A Molecular Basis for Liquid State Information Processors

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DISSERTATION
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PREFACE

Preface contains information and instructions to assist the reader in the intended interpretation of this document.

A paper by Art JJ, in1995 inspired this project by demonstrating the feasibility of melding diffusion, kinetics and electrical phenomena into a single predictive model of channel behavior.[51]

REVISION HISTORY

Event	Date	Description	Location
Committee 4 points	12/13/12	Diffusion EQ, Terse Algorithm, Sim SUR, Validation test	5.1.10, 6.5, 9.18, 11.2.1:3, 11.7.3.1, 12.3

KEY PHRASES

Affine transformations, allosteric modulation, basis for neural networks, binding kinetics, biocomputation, bioinformatics, biological computation, biological neural network, BNN, Brownian dynamics, cellular information processing, channel capacity, channel cluster, channel distribution, channel localization, channel rafts, channel receptor, chemical modulators, closed graph circuit, closed grid circuit, closed surface manifold, collision detection, compartmental model, computational statistics, computational thinking, concentration gradient drivers, conics, diffusion currents, distributed capacitance, electrodynamics, extracellular compartment, finite state machine, geodesics, geometric representation of neuron, graph theory, heterogeneous digital data, hybrid model, interactive computation, ion channel, ion pump, ion sequestration, Kolmogorov stochastics, linear systems theory, liquid state processor, manifolds, Markov chains, massive datasets, membranal biosystem, membranal proteins, membrane computing, microphysiology, molecular dynamics, molecular model, morphometrics, multi-scale modeling, nanoscale model, nearest neighbor algorithm, neighborhood projections, neural informatics, neural ionics, neural modeling, neural process, neurodynamics, neuron simulation, neuron topology, neurophysiology, neuroscience, nonlinear systems theory, open-form iterative equations, parameterization, partition of unity, portless network, probabilistic computer language, quantum statistics, resistive-capacitive grid, SDE, sequestration, simulation of complex stochastic systems, soft matter physics, spatiotemporal dynamics, spiking neural systems, stochastic

differential equation, stochastic dynamics, stochastic protein conformation, subcellular boundary-crossing processes, synaptic cleft model, tessellation, 3-D voltage gradient, transformative multidisciplinary research, two-dimensional propagation, vesicular release information veracity, whole cell model.

PREPARATORY REFERENCE TEXTS

Due to the interdisciplinary nature of the project, it may be helpful to the reader to note a core set of sources containing the general knowledge that support the synthesis of physics, biology and engineering into a coherent, consistent and optimal-to-mission, body of work.

1. Hille B, Ion Channels of Excitable Membranes, 2001.
2. Sakmann B, Neher E, Single Channel Recording, 1995.
3. Weiss T, Cellular Biophysics, 1996, 2 volumes
4. Papoulis A, Pillai S, Probability Random Variables and Stochastic Processes, 2005.
5. Tuckwell H, Stochastic Processes in the Neurosciences, 1989.
6. Crank J, The Mathematics of Diffusion, 2004.
7. Halliday D, Resnick R, Krane K, Physics, 1998.
8. Voit E, Computational Analysis of Biochemical Systems, 2000.
9. House J, Principles of Chemical Kinetics, 2007.
10. Howard R, Dynamic Probabilistic Systems, 1971,
11. Chen C, Introduction to Linear System Theory, 1970.
12. Bhatti M, Fundamental Finite Element Analysis and Applications, 2005.
13. Choma J, Electrical Networks Theory and Analysis, 1991.
14. Griffiths, D, Introduction to Electrodynamics,1999.
15. Noble B, Applied Linear Algebra, 1979.
16. Sperelakis N, Cell Physiology Sourcebook Molecular Approach, 2003.
17. Erleben K, et.al. Physics-Based Animation, 2005.

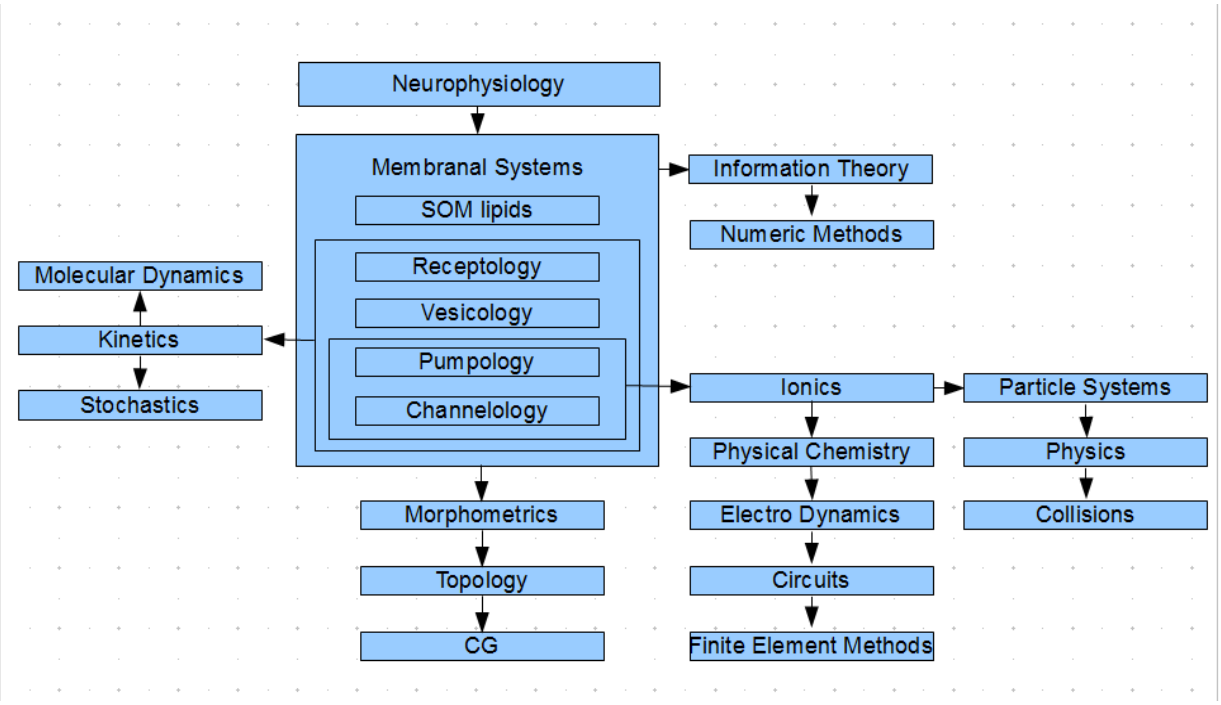
The above collection, or their equivalents, spans the basic science employed in this project, and are not cited on a fact-by-fact basis. Current advances beyond this basis are duly noted and cited in the bibliography.

MULTIDISCIPLINARY MODEL

TABLE 1: CONTRIBUTORS OF PREREQUISITE DATA

CONTRIBUTORS	*This is a multi-disciplinary project. It is acknowledged that the workers in the following fields are contributors to the knowledge pool prerequisite to implementation of this model.*
Physiologists	The general information necessary for whole cell modeling of the information processing by neurons comes to us from neurophysiologists. The data they generate must be culled, conditioned and normalized to appropriately fit the model data structures, constraints and scope. e.g. Eric Kandel
Channelologists	Within the field of physiology is channelology, a specialty providing research findings on cellular ion channels (Similar to the work of receptologists, vesicologists, and pumpologists). Ion channels are the informationally most significant actor in the neuron. They are the modulators, the primary component of the positive feedback loops that must be tamed (for stability), and are responsible for propagation of information along the neuronal processes. e.g. Jon Art Similar proteins include pumps (injecting energy into the system via concentration gradients), and receptors (the input devices to the whole system).
Physical Chemists	Physical chemistry if foundational for the creation of voltage from ionic solutions, for diffusion, and for chemical kinetics and energetics of all molecular interactions and state changes, e.g. Fick, Nernst, Crank.
Physicists	This model relies upon numerous physical constants and formulae. Temperature, force generation, conversion from potential to kinetic energy, conservation of momentum and charge, force fields, energy flows. Also Boltzmann, Planck, Einstein, Faraday, Avogadro constants. In particular, Electrodynamics and elastic collisions are extensively employed.
Circuits Analysts	The voltage sources, the current sources, capacitance of the membrane and the resistance of the saline – all require circuit theory to convert to a mathematical representation for a 2-d closed surface grid of about 1 million elements.
Control Theorists	Stability, limit cycles, positive and negative feedback loops and networks, instability analysis, nonlinear methods, oscillations, consistency, and error – are all considerations and metrics of how the model is designed and performs, e.g. Lyapunov.
Computer Scientists	Software architecture, data design, algorithms, numeric methods, and a plethora of Matlab ™ idiosyncrasies all demand significant effort within the realm of computer science.
Linear Algebrists	All of the diffusion, stochastics, and circuits equations are converted into

	matrix notation, and the solution is derived via matrix inversions. Linear algebra makes for very efficient coding and supports rapid search algorithms.
Statisticians	Kinetics and probability distributions are in constant employment in the model of a neuron. Stochastic Differential Equations are the heart of modeled behavior for receptors, channels, vesicles and pumps, and their binding sites. They are finite state machines, represented as functions in time. There are significant sources and uses of thermal noise in biologic systems. There are also huge variations in the instantiation of cell types. Kolmogorov and Markov methods are used.
Topologists	The shape of the neuron is exceedingly complex. Simplification is necessary to render such data tractable to digital computers. The theory of topology assists in condensing 3-d phenomena down to 2-d matrices, while preserving the essential relationships between the elements.



While admitting extensive reliance upon the above fields, this list is also intended to set a reasonable boundary beyond which raised topics can be held as out of scope for this project.

SYNTAX

SI units are the current standard for all scientific literature and academic dissertations. Regarding biological phenomena, SI units shall be used herein. However, within the realm of modeling all units are synthetic, even when

they purport to mimic some real measurable quantity. Computational loads are sensitive to scale and to frequency of unit conversions. To minimize computational load it is necessary to create modeling units optimal to the model's purpose. These units are created in Chapter 3 Strategies.

The modeling activity described herein is conceived and executed in computer code languages, particularly Matlab and Octave. The syntax of these languages is at variance with SI units and other conventions of the scientific literature. Because the symbols of the narrative and computer code are quite intimate to each other, it would be tedious and confusing to maintain two completely separate and contradictory sets of rules for their use. A singular set of rules is adopted herein which apply to both the coding and the narrative. The following conventions are used consistently throughout this document.

1. Curly brackets "{ }" denote sets. Straight brackets "[ ]" denote vectors/matrices.
2. Comments appended to the right of a formula or equation are preceded by a "**%**" .
3. Return or New_Line is indicated by a semi colon " **;** " . EX f=m*a**;**
   Mathematical equations are typically, but not necessarily, terminated by a semi colon.
4. Single names constructed of multiple words must be connected by "**_**" .
   EX new_name
5. Exponentiation is indicated by "^" . EX 2^2 = two_squared;
6. Multiplication is indicated by "*****". Never by x. EX ans = 2*2;
7. Matrix and Vector values are contained within "**[ ]**" . EX A = [1 2; 3 4];
8. The size of a matrix is indicated by **"x**" . EX A = [1 2; 3 4]; % A is 2**x**2
9. Concentrations are always preceded by "Conc". Never within [ ]. EX ConcNa = 105; % mM
10. Discrete Ranges from *a* to *b* are defined by "a**:**b". Never a-b, never a...b. EX countC = 1:100;
11. Ranges with step values other than 1 are defined by "a:step:b".
    EX rangeD = 3:0.1:5; % rangeD is 1x21
12. Continuous Domains from *a* to *b* are defined by "a .. b" (two periods).
    EX 3.1415962 is_element_of 2..4;
13. Equations that are interrupted by a line break shall indicate such by the ellipsis " **...** " .
    EX e = m * ...
    c^2;
14. The operators AND, OR, NOR, NAND, XOR are in all capital letters.

15. NOT is indicated by ~ EX -1 ~= 1;
16. When a value is approximate, use prefix 'approx' as a function. Never ~.
    EX pi = approx (3.1); EX F = approx(3.1,tol), % where tol = plus_or_minus 0.05;
17. An estimated value is indicated by the prefix “est”. EX est(F) = 3.1;
18. Terms are defined using the symbol ::: EX up ::: following a radial ray away from its center point
19. Typeface modifiers - such as bold, italics, font_size and font_change - are not recognized by the computer languages in use, and therefore are not used in the narrative, except within document headings. Unfortunately, this does not comply with the SI standard requiring all variable names being written in *italics*.

INTENDED USE

The computer program application described herein is a stand-alone application, with no interfaces to other hardware or software. It may be set up to automatically input morphometric data and actor distribution and/or kinetic data from other databases. And it may require a multi-core machine to be practicable for realistic simulations. Its output is quantitative, time-series data, optionally in movie form, to depict a reasonable visual representation of the neuronal structures and dynamic processes. This output is not intended to drive any other hardware system. It may drive clones of itself, that is, several models of neurons that may be wired into a local circuit.

The Usage sequence is straight-line linear (see fig. below). A Data Design phase is necessary to normalize complex patterns available in the biological literature, which are selected, filtered, normalized for compatibility, and simplified so as to fit within the provided parameters of this model. Molecular mechanisms must be scaled in space, time and quantity to render them tractable to current digital computational devices. Additionally, each experimental design is driven by a specific query. Parsimony and alignment to the query involves discovery, culling, cleaning, normalizing, and filling in gaps with hypothetical data ranging across the regions of interest.

Conceptually, the user engages the following sequence of events in a model RUN.

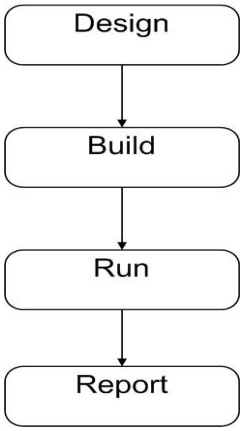


FIGURE 1: USAGE SEQUENCE

USER CONTRIBUTORS

The multidisciplinary nature of this project warrants acknowledgment of the various talents employed. The contributors list below indicates the fields of study from which numerous scholarly papers were consulted. This list also serves as a reminder to the user that liaison to these fields will be necessary to master the potential of this sort of modeling.

User	Any individual sufficiently versed in molecular neurophysiology and numeric programming, and desirous of building predictive, demonstrative, and/or verification models of neuronal behavior regarding information processing potentialities.

NOTES on Citations

Citations are pointers to the List of Cited Literature. As pointers they should be as brief as possible to uniquely specify a single entry in that list. The author has chosen the method of PubMed database numbers, because they are globally unique assignments to peer reviewed scientific literature related to the life sciences. Books have a well established ISBN number with 3 or 4 dashes within a 10 or 13 digit number, easily distinguished from pubmed numbers. Unfortunately, not all cited literature yet has a PubMed or ISBN number uniquely assigned to it. For those articles and books an arbitrary number has been assigned (hopefully only temporarily). These arbitrary

numbers always are prefixed by four 9's followed by four digits, e.g. (99990001). When it facilitates the flow of the narrative to indicate the author and year of the work, as in the historical review of the field, the convention of (Last FM, year) is used. Alternative methods may list all the authors or use “et.al” to indicate more than one author. As used herein, the intention is for these to serve as pointers to the List of Cited Literature, not to pay homage or courtesies to the authors right there on the spot. The List of Cited Literature gives full and proper credit, such that the pointers may remain as brief as possible.

NOTES on Grammar

This topic involves extensive quantitative data, tables, equations and computer code. Conventions are devised to minimize redundancies of representing both the conventional equation formatting and equations as computer code. For consistency, all equations will be presented only as computer code. Numbers less than twelve are not converted to text but rather left as arabic numerals, unless the name of the number is intended. The author does not subscribe to the convention of hanging quotation marks after the period unless the quote is of an entire sentence. The organizational principals of parentheses are adhered to.

ABBREVIATIONS

A2D	analog to digital conversion
AA	actor to actor interactions
aar	spherical coordinates = [angle1 angle2 radius]
Aarz	acceleration, cylindrical = [angular rotation divergent radius axial linear]
AB	actor to particle interactions
acc	set of accelerations
actor	any active protein embedded in the lipid membrane (channel, pump, receptor, vesicle)
afo	as a function of
a/k/a	also known as, alias
allo	actor binding to affect modulation of its kinetics
AN	actor node assignments
ANN	artificial neural network (silicon/oxide based)
ap	action potential, discrete propagation of information, decision
AP	actor position = [x y z, dx dy dz (orientation), pole extents]
arg	argument(s) of a function
arz	cylindrical coordinates
AS	assumption, as enumerated for software module
AT	actor types
autocor	auto-correlation
avg	expected value, mean
avog	Avogadro's number
ax	pertaining to the axis of rotation
Axra	acceleration, cylindrical (axis position, radius, angle)
Axyz	acceleration, Cartesian
basec	basis coefficients
BC	boundary conditions
basef	basis function
bind	coupling function
bio-	indicates empirical data collected from a living sample (not simulated nor hypothesized)
bl	bond length
BNN	biological neural network (water/carbon based)
boltz	Boltzmann's constant
BP	particle positions, velocities, accelerations = [x y z dx dy dz ddx ddy ddz type]
BT	particle types (atomic# mass charge radius etc)

build	population of all data structures within the model to effect all IC's, BC's, and statics.
cart	Cartesian coordinates
cdf	cumulative distribution function, integration of pdf, used to generate instantiations
chan	ion channel type
ci	configurational integral
class	group of software entities treated identically wrt data types and functions called
co	Coulomb operator
collar	ceiling + floor membrane positions for a given particle, or for a given compartment
comp	compartment. Usually comp1= intracellular, comp2= extracellular, comp3 =sequestration
con	cone-shaped compartment or subcompartment
conc	concentration within a specified volume. A vector across all particle types, not a scalar.
concIn	concs in the intracellular comp1 e.g. conc.all = [conc.na conc.k conc.ca conc.cl conc.an]
concOut	concs in the extracellular comp2
concPeri	concs in the perilymph comp3
CPU	central processing unit, main chip type in a computer
cor	correlation function
corn	normalized correlation function
cov	covariance function
covar	coefficient of variation
cp	chemical potential
CP	compartment positions = [x y z]
CPU	central processing unit, main chip type in a digital solid state silicon computer
CT	compartment types
curl	three dimensional net rotation of a fluid about a designated point, curl(v) = cross(del,v)
cyl	cylindrical, especially cylindrical coordinates
d	differential, especially first differential
dd	second differential
D	distribution of
D2A	digital to analog conversion
DE	dependency, as enumerated in each software module
deal	divide a matrix into column vectors
del	three dimensional gradient function, del(t) = [dt/dx dt/dy dt/dz] .* [i j k]
dens	density
densc	charge density
densm	mass density

densn	density by quantity of particles, similar to conc
densp	momentum density
densr	particle volume density
design	formalization of all the biologic and physical data necessary to create a static model
diff	difference equation
disk	planar end of compartment or perforated disk intermediate platen surface of compartment
dist	distribution instantiation
DIST	file type containing one or more pdf's associated with Actors, Interactors, Variables
div	three dimensional divergence function div(v) = dot(del,v) = dvx/dx + dvy/dy + dvz/dz
dm	change in particle mass
dra	draw, as in construct plot points
dry lab	analytic data collected from electronic simulations
dt	time step or time slice for purposes of computational iterations of differential EQs
dx	space step or volume slice for purposes of computational iterations
dX	distance between centers of particles = [x2 y2 z2] - [x1 y1 z1]
e	exp(1) = 2.7183… (not an electron charge)
E	electric field
ed	dielectric constant e_o*er
edge	graph connector between 2 nodes
EM	electromagnetic force
eo	permittivity dielectric constant for a vacuum
EP	electrostatic potential
eps	events per second
EQ	equation
er	relative permittivity
ergbar	energy barrier, especially as a axial profile within an ion channel
ev	model voltage/kelv
EX	example
exop	exchange operator
EXP	experiment, particularly a software run designed to answer a biologic query
F	force or force field
flops	Floating point operations per second, as load on a CPU
fsm	finite state machine
gen	generate
gibb	Gibb's free energy

Goblet	Micron-scale whole cell model
grad	gradient
graphit	generate plot
h	header, column headings for a matrix, or row headings for a matrix
HAD	Hybrid Analog Digital
hamil	Hamiltonian
hc	heat capacity
helm	Helmholtz free energy
horz	processes parallel to the membrane surface, parallel to the axis, e.g. Ri, Ro, Xflux
HW	hardware
ijk	orthogonal unit vector, cartesian
iops	Input output operations per second, as load on a CPU
I	identity matrix
IC	initial conditions
IN	input
int	integrate
interactor	any particle in solution (ion, ligand, ...) which will diffuse and/or bind during simruns
INIT	initialize the model by populating input data into the workspace. First step in BUILD
im	Imaginary values expected (used as part of a variable name)
IP	information process, information processor, information processing
ix	Index vector of a variable (used as part of a variable name)
Jz	horizontal diffusion (parallel to the surface of the membrane)
Jr	flux perpendicular to the membrane, especially through channels
k	index value
KE	kinetic energy
L	size of a rectangular container or voxel = [dx dy dz]
lagran	Lagrange multiplier
lambda	space constant
laplac	Laplacian = $del^2\ t = d^2t/dx^2 + d^2t/dy^2 + d^2t/dz^2$
lim	limits
logi	matrix of logical data type, consisting only of 0 and 1, or true and false, or yes and no
lookup	input to output mapping via a table
lv	latice vector
m	mass
mag	magnitude, radius, distance

M	concerning membrane
MD	molecular dynamics
memb	lipid membrane traits, including thickness, capacitance, permeability, etc
metric	metric matrix per distance type
mi	mutual information
mo	membrane orthogonal process
mob	mobility
mobe	electrical mobility
mobm	mechanical mobility
mod	ligand, interactor or force that modulates the state transition rules of an actor
mp	membrane parallel process
mt	membrane transverse process (perpendicular)
N	concerning Nodes of a membrane
NaN	not a number
NanoNeu	Multi-scale Model combining Patch and Goblet
NIP	pertaining to Neuron Information Processing. Throughput, not internal organization
NIPS	Neuron Information Processing Significance. An inclusion criteria.
node	locus of an Actor on a membrane, pos(actor(N))
norm	normal to a plane
NTF	nonlinear transfer function
O	gating function, as in open/close
OE	operating environment, as enumerated for software module
om	overlap matrix, or 2 or more matrices merged
opq	euler angles
OUT	output: e.g. phenostate, released particles or observable voltage
P	actor poles, actor positions, particle positions
Paar	position, spherical
pack	packing density
pad	fill in vacant elements in a matrix with default values
pair	pairwise collisions or pairwise contractions
param	parametric values
Patch	Nano-scale cuboidal submodel, exemplars for large quantities of similar patches
pc	partition coefficient
PC	personal computer, 1 cpu, 1gbs speed w/ 1 gb memory (for benchmarking loads)
PDF	probability distribution function

PE	potential energy
perp	perpendicular
pf	partition function
pheno	outwardly expressed state
plaid	pattern of actor placements in the membrane, including polyads, interpolated gradations
plank	Plank's constant
plu	input or output plug(s)
pole	Binding/unbinding allosteric sites on an actor. Actors have a pole on each side of memb
pos	position, may be cartesian (x,y,z), cylindrical (r,a,z), or spherical (r,a1,a2)
pres	hydraulic pressure
princ	principle components, ranked
pt	cartesian point
pump	type of pump, cotransporter, exchanger, or ATPase, transporting ions across a membrane
PVA	[position velocity acceleration] vector (1x9)
PVAMR	[position velocity acceleration mass radius] vector (1x11)
Pxra	position, cylindrical (axis position, radius, angle)
Pxyz	position = [x y z]
q	quantity
Q	file containing one or more matrices of state transition rates
Qdt	Function generating Q as a function of modulator values. Q = Qdt(mod1(t),mod2(t)..modn(t))
QED	Quod erat demonstrandum; that which is to be demonstrated or proved
QEF	Quod erat faciendum; that which was to have been done
qm	quatropole moment
qt	quantity of time steps in simulation
RAM	Random access memory of a digital solid state silicon computer
rand	generate random number(s)
RC	resistance - capacitance electric circuit
recep	type of receptor specifically involved in neuronal information processing, metabotropic
rem	remainder
report	collected data from the run can be projected as a movie and graphed.
rgb	color vector = [red green blue]
rin	pertaining to rings, points in rotation
rms	root mean squared
rot	rotate
rt	dt*qt = run time

RT	real time
run	iterative time loop in the program to simulate dynamics.
S	state matrix
SAM	self assembling molecule
sc	similarity coefficient
sd	standard deviation
se	statistical efficiency
sf	substitution function
Sh	parametrized shape
SI	International System of units
simrun	simulation software run, the act of executing full program according to parametric settings
sn	serial number of a model element
SNR	signal to noise ratio
so	spatial orbital
sph	sphere, spherical, especially spherical coordinates
sr	swing radius
state	molecular configuration, represented as finite state subject to transition probabilities
STP	state transition probabilities
substructure	a mathematical component (usually a matrix) of an actor representation
subunit	a biophysical protein component of an actor
SUT	system under test, as enumerated for software module
SW	software
swit	switching function
t	time
tt	period or interval
tau	time constant
te	instantaneous energy (at time t)
TE	test environment, as enumerated for software module
this	reserved word, referring to Norm Dyer's work, so as to distinguish from others' work
thk	thickness
tor	torus shape compartment or subcompartment; may be only quadrants of a torus
tri	triangle
TYPE	stationary intrinsic trait data of an Actor or Interactor (not species)
Vaar	velocity, spherical (angle, angle, radius)
van	radial vane(s) to divide a round compartment into sectors

var	variance
varf	variance function
Varz	velocity, cylindrical
vel	velocity of an interactor, may be Cartesian (x,y,z) or polar (u,v,w)
vert	refers to processes perpendicular to the membrane surface, radial, e.g. Gchan, Cm, Ipump
ves	vesicular mechanism for releasing quanta of neurotransmitter into the synaptic cleft
vir	virial
vol	volume
vox	voxel, unit of volume, especially as a pair centered on an actor, one above and one below
VV	set of all velocities
Vxra	velocity, cylindrical (axis position, radius, angle)
Vxyz	velocity, cartesian
W	momentum, linear = velocity*mass
wet lab	analytic data collected from living cells
wrt	with respect to
xloc	translocation of a particle = [dx dy dz]
xls	spreadsheet
xyz	cartesian coordinates
z	charge or partial charge on particle (valance)
zon	pertaining to zones

One Letter code used in function naming

A	actors = { recep/shuttle chan ves pump }
B	particles, interactors = { ions polyatomic ions ligands messengers }
C	cytological compartments (not Rall compartments nor finite element compartments)
D	1) distribution 2) shuttle data
E	charge, units are count of positrons
F	force field (EM or concentration)
G	conductivity (vector across all particle types, not a scalar)
H	actor subunit
I	current, units = count of net charges per unit time passing through a designated area
J	particle flux, units = count of particles per unit time passing through a designated area
K	1) constant, 2) capacitance
L	logical (includes gating)

M	membrane
N	node
O	molecular phenostates, gating function, transport function, also pivots
P	1) position 2) pole
Q	transition matrix
R	bind/dissociate kinetics matrix
S	state (of actors or actor subunits)
T	type
U	1) instantiations from distributions 2) traits
V	voltages,
W	1) Implicit entities, 2) input signal as modulation values
X	axis of rotation, on or projected to, length of the neuron
Y	perpendicular to the axis, orthonormals
Z	volumes, voxels

One Letter code used in Matrix & Argument Naming

A	actor occupancies, current bindings (M), current state (Q)
B	particle bindings, actor assignments
C	CDFs
D	distances between particles and particles, particles and actors
E	current charge locations = P*z
F	current force field due to charge, electrostatics
G	conductivity profile, particle transport profile
H	maps subunit types into an actor type
I	current charge vectors, as grad, div, and curl
J	delta concs (transports)
K	particles held in capacitance
L	particles held in sequestration
M	modulation combinations per actor type, with map to Qpage
N	Floor and Ceiling for particle reflections
O	actor phenostates
P	current particle positions, actor poles
Q	transition probabilities
R	affinity values for each binding sight, as altered by M state
S	state time series
T	

U	distributions, PDF's
V	current particle velocities (Boltzman distributed)
W	current accelerations due to F
X	contents of each voxel pair, over and under each actor
Y	contents of each affinity hemisphere, over and under each actor
Z	valence of each particle

Terms of Limited or Altered meaning

...noting newly defined terms and rare usages of known terms

actor	a protein molecule capable if significant changes in state (conformation). In particular, receptors, channels, vesicles and pumps are actors in this modeling framework.
capacitated	ions that are prevented from achieving charge space neutrality by a membrane barrier, and therefore collect near the membrane, attracted to opposite charges across the membrane. Charges are effectively bound in the direction perpendicular to the membrane, but are relatively free to migrate parallel to the membrane surface.
channel	unless otherwise specified, an ion channel consisting of protein subunits and embedded in a lipid membrane, and capable of opening a pore through the membrane to selectively allow particles to pass by force of concentration and voltage gradients. Channels are usually modulatable by ligands and/or voltage.
distribution	the statistical positions and densities of a specific actor type on a specific cell type. Includes changes in distribution, turnover, regulation of distribution
element	ion, ligand, membrane, receptor, channel, vesicle or pump. Implicit elements include water, capacitor, resistor. Receptor includes second messenger structure.
engine	portions of software dedicated to advancing simulated process, as opposed to software that manages data transfers, sorts, integrity, etc.
exsert	Tap into a system to realize and output signal; opposite of insert
instantiator	a computational device consisting of a random number generator and a CDF, producing a stochastic output that conforms to statistical parameters. (called Markov propagator function by others)
interactor	see particle
kinetics	probability transition matrix for the significant conformations of an actor as a kinetic scheme, per subunit of actor type, including all significant binding sites and their possible ligands, in various combinations. This more closely matches the chemist's use of the term than the physicist's use of it.

membranal	pertaining to an assembly of a lipid membrane immersed in saline solutions, with embedded receptors, channels, vesicles and pumps. May refer to a membrane patch or a closed cell.
modeling	mathematical models and artificial builds of elements and element assemblies; and runs, wherein processes act upon these elements Meta-modeling refers to the designs of models and the iterative improvements to them.
modulator	any ligand binding to an actor type that would alter its probability transition matrix. Each modulator has binding/unbinding probabilities specific to each actor type. Also force gradients impinging on an actor which alter its probability transition matrix.
number	identification number or serial number, but not quantity.
particle	instantiated ion or ligand entities that are motile in water due to thermal energy, and reflect off container surfaces. They may become bound to actors, transported across membranes, and/or experience drift due to the EM force. Particles have mass, effective radius, and optionally have charge. The word particle is used interchangeably with interactor.
platen	for convenience, the model provides limited planar rings as part of the shape of the plasma lemma. This provides a surface suitable for synapses, without the need to address contours which significantly increase calculations of synaptic processes.
pump	ATPase, cotransporter, exchanger, or electrogenic transporter. May transport ion, ligand or messenger particles in any combination. May be driven by ATP or by concentration gradients. Has kinetic scheme that is modulatable, including binding/unbinding kinetics.
receptor	metabotropic receptors for neurotransmitters and particles that serve modulate ion channels. A transmembrane switchable catalyst. Ionotropic receptors are not included under this term.
responder	given a signal, various actors in the vicinity may or may nor respond to that signal. Those that respond in the earliest physiologic time are called first primary responders. Those that respond on the echo of the primary responders are called the secondary responders.
stateful	an actor with two or more significant states of utility in information processing
systemics	interactions between membranal elements, as expressed in cell behavior or multicell behavior, especially with feedback loops. Includes poly-entity interactions, homeostasis, information processing, learning, role, and modes. As distinguished from process, which involves the interactions between two or three elements, without feedback loops.
tonicity	measured ion concentrations on both sides of an actor, particularly the micro environment (voxel pair) unique to that actor. This includes charge imbalance.
tranche	v. to divvy up the whole in a non-obvious way into a set of abstractions, which as a group contain the necessary and sufficient information to reconstitute the whole. n. one of the several pieces of the whole so divided. This concept is borrowed from the financial community. For example, a particle system may be tranched into its position data, its velocity data, its force data, and its container data, each of which may be processed alone for certain metrics.
type	unique molecular formula for an actor, therefore unique probability transition matrix, defining which subunits comprise it. Characterizing that type, distinguishing it from all others.

vesicle	transducer of information from an intracellular Ca++ ion messenger input to a packet of messenger molecules deposited extracellularly as output. Its informationally significant aspects are the particular contents resulting from the formation system, and the speed and reliability of the vesicle release mechanism.

Other apparent abbreviations may be function names.

SUMMARY

Solid state electronics is reaching developmental limits with regard to miniaturization, clock speed, and heat dissipation. Further advancement in hardware will require a new approach. The miniaturization limitations are breached by exploitation of intramolecular order. The clock speed limitation is breached by asynchronous massively parallel processes. Heat dissipation is solved by avoiding energy consumptive processes, rather powering them by ambient thermal energy. Liquid state information processors combine all of these benefits.

A computer model is devised to represent, at the molecular level, information processing by membranal systems similar to that in neurons. The model consists of membranes, mobile particles in aqueous medium, and stationary membranal proteins (multiple-state actors). The membranes are three-dimensional closed surface whole cells, containing volumes of freely diffusing particles (ion species, neurotransmitter species, second messengers, ATP, etc.). Each species of particle is represented as a large number (1E3 to 1E6, proportionate to *in vivo* concentrations of each) of individual particles with mass, charge, radii, position, and velocity. Particle mobility enjoys diffusion, collisions, viscosity, and drift due to charge fields. Particles collide, reflect, bind, absorb, and transport across membranes. Linear momentum is conserved. Particle mass and radii may be dynamically modified via solvation probabilities. Several relevant characteristics of water are represented so as to replicate the collision paths of particles and maintain the Boltzmann velocity distribution of each species of particle as a function of mass and temperature. Particles experience Brownian dynamics and drift under the influence of all charges in the system, fixed or mobile, as an N-body problem. Particles colliding with a membrane are reflected or absorbed according to oil/water boundary kinetics. Energy-bearing particles (e.g. ATP) may be individually transmuted to alternate forms (e.g. ADP) when binding to a pump or G-protein system.

Four classes of membranal proteins, those that exhibit neuron information processing (NIP-significant) conformational changes, are represented: metabotropic receptors, ion channels, vesicular release mechanisms, and ion pumps (these four types are collectively referred to as actors). Ionotropic receptors are treated as ion channels with modulator binding sites. All actors have the capacity to bind and unbind particles at various binding sites, instantiated stochastically, according to known kinetics as a function of modulation and molecular conformation. Actors each have the capacity to stochastically change conformations according to transition probabilities, as

dynamically modified by voltage and/or allosteric bindings. Actors return instantiated conformations, updated binding affinities and transport actions as outputs (e.g. receptor release of messenger; channel conductances; pump staging, transporting or releasing; or vesicular release of neurotransmitters). Each combination of modulation site bindings plus the impinging voltage warrants a change in the transition probability matrix. These probabilities are instantiated each time step as a function of the prior state, and particle concentrations in the actor's vicinity. Individual particles that are bound have their velocities set to zero until stochastically dissociated. Transported particles are reassigned to the adjacent compartment, then resume a Boltzmann velocity.

The neuronal membranes are represented as closed three dimensional surfaces, with thickness, given shapes that preserve the topological relationships between nearest neighbors of the membrane (generated from contours of revolution). Actors are positioned and oriented embedded within, and permeating, the membranes. Positions are selected statistically per probability distribution patterns equivalent to their spatial patterns in living neurons. Actor position determines the electric conduction between nearest neighbors and the capacitive area surrounding each. Membranes serve as a dielectric barriers, maintaining charge separation.

Digitally, in time steps of about 1E-4 s, the above processes are simulated across approximately 1E6 loci for simulated time duration of about 0.1 s. The time-scale compass is 1E-4 s to 1E-1 s. The space-scale compass is 1E-10 m to 1E-5 m. The quantity-scale compass is 1E1 to 1E5 (one model particle represents from 1 to 1E5 real world particles). Due to the actions of pumps, channels, diffusion and drift, particles are redistributed each time step.

Particle flux alters the local concentrations and charge distribution. These determine Coulombic and Nernst voltages local to each channel and pump. Voltage and concentration gradients between nodes, and thermal energy, drive ion movement through somewhat resistive saline solution, and through selective and dynamically conductive ion channels. Particles passing through ion channels become neutralized by opposite charges if available, else become capacitated at the membrane. However, they eventually are pumped back across the membrane by ion pumps distributed in physiologically realistic patterns. The aggregate effect of this parallel multitude of actions may generate wave fronts of graded responses or action potentials, which may decay or propagate along the membranal surface depending on gain. These disturbances may cause calcium channels located near vesicles to allow Ca++

ions into the neuron which proceed by constrained diffusion and bind to nearby vesicles. This initiates the kinetics of neurotransmitter release into the synapses. The specific mix and quantities of neurotransmitters in a vesicle are determined stochastically. Additional pumps retrieve neurotransmitter and other messenger particles from the synaptic cleft, thus determining messenger half lives. Ion pumps (cotransporters, exchangers and ATPases), and messenger pumps as well, have quantitative affinities for their substrates, demonstrating starvation and saturation kinetics. They pump stochastically according to competing affinities and dynamic transition probabilities. A limited quantity of chemical processes are supported, such that pumps may convert ATP to ADP per cycle (or be driven by the Na+ concentration gradient). The pumps must be adequate to maintain physiologic concentrations throughout physiologic channel opening patterns, except to the extent that fatigue is being modeled. The incoming information to the neurons arrives as ligand particles, is transduced into the motion of four or more species of ions, which each affect their targets differently and are themselves affected by ion channels differently, causing ion channels to "resonate" to inherent patterns of molecular dynamics of their type.

The above aspects are integrated into a software application serving as a neuron design workbench with a parametric domain spanning most neuron types. Cuboidal patches may be excised from a whole cell model for a more rigorous study of molecular interactions. Such patches support 1:1 particle representation, so as to justify the whole cell model which uses one particle to represent thousands of real world ions.

Multi-scaling is supported so as to assemble the results from patches into whole cell models, and for assembling whole cells into local circuits. Thus, channel physiology, pathology, therapies and hypothetical types can be simulated.

Three-dimensional charge flux is emergent. Localized membrane capacitance of charge imbalance is emergent. The zeta potential (fuzzy layer of thermally energetic charges near the membrane) is emergent. The electrical grid implied by a two-dimensional fabric of saline resistances, membrane capacitances and dynamic, through-membrane conductances is emergent. Input signal pattern recognition is emergent from single channel kinetics. Action potential propagation is emergent from the channel refractory kinetics. Propagation velocity is emergent from the membrane capacitance and actor spacings, and actor response times. Antidromic dampening is emergent as a

function of actor refractory times. Lateral and axial flux are emergent from asymmetrical placements of pumps and channels.

Systemic behavior arises from the constellation of actors, and can achieve waves of characteristic opening/closing patterns, with resultant signaling via ion flux. Therefore, information flow is spatiotemporal, with temporal patterns found to be significant to actor behavior. Patterned neuron firing sequences are emergent from channel type kinetics plus diffusive interactions between those types. The constellation of actor type distributions and synaptic connectivity patterns determine the computational role. Liquid state processors harness thermal energy for diffusion and stochastic gating, with only the pumps consuming significant energy, to do work against concentration and charge gradients. The quantity of ions pumped need only be sufficient to drive a quantity of ions through the open channel to create a large enough disturbance of the capacitated charges along the membrane to stimulate adjacent channels. No energy is consumed by the gating mechanisms, which are driven by ambient thermal energy.

The actors are found to act as pattern recognizers and as pattern generators. This potential is rather easily harnessed into single molecule information processors. Ironically, the computational load of a digital representation of such a model is huge. The model of hybrid particle Markov processes captures the informational content of the molecular mechanisms of the neuron, allowing a much more detailed predictive model of neurons in the wide variety, in health and in various pathic states, and the development of the liquid state as a computational machine.

The membrane serves several valued roles, providing accurate capacitance, positional stability and order for the actor processes. Membrane area voltages and concentrations exhibit significant non-homogeneity, which is crucial to their carrying of information. The ions near the membrane are found to commute between actors not via diffusion, but rather by an efficient wave phenomena driven by the EM force and their own mass (together comprising a second order system).

The published data on the four classes of membranal proteins is rarely complete, due to the relative difficulty of measuring hidden intramolecular states, as opposed to the outwardly expressed phenostates. Internal consistency is robust, sufficient to found a science of liquid state molecular information processors, and support the design and development of single molecule information processors.

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1 INTRODUCTION

Neurons are distinct from other cell types by their capacity to process information, not merely for themselves, but as a service for the entire organism. Neurophysiologists have established that it is the excitable membrane of the neuron which receives, processes and propagates this critical information through the cell. Such information processing involves these three processes: (1) particles, serving as charge carriers and messengers, commute in aqueous media, (2) protein molecules embedded in the membrane kinetically change their conformations, and (3) charge fields resulting from non-homogeneous distributions of ions induce currents and settle into capacitance. The physics of each of these is well described in the literature.

These processes combine to constitute the complex molecular systems along the membrane, from which the behavior of bio-computation is emergent. Every computational device must consist of at least these two: well delineated elements, and well defined architecture for the connectivity between those elements. The elements must intrinsically change state in response to inputs, and extrinsically communicate those states to other elements according to the connectivity architecture. In service of these two aims, analysis prescribes the elements and synthesis prescribes the connectivity. The particular types of elements may determine the type of computation to be performed. Alternatively, the particular types of connections between the elements may determine the type of computation to be performed.

How do we assemble the known elements of lipid membrane, ion channels and ion pumps into a model that exhibits bio-computational behavior? The analytic work that has characterized these elements is extensive. However, the synthetic work of defining the possible relationships, the connectivity between these elements, is underdeveloped. The synthetic work is well advanced within the field of computer science for silicon-based computation, but carbon-based computation requires entirely different rules of connectivity. The current challenge is to discover the rules of carbon-based synthesis, fully consistent with the known biology and physics, and sufficient to build operational computational devices.

It is therefore proposed to construct a hybrid model based upon diffusion, kinetics, RC-grid[1], and 3-dimensional shapes, which shall represent a neuron's information processing capability via large quantities of individual dynamic molecular events. It shall have the capacity to implement various channel/pump distributions. Such a model offers a work bench for studying the behaviors of channel/pump constellations.

The utilities of such a model are intended to include:

1. provide a simulation context for interpretation of neurophysiology data concerning receptors, channels and pumps
2. provide a design program for creating and testing simulated therapies for channelopathies and pump pathologies
3. further explore the computational potential of artificial neural networks, especially via the addition of modulation
4. founding the new field of molecular based liquid state processors

The elements of such a model have been under study for many decades. The neural membrane consists of a number of self organizing types of lipids. Embedded within this membrane at various points are a number of types of proteins. The proteins of greatest interest to information processing include the receptors, channels, pumps and vesicle release mechanisms. Their occurrence and physiological roles have been explored over many species. Normalizing such findings for systemic compatibility is prerequisite to the assembly of such components into a model of computation. The quantities and locations of ion channels suggest a massively parallel processor of spatiotemporal input patterns. The complexity of spatial patterns and the depth of temporal patterns remain to be evaluated as to how these impact the output signal of the cell, and what then might be the dynamic range of the cell.

Within the theory of computation, general processors are conceived as suitable for all types of problems. If neurons were fully generalized bio-processors, then there would only need to be one type. However, there are many dozens of neuron classifications, and gradients between those types as well. Why so many specialties? Consider that silicon-based computers in general use have within them a CPU chip with approx. 100 million nearly identical "transistors" (gates) over 3 or 4 types. Such transistors are, *de facto*, general in their processing potential. But at the slightly larger scale of the CPU architecture, one finds those components are laid out across the chip in complex

[1] RC-grid: refers to an electrical circuit consisting predominantly of resistors and capacitors. In this case the capacitor is the lipid membrane, and there are two types of resistors, the saline and the variable resistance of ion channels.

non-uniform arrangements. The details of such order involve highly specialized functions. Thus, even these most generic of processors, built up of AND, OR, NAND, XOR gates, require considerable specialized organization within. The search for a theory of general computation continues, but real instances apparently require specializations. The human desire for the general case is understandable. Else each type requires it own discovery with little benefit from the study of other types. Thus the search for common principles, common themes, common components and common processes from which processors can be built. However, such generalities will not serve understanding of the many biological entities until they can be readily adapted to specific cases with only parametric adjustments. This paper strives towards identifying general principles of carbon-based computation. It also pursues a base set of parametric ranges, with each value set therefrom alone determining the embodiment of a useful processor.

A pragmatic approach is to convert the various aspects of algebraic completeness for a general processor into a list of tests, and then apply these tests individually to each of the bio-processors that comes along - and thereby rate each type for its processing potentials. A caveat is that human notions of mathematical completeness may not be so complete when compared with the full flower of evolved nerve cell functions. To wit, algebraic completeness, which is founded in digital logic (surprisingly, not the other way around), may hold little or no overlap with bio-computational completeness, which operates stochastically and over a hybrid analog digital space.

It is therefore prudent to avoid parsimonious modeling. Simplifications are justified by our notions of logic, logic of a type which may not apply in this case. Any fine detail of the various molecular mechanisms, the chemical reactions and the charge activities and/or patterns may later prove to be significant, though at first man's eyes did not perceive their causal relations. The inclusion criteria must be: preserve the information, that which is held, processed and transmitted. This sets the high priority, which may result in diminishing some of the physical, chemical, or even biological nuances, in favor of preserving the information flows.

Bio-computation is fundamentally different from the logical digital processing of common silicon computers. While all electronic devices move only electrons, bio-processors operate with 4 or more types of charged particle sharing the same conductor. Most often these are Na, Cl, Ca, and K, but dozens of other ion types are present as well. This presents immense complexity (and opportunity) compared to mere electrons. Each of these ionic circuit types is not an independent problem, which would be challenging enough, but rather all are coupled to each other just as partial

voltages integrate into a transmembrane potential. Concentration gradients for each ion type, made dynamic by charge repulsions and attractions, lead to complex temporal-spatial patterns that simply do not exist at all with electron pools.

Also present are dozens, if not hundreds, of messenger molecule types that bathe the logical devices of the bio-processor. Such modulators are instrumental in the neuron's ability to compensate for a changing environment, shifting modes for different processing tasks, or even re-centering drifting input patterns.

Bio-processors also grow (evolve) through various developmental phases, changing their role during each. They self-maintain and self-repair. They are not limited to step-by-step logical problems, and readily tackle problems requiring probabilistic decisions based upon incomplete information. They can process analog problems as readily as discrete problems. They sometimes invent new ways of problem solving. Neurons may serve in sensory, regulatory or motor capacities, all based upon a fairly standard model: A cell that grows connections of chemical diffusion, responds with excitable membranes of ample ion channels and ion pumps, and results in the release of more chemicals for diffusion to the next cell. Specialization then results from varying the parametric values of this plan.

Electronic processors have no such counterparts to these ion types, modulator types, growth patterns, and modalities. Each one of these potentialities presents formidable challenges for those wishing to evaluate the greater information processing scope of bio-processors (upon which silicon-based electronic counter parts shed no light). To preserve the yet uncharacterized phenomena for study, large-scale molecular systems models are needed.

Such characteristics of neurons attracted the attention of computer scientists, mathematicians and engineers who in turn gave birth to the field of “neural networks”, hereafter distinguished from living cells by referring to them as Artificial Neural Networks (ANNs). The efforts of this field have been directed toward exploring connection patterns between large numbers of chosen simple elements - elements that typically sum and threshold. Less well studied is the computational potential of each of those elements being connected. In summary, the silicon processors are very developed in their connection theories, though modest in sophistication of their elements. The study of (biological) carbon processors is very strong in analysis of many sophisticated elements, but yet underdeveloped in the logging and theorizing of connection patterns between those elements. This paper attends to the Biological

Neural Networks (BNNs), by further exploring the expressions of each of the element type with respect to information processing potentials and the practical connection patterns between those elements.

1.1 PRIOR ART

In 1943, Warren McCulloch and Walter Pitts published, "A logical calculus of the ideas immanent in nervous activity," credited with launching the field of neuronal modeling [2] . To explore the consequences of distributed memory and distributed power sources, they applied linear systems theory to neural networks, recognizing that neurons compute statistically- not logically- and that a new mathematics was needed to develop this. They derived values for a number of neuron parameters, such as membrane capacitance, saline resistance, and background noise [3]. Over the subsequent 60 years, the process of modeling a neuron typically began with a considerable list of simplifications. This was necessitated by two deficiencies - (1) early computers were quite modest in their throughput, and (2) there was immense amounts of work yet to be done in neurophysiology to characterize and mathematically represent the receptors, channels, pumps and vesicles. Hundreds of workers chose to collapse the immense complexities of the cell by employing the four Hodgkin and Huxley equations, or even further collapse down to the two Fitzhugh-Nagamo equations. In such renditions, all spatial information was purged, and therefore no effects of shape or channel distribution were considered. The Hodgkin Huxley neural model recognizes only two active elements (one type of Na channel and one type of K channel) and two passive components (a constant voltage source and a single capacitor representing the cell membrane). This is adequate to generate an output wave matching the shape of an action potential.

Another prolific form is the integrate and fire (I&F) model which consisted of an input sum with a time-wise bleed rate (thus the "leaky bucket" moniker), followed by steep sigmoid function (e.g. $y = \tanh(x)$) serving as a threshold, above which an output signal was sent; else not. Such approaches are silent on the underlying physics and chemistry directly involved in the biological information processing functions, in favor of mathematically tractable minimal algorithms that yield output curves with a shape similar to the biological action potential.

Heralded early workers in neurophysiology included Hodgkin and Huxley, who applied electrical circuits to the diffusion of aqueous ions inside and outside the squid axon, so as to indirectly observe some of the aggregate kinetics of the large protein molecules that were acting as current gates, i.e. the ion channels. By methods that

would now be regarded as exponential curve fitting, they determined that the Na channels were comprised of 3 identical subunits ("m") plus 1 quite different subunit ("h"); and that the K channels were comprised of four identical subunits ("n"). ... also that the 3 Na subunits would respond to transmembrane voltage drops between 0.060 V and 0.040 V so as to trigger a dramatic opening of the Na channels in 1E-3 s; that the 4th Na channel subunit would follow this opening by rapidly closing the channel in 0.003 s; and that the 4 K-channel subunits would respond to a voltage reaching 0.0 V by triggering a similar but slower opening of the K channel over 0.010 s, followed by a slower, but inevitable closing of the K channels over approximately 0.040 s. These time durations vary somewhat with temperature and tonicities, but their relative positions hold.

The 4 (1953) Hodgkin-Huxley equations (HH EQs) utilized are as follows:

dn/dt = an(v) *(1-n) - bn(v)*n;
dm/dt = am(v)*(1-m) - bm(v)*m;
dh/dt = ah(v) *(1-h) - bh(v)*h;
dv/dt = 1/C*(k*d^2v/dx^2 + G.k * n^4 * (v.k - v) + G.na * m^3 * h * (v.na -v) + I;

% a and b are the forward and backward rate constants for each of the subunit types.
% the values of m,h,n are created by integrating their initial values and the results of the first 3 EQs
% the m and h curves sum to a Na "spike"
% The K channel consists of 4 subunits of type n
% The Na channel consists of 3 subunits designated type m and 1 subunit type h
% C = membrane capacitance;
% I = stimulus current, (disturbance)
% dv/dt couples capacitance to the channels by ion diffusion.
% k = constant of diffusion
% these curves represent aggregate data for the channel types present in the axon

This equation set can be treated as representing a single node. Such a node can then cloned into a series of nodes, coupled by saline resistors. Such a ladder network can "propagate" signal from node to node as a wave front. It can transmit, but not process, information. Derived from studies of the squid axon [4], the primary function of which is to perform long distance transmission of uniformly shaped electrical spikes, this is not surprising. The exponential curve fitting was justified by the first order chemical kinetics of channel subunit conformational changes, the solutions for which are exponentials. The exponent parameters (floor, ceiling, time constant) were equivalent to chemical reaction rates, modulated, in this case by the transmembrane voltage.

The HH EQs represent an aggregate of hundreds of ion channels as a homogeneous mixture present over a length of axon as excised from a squid and placed under space clamp (in a saline bath with a silver wire run up through the middle of the axon to which voltage is varied). The equations are deterministic, therefore noiseless, so do not

present any variance. They do not take into account the distance between channels, nor any dynamic changes in the tonicity of ions as may effect channels over their physiologic range. They do not take into account the driving forces of concentration gradients nor the depletion of those gradients over the course of repeated channel openings. They do not account for the effects of ion pumps. They do not account for other means of modulating ion channels such as phosphorylation, glycosylation, Mg, neurotransmitters, hormones, etc.

Henry Tuckwell in 1989 noted that, "Because the Hodgkin-Huxley equations are difficult to analyze, a simpler system with only two components has been employed."[5] They became known as the Fitzhugh-Nagamo equations. [6] They further reduced the computational load of the Hodgkin-Huxley equations:

Fitzhugh-Nagamo equations, as based upon the v,m,n,h from the Hodgkin Huxley equations;
$dV(x,t)/dt = d^2V/dx^2 + (V*(1-V)*(V-a)) -W + I;$ % where V= f(v,m); W = f(n,h); I = input current;
$dW(x,t)/dt = b*(V-d*W);$ % a,b,d = constants between 0..1

These equations collapsed the Hodgkin Huxley equations from 4 to 2, at the cost of sacrificing realistic units like voltage and rate constants. These equations can also be treated as nodes, cloned and serialized to support a solitary traveling wave. These equations produce a curve shape similar to the transmission of an action potential. However, they do not constitute a computational device.

These equation sets are worth mentioning because hundreds of scientific papers concerning the topic of how a neuron works have been based upon them.

1.1.1 PHYSICAL BASIS

Ludwig Boltzmann (b.1844 d.1906) gave us the concept of entropy, and a treatment of time, tractable to the requirements of physics. Entropy was originally viewed as waste heat. But it came to be appreciated for the lowest energy state, the most relaxed conformer of a possible set of conformations. This set of possibles came to be formalized as a probability distribution. The concept of entropy predicts that the conformation requiring the least energy to achieve is the one with the highest probability of occurrence. And so entropy has great utility in finding the common conformations of complex bio-chemical systems, indeed the entire distribution of products and byproducts. It has served to broaden our vistas of chemistry, and that has led to a mathematics and stochastics of chemical systems.

Boltzmann also worked out the velocities of particles for a given temperature and mass, as a gas or a liquid. With his velocity distributions, virtual ions can be instantiated and later, after numerous collisions, checked for "sanity" (compliance to real world physics) against his profiles. Such particles are available for free paths, collisions, reflections, binding and/or transport. The collision rates of ions in saline with stationary channels and pumps can then be measured as a function of surface area. Realistic diffusion rates through complex shapes become feasible by open form iterative methods. At the molecular level, concentrations are the trivial result of particle counts within a unit volume. Realistic interactions may be instantiated 3-dimensionally, where shape determines surfaces, volumes and nearest neighbors. Temperature can be calculated backward through the Boltzmann distribution.

Perhaps more important to the purposes of this paper, Boltzmann's work fathered statistical mechanics, providing the mathematical basis for particle systems.

Georg Cantor (b.1845 d.1918) developed a mathematics for treating infinities, paving the way for digital computer algorithms, where incidental division by zero is common enough. He provided an essential set of concepts for converting analog data into digital, continuous into discrete. This finds utility in formalizing the processes by which neurons convert analog events into discrete events, and discrete events into analog events. He also developed a mathematics of set theory, so useful in classifications, especially where there are multiple layers of logic. Set theory reached its limit with Kurt Godel (b.1906 -d.1978), who proved its incompleteness in the abstract. While this disturbed many mathematicians, its real effect was to ground our abstractions, forcing them to be axiomatized from the real world. Engineers have no problem with this.

John von Neuman (b.1903-d.1957) furthered set theory for digital computation, developed cellular automata theory, game theory, and architect-ed the first electronic digital computer, the EDVAC, embodied as the ENIAC. His automata theory, in particular, presaged some of the forms of discrete interactions within networks of pulse-producing "neurons". It is a rules-based version of network, by which the state of any one node is determined by some function of the states of its nearest neighbors. When liberated from its digital origins, automata theory can create games that perform similar to simple neural networks. To perform as more robust networks the nearest neighbor rule must be liberalized to allow connections afar.[7]

Alan Turing (b.1912 d.1954) gave us the applied logic and other key foundations of the digital computer, and various logical tests for insuring computer sanity. In particular, the Turing machine converts a temporal pattern into

a spatial pattern, processes it, then generates a new temporal pattern. This conception of information processing is insightful regarding how ion channels might receive and process information, due to the the spatiotemporal complexities.

Claude Shannon (b.1916-d.2001) applied principles of entropy to the problems of communications, and founded a method of measuring uncertainty in information. He devised optimal coding algorithms, a theory of communication and founded the field of information theory. These milestones prepared the neural modeling field for quantitative studies of cells that compute. His methods presupposed that information was digital (the bit). They were later found to be equivalent to Boltzmann's statistical mechanics. Thus information and entropy are different perspectives on the same phenomena. Fred Rieke et.al. 1997 extended some of these concepts to continuous signal values. A challenge remains to extend Shannon's principles so as to tolerate hybrid analog digital processes (HADs).[8]

Physicists speak of particles, which may possess intrinsic traits including radius, mass and charge; and extrinsic traits including position, velocity, acceleration, collisions, and bindings. Particle systems are usually calculated in computers as matrices of data processed *en block*, by equations that express the various forms of coupling between the particles and their surround. Diffusion is a name we give to the aggregate observations of particles in motion, colliding along the way. Coupling is a name for the force fields acting upon all particles which possess mass and/or charge. Physicists prefer to work with momentum instead of velocity; with Lagrangian constraints instead of containers; and with hyperbolic orbits instead of hard sphere collisions. Regardless of the rendition, particle systems provide a detailed method of instantiating most or all of the events crucial to neuron information processing.

Erwin Schrodinger's time-dependent wave equation of 1926 (applicable to the motion of free particles) addresses the conversion of all waves into digital information. The process is sufficiently tedious, despite its theoretic potential to capture all wave-like properties of matter at scales ranging from subatomic particles to the entire universe. It is not practical as a modeling algorithm. The great attraction to consideration of wave phenomena is that waves are perfect carriers of information, in that there is no loss of information regardless of distance. Consider listening to a Moscow radio station while in Chicago, to appreciate how robust is this effect. What waves accomplish in continuous space-time with zero computation requires very large computational loads to predict in the digital realm (consider the charge and gravity fields as N-body problems, followed by Schrodinger’s wave equation applied to the permutations). Although far fetched for the casual BNN modeler, the questions raised by the physics

of wave-particle dualities lead to insights as to how neurons might be exploiting the nanoscale world of ballistics and collisions. Molecular models are reaching the point where nano effect become relevant.

Which relations between particles and waves are most relevant to neurons? There was never a time nor a place when and where the molecular events of biology were exempt from being fully involved with wave effects, quantum effects, thermal energy effects, and charged particle force field effects. Avoiding them was never an option. Every quanta of energy impinging on an evolving biological entity must be dealt with in some fashion, and the most successful evidently dealt with them to great advantage. So it is ill advised to dismiss the various atomic scale effects as though they have no bearing on how a neuron accomplishes its Neural Information Processing (NIP) mission.

Because thermal motion is absolutely unavoidable, living systems do not ignore it but rather have evolved to utilize it as an energy source. Messenger molecules are moved about by thermal motion, and this costs the cell nothing (no ATP, no sugar, no oxygen is consumed). What the physicist regards as scattering, the neuron regards as its postal delivery system, getting the messages delivered on time. Proteins are constantly bombarded by collisions due to thermal motion, causing them to stochastically change states - endlessly. This phenomenon has been exploited by living cells such that certain proteins have become stochastic computers. Until proven that a physical effect somehow cancels out to zero or else is not a high runner in the list of factors that determine output signals, it cannot be purged from a model purporting to represent the physical bases for its NIP functions. None the less, most models in the literature have purged all of these matters out completely by dismissing them as noise. Why?

Most modelers are confronted with A2D (analog to digital conversion) headaches. There are many burdens to digitizing the continuous, simply because between each two digital points there are an infinity of continuous ones, and because continuity is differentiable (it has a slope or gradient). For homogenous spaces or materials, the Fourier transform can convert the discrete into the continuous and vice versa. The Gaussian curve proceeds through this transform unscathed, suggesting that white noise has no information at all - it is the zero of the information universe The Fourier implicitly acknowledges this fact, but a theory of information values being passed through the transform has not been offered. One can intuit however that if the Gaussian is zero, then the further one distances from from it, the more information value it has.

Development of radio transmission for television and audio signals led to the conclusion that noise is a bad thing. Great effort been made to filter it out and suppress it. The same perspective continues for the development of solid state processing chips, where thermal noise (Johnson noise) threatens reliability. It is somewhat understandable, therefore, that within science and engineering there may be some social inertia to overcome to get to the realization that:

I*n biology, thermal noise is a ubiquitous energy source, not a nuisance.*

When the early deterministic models were found wanting, white noise was added to create variance. Pink noise was added to frequency data (color weight proportional to an exponential decay). Shot noise was used to imitate ions traveling through ion channels. Of course, such addition did not restore the energy source for the system. Nor did it restore the original energy content filtered out in the first place. These are some of the efforts to treat model deficiencies in the aggregate. Once we zoom in on the molecular processes there is no more opportunity to "inject noise". Instead, we must detect and resolve collisions. We must stochastically bind and unbind the various possible encounters according to known probability distribution functions. We must change molecular conformers according to known state transition probabilities. These are not noise - they are the state of the system. And the state of the system is its information. The reason it is quiet, not noisy, inside of every living cell, is because all such "noise" is absorbed and harnessed. It is converted to work. Contrast that with man's machines where no such effort is made.

This problem continues. When the noise had been purged out, we were left with sterile deterministic equations, having lost both their energy source and their real information. Biological data was often "processed" by the application of preconceived mathematical constructs and tools. These constructs were typically originated for other purposes. Axon data was mapped onto the cable equation (originated for the transatlantic telephone cable). Channel openings were mapped onto binomial statistical processes (Bernoulli distributions which originated with coin flips). The "whole cell" behavior was mapped onto an "integrate and fire" equation set, or a "leaky bucket" integrator. Such applications are, *de facto,* filtering processes, whereby the biology is filtered out, leaving only the singular preconceived analytic notion to remain, most often a first order differential equation. Convenient, but not representative of NIP processes.

Physicists, chemists, and computer scientists have sometimes applied patterns found within their own field to the higher levels of organization of living forms, displacing whatever mechanisms the living form actually employs for

itself. Such has often been the nature of modeling. What resulted from such efforts was usually closed form deterministic equations that continued to imitate the original, known lower level functions, but offered little capability for predicting the higher level behaviors of living cells. With analytic approaches, there can be no emergent phenomena, and no information processing capability. Physics and chemistry do indeed apply – at the appropriate levels of organization, especially in defining the elements. But biology offers a number of higher levels of organization upon which physics and chemistry are silent. This is accomplished via the patterns of connections to which the elements are prone. This project strives to fully apply the relevant physics and chemistry as a basis, but is careful to enable the biology to emerge therefrom.

A telltale sign of a deterministic model is that repeated trials yield exactly the same result. Digital computers are so deterministic that their random number generator will yield the exact same result every time. So various tricks, like mixing the current clock reading into the starter equation, must be used to create a different "seed" each time it is used. This is worth pondering. The digital computer needs an externally derived signal (the clock) to generate a random number. That is pretty stubbornly deterministic! Digital computers can indeed perform stochastic equations, but it is not in their nature. The cost is considerable. What the real world (the continuous world) does trivially, such as rolling dice or hitting billiard balls, requires an astronomical amount of digital computing to imitate accurately.[2] Our deterministic neural networks (ANNs) are made to look individualized by variations in the training sequence (again, external source of variety must be provided). With such a deficiency, how then can deterministic neural nets perform so powerfully? And if biological neurons could have been constructed of much more simple elements and still perform so powerfully, then why didn't they so evolve? These questions are the concern of this paper.

1.1.2 MOLECULAR MODELS

Molecular models are, in theory at least, capable of predicting wide ranging behaviors of, in this case, the living neurons they represent. This is particularly valuable when in pursuit of a system's information processing potential.

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[2] Digital computers can handle "ideal" conditions quite efficiently, but the real world is not ideal. A billiard table with slightly worn and irregular felt, balls with slight inhomogeneities and scratches, give the digital computer great trouble in emulating, while the real world takes all such matters in stride, with no additional "calculations" necessary.

Moving beyond the cable EQ, the simple Integrate and Fire models and the flat Hodgkin and Huxley equations, by 1989 workers were assembling sets of parameters needed to model a stochastic neuron. [9] A major effort began to tackle active, rather than merely passive, elements. Nonlinearities, previously only represented by a step or ramp function, were being looked at kinetically. The first individual ion channel current was recorded in 1976, by Neher and Sakmann, and they developed the patch clamp by 1982.[10] By 2001, Bertil Hille assembled hundreds of papers on ion channels into an impressive volume covering the physics, genetics, electrics, kinetics, mechanisms, selectivity, dynamics, distributions, modulation and pharmacology of 43 classes of ion channels. [11] This provides a base library of ion channel types and their performance characteristics sufficient to begin finite state machine models of ion channels. If the receptors and pumps were as well described, then predictive whole cell models of specific neuron types could be constructed.

Lindsay, in 2004 applied Maxwell's four equations as a basis for neuron modeling. [12] This was most welcomed as it provided *terra firma* first principles from which any conceivable hybrid diffusive and kinetic model could be built. It was quickly admitted that the magnetic forces at that scale were too miniscule to carry forward, and eliminating them reduces the problem back to 2 equations (Gauss's law and Ampere's circuit law), looking like traditional electrostatics rather than electrodynamics when the magnetic component of the circuit law is small enough to be ignored.

At last, the Hindmarsh-Rose neuronal model is sufficiently complex, kinetically, to exhibit multiple modalities in its response (burstiness vs single spikes).[13] Though driven by SDEs, it does not take into account spatial relationships nor shape, nor channel density heterogeneity in pattern. Models which exhibit modalities are entering the realm of emergent properties, so abundant in biological systems, and so absent in deterministic models.

The investigation of modalities usually requires sweeping the domain space with a sensitivity analysis, monitoring output to detect qualitative changes. In digital models modes are likely to be unstable, perhaps because they lack continuity; perhaps because they are not finely grained enough to follow the steeper nonlinearities. Computer models often suffer instability problems even when they are simulating biological processes that in the real world are always stable. Is this a digitization artifact, an incompleteness problem, or a misunderstanding of the fundamental physics? Modeling must forever be sensitive to questions like these, posing them both to modelers

and to the biologists, in hopes of avoiding conceptual blind spots, finding resolutions, posing queries worthy of further research, and tuning the modeling methods towards producing high fidelity representations.

In 2003, Hucka produced a mark-up language (similar to .html) dedicated to neural simulations. [14] In this paper, he develops the concepts of particle types and channel types, and seeks to generate a spatial grid of output voltages for the membrane state. While useful for depicting neurons on the internet, web postings might harness idle PC's into *ad hoc* super computers that can support more rigorous models, particularly more complex shapes and greater numbers of actors. It is the matrix inversions, the large scale sorts, the euclidean distances requiring square roots, and the basis conversions that determine a dynamic model's computational load.

Markov processes, by definition, are random processes which have no memory at the elemental level. It will be shown later in this paper that receptors, channels, vesicles and pumps (collectively referred to as actors) may be quite accurately modeled by Markov processes, provided that the kinetic schemes yielded from wet lab work are of sufficient detail to the objectives of the model. This is counter-intuitive, given that a nervous systems is the epitome of a system with memory. However, a molecule in any one conformation has no memory of any of its past conformations. An atom is fungible in that it is no different from any other atom of the same species, therefore it has no states nor memories that could distinguish it from any other. In other words, all of its past is integrated into its current state and position. This continues to be true at the higher organizational levels of the nervous system. It has no access to the past, only to its own (admittedly complex) state. Memories are states. States are configurations. Configurations are positions. There is only knowledge of the current position, not of any past positions. Markov processes employ forward rates and backward rates, analogous to chemical binding and unbinding, a useful fit for modeling biochemistry and conformational changes. Andrey Kolmogorov (b.1903 - d.1987) elaborated upon this such that he could adjust the stochastic probabilities, correct to the chosen time slice. This is critically important in modeling. Bio-data may be offered as events per second, but when modeling at a dt of 1E-4 s the real probabilities are strikingly different from merely taking the per second data and multiplying by the dt value. Such conversions will necessarily be utilized in this project model.

There are several shortcomings with reducing a complex molecule, such as an ion pump, into a kinetic scheme to be modeled as Markov process.

First, the number of possible conformations in a molecule of more than 10000 atoms is held by many workers to be astronomic. To represent all conformations of a single type would require a full Molecular Dynamics simulation.

Second, the intent of the "kinetic scheme" is to collapse the potentially immense number of conformations down to perhaps 10 to 30 significant states. Conceptually, this is done by identifying the "high runners", those states with the greatest impact upon transport. It is the nature of how such data is collected (two-step voltage clamps) that several different conformations might be "read" as the same state, simply because instrumentation cannot resolve between them. Even when it can so resolve, if two or more state have the same effect upon transport then some workers may choose to bundle them together as one state. Then there are the "low runners" apparently of little consequent which may be bundled together, even in large numbers, as "other" or "rest state". While it is generally sound to select only those states significant to the quest (e.g. transport effects), determining such information is tricky. A very rare state might have profound effects when finally it arrives. Only by exercising a model many times through its domain can the observer begin to gain purchase on what is missing or askew, due perhaps to leaving out some statistically "low runner" states. This is especially true for rarely occurring states that tend to toggle. That is, switch on, then stay on for a prolonged period. Another possibility is that two seemingly similar states may be on different paths, exiting through quite different routes, resulting in different temporal patterns. Beware criteria that judges what is "significant". This paper explores the second and third order relationships between states, that predispose state changes to occur as paths and rhythms.

Wet lab work to derive kinetic schemes for the channels and pumps is constrained by the means of taking measurements. In the event of a channel opening, a current is created by the flux of charged particles through the channel, and electrical currents can be measured down to as little as several charges moved several nanometers. Determining which ion types pass requires changing the bath water (Ringer's solutions). Some techniques (referred to as measuring gating currents) detect parts of molecules shifting position ... for example, the arm that opens and closes certain channel types. Because the arm is constructed of amino acids, there are certain to be charges at the polar end. In motion these may be detectible. This technique may not always be adequate to determine the geometric consequences of every charge shift possible for the molecule, nor distinguish which shifts will be the most significant ones to the larger functional role of the actor. When the channel is presumed to be a binary device (open or closed) it is easy to rationalize the collapse of the many states into the few. But if it should be that the ion

channel state transitions are exploiting temporal patterns, then we must preserve as many of those states as is practicable until we can know what those patterns may be.

Molecular Dynamics (MD) rises to help fill this void. It is a new field which harnesses large computers to simulate the atoms and forces within and about a molecule sufficiently complete to determine tertiary and quaternary structure, and also the probabilities of each of its various conformations. The atoms, bonds and energy relationships are processed dynamically to yield a movie of the molecule in action. This rigorous approach is more fundamental than the kinetic schemes derived from the two-step voltage clamps, although MD can use well-reasoned kinetic schemes to validate its own models. Indeed, MD's rigor is far too computational to be included in a whole cell model. A single molecule of hormone colliding with a single receptor molecule can require weeks on a 256 core computer to do an MD simulation. But, the results of such investigations are of great value to neuron modelers. MD can zoom in on a critical interaction to clarify its occurrence, behaviors and outcomes.

By 2002, MD was doing software constructions of ion channels and began yielding the most detailed information available by any means. [15] The workers in this case admitted that MD studies do not yet produce quantitative values about the channel pore binding sites, because the free energy of the aqueous environment may have effects via coupling from beyond the boundaries of the simulation. MD can play a special role in helping select and characterize those chosen few “significant” states that comprise the kinetic schemes upon which the Markov processes operate.

To recapitulate:

Physics provides the rules for particle movement and interactions. Chemistry provides the rules for binding and unbinding phenomena , and MD will eventually elucidate most of the quantitative data to capture the kinetic states of the actors.

1.1.3 MODELING HISTORY

Within the realm of neurophysiological modeling there are several applications currently available: Genesis, and Neuron. GENESIS (GEneral NEural SImulation System) simulates sub-cellular neurons to networks, originated by Bower in 1988. It is written in C language, and assembles prepared blocks of code into models. It can simulate

spherical and cylindrical compartments. In 1997, a software program named NEURON was introduced by Hines, Carnevale and Destexhe. [16] Sponsored by workers at Yale University and Duke University, NEURON is currently perhaps the dominant form in the field. Over 700 scholarly papers have been published as of this date, which cite Neuron as a tool employed to demonstrate or verify some neurophysiological process. [17] None of these papers (to date) attempts a general analysis of liquid state informational processing of those molecular mechanisms employed by neurons. Neuron is coded in C++ programming language, and typically runs on the UNIX operating system. It produced graphs following the Hodgkin Huxley curves of an action potential and propagated them along the cable EQ. In their software documents they define an ion channel as a current over voltage plot (I/V), i.e. a look-up table. This implies there were no time-dependent kinetics. Such a two dimensional simplification does not account for modulation, subunit kinetics, energy barrier profiles, the temporal aspects of state changes and inactivation, nor for the rich behavior patterns and modes of the finite state machines that ion channel actually are. By 1987, it was known that sodium channels were significantly more complex than the HH EQs representations. [18][19][20] Certain intermediate state transitions were occurring independent of voltage, and thus a minimum 12-state kinetic model (Q-matrix) was deemed necessary, [21] and a 30-state model was proposed to account for the channel behaviors.[22] The fact that ion channels are modulatable also requires a larger number of state space dimensions. The dimensionality of the state space increases by one for each allosteric binding site. The vector length of each such dimension is equal to the quantity of possible binding types to the one allosteric site +1 (the +1 is for the empty condition). Each modulator site constitutes an input port. Additionally, the order of the system is increased multiplicatively by the number of time steps required to span all distinguishable input patterns by the system. The set of all input channels, times the temporal order of patterns recognized determines the size of the system array necessary to model an ion channel, pump, receptor or vesicle, as adequate to demonstrate its Neural Information Processing (NIP) capacity. By contrast, a 2-d plot portrays only a 1-dimensional lookup table, with no NIP.

A restricted form of diffusion was added to NEURON in 2007 as equations, not as particles, wherein the concentrations are re-calculated each *dt*. [8] The collaborative efforts of J Moore, M. Hines, T. Carnevale et.al. (at Yale University and other universities) offer an ever increasing library of C++ routines to assist the neural science worker in the mathematical representation of hundreds of neuronal phenomena discovered in wet labs or hypothesized to exist in living systems. This is a numerical methods approach to the neuron, not a molecular model, not a particle system model, not a kinetics model, not a 3-d diffusion model. It serves the need of modeling local

circuits (2 or more neurons connected into communications circuits) at the expense of simplifying many neuron functions down to data-mappings (curve-fits and table lookups) for computational speed.

Current modeling efforts by others are dominated by closed form mathematical equations, by *ad hoc* models of singular specific phenomena. As features and scope are increased, supercomputers have become increasingly necessary.

1.1.4 INSTANCES VS AGGREGATES

Neural modeling has been motivated by wide ranging needs: : genetics, evolution, anatomy, development, proteomics, systems biology, cytology, pathology, pharmacology,physiology, molecular dynamics, statistical mechanics, bio-computation, computer science, mathematics, fluidics, and materials. Each perspective will purge most of the bio-data so as to leave a parsimonious model which contributes to its respective goals. For many, the various analytic techniques which reduce redundant elements to one, and complex processes to equations, yield the answers sought. But information processing often involves large numbers of similar units, being richly connected together as networks, each being subtly “tipped” to indicate its information value. Most of the analytic techniques applied to neurons do not preserve those large numbers of similar units. Rather than distinguishing between them, they are aggregated into “macro” behaviors. The problem with analysis is that it cuts apart the connections and then purges the redundancies in search of essences. If the outstanding trait of neurons is their ability to process information, then models which purge the molecular mechanisms that perform information processing are inherently self defeating.

Simplification is the result of analysis. Analysis works by aggregating like kind events into singular mathematical expressions. But any act of aggregation loses the information of the individual elements. Thus, the study of informational systems must resist the temptation of doing analysis. Rather, synthetic processes must be sought which support the emergent properties from large numbers of simpler elements. As concerns information processing it is not advisable to model aggregates except for those types which must be present as substrate but do not participate in state changes, e.g. water, catalysts.

Consider the absurdity of one running a computer program then claiming to have “gotten the answer” by reading the computer's temperature. Or by adding all the output 1's and 0's into a single net sum. For most operators,

information is lost when two or more values are merged into a single value. It is the numerous unit values which are the essence of the information. To extend the model the axon to include the rest of the neuron (dendritic arbor, soma and initial segment), large numbers of states must be instantiated, and their interactions doing the information processing. Only when state change sequences are demonstrated to occur identically, in parallel, and triggered by the same source, can redundancies be purged from a representative model without loss of veracity. It is the intent of this paper to represent the neuron's fine grain instances of state change, those with any likelihood to impinge upon the output signal.

The behavior of a single ion channel is considerably different from that of the Hodgkin Huxley equations (HH EQs) output signal. While the HH EQs produce exponential response curves, a single channel responds with either full open or full closed, as a somewhat chaotic step function. The durations of openings and closings can span 1E1 s perhaps down to 1E-12 s. The faster the flicker, the greater must be the force/mass of the gating mechanism. Channel activity is practically digital. Given such generation of digital information, and given that ion channels are only known to communicate to each other through the saline between them, there is a grand question as to how the saline passes such digital information between the channels. Is the informational signal filtered? Are there high loss rates? Is the channel digital signal converted back to analog? How saline connects the ion channels by conveying information is a key query of this paper.

Warren McCulloch and Walters Pitts offered a digital perspective on neurons. They proposed simple AND and OR gates as representative of excitatory and inhibitory actions. Then the Hebbian synapse was defined by Donald O Hebb in 1949, now known as the Hebbian learning rule. This allowed learning to take place, such that the excitatory and inhibitory synapses would change their weights as a function of feedback per the “correctness” of their output. Put otherwise, synaptic gains were adjusted by the error signal. Such error signals required “recurrence”, that is backwardly traveling signals, from the output region to the various input and intermediate elements. This architecture also implies a hybrid of analog and digital operations. To wit, the analog sums the many inputs, first weighing them according to their Hebbian values. Then a digital process occurs which evaluates the sum by comparing it to a threshold value. Above the threshold warrants an action potential propagation, else silence or low basal firing rates. (For neuron types without action potentials, the prior sum is passed as a “graded potential”.) The output signal is then measured by some success criteria. An error signal is calculated. The error is feed back to those synapses most active in the processing of that signal. To the extent that the answer was “wrong” all those

synapses can be proportionately diminished in weight. To the extent that the answer is “correct” all those synapses can be proportionately increased in weight. With repeated trials the system gets progressively better at its performance, even across a large number of distinct problems. However, such connectivities have the characteristic that the most recent experiences tends to overwrite the older experiences. Thus memory is not fully persistent, but rather fades with usage.

Many early bio-computation workers treated the whole cell as a sum and threshold device. We now know that each cell consists of hundreds of thousands of ion channels, and each ion channel is a sum and threshold device. One cell is therefore a massive computer, built of a network of approx 1E5 channels, all “connected” to their nearest neighbors by membrane capacitance and saline resistance. Such errors of scale are common place throughout science, gradually corrected as our wet lab instrumentation improves to discern finer detail. Network theory, like many sciences, is moving toward the molecular realm, and in so doing discovering new possibilities. Because of this history, some of the prior art concerns whole cell studies, and some of it multicell studies. As the resolution was not too keen in the beginning, some things that were originally applied as multicell would now be applied as sub-cellular phenomena. This is a bit confusing, so please note that all efforts herein are to build a whole cell model, and that some of the relevant concepts thereto may have been originated at larger scales.

We must distinguish between Artificial Neural Networks (ANNs, silicon based) and Biological Neural Networks (BNNs, carbon based). By 1990, ANNs were making rapid advances, paralleling the advances of conventional digital computers and super-computers. ANNs consisted of 2 to 5 layers of elements whose major connectivity was fan-in and fan out between layers. This is neither a vertical nor horizontal architecture, but rather diagonal. AAN designers often considered the HH EQs as too computationally burdensome for large scale networks, but they were sometimes employed in smaller scale experiments. [23] This is somewhat ironic because the BNN modelers were going in precisely the opposite direction, opening the HH EQs up into numerous single unit stochastic processes, greatly increasing the computational burden. It is indeed an intellectual challenge to explain how the ANNs achieved such stellar successes with such extremely simple “neurons” (sum and sigmoid nonlinearity) while the BNNs were proving to be immensely more complicated devices. It is a concern of this paper to pursue an information theoretic explanation that objectively and quantitatively distinguishes the performance and computational potential of BNN's from ANNs, so as to quench some of the misconceived crossover assumptions.

The first proposed solution to the over-simplification trend was to cut the unitary intracellular compartment into many cylinders, resulting in somewhat arbitrary discretization by Rall. [24] This discretization allowed a more detailed representation of the several chosen cylinders by mathematically collapsing each into a node. It facilitated some accounting for shape and bifurcations. The nodes were then coupled by an extracellular resistor and an intracellular resistor. They could then be solved as current and/or voltage coupled equations (node or mesh). This approach to modeling was an early form of the finite element method. Although in practice this approach cuts the neuron into parts creating unrealistic compartments, in effect it served to increase our resolution of the workings of the neuron because prior to such a technique, workers were treating the neuron as single node.

A subsequent strategy was to take the HH EQs or Fitzhugh-Nagamo equations and add noise back into the model Plesser, [25] and Tuckwell. [5] This strategy is the strange consequence of having first squeezed every stochastic process out of the system, so as to 'fit' into deterministic first order exponentials, and then regretting it. This approach produced output that “looked” more like the original noisy data but recaptured nothing of the original utility of that 'variance' in the neural processing of stimulus to response. Painting noise over a deterministic equation does not compute anything, any more than replacing a 8-bit CPU with an 8-bit noise generator would compute the same “answers”. The signal variance (historically referred to as “noise”) is the means by which a small group of neurons operating in parallel can convert an analog signal into digital pulse coding. They can do this in such a robust fashion that the quantity of neurons can be increased or decreased with little change in the quality of the response. Such a robust elemental group may also act as a fine discriminator – sometimes called 'intelligence' because decisions are being made according to some criteria. When one is in search of the information flows through a neuron, be cognizant that models that replace the acting discriminator with a white noise generator completely miss this point.

1.2 CARBON VS SILICON

Because so much of science and technology today is framed within what is feasible in silicon computers, and because the digital computer has become the metaphor of first resort, let's begin with a comparison between silicon digital processors and carbon associative processors. This is intended to provide a checklist of the ways bio-

computation is not analogous to the domestic computer, in hopes of avoiding the various temptations to assume they are.

TRAIT/FEATURE	SILICON	CARBON
Modulus	Cartesian	Fan-in, Fan-out
Quantity I/O Channel	Equal arrays	Large input, small output arrays
State	Solid	Liquid
Connectors	Point to point (wire), point to many (bus)	Many to many: baths, continuous membrane
Connector materials	numerous individual copper or silver wires	Common saline bath
Gates	Transistors, typically 2 states	Ion channels, approx 30 significant states
Gate types	AND OR NAND XOR	43+ channel types
Charge carrier	Electrons	Ions: Na, K, Cl, Ca,.....up to approx 128
Power source	External battery (or power utility)	Well distributed ATP molecules
Power storage	Battery, capacitor	Concentration gradient, voltage gradient
Capacitors	Discrete, one per gate	Continuous, as complex closed membrane
Inductors	None	None
Resistors	Minimized, point to point	Saline, point to bath, general signal damper
Clock	Master clock synchronized all	Asynchronous, but resonance occurs
Gating heat	Significant heat generation, mandatory	Zero heat generation in gating
Conductor heat	Significant heat in copper resistance	Zero heat generation in diffusion
Battery charges	About 90% efficient	Ion pumps are about 80% efficient
Error rate	Very low < 1E-12	High rates of error <1E-1. Redundancy reduces this problem.
Availability of resources	Memory + logic = 95%	For any one problem only a small % ,< 5%, will be “on task”
Memory transfers	Resource bottleneck, expense in time and heat	Molecular repositioning, incremental
Residual knowledge	Zero, although OS and Apps save form.	complete, but constantly fading with overwrites
Representational scheme	Arbitrary assignment and flow control	persistent spatiotemporal mappings
Representational logic	Boolean discrete	Pattern resonance and pattern generation
Modulation	None	Dozens of modulation messengers in the bath
Modalities	None	Multiples mode of operation set by modulators

TRAIT/FEATURE	SILICON	CARBON
Initiator	External instruction set	Bootstrapping
Time to program	minutes	21 years
General approach	Brute force, costs much energy	Ride the free thermal energy sources
Structural elements	Persistent for life of product	May require steady replacement (costs energy)
Environmental Risks	Overheating, programming errors	Soft tissue damage, infections, denaturing
Centralized control	Established via hierarchy	None
Pumps	Battery charger	Thousands of distributed ion pumps, create a power topology with hills and lateral flows
Power as a carrier	Power is kept clean, free from extraneous signals	Power is highly multi-tasked, with many space-sharing varieties of gradients. There is also a logic of relations between these.
Redundancy	Low, because precision is already high	High redundancy (8 to 32) per accuracy required
Multiplexing	Time sharing allows many signals on 1 wire	Overlapping frequencies = Spectral data. Also, multiple charge carriers with independent signals.
Dimensionality	[x y z t binary_state] = 5 dimensions	[ions mods statespace] = approx 100 dimensions
Nonlinearities	Strictly digital	Adjustable response curves, subtract to sharpen
Auditability	Very good. Core dumps reveal all, but temporal sequence may not be complete.	Very poor. There is no way to read the inner processes, nor to capture them as a log.
Resiliency	Extremely fragile, prone to crashes with total loss of function and total loss of memory	Extremely resilient, can go 100 years with no crashes
Power to computation ratio	35 watts to power: 3.5E8 binary gates * 2E9 clock = 1e16 ops/watt	15 watts to power: 1E11 neurons * 1E5 channels * 1E4 clock = 1.5e19 ops/watt
Completeness	Always incomplete: requiring outside initiator, programmer, maintainer, upgrader, corrector, and output evaluator.	Complete and autonomous. Self evolving. Self regenerating. Self developing. Self repairing. Self programming. Self evaluating.

TABLE 2: TRAITS OF CARBON-BASED AND SILICON-BASED COMPUTERS

Despite the equivalence between carbon and silicon on the periodic table of elements, these two exhibit only a few similarities and many differences. Both can bond 4 ways in a tetrahedral shape. The silicon atom is more than twice

the size of the carbon atom (1.46 :: 0.91) E-10 m, thus their “fit” into various molecular configurations with oxygen, hydrogen and nitrogen are very different. Carbon will sustain single, double and triple bonds. Silicon will only sustain single bonds. Both will support very long chains, into the 1000's. Carbon most easily forms chains of -C-C-, while silicon most easily forms chains of -Si-O-Si-O- . This hints at a second chemical difference: Silicon has a much higher affinity for oxygen. CO2 is a gas due to the double bonds, but SiO2 is sand, because of the single bonds the oxygen affinity is so strong that it pulls other nearby oxygens into a lattice.

Living systems exploit numerous chemical reactions at “near balance”, that state of equilibrium where trivial forces can shift its reactants to one side of the equation or the other. Weak bonds are necessary to facilitate these low energy shifts. In such a system, strong affinities act as poisons. They never let go, such as with chlorine attaching to hemoglobin. Because of high affinities, a lot of silicon chemistry takes place at high temperatures (350C to 1500C) and elevated pressures. All traits considered, silicon is useful in the solid state, but much less so in liquid forms; and carbon participates in thousands of chemicals in the liquid state at room temperature, much less so in solid forms.

1.2.1 SILICON PROCESSORS

A silicon CPU (central processing unit) has an array of input channels, and an equal-sized array of output channels, laid out on a Cartesian grid. The concept of orthogonality spawns its architectural modulus, and therefore structural relationships are the primary relationship. The solid state is necessary so as to hold this structure. The CPU consists predominantly of gates, capacitors and conductors. Resistors and inductors are minimized in use. The gates are transistors, acting as AND, OR, NAND, XOR logical devices. The capacitors are distributed, one per transistor, serving as short term memory. The connectors are copper, silver, or aluminum wires. Most are point to point. A few are buses, one point to many points. The buses distribute at the beginning and collect at the end.

The digital chip has a centralized power source that distributes current to every gate. It has a master clock that synchronizes all processes. The clock speed, currently at about 2E9 Hz, is increased by increasing the power input, and by reducing element size. Every computation generates heat, inherent to the flipping of bits, not an option. Heat dissipation is a major consideration in CPU design. Digital gates are strictly logical, in that any bit can be arbitrarily assigned any consequent. Memory is separate from logic. Therefore, transfers to and from memory require large data buses, and are a major bottleneck in operations. All or most of the memory is completely cleared

after each problem cycle to make room for the next problem. It therefore approaches each problem in complete naivete, and completely submissive to its next instruction set. Signals are conducted internally via small diameter wires oriented point to point. Capacitors are discrete and well distributed. As a system it is most efficient when large blocks of data are sized to fill the gate array, and then uniform deterministic equations are performed simultaneously across that block of data.

The digital chip can produce exact solutions to deterministic problems. Anything more complex than addition requires a hierarchy of logical control to manage the problem in CPU space over the course to solution. Complex or large problems must be converted into temporal sequences by “algorithms”. There are different levels of command language, and different levels of priorities (interrupts). Therefore, all bits are not created equal.

The digital system is excruciatingly sensitive to single bit errors. A single bit can cause a shift to an entirely different instruction set, and quite often a single wrong bit causes the entire computer to seize (become incapable of proceeding) and then require a complete reprogramming from startup. The digital chip is completely dependent upon software instructions to define the problem and the means to a solution. Therefore, the so called 'computer' is only a partial of the problem-solving system. To complete the system human programmers are needed. In this sense, computers are mere dependents, not at all autonomous. They offer logical leverage to their carbon-based owners/ controllers/ beneficiaries.

Electronics involves a singular type of very low mass, high charge particle. Electronic current travels near the speed of light through metals. Inertial effects rise to significance in inductors, otherwise are negligible.

1.2.2 CARBON PROCESSORS

A single neuron processes an immense amount of information: spatial, phase, weighted, patterned, and chromatic. A biological (carbon-based) processor has an input array consisting of thousands of connections, and output array unequal in size to the input array, laid out as a layered graph, not fully connected. Its output array is typically simpler than its input array, as a neuron does not typically generate many completely independent output channels the way a silicon processor does. There are exceptions, however.

The neuron has multiple types of charge carriers freely intermixed, and similarly many types of modulators, also freely diffusing. It consists of predominantly of gates, capacitors and conductors. The gates are complex proteins of many types distributed non-uniformly and non-randomly. Ionics employs charged particles with mass equal to 22000..35000 times the mass of an electron. In some situations, this mass is great enough that inertia becomes a significant factor in creating oscillations and waves.

The neuron has many mechanisms to generate patterns within single molecules. All activity is asynchronous in that there is no master clock, but patterns in time and space are highly correlated none-the-less due to resonance and radiating waves. The equivalent clock speed would be about 1E4 Hz, that is 5 orders of magnitude slower. However, every element is in constant motion - there is no silencing of elements as a majority are at any one time in the digital computer. Memory is widely distributed. Power is widely distributed, and most of its is “free” thermal energy that is not consumed.

The carbon-based liquid state processor is a hybrid analog digital processor that does not employ instruction sets not software programming. It learns by repeated trials, wherein successful trials trigger modulators which alter the synaptic weightings, and unsuccessful trials trigger the release of other modulators which alter the synaptic weightings in opposite fashion. Bits are generally equal, in the sense that the loss of any few of them has little impact upon the outcomes. As a result, it is exceedingly robust, able to recover quickly from almost any kind of error. No outside programmer is required, so it stands as a complete, autonomous machine. All memory is retained, not cleared between problems. However, the newest memories are added to the old, in such a way that the old are gradually diluted down by the new. This implies that every new problem is always introduced to the residual patterns of the old, and must in some way be solved as a subset of the whole of its experience. On the one hand every problem immediately benefits from all prior experience. On the other hand, it is very unlikely that any one problem will have access to the full resources of the processor, as most of the memory is likely to be irrelevant. This is a rather serious limitation, shrinking the efficiency of resource utilization down to a modest percentage of the whole.

Furthermore, the carbon based processor does not produce exact solutions. All solutions are approximate. Higher precision is usually possible by continuing the processing for a longer period of time in an iterative fashion (regeneration). This is an interesting processor trait, that a solution is always available, poor at first, but improving

with iterations. [3] Thus, the quality of the solution is automatically adjusted to the time allowed, without change in algorithm to do so. This has other implications: it can solve problems that are incompletely defined and/or for which there is inadequate information available. The quality of the solution varies with the completeness of the problem and sufficiency of the data available.

The carbon processor can also create new patterns and ideas. Because of the persistence of all experiential memory and treating every new problem as an overlay thereof, problem interruptions and problem multitasking are also easily accommodated without loss.

For completeness it is noted that the system is not a stand alone faculty, but is embedded in a respiratory, circulatory, digestive, excretory, musculo-skeletal, sensing reproducing system, all integrated in highly coupled fashion..

The signals within digital machines typically have values between + or - 5 V. Biological electrical signals often range from -0.100 V to +0.020 V. Sometimes more. But biological signals are also carried by chemicals, which greatly add to the dimensionality of the signaling domain, and thus to the information capacity[4]. Let a container of volume 1 nm^3 contain a variable quantity of particles of 0.1 nm radius, from 0 to 125 (ignoring water). It is then occupied at a density somewhere between a vacuum to a densely packed volume. If all occupant particles were of the same type, then the total number of possible values = 126. Information value is a little less than 10 bits (2^7 = 128). If in that same cube, those particles could be any combination of 8 different types (of the same size), then what is the information value of that space? It is a multichoose combination problem, where r types of objects are taken n at a time, r =8, n= 125. The standard formula for combinations: q = n!/(r!(n-r)!) does not work in this case, but the multichoose function converts n to m = (n+r-1). Then one can proceed to execute the combination: q = m!/(r!*(m-r)!) ; Each of the 125 positions may be occupied by one of the following: (0 1 2 3 4 5 6 7 8). The quantity of combinations (ignoring order) is 1.84E12. The information value is > 40 bits (2^40 = 1.1E12). There is a lot of information available in particle combinations that is simply not there for single type charge carrier systems! Electrons have nothing to offer in equivalence to such degrees of freedom.

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[3] Such iterations are reminiscent of digital algorithms for ODEs. The commonality is their solving for differentials.

[4] Within information theory, the term channel capacity is defined as the maximum quantity of bits/second that a transmission line can carry. Attempts to load more than this will result in data loss. For purposes of this paper, channel capacity is renamed “information capacity” to avoid confusion with the many ion channel traits.

With channels and pumps, there is no centralized control. That is, power is distributed, state is distributed, memory is distributed, and capacitance is distributed. Learning occurs via synaptic growth or atrophy, and/or by altering the quantities and placements of replacement actors. Note that the actors are replaced on a weekly basis regardless, as a regular part of maintenance and renewal. Therefore, to modulate this process to bring about a shift in the distribution of actors is "inexpensive" for the cell.

The energy source for diffusion is "free" in that no cellular energy source need be expended. Transport across the membrane is not free however, because if there are concentration and voltage gradients across the membrane: transport up-gradient requires the expenditure of energy, and transport down-gradient expends that energy. Therefore channels always move ions down-gradient (conc + volt), and pumps are required to move them back up the gradient. Noteworthy is that a lot of pumping goes on via co-transporters and counter-transporters (exchangers) whereby the energy source to "pump" one ion type up-gradient is a trade-off, linked to down-gradient transport of another ion type. Such transporters can be driven "backwards" whenever the gradient ratios cross 1.

In addition to the membrane and its protein actors, there are also the two saline solutions, one on either side of the membrane. While the role of saline is roughly analogous to that of a man-made wire or resistor, it is a multiport resistor, the extent of which is determined by the shape of the extracellular fluid in the upper case, and the shape of the intracellular fluid in the lower case. As a contiguous volume conductor, it is quite unlike a point to point copper wire. Nor is it like a buss bar, due to ionic mass, which expresses as lag, which tends to isolate each region from all the others. Diffusion loses information. Furthermore, the use of multiple ion types whose movement constitutes current in those resistors, creates a greater dimensionality of the domain, and must operate significantly different from copper wires. The nature of these differences can to be investigated such that behaviors are mapped into contributions to the information processing role of the cell, if any.

The ion pumps are roughly analogous to man-made batteries, and often depicted that way in schematics. When not modulated by voltage, they are current sources. A better analogy is that the pump is like a battery charger, because each pump requires a power source, and that power source can vary, thus limiting or modulating the pump performance. The battery is the membrane capacitance, as it is "charged up" by the pumps. The ATPase pumps are driven by binding ATP, and unbinding ADP. Other types of pumps perform co-transport and/or counter-transport according to a logic of ratios. Electrogenic pumps cause the membrane to store up potential energy as capacitance

charge as well as concentration gradient. Electro-neutral pumps consume much less energy because they are not fighting the EM force. The ion pumps are finely distributed, and those distribution patterns can induce complex axial current patterns by generating current sources at various distances away from where the ion channels will complete the circuit.

Ion pumps also are logical devices, in that they require ratios of transport between the ion types. For example, one type of pump binds 3 Na on the inside, 2 K on the outside, and 1 ATP on the inside. The conversion of 1 ATP to ADP provides the energy to move the 3 Na outside and the 2 K inside in a single pump cycle. Another pump may bind 3 Na outside and 1 Ca inside, and employ the Na gradient to drive the cycle, and in so doing pump one Ca out. These pumping ratio rules make for an informationally rich "power source". Not only do they vary each of the ion species concentrations, but they are interlocked in their function in curious ways. The systemic consequences of pump-induced changes in the ion ratios can be investigated for their impacts upon the information processing function of the cell, if any. Perhaps they are modulatory. Perhaps they can cause modality shifts. Perhaps they alter the resonance and damping characteristics of the waves of information carried in the ions.

The neuronal membrane is roughly analogous to a man made capacitor. However the membrane has several significantly different aspects to it. The membrane is one large shared contiguous capacitor covering the entire cell. This would be an impossible arrangement in an electron system, because essentially every node would be short-circuited to every other node through the capacitor. The neuron works with ions rather than electrons, and ions have mass. This mass, at least 22000 times greater, must make its way to the membrane and along the membrane before it can influence its neighbors physically, Ions radiate in concentric circles to generate "horizontal" signal and current. Thus all nodes are separated, not electrically, but in time, by how long it takes to radiate ions to nearest neighbors. There would be immense "crosstalk" of overlapping signals except that each signal is muted by distance, by water collisions, by thermal energies, and by capacitive attraction across the membrane to oppositely charged particles. Such a liquid capacitor allows the charges to "bounce" along the membrane to such a height that the so-called zeta potential is created. These traits can be investigated for their characteristic behaviors vis-a-vis solid state capacitors, and for their impact upon the information processing role of the neuron.

Thermal noise is the nemesis of solid state processors, but is a vital energy source for liquid state processors. More than an energy source, it is also equivalent to the value of zero in deterministic systems. That is, white noise equals

no information (complete uncertainty whether the value is 0 or 1). Zero is a bit and 1 is a bit, so both have equally significant information value.[5]

Although the neuron does consume energy to pump Na ions against the gradient, the major information processing events ride on free thermal energy. It is free because it is not consumed, therefore does not need any replenishment. The liquid state is able to harness the ambient thermal energy to effect movement of messengers from point to point, and the harnessing of thermal energy to effect state changes in the large molecule conformations. No, this does not violate the laws of thermodynamics.

Perhaps the most distinguishing feature of liquid state processors is their ability to exploit the random impacts of thermal energy. For neurons, thermal energy is well harnessed as a stochastic process that drives the two most critical processes of its information processing mechanism.

Consider that 10 identical deterministic elements (e.g. in a PC computer) will all respond to a given signal in exactly the same way. Thus their redundancy adds no additional information. They are best not allowed to act redundantly but rather each assigned to individual tasks. However, 10 identical stochastic processors will each respond differently to the same stimulus, tending to "fill in" the probability distribution curve. As a group, they create as pattern match value to each particular input pattern. It becomes possible that as a group, they can discriminate steeply to subtle changes in the input, and thereby distinguish between several different patterns in the input. Although such complicated responses are theoretically possible with a deterministic processor, that processor would need to be specifically programmed for such increasing the number of elements as the pattern increased in complexity, and concurrently needs more memory to store sought patterns and the logic for switching between patterns. The stochastic counterparts are much simpler to assemble and get working because their genetic history has accumulated into the program what determines their pattern resonances. When a small group of them are placed in parallel, they can perform sophisticated tasks with no programming. Modifications to that program are incremental, or possibly qualitative, via modulator bindings. If one of the group should be lost, the remainder

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[5] If 1's are more rarely used than 0's, then 1's have a higher information value (iv), but the overall value of the code drops somewhat due to inefficient use of letters. For example, if 1's are used 0.1 fraction of the time and 0's used 0.9 fraction of the time, then: iv(1) = -0.1*log2(.1) = 0.152; iv(0) = -0.9*log2(0.9)1. Barch, D., *Characterization of activity oscillations in an excitable membrane model and their potential functionality for neuronal computations*. Neurocomputing, 2000. **32**: p. 25. = 3.322; By this asymmetry, the iv of the running code drops from 1 bit per letter to an average of 0.469 bits per letter.

continue working almost as well, with no obvious change in the response patterns, just somewhat more graininess. This is highly robust.

Ion channel transport is driven by (concentration + partial voltage) gradients across the membrane. Their pore selectivity results in a set of conductances for each particle type. Their opening and closing behavior is modulated by a wide variety of environmental factors. These may be chemical, as with allosteric binding sites, or by the molecular torsion imposed upon them by force-fields, as with voltage sensitive channels. There are only 2 candidate forces, gravity and EM, and at the nano-level gravity is miniscule.

For these and other reasons, we do not yet have a precise abstraction of the equivalence between information processing of a neuron and that of silicon-based artificial processors. The brain is a liquid state information processor. It can process at least 1.2E16 flops per watt of power. Heath 2000,[26] calculated that the theoretical limit for chemical information processors (liquid state) = approx 1E18 bits/second/watt. Neurons however, must expend energy in development and maintenance of the living cell. There may be a lengthy period of support necessary to get to the point of solving significant problems. Current solid state information processors can process about 8.2 teraflops at the power consumption rate of 20000 watts, per SciCortex product specifications, 2009. That is 4.1E8 flops per watt of power consumption. Thus, liquid state processors enjoy an estimated advantage of 3.05E7 times greater computation per watt than solid state processors! There are speculative factors in this calculation, and others have concluded as low as a 1E3 advantage to the liquid state.

Within solids, structure comes free, but movement costs energy.

Within liquids, movement comes free, but structure costs energy.

It costs less energy to hold the ion channels in their place on the membrane in the liquid system than it does to move the electrons from gate to gate in the solid state system. The total energy put into a liquid state system is considerably less than into an equivalent solid state machine. Therefore the liquid state operates at ambient temperature, while the solid state builds up self-destructive heat that must be dissipated via a large thermal conduction system.

1.2.3 ARTIFICIAL NEURAL NETWORKS

Let's consider some of the major forms of "neural networks". Each is a large scale graph of nodes and edges, following certain connectivity schematics. The Perceptron, Hebbian synapse nets, Widrow-Hoff, Grossberg, Hopfield, back-propagation, and adaptive resonance networks were out-growths of the concept of the Artificial Neural Network (ANN) as "sum and threshold" transistors wired together in regular patterns (fan in and fan out). [27] All exploit associative processing, which is a non-rules based method of learning and problem solving. They are able to tackle difficult problems with a strategy that varies the mapping weights from input domains to output ranges according to some measure of success. Each of these is *de facto* a specialist, because each is better at certain forms of problems than others as an accident of its architecture in some way "aligning to" the nature of the problem to be solved. They can all deal with arbitrariness quite easily, e.g. a random input combination associated to a random output configuration. One can also add a random signal to a training signal, and with repetitions, the neural net will still learn the training signal. Where most or all types have trouble is when two inputs are very similar, but the expected outputs are far apart.

Consider the lunch table game of flicking a finger to knock a bottle cap across the table as close to the far edge as possible without falling off. This means that stopping at 99.9% of the table length is a very high score, but 100.1% earns a zero. Digital computers have no trouble at all with this problem (y = 1/(1-x) would give). But neural nets persist with very high error rates even after lengthy training. The situation for them was finally improved by adding a transform to pre-process the problem. The key is to move the input values of successes and failures farther apart. Given the right transform the problem is once again easy. But selecting the right transform required outside intervention. And so a pre-processing unit had to be designed that could create or select an optimal transform based upon the problem type. This finally led to the concept of "self organizing maps" whereby essentially a neural network could learn how to learn. This can be summarized as second order learning, as annexed onto the original first order learning. And for more complex problems, third order learning may be the solution. Eventually, you will have grown some frontal lobes!

To relate this to the realm of how biology operates neural networks, we can consider the complexity depth of the problem, and therefore the requisite complexity depth of the neural network to solve it. Layers of neural tissue, replete with their wiring schematics, certainly add to the complexity depth. A non-rigorous measure of the

complexity of a nervous system might be the minimum number of synapses that must be traversed from the sensors to the muscles. For completeness, it is also necessary to consider the width of the layers (how many neurons in each layer). The widest layer defines the nominal width of the overall system. Then there is also a connection density, between 0 and 1, where 1 = each neuron is connected to every other neuron. There are other measures, e.g. recurrence (feeding back error signals to earlier layers). Each system has a maximum digestible chunk size. A 10x10 grid, 3 layers deep could handle a pattern of 3 frames of 100 pixels each, where the 3 frames capture the temporal nature of the pattern to the second order. (One frame is still, so it is of the zeroth order. Two frames allow calculating the difference. Three frames allow calculating the acceleration.)

Because nervous systems evolved from molecules to larger entities, constantly bathed in thermal energy, stochastics is a necessary inclusion in models of their behavior. Processing steps must be considered as probabilities in time, across a profile of alternative probabilities. In 1986, William O'Neill created a stochastic neuron model. [28] He retained measured membrane capacitance and replaced the three parallel conductances of Na, K and Cl through the membrane with a threshold element. The model provided random inputs to an integrate and fire model with a threshold of randomly fluctuating value, and a reset that occurs at a randomly varying time.

In 2004, Morgan presented a series of differential EQs for whole cell modeling. His stated purpose was to include cell growth and cell division into the model. [29] Synaptic weighting is effected via neuronal growth and retraction. These are important real cell features that effect learning. This might be added as a feature in neuron computation models, but at the present only about 1 s of simulated time is tractable, not enough for realistic growth processes.

Migliore, in 2005, brought complex shapes (e.g. that of a pyramidal cell) into a NEURON program and compared passive dendrites to active dendrites.[30][31] He was also able to administer two stimuli at widely spaced injection points (soma + axonal bouton, dendrite + soma), demonstrating spatial response patterns for each configuration. He simulated membrane with uniform channel densities and also graded channel density. A membrane with two channel types was simulated using a double exponential time course for the aggregates. Both channels and ions were treated in aggregate.

As late as 2008, Terman was making efforts to collapse the entire neuron into a discrete (digital electronic) information processor, declaring equivalence under certain very restricted circumstances.[32] This may have some utility in industry, but does not serve biology, as all of life's variables were collapsed to constants, flattening the

dynamics. As a result this model can only "solve" the same equivalent problem over and over. It does not exploit the multidimensional potential of biological approaches to information processing.

An attempt was made to employ large scale computers to model neurons by Loeb and Schaff in 2001, which takes on a biological systems approach.[33] This particular model is more cytoplasmic than membranal, therefore side steps the information processing aspects of the membrane. But it is noteworthy for its General Systems Theory application, which is excellent at emulating multichannel, highly-coupled, analog problems. It is very efficient at linear equations, progressively slower on the nonlinear equations. High order nonlinear equations can be made to emulate discrete processes quite well, and so the potential is there for simulating a hybrid system. (Hybrid Analog Digital models will be further discussed below.) Traditionally, linear systems treatments have not embedded any stochastic processes within them, although noise was often used as external drivers or signal sources. However, the line between PDEs (partial differential equations - the engine of linear systems) and SDEs (stochastic differential equations - which ultimately are calculated as though they were PDEs) is fading. We can expect that soon linear systems theory will fully embrace stochastics, fully integrated into the large matrix inversions that solve the first order differentials, solving them seamlessly with no special treatment at all *vis-a-vis* the PDEs.

Artificial Neural Networks, as a formal discipline, has drifted independent of the study of biology. It has been driven by the utility of problem solving machines as applied to commercially attractive problems. To the extent that neural network architectures are mathematically sound, each presents a query to those workers pursuing biological computation: Could biology work this way?

The current mismatch between commercial neural networks and what we know about biological networks is so great that we cannot compare the neuron of an ANN to the neuron of a BNN. An ANN "neuron has one summer or integrator, and one threshold function, such as $y = \tanh(x)$. The BNN has a shaped phase array that resonates to spatial-temporal patterns, has variable diodic qualities that meter back-propagation, and employ a variety of filtering processes that cancel out many patterns, while amplifying others. The BNN has approximately 1 million pattern recognition devices each of which may recognize several different patterns and response with yet different patterns. Each of which is modulatable in many ways (multidimensional). The communications between these are not limited to electrons, but rather by many species of ions and messenger molecules, again greatly increasing the degrees of freedom. The BNN neuron is many orders of magnitude more complex, extensively utilizes stochastic processes,

and is of factorially greater information potential. We will have to compare a single BNN neuron to an entire network of ANN neurons to approach some comparable stance between them. The mis-calibration between the two nominal "neurons" is significant.

1.2.4 BIOLOGICAL NEURAL NETWORKS

Biological Neural Networks (BNNs) have many millions of years head start over the ANNs. They serve as the mentor and the gold standard for the ANNs. We can start with the concepts biology contributes to science in its own right, meta to physics and chemistry. Biology recognizes patterns of organization that perform entirely new behaviors, and indeed more complex behaviors than predicted by physics or chemistry. All living cells make extensive use of feedback loops, for homeostasis, for adaption, for learning and for responding. The neuron, for example, is solving numerous environmental problems. Groups of neurons are radically altering the environment, as well. Biological processors are evolved assemblies of particular patterns, selected for their performance in response to very specific survival advantages. Such selective pressures presumably yield variations in each species, each cell type within the species, each stage in development, and reorganization of cells to changing environments.

The sophistication of interaction with the environment is much higher in biology. Among other things, this implies two critical processes: the ability to derive information from the various aspects of the environment; and the ability to generate new behaviors that respond to environmental stimuli. The complexity of information so derived is dependent upon the complexity of the nervous system. In between sensing information and motor outputs must some form of mapping information patterns from input to output, not one-to-one but many-to-many. When various experiential patterns can be recorded, they may utilized in combination to generate new patterns for output trials. The nature of how environmental patterns are recorded, held, over-written and combined determine the "personality" of the organism.

A useful frame of reference might be that each living cell does computations to decide what to do next. Presumably, this is based upon an anticipation of what the environment will do next. What then is a computation? Mathematicians have extensively studies digital computation. There are unary operators, such as looking up the log of a number, or the sine of an angle. There are binary operators, such as addition, division, or exponentiation. Trinaries exist, but they can usually be broken down into two binaries. There are counterparts to these in chemistry.

A zeroth-order reaction is analogous to an unary operator. A first-order reaction is analogous to a binary. A second-order reaction is analogous to a trinary. Thankfully, much of chemistry behaves as first order binaries, and thus the ubiquity of the exponential response curve. It is noteworthy, however, that second order systems are capable of oscillations, and indeed chemical systems have been defined and built that oscillate. From a modeling point of view it is desirable to avoid constraining the system from exhibiting the zeroth, first, or second order reactions and their effects. A good particle system will be capable of emergent oscillations when ever second order effects emerge from mass-force interactions.

Human study of how biologic organisms compute tackles an immense complexity, because every cell type is quite rich in its computational activities, and these are quite varied across the cell types. Researchers have been engaging in drastic simplification measures over almost 100 years in efforts to understand how the neuron works. Most of these efforts can be classified as analytic, to the extent that phenomena were aggregated and homogenized into continuous deterministic equations. Analytic solutions to liquid diffusion problems and molecular kinetic problems strive to treat the particles collectively. They often assume homogeneities of: substance, size, speed, spacing, and time. Such homogeneities provide the substructure, but it is precisely the inhomogeneities that are the information of the system. To the extent that an analytic effort presumes homogeneity, it defines a system without information content in it.

The real world system, minus the analytic representation of that system, equals the information content of that system.

One could begin, conceptually, with a complete molecular-based model of a general neuron, then narrow the input domain to that of a specific type of neuron, then narrow the state space to only those states that are utilized by such an input domain, and finally limit the output range to only that used by the reduced state space. This would be the linear systems approach. By assuming that the entire arrangement of things could be mapped onto a Cartesian grid, and then reduced to eigenvectors, such an elimination strategy is valid.

Off the Cartesian grid, in a network (also called a graph) of nonlinear elements, eigenvectors may not exist. In a system where slight rearrangements of ion channels on the membrane can alter the mathematical function of the cell requires modal analysis. In a system as nonlinear as the neuron, linear approximations and piecemeal approximations are inadequate and misleading.

The matter of frequency analysis is often raised. Anywhere there are masses and forces, oscillations will occur unless damped by friction. Frequencies are the results of mass, force, distance and interference. They are therefore indicative of, or symptomatic of, the entity that generated them. From an informational point of view, it is the changes in frequency that are significant. A molecule in one state may vibrate in a characteristic manner. Then a change in state will most probably change its characteristic frequencies. Fourier transforms are excellent at capturing the steady state frequencies of a system, but lose much of their accuracy in dynamic systems. To solve this problem, wavelet analysis was invented. It offers Gaussian envelopes in time for frequency sampling, so that consecutive wavelets can be compared, so as to detect changes in time in the underlying system. All of this is indirect to the mechanisms of how the system works. A frequency is one value representing 4 values: mass, force, space and friction. Information has been lost because the frequency value cannot be returned to these 4 values. Only if 3 of the 4 remain constant and are known can the frequency be back calculated to the 4^{th}. This makes a point. Why bother with the degenerate information of frequency data when one has access to the underlying entities and the necessary and sufficient values to model their behavior? Indeed, frequency is but an emergent behavior of a mass-force system. It is therefore prudent to focus on modeling the particles and forces.

The most complete model of a thing is the thing itself. And in the case of the neuron, NIP functions will require representation of a charge barrier, individual ion,s and individual channels which gate ionic flow through the membrane. Neural modeling can be furthered by conceptualizing the information processing ramifications of massively parallel quantities of the involved physical processes, as they occur in living neurons. The literature reveals that the vertical flows are quickly grasped, but that horizontal flows are often ignored. Consider that the retina consists of 5 layers of neuron types (there are also several dozen subtypes). The connection patterns between the layers have been traced. But the initial processing of the retina, known to include edge detection, motion detection, angle detection, and others, are accomplished horizontally, via the connections between peers within a layer. When the basal states of peers are delicately balanced, a signal of lateral contrasts and/or temporal dynamics can cause a strong ripple throughout the net, or trigger useful patterns, subsequently linked to specific responses. Studies of the “purpose” of the retina can guide the search for mechanisms within each of the constituent cells. For example, the search for directional sensitivity led to the detection of a particular cell type (amacrine starburst) with a particular distribution of chloride pumps that set up an axial current of ions which in turn determined directional sensitivity.[34] Here again, the patterns first detected at a multicell level have found purchase at the molecular level.

In stochastic systems there is likely to be significant redundancy. If information theory can properly define the purposes of the system, then statistics can measure the amount of redundancy. In modeling, redundancy is computationally expensive, and it is desirable to purge redundancy to the point of holding the desired precision. This is sometimes referred to as finding the point of diminishing returns. However, we cannot suppose that we know all the functions and "purposes" of the neuron signals. We, therefore, must error on the side of greater redundancy, rather than risk (unknowingly) losing critical functionality. To the extent that information theory may be successfully applied to hybrid analog digital systems (HADs), this problem can be settled, and models can be optimized to the minimum redundancy that preserves function.

1.3 APPROACH

Modeling compels one to consider a number of abstract concepts: continuity vs discrete; infinite vs finite; closed form vs open form differential equation systems; deterministic vs probabilistic universes; degree of incompleteness; inherent uncertainty; reversibility vs irreversibility; entropy in cytological systems; asynchronous biologic events vs synchronous digital computer clock events; stationarity vs steady parametric drift (concerning both development and evolution); false classifications and semantics; noise vs thermal energy sources; molecular dynamics vs kinetic schemes. Every attempt at simulating a living system within a computer runs into these, explicitly or implicitly. A conscious effort will be made to address these on their merits, across the alternatives, valued and ranked for appropriateness to the standard of NIP-relevance.

Three of the concept threads that paved the way for the study of cells that compute:

heat > entropy > probability > communications > information theory

number line > continuity > infinities > discontinuities > discrete math > logic > turing machines

linear algebra > general systems theory > control theory > optimal control > systems identification > nonlinear systems > stochastic systems

Several workers, e.g. Voit EO, 2000, refer to the evolution of reductionist models as "reconstructionist" models.[35] Mathematically, this is equivalent to moving from linear systems theory to stochastic partial differential equations (SDEs). But no sooner were SDEs employed to simulate neurons than workers expressed a need of "simplification" so as to handle the immense quantities of elements and their process step iterations.

Hodgkin and Huxley, in 1953 inspired an application of chemical reaction kinetics to large molecule conformational changes. This implied that a molecule was reacting with itself, yet the forward and backward reaction rates still held. Studies of ion channels in the lobster giant axon led the way because the channel state changes were detectable via electric currents passing through the channels when open. As detection methods progressed, such kinetic approaches extended to pumps and receptors, wherein the movement of an "arm" of the molecule was detectable so long as it had a charge on it (so called "gating charge"). Since the early 1990's , workers have been attempting to identify the critical pieces necessary to comprise a whole cell model of neuronal function, [36] and collecting sets of parametric values suitable for such a model.[37]

1.3.1 PARTICLE SYSTEMS

It is recognized that the natural world generates great variety though abundant types of molecules, very large quantities of those types, and superabundant possible interactions between them. The velocities of these molecules ensure extremely high rates of collisions, thus engaging in very intimate interaction rates. A single molecule of O2 at Standard Temperature and Pressure (STP) experiences approx. 5e9 collisions /s. Each one of these collisions is a presentation for chemical interaction. At that transaction rate, in a mixture of 1000 different molecular types, chances are that a single particle will have interacted with 99.5% of all other types within 1E-6 s. (results of simulations) That is, *de facto*, a very high level of coupling. In liquids, the collision rate is much higher, about 1E14 collisions /s. However, due to the close packing distances, the chances of hitting the same nearest neighbors repeatedly are much higher than hitting something new. It can be calculated or simulated the statistical collision rates for various mixes, taking into account temperature, masses, and radii. It is these extremely high interaction rates that allow us to conceive of "high affinity" receptors. To bring about this effect, we need only design receptors to bind a somewhat greater percentage of these high hit rates. No genuine "affinity" (i.e. force) is needed. Note however, that water is a complex solvent, creating several types of transient structures, which tend to reduce novelty in collisions.

The continuity equations break down near the resolution of molecules, at about 10 nm. Below that, a particle model is required to predict outcomes of interactions. Particle models are agnostic with respect to shape, elasticity, diffusion and drift, supporting complex interactions between them all. Particle system models of the neuron can be constructed so parametrized, and so generative, as to embrace this variety of fast interactions. Indeed, they may

create new variety, whenever molecules are conducive to building lengthy chains and branch chains, as indeed carbon can. Particle models have great breadth, allowing highly parallel natural processes to reveal behaviors of massively-coupled ions in charge fields, constrained by container walls and colliding with binding points. Such large scale networks may display dominant patterns in parallel, in series, in systemic loops, or as spatial-temporal patterns. By making the container shapes more complex, e.g. adding topology of arborizations, which consist of numerous bifurcations and tapered shapes, patterns may emerge far more complex that those generated by smaller scale modeling strategies. Contrast that with the analytic methods. J. Crank, in his “The Mathematics of Diffusion” , 1975, is only able to address the primitive shapes of cubes, cylinders and spheres.

Electronic circuits deal in the flows of a single type of charged particle (the electron). These particles may be conducted, resisted, capacitated, inducted, gated, or accelerated (forced). Conduction, resistance and gating are all variations on a single phenomenon. When a gate is open, resistance is minimized (its a conductor), and when a gate is closed, resistance is maximized (high resistance = an insulator). And that leaves four base functions: C,R,L,F (capacitance, resistance, inductance, acceleration). However, man made circuit elements are all designed unidimensionally for point to point connections. That is, they are intentionally constrained so as to minimize dimensionality, maximize linearity, and to separate the functions (capacitance, inductance, resistance).

In silicon chips, capacitance serves as short-term memory for 1's and 0's. Inductance is not practical in microcircuits, because of the required inertia there available is too small to have appreciable effect. Force is provided by a steady voltage from an external power supply. All components are designed to behave linearly - except the gate, a chip's distinctly non linear component. All digital components are deterministic, to the extent thermal noise is minimized. To put it another way, great effort has been made to design out all statistical behaviors and non-linear behaviors of the components, even though at the nano-level uncertainty is inherent and persistent. All of this effort is made in pursuit of reliability, which is defined as precise repeatability. Given current chip architecture, this is a very necessary objective, because in such logical systems a single bit may alter control flow over the entire machine. Consider the single bit setting of the power button, or the single bit setting which determines one of two operating systems to boot. Though digital machines are empowered with general processing ability, certain forms of mathematical completeness and strong leveraged control of operations, this arbitrary bit value situation makes digital processors excruciatingly sensitive to software errors. We say they lack robustness.

While digital machines exploit discreteness a/k/a logic, biology exploits the continuities of saline volumes and membrane surfaces. It benefits from the high orders of resonance that they support, i.e. spatial-temporal patterns. Biologic systems have no master bit for power on and off, nor operating system. However, there are some mechanisms of informational leveraging. For example, hormone molecules can radically change the mode of the cell. Therefore, man made circuit representations are overly constrained, with one dimensional wires and 2-port elements. Such dimensional and linear constraining suffer serious limitations in mimicking biology, no matter how earnest the simulation.

The electrical grid built of of saline resistance and membrane capacitance may be represented by a finite-element triangular-grid surface. This approach is purported to represent distributed discrete capacitances, with lag coupling between. Such a finite element approach can support wet lab work collecting single unit recordings. Single unit recordings on intact neurons are plagued by non-linear capacitance resulting from their complex shape. An equivalent-shaped model to the neuron under study can be "reverse engineered" and then used to subtract out the stray capacitance from the data. Theoretically, this process should leave remaining a clean single channel record.

Electronic conduction through a copper wire is extremely fast, near the speed of light, when all the electrons are constrained within a metal bar, and there is no capacitance to absorb some of the charge. However, any single electron is jostling about very slowly, in comparison, translating less than 2E-5 m/s. It is the incompressibility of charge that determines the velocity of the wave front (conduction velocity). The charge movements of the saline and membrane capacitance cannot be electronic. If they were, then any charge movements would be "shorted out" over the entire surface of the cell (and via the extracellular fluid, to all cells) at nearly the speed of light. The neuron could do no more information processing under these conditions than any number of man-made transistors could if they were all shorted across two buss bars (nullifying any other wiring patterns between them). Therefore, we must consider that ionic conduction is qualitatively different from electronic conduction. The saline *per se* is not a general conductor, as copper would be, because it is conducting ions, not electrons, and because only those areas of charge imbalance are conducting at all. By "areas" is meant membranal charge barriers which prevent unbalanced charges from neutralizing. While conduction may be induced across arbitrary paths by the injection of electrons via mensuration equipment probes, in the natural state, no such electrons flow broadly through the saline.

We observe propagation velocity along an axon in the range (1..100) m/s, depending on neuron type. Biological "conductors" are best conceptualized not as baths but as surface effects resulting from charge barriers (lipid membranes) which conduct to all points along the membrane, and perhaps across to the neighboring cell whenever an electrogenic differential between cells is "pumped". This lack of point to point conduction links implies significant "cross-talk" amongst the nodes of a membrane. How can a system work in which all conductors are significantly coupled? Two obvious possibilities are:

1. Damping effects of distance due to saline resistance cause the signal amplitude to fall below the threshold of all distant responders. This would certainly be sufficient if only one channel could open at a time. But as neural electro-recordings often show multiple channels concurrently open, then the sum of their outputs would be expected to again exceed the threshold of responders.

2. The general mechanism of communication is a grid of point processes capable of emulating a wave front as a group, but are too weak individually to exceed the thermal noise. To generate a wave front, these points must be in phase. In that case, the "cross-talk" referred to earlier is actually a vital linkage to create the wave front. Such synchrony implies redundancy, and redundancy is of lower information content. When nodes are in near synchrony, the information is in the slight differential between them. This set constitutes a wavefront at the macro-level, but the subtleties of timing, direction, shape and amplitude all have informational values because they determine where, how far, how fast and how strong that wave will proceed until terminating.

3. The point processes might have a mechanism for echo cancellation. Indeed the refractory period of ion channels serves this function.

Their 'nonlinear transfer function's[6] vary along many parameters, and these impart significant information processing characteristics to the neuron. Early neuron models have assumed that biology operated analogously to electronic concepts, but in so doing lost many of their biological traits. These traits are not discard-able if one is to capture mathematically, parametrize and design BNN's. This model will of necessity evolve to include ever greater types of membranal proteins involved in channel system behavior.

1.3.2 KINETICS

Kinetics is defined as the velocity of chemical reactions. Because models consist of a set of objects (chemicals?) arranged in a network of processes (reactions?), how we define the objects and how we write the interaction rules will determine the velocities of communication between them. In the case of a homogeneous series of repeating steps, we can speak of 'conduction velocities'.

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[6] Though the term 'transfer function' is passionately reserved for linear systems, a suitable complimentary term for nonlinear systems is not settled.

The modeling challenge includes the problem that a digital universe requires many concessions, leading us away from the continuum of natural interactions. The early definitions of digital process frame the concepts and terminology that we later use to discuss simulation experiments and their performance. The early (less informed) design decisions may have great impact upon what questions we can ask and answer. Graph theory can be utilized to help identify possible optimizations in network designs, derived from the fruits of systems biology. Graph theory provides a calculus of connections in an algebraically complete way, but of course must be carefully aligned to how biology actually is connected, and avoid any functional connections that biology disallows.

Regarding the input to such a model, analytic bio-data must be normalized, generalized and interpolated to span the parametric space. But this time every biological effect is but a mere number, discretely stored in a matrix column, oblivious to the values in any other column. The only interactions allowed within the digital universe are those specifically programmed. In highly complex space, such as the possible conformations of an ion channel protein, modelers must focus on those few conformational aspects most determinant of channel function. Thus, the utility of "kinetic schemes", is admitted, right in the name, to be fabrications. When simplifying, clipping, merging various biological arrangements, what havoc does that reek upon the kinetics of the system? Blessedly, it greatly reduces the quantity of possible interaction types; but dangerously, it may discard significant and even crucial reactions, and may distort the representation of those that remain. How the reduced set of reactions to be modeled are normalized is of great import because most biological reactions "live" right at the equilibrium points. Any distortion in the design process risks creating a model that has lost the delicate balance of reactions, and thereby produces behavior far from homeostatic, far from viable, and far from representing the signals that a biological system actually produces.

Molecular models of ion channels, when successful, may yield millions of "states". A lengthy hydrocarbon backbone is flexible at every joint, and the "radical" arms of the amino acids possess terminal charges that necessarily produce a "stickiness" of certain conformations due to opposite charges attracting. Despite huge quantities of possible conformations, we seek to reduce this list down to the highly probable conformations. Often the case, a huge percentage of possible conformations have no impact upon conductivity so may be ignored in an information model. Some conformations may be so fast or so slow as to be out of temporal compass. Often this leaves us with less than 30 states to model, sometimes only 3. This huge reduction may (or may not) be justified on the grounds that these 30 or so abstracted states each represent a group of states which happen to have a similar

impact upon conductance/transport/ catalysis and have similar transitions to other states. Unpublished results by Jie Liang, of UIC Bioinformatics, show the conformational possibilities for some ion channels to be largely torsional, and not at all chaotic, resulting in only a few states being transitioned in rhythmic cycles of twist close/untwist open. [38]

In 1990, a learning synapse (Hebbian) is modeled,[39] and this requires dynamics of 2 time constants, the spike time and the learning time. The former altered input weights by the ms while the latter took considerably longer. Since then, time constants have been replaced by the stochastic probabilities of state transitions. Kinetics predicts reaction rates, though the individual bindings are the result of stochastic process. Stochastics are handled mathematically in a straight forward manner using stochastic differential EQs (SDE). What means of simplification can be justified in SDE systems? Averaging molecular behavior may not be valid in information processing systems where very small details are significant to model behavior. Complexity demands spatial, temporal, quantitative, and redundancy simplifications. In order to harness stochastic processes in an informational system, we must deconstruct the traditional aggregate methods, and return to statistical instantiation of individual particles, their velocities, their collisions, and their bindings. This involves random number generators driving CDF selection across possible transitions, at a sampling rate of at least 2 times greater than the fastest reaction rate to be modeled. Where frequency phase locks are instrumental to system performance, the sampling rate should be at least 8 times greater, so as to avoid aliasing error which produces “ghost” frequencies and rhythms as artifacts, as well as “missing” many of the phase lock opportunities presented to it.

While physics is currently engaged in divining the predictability and unpredictability of aggregate quantum matter, biology has long inspired this search. It is intended that this model serve as a platform for investigating previously un-noted patterns of molecular systems. Elegance and speed are sacrificed for the sake of robustness and variety. Accordingly, the quantities and placement of elements and their degrees of randomness are critical. For practical reasons, quantities often need be tempered by observations of diminishing returns from shear number. Nature may be far more bounteous and redundant than our present day computers can afford.

Neurons enjoy the complexity of at least 5 species of charged particle (Na, Cl, K, Ca, and organic anions), and most often there are other ion types involved (e.g. Mg, Mn, Fe, NH4, NO2, NO3, CO3, PO4, SO2, SO4). These interact with channels and pumps which are capable of treating each species differentially. They are embedding so as to

penetrate a membrane that serves as continuous capacitor, its shape determining channel and pump nearest neighbors. Each channel and pump type transports some subset of the particle species in solution, in a unique ratio (conductance selectivity profile for channels and ratiometric stoichiometry for pumps). These differential conductivities in turn are multiplied by their net respective ionic partial voltage plus concentration gradient pressures to determine flux rates. They are highly dynamic, as is required of any information processing system.

Unlike digital gates, ion channels do not respond in a one-to-one to their inputs. They are not deterministic as digital computers are, but rather change conformations according to large numbers of transition probabilities (expressions of chemical kinetics of large protein molecules). An ion channel has the potential to require a temporal input pattern which would cause a particular sequence of state changes. Certain sequences of state changes can result in channel openings or closings. Even given a finite number of gate types, the quantity of possible computational systems is theoretically infinite, because conductivity ratios can be set over continuous gamuts. Recall also that our kinetic schemes are gross simplifications of actuality; that the numbers of possible patterns of input recognition and output responses remain astronomic because the number of possible conformations in any large protein molecule (or other large molecule of mixed neutral and polar portions) is 'astronomical'[7].

In common parlance kinetics is a concept applied to the chemical interaction between two or more species of chemical. The genius of the Hodgkin and Huxley team in their early work was to treat conformational changes as the kinetics of one part of a large molecule interacting with another part of the same molecule; i.e. an interaction with self. Such interactions are then recognized as state transitions. A patterned recognition or response of such large molecules to environmental impacts is the direct result of that molecule temporally traversing path through its state space. We may think of this as internal kinetics, a useful concept because the transaction rates are determinant of which path shall be the dominant one, the secondary one, etc.. As kinetic schemes began to be published for channels and pumps, a chemical dynamics approach to neuron modeling became feasible. The number of possible transitions in a state space of s states is s^2. But the number of paths is quasi-infinite because of the possibilities of repetitions and sub-loops along the path. For practical reasons, the paths actually used are the shorter ones, as long paths lower the throughput bit rate (lower the response frequency). Extending the length of the state path may have

[7] Though tradition has it that emphasis on very large numbers employ astronomy as metaphor, in fact the permutations of chemical interactions present in a living cell far exceed the touted astronomic numbers. About 100,000 factorial!

utility if it adds to the ability to process more complex tasks. For example, if a 3-step input pattern was necessary to elicit a 2-step output pattern, then this constitutes a sort of pattern recognition, and therefore is a computation.

1.3.3 SHAPE

By 1980 morphometric 3-d reconstructions from micrograph slices was becoming possible, and by 1990 development of computer hardware and software advanced to the point of a package made available for general lab use.[40] This is germane to modeling because shape constrains the positioning all those ion channel and ion pumps, which in turn determines the nearest neighbors to each, which in turn is a dominant factor in how information is processed. Topology and actor density matter.

Morphometric data from the anatomy of neurons is becoming readily available. But Actor distribution data remains sparse. While fluorescent marker studies can sometimes display whole cell distributions of membrane proteins, the verification of channel function is done via patch clamps, which can only sample about 10 out of about 1 million channels on any given neuron before it dies. Thus extrapolations are made with sample sizes too small to achieve high levels of confidence. However, by modeling hypothesized distributions and verifying their performance against wet lab data, reasonable inferences can be drawn as "place holders" or equivalents. In any case functional configurations can be discovered and employed, even if not an exact match to the biologic ones. Working in the hypothetical may discover significant domains within which biological reality must lie to produce equivalent behaviors.

In this model, the complexity of biologic shape is abstracted topographically into two-dimensional contour lines, which are then rotated cylindrically (i.e. contours of revolution). This shape simplification may realize about 3 orders of magnitude reduction in computational load, by converting the determination of where ionic collisions with membrane (and stationary proteins) will occur into a simple polar coordinates problem. Furthermore, of the three major engines within the model, only the diffusion/drift engine is intimately shape dependent.[8] The electrical phenomena of membranes are completely and accurately captured in the form of a simple plane. The protein stochastics are completely and accurately represented as isolated nodal points of the membrane surface. Membrane

[8] Near-membrane diffusion is amenable to conversion into planar representations via mathematical manifold theory.

bifurcations, however, also determine nearest neighbors for the RC grid, and this 3-D information is mapped into 2-D matrices, albeit with sometimes irregular borders.

1.3.4 MASSIVELY PARALLEL SYSTEMS

Neural modeling can be furthered by conceptualizing the information processing ramifications of massively parallel quantities of ions in solution and channels held stationary in membranes, as they occur in living neurons. When a scientist says "All other things remaining equal, A causes B", he is striving to uncouple the system under test (SUT) from the system's environment (SE). In biology, components are so richly coupled, that the specimen must usually be killed to study it thusly. The act of tackling more complex systems (more coupled systems) exposes the inadequacy of this older version of the scientific method. It might be more fruitful to study creatures while they are alive and then say, as the new version of the scientific method:

"All other things refuse to remain equal. However, I measured a correlation between A and B several times during their motion, and the time sequence suggests causality."

This sounds weaker than the traditional form, and such was shunned in prior decades. But it has now been harnessed in far greater quantities of interactions, recorded *en bloc*, to reveal complex relationships previously unfathomable. So let us revise the claim to:

"All living things are perverted by static conditions; therefore we allow them their normal dynamics. We can monitor large numbers of variables simultaneously, streaming for long periods of time (days). From this massive data can be measured cross- and auto-correlations across all channels , yielding hundreds of coupling phenomena in a single experiment, as chains and networks of systemic regulation and responsivities."

This is essentially the approach of systems biology. Bayesian Network methods applied to rolling systems biology (collecting multiple streams of long run data on groups of living cells) are outperforming the "holding things equal" tradition. This is an important water shed, because it breaks the centuries old scientific "barrier" of doing only nomenclature and analysis, by entering into the creational activity of synthesis. This process of synthesis is necessary to understand cells that compute. Computation, in essence, is synthetic. It is the convolving of two patterns to generate a third pattern. Synthetic, because 2 second-order EQs would convolve into a fourth-order EQ.

Any two streams of information have the potential to interact by some function to create a third stream.

This is the dynamic equivalent of the binary operator.

In the past, major simplifying assumptions were made in the design phase to reduce the number of equations in the model. In so doing, many of the emergent properties of living cells were lost. The many previous approaches did not address the underlying molecular processes directly. The objective herein is to faithfully replicate, in quantity, the 3-dimensional molecular mechanisms employed by living cells to effect information processing tasks, with their topological relationships adequately represented.

The quest for understanding cells that compute can proceed by synthetic means. That is, one can build up from particles, rather than cut down from a living squid. In order to accurately model such complex effects, it is necessary to review the underlying physics, and build up from statistical mechanics. In particular, the physics of how ions and molecules diffuse, drift, bond, organize and build. To rigorously study the information processing capacity of the neuron, a science of synthesis is required that retains the integrity of the biology at all levels - from ion, to protein molecule, to membrane, to synapse, to glia, to brain tissue circuitry. The original stochastic processes must be preserved, because physics at its essence is stochastics, and biology is built up from such processes. What has previously been labeled as "noise" is actually ubiquitous thermal energy, which biology has harnessed as a convenient and free energy source, as a pattern generator, and as a discriminator function. Thermal noise provides the transport of diffusion for messenger molecules, and the energy for effecting state changes in large protein molecules such as ion channels and pumps.

The more advanced models of neural networks employ some form of recurrent wiring. Such feedback offers a way of learning and improving, and also offers fine tuning (high discrimination) which is necessary for intelligent systems.[41] Recurrent wiring of nodes usually transforms time-varying inputs into spatiotemporal patterns of activation. A pattern received can be reverberated about the network so as to elicit a distinctive temporal pattern. When an input pattern stimulates the network, it most often responds with a different pattern, then that second pattern acts as a stimulus to elicit yet a third pattern, and so forth - thereby yielding a train of patterns until they decay or until a new stimulus intrudes to break this reverberating process. Usually there is a "winner-takes-all" mechanism such that only a single most strongly resonating pattern gets to propagate while all others are dampened to zero. This is the same effect of a radio tuner, which may receive 100 stations simultaneously, yet filter all of them

out but one and “play” only one signal at a time. Whenever the output pattern of a neuron does not match the input pattern to which it responded, then one or more transformations must have occurred within the neuron. It becomes possible for such neurons to comprise a concept map and/or a problem-solving map, whereby the output patterns are solutions to the input pattern “problems”. Presumably, each output pattern represents some attempt at a real world solution, that is incrementally “discovered” and improved as feedback is provided from the environment (rewards and punishments) and numerous reties are made. First there is variety, then selection, and then memory (inheritance). It is possible to construct such systems as either deterministic or as stochastic systems.

Given ubiquitous thermal noise, biology chose the stochastic option. Constant driving by thermal noise results in information processing cells that never lie silent. Membranal proteins are rendered in constant state of conformational changes, and some of this results in the transport of ions. This constant state of computation results in a phenomena we might call “anticipation”, as such streaming generates a normalcy that is only disrupted by a failure anticipate how the environment will next impinge upon the organism. Biologic systems come to “resonate” with normal impinging patterns such that they become predictive of “what comes next”. It is the failure of such predictions, the surprises, that perturb the biologic system into strong response. One can sleep near the speakers of a rock and roll band performance when those band members are friends, but if the sounds change to something not predicted, like the sound of police sirens, one is snapped to awakeness with adrenaline pumping.

The arguments of how the nervous system works must traverse the scale from whole organism down to molecule. The history of discovery in neurology has been to attribute function to the largest scale entity (whole brain), and progressively establishing such function at lower orders as instrumentation might allow. Though higher order information processing is tautologically the more complex, it must be built out of elements that compute. Assumptions about neurons as transistors are falling away to ion channels as transistors, which are falling away to ion channels as multi-state Finite State Machines (akin to integrated circuit chips, of say, 100 transistors). Given that ion channels are found to have 7 to 30+ states, and that admittedly, not all states have been found for any given channel type, then it might be difficult to get an ion channel to do mere addition and subtraction. Mere algebra is trivial for a Finite State Machine, and requires some dumbing down to effect it. This is analogous to asking an Integrated Circuit chip to act only as 1 transistor. While most ion channels are found to operate with 7 to 30 significant states, only 4 states are required to add, subtract, or multiply. See the definitional tables for AND, OR,

NAND, NOR gates to verify this. Presumably, the demands for survival over the course of evolution are greater than the demands of the math teacher.

In summary, the nervous system is a massively parallel system comprised of information processing elements. Such base elements must receive an input pattern and generate an output pattern. For information processing to take place, the output pattern must be different from the input, at least some of the time. Else the element would serve as a mere repeater (not processor). The state of the art has it that ion channels are state machines, implying significant potential to process information. As similar protein molecules, receptors and pumps may also serve as repeaters and/or processors. The challenge is to provide a platform for such molecular processors to express their range of potential behaviors, in a recordable maner.

1.3.5 HYBRID MODELS

The information value of the analog signal being collapsed into a digital signal is polluted with distortions. Spectral analysis provides a reasonable limit of the information contained in an analog signal. The faster the rate of change of the spectrum the less accurate the conversion from A to D is. Digital signals pick up multiple forms of aliasing error. Despite the many successes of digital computers they are at their worst when emulating continua.

The ion channel has the gating quality of a solid state artificial transistor, and the flux of ions, both vertically through the channels and pumps, and horizontally along the membrane as capacitated charges. Thus membranal systems possess both discrete and continuous elements, thoroughly distributed amongst each other. Furthermore, the ion channel has far more complexity and modulatability than a single NPN transistor. It is more analogous to a medium scale IC (integrated circuit chip with about 100 transistors). This fact could bump the equivalent “transistor count” for the human brain up to about 1E16. Such ion channel kinetic complexity is probably muted by the typical constellations of channels which apparently can be quite redundant in their function. Especially circumferentially, no patterned variation in ion channel distribution has been reported. This suggests that circumferential distribution lends itself to generating lockstep wave fronts, imparting directionality to the propagating action potential. The degree and distribution of such redundancies may be exploited to support and further plasticity, development and evolutionary processes.

The whole of logic is discrete, but it has sometimes been applied to represent hybrid analog digital (HAD) problems. This is to say that digital logic can be made to (weakly) emulate continuous processes. Such an exercise is sound when the entities of interest can be de-coupled into discretized spaces. [9] Our sense of "particle" holds that each is a discrete entity. We talk of its intrinsic traits: mass, radius, charge, all occupying a single unique location on space. Less often taken into account is that such a particle would not be what it is without its extrinsic traits: gravity, EM force, temperature of its environment, chemical bond potentials, its ability to exert pressure, its ability to cooperatively form gases, liquids, solids - and many others. These often taken for granted extrinsics must be explicitly defined and enacted within any digital simulation, and usually comprise a much larger part of the simulation code than do the intrinsics. This is so because the quantity of relationships is vastly larger than the quantity of entities. Accordingly, problems involving dense coupling between the components become extremely tedious if pursued logically and become intractable for many common problems. Artificial intelligence suffered this set back in the 1980's, when it had to abandon predicate calculus approaches (logically constructed) because the quantity of computations "exploded" for all but the simplest problems. They were replaced by open, continuously coupled systems which employed "field effects" rather than logic.

Biological Neural Networks (BNN's) produce "answers" (behaviors) that are the result of processes more complex than step-by-step logic and qualitatively different from step by step logic. Physicists have been talking about the "field effect" or "mass action" of the brain. (Freeman WJ)[42] Yet, we are today investing great energy to model biology within the confines of wholly digital silicon processors, restricted to step-by-step logic. This occurs merely as a result of the convenience of what is readily available, and the economics characteristic of the greater society in regard to producing computing machines. The digital processor is not the ideal machine for the task of neural modeling. This should give pause, as it forebodes some of the problems that lie ahead. The conversion of bio-data into digital programs will always lose a great portion of the total, and will always add in artefactual errors. Yes, we have developed cautionary rules, like Nyquist's sampling theorem, and algorithms to compensate for aliasing error. But we still suffer from discontinuities that lose the differentiability that was present in the analog form and must continually battle "ghosts" and accumulating "round off" error in the discrete data that are generated by the digitization process itself. More obvious, sampling rates risk missing any event that occurs between samples, and

[9] Consider domains of words or man-made objects. The processes by which they are invented and articulated may be somewhat continuous, but the instantiations are necessarily discrete.

incur hugely burdensome computation loads when choosing high sampling rates to avoid such missed events. This option wastes a majority of iterations wherein no such events occur.

There is significant processing going on throughout the neuron, along its membranes. The arborizations of integration, the soma of inhibitory signals, the axonal hillock performing analog to digital conversion, and axonal nodes acting as contrast sharpeners, are all extra-synaptic operations that constitute definite information processing functions. The neuron also provides parallel processes of widely varying time constants. Fast constants for "propagation", medium constants for short term memory and modulation, slower constants for long term memory, adaptation, plasticity, cell development and repair. This is immensely greater functionality than current solid state processors can offer. Addressing the compass of time constants always requires compromises to get to a simulation. A similar problem presents with regard to the compass of space constants.

1.4 MEMBRANE PATCHES

The obvious necessities of modeling a neuron for its ability to generate an action potential include water, ions, membrane, ion channels. To create realistic input and outputs to the neuron, receptors and vesicles must be represented. To achieve initial conditions across the membrane, "resting potential" tonicities must be establish and restored via the pumps. During action potentials and graded responses, axial flux, neurotransmitter re-uptake, modulation and depletion, must all be simulated.

Because current day computers cannot simultaneously simulate all the ions and actors of a single neuron, one solution is to simulate only a small patch of that membrane at a time. The simulation of a membrane patch of (1E-6 m)^2 surface area within a volume of (1E-6 m)^3 saline solutions might only require 1e9 collisions, which is digitally feasible. If patches were intensively studied, and then somehow abstracted, and those abstracts assembled into whole cells, then we might have an accurate model of whole cell behavior as emergent from molecular events . The art of multiscaling software is applicable to this approach.

Consider a *de minimis* arrangement of two channels, fixed in a membrane between two baths of different tonicities, each bath made up of four separate ion concentration values. Initiated at random states, a steady state is soon achieved, and maintained until some neurotransmitter is added near the receptor sites on the channels. Once bound

to a receptor site a neurotransmitter molecule modulates the transition probabilities, which sets into motion new paths through the state space. There are no clocks in neurons to synchronize events and measurements, as all actors are stochastic over their state transition spaces, and in so doing generate varied complex temporal patterns (state transition paths) in continuous time. Any synchrony that occurs does so via field effects, particularly wave fronts. The radiating outward of signals from each actor type might be exploited by neighboring actors of a different type that exploit such signals. Practical combinations of actor types are those which generate signal values within physiologic range, tending towards homeostasis, responding strongest to input patterns which resonate with high probability paths (patterns); and yield patterns which reflect the paths through relaxation states of the channel and are somehow useful downstream.

There are constraints determined by conductivity profiles of each channel type. There are also constraints determined by the ratiometric pumping of ions up gradient. Channel locations and quantities change more slowly than the tonicities of the compartments, a result of conservation of momentum. Because channels are statistical processors, some redundancy is necessary to average out noise (the hair cell of the inner ear has a redundancy of about 8). In a biological cell of about 1E5 channels, despite the above constraints, there are still astronomic possibilities in information processing potential.

The patch model is sufficiently detailed to represent the difference between ions near the membrane (lipids about 5.6E-9 m thick, hydrated to 8E-9 m) and ions near the ion channel (protein about 1.7E-8 m tall x 8E-9 m diameter). The membrane may be glycosylated to greater thicknesses and those sugar molecules can attract layers of solvation. All of this complicates how ions will behave along the membrane and near the ion channel openings, which is critical to neuron function.

Hodgkin and Huxley, in 1953 inspired an application of chemical reaction kinetics to large molecule conformational changes. Studies of ion channels in the lobster giant axon led the way because it was large enough to stick a wire down the length of it and thus record the channel state changes as electrical signals, via detection of ion currents passing through the channels when open. As methods progressed, such measurements extended to pumps and receptors, wherein the movement of an “arm” of the molecule was detectable so long as it had a charge on it (so called “gating charge”). These very much welcomed sources of data none-the-less are a long way from a complete characterization of actor behavior as relevant to NIP. Determination of internal conformations is an inexact science,

relying upon detectible charge movement which can only “see” those changes that relocate a polar group parallel to the axis of mensuration.

Since the early 1990's , workers have been attempting to identify the critical elements to comprise a whole cell model of neuronal function [36], and collecting sets of parametric values suitable for such a model [37]. These may serve as test cases for a molecular model but are silent on how to construct such molecular models.

This author recommends the rigorous molecular modeling of typical membrane patches on a one-to-one basis *vis-a-vis* ions and membrane proteins. This is offers a method to build towards a complete, predictive model of information throughput for the membranal processor. Simulated patches can be exercised across their parametric space to record their modalities, stabilities, and nonlinearities wrt time-wise variations in physiologic values, especially ligand concentrations and voltage.

Of course, every living cell requires a boundary between self and environment, the plasma lemma, that if punctured the cell dies due to loss of tonicity gradients that drive many of the chemical processes of life. The lipid membrane also provides a role as capacitor for storing electrical charge, and by the ratio of those charges, effect a transmembrane voltage. In addition to the elements of ions in saline volumes, channels and pumps to transport those ions, there is also the matter of how to simulate that lipid membrane, so as to serve as a charge barrier. Such a barrier effects a capacitor continuously over the boundary of each compartment, especially the membrane dividing the intracellular from the extracellular.

The basic sciences implicated in neuron modeling at the molecular level for bio-computation purposes include the mathematics of: diffusion, drift, protein kinetics, stochastics of finite state machines, and topology of shape. Each of these will be developed in the course of this paper.

1.5 WHOLE CELLS

The choice of quantities of moving parts (thousands) being simulated is motivated by a desire to "scale up" the number of elements (particularly ions, ion channels and ion pumps) only as necessary and sufficient to faithfully express the emergent behaviors relevant to NIP. Simply put, the patterns of molecular organization can trump the

intrinsic individual atomic traits, and many of the significant processes of biology are simply not possible at the level of say only 10 elements. Quantities matter, but only to the point of redundancy.

A computer model is limited by the element requiring the largest quantity of computations. In the neuron that would be water. Water molecules are non spherical, non symmetrical, tend to loosely cluster into variable sized spheres of solvation that are easily and frequently altered, and interact with charge in a variety of asymmetric ways. Water molecules collide with other water molecules about 1e14 s^{-1}. [43][44] Modeling an action potential requires space and time of about 1000 (1E-6 m)^3 (cubic microns) and 0.1 s. That infers 3.31E10 H2O/micron^3 * 1000 (1E-6 m)^3 * (0.5)*1e14 collisions per molecule * 0.1 s of simulation = 1.66e23 collisions, for an accurate whole cell simulation. This is not tractable within current digital computers.

This effort strives to employ a bottom-up approach, so as to avoid the oblivious discard of biological function . Although the model is robust, practical limitations of available computer processing power set limits, and demand simplifications of another kind (graininess). In order to address such limitations, multiscale modeling has been resorted to. Rigorous biologic modeling can be achieved at the nanoscale, the results of which can be mapped to larger (whole-cell) scale by inference. Such a flexible approach can produce models which can be then run on various sizes of computers (adjusting parametric “graininess” to suit). One might liken this approach to adjusting the spatial frequency band limits of the Fourier transform of a photograph.

When large scale systems exceed available digital computer power to model them fully, the system can be broken down into its layers of complexity. The highest level remains intact. Successively lower levels are allowed fewer portions to be fully modeled. The unmodeled portions must be either clones of the modeled ones, or stable enough to allow interpolated values to stand in for the unstudied pieces. Presumably, redundancy is highest at the lower level. For example, at the atomic level there may be trillions of oxygen, trillions of hydrogen, etc. It is not necessary to model every water molecule rigorously. The study of water in each of its various roles will do. The rest can be inferred.

A multiscale modeling strategy is employed, with various *dt* and *dx* values selected appropriate to each phenomenon being represented. Smallest scale phenomena are modeled first. Once characterized over the parametric space of physiologic domains, then this data may collapsed into a "look-up" table, or to a curve fit, which becomes "elemental" to the next higher layer of complexity. Such tables or equations are extrapolated to fill in the grid

between the samples. This process can continue all the way up the hierarchy of complexity through the whole cell model, and to cellular circuits.

To manage the large compass in time and in space, multiscale strategies provide computational relief. The question is: can bio-computation be leveraged by multiscale strategies without loss of critical nonlinearities? To answer this the smaller Patch model was created, conceived as a sub-model of the WholeCell model. The Patch works with a minimal number of ion channels (usually < 10) to define the modulus of the membrane plaiting the whole cell. It may then be incrementally enlarged to include larger patterns, checking for continuity of performance along the way.

The power of multi-scaling is that it can model rigorously at the molecular level, then clone those results as tiles into a much larger model. Once the parametric space of the smaller patches is swept, and the output modes characterized, then they can be tiled into a whole cell model, with much of the computational work at the higher level reduced to arrays of look-up tables. The challenge of multi-scaling is to justify the choices made as to how many samples (and which ones in particular) represent that layer, and then to verify the assembled results against found bio-data.

1.6 NETWORKS

For six decades there has been a strong interest in multi-neuron models, more so than single cell models, presumably because of a conceptual bias that a neuron was like a transistor and it would take many transistors to do anything computationally interesting. Frank Rosenblatt, in 1958 contributed the Perceptron, a true three layer neural network wiring summers and threshold devices. Bernard Widrow and Marcian Hoff in 1960 contributed an analog computer design for neural network demonstrations, called Adeline. Marvin Minski, who had been contributing to the field since 1954, in 1969 wrote a book setting forth a short proof that 2-layer neural networks could not solve the exclusive OR problem (XOR). This seriously quenched interest in neural networks for more than a decade. Paul Werbos, in 1974 contributed back propagation schemes, which like the superhetrodyne circuits in radio, employed feedback to intensify and sharpen the selection and classification process, although typically not applied to neuron models. K Fukushima, in 1975 developed large scale (5+ layers of 30,000+ elements) neural networks that performed visual processing tasks, albeit quite inefficiently. He disallowed variety within the middle layers. Teuvo Kohonen, in 1984 contributed self organizing maps. Steve Grossberg, in 1988 published on Adaptive Resonance

approaches. John Hopfield developed self organizing maps, albeit by means not related to biological neurons. As a new and promising field, parallel processing and associative processors received intensive study. These studies are not irrelevant to the intracell studies. Their explorations of connections between active elements formalized analog and HAD computation. A significant difference, however, is that the connections of neural networks are all “wired” as point-to-point links, not via a common saline bath.[27]

1.7 LIQUID STATE

Biology works at the molecular scale (2E-10 m), not at the *in silico* transistor scale (3.2E-8) . Its processes may be divided into two classes: physical electrodiffusion and chemical kinetics. Diffusion may take place 3-dimensionally, 2- dimensionally or 1-dimensionally. Diffusion of charged particles enjoys the adjunct process of drift. There may also be forms of weak transient bindings, such as solvation, structures which float and drift, which impede or facilitate diffusion proportionate to their size. In aqueous solution there may be numerous ions which both generate and respond to a charge field.

The kinetics of the actors is not, strictly speaking, taking place within a liquid state. Classifying the membrane and its embedded actors as 'soft matter' is more appropriate. However, it is indeed significant that both membrane and actors are bathed in liquid. It is the thermal motion of liquid medium molecules which effect the conformational changes in the static actor molecules. It is the thermal motion of those same liquid medium molecules that effect the movement of ions and messenger molecules along the membrane. As these are essential and dominant features of the membranal system, it is justified to refer to the entire ensemble as a liquid state processor, though for completeness one could call it a liquid/soft matter information processor. Precedent has been set by Liquid Crystal display panels, which also are technically liquid/soft matter devices.

The major events of the soft matter actors are three: bindings, conformational state changes, and external effects emergent from those conformational changes. Put another way: inputs, state, outputs. Assuming a higher perspective to these physical phenomena, we see that some systemic support will be necessary to exploit them. Possibilities include that the membrane will support charge imbalance 2-dimensional waves along this surface; that the channels will support some level of pattern recognition; that the pattern of channel and pump placements will set

up some sort of temporal patterns or logic; and/or that the shape of the membrane will define and support some sort of patterns or logic to the information flow.

The realization of liquid state processors is dependent upon the following enabling technologies: production and shaping of lipid membranes into compartments; the production of proteins that become ion channels, ion pumps, and receptors; the molecular machinery to place individual actor proteins within the membrane, with some control over the positioning thereof; some manner of tethering the actors so that they do not float out of the intended constellation. Optionally, there is actinomysin machinery which grows processes that connect to targeted neighboring synapses; the bouton growth and shrinkage mechanism that "weights" the signal strength of each synapse; the genetic machinery to code for the proteins which become actors; and the ribosomal machinery to decode, produce, insert, and manage all the above. Artificial replications of each of these mechanisms are objectives within the general mission of neuroscience.

Silicon technology as of the year 2012, consumes about 25 watts for 2.3E8 transistors at a clock speed of 2E9/s. Silicon chips are produced with up to 820 million transistors on 32 nm architecture at 1333 MT/s . The gate density of silicon processors is about 1E15/m^2.

Solid state silicon chips are reaching their size reduction limits, currently at 2..5E-9 m wide conductors. This implies about 1E5 atoms per bit and 1E-20 Joules to flip that bit, at clock speeds of of about 3E9 Hz. Adequate heat dissipation becomes increasingly impossible at smaller scales. Reliability also becomes impossible at smaller scales due to the uncertainty principle. Does liquid state computation offer any advantages over these solid state limitations?

Computers are not touted for their average throughput, but rather for their maximum potential information handling. By this criteria, ion channels have far greater potential to handle information than they have so far been measured to process. Each channel can recognize one or more complex patterns as input, and generate arbitrarily different (but unchanging characteristics of the type) patterns as output in response. This is the essence of computing, and therefore each ion channel is a computer. However, the biological literature does not yet provide much insight as to the quantity of patterns that a single ion channel can respond to uniquely. We only know that it is kinetically possible and probable. We can also conclude that this potentiality is exploitable.

1.8 IMPACT

Humans are quite a bit more than logical devices. To model the human brain will require more than logical devices. When seeking a model of how humans think, it is hobbling to restrict oneself to digital processing machines. Logic alone can solve the step-by-step problems but not the continuum problems, associative problems, nor the creative problems. Linear systems theory has evolved from its original deterministic form into stochastic partial differential equation systems, and these are making headway in the representations of HAD systems. However, mathematicians have not yet offered a formal system of "hyper-logic" (?) or "continuum logic"(?) that spans the potentialities of HADs. For purposes of this paper, I shall refer to "HAD processes" as a place holder for the greater computability of continuum plus discrete problem-solution spaces.

The brain is not strictly comparable to a digital machine because events a): are not synchronized by a clock, b) are not digitized into numeric values of fixed precision; c) are not forced into discrete positions, values or times (but rather continuous space and time). Concerning action potentials, it is reasonable to treat the quiescent periods between spikes as 0's, and the spikes as 1's. But those 1's occur in continuous time, which is exploited for its phase information , and at a specific location, revealing spatial information, and is part of a time series, which reveals firing rate. These effects sum to make the single action potential worth much more than 1 bit of information. The fan out of a single "bit" may be expressed as part of a complex spatiotemporal pattern, of great significance to cells impinged upon. That is, each neuron is characterized by a unique spatiotemporal pattern in outputting its bit, and often sets up constraints as to how the bits can be sequenced (refractory period, periodicity, burstiness, etc.). Such "restrictions" have been described as limiting function t oless than that of a general processor. But they also establish characteristic response patterns, providing a "signature" of origin. In a realm where some patterns are far more useful than others (see the so called "natural stimuli"), characteristic patterns can have great utility, in a sense setting priorities, and rank ordering the value of information.

Generally, spiking neurons operate over a firing frequency range of 10 Hz to 1000 Hz (slower for the more primitive forms). Maximal throughput does not occur at maximal frequency, but rather at the mid-range, about 100 Hz, because information requires "white space" or foreground/background contrast, to carry information. Periodicity of firing patterns of several seconds or more may still be highly significant information. Evaluating information processing and transfers, we find a maximum bit/second rate of 100 Hz = 2E16 bits/second times 2E14

synapses processing capacity. The lengthwise number of steps (synapses) from sensorial input through the CNS to motor output is greater than 2 and less than 100. The fastest life preserving actions will need to be the shortest possible circuits (length = 2), while the contemplative planning may enjoy the luxury of more circuitous paths. This addresses the verticality (serialism) of the circuits only, not the horizontality (parallelism) of the circuits. The fan out and fan in wiring that characterizes the horizontality of neural networks in immensely higher, about 1000:1 to 10000:1 for many neuron types. This connectivity manifests when the neuroanatomist counts the synapses per cell. If the circuit length is only seven, and each neuron has 1000 synapses, then there must be a connectivity width of nearly 1000. This is a very horizontal architecture. It lends itself to massively parallel processing, and to very fast processing times.

Kety SS, in 1991, estimated that the human brain consumes 14 to 22 watts of power.[45] This energy operates 2.3E9 neurons with approximately 2E12 trillion synapses, about 2E14 ion channels, and perhaps 1E15 ion pumps (calculations below). On an energy consumption per unit mass basis, bio-computers apparently offer 6 to 7 orders of magnitude greater energy efficiency. But they are about 7 orders of magnitude slower, in that an action potential takes about 5E-3 s, while silicon processors consume about 4E-8 s per calculation step (about 5 clock cycles). Because bio-computers require correspondingly less energy to perform equivalent tasks, they do not suffer the overheating problem so prevalent with silicon processors. Despite the soundness of mutual information measures in artificial systems, information throughput metrics have not yet been settled for biological systems because not all information pathways are known. Information streaming along is often “pealed” off for ancillary functions. For example, the left and right auditory signals are read and subtracted to determine location of the source of the sound. All functions of the neuron are not yet known; all input variables are not yet known; and all outputs variables are not yet known. Neurons are certain to garner higher performance ratings as functionality is revealed because a) an action potential is worth far more than 1 bit; b) all processing elements run continuously without pause, without hold states; and c) the bio-gates are second or third order pattern recognizers which would each require about 100 transistors each to emulate.

Given the imminent arrival of ever greater supercomputers (currently planned at petaflop performance), software applications need be written to harness such computational power to further the understanding of biological complexity. This project strives to advance the art by realizing a large scale hybridization of the diffusion, electrochemical and kinetic aspects of neuronal function. This model is highly stochastic, intended to closely mimic

the underlying statistical mechanics of diffusion and kinetics, and eschews the earlier practice of simply "adding in noise" to deterministic equations so as to curve fit prior records of biologic signals. The motivation for the stochastic approach is to advance biologic science towards expression of emergent phenomena of living systems, via large numbers of highly-coupled stochastic difference equations, from which emerge new and significant behaviors.

To the extent that this strategy is a workable and representative one, it is an important one. Only with the dimensional reduction of the "possibility space" can we hope to produce ANN's that exhibit the great variety and flower of BNN's. It is hoped and expected that this strategy will produce "verified" models of biological neuron types, suitable for large scale employment in networks. Distinction is noted between "simplified" (prior art) and "verified" (current efforts).

Although tedious, a large-scale molecular model of biological neural networks is expected to reveal the common ground to all of the artificial networks, and much more. This is a reasonable expectation because it is the BNN, the human brain, that invented all of those ANN types. Those persons wishing to extend, analyze, or justify any artificial neural network design may find utility in this model, due to its flexibility. When wired into “local circuits” as prescribed, the whole cell model below is expected to perform generally, such that a network of such general processors may be taught to embody each of the extant ANN's and fill in some of the conceptual space between them and extend beyond them. The modeling approach produces behaviors of both conventional ANN computations and emergent phenomena of known biological configurations. It is intended to serve as an effective tool for extracting principles of general HAD processors.

Advancements of the whole cell model are practicable in several dimensions. Internally, processes of longer time constants can be added, such as regulations, plasticity, and learning. Externally, the connection and diffusion/drift relationships to neighboring neurons can be built out. Experiments in shape might reveal optimal production designs.

Applications for this work include the study and characterizations of channelopathies, receptor pathologies and pump pathologies; the design and testing of therapies for such pathologies; the design and engineering of new types of receptors, channels and pumps; and the design and testing of liquid state processors as artificial computational devices.

2 OBJECTIVES

2.1 PURPOSE

This document describes the functional and nonfunctional software requirements for a large scale simulation of the molecular events causally involved in the information flow through a single excitable biological cell. Simulations are accomplished within a general model, parametrically defined over sufficient breadth to simulate hundreds of different types of neurons, including hypothetical ones. This model is intended to support the investigation of biological constellations of actors so as to comprise a membranal information processor. It attempts to found a science of liquid state information processors as artificial molecular systems.

2.1.1 NEUROPHYSIOLOGY TO BE MODELED

An engineering approach organizes the biological facts into standardized types of elements and processes. These are constructed sufficiently continuous and smooth to represent biological entities as predictive and distinguishable, instantiable anywhere within their parametric domains. Nonlinear functions are approached with detailed attention, intended to be sufficient to avoid smoothing away biologically significant boundaries or modalities.

The neurophysiological literature is rich with quantified phenomena relevant to the mechanisms of neuronal information processing (NIP). However, there remains the synthetic task of hybridizing diffusion processes, kinetic stochastics, and ionic circuits (RC grids, per electrodynamics) into a single general model of bio-computation. It is found that current art does not offer any compatible set of necessary and sufficient model components from which to assemble this project. Accordingly, this projects proceeds from the primitives and rebuilds what we know about NIP into a single coherent computer program. The model performance traits include:

1. There are multiple charge species. (Electrical theory for electronic networks has no such accommodation.)
2. The curved surfaces of the plasma lemma require a homogeneity for the placement of actors. Node tessellation can be effected that supports statistical placement of actors over complex surfaces.
3. Capacitance is not discrete, but continuous over the entire membrane surface, communicating ionicly.

4. Conductors are not point to point (as with wires), but are continuous volumes and surfaces. This presents a rather unique challenge to avoid echo-ing and shorting.

5. Current sources are also logical devices, pumping ratiometricly. Therefore, they do not allow simple restoration of resting potentials but rather must negotiate ion trades to maintain a homeostasis. This requires feedback and modulation to accomplish. Pumps are stochastic, not deterministic.

6. Particle flows are impeded by: obstacles, temporary bindings and sequestrations, inhomogeneous, torturous shapes of the reticuli, and various protein tethers.

7. The gating mechanisms for ion flow are far more complex than are transistors, as they accomplish selectivity of the pores, and a stochastic logic applied to their open patterns.

8. Channel, pump, receptor and vesicle molecules are too complex to represent thoroughly within a neuron model. The field of Molecular Dynamics strives to model single molecules using super computers. In this model, they are simplified to finite state machines.

The model developed herein is parametrized to span the domains of: biologic neuron species, types, shapes, bifurcations, compartmentalizations, channel distributions, pump distributions, receptor distributions, vesicle distributions, tonicities in each compartment, 3-d diffusion of ions and modulators, second messengers to channels, and connectivities between cells. This model is intended for use by those pursuing neuronal information processing at molecular scale; suitable for dynamic demonstrations, channelopathy diagnostics, and/or computational device designs.

Certain entities are high in NIP value and are given modeling priority. Follows is an initial assessment of the role and value of the various elements when weighed strictly by their contribution to information processing.

1. The neurotransmitter metabotropic receptors serve as transducers, and perhaps do not add new information. They serve as critical input portals and broadcasters of second messengers, thus providing amplification. They cause information to fan out, at the expense of some delay and time smear. A variety of G-protein second messenger systems are enlisted in the fan out function between receptors and ion channels. This may be both quantitative and qualitative. By qualitative is meant a receptor's ability to target different types of actors in varying ways.

2. Of the membranal entities, ion channels are probably the highest valued wrt NIP. They are fast responders that convert input patterns into filtered and patterned binary output patterns. The stimulating input patterns may be as simple as voltage threshold crossings. They also may be temporal patterns. Channels can generate a large number of different patterns per channel type (they express modalities). Their asymmetries in location and refractoriness can radically alter propagation waves in shape and direction.

3. The vesicles serve as transducers, and are low in information value as they (almost deterministically) transduce an intracellular Ca++ signal into a synaptic neurotransmitter signal. There is some time smear, and some uncertainty in performance. By virtual of the large contents contained within a vesicle, they provide great information amplification. If certain vesicle types contained mixed messenger particles within, then the output waves can be quite complex in their effect. But because these mixes are preordained prior to the signal that releases them, they produce a rather fixed and predictable mapping.

4. The pumps are low, but not zero, in the amount of information they inject into the system. They modulate channels via the resultant concentrations and voltage built up. Pumps can respond to messenger molecules, voltages and particle concentrations. They maintain (or at least tend towards) certain ratios between the ions pumped. They can fatigue due to a shortage of energy-conveying molecules such as ATP, with significant lowering of pumping capacity as energy resources become depleted. One of the consequences of them being stochastic devices is they make errors, sometimes pumping the "wrong" species of ion, or pumping backwards, or losing cargo before completion of the cycle. Any asymmetries between pump distributions (location patterns along the membrane) and channel distributions can set up significant horizontal flux. Such flux may be integral to the function of the neuron, e.g. detecting movement or directional sensitivity.

5. The ions are the smallest of the relevant entities. They serve as information carriers - the smaller the mass, the greater the speed. Their information is coded as the ratio between the unbalanced members of the type. A secondary form of information is generated in the aggregate, as the balance of charge across the membrane, determining the voltage potential that modulates actors and drives flux through membrane pores.

6. In addition to the above list of active elements is the passive element of the membrane. It serves to anchor the four actor types, providing positional stability in an otherwise liquid environment. The membrane acts as a charge barrier to the ions, supporting an energy potential proportional useful to do work. The membrane thus participates in organizational information, but not in the dynamic processing of information.

7. Such a system does not work without water. Water provides a large sink of ambient thermal energy. It provides a free transport mechanism, diffusion. It is a medium for drift. It provides viscosity and solvation of ions, which slow down ionic movement (that may be necessary to synchronize with other processes). Water is an enabler but provides no information in the course of dynamic processing.

The elements above are deemed to be a necessary set of elements to mimic the 3-dimensional poly-order pattern recognition of the neuron which enables it to "process" information as well as transmit it. It is not claimed that these are sufficient for all cases.[10] It is highly likely that nature has creatively exploited any number of addenda, alterations and assemblies as to effect wider problem solving potentials than this base configuration might not embody. But this is an ambitious base model, and will serve as a point of departure for subsequent models and extensions.

2.2 CONCEPTUAL PLATFORM

It is intended that the following concepts be integrated into a general modeling approach: a lipid membrane with variously placed receptors, ion channels, vesicles and ion pumps. Each instance of these four actor classes operates independently and kinetically. It is intended that quantities of metabotropic receptors, ion channels, vesicles and ion pumps be embedded within each contiguous, closed surface lipid membrane, and be present in quantities of

[10] It was subsequently found that a second messenger system could be added to the model as a membrane-attached catalytic actor (e.g. cyclase), which provided messenger amplification midpoint between a metabotropic receptor and a set of target channels, and that messenger particles could be made to diffuse 2-dimensionally along the inner surface of the membrane.

hundreds or thousands, as might be necessary to accurately predict the behavior of a specific neuron's information throughput. That the model shall take into account the effects of shape, adjacency and connectivity upon the information throughput of the cell. That each compartment formed as the result of closed membranes shall house a 3-dimensional particle system, representing ions and messengers, each with instantiated mass, radius, and charge.

Such a conceptual platform shall provide an ever growing library of experiments, constructs, entities and assembly blueprints so as to demonstrate molecular behaviors of extent biological forms and to construct hypothetical forms. This model shall be consistent with, and available to interface with other physical models of molecular systems, including representations of glial cells, muscle cells, and various biosensors. It shall be sufficiently general that its engines may be transplanted to other biosystem models requiring 3-dimensional diffusion, chemical kinetics and electrodynamic phenomena.

2.2.1.1 Reduction vs emergent behaviors

Due to the historic lack of computing power available to scientists, previous models of neurons were based upon severe reductions in quantities and functions of the elements, often to merely one of each type. Aggregate behavior came to be represented, through analysis, as functions that mimicked the group, but not the individual behavior. Though representing some physical or chemical phenomenon reasonably, there resulted a loss of the informational role of the neuron. Reduction in quantity of actors and ions is only justified if it does not sacrifice the natural, emergent behaviors of the full set, particularly the information capacity and information transformations.

Information is defined as a change in state. This concept is extended to analog signals by noting the change in the voltage states of a series of samples. Therefore, an expanse of unique states capable of capturing and changing at a rate faster than the impinging environment changes, is prerequisite to a large scale information processing device. Just as one cannot demonstrate the processing power of a computer by averaging, aggregating, or collapsing all of its transistors down to just one gate, so too is the worker disallowed from “analyzing the neuron via a reduction to say 4 or 5 components. The loss of information processing ability undermines the goal of the project. Therefore, each particle and actor capable of distinct states distinguishable from other particles and actors must be treated as a separate information-carrying entity.

2.2.1.2 Analysis replaced with synthesis

Diffusion shall be represented by a 3-dimensional charged particle system. Particles may be ions, messengers, modulators, floating obstructions, or water. Each particle has charge (which may be zero), mass, radius, position, velocity, and acceleration. Particles may collide, reflect off surfaces, become absorbed into the membrane material, become bound and then unbound, and be transported. Mass, charge and momentum are conserved. Electrodynamics and thermal energy shall supply the forces that drive the particle system. Voltage is a consequence of the electrodynamic force of charge inhomogeneities and position resulting in charge density ratios across the membrane (partial voltages).

The membrane shall be represented by a 3-dimensional reflective surface with thickness and capacitance. It shall have addressable nodes for the purposes of placing the actors according to realistic density patterns, and these nodes shall be everywhere evenly spaced. In whole cell models it shall be a closed surface.

Receptors, channels, vesicles and pumps shall be represented individually as trans-membrane entities, each with position, orientation, a modulatable kinetic scheme, particle binding sites, and some outward expression upon the environment. In the case of pumps and channels, they shall have transport functions and transport ports. The particle bindings and unbindings shall be probabilistic, and may allosterically alter the conformational kinetics of the actor. Actor state transitions shall be animated via individual Markov processes.

Key physical concepts to be addressed in the NIP model of neuronal function include:

1. Position, Velocity, Acceleration, which support second order representations of mass and energy
2. Momentum is not often considered in neural models but is necessary to maintain a sane particle physics
3. Charge, electric field, electrodynamics. Coulomb's Law is indispensable in channel to channel communication
4. Particle systems consist of instantiated particles, bounded within 3-dimensional containers
5. Conservation of linear momentum
6. Quantized energy, as the cause of bindings and conformational changes
7. 3-dimensional elastic, momentum-conserving collisions result in hyperboloid trajectories
8. Liquid particle random walks[11]
9. Fields of flow, driven by EM and concentration gradients, give rise to: grad, div, and curl

[11] Subsequently upgraded to Langevin dynamics.

10. viscosity, turbulence and chaotic flow may arise without intent
11. temperature is emergent from Boltzmann velocity distributions
12. Boltzmann velocity distributions are emergent from elastic momentum-conserving collisions
13. Mean Free Path of gas particles is not accurate for liquid particles which must move more serpentinely
14. Mean Free Path of gases can be shown to be an effective substitute for aqueous diffusion (short cut algorithm)
15. Traveling waves may arise from mass-spring grids[12] of like charged ions
16. Hydration shells around ions variably affect mass, radius and viscosity
17. Superimposition is legitimate. Sum of electric potentials from point charges equals the net force.
18. Maxwell's equations determine that magnetic effects in the cell are too small to be significant
19. Electrostatics is a sufficient representation of electrodynamics where magnet effects are infinitesimally small
20. Gauss' Law is emergent, as like charges behave so as to populate the outermost surfaces
21. Reversible and Irreversible processes are present and necessary. Biology uses both very discerningly.
22. Probability and Entropy measures reveal SDE processes, the heart of kinetics.
23. Electromagnetic force is in contest against other forces. It tends to override every other force in the cell.
24. Conduction may be “horizontal” (through saline or along surfaces); or “vertical” (through the membrane)
25. Capacitance may be discrete or continuous. Ionic capacitors do not achieve isopotential, due to mass.
26. Polar heads within membrane determine the dielectric effect of the membrane
27. Dielectrics require that the membrane thickness be modified to an equivalent separation distance of charges
28. Ohm's Law in electrolytes is emergent from nano-scale ion collisions (which in turn determine mobility)
29. Semiconductors are gates to charge flux. Channels act as gates in a far more complex manner than transistors
30. Channels can serve as diodes merely by their funnel-shaped pores.
31. RC mesh (multi-loop) circuits (e.g. grid filter resulting from membrane and channels) exhibit Green's function
32. Large scale portless grids of RC components exhibit complex behavior (3^o, 4^o and beyond)
33. Multi-species ionic currents
34. are not adequately treated in conventional electronics science
35. Membrane surfaces may reflect or absorb. If absorbing, then the membrane itself is a compartment.

[12] resulting from like charged particles on either side of the membrane, forming a capacitor, with attraction across but repulsion between.

36. Active transport is necessary to provide energy for viable concentrations, voltages, and horizontal flux
37. Passive transport is critical to information processing, and is complex

2.2.1.3 Information Theory

It is understood that all changes in state constitute information. This includes every chemical reaction, every conformational change, and some physical events as well (e.g. adsorption, transport, moving from aqueous phase to lipid phase). However, the domain of interest for this project is neuron information processing (NIP). Parsimony dictates that elements not serving the throughput of information from receptors to vesicles be declared off-NIP, and these are intended to be excluded from the model. The information processes of interest include precisely those changes in state and changes in position that are constituent to the flow of information from the synaptic inputs to the synaptic outputs of a neuron. There are many housekeeping functions within any living cell, including neurons. And these all involve information processing in some sense. But neurons are distinguished by the fast (up to 1 kHz) information processing service they provide to other cells and to the organism as a whole. The mechanisms of this service takes place at or near the membrane of the neuron, typified by the propagation of an action potential.

There are other relevant processes (e.g. adaptation and learning) that may involve more interior cytological structures and take place on a somewhat slower timescale (> 1E-1 s). Neurons are distinguished by their persistent alterations in response to signaling patterns, which we call learning. Changes in shape, actor positions and actor quantities are particularly of interest to a NIP model. Though the time constant of change is typically slower than simulation runs, a series of runs can reflect the learning process in a realistic molecular manner. This project cannot become concerned with these processes until after it has stabilized and verified the drift and state transition engines.

Depending on the experimental objectives, unusual entities may need to be added, and perhaps common entities removed. A criteria is needed to distinguish NIP elements and processes from non-NIP cell operations. Careful study of the complex biochemical coupling within the neuron will eventually conclude everything affects everything. The base purpose of this project, however, is to focus those high runners with great significance to the throughput signals of the frequency band (1E-5 .. 1E-2) s^{-1}. That is, for practical reasons, the coupling matrix must be reduced from full to sparse.

The essence of the transfer function is that it specifically addresses the mutual information between input signal and output signal. This is a useful concept in stochastic system metrics. The mechanism between input and output shall be referred herein as nonlinear transfer functions (NTF) in general, and for measurement purposes we may speak of the mutual information between input and output.

There is a large field of study concerning neural coding. The debate has raged on for at least 6 decades as to whether the cell employs temporal coding, phase coding and/or convolutional coding. See Riekec F[46] and Wells RB.[47] This is of direct concern to the application of information theory to NIP functions. If ion channels are the main gateway device in this process, and they operate as Markov processes, then only those coding schemes that can be generated by a Markov process need be considered. Modulation theory and state constraints are relevant. Error tolerant systems are relevant. And there is a likelihood that some form of convolution is going on between the free-moving particles and the stationary kinetics of the actors. Whatever coding scheme is in play, it is only an emergent property of large scale molecular systems. If the underlying molecular interactions are correct, the "code" is merely an observer's metric, not intrinsic. The motivation for divining such a code is to measure the quantity and quality of information being passed along the chain. How much information is actually "read" into the cell; what processing of that information takes place within the cell; and what portions of that information are exported out of the cell, where and how? Inputs and outputs can be determined by the molecular behavior of trans-synaptic processes. But some information is expected to be utilized internal to the cell. Perhaps some dissipates and never makes it to export. Reformation is implied in cellular memory. For example, there are numerous cellular reformation processes triggered by information inputs and through-puts (learning, adaptation, etc.). It usually requires a series of simulation runs to demonstrate it, each with progressive shape/constellation "builds" as samples along the course of plasticity responses. Automation of simulated learning processes is left for others, but various mechanisms of plasticity can be added to this model using a variety of parametric settings, including channel densities and distributions, synaptic size, growing new connections, and changes in tonicities.

This project is not a molecular model for the sake of modeling molecules, but rather is an attempt to account for the neuronal information processing detailed down to the smallest relevant scale. To capture the informationally significant aspects, physical scale need not be uniformly applied; nor molecular traits uniformly detailed. A uniformity in the information metric (bits) may cause distortion in the physical metric (meters). One can imagine a non-linear transform which maps one into the other. The physical size of ion channels and ion pumps is not as

important as their state transition tables. They may be treated as point processes and still wield major influence and serve critical roles in the information realm.

2.2.1.4 Point Processes

There is a question as to whether or not there exists a single optimal kinetic scheme for a given type of molecule. If one knew for certain the complete functional roles of a given actor type, e.g. that a given channel type was only modulated by voltage and noradrenaline and nothing else, then a singular ideal kinetic scheme might be formulated. But in biological systems, it is generally the case that there are hundreds of possible interactions for a given molecule type, each of which could be conceptualized as effecting modulation to some degree. We must, for the time being, allow for an open-ended view towards such interdependencies. A single actor type may have several kinetics schemes proposed for it in the literature. Each scheme can be expressed in model "runs" to determine their behaviors, and chosen according to their utility. Some workers strive to simplify the data they collect on actors, and others seek a full accounting of the many states the data hint at. The more accurate schemes are likely to be the larger (less simplified) ones. It is in those we can expect to find intricate behaviors that go beyond simple openings and closings, into the realm of patterns.

Biology is a space populated by a very large number of very complex molecules coupled in numerous and complex ways. Techniques are being developed to standardize all of that into matrices that render cytochemical systems tractable to super computers. Science is a long way from certitude as to the complete account of molecular species present in a living cell, their reaction rates and their emergent functions for the cell. Until reasonably complete, we must model to narrowly proscribed queries, and yet try to allow models of biological systems sufficient vitality to display emergent properties, especially including behaviors consistent with their living counter parts. It is hoped that exercising such models should make visible the gaps and errors in our knowledge base that will point to needed wet lab research and the next experimental model designs. Exercising particular kinetic schemes will reveal their behavior patterns, and thereby suggest their roles within the cell previously unreported.

The decision as to which kinetics schemes are compatible within a single experiment may be determined on a basis of each entity's contribution to the NIP of the whole cell, or to the membrane patch of interest. Optimization of computational load would tend towards representing critical actors via large numbers of states and less significant

actors with smaller numbers of states. More specifically, the states themselves could be ranked ordered by their significance, and some cut-off point might eliminate all states below the desired significance bar. This approach is unlikely to lead to such "standardization" as trying to make all kinetic schemes fit into the same size matrices (same number of states) - which would have been quite convenient for data handling. Such an arrangement is not easily realized because the significance of each state can only be evaluated in hind sight after many simulation runs doing sensitivity analysis. And as new bio-data becomes available, these schemes may need to be revised. Both qualitative and quantitative changes in such nonlinear systems can jeopardize the prior optimization results. The model, therefore, should support the easy substitution and addition of kinetic schemes, and fully support easy matrix size changes for the state transitions probabilities.

The physical dimensionality of the actor is not NIP significant except as pore size and, optionally, funnel shapes, affect flux. When conductances are known for an actor type as a function of variable concentration and voltage gradients, actor shapes may be ignored. In any case, molecular shape falls into the domain of MD studies and is out of scope for this project. Actors may then be represented as point processes with a binding site on each side of the membrane. Collision rates, although a function of density and velocity in analog space, are calculated in digital space so as to mimic their analog counterparts.

2.2.2 BASIS IN PHYSICS

The biological phenomena of interest include diffusion, kinetics and the electrodynamics of drift in an aqueous medium. These bases are studied at the molecular level, then embodied as entities and processes so as to exhibit some of the emergent qualities of living cells, in particular excitable membrane signal propagation. The loss of emergent properties in models usually occurs due to aggregation. To preserve the individual particle behaviors, and therefore their informational value, individual particles must be instantiated within the model for their positions and states, not merely as aggregate representations (as would be standard in analytic models).

2.2.2.1 Electrostatics

Charged particles in aqueous solutions undergo drift as a function of the sum of the inverse square of the distances between those charges. In the gaseous state, the electromagnetic force causes acceleration. In the liquid state, the

mean free path of particles is so short, acceleration is reduced to viscosity. In fact, mean free path and incompressibility (as ascribed to liquids) are mutually exclusive concepts. Indeed, “fixed center to center distances” is a constraint that directly implies the path is not “free”. It is most likely that ions and molecules in the liquid state move along serpentine paths as they slide betwixt their neighbors while maintaining fixed center to center distances until there is a substitute neighbor ahead taking the place of the neighbor left behind. Model particle systems are usually conceived as ballistic movements interrupted by collisions. This conceptualization must be rationalized wrt liquid state realities. More on this below.

Although Maxwell's four equations of electrodynamics apply to neurons, the scale of events is such that the magnetic effects are not significant to its role as an information processor. Thus the two of Maxwell's four equations applying to magnetism need not be applied at all. By conventions of naming, this reduces electrodynamics to electrostatics, despite that the remaining charge equations apply to moving particles and create forces that induce particles to move.

Charged particles within large stationary molecules have been mentioned above for their role in discretizing that molecule's states. Fixed charges also play a role in ligand affinities for binding and unbinding. Because of the complexities of ligand binding site geometry (recall the “lock and key” metaphor often employed in textbooks), it is overly complex to represent ligand binding in this model as a complex of charge attractions over a fixed socket shape. From a NIP point of view, the significant part is the probability of binding to each site, and the probability of that allosteric binding event causing an internal state change.

2.2.2.2 Water Molecules

The most redundant of all entities in the neuron is water. Those aspects of water that might be NIP-significant need to be identified and extracted for incorporation into the model. Water is a medium and carrier for information, just as a copper wire might be for a land line phone conversation. The electrical conductance of water is directly proportional to the concentration of ions dissolved in it.

Water provides thermal noise, called Johnson noise, by virtue of the collisions an ion incurs along its conductive path. These collisions are proportional to, and indeed the cause of, electrical resistance, and also the viscosity for solutes.

Water is essential in the phenomenon of pH (acidity and alkalinity). The bare proton is considerably smaller than what we think of as an atom or an ion. It therefore creates quite unique effects in regard to electron donors and acceptors.

Water has no dielectric strength, so supports electric fields, and therefore electric gradients.

It is difficult to claim that water is acting in the role of information processing, but its traits mentioned above must none-the-less be represented to allow ions to function properly. So long as the ion mobility and mass characteristics are represented, water may be abstracted.

Scaling back the quantities of the particles and elements is not trivial, but must be thoughtfully determined so as to preserve the NIP characteristics, in time and space. The quantity of water molecules in a neuron may perhaps be reduced in number, reduced and/or abstracted in function, provided that ion collisions that redirect ion velocities, and rates of ion drift, and ion solvation sizes are all maintained.

The ballistic movement of gas particles is relatively simple to execute in a digital computer. However, the liquid state presents special modeling problems, because in liquids all particles remain fixed distances from their nearest neighbors, resulting in incompressibility. The serpentine weaving between one's neighbors is quite complex to model and may not of itself be NIP significant.. The critical question wrt to information flow is: is the net result of diffusion in gases qualitatively different than that of liquids? Lifelong workers in the field of diffusion report no such difference, despite the distinctly different mechanics and path shapes. If the positions of particles (density patterns) with respect to time in gaseous diffusion and liquid diffusion are similar except for the average speed, then there is great computational advantage to be had by treating particles ballistically, rather than as tightly packed sphere slipping along. It is therefore reasonable to treat a ballistic trip as a summary of a more convoluted trip, to get to the net position of a lengthy serpentine path, so long as the distribution generated by such shortcuts is the same distribution of natural liquid diffusion. To the extent that the ballistic shortcut is justified, all of the particles of water interacted with in between the start position and the stop position can also be omitted. This effectively reduces the quantity of particles represented, and therefore effects a significant reduction in model computational load.

2.2.2.3 Saline

Not only is the quantity of water molecules super abundant to the needs of a whole cell model, perhaps also are the quantities of the ions. The number of ions in a model may be reduced to the extent of redundancy in their NIP role, provided that redundancy can be determined. A minimal sufficiency may be determined by empirical performance in a patch model to within range of acceptable error. Because of the complex and nonlinear nature of neuronal behavior, the easiest method of determining sufficiency might be empirical; to run the model as test patches while sweeping a gamut of particle densities and recording sensitivity to changes. Care must be exercised near modal shifts in time (e.g. from periodic spikes to bursts of spikes), and modal shifts in space (e.g. from analog responses to digital responses across the initial segment a/k/a axonal hillock). Indeed one of the objectives of the model is to identify systemic *minima* for element quantities, as preserve the bio-computation functions of the cell. Sampling theory may be applied to the challenge of element count reduction if the dimensionality of the problem is not under-estimated. For normally distributed values, 30 samples per degree of freedom yields 99% confidence levels, but nonlinearities make that an unreliable “rule of thumb”.

The quantities of ions in solution may be reduced to the extent many of them are sufficiently distant to the membrane functions as to render them insignificant. If they are serving as “reserve capacity” or “buffer” for charge imbalances, then they still are not NIP active. Short of compromising axial and/or circumferential flux, their numbers may be reduced. At the risk of some graininess, the numbers of ions may be reduced proportionate to the reduction in the numbers of ion channels and pumps. Then there is the question of quantity of ions that flow through a channel per millisecond of channel open time. If this quantity is, say, 1E3 to 1E7, then couldn't that number be scaled down by one or two orders of magnitude? Only if the capacitance were also scaled down, so as to preserve the resultant transmembrane voltage, and only if the speed of ions through the channel were proportionately slower, so it takes the same amount of time to generate an action potential. There is then the matter of consistent multi-dimensional scaling.

Reduced to a tractable quantity, ions in water might be modeled for the transient solvation shells that accumulate when quiescent and are sloughed off with increasing drift. Neutral molecules are known to be encased in water “cages” that optimize the “hydrophobic” energies. The actions of water are nonlinear and determinant of mobility. The mass of ions is significantly altered by the up to 50 water molecules that might become encased around it.

Given that mass is a strong factor in drift, conduction velocity, and wave shape when charge disturbances occur, the model must accommodate water structures to achieve predictive results.

2.2.2.4 Motion of Ions

Similar challenges present themselves when attempting to simplify the representations of ion movement. Motion has variously been represented as steps within a grid, random walks, statistical scatter patterns, dimensionless spheres proceeding ballistically, two dimensional elastic collisions, three-dimensional elastic collisions, and various modifications of Monte Carlo simulations. The physicist's trick of periodic boundary conditions, whereby a cube of particles is cloned and re-used as a neighbor to itself, is only useful for perfectly homogeneous patterns along the membrane. Most, probably all, neuron types rely upon certain inhomogeneities along the course of neuronal length to accomplish their information processing role. This eliminates some of the easier representations. At the very least, the NIP performance of a neuron must be represented by a series of such cubes made distinctive by the patterns of ion channel and ion pump distributions. The boundary conditions become problematic unless the various cubes are placed continuously adjacent, such that particles can move freely from one to another. Because the particles are carriers of information, and the information content is their position (they have no changeable states), then one must conclude that anything about a model that interferes with their natural flux processes threatens the veracity of the NIP model. For this reason, the Rall modeling method [48], slicing the neuron into segments which are then mathematically coupled, was eliminated as a candidate approach.

2.2.2.5 Membrane Lipid Molecules

The neuronal membrane consists of self organizing molecules. But interestingly, such self assemblies consist of many dozens of types of molecules, some of which alter the thickness and/or the capacitance of the membrane. The lipid molecules are not stationary, but apparently move as adaptive changes to temperature, hydration, pH and other factors. The dielectric strength of the polar heads of the membranal lipids alter the electrical capacitance of the membrane. There may be “rafts” of inhomogeneities floating around 2-dimensionally within the membrane.

It is acknowledged that the quantities of lipid molecules in a neuronal membrane are too great to model all. Therefore, the membrane will have thickness, but not individual lipids. The thickness may vary at each node to mimic the inhomogeneities of the lipid mix.

The membrane also provides various forms of tethering for the proteins active in NIP. In particular, ion channels, ion pumps, metabotropic receptors are among those membranal proteins. Verification of the proposed model wrt reducing quantities of lipid irregularities shall be accomplished by modeling membrane patches small enough that the number of particles is tractable to current technologies. These patches may then be extrapolated in size and complexity, in progressive stages, such that verification work for each stage can be performed by comparing the performance of the reduced quantity model to the performance of the full quantity model.

The roles of the membrane, from a NIP perspective, include: define a compartment shape; reflect particles that collide with it; provide positional loci for each membranal protein (a/k/a actor); define the sidedness of the compartment (inside vs outside) so as to orient pumps and receptor sites; and act as a charge barrier to capacitate any charge imbalance across the membrane. To fulfill all of these roles requires a surface location system, an equivalent thickness that determines capacitance, and the ability to divvy up the surface into pixels suitable for finite element method treatment or tessellation of nodes. It also must allow penetration by the various protein actors embedded in it, for transport. It would therefore seem that the individual lipid molecules are not significant to NIP. The inhomogeneities of constituent molecule types can be represented by pixel-wise variations in thickness and capacitance.

There may be a need to model the membrane as diffusible for some particles, e.g. anesthetics. To accomplish this, the membrane is treated as a compartment and the surfaces treated as the water-lipid partition coefficient, breached stochastically with forward and backward reaction rates.

2.2.2.6 Thermodynamics

There are two types of random process of interest to neuron modelers: Collision events of particles[13] in solution due to thermal energy; and conformational changes within large actor molecules, also due to thermal energy. For completeness, I note that there is chemical conversion of ATP that yields a specific quantity of chemical energy per molecule; ultimately driving the membranal system.

[13] Brownian motion is defined as the random motion occurring with particles too large to move by their own internal thermal energy, but small enough that collisions with solvent particles are sufficient to move them randomly.

The relationship between thermodynamics and information theory is analogous to the relationship between the power supply and the CPU in a silicon computer. The two are linked by the concept of entropy. Just as the 120VAC current must be conditioned via a power supply to drive the gates within the chips, the thermal energy must somehow be limited in its effects upon the decision processes of the cell. This is accomplished by the complexity and strengths of a multitude of chemical bonds which constrain the intra-movements of large molecules. A molecule may be so constrained that the various thermal impacts constantly impinging on it only bring about one of several possible “subsequent states” in the duty cycle of that molecule, but do not break the chemical bonds which constitute the solid. Which state is the “next state” may be altered by modulation of that molecule. Thus, thermodynamics drives an information processing system. The kinetic scheme of each actor is a product of its thermodynamics (some amount of energy is necessary to change state; the higher the energy, the lower the probability of that being the next state). So the thermal dynamics is already implied. To incorporate Gibbs thermal dynamics would in effect generate those probabilities. But as they are already given to us by the published kinetic schemes, most thermodynamics work would be redundant.

A word about the concept of “duty cycle”. If a molecule is of one-time use, then we make speak of the processing steps of its functional role. But for all those molecule types of reuse in living cells, there must be some series of steps that returns to the “start” position, so the process can be repeated. Exploration of the kinetic schemes of the actors reveals that no matter which state you start in, the actor will proceed into one or another limit cycle. (Else, the actor is stuck in a poison state.) The quantity of limit cycles determines the quantity of possible modalities. When a state graph is drawn accurately reflecting the molecule's physicochemical transitions, there must be at least one loop in this graph. If there is more than one loop, then there is variability in the molecule's behavior, and presumably in its role. For purposes of this project, “duty cycle” refers to the dominant loop (path of highest probability), usually directed, in the set of possible states. Multi-loop actors can be discussed as having alternative duty cycles, with criteria or probabilities as to each one occurring. Of particular interest would be modulation conditions which could switch preferences for which of the loops is active. Each of the loops, in turn can express themselves by the impact they have upon the output of the actor, e.g. transport pattern or catalysis pattern.

Significantly, the net Gibbs energy to traverse any complete cycle equals 0. This has a great implication, that the act of conformational changes, though individual steps may be net positive or net negative on Gibbs energy change,

and actor completing a duty cycle consumes no energy. This is significantly advantageous over solid state gating, which must consume energy, and then release heat, with each gate cycle.

There are additional critical processes requiring energy, especially pumping ions up-gradient. Like an ion channel, a pump can be represented by its known kinetic probabilities, a series of which comprises its state paths. Using chemical sources of energy is permissible, as ATPase pumps will convert 1 ATP molecule to 1 ADP + 1 Pi. Th quantum energy released by this reaction is usually spent doing work, pushing 1 or more ions “up-hill”. However, there is almost always more energy released than absolutely necessary for transport. The surplus energy may go to increase the velocity of the transported ion, or increase the “ringing” of energy within the pump. Either way, there is a temperature increase in the system as a result.

Particles in aqueous solution undergo random trajectories because of relentless collisions, most driven by thermal energy, and some by drift. At any point in time, a compartment at uniform temperature will have a velocity distribution that will follow the Boltzmann velocity distribution. The thermal energy affects each mass value differently, and therefore, there will be a Boltzmann distribution for each mass group (particle type). The introduction of new uncharged solute into this solution will result in a Gaussian-shaped spread of that solute, following the heat equation. This pattern of diffusion occurs subsequent to each channel opening or to each pump cycle, whereby transported particles are released to diffuse into the new compartment. In the case of charged particles, the outcome is more complex because Coulomb's law is in effect.

On the inlet side, channels and pumps act as ion species filter drains. The removal leaves a “hole” in the spatial distribution pattern, causing all particles to rearrange themselves in a more diffuse manner. In this case it is the “holes” that rearrange themselves. In a matrix of neutral particles, they diffuse in a Gaussian-shaped spread, and the actual particles act in compliment. The spatial disparities in action between the various channel and pump types result in irregular concentrations over the length of the membrane, rather like the surface of the ocean in response to several winds and vents. Such crests and valleys drive lateral flux of the transported particles. Ion charge adds drift force to these movements. Concentration gradients add another force factor to the determination of transport rates. Concerning non-ionic particles, such as neurotransmitters and second messengers, they are less likely to be transported via channels.

Conformational changes may range from trivial to significant, from continuously flexible (e.g. movement in angles of rotation), to discrete conformers with no intermediary shapes found. At the continuous end, there must be no energy barriers, and many Gibbs-equivalent states. At the discrete end, there will be found significant energy barriers, caused by repulsive charges, and then the discrete states, caused by attractive charges. For example, inverting the "chair" conformer into the "boat" conformer requires energy to distort the bond angles enough to pass between these two "relaxed" conformations. Though apparently a mechanical distortion, the subatomic phenomena involves distorting the electron orbits, distorting charge patterns from one relaxed state to another relaxed state. Fixed charges along the molecule create attractors towards some states (stable) and repulsors away from others (unstable). Of course the greater the energy needed to force a conformer out of its stable state, the more unstable the intermediate position will be, and the shorter lived they will be. These effects tend to cause molecules to snap between states, and the observer sees the stable states as discrete possibilities unless in possession of very fast recorders and clocks. Ambient thermal energy is sufficient to achieve some state transitions, but perhaps not others. When a state is achieved from which there is not enough energy available to get out of, this may stop the biological functioning of the molecule. We say this molecule has become "denatured" or "poisoned". In summary, the human notion of "digital states"is a fiction that conveniently summarizes the high speed with which states are changed and the stability (persistence) of those states when not perturbed.

The energy budget of a chemical system is highly determinant of which reactions transpire and at what speed, which are reversible, which are blocked, and which are poisoned or denatured . Entropy and information are closely related concepts. Entropy can be employed in coding theory, but the contribution of thermodynamics is completed prior to the measurement of information. Its effects are already embodied in the state transition probabilities. It is not likely that thermodynamics will need to be directly incorporated into a NIP model because its effects are implicit in the empirical reaction rates provided, and because information flow is not directly related (not one-to-one) to such energy "costs" as they are rather orthogonal to each other. The model works with transition probabilities, superseding the thermodynamics that underlie them. The risk is that some thermodynamic principles or events would make transitions impossible, especially hypothetical constructs. There is an empirical check for the *in vivo* data, but hypothetical constructs will require verification in the chemical realm if intended to be realized as physical entities. Known thermodynamics can be mapped into the probabilities of the Markov processes.

The consumption of ATP to drive pumps requires thermodynamic phenomena, but those particular aspects of the neuron are not on-NIP. An informational approach creates ATP as particles, with probabilities of binding and unbinding to actors as a modulator type. The ability of a pump to transport against a concentration gradient is clearly a thermodynamic problem. But, once again, the thermodynamics is embodied in concentration gradients times the binding kinetics, which in turn determine the transition probabilities per unit time.

There would have been an advantage to carrying the thermodynamic process along through the simulation, in that it generates the reaction rates of all possibilities dynamically. The disadvantage is that it greatly increases the computational load, without contributing directly to the information throughput. In a future time of lower cost computation, it will become desirable to add a front end model of the thermodynamics to "pre-process" all the likely probabilities and make them available as a library of Q matrices, to be called per parametric combination each *dt*.

2.2.2.7 Kinetic Schemes

Conventional chemistry kinetics refers to reactant A mixed with reactant B to yield Product C (and sometimes Byproduct D) as per the rate constant of this reaction. There are usually alternative (competing) reactions which generate other "side-reactions". In reversible reactions, a backward rate constant may also be determined. When observed at the molecular scale, reaction rates are seen to be probabilities of a binding (forward rate) and/or unbinding (backward rate) to occur. Regarding larger molecules, as are common in biology, the quantity of possible reactions often becomes "astronomic". Large molecules without charge inhomogeneities are pliable, bending and twist like rubber. Large molecules with charge foci at various points are more likely to react extremely quickly, appearing more discrete than continuous. Large molecules with distributed charge loci might react with themselves, thus changing conformations. Such charge mediated "flips" result in a rather discrete number of possible conformations (states), with the time spent in transition between such conformations very short (<1E-7 s).[49]

Though conventional chemical nomenclature may not catalog all these conformational possibilities, the physical reality of their actions is much the same as conventional chemical kinetics. The greatest point of difference is that in biology their are no rate constants. The rates fluctuate due to modulation. This is inherent to large molecules, which will experience changes in the electron cloud at one end due to some binding or unbinding, but this will invariably

affect the electron patterns at all other points on the molecule as well to varying degrees. Thus one site's reaction becomes another site's modulation.

The reactions-with-self are interpreted as “conformational changes”, and the subset of these deemed NIP-significant are assigned state numbers and state transition probabilities. Very complex molecules and structures from a molecular dynamics point of view might be greatly simplified, or even eliminated, if their roles are off-NIP or their NIP-contribution is minimal.

In biological systems, large molecules experience these frequent state changes due to thermal energy. It is not currently feasible to observe these states directly. They are observed indirectly through 2-step voltage clamps and charge movement detectors. As a result, only partial data about states is available. And this data arrives in a mixed format, such that the rate coefficients must be “peeled” out of the aggregate of superimposed exponential decay curves. This results in significant variation in reported results between workers, even when working on the same raw data. Choices are made, which invariable serve as simplifying assumptions. The extraction of significant states and reduction in their number to NIP-significance yields something called “kinetic schemes”. These are the results of attempts to collapse multiple similar states into single states, ignore flutter too fast to be determinant in action potential propagation, and ignore transitions too slow to be found present in any action potential. The result is indeed a scheme, in that many quite different schemes may fairly represent the exact same molecule along its behaviors of interest. Some experimental objectives may require more detailed kinetic schemes than were adequate for prior experiments. This all handicaps the model, which would thrive on a complete, stable set of transition probability tables, including both internal changes and external bindings. We mourn not to greatly however, as one Q matrix is easily exchanged for a new and better one.

Kinetic schemes which capture the most significant NIP conformations (as states) are chosen for representation while insignificant states may be bundled together as the “idle” state or ignored all together. Each of the most significant states is significant precisely because of its effect upon the surround (directly or indirectly). The respective functional role of each state is interpreted and labeled as a phenostate, such as: {channel open, channel closed}. Phenostates are distinct from states because the mapping is not one-to-one. There are usually more than one state that express as “channel closed” and more than one that express as “channel open”.

Kinetic schemes also capture the nature of the transitions between states, as state transition probabilities. Because information is defined as a change in state, these transition rules are of the essence in a model of neuron information processing.

Kinetic schemes are artifacts, hugely abstracted images of the more complete account of bio-molecules as the discipline of Molecular Dynamics might provide. While this abstraction makes the information role compact and representable *in silico*, it renders an impotent output, merely a state number. When a kinetic scheme is employed to represent a receptor, channel, vesicle or pump, it is necessary to add an additional entity which interprets the output state for its "expression". In the same sense as this word is used by the geneticists, "expression" maps the internal state of the molecule to its impact upon the environment. A phenostate table projects the molecule's implicit nature to its explicit nature, as a mapping, or lookup table, which may in turn point to an executable function like, "move ions to other side of membrane".

2.2.2.7.1 Modulation of Kinetic Schemes

Kinetic schemes for large molecules are not stationary Those so called "rate constants" that populate the transition table are not at all constant.. The transition probability values are subject to change, implying second-order transitions. This implies a second order of information , and also implies an increase in the dimensionality of the state transition matrix. These second order effects are usually referred to as modulation, and the input signals causing such modulations are referred to as modulators.

Modulators are entities external to the molecule being modulated, and may be particles (ligands) or forces (voltage, mechanical pressure or heat). In any case, they exert their effect by altering the bond strains and electron orbits throughout the larger molecule, and thereby alter the energy barriers between states. Thus, the probabilities of the molecule's conformational changes are altered. Second order modulations of the kinetic schemes typically operate on the same time constants (just as fast) as the first order conformational transitions. In the case of voltage modification, the second order dynamics can be faster than the first order transitions (regarded by physicists as force field effects). Therefore we cannot demote such modulations to the status of parameters, nor as adaptive signals, nor as compensators. They are full status input signals.

Conceptually (and mathematically) we may say that the state changes of the large molecule are analogous to velocity, and the modulation of those state changes is analogous to acceleration. To complete the comparison, the

modulator particle embodies the potential energy. The chemical bond it makes at the allosteric binding site is the force the modulator brings to bear (force being causal to acceleration). Of course, this is only metaphor, but perhaps useful when later thinking about informational transactions.

2.2.2.7.2Kinetics of the Actor Molecules

Just as diffusion commutes rather simple movement fronts via multitudes of particles, actors accomplish transport functions by passing through a multitude of molecular conformations. That actors are comprised of large number of constituent atoms (about 1E5) might suggest very large quantities of degrees of freedom, reduced by constraints. Large quantities of freedom would present a modeling nightmare except that all but a few of these conformations are either insignificant or insufficient in occurrence. MD studies also suggest that ion channels are quite constrained in their internal motion to rather rhythmic cycles and do not appear chaotic in dynamic simulations.[50]

Beginning with the kinetic schemes published by wet lab researchers on membranal proteins, the nodes thereof as each assigned state numbers. By applying graph theory to the transition links between states, it is not difficult to assess which states can be merged or ignored with no loss in NIP-functionality. The kinetics of receptors, channels, vesicles and pumps may be simplified to such kinetics schemes as sufficiently mimic the dynamic transport behavior of their biological counterparts for purposes of a given experiment. This includes modulator binding behavior, response to force fields, signaling, transport, patterns of receptivity, patterns of response, and refractoriness. Caution must be exercised to avoid assumptions that alternative pathways are redundant and can be purged or merged. It is the alternative pathways that enable actors to exhibit modality. It is prudent to leave all pathways intact until sufficient runs can determine whether or not they express as anything significantly distinct vis-a-vis the modeling objectives. Various modalities are of keen interest to this project because they are implicated in actor pattern recognition and pattern generation.

Metabotropic receptors employ complex G-protein messenger systems that radiate outward along the membrane. They may employ multiple stages, using 2-dimensional and 3-dimensional processes in series. When proteomic and genomic aspects are not considered, they may be simplified to messenger particle shuttles between a single receptor and multiple ion channels, so as to effect signal leverage and some variation in delay, faithful to the spatiotemporal patterns reported in the biodata.

Vesicles are extremely complex, mechanically, chemically, and systemically. Within this modeling effort, vesicle complexities of compartments, subunits, complex control systems for construction, staging, release and recycling, are not tractable. However, the NIP function of vesicles is similar to that of the receptor. To the extent that vesicles are transduction mechanisms from Ca++ signals to neurotransmitter release into the synapse, immense conservation of computational load can be realized by reducing the vesicle to a stochastic point process which merely releases a larger quantity of messenger particles than does a receptor, and at a faster rate (as a batch). To serve the information throughput, the kinetic schemes must yield a release pattern in time that mimics the known patterns of exocytosis.

The vesicles, in particular, lend themselves to NIP-simplification because the molecular mechanisms of construction and release are enormously complicated, while the throughput from Ca++ stimulus to neurotransmitter response apparently is captured in a few statistical equations. This leaves the vesicle as a sort of inverted receptor, transducing an intracellular message into an extracellular broadcast of messengers.

It is hoped that all actor types might tolerate some reduction in quantity without loss of veracity. Although care must be taken to establish the correct scaling factors for each element type. It is notable that Jon Art produced predictive results with a model that scaled actor quantities down to just 3 channels, to conclude that the turtle auditory hair cell could tune to a specific frequency independent of cilia length.[51]

The molecular kinetics of an actor may express widely varying timings between states (about 20 orders of magnitude of time constants are possible between the fastest and the slowest transition). Such a compass must be clipped, for practical reasons. It is possible to tranche the challenge into 3 or 4 orders of magnitude at a time. The tranche of greatest interest is the one that straddles the action potential, about (1E-4 .. 1E-2) s.

From an informational point of view, the actor has an internal 'space' which contains its states and its state transition probabilities. The actor also has an external space within which its impacts and bindings of particles, impinging voltage, and the transport effects occur.

2.2.3 MEMBRANAL SYSTEMS

A membranal system is defined as one layer of lipid membrane between two layers of saline; with active transport molecules embedding in said membrane. Membranal systems have distributed sources of energy, in the forms of:

chemical energy source e.g. ATP (adenosine tri-phosphate) as a for driving ion pumps; concentration gradients (across the membrane and ipsilateral gradients between actors) which determine flux; charge fields which usually produce ions held in capacitance near the surface of membranes; and thermal energy which drives diffusion and actor state changes.

Membranal systems consist of two or more liquid state compartments separated by soft matter partitions which play an active role in systemic function. Generally, the liquid state provides analog communication and convolution, and the soft matter provides discrete state functions. The importance of soft matter as opposed to conventional matter or hard matter deserves mention. Soft matter physics concerns those molecular types which are easily deformed by thermal fluctuations. It is those proteins which have the potential for numerous conformations, and are delicately balanced in the energy needed to effect changes in those conformations, such that these molecules will experience spontaneous alterations due merely to ambient thermal energy. This quality makes them very useful in biological systems, both for their low (often zero) energy requirements, and for their spontaneous traversing of their state space.

The highly coupled nature of membranal systems with respect to receptors, messengers, channels, ions, pumps and vesicles is expressed in a large scale network of interactions, from which emerge copious qualities and quantities of couplings, with causality well distributed and highly non-linear. Membranal systems may possess critical and intricate positional organization of the active elements. Distribution patterns by which transporters are laid out over the membrane determine characteristic behaviors of the membranal system. Indeed it is the intention of this model that it should serve as a tool for studying such characteristic behaviors as distribution patterns are varied.

The communication linkages over the membrane will express feed forward and feedback circuits. Spatial positioning of actors and concentrations of interactors (particles) have consequences with respect to diffusion time, force field intensity, nearest neighbor interactions, and refractory effects. Thus, the local environment to an actor is critical to that actor's behavior and NIP impacts. The natural surficial distribution of actors and particles is significant to the various information processing roles. This justifies the concept of modeling each actor as occupying the center of a voxel, which delineates that actor's “impinging environment” of saline above and below it.

These two, the external and internal environments of each membranal actor, conjoin to produce behavioral patterns, characteristic of each actor type in a given context. These patterns can be mapped across their parametric space,

within physiological domains, pathological domains and hypothetical domains, via combinatorial parametric sweeps.

2.2.3.1 Channel and Pump Performance

Channels, by virtue of their gating function between compartments and the voltage potential they dynamically alter, can pass from 6E1..1E6 ions in a single opening of less than 1E-1 s. They are easily amenable to instrumented measurements of currents, which can be manipulated to detect many of the significant conformational changes that impact upon channel openings. To the extent that a model, by virtue of its accuracy in kinetic representation, becomes predictive of the correlation between molecular design in a given environment and its performance, then that knowledge can incrementally be extended into realms where the functional changes in conformation are not so easily measured in the wet lab. Modeling extends our knowledge by principle. But that must eventually be verified by fact.

2.2.3.2 Receptor and Vesicle Performance

The model membrane may be tessellated according to the biodata on actor distributions. Each actor is represented as a surficial node. These nodes imply a network of edges consisting of diffusion/drift links to nearest neighbors. Receptors act as input nodes for the network. Vesicles act as output nodes. Typically the quantity of receptors and vesicles would be 1 or 2 orders of magnitude lower than the quantities of channels and pumps. This is consistent with the expectations of linear algebra, which would provide for M input nodes, N output nodes, and N **x** M interior nodes. In a neuron there are also interior nodes which neither receive input from receptors, nor pass output to vesicles (the so called middle layers). These can be of arbitrary quantity, as some function of length of dendrites and axons, plus surface area of the soma, times some viable density value.

The kinetic schemes of receptors and vesicles are quite similar to, and fully compatible with, the kinetic schemes of the channels. To pass and process information, the kinetic rates and transition speeds would be expected to be similar for all 4 actors types, else there would be a weakest link which would squander the other resources by causing them to be in wait states most of the time.

Receptors and vesicles each serve two functions. They transduce and they fan-out (amplify). The receptor may accomplish its leveraging role via catalysis, while the vesicle accomplishes the same via a storage reservoir that is released as a batch. Transduction is duplex in role. Each transduction converts one type of messenger to a different type of messenger, and each transduction causes the signal to cross the membrane, i.e. pass from one compartment to the next.

The receptor receives one messenger particle as input and releases numerous second messenger particles as output. The speed of catalysis is critical to the information throughput rate. If the time allotted for message delivery happens to be 1E-4 s (measured empirically) and the time to diffuse from receptor to the target channel is 4E-5 s (constraint of physics), and the quantity of down-stream target channels is 100; then the catalysis of the receptor must produce 100 particles in 6E-5 s, or 1 per 6E-7 s. A seldom addressed implication of this is that there must be a complimentary mechanism for "clean up" that removes all of those 100 wandering particles, where ever they may roam, in about the same length of time they were produced, 6E-5 s. Given their uncertain locations, that is asking a lot. But without so doing, these messengers go forth continuing the message long beyond its currency. They would produce echoes and noise if not removed. Worse, they would act to block the receipt of future information.

The vesicle receives one calcium particle as input and releases numerous neurotransmitter particles as output. The contents of the vesicle may consist of more than one type of particle. The quantity of particles within a vesicle has variance. The timing of release also has variance, and the reliability of release may result in releasing 0,1,2,3, or 4 vesicles per event.

Because of the primary transduction role of these two actor types it is not expected that their kinetics would also perform a pattern recognition role nor a pattern generator role. However, it is certainly possible for them to do so.

2.2.3.3 Pathologies

The ability to model neuronal function as a system of molecules enables workers to characterize, diagnose and design corrective measures for channelopathies. Channel errors may occur in subunit amino sequencing, subunit (mis)matches, channel positioning, multichannel rafting and spacing, channel type ratios, or channel densities that displace membrane capacitance. All can be modeled predictively with the proposed nanoscale particle/kinetic system. Such a general tool can establish the essential and robust parametric values of a channel/membrane system.

It can then explore pathological possibilities, followed by various designs for therapies. For example, excitopathologies involving over-production of glutamate due to high frequencies of ion channel openings could be dynamically modeled in 3-dimensions to determine the root cause down to a specific subunit of the channel. Once the offending protein is identified, then those who develop therapies can focus on replacement methods. Also, alternative kinetics could be experimentally developed. If direct replacement is not possible, then the addition of compensatory actors may be therapeutic. Modeling offers great assistance in developing such compensators, and in reverse engineering the desired effect back to the proteins exhibiting such desired states and state transitions. It is plausible that therapeutic strategies can be worked out for channelopathies, including, but not limited to, subunit replacements, synthetic channel insertions, compensating actor constellations, altering spacing and geometry between actors, altering the messenger environment, and altering the tonicity of one or more compartments.

A similar case can be made for pathologies of receptors, vesicles and pumps. What is learned from the eminently measurable channels is likely to have analogs in the other actor types, though not as easily measured in wet lab. The model, however, is agnostic to such limitations of instrumentation and can assist in the exploration of receptors and pumps just as easily as with channels.

2.2.3.4 Emergent Phenomena

Alan Turing, in his 1952 “The chemical basis for morphogenesis” brought a working definition of chaos and principals of self-organizing molecules into science, (also Robert May, Belusov, Lorenz, Mandelbrot) forever ending determinism as a viable explanation for anything biological. Very simple equations can create immensely complicated and unpredictable behaviors, so long as there is some form of feedback in them. Stochastic feedback is not an abstract mathematical invention, but is in fact abundant in every living cell. And so all of the deterministic approaches are obsolete, even as they continue to yield good results for certain problems of artificial systems. Biology employs multiple forms of feedback to generate patterns that become the basis of yet more complex patterns. They generate novelty and then via feedback select the most useful of those patterns and assimilate them for future and repeated use. To model emergent phenomena, approaches are needed that preserve the chaos, and filtering thereof, and the means of capturing the useful finds into self, processes inherent to biology. See also Steward Kauffman, 1995, for a theoretical justification.[52]

Routine use of the phrase “emergent property” or “emergent phenomenon” is not an evocation of mysticism. It is the consequent of a very down-to-earth process: arranging things. A house is emergent from a pile of bricks and sticks when one particular arrangement is followed (as prescribed by a set of architect's drawings). Emergent phenomena are self evident when concrete, but we do not have a common language for communicating emergent processes that are dynamic. The Niagara waterfall is emergent from a flowing river and a sudden drop in the elevation of the river bed. This is an arrangement which alters the continuity of the water, and we give this striking change a name: waterfall. All aspects of life are arrangements of things, simple things like oxygen, carbon, sulfur, nitrogen, and hydrogen. But some of these arrangements can result in some quite impressive results. Positional organization makes all the difference.

The discipline of molecular biology is on a quest to explain all of life's structures and processes at the molecular scale. This is not to be confused with reductionism. The anti-reductionist argument would look at the pile of bricks and sticks and claim “they can never hop together and spontaneously form a house”. The statistician agrees with him with slight modification. “It is extremely improbable that the bricks and sticks will hop together and spontaneously form a house.” A biologist immediately starts looking for the DNA (blueprints) and the ribosomes (laborers) and sets into motion the construction process that will result in a house, provided there are adequate energy sources (money). New types of entities emerge from the extant entities when the following are available: the building blocks, the patterns of assembly and a mechanism that “reads” the pattern and executes the assembly. This is a synthetic process. Its opposite is analysis, a cutting process, a disassembly. What was missing in reductionism was the acknowledgment that there exist synthetic processes. Physical synthetic processes form rock, mountains, hurricanes. Chemical synthetic processes form plastics and detergent. Biological synthetics form trillions of fascinating entities upon the earth.

What is categorically different in modeling upward from atoms is that the build process is necessarily synthetic. Every form that results from assembly of given smaller/simpler parts is emergent, requiring some information source for the pattern of assembly, and some production mechanism for effecting that assembly according to pattern. This is no surprise to engineers and chemists, but most fields of science are heavy in analysis and silent on synthesis. People trained only in analysis may experience some conceptual friction in accepting emergence as a practical and scientific undertaking.

It is an objective of this project to substantiate in physics several of the emergent phenomena common to neurons, as instrumental to their acquiring the ability to compute. It is a strong motivation of this project to enable simple elements to give rise to complex behaviors.

2.3 DELINEATION OF THE CHALLENGE

2.3.1.1 First Problem Set

1. Create a compartmental surface via rotation of contour points into rings
2. Create loci on this surface, homogeneously spaced (each point on a ring (slice)).
3. Adjust ring width to preserve point spacing. Solve the circum/secant distortion.
4. Tessellate this surface into triangles with nearest neighbor actors as corners
5. Allocate capacitance per triangular face, one actor per face
6. Solve for normals to each triangle, for particle reflections
7. Effect reflections according to normals
8. Collision Detection algorithm determines which face will be struck
9. Collision Detection mechanism for particle-particle hits
10. Initialize particles in solution to randomized Boltzmann velocity distributions
11. Equations for diffusion metrics: flux, grad, dif, curl.
12. Add forces, sources: point, line, plane, uniform, gradient, N-body
13. Mean Free Path algorithm that preserves Boltzmann velocity distribution.
14. Velocity distributions quivers for plotting moving particles
15. Conc tracker per voxel
16. Nernst voltages for ions from concs
17. Vm from weighted Nernst
18. Vm from Coulomb's law

2.3.1.2 Second Problem Set

1. Add membranes for extracellular, core, presynapse, postsynapse plugs
2. Map ceiling/floor surfaces per ring to define compartments, then per particle

3. Calculate likely collisions with membranes (anticipate and optimize CPU time)
4. Add database manager to call any subset of membrane/zone/segment/ring/node/actor
5. Add viscosity of medium, from mechanical mobility and electrical mobility
6. Add library of particles and their relevant traits from periodic table.
7. Parametric control of strength of charge
8. Add library of commonly-used compartments
9. Add membrane thickness and water-lipid partition coefficient
10. Add charge attraction and repulsion between particles, charged membrane
11. Add binding sights and bound particle management
12. Add library of actor types
13. Develop flux and charge metrics on a per voxel basis
14. Develop 2-D grid circuit for membrane and saline RC system (accommodating actor conductivities)
15. Actor PDFs from biodata
16. Actor placements via PDFs

2.3.1.3 Third Problem Set

1. Develop finite state machines for each actor type (M,R,P,Q matrices) M = modulator state; R = open/close table; P = PDF; Q = transition probabilities
2. Instantiator for bindings and state transitions
3. Bookkeeping between bound particles and their binding sites; map B state to A state
4. Extract and normalize PDFs out of bio-data on protein actor distribution
5. Sprinkle actors according to their PDFs (recep, shuttle,channel,vesicle,pump)
6. Avoid overwriting while preserving PDF stats (Alert if insufficient nodes)
7. Add actor normals and poles
8. Identify nearest neighbors and Calculate distances between nearest actors
9. calculate Voronoi areas around each actor. Use to calculate membrane capacitances/actor.
10. Calculate actor-to-nearest actors saline resistances
11. Signal generator to drive model across multiple input ports
12. vesicle simulation: signal to NT release algorithm
13. ATP to ADP conversions as part of pump cycle;

14. Reporting routines, data capture

2.3.1.4 What is Needed from the Biologists

The skills sets for computerized modeling generally arise from engineering studies, but the skill sets for producing the input data necessary to drive models of neurons generally arise from biology. This dependency surfaces as modelers recognize "missing pieces" found necessary to built an integral working model. Follows is a list of the data that would be needed to accurately represent a neuron mathematically and dynamically for its information through-put.

1. The physiologic ranges of intracellular and extracellular tonicities for each cell type, in each species
2. Definition of channel types, pump types, receptor types for each cell type, within each species.
3. Distributions of each of those actor types, for each cell type, of each species.
4. Specific kinetic schemes which determine the input output time function of each actor type.
5. Specific kinetic scheme for the binding and unbinding of each ligand to each actor type.
6. Specific modulation effects upon the kinetic scheme of each binding combination for each actor type.
7. Specific input output function for each vesicle type for each cell type within each species.
8. Distributions of each vesicle type within each cell type.
9. The variability for each of the above.
10. The shapes of each cell type, gradients and variations thereof, including tortuosity of the membrane
11. For local circuits, the connectivity matrix between all cell types of a given individual nervous system.

The above are necessary for both the neurons and the glial that exchange ions or messengers with them.

2.4 MODEL REALMS

The model is nonlinear due to conditional flow control operators. There are two master processes that drive the model: Particle collisions and gating events mediated by stochastic finite state machines. Each encounters frequent and significant extrinsic disruption events that are germane to the transfers of information. As a HAD (hybrid analog digital computer), the continua of space, time and force fields behave linearly for particle drift, while the intramolecular state transitions and binding/unbinding modulation events behave nonlinearly.

Solutions to linear systems are amenable to closed form analytic EQs. As the order increases in polynomial EQs the smooth curve give way to ever sharper singularities, heading toward square and triangular "waves". Where lower order systems abide by continuity, higher order systems tend to emulate the "decision" with sharp modal shifts when a certain combination of conditions is crossed. The nervous system is concerned with recognition and decisions as to how to respond to such recognitions. The study of the nervous system is then, by necessity, a study of nonlinear processes.

Within biological systems there are two dominant circuits. The homeostatic circuit is a negative feedback loop that tends toward equilibrium (set point) after each perturbation. It generates the classic sigmoid response curve. The defense circuit is a positive feedback loop that once perturbed tends to grow very fast to limits of the system. This phenomena can give rise to the startle, the attack, the appetites driving search behavior, and, at a smaller scale, the firing of neurons. Positive feedbacks are inherently dangerous. In every case there must be limits to resources consumed by positive feedbacks, timewise limits to the duration of these circuits in their consumptive process, and some grand restorative negative feedback loops that eventually take over and restore baseline levels for the organism. The membranal actors exhibit distinctly nonlinear behaviors (as finite state machines); and the ecologies of systems of such actors coupled by particle collisions give rise to highly nonlinear behaviors.

2.4.1 ELEMENTS

Physics tells us that everything consists of particles and/or waves. It is convenient, however, to classify element types at a somewhat higher order so as avail them for simulations of the NIP functioning. Considered are particles and their movements within volumes and limited by surfaces. The volumes contain particles (ions and messengers, as solute particles), and the surfaces contain actors (membranal proteins, as point processes). The particles change their positions, and the actors change their internal conformation. The particles are accelerated by the EM and thermal forces, randomized by collisions with water molecules. The actors are stressed by the force of voltage and modulator bindings, and by particle collisions (thermal noise).

The experimental space is divided into compartments (volumes). Compartments are organized by shape. The surface of each compartment is considered to consist of a membrane. Each surface has sidedness (e.g. inside and outside), thereby orienting its actors. Particles within the volumes are significant by their distributions. For

particles, position is information. Velocity may also be information, in that zero velocity indicates a particle is bound, and binding indicates a change in state for the actor to which it is bound. Actors of the membranes are significant by their states. For actors, state is information. States inevitably have impact upon their surround. For example, an open channel effects a leak across the membrane, causing a redistribution of particles, and therefore the positional information of the system.

For convenience, the particles are treated according to two classes: monatomic and polyatomic particles. Though biology makes the distinction between ions, ligands, neurotransmitters, and others, for modeling purposes charge, radius, and mass are the significant constants (traits). For polyatomic particles the radius must be treated as an "effective radius". Ions that solvate by accumulating water shells also require special treatment, because both their mass and radii are varying over time. The particles are present in a number of types the same as chemical names. For example, sodium, chloride, potassium and calcium are almost always present. The actors are represented in multiple classes: receptors, channels, vesicles and pumps. The second messengers are treated as extensions of, as part of, the receptor type which they serve. For example, there are neurotransmitter receptors, ion channels, neurotransmitter vesicles and ion pumps present as membranal actors. In some cases the distinction between classes is blurred. For example there are some pumps that can transform into channels. This may be accomplished by a logical switch.

For completeness, there are several intangibles that need to be considered in a NIP model of the neuron. They are emergent properties of the lower level processes. Positions of particle in a volume determine concentrations, and of course, concentration gradients. Gradients times mobility plus prior inertia determine velocities. Velocities of particles in a volume determine flux, divergence and curl. Positions of charged particles determine an electric field. Electric field sums to apply force to each charge. Force divided by mass plus inertia determines velocity. Positions of charged particles near a membrane determine capacitor charge (coulombs). Velocities of charged particles determine current (amperage).

In summary, all elements have position (shape, position or surface address) and state (capacitance, bindings, and/or configuration). The traits of each element are predefined as TYPEs, and their initial positions are prescribed as DISTs. Each actor must in any given instant be in a certain STATE, which is prescribed by its state transition probabilities.

The terms interactor and particle are used interchangeably in this document. The terms ligand and modulator are used interchangeably in this document, except that, technically, voltage is also a modulator. The prefix B may indicate interactor-related functions, the prefix A may indicate actor functions, and the prefix C pertains to compartment, membrane and capacitance functions.

2.4.1.1 Element Divisions

a) Actors are stationary proteins, affixed to the membrane, and operating as finite state machines;

b) Particles consist of charged Ions and uncharged Ligands dissolved in the water filling each compartment;

c) Membranes serve as compartments for particles, as addressable nodes for actors, and as capacitor for the electrics.

d) Emergent forces and flux are observed via the metrics of voltage and flux.

2.4.1.2 Element Classes

1. Water, as a statistical phenomena of collisions and charge smear, hydration and thermal mass.
2. Ions, any number of species in quantities up to about 1,000,000, as computer capacity allows
3. Ligands, defined as any molecule that can modulate ion channels or ion pumps via binding/unbinding, including all neurotransmitters. Ions may be ligands. Ligands may be charged or neutral.
4. Membranes form closed surface vessels, sometimes nested, which define the shape and volume of:

   a. plasma lemma, as a closed-surface the shape of a neuron, or a simplified version thereof

   b. neighboring neuron plasma lemma, but also forming an outer closed surface

   c. core (nuclear) membrane, creating a central compartment within the neuron for purposes of sequestration, re-uptake, etc. and for limiting the intracellular volume to predominantly a near-membrane layer.

   d. dendritic synaptic “plugs” which provide synaptic clefts and neurotransmitter release sites. This is intended to be the business end of the adjacent neuron, as programmable boutons.

   e. axonal synaptic “plugs” which provide signal detection for received neurotransmitter molecules from as output from the neuron. These boutons serve to listen to the output of the model whole cell at realistic termini.

5. Receptors, metabotropic stand-alone types utilizing second messenger leverage mechanisms to modulate more than one channel. Note that ionotropic receptors are merely binding sites on the ion channels, and for purposes of this model are not referred to as receptors, but as channels.
6. Ion channels of any number of types, defined as: kinetic schemes per subunit, conduction profiles, modulator combinations effects upon state, and state effects upon bind/unbind kinetics; (includes ionotropic receptors)

7. Vesicle release mechanisms are represented simplified to kinetic schemes for release of their neurotransmitter package in a time-wise, and variance-wise, realistic fashion.

8. Pumps, including co-transporters, exchangers and ATPases that selectively move certain ion combinations across membranes. Represented as kinetic schemes. They may run backwards. They may starve or saturate. They may be allosterically modulated. They may pump Ligands. They may replenish the vesicles.

2.4.2 STATES

Compartments are usually considered to be static, therefore of only one state. However, because lipid membranes are prone to act as capacitors, and that capacitance is NIP significant, the state of a membrane may be said to equal the distribution of charge across it. That is, farads * voltage = charge, for each area local to an actor.

Each interactor has the extrinsic state of its position and velocity. The forces impinging on its mass and charge determine its acceleration.

Each actor has as many states as its kinetic scheme requires, and a set of transition probabilities between each possible pair of states. The transition set determines which state the actor will spend most of its time in, down to the state of least persistence. The transition set is usually modulatable via allosteric bindings and/or voltage. And such modulation shifts the proportion of time each state is visited. More subtly, modulation may speed up or slow down transitions without shifting the favoritism of states visited.

Conceptually, there is an analogy between interactor position and actor state; between interactor velocity and actor state transition frequency; between interactor transport and actor modulation. The modulators which modify the transition probabilities are roughly analogous to force, as they alter the state change velocities. All of this has utility when we consider that the information flows necessarily pass from particles through actors and back to particles again. The analogs will map cleanly in and out of the actors.

2.4.3 FORCES

There are many possible forces impinging on a living neuron. However, in modeling parsimonious to the task, the largest force is the electromotive force. This force must be calculated each *dt*. There is also the thermal energy, which is represented as a sum distribution of molecular inertia. Concentration gradient force is an emergent property of diffusion, which in turn is the expression of the thermal energy. Thermal energy is implicit in particle

systems as particle inertia assigned at initial conditions, never needing to be added thereafter throughout the simulation, as momentum is conserved. Ions moving through channels are driven by these two forces: electrostatic and thermal (the actions of voltage and concentration). All other forces are sufficiently small that they may be neglected.

The thermodynamic energy cascade is a fact of any living cell. The energy source for the system may be glucose, which is metabolically converted to ATP, which becomes a convenient packetized form of energy useful for a long list of bio-functions. Some pumps are driven by ATP. These establish a concentration gradient across the membrane sufficient to drive a long list of membranal processes. Pumps that move charges across a membrane are said to be electrogenic. For example, the Na-ATPase pump moves 3 Na+ out and 2 K+ in, for a net charge per duty cycle of 1 +charge out. This has the effect of charging the membrane as a capacitor, but it is a lot of work to fight the EM force to move charges up gradient. The charged capacitive has the effect of producing a voltage across the membrane, and this voltage is a pressure which impinges on the actors. Some other pumps are driven by the concentration gradients, effectively undoing what the electrogenic pumps did. The flux through all ion channels is driven by such concentration gradient and/or by corresponding partial voltage gradients. All of this could be modeled as a thermodynamic model, or by a probabilistic model, or by a deterministic mechanical model (like clockwork gears). An energy cascade can be emulated by a series of kinetic processes with the appropriate kinetic proclivities and ligands passing between them. Each step consumes only a small portion of the energy coming to it, and passes along what's left to the next step. By this means, a single type of pump can provide the energy that drives many other types of channels and pumps.

2.4.4 INPUTS

The input signal to the cell is created by a Signal Generator. In order to be faithful to bio-signals it must produce multichannel releases of neurotransmitter packets into any number of synaptic clefts. The modulation and timing of such releases may be driven by realistic multi-unit neuron recordings or hypothetical data. The Signal Generator shall imitate the lag, time spread and variations in quantity of the various messenger molecules in the vesicle, and be parametrically adjustable over the physiologic domain.

In most cases a new experimental design may be created by modifying a pre-existing experiment. Reusable data characterizing element types, processes (as functions) and experimental designs (each an assembly of types, distributions of types, and input signal set) is stored in libraries, constituting an “experiment”.

2.4.5 MEMBRANES

A 3-dimensional membrane reflecting the significant topological bifurcations and nearest neighbor relations is necessary to study channel distribution patterns, their effects upon neural functions, and their sensitivity to parametric changes (robustness). The patterns of channel distributions are more than mere densities, as mixed channel types may be present as triads or within rafts or other protein structures which fix the distances between certain channel types. Such distances may be critical to resonance frequency and localization detectors, etc..

The 3-D shapes of both the intracellular and extracellular compartments are defined as closed surfaces, each enclosing a fixed volume, derived morphometrically (as provided by the anatomical literature). Such closed surfaces may be nested. Attempts are made to simplify the shape to reduce computational load without loss of veracity. The membrane, of approximately uniform thickness, effects a Resistance/Capacitance 2-D grid, comprised of the insulative/capacitive lipid layer, and two conductive/resistive saline solutions, on either side of this membrane, containing the diffusing ions and ligands of the system under test (SUT). Membranes are herein referred to as M; there volumes within as compartments, or Comps.

2.4.5.1 Neuron Shapes

The phenomena this model intends to demonstrate are shape-determinant. For example, the topology of bifurcations in the dendritic arbor. determine nearest neighbors among the actors, which in turn determine which signals are received from whom. Previous workers have collected high resolution, three dimensional morphometric data on neurons. Instantiations of high fidelity shapes as dynamic information processors are presently computationally daunting.

2.4.5.1.1 Patches

It is put forth as a testable hypothesis that the mathematician's notion of "manifold" applies to the neuron. Namely, that although the closed shape of the neuron is immensely complex (difficult to capture as a mathematical function),

the most significant operations of, and upon, that function are sufficiently local that the mathematics can be reduced to planar operators for all local (nanoscale) effects. And that these planar patches can be assembled (tiled) into more complex shapes that topologically represent the nearest neighbor relationships of the living neuron.

2.4.5.1.2 Zones

The whole cell model membrane has (usually, but not mandated) Nine Zones

1. Dendritic Synapse
2. Dendritic Bouton
3. Stalks
4. Soma
5. Axonal Hillock
6. Axon
7. Node of Ranvier
8. Axonal Bouton
9. Axonal Synapse

These are only a suggestion, as it is very easy to define any number of zones and allocate any portion of the neuron length to each zone. A single zone type may be used multiple times, even separated, over the length, e.g. node of Ranvier.

2.4.5.1.3 Whole Cell

There are two possible approaches to whole cell models. First is a simplified version of down-scaled size and reduced quantities of elements, but otherwise a charged particle system with actor kinetics. The other is to assemble the results of patch simulations, tiled into a neuron shape. This approach treats the patches as lookup tables so as to avoid redundant calculations.

A canonical patch may be used to characterize the zone from which it was excised. A set of zones can be assembled into a whole cell model. The contour of revolution is a compromise shape that represents most of the topological relationships between elements of a neuron, both surfaces and volumes. Use of the revolution of a contour about an axis allows a single basis conversion to cylindrical coordinates to locate membrane surfaces, detect all boundary collisions, and thereby realizes significant reduction in computational load.

2.4.6 MOBILE PARTICLES

Particles = {Water ions ligands}. Particles have size (radius), mass, mobility, and may have charge. They collide with each other, reflect off membranes, and may bind to actors. They may be transported by pumps or channels. They may be bond by receptors, channels, vesicles or pumps. They may, if charged, become solvated with one or more shells of loosely bound water molecules, according to radial distribution probabilities. All unbound particles are subject to the diffusion process. Charged particles are also subject to the drift process. Like charges repel and oppositely signed charges attract, both according to Coulomb's law.

2.4.6.1 Water

Water is an essential entity determinant of saline solution behaviors. There are approx 55.4 moles of water per liter. With Avogadro's number of molecules per liter, that yields 3.34E25 water molecules per liter. A neuron of volume = 1000 micron^3 would have about 96% water, which comes to about 3.2E19 water molecules. Current PC computers can handle about 1E6 particles per CPU core. Therefore, some method of reduction in quantity is necessary. In the case of instantiated water molecules this would be as much as a 1E-13 quantity scaling factor!

Water exhibits several behaviors relevant to the ions themselves. It tends to smear the charge fields. Such that an ion that would have headed straight for an opposite charge in a vacuum, will be diffused randomly (as in pascal's triangle) in a water solution though drift will still bias its direction. Its acceleration will be reduced to a terminal velocity. An ion collides with a water molecule on average every 1E-10 m. This disrupts all straight line and elliptical trajectories, resulting instead in “thermal noise”. There is a net drift of charge if there are asymmetries in the total charge system, otherwise mere Brownian motion. The effects for concentration asymmetries are evolved via diffusion.

2.4.6.2 Ions

Each ion type has a unique combination of mass, radius, charge, mobility. From the modeling perspective, the motile particles present in large quantities (ions, water) are measured in aggregate as concentrations and flux. And the motile particles present in such small quantities that they are individually significant as messengers, make their impact as modulatory bindings (that is, allosteric) upon the stationary protein channels. From the ion channel's point of view, flux entities pass through the channel but do not usually bind to them; and signaling entities which bind to

receptors, but usually do not pass through the channel. Calcium is a noteworthy exception for its flux through calcium channels and its modulatory binding to certain potassium channels.

The extracellular and intracellular saline solutions consist of particles in almost constant motion due to thermal velocities, chemical gradients, voltage gradients, and point-to-point charge forces. They therefore possess individual position, velocity, acceleration, collisions, reflections, binding, and transport.

Diffusion is simulated via 3-d motion of instantiated particles within the various cellular shapes provided. Typically less than 20 types of particles (ions + ligands) are simulated in a single experiment, but the total quantity of particles may be 1E6 or more.

2.4.6.3 Ligands

By definition, ligands are molecules that bind. In this case, any messenger molecule or ion that can bind to any site on a receptor, channel, vesicle or pump, and thereby modify its transition probabilities, is considered to be a ligand. This includes neurotransmitters, Ca++, hormones, phosphates, ATP, cAMP, and other messenger molecules that affect neuron transmission of information. For modeling purposes, ligands are considered by default to be electrically neutral particles, but it is feasible to give them charge when doing so is instrumental to the experiment.

2.4.7 STATIONARY ACTORS

Embedded within the membrane, at statistically determined locations, per probability distributions (PDFs) specified in the physiology literature, are species of proteins that variously act in the capacity of neurotransmitter receptors, ion pumps, ion channels, and neurotransmitter vesicular release mechanisms. Collectively, these are herein referred to as Actors. Actors usually have bindings sites for either ligands or ions. Such bindings are characterized by affinity profiles which are determinant in binding rates and unbinding rates as a function of concentration. The prefix A may be used to indicate actor-related functions.

2.4.7.1 Receptors

A receptor is an actor that binds a ligand (e.g. neurotransmitter) on one side of the membrane, that in turn results in a conformational change within the receptor, that in turn causes the release of a packet of secondary messenger

particles on the other side of the membrane. The receptor, as envisioned in this model, includes some mechanism for sending multiple second messengers to target channels and/or pumps. This may be referred to as a shuttle mechanism, though its biological counterparts may bear little resemblance to shuttles.

2.4.7.2 Channels

Ion channels gate the conductance of passive ion flows through pores in the membrane. The gating decision is stochastic, varied in frequency, duration and pattern by external modulators as they may allosterically bind. And the current combination of such bindings shall determine the state transition probabilities.

Channel openings can result in millions of ions passing per ms. They are the transporters of greatest quantities. As it is the pumps' role to restore what the channels let leak across the membrane, the pumps can be easily overwhelmed if the channels remain open for very long. Viability therefore insists on either there be a high ratio of pumps to channels, or else the open time fraction of channels be very small, say about 1%.

Channel densities cause them to occupy positions along the membrane that leave only so much area of membrane per channel. Membrane capacitance is proportional to this area. Therefore higher channel densities enjoy less capacitance. This can be a big factor in system performance, because capacitance is the buffer that allows both channels and pumps to perform out of synch.

There is more to channel locations than mere density. The fine pattern expressed as the distances between several channels structurally assembled into rafts may not be revealed by density numbers. Zeroth order patterns may be defined relative to the given surficial node locations. Second order patterns may be defined relative to actors of the same type. Third order patterns may be defined relative to other actor types adjacent to it (e.g. triads). It is this fine pattern (second order organization) which in some cases determines neuronal resonance frequencies, or burstiness, or other characteristic behavior. The term ‘plaiding’ is used here to describe second order channel distribution patterns beyond mere channel density by zone or by gradient. Setting up assemblies is necessary whenever such patterns alter the neuronal response to a stimulus in a physiologically useful manner. This modeling approach has the utility of enabling study of a great variety of channel plaiding patterns; physiologic, pathologic, therapeutic and novel design, as distinct and characterizable systems. See “assemblies”below for further discussion.

2.4.7.3 Vesicles

Vesicles are extremely complicated in mechanism, but fortunately much simpler in informational impact. As a spherical container made of membrane, containing some mixture of messenger ligands, it must be released statistically into the synaptic cleft upon the binding of a Ca++ signal. Therefore, its function is to map a single Ca++ ion into a (somewhat variable) packet of messenger molecules, fairly reliably. The uncertainties (for a single action potential) include: sometimes the vesicle does not open, sometimes it opens partially then re-closes, and sometimes more than one vesicle is released. The probabilities of each of these occurring is often known, and so can be programmed probabilistically. For modeling purposes, the vesicular release mechanism can be reduced to something like a receptor inverted in it positional polarity *vis-a-vis* the membrane (that is, mounted inside out). Such uncertainties have often been ignored or consciously eliminated as noise. But the alert modeler will note that all possibilities make up a distribution of responses. The distribution is the whole, and each instantiation is but a part. It is the repetition in time or the redundancy in space, that reveals the whole. It is reasonable to conclude that biology makes full use of this fact because the spatial redundancies are quite consistent, and the temporal patterns are of the essence. Collapsing such nuances out of a purported information model may seriously degrade the veracity of the model, therefore doing so is countermanded.

2.4.7.4 Pumps

Pump require an energy source to transport ions against the gradient. They transport particles in very small quantities per cycle, usually less than six. They more often than not transport more than one type of particle each duty cycle. That is, they transport in ratios. Because of such ratiometric mechanisms, one type may be pumping up gradient while another is being pumped down gradient. The energy source for a given pump type may be an particle concentration gradient or ATP. Pumps may counter-transport ions, or co-transport ions, or both. They may transport in an eletroneutral, or in an electrogenic, manner. A pump cycle may take (1E-3..1E-2) s. Pump densities and distributions may be similar to, or quite dissimilar to, channel densities and distributions. In any viable system, the quantity of pumps must be sufficient to restore what ever quantities of ions the channels let pass passively. It might be expected that the neuron makes efficient use of the significant energy invested in electrogenic pumping by minimizing the ion channel openings as consistent with the neuronal role.

2.4.7.5 Assemblies

This model contains a mixture of channel types of known internal kinetics and transport function, each at known locations (based upon published kinetic schemes and distribution studies). The model also supports assemblies of actors such as rafts, which are positioned as though a single actor, at some specified node, but functionally perform as a set of actors at fixed (small) distances apart. An example is the channel triad. Actors are embedded within a membrane of known capacitance, bathed in solutions of known local tonicity on each side of the membrane, with known concentrations of various messenger molecules local to each actor. The model is expected to produce systemic behaviors, such as action potentials, propagation, and that these may arrange into firing patterns mimicking their biological counterparts. Such a model commands "controllables" and "observables" that may not yet be observable and controllable in the *in vivo* studies in the biological wet lab. Model parametric values can be varied, sensitivity analyses can be performed, hypothetical scenarios can be enacted, and various optimization routines can be run, so as to discover perhaps new modalities of information processing at the molecular level. Exercising such models can also assist the biologist by drawing attention to crucial areas and missing data.

2.5 PROCESSES

All of the dynamics of the model are embodied as particular processes, intended to represent specific physical phenomena. The three base processes are thermal motion, acceleration due to the EM force, and chemical release of energy. The first two of these, in turn, bring about secondary processes of diffusion, drift, capacitance and molecular kinetics. The kinetics in particular brings about tertiary processes of receptor transduction, and channel gating. Finally, the kinetics are supplemented by chemical energy release to make possible pumps which move particles against the concentration gradient and/or against the voltage gradient. These are the necessary and sufficient processes with which liquid state information processors can be built. The challenge of this project is to simulate all of these in a digital computer. As these processes occur in continuous space-time, digitization is certain to bring about some distortions and some inconveniences.

Diffusion in water is occurring at about the 1E-10 m space constant and 1E-12 s time constant. The EM force expresses itself as capacitance along the membrane, the thickness of which is about 1E-4 m. This capacitance, along with channel openings express as action potentials occurring at about 1E-2 s. The wide compass of time constants (1E-12 .. 1E-2) and space constants (1E-10 .. 1E-4) inherent to necessary cellular processes present formidable

challenges in digitization. A variety of methods are applied in attempts to simplify and compress the time and space compasses. The very slow processes can be ignored **if** they are clamped down (held constant) so as to avoid going into some rest state, inactivating state, or other modal shift that would arrest or distort normal physiologic function. Several very fast processes can be averaged into a single average effect as a pseudo-state. For a discussion of techniques beyond these simple expedients, see scaling topics below.

Particles move about in a living cell in response to more mechanisms than mere diffusion and drift. The intracellular membrane and elaborate transport mechanisms serve to rather tightly control the movements of all resources from source to target locations. Because neuronal information function is established as an electrical phenomena that is for reasons of physics considerably faster than all other cellular processes, it can be concluded that the more elaborate intracellular transport mechanisms are not fast enough to directly participate in NIP function. Of course they may play supporting roles, but are out of scope for this project. That lease the fast processes of drift and kinetics, but does not rule out structures and impediments within the cell that would disrupt, divert, or thwart diffusion and drift from their straightforward effects. In other words, living cells may employ diffusion and drift, but these may be biased by a plethora of membranes and fibers. If it is found that particles relevant to NIP modeling do not move quite randomly, perhaps a bias can be introduced which will increase the success rate in arriving at target locations. For example, the concept of affinity implies the equivalent of an attractive force. Physics offers no such a force, only a net performance of combined diffusion and the EM force that results in movement as though there had been one. Biases in velocity can enable the model to get target arrivals up to frequencies similar to those of living cells. Attractor/repulser forces, or even shuttles, can assist the model in successful point to point transport. Simplifications can lead to deficiencies and flaws, and so a careful approach would try to replace the most complex mechanisms with the simplest digital mechanisms that would still accomplish very similar phenomena. Some instances of such considerations follow.

2.5.1 DIFFUSION

True diffusion in water occurs in picosecond frequency of collisions. A digital model cannot faithfully embody such events, in multitude, for much more than a nanosecond of simulated time. This is not sufficient for NIP purposes. Therefore, justification is sought to rescale the time constants of diffusion to frequencies closer to 1e-5 s. Diffusion results from a particle system consisting of spheres with varying radii, mass, charge, and velocity, colliding into each

other at high event rates (equivalent mean free path is about 1E-10 m), as fully elastic, momentum-conserving 3-dimensional collisions. The question is: what reduction in particle quantities will still perform in similar fashion for the actor kinetics they impinge upon?

2.5.2 DRIFT

Charges are ubiquitous and this requires the N-body problem be resolved each *dt*. Charges may be neutralized by binding to oppositely charged particles or actors. When actors possess charged binding sites, those charges are included in the N-body problem. The membrane is a barrier to charge flux and results in capacitated charge whenever there is charge imbalance across that membrane. Presumably, the quantities of charged particles can be proportionately scaled down, but simulations for sensitivity to charge scaling must be performed to determine empirically the practical limits for a desired level of confidence.

2.5.3 KINETICS

Each actor may have multiple configuration states, presumably altering the functioning of that actor wrt particle binding, transport, and release. The kinetics of each is mathematically represented by transition probabilities table. This table may be uniquely modified by each combination of bindings of the various modulators. The table is "read" by the current state, and outputs a row, which constitutes a PDF as a set of possibilities for the next state. The PDF is instantiated to determine the subsequent state. That state is then "read" for its phenostate (functional implications). The phenostate calls some set of executable functions to carry out the transport operation for that type of actor.

2.5.4 ELECTRODYNAMICS

The membrane creates a portless, closed-surface, electrical network of resistors, capacitors, and current sources. The variable resistors are the only input signal into this circular grid. The most common electrical representation is a ladder filter. Driven by a voltage source on the left, repeating units are equal (or nearly equal) filter stages. The variable resistors are not usually present, but are added here in anticipation of ion channel conductivities. This circuit represents either electronic flow, or else a single type of ionic flow.

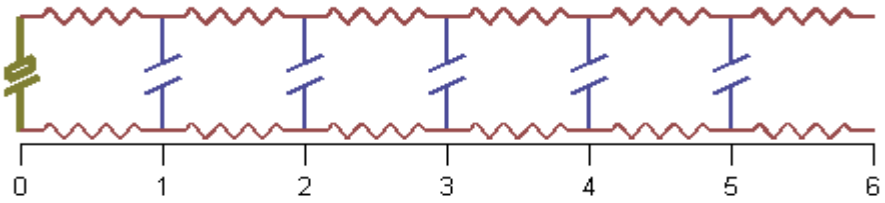

FIGURE 2: RC LADDER FILTER REPRESENTING A CABLE

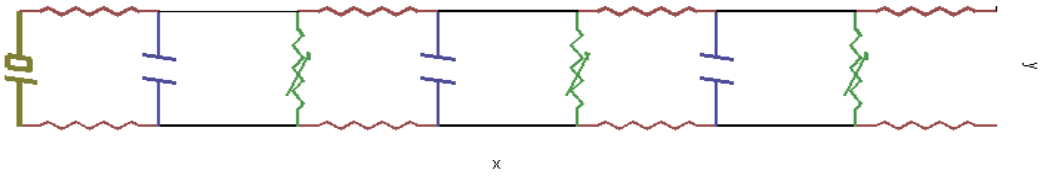

FIGURE 3: RC LADDER FILTER WITH VARIABLE RESISTORS

This can be extended from linear string to 2-dimensional grid, so as to represent the membranal system

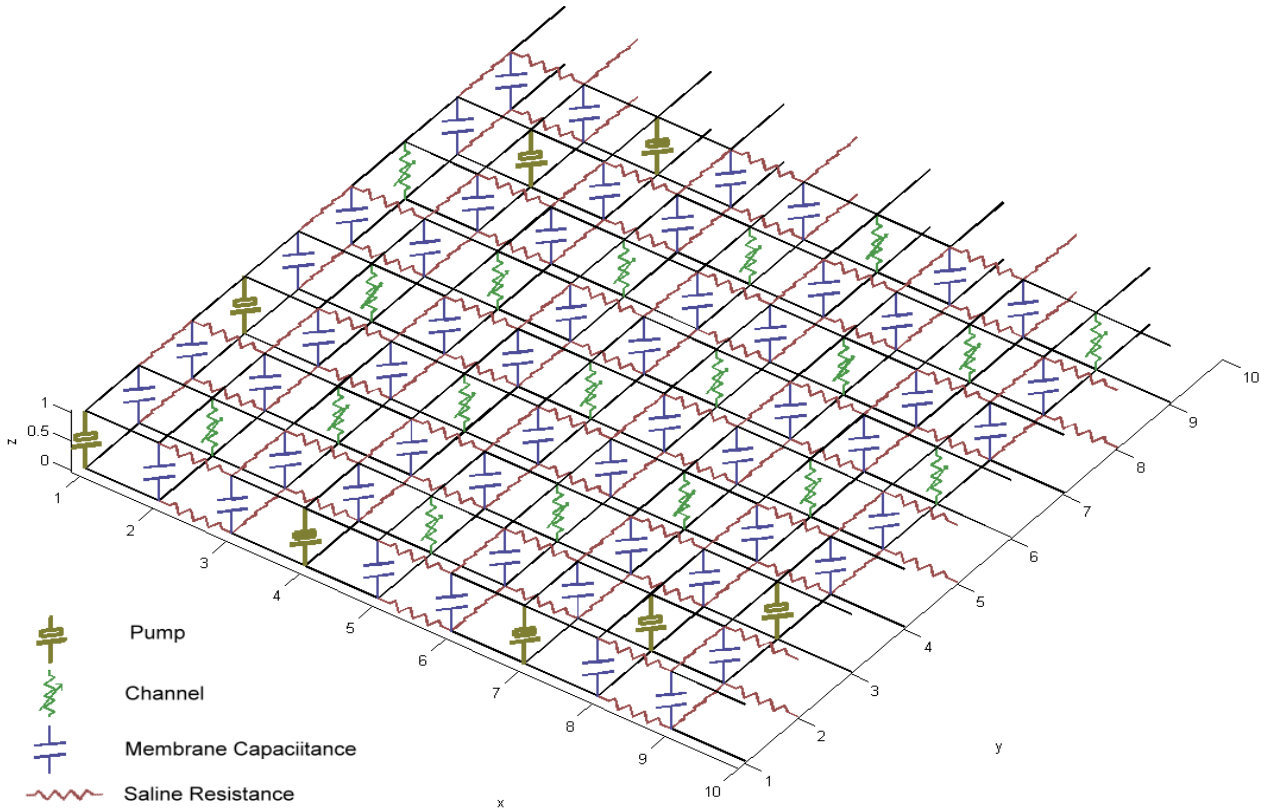

FIGURE 4: RC LADDER CIRCUIT AS A 2-D GRID

The edges of the grid wrap so as to form a closed surface. The depiction of a neural membrane as an XY Cartesian

grid is unrealistic in that the positions of the channels and pumps are semi-random. Positions are none-the-less significant to function. A grid is helpful, though not Cartesian. Tessellation can come a lot closer to the natural arrangements of actors. The variations in nearest neighbor distance, and the pattern of heterogeneity among the actor types, are highly determinant of systemic behavior, given actor strong nonlinearities. The capacitance per node varies with the area per node, and to a lesser extent with variations in the lipid makeup which determines membrane thickness and "polar head" dielectric coefficients. The saline resistances vary with salinity * internodal distance. And due to channel and pump activities, those salinities are local to the actors, not general to the compartment.

For electricity to move at all, there must be a "complete circuit". Because channels have duty cycles that are most of the time closed, it is not a given that circuits are completed with nearest neighbors. For example, If chanA has a duty cycle of 0.12 and chanB has a duty cycle of 0.07, then they share open time only 0.0084 fraction of the time, assuming they are completely independent. But they are not independent because of the refractory period. Whenever the refractory period initiates before propagation to the neighboring cell, then chanA will always be closed for chanB openings when signals are passing in the orthodromic direction, and *vice versa* for the antidromic direction of propagation. Only when propagation is perpendicular or near perpendicular to the axis between the two channels can they both be open at the same time. This might tend to support wave fronts, but it does not complete the circuit very often so that channels can conduct current. Thus, current must be conducted to some other sink.

As it turns out, membrane capacitance is crucial as a current buffer. It absorbs particles as they are pumped across the membrane, and releases them when the channels open. Without membrane capacitance, the membranal system grinds to a halt.

Pump density is significant to membranal system performance. As pumps only transport at about $1/1000^{th}$ the rate of open channel flux, then even if the channel duty cycle was only 0.01, there would still need to be 10 times as many pumps as channels. There is another factor that increases the need for pumps. The sodium pumps generate a sodium gradient that is used to drive a number of co-transporters and counter-transporters. These are types of pumps, being driven ultimately by yet another type of pump. This pump cascade adds load to the total Na pump load, further increasing the quantity of pumps required. The sum or all energy drains upon the Na-ATPase determines how hard they must work and how many there must be.

Some pumps are electrogenic and others are electroneutral. The electrogenic pumps alter the charge balance across the membrane. This charge imbalance cannot diffuse freely into the electrolytes due to the strong EM force. Rather it will quickly become capacitated at the membrane. All charged particles, both stationary (as protein or lipid heads) and mobile (as ions and dissolved polar biochemicals) contribute to the charge field, even across membranes. Therefore the whole model is an N-body problem to determine the resultant forces on each particle. Although water molecules tend to "mask" or "smear" the charge effects, this effect offers no short cuts to the calculations of accelerations when requiring conservation of charge. Compartments cannot be calculated for charge fields separately, least all capacitance be nulled by so doing.

Maxwell's 4 equations drive the entire field of electrodynamics. They include magnetic and inductive effects. But the molecular systems within neurons generate infinitesimal magnetic effects, so magnetism may be dispensed with in the NIP model. Eliminating 2 of the 4 equations reduces the system from electrodynamics to electrostatics as far as physics is concerned. But in the neuron, the charges are still very dynamic, and critically so. Charge movement due to the accelerating forces caused by the general charge field are of the essence as to how the neuron functions. Because membrane capacitance is ever present in the proximity of those ions effecting the action potential, there is no opportunity to ignore the surround and calculate only the charge in a local vicinity.

Investigations are warranted to determine how much of the RC grid is emergent behavior from the EM force. A particle model may investigate the consequences of treating capacitance as discrete (near each actor) *vis-a-vis* continuous capacitance.

2.5.5 TRANSPORT FUNCTIONS

The phenostates of each actor serve to trigger the appropriate function of impact to the outside world, when appropriate.

Certain receptor states trigger the release of the messenger particles, or begin the catalysis function that generates messenger particles. Particles are released at random velocities consistent with the Boltzmann velocity distribution for each mass, at the system temperature.

Certain channel states result in channel openings. This triggers calculations of the partial voltages across the membrane (via the Nernst EQ) the aggregate voltage across the membrane (via Coulomb's law) and the difference is multiplied across the conductivity profile of the channel type, then multiplied by the open time, to calculate how many particles were transported. Those particles are identified by serial number and are reassigned to their new compartments. Their velocities resume as they were before transport so as to preserve temperature and conserve energy.

Certain vesicle states trigger partial or complete exocytosis into the synaptic cleft of the contents (release of messenger particles). Stochastic EQs determine the timing, and portion of contents released., so as to mimic biological counterparts.

Certain pump states trigger the reassignment of bound particles from one compartment to the other, and cause the release of those particles, resuming their old velocities from just prior to binding. This is done to preserve the Boltzmann velocity distributions, which in turn preserve temperature, and conserve energy.

The price paid for working within a discrete computational space is the incursion of logical functions to handle the necessary switching from class to class, type to type, compartment to compartment. Each of the modeling phases has a set of functions to create, maintain, and deliver data. By definition the RUN phase is heavily iterative. Therefore the RUN functions are the most sensitive to numeric methods regarding opportunities for model efficiency.

Functions maximize their reuse potential via an object oriented approach. Care must be taken to conceive of each function in its most general form, spanning the likely parametric space of neurons to be modeled. This implies an additive (constructive) rather than subtractive (analytic) approach. The model must be open to the addition of new structures and compounds found within cells, without having to tear apart existing functions. This strongly suggests a physics (first principles) basis for each function, and an object-oriented coding approach.

2.5.6 OUTPUT SIGNALS

Of the many variables involved in running a hybrid particle and kinetics model, certain of them are chosen for capture as the “results” of the experiment. These variables must be interpretable in the context of the biological

literature from whence it all came. Therefore they must not be some abstracted convenience that has not physical meaning, and they must be converted back from modeling units to SI units. The very large data-series with heavy repetition are collapsed into some reduced form via sampling, smoothing, threshold crossings, statistical measures, or curve fits. The human interpretation of the data is after all, the critical last step, and this often requires visualization of the data so as to accentuate the differences between two or more comparison cases.

For the mobile particles, position is information. The position of charges in a capacitor. The position of neurotransmitter molecules *vis-a-vis* the receptors. The position of ions *vis-a-vis* the ion channels and pumps. The position of neurotransmitter molecules *vis-a-vis* the vesicle they were originally contained by. The positions of charges determine the forces, therefore the accelerations, therefore the velocities. Charge positions and the densities implied by particle positions together determine how much flux there will be upon a channel opening. The position of the channel gates within each the ion channels is also necessary to complete the positional information that makes possible predictive constellation.

State is information. Each actor has proceeded through limit cycles, and these reflect the modalities of that actor. Transport patterns are emergent from those state patterns. Transport has a high impact upon particle flux.

One may choose the graininess of data presentation. For example, one may choose to look at only every tenth frame of the simulation to get a reasonable picture of what transpired.

2.5.7 TIME SEQUENCE

Follows is a sequence of events that comprise a minimal set of functions which the model must be capable of executing consecutively.

1. A neurotransmitter packet is released into a synaptic cleft
2. The neurotransmitter particles diffuse across the synaptic cleft, exposed to removal mechanisms, re-uptake, conversion, binding to non-informational elements
3. Some neurotransmitter particles bind to those receptors for which there is a binding affinity
4. A binding event is competitive and stochastic, proportionate to local concentrations of competing particle types
5. Receptors change kinetics when bindings occur

A. metabotropic receptor (includes second messenger system to nearby channels)

B. ionotropic receptor (treated as part of modulatable channel, with no separate receptor entity)

6. Various modulator concentrations in the compartments alter molecular kinetics of channels and pumps

7. Second messenger systems leverage one receptor signal into hundreds of ion channels. There may also be phosphorylation in a radial pattern around the receptor (2-d effect for g-proteins, 3-d effect for PO3)

8. Receptor, channel and pump kinetics are instantiated as a function of their prior state, kinetics, modulation combos

9. Ion channels flutter open and closed ; pumps proceed through duty cycles

10. Ion channel conductances as a function of conduction profiles, times sum of forces from partial voltage gradients plus concentration gradients impinging on each particle type at the two ends of the pore

11. Ion flux through channels immediately impacts local capacitance at the membrane as a charge imbalance

12. Charging curve of local membrane capacitance is a significant determinant of action potential shape

13. Resultant local voltages are “read” by all voltage sensitive actors, resulting in intra-molecular torsion

14. Saline resistance conducts ionic current to nearest active neighbors, above and below the membrane

15. Nearest neighbors are modulated by voltage changes, and their open-close times are altered

16. This process repeats, resulting in ion flux between channels (repeat 8-15 for nearest neighbors)

17. Propagation proceeds bilaterally around the perimeter and down the axis in a wavefront. Directionality is determined by the kinetics of the relaxation/return-paths to resting state, and refractory periods, which tend to be unresponsive to external stimuli

18. Calcium channels allow calcium influx, which in turn serve as a messengers to cause the release of vesicles

19. Vesicular contents diffuse out into the synaptic cleft

20. Pumps work towards reestablishing membranal system equilibrium states for each particle type.

2.6 BIOLOGICAL ENVIRONMENT

For convenience, the standard whole cell model is referred to under the name of Goblet (for its initial shape). The nano-scale patch of membrane with one or several embedded actors is referred to under the name of Patch. A constellation of Patch instances can be brought together to interact as a multi-scale model, when the several canonical patch models are archetypal of the many patches around them. The many patches located between canonical patches are created as interpolations. After confidence is gained through modeling experience, only key regions of the whole cell need be sampled to produce a representative membrane fully populated with channels and pumps. It is expected that 10..50 patches would suffice to characterize the entire membrane of a neuron,

corresponding to known zones, and also to establish gradients where found. The individual patch performances can then be cloned and/or graded via interpolation, so as to tile the Goblet. The resulting fine pattern of nearly repeating channel types is herein called “plaiding”.

All of the nearest neighbor relationships between surficial nodes emerge from the shape of the Goblet. Patches then extracted as samples from this nodal fabric. Certain simplifying assumptions for the patches are justified by the mathematics of manifolds.

Information processing events at the molecular level of a single neuron are to be modeled, conceptualizing the whole cell as an input/output device, such that multiple instances of this model can be wired together, via synapses, according to a connectivity matrix, so to simulate local circuits. Such modeling requires the inclusion of a membraniform system defining shaped saline compartments for extracellular, intracellular, synaptic, vesicular, and sequestration functions. The closed-surface membraniform system shall have means of input via receptors and output via vesicles, receiving and emitting neurotransmitter molecules across synaptic clefts, respectively.

2.6.1 ADJACENT CELL MEMBRANES

As an extracellular membrane is provided to contain the extracellular fluid to a prescribed thickness around the cell, that membrane is available for pumps, channels, receptors and vesicles. This surface is completely addressable so that placement of actors can simulate neighboring neurons or glial. While many models assume the extracellular fluid to be at zero volts (grounded), it is obvious to modelers that the extracellular fluid is even more dynamic in it voltage swings, fluxes, and concentrations than is the larger volume of intracellular fluid. This model supports the investigation of the role of extracellular dynamics.

2.6.2 ADJACENT CELL SYNAPSES

A signal generator (SigGen) is provided to simulate the presynaptic signal set. This signal is a spatiotemporal, multi-channel stream. It may be used to convert any reasonable bio-signal, like a noisy battery of spike trains or audio music phase lagged to the various distances, into a series of vesicle releases of neurotransmitter into the synaptic cleft. This is accomplished through the use of “synaptic plugs” which simulate “intelligent” boutons.

For computers large enough to run simultaneous 2 or more Whole Cell models, the outputs of some may serve as the inputs of others, so as to form local circuits, and at greater quantities of cells, connected formal neural networks as constituted in layers.

In any case, the whole cell outputs are captured as streaming data into flat files, containing the particle positions, fluxes, transmembrane voltages, forces, and actor states wrt time. Output Reports, as graphs, and movies of particle positions and actor states are provided for visualization of the data.

2.6.3 DENDRITIC ARBORIZATIONS

Representation of the many shapes ad bifurcation patterns of dendritic fields requires radial partitioning (herein accomplished by inserting vanes into the dendritic "cones"). The taper rates and bifurcation points are represented via vane placements. There may be as many dendritic cones as necessary to reasonably represent the shape being modeled.

2.7 CAVEATS AND ISSUES

Irrespective of the biology, the modeler runs into several issues concerning the numerical methods and hardware constraints.

2.7.1.1 Deterministic vs probabilistic universe

Already discussed, determinism is apropos for the very simplest of mechanisms, like the lever and the gear. But as complexity rises, even the smallest probabilities can express as some degree of variance or chaos. Take for example printed circuit boards in computers. Every component on them is intensively designed to operate deterministically. And indeed they do, most of the time. But the very "deterministic" calculations of failure analysis reveal that every board will fail sooner or later, and that the exact time cannot be predicted (violence excepted). Everything is built out of components that have some thermal "noise" in them, which is inherently random. This randomness is mostly tamed by design, but never 100% contained. Thus, it is wise to acknowledge the inherent randomness (uncertainty) in everything, and design accordingly. Variance can be rationalized as multiple state paths, with each path resulting in a somewhat different outcome. The qualitative difference between solid state silicon and biological membranal

systems is that random processes are embraced and harnessed in biology. That is the various states paths each serve some utility; usually described as shifts in mode. This makes many wondrous things possible, and, by the way, transcends the narrow view of the determinist.

2.7.1.2 Incompleteness: incomplete physics, incomplete biology

See the abductive modeling approach described above as to how humans deal with incomplete information. Beyond the scope of this model, multicell networks processing large block of information develop an innate ability to think across missing information, and do so effectively, in a useful manner.

The incompleteness problem deserves some thought because the available data from the literature on membranal proteins is rarely complete. The kinetic schemes are not only simplifications in their own right, but often stop short of a complete scheme due to practical limitations in mensuration. The modeler will often be confronted with missing reaction rates, and missing states. This sometimes becomes quite obvious in the simulation, wherein actor performance does not match the biological single channel recordings. The verification process is dedicated to answering the question of completeness and accuracy of input data. The "art" of modeling is called into play when there simply is not the necessary data to complete a duty cycle. Then the single unit recordings must inform the modeler as to what is missing and within what range the missing values must lie. There are several aspects to the treatment of missing values to be treated later: First, is the need for a clear marker that tags each estimated value, that they not be passed as biologically derived. The second is a sensitivity test to determine the plausible range for the estimated value, serving to limit the model and to inform the biologist as to what is expected, should the additional wet lab work be performed to measure that value. Third is a contemplative analysis for alternative explanations of the single unit recordings. In all likelihood there are more than one way to achieve a given single unit behavior trace. What subtleties of the bathing solution could affect the data? What possible denaturing of the actor might alter the results? What degradation takes place over time since the preparation was made? What was missed in the search for hidden states comprising a kinetic scheme?

The biological aspect of incompleteness acts as a frontier, inviting wet lab workers to proceed onward into uncharted domains of mensuration. The modeling aspect of incompleteness requires a careful compliance with known physics so as to avoid creating fiction and then presenting it as emulations of science. The good news is that neural

networks, more than any other type of processor, are known to perform well in the face of incomplete data to solve the assigned problem.

2.7.1.3 Entropy in cytological systems

Entropy is the opposite of information. Therefore any loss of information is entropy. It is a very relevant concept to this model because there is an interest in identifying information that is redundant, dead-ended, or corrupted along the process path. Failure to identify these types will result in an over-stating of the throughput information of the system.

2.7.1.4 Asynchronous biologic events v synchronous digital events

Digitization of time leads to aliasing error, the cure for which is smaller *dt* size.

2.7.1.5 Steady parametric change (development and evolution)

Postponed for future releases.

2.7.1.6 Noise vs thermal energy source

It is probably for the better if those modeling biologic processes discard the term “noise” once and for all. Living cells simply do not see thermal energy as noise. It is exceedingly useful free energy, and it is harnesses in many ways within each cell. No living cell is viable without it. Period. Perhaps “ambient thermal energy” is a suitable replacement.

2.7.1.7 Molecular dynamics vs kinetic schemes

Molecular dynamics are based upon first principles of physics and are far more accurate and predictive than kinetic schemes. Kinetic schemes are abstractions that are subject to the whim of their creator, much as curve fits may be accomplished by several different strategies. However, the computational loads of MD make them far too intensive to include in a whole cell model. And most of what they calculate must be irrelevant to the NIP function of the neuron. The best usage is that the MD simulations are used to validate and choose amongst the proposed kinetic

schemes such that the best in class is being employed in the model. This model is built such that any improvements in kinetic schemes at any time can easily be submitted to the model library for easy utilization.

2.7.1.8 Unsettled Classifications, Ambiguities, and Conflicting Characterizations

Biological data solidifies over the time from the first discovery, through characterization, to a well characterized and generally agreed upon entity. There is always a period of uncertainty and conflict about distinguishing characteristics. This is a meta-problem in that it occurs before the bio-data gets into a model. It is for others to argue out the classifications and variations on biologic themes. It is for those interpreting the results to determine its applicability to biologic systems, whether physiologic, pathologic or pure fantasy. It is for the modeler to to carefully label the hypotheses and competing representations of actors as alternatives, and is encouraged to run competing models to determine which exhibits behavior most closely matching biological reality.

When ever there is ambiguity or dispute about types and classes, it is recommended that both be entered into the library, with distinguishing names. Then comparison RUN can be executed, and the performance rated to the objectives. At some point of model confidence it should become the arbiter of such disputes, The proof of claims is in its performance.

2.8 JUSTIFICATION

Justification concerns the physical, chemical or biological basis of entities and processes selected for inclusion in the model, and the veracity of the representations of same. This is a general theme throughout the modeling process. The metrics for justification are discussed in Chapter entitled Architecture.

2.9 VERIFICATION

Verification concerns the performance of each aspect of the model. Each function must be verified over applicable physiological ranges for its veracity of performance, stability and graceful recovery from errors. Then assemblies of functions that typically work in concert are verified. Finally, all the called functions of a RUN are exercised over extreme and normal parametric settings to build confidence that the model is stable, reliable, repeatable, and representative of that which it claims to model. Verification goes ultimately back to the literature of the biological

phenomenon which the model purports to simulate. The metrics for verification are discussed in Chapter entitled: Architecture.

2.10 MODELING TEMPORAL PHASES

Living cells enjoy many time constants that digital models cannot span. The growth and development of cells, responsive widening and retraction of synapses in "learning", and a lot of compensating and adaptive strategies so as to continue functioning over widely varying conditions. At this point in model development, it is straightforward to define a single distinct scenario (cell condition), and run it as a separate model experiment. When a cell shifts modes for reasons other than the direct result of protein conformational kinetics, then some re-architecting of the cell structures and processes is often involved. This may be regarded as meta-programming to a NIP model. It is possible to effect structural changes within a modeling run, but out of scope for this project. For the time being, multiple runs across a series of scenarios of changing parameters will approximate these higher order processes.

2.10.1 MICROSCALE MODELS

A neuron can be designed or analyzed from the bottom up or top down. A top down approach would implement the whole cell model first (microscale), then progressively add more elements and features. The patch model (nanoscale could be used selectively to verify the validity of representative patches from the whole cell model. Once the various patches of interest have been modeled at the nanoscale, they comprise a library of re-usable blocks for the large-scale whole-cell simulations. A means for exchange of particles between patches is necessary for them to work as an integrated whole. Given that patches are collapsed to lookup tables for purposes of tiling a whole cell, such particle exchanges would simply be numeric values.

Distortions arise from a reduction in particle densities. If one model particle represents a million real ions, then there are a number of other compensations in the model that must be made. The channel conductivities then transport very grainy amounts of charge, resulting in rather abrupt changes in voltage, called shot noise. Also, a recalibration of membrane capacitance, receptor bindings, and pump function are all necessary if the results are to be meaningful to biologists.

2.10.2 NANOSCALE MODELS

It is intended that the nanoscale model of a patch of membrane represent real ions one to one. If all the physical constants are preserved in quantity in the nanoscale model of membrane, ions and ion channels, then the causal and spatial relationships between the key elements remain intact. The price paid is that only about 1 millionth of a neuron can be modeled this way. It is possible and advisable to model a smaller portion of the neuron where the physics is tractable to computation without scaling. Patches of 10 by 10 voxels of 0.01 micron edge length would, on average, have only 1 channel. In busier areas, near synapses, this density could rise to a max of 25. A patch of 16x16 voxels, one layer deep on either side of the membrane, would allow the study of Hodgkin-Huxley type action potentials. A typical rendition of this size would have about 92,000 particles, 256 membrane addresses and 12 channels. Note that this is 10 times the average channel density but typical of the more informationally active regions of the neuron. Note however, that high channel densities imply low capacitance per channel, which have significant consequences upon the ability to generate an action potential and the propagation thereof.

2.10.3 MULTISCALE MODELS

The solution to the overwhelming computational load of rigorous whole-cell simulations is multiscale modeling. The microscale and Nanoscale simulations may be used in concert. Certain representative “patches” of membrane can be incrementally increased in size and counts until a point of diminishing returns is reached in the input/output relationships. This nano-patch can be expanded until propagation is consistent with up-scaling. That is, if increasing the number of components does not add appreciably to the generated results, then that patch can be held at its point of diminishing returns. Such an exercise provides valuable insight for both ANN and BNN designs.

1. When such a size is reached it can be “cloned” around the circumference of cylindrical shapes as an accurate predictor of what actually transpires in an axon.
2. To the extent that the parametric space is exercised and consistent between ANN and BNN, such patches can be collapsed into look-up tables, and then stitched together in much larger quantities. accurately modeled at the nanoscale of ions and ion channels, including the nearest neighbors, membrane capacitance and chan type mixes/patterns.
3. A design can mix-and-match canonized patches to mimic the BNN distribution patterns.
4. patches that do not add anything to the output signal can be eliminated. For example, can a thin radial slice down the entire length of a neuron accurately mimic the BNN performance? If not, can the edge-dissipation effects be negated via mathematical stitching so as to improve the model’s veracity?

Multiscale modeling will play an important role in capturing the information processing capabilities of neurons. Because a full-scale model will involve perhaps 1e12 particles, 1E8 locations, and 1E6 actors, over a series of 1E6 time steps. every opportunity to reduce computational load in the ANNs is to be fully exploited. Aside from the Computer Science contributions to numerical methods, there are several higher level strategies that can gainfully be employed.

1. Reducing patch size to its minimal informational character.
2. Eliminating all patches shown not to contribute to the out put
3. Cloning all homogenous patches alone a wave front (only the locations of the wave front need be computed)
4. Correcting for edge artifacts allows modeling of only a radial slice of circular profiles
5. Studying complex local phenomena and then collapsing the results into look-up tables to be libraried for future use.
6. the 'digestion' of relevant phenomena at a lower levels for preprocessed use in larger quantities at higher scales.
7. the automatic detection of violations of canonical forms. This is critical to avoid bad science. Any emergent phenomena not consistent with previously characterized behavior must be detected and alerted. This should trigger additional intensive study into the local behaviors so as to add more possibilities to the library of low level routines. The essence of multi-scale modeling is that the unanswered question drops down to a lower level of analysis, on a type-by-type basis
8. At each level, parametric sweeps need to be performed across each of the likely permutations in assembly of parts. Distinct modes, if any, should be mapped.

The whole cell model can be realized as a projection or clones of patches. As this is a tedious method, it is anticipated that over time, the bottom up approach will need not be repeated with every experiment. Stable performance of certain parametric domains would justify direct to whole cell modeling which represents ions perhaps 1:10,000. Random checks can be performed on several patches from that whole cell to insure that performance between the rigorous nanoscale model was being matched by the less rigorous whole cell model. Some minimal quantity of patch types with a placement map can capture the input-output relationships of that particular species of neuron. The levels of confidence of such whole-cell simulations are dependent upon how exquisitely the whole cell is calibrated to the lower scale patch models.

A question arises as to whether intermediate assemblies of patches could effect any computational efficiency. For example, might one patches be cloned into a 5x5 array of 25 patches; and these assembled into grids of 625. The problem is that portions of the larger grids must be discarded to achieve the shape of the neuron, and this fitting of

square tiles onto an irregular surface could become more tedious that its worth. The solution to tiling irregular shapes is called tessellation, and it works with triangles, not squares. Conveniently, every square can be cut diagonally into two triangles, and triangles can always be stretched to fix the contour. It would still be an algorithmic challenge to decide how to fit all the tiles onto a cell surface. It is much easier to tessellate the cell surface first, and then map 2 adjacent triangles down into a square patch.

2.11 APPROACHES

The activities of science are for the most part analytic. Analysis seeks the uniformity of an object or process so as to collapse all instances into a single compact form. It thrives on homogeneity, and indeed strives to reduce all equations to their homogeneous form. There have been thousands of attempts to analyze the neuron for the mechanisms of its functional role. However, there is this problem: information is precisely the non-uniformities. Information is the non-homogeneities. If you could take all of the analytics out of a neuron, and throw them away, what is left is the information. It may be that some of this information remains un-read; and so we think of it as waste or noise. But all of the important information being processed and throughput by the neuron lies outside of analysis. To be fair, one could employ analytic techniques to characterize the building of the mechanisms. But this will not deliver to you the content. Any more than studying a TV schematic will ever tell you what shows will be aired tonight. What is needed is the further development that focuses directly upon the non-uniformities, as a complement to traditional analysis. We have a word that serves to name its complement: synthesis. Which of course means to build. Structure is a zeroth-order activity, and information is a first-order activity, as it is a differential. This raises the conceptual question: what is a proper way of studying the information processing potential of a living cell? On a spectrum from uniformity (e.g. a salt crystal) to pure white noise, are various patterns. There must be “degrees” of patterns, as there are for example, degrees of symmetries. Simple patterns are of low information content, while extremely complex patterns (e.g. the distribution of ones and zeros in a large computer memory) can contain maximal quantities of information via efficient coding.

But humans come to the table with a bias. They tend to read simple symmetries as “good” and rich symmetries as noisy, wild, undesirable. For this reason Albert Einstein's e=mc^2 is celebrated, but Erwin Schrodinger's wave equation for a single particle in a potential

$$i*\hbar*\partial/\partial t*\Psi(x,t) = -\hbar^2/(2*m)\nabla^2\Psi(x,t)*+V(x)*\Psi(x,t);$$

where:
i = imaginary input;
h = reduced Plank constant;
Psi = probability amplitude;
del^2 = Laplace operator;
m = mass;
V= potential Energy;

is much less so, despite that Schrodinger's equation is arguably "more important to the betterment of mankind". This attests to our preference for simple patterns, even regarding erudite theoretical physics. This same bias may cause us to expect simple equations to explain neurons, and regard information-rich processes as noise, or somehow unclean, or unfinished or held suspect.

To find the information of a membranal system we must go hunting for its most complex patterns. It is not the job of analytics to do that. Our current state of reports on neuronal pattern recognition is based upon preconceived notions of known patterns to be searched out. That is, few investigators have applied means to find previously unknown patterns. Feature extraction is based upon preconceived definitions of such features. As a departure from this limitation, the coding applications of information theory can find patterns without *a priori* definitions, as arbitrary digital codes, or as self organizing maps. It is possible to sample analog data to force it into digital data, but the sampling method chosen strongly biases the outcome of patterns subsequently found.

One approach that aligns quite closely to the task of discovering how neurons use information is System Identification. It begins with no preconceived notions, and works on analog data. Its typical goal is to create a black box that imitates the functions of the System Under Test. This requires a complete knowledge of the input and output signals and a rather complete exercising of the parametric space. It is effective for linear systems, but increasingly ineffective with increasing nonlinearity of the system.

The content that is generated by a neural information processor is all the non-uniformities to the neuron' otherwise steady state. And the value of that content depends upon whether and how it is read. That implies that the information values are extrinsic to the mechanisms that created it. The search for a concrete litany of what information is actually produced by neurons may be frustrating because it may produce far more than is actually "used". A biological process which simply generates abundant information in response to perturbations from the environment creates a ready pool of internally measurable data that correlates with "outside". It could be that only a

small percentage of these are actually “read” or “peeled off”. This is not unprecedented. How many pollen grains are produced per stamen that might receive one of them? Obviously to the stamen that one grain carries a lot of valuable information. But what is the information values of all the pollen that will never see a stamen; the pollen that will never be read? Nature often creates redundant information, to succeed in a noisy environment.

In like fashion, the neuron may produce information as ion movements, in abundance, even though only a tiny percentage result in bindings, or triggering output signals. We would then expect significant redundancy of information content. But there may also be variety. The ability to generate “bits” as ions moved across membranes varies from cell to cell, and from situation to situation. We therefore need a generous approach to modeling neurons that allows for such a possibility, and preserves such nuances, without attempt to aggregate any of these information carriers.

2.11.1 DISCIPLINARY SPAN

This project specifically tackles the following challenges in modeling neuron information flow:

Class	Problem Class description
Software Architecture	Over-arching structures of the model and its processes that define the domain and range spaces
Geometry & Topology	Primitives for the various shapes, distances and neighbors of and between the elements.
Algebra	Basis changes, eigenvalues, inversions, determinants
Physics	Constrain all operations for consistency to applicable laws of physics. Mass, inertia, momentum, size, charge, force, elastance, drift.
Forces & Collisions	Position, velocity, acceleration, momenta, reflection, absorption
Kinetics	Molecular states and bindings; stochastic processes, Markov, Kolmogorov
Biodata2model	Convert bio-data received from literature into normalized compatible optimal library of types
Design and Logic	Continuous and discrete bio-processes which identify necessary and sufficient elements and relationships for information processing.
Digitization	Continua of space-time reduced and compressed into digital representations, topology
Numeric Methods	Sampling and aliasing error , integration and differentiation, random distributions
Build	Populate data structures with instantiations of types per the experimental design.
Phenomena	Map out the flux, current, charge field, voltage, forces, acceleration, barriers, binding, transport, capacitance
RC Grid	Electrical network representation of a wet circuit, over a portless closed surface
Signaling	Input Signal Generators and output signal capture devices
Information Theory & Stats	Metrics on the channel capacity of elements, patch and whole cell
Iterations	All functions within a time loop are difference equations
DataBase Management	All data structures to be populated and their integrity insured
Graphics	Presentation functions
Testing	Each function must be justified and verified
System Optimization	CPU and memory resource management

2.11.2 LIMITATIONS

There are, of course, many limitations on the construction of such a neural model as described herein. It is helpful to sort them out and identify which are hard constraints and which might offer opportunities for future study.

1. Physical basis of biology
2. Biological data as driver
3. Mathematical constructs
4. Available hardware resources
5. Available software resources
6. Quantities of elements and processes
7. Qualities of elements and processes
8. Author's time

The biology addresses an immensely complex space, and a constantly evolving one. Biologic data generation will always be both voluminous and inadequate. As Thomas Weiss has compiled [53], the underlying processes of NIP are fairly well established, with the exception of protein kinetic schemes. As these proteins are assembled out of subunits, and often modified (e.g. tail snips), tethered, and recycled, the kinetic schemes are greatly simplified representations of what is really transpiring within living cells. The challenge is to capture the NIP significant aspects of transport phenomena and to handle the very large quantities of elements and their processes in the form of a large scale model. Any treatment of missing data will be risk-prone, yet to get actors working some of the blanks will necessarily be filled in with tentative data.

This project will of necessity develop geometric functions, collision detection algorithms, Kolmogorov processes, N-body charge fields, complex data structures, topological mappings, and visual representations of the output data.

In the modeling of information systems, redundancy of the form does not necessarily indicate redundancy of the function. In a digital computer, for example, despite millions of identical transistors (redundant form), they are each assigned a unique task when under full load (no redundant function). In the neuron the case is not so clear. There may be 1E16 water molecules, 1E13 ions, and 1E6 channels. How many of these could be eliminated with no loss in function? Given a fixed and known information transmission capacity, then redundancies could be identified in a straight forward manner. But in a yet-to-be-explored analog environment of living cells, where a wave front

(propagation) can take any shape and proceed in any direction, by what criteria can we declare redundancies? We do not yet know how much information each downstream neuron extracts from the signals impinging on them. Many modelers have purged elements only to discover later that doing so lost the essential qualities that were being sought.

At the molecular level, information content is more certain because the entities and interactions between them are fewer in type and better characterized as to mass, charge, radius and affinities, and bonds. A sampling theory is needed to determine how many elements performing the same function are necessary to achieve some define standard of reliability.

Super computers are in development that promise to handle an adequate number of elements so as to mimic neuronal information processing behaviors of whole cells and local circuits of cells. What has not stabilized is the computer programming languages, compilers and higher level applications that are most conducive to multi-scaling of whole cells from the molecular scale up. Trends are towards human productivity tools, but we do not yet have an adequate set of geometry tools for physics-based modeling and sparse matrices. We do not yet have an adequate representation *in silico* of the continuity of space-time.[14]

The quantities of elements and processes are easily scalable. The only challenge is to determine the confidence levels for consequences each simplification procedure and to resist any reduction, either quantitative or qualitative, which cannot be justified by underlying physics and performance to match the biology.

In NIP modeling it is necessary to rank order all elements and features as to their relevance, then delineate cut-off lines, below which traits are purged from the model as not justified given their low significance. The notion of "relevance" is not simple. If, for example, we were to choose element size, then the first thing to go would be the ions. Clearly not a workable strategy. If we were to choose the ratio between modeling cost and information processing gained, then the vesicles would be the first to go. Also not advisable. This author proceeded as follows:

1. Identify the necessary and sufficient chain of events between input and output, of which any missing link would cause the neuron to fail in its roles.
2. Identify the elements along this chain.

[14] The historic analog computers are acknowledged, with production peaks in the 1960's. They were abandoned as not cost effective before they could be miniaturized down to the nm scales of current digital machines.

3. Identify the necessary and sufficient processes of interactions between these elements to effect neuron function.

4. Identify the internal processes of elements necessary to neuron function.

5. Identify the quantities of each element as present in living cells and explore the consequences of reduction in quantities, as individual types of elements, and as ratios between the element types.

6. Consider the adequate representation of an element to be its bio-inputs and bio-outputs with an adequate state graph in between to mimic the NIP relevant behaviors of that element. For example, a vesicle need not be represented as a bag of solute, but rather as a stochastic device that releases a varying quantity of particles in response to successful bindings of its appropriate ligands.

2.12 MOTIVATIONS

The motivations for this project are three-fold:

1. To provide a conceptual platform for studying the dynamic interactions of membranal information processing systems at the molecular level, consisting of receptors, ion channels, vesicles and pumps, one that is physics-based and information theory constrained, so as to yield predictive behavior over wide parametric domains;

2. To provide a method of extending the parametric domain for the above modeling of biological membranal systems, such that their normal and pathologic functioning can be simulated, such that therapies can be designed and tested within the model;

3. To develop a molecular basis for liquid state processors. To the extent that biological neuron information processing is parsed down to its molecular minimum, and the varieties of mechanism and function are explored for their utility, a molecular model is the blueprint for the physical construction of artificial liquid state processors.

These three do not necessitate separate efforts for each but rather are the benefits of a singular effort to model information processing at the molecular level of charge, diffusion, and kinetics in 3-space.

2.12.1 CONTRIBUTIONS TO SCIENCE

This model is intended to enable researchers and modelers to mathematically simulate single neuron information processing, based upon the movement of large quantities of ions and ligands in solution, (>5000) between large numbers of membrane-embedded proteins (>500) which experience significant quantities of state changes, and extensive coupling between these elements via electrical and flux phenomena. This model intends to employ a Finite Element Method (FEM) approach to the electrical circuits of membranal systems, a free path to collisions approach to the saline solutions on either side of that membrane, and a stochastics approach (per Andrey Kolmogorov and David Colquhoun,[54] to the proteins as finite state machines.

The objective of modeling a viable system requires, at the very least, sustainable dynamics. In this case, that implies a closed system with a compliment of ionic pumps, restorative of, and sustaining, normal ionic gradients across the plasma lemma. This project is intended to move the art beyond prior tendencies to impale the neuron with micro-electrodes and then to, in effect, model its death, or to treat ionic concentrations as infinite sinks, or record only the effects of injecting electrons into an otherwise ionic circuit. It also recognizes the topological relationships between ion channels and bifurcations in the dendritic arbor. It strives to support a number of emergent phenomena, including propagation, capacitance, refractory periods, resistance to antidromic conduction, and poly-channel behaviors like resonance and burstiness.

2.12.2 PRIOR ART ON LIQUID STATE COMPUTATIONAL MACHINES

Heath in 2000 discussed step by step enzymatic processes, as chemical machines.[55] Kaminski and Wojcik proposed a liquid state approach to artificial retinas.[56] [57] An M.S. thesis by Vreeken at Utrecht University described temporal pattern recognizers in the liquid state.[58] As yet there is no literature on BNN's construed as liquid state information processors. This project seeks to found the field of liquid state information processors with a firm foundation in physical first principles at the molecular level.

2.12.3 END USES

Information processing events at the molecular level of a single neuron are to be modeled and packaged as an input/output device, such that multiple instances of this model can be wired together, via synapses, as per a connectivity matrix, to simulate local circuits. Libraries shall be kept and accumulated for the various interactor, actor and compartment types, for re-use.

2.13 EXTRACT

There are 4 main areas of effort in this project: Physics, Modeling, Informatics, and New Concepts.

The physics concerns particle systems, surfaces, kinetics and transport. The modeling concerns geometry, homogeneous surfaces, computer graphics, numerical methods, and multi-scaling. The information theory concerns transduction, leveraging, diffusion, differentiation, stochastic processes, integration, and waves. New concepts

include liquid states information processing, continuous capacitance as a conductor, particle wave transmission, designer kinetics, molecular pattern recognizers and generators, and hybrid analog digital (HAD) system computation in the wet.

3 STRATEGIES

3.1 MASTER QUERY

Q: Can a software model of the neuron be designed suitable for the study of ion channel and ion pump distributions in 3-space, sufficient to generate the input/output information function predictive of the behaviors of a particular living neuron or type of neuron?

A: It would require a synthesis of the necessary and sufficient processes of:

1. diffusion and drift of ions in aqueous solution
2. kinetics of channels, pumps, receptors and vesicles, and their resultant transport functions
3. electrical voltages and currents of extensive capacitance in 2-space and resistance in 3-space
4. topology that preserves the positional relationships of elements via analogous shapes

3.1.1 COROLLARY QUERIES

Q: Can the set of all extent neurons be parametrized such that a general model can be designed to span the domain space of those parameters?

A: The complete parametric space of neurons is not yet known. However sufficient data has been collected and analyzed that models are approaching (asymptotically, it is presumed) the performance of living cells. A base model must represent: dendritic synapses, dendritic arborization, soma, initial segment, axon, nodes of Ranvier, and axonal synapses. This base model must be built of the physics of diffusion and electrodynamics, and the chemistry of kinetics. The base model is then modified and expanded parametrically spanning the measured performance of living cells. The base model must be amenable to new features as more becomes known about membranal systems.

Q: What superfluities may be purged to reduce the computational load of the model?

A: First, to include only those mechanisms which are the high runners in the causal map between input stimuli to the neuron and that neuron's output. Second, to incorporate such numerical algorithms and heuristics as developed

by computer scientists that most faithfully perform the desired tasks via minimal computational load. Performance tests will be necessary to demonstrate the veracity of each such method.

Q: What are some of the methods by which the model can be made efficient enough to be realizable?

A: Coding efficiencies at the machine level are inherent to any modern computer language compiler. Compression strategies reduce the quantities that have some quality of redundancy to them. Shapes can be simplified so long as the nearest neighbor relationships are preserved, and the relative distances between them. Various cytological obstructions to diffusion can be imitated by increasing the viscosity of the cytological fluid. Bases can be converted from Cartesian to spherical to resolve collisions. Data can be normalized and held in units most convenient to the CPU. Computationally awkward configurations can sometimes be transformed. Biological complexities that are of low consequent to the flow and processing of information service that the neuron performs can be purged. Some problems are divisible into sub-problems, so as to eliminate memory overflows, by reducing the focus, scale and scope of each piece. Then results can be reassemble, re-scaled to the whole.

Q: What approach would proceed toward optimal (or at least competitively fruitful) models of neuronal information processing, available at this time?

A: To fully employ currently available digital computers, and to best prepare for those more powerful digital computers likely to become available in the short term, massively parallel processes can be addressed directly. Large scale depictions of information flowing through the neuron would entail large numbers of states, large numbers of links between those states, and large numbers of transition rules for changing states. Each molecule of informationally significant types can be instantiated for its information role. Thus the physical basis of life at the molecular level is nearing tractability. Because life is necessarily built of, and organized at, the molecular level, it is desirable, perhaps necessary, to found the modeling effort at this level. Because life is also organized at progressive levels above the molecular level, it is also necessary to accommodate a multi-level model. Every level of organization should be consistent to the known biology. This generally involves concepts of sub-assemblies, then assemblies, all arranged in a connection grid. Connection networks inevitably gives rise to feedback loops, which in turn give rise to behavior.

Q: What are the likely limitations to this approach?

A: The quantities of ions, channels and pumps in 1 neuron are significantly greater than can be individually modeled by currently available computers. Multiple simplifications will be necessary, justified if such simplifications can be demonstrated to yield substantially the same results as would the full quantities *in vivo*. Sampling theory is useful in justifying quantity reductions.

3.2 PERSPECTIVES

The first step in modeling is to set forth the criteria by which all possible elements and processes are rank ordered for importance of inclusion. This is the same criteria around which all representations within the model of elements and processes will be optimized. This criteria deserves careful thought, as it determines the nature of the model. If a model is expected to yield emergent behavior, then its kernels must be precise and complete.

The prime criteria that defines this project is neuronal information processing (NIP) service. This concerns 2 fundamental roles of neurons: Computation, whereby many input signals are processed into a smaller number of output signal patterns; and Connections to other cells in ways that imply timing and positioning of output signals. The literature is more prolific on the matter of signal transmission than on signal computation, probably because the mathematics of transmission lines is well established (cable EQ, information theory, and the Hodgkin Huxley studies). Bio-computation is still a nascent field, with little yet proven to serve as settled art. Nor are there crisp definitions as to what exactly constitutes information processing operators in biological entities. Neurons clearly are not digital processors, and so the computer sciences are as likely to mislead as be helpful in the characterizing of bio-computation events.[15] For example, 1 leaky bucket mechanism is a transient summer, an integrator, and an averager, all depending on when you read the output value.

The conceptualization of biochemicals as information processors and information carriers requires an interesting perspective that is not widely voiced. Let us start with a simplest case. Proposed is a water/ice integrator. Given a fixed mass of water at 0 degrees Centigrade in a near-perfectly insulated container, then any heat removed from the system would result in the formation of a precise amount of ice, 0.0003 g/J. In such a system weighing the ice would answer the question “How many Joules of heat, net, have left the system? Each gram of ice indicates 334

[15] In a neuron, there is no clock, no wires, and only one large capacitor. Its power source is distributed. Conduction takes place in contiguous 3-d liquids, and there are at least five flavors of charge. Gating logic is driven by thermal noise. There are many mechanisms of modulation. There is rapid turn-over of the gating elements (short life span). The architecture is in a constant state of reshaping. Communication between cells is chemical.

Joules. It is a very accurate integrator, albeit with an upper and lower limit to its range. This measuring device can be augmented with a steady known heater, melting the ice at a steady rate. Then the device would act as a leaky bucket integrator. It would be measuring heat removed at a rate above some set point (equal to the Joules injected by the heater).

Let us now move to an analogous computational system of salt water in two compartments, with an ion pump between them. We will pump ions rather than heat, so instead of analog temperature scale we have the discrete count of ion particles to measure. Let the initial conditions in each compartment be: 1 liter of 1 molar NaCl. Let the pump transport ions individually between the two compartments, leaving the water where it is. Then the tonicity in either compartment, at any point in time, represents the integration of the pump flows. Given a pump that can run at a variety of speeds and in either direction, the resultant tonicity can be subtracted, divided by 2, and multiplied by Avogadro's number to get the net quantity of ions pumped. In a realistic case, both negative ion Cl and positive ion Na would need to be pumped to avoid the very large forces of charge separation incurred when pumping against the EM force. Electrogenic pumps do a lot more work for the same quantity of particles moved, so we shall not do that here. We use an electroneutral cotransporter.

Next, let's add a small permanent pore between the compartments. Then our system would constitute a leaky bucket integrator, analogous to the ice system with a heater.

Next, let us elaborate our processor by setting the pump to a steady rate of ion transfer, and add an adjustable valve that for each setting allows a rate of “leakage” across the membrane. In this arrangement, a rapidly varying valve position constitutes a “signal”. The tonicity of the compartment then may be seen as a “moving average” of the ion flows through the valve. We could have varied the pump rate while holding the valve at a constant “leak”and gotten the same effect, but for practical reasons it is easier to open and close a valve quickly than it is to vary the pumping rates quickly. We can transmit higher frequency signals with the valve, but interpretation is a bit more difficult. A simple valve allows flow through it proportionate to the pressure differential across it, and that pressure accumulates to higher values when our “signal valve” is open less.

Additional complexity is introduced when we separate the way the cation and anion are transported. Suppose that the Na is pumped, while the Cl is passively “leaked” through a second valve with a flow rate equal to one half that of the Na pump. In this manner, a charge differential accumulates to the extent that the signal valve does not pass a

quantity of cations equal or greater to the Cl leak quantity through the leak valve. The charge differential constitutes a voltage across the membrane, which may also be used as a signal. There exists a mathematical transform that converts the input signal of the valve position into this voltage signal. This arrangement is also referred to as a "leaky bucket" or decaying average.

So far, these processors convert 1 input signal to 1 output signal. Can 2 independent input signals be operated upon so as to generate a unique output signal? Suppose there were 2 different types of Na valves, each controlled by a mechanical linkage to outside the system. If 1 of these modulated valves was moved only rarely or slowly, it can be said to add a bias flow to the signal of the other valve. If both valves are changing positions at similar speeds, then there is an additional parallel operation taking place. Subtraction could be accomplished if one input was an Na valve and the other input controlled the rate of Na pumping against the gradient. When ever the quantity of cations moved is not equal to the number of anions moved in the same direction, we have an electrogenic process. The results of electrogenic process can be measured as q = voltage* capacitance; where q= net quantity of charges moved.

All the above are linear systems. If we add yet another valve that passes only Na, but its position (fraction of opening) is controlled by the voltage accumulated by the system, then what would be the transform function? The voltage is a sort of feedback of the accumulated concentration differential. If increasing voltage gradually opened this second valve until it passed a quantity equal to the pump rate, then that would set an absolute limit to the pump's ability to accumulate voltage. Such a valve would act as a "relief valve" or high limiter. The combination of the two valves sums to a non-linear relationship.

A voltage low limit would not be quite so easy because it would require our signal valve to shut completely whenever the voltage dropped to the "low limit". This would require a series mechanism, most easily realized by a channel with two gates. One gate would be the normal signal modulator as described above, and the other would close when ever a low-limit threshold was crossed. The combination of a high and low limit tend to produce sigmoid response curves. These are noteworthy because such curves are prevalent in biology, as self regulating (homeostatic) processes.

While the sigmoid curves essentially flatten the input response, it is possible to go the other way, to accentuate the input. If a small change in input signal results in a large change in the output signal, we can say that we have an

amplifier, or we could say we have an excitable system. Man-made amplifier circuits usually are designed for linearity, while many biological excitable membrane tend to perform with distinct nonlinearities. In fact, there are two general types of neurons: those with graded responses and those with action potentials. The graded responses are near-linear, while the action potential generator closely matches the functioning of an analog to digital converter (A2D). An all-or-nothing response is an acute nonlinearity. Thus, process of digitization is highly nonlinear. Note that a point of confusion arises when the digital pulse generator produces a pulse rate proportional to the analog input magnitude. In this arrangement a very nonlinear process is used to produce a quite linear response curve, albeit in a different format.

In the simplest A2D case, an analog signal voltage is transformed into a "spike" rate. Accordingly, many modelers were content to model the neuron as linear summers on the dendritic side and as A2D converters on the axonal side. When observing neurons at the molecular level, it was found that the mechanisms in play are much more numerous and much more varied. Ion channels and ion pumps both number in the thousands per neuron, and there are dozens of types. If all that was transpiring was a linear A2D process, then 1 or 2 types of channel would have been quite sufficient.

Popular amongst physicists is a way of approaching the complexity of molecular systems by considering how earthquakes work. They are characterized by very slow accumulations of energy, held from escaping by some "stiction". At some point the accumulated potential energy exceeds the stiction, and sudden movement results. This releases a large portion of the potential energy until things settle into a relatively "relaxed" state, quiet and slow enough for stiction to set up again. And the process renews. It is very difficult to predict the precise moment of the release. The earthquake is thought of as not having an input signal, only a steady injection of energy into the system. They are capable of generating erratic spasmodic behavior autonomously, given only this steady pumping in of energy.

The precise moment of the beginning of the release is called the criticality. The precise moment of the first ice crystal in water being chilled is another criticality. Such critical behavior requires a barrier of some sort, that gives way when potential energy builds up too much. The physicists call this the "partition function". This function is characterized by this trait: at the criticality a local disturbance can propagate throughout the entire system. This

implies that at this brief release period, all elements are tightly coupled, while at most other times they are hardly coupled at all.

It is interesting to note that such partitions can be in space and/or in time. A membrane is an obvious partition in space. When pumps operate at $1/1000^{th}$ the transport rate of the valve openings, the two processes are partitioned by their difference in time constants. If the valve openings can be triggered by disturbances in adjacent valves, then the pump-valve system exhibits criticalities. Neurons have such elements and resultant behavior. A signal can propagate through a system whenever there is one or more paths (connected nodes) of at-threshold potential energies. There need not be a defined pathway of propagation. Critical systems usually percolate through multiple semi-random paths, a changing subset of all possible paths. In the absence of an input signal the various nodes tend to release randomly, and will also propagate to their neighbors to (randomly) varying chain lengths. Such systems are "at the brink" most of the time, and can be exquisitely sensitive to external disturbances, unleashing the total store of energy in response to a tiny perturbation. The system "quiets down" after each release, until the pumps can rebuild some pressure. An excitable system may be described as being refractory during this after-potential phase.

Despite the chaos described above, a quantity of such mechanisms operated in parallel can often perform as reliably as a single linear deterministic mechanism. That is, multiple chaos processes in parallel can be wired to emulate determinism. The law of numbers is in effect. Thirty random processes giving way to release their energy at random times can all sum to a beautiful ramp function. Or to an exponential function. The quantity of parallel redundancy can be adjusted to achieve arbitrary accuracy to the linear function. Achieving and maintaining 99% repeatability is quite easily accomplished. And as few as eight random processes in parallel can generate a linear signal adequately precise for most organismic purposes.

Another feature of parallel random processes is that as a group they can multiply their top end frequency response over what they can detect individually. Stochastic resonance is the ability of large numbers of parallel random processes to tune to certain frequencies, yielding a characteristic frequency spectrum. This arrangement can be likened to a noisy electrical circuit, in that the circuit resistances and capacitances are determinant factors in the resonant frequencies. However, in biological systems the thermal noise is harnessed as an energy source. The noise reduces the stiction, which increases the response frequency, and the accidental phase locks with different peaks

allows the group to pick up all of the peaks where a single actor may be fast enough to only pick up ½, ¼, $^1/_8$ or $^1/_{16}^{th}$ of the peaks.

The temporal partition functions of the neuron are the ion channels. They are variously configured to undergo strong nonlinear changes in response to mild temporal inputs. There may be a small voltage band that triggers an ion channel to open.

Random processes, of course, are not restricted to uniform distributions between 0 and 1. They have achieved great utility by employing rather unique distribution patterns and then being able to significantly modulate that pattern. These distributions express as characteristic responses, and modulating them to alternative distributions express as modalities of performance. This goes far beyond the textbook techniques of fiddling with the mean, variance, curtosis and skew.

These observations lead to identification of the linkage between nano-processes and the macro-processes. At equilibrium, macroscopic variables will evaluate to the same solution as the microscopic variables will. Thus, the plethora of macroscopic equations in the literature being applied to neurons. See, for example Johnson & Wu's textbook teaching neurophysiology from a macro point of view.[59] However, the essential function of the neuron requires it to be in non-equilibrium states to create and delivery information; and the information may not exist at all at the macro state where it may be averaged to zero. To secure the information, the system must be modeled at the molecular level, instantiating each molecule. Non-equilibrium states are of the essence in neuronal mechanisms, and so representations which aggregate nano events into macro behaviors will not be able to demonstrate how information is processed.

Let us return to our construction of a liquid state processor. Nonlinearities may serve either as regulators or serve to make the system excitable. Regulator functions are negative feedback functions, and exhibit inherent stability. Excitable functions are positive feedback functions, and are inherently unstable. Instabilities are dangerous to organisms unless they are strictly limited. This implies that for every excitability function there is at least one over riding regulatory function. For example, many Na and Ca channel types are excitable. If these channels were simple positive feedback loops, they would bleed the neuron of its membrane voltage and in effect kill it. The limits to excitability may be: depletion of the particles in flux (fatigue); a complimentary compensating action (e.g. the K channel, which moves positive charges in the opposite direction of the Na channel); or a kinetic cascade of

conformations within the channel itself that simply makes it impossible for the positive feedback circuit to continue (self timing the event, as the Na channel fourth subunit does), or inherently unstable (short-lived) excitation events (as the first 3 subunits do in the Na channel).

Noise and instability are closely related. It is usually noise that initiates an instability event. Working at the macro level (human scale), engineers have considered noise to be their nemesis. Biology, having evolved at the nano scale, is thoroughly immersed in thermal noise. Biology "considers" it to be the force that renders everything dynamic. One of the great differences this makes is that biology harnesses thermal noise as a ubiquitous energy source, to provide continuous liquid state transport and continuous conformational change.

In such a dynamic environment, the key to design is selective partitioning: a sort of management system for ubiquitous and continuous transport and kinetic activity. Better put, biology is made possible via optimal partitioning.

Spatial partitioning is provided by the lipid membrane, which sets up the hydrophobic/hydrophilic gradients and transitions. Such spatial partitioning determines shape, which in turn determines connectivity with one's neighbors. This is another conceptual inversion from the macro to the nano: that the partitions might determine the connectivity.

Temporal partitioning is brought about through many mechanisms, beginning with ontology (genetic operons), expanding fractally to organismic life cycles and ecosystem evolution. The temporal partitioning of interest regarding NIP is that of ion channel kinetics. Of secondary interest is the durations of each of the events in the cascade of information through the neuron from tip to tip: bindings, releases, diffusion, and conformational changes of receptors, channel gates and refraction, pump cycles and vesicle releases and reconstruction. In the case of the G-protein systems, there is also a rate of catalysis that is critical to the fan-out speed of signals.

The concept of a liquid state processor may harness the strong nonlinearities of excitability so long as safeguards are in place to limit that excitation and restore the steady state quickly thereafter. If biology had not been able to incorporate sufficient redundant safeguards against runaway positive feedback loops, then life would be fragile indeed, prone to self-destruction. So critical is it that positive feedback loops be checked, neurons employ at least 4 mechanisms to restore the steady state after a Na influx due to channel opening. First, the channel itself has a

subunit, (named “h” by Hodgkin and Huxley) that shuts down the channel after only a few milliseconds. Second, there are K channels nearby, which are triggered by the depolarization effect of Na influx, to counter the cation influx with cation efflux. Third, the Cl leak channels allow anion flux to compensate for charge imbalance across the membrane, thus easing the amount of energy necessary to reset the cations. This Cl flux often passively parallels the Na flux, reducing the electrogenesis of the Na flux, which in this case mutes the depolarization effect. And fourth, the ion pumps are constantly at work towards restoring the steady state (membrane resting potential). The Na channels are only viable when their open times are small enough that the integrated Na influx due to all channel openings (summed with all other Na-influx mechanisms e.g. co-transporters) is less than the pumping capacity of the Na pumps. As a practical matter, it is easier to limit the firings of the Na channels than it is to increase the metabolically expensive pumping capacity.

The addition of pumps create a need for an energy source for the liquid state processor. Providing energy, packaged and transported as ATP molecules, to various actors allows for the active processes of signal amplification, signal modification and system sustainability via reestablishment of steady state conditions after every perturbation. The ion pumps are therefore working as active compensators.

Although pumps are necessary for electrogenic transport, the intricate gating service provided to the neuron by the ion channels, namely the high speed openings and closing in response to complex stimuli and parametric changes, is operated mostly or totally by thermal energy. That is quite surprising, especially when contrasted with solid state gates in silicon computers, which are physically bound to consume great amounts of energy in gating and thus generate great amounts of heat. Neurons, of course, are not driven exclusively by thermal energy, as thermodynamics requires that chains of chemical and physical events acquire their directionality via increasing entropy. But the most crucial part, the logic gates, are driven by thermal energy, at no caloric cost to the cell. And this fact, combined with the “free” conduction of liquid diffusion, allows the entire human brain to operate on less than 25 watts.

The next feature we can add to our liquid state processor is modulation. The gates may have their opening statistics altered in several ways: Frequency response may be altered. The refractory period may be lengthened (forces ignoring the near term input pulses). If the modulator is quick enough acting to match the original signal, then the

modulator signal may be multiplicative to the original signal (as it is in analog solid state gates). We now have a multiplication function.

An input signal may be excitatory or inhibitory. Inhibition can be accomplished by opening Cl leak channels rather than opening Na channels. Or it could be accomplished by an allosteric binding site on the Na channels that requires larger perturbations to the Na channel to get a channel opening. Either way, we now have a subtraction function. There are many other ways to inhibit. Almost anything that breaks the excitatory chain of events can be called inhibition.

A chain reaction of channel openings can be accomplished when the flux through one opening serves as the trigger for the adjacent channel to open. A flux of charged particles constitutes a current. A current necessarily alters the aggregate charge on each side of the membrane. The altered charge ratio alters the voltage generated across the membrane. This change in voltage, also a pressure, is remotely sensible by those large molecules which traverse the membrane and have asymmetrically distributed charges affixed within them. Whenever the output signal is greater than the input signal, fields of such mechanisms could generate chain reactions, as reverberations that would not stop unless there were some damping or limiting mechanism present as well.

Ion channels usually include a mechanisms to shut down the channel. They do not hold open as long as there is a stimulus, nor do they stick open beyond the stimulus time. The primary closing mechanism merely closes the gate. The secondary mechanism renders the channel unresponsive to future stimuli for some duration of time, called the refractory period. This is interesting both for its internal effects and external effects. Internally it creates a period of silence thereby enforcing a separation of stimuli. This would be necessary if the ion channel were acting as a pattern recognition device, for which a start and stop code make the recognition function far more efficient. Externally, it silences the channel just after a wave front has passed over. Without such refraction, there could be no directionality of disturbances, and therefore no propagation. The neural membrane would just be a dance floor with all kinds of actions and interactions, but no net movement from in-port to out-port.

We can further enhance the computational power of our liquid state processor by building kinetic schemes within the channel that require temporal patterned input to get a response. Kinetic schemes with greater than 2 or 3 states have the potential to generate a patterned response. For example, one can design a channel that requires, as a stimulus to open the channel, a two-spike pattern with a certain temporal spacing. Subsequently, the channel could be designed

to output a triple opening pattern. This maps a unique input pattern to an arbitrarily different output pattern. It implies that the channel is in the pattern recognition business and in the pattern generation business. As channels have been found to have more than 30 states, there is adequate state space there to accommodate both of these. It remains to be investigated the extent of such phenomena in nature.

And finally, for completeness, we will consider spatial patterns. The distributions channels and pumps are neither uniform nor clustered - they apparently are distributed in elegant patterns that reflect function. Although the synaptic receptors and vesicles are clustered at the boutons, what happens over the rest of the neuron is more complex. It is the purpose of this model to enable the investigation of the consequences of various channel and pump patterns upon neuronal information processing. For example, varying the types and quantities of channels in the dendritic tree can support or thwart antidromic conduction. The layout of the channels over the vast topography of a neuron *de facto* gives us gives spatial patterns. The question is, what consequence do such spatial patterns have upon the temporal performance of the channels, and how do they act in concert to process spatiotemporal information? Can a single neuron, due to such spatial patterns of channel layouts, perform special pattern recognition?

This work is an independent effort, not an extension of any known strategies or frameworks for mimicking the information through a 3-d shaped neuron. It is therefore burdened with significant “re-inventions” of computer functions for geometry, physical principles, electrical circuits, information theory, stochastics, topology, and graphics - into an integrated coherent whole. At the onset, it was expected that most of this art was already completed, stable, computationally efficient, portable and available for reuse. Unfortunately, searching, translating, testing, and integrating such pieces (when indeed they existed), took more time than simply writing them “from scratch”. Integration of such a diverse collection of functions is a major challenge, and there was no hope of finding other people's work gleaned from diverse fields that was inter-operable.

This work is a multidisciplinary hybridization of biologics, engineering, physics-based computer graphics, stochastic systems, electrochemistry, statistical mechanics, and small amounts of topology. It is intended to advance computational thinking by scaling up the parallelism of neuron sub-elements consistent with the biology, and providing a software platform for studying neuronal function and design in a high dimensional parametric space. A library of algorithms simulating physical phenomena are provided at a level consistent with numerical methods

optimization. That is, the simplifying assumptions are “leveled” so that the precision is maintained with equal rigor across the model library.

It is intended that this whole-cell model serve as elemental to the development of Designed neurons, and that these can be assembled into local-circuit canonical forms for neural networks.

3.3 APPROACHES

Biological models have traditionally been regarded as parsimonious representations of the system under study so as to yield an answer to a singular query. Such minimalism was advocated to ease the human effort of model construction, require a minimal computational load when such was expensive in time and resources, and to present an unfettered case of a particular mechanism with all other influences stripped away. After some set of bare mechanisms has been accumulated and exercised, interest grows in assembling these mechanisms as they are connected and interact in living cells. As digital computers advanced and enjoyed gradual reductions in cost, and the science of software algorithms advanced for increasing re-use and generality, the quest for general models became feasible. Let's define a general model as a persistent model that can exhibit multiple behaviors, and therefore answer multiple queries, accomplished by only changing the parametric values that drive the model. (as opposed to having to rebuild the model with each different query). This general ability is ideally expanded to fill a defined parametric space (corresponding to physiologic ranges). The over all trend of science might be summarized as an evolution from simple, short sets of analytic closed form equations, towards an exhaustive, large scale, open-ended representation of a whole system. This expansion is taking place not merely in quantities of elements, but also expanding down-scale to the atomic level (or sub-atomic if those processes are relevant to the system under test).

3.3.1.1 Analytic Approaches

The history of science is for the most part the history of analysis. The greater quest has been to discover the most prevalent patterns of nature, and reduce them to the simplest mathematical representations, traditionally called laws. This act of cutting the problem down into simple calculus problems relies upon the redundancies and homogeneity of nature, and goes on to represent all of a type as though there 1 instance of that type was sufficient for questions of

science. Alternatively, the aggregate group behavior generated a quite different stimulus-response pattern from the singular instance, which was regarded as more valuable than singular studies. Thus, trillions of gas molecules in motion could be reduced to a single scalar, temperature. The material called steel could be reduced to a compression strength, a tensile strength and a shear strength. The macro world view necessarily works with measures of aggregates.

We might ask: Given that analysis means to cut, just what is it that's being cut? It must be the links or relationships between the smaller parts. It must be the more intricate and subtle forms of organization. Although the defining characteristic of information is changes in state, a pronounced secondary characteristic is its portability, its transmissibility. This implies links or channels of communication. The utility of information stems from its conveyance from a source to a user. So might the act of cutting in analysis sever those lines of communication, so essential to information processing systems? If the purging of redundancies and the cutting of higher order relationships is performed in analysis, then might analysis be the wrong approach for the study of information flows through the neuron?

As the scale of examination has been reduced down toward the atomic and subatomic levels, the analytical forms based in continuous math begin to fail. The quanta effects are categorically not continuous. At the atomic level things become much more discrete, and there one is forced to reconsider what analysis means. Need one only shift from continuous math to discrete math to continue on downward? Or does one reach the bottom of analysis, after which it is most fruitful to undertake the return trip, the journey through synthesis?

What analysis taketh away, might synthesis restore? Synthesis is the stepchild of science, most often written off as technique, or as engineering, and therefore not “pure”. But synthesis has played a role all along in science, albeit not as prominent of one. Considerable synthesis was necessary to design and produce the instrumentation and apparati that enabled a lot of the experimentation. More to the heart, the act of interpretation of experimental results subsequent to any analytic investigation is indeed synthesis. To understand any system requires both the characterization of the elements and then the reconnection of those elements to the point where they generate predictive behavior. In the past that was called interpretation. As systems science has matured and computational machines grown, that work is now more often done as modeling. Modeling is the hard science that has vanquished the soft science of pondering possible interpretations of the empiric data. Modeling improves on the static logic of

text by offering dynamic demonstrations of logic in full flower, developing and evolving complex forms, including living forms. The logic of Boolean algebra is not robust enough to represent the varieties and distributions of living processes. It has often led to erroneous conclusions when so applied. However, stochastic systems has come to the rescue, opening up the severe limits of 0's and 1's to the colorful PDFs so abundant in nature.

With the physicist's development of quantum theory in the first half of the twentieth century, and its implications of uncertainty, leading to complexity theory - it dawned on most workers that determinism was incorrect. Especially Godel's proof made this conclusion unavoidable. This opened up a conceptual space for bottom up models of physical systems, indeed of the universe. That very act we can call synthesis. The probabilistic assembly of things (subatomic particles, atoms, molecules), brought attention to the self-organizing qualities of matter. This was furthered by general systems theory and its stochastic variants, which in turn reached upward from physics into chemistry and biology.

Modeling is often defined as an exercise in parsimony. We set up constraints. We do linear programming. We exclude components that are deemed to be of low significance to the desired outputs. We often squeeze out the variance so as to employ ideal equations to represent non-ideal reality. Models will fall short of expectations when they analyze out what they seek to observe; when they collapse the variance of a population into an aggregate form.

But there are alternative approaches to modeling. One is to employ generative equations that give rise to immense complexity emerging from their own simplicity. Two very simple equations can interplay iteratively to create nearly infinite complexity. This observation led to the development of the field of fractals. The essence of fractal patterns is that there is an additive equations counterbalanced by a subtractive equation. The subtle net value between these two can flutter into very large scale patterns. Biology, of course, is also generative; from compact, simple, static DNA, to proteomics, to living cells. Within a nervous system, a simple excitatory mechanism plus an inhibitory mechanism can synthetically create nearly infinite patterns. Then might not such generative processes be relevant to the study of neuron information processing and transmission?

Analytic models have oft encountered limits. They fail at the 3-body problem, to say nothing of a particle system of say 1 million charged particles with size and mass. They fail at the inherently nonlinear and dissipative nature of living systems, as analytics tends toward the linearity of its base methods. They fail at encounters with

discreteness, which appear as singularities. They fail at the uncertainty of outcome distributions. They fail to generate the emergent phenomena that are rife in biology.

Biology does not require dualism - that is, it does not break the laws of physics nor exempt itself from them, nor even transcend them. But biology is synthetic, building up elaborate layers, meta-layers, rich coupling and feedback loops. And accordingly, to establish these phenomena within a model is an exercise in synthesis, not analysis. Yet we still find most models of biologic phenomena employing analysis, so as to simplify the challenge and reduce the computations. For these and other reasons, it is deemed germane to this project's objectives to build up from physics first principles processes and allow them to run free, to see what they can do.

3.3.1.2 Exact Solution based Approaches

Exact solutions overlap with the analytic approach. They are closed-form equations models well suited for the study of properties of materials, and to a lesser extent properties of waves. They characterize entities effectively, by abstracting the repetitive patterns of those entities. This, of course, requires deterministic concepts and equations. Even as statistics evolved over the second half of the nineteenth century, the objective was to yield exact solutions, usually the moments of a set of points: mean, variance, skewness and curtosis. Then the particular form of distribution pattern could be selected: uniform, Bernoulli, binomial, exponential, gamma, Gaussian, Poisson, Boltzmann, Cauchy, Weibull, etc., so long as one is satisfied with a parametrized set for a solution.

Conveniently, the mathematics of stochastic equations, the handling of systems of random variables, reduces to partial differential equations. These perform not as a short cut nor approximation, but are complete. Nonetheless, they work with the aggregates, not the particulars. They do not attempt to represent instantiated particles within a large scale system.

Concerning biology, how many such layers are there from atoms to whole cells? Atoms spontaneously form chemical systems that evolve into ever greater complexity. Modeling the neuron requires a multilevel representation: ions, molecules, molecular state changes, molecular networks, membrane surfaces, compartments, shapes. At every physical level there are novel patterns of interaction and association. Between every two adjacent levels there is a transition of chaotic behavior. This interface (which generates chaos) gives rise to stochastic systems, but it also creates an information barrier between layers. This is why no one layer can serve as the sole

basis for any other. Every layer is a stochastic system to the extent there is variance. Some types of query can justify simplification to exact solution analytic equations, as PDEs. But tracing information processing is not one of them.

The intent of exact solutions is to apply analytic EQs which represent the aggregates. They are therefore deemed inappropriate to this project.

3.3.1.3 Geometric Approaches

The field of anatomy is heavily invested in the shapes of things, but it is a static study. Physiology, biochemistry, pharmacology and genetics do not normally consider the matter of shape as germane to the processes under their study. As greater biological complexities are tackled, shape does become significant, even within these fields. The caveoli alter diffusion patterns. Bifurcations in the dendritic arbor alter propagation. Drug delivery is determined by the shapes of compartments and the flow patterns those shapes dictate. And of course, shape is determinant in connectivity of one neuron to its neighbors. The changing shapes of the developing and "learning" synapse may be dominant determinants of function. As modeling builds towards large scale representations, shape becomes a necessary consideration.

Although the mathematical basis for the several geometric systems is presumed to be well understood and complete, geometry is not as model-ready for neuron information processing as was hoped. The requirement for a homogenous membrane (of consistent graininess throughout) disqualifies all Cartesian, cylindrical and spherical coordinate systems. Topological approaches are necessary. Geometry is a necessary aspect of neuronal modeling because it establishes the nearest neighbors between all the actors, and the thickness of the saline above and below the membrane. It is the carriage upon which all else is affixed.

The strong nonlinearities of membranal system dynamics may produce spatial regions that appear continuous but none-the-less form functional separatices, whereby the activities on one side are partitioned away from the activities on the other side. This is found, for example in the star burst amacrine cells of the rabbit retina, where one cell acts functionally like 12..16 separate cells, related only by their radial positioning.[60]

The dimensionality of a model neuron is not simple. There are 3-dimensional volume processes, e.g. diffusion. There are 2-dimensional surface processes e.g. capacitance. There are 1-dimensional processes like axonal transport. Each will require separate mathematical treatment. And then there is a need for some manner of integration of these three into a working whole.

3.3.1.4 Topological Approaches

The morphometric studies of neuron shapes and connectivities enlisted several geometric approaches, the main problems being the statistical algorithms to connect the microtome slices for 3-dimensional reconstructions, and to what resolution texture can be captured. A static shape can be captured down to a resolution of about 1E-8 m in electron micrographs, and this data may be represented in digital form. The computational load to maintain such a neuronal 3-dimensional surface in a dynamic model is enormous, and such resolution of shape is not yet practical.

Neurons consist of several volumes made distinct by closed surfaces. The cell, the endoplasmic reticulum, vacuoles, vesicles, and other compartments. A neural shape represents a compartment or container, to be bathed in aqueous solutions on either side of the surface. Of the essence for particles in motion is the volume shape and the detection of collisions with the boundaries of each container. The biological data of cell shapes is often "smoothed" via software filters. Reducing the tortuosity makes the surface more differentiable and requires less computational load to represent it. But care must be taken that the loss in area does not alter the characteristics of the system, especially capacitance.

Topology may lend its methods and justifications for certain simplifications of the shape that retain essential characteristics. Topology is a necessary but not sufficient aspect of neuronal modeling. It is of great service in determining which shape simplifications are justified.

Projections can collapse 3-dimensional space into 2-dimensional space, assisting in computational load reduction. Manifolds, among their many salient characteristics, are concerned with mapping or projecting a surface in 3-space (or N-space) onto a 2-dimensional plane. The distortions of such a transformation are minimized by restricting the portion of the surface to be projected to that which is most parallel to the plane of projection. A series of such projections created to variously oriented planes, such that no one of them suffers perpendicular areas nor folded areas. These matrices are then "stitched" together via links at their adjoining edges. The more torturous the shape,

the greater quantity of such projections are necessary. The benefits of reducing the dimensionality to two, are offset by the artefactual overhead of transitioning between the various planes of projection. Simplification of shape to a convex surface can reduce the number of projections to six in a Cartesian frame or to four in a tetrahedron frame. To what extent such simplification is justified depends upon its ability to preserve the nearest neighbor relationships, comparative model performance, and acceptable levels of error.

3.3.1.5 Dentograms

One form of abstraction or parametrization of the dendritic arbor measures the lengths of each leg, the bifurcation points, and the synapse locations along these legs. The visualization of this data usually lays all dendrites parallel, with a small lateral offset at each bifurcation. Diameter data may also be preserved. This scheme works best when all the dendrites converge to single trunk at the soma. This is essentially a method for collapsing 3-dimensional data into 1-dimensional representation. It is especially convenient for studying the effects of bifurcation locations and density, but does not offer much for the soma and axon. It also offers no adequate means for preserving the inhomogeneities of channel and pump distributions along the dendritic surfaces. This technique, though instructive in visualizing the bifurcation patterns, may have purged too much information to find utility in models of neural information processing.

3.3.1.6 Tiling

If electron communication was involved in NIP, then the whole of the contiguous extracellular fluid would be implicated, and the whole of the contiguous intracellular fluid as well. For that to be the case, there would need to be an electron source, such as an electrochemical battery, driving the system. What is found, however, is that charge movement occurs by ion flux through ion channels and ion pumps. Considering the speed of the neuronal response (1E-3 s) and the inertia of the ions known to be involved, it is probable that only liquid components very near the membrane are involved. This would allow NIP models to be construed as a 3-layer sandwich of saline-membrane-saline. Some thickness of saline could be chosen, arbitrarily thicker than known ionic involvement in an action potential, and from that a “standard model” of membranal NIP could be designated (e.g. 5E-8 m thick extracellular saline, the membrane, and 5E-8 m thick intracellular saline). If NIP is accepted as primarily a phenomena of the plasma lemma and its 2 para-membrane solute blankets, then models would necessarily focus on this laminated

“surface”, i.e. treating NIP as 2-dimensional phenomena (sometimes referred to as a 2.5 dimensional model. This lends itself to divisions of unity for surfaces. Each resultant from the division of unity is called a “tile” or a “patch”.

In the pursuit of the molecular basis of NIP, high levels of detail are required at the smallest scale. It is therefore convenient to “zoom in” to model small portions or patches of the cell surface. This affords the computational power to model every particle and molecular protein within that small volume. Given that the neuron is a densely coupled system, the primary challenge with the patch is the boundary conditions.

The simplest solution is to fold the upper edge to the lower edge and the left edge to the right edge. This creates spatial periodicity (as an artifact). Though computationally efficient for characterizing certain behaviors of the tile, traveling wave fronts across many tiles are not possible in this arrangement without severe distortion. To the extent that patches can feed back as well as feed forward implies difficulties in stimulating the sole patch with realistic inputs, outputs, and the reverberations therefrom. However, if the parametric space of one patch is thoroughly exercised, then the output data of that patch may be used as the input data to a neighboring patch, and systems of patches can thereby be assembled and tested.

Alternatively, the entire plasma lemma can be divvied up into, say, 1E5 nearly equal patches. The make up of each such patch can be quantified by a set of parametric values: e.g. quantities of various actor types present plus membrane capacitance. The differentials in actor counts and ion counts between adjacent patches reveals the gradients. Where the gradients are small, then few sample patches might well represent a large number of patches. Where the gradients are largest, the patch sample rate must be high enough to capture the modal shifts and any other nonlinearities of performance. One can adjust the sampling rate proportionate to the rate of change, which would yield variations in sampling densities much like the finite element method does to determine node location. For long stretches of homogeneous membrane, such as with a non-myelinated axon, few patches (maybe as little as 1 in 1000) would be necessary to characterize the behavior of the entire expanse. In areas of sharp transition, more patches would be necessary to accurately represent, with a worst case of all patches required to be modeled individually. The strong nonlinearities of neuronal behaviors suggest the most important metric is the response to natural stimuli. A superior metric for patch sampling density would be the differential between the responses of adjacent patches.

By this means some minimal set of patches, called the canonical set, can be identified as sufficient to reconstruct the entire cell by positioning them back to their original positions, then tiling in all the intermediate patches by interpolation. This would require verification testing between the original model and the reconstituted interpolative model to gain confidence in the method and establish a relationship between sampling density and error levels.

3.3.1.7 Contours of Rotation

The simplest of models are the 1-dimensional representations. These consist of a series of nodes from dendritic origin to axonal termination. Compensation must be made for the lack of circumferential neighbors, as propagation is found empirically to not occur without nearest neighbor synergies (sympathetic resonance).

The 1-d series of nodes can be bent into a contour, i.e. repositioned in 2-space so that each assumes its true distance from the axis of the neuron (radius), as well as retaining its true position along the length of the neuron. These points form a thread representing the diameter of the neuron along its length which affords opportunities to distinguish by shape dendrite from soma from axon, and to add finer detail such as caveoli.

Such a contour line can be rotated to generate a 3-d cylindrical shape. Doing so eliminates the boundary value problem of the lateral spaces adjacent to the nodes by forming a closed surface. Furthermore, a closed surface clearly delineates the inside volume from the outside volume, as is critical for any living cell. While lacking the arbor of the dendritic processes, giving the neuron such a shaped volume does support the study of a number shape-induced phenomena. (Examples: thickness of the extracellular fluid, effects of the dendritic trunk signal being diffused cross the expansive soma, bifurcation tendencies to back-propagate, effects of increasing the axon diameter, or altering the taper of the dendrites, and the channel density variations at bifurcations.)

3.3.1.8 Tessellation

An alternative approach to manifold projections is to convert all surfaces into a triangular grid, with the nodes determined by the locations of actors. Tessellation is rather well developed in the Computer Graphics field, and especially well behaved for convex hulls. Neurons, however, are anything but convex, and each exception to convexity requires more computation, suffering the same problem of the proliferating projection planes. Both

systems, manifolds and tessellation, enjoy great computational reduction when the shapes can justifiably be simplified and smoothed.

Finite element approaches developed by the mechanical engineering field have found application in a variety of 3-d models. The strategy is to represent solids as a finite number of nodes spread sparsely in uniform areas and more densely in areas of heterogeneities, sharp turns, rapid changes, etc.. The nodes are then connected by equations that express the nature of the coupling between the nodes. This could be strain, friction, or other effect of force. These couplings to nearest neighbors result in triangles. Connected triangles in 3-space necessarily produce tetrahedrons. So any surface can be represented as a sheet of triangles, and any solid shape can be represented as a large number of tetrahedrons. These nodal relationships provide the structure through which various forces interact.

The tessellation approach feeds into a finite element approach. (see below)

3.3.1.9 Dynamical Systems

The application of general systems theory to biology requires limiting processes and random variables. Arrays of point processes in space may drive the state space matrices solvable with iterative differential equations. The first and common problem is that the wet lab workers do not have a way to observe all of the relevant variables. This results in a model of insufficient observables, even when there are adequate controllables. The primary benefits of this approach are the applicability of Liapunov stability analyses and Riccati optimization methods. It is a fast and efficient representation of complex systems. Usually, stochastic processes are not included in such models, except as “noise” components added to certain variables.

Perfect equilibrium renders a system timeless. It is the slight disequilibria through networks of interactions that produce the sensation of time, the dynamic patterns by which we can measure time. Therefore, dynamics is the study of the consequences of disequilibrium. Biology has thousands of processes that are on the one hand so balanced as to be near the equilibrium point all the time, but on the other hand exquisitely responsive such that they tip to either side of the equilibrium to effect vital processes of homeostasis and/or action. It is a fascinating area of study, in its infancy, with much investigation to be done. Dynamical systems, if expanded to fully embrace stochastics can serve this field well.

3.3.1.10 Finite Element Methods

The finite element method clones simple mathematical representations into a large scale network of similar representations, coupled together by the forces that couple them. These couplings are not NxN in quantity (which would be fully connected), but only connect to nearest neighbors, usually 2 to 6 per node (quantity of links = approx. N*4). The finite element is embodied easily within digital computers because it is a discrete representation of what is in reality a continuous solid material. This is to say, the method itself has already born the distortions of digitization, and the digital computer can perfectly carry out what the method specifies. This doesn't avoid those distortions, it only shifts the blame. This method is efficient because it provides for a sparsity of nodes where not much is happening and a high density of nodes in the most critical and interesting areas. This approach also tends to simulate nonlinearities well, as the node density is automatically increased to the point where a piecewise linear representation yields results within error tolerance.

Engineering finite element approaches typically involves converting a homogenous solid of a complex shape into a set of nodes and edges. A significant part of the effort is the optimizing node density to the objectives of the problem. As concerns the neuron, no such routine is necessary because the neuron comes to us with its nodes already defined and positioned. The membranal location of each actor (receptor, channel, vesicle and pump) constitutes a node. And the lipid and saline expanses in between these actors may also serve as couplings between nodes.

Finite element methods include iterative simulations, producing time series as their results. This method supports non linear phenomena modeled as piece-wise linear equations (just as a curved arc can be simulated by a polygon of hundreds of short straight edges). The finite element method has typically not been applied to liquids and gasses because nearest neighbors would be constantly changing, requiring rewrites of the nodal tables of triangles and tetrahedrons with each *dt*. However, it is well suited for the stationary proteins embedded in lipid membranes.

3.3.1.11 Particle Systems

Particle systems seek to represent real particles as either dimensionless points,or as spheres with fixed radii. They may be built in 1-dimensional, 2-dimensional, or 3-dimensional spaces. The growth in computation from 1 to 3 dimensions is not additive as with vector addition and inner multiplication. This is because 1-dimensional collisions

are trivial; 2-dimensional are algebraic, and 3 dimensional require 2 basis conversions, unique to each particle pair in collision. Particles system models may or may not include representation of radius, mass, charge, angular momentum, elastic or inelastic collisions, gravity, magnetism, drift, temperature and/or pressure. Particle system representations are a hybrid of continuous Newtonian ballistics and discrete collisions. Particles collide with each other and with the container walls. Container shape and container wall elastance/absorption may be an important feature of the system under test. The standard diffusion models championed by John Crank[61] succeeded in solutions to only basic geometric shapes (cubes, cylinders, spheres) and grew overly cumbersome when attempting the irregular shape of a neuron.

The particle system about the membrane of the neuron is a coupled electrical-mechanical system. It can produce non-stationary cycles. This can be viewed as mere turbulence, often done in thermodynamics, or as "data transmission", as in the case for action potential propagation. This difference of "interest" has strong implications for the choice of modeling strategy.

The continuous trajectories of particles may be digitized, but at the price of extra computations to detect collisions accurately in time and space. Mass may be conserved, or alternatively particles are added or removed from the space according to certain rules or conditions.

There may be several compartments, with transport between adjacent compartments according to specific processes. Particle systems are generally employed to model liquids and gases, but may also model diffusion in solids.

The N-body problem is implied in the charge field acceleration of every non-fixed particle with charge. Charge effects cross over the membrane, so a compartment by compartment calculation yields incorrect results.

3.3.1.12 Stochastic Differential Equations

In biochemical systems, there are reaction processes where chemical bonds are made and/or broken. Chemical kinetics may be a zero-order, first-order or second-order reaction., depending upon the sensitivity to the concentration of the reactants. Reactions are stochastic in that there is a randomness as to which particles will bind when. Unbinding experiences a similar random process, perhaps due to collisions from surrounding particles that may knock a reactant lose.

Point processes, for purposes of this document, are nodes that consist of state transition rules, that in turn result in a time-series of state changes. There are also point processes wherein a given moiety is regarded to remain the same chemical while it in fact changes internal conformation. Among smaller molecules these are called stereo-isomers and enantiomers. But at the larger scale of membrane proteins, (> 100,000 Daltons) conformational changes may be machine like: opening and closing gates, pumping particles across a membrane, triggering release of a messenger,etc.. While the effects and implications of such changes may be mechanical in nature, the particular timing of events are determined by stochastic processes. All of this is inherently a chemical process, and all the rules of chemistry apply.

If a molecule has N states of interest, then there are NxN possible transitions between states. Some of these may be null (impossible). The remainder have some probability of occurring, some more likely than others. These transition probabilities predispose the instantiation of which and when the next state will be. These transitions are in effect the differentials of the states, and can be expressed as partial differential equations. The instantiations involve a random number generator mapped onto the cumulative distribution function of the next possible states, so as to choose one.

The likeliest transitions in large molecules proceed through a series that must eventually complete a cycle by returning to some repeated state. For any molecule to be used more than once this is necessary. With each state assigned a number, there exists one or more paths from state to state that constitute a loop. This loop along with its side chains constitutes a directed graph. Graph theory develops the characteristics of such duty cycles, their stability, variety, speed, and variability. It can identify limit cycles, attractors, divergence and trapping states. As biology consists of thousands of delicately balanced and inter-coupled equations, a tool for establishing the legitimacy of a model is appreciated. Graph theory assists in generating Markov chain models of molecular conformational changes that are relevant to many membrane proteins. They can determine what level of complexity is possible for the behavior of a single molecule.

3.3.1.13 Kinetic Schemes

The problem with a consistently atomistic model of the neuron is that while doing so may lead profitably to the molecular dynamic models of large molecules, this overburdens the pursuit of information flow along the vast

membrane populations of actors. Workers have responded to this handicap by inventing Kinematics, the study of motion in the abstract.

A system of motion may be characterized in time and space without accounting for the underlying forces that may ultimately be responsible for that motion. In so doing one layer is transcended by entering the next. In this case molecular dynamics is collapsed into kinetic schemes, no one of which perfectly represents the molecular dynamics which it abstracts. The complexity of the chosen scheme must be calibrated to the desired accuracy of the model.

The field of logic is just such an abstraction. Its discrete set of rules are built out of discrete elements, and as a result output discrete decisions. Such strict determinism fails in any multilevel system. To cross any chaotic barrier, the "clean" analysis of logic must be sacrificed for less certain probabilistic logic. Stochastic systems are built of this, and they more closely resemble reality. While the culture of science often regards the addition of noise to cause a "loss" in precision, formality and elegance, real systems are far richer and more intelligent than the logical systems that have been employed to represent them. The replacement of deterministic equations with probabilistic transitions gives rise to the "state transition probabilities matrix" for each molecule or subunit thereof (hereafter called the "Q" matrix). Workers may attempt to hybridize simple particle models with stochastic models of complex molecules so as to optimize the information exchange between the two.

3.3.1.14 R-C Grid (Resistance Capacitance Circuits)

The concept of the Resistance Capacitance grid may be said to begin with the cable equation. Because long electrical cables, such as the transatlantic cable were imagined as an infinite number of filter stages in a ladder formation, an analytic solution was sought.

$$1/rx*dV/dx2=Cm*dV/dt+V/ry;$$

where:
rx = axial resistance
dx = length constant
dV = the change in voltage with respect to time
Cm = capacitance of the membrane
V = voltage across the membrane
ry = resistance through the membrane

Passive membranes and non-thresholding active elements Decremental conduction, graded potentials. Decrement-free conduction requires active membranes

Ephaptic transmission to neighboring cells occurs merely through extracellular charge imbalance. For example, suppose two adjacent cells have intracellular conc.Na of 50mM Na and extracellular conc.Na of 0. 150 M. If one of the cells is perturbed such that a sodium flux occurs of one half of the (shared) extracellular Na moves inward, then the extracellular conc.Na drops to 0.075 M and the interior or the cell rises (depending upon the ratio of volumes intra to extra) to say 0.0 70 M. The first cell changes in conc ratio from 150/50 = 3 to 75/60 = 1.25. Meanwhile the neighboring cell experienced a shift from 3 to 75/50= 1.5. At 293 kelv, voltage = -.02524*ln(conc.ratio) for valance=1. The voltage drop in the first cell is 0.0221 v (22.1 mV) and in the second is 0.0102 v (10 mV) Neighbors might then feel about ½ the effect of the disturbance. This author claims this to not be the case, because the voltage disturbance is instantly "capacitated" at the membranes due to the over-powering EM force, whereby all charge imbalances are relegated to a near-surface phenomenon, not turned lose into the extracellular volume. Therefore there will be no free charges to migrate across the extracellular cleft and alter the voltage experienced by the second cell. QED

3.3.1.15 Constraint-Based Multi-bodies

Linear programming addresses multidimensional constraints on a system. If one defines the container shape and eminent collisions as constraints, then linear programming can be employed to model a neuron's information processing capabilities. Improved constraints narrow the possibilities for a solution. The remaining volume within and between the constraint planes represents the solution range. One can stochastically choose any point within this volume and yield a correct instantiation. Multi-modal neurons must have multiple solution volumes. To the extent that a neuron is information generative, constraints alone do not tell the whole story.

The field of differential equations concerns itself with boundary conditions and boundary value problems. They deal with the edges to the main body of interest, and how they might misbehave or cause trouble mathematically. But in neuro-informatics, the boundary problem is the whole of the problem. That is, the membrane is all boundary. All the information processing and flows may be deemed as boundary processes. The major concern is with limit cycles (not static rest states, nor unstable explosions). These "cycles" are near-neutral states, but with a "wobble".

Only non-conservative nonlinear systems can generate limit cycles. The wobble is complex, and is the "answer" to the "query". Accordingly, we must be sure that all of this information is preserved.

Containment is of the essence in the construction of information processors. They occupy a niche of non-conserving nonlinear systems that are very nearly conserving, by the nature of their containers. That is, they are highly constrained so that "flows" occur in certain directions and do so over very gentle gradients. Information is represented not by "major leaks" but rather subtle cascades and stops along the way (memory) that employ tiny efficient storage schemes. These are systems with a minimal amount of energy input, and result in a a maximum quantity of state changes. These state changes are patterned as a function of perturbation types.

Perfectly reflecting walls can produce cycles, as within a flute. Imperfectly reflecting walls can produce a computer, as with a neuron. The wall contributes to the nonlinear character of the system in widely varying and potentially useful ways. The ability to alter the porosity or texture of the walls changes the limit cycles. Added to this static character, the changing the patterns of channel openings in a neuronal membrane radically alters the system limit cycles and provides a means for generating a large number of limit cycle patterns.

Unfortunately, the free path plus collision events of ions in solution do not lend themselves to Lagrangian dynamics.

3.3.1.16 Event-based Modeling

In iterative models the time slice (the *dt*) is a heavy determinant of the computational load to run a simulation. During ballistic trajectories the *dt* can be extended so long as there are no collisions, thus economizing on computation. The calculation of when collisions will occur allows them to be rank-ordered in time, and become flags on the time line as to when to trigger the collision algorithms. This arrangement Ballistic movement is inexpensive wrt the computations involved in collisions. In models with few moving particles, collision detection and event-driven algorithms can realize significant reduction in computational load. However, in large scale particle systems collisions occur at a higher frequency than any practical *dt* duration. This allows multiple collisions to be processed in 1 *dt*.

There are in this model extrinsic events, e.g. mobile particle collisions, and intrinsic events, e.g. actor state transitions due to thermal noise. If a neuron could perturb an adjacent neuron so as to cause it to "provide a service" e.g. action potential, then we might say this is an event driven model. But if the detailed sequence of events within the neuron that carry out that service are of sufficient length of time to overlap with any other perturbation; or if those processes are more or less on-going, acting as a carrier for any perturbations, then the model is simply dynamic, not event-based.

3.3.1.17 Feature-based Modeling

A feature based approach to modeling divides the model into stand-alone objects. Each object, which presumably has a single function (providing a service or feature to the overall model), operates according to its needs: its own clock, timers, triggers, memory, rate of iterating, etc. Because most features are not drafted into use each and every *dt* they lie dormant until called, intended to cut the computational load down to only the high runners. This approach is common in social service software, because it is customer driven. The neuron may not fire every *dt*, but there are information processing activities every *dt*. That is because diffusion is a time-continuous process, and because all of the stochastic actors are generating state transitions continuously in time. Given that both diffusion and stochastics are present large scale, it is unlikely that a feature-based approach can conserve computational load to any effect out weighing its overhead.

In some sense, a model of something as complex as a neuron must necessarily evolve. It may start out with only channels, then add pumps, then add receptors and vesicles, then second messenger systems. Other features sure to be desired include sequestration, ATP energetics, Gibbs accounting, dendritic spines, caveoli, ribbon synapses, process growth and retraction, plasticity and learning mechanisms, channel turn-over, channel rafting, In this sense, at least, this model is feature-driven. The core, however, must include an ion particle system, actor kinetics, and the effects of charge force fields. These are "always on".

3.3.1.18 Volume-based Modeling

Voxels are the 3-d equivalent to 2-d pixels. A 3-space model can be digitized by cutting it into voxels, and calculating the processes within each separately. Voxels are often cubes, but can be cut as tetrahedrons. The tetrahedrons are more adaptable to irregular shapes and to the finite element method (FEM). As some voxels are

more important than others, a binary tree approach is often used. The very largest possible voxels are left large as long as they are not near the critical actions of the model. Else they are divided into 8, then 64, then 512 smaller voxels ... 8^n until the graininess (resolution) is sufficiently detailed to yield results within acceptable error levels. For non-moving or slow moving particles, this can be an efficient approach. There is an overhead of determining particles crossing from one voxel to a neighboring one.

The operation of membranal systems is inherently a surface phenomenon. As a 2-d structure, albeit a 3-layer surface (saline above, lipid in the middle, saline below). So might not the entire neuron be modeled as a 2-d structure? Perhaps surface area is far more significant than cell volume. Indeed, most of the volume of a cell is occupied by obstructions to ion diffusion. And the extracellular "volumes" outside of most cells are quite thin and somewhat uniform.

One of the problems with collapsing the model to 2-d concerns the behavior of ions near the membrane. The capacitance effects strongly vary perpendicular to the membrane (in the third dimension), and it is not clear that the behavior of ions being "spouted" out of an ion channel can be "flattened" without loss of the membrane's information processing character.

An alternative to the full volume and b-tree approach to volume management, manifolds can be used to project the surface membrane of the cell onto planes, retaining a sufficient thickness of water on either side to perform its functions. All the remainder of the volume is sliced off and ignored. However, to the extent that the greater volume acted as buffer and slow transport, those actions can be simulated by an active membrane at the outer surfaces of the water layers. They can algorithmically remove or add particles so as to mimic the effects of greater volume.

While the voxel approach is the traditional numerical method for 3-d liquid models, it does not optimize to information flows. It may be prudent to allow whole compartments to operate as wholes, with only special samplings of nano-environments around each actor.

The wave -particle duality problem of physics has ,this far, found to not to impact the design nor output data of this model.[16] By moving up the size scale to where probability distributions serve as data sources, we are deprived of

[16]Physicists may argue that all particles are composed of energy and therefore energy is the most important measure of the model entities. Particles, in this view, are discrete packages of energy. At any subatomic levels wave effects and quantum effects must be taken into consideration, as they determine the transformations of the particle. EM waves interact with particle quantum states to determine only the probability distribution that certain atomic events

the analytic solutions, such as the heat equation and the wave equation. From this point forward we must rely upon stochastic differential equations to resolve outcomes.

Perhaps the most significant phenomenon to emerge from energy discretely packaged into particles is that particle collide. Most renditions of colliding particles regard the collisions as Brownian motion, closely related to Gaussian white noise. Indeed, when taken in aggregate, there is only noise and temperature to measure. But what if each particle was a unique individual. It would have a unique trajectory, and a unique series of relationships with other particles along its path. Is the list of interactions true information? Is the path information? Is the velocity information? Is the final position information? Is the timing of arrival of a particle type the information? Somehow the neuron is transmitting information through the collisions of ions, and a demonstrative model might reveal just which of these, if any, is the significant one to the neuronal role.

3.3.1.19 Information Theory

Information theory was born of that smallest bit of information, the yes-no decision. That is, it lives in the base-2 discrete number system. Information is defined as the change in state. One large state, such as an electric power switch, is only one bit of information, no matter how large the amperage. We might say that coherence is the opposite of information, because by definition, all travelers are in precisely the same state. What then might be the opposite of coherence? Is it chaos? What is the difference between white noise of say 1 trillion bits and the library of congress 1 trillion bits? Information requires writable and readable states. If our chaos is writable, as with a random number generator, and readable, as with the random number generator output being placed in memory, then that "noise" of randomness has become information. How can pure noise be distinguished from information if a random number can be declared as information? If I generate a random number and then use that number as the password to my bank account, is that not important information? If it has the quality of write once and read many times, then certainly is has the potential of being information. Of what importance or significance is a function of downstream processes, no concern of the generator.

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will take place. At the slightly higher perspective of whole atoms and whole ions, we see only the probability distributions of events, not the underlying wave equation mechanisms, not the energy that drives them. Such distributions are kinetic abstractions of the underlying energetics. Although losing Gibbs information is mourned, the energetics of the molecule is implied in its kinetics. If the available energy for a transition is high then the probability of transition goes to near 1, while if low it drops to near zero. By this means, it is argued, aspects of energy flow relevant to information flows are preserved within kinetic schemes. Carrying forward the bookkeeping of the thermodynamics of each chemical reaction is therefore somewhat redundant, and an unnecessary computational burden to the information processing model.

And so, with regarding the neuron, we look to measure the maximum input information, no matter how chaotic it might look to us, then measure the output information in similar fashion. The mutual information between the two is a reasonable measure of throughput, but how might information have been processed between the two measures? Is it possible to generate and utilize information that would not show in the mutual information metric? This is the challenge of a model of neuronal information processing. We do not yet know what all is information, We do not yet know how many ways a biological system might "peel off" information along its course. We do not know the "depth" of the information (as in the order of distinguishable patterns). We talk about temporal, spatial, frequency and phase metrics. But do we know that these are exhaustive?

Were we to model at the subatomic level, quantum theory excludes structureless media. This implies discrete space, time and energy levels. But up at the level of whole atoms and molecules, that handy arrangement vanishes in the aggregation, and the space-time behavior is quite continuous. It may be a significant distortion to impose discrete voxels or nodes upon what is genuinely continuous movement and charge fields.

Information Theory does not lend itself to continuous time and space, nor to any analog systems. One would have to contrive a graininess that would surely distort the system. For systems of continuity, General Systems Theory might be the better choice. Information Theory addresses the discrete while General Systems Theory addresses the continuous. Neurons are hybrids of both. It has proven difficult to apply either of these to the neuron precisely because of their inappropriateness and weakness at incorporating both. It might therefore become necessary to apply them piecemeal, in discrete-continuous-discrete fashion through the information flows along the membrane. If an action potential traversed along an axon, crossing over 1000 ion channels along the way, then that would require a model of 2000 mode changes between analog and digital representations, in series! It would be superior indeed to discover a mathematical tool that could handle and measure the throughput of systems comprised of a distributed arbitrary mixture of both continuous and discrete processes.

It might be possible to discount the informational role of the ion waves radiating out from each open ion channel and focus solely on the kinetics of the actors as the most informationally significant features of the neuron. This is only conjecture however, and it remains to be demonstrated and proven that this would be a justified approach.

In any case, Information Theory has its utility in evaluating the the throughput of action potentials through a neuron, even when the dendritic arbor may not use action potentials. The mutual information measure allows “skipping over” the analog bits and measure the differential between two discrete nodes.

3.3.1.20 Complexity Modeling

Physics has done an excellent job of orthogonalizing the variables and standardizing the working set as the necessary and sufficient set to completely represent the real system under test to the desired echelon (Newtonian, relativistic, quantal, etc). Accomplishing this for biology is a much larger task, and currently beyond our reach. Absent such a 'clean' perspective, it has been overlooked that many representational mathematics do not meet the above criteria. If one represents a fourth order process with a first order equation, then serious information has been lost, and the model can only be correct at a few incidental points. This is especially a problem when ion channels are represented as I/V plots or as first order exponential equations. It is simply impossible to capture the behavior of the high order systems by simulating them as low order equations. To address this we need a metric for the veracity of a representation vis-a-vis the living instance it represents. The first problem is that most biological processes are not known completely. Thus, workers resort to 'kinetic schemes' to reduce that order to some tractable dimensionality, for modeling purposes.

Once the practical order of each individual process to be included in the model is ascertained, then the flows between these processes must be considered. If a 4-order process flows only into a 1-order process (in series), then most of the informational richness of the former will be lost. However, at least within the mathematical realm, certain tricks can be applied by lower order systems to pass information of higher order systems. For example time-sharing. A 1-channel input can carry all the information of a 4-channel output if the 1-channel system is 4 times as fast and can do the bookkeeping to track which time slot is assigned to which channel. Another sample problem would be a mismatch between processes. If system A is 4-order and system B is 4-order, each with 4 inputs and 4 outputs, but the nature of the connections between them can only transfer 3 output channels from A to 3 input channels of B, then again information is lost. For this and similar reasons, it is not sufficient to compare matrix sizes alone. It comes back to channel capacity for each process and the all-in transduction process between processes.

3.4 MODEL TYPES

In the past, models have been parsimonious to very restricted queries or purpose.

3.4.1 DESCRIPTIVE

Descriptive models may be static, incomplete, simplified renditions of the real thing - for purposes of teaching or communicating to others some aspects that would otherwise not be assessable to the casual viewer. The purpose is the appearance of the thing - how it is perceived by others . May be words only, or picture only representation.

3.4.2 EMPIRICAL

The objective is to be faithful to the data. The data is often incomplete, so holes are present. The purpose is usually to present to others in the field a form of progress report: We have completed this part, but are still missing that part. They do not concern themselves with causality, only results.

3.4.3 DEMONSTRATIVE

Similar to Descriptive, but must include some dynamics or process. Demonstrations are contrived so as to a very high chance of performance success, so so all unreliable data is filtered out, and the demonstration is practiced before public presentation.

3.4.4 CONCEPTUAL

Concepts can be visual, auditory, logical, math equations, or abstract. A new concept is usually rooted and justified in the context of the pre-existing concepts. A strong biological concept is founded on the concepts of chemistry. A strong chemical concept is founded upon the concepts of physics. A strong physics concept is founded upon the concepts of mathematics. Concept models are usually not dynamic, although concepts can be extended into a demonstrative model by making them dynamic.

3.4.5 PREDICTIVE

The standard for a predictive model is quite high. It must capture the patterns of behavior of the real thing well enough to elicit them under similar stimulus conditions. This can be accomplished via a faithful rendition of the underlying first principles, be a curve fit to the empirical data of input output relationships, or it can be a blind optimization of performance to mimic the real thing without any understanding of its mechanisms. Predictive models are often the “holy grail” in modeling, because it is accurate predictions that empower the clinician, the economist, the engineer, the psychologist to succeed at their tasks.

3.4.6 NUMERICAL

Any modeling done within a digital computer necessary involves numerical methods, directly or indirectly. The primary purpose of numerical models is to improve the algorithms and heuristics of getting to the solutions so as to minimize resources consumed, especially time and CPU size needed. Numerical models often enjoy high re-use potential and are added to libraries of routines that can be stitched together into many variations and more complex models.

3.4.7 PHENOMENOLOGICAL

Models have the purpose of distinguishing between competing explanations and concepts so as to determine which is the most accurate abstraction of the real thing. These may be regarded as tests of concept. They seek veracity through mimicry.

3.4.8 ITERATIVE

Iterative models are concessions to the limitations of closed form analytic equations and digital representations. For complex shapes, hybrid processes, unrefined concepts, it is often productive to iteratively “hill climb” toward one's goals. In the digital world where most differentiability is lost, this may be the only option. Difference equations have proven themselves to be powerful in solving very complex problems, but consume huge computational resources to do so. Specialized PDE processors have emerged to fill this niche. One may argue that continuously streaming processors are not iterative, but representing them digitally remains an iterative program.

3.4.9 STOCHASTIC

An extension of the PDE processors is to pursue solutions to iterative problems with integral processes involving random number generators. There are many stochastic processes in nature and at the molecular level and below, it can be argued that every process is stochastic. Fortunately the solutions to stochastic differential equations (SDEs) is, from the computer's point of view, the same as solving PDEs, and so the transition has been an easy one.

3.4.10 ABDUCTIVE

Making a case on incomplete information for purposes of making timely probabilistic decisions. It is a means of jumping up a level in complexity, perhaps prematurely, perhaps incorrectly. We may regard the output decisions as trials, hypotheses or as commitments. By this means one might “operate at a higher plane” until falsified. It is yet another stochastic process, capable of generating new hypotheses with each falsification of the old.

3.4.11 HYBRIDS

Increasingly the problems confronting us no longer remain of one type. We no loner enjoy diffusion only problems or ballistic only problems, or edge-detection only problems. Hybrid models recognize that the nature of the implicated computations divide into rather distinct types. These types require different algorithms, and may be optimized on different hardware. For example their are dense linear algebra and sparse linear algebra, procedural and associative, random search and binary search.

3.4.12 LARGE-SCALE

With the failure of analytic methods to solve the complex problems, a new approach of massively parallel open-end equations is being tried. Paralleling the development of CPU transistor density, the term “large scale” was picked up. Given the history of chip development, what is today large scale is sure to be tomorrow's small scale. Generally, large scale approaches attempt to solve he whole problem in parallel. Problem types include earthquake modeling, weather modeling, astrophysics problems, biological cell simulations, medical diagnosis.

3.5 MODELING SCALES

Consider the following 4 perspectives on size of the model. At about 1E-4 m there is the local circuit of several neurons. At bout 1E-5 is the whole cell model. At about 1E-6 m is the excised membrane patch. At about 1E-8 m is the large protein molecule, a channel o a pump. This model focuses on the physicality of the whole cell and patch, and on abstractions of local circuit connectivity and molecular state transitions. Little will be said about local circuits, but molecular state transitions comprise a major, crucial portion of the model.

3.5.1 MICRO-SCALE

The whole cell present the "main" perspective of this modeling exercise. Everything else exists to serve this entity. The whole cell is a closed membrane living entity that completes the information processing role from input synapse to output synapse over continuous forms of membrane and saline. Every other perspective involves unrealistic cuts and/or other discontinuities. Therefore, all design effort should first go to a reasonable whole cell as a test case for the problem or quest at hand. Once readied, then that problem may be broken down into canonical patches and mathematical abstractions as available modeling computers may constrain.

Once the various patches of interest have been modeled at the nanoscale, they comprise a library of re-usable elements for the large-scale whole-cell simulations. It is anticipated that the behavior of patches can be scaled up in size (not quantity) without much lost in veracity, per the findings of general physics. Thus the whole cell model will be realized as an assembly of patches, some minimal number that none-the-less captures the input-output relationships of that particular species of neuron within tolerable error levels. The levels of confidence of such whole-cell simulations are, of course also dependent upon its constituent lower scale sub-models.

If the whole cell model is to embody sufficiently large quantities of particles and actors that it cannot be robustly modeled at once within available computers, then a select number of canonical patches of membrane are excised out, modeled and characterized. A sufficient number of canonical patches must be chosen such that all the patches are accurately represented by gradient forms interpolated between the 2 nearest canonical patches.

3.5.1.1 Bio-Data Conversion

The highest veracity model of a living cell is the cell itself. But the biodata cannot be made dynamic without a model. The modeler receives data on a "catch as catch can" basis. It is always incomplete from an engineer's point of view, because it is not yet feasible to observe and measure all the relevant values of a living cell. Results are not always quantified. Bio-data is not usually in a form that directly applies to the model (must be interpolated, extrapolated, converted, normalized and/or estimated).

Biologic data as it becomes available will fill in the shape details, locations of actors, state behavior of those actors, and constellations of modulators. As the biologic database is currently incomplete, and the computational loads astronomical, the whole cell model stands as fragmentary and weakly operable, except as a few classroom demonstrations or great simplifications to elucidate singular events. It does however serve well as that point on the horizon to which workers aspire. The whole cell may be considered to reside at the micron level, in its full biological complexity and diversity, and thus is sometimes called the microscale perspective.

3.5.1.2 Whole Cell Normalization

The greatest computational load in a whole cell model may not be with the actors, as one might expect. Actors are relatively low in number compared to particle collisions and particle reflections. The particle quantities as up at 1E11..1E14. And so all simplifications which reduce the computation of particle motions without losing the veracity of flux, current and capacitance are highly valued. The argument is made that while the axial shape of a neuron is critical, the radial shape is less so. The greatest simplification of radial shape can be accomplished via a contour of rotation. The computation of particle reflection then reduces to a radius check and a polar coordinates conversion. The goblet easily supports 1e5 membrane locations (addresses); 1e5 particles and 1e3 actors. With larger computers these *maxima* rise 1 to 3 orders of magnitude. This level, like the first, takes place at the micron level, but strives for great simplicity within that realm. In particular, the computationally intense phenomena are focused upon by "zooming in" to a small patch. rescaled where possible to this higher level, and thereby reduced in quantity.

The goblet features an anomaly, and that is the shape of its dendritic "tree" , which is represented as a thin cone. What information processing distortions may arise from this shape is yet to be determined. It is hoped that by making the cone thin enough, the lateral "short-circuiting" between inputs will not distort the neuronal output. If

necessary, radial partitions can be placed within this cone to mimic individual processes and their bifurcations. The great advantage to the cone is computational efficiency in particle motion calculation.

3.5.2 NANO-SCALE

At the nano-scale is the patch. It consists of a rectangular patch membrane replete with voxels of water above and below, from 8 to 1024 in number. This third level takes place just above the nanometer level, and is particularly faithful to individual ions and channels, as a excised system of particles and stochastic kinetics. It is concerned with both 3-dimensional and 2-dimensional processes (diffusion and capacitance). An isolated patch can faithfully model ions and ion channels 1 to 1, and can reproduce Hodgkin-Huxley action potentials and a little propagation thereof. The mission of the patch is to drill down to statistical mechanics for an accurate account of channel behaviors interacting in a membranaform system. The particular pattern of mixed channel types at this scale constitute the plaiding of the plasma lemma.

Its secondary purpose is to support the characterization of a select few “high runner” or canonical patch configurations, and rigorously model these prior to the simulation run. If each patch can be exercised through its domain, producing a input/output map, sans all the differential equations in between, then they do not have to be completely recalculated real time during a whole cell large scale run. If canonical patches are chosen careful at each end of modest gradient changes in channel densities, then some interpolation of patches in between can save immense amounts of computation. This “short cut”, of course, must be verified as free from non linear surprises. Patches should contribute to the computational reduction of larger scale models through compression. That is, the whole cell model might end up being entirely tiled with patches, each of them consisting of look-up tables that immediately predict the patch output without computation.

If all the physical constants are preserved in a nano-scale model of membrane, ions and ion channels, then the causal and spatial relationships between the key elements remain intact. The price paid is that only about 1 millionth of a neuron can be modeled this way. It is possible and advisable to model a smaller portion of the neuron where the physics is tractable to computation without scaling. Patches of 10 by 10 voxels of 0.01 edge length would on average have only 1 channel. In busier areas, near synapses, this density could rise to a max of 25. A patch of 16x16 voxels, 1 layer deep on either side of the membrane, would allow the study of Hodgkin-Huxley type

action potentials. A typical rendition of this size would have about 92,000 particles, 256 membrane addresses and 12 channels. Note that this is 10 times the average channel density but typical of the more informationally active regions of the neuron.

3.5.2.1 Relevant Chemistry

Zero order reactions are controlled by some factor other than reactant concentrations. Usually, they are catalyzed reactions, especially fixed surface catalysts.
dA/dt = -k; % where k = reaction rate that the catalyst produces whenever reactant is present.

First order reactions are by far the most common, suitable for particle-actor reactions. They have specific reaction rates according to:
dA/dt = - k*A; % where A = concentration of the reactant, k = reaction rate, t = time

Its solutions are:
A = A0 * exp(-k*t); % where A0 = initial concentration, A = final concentration
tau = (1-1/e) / k; % where tau = time to 50% of reaction, e = natural log. tau = approx(0.693/k)

Second order reactions have reaction rates according to:
dA/dt = k*A*B; % where A and B are reactant concentrations, suitable for particle-particle reactions

t = 1/(k*(A0-B0)) * ln((B0*A) / (A0*B))

Most reactions are first order and most second order reactions can be computationally broken down into 2 first order reactions in series (multiplied).

3.5.3 MULTISCALING

3.5.3.1 Spatial Multiscaling

For those problems inherently too large for today's computational devices, certain compromises can be made if at the finest granularity of the problem, small bits or patches can be modeled intensively, and then represent a large number of the other one's similar to the patches. These many cloned and graded bits can then be re-assembled into the whole. It is possible to maintain several levels by this means. For example, modeling the human body down to the molecular level would certainly require a multiscale approach: molecules, organelles, cells, tissues, organs, whole. At each level only a representative sampling of its components would be modeled.

The solution to the overwhelming computational load of rigorous whole-cell simulations is multiscale modeling. I use both the Microscale and Nanoscale simulations in combination. Certain representative “patches” of membrane

can be incrementally increased in size and counts until a point of diminishing returns is reached in the input/output relationships. This nanopatch can be expanded until propagation is consistent with up-scaling. That is, if increasing the number of components does not add appreciably to the generated results, then that patch can be held at its point of diminishing returns. Such an exercise provides valuable insight for both ANN and BNN designs.

1. When such a size is reached it can be "cloned" around the circumference of cylindrical shapes as an accurate predictor of what actually transpires in an axon.

2. To the extent that the parametric space is exercised and consistent between ANN and BNN, such patches can be collapsed into look-up tables, and then stitched together in much larger quantities. accurately modeled at the nanoscale of ions and ion channels, including the nearest neighbors, membrane capacitance and chan type mixes/patterns.

3. A design can mix-and-match canonized patches to mimic the BNN distribution patterns.

4. patches that do not add anything to the output signal can be eliminated. For example, can a thin radial slice down the entire length of a neuron accurately mimic the BNN performance? If not, can the edge-dissipation effects be negated via mathematical stitching so as to improve the model's veracity?

Multiscaling modeling will play an important role in capturing the information processing capabilities of neurons. Because a full-scale model will involve 1e12 particles, 1E8 locations, and 1E6 actors, over a series of 1E6 time steps. every opportunity to reduce computational load in the ANNs is to be fully exploited. Aside from the Computer Science contributions to numerical methods, there are several higher level strategies that can gainfully be employed.

1. Minimizing patch size to their informational character.
2. Eliminating all patches shown not to contribute to the out put
3. Cloning all homogenous patches alone a wave front (only the locations of the wave front need be computed)
4. Correcting for edge artifacts allows modeling of only a radial slice of circular profiles
5. Studying complex local phenomena and then collapsing the results into look-up tables to be archived in the library for future use.

6. the ‘digestion’ of relevant phenomena at a lower levels for pre-processed use in larger quantities at higher scales.

7. the automatic detection of violations of canonical forms. This is critical to avoid bad science. Any emergent phenomena not consistent with previously characterized behavior must be detected and alerted. This should trigger additional intensive study into the local behaviors so as to add more possibilities to the library of low level routines. The essence of multiscale modeling is that the unanswered question drops down to a lower level of analysis, on a type-by-type basis

8. At each level, parametric sweeps need to be performed across each of the likely permutations in assembly of parts. Distinct modes, if any, should be mapped.

3.5.3.2 Temporal multiscaling

There are at least 3 distant time domains relevant to the neuron. The fastest is the particle collisions, taking place in picoseconds. The second is action potential generation and propagation, taking place in milliseconds. And the third is adaptation/learning, taking place in seconds to hours. It is not at all feasible to accommodate all 3, or even 2, in a single model run. However is is possible to focus on 1 of the 3 at a time, characterize the performance patterns, and capture them in such a way as to render them portable to the slower process runs.

The strategy is to capture the results of each run in such a form that it can be rescaled temporally. Given a diffusion pattern resulting in a run of 1E-6 s, is there as function that can accurately extend that pattern to 1E-3 s without lose of veracity? The key to multiscaling is to avoid surprises. So long as a process is applied iteratively, without change in parametric values, then it becomes predictable and amenable to such extensions of results.

Temporal multiscaling is expected to be especially useful when the model is applied to adaptation and learning. As the molecular processes are complex, great in quantity, and tend to accomplish adaptation over immense numbers of cycles, heuristics will be necessary.

3.5.4 MODELING UNITS

Modeling requires consistent units which are compatible with the various simplifications and digitization of the problem space. Use of conventional macro units results in a heavy computational load over whatever units might be most “natural” to the model. For example, amperage, which is based upon Faraday's conversion from the mole, which is based upon Avogadro's number of molecules, implies carrying around 1E-19 with every count of particles. It is much more straight forward to simply track N, an exact particle count per *dt*. This new unit for current is named 'ea'.

The original and various sources of voltage definitions were reviewed. Most were simply based upon some historical standard. Two candidates present themselves for model voltage: Coulomb's law and the Nernst equation. The Nernst is quite relevant to ion channel flux, and is specific to each ion type. But it is peculiar that the Nernst is temperature dependent, while Coulomb's law has no temperature dependence. A configuration with one charged particle on one side of a barrier and zero particles on the other side calculates to an infinite voltage, according to Nernst. A configuration with one charged particle on one side of a barrier and one particle on the other side calculates to a zero voltage. The very simplest configuration of particles that yields a practical voltage value would be two charged particles on one side of a barrier, and one charged particle on the other side. This yields :

voltage = (kelvin/valance) * log(2/1) * arbitrary constant;

Note: Following Matlab™ conventions, log = ln.

If we remove the old constants because they are unit conversions and therefore arbitrary, then replace ln with log2, for cause and for a basis set kelv=1, then

ev = (kelv/z)*log2(2/1) = 1; % new unit of ionic voltage, where 1 volt = 16742 ev, and 1 ev = 5.973E-5 v.

Nernst voltage is proportional to temperature, so there is no natural unit, and it is stable where temperature varies. This is characteristic of differential forces, like pressure. Because this model deals with discrete particles to calculate voltage, rather than some continuum, log2 is preferred over ln (natural logarithm). Log2 is also useful for its role in information theory EQs. Thus it is trivial to read the change in ev voltage (derived from log2) directly as information. For charged particle concentration ratios of 4:1 the ev voltage = 2, and for 8:1, ev = 3 (when kelv =1, and valance =1). This is computationally quite compact and lends to intuitive interpretation of results in model design and performance. (Note that this applies during the design phase where temperature is set kelv =1. During the Run phase, at kelv =293 or 307, ev values will be proportionately larger, with values in the thousands.)

Capacitance then is merely the bound charges / membrane unit area / ev volt. The unit of capacitance is defined herein as the binding of one charge pair across a barrier per ev.

Alternatively, voltage is defined by Coulomb via his F = (1/4*pi*e0)*(q1*q2)/r^2;

Strictly, voltage is the field potential impinging upon an infinitesimally small test charge, and so acts as a half cell:

V = (1/4*pi*e0)*(q1/r);

However the model is interested in the explicit force been specific particles. And so Coulomb's law applies.

Modeling at molecular scales and entailing large numbers of particles necessitates the use of units optimized to computational algorithms. The hydrogen atom was chosen as a basis for all model units.

As the published data is presented in hundreds of varying unit systems, all will first be converted to SI units for the sake of standardization. This is the human-readable format of choice, and supports the comparison between sources and mergers of data sources into a coherent whole. Then that data must be normalized to the extent that two sets are incompatible with a merge for any of a variety of reasons. Compatibility and interoperability within a single model is necessary, or else the concept of a library of types is flawed.

However, the human-readable form of SI units can be terribly inefficient in large scale computer simulations at the molecular scale. Because the model is particle oriented, it measures by counting particle quantities instead of amps or moles. Forces must scaled down to transport events, such that voltage tells how many particles will pass through a channel per 1E-3 s.

Although several popular physics units systems are based upon the electron, that does not work for ion systems, as it places everything 3 to 4 places off. This model needs units based upon the ion, and so a common ground was selected in the Hydrogen atom:

distance = angstrom

charge = electron

time = frequency of Hydrogen (1 cycle)

temperature = Kelvin (in terms of melting and boiling points of Hydrogen)

quantity = particle count

quantity	SI unit	converted to	model unit
distance	Meters	nm	nm = 1.00E-9 m
mass	Kg	Daltons	em = 1.660565586E-27 kg
time	Seconds	(frequency of H)	et = 7.04024183762482E-10 s
temperature	Kelvin	(no change)	kelv = 1.0E0 K
chemical quantity	Mole	Quantity of molecules	qm = 1.6605400000E-24 M
electrical quantity	Coulomb	e-	qe = 1.60218E-19 Coulombs
electrical force	Volts	Not electron volts	ev = 5.9727065680E-05 V
mechanical Force	Newtons		en = 2.5634272968E-25 newtons
electrical current	Amps	charges/et	q/et = 2.2757456874E-10 amps

TABLE 3: BASE MODELING UNITS AND FACTORS

Such a unit system does not guarantee against large exponents. It only provides a very immediate measure of quantities of particles in the system, and a 1-to-1 basis for the operators. This system of units greatly improves the intuition during the experimental design, because one is working with specific particles and the response of each to its immediate force vectors. The SI system requires dealing in aggregates that blur the notion of atomistic phenomena, or else require and endless effort of converting and de-converting units with each of about 100 operations per time step. See chapter " Design Elements" for a full development of units. Note that in the model units, most constants are dispensed with: no more Avogadro's number, Faraday's constant, gas constant, Boltzmann's constant, coulomb, mole, nor farad. These were all crutches to allow the SI system to reach the molecular scale from the macro units.

These selections carry through the SI Base Units and SI Derived Units with significant impact, especially because time is no longer in seconds. Mechanical force (the SI newton) is redefined as the attraction between 1 electron and 1 proton separated by 1 nm. Voltage (the SI volt) is redefined as the force between 2 protons on one side of a barrier and 1 proton on the other side. Voltage is proportional to temperature.

New model units will each be a 2 letter code beginning with *e. (ea, ef, eg, ej, en, ep, et, ev, ew)*

All source data shall be converted to SI units and stored in the Types library. This is to support comparisons between held data and new literature within a singular, widely accepted unit set.

Model units, however, are geared to efficient computation of molecular scale events, and as such are quite different from SI units. SI are automatically converted to model units when the bio-data libraries are read into the Experimental Design and Build.

Note: It is common practice to apply statistical techniques to biodata so as to compress it and to standardize the metrics for comparison purposes. However in this modeling process, fitting the raw data to commonly used distributions, such as means, standard deviations, and normal curves, is undesirable. The model requires the raw data, instantiations. Given the diversity of bio-data, it is prudent to let go of the canned distributions like uniform, Bernoulli, binomial, Poisson, beta, F, gamma, etc.. but rather accept the distributions as empirical. This is to avoid the temptation to impose preconceived notions about what the data "should look like", and to avoid squeezing out the "best part". Just take the direct measures of natural conditions and store them without collapsing any of the dimensionality until it is to be applied to a specific model function. At that time care must be taken to preserve the salient features as represent the intended function. There are a LOT of interesting distributions out there, and it is often the unique distribution of things that characterizes the function of those things. That is, distributions in space and state are not incidental, but are definitional. The phenomenon of modalities implies more than one distribution, so care needs to be taken to capture all of the modes in uniform units, and keep them associated as a single state transition set.

3.5.4.1 Base Units

Measure	Unit	Action
length	nm	adopt existing unit
mass	amu	adopt existing unit (amu = Dalton)
time = et	et	create new unit from frequency of Hydrogen
electric current	q/et	create new unit by switching time unit
temperature	K	adopt existing unit (H melt = 14; H boil = 20)
amount of substance	q	adopt existing mole/Avogadro's number
luminous intensity	photon/et	create new unit as photons / et (at std freq)

TABLE 4: BASE UNIT ACTIONS

1. The frequency of Hydrogen (as measured in coherent maser for the most accurate clocks to date) is: 1.4204057518E+09 Hz. Accordingly, model time = 1 et = 7.0402418376E-10 second
2. Amps are replaced by charges / et = 6.2414959618E+18 / 1.4204057518E+09 coulomb/second
3. 1 Candela[17] = 1.9682193364E+09 photons/et at freq 5.4E14 Hz (3.8E5 /et)3.

By convention, all model units will be named as 2-letters, the first of which will be "e" and the second of which will be derived from the macro unit of its type. Thus:

1. Newton :: en
2. Voltage :: ev
3. Joule :: ej
4. Pascal :: ep
5. Farad :: ef, where :: = is proportional to

[17] *the candela is the luminous intensity, in a given direction, of a source that emits monochromatic photons of frequency 5.40E14 hertz and that has a photon intensity of 6.81E13 moles of photons per second per steradian. (cone of 32.77°), equaling radiant intensity of 1/681 watt per steradian.*

Measure	SI	model	factor
Distance	meter	Ang	1.00E+010
Mass	kg	amu	6.02E+026
Time	second	et	1.42E+009
Current	amp	q / et	6.24E+018
Temperature	Kelvin	Kelvin	1
Quantity	mole	q	6.02E+023
Luminosity	Candela	photons@3.8E5 /et	1.9682193364E+09 photons/et

TABLE 5: CONVERSION FACTORS

3.5.4.2 Derived Units

3.5.4.2.1 Derivation of EM Force Unit

Coulomb's law states:

1. F = 1/(4pi*e0)*(-e*e/r^2) (kg m / s^2) where
2. e0 = 8.85418781762E-12 * c^2 (1 / N m^2)
3. c = 3E8 (m / s) speed of light
4. e0 = 7.9687690359E+05 (F / m)
5. r = 1E-10 (m)
6. e = 1.60218E-19 (coulombs)

Therefore, the force between 2 charges 1 angstrom apart = 2.5634272968E-25 Newtons

Define en = 2.5634272968E-25 newtons

3.5.4.2.2 Derivation of Voltage Unit

The Nernst equation, used for determining the partial voltage contributed by 1 species of ion, states:

1. V = R * T / (z * F) * ln(conc2/conc1) where
2. R = 8.314 Joules / mole Kelvin
3. T = kelvin

4. z = valance of ion
5. F = 96486

In the case where there conc2 = 2 and conc1 = 1 (no matter the units) at K = 1 and z = 1

V = (8.314 * 1) / (1 * 96486) * ln (2/1) = 8.6168E-05 * 0.693147 = 5.9727065680E-05 volts

Define ev = 5.9727065680E-05 volts

From these new Force and Voltage units, all others can be derived algebraically. Unfortunately, the time unit of 1.42E+009 s is going to have to wait for larger computers. Compromises must still be made to get the simulation *dt* to about 1E-4 s. And so the time unit *de facto* is the *dt* of the RUN. It may for convenience be defined in terms of seconds, but as far as the computer is concerned dt=1, period. 1 timestep = 1 iteration. The key is to adjust all velocities, accelerations, state transition frequencies and conductance units to *dt*. This also affects the readout, such as current (q/dt) and propagation velocities (nm/dt)

derived quantity	SI Unit		Model to SI	SI to Model	Model Unit
distance	meter		1.0000000000E-10	1.0000000000E+10	Ang
mass	kg		1.6605400000E-27	6.0221373770E+26	Daltons
time	second		7.0402418376E-10	1.4204057518E+09	et
charge	coulomb		1.6021800000E-19	6.2414959618E+18	e-
quantity	mole		1.6605400000E-24	6.0221373770E+23	q
temperature	kelvin		1.0000000000E+00	1.0000000000E+00	kelvin
luminosity	candela	@ 3.8E5	5.0807345578E-10	1.9682193364E+09	photons / et
area	m^2		1.0000000000E-20	1.0000000000E+20	Ang^2
volume	m^3		1.0000000000E-30	1.0000000000E+30	Ang^3
velocity	m/s		1.4204057518E-01	7.0402418376E+00	Ang / et
acceleration	m/s^2		2.0175524997E+08	4.9565005132E-09	Ang / et^2
density	kg/m^3		1.6605400000E+03	6.0221373770E-04	Dalton/Ang^3
concentration	mole/m^3		1.6605400000E+06	6.0221373770E-07	q / Ang^3
plane angle	radian		1.0000000000E+00	1.0000000000E+00	plane angle
frequency	hertz		1.4204057518E+09	7.0402418376E-10	1 / et
force	newton	N	2.5634272968E-25	3.9010273521E+24	en
pressure	pascal	N/m^2	2.5634272968E-05	3.9010273521E+04	ep

derived quantity	SI Unit		Model to SI	SI to Model	Model Unit
energy,work	Joule	N m	2.5634272968E-35	3.9010273521E+34	ej
power	watt	N m/s	3.6411068766E-26	2.7464175974E+25	ew = ev*q/et
current	amp	C / s	2.2757456874E-10	4.3941640999E+09	q/et
emf	volt	N m / C	5.9727065680E-05	1.6742828207E+04	ev
capacitance	farad	C / V	2.6825024497E-15	3.7278623925E+14	ef = q/ev
resistance	ohm	V / A	2.6245052780E+05	3.8102419087E-06	1 / eg
conductance	Siemens	A / V	3.8102419087E-06	2.6245052780E+05	eg = q / ev et
catalysis	katal	mole / s	2.3586405670E-15	4.2397303513E+14	q / et
viscosity	pascal s		1.8047148103E-14	5.5410416887E+13	ep et
moment	N m		2.5634272968E-35	3.9010273521E+34	en Ang
surface tension	N / m		2.5634272968E-15	3.9010273521E+14	en / Ang
angular velocity	radian / s		1.4204057518E+09	7.0402418376E-10	radian / et
angular acceleration	radian / s^2		2.0175524997E+18	4.9565005132E-19	radian / et^2
specific heat capacity	J / kg K		1.5437311337E-08	6.4778119593E+07	
specific energy	J / kg		1.5437311337E-08	6.4778119593E+07	ej / Dalton
thermal conductivity	W / m K		3.6411068766E-16	2.7464175974E+15	
energy density	J / m^3		2.5634272968E-05	3.9010273521E+04	ej / Ang^3
electric gradient	V / m		5.9727065680E+05	1.6742828207E-06	ev / Ang
electric charge density	C / m^3		1.6021800000E+11	6.2414959618E-12	e / Ang^3
electric flux density	C / m^2		1.6021800000E+01	6.2414959618E-02	e / Ang^2
permittivity	F / m		2.6825024497E-05	3.7278623925E+04	ef / Ang
permeability	H / m				
molar energy	J / mole		1.5437311337E-11	6.4778119593E+10	ej / q
molar entropy	J / mole K		1.5437311337E-11	6.4778119593E+10	ej / q K
catalysis concentration	katal / m^3		2.3586405670E+15	4.2397303513E-16	
speed of light	c m/s	3.0E+08	2.1120725513E+09	4.7346858392E-10	c Ang / et

TABLE 6: MODELING UNITS

Note that the largest unit reduction, 2.56E-35 J = 1 ej, is quite close to plank's constant, which gauges the energy of a photon in Joule seconds. Most reductions are fairly intuitive, reducing by Avogadro's number or charges per coulomb.

Working in a straight forward manner with quantities of particles dispenses with moles, coulombs, gas constant, Faraday's constant, Boltzmann's constant and Avogadro's number. Furthermore, the units of amps, farads, and Henry's are reduced to mere quantities of particles per unit force and/or unit time.

3.6 UNITS FOR ACTORS

3.6.1 ACTOR KINETIC SCHEMES

Out of range of of SI units are the kinetic schemes of the actor state transitions. While most of the phenomena down at the nano-level obey physics conservation laws and are otherwise stochastically well-behaved, the large protein molecules are cities unto themselves, rife with far more complexity than is relevant to NIP. So called point processes are considered to have zero physical dimension, but this is misleading regarding their informational dimensionality. They act finite state machines, and their dimensionality corresponds to their internal degrees of freedom.

If an analysis were to be undertaken as to the optimal kinetics for a given actor type regarding its role in the neuron's information processing; there would need be full parametric sweeps for empiric data, sensitivity analyses, simplification of the state space to purge irrelevant but computationally costly states, and design to fill in the gaps with reasonably conceived duty cycles for each modality. There would need to be careful mapping of all possible modulation combinations to their effects upon the kinetics, and *vice versa* of the impact upon the kinetic state upon the bindings and unbindings of the modulation sites.

In general, the modeler is at the mercy of the biologists' findings, and usually will not be in a strong position to advance the knowledge of the correct kinetics without collaboration with biologists or molecular dynamicists.

3.6.2 ACTOR POSITIONAL RELATIONSHIPS

How sparse of a representation of reality is statistically sufficient to reveal the patterns of diffusion and charge behaviors typical of neuronal information processing? This question is answered empirically.

About 1E2 actors and 5E3 particles are implemented in the first series of instantiations. After debugging, verification, and multi-core machine availability, these numbers are increased to as high as 1E6 interactors and ten thousand actors. Before reaching such high scales it is expected that at least some of the quantities will have reached their points of diminishing returns. Such discoveries are of import, as quantities can be held to their optimal levels and thus free up computational resources for particular phenomena of interest.

Further simplifications are justified where ever there is a homogeneity or repeating pattern of Actor distributions. It is further hoped that certain gradations of actor densities can be interpolated without nonlinearity problems. Sensitivity tests are performed to validate that such reductions do not incur loss of predictive value for the model. For example, if a representation of an axon happens to have a uniformity of channel distributions along its length, then it is easy to design a series of runs that will determine how short that axon can be made and still preserve the shape of the propagated signal. Then all of that axonal length in excess of that minimum can be collapsed into a simple delay function.

It should be possible to study the plaiding patterns so as to determine the "unit" of pattern. If this is successful it will, in very straight forward fashion, determine the optimal scaling factors.

3.7 UNITS FOR PARTICLES

3.7.1 REPRESENTATIONS OF IONS AND MESSENGER MOLECULES

Having determined that the actors need be represented individually and in 3-space, there is next the question of how best to represent the freely mobile particles in aqueous solution, including ions and messengers. As the information of the actors is determined to equal the number of states, how is that quantity of information to be communicated via the interactors? If there there are n actors with m states each changing states at a peak significant rate of r; then the rate of particle interaction (bindings and unbindings might need to be n*m*r. In a membranal system with 1000 actors, and average of 10 states each, changing states at a peak rate of 1E5/s, then particle communication requires a collision capacity of 1E9/s. However, in a stochastic system, 1 collision does not mean 1 binding event. In a plume or bolus of particles, not every one can collide with an actor binding site. Therefore we need to add the factors of fraction collided c, and fractions of collisions that bind b. Particle incremental motions Bt

= n*m*r/c/b. If c = 0.01 and b = 0.1, then Bt = 1E12/s. If dt = 1E-4 s, then the quantity of particles = 1E8. Also to consider is the communication distance between actors, because for short hops the same particle can serve multiple messages in a second. If the drift velocity is 1E7 nm/dt, and the average distance between actors is 100 nm, then one particle can visit 1E5 actors/s ! That reduces the required particle quantity from 1E8 to 1E3. So at a very minimum, the model must support 1E3 separate independent representations of information carriers between actors. This rules out analytic solutions to the diffusion EQ. Some form of particle systems is indicated. Their individual ability to carry information must be some function of the particle's type, position, velocity, and whether or not it is bound, because ions do not have any internal states. That is, mobile particles can only carry information by their external states, most likely their position, because velocity is continuously disrupted by water molecule collisions. Velocity expresses itself by impact force. Position expresses itself by binding events. We know that binding events serve to modulate actors.

It is therefore concluded that diffusion and drift must be represented as a particle system, not by the conventional aggregate equations.

3.8 ELEMENT SIMPLIFICATIONS

In addition to the specifics of neuron simulation there are the considerations inherent to digital modeling.

1. Scaling Factors
2. Digitization & Numeric Methods

The subset of neurophysiology that applies to this modeling effort is constrained in scope by the following:

1. Limited number of types of elements: Membranes, four types of embedded proteins, and the adjacent ionic solutions are modeled. Other cytological structures are not included.
2. Simplified shapes: Membranes have shape, and those shapes determine both the actor nearest neighbors on its surface, and the define the ceiling and floor of each volume compartment.
3. Limited number of processes: Those processes directly implicated in the information processing role of the neuron are included: diffusion, charge fields, binding/unbinding, conformational changes, voltage-induced drift and torsion.
4. Down-scaling of quantities: To model a neuron at nanometer scale poses computational difficulties unless a reduction in the number of Patches (and processing steps) can be justified and effected without loss of veracity and reliability. Therefore multiscaling is employed. Nanoscale patches of membrane are modeled one-to-one wrt ions, channels and distance.

5. Re-use of oft-repeated computations: Once characterized and verified to the biologic literature, patches may be cloned and collapsed from a system of equations to data mappings, for use in large scale tiling over closed membranes at the micron scale, to effect whole-cell models.

6. Log-scaling of time and space: Because of the very large compass in time (1e-12 .. 1e0) s and in space (1e-10.. 1e-5) m, some form of compression is needed. Log scaling may be justified empirically through the use of multiscaling between patch and whole cell models.

   Only those processes taking place on timescales near to that of the action potential are considered. Typically events between 1E-4 and 1E-1 seconds are included. Nanosecond molecular vibrations, and 28 day learning cycles are far out of scope. It is possible to have the Patch sub-models and the whole-cell Goblet sub-model calculating at different time resolutions.

3.8.1 SCALING CONSIDERATIONS

Scaling within the model is of great import. There are several aspects that need be distinguished:

1. time scaling
2. space scaling
3. quantity scaling
4. force scaling

3.8.1.1 Time Scaling

Simulation Time scaling: because real-time speed of ion collisions and diffusion in solution cannot be modeled, some conversion is selected. Typically microseconds of nano-scale events are expanded to seconds in presentations, and milliseconds of micron-scale events are expanded to seconds in presentations. These are arbitrary and of little consequent because they do not alter the mathematical consequences.

1. Biological time
2. Simulation time
3. CPU time
4. Time Resolution

3.8.1.1.1 Log Scaling of Time

Time cannot be log scaled dynamically without awkward acceleration distortions. Although these can be corrected, it adds to the computation that log scaling was meant to reduce. However, because of the existence of very fast processes (1E-12 s) and very slow processes (1E1 s, both within the same model, it is proposed that the time constants of these processes be rest, according to formula, so as to compress the compass of frequencies of

phenomena. If the 1E-12 s events were compressed so that they were modeled as 1e-4 s events, and everything else geometrically scaled for consistency, then such a model becomes computationally tractable.

If transport takes place *in vivo* at much higher rates than the *dt* of the simulation can possible negotiate the various state changes implied in the duty cycle, either the model is tolerant of the sluggish digital simulations, or else special small *dt*'s must be used for such actors, separate from the normal *dt* used for particles and capacitance.

3.8.1.2 Spatial Scaling

Spatial scaling addresses the question as to how can the size of a neuron be reduced while preserving its functional role precisely? Can the same job be performed with less water, fewer ions and less lipid to make a smaller membrane-enclosed compartment?

3.8.1.2.1 Volume Scaling

A voxel is typically 10 nanometers ^3 and this is scaled to ~ 1 cubic centimeter in visual presentations. The utility of voxels is limited when implemented in a realms of cylindrical coordinates. It may be computationally efficient to calculate only hemispheres around active actors, the size of which is determined by their attractor radius. The attraction radius is an artificial construct that adjusts the model to attract particles of types on the binding profile of that actor. The attractor radius is set so as to effect a collision rate equivalent to the *in vivo* rates, in compensation for when the particle quantities have been scaled down.

3.8.1.2.2 Volume Resolution

The voxel serves several purposes. Reducing the computation for collision detection. Calculating (counting) concentrations. Determining flux and current. Determining voltage across each actor. Harvesting pools for affinities. The voxel must be small enough to represent a single actor's nano-environment, but large enough to yield reliable counts for voltage and concentrations, the values of which are modulators. Voxels are especially useful in the construction of patch models.

3.8.1.2.3 Size scaling

One can reduce the gross size or increase the voxel size, and either way, the picture becomes more grainy. In a complex system of non-linear equations, such “simplifications” are fraught with dangers.

One hundred patches of axon, 1E-8m^2 in size, can be replaced by a single patch scaled such that the action potential retains the same shape and the propagation time across the length is 10 times as long. Each particle would represent 10 ions, and each simulated channel would have a flux 10 times the amperage of the *in vivo* channel. With such scaling, there are implications for radius, mass, charge, and delay functions. Uniform scaling in all dimensions may be intellectually pleasing but may not be the most computationally efficient use of resources. surface to volume ratios are distorted by such "uniform" scaling. Verification is necessary for mixed scale combinations. Recommended is gradual deviations from real numbers, sizes, and speeds noting performance similarities, until the extent of unacceptable error levels (in comparison to the highest veracity RUN).

3.8.1.2.4Membrane Surface Scaling and Smoothing

Biological membranes often have significant irregularities and texture. These have caused great problems in the morphometric efforts, because when tissue is sliced it becomes quite difficult to correctly assign continuity. A small fragment of membrane could even be assigned to the wrong cell, or be recorded inside out. Such roughness increases the surface area, and probably hinders diffusion. The modeler can design a smooth differentiable membrane and then parametrically add texture until model performance matches *in vivo* performance. Mathematicians have developed metrics for tortuosity of a surface. This may be summarized by the increase in surface area. Increased tortuosity implies increased capacitance, and that can be a dramatic factor in membranal system performance.

On the other hand, building a model with genuine surface texture is feasible but computationally costly. In many cases, large computational savings can be realized by smoothing the membrane down to a contour of rotation. This may measure to a smaller membrane area than is needed, so a scaling factor on capacitance may be needed to compensate.

3.8.1.2.5Membrane Surface Resolution

The quantity of addressable nodes on a membrane must produce a density high enough to accommodate the highest actor density in the experiment. When specific actor plaiding patterns are specified, the nodal density may need to be higher to reasonably coincide with the pattern. For a list of reasons, the membrane needs to be represented as a homogeneous surface of a quantity of nodes several times larger than the total count of all actors. This allows

distribution patterns that are not compromised by competition for scare nodes. The nodes are not expensive because they play a role only in the build. After that it is the quantity of actors that determines computational load.

3.8.1.2.6 Membrane Thickness Scaling

Membrane thickness determines dialectic strength. In reality, the polarization of molecular heads of the lipids comprising the membrane alter the effective electrical thickness. However for modeling purposes the extra computational load does not seem warranted. One can merely set the model thickness to the effective thickness. The thickness may easily be varied from node to node, when experimental purpose warrants this.

3.8.1.2.7 Shape Scaling

We do not often think of altering the shape as "scaling". Shapes have spatial frequencies. Scaling back on the frequency range of a shape often smooths the shape (at the high end) and flattens it out (at the low end). The latter is useful for manifolds. The projection of some portion of shape onto a plane has the same effect.

Another approach is to assume some degree of radial symmetry. Although not valid for the dendritic field, once a signal is summed in the soma, then a single wave front proceeds down the axon. For most of the length of the soma and axon, radial heterogeneity effects may be minimal, although not zero.

In any case, when shape is simplified to a contour of revolution the computational load is greatly decreased. The task then is to select a contour which best captures the topological relationships between all the actors, and provides for particle movements between those actors in realistic patterns.

3.8.1.2.8 Spatial Log Scaling

It is proposed that all of the above spatial aspects may be uniformly compressed via log scaling. Thereby the smallest entity of 1E-10 m and the whole cell of 1E-4 m might be compressed to 1E-7 .. 1E-4 m. This will distort the timing of all phenomena that transverse space, including diffusion and drift. This will require empiric studies to to account for the effects and distortions to determine if they can be compensated for without adding back the computational load that was to be saved by compression. The effects of spatial log scaling and temporal log scaling tend to correspond so as to cancel out each other's distortions.

3.8.1.3 Quantity Scaling

A reduction of particles by 1E-6 would result in about qB = 3.6E5, a tractable number on today's PC's. The consequences of such a reduction are considered. The many impacts include:

1. channel flux becomes highly quantized, and incapable of passing less than 500,000 ions in an action potential, or other gating phenomenon. This could result in very grainy transport.
2. shot noise is greatly increased and distorted, in magnitude and altered frequency
3. Membrane capacitance is zero for less than 1 million particles, and
4. very "chunky" thereafter.
5. Diffusion to nearest neighbor may be altered in speed and delay.
6. The effects of water upon such chunky ions needs to be re-evaluated (solvation shells, charge smear, etc.)

Thus, much verification and recalibration work are needed to justify a model with its quantal nature rescaled one million times.

If the ion channels are to be scaled accordingly, what should be their relationships to the modulators? Lowering the concentration of particles that bind to actors would reduce the collision rate irrespective of the quantity of actors.

3.8.1.3.1 Water Scaling

Water molecule quantities are too high to be modeled. They must be simulated by their effects upon the interactors. This implies pseudo collisions that conserve momentum.

3.8.1.3.2 Interactor Quantity Scaling

Each computer, as a function of core count, has a practical limit to the number of particles that can be simulated in a charge field. It is not a matter of waiting twice as long when you double the particle count. Once the RAM memory is exceeded, performance may drop 100-fold, waiting for disc calls every *dt*. Each relocation to a different computer should be tested for its own particle count limit. This determines the practical ratio between biological counts and simulated counts. This ratio determines the graininess of the model. If such graininess is unacceptable, then the model must be cut down in volume, or moved to a larger computer. The neuron can be shrunk, of the neuron cut into Rall-like sections. The latter presents interface problems (boundary value problems) between the sections. It is possible to record the particles leaving each section, but not always know which are entering, except by a rather torturous iteration of simulation sets. It is advisable to restrict model complexity to the capabilities of the machine that will run it. Patience will not compensate for an element count set too high.

3.8.1.3.3 Actor Quantity Scaling

When actors are homogeneously distributed, and the signal measured in vivo to be “propagated” rather than processed, then considerable reduction in actor quantity can be effected without loss of information. Taken to the extreme the entire length of the axon can be replaced by a lag function. But in the case of information processing (as opposed to transmission), small changes in the positions of actors, longitudinally or circumferentially, or in the ratios between actor types, can have profound effects upon the output signal. It is the purpose of this model to provide a platform for investigation of the effects of actor quantity reductions upon model veracity.

3.8.1.4 Force Scaling

3.8.1.4.1 Concentration Field Scaling

This is implied by the ion quantity reduction factor. The problem is that concentration is used to determine flux rates through open channels, and care must be taken to preserve the net effects of that flux upon both voltage and concentrations. Concentration also has implications for diffusion rates. And saturation levels for actors. And starvation levels for transport phenomena.

3.8.1.4.2 Voltage Field Scaling

The Nernst voltage is determined by the log of the ratio of charges across a membrane. This nonlinearity makes scaling the concentration proportional to scaling the voltage impossible. Therefore, voltage must be calculated, not off the model interactor counts but rather off the *in vivo* counts which they represent. The true voltage pressure on the membrane is determined not by the Nernst, but by Coulomb;s law. The Coulomb's calculation and the Nernst calculation are not reconcilable because only the Nernst is proportionate to temperature. The Nernst can only apply to chemical like generation of voltage and applies only to one type of particle at a time. Coulomb's law applies to free ranging particles, whether of one type or mixed. Nernst applies to channel pores and Coulomb's applies to membrane capacitance. To the extent that these do not predict the same outcomes, empirical tests may be necessary to resolve them.

3.8.1.4.3 Affinity Scaling

In chemical reactions, each molecular type is said to have an affinity for its substrates. This is a misconception as the actor has no such power to “attract” interactors at a distance. Rather, the interactor speeds are so high (say 1E12/s) that many collisions occur with the actors, but only a portion of them actually result in a binding event.

Affinity, therefore, is a collision yield. In modeling, however, with slower and fewer interactors, the archaic notion of "affinity" regains its usefulness. In order to effect a frequency of bindings equivalent to that of *in vivo* binding rates, it is necessary to "attract" freely diffusing interactors to the binding site. Although this could be done by choosing the closest interactor of the right type, that would violate the stochastic nature of the process (eliminating the accidental bindings of "similar" interactors as sometimes happens between Mg++ and Ca++. The attractor concept preserves the chemical stochastics, not by predetermining which exact interactor will bind, nor even when a binding will occur. It merely increases the chances of a binding across the actor type binding profile until an event. It borrows the mathematics of a charge field to accelerate interactors towards the binding site. Those which do not bind are reflected off the membrane and return to freely diffusing. The affinity then is a force, and that force magnitude can be adjusted to compensate for fewer and slower particles.

3.8.1.4.4Transport Scaling

The number of particle *in vivo* per unit area of membrane per unit time should normally be preserved. Therefore the number of interactors is transported according to their scaling ratio, corrected for any change in actor density.

3.8.2 DIGITIZATION & NUMERICS

For practical reasons, numeric methods are always near the surface when implementing digital models involving time and space. It is not the purpose of this model to develop numeric methods for efficient use of computational facilities, nor to develop new algorithms to facilitate models of neurons. If either happens they are incidental to the quest to model information through a neuron, regardless of the characteristics of the computer used in the implementation. Each of the functions is intended to demonstrate proofs of concept, leaving optimization of computational resources for others in the computer science disciplines. The model is intended to be an accurate representation first, and computationally straightforward, if not efficient, second. There are occasions when computational speed is disregarded in favor of exploring emergent behaviors or any relevance to how the neuron might be processing throughput information. Because this project is an exploration of both phenomena and methods, documentation is necessary and copious. Documentable code must be readable for the uninitiated. But the most efficient code is the most unreadable. Because the greatest amount of function is packed into the fewest large matrices, to all but the expert, the code looks like a black box. Thus, for the early versions, code is often less efficient for the sake of traceability and understanding.

3.9 METRICS

The adaptation of the mathematics of electronic circuits to neurons may more properly be called the "ionics of liquid state information processors". In a neuron, there is no clock, no wires, and only one large capacitor. Its power source is distributed. Conduction takes place in a 3-dimensional liquid shared by all, and there at least five flavors of charge. Gating logic is driven by thermal noise. There are many mechanisms of modulation. There is rapid turn-over of the gating elements (short life span). The architecture is in a constant state of reshaping. Communication between cells is chemical. So how best can a mensuration system be applied to this variety?

Modeling particle by particle expresses, without any particular intent to do so, for example, the shot noise of ions passing through ion channels, complex wave phenomena in irregular vessel shape, the vagaries of ionic particle diffusion via elastic, momentum-conserving collisions, graded capacitance of charged particles along the membrane surfaces, and non-linear resistance through saline. Flux is easily collapsed into "amperage", which integrates into dynamic charge potentials, regardless of shape.

The imposition of preconceived mensuration blinds us to things we do not know are there. For example using the FFT to find sines will blind us to any patterns in the signals. We will hear the chord, but never the music. Using curve-fitting and exponent peeling algorithms blind us to the presence of any pattern recognition abilities of the actors. Measuring channel open time fractions blinds us to any pattern generation that's driving those open times.

The primary contribution of this model is the merging of 3 previous approaches: diffusion, RC grid, and stochastic molecular states. In reality, these each operate on different time scales (periodicity of significant events), and thus an argument can be made for operating three separate computers, each optimized to their task. However, the universe consists of highly coupled particles, forces and events. The interchange between these three sub-models is sufficiently rich that synchrony becomes a critical requirement. Given that, there is no longer much advantage to running the three sub-models asynchronously, except maybe as even multiple in speed. Given the current technologies of Linux cluster realizations, there will not be much choice in this matter anyway. The various CPU cut through, cache and buffer memory designs will dictate.

Back propagation can be a significant mechanism of the cell, particularly the dendritic arbor. How will you measure that, and its effects?

The base measurements must be particle positions and actor states. Just those and the original compartment positions should capture the entire system. From those three, all other metrics should be derivative. Of course, some of these derivatives will be more convenient and telling than others, but they will come and go with the nature of the query. It is therefore recommended that the metrics be standardized as positions and states, following by a terse library of function available to quickly generate the derivatives of choice.

Of special interest at this time are metrics that detect the higher order patterns above the first order exponentials and second order sines.

3.9.1 COMPLEXITY

Because knowledge of the information processing role of the neuron is imprecise, various computational statistical metrics can be applied in the search to discover a more complete accounting for neuron functions. The neuron can be characterized as highly dimensional, computationally intensive, highly nonlinear, makes extensive use of iteration, is highly robust in the face of damage and structural variation, is highly non-homogenous an irregular in the distribution of its elements, and is somewhat uncertain as to how many input and output ports it may have. Such ignorance of the system under study requires very broad and inclusive approaches, because preconceived and over simplified assumptions have in the past purged out many of its known behaviors. The usual distributions do not apply, but instead must be empirical to the neuron type. The sampling methods must be pursued to high dimensional very large sample sizes. Parameter estimation must proceed via maximum likelihood estimations and similar approaches. The multivariate computational processes require large computers to handle the high dimensionality. The random variables must be generated by authentic physics-based simulations at the molecular level. Precautions must be taken to determine the presence of memory or hysteresis in living neurons before applying Markov processes in representation thereof.

Models must be justified and verified, evolving from the simplest viable forms, and gradually adding the complexities of living cells. Error detection and correction techniques are a necessary part of the modeling process. Designing across incomplete data sets is a necessary risk to further the field. Therefore each model based upon hypothetical values used to fill in missing wet lab data must be so construed and tested to reveal the consequences of various possible ranges of hypothetical values. What is learned from such exercises should be brought back to the

wet labs to assist in determining future experimentation and data collection. The presence of "trees" explicit in the dendritic arborization and the abstract "trees" implicit in the "decision" processes of neurons with action potentials greatly complicates the interpretation of model behaviors. It is therefore prudent and probably necessary to begin with the simplest of arborization and actor plaiding patterns until this factor is understood and becomes predictable. Although this model is intended to be parametrically controlled, it is acknowledged that such highly non-linear systems as neurons can operate in sparse realms where parametric control is not appropriate nor feasible. Although such challenges can only be addressed once incurred, it is prudent for the investigator to be watchful for complex behaviors that exhibit modalities, and that these not be discounted as noise.

3.9.2 PERFORMANCE

Because only the ion channels and ion pumps are emphasized in this first version, critics may voice concerns about the inadequate treatment of the many other membranal proteins which *in toto* comprise a whole for the membrane's information processing capabilities. Indeed there well may be non-channel proteins which have fast enough time constants (approx 1E-3 s) to qualitatively alter the "transfer function" of the whole cell. In this first version, however, all such effects will be bundled as "modulators". To the extent that the model cannot reconcile with the bio-data, that gap may indicate the nature of missing components, and hopefully will be suggestive of what needs to be corrected and/or added. In any case the model supports such additions.

Despite the immense complexity of such an undertaking, the real world cell exhibits some number of "high runner" states, that are constantly in play and determinant of the role that the cell plays in the nervous system. The other approx 99.9 percent of the possible states are low impact events, and can safely be regarded as noise, until proven otherwise by biological phenomena of note. Low probability states are mathematically problematic, as they can serve to shift the "mode" of a complex molecule to some completely different behavior pattern for a while. Thus, low frequency is not a criteria for dismissing it in the model.

Neural Ionics is intended for the investigation of parametric sensitivity, stability and mode identification of whole-cell filters. It will serve in the design of novel channel/membrane systems towards increasingly competent neural networks, by evolving membranal systems behavior towards useful patterns. Neural Ionics offers the possibility of specifying simplified artificial assemblies of cytological elements, that none-the-less capture most or all of the

information processing capabilities of the living cell counterparts. For example, once a channel location pattern has been verified to propagate a particular *in vivo* signal shape at a particular velocity (presumably consisting of thousands of channels), one can then find, via Neural Ionics, the minimum number of actors to duplicate this effect.

This model serves to discover the minimal number of elements plaiding a molecular pattern to achieve a desired reliability of any of hundreds of novel biologic neuron behaviors. This is useful information in at least three ways: the screening out of hypotheses which map channel constellations to neuronal function; the design of artificial neurons; and in the design of therapies for dysfunctional living neurons. Because nature is bountiful in its quantities of components (1E6 ion channels and 1E13 ions), it is presently impossible to model all of the molecules on a one-to-one basis. It is therefore necessary to discover how few of these components will retain the information processing characteristics of the larger numbers. Such found minimal quantities allow for more efficient modeling, which in turn makes possible building to ever higher levels of organization. The most obvious application of such whole cell models as these would be assembly of quantities of them into local circuit networks.

Information theoretic analyses are applied so as to insure that the several simplifying assumptions that do not compromise the output behavior of this dynamical model of a complex 3-d shape of significant heterogeneity.

We do not yet have an accounting of the neuron's information processing capacity by a quantitative measure. We do not yet have an account of the information processing capacity of constellations of ion channels via their stand-in kinetic schemes and the peculiar interactions between adjacent channels of differing types as they may be variously distributed across the membrane. We do not yet have each of the functional areas of the neurons (distal dendrites, proximal dendrites, dendritic spine, soma, initial segment, axon, node of Ranvier, myelinated internode, bouton) characterized for their modalities and information processing capacity. We do not yet have the effects of shape upon all of the above, their modalities and information processing capacity. A programmer's workbench is needed that will support a full compliment of receptors, channels, vesicles and pumps, distributed in a realistic fashion over a neuron shaped compartment, filled with a particle system of ions that are transported across the membrane.

3.9.2.1 Viability Testing

Viability requires one or more forms of stability. Viable ranges are achieved by enacting upper and lower limits on the physiologically significant parameters. These are curbs to activity. The region between the curbs is “free”, in

that any possibility and combination is allowed. But having reached a curb, the system will expend energy to resist any further deviation and will return to values within the curbed domains (if possible). We call this homeostasis. Two nearly equal but opposing forces leave a band of freedom in between, the width of which is a function of the inequalities.

Viability testing for biological parameters grows out of physiology. Physiology has produced a number of system models that are predictive of organismic function. But their viability is usually determined empirically, not yet by criteria within the model. Lyapunov stability makes significant contribution to our understanding of systems that "crash". Iberall contributed a general theory of viable systems in 1972.[62] It is yet a young science. Because a living cell consists of a biochemical network of hundreds of thousands of types of molecules, systems biology does not yet rise to the challenge of determining the viability of any configuration or modification thereof. So far we have only grossly simplified systems like lung capacity and kidney clearance, but Bayesian Networks are making strong headway into predicting the behaviors of ever larger quantities of elements and their relationships.

As a base case for viability, a model needs to conserve matter, hold Boltzmann temperature, pass energy such that energy in = energy out; conserve momentum; be capable of maintaining rest tonicities by pumping across the membrane; and in order to qualify as a neuron, show some effect at the output synapses in response to perturbations at the input synapses. In addition, one might add that neither particles nor the actors should lock up (become frozen in some position of state that would thwart their ability to serve as a neuron).

3.10 SCOPE

This project provides a test bed for ion channel constellations. Ion channels and their receptors critically determine both the trans-cellular information flows, and the trans-synaptic information flows. Biological neural networks receive complex natural stimuli via a huge variety of bio-transducers. These transducers each have unique "filter functions" or "nonlinear transfer functions", and may have unique synaptic chemistry and geometry as well. They are wired into the neural networks with complex phase and spacial relationships across perhaps thousands of inputs per neuron. The connectivity patterns between neurons may be repetitive but are always complex. Nature offers a large library of such patterns to study. Neuroscience therefore needs a simulation environment that gives equal weight to both the mechanisms of synapse and the mechanisms of propagation along shaped, bifurcating

membranes. Both synaptic and cell surface processes consist of diffusion, kinetics, and electrical phenomena. A broad physics-based approach can smoothly incorporate both synapses and whole-cells into an information-flow model.

This model supports the design of novel (hypothetical) ion channels engineered to specific functional requirements. The ability to create a full constellation of functional types of neurons by design, becomes tractable when modeling takes place at the molecular level. There are direct one-to-one correspondences between model elements and molecular species, although actual amino acid sequences may or may not be capable of replicating desired conformational stabilities, and to this extent limit designs. The model is initially built of representations of molecular types already known and synthesized. It then directly supports efforts by others to design new functional types of channels, pumps, and receptors by providing a simulation of molecular system performance and behavior. It provides the tools and test bed for the development of new computational functions for neurons.

Engineered neurons following biologic designs are valued for 4 important features.

1. They can process up to approx.10,000 inputs in a great variety of mathematically distinct ways;
2. They can be wired together into a huge number of possible schematic patterns which predispose their logic and function;
3. They can be chemically modulated in function and mode, speed and priority (locally to globally in effect); and
4. They can learn over a variety of time constants, from short-term to long-term, via a very long list of plasticity mechanisms.
5. Theoretically, at least, a fifth function would be that they can evolve in the Lamarckian sense into a better processor to the task, and then be cloned.

There are several advantages to this (admittedly tedious) approach.

1. Robust and representative molecular physics and kinetics reveals the biological nuance, even if not understood, so long as the shape chosen is adequately representative of topological relationships between actors.
2. Multiscale modeling lends itself to assembly of synapses and membranal patches into whole cells; whole cells into local circuits; local circuits into ‘cortex’, and cortical organs into nervous systems.
3. Advances in large-scale computing do not require the model to be re-designed; only several global parameters adjusted, like *dt*, *dx*, N.

Some of the impediments to progress in the study of cells that compute have been self inflicted. For example, the metrics of channel capacity (rather than computability) were often applied to computational machinery. That is like

trying to measure how much a computer is like a copper wire! A great computer cannot be a great conductor. Already mentioned: treating variance as noise, and treating thermal energy as noise. Also: treating ion channels as I/V plots (current on the y axis, voltage on the x axis), and ignoring the fact that neurons have shape, which is highly determinant of information flows, strengths and phase.

In the view of analytics, the terse equations of the “integrate and fire” neuron are potent in that they can simultaneously represent millions of elements, as the cable equation represents millions of lipid, protein and ion particles within an axon. Analysis seeks the most deterministic, stable, repetitive aspect of the item under examination, such that it may be 'reduced' to a few short equations. But in the analysis of biological neurons, those aspects which often lend themselves to being culled out as redundant are precisely those which are informationally significant. That which is 'analyzable' (capable of being collapsed) is the carrier (in the sense of radio transmission consisting of the station frequency carrier, modulated by an audio signal). The carrier is the underlying structure and matrix for transmitting information. Note that the carrier is not the content. Information theory – particularly coding theory – makes this clear. Information <u>is</u> distinguish-ability; changes in state, the uniqueness of the thing in time, the variance. The carrier is stationary, while the content is volatile. Therefore, the information is that which is abstract-able from its carrier, and the information content of an entity is independent from its stationary physical embodiment. Information content is likened to surprise value. If a neuron could be stripped of all its analytic information (all the patterns inherent in aggregates), one would be left with a remainder of novel, unpredicted patterns, the variance. This variance is the very quality a responsive organism requires for alerting to the changes in its environment, and is the essential activity of computational cells. This has implications. It requires the abandonment of the Hodgkin and Huxley model, and of the I/V plots representing ion channels. This project responds to that awakening.

3.10.1 <u>OUT OF SCOPE</u>

The model shall be of a sufficiently general basis to be amenable to eventually include nutrient systems, electrochemical signaling systems, cell development, plasticity and learning systems, cellular housekeeping, turn-over and repair systems, and molecular memory systems.

NOT considered in this version: Development, Genetics, Proteonomics, Enzymology, Pathology, Structural considerations, channel turnover, and vesicle production/recycling. Processes not included because they typically are not dynamic determinants of the computational information flows through the neuron are: osmosis, hydrostatics, pH, aquapores, metabolism, growth, actin/kinesin/myosin mechanical effects upon shape and connectivity, acidic vacuoles, endosomes and lysosomes, cytoskeleton, contraction, support cell interactions, respiration.

Processes that typically are not dynamic determinants of the computational information flows through the neuron are NOT considered : Development, Genetics, Proteonomics, Enzymology, Pathology, Structural considerations, hydrostatics, channel and pump turnover, and vesicle production, osmosis, pH, aquapores, metabolism, growth, actin/kinesin/myosin mechanical effects upon shape and connectivity, acidic vacuoles, endosomes and lysosomes, cytoskeleton, contraction, support cell interactions, respiration.

Also out of scope are the many artifices that comprise the tools of neurophysiology: micro-electrodes, patch clamps, EM stimuli, pharmacological agonists, blockers and mimetics.

4 SOURCE ELEMENTS

4.1 BIOLOGICAL SCIENCE OF ELEMENTS TO BE MODELED

4.1.1.1 Whole Cell

Cell morphology among nerve cells is as varied as in any aspect of biology, except perhaps the complexities of the immune system. The shape of the various neuronal features may have either excitatory or inhibitory influences, spatially and/or temporally. The pattern of ion channel distributions is expected to interact with shape to produce a characteristic behavior of the membrane in response to stimuli. The axonal fan out provides an obvious distribution in space, with some implied phase discrimination along the varying lengths. The fan out also provides the opportunity for differentiation (between the signals of two parallel or perpendicular axons, immediately or temporally). The radius of a bifurcation crotch may determine antidromic propagation, or lack thereof. Caveoli are yet to be investigated as to their effects upon signal processing. They increase surface area, therefore capacitance, and tend to isolate each "pocket" of such area electrotonically, encouraging local effects without far reaching propagation.

For these and other reasons, it is useful to design a model that represents the channel distributions realistically positioned upon a simulated membrane of various shapes typical of neurons. To capture only the topological aspects of neuronal shape, simplification is indicated. To study the exact intricacies of neuronal shape features, partial models, called patches, are indicated.

4.1.1.2 Shape and Texture

The fine texture of the plasma lemma as appears in micrographs often is rough and perhaps distorted by the fixative or other handling. In any case, such texture makes it difficult to follow the membrane as a continuous 2-d sheet. Computer algorithms often must make creative leaps to assume membrane continuity between the slices. [63] As a result it has come into practice to smooth the membrane texture data sufficient to make the continuity obvious in all

modeling calculations. Such a reduction in tortuosity has the unintended effect of reducing the surface area, which in turn reduces the capacitance per channel unless the channel quantity is reduced proportionately.

To support varying shapes of neurons and their processes, various algorithms were trialed to generate stochastic shapes. [64] By 1999, dendritic tree bifurcation points were being randomly simulated, parametrized to mimic several neuron types.

Membranes of interest are closed-surface vessels and support lateral diffusion of ions both over and under the membrane, by virtue of the thickness of the extracellular space, and an implied "thickness" of the intracellular space due to the presence of the nucleus and reticulum. Where ever ion channels provide ion diffusion through the membrane, "complete circuits" (in the electrical sense) are prolific. Unlike electrical circuits, there are no formal input or output ports, academic notions of boutons not withstanding. Despite the conception that dendrites are inputs and axons are outputs, the membrane itself is continuous and "circular" (spherical, closed surface). An input occurs anywhere there is a receptor, and an output occurs anywhere there is exocytosis. As the inputs are chemical signals acting as modulators and the outputs are again chemical signals, it is not electricity that is being passed on from neuron to neuron. Indeed, when there is voltage being produced, as in the electric eel, it is emitted from the entire plasma lemma, not limited to axonal boutons. Thus, the membrane shape does not imply a ported linear system, as do man made electronic circuits. Antidromic conduction is trivially accomplished in a quiescent cell by stimulating it at arbitrary locations. In theory, at least, the membrane serves as an excitable surface upon which one can insert input signals or "exsert" outputs at almost any location (tap into the system to realize an output signal). It is the patterns of those locations which in good measure determine the flow patterns of information, and therefore the role of that neuron type.

4.1.1.3 Extracellular Compartment

Extracellular water between neurons (not in blood nor lymph) is estimated to be about 14% the total brain water volume.[65] This model is interested in only that water which is juxtaposed to the neuron plasma lemma, on both sides. As a starting point, it may be assumed that equal volumes of water inside and outside the membrane participate in ion exchange across it. Thus, doubling the 14% to 28% indicates how much of brain water volume must be accounted for in modeling membranal function. It may be demonstrated via physics-based models of the

zeta potential that somewhat less volume is active in neuronal information processing because of membrane capacitance which holds a large number of ions very close to the membrane. The rapidity of transmembrane transport also tends to keep active ions close to the membrane.

The thickness of the extracellular compartment is about 10 microns. It contains not only the ions as determined by the pumps and channels on the neuron under study, but also by all of its adjacent glia and neurons; their pumps and ion channels. The synaptic clefts are rather specialized patches of extracellular fluid, rich with vesicles, ligands, receptors and ligand-pumps. The cleft thickness is evidently held rather constant by protein structure. The remainder of the membrane is likely to consist of a set of: channels and ion pumps embedded in the membrane with ions and ligands on either side of it. The tonicities of course are not the same outside and inside, and there is a higher protein concentration inside. Intracellular ligands are necessarily for intracellular communications and extracellular ligands for cell to cell communications. It is likely that the glial cells, which outnumber the neurons are pumping both ions and nutrients into the extracellular spaces, as well as removing metabolic byproducts. For purposes of this model, such housekeeping functions will be ignored.

4.2 MEMBRANE GEOMETRY

The membrane may be smooth , rippled, folded or convoluted into caveoli. Fold overs are problematic for the morphometrics. Workers often apply smoothing functions to flatten out the bio-membrane in an effort to avoid mistaking a fold for a neighboring cell. One can view the spatial Fourier transform of a whole cell membrane and see that the highest frequency components represent the texture or nano-folding. In the mid frequencies are the bifurcations and terminations. The lowest frequencies represent the overall shape of the cell.

Geometrical representations are not trivial, as digitized geometry algorithms are not yet advanced enough to generate neuronal shapes without tedious manual work. In addition to a geometric surface, the membrane serves as the boundary to the volume within. Thus, the surface is the differential of the volumes on either side. As one zooms in on any particular location on the cell membrane its curvature becomes more planar. This suggests employing manifold theory to reduce the three-dimensional patch to two dimensions for computational purposes.

4.2.1.1 Manifolds

3-D shapes maybe mapped onto 2-d matrices if there are no sharp corners and if there are no fold-overs in the projection. There is a significant computational advantage to doing so: 2/3 *N. However the gain is partially offset by the extra bookkeeping of stitching the several patches together again. A greater gain is realized when the projections (accomplished by merely ignoring one of the x,y,z dimensions) can be processed so as to avoid the forward/backward transformations of basis from Cartesian to polar every dt.

4.3 MICRO SCALE ELEMENTS OF THE NEURON

By microscale is meant those features of a neuron that are typically measured in units of microns, as opposed to nanoscale, intended to address molecular features.

4.3.1 SYNAPSES

As synapses are concentrated nodes of information transfer between cells, they are very high in NIP relevance. The synapse is characterized by membranes and actors similar to the general plasma lemma, except that the actor density is typically much higher, especially receptors and vesicles. Therefore, concentrations of neurotransmitter can rise much higher, and the pumps and catalytic mechanisms to recover spent neurotransmitter must also be much denser. There may be types of actor that are present only in synapses. Biologically the synaptic cleft is not a separate compartment from the extracellular fluid. However, for modeling purposes there might be reasons to treat it as a separate compartment. Cleanup computation of specialized synaptic particles that leak out the edges of the synaptic cleft into the extracellular fluid can thereby be avoided, unless such leakage is a feature of what is to be modeled.

Diffusion time across the synaptic cleft is less than 5E-4 s. Therefore the model distance cross the synaptic cleft cannot be greater than what model particles can cross in that time. The time smear from first arrival to last arrival also may be informationally significant, forming the temporal envelope of the signal. A model of this process must include ligand recovery else they go on to create spurious signals (echoes). There are some open questions about the role of charge effects within the synapse. The presence of any ions at all implies an EM force is present. Creative use of drift could speed the transit of particles.

4.3.2 DENDRITIC ARBOR

For several decades, dendrites were thought of as Rall compartments strung together, each performing as an RC node, or according to the cable EQ for the longer compartments . Such embodiments supported a deterministic response curve to be propagated along a dendrite, but left no room for the dozens of ways that living dendrites modulate, adapt, alter modes, and fine tune the balance between competing, synergistic and canceling signals. In other words, all of the information had been purged from the model by design. [Note that information is the "surprise" value of a system.]

It was found in 2000 by Archie, that the distal dendrites serve functions different from the proximal dendrites.[66] This is obvious in one way: there is no need to inhibit anything until there is something there to inhibit. Accordingly, inhibitory synapses are usually found more proximally in the dendritic arbors, and on the soma as well. Inhibitory inputs can be processed to increase the contrast, and to sharpen the frequency tuning.

There are numerous ways to collect morphometric data for modeling. Electron micrograph slices were traced and reconstructed into 3-d models of arborization.[67] Shapes can be three-dimensionally complex, with the important feature being their connectivity. Once connected, the significant features suspected of signal processing are diameter taper, length and bifurcations. The length and bifurcations are captured in dendritic profiles similar to the genetic dendrograms.

Geometry, by virtue of conduction velocity times segment lengths, determines phase relationships between the branches, and phase can make a huge difference in neuronal response.[68] Whether or not there is back propagation also depends upon dendritic geometry, and upon channel positioning patterns. Changing the shape of the dendritic tree can alter the propagation threshold and wave shape, without any change in the channel densities. [69] The dendrite diameters, taper rates and bifurcation points influence firing patterns and basal rates.[70][71] All of this implores the modeler to find ways to include the effects of shape in whole cell models.

Randomness (variance), in diameter, length between bifurcations, and channel placement, all contribute to a graded response. Rigidity of form yields narrowness of responses. If the dendritic branching and actor placement pattern was perfectly homogeneous, then neurons could offer little more than an "all or nothing" response. In the lower animals (turtle) randomness is a primary strategy for information processing, whereas in higher forms (rabbit)

differential inhibitory fields are more responsible for information processing (creating moire patterns between excitatory and inhibitory arbors).[72]

The initiating nodes are depicted by spherical coordinates on the soma. Then lengths are denoted in 1E-6 m (microns). Note that the vertical lines are considered to be of zero length. Bras in 2003 determined that the bifurcation pattern is the single largest determinant in dendritic tree performance.[73] Dendrograms can then be embellished with diameter data, and locations of synapses.

Additional necessary information to embody the dendrite is the actor distribution densities. This is often accomplished by fluorescent marker micrographs, and verified by random patch clamps. In particular: the number of vesicles and their contents, the number of receptors and their fan out capabilities, the number of ion channels, their locations and their types, the number of pumps, types and locations. This information at synapses serves to determine whether a synapse will function in an inhibitory manner, or excitatory. This information, along the dendrites between synapses serves to characterize the excitability and the speed of response, the propagation velocity, and whether a response is graded or an action potential (digital spike). When the dendrite composition is consistent in pattern from soma to distal tip, then only one representative segment need be mapped as to actor densities. This pattern can then be mapped onto all the other neuron shapes and sizes, scaled in length and diameter, stretched between bifurcations.

Some dendrites have spines, which are small hollow processes budding out from an otherwise smooth cylindrical or conical shaped membrane. Spines may be spherical or irregular in shape, but are usually characterized by a stalk diameter smaller than the head diameter.

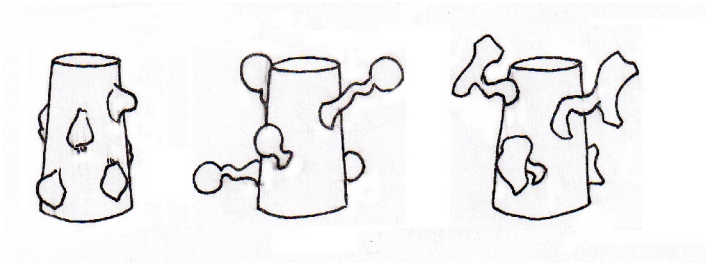

FIGURE 5: DENDRITIC SPINE SHAPES

Dendritic spine shapes: buds spheroids irregular

This complicates the diffusion problem, as spines act to isolate much of ion diffusion from the main channels. The capacitance of the spines has been measured at 1.5e-2 farads / m^2.[66]

In pyramidal cells, the spines contain four times higher channel densities than the rest of the shaft. The excitable dendritic spines are found to be necessary to effect back propagation in the dendritic arbor.[74][75]

4.3.2.1.1 Inhibition

When the mathematics of signal transmission along a neuron is considered, a rather delicate consideration arises. The amount of inhibition needs to be quite accurately matched to the amount of excitation. Every process described above, though described as a stimulus, most likely consists of two types, excitatory and inhibitory. The role of two inhibitory neurotransmitters is well known (glutamate and GABA), but systematics reveals that inhibition can be accomplished any of a long list of ways. A complex system can be disrupted from passing an excitatory (or basal) signal by any of a variety of disruptions, each of which can classified as inhibition. Too great a distance between channels; too long of a refractory period; fatiguing out the pumps, allowing chloride to cancel out the positive charge differential; too much capacitance per channel; membrane texture (shapes) that tend to dampen out the signal as sinks; allowing in the Potassium too soon will cancel out the Sodium in rush; diffusing the signal across the great expanse of the soma; geometry that causes a split signal to collide with itself; too high of a propagation threshold; too small of a channel conductance; molecules that tend to block the channels shut; pumps that make type of messenger molecules unavailable; glial the modify the extracellular tonicity. There are probably many more opportunities to reduce a signal. From a modeling point of view, getting the excitatory mechanisms to all work properly is the challenge. Inhibition is easy, just break something. To be faithful to the biological mechanisms of inhibition, the modeler chooses which way to break things in correspondence to the biological effect. One can modulate ion flow or actor kinetics.

4.3.2.1.2 Back propagation

Although a theory of back propagation is available for networks, the role of back propagation within a single cell is a largely unexplored area. Where ever the output of one channel (ion flux through the membrane) is sufficient to serve as an adequate input for its neighboring channels, then a “chain reaction” (via voltage thresholds being crossed) can occur, thereby sustaining a wave front of channel openings along the surface of the membrane. Because the axis of the channel is always perpendicular to the membrane surface, the channel has no capacity to

sense which way is “forward” (towards the axonal bouton output vesicles). Channels should be considered as omnidirectional receivers and as radial transmitters. Despite that the receptor sites on the channels may be eccentric, that does not make them unidirectional. Ligands arrive by random walk processes due to collisions with water molecules, so the direction of the hit is unpredictable, therefore lacking in information. This raises the profound question: given an excitable membrane consisting only of of lipid membrane and such channels, how does it reliably produce dromic propagation of signal from dendritic end to axonal end?

First of all, there must be initiators. The loci of initiation are typically at the dendritic synapses. The various receptors initiate ion channel openings, which in turn initiate the voltage wave. Though the voltage waves radiate out in concentric rings, the only channels responsive to these waves are those not in refraction and close enough that the wave strength is greater than the channel threshold. For the signal to propagate, there must be signal repeaters. An ion channel type is a repeater if its output is of the same character as the input stimulus. Most commonly, a voltage change from high negative numbers to near zero values will cause the channel to open, and such opening also causes a similar voltage change. Clean repeaters can continue high fidelity signal transmission over very long lengths of membrane. Then there must be terminators. The vesicles are sensitive to rather weak signals, in the form of a few Ca++ ions, which trigger exocytosis of a significant quantity of neurotransmitter molecules into the synaptic cleft from the presynaptic side. There is one other feature of this system of propagation. There needs to be some mechanism of dampening echoes. Without this feature, one disturbed channel would trigger all its neighbors in all directions, which in turn would trigger all their neighbors. And so forth, *ad infinitum*. This would be a sort of nano-epilepsy, with no way to stop it short of exhaustion of the energy supply. However, ion channels have a solution to this problem. It is the refractory period, the effect of which is to fail to respond to an echo, and thus to quench any back propagation over areas the wave front has just covered.

That works fine for the singular axon, but what about the arbor of dendrites? If a small number of branches are stimulated and a wave proceeds toward the soma, what happens at the bifurcations? There will be some branches not participating in the original stimulus, therefore not in their refractory period when the wave arrives. Based upon the repeater model the wave should proceed both ways: onward toward the soma, and around the corner, back up the quiet branch. The channels on the quiescent branch will respond to the propagation even when serving to move the wave backward toward dendritic tips of the unstimulated branches. This particular form of antidromic propagation applies only to peer branches that did not receive the initial dromic signal.

Therefore back propagation is possible. Some types of neurons might employ such back propagation in adaptation. Other may dampen out the signal such that back propagated waves quickly die out and have no effect. Some may recruit the quiescent branches simply to build the strength of the wave front. Some may use the back propagation as a way to put the quiescent branches into refractory period so as to block out competing (but slightly late) signals from other locations on the arbor. The model must accommodate all of these possibilities, as a function of channel types, channel densities, shape of the dendritic bifurcations, tonicities at the bifurcations, and the possible presence of modulator particles at the bifurcations.

4.3.2.1.3 Arbor Fan-in, bifurcations

The dendritic arborizations typically channel information towards the soma, and perhaps also antidromically to adjacent dendritic branches. How much information is propagated antidromically and what becomes of it is something models like this one should be capable of answering.

4.3.2.1.4 Arbor Shape

A dendritic tree is often assumed to communicate information from the distal synapses towards the soma. Why a response wave proceeding alone one branch does or does not turn at the next bifurcation with another branch is determinant on the channel distribution pattern around the bifurcation. One measurable difference between the orthodromic wave and the antidromic wave is increasing diameter vs decreasing in diameter. Can such a shape gradient quench anti dromic discharges? If the larger diameter responded quicker, can this quicker response serve to mute the sightly slower response of the upstream branch? Theoretically, it is possible to place ion channels of different kinetics on the larger downstream segments, than on the sister upstream segments. Kinetics that are such that all the upstream segments respond with a slower lower voltage and the downstream large section responds with a faster higher voltage. If the low voltage signal arrives first and then the channels respond normally to propagate the wave, strong enough to depolarize only a few of the sister branch putting a portion into refractory state. Then the larger fast signal is triggered, on the downstream branch then the sister branches will receive the higher voltage. But given that a portion of them are in refraction, the response will be incomplete and fail to back propagate.

Bursting neurons tend to be larger with thicker dendritic arbors.[76] Can shape determine the presence of the bursting modality, or is bursting determined by the channel types and distributions? It is possible for one ion type

(calcium) to bind and thereby modify another channel type (sodium) so as to shift modes (from spiking to bursting). [77]

4.3.2.1.5 Arbor Size

Dendritic arbors vary almost a hundred-fold in size. The axons vary at least 10000-fold in length. This raises an issue of scaling factors. Is the arbor strictly a mono-signal carrier to get from point A to point B? Is an arbor only a bifurcation map? Can a dendritic arbor 100 times as big be made to perform exactly the same NIP function? If so, what changes in tonicity, channel density and channel kinetics compensate for changes in length? In diameter?? These are valid and important questions for the model to answer. It should be capable of sweeping parametric values so as to "hill climb" (optimize) toward answers to these questions. The challenge remains to determine what effect sweeping the value of each parameter has upon the NIP behaviors of the cell. A cautionary note: to the extent that the arbor is an information processor, as opposed to an information conveyor, necessitates a much more intricately faithful model. Parametric tradeoffs that preserve conveyance may disrupt or alter the processing function.

4.3.3 SOMA

Somas, though usually located axially, in some cell types are off to the side on a stalk, out of the information flow ways (e.g. bipolar cells). Each cell type will require a mathematical function that can generate the soma shapes and placements over the domain of variability. Synapses on the somas often play inhibitory roles or otherwise modify the signal that has been integrated by the dendritic arbor.[78] Some cell types receive both inhibitory and excitatory synapses on their somas.[79]

4.3.4 HILLOCK

The axonal hillock, also called the initial segment, is noteworthy because it often hosts a special selection of channel types in high density so as to effect an analog to digital conversion of the signal. This requires the following: First that an analog (graded) propagation wave arrives (usually from across the soma), converging and concentrating at the initial segment. Second that the next channels downstream have a rather high threshold. If the signal falls short of this threshold, they do not respond at all, and the signal fails to propagate. It damps out to zero. If the signal

voltage exceeds the threshold, then this concentrated mass of ion channels all respond strongly. The response is a Hodgkin Huxley type that is fixed in its strength and duration. The shape of the response is determined by ion channel internal kinetics, not by the strength of the incoming signal. Therefore, any further increases in the graded input signal above the threshold will not alter the height nor the speed of the response signal. The temporal shape of this response is called the "action potential". It is strong enough, that in the presence of the same type of ion channel evenly spaced downstream, it will reliably propagate down the entire length of the axon. Thus, the hillock is the a2-d convertor of the cell. It is expected, but not proven, that the quantity of actors to accomplish the A2D conversion will be the necessary and sufficient set, i.e. near the minimum so as to conserve metabolic energy.

4.3.5 AXON

In those neuron types that sport action potentials, the axons are populated by very uniform identical ion channels and channel densities all along its length. Although a neuron is typically depicted as having a thousand synapses on its dendritic tree, and only one lonely axon, simple logic dictates that the aggregate of all axons must have just as many synapses as the aggregate of all dendrites. For every connection there must be a presynapse and a post synapse. The only exceptions are at the two edges of the network, the connections to the sensors and to the motor end plates (muscles and glands).

Therefore, models must begin to accommodate this fact of connectivity. A complete nervous system will fan out for the first half and fan in for the second half. If there happens to be five layers in and five layers out, and a 1:10 overall fan-out , then the first half neurons will have on average 1:10^(1/5) ratio of dendritic connections to axonal connections. That is 1.58 times as many axonal synapses as dendritic synapses on each of those neurons. For the entire second half, this ratio will be inverted. For completeness, it is mentioned that certain nerve types specialize in horizontal connections. In the horizontal plane, there are no constraints as to the ratio between inputs and outputs. Decisions are made by fanning in, and general alertness is effected by fanning out. For stability a horizontal plane may be modeled from a low quantity with a 1:1 ratio of dendritic to axonal synapses, and then parametrically swept as the quantities increase to note the effects. The quantities of horizontals simply are in addition to the quantities of verticals, with no implied displacement. Of course, the vertical cells must sport what ever additional synapses are needed to connect the horizontals into the network.

4.3.5.1.1 Nodes of Ranvier

The myelinated axon may be interrupted by any number of Nodes of Ranvier. They are characterized by a sharp increase in capacitance, and dense clusters of Na channels. Myelin adds many layers (5 .. 200) of lipid membrane wrapped tightly around the axon, but only for discrete, partial lengths of axon, leaving a short gap of nude axon (the node of Ranvier) before another myelin wrap begins. These many layers have the effect of greatly reducing the capacitance of the axonal membrane over myelinated portions. Capacitance acts as a low-pass filter in the neuron, so long naked axons will lose their signal within about 1E-3 m. Longer lengths of axon can carry a signal by virtue of a very high channel density, high pump density, high energy consumption, and high transport rate of the energy source molecules (ATP) to drive all of this. The increased axial transport requirements to fuel all of these mechanisms force the axon diameters to get quite large. Such is the case of the giant squid axon. At some point, such arrangements become impractical (too high energy consumption) or even impossible (not enough cross sectional area for the needed transport). The larger life forms (think giraffe and blue whale) require axons several meters long, and myelin makes them possible. The effect of myelination is to create a concentrated spike at the nodes, followed by a long stretch of very low resistance, low capacitance, saline conductors to the next node. This arrangement increases conduction velocity while decreasing energy consumption.

For myelination to greatly extend functional axon length, good conductivity is needed both axially within the axon and extracellularly along the length of the axon extracellular saline. These two support a “complete circuit” from node to node. Every node is packed with ion channels so as to concentrate current flow at the node, which in turn creates the largest voltage disturbance practical (so the signal can make it to the next node). Saline conduction occurs much faster than channel kinetics, so length, *per se*, does not slow delivery times very much. Channel kinetics are rate limiting and therefore determine conduction velocity. To a lesser extent increasing channel density increases conduction velocity, and lengthening the node-to-node distance of course increases conduction velocity (but decreasing the quantity of channel kinetics in series). Nodes of Ranvier can be modeled by distributing channels at the nodes only, and decreasing the internode stretches to the very low capacitance value by setting the membrane thickness to a much higher value. There are some ion channels under the myelin, too, but they cannot move many ions in their smothered situation. Consider that after every action potential, pumps are necessary to reset the “rest” voltage, and where they are located will determine the extent of axial current.

4.3.5.1.2Boutons

The receptors of the post synaptic bouton are part of the so called G-protein systems which fan out a signal via catalysis of messenger molecules, which then travel under the membrane until they bind to ion channels with the complimentary receptors in the vicinity. The vesicles of the presynaptic bouton, by releasing a bag full of neurotransmitter molecules into the synaptic cleft, realize a fan out of the signal, so as to stimulate receptors across that cleft. The biological perspective sees vesicles as very different mechanisms from receptors. Their mechanisms are radically different. Their sizes are radically different. The complexity is radically different (vesicles being the more complex). From a strictly information theoretic view, however, they are both transducers, that effect some chemical leverage of the signal across a membrane. The modeling considerations for axonal boutons are quite the mirror image of that of the dendritic boutons.

There are several issues concerning the synaptic cleft. Apparently, the gap is held at a fixed consistent distance, perhaps by protein chains or pillars. The diffusion across the gaps is fast and the diffusion out of the cleft at the perimeter is slight. The reuptake mechanisms must be as fast as the release mechanisms, else the cleft will become polluted with lingering messenger molecules (echoes).

Presynaptic boutons must accommodate vesicular traffic. These are either produced locally or conveyed over the length of the axon. Either way, significant machinery must be present, requiring space and support. Post synaptic boutons usually operate catalytically. There must be sufficiently large “ways” for the flows of precursors and product, that typically transpire in bursts. In addition, even if the mechanisms of the postsynaptic bouton could be packaged smaller than the presynaptic bouton, there is a requirement of mating surface matches in size, shape and opposition.

4.3.5.2 Glial Membrane

Role of the glial cells in NIP.

The outer most membrane of a whole cell model contains the extracellular fluid. This fluid is often about 2.0E-8 m thick. This outer container may be modeled as a larger than, but similar shape to, the whole cell plasma lemma. However, it is most representative of the glial cells which surround and support the neurons. Therefore, the so called “extracellular membrane” should operate as the glia do: providing nutrients, and removing waste products,

and maintaining tonicity of the extracellular fluid. The effects of the glia are not restricted to housekeeping chores. Glia are found to employ ion channels to buffer K+, and in so doing modify the potassium repolarization after an action potential. The glia therefore alter the voltage, alter the firing patterns of the neuron, alter the duration of firing, and can move the foci of spreading depression.[80][81][82]

4.3.5.2.1 Glial Ion Channels and Pumps

A demonstrative model of receptors, channels, vesicles and pumps on a neuron would probably not be viable without the contributions from the adjacent glial cells. The extracellular membrane in the model will typically represent glial neighbors. As it becomes known which pumps and channels are present on glial membranes facing neurons of interest, their membranes can be modeled so as to serve in regulation, modulation and recovery of the tonicity of the ions and messengers in the saline fluid between the cells. From a modeling standpoint the glial membranes are treated nearly the same as the neuron membranes. However there need be no diffusion compartment on the other side. The glial will use ion pumps to maintain tonicity, and messenger pumps to recover and recycle messenger molecules. Particles could be released and absorbed much as receptors do (without transport).

4.4 NANO SCALE ELEMENTS OF THE NEURON

1. Water: determines mean free path of particles, determines temperature
2. Ions: monatomic and polyatomic (mass, radius, charge)
3. Ligands: modulators, messengers and neurotransmitters (mass, radius)
4. Membranes: closed surfaces, consisting of lipid mixtures (thickness is of the essence, also polar heads)
5. Receptors: transduce chemical message, includes associated second messenger mechanisms
6. Ion Channels: modulated, selective permeability, kinetically gated
7. Vesicles: triggered stochastic release of ligand packages, includes mechanism to fill those packages
8. Ion Pumps: modulated, kinetic transporters of ions, ligand combos to steady state, needs energy

4.4.1 WATER

1. Moles water per liter = 55.45 at 293K
2. Water molecules per micron^3 = 55.45 * 6.022144E23 *1E-9 = 3.34E+016
3. For contrast, a type of ion present at a concentration of 0.100 M = 6.022E+013

4. Water molecules per neuron of 1000 micron^3 = 3.34E+019
5. Radius of a water molecule is about 2 Ang . The equivalent mean free path is about 10 Ang
6. Ions per neuron of 1000 microns^3 = 6.02E+016
7. Radius of an ion is about 1 Ang . The equivalent mean free path in water is about 10 Ang
8. Neuron volume range (1000:50000) micron^3
9. Extracellular volume range (100:10000) micron^3

As the total quantity of ions is too great to model 1:1, and the quantity of water molecules is about 3 orders of magnitude greater than that of ions, it will be beneficial to develop a way to simulate the effects of water other than instantiate every individual particles.

4.4.2 IONS, MONATOMIC

1. TYPE = { monatomic forms polyatomic forms }
2. TRAITS = { name atomic_number mw atomic_ radius hydrated_radius valance mobility_e mobility_m }
3. DIST = { list of typical concentrations for various species> cell types> compartments; include also sea water, pond water }
4. Special treatment of ions: aqueous diffusion, drift, transport through pores, capacitation, charge transfer in chemical binding, water hydration shells that vary in ratio H20:1 ion.

The monatomic ions vary considerably in size. This is particularly important with respect to the ion channel pores. There is a 6-fold variation from smallest to largest atom.

Atomic Numbe	Formula	Atomic #	mass, amu	valance	radius calculated	radius VanderWal	radius Atomic n
1	H+	1	1.00	1	0.156	0.120	0.025
2	H-	1	1.00	-1	0.150	0.140	0.031
3	Li+	3	6.94	1	0.263	0.182	0.123
4	Be++	4	9.01	2	0.223	0.350	0.089
5	B+++	5	10.81	3	0.205	0.200	0.082
6	C	6	12.01	4	0.196	0.170	0.070
7	N---	7	14.01	-3	0.179	0.155	0.056
8	O--	8	16.00	-2	0.171	0.152	0.060
9	F-	9	19.00	-1	0.165	0.147	0.050
10	H2O	0	0.00	0			
11	Na+	11	22.99	1	0.277	0.227	0.180
12	Mg++	12	24.30	2	0.242	0.173	0.150
13	Al+++	13	26.98	3	0.240		0.125
14	Si	14	28.08	4	0.226	0.211	0.117
15	P---	15	20.97	-3	0.214	0.180	0.110
16	S--	16	32.06	-2	0.206	0.180	0.100
17	Cl-	17	35.45	-1	0.205	0.175	0.099
18		0	0.00	0			
19	K+	19	39.10	1	0.302	0.275	0.220
20	Ca++	20	40.08	2	0.278	0.990	0.180
21	Sc	21	44.96	2	0.262		0.160
22	Ti	22	47.87	2	0.244		0.140
23	V	23	50.94	4	0.227		0.135
24	Cr+++	24	52.00	3	0.223		0.117
25	Mn++	25	54.93	2	0.225		0.140
26	Fe++	26	55.84	2	0.227		0.140
27	Co+++	27	58.93	3	0.225		0.135
28	Ni	28	58.69	2	0.223	0.163	0.135
29	Cu++	29	63.55	2	0.227	0.140	0.128
30	Zn++	30	65.40	2	0.224	0.139	0.135
31	Ga+++	31	69.73	3	0.241	0.187	0.130
32	Ge	32	72.64	4	0.232		0.125
33	As---	33	74.92	-3	0.225	0.185	0.115
34	Se--	34	78.96	-2	0.218	0.190	0.115
35	Br-	35	79.90	-1	0.205	0.165	0.114
36	Fe+++	26	55.84	3	0.227		0.140
37	Rb+	37	86.47	1	0.315	0.244	0.235
38	Sr++	38	87.62	2	0.294	1.480	0.191
39	Y	39	88.90	2	0.271	1.120	0.180
40	Zr	40	91.22	2	0.257		0.155
41	Nb	41	92.90	1			0.145
42	Mo	42	95.94	1			0.145

TABLE 7: PARTIAL LIST OF MONATOMIC ION TYPES

Element	radius	ratio2H
F	0.57	1.16
O	0.65	1.33
N	0.75	1.53
H	0.79	1.61
C	0.91	1.86
Cl	0.97	1.98
S	1.09	2.22
P	1.23	2.51
I	1.32	2.69
Si	1.46	2.98
Zn	1.53	3.12
Mg	1.72	3.51
Fe	1.72	3.51
Mn	1.79	3.65
Al	1.82	3.71
Li	2.05	4.18
Na	2.23	4.55
Ca	2.23	4.55
K	2.77	5.65
Ba	2.78	5.67

TABLE 8: MONATOMIC RADII COMMONLY ENCOUNTERED IN BIOLOGY

This 6-fold span of atomic sizes has implications for collision rates, viscosity, and transport.

4.4.3 IONS, POLYATOMIC

1. TYPE = { polyatomic ions }
2. TRAITS = { name atomic_number mw atomic_ radius hydrated_radius dipole valance mobility.e mobility.m }
3. DIST = { list of typical concentrations for various species> cell types> compartments; including sea water, pond water }
4. Special treatment of ions in water, diffusion, electrophoresis, movement through pores, capacitation, loss of electrons

Name	Atomic number	*TypeIon(Index_colu*	formula	mass, amu	charge
		115	NH	15.0	-2
		116	NH2	16.0	-1
		117	OH-	17.0	-1
		118	NH4+	18.0	1
		119	H3O+	19.0	1
		126	CN-	26.0	1
		128	CO	28.0	2
		130	N2H3	31.0	-3
		131	CH3O	31.0	-3
		132	NHOH	32.0	-3
		133	HS-	33.0	-1
		134	N2H5+	33.0	-1
		142	OCN	42.0	-1
		143	CH3CO	43.0	1
		144	CS	44.0	2
		145	C2H5O	45.0	3
		146	NO2-	46.0	1
		147	ONO	46.0	1
		148	NS	46.0	3
		149	PO	47.0	3
		150	CH3S	47.0	-3
		151	SO	48.0	-4
		157	CH3CO2	59.0	-1
		158	CO3--	60.0	-2
		159	CO3	60.0	-2
Urea		160	(NH2)2C1O1	60.1	0
		161	HCO3	61.0	-1
		162	C2H5S	61.0	3
		163	NO3-	62.0	-1
		164	PS	63.0	3
		165	SO2	64.0	2
TMAO		175	C3H9N1O1	75.1	0
		176	N2O3	76.0	-4
		179	SO3	80.0	0
		180	PHO3	80.0	0
		181	HSO3-	81.0	1
		182	PH2O3	81.0	1
		188	C2O4	88.0	0
lactate		190	C3H6O3	90.1	-1
		195	PO4---	95.0	-3
		196	SO4--	96.0	-2
		197	HSO4-	97.0	-1
		212	S2O3--	112.0	-2
betaine		217	C5H11N1O2	117.1	-1
		239	ClO	138.9	0
		243	IO	142.9	2
		259	IO2	158.9	0
		271	ClO2	170.9	4
		287	ClO3	186.9	2
		303	ClO4	202.9	0
Carnosine		326	C9H14N4O3	226.2	-1

TABLE 9: PARTIAL LIST OF POLYATOMIC PARTICLES

4.4.4 SALINE SOLUTIONS

As stated above, water is a challenge by virtue of the large quantity of molecules. The simplest hard sphere particle systems are tractable to about 1E7 quantities of elements in a common computer. That is, patch models qualify. Attempts to model saline as it pertains to a neuron have employed diffusion by hard sphere collisions. Later additional features were added: an electric current [83] and Monte Carlo methods [84], radial distribution functions, and force field for n-body solutions have been described by [85]. Saline solutions are driven by at least five forces: thermal vibrations, linear momentum, angular momentum, concentration gradients, electrostatic force fields acting upon all charged particles, and the bindings and unbindings of solvation which form shells of varying radii around charged particles. In addition, some bound particles may be transported across the membrane.

There must be a container, and there will be one or more interaction types with that container wall: reflection, absorption, or transport through it. Lipid membranes are very good insulators, with resistances to ions in the vicinity of 100 ohms / m^2. (= 1E7 ohms per cm^2 = 1E14 ohms / micron^2 = 1E20 ohms / nm^2)

As long as a cell is alive, ion tonicities are different on each side of the membrane (plasma lemma). These tonicity differentials produce potentials in voltage and concentration that are sufficient to drive a variety of cellular functions, especially ion transporters and flux through ion channels.

Full electrodynamic simulations employ all four of Maxwell's equations. However at the molecular level the magnetic forces are minuscule which leaves only the two electrostatic equations.[86]

The mean squared velocity of an ion in thermal equilibrium does not decay due to friction, nor does it accelerate due to the force field. It engages in endless elastic collisions but remains near an average velocity of <v^2> = 3*boltz*kelv/mass. The velocity distribution of each ion type, in liquid water, is determined by Boltzmann's velocity distribution as a function of mass and temperature:

vel = 4*pi*v^2 *(0.001*mass/(2*pi*boltz*kelv)).^(3/2)*exp(-0.001*mass*v^2/(2*boltz*kelv));
The modal velocity of water at 293K is 505 m/s; the mean free path is 1E-9 m.

Individual ion velocities can be realized by instantiating its Cumulative Distribution Function (CDF) This action is sometimes referred to as the propagator function. It is generated as the integration of the PDF of velocities for each type.

4.4.4.1 Saline resistance/Conductivity

Understanding ion behavior at the nanoscale requires knowing mean free paths and effects of a charge field through water. While gaseous systems enjoy copious studies, the mathematics of liquid state particles is sparse. Monte Carlo methods are perhaps the most common method of modeling liquids, but these do not track individual particles. Individual particles become important when serving as messenger molecules, i.e. serving as information carriers. While it is possible to avoid tracking individual particles, whatever short cuts might be realized through analytics might fall short of the information capacity to communicate between the actors, and also may squelch emergent phenomena that might be vital to biological arrangements. Given how little is known about information processing in neurons, the discovery of such emergent phenomena is highly regarded.

The concepts of mean free path and incompressibility of liquids are mutually exclusive concepts.

A straight forward physics approach calculates the electrostatics each time step, and derives the net force on each charged particle.[83] These forces accelerate the particles until they collide with another particle, charged or not. Most frequently they collide with water. Conservation of momentum dictates that collided particles reflected at an angle that resolves the transfer of momentum along the axis of collision. Collisions disrupt coherency, thus appearing as deceleration for a coherent group. By this means, three dimensional flux is accomplished, and there is no need for a viscosity factor to set maximum velocities for particle types. Viscosity, for purposes of this model, is a function of size, temperature and density. Long chains that can knot up to increase viscosity, and charge stiction are not considered.

When examining phenomena at the molecular level, ideal gas laws do not hold. Even Ohm's law becomes non-ideal. [87] The effective radii of ions vary with their environment. Pauling found that Van der Waals radii closely match the ionic radii, before solvation.[88] This is where continuum theories must break down, and quantum effects begin. When a neurotransmitter molecule nears a complex protein, the fixed charges in the protein come into play, and these charges may be altered by induction. As contact is made, shape plays a critical role, and Molecular Dynamics may be necessary to depict an accurate account of what is happening. Some models switch modes from continuum theory to stochastic dynamics as a particle approaches a fixed protein at the Debye interaction distance.[87] This is usually somewhat less than 1nm.

While stochastic dynamics can capture the statistical properties of the fixed large proteins it does not track individual particles in diffusion. It is assumed that the largest mobile particles are too slow to be significant in NIP. Diffusion times between actors must be fast enough to execute the functions of information processing in a timely manner.

For ion flow through an ion channel it is necessary to take into account a variety of three dimensional charge effects along the path. They create energy barriers and repulsive accelerators. They are believed to competitively strip off the water molecules of hydration such that the bare ion moves faster and more selectively through the pore. Brownian Dynamics has been employed to model ion channels but falls short of generating the energy barrier profiles needed for accurate depiction. So far, only the most detailed structural models of the pore, e.g. Molecular Dynamics, have been predictive in ion flux as a function of protein conformation.[87]

The underlying physical concepts of translation in fluids are four: diffusion, charge field drift, chemical kinetics, and solvation (which dynamically alters the size and mass of each ion). To the extent that a model can faithfully represent these, it is likely to have excellent predictive value. The simple reason why this is never done for a complete whole cell is the immensity of the computational load.

Saline is represented as a thermally driven set of particle velocities interrupted by collisions with water molecules. This makes for very short mean free paths between momentum transfers. At 293K, the equivalent mean free path is about 1E-9 m. We speak of equivalent mean free paths because in a incompressible fluid the path must be serpentine. It is the change in net vector that represents an equivalent collision. Conductivity of saline is proportional to the concentration of charges in solution, times the cross-sectional area of conduction. But a nonlinearity occurs when the sources and sinks are significantly smaller than the cross-sectional area of the conductor path, because the electrical forces to concentrate at the sink are significantly greater than the force necessary to effect drift along the conductor path. Therefore the local conditions are dominate in determining point to point resistant, with distance apart having little effect. Heavier mass ions move more slowly, according to Boltzmann's distribution of velocities, and therefore must carry less current (charges per unit time arriving at the sink).

The Nernst Equation is fundamental to neural function. It expresses the electrical pressure through an ion channel as applies to each type of ion. It relates the ratio between the two concentrations to voltage, proportional to absolute temperature. Unlike Ohm's law, this voltage equation is non-linear, being derived from first order chemical kinetics.

V = K*kelv*log (C1/C2)/z,

and derives directly from the electrostatics of charge, where z = valance of the ion. Because Nernst forces are critical to ion flux, the extracellular fluid is a necessary part of the model of a neuron.

The velocities of individual ions as an ideal gas are predicted by the Boltzmann distribution equation:

n = n0*exp(-e*v / (k*kelv), where n0 = average density of particles in solution;

In a liquid, such velocities are not apparent due to the high packing density, which by virtue of numerous collisions, randomizes the path of each particle. The net movement by random walks is considerably slower that a ballistic trajectory. At the macro scale, the high velocities appear to be clipped, as per the measure of viscosity, about 1000 times slower. In aqueous solution, the mean squared velocity of an ion is:

<v^2> = 3 * boltz * kelv / mass;

4.4.5 LIGANDS

1. TYPE = {urea TMAO lactate Gly GABA Ach GLU HIST NE 5HT Epi DOPA cAMP cGMP IP3 ADP ATP}
2. TRAITS = { name mass size charge mobility}
3. DIST = {conc's intracell extracell actor_bound and sequestered in vesicles }
4. PATH = physiologic domain for all relevant factors: kelv pH concs, mods, kelators, bindings, membrane polar heads, production rates, release mech's and speeds, re-uptake mech's and speeds,

Ligands may be any mobile particle that is capable of binding to an allosteric site on an actor. For convenience, within the context of this model, the term ligand will be narrowed to apply to particle types with zero charge, so as to address that group of particles whose motion is driven by diffusion, not by drift. The ligands of primary interest are the extracellular hormones and neurotransmitters, and the intracellular second messengers. That set of second messengers called G-proteins require special treatment because they are known to move along the surface of the membrane, rather than diffuse 3-dimensionally. This may be due merely to the fact they are small molecules with charge, and become capacitated at the membrane, or may be due to more complex mechanisms. In either case, the

motion of these particles more efficiently arrives at target molecules than they would when diffusing in 3-d. G-proteins consist of alpha, beta and gamma subunits, originating from at least 33 genes. The combinations are too many to catalog here. Hopefully, a G-protein system can be represented as a 2-dimensional diffusion along the membrane, or as 1-dimensional vectors straight towards their target actors.

TypeLigand	Name	Formula	mass, amu	charge	recep	ion flux
129						
130	co	CO	28			
131	no	NO	30			
132						
133						
134	hco3	HCO3	61			
135						
136	Gly		75		GlyR	Cl
137						
138						
139	hpo4	HPO4	96			
140	h2po4	H2PO4	97			
141						
142	AABA		103			
143	GABA		103		AMPA, NMDA	Cl
144						
145						
146	Ach		130		nicotinic	Na K Ca
147	Glu		147		AMPA, NMDA	Na K Ca
148	Hist		153			
149	NE		166		Beta, Alpha2	G-protein
150	5HT	serotonin	172		5ht3	Na K
151	Epi		180			
152						
153	dopa		194			
154						
155	cAMP	G-protein1			chans	K down Ca up
156	cGMP	G-protein2			chans	Ca down
157		G-protein3			chans	K up
158						
159	ADP					
160						
161	PIP2				Kg chan	K
162	ATP				purineP1	Na K
163	MgATP					

TABLE 10: PARTIAL LIST OF LIGAND PARTICLE TYPES

4.4.6 MEMBRANE, AS MATERIAL

Membranes consist of self assembling molecules of lipids. The most common of these are:

lipid	neuron plasma lemma	thickness	protein affinity	capacitance	dielectric strength
cholesterol	1 to 20 %				
sphingomyelin	3 to 12 %				
phosphatidylcholine	30 to 60 %				
phosphatidylethnaolamine	15 to 25%				
phoshatidylserine	2 to 8 %				
phosphatidylglycerol	0 to 2 %				
phosphatidylinositol	0 to 12 %				
diphosphatidylinositol	0 to 2 %				
phosphatidic acid	0 to 1 %				
glycolipids	10 to 20 %				

TABLE 11: MEMBRANE LIPID CONSTITUENTS

The types of lipids found in membranes may number more than 1000, according to Raetz, 1986. Values for blank fields are not yet found to be reported.

Membranes also consist of 20% to 50% protein, but these proteins are best treated as separate entities, inserted and removed actively from an otherwise relatively stable lipid matrix. For purposes of this model, all lipids are considered as membrane, and all proteins are considered as actors (see below). The above table is incomplete, as the author has not found reports of variations in capacitance and thickness as per the listed chemical constituents. It is probable that the thickness is proportional to the molecular hydrocarbon backbone lengths, and for modeling purposes this is an acceptable point of departure.

The dielectric constant of a vacuum =1; for a lipid membrane Dm = range (3 : 5)

The capacitance of lipid membranes Cm = range (0.4 : 1.0) F / m^2.

Membrane (phosphadydalcholine +cholesterol) capacitance: 5.4E-7 F/cm^2.[89]

The resistivity of pure lipid membranes Rm = range (1 : 1E3) ohm m^2

Most relevant to the model, data is needed of the capacitance of the various mixtures of lipids tabulated above. Ideally, one could parametrize the capacitance value per unit area, and a model function would calculate what mixture of lipids would result in that capacitance value.

4.4.6.1 Membrane Thickness

Membrane thickness determines the minimum distance opposite charges will be held apart. This distance determines the maximum force of attraction between the those particles (per the inverse square of that distance). The maximum force determines the maximum acceleration, and the maximum acceleration determines the terminal speed, as a function of viscosity. The maximum speed determines how small *dt* must be to detect collisions. Because the triglycerides have polar heads, and voltage differential across the membrane will tend to charge those heads. This has the effect of increasing the capacitance by reducing the effective distance between the two surfaces. In effect the charge density has penetrated the membrane somewhat. So long as the non-polar portions of the lipid membrane are strong enough that the charges cannot break through the membrane, then the membrane is said to have a high dielectric strength. The voltage across the membrane is usually 0.1 volts and never greater than 0.5 volts. The thickness of the membrane is 7.5E-9 .. 1.25E-8 m. The portion of that thickness fatty acid polar heads comprise is about 2E-9 m on each surface of the membrane, leaving a minimum charge free insulative barrier of only 3.5E-9 m, based upon stained tissue viewed under the electron microscope. But staining techniques for the electron micrographs may exaggerate the polar layer thicknesses. Molecular space models suggest the pure lipid center portion is at least 4.5E-9 m. The polar heads of the fatty acids form a thin film conductor of tethered but somewhat mobile electrical charges. Though tethered, the flexibility of the fatty molecule allows the polar head to move as though a free ion. This movement supplements the capacitive effects. This increases capacitance because the polar heads are closer together across the membrane than the ions can get. In computer models, over representation of the thickness of the pure insulative portion is of little consequence, but too thin leads to excessive computation and possible breakdown of the membrane. The thinner is the membrane, the greater the attractive forces, which increase acceleration, which increase maximum velocities, which require shorter *dt* values to model without physics-violating behavior.

4.4.6.2 Membrane Structures (rafts)

Note that the capacitance values are for lipids only, not taking into account the variously spaced embedded proteins. Increasing the protein content reduces the lipid area remaining for capacitance. Because proteins have charged radicals all along their length, it is a bit like having a "polar head" that penetrates all the way though the membrane. It then acts as a high pass filter, passing high frequency charge shifts, but muting low frequency shifts. Put another way, voltage changes tend to put shear forces on the molecule.

The lipids, and the proteins "floating" in those lipids, can diffuse laterally. Vertical diffusion (from inside to outside the cell, or *vice versa*) is extremely rare. Floating molecules may be tethered together by protein strands to form rafts. Protein molecules may be tethered to underlying structures to form cellular "poles" or stationary specific function sites.

Protein affinities are relevant to the existence and operations of second messengers. Charged messenger molecules tend to move via 2-dimensional "diffusion" along the inner surface of the membrane, and therefore encounter target ion channels at a high rate. Uncharged messenger molecules tend to diffuse 3-dimensionally to all parts of the compartment, and are useful for broad spectrum effects (multiple types of targets located both in the membrane and at reticulum membranes below).

4.4.6.3 Transmembrane Transport

Passage through the membrane by ions or molecules is possible by five means:

1. Dissolution into and through lipids. EX anesthetics
2. Open Pores made of protein subunits. EX water through aquapores
3. Ion passage through gated channels. EX KcaV channels which pass K+ when CA++ is present.
4. Gradient driven exchangers and co-transporters. EX all gradient driven exchangers and co-transporters
5. Energy-driven pumps: EX sodium ATPase pumps

A sixth possibility is mentioned: tears or perforations in the membrane by mechanical damage or by disease. But these are not sustainable and kill the cell.

The forces attempting to move particles across a membrane are three: concentration gradient, charge gradients.

```
phi = potential gradient          %
E = del(phi);                     % defines the 3-d force field due to charge.   phi>0 indicates anions
rho = quant ions/m^3              % density of the ions
vd = t*e*E/mass                   % drift velocity at time t, until a collision occurs
g =  rho*e*vd;                    % conductivity of the electrolytic solution
```

Membrane conductance: 1.381E-6 /ohm cm^2 (resistance: 1.85E14 ohms/micron^2).[89]

Each polar head on a lipid molecule occupies about 7E-9 m^2 of membrane area

Each ion channel occupies about 3.8E-8 m^2 of membrane area. This allows the calculation of remaining capacitive area as ion channel density is increased.

4.4.7 KEY PROTEINS

A neuron must have information inputs. These may be electrical, but the dominant mode is chemical. Although there are many variations, let us consider the standard case. A chemical messenger molecule binds to a receptor, the first type of membranal actor. The receptor triggers events that either open an ion channel or send out messenger molecules that modulate ion channels. Specialized G-protein second messenger systems are the second type of actor. Ion channels are the third type of actor. They are sufficiently active that they often set off chain reactions that cascade down along the membrane. There are often mixed types of channels along the way. Eventually the neuron must output its information. This is usually accomplished by vesicles, the fourth type of actor. They emit chemical messengers when triggered to do so. Because energy was depleted in this process, especially concentration gradients are reduced, pumps are needed to restore "rest conditions". The "rest state" is defined as that state which is ready to receive and process the next incoming signal. Pumps are the fifth actor type.

4.4.7.1 Receptors

Receptors have been designated as Actor class 1.

1. TYPE = { A1. type# }
2. TRAITS = { name species family modulator_profile kinetics conductivity_profile releasing_function messenger poles }

   2a. bindings with stimulus molecule, function of ligand concentration

   2b. release/catalysis of messenger molecules, how many?

2c. release of stimulus molecule, must free up the receptor for next time. Is there a refractory period?

2d. reset messenger generator. The messenger molecules must somehow be recycled

2e. messenger target types. Where are the messenger molecules going to?

2f. messenger velocity to targets. How fast, How far?

2g. messenger limits (maximum distance). messengers cannot be allowed to wander around (spurious signals)

2h. messenger reset speed, the entire second messenger system must recycle to reset

3. DIST = { membrane axial distributions complexes development_age }
4. PATHOS = physiology/pathology domain for all relevant variables: kelv, pH, concs, mods,

The entire receptor and its second messenger system acts as a fan-out leverage to some quantity of ion channels. It takes a certain minimum of time to accomplish this. There must be some time spread to the arrivals at the target channels, and the duration of the modulation effect upon them must be limited. The receptor must get ready for the next signal, and there is some minimum time necessary to complete a message cycle. Can the receptor reset faster than the channel? The system would work best if the receptor took slightly longer to reset than the channels. That way the receptor would never waste a whole batch of messengers being sent to channels that are still lingering in a non-receptive state.

Receptors bind chemical messenger molecules allosterically. The resulting conformational change in the receptor plus the subsequent release time determine the period of the transduction cycle. The inverse of this period is the maximal frequency that a single receptor can receive. To avoid echo signals after the receptors release the neurotransmitter molecules, there must a local, rapid re-uptake mechanism, by pumps, catalysis, or other means of sequestration.

The significant function of receptors is that they kinetically bind certain messenger molecules allosterically (a stochastic process, not a deterministic one); and this binding causes a shift in the state transition probabilities for conformational changes of the large protein assembly of the receptor.

The life sciences literature classifies receptors into metabotropic and ionotropic types. The ionotropic types are actually part of the ion channel, while the metabotropic receptors are stand alone membranal proteins. Because most or all ion channels may be modulated by ligands and force fields, the term “ionotropic receptor” is just another name

for “ligand modulated ion channel”. For purposes of modeling, it is convenient to reclassify all ionotropic receptors as ion channels. In this paper, all mention of receptors refers to metabotropic receptors.

4.4.7.1.1 Second Messenger Representations

These are associated with their affiliated Receptor mechanisms. There have so far been found 20 types of G-protein systems that give leverage to a neurotransmitter signal arriving at a metabotropic receptor.

The change in state in (metabotropic) receptors alters the release of secondary messenger molecules, that may be produced enzymatically or by simple release. There are at least 20 found “G-protein” chemical systems by which receptors leverage their signal into multiple messenger molecules. These messengers may diffuse two dimensionally, trolleying along the surface of the membrane; or diffuse three dimensionally in the cytosol. Such secondary messengers may bind directly to some ion channel types or may bind to some intermediary enzyme which further leverages the signal, by producing multiple output molecules for every one input. By such multiple leveraging, a ratio of up to 30,000 :1 may be reached.

For modeling purposes, we can say the receptor is a finite state machine of transduction. It usually does not operate as a simple one-to-one pass through. It may delay signal transmission, combine two or more signals logically, prolong transmission, or be modulated in its response by other allosteric bindings. It most often serves to leverage transmission by releasing many times more messengers than it received. Its broadcasting capacity is large, but comes at the price of several milliseconds delay for each step to accomplish this. Therefore, simple linear models of receptors cannot mimic the behaviors of the more complex receptors.[90]

The mechanisms and timings by which a metabotropic receptor change conformations and eventually release messenger molecules shape the ion channel response. Additionally, a flood of messenger molecules from a receptor will likely prolong the channel opening where a single messenger molecule would not. These are significant effects impacting the the phase and shape of action potentials, and even if there will be an action potential.[91]

Some receptors participate in longer term processes, like learning. They are part of logical systems that trigger restructuring of the synapse when certain conditions are met. In particular NMDA and AMPA receptors are found to be instrumental in neuron plasticity. They trigger more than one response, some moderately fast and others much slower (up to 28 days). In addition to the slower restructuring of synapses, they may also participate in modulating

the fast ion channel responses to signals.[92] Long term potentiation is accomplished via elaborate chemical systems involving AMPA and NMDA receptors. To model the effects of this system upon ion channel distributions, receptor quantities, synaptic growth and shape, generation of new neural processes and synapses - requires simulated time of minutes to days.[93]

Real time information processing requires 1E-4 s (or less) time steps, and plasticity requires perhaps weeks of simulated time. Practical limits in computational load dictate that action potentials be modeled separately from plasticity. The compass between the fastest processes and the slowest is sufficiently great to make it rare for them to be accomplished in the same model.

Receptors may have more than one allosteric binding site for signal inputs; and may have more than one type of output messenger. One receptor type may impact several types of ion channels and pumps. They may affect numerous other processes off the membrane (development, housekeeping, turnover, plasticity, etc.) [94]

Ligands may bind to receptors as a second order reactions. When there are two sites, and the sites have identical affinities, the order remains second order. But as Hill described, when the affinities are unequal, the reaction rates fall short of ideal, effectively reducing the reaction to some fraction less than 2nd order.

Bound fraction = conc.B^2 / (conc.B^2 + dissoc.B^2);

The Hill EQ varies the exponent : Bound fraction = conc.B^h / (conc.B^h + dissoc.B^h); % where 1>h>2;

Receptors are usually comprised of about 5 subunits. Some receptors have all five subunits the same (homomeric), and other are something of a "mix and match" of subunit types to vary the functions (heteromeric). There are at least 20 different G-protein systems that communicate between receptors and other actors, to determine modulator to channel function. A single G-protein system may involve ten or more stationary proteins that are modulated by a single incoming event, and involve 3 or more messenger molecule types moving between the ten. Receptors may modulate ligand-gated ion channels and/or voltage-gated channels.[95] Thus, the naming of receptors and channels after one dominant modulator is usually an over-simplifications of their complex interactions.

The receptor-messenger complex may be repeated in series to effect a cascade, whereby one type of receptor has a messenger output that becomes the ligand input for another (nearby) type of receptor. In this way, the information fan out of the 2 G-protein systems are multiplied.

The operation of a second messenger system requires the physical supply of the precursor particles, the turning on and off of a catalytic process which converts the precursor particle type into the messenger type; the diffusion of the generated particles towards the target bind sites on neighboring actors; the bindings of messenger particles to those actors with corresponding bite sites (high affinities for that messenger type).

4.4.7.1.2 Receptors on Ion Channels

Many ionotropic channels have multiple modulator sites, for ligands such as Mg++, Ca++, Zn++, Cu++, H+, phosphorylation, and glycosylation. These are allosteric modifiers of ion channel opening, and they usually reduce opening probabilities.

4.4.7.2 Ion Channels

Ion channels have been designated as actor class 3.

1. TYPE = A3.type# = { 1100 types over at least 43 families, according to Hille }
2. TRAITS = { name species family subunits modulator profile kinetics conductivity profile gating function poles }
3. DIST = A3.type#.dist# = { membrane axial distributions complexes development_age }
4. PATHOS = physiologic domain for all relevant variables: kelv pH concs, mods

Channels are more thoroughly studied than receptors. Sufficient data is available to organize the following table. In the literature the kinetics and modulation effects upon state change probabilities are usually shown combined into 1 kinetic scheme. For modeling purposes these two must be separated because state to state changes require an s x s square matrix and special treatment of the diagonal (hold states); while modulation effects requires a B x d rectangular matrix and no special treatment of the diagonals. Bind/Unbind probabilities are contained in R. State change probabilities are contained in Q. These two are interlinked. They in fact point to each other. The output of R points to a page in Q. The output of Q points to a page in R.

TYPE Chan					
Name of type	**subunits**	**modulators**	**kinetics**	**Gating func**	**Conductivity**
AQP/MIP		R3.001	Q3.001	O3.001	G3.002
CIC		R3.002	Q3.002	O3.002	G3.002
CFTR		R3.003	Q3.003	O3.003	G3.003
SUR		R3.004	Q3.004	O3.004	G3.004
Kir		R3.005	Q3.005	O3.005	G3.005
Kv		R3.006	Q3.006	O3.006	G3.006
TRP		R3.007	Q3.007	O3.007	G3.007
CNG		R3.008	Q3.008	O3.008	G3.008
Cav		R3.009	Q3.009	O3.009	G3.009
Nav		R3.010	Q3.010	O3.010	G3.010
GluR		R3.011	Q3.011	O3.011	G3.011
GABAaR		R3.012	Q3.012	O3.012	G3.012
GlyR		R3.013	Q3.013	O3.013	G3.013
nAChR		R3.014	Q3.014	O3.014	G3.014
5HT3R		R3.015	Q3.015	O3.015	G3.015
IP3		R3.016	Q3.016	O3.016	G3.016
RyR		R3.017	Q3.017	O3.017	G3.017
ENaC/degen		R3.018	Q3.018	O3.018	G3.018
Connexon		R3.019	Q3.019	O3.019	G3.019
Proton Ch		R3.020	Q3.020	O3.020	G3.020
Cl(Ca)		R3.021	Q3.021	O3.021	G3.021
mAchR		R3.022	Q3.022	O3.022	G3.022
GlyR - NMDA		R3.023	Q3.023	O3.023	G3.023
Kv1.1		R3.024	Q3.024	O3.024	G3.024
Kv2.1		R3.025	Q3.025	O3.025	G3.025
Kv3.1		R3.026	Q3.026	O3.026	G3.026
Kv4.1		R3.027	Q3.027	O3.027	G3.027
Kv5.1		R3.028	Q3.028	O3.028	G3.028
Kv6.1		R3.029	Q3.029	O3.029	G3.029
Kv8.1		R3.030	Q3.030	O3.030	G3.030

TYPE Chan					
Name of type	**subunits**	**modulators**	**kinetics**	**Gating func**	**Conductivity**
Kv9.1		R3.031	Q3.031	O3.031	G3.031
HCN		R3.032	Q3.032	O3.032	G3.032
CNG		R3.033	Q3.033	O3.033	G3.033
eag		R3.034	Q3.034	O3.034	G3.034
BK(Ca) mslo		R3.035	Q3.035	O3.035	G3.035
SK(Ca) SK1		R3.036	Q3.036	O3.036	G3.036
KCNQ		R3.037	Q3.037	O3.037	G3.037
Kir1		R3.038	Q3.038	O3.038	G3.038
Kir2		R3.039	Q3.039	O3.039	G3.039
Kir4		R3.040	Q3.040	O3.040	G3.040
Kir5		R3.041	Q3.041	O3.041	G3.041
Kir7		R3.042	Q3.042	O3.042	G3.042
Kir6.2 - ATP		R3.043	Q3.043	O3.043	G3.043
Kir3 - GTP-aa		R3.044	Q3.044	O3.044	G3.044
TWIK		R3.045	Q3.045	O3.045	G3.045
KA		R3.046	Q3.046	O3.046	G3.046
Nav1.1		R3.047	Q3.047	O3.047	G3.047
Nav1.2		R3.048	Q3.048	O3.048	G3.048
Nav1.3		R3.049	Q3.049	O3.049	G3.049
Nav1.4		R3.050	Q3.050	O3.050	G3.050
Nav1.5		R3.051	Q3.051	O3.051	G3.051
Nav1.6		R3.052	Q3.052	O3.052	G3.052
Nav1.7		R3.053	Q3.053	O3.053	G3.053
Nav1.8		R3.054	Q3.054	O3.054	G3.054
Nav1.9		R3.055	Q3.055	O3.055	G3.055
Ca1.x HVA L		R3.056	Q3.056	O3.056	G3.056
Ca2.2 HVAN		R3.057	Q3.057	O3.057	G3.057
Ca2.1 HVAQ		R3.058	Q3.058	O3.058	G3.058
Ca2.3 HVAR		R3.059	Q3.059	O3.059	G3.059
Ca3. LVA T		R3.060	Q3.060	O3.060	G3.060

TYPE Chan					
Name of type	**subunits**	**modulators**	**kinetics**	**Gating func**	**Conductivity**
TRP		R3.061	Q3.061	O3.061	G3.061
CRAC		R3.062	Q3.062	O3.062	G3.062
GABA		R3.063	Q3.063	O3.063	G3.063
Gly		R3.064	Q3.064	O3.064	G3.064
Glu		R3.065	Q3.065	O3.065	G3.065
Gly NMDA-Ca		R3.066	Q3.066	O3.066	G3.066
nAch		R3.067	Q3.067	O3.067	G3.067
mAch		R3.068	Q3.068	O3.068	G3.068
Ry-Ca		R3.069	Q3.069	O3.069	G3.069
IP3-Ca		R3.070	Q3.070	O3.070	G3.070
SO Ca		R3.071	Q3.071	O3.071	G3.071

TABLE 12: CHANNEL TYPE DATA MATRICES

Modulation tables map possible ligand bindings to each allosteric site of a molecule and modulate the forward and backward binding rates as a function of molecular state. The Q matrices contain state transition probabilities as a function of current binding combinations and prior state. The O table maps internal state to external expression (e.g. channel openings, pump transports, etc.) The O values are maps from internal configuration to external effect. The G values are conductivity profiles for channels, catalytic rates for receptors, pumping rates for pumps, and vesicular contents for vesicles.

Channel type variations may be produced by: alternative splicing, subunit permutations, phosphorylation, disease-induced alterations, or pharmacological blocking and agonist agents.[96]

4.4.7.2.1 Channel Subunits

Channels are built of four to six protein subunits around the pore, and sometimes additional subunits attached thereto. Each channel gating function belongs to an individual subunit type. It may be efficient to maintain the details of channel function on a subunit basis, and define a channel as a list of subunits from that library. Doing so feeds into the logical results of multiple openings and closings.

Some of the subunits assemble so as to form a tight grid of pores from one cell straight into a neighboring cell, with no leakage to the extracellular fluid. These gap junctions allow electrical conductivity between cells.[97] They consist of hundreds of channels arranged in a tight circular grid, and are stacked two high, to accommodate the two plasma lemmas of adjacent cells.

Available subunits data is incomplete. When available, it may facilitate mix-and-match characteristics of hypothetical receptors.

4.4.7.3 Vesicles

1. TYPE = A4.type# = { size contents staging triggers restore_speed }
2. TRAITS = { name species family modulator_profile kinetics conductivity_profile releasing_function messenger poles }
3. DIST = A4.type#.dist# = { membrane axial distributions complexes development_age }
4. PATHOS = physiologic domain for all relevant factors: kelv pH concs, mods,

Vesicles are the output mechanism of the neuron. They are extremely complex systems of molecules that effect : the construction of vesicles; filling them with a mixture of neurotransmitters; the hair trigger release of the vesicular contents via exocytosis; and the recycling of the membrane for the next cycle. In addition, there are other mechanisms found: vesicular delivery conveyors for rapid fire (ribbon synapses)[98][99]; partial releases (kiss and run); and re-uptake of the neurotransmitter soon after its release (est 1e-2 s). All vesicles found to date are triggered by one or a few calcium ions. The calcium binding sites of vesicles are held physically very near to the voltage gated calcium channels that will admit calcium into the cell, insuring rapid and reliable messenger communication. Despite their complexity, vesicles are primarily a chemical transduction mechanism, not performing much of an information processing role except fan out. They do introduce some lag, some temporal spread, some variability of contents quality and quantity, and some randomness in the number of vesicles released per action potential. Vesicles are not often portrayed as being allosterically modulated, except as triggered by the presence of Ca++. But it is certainly possible. Modulators could theoretically slow the release of vesicles, reduce or increase the contents of a vesicle, randomize whether or not a vesicle will be released. All of these can be modeled with the components already described above. The most dominant form of vesicle modulation is the tight control of Ca++ ions in the vicinity.[100]

The modeling of a single vesicle in molecular detail would be a significant project unto itself. Therefore, vesicles are not modeled in detail as part of whole cell models. They are simplified.

Although vesicles and metabotropic receptors appear to be quite different in shape and methods, they are surprisingly similar wrt NIP.

The conductivity profile G of particles available to an actor assists in setting up the relationships between actors and particles. Just as R concerns itself with particles as input devices, G concerns its self with particles as output devices. G determines the quantities and ratios of particles to be processed. In the case of a receptor, G reveals the type and rate of messenger release. In channels, G reveals the through the pore conductivity values of each particle type. For vesicles G reveals the contents of each vesicle. And for pumps G reveals which particles are to be transported. A non-zero variance value causes randomization of the actual particle counts per release packet. G is based upon a single master list of all the particle types in the system. This list is ordered by molecular weight, and the position in the vector indicates the type of particle.

G =

H	Li	Be	B	C	N	O	F	Na	Mg	Al	Si	P	S	Cl	K	Ca
0	0	0	0	0	0	0	0	5	0.1	0	0	0	0	1	1	1

...

GABA	Ach	Glu	Hist	5HT	Epi	Dopa	cAMP	cGMP	G2	G3	G4	I1	ADP	ATP	MgATP
0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0

Fractional values in G force an instantiator to randomize the transport, with the indicated probability of success.

In a mass conserving system, particles must be retrieved via pumps and sequestration. In the case of a sparse particle system, it may be necessary to set up a reverse vesicle process, whereby the receptor sets very high affinity radii within which it collects the particles it needs for future release.

4.4.7.4 Ion Pumps

This Class includes electrogenic pumps, co-transporters, exchangers, passive transporters.

Energy sources may be chemical or gradient.

1. TYPE = A5.type# = { Those transporters which participate in determining the ion and ligand concentrations in each compartment.
   There are about 20 type of pumps considered for modeling}

2. TRAITS = { Stage1 Affinity1 Bind1 Stage2 Affinity2 Bind2 state_kinetics un/bind_kinetics poles }
3. DIST = A5.type#.dist# = { membrane axial distributions complexes development_age }
4. PATH = physiologic domain for all relevant factors: kelv pH concs, mods,

name	*in-bind*	*out-bind*	*energy source*	*mods*	*kinetics*	*gating*
NaK	3 Na	2 K	1 ATP	R5.001	Q5.001	O5.001
Ca high	1 Ca		1 ATP	R5.002	Q5.002	O5.002
NaCa	1 Ca	3 Na	Na conc	R5.003	Q5.003	O5.003
NaHCO3	1 Cl	1 Na 1 HCO3		R5.004	Q5.004	O5.004
NaKCl		1 Na 1 K 2 Cl		R5.005	Q5.005	O5.005
Cl HCO3	1 HCO3	1 Cl		R5.006	Q5.006	O5.006

TABLE 13: COMMON PUMP MODES

The term “pump” for purposes herein is intended to include all forms of active transport, including ATPases, co-transporters, exchangers, electrogenic transporters,, electroneutral transporters, ion transporters and ligand transporters. Every material entity in the cell must be recycled. Although there are many “down hill” (energy wise) cascades, there must be a corresponding equal amount of energy consuming processes to close the loop on each entity.

Concerning the propagation of information across the neuron, Crotty in 2006 calculated how much energy it takes to effect a single action potential.[101] He found, not surprisingly, that energy cost is a function of diameter and channel density. His model axon, with diameters: 4.07e-4 .. 5.5e-4 m consumed 3.8e-6 .. 5.0e-6 Joules/m length, after optimizing the channel density for minimum consumption to: 1.7e3 .. 1.6e3 S/m^2. This exercise reminds the modeler that hypothetical arrangements far off the energy *minima* are increasingly unlikely to exist in nature.

Once such an energy requirement is established, then the need for pumps is likewise established. If the pumps are present in surplus pumping capacity to the channel drain, then the neuron will recover from bursts almost immediately, and never fatigue. If they are short in capacity, when ever the neuron is firing at or near maximal rate the cell will experience fatigue via the gradual depletion of the Na partial voltage. How long this takes depends upon the two volumes of saline (the larger the slower). Fatigue is proportional to the drop in the Nernst potential. Be aware that the sodium pumps serve to drive mush more than the sodium channels. There are numerous exchangers

and co-transporters which are driven by the concentration gradient of sodium. The sodium pump load must add these in as well.

Pumps require 2 G matrices, one for the transport from comp1 to comp2, and one for transport from comp2 to comp1.

In a deterministic transporter, G values are whole numbers.
G =

	H	Li	Be	B	C	N	O	F	Na	Mg	Al	Si	P	S	Cl	K	Ca
AB	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
BA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0

	NT1	NT2	NT3	L1	L2	L3	M1	M2	M3	G1	G2	G3	G4	I1	I2	I3	I4
AB	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
BA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

In the case of pumps the transported ions also act strongly as allosteric ligands, modifying the transition probabilities significantly. Of course, there are still regular ligands, like ATP, Mg++, Zn++, PO4.

In a probabilistic transporter, G values may be fractional.
G =

	H	Li	Be	B	C	N	O	F	Na	Mg	Al	Si	P	S	Cl	K	Ca
AB	0	0	0	0	0	0	0	0	0	0.1	0	0	0	0	0	0	1.9
BA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0

	NT1	NT2	NT3	L1	L2	L3	M1	M2	M3	G1	G2	G3	G4	I1	I2	I3	I4
AB	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
BA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

These will be further elaborated upon in the next chapter.

4.5 BIOLOGICAL DIVISIONS

We may now summarize and formalize the above tour of the elements. There are 4 classes of actors: { receptors, channels, vesicles, pumps } (G-proteins may be considered a separate fifth class)

Each Class consists of a library of **Types**: 1:256 types are supported

EX: B.Ions = { Na K Cl Ca ... },

Each Type may have any number of **Traits:** 1:256 traits are supported

EX: intrinsic traits: B.Ion.Na.type = { # mass radius charge mobility }

EX: extrinsic traits: B.ion.Na.dist = { position, velocity, acceleration, compartment#, bindings, transports }

The intrinsic traits of a type of actor, interactor or compartment are supplied from the literature. The extrinsic traits are initiated based upon data from the literature, but then are rendered dynamic, instantiated, moved and tracked.

4.5.1.1 Element Distributions

a) actors are assigned node locations on the Surface of shapes

b) particles receive Compartment Assignments

c) membranes are assigned Shape

d) particles are set at an initial temperature

e) particle accelerations are initialized by the physics of the EM Force field

f) the EM force determines gradients, divergence and curl of particle flux

4.5.1.1.1 Assemblies

Shapes are assembled to form membranal systems (e.g. neuron, core, extracellular envelope, boutons)

Neuron shapes may be created via the concatenation of primitive shapes: cone, cylinder, sphere .

Actors may be assembled into rafts that can drift around in the membrane. Rafts may be tethered to restrict region.

Each Experimental Simulation is an assembly of elements, parametric values, and driver input signal

4.6 GENERAL DESIGN DATA FOR A WHOLE CELL MODEL

To drive the model with biological data, the following table can be completed, once for each cell type. A diffusion-based approach to surface smoothing is presented. Surfaces are represented as scalar functions defined on the sphere. The approach is equivalent to Gaussian smoothing on the sphere and is computationally efficient since it does not require iterative smoothing. Furthermore, it does not suffer from the well-known shrinkage problem. Evolution of important shape features (parabolic curves) under diffusion is demonstrated. A nonlinear modification of the diffusion process is introduced in order to improve smoothing behavior of elongated and poorly centered objects.

Neuron design dimensions	**units**	**min**	**max**
volume of entire neuron	micron^3		
surface area of entire neuron	micron^2		
volume of juxtaposed extracellular compartment	micron^3		
quantity of water molecules intracellular	moles		
quantity of ions intracellular, by type	mM		
quantity of water molecules extracellular	moles		
quantity of ions extracellular, by type	mM		
diameter soma, mean & variance	micron	4	100
volume, soma	micron^2		
diameter nucleus core	micron	3	18
volume nucleus core	micron^3		
thickness of extracellular fluid, distribution	micron	5	20
dendrite bifurcations, length distribution	micron	0	5
dendrite taper rate	ratio		
plasma lemma tortuosity (fraction area increase)	ratio		
area, one synapse, mean and variance	micron^2		
volume of dendritic arborization	micron^3		
surface area of dendritic arborization			
volume of axonal hillock (initial segment)			
surface area of axonal hillock			
volume of axon			
surface area of axon			
quantity of nodes of Ranvier			
volume of node of ranvier			
surface area of node of ranvier			
Thickness of neuronal membrane	micron	0.01	.01
capacitance of bare membrane	F/micron^2		
capacitance of myelinated membrane	F/micron^2		
synaptic cleft distance across	micron	0.01	.02
quantity of dendritic synapses		1000	10000
quantity of soma synapses			
quantity of axonal synapses			
ratio of inhibitory inputs to excitatory inputs, distribution	ratio		
length axon(s)	micron	5	5e6
resting potential	mV	-130	-20
conduction velocity of action potential	micron/msec	600	120000
internodal Length (depends on fiber diameter)	microns	150	1500
quantity of types of receptors in a single neuron			
quantity of types of channels in a single neuron			
quantity of types of pumps in a single neuron			
quantity of types of vesicles in a single neuron			
quantity of types of channel modulators in a single neuron			
quantity of molecules of neurotransmitter in one synaptic vesicle			
quantity of types of pump modulators in a single neuron			
Axial pdf for each receptor type	1/sq micron		1e-7 .. 2e-7
Axial pdf for each channel type			
Axial pdf for each pump type			
Axial pdf for each vesicle type			
Bind & Conformation kinetics for each receptor type			
Bind & Conformation kinetics for each channel type			
Bind & Conformation kinetics for each vesicle type			
Bind & Conformation kinetics for each pump type			
Single sodium pump maximum transport rate	ions/msec		0.200 Na
Single potassium pump maximum transport rate	ions/msec		0.130 K
Single chloride pump maximum transport rate			
Single calcium pump maximum transport rate			
quant sodium pumps per neuron			1E6 .. 5e6
quant potassium pumps per neuron			
quant calcium pumps per neuron			
quant chloride pumps per neuron			
quant receptors per neuron	micron		
quant synaptic vesicles			
fanout factor of each second messenger mechanism			20 : 4000
quantities of neurotransmitters in 1 vesicle, mean & variance			1e4 .. 1e5
diameter of synaptic vesicle, mean and variance	micron		0.050 .. 0.200
fast axoplasmic transport rate (peptides, glycolipids)	micron/msec		2e-3 .. 5e-3
intermediate axoplasmic transport rate (mitochondrial protein)	micron/msec		1.5e-1 .. 6e-1
slow axoplasmic transport rate (actin, tubulin)	micron/msec		2e-12 .. 4e-12

5 SOURCE PROCESSES

5.1 ELEMENT TRAITS

5.1.1 ELEMENT TYPES

a) Actors are stationary proteins, embedded in and through the membrane, and operating as finite state machines;

b) Interactors: Water, Ions & Messenger molecules filling each compartment, operating as a particle system;

c) Membranes, serve as surfaces and volume delimiters; compartments and capacitors; voxels and surface nodes.

d) Forces: Thermal Energy and EM force; generating diffusion and drift.

5.1.2 ELEMENT PROCESSES

5.1.2.1 Particles

a) position, velocity (velocity profile arises from thermal energy)

b) motion and particle-particle collisions
collisions are necessarily elastic, else the system quickly depletes to absolute zero
diffusion is emergent from collisions

c) particles may possess charge
charges come in only 2 values: + and -
charges are discrete, equivalent to the charge on one electron
charge is conserved. Each system cannot create nor lose charge.

d) voltage gradients and concentration gradients
these are emergent phenomena resulting from thermal motion and the EM force

e) drift and diffusion are additive
it is critical for modeling that:
the sum of the forces on one particle add and convert to an acceleration per its mass (A = F/m)
the instantaneous accelerations are added to the current velocity

5.1.3 ACTORS

5.1.3.1 Conformational kinetics

Every large protein can be represented as a transition probability matrix. Each possible conformation has some probability of occurrence. When it does occur, then the consequences of that conformation can can impact the immediate surround. The duration of each conformation is determined stochastically. State instantiations are derived from transition table probabilities.

In addition, there are usually allosteric binding site affinities. Release phenomena is emergent from the backward rate coefficients.

These 2, states and bindings, represent the internal transitions and external transitions, respectively. As these two aspects play major roles in this model, they deserve some thoughtfulness as to their traits and ramifications.

ACTOR relations	External	Internal
state	d Binding sites	s Conformations of the molecule
quantity at any one time	0 .. d	1
quantity of possibilities	d * B	s
driver	collisions, B hitting A	Thermal energy
static	bind combo = 1 of R states	State = 1 of Q states
dynamic	R kinetics	Q kinetics
mass	+ with bind, - with unbind	constant
matrix size	B*Rstates*Qstates	Rstates*Qstates*Qstates

TABLE 14: ACTOR INTERNAL AND EXTERNAL EVENTS

Given s states, then the state transition table Q = s x s. If there are allosteric binding sites, then Q = s x s x dc, where dc is the quantity of possible binding site combinations. Th is necessary because each binding combination constitutes a unique modulation state. By definition, modulation means to alter the s x s matrix. This is conveniently handled by increasing Q to a 3-dimensional matrix and using dc to point to a page in Q.

5.1.3.2 Membrane – Actor Interactions

a) Actor positions, imply: Actor density, Actor nearest neighbors, Actor patterns

b) Actor drift, rafts, turn-over, tethering.

5.1.3.3 Membrane – Particle Interactions

a) particle collisions with compartment walls, elastic reflections

b) membrane capacitance charge (membrane determines capacitance, particles determine voltage)

5.1.3.3.1 Absorption

A particle striking a membrane might be reflected, bound, or absorbed. Absorption is an option when the membrane is modeled as a compartment, albeit a thin one. The substrate of membrane compartments is not water, but viscous, nonpolar lipids. The diffusion rates within the membrane are determined by molecular weights and sizes. The hydrophobicity is determined by the forward and backward kinetics of the particle type across the water/lipid interface.

5.1.3.3.2 Water/Lipid partition coefficient

For membrane studies where particles pass from the saline into the lipids via solvation, the lipid layer is treated as a separate compartment. The water collisions are replaced with lipid collisions (of considerably greater mass). The partition coefficient is treated according to kinetics similar to the standard forward and backward rate reactions. Because of the self-assembling nature of the fatty acids, variations in chemical makeup of the lipid layer non-uniformly over the cell area, various rafting structures of proteins present in the lipids additional code will be required depending upon which aspects of the membrane are to be modeled and what is the query.

Generally, there are three considerations. The first is the percentage of membrane collisions that penetrate into the lipid layer, for each particle type (and the reverse of this reactions, escaping out of the lipid layer). The second is the transit time across the membrane via diffusion. The third is the diffusion rate horizontally within the lipid layer. The second and third considerations are not identical because the lipid layer is not isotropic.

5.1.3.4 Actor – Particle Interactions

a) particle bindings and unbindings to actor binding sites (see R Tables)

b) actor ability to catalyze conversion of particles (requires a function to convert particle types)

c) transport capability by channels and pumps (impacts the particles)

5.1.3.4.1 Transport

Transport concerns the movement of one or several particles from one compartment to another by the mechanics of certain actor types. Transport is one form of an actor's impact on its environment (a/k/a actor "expression").

a) mechanisms which move individual particles across the membrane against the gradient are called pumps

b) mechanisms which open pores to release bulk movements of particles across the membrane are called channels

c) pump transport requires bindings and unbindings of each particle to be transported

d) flux through open pores requires voltage gradient and/or concentration gradient to transport particles

e) unbinding of multiple particles at once constitutes a messenger package release (as with vesicles and receptors)

e) second messenger transmission of particles constrains the paths of released particles towards their targets

5.2 DIMENSIONALITY OF THE VARIOUS PROCESSES

For purposes of planning a software project, it is helpful to classify each of the process types according to their dimensionality and usage rate. Usage rates must necessarily be determined after the algorithms are established.

5.2.1 0-DIMENSIONAL PROCESSES

Zero-dimensional processes are a convenience for calculations of change that do not express as physical displacement at the resolution of the model.

1. Molecular conformational changes
2. chemical binding
3. point charges
4. 2-point convergence for charge neutralization by co-location

5.2.2 1-DIMENSIONAL PROCESSES

1. point-charge to point-charge force vector
2. velocity vectors
3. accelerating force vectors
4. voltage across a barrier
5. molecular shuttles

6. energy barriers through channels
7. conductance, net current
8. pumping across membranes (transport)
9. axial transport

5.2.3 2-DIMENSIONAL PROCESSES

1. membrane capacitance
2. membrane associated diffusion
3. containment barriers
4. nearest neighbors on a surface
5. solvation (varying quantities of water molecules forming hydration shells around ions)

5.2.4 3-DIMENSIONAL PROCESSES

1. diffusion
2. emf fields
3. flux: gradient, divergence, curl
4. particle-particle collisions (as discrete or hyperboloid orbits)
5. particle-surface collisions (reflections)
6. nearest volumetric neighbors (voxel maps)
7. frictionless orbits (charge pairs, dipoles)
8. resistance (Johnson noise, from collisions)

5.2.5 SIGNALING

Signaling refers to the dynamic variables that drive the model, and by compliment, to the output signal of the model which may serve as the input to another model via a connectivity matrix. Signaling implies streams of information. A steady state is not a signal. For example, DNA as it sits is not a signal, but the act of reading the DNA generates a signal. For purposes of this model, signaling entails:

1. Input Signal Generators and output signal capture devices
2. Signal Generator Drivers

3. Information capacity and throughput gauge the signal handling capabilities
4. Information processing is measurable to the extent that the input and output are not a one-to-one mapping.

5.2.6 MEMORY

Where is the memory of a physicochemical system that is found to be a Markov process? It is not in the membrane capacitance, because there is only one singular, continuous capacitor, so will not hold charge packets discretely per ion channel, (as is necessary in solid state digital processing chips). This continuous capacitor is very leaky, so can only work as a transient signal carrier, but will not hold information. Memory is not in the protein conformations. They are in a constant state of thermal flux, causing state transitions at rates more rapid than the neuron fires. Memory is not in the refractory periods of the action potential. They are inherently transient, and are merely the shadow of the wave that just passed over. Memory is not in the ion concentrations. They are very transient, undergoing constant diffusion, which is the enemy of information. Memory, if it exists at all, can only be in the shape of the neuron and in the actor distributions along its membrane. These actor positions are a kind of higher order shape. Both membrane shape and actor positions are static, surviving the constant wave action of particles and actor state changes. This notion may sound peculiar to many, as shape and position are regarded as too static to serve as memory. And indeed, in solid state devices, shape *is* too static to serve as memory, where the persistence of memory is strictly controlled (by operations: save, read, erase.)

All of the dynamics of an action potential are transient Markov processes (with no opportunity for memory) or else are particle surf. The memory of a cell must be amenable to change upon certain triggering events, but otherwise in a persistent state. Unlike solid state digital processors, the cell is not reprogrammed for each input set. Therefore there is no need for an erase function. Biological memory is cumulative, and its incremental. Usually big lessons are not learned in one event. It is the repeating parts of patterns that tend to modify the system so as to adapt to the consequences of that pattern. Thus, cell growth, making and retracting connections, enlarging or shrinking boutons, enlarging or shrinking vesicles, in contents and quantity of vesicles, altering the releasable contents of vesicles and receptors; altering the distances that messengers must travel; altering the speed of re-uptake; altering the quantities and positions and types of ion channels; altering the quantities and positions of pumps – are all options for altering the cell, and to the extent that they adapt the cell to external conditions, they are indeed memory. Various patterns of input need to be recognized and caused to generate useful patterns of output. To accomplish this no more is

necessary than the above. Does biology have any use for token systems? (like creating molecular markers to represent external objects, one-to-one). None have been found, so far.

The neuronal signaling traffic spins off genomic and proteomic effects which manage the turnover, building and shape altering processes of cell development and plasticity. As the shape of the neuron comes to be altered, changes in connectivity to nearby neurons may be altered, actor distributions may be altered, actor functions may be altered. The prominence or meekness of effects of such structural changes is a measure of its memory significance. The nature of its information processing is determined by shape-determined connections, the types and ratios of the actors, and the sequence of their encounter. Memory, therefore, to the extent that it is to be modeled, exists as a feedback loop that alters the neuron shape and or actor distributions as a function of signal traffic patterns. All of this implies recurrence. Learning is not a valid process until the success or failure of the output is known. It is not known until that output tests against some relevant aspect of reality. That having been done, such test results must be fed back to the input weightings, or actor positioning. Assuming that each neuron is capable of learning, then there must be one feedback circuit for each feed forward circuit. Under this assumption, we would expect the recurrent fibers of the nervous system to equal the feed forward fibers.

5.3 STEP-WISE PROCESS OF NEURON SIMULATION

This lists the processes necessary to simulate one complete cycle of a hypothetical action potential propagation passing by one node, as initiation node > propagation node > termination node. In a whole cell there would be M input nodes, N output nodes, and at least (MxN + L) propagation nodes, where L = internal repeater nodes.

1. compartment shapes initialized
2. ion tonicities initialized to steady state concs in each solution (tonicity profile)
3. ion diffusion in water, in each compartment – with charge, acceleration and collisions, reflections
4. ligands concs initialized to steady-state concs in each compartment (modulation profile)
5. ligands are released into synaptic clefts per input signals from presynaptic cells (via SigGen)
6. ligands diffuse in water, in each compartment (3-d diffusion)
7. actor affinity profiles activated, for ligands and other modulators (e.g. voltage)
8. ligand bindings to receptors, kinetics as func of concs and Q-modes

9. actor Q-matrix changes mode per modulator combo
10. actor state changes, per dt
11. actor phenostate = gating function, transport function, messenger release, vesicle release
12. ligand unbindings from actors kinetically per concs
13. ligand “reuptake” pumps restore ligands to original positions, kinetically, per concs
14. receptors release second messengers upon ligand bindings (1:5 ... 1:20 leverage ratio)
15. second messengers migrate along membrane (2-d diffusion)
16. second messengers bind to cyclases kinetically, as a func of concs
17. cyclases enzymatically produce phosphates (rate = by the hundreds /ms)
18. phosphates diffuse in water (3-d diffusion)
19. phosphates may bind to ion channels (phosphorylation) kinetically per concs
20. modulation combos (including voltage) > Q-matrix change, Ion Channels
21. actor state change, per dt
22. instantaneous conductivity of ion channel G = channel gating function * conductivity profile
23. Nernst potential + concentration potential drive flux: I = (E+C)*G
24. ion affinities to ion channels vary with gating function
25. ions transported through channels per I
26. ions diffuse out of ion channels
27. change in local ion concs (and by implication, change in local charge density)
28. change in Nernst voltages
29. change in Vm as weighted sum of Nernst voltages
30. dV > change in capacitance charge > current in and out of capacitance I = C*dV/dt
31. saline resistances between voxels result in ion currents: I12 = (V2-V1)*(1/R12)
32. horz flux changes Nernst voltages and capacitance charges
33. vesicles bind Ca++ as a modulator, kinetically, per conc
34. vesicles change state per mods
35. vesicles release ligands kinetically into synaptic cleft
36. vesicles reset their state (recycling sequence)
37. pump affinity1 profiles, per mode

38. pump bind1 staging, kinetically
39. pump bind1 state alters Q-mode, also mods and concs may alter Q-mode
40. pump state change kinetically, may transport across membrane (forward) or unbind (backward)
41. pump offload at side2 after transport
42. pump affinity2 profiles, per mode
43. pump bind2 staging, kinetically
44. pump bind2 state alters Q-mode, also mods and concs may alter Q-mode
45. pump state change kinetically, may transport across membrane (forward) or unbind (backward)
46. pump offloads side2 after transport

5.4 QUANTITATIVE INTRODUCTION TO THE PROCESSES

5.4.1 DIFFUSION

Aldolf Fick's contribution (1884) to flux calculations was to observe that aggregate diffusion in liquids is analogous to the heat conduction in solids. Heat flow is directly proportional to the difference in concentrations, and inversely proportional to the distance of elements from one another. This is a basic first order differential that represents any potential energy across a barrier being allowed to convert to kinetic energy.

Fick's first law:
J(t2-t1) = -D*∂ϕ(t1)/∂x; % where D = diffusion coefficient,
Flux = −D * (dC/dx); % C = concentrations at measured points, dx = distance between points.
This is appropriate to calculate the quantity of particles moving through a gateway or across a threshold.

Fick's second law:
$\partial\phi/\partial t = -D*(\partial^2\phi/\partial x^2 + \partial^2\phi/\partial y^2 + \partial^2\phi/\partial z^2)$; % the first law generalized to spatio-differential form

The resulting positions are defined relative to the initial position. This EQ would be repeated for each bolus or voxel, and the results stitched together with voxel superpositions, then hand-offs for boundary crossers.

Albert Einstein (1905) derived D as a function of Boltzmann's constant, thus relating the macro to the molecular phenomena.

D = boltz*kelv*mob / q; % where boltz = Boltzmann's constant;
% kelv = absolute temperature, mob = mobility coefficient

George Stokes (1851) derived an equation for the viscous drag component of a particle moving in water, which converts the accelerations due to forces into terminal velocities due to viscous drag.

```
mob = q / (6*pi*visc*r);       % q = ion charge, visc = viscosity;
    % mob is the ratio:   drift velocity/force
```

Lemons DS (2002) revisited Brownian motion. The position of a particle at time t is:

X(t+dt) = X(t) + Ntt+dt(0,1)*sqrt(t*delta^2); % which fills a PDF of: $\partial p(x,t)/\partial t = delta^2/2*(\partial 2p(x,t)/\partial x2$;
where p(x,t) = exp(-x^2/(2*t*delta^2) / (2*pi*t*delta^2);

Brownian motion with drift is more important to NIP.

$X(t+dt) = X(t) + acc*dt + sqrt(delta^2*dt) * N_t^{t+dt}(0,1)$; Where acc = F/mass;

Although Cartesian methods of performing the above EQs three times – for x, y and z axes – are commonly published; they produce cubic distortion. A superior method randomizes the two spherical angles uniformly, and treats the radius as X above, with each step.

Langevin (1908) solved for viscous drag and velocity fluctuations as the molecular collisions of Brownian movements:

$V(t+dt) = V(t) + drag*V(t)*dt + N_t^{t+dt}(0,1)*sqrt(dt*beta^2)$; % where beta=velocity fluctuation;
drag = 6*pi*visc*r / mass; % where visc = viscosity of water, r = radius of the particle;

Note that mass of solvated ions (Na+,K+, Ca++, Cl+) may be as large as: mw(ion) + 20*18, in the case of 6 H20 in inner shell and 14 H2O in the second shell).[113] Na+ has been found hydrate with 18 H2O.[114] Both K+ and CL- were found by x-ray phase analysis to hydrate to 45 H2O.[115] There may be high speed "flickers" within these water structures. It is known that the ion channel pore has fixed charges that substitute for the hydration molecules, thus stripping ions down to their bare mass while they pass through the channel pore. Whenever the EM force impinging upon a single ion is stronger than the energy of hydration, then the Newtonian acceleration of the ion is expected to leave the water molecules behind via substitution. With structures of 18 to 45 H2O the viscosity goes up disproportionately, as constant asymmetric collisions with the the smaller solitary water molecules are

unavoidable. The temporal dynamics become relevant to various velocities of drift. That is what is the solvation change rate as a function of ion velocity?

Given the position p1, velocity v1 and acceleration a1 of any particle at time t1, find its position at t2,

p2 = p1 + (v1 + a1*dt)*dt ; % where a1 = sum(force)/mass = sum(e0*q1*q2/(r^2*mass)).

However there is also some probability that the particle will become chemically bound, or physically transported by some membrane process. In aggregate, we can track concentrations as particles thusly:

C = concentration of one species of ion in one voxel
D = diffusion constant
Y = a transmembrane vector that moves particles out of the compartment (channels + pumps)
X = [x y z]
xy = area of membrane
a = rate coefficient for binding of particles
b = rate coefficient for unbinding of particles from membrane surface
P = particles bound to membrane proteins
K = capacitivity (capacitance per unit area of membrane)
dv/dm = voltage across the membrane

dC/dt = dA/dt + dB/dt+ dR/dt + dQ/dt: % where
dA/dt = + D* d^2C2/dX^2 – D* $d^2C/dX^{2;}$ % diffusion in and out of the volume
dB/dt = + Y*dC/dX – Y*dC/dX; % transport in and out of the volume
dR/dt = + b*P – a*C; % binding and unbinding of particles
dQ/dt = - dv/dm * K*xy /z; % capacitance charges from the membrane

There are implied additional factors in the above EQs. Transport may be contingent upon the presence or absence of other particles or modulators. Capacitance is shared amongst the various species of charged particles, so only a proportion of any one species will be involved.

Particles are represented leaving by diffusion, transport and binding, and then Diffusion, transport, and unbinding of those particles entering from adjacent compartment(s) .

5.4.1.1 Collisions

The diffusive process in a liquid is essentially mean free path trajectories interrupted by collisions. Collisions occur at extremely high frequencies, perhaps 1e14/s/particle in aqueous solutions at room temperature. Momentum conserving collisions entail mass, velocity, charge, and radii. Spin, and therefore angular momentum, are not considered.

Paul Langevin (1908) worked with Albert Einstein to derive an equation for collisions of particles in water.

```
A = F/M;                                        % where F = ballistic force + collision force
M*d(x)^2/dt^2  = −6*pi*r*mob*dx/dt + W;         % V = velocity;   W = white noise;
dV/dt = -drag Vdt + (beta^2 * dt)^0.5 * N(0,1); % where beta = scales the normal distribution to
velocities
                                                % N = normal distribution with mean=0, sigma =1
```

Langevin brought into existence terms for white noise (W), acting as a stochastic force (process).[116]

Leonard Ornstein and George Uhlenbeck, 1930 clarified the stochastic differential equation as:

```
dx(t) = S(mean-x(t))*dt +sigma*dW(t);           % where S = rate of shock dissipation, sigma =
variance;
```

All of these are attempts to predict the behavior of aggregates of particles without having to actually model the particle system. By instantiation the particles in a 3-d simulation, all of the above are emergent properties, and in fact metrics on the group of particles, per Uhlenbeck GE, Ornstein LS.[117]

5.4.1.2 Resistance

Axonal resistance has been measured at 250 ohms cm^2, and membrane resistance (in the absence of channels) 1E4 ohms / cm^2.[118] But membrane is not smooth. The surface area of a rough membrane is much greater than the area calculated on the assumption of smoothness implied by lineal measurements. Electron micrograph studies reveal the texture and irregularities of neural membranes.[119] These contribute significantly to both the resistance and capacitance of the membranal system, and must somehow be accounted to produce predictive models. After correction for roughness, membrane conductivity was characteristic of the function of that area of membrane; i.e. was determined by ion channel densities.

Resistance is taken into account as viscous drag, which breaks down into Johnson noise plus drift. Therefore, resistance is a consequence of the Langevin equation. In a particle system, it is the diffusion resulting form ions in drift colliding with non-drifting atoms or molecules along the path. Although resistance is presented as linear in Ohm's law (I = V/R), in a 3-dimensional liquid space resistance is a non linear diffusion problem, emergent as the delay, lateral spread, and net displacement of ions under a drift force.

5.4.1.3 Binding/Dissociation

Kinetics of modulators is critical to channel and pump performance. Ligands bind to receptors as a first order reaction, dependent only upon the concentration of the ligand. When there are two sites, and the sites have identical affinities, the order remains second order. But as Hill described, when the affinities are unequal, the reaction rates fall short of ideal, effectively reducing the reaction to some fraction less than 2nd order. The Hill EQ varies the exponent :

```
Bound fraction = conc.B^2 / (conc.B^2 + dissoc.B^2);
Bound fraction = conc.B^h / (conc.B^h + dissoc.B^h);    %  where 1>h>2;
```

Particles collide because they are driven thermodynamically to move at Boltzmann velocities. The packing density determines the length of the equivalent mean free path. At collision, one of several outcomes will occur: elastic rebound and conservation of momentum; a phase transition from aqueous solvation to lipid solvation; or a chemical binding that converts the two velocities into one, conserving momentum. If one of the collision pair is stationary, it is a bit more difficult to account for the momentum transferred by the moving particle. It is possible that some of this kinetic energy is transformed into potential energy, mostly mechanical energy ripples outward adding to the rebound velocity of near by rebounds. For modeling purposes it may be consistent with information flows to store the incoming velocities upon binding, and then when unbinding occurs restore those velocities reflected.

Whether or not there is a binding is determined stochastically, according to the affinity value (which acts similar to a forward rate coefficient). And its release determined stochastically by the backward rate constant. If the resident time turns out to be shorter than that necessary to allosterically set forth transitions as normally follow such a binding, then the molecule will not follow through to its physiologic function (releasing messengers, opening, exocytosis, pumping, etc.). The actor molecules are finite state machines, and the transitions between some characteristic fixed quantity of states are determined according to probability density functions. Thus, we can say actors are stochastically driven finite state machines.

5.4.2 KINETICS

Most kinetics is temperature dependent. Probability transition matrices may have kelvin modulators, unless the temperature is to be held constant for the simulation run. Another aspect of any binding is the energetics of making and breaking the bond. Energy required is heavily determinant of binding probabilities, and is reflected in the

forward and backward rate coefficients. Making matters much worse, in biological molecules, the so called rate constants are not at all constant. They are some of the most dynamic phenomena in living things. The action potential of the neuron is accomplished by 1E-3 s changes in the actor “rate constants”. Not at all subtle, these are some of the most nonlinear, widely swinging effects in the cell. They are more accurately described as dynamic transition probabilities.

The tracking of energetics requires a separate parallel set of data to the state matrices, because the exothermic and endothermic reactions will modify the temperature. Destexhe in 2000 attempted to model the energetics of an ion channel. The free energy profile identifies the barriers to channel activation and inactivation.[120] As this study was based upon the 1953 Hodgkin Huxley equations which employed a 2-state kinetic scheme, it did not include the kinetics of the non-voltage modulated states of the protein molecules, and therefore could not represent the deactivation path.

There are not many irreversible reactions in biology. Most of the time when they occur we call it a poison. Biology thrives on thousands of reactions that are rather delicately balanced such that not only can a molecule hitch a ride on a production circuit, but it can also get off the bus at the most fruitful stop. Most reactions of such delicate balances are reversible when the concentration ratios become inverted. When ever there is some ion translation driven by thermal energy, it only takes some conformational torsion of a target protein to bias in favor of binding that ion, then some relaxation to move it across the membrane, and finally a new relaxed bias in favor of releasing the ion. And that would be a pump. Any effective pump must have a forward bias and have the energy to pump against the concentration gradient. This requires sufficient supplemental energy so applied as to make the duty cycle irreversible (or almost irreversible). This energy usually is derived from the concentration gradient of another ion, or from ATP breakdown to ADP. Thus, a pump is two or more processes coupled such that the energy donated by one is employed by the other to move particles against its concentration gradient. Despite this coupling mechanism, a molecular pump is stochastic, and every move determined statistically. Therefore pumping performance is not 100%, and is reduced by higher concentration gradients. Pumps will stop, spill, thrash, and/or run backwards when pumping against the concentration gradient requires more energy than the donor can deliver.

Receptor kinetics may be treated as a standard chemical reaction.

B + A <-> BA, where

B = a particle, A is an actor (with allosteric binding site for B)
k.AB = the forward rate coefficient
k.BA = the backward rate coefficient
At steady state, there will be:
fraction bound = k.AB/(k.AB + k.BA) % fraction of B bound to A (barring any other competitive Rx's).
Time constant of binding = tau = 1 / (k.AB + k.BA);

These apply when a collision occurs. How many collisions occur is a geometric problem.

A similar sequence of equations was followed by Destexhe in 1994[121], but he used :

fraction bound = Bmax*k.AB/(Bmax*k.AB + k.BA);
tau = 1 / (Bmax*k.AB + k.BA); % includes a term to predict the number of collisions.

This acknowledges that the forward reaction is proportionate to the concentration of available binding particles, while the backward reaction in not. Because the binding event consists of a particle attaching to an allosteric modulation site, the kinetics of the entire molecule must be altered thereby. For each such allosteric binding site the number of state transition probability matrices doubles. Follow through dictates that the unbinding is also a stochastic event, requiring its own probability of releasing of messenger particles. Making things more complicated, the binding and unbinding at other allosteric sites may alter those unbinding probabilities. The receptor molecule has two or more conformations in response to the neurotransmitter binding. Via some path of conformation transitions (according to modulator altered probabilities) a conformation is reached that is conducive to releasing or catalyzing messenger particles. These particles, too, are stochastic in their release, albeit rather reliable (high) probabilities.

The logical flow is:

1. Let the set of B1 be all the neurotransmitter molecules for which there is an allosteric binding site on actor type A1.
2. Let B1 move in a Brownian fashion, occasionally colliding with instances of A1.
3. When a B1 collides with an A1, let the forward rate coefficient k.B1A1 determine statistically if a binding occurs. If a binding occurs, then swap out the transition probability matrix for A1 from un-modulated set to modulated set of probabilities.

conc.B1 * k.B1Ai = rate of binding = dQ(B1A1) = -dQ(B1);

In complimentary fashion, there is a reverse reaction whereby B1 unbinds from A1.

conc.B1A1 * k.A1B1 = rate of unbinding = dQ(B1) = -dQ(B1A1);

Run *dt* several cycles so as to realize the probable conformational changes until reaching a "release messenger" state. Let the backward rate coefficient for messenger binding determine statistically if a release occurs. Messenger velocity may be anything under the Boltzmann velocity envelop as a function of mass and temperature.

By 1983, the theory of how to extract kinetic schemes from single channel recording data had been worked out. [122] [123] Later that year, Moczydlowski found that potassium channels (Kcav) required at least 6 conformational states to fit their behavior[124] and explored the likeliest pathways through the transition probabilities. In 1991, Vandenberg [125] found that the lobster giant axon sodium channel had at least seven conformational states, more than could be inferred from the Hodgkin and Huxley equations (which represented groups of channels rather than single unit channel's inner states). Gating currents were measured and employed to find the conformations. Vandenberg attempted to fit 10 different kinetic schemes, with up to nine states. He concluded that a 9 state scheme was the best fit to express the observed behavior. All of his transition probabilities were assumed to be voltage dependent, but admits at the end that the supposed voltage dependence of inactivation was becoming controversial.

He then states: "*most of the voltage dependence of the inactivating phase of macroscopic sodium currents in the squid is not due to an inherent voltage dependence of the inactivation rate. The rate of macroscopic inactivation largely is due to a combination of rates for transitions between states associated with activation, deactivation and inactivation pathways.*" This implies that the state path of closing is different from the state path of opening, thus establishing the "duty cycle" of the actor. It further establishes that while openings may be voltage sensitive, the closing and refractory periods are larger voltage insensitive.

In 2006, Kuo found that the lobster giant axon Sodium channel required a 12 state kinetic scheme to fit the data revealing non-voltage dependent inactivation.[126]

Because a kinetic scheme is only that, a scheme, each bio-actor can have many different schemes proposed to represent it. Models should be able to accommodate multiple schemes for each actor type, choosing one for the experimental design to be run.

Astumian, 2008, states that ion pumps, e.g. Na,K ATPase, cycle in about 1E-3 s (moving ions both ways across a membrane 1E-8 m thick. This implies a velocity of the transport arm >1E-5 m/s, and a Reynolds number of 1E-9. Such a small Reynolds numbers indicates that inertia is completely muted by viscosity. ATP

hydrolysis is stochastic, and its coupling to mechanical events of ion transport is not deterministic. The kinetic sequence is not strictly ordered, but rather is probabilistic. Allosteric interactions between the pumps and its ligands do not insure that ATP hydrolysis and transport must be executed together, but they do bias the conformational transitions such that more ions will be pumped one way than the other.[127]

Pump affinities and selectivities for transport particles and modulator molecules is little reported across the various pump types.

Each vesicle has one (or more) binding site(s). In the simplest case:

AB = {Ca++}; % set of particle types B that are capable of binding to actor type A

R = (for each binding site there are forward and backward probabilities of binding certain B types) = B x d x fb.

The size is therefore qB x qd x 2.

R =

	d1 fwd	d1 back
B1	0.7	0.7

Where d1 = bind site on Actor; B1 = particle type that will bind to bind site; fwd = forward reaction rate, to be multiplied by concentration; back = dissociation rate.

If the receptor possess static bind/unbind probabilities, then those probabilities must be mid range to high range in values, else they spend time in stuck in hold states and fail to perform transduction. Where the backward rate is slower than the forward rate, then the receptor will continue catalyzing for a longer period than the duration of the presence of the stimulating particle. If the backward rate is faster Each of these combinations may alter the affinities R that the vesicle has for its binding sites.

R =

	s1		s2	
	d1 f	d1 b	d1 f	d1 b
B1	0.9	0.1	0.1	0.9

However if these bind/unbind probabilities are dynamic as a function of actor states, then R = B x d x s x fb, a 4-dimensional matrix. Let's next consider an actor with 2 binding sites, each of which can bind either of 2 particle types, and furthermore this actor has 3 states (called “ready”. “release” and “rebuild”).

R =

fwd

	s1		s2		s3	
	d1	d2	d1	d2	d1	d2
B1	0.9	0.1	0.1	0.1	0.1	0.1
B2	0.1	0.1	0.1	0.1	0.1	0.9

back

	s1		s2		s3	
	d1	d2	d1	d2	d1	d2
B1	0.1	0.1	0.9	0.9	0.9	0.1
B2	0.1	0.1	0.9	0.9	0.9	0.1

For instructional purposes, values of 0.1 indicate low probability events and 0.9 indicate high probability events. In actuality, these number vary wildly, and in any case are scaled to the size of *dt*. These matrices represent a stochastic machine's bindings and unbindings as a function of state and concentration of available particles. Therefore, the forward reaction probabilities must be multiplied by the B concentrations, while the backward probabilities are not.

Once we have determined the bind state of the actor, then we can address the internal state changes of the molecule. In the earlier case of one bind site and one particle type that will bind to that site, there are only 2 R-state possibilities: vacant or occupied. Therefore, there are only 2 pages in Q, the state to state transition probabilities matrix.

Q = [Q1 Q2];

	Q1	s1	s2	s3
ready	s1	1	0	0
release	s2	0	0	1
rebuild	s3	0.5	0	0.5

Q2	s1	s2	s3
s1	0	1	0
s2	0	0.3	0.7
s3	0.5	0	0.5

In the second case, there are 3 possibilities for bindsite 1 and 3 possibilities for bindsite 2. Each can be vacant, bound to B1 or bound to B2. This create 9 possible configurations for bind combinations. Therefore, the second version of Q must have 9 pages. It is helpful to create a pointer table from R to which page in Q is in effect. This can be rendered unnecessary by increasing the dimensionality of R such that each degree of freedom gets its own dimension.

The current state determines the row in Q in effect. The transition probabilities in Q determine state changes stochastically. That row is read as a PDF, and is integrated into a CDF. An instantiator chooses randomly across the CDF, and the outcome is a column number, the new state. This 'expression' of Q is a mapped to its phenostate, which in the case of a receptor could be the release of a second messenger or the activation of an enzyme. This information is transmitted via the O matrix.

O = | | 0 | 0 | 1 | where non-zero values indicate action # to be taken for each state arrived at

The action taken may be a release of contents, a turning on of a catalytic process to produce messenger particles, or a transport operation. A receptor triggering event (exocytotic binding) may cause a group of particles which positions at the interior pole of the receptor to change their velocity from zero to Boltzmann.; or cause a catalytic reaction whereby messenger molecules are rapidly created so long as the triggering binding persists. There follows some lag time to release sufficient particles, then there must be some recovery time to reset for the next event.

5.4.2.1 General form for kinetic state transition probability matrices

A generic treatment of the scheme above for modeling purposes would renumber all the states and rates:

Then map the transitions into matrix form (transition probability matrix Q). In the case where there is found only one duty cycle state path, those states can be ordered thusly.

Q =

Q1	1	2	3	4	5	6	7	8	9	10	11	12
1	k0101	k0102										k0112
2	k0201	k0202	k0203									
3		k0302	k0303	k0304								
4			k0403	k0404	k0405							
5				k0504	k0505	k0506						
6					k0605	k0606	k0607					

7						k0706	k0707	k0708				
8							k0807	k0808	k0809			
9								k0908	k0909	k0910		
10									k1009	k1010	k1011	
11										k1110	k1111	k1112
12	k1201										k1211	k1212

The size of Q is qs x qs where qs = the quantity of states. Units for Q are the probability of an event occurring per second. In other words, frequency. Note that the probability of remaining in the same state i is the remainder: of 1-sum(row i). k0202 = 1 - k0201 - k0203. Each rate function is found to be either a constant (rate constant) or a function of the various modulator values which vary this rate: f(voltage, Ca bindings, PO4 bindings, Neurotransmitter bindings, etc.). Empty cells are zero valued; or as low background noise probabilities. The fastest speed of conformational change determines the maximum *dt* value. Interspike intervals are determined to be caused by channels kinetics.[128] The first upper band is the duty cycle. The diagonal band contains the hold state probabilities. The first lower band are the reversal probabilities.

Biodata almost always reveals more than one path through the state space. Lets take a simplest case to consider the implications. Let path 1 = [1 2 3 4 5 6 7] and path 2 = [1 8 9 10 11 12 7]

Q1	1	2	3	4	5	6	7	8	9	10	11	12
1	k0101	k0102					k0107	k0108				
2	k0201	k0202	k0203									
3		k0302	k0303	k0304								
4			k0403	k0404	k0405							
5				k0504	k0505	k0506						
6					k0605	k0606	k0607					
7	k0701					k0706	k0707					k0712

8	k0801						k0807	k0808	k0809			
9								k0908	k0909	k0910		
10									k1009	k1010	k1011	
11										k1110	k1111	k1112
12							k1207				k1211	k1212

Such a major change in the state flow paths does not show up very strongly in the transition matrix. One must look for the redirects at (1,8), (12,7) and note their high probabilities to identify the second path. It is possible to write an algorithm that will find all of the possible state flow paths and rank them by probability of occurrence.

5.4.3 RECEPTORS

Ligands are modulators of the actors. In particular, the neurotransmitters are those molecules arriving from the extracellular fluids to influence (excite, inhibit, block) actor activities as high frequency signals from other cells. At a lower frequency range, modulators may set the cell mode , as with glycosylation.

Q1	s1	s2	s3
s1	0.36	0.9	0.13
s2	0.16	0.55	0.48
s3	0.32	0.64	0.46

Q3	s1	s2	s3
s1	0.33	0.6	0.19
s2	0.55	0.42	0.33
s3	0.58	0.91	0.07

Q4	s1	s2	s3
s1	0.32	0.67	0.44
s2	0.54	0.84	0.36
s3	0.47	0.79	0.28

The current state determines the row in Q in effect. In this case Q2 is never visited due to an impossible combination of bindings. The transition probabilities in Q determine state changes stochastically. That row is read as a PDF, and is integrated into a CDF. An instantiator chooses randomly across the CDF, and the outcome is a column number, the new state. This 'expression' of Q is a mapped to a phenostate, which in the case of a receptor could be the release of a second messenger or the activation of an enzyme. This information is transmitted via the O matrix.

O = | 0 | 0 | 0 | 1 | where 1 indicates some external action is to be taken when in state 4.

An actor may have more than one output. For example, a receptor releases a molecule and then becomes enzymatic.

O =

mes	0	0	0	1
enz	0	0	1	1

would indicate enzymatic activity in states 3 and 4, with messenger release in state 4;

where mes = messenger, enz = enzymatic process

Messenger release phenomena are handled similar to vesicles. An input triggering event causes a group of particles to change their velocity from zero to Boltzmann. There follows some lag time, then a staging of particles for the next release. The profile G of particles to be staged is similar to channel conductivity profiles. It determines the quantities and ratios. A non-zero variance value causes randomization of the actual particle counts per release packet. G is based upon a single master list of all the particle types in the system. This list is ordered by molecular weight, and the position in the vector indicates the type of particle.

G =

H	Li	Be	B	C	N	O	F	Na	Mg	Al	Si	P	S	Cl	K	Ca
0	0	0	0	0	0	0	0	5	0.1	0	0	0	0	1	1	1

...

NT1	NT2	NT3	L1	L2	L#	M1	M2	M3	G1	G2	G3	G4	I1	I2	I3	I4
6	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0

G extends to include all particle types (ions, neurotransmitters and other messenger molecules). Fractional values in G force an instantiator to randomize the transport, with the indicated probability of success.

In a mass conserving system, particles must be retrieved via pumps and then sequestration or binding to hold them ready for the next duty cycle to begin. In the case of a sparse particle system, it may be necessary to set up a high affinity process, whereby the receptor quickly retrieves the particles it needs for future release.

Each receptor has one or more allosteric binding sites. For the case of 2 binding sites:

RQ = (combinations of ligand bindings)

RQ	m1	m2	m3	m4
Ca++	0	1	0	1
NT	0	0	1	1
Qpage	1	2	3	4

Each of m combinations may alter the affinities R that the receptor has for the other binding sites.

And each of these columns must correspond to a page in the Q matrix of transition probabilities.

R = (arbitrary affinity values for display)

R	m1	m2	m3	m4
ATP	1	0.13	0.71	0.05
NT	0.3	0.52	0.07	0.02

These affinity values are employed in the stochastic machine determining bindings and unbindings, as a function of ligand collisions. This allows the state (s) to feed back to the affinities in R so as to predispose bindings and unbindings in correspondence to actor state.

Q = [Q1 Q2 Q3 Q4]; (pages of transition probability values as a function of modulation)

Q1	s1	s2	s3
s1	0.8	0.32	0.25
s2	0.41	0.22	0.85
s3	0.48	0.65	0.79

Q2	s1	s2	s3
s1	0.58	0.93	0.7
s2	0.16	0.33	0.13
s3	0.41	0.17	0.53

Q3	s1	s2	s3
s1	0.27	0.17	0.92
s2	0.23	0.52	0.74
s3	0.87	0.31	0.42

Q4	s1	s2	s3
s1	0.01	0.64	0.54
s2	0.85	0.23	0.67
s3	0.6	0.62	0.84

5.4.3.1 Receptor Activation (page-swap within Q-matrix)

For *d* allosteric binding sites on a receptor, and only 1 type of particle will bind to each, there are 2^d possible combinations for occupancy of that site. When a single site can bind several different ligands and have different kinetic modifications as a result then there is an even greater quantity of combinations. Each such combination presumably modifies the kinetic transition probabilities uniquely, and therefore requires a separate transition matrix. A receptor, then, is defined as a stack of transition probability tables, one table for each modulation combination.

5.4.3.2 Affinities

Affinity is the probability that a ligand in the immediate vicinity of a receptor with bind to that receptor. In a particle simulation environment, the probability of an exact collision for a binding is far too small to wait for, and so

a binding is considered to have occurred if the ligand happens within a specified radius of the receptor. The radius is adjustable as the affinity value. Empirical determination of *in vivo* binding performance to an equivalent affinity radius may be necessary. Affinities for each receptor are stored in the R matrix. Affinities are not constant, but rather can be swapped each dt as a function of the binding state M, and the internal state Q.

There are two volume shapes that may be employed in affinity calculations: the cubic voxel and the hemisphere. The hemisphere is the more accurate, especially when all particles on one side of the membrane within a certain distance of the actor are considered eligible for binding. The cubic voxel is much faster to compute, but care must be taken not to introduce a biasing error that cleans out the 45 degree angles (corners of the cube) disproportionately to other angles.

The X matrix reports all particles within the voxel above actor A1. The affinity value for particles above A1 is read in R1. Any matching particle within the affinity radius will be instantiated (bound randomly). The advantage of this two step is that the spherical distance of each particle to the actor need only be calculated for the very small number of particles within the voxel, not the entire whole cell system. This can be organized such that all actors are so affined and bound as a single system matrix via logicals.

5.4.3.3 Modulation

Channels may be modulated by specific allosteric binding sites, voltage forces or concentration forces. Most voluminously studied are the voltage gated channels, but this is only a sampling bias. Models must take into account all of the methods of modulation relevant to neuronal function. Because the term “modulator” describes an extrinsic quality, the effect of some input upon an actor, it is not a useful noun in modeling, but is useful as a verb “to modulate”. There are particle bindings that modulate and there are force fields that modulate. Because one particle species may serve multiple roles as: an ion in drift, a messenger released from a receptor, a ligand that allosterically modulates an actor, and one of the contents within a vesicle release, it would be ambiguous to name a particle as a “modulator”.

For continuous variables, such as voltage, the effects upon the transition probabilities may be represented as functions wrt voltage within the tables, or as binned values, with each bin earning a separate table. This is convenient because long stretches of dead zone can be represented as 1 bin, while sensitive volatile areas can be

split into many bins. But it does cost the computation of logicals to determine which bin a particular voltage value belongs in.

5.4.4 EXTRACELL TO INTRACELL TRANSPORT

5.4.4.1 Passive transport

Most of the NIP actions of the neurons are passive. The ion channels, receptors, diffusion of ions and ligands, and the catalysts of the G-protein systems, the co-transporters and exchangers are usually passive. Model elements therefore need not track the ATP consumption nor the Gibbs energy to represent their actions in NIP functions.

The mean permeation time of an ion through a channel is about 10E-9 s.[129] About 1E7 ions pass through a channel per second (dependent upon gradient driving them). That is about 1E4 sodium ions per action potential, then about 1E4 potassium ions in the opposite direction. The average channel density is 2E-5 m^-2, leaving an area of membrane 5E-8 m^2 for capacitating. Capacitance absorbs the currents of both channel and pump transports.

5.4.4.2 Active transport

Ultimately the NIP function is driven by ion pumps. And those ion pumps are ultimately driven by ATP molecules being reduced to ADP, making available 30.5 kJ/mole. Active transport is a relatively steady pumping action tending to return the membrane to its resting potential. Different physiological conditions may modulate the pumps to move the resting potential somewhat. And especially altering the tonicity of the extracellular fluid might cause pump modulation to compensate for any deficiencies. Compared with the number of ion channel types (43 main categories) , there are relatively few types of pumps, doing the active work (5 main types). When ever fatigue or ATP depletion is to be modeled, then a species of particle representing ATP is needed, and this particle must transmute into a different type of particle (ADP) whenever it binds to an active process. In a good kinetic scheme, the bindings of ATP will sometimes not release energy, and at other times will run backwards, making an ATP out of an ADP.

5.4.4.3 Tonicities

As seawater is predominantly NaCl dissolved in water, cells are often bathed in saline high in sodium and chloride. The living cell pumps down the interior so as to minimize sodium and chloride while pumping up the potassium concentration. Reserved for special treatment is calcium, which is in low concentrations outside and extremely low concentrations inside. It is in most neurons used as a messenger molecule, valuable as single individual ions. When a Ca++ ion is admitted to the cell, it is usually done so very near to the site that Ca ion is destined to bind to. It is then very efficiently removed, often sequestered in special vesicles for the purpose. Although the calcium ions are thought of as diffusing, their travel is so constrained that they might as well be piped from point to point. Ca++ does not live in an open system, as do Na+, Cl^- and K+. Sequestration and buffering assure that all calcium are accounted for. This is true also for ion channel clustering, which tightly control calcium influx and messaging.[130]

The early Hodgkin Huxley work characterized ion channels as exponential curve fits of the fourth order (sodium channel: g = gmax*m*h^3 and potassium channel: g = gmax*n^4). Since then the kinetics of these two channel types from the lobster giant axon have been elaborated to as many as 30 conformational states. The original voltage dependencies of inactivation were found to be incorrect, as the inactivation is "triggered" autonomously by its own transition probabilities, not by a voltage shift. Therefore, these sodium channels will inactivate regardless of what the voltage is doing.[131] The lesson learned is that a curve fit to normal performance does not reveal the mechanism, and therefore is not predictive out of those limited physiologic conditions. Far more predictive is a molecular dynamics model but these must be verified by the wet lab data collection. The multistep voltage clamps theoretically can find many of the conformational states of the actor, so long as each conformational change involves a charge shift. But the results are not guaranteed for a number of reasons: some conformational states are too fast to be detected; some transition probabilities are too slow to be detected; some conformations happen to have a net charge configuration very similar to other states and therefore are indistinguishable; there may be state groups which flutter between the group members; there may be alternative state transition pathways that are masked by the dominant ones; motion may occur orthogonal to the detection equipment; uncharged arms may move; the shear number of states is far to large to map out completely. For these reasons, ion channels (receptors and pumps as well) are being defined in the literature as "kinetic schemes". Schemes because they always involve some short-cutting of the true conformational states. Assuming that a protein of 1e6 Dalton has N possible conformations, then there exists an N x N table of possible transitions between states, some of which may be null. While the quantity of

articulating bonds of such a large molecule is huge, so its the interference of those articulations huge. Molecular dynamics simulations seeking energy *minima* show a Calcium channel twisting like a "Chinese handcuff" without any visible flopping about of random processes. Its very orderly nature suggests a low number of conformational states. [Jie Liang, 2007, UIC Bioinformatics, personal communication]. The modeler must accommodate wide compass of possible actor states, from 2 to 100 or more. And that the transition probabilities may or may not be modified by any of the binding sites or force fields. And that some, even many, of the transitions that actually occur are the result of intrinsic probabilities, not requiring a change in the environment to trigger them.

Of all the possible configurations of a molecule, each may be ranked by its order of occurrence (duty cycle) and by its physiological significance. If there are 100 states of absolutely no significance to the experiment, then mightn't they be bundled into a single "garbage" state to save computation? Well, so long as the input/exit probabilities are preserved. Groups of very fast states can often be merged into a single state with no loss of informational significance. Slow states, with a probability near zero over the entire length of the simulation run can be ignored unless they serve as a physiological switch of modalities. In which case, they may need to be manually switched so as to explore both modes over predictable time courses.

There are 3 aspects of states that need individual treatment. The first is the binding of ligands, where external concentrations and collisions are factors, and particles must be bound and tracked for release. The second is the traditional internal states of the molecule, or at least the high runners. The third is what this author calls the phenostate (pheno = to show forth), referring to the impact a particular conformation has on the outside world. For example, a channel may have 4 different open states. These must be kept separate because the in/out state transition pairs are unique, and mixing up the transition paths changes the behavior of the channel. A simple mapping table expresses the relationships between internal conformations and output effects.

There are at least 43 types of ion channels in a single mammalian species.[132] Although useful to have ion channels identified by a fixed number or types, this does not capture the true variety of channels one may encounter. For example, in the auditory system, the Kca channels are individually tuned to a specific frequency by getting their tails enzymatically clipped to many different lengths.

5.4.4.4 Conductivity Profiles

Channel conductivity is determined by the complex interactions of the ion with the fixed charges of the channel protein along the pore. Channel conductivity may require an amount of excess free energy to keep the side chains protonated.[133] Selectivity is determined by ion size and the energy of hydration. For example, the hydration free energy of Na+ is about 20 kcal/mole more favorable than that of K+. For K+ to be selected in preference to Na+, a channel just needs not over-solvate Na+ ions.[134] At the mouth of the ion channel has its own nano-environment electrodynamics, and voltage varies widely with the presence of chemical buffers.[135] Conductivity may be altered by certain ion concentrations at the pore, not merely by internal kinetics.[136] Once an ion is in a pore, the shape of the pore, and the charges along the way determine an energy barrier profile along the axis. Usually the maximum repulsive force along the way determines the conductivity of each ion species.

A physically open channel may be functionally closed, either by hydrophobicity, by solvation of the ion making it too large to pass, or by charge gauntlets the produce an energy barrier too high to pass.[129] Thus conductivity ratios are unique to each pore chemistry. And molecular dynamics are necessary to find the gating mechanisms, how they work, and what the energetics are. From and informational point of view, going down to the detail these mechanisms is not necessary if the conductivity to each ion can be known at physiological concentrations and modulation.

5.4.5 SYNAPSES

Synapses are specialized zones of membrane, characterized by their facing a mating surface from a neighboring cell. Synapses are zones. The distributions within any one zone are uniquely characterized, independent of any other zone type.

The peculiar distribution of channel types about the bifurcations of dendrites determine the degree of antidromic propagation.[137] Some dendritic channel constellations serve to compensate from geometrical factors like dendritic diameter, to grant the smaller dendrites a near equal effect on signal contribution. This is sometimes referred to as “synaptic democracy”.

5.4.5.1 Second messenger 2-d diffusion

The G-protein systems are not of one form. They may be one-step or two step processes. Each step provides a quantitative leverage from 1 to 200 times its input particle binding. The first step of both consists of the release of messenger particles that tend to ride along the polar heads of the lipid molecules. This is an unusual phenomenon: 2-dimensional diffusion. Of course it greatly reduces the quantity of messenger particles required, greatly improves their chances of colliding with a target ion channel, provides for shorter travel paths, and aids in clean up (retrieval via pumps or denaturing enzymes). Some of the G-protein systems do not target ion channels directly, but rather trigger an intermediate catalyst to generate third messengers. Each such step acts as a messenger multiplier. Such intermediate catalysts often produce particles that diffuse 3-dimensionally.

5.4.5.2 Enzymatic production of phosphates

The third messenger systems establish the communication link to the target ion channels nearby. The G-protein system intermediate node may be kinases, which are rapid enzymatic producers of phosphates. The phosphates act as the third messenger particles.

5.4.5.3 Third messenger 3-d diffusion

Typically, the third messengers are released to diffuse freely in the intracellular saline. This 3-dimensional release affords the opportunity to modulate off-the-membrane processes, such as endoplasmic reticulum and nucleus membrane binding sites.

5.4.6 TRANSDUCTION

For purposes of this modeling effort, transduction refers to a process by which the arrival of one messenger on one side of the membrane results in the release of a different messenger on the other side of the membrane. In many cases, there will be one input binding resulting in many output releases. The ratio of input quantity to output quantity may be referred to as the leverage or fan-out characteristic of the process.

5.4.6.1 Modulator / target pairings

The concept of modulators is awkward because a ligand, an ion, a force gradient, temperature, mechanical disturbance, photons, pH; can all be modulators. For purposes of this model, we can consider fast signaling (electrical, photons, neurotransmitters, and second messengers) as constituting the direct path of information transfer and processing in the neuron. We can consider medium signaling (hormones, drugs, accommodation) which maintain the neuron, supporting the steady state and providing a dynamic mid-range for fast signaling. And then we can consider slow signaling (learning, developing, diseasing [sic]) and the constructive and destructive processes which produce the neuron. Although convenient for classifications, this scheme is an over-simplification, as biology employs processes of time constants ranging perhaps 20 orders of magnitude, exploiting a huge array of time constants.

For purposes of this model, modulators serve to alter the actor conformation transition probabilities.

5.4.7 CAPACITANCE

A membrane of constant thickness placed between two saline baths of different tonicities will experience opposite charges attracted to each other from opposite sides of the membrane. This arrangement produces a natural capacitance. The actual capacitance of the membrane is a function of thickness of the lipid layers, and of any induced charge in the polar heads. The higher the induced charges, the higher the dielectric strength, and the greater the quantity of ions that can be held per unit area, per volt of charge imbalance. Capacitance is temperature independent. The voltage across a capacitor is a function of the ratio of charges on either side; to wit, proportional to the log of the ratio of concentrations, and proportional to absolute temperature.

By 1989, measurements were taken to detect the inhomogeneities of capacitance along the surface of the membrane, and that the capacitance surrounding one event (e.g. a channel opening, or pump cycle) faded with the saline conductance that serviced that capacitance.[138] Not yet determined was if there occurred simple lateral surface movement of charges as a 2-dimensional charge diffusion.

Attempts have been made to measure the capacitance of the living neuron membrane for about 4 decades. The problem is that the neuron is not a sphere. Irregular shapes, especially elongated shapes, results in significantly non-uniform charging curves, and they become increasingly uncertain as to their interpretation with complexity of shape.

The axon, as a regular cylinder, is much more tractable to consistent interpretation of capacitance, found to be 9E-3 farads/ m^2. [118]

The current transferred in and out of capacitance across a membrane that results from a voltage change[139] is expressed as:

I = Cm * d(Vm)/dt + Faraday * summation(z.i * dielectric * del(V) * del(C.i))

The membrane is a mixture of self organizing lipids, each comprised of one or two hydrocarbon chain of certain length (C11:C22) with a polar head (carboxyl, saccharide, phophatidylethanolamine, etc). The lipid types within the mix varies from species to species, changes in response to external conditions (temperature, pH, tonicity, etc.) and vary within a single neuron for a number of reasons. Therefore, membrane capacitance is not quite homogeneous across the cell surface. In some circumstances, models may need to account for local variations in thickness and capacitance to accurately predict voltage pressures on ion channels. Rafting implies a dynamic change in thickness and therefore capacitance. Because ion channel responses to voltage changes are highly non linear, such variations in capacitance are sometimes of the essence.

The capacitance of the neural membrane is a critical factor determinant of voltage and propagation, due to its position in the (equivalent electrical) circuitry, which serves as a low pass filter. Eliminating high frequencies can easily eliminate action potentials if the cut off frequency is too low (say 500 Hz). It is the capacitance of the membrane that makes propagation impossible for long distances. The most significant function of myelin is to reduce the capacitance. By adding 100 or so layers of lipids, opposite charges are held much farther apart and the strength of the attractive force between them diminishes with the square of the distance.

Chen in 2000 developed techniques to measure membrane capacitance by varying the frequency to detect non-ideal behavior.[140] Induced surface charges were studied by Chung in 2002[141] in attempts to refine modeling of membrane capacitance. Destexhe found in 2008 that at frequencies higher than 50 Hz, the traditional cable equation approach to axonal modeling broke down.[142] He attempted to improve the capacitance model by measuring some of the non-ideal capacitor behaviors of surface molecules, like the polar heads of the lipids, and attached sugar molecules.

Despite many indications that membrane capacitance mutes the signal, fast changes in current result in local voltage spikes that “beat” the capacitance (charging curves take some time). And these fast changes do cause ion channels to respond strongly and quickly. This is a non-linear effect not predicted by the measurements of RC time constants (tau). Channel responses are sometimes measured to be much shorter than the calculated time constants.[143]

Any movement of charge within and about the ion channel constitutes a current. And that includes the gates themselves. Instrumentation is sufficiently sensitive to detect the moving of an ion channel gate by the current it generates (approx 2 electron charges moving 1 nm). As current, these gating charges can also experience capacitance, in that they are attracted to their opposite and held there. Given that a brief channel opening may flow as few as 6 ions, the gating current and capacitance may be significant in a predictive model. Total membrane capacitance determines depolarization energy, and energy-optimal information transmission rates.[131]

5.4.7.1 Coulomb's Law voltage creation

A voltage is a pressure resulting from a charge differential across some barrier. Coulomb's law takes into account the placement of charged particles and returns the force between them. Its only variable is the permittivity of the medium.

```
F = k0*q1*q2/r^2;     % Coulomb's calculation of voltage
      where k0 = 1/(4*pi*e0*er),  e0 = 8.85418782E-12 F/m              % farads/meter
```

It makes no distinction between types of ions, nor is it a function of temperature. It is accurate in vector form, and the law of superposition holds, such that every pair of charges in a system can be calculated for V via Coulomb's law, and then these vector forces summed to yield the net force upon any one particle, and the net forces on a group of particles summed to yield the physical force tending to accelerate them.

```
F = 1/(4*pi*e0) * q1*q2*(p2-p1) / (abs(p2-p1)^3) =  k0 * q1*q2*N / (abs(p2-p1)^2);  % where N = normal
% The surprising cubed term in the denominator arises from the way a normal is calculated:
N=(p2-p1)/abs(p2-p1)
```

This physical law is the backbone of much of physics. It is basic to Maxwell's equations and to Einstein's relativity. It has been verified accurate to at least 14 decimal places. Yet, it is in seeming contradiction to the Nernst equation. The conflict arises because the Nernst equations says that voltage is proportionate to the temperature and is inversely proportionate to the valance of the ions. Coulomb;s law applies to any group of charges whose positions are known.

The Nernst EQ applies to what amount to chemical reaction rates. In this case with the pores within the ion channels. Coulomb's law can calculate the voltage as the actual pressure against the membrane, not against some electrodes (presumably at distances from the membrane). Coulomb's law is not temperature sensitive.

5.4.7.2 Nernst voltage creation

The various bureaus of standards prefer to define voltage in terms of batteries (wet cells) . However the Nernst EQ is a direct adaptation of chemical kinetics EQs that would predict such battery performance. The Nernst does not address a physical charge density calculation, like Coulomb's law. It says that the ratio of concentrations across that barrier, and temperature, determine the voltage across that barrier. The Nernst partial voltage is directly proportional to temperature, and is directly proportional to the log of the concentration ratio. For completeness, the Nernst partial voltage is inversely proportional to the ion's valance. The Nernst EQ only returns partial voltages, one ion type at a time, and must involve two separate concentrations of that ion type, held apart by a barrier.

```
E = (kelv*gask / (z*faraday)) * ln(conc.in/conc.out);    % for one ion type at a time, where conc = concentration
 % where kelv = temperature; gask = gas constant; z = valance; faraday = 96480 C/mole; ln = natural log
```

Voltage production of partial voltages via the Nernst is in contradiction to Coulombs law because the Nernst is proportional to absolute temperature, and Coulomb's law is independent of temperature.

The measured voltage across a living membrane is not merely a function of the sum of the Nernst partial voltages. The so called “resting potential” can only be maintained as a function of “leakage” of certain ions. Thus the resting potential is closest to the Nernst potential of that species of ion “leaking” the most. Therefore, “leakage” is a poor choice of terms, and “maintenance” or “basal” would be a better description. In any case such ionic flux is an absolutely essential process in the normal functioning of neurons. The Nernst voltage is measured through an electrical instrument with probes in the extracellular and intracellular fluids. Such instrumentation must induce an electron flow through an ionic system. The reading is very sensitive to distance from the membrane as the zeta potential experiences a log decay with distance from membrane.

5.4.7.3 Voltage effects upon membrane lipids

The GHK voltage EQ, which yields a voltage value as the sum of all the Nernst potentials weighted by their currents through the membrane, is only valid in the steady state. In any period of changing voltage those charges in capacitance at the membrane will contribute to both the currents and the resulting voltage. Follows is the GHK for 3 ion types:

```
numer = perm.k*conc.out.k + perm.na*conc.out.na + perm.cl*conc.in.cl;
denom = perm.k*conc.in.k + perm.na*conc.in.na + perm.cl*conc.out.cl;
V = (gask*kelv/faraday)* log(numer/denom);    % where log = natural logarithm
```

The addition of any divalent ion requires taking its terms to the 1/2 power. An accurate simulation of the membrane capacitance involves the non-uniform thickness of the lipid bilayer, the dielectric constants of the various lipid species, the effects of the fatty acid polar heads upon charge retention and fluidity, the mobility of ions in the saline above, the mobility of ions diffusing two dimensionally along the surface of the membrane, and the spatial log decay of charge density away from the capacitive membrane.

5.4.7.4 Voltage effects upon membrane proteins

As there is always a voltage gradient across the membranes of living cells, and there is always various charge concentrations on protein carboxyl and amine groups, then there will always be some contortion of protein molecules as the voltage potential changes. The question is whether or not such charge shifts will affect the actor functional role in any significant way. Because of this ubiquitous effect, it is not surprising that many ion channel gating functions are voltage sensitive. Perhaps we should be surprised when we find an ion channel or pump that is not voltage sensitive. The effects of voltage upon the conformation transition probabilities are of interest.

5.4.7.5 Voltage gradient force

Given an charged particle system, the introduction of a charge imbalance will have immediate effects upon the particles according to the inverse square law. At the nanoscale, voltage gradients may not be linear nor exponential wrt to distance from the membrane. Ion repulsion forces the like charges into layers, with the densest layer right at the membrane, and progressively sparser layers away from the membrane. Each such layer has a precisely corresponding opposite charged layer on the opposite side of the membrane.

5.4.7.6 Concentration gradient force

The particles in solution undergo thermal movement, the velocity of which are determined by Boltzmann's distribution as a function of temperature and mass. The velocity times mass determines the momentum of impact force against the membranes and actors. The aggregate of these impact forces on a surface we call pressure. When the concentrations of a particle species are graded, the so to is the pressure graded. Along such gradients, the difference in pressure wrt x sets up a force that moves those particles down the gradient. That force is countered by the viscosity of water, and together they determine the rate of flux due to concentration differentials.

5.4.7.7 Concentrations altered by buffers

Any particle species may be rendered unavailable by temporary binding to a buffer. A buffer has a bind/unbind equation factored by charge, voltage, pH, temperature or some other criteria. It is usually a simple kinetic with a forward and backward rate constant.

5.4.7.8 Flux

Flux is the diffusion of a species of particle under the influence of force gradients. It is formulated as partial of diffusion in the direction of interest. It is measured as a quantity of particles crossing a square micron of areas perpendicular to the axis of desired measurement of travel. In a cylindrical coordinate system, we may talk of radial flux, axial flux, or circumferential flux. Circumferential flux is best thought of as curl, not straight line diffusion.

5.4.7.9 N-body charge acceleration system (electrodynamics)

Charged particle systems $F_i = -\sum(g \cdot m_i \cdot m_j \cdot R_{xyz} / R_{ij}^3);\ i \sim= j$

where F=force, m=mass, R=distance, g=conversion constant, Rxyz is the directional vector

The inverse square law between each pair of charges is applied. The magnetic forces are sufficiently small at the molecular scale to be ignored.

5.4.7.10 Capacitance on the polar heads of fatty acids

Membranes may have a higher capacitance than would be predicted by their thickness. This is due to charge shifts within the membrane molecules that shift opposite charges near to ions in solution, thus binding them tighter than could ions on the other side of the membrane. This creates an effective charge field penetration of the membrane to the depth of the polar heads.

5.4.7.11 Charging curves in electrolytic solutions

Membranes are non-ideal capacitors, and empirical data is needed to capture the nonlinearities of charge to voltage, timing delays of diffusion, and the various effects of mixed species of charged particles. The fact that ions have thousands of times more mass than electrons (about 42200 times the mass of Na) brings into play the mass spring effects of a second order system. The greater the mass, the slower the charging curve, and the more prone to wavelike behaviors as mass overcomes dampening effects of water collisions.

5.4.7.12 Saline electrical resistance (Ionic flux resistance)

While most measurements of saline resistances were measured plate to plate, the relevant resistance in a neuron is point to point in a half cube (membrane dividing the cube in half). Most of the resistance is very near the points, thus muting the effects of distance between the points.

5.5 ACTOR PROCESSES

5.5.1.1 Ion channel conductivity flutter and drift

The time compass is chosen such that faster events do not correlate to the information throughput of the neuron, and slower events are concerned with out-of -scope development, learning, housekeeping, and adaptation. Most actor flutter is digitally smoothed over by the length of *dt.* However, flutter can be studied if the *dt* is shortened sufficiently, and the kinetic values in Q are sufficiently accurate.

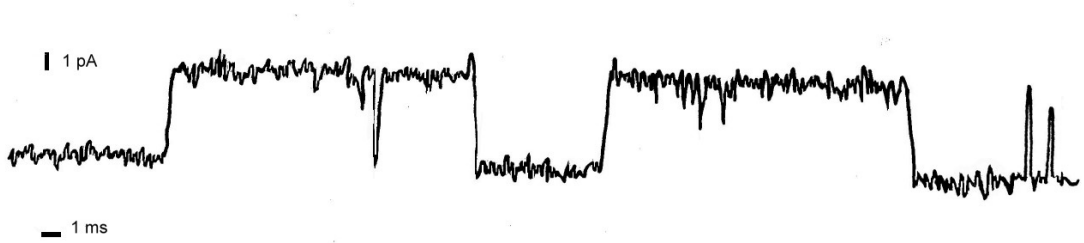

FIGURE 6: Single Unit Recording trace

Shown are 3 instances of flutter (singular spikes), a slight downward drift of the baseline, and low level back ground noise. (from Ach activated motor end plate in frog).

Single unit recordings incur background noise and ion flow through the pore noise. The most common data filters for biological ion channel recordings are Bessel for time domain and Butterworth for frequency domain. The Bessel shifts all frequencies equally so is good at preserving square waves characteristic of channel openings. The ion flux noise can be the largest component.

From the modeling point of view, most signal conditioning is at the discretion of the wet lab worker, not the modeler. However, one factor is particularly relevant: the high end frequency cut off. If the kinetic scheme generate speed of activities at frequencies above what the wet lab instrumentation could capture, then there obviously will be a mismatch between simulation and bio-data. It is prudent to note the upper frequency limit of the instrumentation when entering the biodata into the model libraries. Then a decision must be made either to value any high frequency data generated by the model as potentially useful, or to filter (smooth) the kinetics down to the frequency band of the data so as to have the model behavior match the bio-data. In most cases, this will not be an issue because the kinetic schemes are usually derived from the same biodata as are the traces.

5.5.1.2 Ion channel conductivity profile consequences

Each species of ion channel is conductive to more than one ion species, but to varying degrees. To treat an ion channel as only a sodium channel, potassium channel, calcium channel or chloride channel can accumulate error that rapidly throw the model out of physiological range. The current problem is, not enough data has been collected to accurately portray channel conductivities across all relevant ion species. This missing information will result in

inaccurate channel behaviors that in turn will force the pump performances to be distorted in compensatory manner, or else the systems will drift away from physiological representations.

Several of these were posted in the previous chapter.

5.5.1.3 Exocytosis of vesicles

The exocytosis process may be looked upon as a compartment merge (vesicle contents with synapse contents) or it may be looked upon as a transduction from intracellular Ca to extracellular neurotransmitters, with fan out. The former is a complicated set of processes, and could become a huge undertaking all by itself, if rendered faithful to known biology. For purposes of narrowing the modeling elements to those best serving the NIP functions, it might be possible to replace the vesicle as a compartment with the vesicle as an inverted receptor. As the receptor can be represented by a kinetic scheme, considerable reductions in computational load can be realized. Justification will depend upon modeling both renditions and determining an acceptable match of the inverted receptor to the *bona fide* vesicle.

5.5.1.4 Vesicle release of ligands

A vesicle is a pre-packaged bag of messengers. It may contain only one type in regular quantity, or it may be a mixture of types in various ratios, with variance. Vesicles may vary in quantities from vesicle to vesicle, according to given variances. The releases may exhibit some degree of uncertainty, and the emptying of contents may not be complete. These variations may all be prescribed via PDFs.

After the release of a vesicle there is a half life of each of the content (particle mix). This half life is determined by some combination of binding, pumping (re-uptake) converting (chemically denaturing) and escape (diffusion into the larger compartments). For maintaining steady state conditions only the re-uptake and the conversions are effective. Somehow the vesicles must be rebuilt after each use. In a kinetic scheme this could be as easy as running the release mechanism backwards. Of course reality is much more complicated. But the mechanism of reconstitution for vesicles is not direct on the NIP pathway. The significant factor is the vesicle production rate and any readiness factors for vesicles to release into the synapse when a Ca++ binds.

5.5.1.5 Re-uptake of ligands

Not much discussed in the literature and texts, but the reuptake is equally critical to synapse functioning as the vesicular release. If the synapse is to be efficient, the reuptake speed will math the release speed. The bursting open of a vesicle via exocytosis is a non-reversible process. A corollary to this fact is that it is easier to release than recover, and therefore faster to release than to recover. This suggests that for every 1 vesicle being released there are probably many reuptake mechanisms in the vicinity. For modeling purposes, reuptake of ligands is accomplished via pumps. Large quantities of ligand may be sequestered. For small quantities, high affinity binding sites on an actor can thereby recharge and it will later release them as messengers. Rapid uptake requires fast backward reactions at the binding site and close proximity of the pumps to the binding sites. Couplets may be formed in solution to deactivate and/or neutralize a B type.

If it is found germane to the modeling query, a mechanism may be added that traces the path from the point of reuptake to the manufacture of vesicles, so as to complete the recycling.

5.5.1.6 Resetting ligands to initial positions

In any model that runs more than a few seconds of simulated time, the ability to maintain steady state is crucial. Just as the ion pumps maintain the membrane resting potential, so also pumps retrieve ligand molecules and pump them back into their original compartments. If ligands are released from stationary positions then those release sites need affinity and binding powers to recharge sufficiently fast. Getting particles near such an actor binding site may require nearby pumps to get particles in the correct compartment, and near to the actors that will bind them.

5.5.2 ACTOR DISTRIBUTIONS

The locations of the various types of actors are of the essence regarding neuron information processing. Yet there is very little rigorous data on the precise locations of actors by type. The fluorescence marker data is the current best source. Sometimes it can be corroborated with random sample patch clamps to confirm the functional behaviors of that which was marked. Some channel density variation can be explained as an optimization of impedance, energy cost , transduction speed, or nodal clusters. Much of the spatial variations in dendritic and somatic membrane function are accounted for by channel densities varying non-uniformly, neither with respect to other types of

channels, nor with respect to shape. Beyond the general physical design parameters, local variation represents information.

While some positioning is obviously restricted by its very function (receptors at dendritic synapses and vesicles at axonal synapses), there is plenty of room for subtle asymmetries of actor placements. The individual specific distance from one actor type to another actor type may be critical to cell function because the diffusion from one actor to the next may determine the response frequency of the cell. In particular the channel distributions at dendritic bifurcations determine to what degree there will be antidromic propagation.[144]

Ample evidence is found that changes in the channel distributions will change the shape of the neuron electrical response wave.[145]

Complicating matters is that some channels are present within protein structures that fix the distances between dissimilar channel types. These clusters may be tethered or free floating in the membrane.[130] This is particularly crucial when one type is admitting an ion type that is the modulator stimulating the receptor of the other type. The distance between them determines the diffusion time, and thus the delay. Often these are part of oscillatory response mechanisms.[146]

Channel types are plaided on the membrane in patterns that can produce oscillations. This requires one type of channel with a net charge inward and another type with a net charge outward, and the two are triggered at alternate times.[147]

The actor distribution function reports the actor density over the length of the neuron. A 2-dimensional distribution function would also take into account the angle of revolution, in the case of radial asymmetries. A 3-dimensional distribution function would support mapping every voxel of neuron separately in complex arborizations. However, the 3-dimensional version requires a mapping of volume to surface, as the membrane passes through each voxel (or not) as a warped plane, not as a volume.

There exists 1 actor distribution function for each actor type, per each cell type. For convenience all actor types of a single cell type can have their distributions stacked into a single matrix, then be called by row number (actor type). For consistency, all actor distributions are binned into 100 values, corresponding to percent of axial length of the neuron.

5.5.2.1 Densities and gradients

Found densities from biological data can be preserved as empirical points, interpolated between them, or otherwise curve fit so as to span a variety of model shapes and sizes.

5.5.2.2 Clusters and distance-fixing structures

In the event two or more actors are found within structures that fix their distances from each other, randomly distributing them will not yield the desired result. They must be treated as one, then given a distribution function for the cluster. After cluster positions are substantiated over the cell surface, then from the cluster center points, each of the individual actor points must be calculated. This is best done in cylindrical coordinates, as this allows arbitrary rotation of the cluster while preserving the actor intra-relationships.

5.5.2.3 Exothermic and endothermic bindings and conversions

As this is a model of information flow through a neuron, energetics are not directly considered. The energetics determine the probability of occurrence and the dwell time of each state. In subsequent phases of development, an energetics analysis may be deemed necessary to identify feasible and practicable designs, for which probability data is not yet available.

5.5.2.4 The Outermost Envelope, containing the entire Experiment

Any particle system must be bounded by a closed surface, else particles will leak out of the system under test. For purposes of this model, and "extracellular" membrane is designated at the outer boundary of particle movement. It represents the plasma lemmas of neighboring cells. The extracellular membrane is an active membrane, with the same capabilities as the plasma lemma (main membrane of the model). The core membrane also has full functionality available to it. This enables them to regulate tonicities, set up fluxes, supply needed particles, clean up waste particles, and set up charges along the membranes.

5.5.3 TRANSPORT

Two types of transport are of interest: passive (open pores) and active (pumps). It is possible to represent molecules that convert between channel and pump functions by switching actor trait sets conditionally or stochastically.

5.5.3.1 Channel Conductivity

The pore through ion channels is sufficiently small, convoluted and charged that most pores are particle type selective. However, we begin with the simplest case, the unselective pore:

```
G =  pi*r^2*g/length                  % conductivity of an uncharged cylindrical pore
je = -g*E;                            % current due to the force field (Ohm's law, relates KE to PE)
jc = -D*z*del(rho);                   % current due to concentration gradient (Fick's law, relates KE to PE)
jc.chan = D*(rho1-rho2)/length;       % concentration flux through a channel
j = jc  +  je;                        % Nernst and Planck do addition
j =  -D*z*del(rho)  +  -g*E;          % Nernst and Planck do substitution
g = D*n*z^2 / (boltz*kelv)            % Einstein related conductivity to diffusion
j = -D*z*del(rho)  + -D*n*z^2 / (boltz*kelv) *E;          % substitution
j = -D*z* (del(rho) + rho*z* del(phi) / (boltz*kelv));    % substitution
```

The Poisson equation relates the charge field to the densities of mobile and fixed charges to yield the net effect upon an ion. It calculates the flux through a pore as a function of radius and length, and gradients.

```
rho.saline = rho from Fick's law above
rho.pc = the density of charges within the protein
dielec.water *  dot(del , (dielec.protein * del(phi)) = - (rho.saline + rho.pc);
```

Combining the Nernst-Planck equation with the Poisson equation calculates the channel energy barrier function. [141] At distances greater than the Debye length, the Poisson approach is accurate. However, for interactions shorter than the Debye length, there are induced charges and quantal effects. It is necessary to take a finite element approach to model the entire pore. Molecular Dynamics addresses these issues. For purposes of this model, energy barriers will be taken in summary, as the full Molecular Dynamics model cannot be supported over the dynamic computations of hundreds or thousands of channels.

For reference, consider an ion channel pore of 2E-10 m diameter x 2.5E-9 m length in a 150 mM solution of K+. Conductivity of this solution was empirically measured to be g = 8.4E-3 S/cm. Conduction of the ion channel therefore is G = pi*r^2*g/length = 4.2E-11 Siemens. This smooth pore calculation yields conductivity about 3 times the conductivity of a K channel with shape and charges.

No type of channel is perfectly conducting for one species of ion and perfectly blocking for all the others. Determining the conductances of any given ion channel type requires a series of baths of varying tonicity combinations, deleting some ion types, and substituting like ion types from the atomic table. As the *in vivo* data is so far sparse, modelers often need to hypothesize or extrapolate missing data. In any case place holders are needed to represent known channel types even when specific conductance profiles across all present ion species are not yet available.

Molecular Dynamics models are being constructed to predict some of these conductivities. For example, Noslov in 2006 modeled the ion selectivity of a potassium channel (KcsA), and in the process discovered mechanisms as to how some of the selectivity occurs due to the effects of ligands coordinating the rhythm of binding sites along the pore.[134] Na conductivity, by comparison is enhanced by ligand-ligand repulsion. According to this interpretation, the channel is somewhat like a rubber tube, and the ligands provide the hard pressure points holding the shape of that tube, especially as pinch points. Selectivity is not arbitrary. Given 5 cations {Li Na K Cs Rb} there are 120 possible conductivity-ranking sequences, but only 11 are found in simple pores, varying only diameter. [148] Ion channels must either conform to these 5 or employ significant charge gauntlets to overcome them.

Channels often have conical shaped pores. This is an inexpensive bio-diode that favors movement of ions down the funnel, such that, if left continuously open between two equal sized chambers, the steady state would find a ratio of about 1.15 : : 1 (small end :: big end) for permeable ions in the two compartments (in particle simulation experiments by the author).

Channels vary in the pore height off the membrane surface. Some pores, like the 5 side ports of the nicotinic Ach cation channel, are right at the membrane's intracellular surface, immersed in the highest charge density the membrane can muster. In contrast, the other end of of that same channel rises about 7 nm above the extracellular surface which is far above the 3 nm thick charge density zone, and therefore in neutral territory with little voltage to push ions through. Thus this channel can act as a diode, on basis of shape alone.

5.5.3.2 Pump Ratiometrics

Pumps are actually logical devices whenever they transport more than one type of ion and do so in ratios. Think of a card game when certain players must trade 2 for 3, and other players required to make other ratiometric trades.

After a long series of trades, some characteristic steady state might emerge. There is a logic to how the steady state is arrived at. It may be modulated by slowing some pump cycle rates down, or by increasing the error rate of stochastic pumps.

When pumps are turned on prior to the channels, their tendencies to head for one or more equilibria can be observed. It is possible that the pump system acts modally, or acts homeostatically, or acts adaptively. This model study promises to elucidate the systemics of ion pumps.

Note also that non-electrogenic pumping requires far less energy that electrogenic pumping. It is of interest to determine which aspects of the cell's work can be accomplished non-electrogenicly, and what might be the least energy cost path to achieve electrogenic pumping as necessary for cell vitality. However, the Na pumps are known to build up a gradient that is tapped as an energy source to drive a great number of processes. These include processes out of scope to NIP functions. Accordingly, a model attempting to account for all Na pumping will require a reasonable factor for off-NIP consumption.

Pumps may participate in ratiometric information processing. However, it is presumed that it would take hundreds of pumps to transport a significant quantity of ions in a timely fashion to match the transport of a single channel.

5.5.4 TRANSDUCTION

5.5.4.1 Receptors

A receptor is a stochastic device which rapidly responds to a binding event outside the cell with a multiple event inside the cell. This describes receptors in the plasma lemma, but receptors may be found in other membranes as well. They transduce spatially across a membrane, and they transduce quantitatively to leverage a very small signal into a much larger one. Kandel, in 2000, reports this leverage at approx. 200::1 for single stage messenging, and as high as 30000::1 for 2-stage messenging. [149] Receptors by one of several possible mechanisms release second messengers in quantity. These messengers quickly arrive at nearby actors, especially certain types of ion channel with binding sites for those messengers. This all takes place in about (1E-4 .. 1E-2) s. There are at least 20 different configurations for second messenger systems found to date. Some employ intermediate cyclases to

catalyze the production of third messengers. This takes longer but greatly increases the leverage in quantity. Such leverage can, for example, enable a retina to detect a single photon.

5.5.4.2 Vesicles

From an information perspective, a vesicle is a transducer, much the same as a receptor. They appear physically very different, but the signaling results are quite similar. It may be that the simpler mechanism of the receptor is not available outside the cell, as G-protein systems might be far too fragile to build and maintain on the outside surface of cells. The vesicle mechanism is metabolically much more expensive but had already been developed for endocytosis and exocytosis in eating and excreting. As an already evolved, stable and robust mechanism, it was adapted to the neuronal function of signaling.

5.6 PROPAGATION

Ion flux alters the quantity of charges stored at the adjacent capacitive membrane surface. Ions not bound in capacitance diffuse spherically, yielding non-linear gradients according to the sum of the charge products, inversely proportional to the squares of the distances between those charges (E = ko*q1q2/r^2). The aggregate of these accelerations due to Coulomb's law determine voltage changes that immerse nearest neighbors. When the rate of change is strong it is likely to effect a change in mode of the Q-matrix of those nearest neighbor actors. Such shifts predispose the ion channel to change it open/close time ratio. If the flux quantity from one ion channel is sufficient to cause an equal or greater flux quantity from one or more adjacent ion channels, then a chain reaction ensues. The speed of conduction is not determined electrically, because the rate limiting step is the state changes of the ion channel. These are determined stochastically as a function of the Q-matrix. The conduction velocity is determined by the number of conformers an ion channel must pass through between closed and open states. Similarly, the refractory period is typically determined by the number of conformations that the counter-valent ion channel must pass through. Furthermore, capacitance, by temporarily binding charges, has the effect of delaying flux radiations, thus its “low pass” filter role. When the ion channel flicker is significantly faster than capacitive delays, then capacitance is the dominant determinate of conduction velocity.

Hybrid continuous/discrete cascades will radiate out from a point source. But such point sources do not contribute to information processing of neurons. In purely passive systems, the signal is expected to damp out along an exponential temporal decay curve and to spread out spatially along a flattening Gaussian curve. The neuron does not act passively with regard to signal propagation, despite the descriptions in the literature of dendrites being passive. Where ever there are ion pumps, there will be stored energy in the form of concentration differentials and voltage differentials. This stored energy is held in place by the capacitance of the membrane. Whenever an ion channel opens, some of this potential energy is released. Furthermore, the adjacent ion channels may be sufficiently sensitive to respond to a perturbation that is lower than the one it will produce. When this occurs the ion channel is adding energy to the signal as it is passed on. Technically, the ion channels are acting as repeater stations, each one restoring the signal to full strength. Which such an arrangement, the signal could be propagated for any length of axon without any deprecation in signal strength.

Propagation is not a simple yes or no phenomena when the neuron surfaces are not uniform. Gradients in channel density, channel types, membrane cross-sectional diameter, tonicity on either side of the membrane, ligand concentrations (as modulators), and the immediate prior states of the ion channels all are factors in propagation velocity and amplitude. These are the same factors which determine the information processing role of the neuron.

In sensitivity analyses varying tonicities and channel conduction rates, the Na channel is found to express a “go – no go” threshold concerning its ability to effect a second action potential from the first. Ionic currents of Na,K, and Cl using the Hodgkin Huxley EQs. In repetitive trials revealed a critical point at which propagation occurred.

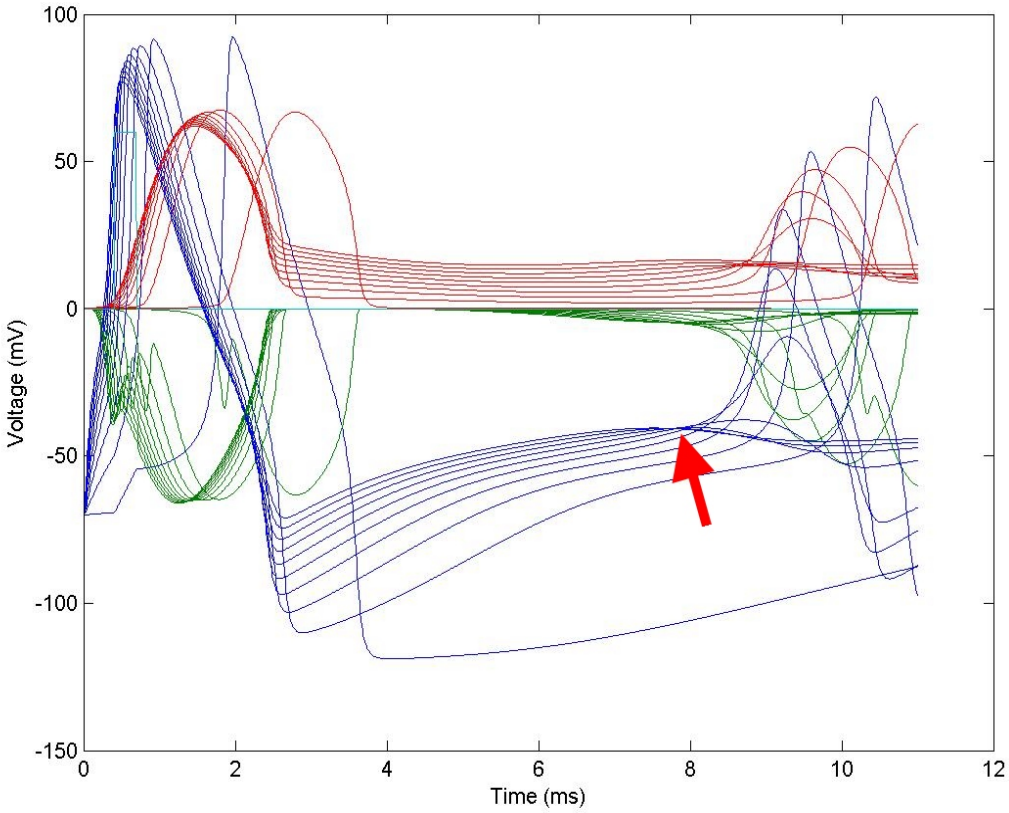

FIGURE 7: NA, K & CL CURRENTS, HODGKIN HUXLEY EQS

The above plot was created by Kirsteen Lugtu, a student of mine at the time. This simulation demonstrated that in a fourth order model, parameters could be swept (ion concentrations, conductivities, and time constants) so as to determine the domain within which propagation occurs. The red arrow points to the time when either there is or is not sufficient signal generation to stimulate the next channel, or to repeat firing the same channel. For axonal propagation, where no signal processing is expected, simple consistent kinetics are desirable. To process information, as with mathematical operators, this approach is inadequate.

5.6.1.1 Wave fronts

Excitable membranes are characterized by the triggered release of energy packets which serve to sustain a chain reaction of such releases. The direction of travel of this chain reaction over a 2-d structure is called a wave front.

The shape of a wavefront is only perfectly uniform (straight or circular) when all of the elements are identical and in exactly the same state just prior to excitation. In a stochastic system this is not what occurs. The states are in various recoveries from previous activities, tonicities, modulator bindings, .

5.6.1.2 Inactivation fronts

Refractory periods are essential for the directionality of propagation. It is a cost of silence paid to insure against back propagation. Just as there is a propagation wave front, there is an inactivation wave front following it. The shape of this wave front determines which excitations and inhibitions will be ignored and for how long. This shape determinant has implications in the responsivity patterns and basal firing patterns of neurons, as secondary effects beyond the channel kinetics.

5.6.1.3 Escapements

A significant phenomena in biology is the manner in which energy is released, i.e. .in a highly controlled manner. In most, if not all of biochemistry, energy can be said to be released in packets. In those few processes where energy is more or less constantly flowing, we call those “leakage”. In neural processes it manifests itself in the discretization of analog signals. The flux of ions through an ion channel is quasi analog. Although ions themselves are discrete, the numbers involved are usually large enough to be treated as analogous to electrical current. While the individual ion channels are discrete and binary in their gating (open/closed step function), the action potential is most efficiently simulated in its 4^{th} order differential equation analog form. At such an aggregate scale the action potential sodium influx within 1 to 3E-3 s is immediately and causally followed by the nearly simultaneous shutting of the sodium channels and opening of the potassium channels to allow potassium efflux. This quick succession serves both to “digitize” the signal and to nearly double the steep dV/dt disturbances to the surrounding local region.

5.7 MODALITIES

In 1990, Shrager did a computer model of a demyelinated axon.[150] He divided it into 20 equal length compartments, modeled Calcium effects upon the axon membrane, and produced oscillations as extracellular calcium concentrations were reduced to near zero. Calcium modulated the behavior of sodium channels and potassium channels. An oscillation requires two opposing forces metered by each other so that each limits the other.

If potassium current consists of positive charges outward and sodium current consists of positive charges moving inward, then these two forces are opposing. We already understand that the depolarization of the resting potential by sodium influx triggers the potassium channels, after a 1E-3 s delay, to open. If a mechanism is added whereby the action of the potassium channels, after a delay, triggers the opening of the sodium channels, then a sustainable oscillation should occur. Normally sodium channels have a refractory period to prevent this. If a modulator of sodium channels were to have the effect of shortening (or eliminating) the refractory period to where the sodium channel could respond to the voltage changes induced by the potassium channels (about 3E-3 s), then an oscillation were occur until some change broke that cycle. Bursts are characterized by very distinct on and off events, not gradual and not chaotic. The sharp modal change from quiescent to rapid fire would require either a sharp voltage range shift (unlikely) or a modulator that could be released near the ion channels to turn on the oscillation, and then somehow become sequestered again to turn it off (or vice versa, where a modulator is removed from an ion channel to start a burst, and replaced to turn it off). Models that represent modalities mark entry into ion channel kinetics of multiple state path circuits, and they also require the modulation mechanisms to reliably switch between those circuits (modes).

Focused, synchronized activity in a dendritic tree can be arranged so as to maximize the wave peak just as it reaches the soma[151] Many dendritic arbors consist of two zones, the distal and the proximal. The proximal acts to suppress the inherent nonlinearities so as to emulate a linear response fro all points in the tree. The distal end is variable, modified per learning and plasticity.[152] Workers are variously aware that the modalities of firing patterns cannot be modeling by stipulating average firing rates. Nor can they be replicated by binary open/closed kinetics.[153] Workers had noticed that the activations and deactivations of sodium channels were often incomplete and chaotic,[154] and this suggested that kinetics was playing a role more complex than the Hodgkin Huxley equations could generate. They responded by building stochastic models to mimic the kinetics of modal shifts, switching between single spikes, oscillations and chaotic firing.[155][156][157] Out of this came the concept of "kinetic schemes", so called out of modesty that there must be immensely more complex kinetics yet unobservable within the molecule, and that the observable bits were but a cartoon of the whole.

The fact that some potassium voltage gated channels have I/V plots that are monotonic, and other channel types that present second order curves, suggests that there are not many significant molecular conformations in those channel types. Some sodium channels have I/V plots that appear to be third order (display two inversions). We can only

measure the openings and closings of the channel (gating currents), and will therefore be tempted to see only those two processes in an I/V plot. Not present in the I/V plot are the time lags between stimulus and response. Not present is the inactivation function. For these and other reasons, two-dimensional plots are not adequate to model channel modulation. All such curves are of aggregates of large quantities of channels. The single unit recordings display greater subtlety. The many found allosteric modulation sites present on most ion channel types, are usually found to alter the state transition probabilities. To discover what might be the states of an ion channel, 2-step voltage clamps attempted to map various combinations of torsion put on the molecule to see where it might jump o when relaxed a little. Every state transition requires time, and reversible processes make the outcome a bit uncertain. But the data were such that exponential curves could be pealed off, each one suggesting the existing of a conformational state. They could then be trialed to establish sequences, and by that a state path chart could be drawn.

Protein molecule state transitions are analyzed as first order processes, with an exponential curve wrt time as their solutions. Given complex data, a number of exponential curves can be "peeled" out by subtraction, leaving a remainder from which more exponentials can be peeled out. This can be repeated to some level of accuracy or diminishing returns. Each found exponential is weighted in amplitude and by time constant. The measurable current is then presumed to be:

I(t) = I(inf) + w1*exp(-t/t1) + w2*exp(-t/t2) + ... + wn*exp(-t/tn); % where I(inf) is steady state

This is only a curve fit of exponentials, but is justified by kinetic first order reactions. The problem is that it is not the conformational change that is being measured, but rather the effect that conformational change happens to have on conductivity of the channel. In many cases that would be none, and so those conformations are invisible and ignored.

The problem is that once terms are added together, information is lost, and even more so when the quantity of terms is unknown. Given a sum of 7, what originally comprised it? 1+6, 2+5, 3+2+2, 1+1+1+1+1+1+1 ? Using only integers, there are 14 possibilities, and of course using decimals, there are an infinite number. We receive the sum effects of conformational changes as a measurable current through the open pore. Teasing them apart leads to what are called "kinetic schemes"

The argument is made that to achieve higher frequencies of flux across the membrane, one cannot reduce the mass of the ions, so there must be greater forces brought to bear. Higher voltages were found to support higher frequencies by Buckingham.[158]

The input waveform is the spatiotemporal integration of spikes, and may present as rather sinusoidal (single frequency) or more jagged (mix including high frequencies). It is the high frequency part of the spectrum that can most easily trigger the rate-of-change sensitive ion channels. Therefore the temporal shape of the input wave makes a difference. Some of these effects can be mimicked spatially. With inputs converging from various length dendrites, they assemble in a phase pattern that can shape waves over a wide range of possibilities.[159] To probe for the temporal shape domain of various dendritic spatial field shapes, various patterns across the field were stimulated.[152]

Given one channel with faster kinetics and another channel with slower kinetics, they can be set into opposition, and together produce an oscillator.[147]

Each of the historic models has been reviewed for its ability to exhibit multiple modes.[160] The HH, Fitzhugh-Nagumo, Morris-Lear, Hindmarch-Rose, Conner were analyzed mathematically for limit cycles. These EQs can imitate the aggregate response, but cannot simulate the unitary channel behaviors.

The mechanisms of neuron ad neural tissue behavior take place at smaller scales than previously thought. A single cell has been shown to be capable of a seizure.[161] A single channel can act as a pattern recognizer. A single channel can act as a pattern generator.

Modalities are significant because neurons are well known to shift between several characteristic response patterns. A model is desired which can represent the neuron dynamics sufficiently to reproduce the mode shifts of that neuron, say from random basal firing, to rapid bursts, to regular rhythmicity.

5.8 ANALOG VS DIGITAL PROCESSING

At the nano-level, a hydrocarbon is an analog molecule. Like a wet noodle or gummy bear, it can be moved and bent continuously over an infinity of conformations. At the nano-level, a molecule with numerous fixed charges

(like a protein) is a digital molecule. Like a toggle switch, when force is applied it either remains in its current conformation or snaps to some other conformation that relaxes some of the energy being applied to it. Such digital events are merely movements through space in very short times relative to other significant processes.

The realm of artificial information processors has been divided into strictly two approaches: analog and digital. The design objective of analog processors is to be as linear as is practicable in the processes of amplification, summing and subtracting of signals. The design objective of digital processors has been to achieve as non-linear as is practicable the flipping of gates in response to various input combinations. We are comfortable with these two extremes only because discrete math has worked out very neat conversions between the two. We tend to regard this arrangement as two for the price of one, because we can always convert the one into the other whenever it is handy to do so. But this skirts a philosophy of science question: What is the natural basis of these two concepts? Are they two extreme points on a continuous gamut? Is one of them the "real thing" and the other but a shadow or emulation? Is it possible to build a processor somewhere in between analog and digital? What sorts of entities live in between? What can we learn from mixed analog-digital systems about the potential of dissolving the distinction between the two? What is the information processing potential of function which have both linear ranges and non-linear ranges? For example, the tangent function can be scaled such that it crosses zero at 45 degrees (perfect linearity) but then soars off to infinity before it reaches 1 or -1. Can a computer be built of such functions, rather than op amps or transistor gates?

The free roaming particles are responding to diffusion and drift. Both thermal energy and EM force are operating as analog forcers. But any binding events are clearly digital functions. Any duty cycle of a particle which involves both drift and bindings (e.g. for transport) is necessarily operating in both analog and digital modes. The question is: are these NIP significant?

Now, let's take a look at those oh so digital actors. The state path diagrams reveal that most (probably all) actors proceed around a duty cycle in digital fashion. However, the state transition probabilities can be modified. They can be modified by allosteric bindings, or they can be modified by the impinging voltage. The bindings are digital but the voltage is analog. Even at the nanoscale of individual charges, voltage is necessarily analog because they are positioned in continuous space, and moving in continuous position trajectories.

Does this mean that voltage-modulated actors have an analog component to them? Perhaps it is more accurate to say they serve as an A2D converter, from voltage to threshold of state change. Then isn't the converse necessarily true, that particles that become bound along their cyclic paths must be acting a D2A converters? Yes, this appears to be a sound conclusion.

Is it possible to build an information processor with strictly only digital, or strictly only analog processes? If not, is what we are calling "information processing" merely an alternative name for continuum/discrete interaction rules? The inner workings of a CPU consists of gates, conductors and capacitors, and occasionally resistors. For these, all are inherently analog except the gate. So here is this strictly digital device, built up of mostly analog components.

Analog processors can add, subtract, multiply and divide without digital components. Evidently 2 or more data streams can be merged to form a third composite stream, all in continuous space and time. But all discrete elements and discrete events are embedded in continuous space and time. They cannot exist independent of them. Therefore, analog is the more fundamental domain. It must quickly be admitted that such strictly analog view only gets so far as we have not encountered any particles, surfaces or bindings. Matter itself is the discontinuity of continuous space and time. Every collision is a discontinuity in momentum and of course they are disruptions in time. Matter may come and go, but space and time remain continuously there. Matter is discrete, and it engages in discrete behavior. That is, it is discrete in space and can be discrete in time (with every collision, binding, or conformational change). As we increase the resolution, those supposed discrete collisions become hyperboloid orbits. This is revealing, because it says that "discreteness" is really an illusion of poor vision. But the concept of discreteness is handy, none-the-less, because indeed, that brief period of elastic collision had things moving very differently from the straight ballistic trajectories before and after.

Well, to continue our probe, we would have to admit that those straight trajectories were not at all straight, being subject to an N-body problem of all the charges in the area impinging upon its trajectory. This must yield something much more serpentine than a straight line. And so there is less of a qualitative difference between "free path" and "collision" at the nano-level. Perhaps the difference is merely between the dominance of the EM force vs. the nuclear forces which hold atoms together.

If processing information is accomplished by digital events, and digital events are collisions, then why is not diffusion a type of digital processing? Well, diffusion is the answer to one type of problem, the spread of the

Gaussian curve over time. But of course, it proceeds to white noise, defined as the absence of information. Its solutions are various paths to zero. In a sense, diffusion erases the chalk board, readying it for the next problem. How then, is one to make a problem solving device out of collisions? The answer is: by ordering the playing field of those collisions. A game of bowling proceeds by ordering ten wooden cylinders in very certain positions. The "answer" to each roll is the disorder created by knocking some down. It is a subtractive process. Disordering all 10 is interpreted as a "high value" action. All of this is arbitrary, a product of: a) certain pattern of order to pre-set the field, then b) accommodating a narrow domain of input signals (sphere with direction, speed, spin, and weight), that c) yield various "solutions" according to the rules of scoring. The rules value some outcomes more than others.

A neuron is more like a game of bowling than it is like a digital computer. The digital computer attempts to be a general processor, which means it tries to allow any possible digital input, and claims to be able to generate any possible digital output without prejudice. It facilitates altering the internal order before every action, and encourages the changing of the rules of how to evaluate the answer with every action. Neurons, as a group have but 3 tasks: to represent (in space, time, and quality) those aspects of the outside environment that are of consequent to the organism; to represent those aspects of the organism itself for possible responses to the environment; and to forecast how these two might interact (anticipate, plan, etc.) . To this end, neurons need to order themselves and their constituent parts so as to perform 1 of these 3, and then connect so as to generate useful behavior via the integration of all 3.

Information processing then, is a matter of order. In particular, the internal order is preset, ready to interact with an external order that is lensed into an "input signal". The internal order is stationary, and the environment is rendered as the dynamic streaming data. This stream literally collides with the stationary order of things. Whatever consequences of those collisions make it out the other end we call "the answer". The imposed order defines the "problem type" or algorithm.

Each encounter of the internal order with the incoming signal pattern results in some "result" or output signal. The output signal is a refraction off the order. In a second-order domain, this could all be done with light, sound or electricity. But the neuron offers a higher dimensionality of pattern space. This is emergent from its complex shapes and complex molecular state changes. A simple analog computer is the still surface of a large pool of water, interrupted only by point disturbances.

A simple digital computer is a grid of transistor gates with open and closed states. But the complexity increases rapidly when tortuous topography is added to the surface, and randomized dozens of state transitions are added to the gates. We then transcend the realm of waves and bits, and enter the realm of pattern recognition and pattern generation. In mathematical terms, neurons operate in higher order spaces, and therefore are capable of processing higher order problems. The terminology for second order phenomena is based on the sine wave; but we have no such clean basis for the third, fourth and higher orders, so they are merely referred to as "patterns. What order of pattern would be symphonic performance of Beethoven's Ninth Symphony?

Neurons are not, however, general processors. They come highly biased, and become progressively more biased with experience. Because their role is to represent the external and internal environments, their order is adjusted to optimize these representations, and this order stands as the static portion of the processor, against which novel stimuli are refracted. There then proceeds steps to extract features and classify those features of the input. Eventually the input pattern is mapped to an output of choice. And that output choice is mapped to a choreographed muscle/gland sequence to effect action. This is an daunting undertaking under any circumstances. Fortunately it is reduced to a "starter position" plus feedback loops (nature + nurture), giving every animal instincts at birth, then time to learn and adapt.

All of this informs the attempt to model of molecular events of the neuron. Neurons are HADs (hybrid analog digital information processors). The analog portion is the field which is rich in overlapping waves arriving from far away, that left to their own devises will dissipate via the diffusion process. The digital portion begins with the order imposed on the system by the placement of certain actor types over the membrane surface. This static order gives rise to dynamic order when the analog pattern washes over it, and in turn the actors respond with internal digital events (conformational changes). Such internal events are "valued" according to their "expression". An internal event with no impact upon its environment is valued "zero". And an internal event that throws open a large channel across which there is a high pressure differential results in a very significant flux through that channel. Such opening/closing events in near synchronicity constitute a "discharge" which we say has high information value. The value of information in the nervous system is not determined by written rules but rather by how loud its response is. Louder responses often carry a lot further down stream. They have impact. It is not the neuron *per se* which determines the value of the message. Rather, it is whatever happens to that message down stream that gives it value. Value is the name we give to consequences.

Ultimately, it can be argued that all so-called digital events are really analog, just at a finer time scale. But it is the sharp contrast in scale that makes one perspective see it as analog and another perspective as digital. Digital need not be qualitatively different. It only need be a steep change in gradient that forces a change in behavior when it is encountered.

5.9 LEARNING

Because biological systems learn over seconds to weeks, the time constants are a bit too long for this model to run in reasonable time. However, the knowledge gained in modeling the action potential (time compass 1E-4 : 1E0) in this model is foundational to future studies of learning. Learning may decrease the amplitude on one neuron's input while increasing that of another, but the mechanism and speed of processing within each neuron need not change. The parameters of this model may be incrementally altered to move it towards a model of the processes of long term memory. All of the parameters of a single neuron may be alterable within the larger context of an organism adapting to changes in the environment. A good basic model already has the most significant parameters built into it, and they are available for future tweaking by meta-models. This model thus exhibits plasticity.

6 ARCHITECTURE

Software architecture contemplates the organization and strategies for converting biological information into a digital model. It adds nothing to the knowledge of biology, but rather grapples with the limitations and forms of digital computers, and how they might emulate types of process other than their own inherent proclivities.

How do the forms of software architecture support the scientific mission? The living cell employs no central control over information processing, nor does it employ any synchronizing clock, which would require wait states and coherence. In the living cell, mass and energy are commingled, such as with the ATP molecule, and information is merely the change in either energy or matter. Information is thoroughly distributed and autonomous. Chemistry is the change in order of the atoms of the system, and this change constitutes information. The digital equivalent to chemistry of the cell might be automata, where all processes are merely interactions with adjacent neighbors according to certain rules. Rules emerge from the order of the system. Order is information in stationary form. Architecture seeks out the natural order of the thing to be modeled, and strives to mimic that order in the design of a model, as best the resources of a digital machine can accommodate such.

6.1 SOFTWARE ARCHITECTURE

The design of this model must confront the challenges of digital representation of certain aspects of a neuron, as needed for the study of ion channel distributions along 3-dimensional neuron shapes. Neurons are hybrid analog digital processors (HADs). The digital computer is handicapped in its ability to perform analog processes and is particularly inept at modeling hybrid, distributed analog digital processes. It must be brought to emulate processes not natural to it, and this typically costs much computation time. SW (software) requires an organizational framework to render it buildable, auditable, modifiable and maintainable. SW Architecture begins with a set of forms, standards, and design rules which insure a uniform, consistent, cohesive product that is not entangled in arbitrary growth.

Digital computation is efficient only when like-kind processes are computed *en bloc* and simultaneously. To accomplish this requires the over-constraining of the great variety of biological entities into a short list of digital

forms, relying upon only the parametric values to express biodiversity. Much or all of the analog nature is squeezed down to discrete entities. Therefore the first business of software design is the reasonable representation of analog processes, and how they interact with the (easier to represent) discrete processes. This involves a dedication of resources to those few critical analog processes, while allowing less significant analog processes to be simplified and digitized.

The formality of digital machines is qualitatively different from the variety of biology. Standardization practices common in computer science will filter out the essential processes of life when applied to modeling living cells. Conversely, when the full variety of living cell variety is modeled the code can grow chaotically and become nonsense. Therefore, it is helpful to recognized that computerization tends to over-constrain biology, much the same as the set of counting numbers are a highly constrained version of the continuous number line.

A failure of sound architectural practices results in something often called “spaghetti bowl” code, which is famously unmaintainable and even unknowable as to what it is really doing. This is a concern regardless of the entity to be modeled, biological or not. Architecture, then, can define the rules of object-oriented practices which will rationalize the linkages, minimize change management headaches, improve readability and maintainability.

6.1.1 CONCERNS OF SW ARCHITECTURE:

1. provide the major Organizational Scheme
2. elucidate the scientific view and benefits
3. identify and select the enabling technologies
4. sketch a data in / data out view
5. trace a schematic of causality
6. structure the challenge into a hierarchical view
7. provide a minimal set of use cases
8. limit the scope via domain definitions
9. characterize the rules engine
10. plan the re-use potential
11. capture scientific information into repositories

12. define the justification process
13. establish criteria for verifiability
14. provide the design view
15. benchmark the major phases in the software process
16. define metrics for performance and set standards
17. provide the means and plan for scalability
18. determine the degree of flexibility that is likely to be achieved
19. calculate reliability factors
20. offer hardware optimization and load leveling strategy
21. define how auditability is to be sustained
22. set coding methods for maintainability
23. provide fail-over and disaster recovery code
24. define the user-interface requirements
25. import capability of relevant data in various formats
26. export capability of data to relevant users
27. make explicit software function priorities

6.2 MAJOR ORGANIZATIONAL SCHEME:

1. Divisions:
    - Physics
    - Actors
    - Membranes
    - Interactors
    - Emergent properties

   Physics provides the forces and rules of engagement between the elements
   Actors are extensively covered throughout this text
   Membrane shapes and positions imply cells, organelles, and interconnections between cells
   Interactors imply both neutral and charged particles,
   Emergent properties include: capacitance, voltage flux, and currents

2. Classes: each division has several classes
   Division Interactors
    - Class 1: Monatomic Ions
    - Class 2: Polyatomic Ions
    - Class 3: Ligands

   Division Actors
    - Class 1: Receptors
    - Class 2: Second messengers
    - Class 3: Channels

Class 4: Vesicles
Class 5: Pumps
Division Membranes
Class 1: membranes
Class 2: compartments

3. Types: Each Class may have any number of functional types, as biologists may identify
EX: Actor Class 5, Type 1: NaK ATPase

4. DESIGN Distributions: positional PDFs for each type of element, prescribe patterns of placement in each experiment
The actor density along the length of the cell is often available as quantity / sq micron
This piecemeal information can be assembled into a contour that represents densities along the axis.

5. BUILD Instantiations: create individuals, initial locations and initial states
The PDFs for each actor can be instantiated stochastically, placing and positioning actors on a shape.
All statics are instantiated in the build.

6. Scaling Factors: map biological conditions into the confines of digitized discrete space
Necessary compromises in large scale molecular models require reconciliation between surfaces, volumes, quantities.

7. RUN Logic: the rules and patterns by which states transition
All conditional switches; all logical processes to identify events; transition probabilities matrices

8. RUN Dynamics: difference EQs and non-linearities employed in iterative RUNs
All dynamics are iterated in the RUN. The *dt* value is critical to nonlinear EQ stability.

9. States: values that are determinant of all timely characteristics on an instantiation
particle positions and actor states are of the essence in systemic behavior and information processing

10. State Transition Probabilities: equivalent to state change rules.

11. Implied Variables: flux, voltage, current, capacitated ions, states

12. REPORT metrics, patterns, and forms
Output variables are collected as time series.
Visualization of large quantities of data via 3-d mesh plots
Movies of particle motions and actor state changes (by color)

6.3 FOUR ELEMENTAL DIVISIONS

Each Division consists of functional classes

EX actors = { recep, shuttle, chan, ves, pump }; EX A.Chan.001 = actor.channel.first type in list

Each Class is a library of a number of Types. For example:

B.Ions = { Na K Cl Ca ... }, up to 256 types

Each Type may have any number of Traits. These are the intrinsic qualities of a type of actor, interactor or compartment. For example:

B.Ions.Na.traits = { mass radius charge mobility }

Each Dist is a distribution pattern along the length of the cell, associated with a Type

Each Type may be assigned any number of Distribution patterns across any number of cell shapes

6.3.1 STATES

Each class of element has a unique data form which must be maintained over the run of the model.

Each actor **A** (receptors, channels, vesicles and pumps) has, for modeling purposes, some fixed quantity of internal states (conformational state **Aq,**). These correspond to the high-runner molecular conformations of greatest significance to the actor behaviors of interest to the model. Typically these high-runner states are garnered from published kinetic schemes or more likely in the future from the results of MD (molecular dynamics simulation studies of the molecule). Each actor interfaces with its environment via bindings and impinging forces. The bind/vacancy states are captured within **Ar**, which are treated as inputs. Each actor has a phenotype state **Ao**, corresponding to its outputs. Additionally, each actor is tagged with extrinsic states: position **Ap,** orientation **Av.** **Ap** contains the locations of 1 centerpoint, 2 axial poles used in transport (Ao), and 2 eccentric poles used for modulation bindings (Ar). Ap may be conveniently summarized as a pointer to a known node location from a fixed set of node numbers **Cp.**

Each interactor **B** (ions, ligands and messengers) has several extrinsic states: position **Bp**, velocity **Bv**, acceleration **Ba**, binding **Bd**. Additionally, interactor polar coordinates are kept: position **pol**, velocity, **pel**, and acceleration **pal**. These are redundant to the Cartesian coordinates, but are convenient for rapid processing.

Each compartment **C** has extrinsic traits: node position **Cp**, are found homogeneously covering each membrane surface. Each node is pre-constrained to a position and orientation. It must be oriented perpendicular to the tangential plane of the membrane surface at that point. Node normals are captured in **Cv**, and the contour equations

used to create those nodes are captured in **Ca**.

Additionally, there are several types of membrane states: capacitance **Cq**, and voltage potential **Ce.**

6.3.2 FORCES

Forces are expressed as acceleration of a mass due to Newton's A = F/M. Forces include the inertia of thermal energy effecting diffusion of all non-fixed particles; and the EM force acting upon all charged particles, as a whole system charge field calculation. For purposes of this model, the thermal energy is the average particle momentum, expressed as a Boltzmann's distribution of particle velocities. The EM force is the net vectorial particle acceleration. Concentration gradient is an emergent property of the transported particles, which then dissipate at the diffusion rate. Transport rates may or may not be proportionate to temperature, depending upon the internal kinetics of the transporter molecule.

Force sources may be point, line, planar, 3-D uniform or 3-d gradient. For purposes of this biological model, the point source is all that is needed. Each particle that has a net charge exerts a force. Such forces integrate into net accelerations for each motile particle, proportional to the inverse of their mass. Forces within a channel may be aggregated into contours of energy barriers.

When particles become bound, the force of deceleration is presumably stored as potential energy within the host molecule. Therefore, an equal amount of energy must be released when that particle dissociates.

6.3.2.1 Water, effects of

Water is not modeled explicitly, because of the large quantities of water molecules relative to all other types of molecule. Water is implied in several ways:

1. Charge attractions are heavily muted in the distance through water.
2. Interactor acceleration due to impinging forces is muted into a velocity as a function of viscosity. See mobm.
3. Velocity vectors are scattered by the collisions with water molecules.
4. Thermal conductivity is implied by the transfer of momentum in all collisions.

6.3.3 MESSENGER INPUTS

Input signals are introduced only as ligand concentrations at synapses. They may be generated by a spaciotemporal signal generator. The release dynamic in time and space shall match or exceed the dynamic domain of the particles (time x bouton surface area x quantity of boutons). For example, an audio signal driving presynaptic Ach concentrations may be spectrally filtered tonotopically across a line of synapses and/or cells, so as to mimic the auditory tonotopic map.

6.3.4 MESSENGER OUTPUTS

Similar to messenger inputs, messenger molecules released at the vesicles may be identified in position and quantity each *dt.* It is necessary that the reuptake mechanism is sufficiently fast to derive a "clean" signal. That is, the concentrations of neurotransmitter in the synapse should always be proportional to the known biological signal, not drifting upward or downward of physiological range. Such regulation can only be accomplished by the reuptake mechanism, as the production system is free to vary arbitrarily to generate a signal. The reuptake process is modeled by high affinity pumps that return the released particles to a useful position, thereby employing already defined actor types without the need for special mechanisms.

6.3.4.1 Other Outputs

A very convenient characteristic of digital models is that all aspects are observable. Outputs may be any variable at any node in the system, whether representing physical or abstract information. Complete time series of hidden variables are easily captured. Additional variable may be derived therefrom, such a voltage. For examples, the model easily generates Nernst voltage values per ion channel, flux grad-div-curl, action potential propagation, vesicle release, changes in extracellular tonicity.

6.4 STANDARDS

This chapter concerns primarily the Nonfunctional Requirements of software development. However, model functions are also addressed for purposes of framing the support structures. In addition there are a number of lesser

but common details, sometimes referred to as boilerplate. Several of these standard software metrics that have merit, and accordingly a brief attempt to address them follows.

It is necessary to set up strict conventions that define the placement and usage of data concerning each of the element types, e.g. channels, pumps, receptors, vesicles. This is accomplished in a straightforward manner by working toward generic forms for each type, identifying the sufficient traits for each type, and organizing them into matrices. Each matrix is composed of fixed columns for reserved traits and variable rows for instances of trait value sets. The necessary and sufficient data on each actor type must be tabularized until a generic scheme emerges.

The structural challenge may be depicted graphically as follows:

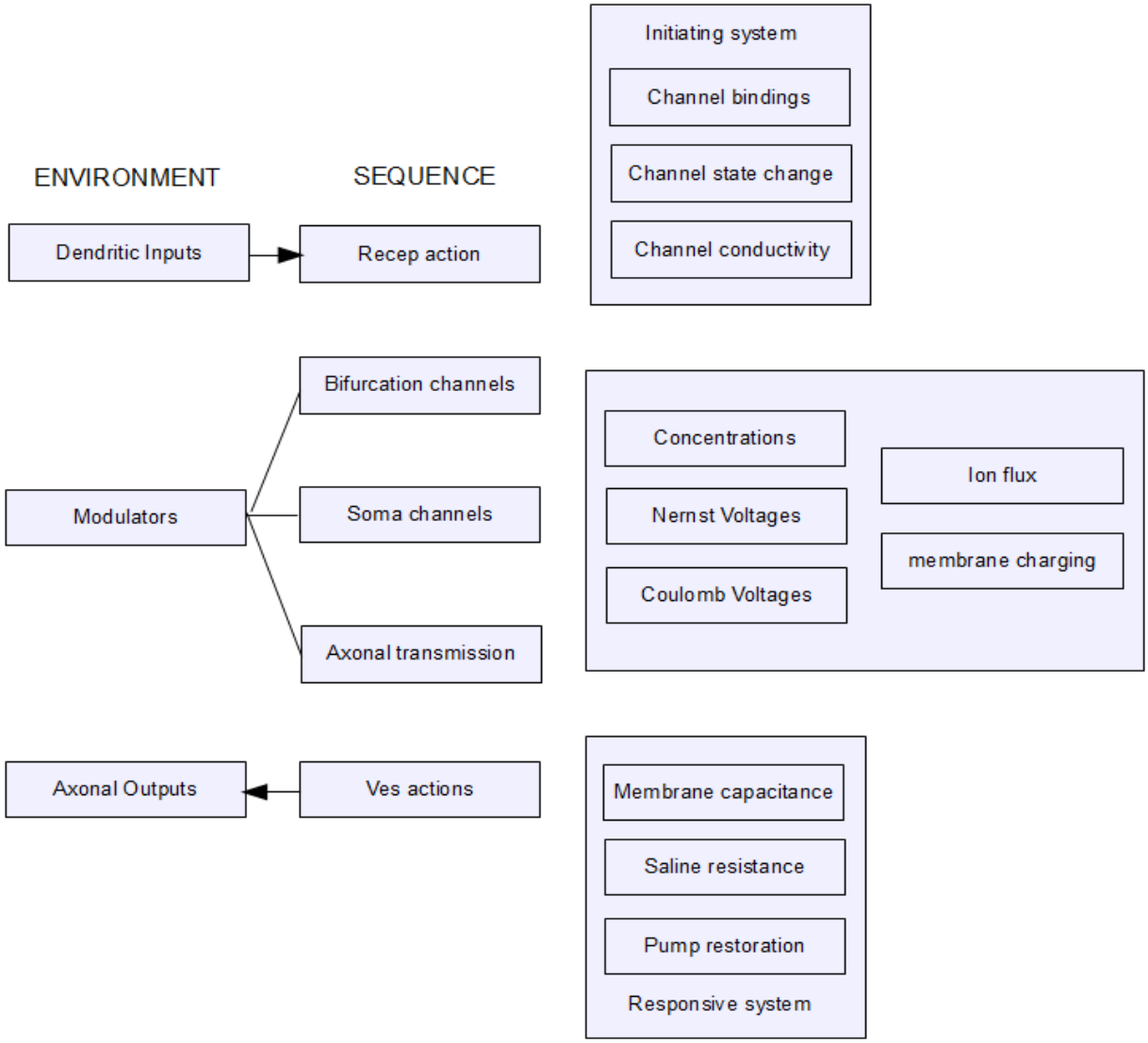

FIGURE 8: Generalized Processes of the Model

The support framework shall be build around the neuronal processes depicted above. There are steady state processes and processes disruptive of the steady state, usually due to receipt of a signal. I am calling the disruptive processes the "initiating system" and those supporting the steady state the "responsive system". he initiating system consists of 3 processes: channel modulation events, channel state changes, and channel openings that result in conductivity to certain types of ions. The rest state for these 3 processes includes background noise, and consequent random channel openings. In response to the channel openings and resultant flux of charged particles, there is a saline resistance to current, a membrane that serves as a capacitor to charge imbalances, and a set of ion pumps that tend to restore the steady state.

There are several metrics of such a system that are useful in producing a dynamic model. We must know the local concentrations of the ion types; the local voltages that result from charge imbalances, the currents through each channel and along the membranes; the partial pressures to move ions through the channels; and the amount of charge on the capacitive membrane.

Zooming out to a more aggregate view, all of the above, as local events, have unique characteristics in each zone. The dendritic synapses are dominated by receptors which directly or indirectly modulate ion channels. The topology of dendritic bifurcations has impact upon how perturbations may or may not propagate. The soma forces an integration of all input into a single signal. By this time most or all of the information processing is complete. The axonal hillock, in many neuron types acts as an A2D converter, producing a digitized signal that is propagated by the axon. This signal is transduced out of the cell by the vesicles, whereby a voltage signal is converted to a Calcium signal, which triggers an exocytotic neurotransmitter signal.

6.4.1 CLASSIFICATION

To build a model, a fixed number of types of elements is defined. There are classes of elements, and within each class any number of types, as they may be found in nature or hypothesized.

6.4.1.1 Actor Classes

A class is a group of elements regarded as serving the same cytological function. The actors are divided into five classes: receptors, channels, vesicles and pumps. Optionally, second messengers may have enzymatic broadcasting stations e.g. cyclase, that require an entity midway between receptor and its target actors.

1. receptors: bind/unbind kinetics, second messenger fan-out, temporal profiles, target profiles
2. shuttles: serve to receive second messengers and catalyze the production of third messengers
3. ion channels: with conductivity profiles, Q-matrices, gate vectors, modulator profiles, subunits
4. vesicles: as output devices with statistical properties
5. ion pumps: with transport profiles, states, saturation profiles, modes, affinity profiles, staging, rates, bind/unbind kinetics

6.4.1.2 Actor Types

An actor type consists of a set of intrinsic traits of an element, one column for each trait, one row for each entity. For example, each channel type has a conductivity profile, modulator binding sites, and probabilities of state change. All actors are point processes. All are stationary membranal proteins that have multiple states. All are modulatable via allosteric binding.

The software must insure the preservation of channel and pump distributions, the use of receptors and modulators for inputs, and the use of vesicles and their content particles for outputs. As the vesicles are of considerable complexity, reasonable means must be found to simplify vesicle functions.

6.4.1.3 Interactor Classes

A particle system consists of large quantities of points, each with mass, radius, charge, position and velocity. Each particle must independently be capable of participating in motion, collisions, capacitance, and binding. Each particle may participate in several collisions: particle-particle, particle-membrane, particle-water. Each particle must

be capable of binding and unbinding to chemically compatible sites upon collisions with that site. Therefore a particle may be in: free liquid state, bound to an actor, in transport to another compartment.

1. ion species:
   minimum trait set: atomic number, mass, charge, radius, mobility
   See Data Structures for a more complete set of traits

2. ligands: modulators, neurotransmitters, hormones:
   minimum trait set: sum atomic numbers, mass, charge, equivalent radius, mobility
   See Data Structures for a more complete set of traits

6.4.1.4 Interactor Types

Ion types include all monatomic ions found in biological systems; polyatomic ions,

6.4.1.5 Interaction Systems

1. voxels: some means must be provided for interpreting position as 'near to' or 'pending collision with' other elements.

2. pixels: some means must be provided for interpreting surface phenomena, an for nearest neighbor coupling.

3. Bind sites: some means must be provided for the capture, ownership and release of particles by actors

4. Bind site dynamics: the bind and unbind kinetics are dynamic. Subject to modulator-actor kinetic changes

5. Actors may function to transport particles across the membrane. The transport rates must be gauged (may exceed diffusion pressures)

6. Energy economics is not an explicit objective of the model but is implied by transition probabilities. In addition, energy depletion, and actor fatigue, are simulated via particle availability (especially ATP) and the Na concentration gradient across the membrane.

7. Energy barriers, when germane to an experiment, must be mapped to a conductivity value as a function of the parametric determinants of that conductance (e.g. voltage, allosteric bindings). This model utilizes only the net effect of an energy barrier upon conduction, rather than the full simulation an ion passing along the energy barrier profile of repulsion and acceleration.

6.4.1.5.1.1 Energetics

It is not the intention of this model to track the energetics of the various reactions, bindings and transports. However, the pump curves require curve-fit EQs, and such EQs will often mimic the free energy EQs, because the pumps may reverse direction when the delta G reverses sign.

Generally, the energetics are implied by the momentum of the particles and the transition probabilities of the actors. That is, a change in energetics will result in certain changes to these variables which are completed prior to the model build.

6.4.1.6 Distributions

The positional distribution of a particle describes the probability of finding one at a given distance down the length of a neuron. Although the initial position of ions needs to be a homogeneous concentration throughout the compartment, this can be achieved by injecting particles into the compartment and allowing time The conservation of energy requires that the system total momentum + system total chemical potential = constant. All charge interactions lead to accelerations, and to capacitance when there is a barrier to that acceleration.

Particle system diffusion serves to deliver messenger particles. Particles with charge and mass participate in second order behavior, waves and oscillations. Particle velocities must remain true to Boltzmann velocity distributions. Other traits will also be attributed to them. They serve both as charge systems and messenger particles.

There shall be a probabilistic distribution for each element type, per each cell type to determine the actor densities per zone and/or gradient. There are several uses of probability distributions within this model:

1. distribution in space
2. distributions in velocity
3. distributions in orientation
4. distributions in initial state
5. distributions in resultant behaviors (state paths)
6. distributions in lag time (phasic information)

6.4.1.7 Zones

Shapes are usually divided into functional Zones. For example, the whole cell model may be depicted as Nine Zones:

1. Dendritic Synapse
2. Dendritic Bouton
3. Stalks
4. Soma
5. Axonal Hillock
6. Axon

7. Node of Ranvier
8. Axonal Bouton
9. Axonal Synapse

The choice of zones is completely flexible. The above default set may be replaced by any other set, fo any length, on a per shape basis. Subzones may be applied to particular areas of interest. For example, the Node of Ranvier may have subzones: prenode, internode, postnode.

6.4.1.8 Workbench for Ion Channel Distributions

Actors are depicted as point processes. A point process is defined as an abstraction of an entity that changes state with no visible change in position or shape. It is a convenience in modeling that treats, for example, a large protein molecule as a mere point in space, but none-the-less capable of changing internal configuration and binding conditions. Stationary membranal proteins that have multiple states, some of which express themselves via special interactions with their environment. These may be calculated probabilistically and simulated without addressing the internal atomic bonds and intramolecular force interactions.

In this model, the following are regarded as point processes:

1. ion channels: with conductivity profiles, Q-matrices, gate vectors, modulator profiles, subunits
2. ion pumps: with transport profiles, states, saturation profiles, modes, affinity profiles, staging, rates, bind/unbind kinetics
3. receptors: bind/unbind kinetics, second messenger fan-out, temporal profiles, target profiles
4. vesicles: as output devices with statistical properties
5. modulation of receptors, channels and pumps
6. binding of interactors to actors
7. transport of interactors by actors to another compartment
8. actor internal conformational changes
9. chemistry: modulator-actor kinetics and conversions. e.g ATP to ADP conversions

6.4.1.8.1 Space representation systems

1. voxels: cuboidal division of unity for volumetric tracking; alternatively, hemispheres at each actor.

2. pixels: square division of unity for surface tracking. Alternatively, voronoi areas, hexagrids, radii of influence.

3. bindings: capture, ownership and release of particles by actors per reaction rates that are not constant.

4. transport: transport rates (that may exceed diffusion pressures)

5. barriers: surfaces that reflect particle movements and provide locations for transport of particles

6. nodal addressing homogeneously covering all surfaces, each provided with an orientation normal, and identification of which volume numbers are present on each surface of the membrane. This implies a concept of inside and outside, by convention.

7. Membranes have mechanical thickness and equivalent electrical thickness

6.4.2 FUNCTIONS

The model, at a minimum, must execute the following biological functions:

function Passive Cl- pores, allowing Cl- anions to pass from one compartment to another as leak current

function Passive “leak” pores, allowing a fixed low conductance of the ion to dominate the rest potential

function pump, 3 Na, 2 K ATP pump, modulatable by ([K+],Ca++, Mg++, dV)

function pump, 1 Ca++ out, 3 Na+ in,

function pump, 2 Ca++ into sequestration, 1 ATP consumed pumps down to [Ca++] = `e-7 M
modulator types = [phosphorylated phospholamban]

function pump, 1 Cl- in, 1 HCO3- out, exchange carrier

function receptor, excitatory, so as to transduce a neurotransmitter outside into a channel opening rate

function receptor, inhibitory, so as to transduce a neurotransmitter outside into a channel closing rate

function Na Channel, modulatable by voltage, by receptor messengers

function K Channel, modulatable by voltage, neurotransmitters, Ca++

function Ca Channel, modulatable by voltage

function vesicle exocytosis, so as to release its contents of neurotransmitters, triggered by Ca++

function neurotransmitter re-uptake in a timely fashion

function vesicle recharge with neurotransmitter, staging for the next release

function Ca++ sequestration, to temporarily remove Ca++ cations from mobility and charge effects

function EM force, applied to all charged particles

function Thermal motion, applied to all particles, per Boltzmann velocity distributions

This is a minimum starter set, intended to be greatly extended as the biodata is available and normalized into the model libraries.

6.4.3 INITIALIZATION

Initialization is easily done wrong; for example if every channel was initialized in state # 1. The correction is easy if there is no coupling between actors: instantiate each actor external state across its PDF of modulator bindings, and then choose some internal state across its current internal PDF wrt modulation state. In the case of G-protein messenger systems where there is some degree of coupling between a receptor state and channel state, a longer sequence of probabilistic instantiations is prudent. It can be argued that no matter what states are chosen for the start states, the system should stabilize to a steady state consistent with physiology after some period of time. However,

the extreme nonlinearity of membranal systems might accidentally find new modes whose attractor is not representative of bio-systems. This is especially a risk when model are constructed with incomplete starter information, and hypothetical values are used to "fill in the blanks". The state probabilities at $t = \inf$ usually yield the "rest state" PDF.

6.5 MODEL REALMS

The model is nonlinear due to conditional flow control operators. There are two master processes that drive the model: Particle collisions and gating events mediated by stochastic finite state machines. Each encounters frequent and significant extrinsic disruption events that are germane to the transfers of information. As a HAD (hybrid analog digital computer), the continua of space, time and force fields behave linearly for particle drift, while the intramolecular state transitions and binding/unbinding modulation events behave nonlinearly.

Solutions to linear systems are amenable to closed form analytic EQs. As the order increases in polynomial EQs the smooth curve give way to ever sharper singularities, heading toward square and triangular "waves". Where lower order systems abide by continuity, higher order systems tend to emulate the "decision" with sharp modal shifts when a certain combination of conditions is crossed. The nervous system is concerned with recognition and decisions as to how to respond to such recognitions. The study of the nervous system is then, by necessity, a study of nonlinear processes.

Within biological systems there are two dominant circuits. The homeostatic circuit is a negative feedback loop that tends toward equilibrium (set point) after each perturbation. It generates the classic sigmoid response curve. The defense circuit is a positive feedback loop that once perturbed tends to grow very fast to limits of the system. This phenomena can give rise to the startle, the attack, the appetites driving search behavior, and, at a smaller scale, the firing of neurons. Positive feedbacks are inherently dangerous. In every case there must be limits to resources consumed by positive feedbacks, timewise limits to the duration of these circuits in their consumptive process, and some grand restorative negative feedback loops that eventually take over and restore baseline levels for the organism. The membranal actors exhibit distinctly nonlinear behaviors (as finite state machines); and the ecologies of systems of such actors coupled by particle collisions give rise to highly nonlinear behaviors.

6.5.1 USAGE PROCESS

Usage process consists of archived elements in the model library selected for an assembly into a whole cell or patch model. The various types and patterns are instantiated in a build, and then the dynamic equations drive the run, generating a time series for all dynamic variables. This assembly is driven with an appropriate input spatiotemporal signal set.

6.5.2 IMPORT CAPABILITY OF RELEVANT DATA

The bio-data must be manually processed to make it compatible with the model. There are a number of steps to adapt disparate data to a singular entity. Assumptions must be made (and later verified). Normalization can be a significant chore, risky for its "collapse" of variety. But despite these caveats, the models do run, are predictive, and with proper care can duplicate the wet lab results.

Normalized forms must be established after consideration of the domain of possibilities for each element type. Then the biodata on each type must be fit into these forms in a consistent and realistic manner. Normalization involves, units, species types, age and sex of animal and cell types. It also involves physiological and pathological condition.

6.5.2.1 Biodata conversion

The DESIGN phase converts biodata into normalized units in regular formats. Interpolation across the missing bits, and/or simplifying the data for tractable computational time may be needed. In the case of hypothetical studies, artificial data must be reasonably generated constrained by the statistical traits of the natural world equivalents. The shapes of the membranes and compartments must be selected prior to the generation of nodes over the surface of the membranes. Then can the positioning of all actors according to realistic PDFs be established, and boli of ions set lose within each compartment. All such design data is captured for the library as new types and dists.

6.5.2.1.1 Seed

The Seed is a virtual data block, consisting of a list of each Type and Dist that comprise an Experimental Design. Optionally, it may contain a pointer to an input signal from the library to be run.

6.5.3 BIOQUERY TO EXPERIMENTAL DESIGN

Biologists are pursuing millions of questions concerning how living cells and tissues develop and perform. Neuroscience is the busiest sub-specialty within biology, in this regard. There are thousands of opportunities for modelers to assist in the understanding of live processes, by assembling known facts together into a system that exhibits behavior. The behavior of the model is revealing in both its likeness to bio-behavior and in the gap between model and life (error). The gap is an indicator of what is missing, and suggestive of which bio-queries might next be pursued to improve our understanding of the involved systems.

If a model generates predictive behaviors of a biological entity, then it is likely to find itself starved for data to set up its experiments realistically. Such models would ideally point out the greatest deficiencies and thus inspire biologists who share interest in the results of such models to help contribute the wet lab data. Indeed the modeling spirit is best embodied by a wet lab immediately adjacent to the the simulation lab, with several iterations between the two each day.

It is the intent of this model to avoid compromising the biological phenomena for the convenience of reduced computational loads. When the modeling schemes are so reduced there comes into play some loyalty to the silicone system rather than the living systems. By investing a lot of time in computer programming, it is tempting to abandon the biological traits that are difficult to simulate. But as modeling drills down to the physical basis and that physical basis is robust enough to emulate complex phenomena without having to detail it as a brute force fit, the model itself becomes generic, adaptable and widely accepted as a standard approach. And at some point it is easier to use, because all of the emergent phenomena require no programming.

6.5.3.1 Reverse engineering from a scientific query

There is a second phase to the experimental design, which requires judgment. The user must choose what phenomenon is to be modeled, how to isolate the “interesting” aspects, how to parse the biological system under study down to tractable quantities, and what queries are to asked of it. A model may consist of about a million particles and links, while a living cell consists of about 1E18 molecules and ions. The process of paring must be justified by demonstrated preservation of function despite reduction in quantities. In nonlinear systems this process must be far more exhaustive across the parametric space, and across all patterns of behavior of interest. There are

most probably aspects of cell performance not yet discovered. Particle system models have the potential to reveal some of these as emergent properties. Optimal quantities and positions of actors are yet to be found. Accordingly, flexibility is needed to “backtrack” or “float” in the process of parsimony, increasing the quantities and types of elements, as necessary to find those optima. This optimization process should be graceful, not requiring a large redesign. Good parametric design can achieve that grace.

Desired levels of confidence can drive the scaling factors. Justification is often an iterative process. It should be expected that some early dismissals of data will later need be reintroduced, and that some early simplification strategies will fail, and need be replaced.

EX The classes and types of components of the auditory hair cell may be modeled for their resonance frequencies.

1. The whole of the intracellular fluid is represented as a compartment.
2. The membrane is represented as a compartment, full of lipids, not water
3. The synapse is represented as a compartment, for convenience in reuptake of neurotransmitters
4. The extracellular space is represented as as 1 or more compartments. e.g. paralymph, endolymph
5. The nucleus of the cell is represented as a compartment. includes reticuli and other obstructions

However, the earlier traditions of "compartmentalizing" various sections and slices of the neuron (e.g. Rall) is NOT done. All compartments are a one-to-one mapping of biological compartments of contiguity. This is to enable and ensure free particle motions as it is in the living cell. Membranes are barriers to particle motion so must be placed only as they form closed volumes in the cell.

An elemental scheme can be implemented in three adjacent containers, the simplest being cuboidal compartments, and the most complex might be the actual biological neuronal shapes taken from morphometrics.

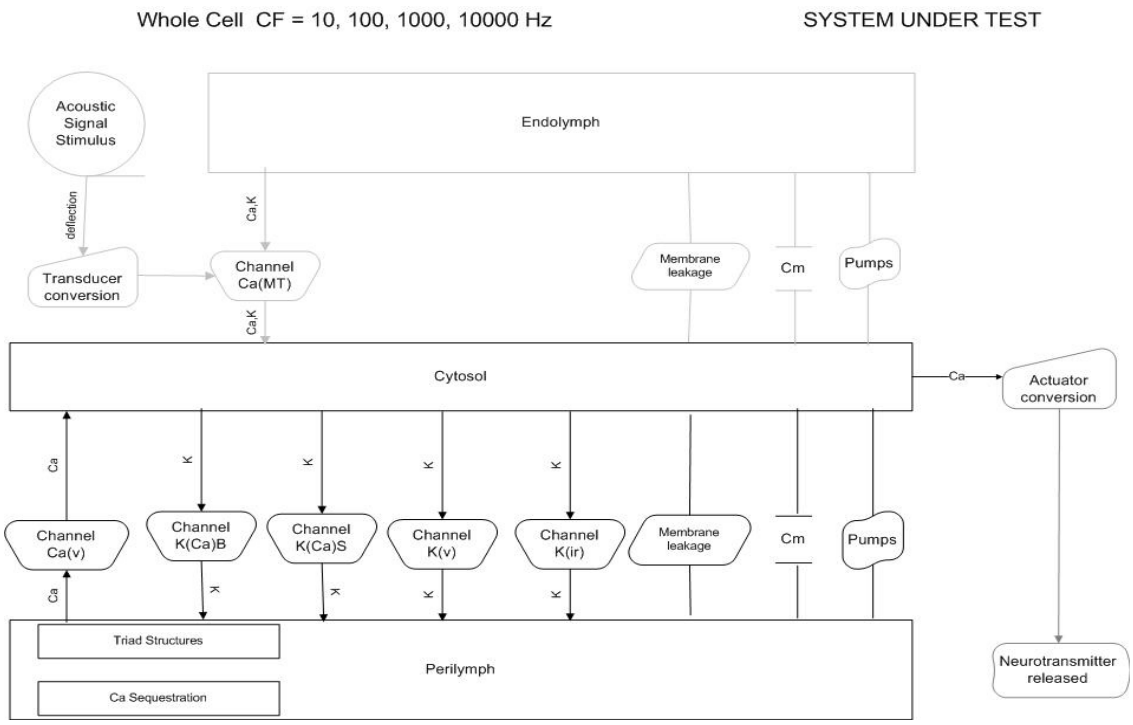

FIGURE 9: EXPERIMENTAL DESIGN OF AN AUDITORY HAIR CELL, ACTOR TYPES

The design above does not show the physical membrane, nor quantity and distribution of each actor type. This design must be instantiated to build out the full number of actors and the spatial positioning between them over membrane surfaces.

6.5.3.2 Parsimony

Conceptually, an experiment begins with a query concerning the shape of, actor distributions on, tonicities about, and input signal to, a neuron. Then the libraries of pre-existing elements and parameters are selected as a point of departure. These are then modified and appended to define an experiment. This initial work creates a starter block referred to as the Seed. The Seed drives the build, which instantiates all the elements, and returns a graphical representation for the user to confirm his choices. The seed consists of Types and Dists for physics, compartments, particles and actors.

6.5.4 EXPERIMENTAL DESIGN

An experiment consists of the selection of the actor and interactor types and their distribution patterns onto a specified shape. The extracellular compartment and synapses are also specified. An input signal set is provided, and

the output data to be collected is specified. In addition some numeric parameters concerning time and space resolution are specified. It is a combination of newly defined entities (if any), library choices (Design), Input signals, and choice of Output variables to be recorded.

The objective of the experimental design is to prepare the basic forms, assembled and made ready to feed to the build process. The build is a compilation, largely automated, of all the specified elements and processes, each instantiated into large scale collection of particles and actors, as an executable simulation. The data for all of these are assembled into like-kind matrices for efficient processing. Recall the abbreviations: A = actors; B = interactors; and C= compartments.

1. Each **C type** is instantiated via **Sh**, a shape generator, typically originated on a spreadsheet
2. Shapes consist of any number of functionally significant Zones, Vanes, Plugs
3. for example C.main.zones = { dendrite soma axon bouton }
4. each **Zone** consists of any number of line Segments which determine their shape
5. each **Segment** consists of a number of Rings (slices), quantity determined by node spacing
6. each **Ring** consists of a prescribed number of Nodes, so as to maintain homogeneous spacing
7. each **Node** may be vacant or occupied by any instantiated Actor
8. In addition to providing Nodes, a compartment also provides a surface capable of particle **reflection** and holding an electrical charge (**capacitance**).
9. The dendritic cone(s) may be divided by radial vanes to separate the cone into sectors, so as to simulate bifurcations.
10. The whole cell may be simulated with an environment of neighboring cells, or else been closed in an extracellular envelop and communicating with small plugs that represent input and output synapses.
11. Each **B type** (interactor) is instantiated from a Molar Concentration per compartment via a Boltzmann velocity **Distribution**.
12. Each **A type** is instantiated via a Spatial Distribution on C and a State Initializer.
13. Spatial **Distributions** are PDFs specific to a neuron type, neuron zone and specific to an A type.
14. Actors are stochastic-driven finite state machines that probabilistically receive inputs and modifiers via **AR**, probabilistically change states via infinitesimal probability matrices **AQ**, which map to effect some external condition via **AE**.

EX Acetylcholine may bind to an ion channel receptor according to the AR matrix for that channel type, which causes the instantiated channel AQ values to change, which begins a probabilistic drift in molecular states over time, which eventually changes the ion channel from closed to open, according to AE.

6.5.5 DESIGN QUANTITIES:

Each experimental design must determine the quantities of:

1. ions per neuron
2. channels per neuron
3. channels per synapse
4. pumps per neuron
5. receptors per neuron
6. vesicles per neuron
7. second messenger shuttles per receptor
8. minimum channel conformational changes per event (e.g. an action potential)

While modeling on personal computers, it is advisable to restrict particle counts to about 1E5, and the number of actors to 1E3. This is but a tiny fraction of bio-reality for a neuron. The use of super computers can increase these quantities 100-fold, or even 10,000-fold if month-long runs are tolerable. (2,592,000 sec/month)

6.5.5.1.1 Shape simplification

Shape simplification opportunities include:

1. axis of transmission, radial symmetry, contours of rotation
2. fan-in and fan-out of inputs and outputs
3. preservation of bio cross-sectional area
4. preservation of nearest-neighbor relationships amongst nodes
5. preservation of contiguous compartments: intracell, sequestration, extracell, in-syn, out-syn
6. homogeneous membranes with addressable node

6.5.5.1.2 Space Scaling

1. Whole Cell dimensions, in microns
2. Patch dimensions, in nanometers
3. Voxels – volume units within the Whole Cell, for purposes of flux measurements
4. Pixels – surface units at the membrane which correspond to the face of an adjacent voxel
5. Flux – net movement of ions, parallel or perpendicular to the membrane

6.5.5.1.3 Space criticalities

A diffusion model is acutely sensitive to distance between actors. For example high concentrations of Ca++ sufficient to trigger vesicle release are only possible when the source of the Ca++ is very close to the vesicle Ca binding site. Nature often deals with this problem via structural links that tether and hold the distance between two such parts as fixed. This may be true for channel parings as well. Another solution nature provides is"rafting". As a result the rates of diffusion and the geometry of diffusion are critical to the ability of the model to mimic biologic "degrees of coupling" between components. Actor assemblies may be necessary to replicate biologic conditions.

As the the distance between 2 oppositely charged particles goes to zero, the attractive force between them goes to infinity. Limits must be set on inter-particle spacing to prevent this., because a single value of infinite attraction will overwhelm every other force vector and reduce the entire model to a single point. Sum of the radii is the limit, and the radii become larger with the solvation qualities of attached water molecules, up to about 45 per ion. Ions must be enlarged to their solvation radii and solvation mass to depict reasonable liquid interactions.

6.5.5.1.4 Quantity Scaling

The extent to which quantities and volumes can be down-scaled must be determined empirically. However, the parameters to not vary independently. Collision rates are a function of particle size, velocity and density. Binding rates are a function of densities and velocity. Scaling a shape alters volumes by the cube, and surfaces by the square. This distorts scaling intent in systems where both the volume and the surface area are critical parameters. The EM force is extremely strong compare with every other force available within the cell. Small EM imbalances would do damage to membranes and proteins. Therefore, limits should be adhered to to avoid unrealistic model behaviors. General, the plasma lemma cannot withstand more than 1 volt.

Opportunities to downscale the model include:

1. Actor quantity reduction
2. Particle quantity reduction
3. Volume reduction
4. Collision rate reductions
5. Quantity of synapse reduction, particle size increases
6. Thickness of membrane decreases.

7. Quantity of phosphorylation and/or glycosylation sites on an actor

A careful accounting needs be done with each scaling change, as to volumetric, surface and point process effects. Coupling and compensation formula must be developed to support such scaling with a minimal loss in levels of confidence. When a full accounting has been made of the scaling factors across all units of measure, then a single amalgamated function can be rationalized and coded which can zoom in and zoom out with minimum distortion to performance.

Some actors have multiple receptor sights for sugars or phosphates. When these quantities are high, there is opportunity to reduce the number while scaling up the modulatory effect of each. This results in a more grainy modulation curve but can be arranged so as to achieve the same wide compass of effects.

6.5.5.2 Assumptions

Assumptions and dependencies of this application as a whole include:

AS-1: The user is presumed to have a working knowledge of Matlab ™, Octave ™ or C++ programming skills.

AS-2 The user is assumed to have access to the scientific literature regarding quantified performance of the various neuronal organelles and molecules.

AS-3 This application shall maintain certain scaling factors in space, time, force and quantity between reality and the model representations. These shall be noted in the Report, and the consequences of such shall be measurable.

AS-4 For visualization consistency, space shall have a scale that is maintained, e.g. 1 cm n screen= 1 micron. However, there may be a need to consider log scaling of space (to be discussed later).

AS-5 Time scale will be noted in displays and movies. Any differential is time scales between processes is particularly prone to creating artifacts, so must be noted, and the consequences of such measurable.

AS-6 Quantity of ion species shall be scaled proportionately except for trace elements, like Ca, which may need to be modeled disproportionately highly in quantity to be effective. The consequences of such measurable.

AS-7 Careful consideration shall be given to the consequences of reduced collision rates between particles and actors. As this affects actor stimulation, which is critical to the information processing function.

AS-8 Careful consideration shall be given to the half-collisions that represent the effects of water molecules in the model, so as to justify such simplifications. Additional traits of water may need to be incorporated into the model,

6.5.5.3 Dependencies

DE-1: The functional ability of future versions of Octave and Matlab ™ will maintain backward compatibility with this code. Note that there are various idiosyncrasies between these two platforms which must be remedied for a fully working bug-free application.

6.5.5.4 PROCEDURE to create a compartment system

1. DESIGN or choose the cell type and shape
2. Starter = write a list of working points for the contour
3. save TypeC
4. load DistC = call default values for spacing off extracell and core
5. Main2Extra = generate extracell and core points. Add to Starter
6. use Starter + PlotC to generate a wireframe plot of what's been designed
7. use Starter to generate SEGMS
8. use SEGMS to generate ZONES, MEMBS and NEURS
9. use SEGMS to generate RINGS
10. use RINGS to generate NODES
11. load TypeA = classes and types of actors
12. load DistA = PDFs to distribute actors according to a cell type
13. use NODES and PDFs to generate ACTRS placements
14. use ACTRS to populate and INIT all the actors
15. use SEGMS to generate SH for particle reflections
16. merge SH into Comp ceiling and floor vectors
17. choose the saline concentrations for each compartment
18. load TypeB = library of particle types
19. load DistB = compartment concentrations and bound ligands
20. populate each compartment with interactors
21. RUN to diffuse and establish Boltzmann velocity profiles
22. capture steady state values
23. initialize the states and turn on pumps
24. RUN to achieve new steady state
25. capture steady state values
26. initialize the states and turn on channels
27. RUN to achieve new steady state
28. capture steady state values

29. initialize the states and turn on receptors and second messenger systems
30. initialize the states and turn on the vesicles

The RUN phase executes the digital code of massively parallel algorithms. Numeric methods must be devised to keep the total CPU time to usefully short intervals (hours, not months). Early concept code may be inefficient, iterating in small time and space steps, with little or no simplifications yet justified. A variety of numeric methods can reduce CPU time about 4 orders of magnitude from the raw physics algorithms. Most importantly, a library of proven routines is accumulated in minimal form, such that their re-use may be reduced to a look-up table.

A run typically requires a driver, i.e. an input signal. This can be in the form of a perturbation, as a step or pulse function. It could be a time-wise transition, a ramp or sinusoid function. Or it could be more complex, such as music, white noise, or "natural" sounds, if auditory. Alternatively, certain sequences of input could be designed to reveal the states of the actors, as in solving a puzzle. For example, 2-step voltage clamps serve this purpose.

Time is modeled consistently within one submodel. Usually *dt* will equal 1E-6..1E-4 s for actors and interactors. Although numeric methods can realize great efficiency via dynamic *dt* parametric values, this creates serious complexity when it comes to synchronizing between massively parallel calculations across all particles and actors, and then up the scaling hierarchy to assemble the WholeCell model. As the primary goal of this project is biologic veracity, not numeric methods for computer science, the code is written to the biology, not to the conventions of computer science. Verification to the biologic aspects is mandated in this type of work. A high-veracity model can serve as a point of departure for those wishing to minimize computational load to effect novel information processing stratagems.

6.5.6 BUILD

The build is a compilation, largely automated, of all the specified elements and processes instantiated into an executable simulation. The build consists of data retrieval from the libraries, then an execution of the static equations of the model.

The BUILD phase initializes the compartments and membranes, populate the volumes within those compartments with ions and messengers, and the surfaces of those compartments with constellations of receptors, shuttles, channels, vesicles and pumps. All of the Boundary Conditions and Initial Conditions must be set here. Also, certain

preferences must be defined, such as *dt*, *qt* (length of run), which data to capture, and to what graininess. The membrane shall be fully addressable, and hemispherical volumes around each actor shall sample concentrations and voltage gradients.

All actor states require initialization. Initializing all instances of a type to the same state would be very unnatural, given that in nature such a group is always distributed across its state space according to their 'resting condition' PDF. Generally, actors are ergodic, meaning that their spatial distribution in aggregate is identical to their temporal distribution for a single entity (when conditions are constant). All Interactors are initialized with velocities according to Boltzmann PDFs.

Initial conditions are not trivial in a digital computer simulation because aliasing error can place immense biases upon differential equations. The living cell does not experience any equivalent to “initialization” nor “reboot”, nor A2D conversion error. Because the entire modeling process can suffers from these artifacts, great care is necessary in the algorithms, and regular verification is necessary to gauge the veracity of the model.. Veracity is sought via parameter optimizations. The A2D errors, which abound in the modeling of biologic processes, must be detected, reduced and managed such that the model results achieve required levels of confidence for each experiment (typically the targets are 95% or 99%).

Though it might be possible to initialize each actor in a rest state, and merely wait for a “warm up” period for the entire system to achieve a steady state, such a “dead” initial state is physiologically unrealistic. Due to the significant nonlinearities of both the elements and the system as a whole, it is desirable to initialize across the probabilities of an element being in a particular state. That is a probability distribution can be generated for the state dwell times, extracted from the Q matices. Thus, there are both position distributions and state distributions.

Because the actors are placed statistically, and their initial states determined statistically, each BUILD of the model is a unique instantiation of the design rules. Therefore, no two BUILDs will yield identical RUNs. The variation amongst repeated BUILD-RUNs is an indicator of all-in system variance, analogous to bio-individuality.

Procedure:

1. The Experimental Design directs which elements and at what membrane densities shall be instantiated.
2. Positions of each actor are determined stochastically

3. The initial states of each actor are determined stochastically

6.5.6.1 Experiment Formality

EXP1 = { CELLS COMPS ACTORS PARTICLES SIGNALS }

6.5.6.2 A. Actors, Point Processes, 0-Dimensional

6.5.6.2.1 Classes = { recep, chan, ves, pump }

6.5.6.2.2 Subunits, logical relationships between them

6.5.6.2.2.1 Mod profile

6.5.6.2.2.2 Bindings

6.5.6.2.2.3 Kinetics

6.5.6.2.3 Assembly

6.5.6.2.3.1 Xport profile

6.5.6.2.3.2 Bindings

6.5.6.2.3.3 Kinetics

6.5.6.2.3.4 Gating function

6.5.6.2.3.5 Conductivity profile

6.5.6.2.4 BUILD Actors

```
EXP.ACTORS = {ACTOR_TYPE.CELL.MEM.ZON.PDF, ...
                    ACTOR_ENSEMBLE.CELL.MEM.ZON.PDF, ... }
        INSTANTIATION ( PDF, NODES)
        INIT_STATES (ACTOR_Q)
```

6.5.6.3 B. Interactors, in solvents, 3-dimensional

6.5.6.3.1 Define solutions: ionic concentrations in water

Note also that the lipids comprising the membranes are themselves compartments with solubility and mobilities for each ion and ligand within them.

A library of ion types, both monatomic and polyatomic ions, is maintained. This supports the use of logicals in selecting which ions will be modeled.

6.5.6.3.2 Type = library of traits

6.5.6.3.3 Compartment assignment

6.5.6.3.4 Position and velocity

6.5.6.3.5 Forces, Acceleration and resultant flux as a function of viscosity

6.5.6.3.6 Mean free path, Collisions

6.5.6.3.7 Bindings, Capacitance

6.5.6.3.8 Resistance

6.5.6.3.9 BUILD Particles

```
EXP.PARTICLES  =  {INTERACTOR_TYPE.CELL.COMP.CONC,  ...  }
          INSTANTIATION ( INTERACTOR_TYPE. COMP.CONC,  ...  )
          INIT_STATES ( INTERACTOR_TYPE. COMP.BINDINGS,  ... )
```

6.5.6.4 C. Membranes, Compartments

6.5.6.4.1 Define membranes

6.5.6.4.2 Define compartments

Each ionic solution needs a container. These containers may be simplified, as in boxes, cylinders, cones or or spheres. Or they may be faithful morphometrics shapes derived directly from living neurons. To get started we will use cuboidal shapes for the patches of membrane, followed by contours of revolution for the whole cell model.

Cubes can conveniently be defined as extents: [xmin xmax ymin ymax zmin zmax], Extents are generated by a basic cube of unity scaled to size, then displaced by position: basicCube*siz + pos. When the max of one cube extent is equal to the min of another cube, then the possibility of adjacency exists. More explicitly, if there is overlap in the x dimension and in the y dimension between two cubes, and zmax of the first cube is equal to zmin of a second cube, then the cubes are adjacent.

Adjacent surfaces may be made to share one or more perforations between them. A perforation can be conveniently expressed as a disc, which is subtracted from the surface of a cube. By this means of adjacent cubes of various sizes, and various perforations between them, a system of compartments can be constructed.

6.5.6.4.3 Membranes, shape simplifications

6.5.6.4.4 Zones, PDFs

6.5.6.4.5 Segs, geometric primitives

6.5.6.4.6 Rings, homogeneity

6.5.6.4.7 Nodes, addressing service

6.5.6.4.8 Occupancies

6.5.6.4.8.1 Nearest Neighbors

6.5.6.4.8.2 Area Allocations

6.5.6.4.9 Generating Contours of Revolution

Parameter vectors for the container shapes have the following columns.

compartment shape parameters =
[neu mem loc zon vane x2 y2 h th1 th2 dx dc]
where
neu = neuron ID #; mem = membrane ID #; loc = multiple unit location #; zon = zone #;
vane = vane #; x2 = distance along axis; y2 = radius; h = arc height; th1 = thickness below;
th2 = thickness above; dx = axial spacing; dc = circumferential spacing;

There is a shape param for each membrane = { main extra core pre post }
Each of these these membranes may have multiple zones, one row per zone.

A neuron can be divided into any number of zones. Nine commonly used zones are:

{ Dsynapse Dbouton Stalk Soma Hillock axon node Abouton Asynapse }

The bouton zones can be joined into the Stalk and axon zones respectively to reduce to seven zones.

A function named getspreadsheet.m reads data into the Octave™/Matlab™ script. From the working points, line segments are generated. Segments are divvied up into rings. Rings are divvied up into nodes.

Next, plugs and vanes shall be added. Various measures are taken of the new shapes: area, volume, centroids, quantity of nodes, zones.

The volumes within the compartments are populated with particles. The buildB function accomplishes this by reading a spreadsheet with various tonicity profiles for intracellular, extracellular, and other compartments.

Particles for one compartment are “injected” into center nodes, and then allowed to diffuse throughout the container until a steady state is reached.

Actor Distributions are represented in the library as vectors of density values along the length of the neuron.

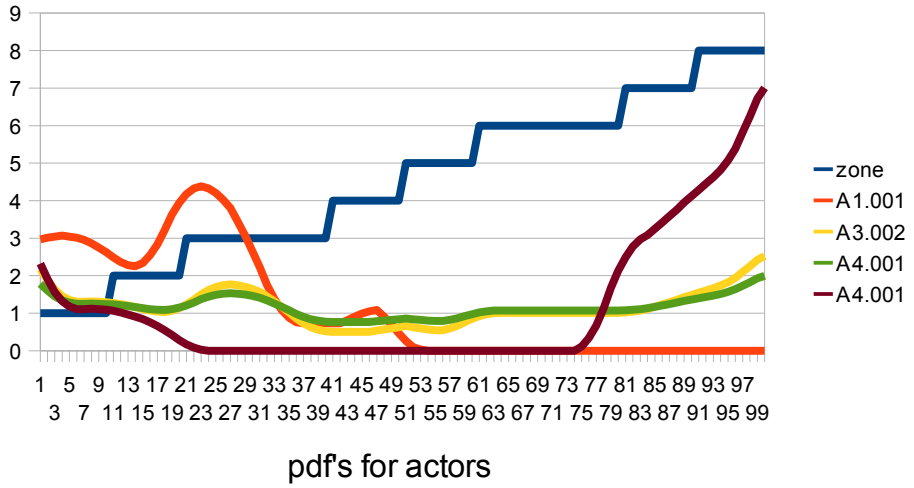

FIGURE 10: NEURON WITH SEVEN ZONES AND 4 ACTOR TYPES

X axis represents fraction of neuron length from longest dendrite bouton to longest axon bouton.
Y axis represents actor density per sq micron.
This data can be “stretched” to fit any shape created as a contour of revolution, on a zone-by-zone basis.

In order to instantiate the various actor distributions provided, they must be mapped onto membranal surfaces in a uniform manner, regardless of shape and tortuosity. Thus, homogenous node placement on primitive shapes is needed: disk, cone, cylinder, sphere, torus.

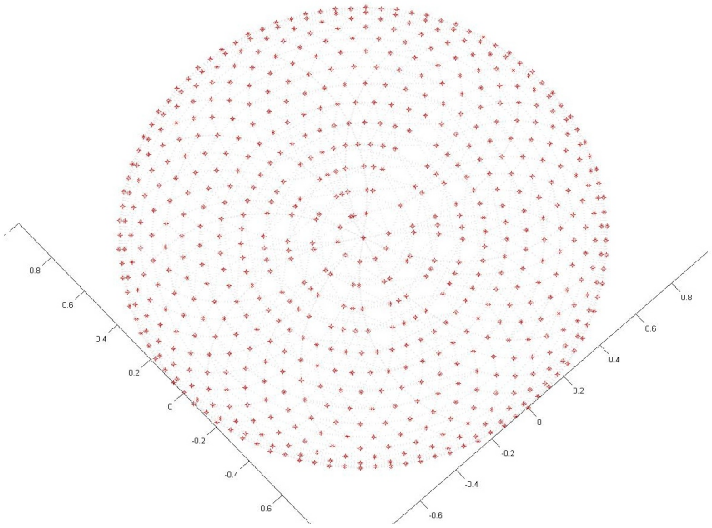

FIGURE 11: Homogenous Node Placement on a Spherical Surface

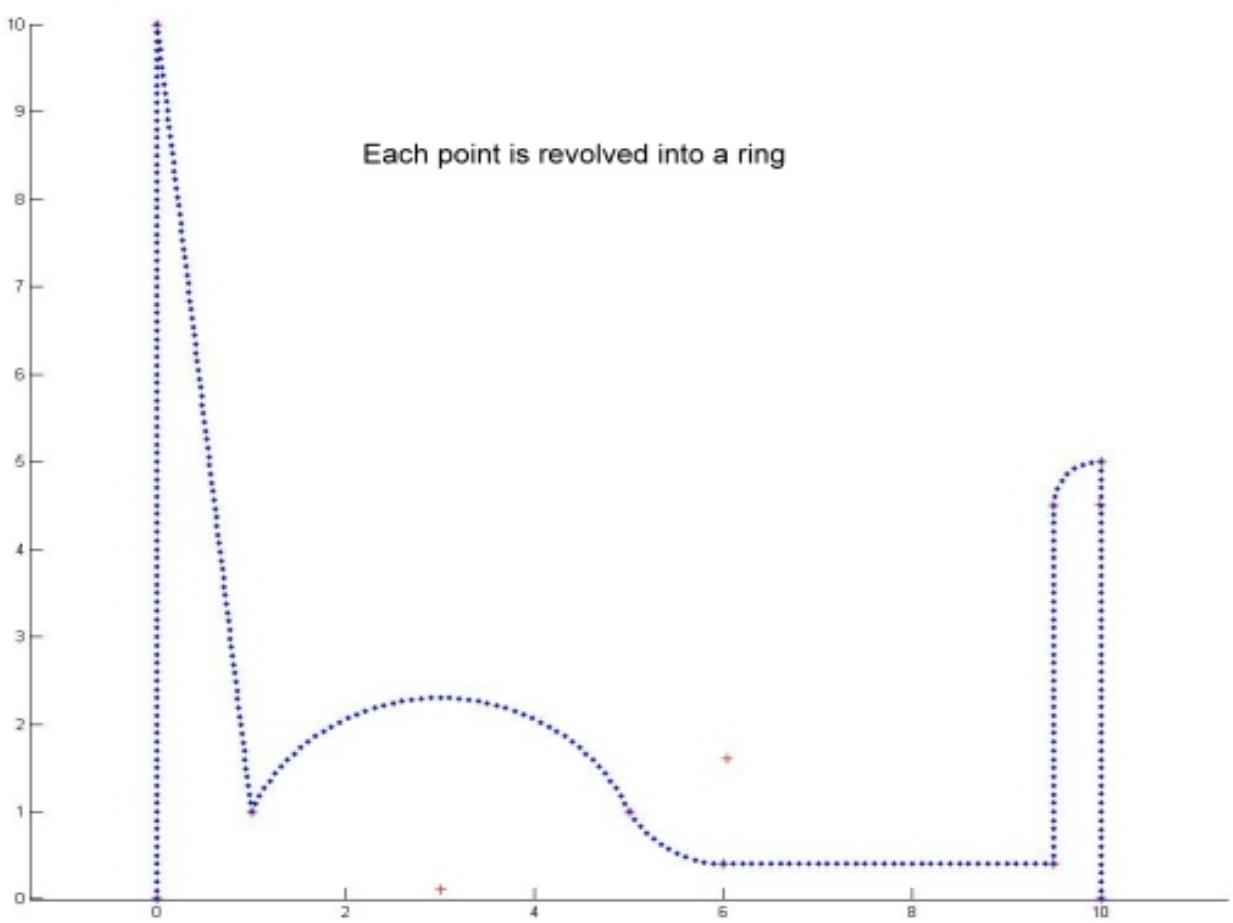

FIGURE 12: CONTOUR OF REVOLUTION FOR CELL

6.5.6.4.10 Whole Cell Shapes

Once a contour for the main plasma lemma has been created, the thickness of the fluid compartments above (extracellular) and below(intracellular) can be specified. The thickness of the extracellular fluid may vary from zone to zone and be graded over the zone.

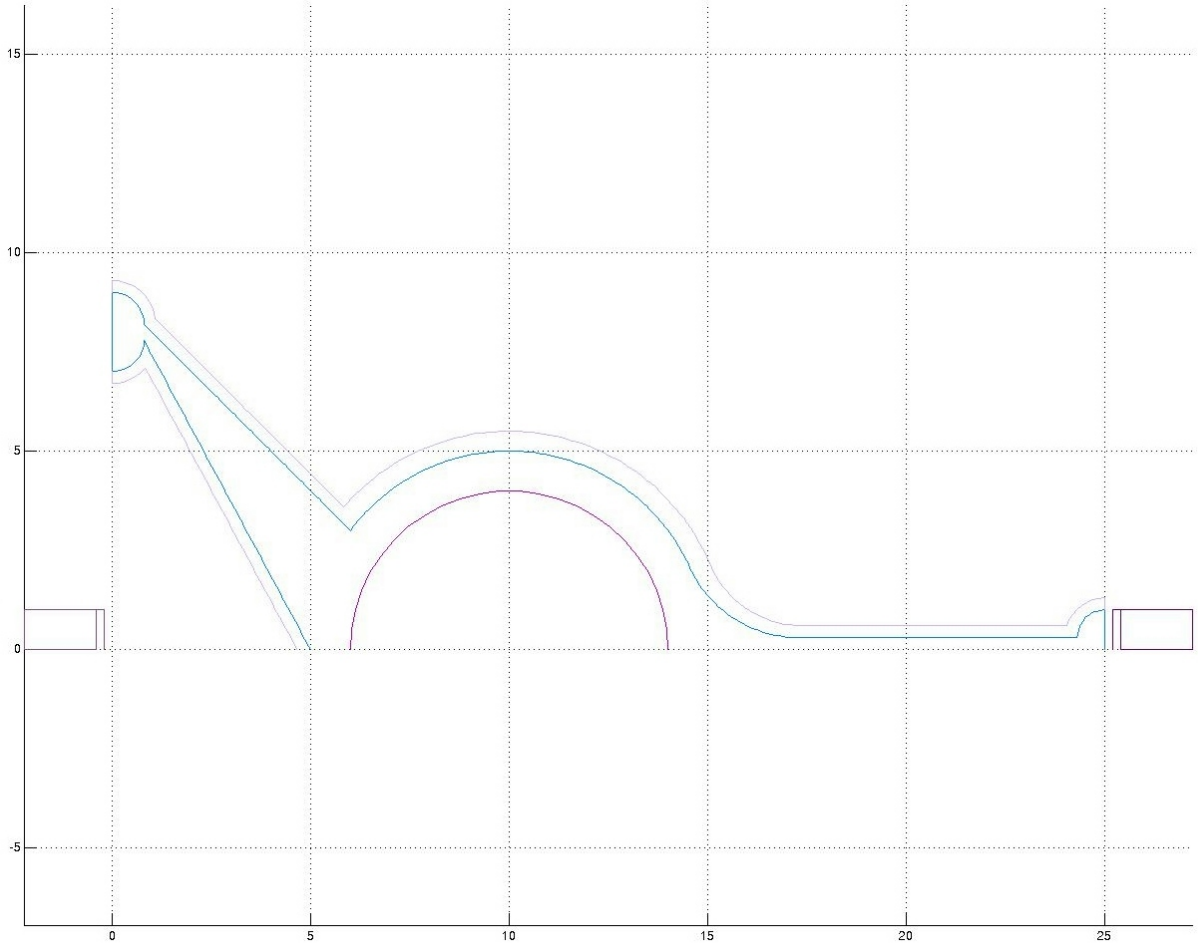

FIGURE 13: CONTOURS OF REVOLUTION FOR CELL, EXTRACELL, CORE AND PLUGS

Contours of rotation are amenable to the cylindrical coordinate system. This works fine for all but the spherical soma (and its core), which is best treated in a spherical coordinate system. As particles travel in straight lines, the Cartesian coordinate system is appropriate for collisions. Thus, there is a heavy conversion-of-basis load placed within a single *dt* cycle.

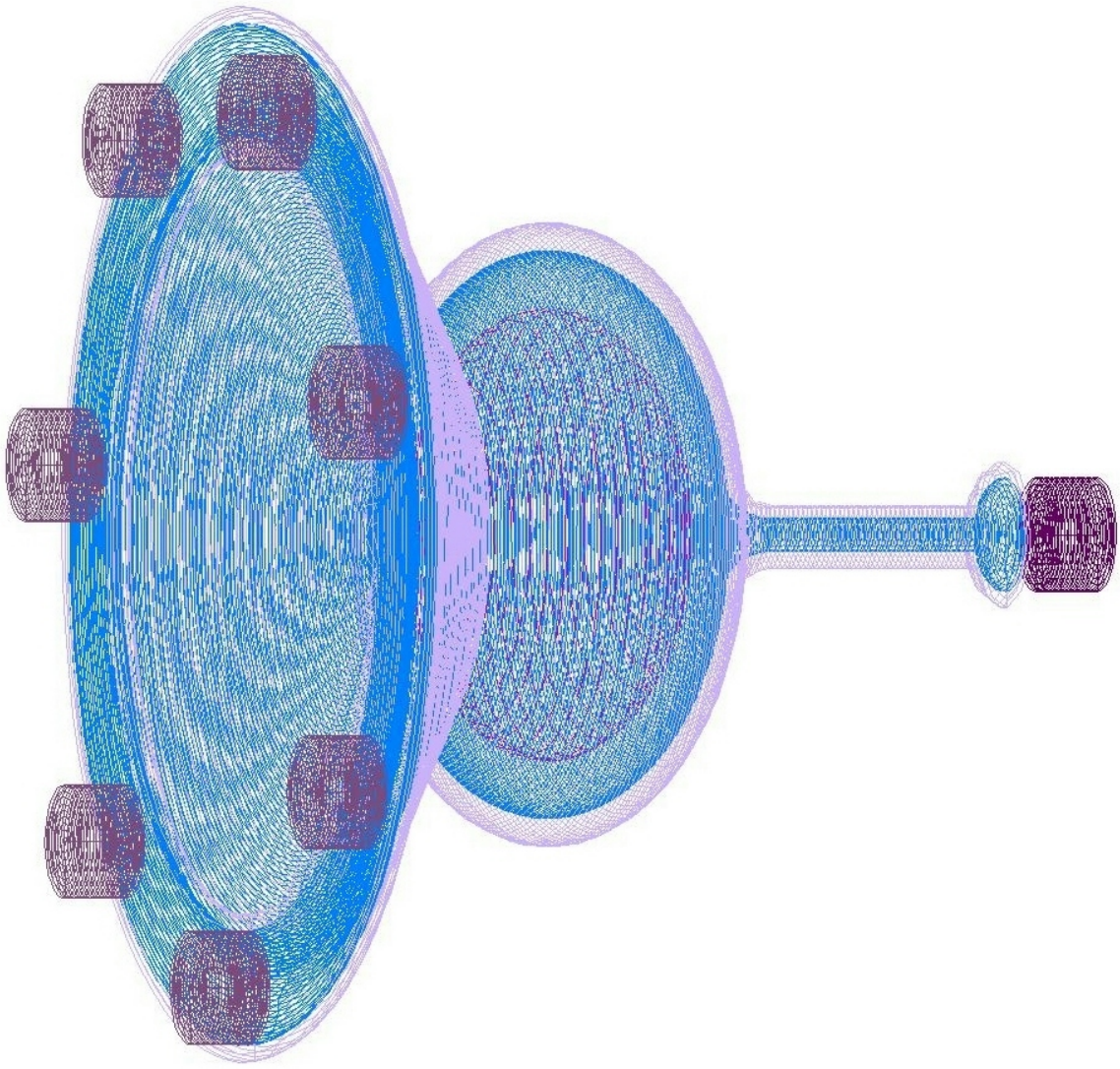

FIGURE 14: CONTOURS OF ROTATION, POPULATED WITH HOMOGENOUS NODES

6.5.6.4.11 Generating Vanes

Starter data originates on a spreadsheet, including working points for all of the compartments, and statistical parameters for distributions and stochastic processes.

Statistical parameters for vane generation =
[segstart segstop xstart xstop rstart rstop Lvar Wvar Lsec2 Lsec4 Lsec8 Lsec16 Lsec32 Lsec64 Lsec128]

6.5.6.4.12 Compartment Volumes

Each contour of rotation is integrated for its volume contained. The largest nested shape within is subtracted from that volume.

6.5.6.4.13 BUILD Compartments

```
EXP.COMPS = { Comp1  Comp2  Comp3  Comp4  Comp5 }
extracell     Comp1 = MEM3 - MEM1
intracell     Comp2 = MEM1 - MEM2
sequest       Comp3 = MEM2 - MEM0,   where MEM0 = the center point
insyn         Comp4 = MEM4 - MEM1.partial
outsyn        Comp5 = MEM6 - Mem1.partial
```

6.5.6.4.14 BUILD Membranes

```
EXP.CELLS = { CELL1  CELL2  CELL3 CELL4 ... }
main      CELL1 = { MEM1  MEM2 ... }     EX  mem1 = plasma lemma; mem2 = core SR
extracell CELL2 = { MEM3 }
incell    CELL3 = { MEM4  MEM5 }
outcell   CELL4 = { MEM6  MEM7 }
          MEM1 = { ZON1  ZON2  ZON3  ZON4  ZON5  ZON6  ZON7  ZON8  ZON9 }
insyn               ZON1 = { SEG11  SEG12  SEG13  ... }
dendrite            ZON2 = { SEG21  SEG22  SEG23  ... }
stalk               ZON3 = { SEG31  SEG32  SEG33  ... }
soma                ZON4 = { SEG41  SEG42  SEG43  ... }
hillock             ZON5 = { SEG51  SEG52  SEG53  ... }
axon                ZON6 = { SEG61  SEG62  SEG63  ... }
Ranvier             ZON7 = { SEG71  SEG72  SEG73  ... }
bouton              ZON8 = { SEG81  SEG82  SEG83  ... }
outsyn              ZON9 = { SEG91  SEG92  SEG93  ... }
                        SEG1 = { RING1  RING2  RING3 ...  }
                               RING1 = { NODE1  NODE2  NODE3 ...}
```

6.5.7 CELLULAR INTERFACING

6.5.7.1.1 Cell-to-cell connection matrix

6.5.7.1.2 Shared extracellular compartment

6.5.7.1.3 Input Signal

The input signal to neuron models is not electronic, nor is it ionic. It is a process of ligand bindings which indirectly modify ion channel conductance values. This is very unlike traditional electronic circuits which receive their signals as voltages to designated ports. Imagine that your home music stereo has no radio nor a household CD input signal, but rather you turn the volume control up and down - and THAT is the input signal. The neuron is a closed quasi-spherical surface with ion channels sprinkled irregularly over it. To the extent that ion channels are modulatable, signals can be introduced, altered or quenched at just about any point over the entire surface. It is not necessary to designate specific ports, although dendritic synapses may be considered as such for convenience. It is worth noting that in electronic circuits, the nature of the active components, especially op-amps and diodes, determine what is input and what is output. With the neuron, this is generally not the case. Orthodromic and antidromic propagation are necessarily relativistically defined because the effects of ion channel conduction radiate out circularly. There are no wires to limit and direct the signal to specific next elements. This characteristic is very

unlike conventional circuitry but none-the-less produces general networks which can receive, process and propagate in any surface direction. The “forward” nature of the signal is determined by the refractory period in the wake of the propagation front which mutes any “backwards” conduction. Thus “forward” covers 180 degrees, or slightly more.

6.5.7.1.4SigGen

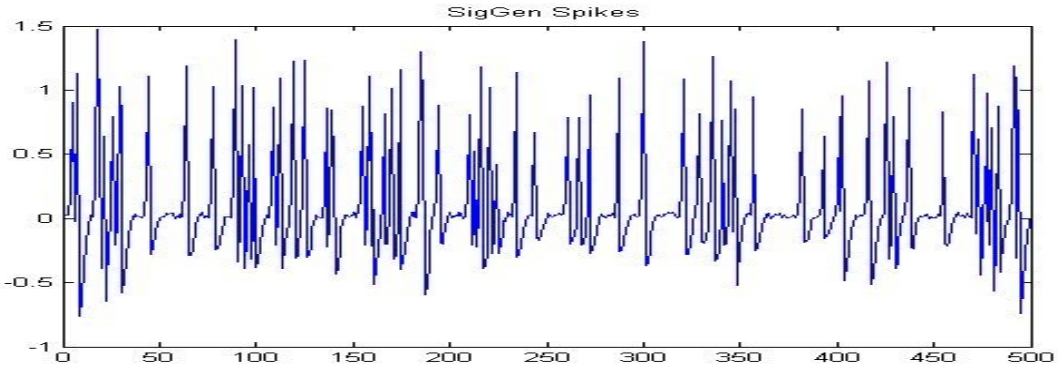

FIGURE 15: SIGGEN GENERATES A SERIES OF ACTION POTENTIALS STOCHASTICALLY

SigGen is a function that serves as a signal generator to create spike trains within given statistical parameters. It can drive the temporal release pattern of neurotransmitter molecules at a synapse. Several synapses can receive correlated signals, lagged, inverted, noisy variations, etc.

Signaling typically begins with ligand molecules which act as Modulators, (Hormones, Neurotransmitters)

Signaling begins at Synapses, via specialized small compartments, called plugs (excised intelligent boutons)

SigGen, a signal generator may be used to drive the neurotransmitter release patterns

Output Reports, as graphs, movies and raw data on particle positions and actor states wrt time

6.5.7.1.5SigGen sets

Multiple inputs often require realistic relationships between them. They may be component feeds from auditory, visual, or tactile inputs. It is a straightforward matter to compose a line of auditory signals tranched into a tonotopic map. Similarly it is not difficult to compose a grid of inputs across a visual pattern. First scale the graininess of the information to the quantity of inputs desired. Create a basal noise to each feed then add a physiological representation of the information to each feed from the adjusted resolution.

6.5.7.1.6Signal Outputs

Where there are more than one output bouton in the run, data needs to be collected from each if they are to be reassembled into “pictures”. The output consists of a count of messenger particle release, sampled about every millisecond. It is therefore necessary that removal/recycling of such messengers be fast enough to support such signals without unrealistic accumulation and dilution.

6.5.7.1.7Internal Observables

One of the strengths of the model is realistic depiction of individual molecules and their states. Output series can be collected on each actor, their states, their bindings, and the local concentrations around each. Additionally local voltages and currents of charged particles can be summed. They can be depicted 3-dimensionally over a time series.

Type	value	comments
Attracts	Ach	(Modulators may be assigned a serial number)
Attraction Force	0.01	(scaled relative to velocity)
Binding alpha	0.6	
Binding beta	0.3	
messenger	Ca++	
release amount	7	(ions)
noise	0.2	fraction of max signal
release time alpha	0	delay
reset time beta	0	delay

TABLE 15: OUTPUT REPORT ON AN ACTOR

Each actor type offers a list of observables. The experimental design may choose from these as relevant to the query.

6.5.8 RULES ENGINE

The sanity of the model is preserved by several methods:

6.5.8.1.1 Tabular and parametric inputs support values within acceptable ranges, datatypes

6.5.8.1.2 Extensive use of logical datatypes that permit yes/no selections within a control flow map

6.5.8.1.3 Experiment Design by choosing formatted types of elements and processes from library

6.5.8.1.4 Function argument formats which accept only well-formed input

6.5.8.1.5 Error legs within function code that catch common errors of arguments or usage

6.5.8.1.6 Warnings on certain output patterns: infinities, infinite loops, negatives, imaginaries

6.5.8.1.7 Access to database only via put and get functions, which limit corruption potential

6.5.9 RUN

The run simulates time, therefore consists of the dynamic equations of the model. A run is an iterative process by which particles move, and the finite state machines call relevant functions to effect collisions, bindings, transport, capacitance, voltage and current. Data is collected raw.

A run generates a time series over which particles move, states migrate, and the finite state machines call relevant functions to effect collisions, bindings, transport, capacitance, voltage and current. Data is collected raw. See Simulation Runs.

The primary architectural challenge of the Run concerns causality. How can the various dynamical functions be ordered and related such that they do not violate causality? Whenever time-wise or space-wise violations occur, a detection mechanism must be exercised. Those instances detected must be backed up to the threshold point so as to preserve the physics of the model.

6.5.9.1 Data Capture

Biology in the wild is enormously rich in data, or at least in potential data. If a non-invasive remote sensing technique were available for every ion and molecule position, velocity, collision and binding, then the work of biology would only be algorithmic - to tease patterns out of the data.

Instead, we move living forms into the laboratory, constrain their activities and environment, the first distortion of that original pristine data. Then we subject the “specimen” to invasive instrumentation, the second distortion. The instrumentation itself has many limitations in converting living organisms into measurable argument values, and almost always filters those few dimensions that it can detect, the third distortion. That data, as soon as it is removed,

is decoupled from the original experiment, and from that point forward relies upon the collective memory of scientists to envision the proper aspects of that experiment when ever reading this bio-data. This is a potential distortion, but let's park it on the side so as to continue down the course which the data itself follows.

That data, to serve modeling, must become normalized into s singular coherent data base. This implies some human judgment in correcting for age, sex, size, location, diet, history, quantities, and other variations such that each element of the database somehow "fits" with all the rest of the data, the fourth distortion. In the construction of a model, one selects from the available data but must interpolate some presumed filler data. Where there is a missing piece, extrapolation is especially risky in such a nonlinear realm. The selection process of which from the literature shall be employed in a model has some arbitrariness and error, as the modeler almost never has the experience of all the wet lab workers so as to appreciate every nuance of the choices to be made - the fifth distortion. Then, to adapt the base data into a specific experiment, there will be a conversion of units, scales, quantities, and shapes, some of which are significantly different from the size, shape and quantities of the original organism - the sixth distortion.

Given that computer resources are limited, some veracity is sacrificed to reduce the computational load - the seventh distortion. Then the big one - digitization - the eighth distortion. Digitization creates a whole new list of problems, biases, lost data, ghost data, and serious nonlinearities. Then there are limits of run time and data to be captured as outputs and how it will be stored, such that the "results" are only a sample of the whole of what was simulated - the ninth distortion. Then there are the software choices of how, in the name of user friendliness the data will be visualized. There is plenty of leeway to filter and contort the data to "look interesting" - the tenth distortion. And finally, there is the audience and writer's interpretation of what these "findings" mean, as lensed through the personal experiences of each observer- the eleventh distortion.

A significant part of the work is getting the model experimental design to RUN benefits from pre-existing libraries of TYPEs. From the physics of ions to the neuronal cell types, the discovery, translation and formatting of such data is a valuable resource to the modeler. Conversely, there is always more such foraging to be done, and so it must be convenient and appreciated that interested parties contribute what they find in the biological literature to the base info within this model.

Beyond the elemental types, there are the DISTs that can also be preserved in the library. DISTs are the PDFs of elemental placements within the neuron. They include ion concentrations, membrane shapes, actor placements and

initial states. At a slightly higher order of capture. A set of Types and DISTs may constitute an “neuron type” or “neuron type instance”.

Furthermore, this model is evolving new functionality. The available set of functions is also part of the “library”of choices that enables a user to tackle increasingly complex phenomena. A readme.txt file shall be maintained that announces at the top new functionality.

6.5.9.2 Quantitative output to information theoretic throughput

So far, biology has been consistently found to be exquisitely efficient in its exploitation of resources. This is a great challenge to human designers, whose engineered products typically are orders of magnitude less efficient. Most of these comparisons are based upon energy consumption or material consumption. Less has been said about information processing efficiency. This is mainly due the uncertainty about just what information the cell is processing. We measure the obvious, but miss the subtleties. Because information is merely the change in state, and every large molecule changes state significantly, we are a long way from logging the entire set of information processed by a neuron. There are strategies for moving closer to that measure. Particle systems offer a reasonable approach to simulating massive data processing in a manner that can be fully captured. And various metrics over many simulations can begin to find the high runners of significant state changes among the cell's chemical machinery.

6.5.9.3 Quantitative output to bio-performance comparisons

The great difficulty in determining how neurons process information lies with the nonlinearities stretching over immense quantities of elements. With such order, the so called “butterfly effect” is a real concern. Very subtle changes in the element parameters can eventually result in emergent assemblies and behaviors radically different from case to case. A viable strategy is to avoid locking all elements into the identical parametric set (stochastic though they may be). The domain of doubt can be applied experimentally by varying the parameters across the group over that range, with particular metrics to track the outcomes of each setting. One can do sensitivity analysis by gradually sweeping the entire group, or do a competitive run with all types intermixed to observe the “winners”.

6.5.10 PERFORMANCE REQUIREMENTS

PE-1: The system shall accommodate 1 user at a time.

PE-3: Responses to queries shall be limited by timers set by the user prior to RUNs. Such timers shall return control back to the keyboard when their values are exceeded, and a message provided with timer name and setting.

PE-4: The system shall display all messages per Matlab ™ messagebox standards.

Generally, there are 4 types of time to be discussed:

1. biological time (that of the empirical data on wet neurons);
2. simulation time (that particular slice of biological time to be modeled)
3. computer time, the quantity of clock cycles consumed to perform a simulation
4. user time, the length of time required to perform certain human tasks and waits to effect a simulation

Most design work is concerned with simulation time. For example, let one second of model simulation playback equal 1 biological millisecond.

Computer time will necessarily be many orders of magnitude slower than biological time. Digitization suffers a total loss of continuity in space and time. This implies a large computational load to recalculate inter-particle distances and forces each *dt*. This leads to the conclusion that biological systems are not at all slow. The massively parallel architecture of neuronal processing, combined with the molecule-sized elements, effect an immense amount of processing in micron-scale space-time. Popular comparisons to computer clocks and bits avoids the fact that a single neuron is doing a lot more than a common computer. By assigning a neuron an arbitrarily simple task, like a "yes or no" decision, we trivialize the work load of a neuron, and then wrongfully declare it to be "slow". Computer time rapidly becomes a limiting factor for practical reasons.

Performance refers not to model veracity, but to the host computer's ability to handle the computational load. Of interest is the ratio of biological entities to digital computer loading. Because the goal is to employ supercomputers to model ever greater numbers of elements and processes in parallel, performance considerations are inherent in the project. While the first task is to create a set of processes faithful to the underlying physics, the second task is to make these processes tractable to currently available computers via numeric methods, and justified simplifications and compression.

Several standards of performance are worth discussing. First, the ability to model certain complex biological molecular systems stands itself as a achievement, and needs only be performed in times within our patience, say a month per experiment. The moment one such success is accomplished, the tendency is to make the experiment even more complicated, so as to consume all new available resources. This is human nature.

However, the more interesting and challenging standard of performance is to pit the supercomputer running its model of the neuron against the living neuron itself. Which is faster? Which can do more (breadth of problem space)? To this end, information theory is employed to measure the channel capacity and the mutual information between inputs and output.

Benchmark quantities of actors and interactors are defined. Runs are conducted with timers across every significant function. The functions are then rank ordered by their consumption of CPU and memory resources. High runner functions are examined for opportunities to perform more time-efficiently. Short-cut algorithms might be employed after justification runs.

Experiments are run with increasing quantities of elements, plotting the results. Most computing machines hit sharp performance drops when they begin relying upon calls to hard drives each iterative cycle. This may be a hundred-fold drop in speed. At that point, if a larger machine is not available, then the software command sequence may need to be broken down into separate processes to the extent they are not coupled. If interactor movements can be executed on one CPU, actor states on another, and the electrical grid on a third, then swaps are greatly reduced and efficiency returns.

6.5.10.1 Scalability

Scalability is the ease with which a model is increased in quantities of elements and in the complexity of its internal interactions (richness of functions).

In this particular model scalability is found to be almost trivial in most respects. The number of uniformly spaced addressable nodes over the entire surface of a shaped membrane requires only the entry of one number (internodal spacing). The definition of complex neuron shapes is accomplished by the entry of a few data points indicating either a line segment or arc between them. These form a contour of rotation, done automatically. The extracellular

thickness is specified with one or several thicknesses, and the extracellular membrane (neighboring cells) is generated automatically. The input synapses are specified either by position or by PDF and they are generated and placed automatically as "plugs". Actors and Interactors are created, placed and initialized automatically by merely specifying quantities and pointing to the chosen PDFs. RUNs are conducted automatically merely by specifying the quantity of iterations. All of this is irregardless of size, quantity, resolution, complexity of distribution patterns, or even number of cells. The extensive use of stochastics produces very lifelike behaviors, including many emergent phenomena.

6.5.10.2 Auditability

Audits are set up as needed. Timers can easily be set on the processes in question. "Catch conditions" can be set as well. The data captured is usually sufficient for verification work. Stop points can be set in the code to look at the set of variables time-progress. And the overall data to be captured can be set in REPORT to collect any function output argument.

Functions shall be written such that only those variables which are not instrumental to model diagnosis may be written as transient (values over-written each *dt*).

6.5.10.3 Flexibility

As a first release, this "toolbox" is only being asked to serve its sole original mission. Thus "flexibility to what?" remains unanswered. As a set of functions enacting basic physics, most of this model is re-usable without alteration. The particular points where simplifications are made (e.g. that one model particle represents 1000 ions in the bio-neuron) are contained and explicit, so that these can be altered or eliminated with no loss in functionality of any kind. The methods of shape generation could be altered and yet most functions would serve without alteration. However those functions relying upon an axis of rotation of course would be affected.

For further details on re-use and extension of generality see the chapter 9 Algorithms.

6.5.10.4 Reliability

General reliability benefits from the current state of the art in commodity computers, which in most cases perform mathematical and string operations reliable to better than seven places. However, delays due to “crashes”, stoppages due to missing or inappropriate functionality, are quite another matter. This worker has |”fried” (over-heated to permanent failure 3 CPUs so far. And hundreds of crashes and data losses have occurred primarily due to overloading systems not quite ready for massively parallel processing. The good news is it is quite rare for them to produce a “wrong” answer due to hardware mis-design. But it is surely common enough to get wrong answers due to software functions written to serve other purposes than this model. As a result it has become the habit of this worker to write entirely new functions “from scratch”, even when it would save time to draft someone else's code into re-use. More often than not the employment of another's work has led to (if lucky) serious problems and (if not lucky) to hidden problems that do not surface until the errors become deeply embedded in some complex operation that requires weeks to de-bug.

Coding from scratch has its own pitfalls, namely that either a rigorous independent testing program must be faithfully implemented, or else there are going to be a steady snowfall of nuisance bugs that always get fixed, but not soon enough for the user to enjoy a totally bug-free experience.

6.5.10.5 Maintainability

As a software “toolbox” or “package”, such applications are maintained as users demand and contribute. In this sense, this model is a “beta” version, enjoying liberal sharing of code and data, in exchange for contributions of criticism, functionality and additional library-compatible bio-data.

6.5.10.6 Fail-Over and Disaster Recovery

This is not a life-safety application, nor a secure-financial handler, nor a real-time agent for any other system. Therefore, failures are not critical. Accordingly, error-leg handling is not the highest priority, although reasonably considered throughout. In an experimental and learning environment, the model code should not over-constrain the users options to try out hypotheticals that may fail. Model RUN failures, *per se,* are not costly, and are usually a learning opportunity in themselves. Modeling is an iterative process, and proceeds by incrementally improving the code veracity to certain biological events and behaviors.

Most of the error handling is performed by the operating system, and the application implementing the programming language. And all within those two are inaccessible to this project. However, within the model algorithms, care shall be taken to provide the following:

1. General BUILT failures
2. Warning messages for ill-formed input that is likely to lead to misleading results. Error messages shall be triggered by the most commonly encountered mistakes in the experimental design and data inputting, as would otherwise impact the code in any way likely to cause lock-ups or other forms of nuisance failure.
3. Generally, RUN failures shall trigger the presentation of descriptive specific error messages, that instruct he user precisely what went wrong and how to remedy it. The code must be transparent enough, and correspond to external reality well enough, that such remedies are grasped intuitively and easily implemented.
4. However, by the time this model has risen to the various missions of prescribing channel alterations for therapies in disease, or for the design of liquid state processors for mass production, then a significantly higher life-safety standard of error-detection will need be applied. Detection and Recovery Modules will need to have been written in and rigorously tested so as to attain the desired levels of confidence.

6.5.11 REPORT

The interpretation of an experiment requires the capture of all the parametric data that defined and set up the experiment, the generated data of motion of interactors and states of actors. Motion of particles, of course lends itself to visualization of data as a movie. Visualization of actor state may be visualized by color changes, icon changes, or by plots. The emergent properties are also critical to understanding the behavior of the neuron. Voltage can be visualized as background color of voxels and current may be visualized as quivers. Both may be plotted in 3-d. Arbitrary time and space scaling need to be offered to the viewer. The results of an experiment must be captured in such a form as to be measured for performance and error to the original design.

6.5.11.1 Information Throughput

Mutual information is applied to synaptic information theory by London in 2002.[162] For some neuron types, as single synaptic input can trigger a whole cell response.

6.5.11.2 Visual Presentations

Insightful interpretations of the model results requires demonstrative graphics. Although from a strictly scientific perspective, graphics are a luxury, it may be argued that the value of the model and the contributions to science of

the model are directly related to the quality of the machine-human interface, and the ability of the model to communicate behaviors, [patterns and emergent phenomena in a manner that strongly suggests the causality of what is seen.

Ions are easy to visualize because they move. But actors states do not show well, as they are static in space and have rather complicated, semi-chaotic state changes internally, though they be of great significance. Even a time-line plot of one's states is weakly informative, in that the number of the state does not reveal what the actor is actually doing. One method of presenting state data is to give each state an audio frequency, and allowing the user/audience to listen to its melodies. This is useful in that the ear is accustomed to detecting rhythms, distinguishing between thousands of them, and quickly detecting a change in melody. Every change in modulation of an actor precipitates a change in melody, often quite dramatic changes. The sequence of notes, the rhythm, and the tempo can change. States of open channel or pump transport may be presented as louder volumes and/or distinctively high or low notes, that the listener may know what the actor is doing by these. One can then listen to an orchestra of actors to hear the wave of information rolling over them. Stereo sound could be calculated by proportioning delay to the distance away from the perspective point. Reinforcement of events could be accomplished by making openings and transports displays as icons growing larger and brighter.

In addition to the movie, important analyses of information can be done on the captured information of ion positions and actor states, all time stamped. Correlations may reveal the effectiveness and sensitivity of certain ion patterns upon actors, and actor patterns upon ions. Cooperation and antagonisms between actor types and actor positioning patterns could thus be revealed. And perhaps most significantly, information content, transmission, and modification could be traced over repeated trials so as to filter out the noise.

Ergodicity addresses the relationship between the output of a single element in repeated trials and the output of multiple elements in a single trial. A simplest case might be one die rolled 6 times compared to 6 dice rolled once. The ergodicity of this system is very high. What is the ergodicity of a river? Is the wavy output of one large river the same as that of many small rivers? We can expect the ergodicity of rivers to be much lower than that of dice. Now what about neurons? Eight identical neurons in parallel may produce similar results to a single neuron stimulated eight times. This is often true if the stimuli are spaced temporally so as to not overlap the refractory

period. For well spaced stimuli, ergodicity of neurons is very high, but as the data stream fills into the refractory periods, it drops. Ergodicity can be exploited in modeling, trading off parallel processes for time, or *vice versa*.

Phase information is regarded as a valuable component in neural systems. This is obvious in source of sound location, where the slight phase differences allow an animal to quite accurately guess which direction, and to some extent how far away, the sound emanates from. Such abilities imply that nervous systems are processing to less than thousandths of a second, and perhaps millionths. The differential is discernible to several orders of magnitude finer than the ordinal. From this one could argue that there are orders of magnitude more phase information in a neural signal than there are in processing a straight signal. However, in digital systems phase information is prone to distortion through aliasing error. To pursue such sensitive phase effects requires proportionately great *dt* size reductions. The modeler should be aware of this effect and design experimental runs accordingly .

It is not trivial to say that the purpose of the Design is to realize the Build; The purpose of the Build is to realize the Run; and The purpose of the Run is to generate the Report. Thus, the Design does not concern itself with the Run nor Report. Neither does the report look back any earlier than the Run. The Run should be an emergent property of the Build.

The report addresses the sub-models Patch and Goblet. Generally the user plays a movie of Goblet responding to some input signal. Banner plots of voltage and current may be selected as well. Because both voltage and flux are three dimensional, slices may be taken through the shape, and values presented in cross section.

Visualization of data is chosen as output in movie and graphs. Raw data is processed as prescribed in the experimental design. Usually, the output signals are specified to be displayed in both tabular and graphical formats. After which, time and space scaling are performed. The output error gaps are then pondered as to causes. Hypotheses may be formulated into revised or totally new experimental designs. Notes on model performance as may verify the model to predict biological performance are noted in the Experimental Results log.

6.5.11.2.1 Multiscale viewing

To zoom in on nano-details, a means shall be provided for the user to select that movies be generated of selected constituent Patches. The screen shall display up to 12 such Patches simultaneously, running in synchrony.

6.5.11.3 Actor States Display

Each actor state may be assigned a color. Black for rest state, Red for blocked state. Green for open or transporting state. Yellow for reset states.

6.5.11.4 Bio-Relevance

This topic was largely covered in the earlier chapters. Architectural considerations include span of the domain space, predictive powers (or lack thereof, pathologies to be accommodated in models, types of therapies and repairs to be supported in models, the mapping between biological action and mathematical computational functions, the treatment of missing data in actor kinetic schemes to complete model entities, the challenges of multiscale coupling between molecular events and whole cell behaviors. All of this boils down to practical veracity.

In addition, their are frontier considerations, like: gap identification strategies – pointers for new wet lab research, development of practical logical processors out of liquid state processors, and design of new channels and assessment of their effects in the whole cell.

Criteria shall be set forth for metrics on the output, which shall yield error data suitable for designing modifications to the experiment for subsequent runs with reduced error.

Thresholds shall be set to levels of confidence and/or ranges of expected output values prior to the run, and exceptions to those rules appearing in the output triggers some corrective measures to be taken. This may be abort, flags, or alternative parametric values. In the case of alternate values, messages must be sent to the user to notify of such changes.

6.5.11.5 Hypotheses suggested by modeling exercises.

With a modeling approach, one can step incrementally through the neuron, tracing every transfer of information along the way. Because it must be represented mathematically, and operate dynamically and sustainably, at the very least, plausibility is achieved. In the case of missing bio-data, the signaling “needs” on either end of a gap suggest likely mechanisms in between. Nature is surely more creative than man's ideation, but man's hypotheses suggest experimental design to test those hypotheses and in the process discover more of nature's true methods.

A stepwise account of a signal arriving at a neuron dendritic field of synapses can be represented thusly:

Some fixed number of vesicles are manufactured and poised at the pre-synaptic membrane. Each vesicle contains a somewhat variable amount of one or more neurotransmitter molecules, on Gaussian distribution curves for variance. The “all or none” action potential that propagated down the axon to the bouton, causing the influx of calcium, will bind stochastically to the vesicular release mechanisms, and these mechanisms will stochastically undergo exocytosis, releasing their contents, or some of their contents, into the synaptic cleft.

The somewhat variable number of vesicular molecules, released at somewhat variable lag time after calcium influx, begin diffusing within the synaptic cleft. In a liquid state, diffusion encounters collisions with water molecules (and others) , which spread the charges and the trajectories radially. A wave of arrivals “washes” up upon the distant membrane. These collide mostly with membrane, but the affinities of certain receptors accomplish hit frequencies sufficient to bind a ligand to a receptor a certain percentage of the time, as a function of ligand concentration and receptor state.

Load TypeComp	contains data on shape of each compartment, also membrane type
Load TypeRecep	contains traits of each receptor type present in this experiment
Load TypePump	contains traits of each pump type present in this experiment
Load TypeChan	contains traits of each channel type present in this experiment
Load TypeVes	contains traits of each vesicle type present in this experiment
Load TypeIon	contains traits of each charged particle type present in this experiment
Load TypeLigand	contains traits of each messenger particle type present in this experiment
Load DistComp	contains data on size, position and orientation of each compartment in this experiment, noting juxtapositions
Load DistRecep	contains data on the density of each receptor type present, as varies along the length of the neuron
Load DistPump	contains data on the density of each pump type present, as varies along the length of the neuron
Load DistChan	contains data on the density of each channel type present, as varies along the length of the neuron
Load DistVes	contains data on the density of each vesicle type present, as varies along the length of the neuron
Load DistIon	concentrations of each particle type in each compartment and binding site
Load DistLigand	concentrations of each messenger type in each compartment ad binding site

The DESIGN of an experiment allows the user to fill in biologic data according to prescribed data formats for each actor type. This is a flexible scheme that can accommodate a huge variety of possible configurations, and a huge variety of experiments to perform on each configuration. This is intended to support the potential to mimic the huge variety of arrangements of biological neuronal types as they may distinguish themselves in the various roles played in information processing.

6.5.12 DOCUMENTATION REQUIREMENTS

All coded functions shall contain text within them that documents the inputs, outputs, dependencies, processes or algorithms in text, the version and the date. Additionally each line of code shall be commented so as to make the intent clear, and to link processes, reveal logic, and quantify limits.

This multi-scale neuron model consists of a whole cell closed membrane with saline solutions on either side of it. Because of the immense quantities of ions and ion channels comprising a whole cell, computational reductions are realized by focusing on nanoscale patches of membrane, so as to characterize local performance. These patches are then cloned and stitched together to comprise the whole cell model

6.5.13 PLATFORM

For the software development phase, Octave ™ and Matlab ™ are recommended. They provide a computing platform for rapid demonstrations of concepts, despite their implications of computationally heavy algorithms. Because the primary attention goes to the neurophysiology, not the computer science, intellectual leverage over the machine is sought out via high level programming languages.

As the model migrates to supercomputers, a greater emphasis must be placed upon task scheduling, and thus Linux and C++ code are the methods and language of choice.

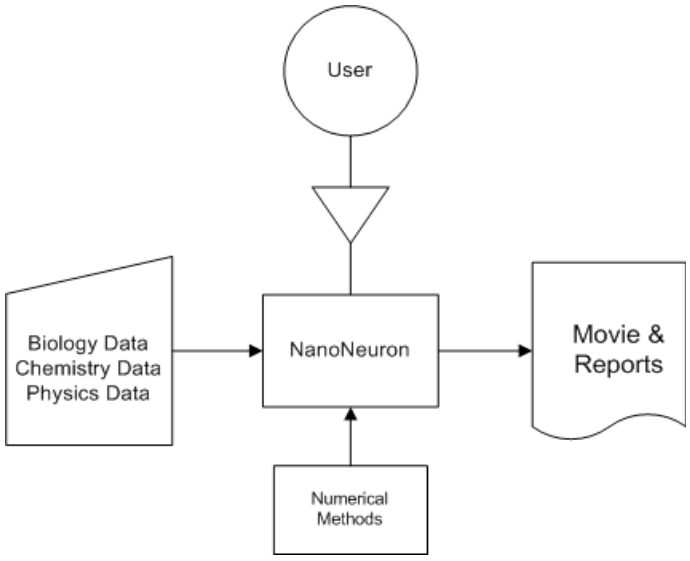

FIGURE 16: SINGLE CPU CONTEXT

Context Diagram for this model on a single processor, in development mode

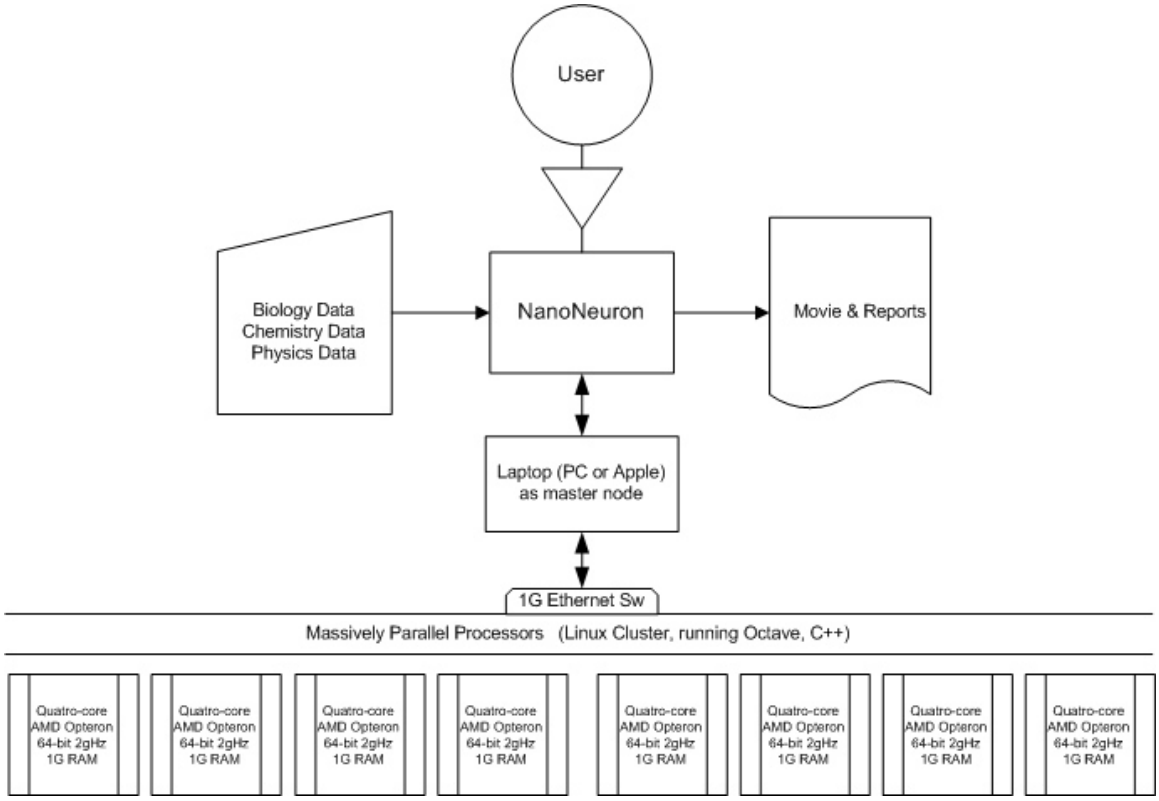

FIGURE 17: CLUSTER CPU CONTEXT

Context diagram for this model on a Supercomputer

Employing computational leverage via task allocation software, thread optimization, and 1gb Ethernet link to the master node. Not shown, a test and metrics processor will be necessary to measure and optimize performance.

6.5.13.1 Enabling Technologies

Modeling, as herein implemented, is restricted to digital computer simulations. Particularly, the so called PC (personal computer), built upon Motorola, Intel, AMD or SciCortex manufactured CPU chips, may employ one of various operating systems, e.g. Apple's Macintosh, GNU's Linux, or Microsoft's Windows. The modeling herein is agnostic to these operating systems, but experience finds Linux to be the fastest in execution.

The computer code is written in Matlab/Octave coding syntax. Matlab is proprietary and Octave is Open Source, under the GNU protocols. The code written herein, to the best of the author's experience, is not specific to particular versions or releases, and has run on Matlab 6.1,6.5, 7.0, 7.5 and Octave 2.1, 2.9 and 3.0 versions. It is not dependent upon any Matlab toolboxes, nor upon any Octave packages. Rather this model constitutes a “toolbox” or

"package" of its own, as a group of interdependent functions and documentation for use, all serving a related purpose. The algorithms are well documented and thus may be translated to C, C++ or Fortran™ in a straight forward manner.

Such a molecule-vigorous model is highly useful in establishing the true nature of neuronal information processing, but once accomplished its results serve as the standard against which various compression strategies will be measured and justified. That is, heuristics must be justified by the computationally heavy models. But then those computationally heavy models must give way to which ever computationally lighter algorithms that can be justified.

EX (q x sf^2 x ops)

	q	sf	ops	ext
Ions	100000	1	7	700000
collisions	100	10	36	3600000
plugs	110	2	8	3520
recep	500	2	5	1000
shuttles	100	10	21	210000
chan	10000	10	56	56000000
pumps	1000	6	45	1620000
ves	100	4	22	35200
erg				126
aff				62178720
eff				0.03
Op / dt				2072624000
CPU cap				360000000
dt / sec				0.17

TABLE 16: ESTIMATED CPU OPERATIONS

q = quantity of element
sf = scaling factor for measured operations complexity handling that type of element
ops = usual number of operations per dt per element
eff = the measured efficiency of the computer hardware/software combination
CPU cap = RAM memory

dt/sec = simulation cycles per second of CPU time

Note: Approaching RAM memory limits has a very serious deprecation of performance effect, and exceeding memory limits can result in a 100-fold decrease in performance, as the ratio of time for disk calls over the time for RAM reads.

Given that solid state CPU technology is reaching its minimum size limits, consideration need be given to the near term future of super computing. The need of this modeling approach to allocate at least one CPU per model neuron (and more probably dozens) does not bode well for this model's ability to compete on a practical level with terse analytic approaches. That is, this modeling approach is not proffered as a final form, but as an intermediate form serving to justify future forms.

This contrasts with the biological neuron, which although lacking a gigahertz clock still outperforms silicone by several orders of magnitude.

Variable precision needs vary from binary to 8 bit to 64 bit. Most parametric values can be course, perhaps 256 values suffice. When the coding is carefully specified to the necessary and sufficient data types, then several classes of efficiency are realized. The important ones are the N^2 and N!. This model does not have any significant factorial load It is speculative to offer a number, so I'll conservatively use only one order of magnitude of computational reduction.

A primary function of this model is to explore the biological configurations that express differing types of information processors. By exploring the entire family and characterizing the mechanisms of each will undoubtedly be informative in the subsequent of engineered neurons for neural networks.

This project writes a modeling program intended to assemble the findings of a variety of analytic papers from prior biologic art. This project is to synthesize biologic findings into a predictive model of how, given the variety of ion channel types, and variety of cellular shapes, can be predicted the information processing function of each cell type. Computer simulations may be written in C++, the Octave ™ 3.0, or Matlab ™ language (Version7), on either Linux, Mackintosh, or Windows operating systems. Other languages are possible, however they are not taken into account herein. The high level platforms for coding linear algebra have been run on PC's and Apple computers during development. Their convenience and portability support rapid proofs of concept. Once debugged and

assembled, the code may be ported onto a Linux cluster, server, or supercomputer for full scale modeling of the information processing function of a single neuron. Use of lower level languages such as C++ for bit-managing the numeric methods and parallelizing the algorithms on machines of say, 50 gigaflops, can simulate one second of biological time in several hours of CPU time.

6.5.13.2 CPU sizing

As a particle-system model, the computational load is high. The single CPU desktop or laptop of the year 2008 can model up to 5000 particles. Models of high veracity will entail about 100 000 particles. Therefore multi-CPU, multi-threading machines are desirable for scientific quality modeling. For example, a machine with 16 cores and 16 gigabyte memory, is estimated to model 100,000 particles in about 11 seconds per model *dt*. Thus, a run with dt=1e-4 seconds and a time simulation length of 10 biological seconds would take about 11.8 days (1,020,000 seconds).

There are 4 major strategies for reducing the above CPU time. First is the implementation of sparse matrices for collision detection. Theoretically this could reduce computations by about 2 orders of magnitude because each particle can only reach a very local area to it in one *dt*. *(This gets us down to ~ 10,000 seconds)*

Second is the multi-scale approach whereby only sample patches would be modeled rigorously and the spaces in between filled in with graded clones as I/O maps (lookup tables created on a basis of the rigorously modeled patches). This method could also realize 2 to 3 orders of magnitude reduction in computational load, albeit at the cost of much more preparatory verification work in the initial phase to optimize the many parameters so as to mimic live cell performance. *(We are down to ~100 seconds.)*

Third is a verification of the redundancy of particles and actors in the derived information processing of a single neuron cell, and subsequent purging of those redundancies. Not known at this time, but it might prove to be true that only 1000 particles can accurately predict the behavior of 100000 particles (law of numbers). This may support a reduction in computational load of 1 to 3 orders of magnitude. This is not trivial because of the interaction between diffusion collisions and protein kinetics, by which modulators leverage the significant process rates of the cell. *(We are down to ~ 10 seconds; which is 'real time').*

6.5.13.3 Optimization and Load Leveling

Optimization to the hardware has two aspects. The larger aspect is out of scope in that it is handled by the operating system, which assesses available resources, and assesses assigned tasks and attempts to divvy up the tasks to use all resources nearly level.

The second aspect concerns the style of code writing. The generally preferred style is to write code for generality, readability and maintainability. But for those few functions which receive inordinately heavy use, there is great need to apply the best numeric methods to minimize CPU time. In those cases, a second version of the function is written, stripped down to the bone. These _fast versions of functions use:

1. base2 quantities
2. multi-dimensional matrices in preference to many smaller matrices
3. logicals in preference to inequalities and "finds"
4. minimal redundancies of variables (this implies the compression of many lines of code into one)
5. Heavy use of the deeper structures of linear algebra and topology
6. The result is that this code is not readable, except as an "exploded view" portrayed in the comments.

6.5.13.4 Priorities

Interrupt priorities determine which shall prevail in a contest for software control

Interrupt Priority	Code blocks
Priority 1	abort via keypad
Priority 2	error legs: detection, resolution, reporting
Priority 3	User parametric settings, data base sanity
Priority 4	normal build and run
Priority 5	capture and reporting, housekeeping

Note that in any interval of critical software continuity, higher priorities may be briefly locked out.

6.5.14 SOFTWARE INTERFACES

SI-1: There are no Software interfaces. The platform is the latest version of Matlab ™ as of Dec 2007. Octave is a very similar application to Matlab; however, some syntax may vary. This code may be re-compiled as C++ code [by others]

6.5.14.1 Security Requirements

Matlab ™ .m files can be converted to .p files for greater source control. P files are compiled binary images, and intended to be difficult to "reverse engineer". Users who produce sensitive modeling runs should take additional precautions to encrypt or otherwise sequester their Design files and Reports.

6.5.15 BASIC EXPERIMENTS

Follows are a starter set of experiments to exercise the functions and adjust scaling parameters for veracity.

1. Moving ions in concatenated shapes. Create a cone and a sphere. Join them. Add a mix of particles. Verify that they are uniformly distributed after a reasonable time. Verify that their Boltzmann velocity distribution is stable over time.
2. Two compartments with funnel shaped pore between them. Determine whether a funnel can passively build up pressure on one side. Vary the angle of the funnel wall and record the differences in results.
3. Two compartments with selective pore between them. Introduce a mix of charged particles (quantity of positive equal to quantity of negative on each side). Will a passively selective pore result in a build up of pressure? charge a capacitor?
4. Check your membrane capacitance and saline resistances. How do these phenomena scale to the biological neurons? Can you justify a scaling down of particle quantities? 1:10? 1:100? 1:1000? 1:10000?
5. Two compartments, set up the passive steady state that mimics a dead squid axon (no pumps). Do your ion concentrations, pore conductivities match the squid? What was the final resting state?
6. Two compartments, turn on the squid pumps in the above experiment.
7. Add ion channels to the above experiment. Vary their spacing and densities. Try to perturb them to create and action potential. Can you get propagation?
8. Add interesting shapes to your quid neuron. How does a signal pass over the soma? You must now add the extracellular compartment to closely conform to the neuron shape so as to produce a realistic “layer” of saline.
9. Add a dendritic arbor, and synaptic boutons. Add an axonal recording bouton.
10. Experiment with varying patterns of channel distributions. Record which propagate.
11. Starting with your most robust patterns from above, experiment with varying channel kinetic schemes. Can you get burstiness? rhythmic? Lags?
12. Add inhibition to your neuron. What is the maximum ratio of inhibiting channels to excitatory channels before your neuron is unresponsive?
13. Move your pumps around to create end to end flux of chloride. How does this change the shape of the signal being processed?
14. Make an adding neuron. A subtracting neuron. A multiplying neuron. A dividing neuron.
15. Make an integrating neuron, a differentiation neuron.

16. Create two neurons and wire them for a coincidence detector, as a component in localization from the two signals of the ears.

6.5.15.1.1 Instantiation model

Instantiation model consisting of the available actors as defined herein:

1. A precedent neuron may release neurotransmitter particles into the extracellular space.
2. It will diffuse very rapidly (0.5 msec) across the fluid incidentally colliding with receptor binding sites.
3. There particle-site matches may bind, causing a Na chan to open via stochastic state transitions.
4. Na fluxes into the intracellular space causing a voltage disturbance across the membrane.
5. This triggers the K chan to begin opening which allows K flux outward.
6. These two disturbances set forth a "wave" of propagation to other Na and K channels.
7. The second to last chan at the right is a Ca channel.
8. It releases Ca into the intracellular compartment very near to a vesicle.
9. The last element is a vesicle, which releases GABA into the extracellular space.
10. This diffuses to the antecedent neuron's receptors.
11. Sequestration maintains the low levels of Ca in the intracellular compartment.

6.5.15.1.2 Modalities

Non-linear systems are prone to limit cycles. Stochastic systems randomize those limit cycles into modal domains, which serve rather like corals or valleys. If enough energy is added, the trajectory can “jump” the boundary of the modal domain and enter an adjacent domain. Examples might by a chaotic basal firing rate, stimulated to jump into a burst of firings, then dropping back down into the chaotic basal firing rate. Other commonly encountered modes include periodicity, phase locking with neighboring cells, proportional response. Because of the ubiquitous thermal energy, significant activity is that which is rises above the basal rate. Though neurons may be firing at some basal rate all the time, the local group of these does not sum above the threshold necessary for signal transmission to downstream groups.

6.5.15.2 Minimal Model

6.5.15.3 Patch : Nanoscale

The whole cell model may be comprised of an assembly of patches into a cylindrical shape conducive to numerical methods for 1E5 interactors and 1E3 actors. Each patch model is intended to contain some minimal quantity of actors as necessary to study information transmission between the actors and ensemble behaviors. The size of the membrane to be modeled is usually less than 1 square micron, or that sufficient to include 2 to 20 actors in their normal distances apart.

6.5.15.4 Goblet : Microscale

The whole cell model is suitable for about 1000 actors positioned in any of about 100000 membrane nodes, of which about 5000 are occupied by actors. About 20000 interactors participate in diffusion and charge flux.

Vivo-shape modeling is pursued for purposes of justification of scaling and shape simplifications. Such studies must be conducted piece-meal however as full scale runs would be computationally prohibitive, even for world class super computers. The Vivo-shape models serve as organizational schemes for normalizing biological literature into single coherent cell types.

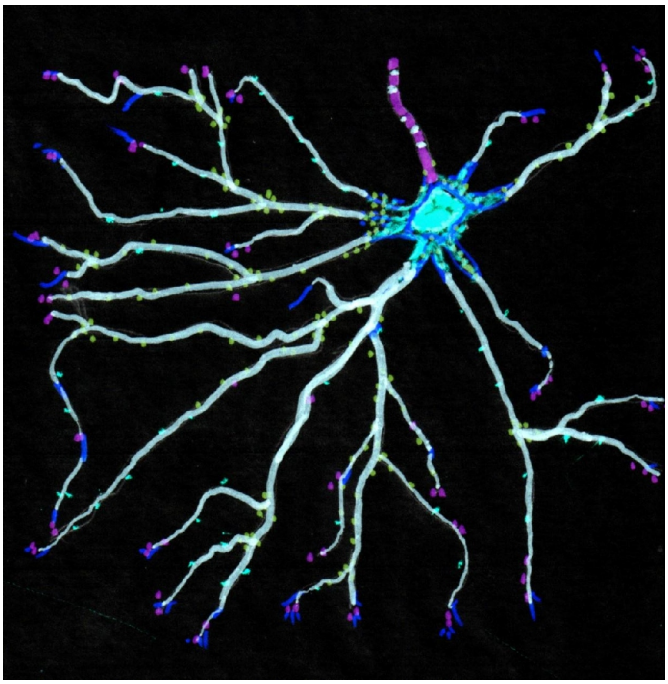

FIGURE 18: COMPLEX NEURON SHAPE WITH SYNAPSE MARKER

Ideal wet lab data would include a uniquely colored marker for each channel type, pump type, receptor type, and vesicle type. Diameters of each process measured, and from them surface areas calculated, and then the actor densities calculated for each type, as a function of actor counts. Bifurcation pattern would be measured for vane placements. Further metrics on the size of the soma and axon would reveal volumes, surface area , and lengths of each.

Full scale neuron shape complexity is extremely heavy in its computational load. One estimate required an 800 gigaflop computing machine, to manage 1e5 actors, 1e6 interactors, and membrane with 1e6 nodes. However, when whole cell neuron data is available with fluorescent dye markers on receptors, channels, pumps, vesicles and/or second messenger components, valuable distributions can be gleamed from it. Also valuable are data that identify the locations of synapses, bifurcations, and specific types of actors. Color thresholds can then be set to find the locations of each actor type so marked. From this their densities and distribution profiles can be generated.

6.5.15.5 Multicell Models

The fourth opportunity for computational load reduction is an information theoretic approach which captures the final results of a simulation run as a input to output mapping across parametric sweeps. This would preserve the mutual information between input and output, and purge the entire model down to its essential (nonlinear) transfer function. Although its original veracity is then deadened, the residual map provides a fast and accurate mimic of a 3-D neuron, for purposes of predictive models of local circuit neurons. In the multi-scale modeling strategy, this represents the next layer. *(This is not to reduce CPU time, but rather to support parallelism of multiple neurons simultaneously. The potential here for compression is quite high because we will be generating an interpolation on an N-space lookup table, where N is the quantity of parameters.)*

The fifth opportunity for computational load reduction is strict parsimony regarding datatypes. First, convert all variables that can be expressed as binaries to logicals, then all for which precision is not critical to more than 8 bits integers; then floating point 8 bit; then 16 bit; then 32 bit; then 64 bit.

Even after combining all of these strategies, what are the theoretical limits to reduction? The simplest neural net model (by others) reduces the neuron to an “integrate and fire” function. Thousands of such “logical units” can be

arranged in layers, and have already proven they can parallel process complex information at gigahertz clock speeds (faster than the human brain), in special use configuration (e.g. face recognition, biochemical configuration dynamics, battle scene analysis). However, it is the stated purpose of this model to capture the full molecular veracity of neuronal information processing, and thus the degrees of freedom necessary to maintain the *in vivo* mutual information is the criteria of veracity. The ability to reduce or simplify such a model is limited to the information throughput (channel capacity) plus the operations performed on the input information as necessary to generate the desired output. Such a limit will necessarily float with the task assigned the neuron. Thus the reduction strategies must be flexible and responsive to this end.

6.5.16 NEURAL NETWORKS

When neurons are simplified down to sum and threshold elements, then a network of "neurons" are required for pattern recognition, movement detection, etc.. A large number of articles have been published concerning the computational power of various wiring schemes of such simple elements into networks. In 1987, investigation of neural coding strategies led to the Hopfield net.[163] In 1994, Destexhe studied oscillations in networks of excitatory and inhibitory neurons.[164] Several times, workers reported that neural nets were severely limited in the types of problems they could solve – so discouraging that most funding sources withdrew support for such research.[165]

By 1996, training algorithms existed to help neural nets continuously and incrementally improve their performance.[166] And neural networks were back on track to solve ever more complex problems. Mathematicians blessed them as being able to solve a greater number of classes of problems than could a digital step-by-step computer. By 2003, a primitive worm, Caenorhabditis elegans was the first creature to have all its neurons mapped and all of its synaptic connections.[167] This provided an intact, complete, tractable nervous system for systemic study and modeling of a computational biologic system.[168] Connectivity of higher forms is being gradually mapped.

It has gradually come into our awareness that simplifying the neuron is directionally incorrect. We should be increasing our abilities to master their full complexity. There are serious challenges to our hardware as to how to accommodate such large set of data and processes. One fruitful avenue which this author is pursuing is called

multi-scaling. Rather than compute every ion in a neuron, representative patches of them can be intensively studied and mapped across the closed surface of the membrane.[169]

At the level of local circuit neurons the issues are mostly synaptic transfer functions and connectivity. At the next level up things are sufficiently organized that control systems theory can be applied to model high level functions, such as sound location.[170]

6.5.16.1 Artificial neurons

Quist in 2007 burnt holes in artificial lipid bilayer membrane to simulate channels.[171] He advocates that saline/membrane artificial neural networks could be interfaces with conventional silicone chips and provides suggestions how to do this. As manufacturing CPU chips becomes more an exercise in chemistry, then so the assembly of nano molecular gates becomes nearer to feasible.[172]

6.6 RE-USE

All algorithms shall be written across the most general usage space except when doing so incurs computational inefficiencies detrimental to the model. In such cases, the commentary within such functions shall clearly indicate the compromises made in the interest of speed, and document the code (as comments) that would serve a more general case. Where both the specific heavy use case and a lighter use more general case would both be used, then two functions shall be written; the general one by the standard name, and the specific one written with the same name but tagged "_fast".

Those functions and variables which serve to operate and maintain the database and data structures shall be set up as globals. Most other functions shall be set up as local operators, to avoid the accidental overwrite of far off variables that happen to have the same name.

6.6.1 LIBRARY

The static part of the model is its libraries of types of actors, their trait values and their parametric domains. There are also libraries of interactor types, membrane types, compartmental shape types. The first phase is to insure that the libraries are adequately stocked of all the types needed for the experiments to be conducted.

1. **Type:** intrinsic traits of an element type:
   A: affinities, binding kinetics, conformational kinetics, phenostates,
   B: mass, charge, radius, mobm, ...
   C: shape, zones, thickness, capacitance
2. **Dist:** probabilistic distributions in space, orientation, and initial state of an element type
3. **Design:** a set of parametric values that define an experimental run. A selection of types and dists that uniquely characterize a single neuron..
4. **Exp:** collection of elements, processes and signals that comprise an experiment, benefiting as much as practicable from lessons learned from experiments already in the library.

The static part of the model is its libraries of types of actors, their trait values and their parametric domains. There are also libraries of interactor types, membrane types, compartmental shape types. The first phase is to insure that the libraries are adequately stocked of all the types needed for the experiments to be conducted. Libraries of elements shall be provided as starter sets.

6.6.2 CAPTURE OF EXPERIMENTAL PARAMETERS

An experiment consists of the selection of the actor and interactor types and their distribution patterns onto a specified shape. The extracellular compartment and synapses are also be specified. An input signal set is provided, and the output data to be collected is specified. In addition some numeric parameters concerning time and space resolution are specified.

1. Any newly defined entities must be entered into the libraries, properly classified and characterized by trait values
2. Chosen elements from the libraries for an experimental design
3. Input signals to exercise the model designed and entered into the library
4. Output variables chosen to be captured and recorded.

6.6.3 EXPORT CAPABILITY OF DATA TO RELEVANT USERS

Currently, the output data is not in a standardized format for neural models, if indeed one exists. The output is raw position and state data which supports the reconstruction of events as a movie and/or plots of voltages, currents, flux, capacitance, etc. It is meaningful only in the context of the input set, which includes both design and signal information. The field awaits the proposal of standards in neural modeling that would enhance rather than limit scientific efforts.

6.6.3.1 Digitization and Computational Compression

Due to the large quantity of elements, there is a strong need is to eliminate redundant calculations, and to simplify necessary calculations. As the total list of computational steps per *dt*, per actor is about 100, simulations can consume weeks of CPU time. Size scaling is analogous to voice compression by clipping out the repeating patterns, and pasting copies of the unique patterns back in at the end to reconstitute the original signal. It is anticipated that the molecular pattern redundancies in the neuron are large, and thus much computational compression may eventually be justified.

However, all of this comes at a price. Reliability is threatened by any heuristic, short-cut, compression, linearization, classification, interpolation, extrapolation or estimation. This model, necessarily will do significant amounts of all of the above if it achieves large scale representation of the whole cell or multiple cells. Therefore, it is necessary to proceed with each of these incrementally, to verify the fidelity of the model as it departs from one-to-one correspondence with known biology.

6.6.4 FEEDBACK & ERROR CORRECTION

Design and performance metrics set forth criteria to be used applied to output so as to yield error data for purposes of causing modifications to the experiment for subsequent runs. Generally, levels of confidence and/or ranges of expected output values are defined prior to the run, and exceptions to those rules appearing in the output trigger some corrective measures to be taken., and generate a report of what was done. A modeling phase in which the researcher ponders the output error gaps and hypothesize their cause is needed to point the direction for future

metrics of performance. Sensitivity analyses that sweep some portion of the parametric space are needed to validate the model as representing some physiologic counterpart.

In some instances modeling will discover missing elements, processes or values thereof. This may be useful feedback for wet lab researchers, indicating possible areas of investigation so as to more completely understand some cellular process. It may also reinforce or challenge prevalent working models that drive wet lab experimental design.

6.6.4.1 Statistical Assessment of parametric domains

In a sense, this project is statistics-adverse. This is so because all statistical measures involve collapsing large numbers of events into aggregates. There are still a few of these of interest to information flows, however. It is presumed that information is communicated to a neighboring cell via particles small enough to diffuse/drift between cells within the timeslice of interest. That is, the crossing time is the period, and its inverse is it maximal frequency.

To insure that nothing significant is missed in this accounting of information flows it is prudent to run sweeps of parametric value combinations over all physiological ranges. Doing so increases one's confidence that all the common modes are discovered and characterized, with the boundary of each mapped. One then has many sets of input particle patterns and their corresponding output particle patterns. From these mutual information measures can be taken.

```
MI(in,out) = sum(p(in,out)*ln(p(in,out)/(p(in)*p(out))));
% MI = mutual information
% in = system input signals
% out = system output signals
% p(in,out) = joint probability of in and out
% ln = natural log
% p() = probability of occurrence
```

Solving this EQ is greatly simplified when the observer declares that only dendritic spikes count as input, and axonal spikes count as output. However, in this model, the positions of all unbalanced ions are considered to constitute information; and the states of all actors constitute information. For each of these some information is lost at the time of bio-data collection because, only that percentage of ions which become bound or transported are measurable.

And due to the use of kinetic schemes, only a few of the high runner states, some combined, some ignored, are measured.

One could detect and mark which ions are not charge balanced. But I fear this is not of significance because several partially balanced can add up to one fully unbalanced. There is an analogous concern for actor states. The several most similar states might be expressed as combined into a single state. Can these partials become significant to model behavior? A theoretical answer: Depends how far in space the ions are separated, and how spread in time the partial states are. It is a divergence problem. Are the numbers great enough that they average out to orderly behavior? That would be an ergodic problem. In this model such concerns are addressed empirically.

For purposes of the first development round, it is assumed that partial charges and partial states are not significant in altering the outcomes, within the resolution of the overall model. In future releases it may be found that with increased precision such effects become significant and need be accounted for in model behavior. It is reasonable to claim that the charge field will be accurate, including partial charges, down to the *dt* selected; and that the kinetic scheme will behave accurately over any number of states in the Q matrix, down to the *dt* selected. That leaves only two variables: the detail of the model design and the fineness of the *dt*.

Sensitivity sweeps may be designed to measure the robustness of a parametric set of model scaling and mapping from wet lab data.

6.7 DATA BASE MANAGEMENT

Each line segment of the contours of rotation that comprise a compartment has unique normals, necessary for determining particle reflections. Each particle must know which surface is it floor and ceiling (limiting membranes). Each particle must be tagged as to which compartment it belongs in, to detect escapees. Each particle must be tagged whether or not it is bound and to which actor and which binding site on that actor. Each actor must track its state, and track which particles, if any, are bound to each of its binding sites. Voltage and current need to be instantaneously measured for each *dt* on a per actor basis. Each zone has different characteristics and thus tracked as separate grouping. Each ion channel and pump must be able to attract and receive realistic quantities of particles for transport so as to achieve a sustainable circuit of particles.

All such data shall be organized into matrices. Pointers shall be provided to determine the relationships between unequal sized matrices. The details of database design and management are treated in a subsequent chapter. Covered below is the context within which database design can proceed.

6.7.1.1 Operating Environment

Operating Environment requirements include:

OE-1: The Patch model is completely contained within a single software application in the programming language of Octave or Matlab. As such it is portable to many platforms including Windows, Mac, Linux. At the small end of implementations, only a single laptop with Matlab ™ is required. In larger implementations, this model can be adapted to C++ over Linux on a processor cluster.) As the hardware environment is a rapidly evolving craft, it is presumed that interested parties will be versed in some version and rendition of the feasible program language embodiments as appropriate for its implementation and maintenance. The program lends itself to adaptation and expansion, so as to render an ever larger problem space tractable by expanding the libraries of actors, interactors and compartments..

OE-2 The program is driven by biological data. Concerning the anatomy, physiology and chemistry of the neuron. Only components and processes directly relevant to the information processing capabilities of the living cell are considered. It is flexible enough to handle variety of neuronal shapes and actor distributions within a cell type; a rather complete variety of cell types within an individual organism; the variance of nervous system cell instantiations within a species; and the variety of neurons possible across the animal kingdom. One celled organisms and reactive plant cells can also be modeled for their ion channel activities, and consequent voltage and concentration changes.

Several values of physical data are needed as well, such as temperature, various traits of water, and the periodic table.

OE-3 There is a small amount of physical data needed as well, such as temperature, various traits of water, and the periodic table.

6.7.1.2 Inputs

Input requirements include:

IN-1 Input is biologic data concerning the shape of neurons and the placement of Actors throughout that shape, and the initial positions and velocities of solute particles. Input data is divided into to classes: intrinsic data is called Type data, and extrinsic data is called Dist data.

IN-2 Input may also be artificially generated via statistical approximations of live cell data. These may be referred to as "simplified designs". All Input preparation is called the Design, regardless of biologic source or fabricated hypotheticals.

IN-3 Input to the model may also be generative. That is, instead of mere data, it may be formulaic The Q matrices for Kolmogorov states are generative. Such functions produce DIST files, either static or dynamic. Obviously, formulaic generators are an efficient mechanism for producing dynamic Distributions for the model. This would be of obvious utility in setting up state machines, or for simulating the response of a neuron to a changing environment.

6.7.1.3 Outputs

Output requirements include:

OUT-1 Output is a movie of the diffusion model, showing particles in motion, marking key events in color, and plotting selected key values, e.g. voltage, current, flux, concentration wrt time.

OUT-2 Output also consists of data files which can be stored and processed in a variety of ways. They include traces of all dynamic variables generated during the Run. Output visualizations may be customized to emphasis the phenomena of interest, and calculate some metrics that might best indicate what the next step should be.

6.8 WORK FLOW

1. Standardize the numerical treatment of all charged particles
2. Standardize the numerical treatment of all non-charged particles
3. Develop a function set for particle movements, collisions, bindings, unbindings

4. Add a sanity check for particle physics and conservation laws
5. Write a CAD program for shape generation: as volume, as surface, as addressable nodes, as NN
6. Coordinate routines between particle reflections off surfaces and particle transport through nodes
7. Standardize Actor defining traits, so that any type can be called into service merely by type #
8. Manage scaling problems, space, time and quantities, for motion and states.
9. Manage meta layers of model administration: libraries, design, build, reports
10. Map each of the created functions into the data structure needs, inputs and outputs (merge these)
11. Identify the heaviest use functions and rebuild them into highly efficient engines
12. Develop a test routine for each function over its usable domain
13. Identify opportunities for sub-assemblies for frequently called groups

6.8.1.1 The Load sequence shall be:

Load TypePhysics	Physics and Chemistry basics, constants, conversions, default values
Load TypeComp	Shape and perforation choices
Load TypeMemb	Surface and membrane characteristics, including rafts and capacitance
Load TypeIon	Periodic Table info on mono-atomic ions
Load TypeIon2	Table on poly-atomic ions
Load TypeLigand	Table on ligands: neurotransmitters, g-proteins, phosphates, glycosylates
Load TypeRecep	Library of Receptors, traits, inputs, mods, states, transitions, outputs
Load TypeChan	Library of Ion Channels, traits, inputs, mods, states, transitions, outputs
Load TypeShuttle	Library of shuttles, and their traits
Load TypePump	Library of pump types, inputs, mods, states, transitions, outputs
Load TypeVes	Library of Vesicles,traits, inputs, mods, states, transitions, outputs

6.8.1.2 The Design sequence shall be:

Input DistComp	% parametric values for compartment shapes, sizes and placement
Input DistConc	% concentrations of particles within each compartment at INIT
Input DistActors	% distribution functions determining placement of actors
Input ReportParams	% choices on how to present findings

6.8.1.3 The Build sequence shall be:

BuildC	% define compartments as a list of points, lines, surfaces, volumes
BuildB	% define positions and velocities of all particles for INIT, per biodata
BuildA	% locate actors per PDFs, set INIT states, forces, create icons for each
BuildRepor	% sets up data capture tables for future reports

6.8.1.4 The Run sequence shall comply with the following rules:

1. Start-up sequence first allows the particles to diffuse within their respective compartments, until steady state is achieved. Movement of all interactors shall be executed, then the consequences of those moves calculated: collide, reflect, absorb, bind

2. Then turn on the pumps. Run until steady state is achieved (all ion channels closed, all ligand vel=0, attractors off, binders off)

3. 3All state machines (actors) shall individually initialized have their initial states determined statistically. This includes some binding of ions and ligands at this time.

4. The collide, reflect, absorb, bind processes to be simulated within the time loop shall be rank ordered by speed, fastest first. This is to ensure the preservation of reasonable causality. Aliasing error must be compensated

5. To the extent possible, all coupled EQs shall be implemented within a single matrix, such that its inversion solves for dALL/*dt*.

6.8.2 DATA IN – DATA OUT PERSPECTIVE

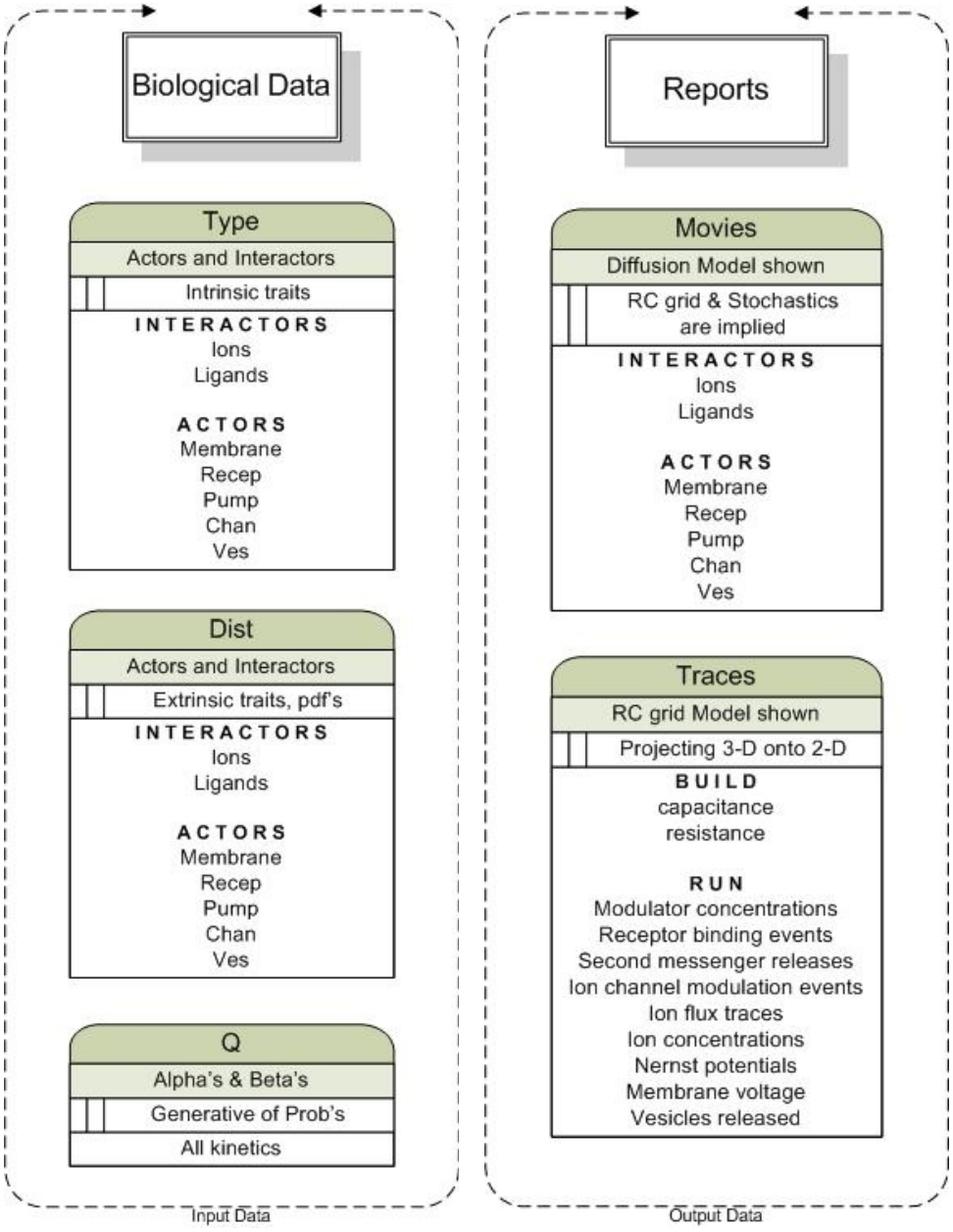

FIGURE 19: Data In **FIGURE 20: Data Out**

DATA_IN AND DATA_OUT DIAGRAMS FOR NEURAL IONICS

This is a black box approach to the model which soft ware coders like to see at the onset to get the span of the model. Software builds the bridge between these two, complying with a set of rules, mostly physics and conditional logic.

6.8.3 INFORMATION FLOW PERSPECTIVE:

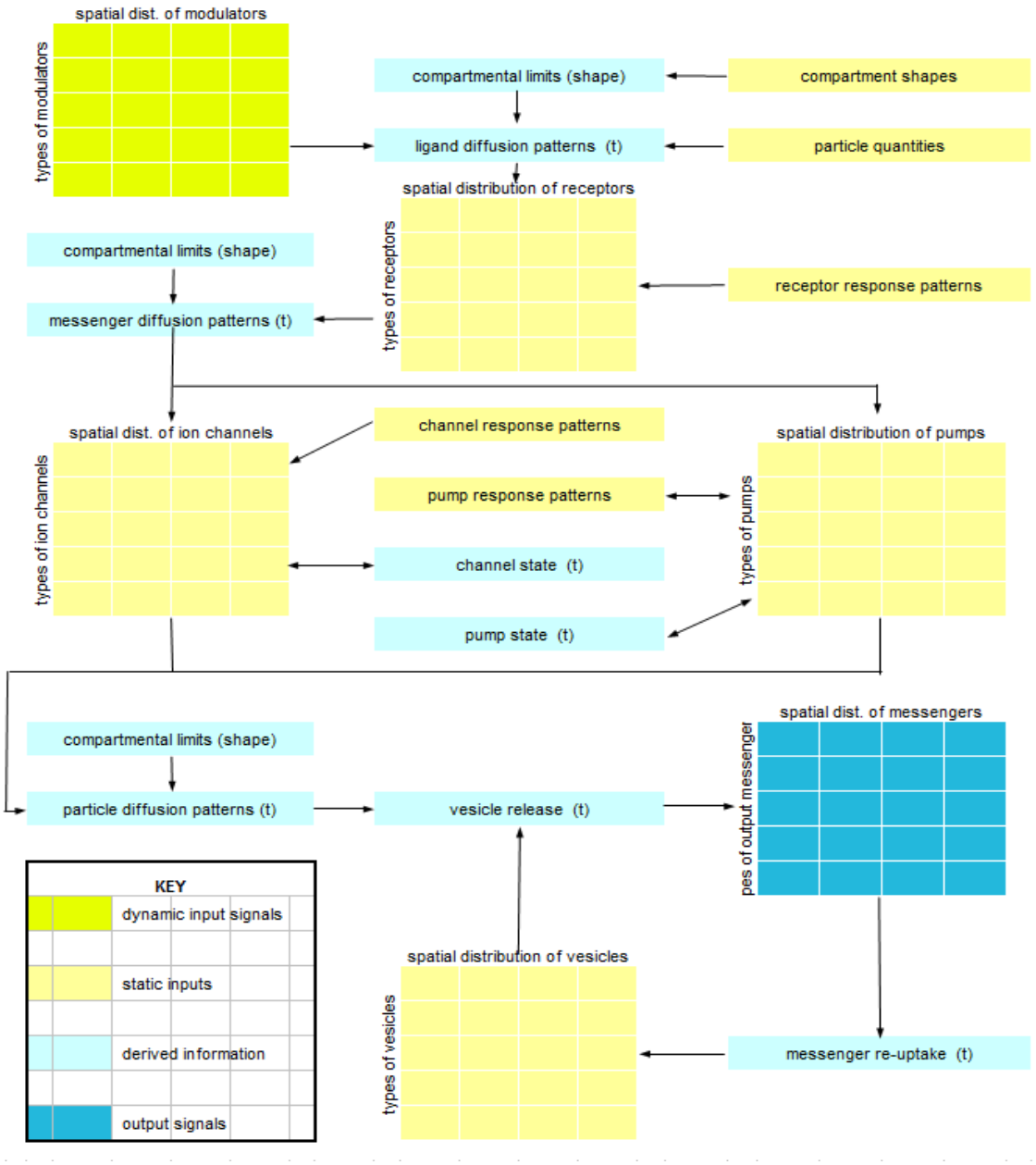

FIGURE 21: Information flow, setting aside the ions

The Information flow above invites consideration the way different sources of information convolve with each other. As the essence of the model is to map and functionalize information flow, this brings us closed to that goal. It will become the basis for the design of the data structures, which represent physical reality at the molecular level. The functions which act upon these data structures are the laws and forces of nature, moving through time.

6.9 TESTING

Each function shall be justified and verified. Each function has a set of precedents, dependents and downstream recipients. Each of these relationships shall be tested over physiologic ranges.

6.9.1 FUNCTION TESTS

T1 - Each function shall be tested for required operations over defined arg ranges, out of context, for expected deliverables, prior to insertion into the model code.

T2 - Arg ranges and dimensions shall be extensive enough to accommodate all likely uses within this modeling environment, including anticipated increases in model sizes and complexity as hardware computing power evolves.

T3 - Each function shall be tested, in context, for receipt of defined args, and error free creation of defined deliverables over the defined domain and range.

T4 - Error legs shall be added to prevent SW crashes over a reasonable range of likely user parameter entries over algorithmic "out of range" conditions.

T5 – "Divide by zero" warnings shall be suppressed, as there are numerous zero-crossings implied in reversing currents.

T6 - Timers shall be set on all RUNs, so as to measure CPU resource consumption, and report same. When multiple CPU's are employed, each shall be metered separately.

T7 - Threshold values shall be set on max length of RUN in seconds, after which control is returned to the keyboard, and an announcement to the screen indicating such.

T8 – Task allocation routines for multi-core machines (or Linux clusters) shall be bench-marked against the solo laptop performance o f the same run. Available optimization routines shall be applied as appropriate to identify and adjust the algorithms of dynamic thread allocating so as to maximize CPU resource efficiency and to realize parallelism with minimized “bottlenecks” (rate limiting processes) and optimized load leveling.

T9 – Metrics shall be installed into the software so as to recognize that resources are overwhelmed, and a warning issued to the screen that a reconfiguration of the RUN and/or hardware is necessary to avoid grid-lock, excessive hard drive calls, or unacceptably long run times. Suggestions shall be provided in this warning to raise priorities, increase memory allocation, improve load leveling, alter parametric values - so as to improve performance.

T10 - Any routine called more than once shall be written as a separate Octave ™ or Matlab ™ function.

T11 - No function shall be allowed to cause another function to abort the program due to errors.

T12 - Units conventions shall be maintained by a single directory of assignment, definition, scope and limitations.

T13 - Feedback loops shall be sufficiently stable so as to avoid freeze-ups, crashes, and infinities.

6.9.2 JUSTIFICATION

Justification is the process of selecting particular representations and algorithms as entities and features of the model. Justification does not apply to the the model as a whole, only to specific functions, steps, or parts.

Justification is integral to the design and build process, not to the usage of the model. Justification is accomplished by comparing the model element and process performances to the principles of physics or to living cell equivalents over the physiologic domains of interest.

Justification is the process of comparing modeling assumptions against fully robust renditions, theory and empirical data on principles. The purpose of justification is to insure that the simplifying assumptions do not produce distorted or inaccurate predictions on how the neurons they represent will behave. Justification applies to individual components, functions, subroutines of the model, step by step through the development phase. The purpose is to achieve heuristic performances of a required level, usually 99% confidence levels. However, iterative functions must be free from cumulative error, least they rapidly drift into unrepresentative spaces.

Each function, during the coding activities, shall be defined as a testable operator. Arguments and their domains shall be checked against best known biological data, domains, and principles. Outputs shall be verified to be reasonable and within biologic ranges.

A cautionary note: Aspects of the model may be justified over defined physiologic domains, and at some later time the model may be employed outside of that domain, and thereby be unjustified. Notes must be kept of the justification procedures conducive to extending those teats whenever the model is to be exercised outside of those domains.

6.9.2.1 Justification Requirements

Each simplifying assumption shall be tested statistically.

Justification is integral to the design. When each function is based on underlying physics then the remaining question is: To what real world situations does it apply? One the one hand, a model can be justified by its close compliance to the bio-data, especially dynamic and parametrically swept. But a good model has utility beyond the currently available sparse wet lab data. Care should be taken to orthogonalize the parameters, not as eigenvectors, but as real world independent variables.

Justification is a process that takes place during the original coding of this application. It is best performed on each function or functional set, whereby the expected result would be true to natural principles. The most common

challenge is that an exacting model would require too many particles and too many states to be computationally tractable at this time. Therefore reductions in quantity, culling out of insignificant states, increases in the time slice, and short cuts in collision detections are very much needed to achieve utilitarian performance.

Justification is accomplished by employing additional models that run individual phenomena more rigorously. These are the test standards. For example, if a real cubic micron of water has 600,000,000 molecules, how different would our model perform if the model had only 60,000 molecules? Would any compensating factors be required to decrease its error? If we set an acceptable level of error, say 1%, how low can we go in particle count? There are well established analytical approaches to linear systems, but in these highly nonlinear systems it is easier just to run the simulations and compare the outcomes.

1. Parametric sweeps shall be conducted over the N-space of a given actor's I/O relationships, to determine the degree of graininess that results from reducing the quantity of interactors and/or actors. Results shall be incorporated into the instruction text accompanying each actor.

2. Parametric sweeps shall be conducted over the N-space of a given actor's I/O relationships, to determine the degree of stability and non-linearity that results from reducing the quantity of interactors and/or actors. Findings of instability shall be incorporated as warnings whenever design sets have a likelihood of resulting in unstable results.

A log shall be kept that notes the software performance measurements with each run, specifically organized so as to contribute to the mapping of ranges of emergent behaviors, especially if not predicted by linear simplifications of that set.

The choice of modeling scheme first involves some test cases; each measuring performance, error and computational load. From these initial studies, some of the obvious losers can be weeded out. But for those that some performance has been achieved, there is a mater of veracity. Modeling is not seeking an efficient curve fit but rather an analogous mechanism that will continue to behave in a similar way as its bio-counterpart over a full range of conditions. To this end modeling is rapidly headed towards physics-based animation. The more firmly a model is based upon the physical underpinnings, the easier it is to justify. In fact, one of the best working definitions of model justification is a 1-to-1 correspondence with its physical counterpart components and processes.

6.9.3 VERIFICATION REQUIREMENTS

The purpose of verification is to rate the model's veracity to biological phenomena. It consists of comparing a simulation (Report from a Run) to the original bio-data. In most cases the model is expected to exhibit considerable error in the first and early runs. It is the nature of this error that is suggestive of what aspects of the model can be improved to better match biologic events. As nature is a variety generator, we should expect that some biologic processes will lie outside of the modeling toolbox, and may motivate us to write additional functions. In any case, it is the iterative conversation between wet lab and simulations that enlighten both efforts. The model poses questions about how and which bio-data is being collected, and the bio-data poses questions about how the simulation experiment is defined. The researcher benefits from both, and participates in hypothesis generation.

Means shall be provided to fully support the verification process for each simulation run. In preparation, bio-data shall be mapped into precisely the same formats as the model generated data, then the two compared for variance.

Functions shall be provided to automate the conversion from the common formats of biodata into model forms.

Functions shall be provided to perform the following statistical measures on the model performance: variance to biodata, confidence levels, chi-square tests on multivariate domains.

6.9.3.1 Validation Plan

In particle models, the computational load can easily grow to something greater than any available computer can handle. The current day battle in not so much one of achieving veracity as it is of cramming a good model into a smaller CPU than is really needed. That is where the compromises begin. And is where serious error can start to creep in. The very largest of these compromises is the mere act of digitizing the data. It is so common place most workers take the sampling process for granted. But the very essence of mathematics, the very essence of physics is firmly and utterly dependent upon the continuity of space and the continuity of time. Discrete objects may exist in those spaces and time, but their position velocity and state can be measured only because of the continuity of the number line, the time line, the gamut of possibilities. Even random processes in physics require continuous time domain and continuous process variable domains e.g. Markov processes). Their loss, necessary to transfer them into a digital computer, is grave.

Validation, foremost, must compare digital performance to known analog (real world) performance. This step often reveals the "ghosts" of aliasing error[18] (reflected data). Cumulative error easily crashes modeling programs because they are intensively iterative. Methods for eliminating (not merely reducing) sources of cumulative errors shall be pursued. Next comes parametric sweeps to demonstrate reasonable function behavior in isolation, not yet installed in the model. For each function reasonable input and argument sets must be created though many of these will later be generated by the intermediate steps of the algorithms. It is critical to well understand the behavior and span of each function before its goes into service, because once in the complexities of a system, root cause analysis is very expensive in time and effort. The edges, minimums, maximums and inflections all deserve enough attention to determine the smoothness of crossing these values. Programming for real time diagnostic plots of signals as they winnow through the system, with slider bars to adjust the input values, are fast ways of spotting anomalies for further investigation.

To the extent possible, small groups of functions should be stitched together into cooperative families. Tests can then be designed to exercise the group as though a single entity. The challenge here is to tease it in ways to assure that the innermost components are operating correctly in this environment. This challenge is not unlike the voltage 2-steps to tease out the kinetic schemes of ion channels. It is usually not possible to test all the permutations, but the likely use cases are a must, as are points either side of the steepest nonlinearities. In such nonlinear realms as neurons live, the challenge is to find the perimeters of each modality (when often one does not know how many modalities there just might be, or what their characteristic behaviors look like.

Once the subgroups have been assembled into a full model, the serious worker starts with the simplest possible experiments, and gradually works to greater complexities only when the confidence levels have been established across the simpler levels. Confidence is quantifiable, so log as the domain of each argument is defined. Standard procedures for failure analysis in hardware products apply to software as well. The digital constraints of software make for quite precise assessments, if only the time can be availed to track down all the legs.

Sensitivity analysis attempts to find unstable regions and parametric regions of higher error.

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[18] In the digitization of analog data, one of the several artifacts is that data may be reflected about a sampling point, in its effects upon EQs. An image of the data therefore is placed in an illegitimate position, and may show up in visualization as a transparent reversal of its legitimate counterpart.

Verification is the process of designing experiments to run on the model, then to measure their performance and predictability as compared with empirical data. Early verification certifies the model as a whole on benchmark tests. This is done to ascertain whether the model meets requirements for veracity to nature, and therefore holds promise for producing predictions about nature. Subsequent verification work is performed on a variety of experimental runs. To the extent that the model is already qualified, then the results are measuring the veracity of the experimental design, a user input. To the extent that the model has not yet been verified in this area and the experimental design is a faithful representation of natural phenomena, then the verification is a measure of the weakness or strength of the model itself in this area. Results may suggest ways to extend the model to make its parametric space larger or more complete.

Verification takes place after the model is operable. Performance is gauged against reliable bio-data scenarios of the equivalent cell type, its adjacent cells, its environmental factors and its physiological input signals. Because it is impossible to test all of the permutations across the full parametric range of each, reasonable samples need to be taken, especially near strong nonlinearities. An active search needs to be made to detect problem areas, or areas which are under-represented by the model. It is not necessary to have a perfect model that does everything - only that the limits are determined and announced to users. It is wise to constrain the model from "going there" (into poor performing territory) by setting limits with messages to explain to the user why certain parametric combinations have been shut off. Documentation may note how to remedy certain short-comings. For example, dendrites might require the addition of caveoli structures to perform as cell types that utilize them.

Verification refers to the model as a whole, not to individual elements or functions of the model. Verification is the process applied to a simulation run, measuring whether it is a useful representation of that which it was intended to mimic or predict. Certain parameters of the model may be adjusted to improve the veracity of the model performance, but just as importantly, the error gap between model performance and live cell performance may be useful in suggesting where to look next for unknown phenomena of that cell. That is, the model is always acknowledged to be incomplete, and yet is useful in assisting in the next wet lab experimental design.

A valid scientific hypothesis must be disprovable. Each model RUN is a hypothesis. It is shown to have a strong or weak veracity by its comparison to living tissue under similar conditions to the parametric representations that drive the model.

6.10 GENERAL REQUIREMENTS

1. Any routine called more than once shall be written as a separate function, suitable for general reuse.

2. There are no backward compatibility requirements regarding Version01. This grants freedom for a completely fresh design to best and current practices. This is a desirable standard for pre-release development versions. It allows complete correction and alignment to first principles without encumbrance by previous practices.

3. difference equations are the necessary representation of differential equations in digital machines. They are not exact solutions, and are prone to extreme error near regions of greatest nonlinearities. Procedures must be in place to detect such sensitive domains and to adjust the *dt* and *dx* to finer values accordingly.

4. iterative equations are the necessary representation of closed-form analytic equations in digital machines. Such iterations demand large computational resources and are grainy. They have the advantage of often revealing emergent properties of the underlying physical principles. They are prone to drift error that must be compensated for, but are less likely to lose behaviors due to the user's assumptions. This is true to the extent that all such iterative processes refer back to first principles.

5. No function shall be allowed to cause another function to abort the program due to errors. That is, each function shall have adequate error legs to handle un-executable requests gracefully. A pause for user intervention is acceptable, with screen prompts as to what value is out of bounds and how to correct it.

6. Naming conventions shall be maintained by a single directory of assignment, definition, scope and limitations. Long name conventions tend to have less occurrences of ambiguity, but become cumbersome in writing lengthy code of tens of thousands of lines. Short names can be quite efficient if the conventions are strictly adhered to.

7. Units conventions shall be maintained by a single directory of assignment, definition, scope and limitations. Units are critical to model efficiency and sanity. Model units appropriate to scale and for matrix inversion are necessary to avoid ill-formed matrices and spurious results.

8. All feedback loops shall be analyzed and tested for code stability, and any tendencies to abort or lock up shall be remedied inherently, or if that is not possible, then by reverting to keyboard control. Flow control shall count all iterations and provide for an exit when the code is repeating longer than expected.

9. SW Process = { LIBRARY > DESIGN > BUILD > RUN > REPORT }

6.11 USE OF SUPERCOMPUTERS

Single processor PC's are limited to about 1000 particles and 100 actors before they bog down or freeze due to excessive disk calls. Computers running out of RAM will slow down to only a few percent of their former speed rendering them unsuitable for large scale models. With experimental designs using the full rigor of shape, collisions, forces and kinetics (without heuristics), 500 particles and 50 actors may be the practical limit for single processors.

With the advent of machines with 64 to 5000 CPUs, large scale experiments become practical with quantities of particles and actors that substantially cover the salient aspects of a neuron. 64 CPU's with 128 gb of RAM will run

about 50000 particles and 5000 actors. 1024 CPU's will run about 500000 particles and 50000 actors. Performance can be improved several orders of magnitude with sparse matrix handling, incorporation of collision heuristics (not yet developed), and a rewrite of all functions for speed, rather than for readability and maintainability.

6.11.1 CLUSTER ARCHITECTURE

The Intel T8100 duo-core CPU with 4 gigabyte of RAM runs at 0.18 gigaflops, according to the LinPack Benchmark test, which solves a 500x500 simultaneous EQ problem in 0.47 seconds. At some quantity of actors and interactors, PC's performance will plummet due to disk calls and/or memory overflows. The question is one of scalability, from the 500x500 matrix of the benchmark test to ever higher quantities of elements in the model.

A reasonably complete model of a neuron might have 1E6 particles, and 1E5 actor states, 10 full-size matrix inversions per *dt*, and 1000 *dt* per run. That is 1E16 flops, or 10 petaflop.

Accepting 16 hours as an acceptable run time (64800 seconds), which calculates to 154 gigaflops. That implies 154/0.179 = 862 CPU = 1734 cores. Making the crude assumption that software and hardware efficiencies and heuristics can achieve an order of magnitude improvement, and that sparse matrices can realize another order of magnitude improvement, then 18 cores are indicated for a fully optimized run.

Efficiency opportunities include: stripping out all unessential tasks; Rewriting all function code avoiding algorithm serialization; setting up the operating system for real time processing; hardware for maximum bus transfers between CPUs and memory without wait states; adequate RAM to avoid rate-limiting hard drive calls; logical short-circuiting of unproductive areas of large matrix operations.

Prior to major purchases of hardware, benchmark tests should be run while varying the ratio of cores to RAM, then cost-optimize that ratio.

While Matlab ™ over Windows may be running in the user's laptop, Octave ™ and C++ over Linux may be running in the user's supercomputer. Care must be taken that the task manager maintain dual compatibility, else convert syntax between the two. Simplified task management can be realized by replacing Matlab ™ code with C++, which

is portable to both platforms. An advantage to leaving Matlab ™ on the master node is that it may receive the output files and easily generate sophisticated movies and plots.

6.11.2 CLUSTER OPTIMIZATION

An additional node is necessary during the early phases of task allocation algorithm for the cluster optimization. A processor for software metrics and hardware tests is needed to monitor the traffic and performance of each of the processing nodes. An optimizing program will benchmark and incrementally adjust the parameters of the task allocation strategy until all resources are well balanced for purposes of neuronal simulations. This is accomplished by adapting some average simulation run to generate benchmark metric values. The benchmark is scaled to determine what the largest practical model might be on a given cluster, and that performance remains high as the scale of the model is reduced below the maximal one (no "valleys of death", etc.).

No matter how carefully crafted, the test node itself is an additional tax on cluster performance. Such test nodes are also tested for their burden to the system, and this is subtracted from the performance ratings of the completed system.

6.12 TROUBLESHOOTING

6.12.1.1.1 Software logic and syntax errors

Error legs are written into each .m function at test time, so as to avoid unresponsiveness that may result from common user input mismatches.

Data Structures shall be designed in regular and standardized tables with restricted additions and alterations such that data corruption does not occur, and so as to minimize input error-caused aborts.

6.12.1.1.2 Biological misrepresentation errors

Warning legs are written into those .m function for which there is a likelihood that entered data will run normally but produce spurious results. This is a duty of the biologist during the verification phase of testing.

7 DESIGN ELEMENTS

This chapter covers aspects of the design elements as needed for:

1. Experiment Design
2. Build instantiation
3. Run dynamics

Design Elements are the products of efforts to define canonical forms, distilled from the great variety of biological expressions. This is done not to advance the understanding of biology, but rather to accommodate the limitations of digital computers. The goal is to define a general form that can be caused to express over a wide range of biological types by merely adjusting parametric values. A group of biological entities under study is generalized by measuring each according to known distinguishable features, quantifying the variation in each feature. The necessary set of variables to record these features spans a domain, the parametric space. Often, the eigenvalues on the data can be useful in finding a minimal set of maximally uncoupled variables that spans the space. Thus, a core form is required, and that core form is parametrized so as to facilitate the speedy creation of new types merely by providing a set of parametric values. Parametric domains usually have defined limits such that type varieties insane to the intended environments are avoided.

Elements are objects. They are the nouns of the system. Elements may be passive or active. The passive elements do not expressive behavior except movement induced by external forces. Passive elements do not change state. Active elements have 2 or more states, and the transition from 1 state to another we call behavior.

Elements do experience actions, which we call processes. This chapter addresses element traits, and the following chapter addresses the processes that may act upon them.

7.1 DESIGN PARAMETERS

Design parameters must safeguard the essence of each element type, while expressing all allowable variations on that type. Each satisfactory parametric set, expressing a useful variety of element, is recorded in the library for

future use. Each created/designed variety should be valued for consistency of behavior over the span of all supported modeled environments.

Following a set of parametric values, element types are selected and their traits defined, their quantities and positions defined. As a set they define one another's environment, and will influence each other's behaviors. There is either explicit and/or implied a set of rules of engagement between these elements. Often these are the "laws of physics", or else compromised alterations of such laws. The model system is conservative regarding the total quantity of elements.

7.2 FOUR ELEMENTAL DIVISIONS

At the very highest classification level of elements are the divisions:

A. Actors – there are five classes of Actor: Receptor, Shuttle, Channel, Vesicle, Pump

B. Interactors – there are three classes of Interactor: Monatomic Ion, Polyatomic Ion, Ligand

C. Compartments – are built of primitive shapes: Box, Cone, Cylinder, Disk, Sphere, Torus

D. Implicit entities – charge, flux, current, voltage, capacitance, resistance

7.3 ACTORS

Actors are defined as large proteins embedded in the lipid membrane, stationary in position, receptive to their surround, and capable by one means or another of influencing that surround. The parameters of Actors concern their intrinsic traits, bundled as Type, and their extrinsic positions, orientations, etc., bundled as Dist. For convenience, a set of physiological limits may also be set for each actor type, bundled as Pathos. These provide distinguishing information that determine function and behaviors of each actor. Types are collections of physical, chemical and biological data, to be held in a library (a hierarchical cell structure), for ease of use.

In the design phase, types are chosen from the library and applied to the model via distribution functions that statistically place them and orient them.

In the build phase, each individual actor is instantiated by initializing its bindings and state. This information is held at the beginning of Inst.

In the run phase, bindings and states become dynamic, recalculated each *dt*. The run generates a time series, recorded in Inst.

Within Type, the following traits are generalized:

Type Information necessary to distinguish the functionality of each type from all the others, including its kinetics, bindings, chemistry, and mechanical actions.

Intrinsic operations, defined in matrix forms

Bind Kinetics **R:** kinetics of bind and unbind at each allosteric site, (binding site x BT x State)

State Kinetics Q: quantity of states = qS. (qS x qS x dc) = state transition probabilities

Phenostate O: lookup table for current state to be read for its expression upon the outside world, e.g. channel opening or closing, pump transport events

Transport O: lookup table from current phenostate to function calls necessary to effect a process , e.g. move particle from one actor pole to its other pole for release. Pumps and channels effect transport. O = [side1 thru side2]; Pumps use side1, side2; Channels use thru. This data arrangement supports molecules that convert between pump and channel.

Conductivity G: profile of particles for channel selectivity: BT x Siemens. G serves vesicles by enumerating contents. G serves receptors by enumerating catalytic rates.

Extracurricular operations, functions defined by parametric values

Affinity aff: radius of attraction (r5xBT), binding radius (r4xBTx binding site)

Catalysis erg: pumps and vesicles may require binding ATP and then release it as ADP, transmutation

Targets eff: receptors and vesicles may accumulate B and target actors within r9 messenger shuttles

BT = particle types; dc = bind combinations; r4 = collision radius; r5 = affinity radius; r9 = shuttle reach;

Dist All information as necessary to position (and orient) each instance of a type within a particular membrane

PDF density of occurrence wrt axial length of the neuron, per type, per zone

PDZ zone demarcations along the PDF, allows the PDF to be sectioned by zone and then "stretched" zone by zone, across appropriate portion of the selected shape. Each shape must designate the same set of zone over its length for this operation to function properly.

In the Design phase, Type and Dist are selected sufficient to comprise an experimental design. They are parametrized and scaled per the needs of the experiment.
In the Build phase,the Types are instantiated across all positions they are to occupy. Positions, velocities, orientations, states, etc. are all instantiated stochastically.

Patho Allows user to set min and max values on local conditions, outside of which functions may be called to denature the actor. The primary use of this feature is to define physiological ranges, outside of which the model is flagged as being invalid. Each venture outside of physiological range requires non-linear treatment as to what qualitative shift is necessary to reflect change in character of the system. The study of pathological scenarios is facilitated when the model provides modal shifts from "normal" to "abnormal" under quantified conditions. Pathos data takes the form: A1.type#.Pathos = [min max] x [kelv pH ...];

7.3.1.1 Distance Conventions

r1 = radius of the naked particle
r2 = minimum hydrated radius
r3 = maximum hydrated radius
r4 = collision radius, effective
r5 = affinity radius, artefactual
r6 = nearest NN
r7 = furthest NN
r8 = shuttle catalyst station radius
r9 = shuttle max reach to actors

7.3.1.2 Mass Conventions

m1 = naked particle
m2 = minimum hydrated particle
m3 = maximum hydrated particle

7.3.1.3 Chemical Conversions

Mass, charge and size of molecules usually change upon chemical reaction. For modeling purposes, a particle exchange takes place. One or two reactants (instantiated B types) are exchanged for one or two products (also instantiated B types), according to lookup tables that specify what the event triggers are, and what reaction type is being triggered. Each chemical conversion is tracked and reported as experiment output data. Most chemical reactions are reversible. Forward and backward rate coefficients are provided where ever possible. The execution of the forward reaction also calls into play the probability of the backward reaction. Thus, for example, ATPase

pumps can be run backward when the gradients are not favorable to forward transport, in which case they produce ATP from ADP.

Build All information is read and instantiated into a complete compliment of compartments, particles and actors. Specific locations, orientations and initial states are generated to realize the entire neuron.

Compartment Segs are assigned to zones

Compartments are generated by Segs, Rings, Nodes.

Each node has position, orientation, nearest neighbors

Membrane/Node Assignment, pole compartment assignments

Each Actor binding site is given Pos and Affinity, state, id# of particles bound

Particles are initialized as boli in compartments, as bound to bind sites in actors

Build converts a prototypical set of Type traits, the values of which may be instantiated into actors.

Inst { Actorclass Actortype Node# orientation state bindcombo } % qualities of the actor

% orientation assigns each pole of the actor to a specific compartment#. It also holds specific xyz locations of the poles

% bindcombo serves as both the bind state of the actor and the contents of the messenger package.

Inst2 { r5particle#s1 r5particle#s2 r4particle#s1 r4particle#s2 voltage } % relationships of the actor

% voltage is calculated from r5 qB;

Run beginning with the initial conditions, initial particle locations, and initial actor states, a set of functions is executed through a single *dt*. The outcome of each *dt* is recorded. Dynamic functions are executed iteratively, as difference equations. Each individual element carries type, state, bind, and force information with it, either directly or as pointers. All dynamic EQs are evaluated each dt. However, multiscaling is supported, whereby the actor EQs may be calculated on a different *dt* than that of the particle EQs.

Multiscaling is of use in the long stretches between particle-actor collisions. It is possible to iterate the diffusion EQs on a *dt* of some ratio to the *dt* of the actor state changes. In that case we speak of Bdt and Adt values. Whenever there is a binding or transport event, requiring joint action of both A and B, the 2 *dt*'s must be in synch. Which ever of these 2 is the more informationally intensive will receive the finer resolution (smaller *dt*).

Because bindings are of the essence of the system, it may be desirable to have both particles and actors on the same clock (same *dt*). Rather than set Adt multiples apart from Bdt, it may prove better to adjust particle quantities such that the amount of information processing is balanced between particles and actors each *dt*.

Bindings	**R:** Each actor may at any time bind and unbind at its allosteric sites, according to kinetics
State	Q: New states are instantiated each dt, per state transition matrices + current bindings
Phenostate environment	O: The current state is read into a phenostate which directs its impact upon the
Transport	O: Certain particles are available to be moved and/or released into a compartment
Accum in R)	G: profile of particles accumulated in bulk, for receptors/vesicles (This may be handled
Conductivity	G: profile of particles for channel selectivity: BT x Siemens
Affinities	aff: Identifies particles by type within r5 for certain chemical affinities to its binding sites
Shuttle messengers	eff: (optional) receptors may target certain actors within r9 for 2-d diffusion of
Energy transmutation	erg: (optional) pumps may require binding an ATP and then release it as ADP,

Follows are the five Actor Classes.

7.3.2 RECEPTORS

Receptors are point processes that transduce the concentration of an extracellular messenger concentration into the release of a quantity of intracellular messenger molecules. They accomplish this by switching on and off a catalytic function which rapidly produces messenger molecules. Receptors are metabotropic, and stand apart from channels. They utilize second messenger leverage mechanisms to modulate more than one channel (see Shuttles below). Bio-receptors that service only one channel (the ionotropic kind) are treated within this model as channels with allosteric binding sites. That is, there is no separate element for the receptor on that channel.

Metabotropic receptors release messengers to a 2-dimensional diffusion along the inner surface of the membrane. Of these, relatively few hit downstream targets that are channels. For modeling purposes, only those that will hit their targets are modeled. For purposes of the model, the entity “receptor” refers only to metabotropic receptors,

and also includes the second messenger system, which consist of rays pointing to target actors in the vicinity. These rays serve as tracks (ways) for the second messengers to travel. Their communication velocities vary stochastically. Their success rates are also stochastic, reduced by distance. Each receptor is assigned a shuttle mechanism that releases its second messenger molecules in a fan-out so as to target a pre-identified group of nearby ion channels. The shuttle mechanism restricts messenger diffusion as 1-dimensional travel toward a channel bind site, but does support variations in speed and reliability.

The NIP significant features of receptors include the binding/unbinding stochastics of ligands, the internal stochastics of state transformations that reconfigure the molecule; the consequences of such reconfiguration upon the probabilities of second messenger release; and finally the stochastics of release. The actual quantity of release is subject to some variability, and maybe defined as modulatable.

For modeling purposes, there are two options as to how the messenger particles are produced and released. For fine-grained time (dt < 1E-4 s), the receptor can be modeled as a catalyst. For courser grained time, the receptor can be modeled as a packet release mechanism, similar to the vesicle.

Recep.Type is defined as:

1. Represented as 1 subunit. Biological receptors comprised of many subunits may have their kinetics merged.
2. R: Bind kinetic scheme, (d x BT x s) matrix, where d = quantity of binding sites, for particles <r5 distance
3. Q: Conformational kinetic scheme, (s x s x dc) matrix, where s = quantity of internal states; dc = bind combos
4. O: Phenostate map: indicates which state number causes an external impact, e.g. release of messengers
5. G: Messenger release profile (q x t)
6. aff: One affinity profile for the modulator (un)binding sites and particles within r6
7. eff: Shuttle type (r9, BT, speed, variance, back-speed)

Receptors are present in the neuron membranes in distinctly inhomogeneous patterns. These patterns are significant to the NIP function. For every release of messengers, there must be an equally speedy mechanisms for removing them message duty. Indeed the removal mechanism is move challenging than the release mechanism. This is because finding them and returning them to some recycling process is more expensive than merely releasing a

packet. The simplest way modeling the withdrawal of messenger particles is to reverse the shuttle mechanism. To adjust it to realistic timings, this back speed is adjustable independent of the forward speed. This back-speed represents the rate at which the living cell is capable of scavenging released messenger molecules, and going through the entire recycling chemistry such that particles are delivered to the receptor for it's next release. A back-speed slower than the shuttle messenger delivery speed to target actors implies a depletion/fatigue phenomena will occur with high volume messaging.

Recep.Path lists the limits to conditions of the actor: [min and max] for {kelv pH … } as the user may require

Recep.Dist is defined as follows:

1. PDF = distribution by type of receptor as density along axial length of neuron
2. PDZ = zone delineations of PDF, along length of neuron (similar for all actor types)

Receptor locations are instantiated by placement PDFs characteristic of the neuron type for that actor type.

Recep.Inst is defined as:

1. Type_call info: actortype#=1, receptor type#, shuttle type#,
2. Type_return info: Rkinetics, Qkinetics, Otable, Gprofile, aff_params, erg_params, eff_params,
3. Build info: node#, pole positions, compartment#s, initial state, initial bind, initial force
4. Run info: B(r5,comp1), B(r5,comp2), B(r4,comp1), B(r4,comp2), Bindcombo, state#, phenostate#, xportEQ
5. Report info: list of variables to keep as a time series
6. Report return info: icon type, icon geometry, icon colors, icon size, quivers_onoff

Recep.Patho = [min max] x physiological ranges over: temperature, pH, voltage, etc.

Crossing a pathological threshold triggers a function. Pathos supplies a pointer to which process is to be triggered. Pathos triggered functions can operate on elements to: inactivate, bind, sequester, convert, or otherwise tag the element as having been exposed to pathological conditions.

7.3.2.1 Receptors, metabotropic

Metabotropic Receptors release secondary messengers (usually G-proteins), which diffuse 2-Dimensionally along the membrane surface to nearby enzymes (cyclases) which in turn produce phosphate modulators to those local ion channels responsive to the messenger produced. These shuttles serve as transport links between metabotropic receptors and channels, in a one-to-many fashion. They are slower than ionotropic receptor-channel complexes, but provide quantitative leverage. Receptors are the primary input mechanism of the neuron. Receptors behave according to transition probability kinetics.

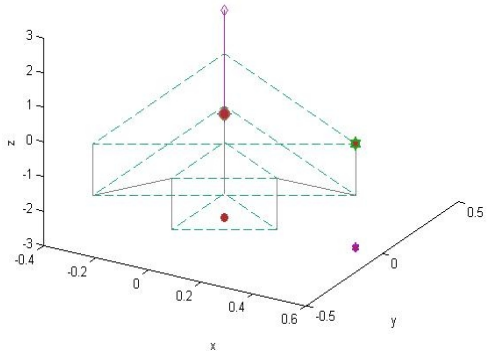


FIGURE 22: ICON FOR A RECEPTOR, 3-D

Icons chosen for Receptors have a 3-point circumference, but may vary in color and other parameters, so as to visually distinguish types. Icons for receptors are 3-D shapes They have input and output poles, normals for orienting them to the membrane. The axial poles (round) are loci for ion transport. The eccentric poles (asterisks) are the binding sites for modulating ligands. Z=0 is the membrane plane. X,Y=0 is the axis of the actor. A function is provided, named IconGen.m, that easily generates any of thousands of 3-dimensional icons from merely 3 argument values.

7.3.2.2 Receptors, ionotropic

The binding sites for ligands on ion channels are referred to by others as Ionotropic Receptors. These are not treated as separate entities but rather as part of the channel. As allosteric binding sites they induce immediate modulation of the Q matrix element values of that ion channel.

7.3.2.3 Shuttles (G-Protein Messenger Systems)

The second messenger systems of neurons are understood to perform a fan-out of the signal such that the stimulation of one receptor can modulate up to about 30000 channels. It is also allowable to modulate pumps this way. A single fan out provides leverage of up to 1:400, and a duplex fanout would then support up to 1:(400)^2. Which actors are modulated depends upon the type of messenger particle, and the binding site affinities on each actor. It also depends upon the distance between the two, with a decreasing chance of binding a modulator as the distance increases. The particular effects of distance are tempered by the locations of reuptake pumps for the modulators as they may impact the concentration of modulator particles at the various actor binding sites.

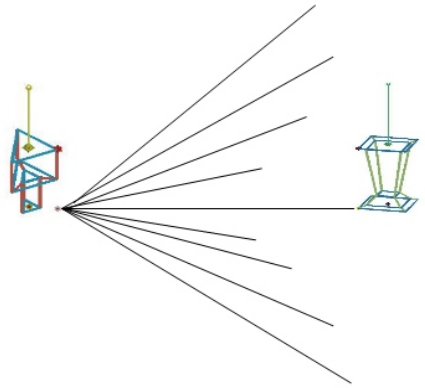


FIGURE 23: SHUTTLE SECONDARY MESSENGER FAN-OUT

A fan out from receptor to 9 channels.

Receptor Second messengers Catalysts Third messengers Channels

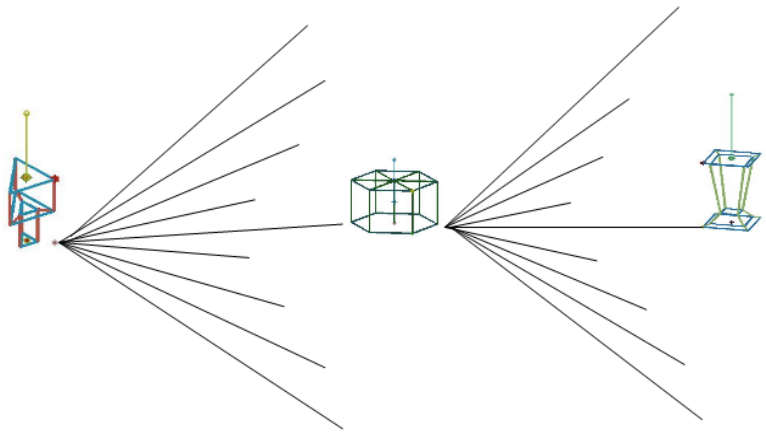


FIGURE 24: SHUTTLE DUPLEX FAN-OUT TO CHANNELS

Duplex links require additional time for each link, as each actor has stochastic conformations to proceed through.

Shuttles are simplified mechanisms representing the second messenger systems, particularly the G-proteins.. There are a variety of possible organizational arrangements of chemical components that constitute a message fan out. The processes by which they generate and more messengers are complex. There is often catalysis and charge transit mechanisms. These mechanisms vary considerably in the number of steps, the quantities of elements, the dimensionality of the flows, the overall leverage ratio, the types of targets that they impact, and the time spread of messenger arrivals. They may have additional impacts upon cytological sites other than channels and pumps.

However, for purposes of this model, shuttles are simplified to a set of links from one receptor to actors of a specified type within (r5) distance. The selected actor type must have allosteric binding sites for the messenger being sent down the shuttle to have any effect. The shuttle simply serves to deliver the messenger particles to positions within the collision radius of the actor. From that point it is up to the actor to engage the messenger kinetically to determine binding and dissociation events.

Each shuttle type represents 1 of about 20 G-protein schemes. Because each shuttle mechanism is the broadcast mechanism of a particular receptor, shuttles are defined as a subset of the receptor type, not as independent entities.

Once a receptor releases a packet of messenger particles, those particles will follow the G-protein scheme of that receptor type. This will effect a fan-out information leveraging mechanism to targets within certain radius (r7) with certain modulator sites (allosteric BT = shuttle messenger type). The messenger arrival times may be set with variance so as to best represent the bio-data. Arrival of messenger particles at the actor allosteric sites leads to stochastic binding, which will modulate the kinetics. Fan out leverage from receptor to target channels may be from 1:1 to about 1:30000. Which channel types are targeted is determined by the BT profiles of the actor bind sites, not by any shuttle parameters. It is permissible for shuttle messengers to modulate channels, pumps, vesicles or even other receptor types, provided they have the appropriate modulator binding sites to receive the messenger particles.

Shuttle.Type is defined by:

1. r9 distance - sets the probability of communicating to an actor type up to r9 distance away
2. Speed PDF distribution - sets the probability of delivering a message at a certain rate of speed, includes 0 (failed delivery)

3. Modulation kinetics - modulation of the intermediate G-protein cyclases result in altered catalytic production rate of the tertiary messengers. But as we are only modeling those few that hit target channels, adding more will not impact anything. Such modulation must be made to increase the speed of messenger delivery and/or the quantity of target actors to have any effect. In the case of a batch release, the quantity of particles per release must be adjusted in such a way the quantity of actors targeted is increased, so that the end result best mimics the biological phenomenon.

4. Reset action and timing: defines begin time and end time, so as to reset receptor for next duty cycle. If some receptor types can be reset and be retriggered while the prior set of messengers is still bound to actors, then surplus messenger particles must be available for the replenishment step. Replenishment will call the nearest messengers of the necessary type via affinity force.

Shuttle.Dist is defined by:

1. ReceptAssignment = position is equal to the Recept.Dist to which the shuttle is assigned.
2. Links are defined as a list of begin-end node pairs.

Note that every particle unbound is set free into the aqueous environment. In order to maintain normal concentrations, to remove messenger particles, and to keep them from sending rogue messages, they must be promptly sequestered. This is accomplished by receptor affinity force or by pumps, which collect the spent messengers and return them to the receptors for reuse. This conservation of mass is inappropriate when representing messengers that are chemically synthesized as needed in the bio-cells. To avoid carrying the entire synthetic/degradation chemical system that is not mainline NIP, it might be appropriate to sequester via pumps all messengers not in use. There are critical issues of timing, in that echo effects will occur if messengers are not promptly removed from the target areas.

7.3.2.4 Receptor-Shuttle states

1. Idle
2. affinity on for modulator from modulator profile
3. binding modulator
4. altering kinetics
5. releasing second messengers
6. unbinding modulators
7. re-affixing second messengers

7.3.2.5 Ideal Receptor

Follows is a cartoon of an ideal receptor, to serve as a point of departure for development of R,Q,O,G matrices and the aff,erg,eff parameter sets.

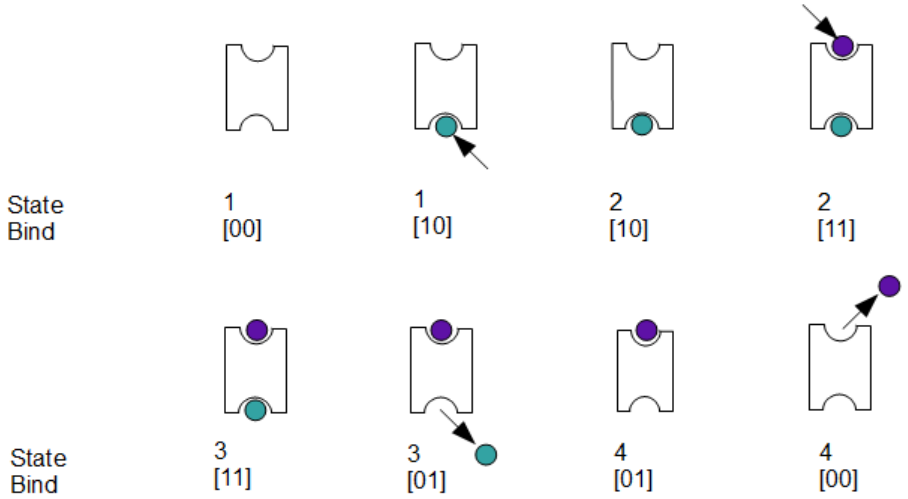


FIGURE 25: IDEAL RECEPTOR, STATES AND BINDINGS

The states are internal conformations of the molecule, and are not shown explicitly in the drawings above. State 1 is the recharge time to get all messengers ready for release. In the case of a catalytic release, then only the precursors must be in the immediate vicinity. The lower (green) binding particle represents a complete set of second messenger particles. The types and quantities are defined in Actor1.Recep#.G. When there are groups of particles to be gathered, as in receptors and vesicles, there must be 3 stages of binding: empty, partially full, full. The second frame in the figure above repeats with each addition until the quantity qualifies as complete. For modeling purposes this may be "speeded up" by increasing the affinity parameters in aff. The objective is to get the recharge time to a realistic interval. When the charge is completed, the receptor shifts to state 2, the "ready" state. At any time during this state, the receipt of a first messenger particle (often an extracellular neurotransmitter) may bind according to R kinetics and serve as a trigger. Such a binding causes a change to state 3, the "release" state. This causes all of the held second messenger particles to be unbound, by shifting the R kinetics from high binding probability to very low binding probability. The final exiting of the second messengers leaves the receptor unbound at site1, which causes a shift to state 4. State 4 releases the original trigger particle at bind site 2. The eventual unbinding of the stimulus particle causes a shift to state 1.

7.3.3 ION CHANNELS

Channels are proteins "floating" in the membrane, that enable the passage of one or more ion types from one compartment to another. Channels are the most dynamic class due to their rapid kinetics varying their conductance, and their frequent and multiple modulation. Modulation is due to chemical modulators (Ligands, second messengers, or Ions) and/or membrane voltage, pH, concentrations or mechanical pressure. The conductance of a channel (times the driving forces) dictates the amount of ions that pass from one compartment to another. The interior energy barriers of ion channels determine the direction, rectification, types and quantities of ion species allowed to pass. While ions are the fundamental mover in neuron communication, channels are the controllers of that movement. Channels behave according to Kolmogorov kinematics. There are at least 50 classifications of channel per species, and these are multiplied across the species varieties of the plant and animal kingdoms.

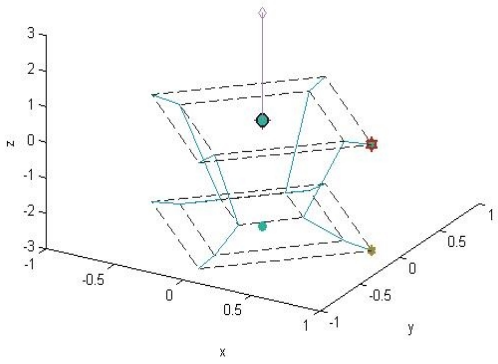


FIGURE 26: ICON FOR A CHANNEL, 3-D

Icon for the channel has a 4-point circumference, but may vary in color and other parameters. so as to visually distinguish types.

Icons for actors are 3-D shapes that can be unique to each actor type. A provided function easily generates these with just 3 numbers. They have input and output poles, normals for orienting them to the membrane.

A library of channel types is maintained. Each is characterized by an ion conductivity profile, an instantaneous state transition matrix, and a P vector for state to gate mapping. The Q- matrix is one of 2 types, variable or discrete. A

discrete Q is a set of several Q matrices consisting of fixed element values, chosen according to modulator bindings, if any. A continuous Q-matrix is a single matrix consisting of elements that are functions of a modulator value, such as voltage. The discrete corresponds to metabotropic and the continuous to ionotropic channels. For discrete Q's there is an R function which translates the modulator state into a choice of Q matrices each dt. For continuous Q's the variables within it are re-evaluated each dt. Ion channels open and close stochastically as a function of state transitions within the Q-matrix.

o = O(Q(R(d),s), where
R = binding site binding probabilities
d = currently bound particles
s = current molecular conformation
Q = infinitesimal transition matrix (as determined by R)
O = functional expression of any given conformer
o = open/close status of the ion channel
So = stochastically determined initial state of each channel

Practically, ion channels usually consist of 1 to 6 subunits which are protein molecules changing conformation somewhat independently. It requires less computation to treat each subunit separately and then take the product of their conformers, than it does to process a single large joint matrix representing the whole channel.

Channel opening and closing rates are measured as alpha and beta, so called “rate constants” from the traditions of chemistry. Unfortunately they are not at all constant, and their consultancies are of the essence. So let us call them rate functions.

$$h1(t) = h1_{\infty} + (h1_0 - h1_{\infty})e^{-t/\tau_{h1}}$$

$$\alpha_h(V) = \alpha_h^0 e^{\delta zFV/RT} \qquad \beta_h(V) = \beta_h^0 e^{-(1-\delta)zFV/RT}$$

Where
h = the aggregate performance of one type of channel subunit, as fraction open.
t = time (sec)
tau = time constant = 1/(alpha + beta);
alpha = forward rate (opening time), as a function of voltage across the subunit
beta = backward rate (closing time), as a function of voltage across the subunit
delta = center of action as fraction of the thickness of the membrane
z = charge count on the mechanism of action
F = Faraday's constant
R = gas constant
T = degrees Kelvin
V = voltage

Andrei Kolmogorov's contribution to channelology supports the adjustment of a Q matrix from frequencies of occurrence to the probabilities of occurrence during *dt*:

$$\frac{dp(dt)}{dt} = p(dt) * Q$$

where
Q = instantaneous transition probabilities
p = instantiated state of the molecule

The solution for which is:

$$p(dt) = p(0) * e^{Qdt}$$

Q matrix is a table of state transition probabilities. These probabilities may be constant or variable. For example, ion channel probabilities are modulatable, by voltage and concentrations. EX below.

Q = % Kv Channel

		c0	**c1**	**c2**	**c3**	**c4**	**o2**	**o3**	**o4**	**b4**	**b5**
		1	2	3	4	5	6	7	8	9	10
c0	1	0	.007*e^ (v/91)	0	0	0	0	0	0	0	0
c1	2	.002*e^ -(v/65)	0	.112*e^ (v/81)	0	0	0	0	0	0	0
c2	3	0	5.0*e^ -(v/112)	0	.212*e^ (v/91)	0	3.28	0	0	0	0
c3	4	0	0	1.65*e^ -(v/38)	0	.246*e^ (v/73)	0	1.06	0	0	0
c4	5	0	0	0	5.61*e^ -(v/70)	0	0	0	8.37	0	0
o2	6	0	0	5.06	0	0	0	.027*e^ (v/93)	0	0	0
o3	7	0	0	0	4.38	0	0.561*e^ (v/39)	0	.012*e^ (v/72)	.07*e^ (v/88)	0
o4	8	0	0	0	0	2.44	0	0.019*e^ -(v/68)	0	0	.00003*e^ (v/130)
b4	9	0	0	0	0	0	0	0.6	0	0	0
b5	10	0	0	0	0	0	0	0	0.08	0	0

c = closed state
o = open state
b = refractory state

This is a voltage gated potassium channel kinetic scheme adapted from the literature.[173][174] The only modulator acknowledged is voltage. No subunits are distinguished, so this is the merge of all. Note that the zeros along the diagonal will be replaced by Kolmogorov values as a function of dt. In the bio-channel which this scheme represents, there may be more modulators, and therefore requiring more states and more complex formulas to determine the transition probability values. When broken down, it is likely that there will be fewer states per subunit. Identical subunit types will have identical kinetic schemes, but once instantiated will have different state sequences over time, and are likely to vary somewhat in bindings and unbindings.

The O vector interprets internal state for actual channel openings and closings. For the Kv channel, O is:

```
O = [ 0 0 0 0 0 1 1 1 0 0];        % indicates that states 6,7,8 are open states, the rest closed.
```

The current state P determines which row in Q will be calculated to the current voltage. Only those rows with modulator variables need to be calculated each *dt*. If the current state is known precisely, then only that one row will be evaluated. Where the Q transition frequencies are faster than the *dt*, then the current state is not precisely known, but only probably known. In that case all non-zero probability rows must be evaluated as a function of the modulator values.

Once evaluated, the row becomes a PDF for transition to the next state. When multiple rows are evaluated they are weighted summed for a composite probability. The next state is determined by converting the PDF to a CDF (via integration), then generating a random number to determine where along the CDF the instantiation lies, and thus which will be the next state (s(t+1)).

There are at least 50 types of of ion channels, all or most of which may be present within a single species. Each species may have variants on these types, and one type may have variable characteristics, such as various clipped tail lengths that may alter its kinetics as a gradient. For modeling purposes, each such variant is treated as a separate type.

Channel.Type is defined as:

1. Consists of 4 to 6 subunits. Subunits may be of the same or different types.

2. One internal kinetic scheme per subunit, an (s1 x s1 x c2) matrix, where c2 = quantity of binding combinations
3. One external kinetic scheme per subunit, an (s2 x BT x s1 x c2) matrix, where s2 = quantity of binding sites
4. One affinity profile per subunit for each of the binding sites [r5 F r4] x BT
5. O: Phenostate map s1 x gate, identifies which states result in an open pore trough the membrane
6. The subunits operate logically in series
7. G: channel conduction profile

Channel.Dist is defined as:

1. PDF = distribution by type of receptor as density along axial length of neuron
2. PDZ = zone delineations of PDF, along length of neuron

Each type of ion channel is instantiated at locations according to a probability distribution function which profiles channel density along the length of the neuron. Channels are present in the neuron membranes in distinctly non-homogeneous patterns. These patterns are significant the to NIP function.

Channel.Inst is defined as:

1. Positions + Orientations
2. Pole to Compartment map

Channel.Pathos = [min max] x physiological ranges over: temperature, pH, voltage, etc.. Crossing pathological threshold triggers functions via pointers. These functions can operate on element to: inactivate, bind, sequester, convert, or otherwise tag the element as having been exposed to pathological conditions.

7.3.3.1.1 Conductivity Profiles

Channel conductivity is highly selective, determined by the complex interactions of the ion with the fixed charges of the channel protein along the rather tortuous pore. Channel conductivity may require an amount of excess free energy to keep the side chains protonated.[175] Selectivity is determined by ion size and the energy of hydration. For example, the hydration free energy of Na+ is about 20 kcal/mole more favorable than that of K+. For K+ to be selected in preference to Na+, a channel just needs not over-solvate Na+ ions.[176] The mouth of the ion channel

has its own nano-environment electrodynamics, and voltage varies widely with the presence of chemical buffers. [177]

Conductivity may be altered by certain ion concentrations at the pore, independent of internal kinetics.[178] Once an ion is in a pore, the shape of the pore, and the charges along the way determine an energy barrier profile along the axis. Usually, the maximum repulsive force along the way determines the conductivity of each ion species.

A physically open channel may be functionally closed, either by hydrophobicity, by solvation of the ion making it too large to pass, or by charge gauntlets that produce an energy barrier too high for the ion to pass the full length of the pore.[179] Thus conductivity ratios are unique to each pore's chemistry. Molecular Dynamics studies are necessary to find the gating mechanisms, how they work, and what the energetics are. As of this writing , the field of Molecular Dynamics has not tackled the aqueous environment with its ions and solutes impinging on the molecule. However, the Poisson Boltmann EQ has been employed in models that have done so.[180] From an informational point of view, it is not necessary to go into such detail. Selectivity mechanisms are complex, but they result in conductivity values, which are easily handled by this model as such. Any function that calculates the correct conductivity value under the physiological conditions of the moment will do.

For purposes of this model, channels are point process Markov chains and the pore dynamics are not represented. The conductivity values will be taken from the literature and applied as Ohm's law plus a flux due to the concentration gradient.

7.3.3.2 Subunits of Ion Channels

An ion channel may consist of 1 to 6 main, columnar subunits which penetrate the membrane, and a variable number of ancillary subunits that typically do not penetrate the membrane. Each subunits may or may not be active in determining whether a channel is open or closed. Each subunit may or may not have allosteric binding sites. Subunits are often autonomous enough in modulation and action to warrant their own Q matrices, but data is rare from the wet lab work in this regard. The model provides the option to treat a channel as a single Q matrix, or as a set of smaller Q matrices that operate logically in series. That is, all subunits must be open for the channel to be open. Any one subunit can block the pore.

It is desirable for each subunit to be explicitly instantiated and calculated separately for its phenostate function. This is especially appropriate for channels, but may be applied to any actor class, providing the wet lab work as discerned specific subunits by function, modulation, dynamics, and impact. For example, the mathematical relationships between channel subunits are as follows.

Each subunit has a state s, and each state maps to a phenostate h.
Output of 4-subunit channel: Y = h1*h2*h3*h4.
Conductance of the channel: G = Gmax(ions)*Y;
Current through the channel: I = (V-Eions)*G;
Flux through the channel: J = I/z.ions;

Most of the mathematical description above for an actor applies to a subunit. The difference is that the subunit state h may not map to a phenostate. Instead, the subunit states are logically combined into a whole channel state, usually in series, and then the channel is mapped to a phenostate.

7.3.3.3 Channel states

As channels are composed of subunits, some experiments may need to portray the individual subunits stochastics, rather than a combined matrix. Instantiating the subunits separately produces accurate gating patterns and allows the modulators bound on each unit to alter only the kinetics of that subunit without altering the kinetics of any of the other subunits.

Data that must be collected to support subunit kinetics and a logical merge

1. Subunit types per actor type
2. Modulator Binding Profile per subunit per pole
3. Q matrices for each subunit
4. Current Modulators Bound per subunit per pol
5. Modulation may be per subunit, and then requires a Q for each subunit type
6. Current State Numbers, one per subunit
7. Gating Function = logic between subunits > expression
8. Conductivity profile, one per actor

These are integrated over the time envelope of channel openings. Although the subunits appear physically as parallel cylinders, their operations are logically in series.

An example of a kinetic scheme with 24 states:

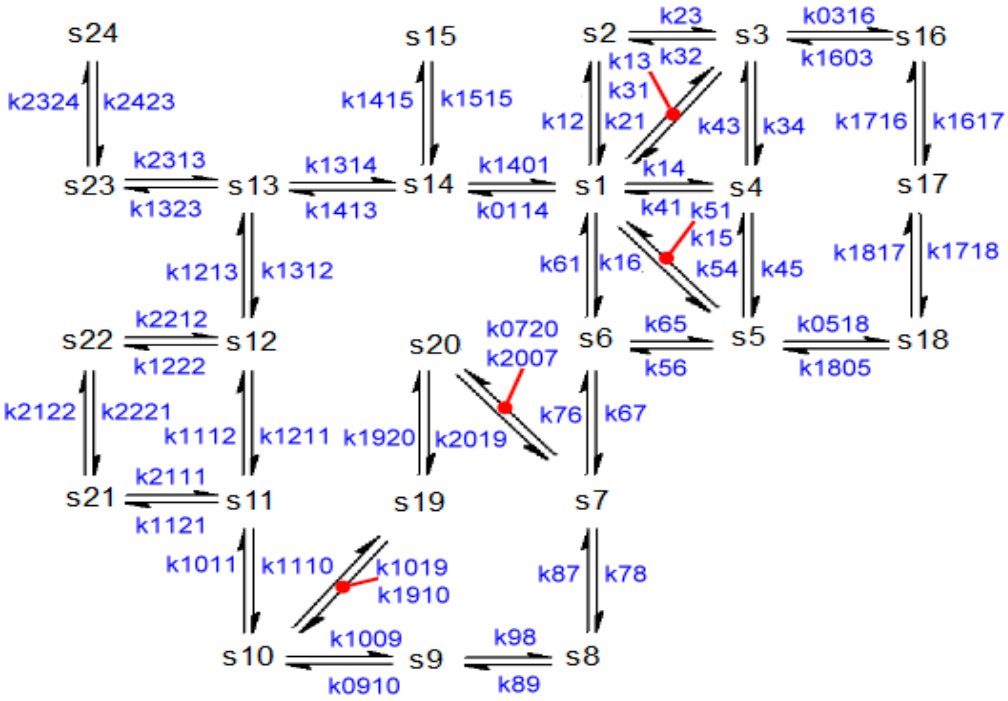


FIGURE 27: Kinetic Scheme with 24 states

Kinetic schemes are the source of molecular behavior. Each of the rate coefficients (k- numbers above) translates to a probability of state transition

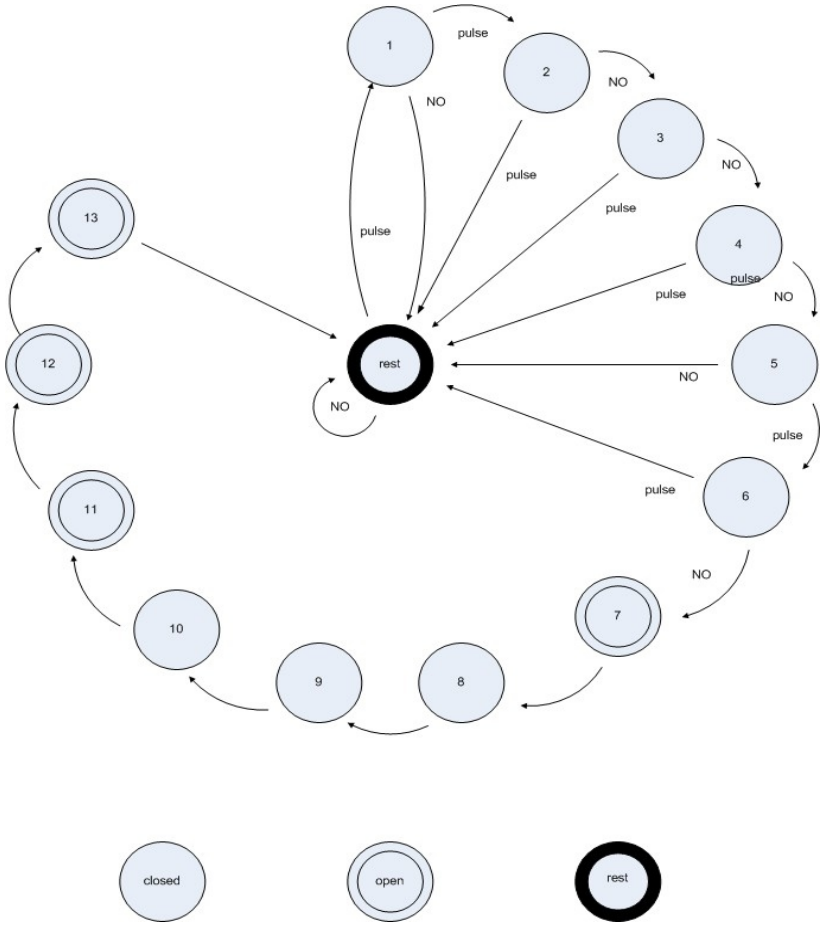


FIGURE 28: CIRCULARIZED STATE FLOW OF CHANNEL WITH 14 STATES

With minor design changes any input code could be mapped to any output code. The temporal quality of performance degrades with cumulative error because of the stochastic nature of transitions, and thus only the shorter sequences are expected to be practical. Th state flow above does not add nor subtract from the kinetic schemes, but is merely a mapping of the same information for visualization of the duty cycle and rest state. This form makes it easier to add alternative paths in a way that they are seen as separate from the main path.

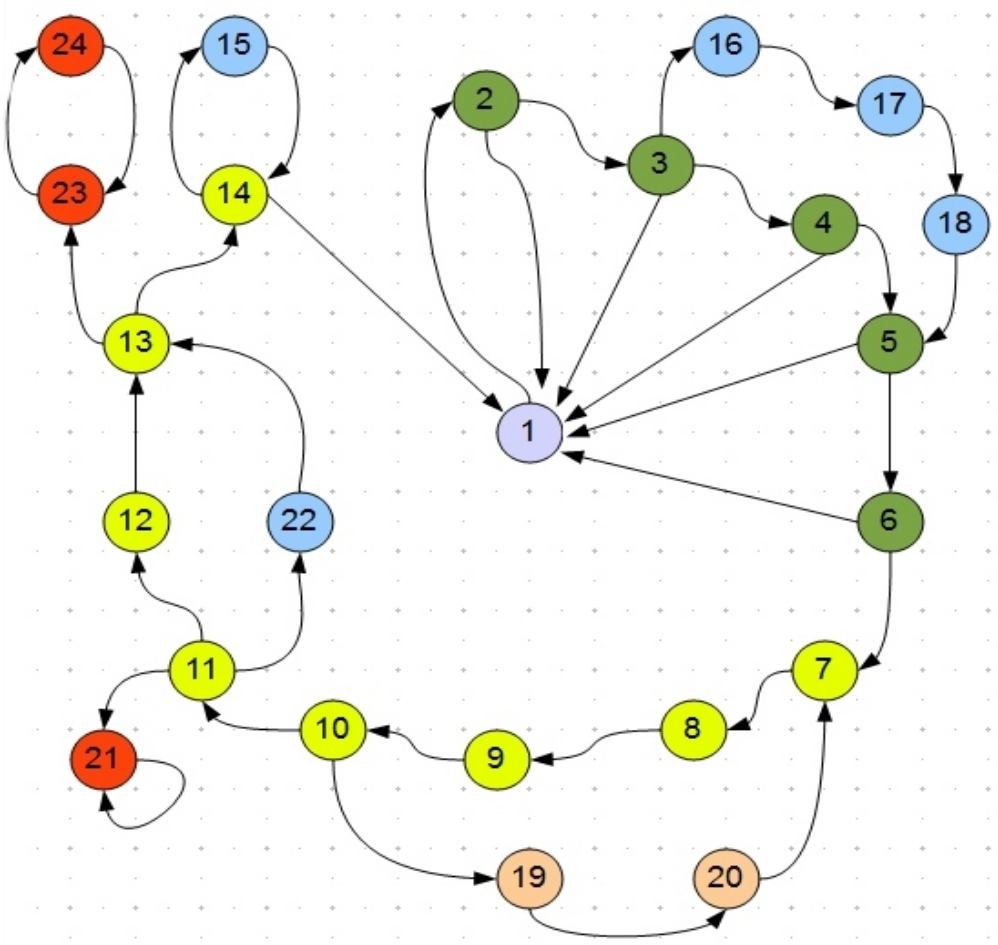


FIGURE 29: Auxiliary Paths added to duty cycle

A kinetic scheme becomes "readable" when the duty cycle is clearly visible, and the lesser traversed paths are added distinctive from the main path. The probability of the main path determines the reliability of the actor. State =1 is presumed to be the rest state. In this matrix, and failure to match the input pattern results in a failure back to rest state. The output pattern has 2 openings with an interim closing at state 10. In the event of a 19,20 back path, the first opening (states 7,8,9) gets repeated. States 21, 23,24 are poison states because there is no way out, to resume the duty cycle. These must be exceedingly rare events because they kill the actor.

Q = % Bare Q matrix for Main 14 States

Q	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	***11***	***12***	***13***	***14***
1	0	v	0	0	0	0	0	0	0	0	0	0	0	1-v
2	0	0	1-v	0	0	0	0	0	0	0	0	0	0	v
3	0	0	0	1-v	0	0	0	0	0	0	0	0	0	v
4	0	0	0	0	1-v	0	0	0	0	0	0	0	0	v
5	0	0	0	0	0	v	0	0	0	0	0	0	0	1-v

6	0	0	0	0	0	0	1	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	1	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	1	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	1	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	1	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	1	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0	1	0
13	0	0	0	0	0	0	0	0	0	0	0	0	0	1
14	v	0	0	0	0	0	0	0	0	0	0	0	0	1-v

The zero values will become occupied by low level noise in a molecular embodiment. V values are for design purposes, considered to be 1 if a pulse is present at that time, 0 if no pulse is present. Input values 0<v<1 act as noise, sometimes read as ones, sometimes read as zeros.

The O matrix is a phenostate lookup table (For channels, disclosing which states are open). In this case it would be:

O = % O matrix For Channel with 14 States

O	***recep***	***pore***	*value*
1	read pulse	closed	0
2	read pulse	closed	0
3	read pulse	closed	0
4	read pulse	closed	0
5	read pulse	closed	0
6	read pulse	open	0
7	block	open	1
8	block	closed	0
9	block	closed	0
10	block	closed	0
11	block	open	1
12	block	open	1
13	block	open	1
14	block	rest	0

The blocked state of the receptor(s) is the time of the refractory period during which the ion channel is not responsive to input stimuli. It is blocked in the sense that changes in the voltage do not alter the course through the state changes back towards the rest state. Once back to the rest state then responsivity to voltage changes returns.

7.3.3.4 Ideal Channel

Follows is a cartoon of a simple ion channel, its bindings and requisite states. This is regarded as a point of departure for development of more complex channel kinetics. Because of its simplicity, this channel type is weak in information processing potential. A robust general channel would be one with a mode for each of the mathematical operators, a modulator bind combination that would engage that mode; then a characteristic output pattern that revealed which mode it was in, as well as an amplitude "answer" to the inputted "problem". Because living systems receive inputs as continuous streaming, the channel evidently requires a refractory period to slice the input stream into processable time segments. This discretizing of an analog stream allows the actor to proceed through its state path, including possible modal shifts, before eliciting its response of pore openings. The response openings are characterized by lag, duration, and pattern.

State =1 is presumed to be the rest state, even if it is not the state of greatest residency time. The rest state is usually characterized as the state possessing lowest Gibbs energy. A low energy barrier translates to a high probability of occurrence of this state. However, thermal motion, and the effects of certain binding patterns, can alter the Gibbs energy of each conformation, setting the molecule down a state path of variable predisposition. Each binding combination requires its own transition probability table, and there is the potential, if not the necessity, for each combination to result in a unique modality for the molecule. Generally, the state path is being forced up the energy scale along the "input" portion of the path. During this portion, modifying bindings matter. This is particularly true under voltage pressure. Then, having reached some peak energy content about mid way around the duty cycle, from then on the potential energy must be released along the main state path , running slightly down hill, until it arrives back at the rest state. All of this comprises a duty cycle. There may be more than one duty cycle within any actor type, each one referred to as a different mode.

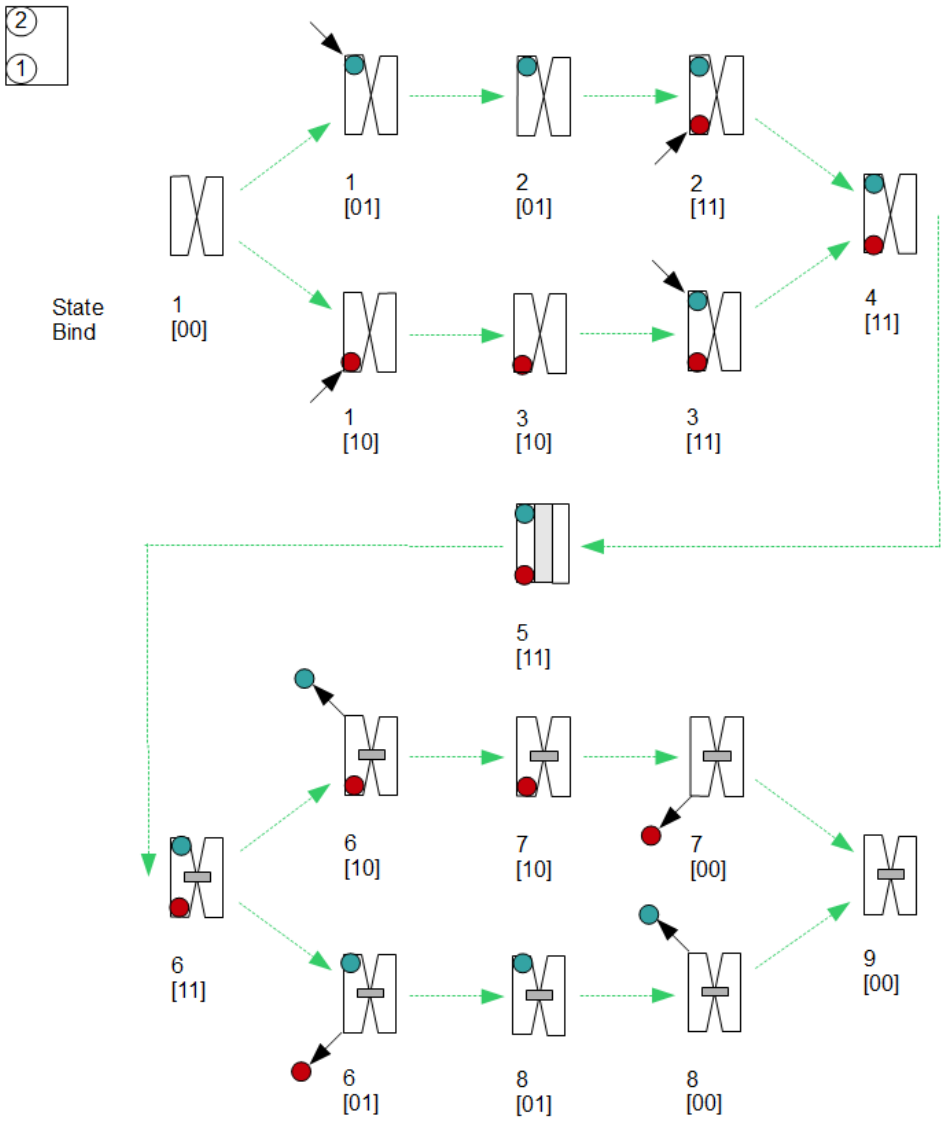


FIGURE 30: Ideal Channel, Bindings and States

Modulation may alter the input characteristics or output characteristics. Altering the input will change what may bind to the various binding sites. Altering the output will change the timing and pattern of the channel opening.

In the above cartoon, it is acknowledged that binding order may be reversed to achieve the same results. Different channel types will vary in sensitivity to binding order. Some channel types may bind 2 or more types of particle at a single binding site. Channels also exhibit different responses to different ligands binding to the site binding site. When an Mg++ binds at what normally is a Ca++ binding site, there is the possibility that the channel will behave differently. It is known that Mg++ can block what Ca++binding enables or stimulates.

The internal conformational states of a channel are the heart of the model, holding the greatest potential for information processing at the molecular level found so far.

In the above example the rest state awaits 2 bindings, one each of intracellular domain and extracellular domain. When both sites are activated the molecule shifts to state 5, which is the pore open state. Pore open states are extremely unstable states, causing channel closings within a few milliseconds of open time. This is essential to life, as an open pore will bleed the ionic transmembrane potential to death. Consequently, state 5 quickly transitions to state 6. States 6, 7, 8 are shown with a blocking bar to indicate the refractory period. During these states, the molecule will not respond to any stimuli nor modulation. The refractory period after the open state indicates that the state path is not reversible – the leg from rest to open must be different than the leg from open to rest. The timing of the refractory period during the state path is critical; if the channel goes through a refractory period before opening, then it will never open (do you want to state why?). State 5 marks the beginning of the channel's journey back to the rest state. Until the rest state is reached, all other states will be predisposed to unbinding, promoting faster arrival.

In a simple kinetic scheme, the pore only opens once during a duty cycle. It is quite possible that the state path could proceed through more than one pore opening before arriving in the rest state or refractory state. Doing so would produce a temporal pattern, characteristic of the modality of that type.

7.3.4 VESICLES

There are a wide variety of cytological mechanisms for exocytotic release of messenger products out of the cell. The key statistical features of the vesicles relevant to NIP are the binding/unbinding stochastics of calcium, the variability of the contents of the vesicle, the exocytotic release timing and variability, and the distribution of release portions (partial, full, none). Although they could be modeled as compartments with dynamic membranes, that would be computationally prohibitive at this time. Instead, a statistical representation of their neurotransmitter release function is modeled, much the same as that of the receptors. Vesicle release mechanisms are simplified to their intrinsic information flows, as a transducer converting an intracellular Ca signal into an extracellular neurotransmitter signal. As typical with transducers there is also a fan-out leverage mechanism whereby a single Ca arrival triggers a massive release of particles. The leverage may be set from 1:1 to 1:30000.

Vesicle.Type is defined as:

1. Consists of 1 subunit. The many sub-components have their kinetics merged. All aspects not significant to the release timing and quantities of particles are purged. Replenishment mechanisms are greatly simplified.
2. R: One bind kinetic scheme, an (s2 x BT x s1) matrix, where s2 = quantity of binding sites
3. Q: One conformational kinetic scheme, an (s1 x s1 x c2) matrix, where s1 = quantity of internal states, c2 is the quantity of binding combinations
4. O: One Phenostate map: each state number may be scheduled to initiate causes a release
5. G: Messenger release profile and reuptake profile (BT x s2 x 2)
6. M: timing issues on reuptake (should be implied by s1 kinetics), but special mechanisms may be entailed
7.

Vesicle.Dist is defined as:

1. Position + Orientation
2. Pole to Compartment map

Each type of vesicle is instantiated at locations according to a probability distribution function which profiles channel density along the length of the neuron. The locations of vesicular releases are also critical to NIP function by determining the output signals to which downstream cells.

Vesicle.Inst is defined by:

1. Positions + Orientations, usually as a function of zone
2. Pole to Compartment map

Vesicle.Patho = [min max] x physiological ranges over: temperature, pH, voltage, etc.

Crossing pathological threshold trigger functions via pointers. These functions can operate on element to:

inactivate, bind, sequester, convert, or otherwise tag the element as having been exposed to pathological conditions.

Vesicles are present in the neuron membranes in distinctly non-homogeneous patterns, usually only in presynaptic zones. These patterns are significant the to NIP function.

Vesicles are comprised of membrane lipids, with a constellation of specific proteins bound and/or associated thereto. They contain chemical modulators, especially neurotransmitters, and undergo controlled exocytotic into the synaptic cleft. Known vesicles respond to Ca++ concentrations (in very low concentrations), according to their kinetic schemes; There is some variation (noise) in whether or not a vesicle is released, how many vesicles are released, the exact timing of release and how much neurotransmitter is present within each vesicle. This information is captured in the kinetic schemes. Vesicles act as the chemical output device for the neuron. A faithful model of the vesicle is a complex undertaking. For purposes herein, only the information-aspects of the passing vesicle are represented. This allows the mechanism to be reduced to that of a receptor in reverse. The recycling of vesicles is simplified to pumps, which reset conditions for the next release.

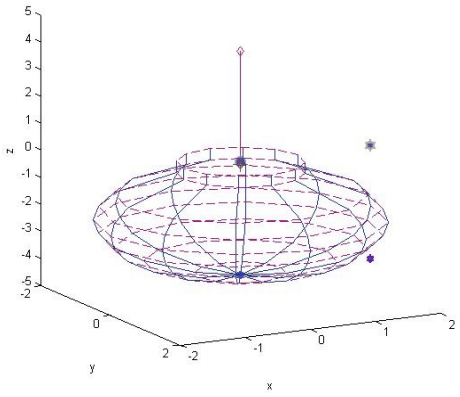


FIGURE 31: ICON FOR A VESICLE, 3-D

Icon for the vesicle is globular (10 sided), but may vary in color and other parameters to visually distinguish types.

Vesicles may be considered as compartments made of capacitive membrane filled with water, ions and ligands. This is however yet another cell, with all of its computational load. To manage a complete set of vesicles, say 100, would not be computationally tractable at this time. Given the information processing role of vesicles, it is concluded that they may be simulated as particles. That is, if a vesicle were a ligand molecule bound to a receptor, and released upon modulation, the the stochastic effects could be made to mimic those of vesicles, given that a large number of such releases could be managed. Therefore, vesicles will be simulated much the same as receptors, described above.

7.3.4.1 Vesicle states

1. Idle
2. binding Ca++
3. exocytosis of neurotransmitter into synapse
4. unbinding Ca++
5. reloading neurotransmitter

7.3.4.2 Ideal Vesicle

The cartoon below depicts a simple case of vesicle kinetics. It is the compliment of the receptor kinetics, so the details need not be repeated here.

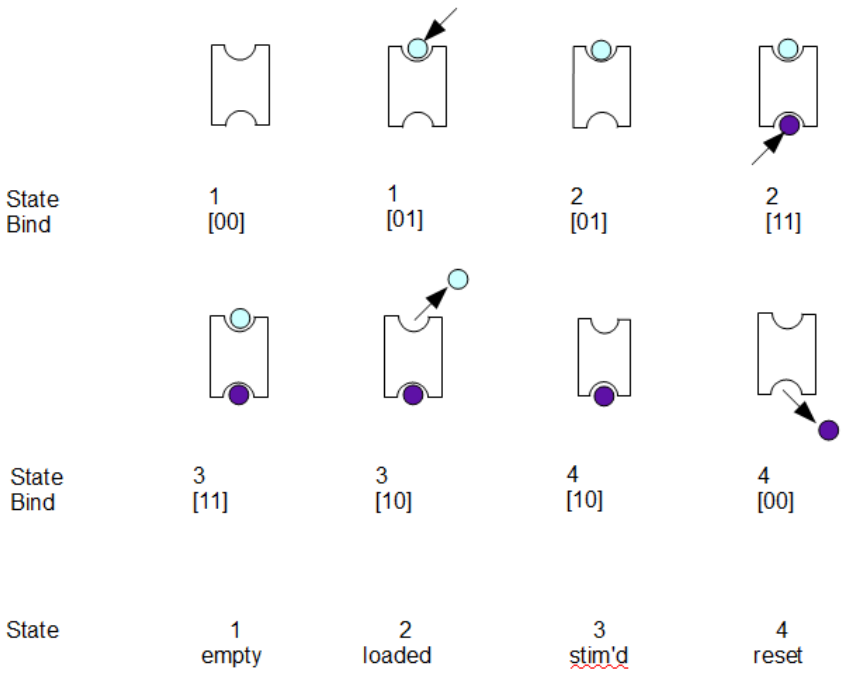


FIGURE 32: Ideal vesicle kinetics, its states and bindings

This is admittedly a great simplification of the immense complexity of the vesicular exocytotic mechanism. This representation focuses on strictly the informational events and conversions, setting aside all of the vesicle building, managing, moving, opening, and recycling mechanisms. From the information standpoint, the vesicle is a transducer with some amplification. Vesicles contain a large amount of variability, which is handled by the aff params and the functions that implement them. Some of the variable properties of vesicles include: the type of

particles within a vesicle, the number of each type of particle contained, the timing of vesicle release, and the reliability of release.

7.3.5 ION PUMPS

Pumps are proteins "floating" in the membrane, that enable the passage of ions from one compartment to another. Pumps can transport ions from a low concentration to a higher one. Pumps enable the compartments to maintain the concentrations of ions at a “resting state levels” as necessary to support multiple action potentials or graded depolarizations. There are at least 6 types of ion pumps, and a number of ligand pumps which are created for a number of utilities. The class Pump includes all co-transporters, exchangers, active transport, re-uptake, reset, and sequestration mechanisms. The energy sources include ATP dephosphorylation, concentration gradients, or “hidden” re-uptake mechanisms that are modeling shortcuts for necessary processes that are not directly information processing.

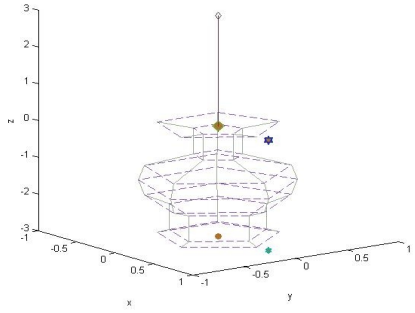


FIGURE 33: ICON FOR A PUMP, 3-D

The icons for pumps will have a 5-point circumference, and may vary in color and other parameters to visually distinguish types.

A library of Ion Pump types is maintained. Ion pumps are indispensable in many modeling queries. Firstly, they determine what the steady state is regarding tonicities. Therefore they determine the resting potential. One definition of clinical death is the cessation of ion pump activity, so critical is their contribution.

Secondly, pumps are logical devices, whenever they co-transport. Rather than merely pump one or another ion to desired levels, they force ratio-based movements, more apt to preserve the ratio between species of ion than set the absolute concentrations. Further complexity arises by the interplay of various types of pumps, each with its own idiosyncratic ratio. Tonicities can be shifted to different concentration profiles by re-weighting pump type activities. This can play a role in shifting the functional role of the cell across several "moods", by altering tonicities along viable paths to modulate the Q-matrices of ion channels (and other actors).

Thirdly, pumps fatigue, presumably due to energy shortages. This effect is certainly relevant to neuron behavior. Pump fatigue can be simulated by giving them receptors which modulate pumping rate, and causing them to become starved for ligands. Thus ligand concentration controls pump rate. If modulators alter or switch pumping curves, then ligands can alter the steady state conditions as well.

Fourthly, pump distribution can set up significant effects for information processing. A cluster of ion pumps at one end sets up an ion current down the entire length of a process. Such currents are instrumental to determining many processes such as motion detection.

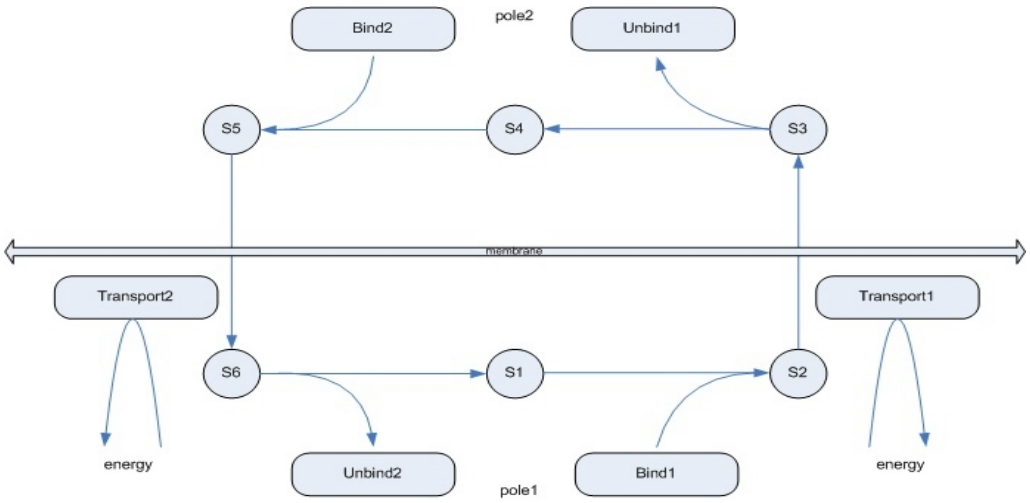


FIGURE 34: PUMP STATE DIAGRAM, UNIVERSAL

The pump state diagram above traces the state path of a Na K pump driven by ATP. Its kinetic scheme has 6 states. The lower traces from bottom to top, are: intracellular Na bindings, extracellular Na unbindings, extracellular K bindings, intracellular K unbindings, intracellular ATP bindings, intracellular ADP unbindings. Run length is for 0.5 seconds.

As the number of side chain conformations in the molecular organization of the pumps increases, the pump performance may diminish. Below is the same type of pump but with a Q matrix of "noisier" values (less deterministic).

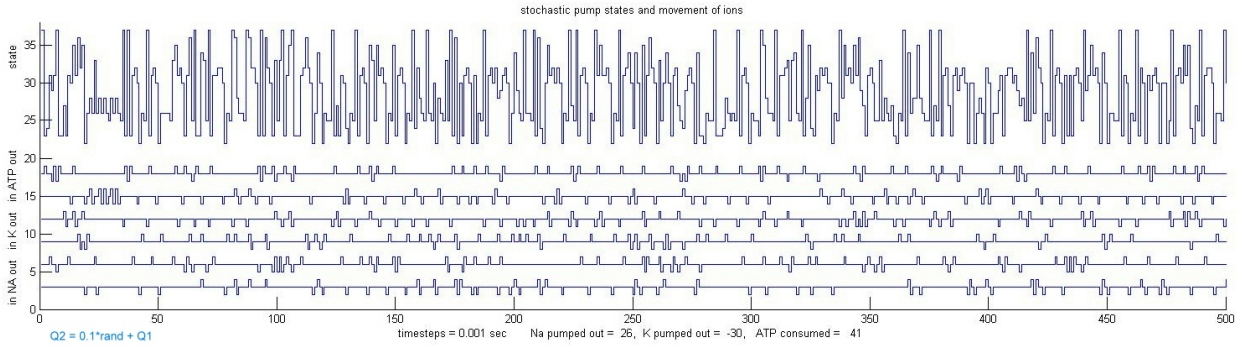


FIGURE 35: PUMP STATE TIME SERIES WITH Q MATRIX AT INCREASED NOISE LEVEL

Trace of Na K pump driven by ATP, with 5% more randomness in its Q matrix. Note the increase in flutter, and decrease in successful ion transports.

Pumps include co-transporters, exchangers and ATPases that selectively move certain ion combinations across membranes. As kinetic devices they may run backwards. Every ion that is allowed to passively cross the membrane must be pumped back in a timely fashion, so as to maintain the physiologic tonicities of life. Clinical death is defined as a loss of pump function.

Pump.Type is defined as:

1. Consist of 1subunit. When comprised of multiple components, their matrices are merged.
2. aff: One affinity profile matrix, one row for each of the binding sites
3. R: One external kinetic scheme, an (s2 x s2 x s1) matrix, where s2 = quantity of binding sites
4. Q: One internal kinetic scheme, an (s1 x s1 x s2) matrix, where s1 = quantity of internal states
5. O: One Phenostate map, which identifies which binding sites move upon which state transitions
6. One pump transport standard sequence (optional for diagnostics)

Pump.Dist is defined as:

Pumps are present in the neuron membranes in distinctly non-homogeneous patterns. These patterns are significant the to NIP function.

1. Positions + Orientations
2. Pole to Compartment map

Pump.Patho = [min max] x physiological ranges over: temperature, pH, voltage, etc.

Crossing pathological threshold trigger functions via pointers. These functions can operate on element to: inactivate, bind, sequester, convert, or otherwise tag the element as having been exposed to pathological conditions. Each type of pump is instantiated at locations according to a probability distribution function which profiles pump density along the length of the neuron, usually according to zones.

7.3.5.1.1 Re-uptake

If neurotransmitters were allowed to accumulate in the synapse, then every receptor would be completely on, and stay that way; this would not facilitate information transfer. For information to traverse the synapse, a neurotransmitter molecule must be released, diffuse across the cleft straight away, bind to an appropriate receptor type, unbind from the receptor site as soon as the receptor has triggered its mechanism to release its second messenger, get captured by a pump and returned to receptors for restaging.

Theoretically there are several ways to disable a neurotransmitter once it has bound to a receptor: It can be sequestered within a vacuole; denatured; pumped into the post synaptic cell; and/or pumped into the pre-synaptic cell. From an information point of view, placing a pump right next to the receptor, such that the angle of receptor release pops it right into the pump, would minimize the echo of allowing the neurotransmitter free to bind again to a receptor. From an energetics point of view, the presynaptic cell should pump neurotransmitters back its intracellular derivation, recycling for re-use, used to recharge vesicles in the making. This process involves another journey of diffusion back across the cleft, which raises questions: By what means is neurotransmitter prevented from returning to another receptor and giving a “ghost” signal?

If the receptor were to act enzymatically to bind the neurotransmitter to some deactivating molecule, then the complex could be left to diffuse at a leisurely pace back across the cleft. There, a pump recognizing only the complex, not the naked neurotransmitter, would return them to the presynaptic vesicle production machinery.

There is a similar problem for secondary messengers. The uncharged particles cannot partake in the voltage gradients nor the N-body charge field. Therefore, the value of each type must be informational or serve as an energy carrier. Informational particles need to effect an "on" signal (bind event) and an "off" signal (dissociation event). The "on" signal is the obvious one, but the off is a bit more subtle, requiring 2 steps: the backward kinetics for dissociation, and then a removal from the area by pumps, affinity to other bindings (sequestration), or enzymatic degradation.

7.3.5.2 Pump states

5. Idle on side 1
6. affinity on for stage1 profile
7. Staging on side 1 bindings
8. Transporting 1 to 2
9. Releasing on side 2
10. Idle on side 2
11. Staging on side 2 from stage2 profile
12. Transporting 2 to 1
13. Releasing on side 1

Note: pumps are often modulated by concentrations they are pumping against, to the point where they can be made to run backwards. The kinetics must reflect this reality.

7.3.5.3 Ideal Pump

The pump has the opportunity to bind on both sides of the membrane. Various pumps, cotransporters and exchangers may bind 0 to 3 particles on one side, and unbind them on the other side. The cartoon below shows these bind groups each as a single particle on each side of the membrane.

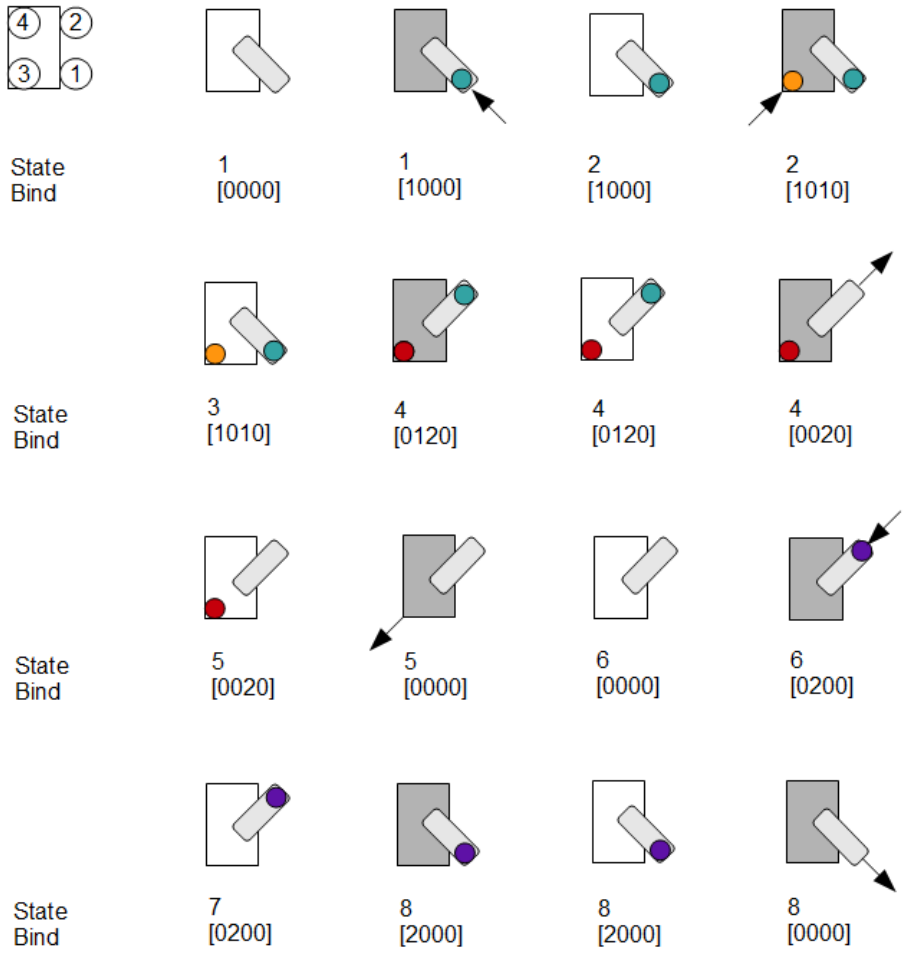


FIGURE 36: Ideal Pump, States and Bindings

The interpretation of the 4 values of the bind vector is assisted by the key in the upper left corner. The primary challenge of modeling pumps is to seize control of individual ions, particular to type, and physically move them through the membrane to the other side. Once on the other side the binding rules are changed such that some different ion will bind on side 2 and be precisely moved across to side 1 and released. This seemingly simple motion has consequences for the model. First, mass is conserved only when a precise number of a precise type is subtracted from 1 compartment and added to an adjacent compartment. This requires Cartesian reassignments from pole to pole, and compartment reassignments for each of the particles. Second, ion charge alters the space charge neutrality of each of the two compartments. Third, pumps can only run "up stream" (against the energy gradient)

when there is an immediately available source of "boost" energy. This source can be chemical, as with ATP to ADP conversion, electrical, as with a voltage gradient, or "mechanical" where the concentration gradient of one ion type is great enough to push the pump in a direction that pumps another particle type uphill against its gradient. The change in color at bind site 3 indicates a conversion from ATP to ADP.

In the simplest kinetic case, the internal conformations only reflect the external conditions of bindings and arm positions. Given the immense size of the pump molecules, it is quite possible that there are more internal states than those external events depicted. Such supernumerary states offer alternative state paths, modulation and modalities of operation. They also offer the possibility of regulation and compensation for external conditions. The number of modulator sites on an actor is some indicator of such possibilities. Few modulation sites would limit the pump's responsiveness.

7.4 INTERACTORS

Interactors are motile particles. They may be charged (ions) or uncharged (ligands). They may be a) mobile within a compartment, or b) temporarily bound to an actor. They may be sequestered into small compartments (vesicles or core reticulum). Their primary roles include:

1. communicate between actors, via diffusion and/or waves (thermal energy or EM force)
2. serve as charge carriers, determining voltage and capacitated charge
3. pass through open pores per gradient pressures, causing current disturbances
4. serve as messengers, being released from certain actor types and binding to certain actor types

Their secondary roles include:

1. setting up delicate capacitated pools that disturb easily and therefore are efficient wave generators
2. forming waves fronts that may propagate along the surface of the membrane
3. convolving their motion with the actor responses, which modify that motion
4. resolving multiple waves into constructive/destructive composite waves that serve as analog computation
5. effecting the gradual decay of all waves into back ground noise, so as to provide substrate for future waves

7.4.1 INTERACTOR CLASSES

There are 5 classes of Interactors:

1. Water
2. Monatomic Ions
3. Polyatomic Ions
4. Ligands
5. Second Messengers

For most purposes, Monatomic and Polyatomic Ions can be merged into a single group. Only when shape factors are a consideration need they be processed separately. Note the water hydration shells move monatomic ions into the polyatomic category. Hydration shells are dynamically built up and torn down.

7.4.1.1 Water

Water is represented as a statistical phenomena of mean free paths, interrupted by collisions with other water molecules, ions, and surfaces. Its velocities are Boltzmann distributed per its temperature and viscosity. Particles proceed in random walks. The charge effects of water smear the charge effects of ions. Water has thermal mass, constructs hydration shells of varying thicknesses around ions (easily stripped off by collisions). Water molecules have an effective radius, are soluble to ions, conduct electricity proportionate to the ion concentration, and are the primary determinant of diffusion rates of ions. In liquid state, the density is nearly constant (varying a little with temperature) and therefore the inter-molecular spacing can be treated as constant.

The most redundant of all entities in the neuron is water. What might be the NIP contribution of water? It is a medium and carrier for information, just as a copper wire might be for the telephone messages. It is an electrical conductor proportionate to the ion concentrations, acting as solutes. Aside from determining the pH and the viscosity, it is difficult to argue that water is acting in the role of information processing. Its charge “smear” effect is losing information, and diffusion in general loses information. Much more consistent with its traits, it provides a matrix which mobilizes the ions to perform their roles. It provides a pool of ions, neutralized by opposing charges. But whenever there is a voltage gradient or a charge imbalance, a proportionate number of charges come out of solution. So long as these mobility factors are preserved, the quantity of water molecules in a neuron may be

reduced in number, reduced in function and/or abstracted, just so long as maintaining ion mean free path lengths, ion collisions that redirect ion velocities, and ion solvation sizes.

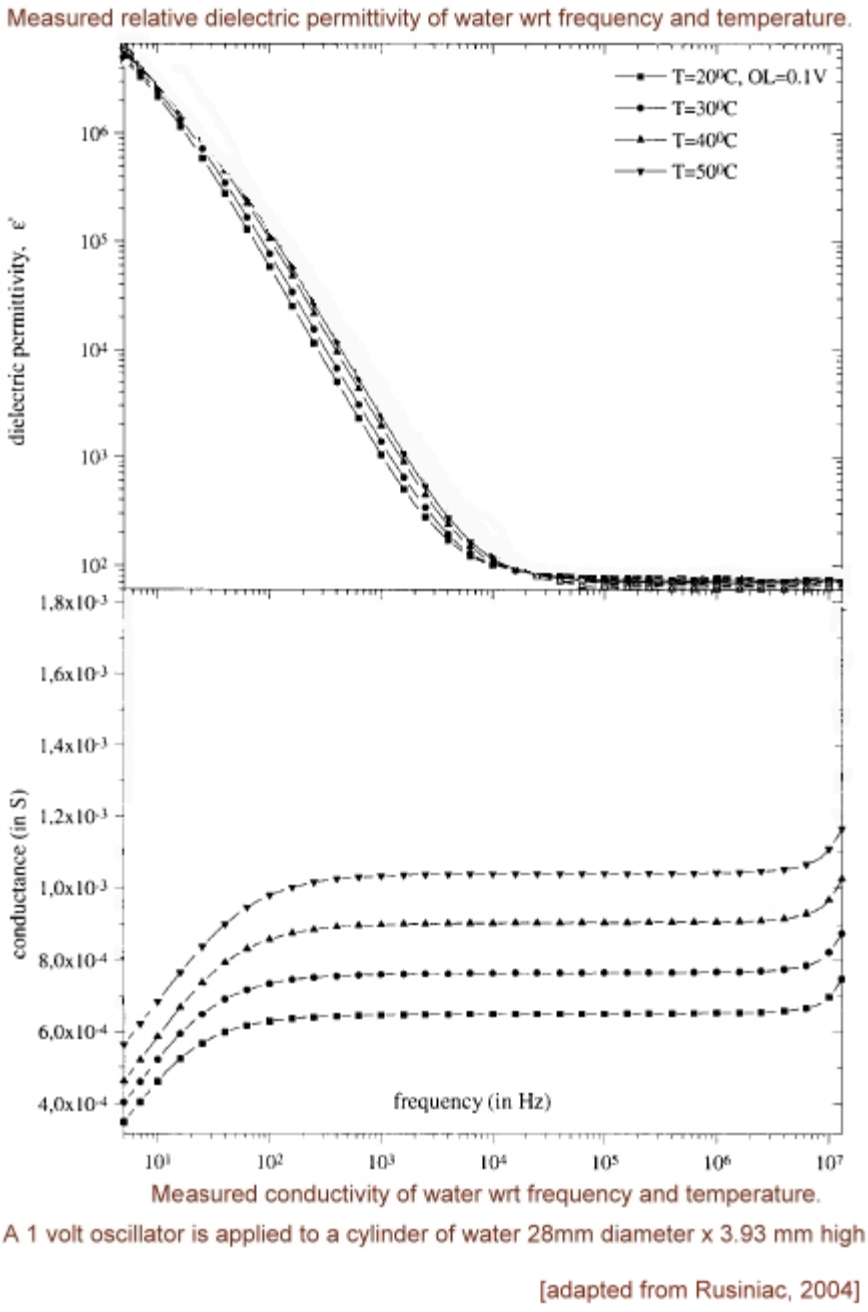


FIGURE 37: Conductivity of Water wrt Frequency

Although pure water is an outstanding insulator, very small amounts of salt render it a great conductor. Measurements of conductivity reveal it proportional to the ion quantity, as every ion is a charge carrier and is capacity limited by that ions mobility. However, as the frequency of the signal increases, mobility becomes less of a

factor. See the figure above, from Rusiniac, 2004, which reveals the variability of conductivity wrt frequency and temperature. A particle system needs a variable mobility to duplicate these results. It is not easy to know the "frequency" of individual ionic collisions, unless their is coherence due to a strong driving signal.

It turns out the conductivity of water is quite sensitive to frequency. (see Rusiniak below) One can see that if the conductivity of water were the primary determinant of inter-actor communication life would be a lot warmer (90C?) and would restrict all actions to below 100Hz. While these curves have implications for liquid state processor design, the range of conductance varies only about ½ order of magnitude wrt temperature and much less wrt frequency. The dielectric permittivity varies widely, almost 4 orders of magnitude, wrt frequency, but is not temperature sensitive. As many neurons are operating at about 30C and frequencies between 100 Hz and 1000 Hz, conductance is low (7e-4 Siemens/test cylinder) but stable. The effects of the EM force are surprisingly variable. At 10 Hz, εr = 1e6; while at 1000 Hz, it is down to 1e3. This effect acts as a high frequency filter, and higher energy efficiency would be achievable at the lower frequencies.

7.4.2 IONS

Ions are represented as individual particles, present in any number of types, in quantities up to about 1E6 for PC computers, or as large scale computer capacity may allow.

Not only is the quantity of water molecules super abundant to the needs of a whole cell model, so too are the quantities of ions. The number of ions in a model may be reduced to minimal sufficiency as determined by performance within range of acceptable error. Because of the complex and nonlinear nature of neuronal behavior, the easiest method of determining sufficiency is to run the model as test patches while sweeping a gamut of particle densities and recording sensitivity to changes. Particular care must be exercised near the boundaries of modal shifts (e.g. from periodic spikes to bursts of spikes). Indeed one of the objectives of the model that can help our understanding of NIP phenomena would be to identify minima in element quantities that preserve the bio-computation functions of the cell. Sampling theory may be applied to the challenge of element count reduction if the dimensionality of the problem is not under-estimated. For normally distributed values, 30 samples per dimension yields.

The quantities of ions in solution may be reduced to the extent that many of them are sufficiently distant to the membrane functions as to be insignificant. If they are serving as “reserve capacity” or “buffer”, then they are not NIP active. Short of compromising axial and/or circumferential flux, their numbers may be reduced. At the risk of some graininess, the numbers of ions may be reduced proportionate to the numbers of ion channels and pumps. Before deciding on a reduction number, the quantity of ions that flow through a channel per millisecond of channel open time must be considered. If this number is, say, 1E3 to 1E7, then couldn't that number be scaled down by one or two orders of magnitude? Only if the capacitance were also scaled down, so as to preserve the resultant transmembrane voltage, and only if the speed of ions through the channel were proportionately slower, so it takes the same amount of time to generate an action potential. Scaling back the quantities of the elements is not trivial, but must be thoughtfully designed to preserve the NIP characteristics, in time and space. Similarly, the quantities of receptors, channels, vesicles and pumps may be reduced short of misrepresenting the information throughput function of the cell.

7.4.2.1.1 Monatomic Ions

From the periodic table there are about 64 possible ions that could conceivably be found in biologic systems. Several of the elements can be found in more than one ionic form (different charges). Each element has these traits: radius, mass, and charge. Monatomic Ions are the dominant movers in neuronal information processing. Their action is predominantly a function of their charge. The flux of ions, (especially of K, Na, Ca, Cl), is sufficient to create high voltages (consider the electric eel). Ion concentrations are built up and maintained via the pumps, and their occasional flux through channels results in cascades of events that usually result in chain reactions that carry down the entire length of the neuron. Each ion has its own mass, charge, velocity, and position. Ion concentration is the quantity of ions, by type, in a voxel.

7.4.2.1.2 Polyatomic Ion

Polyatomic ions are numerous in quantity of types, and are irregular in shape. They usually have rotational bonds that allow some change in shape, and their stereo-isomers may be significantly different in action. Therefore, the traits include mass, charge, size and conformer. The conformation of a polyatomic ion is regarded as static. They must be treated slightly differently because they do not have a radius, and may have multiple binding configurations. They are treated separately only to tabulate these additional traits. Ion2 species are not merged with the larger Ligands because their action is predominantly a function of their charge and chemistry.

7.4.2.2 Intracellular proteins

Intracellular proteins may serve any of several functions: obstacles, viscosity, buffering, bind/release sites, sequestration, chemical transformation, shuttle, scaffolding and rafting. Other functions are not considered by this model. Proteins, in general are modeled with mass, a single net charge valance, and an equivalent radius that would calculate to realistic viscosity and collision values.

7.4.2.2.1 Second messengers

Metabotropic receptors will release messenger molecules into the intracellular compartment. These G-proteins usually participate in leveraging mechanism which involve intermediate catalytic production and removal systems. Numerous Ion channels (and other actor types) may be modulated by the stimulation of a single receptor, up to about 1:30000 fan out. For modeling purposes, any molecule that can allosterically bind to an actor on the intracellular pole may be considered a messenger molecule, or ligand.

Second messengers work by multiple mechanisms. For example, and initial 2-dimensional diffusion of second messengers from the receptor reach catalytic intermediate nodes which release third messengers diffusing 3-dimensionally. The second messenger may have one group of targets and the third messenger quite a different group. The second messenger may be leveraged 1:100 and the third messenger may be leveraged wrt to the receptor 1:10000.

The library of Interactors in this model consists of three Types:

```
Interactors = { Ions  Ligands }
Ions = { K Na Cl Ca H An ... }
Ligands = { Ach Ne Gaba Glu 5HT ATP GLY ... }
```

7.4.2.2.2 Obstructions

The intracellular space is populated with protein structures, both static and dynamic. These will impede the diffusion and drift of the smaller particles. To the extent that this effect is isotropic, then arbitrarily large motile protein molecules can be introduced into the compartment. Their mass will render them slow moving according to Boltzmann's velocity distribution. Their size with increase the collision rates and therefore slow both diffusion and drift of the charged particles. However, anisotropic effects may require the addition of vanes protruding into compartments to direct flows. Vanes may be installed with various perforations as well. These can imitate in simple form some of the effects of reticuli and structural proteins.

7.4.2.3 Extracellular proteins

Extracellular fluid may contain motile proteins, which contribute to general viscosity. They may also serve as Ligands needed for specific messenger duty. Additionally, glycosylation of channels and pumps may serve as modifiers to their Q matrices. Extracellular protein particles may be created and simulated by the same means as intracellular particles. The outermost experimental membrane may be made active in the release and the reuptake of those proteins so as to maintain tonicity or messenger traffic as needed.

7.4.2.3.1 Ligands

Ligands are medium-sized soluble molecules which serve as messengers between Actors. They bind reversibly. Their action is predominantly a function of their shape. Ligands are released by a variety of mechanisms and bind to Receptors for a short time. Such bindings act as signals, inhibitors, activators, neurotransmitters which cause the Actor to change state. The binding and unbinding of the Ligand to a Receptor may be handled mathematically as a forward and backward Kolmogorov process.

Ligands, for purposes of this model, are uncharged particles. A ligand is defined as any molecule that can modulate ion channels or ion pumps via binding/unbinding, including all neurotransmitters, hormones and messengers. For purposes of modeling a ligand is the same as polyatomic ion, except with charge = 0.

7.4.2.3.2 Neurotransmitters

Many of the ligands in the extracellular compartment and in the synaptic clefts are called neurotransmitters. For modeling purposes, any molecule that can allosterically bind to an actor on the extracellular pole may be considered a messenger molecule, or ligand. A particle without charge diffuses via a Boltzmann distribution of velocities in spherically-random directions, colliding with other particles and and reflecting off surfaces. For each dt, any ligands within the affinity radius of an actor pole will be considered for binding/unbinding per the binding profile.

Neurotransmitters are particles, that can act as ligands. They may or may not have any net charge. Their primary function is to modulate actors, although they also perform many longer term functions not represented in this NIP model. Modulators, by the act of binding, introduce new stresses into the actor molecule, and thus change its conformation. This shifting, bending, and moving of molecular parts is often instrumental to the actor's role. Most often, the binding of a modulator does not directly change the actor's phenostate, as would say turning on a light switch result in instant light. Rather, modulator bindings create a new set of probabilities, that determine whether

the molecule will arrive at some new phenostate. Its rather like asking a bureaucracy to turn on the light. “Your request will be passed along through several desks. We hope to have it on by Wednesday.”

In similar fashion, voltage works as a modulator. Voltage as an omnipresent force field has the advantage of affecting an entire molecule thoroughly and instantly b exerting torsion on every charge in the molecule.[181] Such force will still require time for the molecule to find its new equilibrium (lowest energy state), and this will still follow a Q matrix of transition probabilities.

7.4.3 PARTICLE STATES

Particles may be simple, with only size, mass and charge, but tracking them through a digital model requires a great number of values, nearing 100 columns of data per particle. The basics to get started are:

1. Compartment number assigned to
2. Actor number bound to
3. position, velocity, acceleration
4. Voxel number passing through
5. Capacitance pixel number captured within

In addition, there are some historical aspects of particles that must be tracked in digital models. For example, when a particle is bond to an actor, it loses its momentum. To avoid violating the conservation of momentum law. This momentum is stared as a value, and returned to the particle upon its release.

Concerning particle collision detection and resolution, there are test cases that require additional data, including backing up in time to before the collision took place. These will be treated more formally in subsequent chapters.

7.4.4 PARTICLE BUILD

TypeB.mat is the Library data set for all Particle Type archival information. Within the data package of TypeB is the main traits file TB, which list all particle types by row and 32 traits by columns. The user selects from TB which particle types are relevant to a given experiment. These need not be all used. For, example, if Mg is selected, the

concentration of Mg in a given compartment could be specified as zero. The particles selected are usually specified as concentrations.

BT					Concs	
					comp1	comp2
Type	a.n.	mass	valance	radius	conc mM	conc mM
Na	11	23	1	0.28	12	145
Mg	12	24.3	2	0.24	0	0
Cl	17	35.45	-1	0.21	4	110
K	19	39.1	1	0.3	140	5
Ca	20	40.08	2	0.28	0.02	3.5
PO4	49	95	-3	0.81	0.1	0
SO4	50	96	-2	0.8	4	0
An2	256	256	-1	1.5	141.13	46.49

Only 4 columns of the 32 traits in BT are shown here. The Concs are converted to particle counts in each compartment in preparation for use in the model

Dens: From the molar concentrations, calculate the quantity of particles per cu micron.

BC: Multiply those density numbers by the volume to be modeled (in the EX the volume is 0.001 cu microns)

N: Multiply the quantities by the scaling factor to reduce particle counts (in the EX this is a 100-fold reduction)

Dens		BC		N	
60230	N/cumicron	0.0010	N/0.1micron^3	100	sfN
722760	8733350	723	8733	7	87
0	0	0	0	0	0
240920	6625300	241	6625	2	66
8432200	301150	8432	301	84	3
903.45	210805	1	211	0	2
6023	0	6	0	0	0
240920	0	241	0	2	0
8500000	2800000	8500	2800	85	28
				180	186

This brings us down to 7+84+84 = 175 particles in compartment 1, and 186 in compartment 2. Next, the charge imbalance is checked. For the valances given in BT, the charges are summed per compartment.

At initial conditions, in this EX, there is space charge neutrality in each of the compartments. Any manner of transport, by pumps or channels, can alter the charge imbalance near the membrane however. This results in a capacitated surplus charge near the membrane between the affected compartments. Initial conditions require a

membrane with a charge resulting from ion imbalance within physiological range. This is called the resting potential, and actors should not be turned on until this potential is established, least the conformations be denatured.

	E	charge	
Na	7	87	
Mg	0	0	
Cl	-2	-66	
K	84	3	
Ca	0	4	
PO4	0	0	
SO4	-4	0	
An2	-85	-28	
	0	0	Charge neutral

E	charge	
7	87	
0	0	
-2	-66	
84	3	
0	4	
0	0	
-4	0	
-113	0	
-28	28	Charged

membrane

The left set of values initialize the model with space charge neutrality. Any pump or ion channel activity will unbalance the charges and result in some capacitated charge across the membrane that separates the two compartments. The second set of values initials the model with a charged membrane. Given a set of empirical data to hold to, only the residual values of An (a catch-all for unspecified negative ions) is adjusted. This adjustment is necessary, however, to avoid physically impossible or unrealistic conditions of charge imbalance.

This count of particles is introduced into each compartment near the center of the volume as a bolus. A bolus is a spherical cluster of randomly placed, non-overlapping, mixed types. The bolus is usually a fraction of the volume, from 90% down to 1% of the compartment volume, depending on the intricacies of shape.

7.5 COMPARTMENTS

Compartments are created by membranes formed into closed surface vessels. One membrane may be nested within another membrane. The membranes define the both the surface and volume of each compartment.
Typically, the following membranes are created for a single neuron simulation:

7.5.1.1 Plasma lemma

A closed-surface delineating the shape of a neuron, or a simplified version thereof

7.5.1.2 Neighboring neuron

The plasma lemmas of adjacent neurons may be represented as a compartment so shaped as to hold a realistic thickness for the extracellular fluids. This is the outermost surface of the whole cell model It is a closed surface.

7.5.1.3 Core (nuclear) membrane

The core is a central compartment within the soma for purposes of sequestration, re-uptake,etc.. It also serves to obstruct most of the center of the soma, so as to disallow diffusion straight across the center of the cell. Due to the presence of the nucleus and reticulum, most ionic diffusion is near the plasma lemma and circumferential in direction, and the core compartment helps to enforce this pattern. Finally, the core membrane reduces the volume of the cytoplasmic fluid to be modeled, reducing computational load.

7.5.1.4 Dendritic synaptic plugs

Dendritic plugs are simplified synapses which provide synaptic clefts and neurotransmitter release sites (vesicles), and sometimes re-uptake pumps. When the whole cell model is the subject of study, it is often necessary to provide realistic inputs to the cell. Most wet lab work stimulates electrically or pharmacologically, but computer models support the representations of synapses and neurotransmitters so as to correspond to bio-functions of same. The dendritic plug is a simulation of the pre-synaptic bouton (without the rest of the cell). It is driven by a signal generator, or by a pre-recorded temporal pattern. A set of such patterns can drive any number of dendritic plugs, and thus represent a spatiotemporal pattern. Plugs can be placed on any planar surface of the cell.

7.5.1.5 Axonal synaptic plugs

Axonal plugs provide signal detection for received neurotransmitter molecules as output from the neuron (receptors), and may also possess re-uptake pumps. They represent the synaptic cleft and the post synaptic membrane, and as such reveal the lag time and noise of the synapse. They may be parametrically modified.

7.5.2 MEMBRANES

The membrane is a uniform curvi-planar structure of lipid material that forms closed surfaces which define the compartments, their shapes and volumes. The membrane supports within it important proteins such as channels,

pumps, and receptors that enable the neuron to act as an information processing system. The membrane may reflect ions, or absorb them, according to beta partition factors. The membrane is considered to be an Actor because it serves as a capacitor, a dynamic element. Membranes have important 2-dimensional properties (e.g. addresses for actors); 3-dimensional properties (e.g. reflections of particles); and important abstract properties (e.g. Resistance Capacitance grid).

7.5.2.1 Membrane Traits

Membrane.Type is defined as:

1. Contour working points. These are for design convenience, and library portability. They constitute the minimum data to generate a closed volume as a contour of revolution.

2. PDC = zone designations along axial length of neuron per a given shape (C compartment).

1. Intracellular This is the main plasma lemma of the cell. There is one per cell in a multicell model.

2. Extracellular This is the outermost membrane in the experimental setup. It represents the boundary of extracellular fluid, and therefore determines the thickness of the extracellular fluid.

3. Sequestration core This is roughly the nucleus of the cell but serves the model in a different capacity: to determine the thickness of the intracellular fluid to be modeled as a thickness below the membrane, and as a compartment of sequestration for particles rendered temporarily "out of circulation".

4. Input Synapses The synaptic clefts are of regulated gap distances, and of limited "leakage" at the edge of the synapse. The post synaptic membrane is one or more circumscribed areas on the plasma lemma that typically are rich in receptors appropriate to the vesicle content releases across the gap on the pre-synaptic cell.

5. Output Synapses Each synapse consists of a pre-synaptic membrane, and fluid gap of fixed distance, and a post synaptic membrane. Particles may be exchanged both ways, depending upon the placement of actors of release and actors of uptake. As receptors are not known to recycle messenger particles, there must be present a third type of actor which "cleans up" the cleft at rates comparable to the release rates. The output synapse is structurally the same as the input synapse, but is not always necessary. This is because voltage readings can be taken from the model membrane near the output pole(s) and this would yield an accurate signal of cell production, that the addition of an output synapse is unlikely to alter much, unless specific maladies of the vesicles were under study.

7.5.2.2 Membranes present in Whole Cell Model

7.5.2.2.1 Plasma lemma main region of computation

7.5.2.2.2 Core serves only as a parking lot

7.5.2.2.3 Neighbor sets up the connectivity of the neuron under study and therefore the many signals

7.5.2.2.4 Pre-synaptic vesicle releases and neurotransmitter reuptake, followed by vesicle reconstruction

7.5.2.2.5 Post-synaptic cell input reception

7.5.2.3 Membrane Hierarchy of Spatial Relationships

7.5.2.3.1 Membranes

7.5.2.3.2 Zones these are functional areas somewhat arbitrarily defined by human observers

7.5.2.3.3 Segments these are strictly conveniences of geometric construction of contours of revolution

7.5.2.3.4 Rings come into being as a contour is rotated. A ring is populated with nodes for homogeneity

7.5.2.3.5 Nodes the addressable points for actors to be populated per the pdf's

7.5.2.3.6 Occupancies instantiation of actors results in certain nodes to be occupied

7.5.2.3.7 Assemblies actor groups - some actors must act in concert and maintain fixed distances between them

7.5.3 SYNAPSES

Synapses are specialized zones of membrane, characterized by their facing a mating surface of a neighboring cell. Synapses are zones. The distributions within any one zone are uniquely characterized, independent of any other zone type.

The peculiar distribution of channel types about the bifurcations of dendrites determine the degree of antidromic propagation.[182] Some dendritic channel constellations serve to compensate from geometrical factors like dendritic diameter, to grant the smaller dendrites a near equal effect on signal contribution. This is sometimes referred to as “synaptic democracy”.

7.5.3.1 Cleft

Synapses are defined structurally in that the cleft is held as a fixed distance, thus ensuring a constant diffusion time across it. Synapses may form separate compartments, such that neurotransmitter molecules cannot leak out the edges into the general extracellular fluid. The decision must be made as to cleft perimeter porosity. If messenger

particles are allowed to drift outside the cleft, then appropriate reuptake mechanisms may become necessary in locations remote to synapses. If the cleft perimeter is closed, then all synaptic activities are isolated from the greater extracellular fluid.

7.6 SHAPE SIMPLIFICATIONS

The subset of neurophysiology that applies to this modeling effort is constrained in scope by the following:

1. Only the membrane, its embedded proteins, and the adjacent ionic solutions are modeled. Other cytological structures are not included, except as shape-wise obstructions to diffusion and conductivity, or as compartments for sequestration of ions.
2. Only those processes directly implicated in the information processing role of the neuron are included.
3. To model a neuron at nanometer scale poses computational difficulties unless a reduction in the number of Patches (and processing steps) can be justified and effected without loss of veracity and reliability. Therefore multiscaling is employed. Nanoscale patches of membrane are modeled 1-to-1 wrt ions, channels and distance.
4. Once characterized and verified to the biologic literature, patches may be cloned and collapsed from a system of equations to data mappings, for use in large scale tiling over closed membranes at the micron scale, to effect whole-cell models.
5. Only those processes taking place on timescales near to that of the action potential are considered. Typically events between 1E-4 and 1E-1 seconds are included. Nanosecond vibrations, and 28 day learning cycles are far out of scope. It is possible to have the Patch sub-models and the whole-cell Goblet sub-model calculating at different time resolutions.

7.6.1.1 Shape factors

The inclusion of shape was first made necessary by the inclusion of raw diffusion process represented as a set of particles with random positions and initial velocities determined by Boltzmann's velocity distribution equation. Of the essence are the boundaries that determine reflections, and the flux routes between sources and sinks. This cannot be realized without a representative mapping of shape and its bifurcations. A great deal of effort was expended on what, if any, shape simplifications might be justified. It was eventually decided that up to some point of spatial complexity, a neuron might be "flattened" to a 2-dimensional projection and still perform quite close to how it did in its original 3-dimensional shape. Once flattened, the whereabouts of the neuron membranes must be computed for purposes of particle reflections.

Modeling only the information processing of neurons, it is presumed that most representations would have a minimum of a dendritic arborization, a soma and an axon, as its functional sections. Various trials led to the following generic shape for modeling purposes.

There is a second implication of shape, perhaps more determinant than even the consequences of routing ionic flux. And that is the "nearest neighbor" relationships between the ion channels. Obviously, beyond any bifurcation point, ion channels on different branches rapidly become "uncoupled" from each other, and this fact has great weight in determining the temporal behavior of the actors. Replace such bifurcations with a continuous "sheet" and the systemic dynamics will be something all together different. Thus the agony between the computational impossibility of preserving the natural shape of living neurons and the loss of bifurcation data when employing a contour of revolution. The modeling strategy is to begin with the simplest of shape and work toward biological veracity as the availability of supercomputers may allow.

Although there must be considered both the volumetric effects of flux and the surface effects of actor nearest neighbors, these two present in parallel fashion, as something of a sandwich. It should therefore be possible to take them as a single "pattern" or fabric (mathematically) which needs only be represented in 3-D in the micro-perspective, and as planar in the nano-perspective.

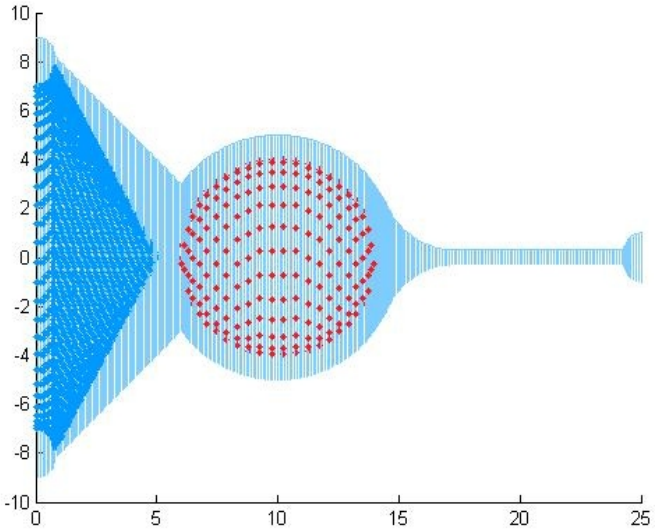


FIGURE 38: WHOLE CELL WITH CORE COMPARTMENT

7.6.1.2 Shape smoothing

It is advisable to begin a complex model in its utmost simplest rendition, and gradually work towards fuller detail. Original bio-shapes can be smoothed repeatedly, until the series yields a result but a mere cartoon of its original self. What is lost in such an exercise is the spatial high frequencies. What purposes might the high frequency spatial data serve? The development cycle of a model would employ this series of smoothings in reverse order. Because the dimensionality of parametric space is so large, and the dangers of A2D so very unpredictable in the highly nonlinear space of action potentials, there is considerable verification work to be done along the path to a useful membrane texture in the model. Teasing apart all the possible opportunities for misrepresentation, and therefore erroneous results, in a large scale model can be reasonably said to be impossible. A superior approach is to verify "developmentally", over a process of gradually adding complexity, both quantitatively and qualitatively. Such an approach serves the additional interest of finding points of diminishing returns on computational load for each added feature. The goal is to find necessary and sufficient models that consistently and accurately predict cellular information processing. The suspicion is that there will be very little of the living cell found to be dispensable, and therefore that modeling complexity will continue to grow for some time.

7.6.2 COMPARTMENT PRIMITIVE SHAPES:

7.6.2.1 Box

The cuboidal compartment shapes are used for patch models. Typically one above and one below a surface of membrane.

7.6.2.2 Cone

Conical compartments are often used to mimic dendritic arborizations. Cones may be made hollow by subtraction of a second smaller intersecting cone. Cones may also be bifurcated via vanes (see below).

7.6.2.3 Cylinder

Cylindrical compartments are often used to mimic axons. A series of cylinders may imitate the nodes of Ranvier. Hollow cylinders may imitate myelin.

7.6.2.4 Disk

Disks are planar surfaces suitable for synaptic connections. Typically there are dendritic disks and axonal disks. A larger disk minus a smaller disk creates a planar ring which may be positioned anywhere along the length of the neuronal shape, so as to receive inputs and/or transmit outputs. The subtraction of a disk equals a perforation.

7.6.2.5 Sphere

A spherical compartment may be used to mimic the soma. It can also be used to imitate spherical-shaped dendritic arbors. Spheres may be truncated any where perpendicular to the long axis of the neuron. The offset soma of the bipolar cells does not quite lend itself to generation via contour of revolution.

7.6.2.6 Torus

Torus shaped compartments are typically used truncated to help form synaptic boutons. They may also be used to create toroidal shaped dendritic fields. The various quadrants can be specified so as to fit as fillets and bulbs.

7.6.2.7 Vanes

Vanes radially section any other shape so as to mimic arborizations. Various bifurcation patterns, including randomized patterns are possible so as to imitate the tapered cross sectional areas of dendrites.

7.6.2.8 Perforations

Any shape above may be perforated so as to juxtapose any two shapes together with a continuous interior of specified area at the interface. The union of two shapes requires the perforation shape at their common border. Typically perforations are not used as leaks to the exterior, as that would kill the cell.

7.6.3 COMPARTMENT SURFACE DETECTION

Ceiling and Floor detection of each compartment

7.6.3.1 Zones

Zones are provided as markers along the length of the neuron, arbitrarily set, both quantity and location. When actor distribution data is provided it may be assigned on a zone-by-zone basis, such that the PDF is stretched to fit the model zones. This makes automatic the mapping of actor distributions onto a wide variety of shapes. Section 7.8 below addresses zones in greater detail.

7.6.3.2 Radial symmetry

Irregular shapes consume inordinate processing time to determine particle-membrane collisions. At the risk of some veracity, shapes are simplified such that membrane collisions and absorptions can be computed efficiently. This is the single greatest numerical methods benefit within the model. The employment of contours of revolution into cylindrical shapes allows *en bloc* Cartesian to polar coordinates conversions to determine membrane collisions. Cylinder shapes generated via contour of rotation yield cylindrical coordinates.

x	axis of rotation	(as length of neuron)
y	meridians	(radius)
z	circles of latitude	(circumference)

Transformations between Cartesian coordinates other coordinate systems may be orientation-preserving, and/or distance preserving. An axis is a directed line, and so reorienting various elements can be accomplished as a vector transform, without the use of sines and cosines.

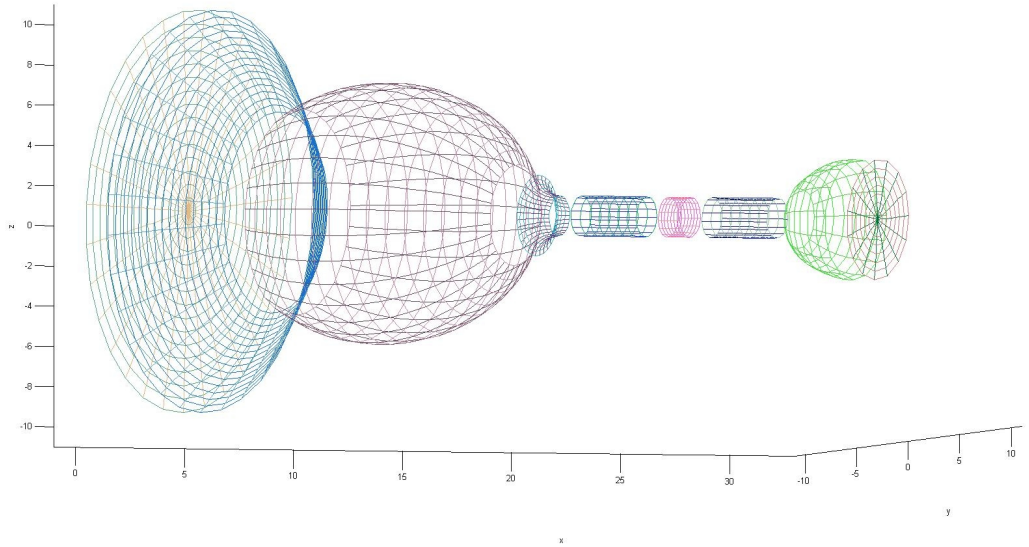


FIGURE 39: WIRE FRAME OF WHOLE CELL

Morphometric data is available to capture quite accurate shapes of neurons. However, to digitally implement a dynamic model of such shapes is beyond the capabilities of current computers. I have agonized over shape simplification for several years, with an eye towards optimizing between essential neuronal topology and computational tractability. How can the behaviors of the various functional zones of neurons survive changes in shape?

7.6.4 DENDRITIC ARBORIZATION

It is anticipated that eventual demands for greater veracity to the shape and functioning of the dendritic field will cause a severing of the goblet into 2 parts. The dendritic cone will be replaced by a dendritic arborization according to characteristic branching and taper patterns. An efficient algorithm for interactively computing the dynamics of such an arrangement is not yet worked out. The soma and axon will remain as they were, because as coaxial concentric shapes, they are computationally less costly.

7.6.5 VESICLE SIMPLIFICATION

The complexities of vesicular release mechanisms rival that of the entire cell. They have a membrane, compartments channels pumps, receptors, structures, messenger systems, complex opening and closing mechanisms, enzymes, recycling mechanisms and more. But true to the original mandate of purging all but informational relevant phenomena, the vesicle shall be greatly simplified, down to something like a receptor. It need only have an input binding kinetics, and output release kinetics that mimic the natural time course of events. Re-uptake and vesicle recycling will only be represented by a pump.

7.6.6 INPUT-OUTPUT SIMPLIFICATIONS

The essential mechanism of the synapse includes 2 membranes of fixed distance between them, and the gap filled with saline, often at extracellular tonicity. The presynaptic membrane releases vesicular contents into the gap, and has re-uptake mechanisms to recover those contents after they have served their messenger service. The contents diffuse across the gap, perhaps motivated by a charge field, and may bind to receptors on the post-synaptic membrane. There is also the possibility of feedback. Plugs have been devised to provide arbitrary input at various locations, and to receive output at arbitrary locations.

7.6.7 OMITTED COMPONENTS AND THEIR COMPENSATIONS

The cell interior is not a simple saline solution, but is chemically and structurally complex. It is comprised of membranes, vesicles, a wide variety of protein objects, structured means of transport, and free roaming moieties. This immense complexity is relevant to this model in three ways:

1. major obstructions, which can be modeled as “core” compartments: nucleus, endoplasmic reticulum, micro-tubules, etc.
2. binding/release sites, such as calcium chelation and buffering, which can be modeled as binding sites and/or by pumping into sequestration.
3. minor obstructions, which can be modeled as increased viscosity. Protein cyto-structure delays the diffusion process by forcing molecules to randomly “walk” around obstructions.
4. recycling of membrane and vesicle contents is immensely complicated in the living cell. These processes can be simplified into a release packet, reuptake pumps, and restaging of contents for the next release. Timing and variations on each are NIP relevant, but the how they are performed may not be relevant.

7.7 WHOLE CELL

A neuron of 10 microns diameter soma and 10 processes of 100 micron length must have a volume of at least 2333*pi Micron^3, and an area of at least: 1110*pi Micron^2. 10 processes is a very simple case, with bio-neurons easily sporting 1000 processes, to say nothing of the complexities of bifurcations and tapers. The surface area expands proportionately (100-fold), although the volume may not go up significantly. Thus, dendritic trees increase the chan to ion ratio.

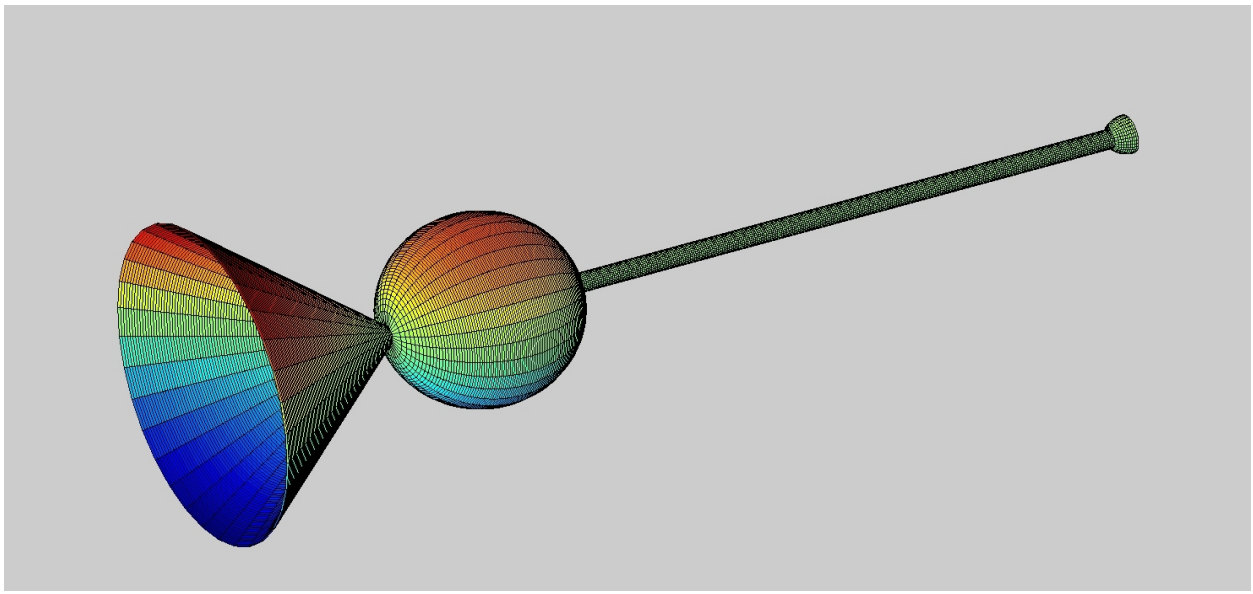


FIGURE 40: FIRST CAD RENDITION OF THE WHOLE CELL

Conventional computer graphics produces widely varying size pixels, which are unsuitable for mapping Probability Density Functions onto. And also unsuitable for manifolding from 3-d to 2-d surfaces.

The volume of a neuron is often greater than 5000 Micron^3. To which must be added an extracellular compartment, synaptic clefts (and note intracellular sequestration compartments as well). And from which should be subtracted all of the organelles and sub-cellular structure. It is not unreasonable to allocate 1000 intracell and 1000 extracell Micron^3 for modeling purposes. That translates to:

Nmanaged = 2000*1.8E8 = 3.6E11 % quantity of particles present in the compartments

The Goblet model is a whole cell model consisting of Patches. Because the quantity of Patches is large, some means of reducing the computation of individual patches must be justified and implemented.

7.7.1.1 Compartment Volumes

Interactors (ions and ligands) and compartments, of course, are volume-dependent phenomena.

NperMole = Avogadro*particles % in one liter. This is ion count (not including water).
NpermiliMoleperCuMicron = NperMole * 1E-6^3 * .001 / 0.1^3 = 602300 ions/mMole

The molarity of cytosol is generally between 150mM and 500mM. We therefore must manage about 180 million particles per Micron^3. A small neuron could have a volume of 100 Micron^3, which brings the particle quantity to 1.8E9. We also have extracellular fluid to manage in about equal measure, so we are at 4E9 particles. As the PC computer is limited to about 10,000 particles, we need to scale down by a factor of 1E5. This first appears to be an extraordinarily large scaling factor. It can be justified if the redundancy of particles is great, and the quantity of information being conveyed by then is comparatively small.

If the neuron were carefully rescaled for about 100,000 patches, then each particle could be rigorously modeled. However, the challenge is in evaluating the effects of surface reduction verses volume reduction. Also, rendering particles sparse can greatly reduce the collisions rates, which reduces the binding rates. This can be a serious distortion unless compensated for by means of affinity, \velocity, or size of objects to collide.

For practical reasons, a voxel of size 0.01 microns^3 is chosen. Voxels serve double duty. They track concentrations and flux through space, and to the extent that they impinge upon surfaces they constitute addresses. An actor may be situated at the center of the face of any voxel impinging upon a membrane; else upon a predefined nodal position.

NperCuMeter = mole*1E3;   cuMicron = (1E-6)^3;   milimolar = 1E-3;
voxel = 0.01 micron cubed = 0.01^3 cuMicrons = 1e-6 cuMicrons = 1e-12 cuMeters
Then a voxel has 0.602 particles per mM

Biosolutions often carry a sum of the partials = 300 mM, or 180 particles per voxel
Under these conditions, a PC can only model about 50 voxels for runs of 100 seconds.

It was later found that voxels invariably pick up computational load as they do not fall conveniently around the actors. It was subsequently decided to abandon voxels for hemispheres specifically around each actor. This incurred the computational load of polar coordinates conversion,but yielded precisely the information needed to interact with each actor in a physically realistic manner.

7.7.1.2 Membrane Areas

Actors (receptors, channels, pumps and vesicles) and membranes produce surface-dependent phenomena. Voxel edges of 0.01 micron imply 10000 voxels on the surface of one sq micron. Voronoi methods are applied to determine the "fair share" area around each actor. Despite the homogeneity of the membrane and node locations, the actors impacts upon membrane areas vary widely because actor densities vary widely. Furthermore, each actor is an intermittent transporter. When quiescent, it is effectively not there, abandoning membrane area to other nearest neighbors. This poses a problem that eventually rendered the Finite Element Method approach to modeling ineffective in capturing the biological processes under study.

Ion channels densities are often about 20 chan per Micron^3 of membrane. (min=0, max = 10000), Given that there are usually 3 or more chan types present, 60 out of 10000 surface voxels implies that 0.006 fraction of all addresses (voxels) are occupied by a channel. This is a manageable and useful ratio, serving the need to distribute channels over a wide variety of patterns across the membrane.

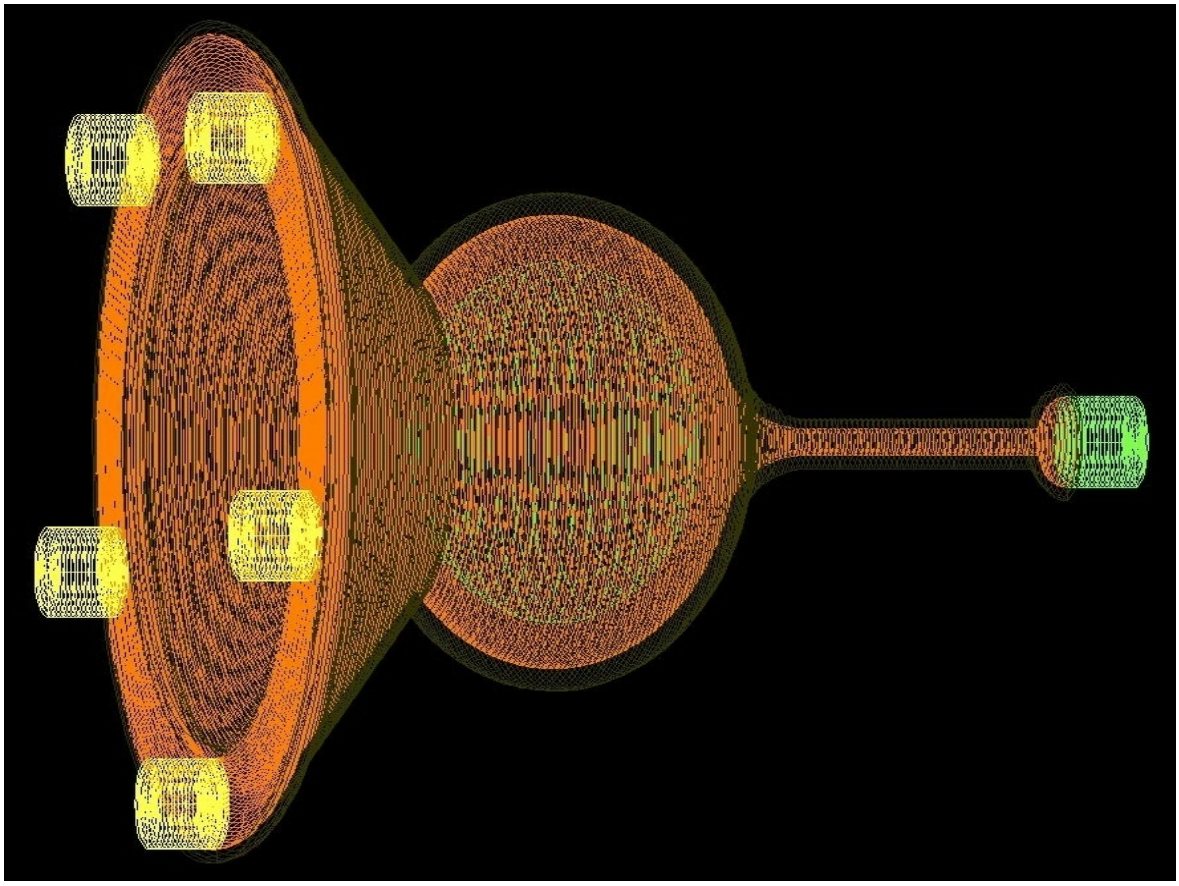


FIGURE 41: CREATION OF 9 COMPARTMENTS VIA CONTOURS OF REVOLUTION

The Goblet is a Whole Cell model. It usually involves sufficiently large quantities of particles and actors that it cannot be robustly modeled at once. Rather a select number of canonical patches of membrane are excised out, modeled and characterized. A sufficient number of canonical patches must be chosen such that all the patches in between the canonicals are accurately represented by gradient forms between two canonicals.

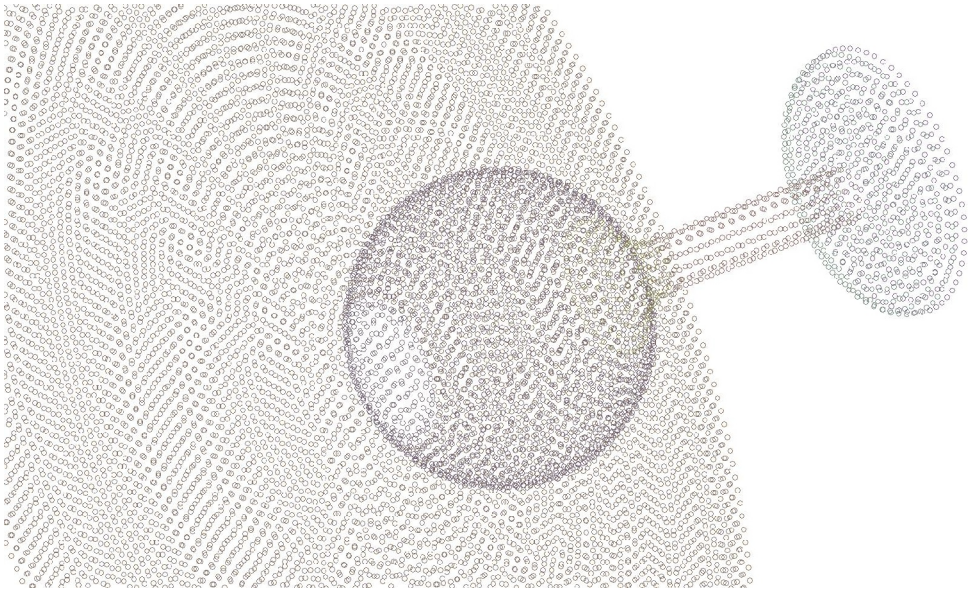


FIGURE 42: HOMOGENEOUS NODE PLACEMENT ON CONTOUR OF REVOLUTION

Each open circle is an available site for an actor.

7.7.2 ACTOR PLACEMENT

Occupied Nodes are represented by placing markers at select nodes. Actor placement is accomplished by applying the PDF for each actor type across the zones of the shape. [See node of Ranvier for a sketch of how this is done].

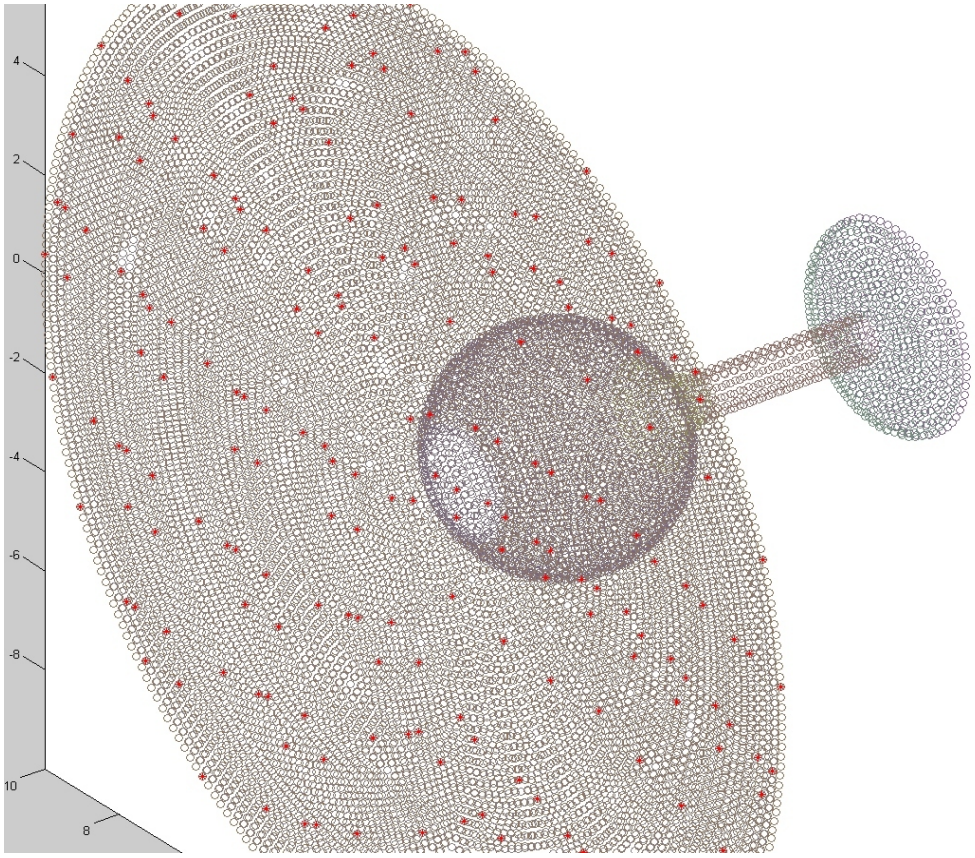


FIGURE 43: ACTOR PLACEMENT VIA INSTANTIATION OF PDF'S

To extract an ion channel placement PDF from the biological data, take a longitudinal slice through the center line of florescent marker images and read the marker density values as vectors along the length of the slice (in this case a node of Ranvier).

FIGURE 44: FLORESCENT MARKER DATA ON NA AND K CHANNELS AT NODE OF RANVIER

This slice is read spectrally for each of the tag frequencies of interest. In this case Green is a Na1.6 chan, Blue is a Kv1.2 chan, but red is not a chan (only a protein glue that seals the ends of the myelin layers to the axon).

direct from the photograph

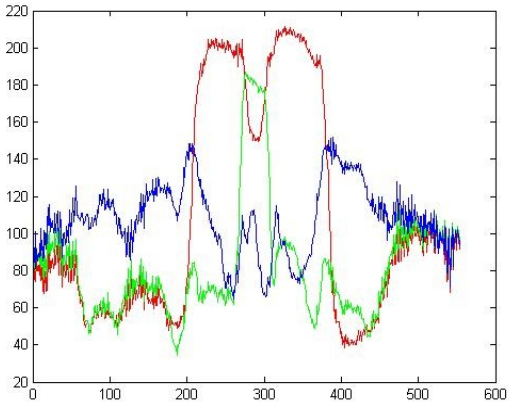


FIGURE 45: ACTOR DISTRIBUTIONS, RAW

PDFs normalized to model

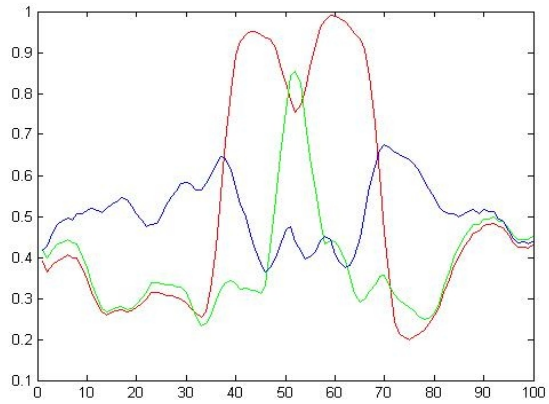


FIGURE 46: ACTOR DISTRIBUTIONS, SMOOTHED

7.8 ZONES

Each membrane is conceived as a concatenation of functional zones. This is for the convenience of the modeler, despite that both the biological neurons and the modeled neurons may have gradients and transitions between zones that blur their distinctions somewhat. Zones are useful for organizing and storing bio-data, for checking the functionality of membrane regions to the extent it is required to act with distinctive behavior from other regions and most importantly, for adapting limited biodata to "Stretch" across arbitrary and artificial shapes. This approach gives wide utility to the biodata of a few cells. The interim concern is that there is often insufficient biodata to ascertain the characterization of zones by actor densities, and therefore the modeler must work in hypothetical space until it does become available.

The modeler may define any number of zones, for each membrane separately, over any combination of shapes and distributions of actors thereon.

7.8.1 DENDRITIC PLATEN

The platen serves as a circular input face for the dendritic "field", and is attached to a cone serving as the dendritic "Stalk". The platen and cone combination construct a conical chamber intended to capture several of the topological relationships of the dendritic field while maintaining very fast computations for a dynamic simulation. This shape has evolved from a rim-only towards mimicking the tips and tapering thickness of the dendritic branches so as to

slow diffusion at the periphery. The filling in of the center of the rim (to become a solid circle) supports modeling the very short dendritic branches terminating close to the soma. Lateral (circumferential) diffusion can be further limited by inserting vanes into this conical chamber. The platen can accommodate several hundred dendritic "plugs" which produce synaptic signals.

7.8.2 SYNAPSES

Synapses are represented as plugs. They are cylindrical compartments with vesicles on the pre-synaptic membrane and receptors on the post-synaptic membrane. Diffusion across the gap is supported. Re-uptake of particles is supported via pumps. Realistic signals, for example voice or music, can be simulated via ligand release rates.

7.8.2.1 Synaptic Plugs

The plug consists of a cylinder divided into 2 compartments. The larger compartment is for storage (sequestration). The thin compartment is the synaptic cleft. The cleft has saline in it. Neurotransmitters can be released by the vesicles, bind across the cleft at post-synaptic receptors, then re-uptake accomplished by pumps located on the pre-synaptic membrane. The concept behind the synaptic plug is the analogy to the headset a human communicator may use on the telephone. The ear piece provides an input signal and the microphone captures the output signal. This skirts the geometric problem of getting many neurons to interconnect via contorted shapes. It reduces the local circuit connectivity challenges to a connectivity matrix, even though most of the physical intimacies of diffusion and tonicity are preserved.

Synaptic plugs are diffusion/kinetic compartments that can have tonicity, actors, binding, release, and re-uptake.

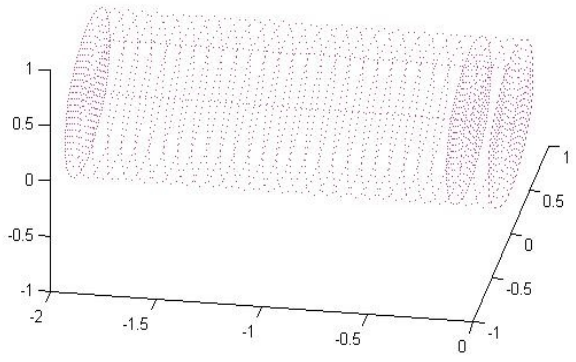


FIGURE 47: INPUT PLUG WITH SYNAPTIC CLEFT

7.8.3 BOUTONS

The portion of plasma lemma facing a synapse is characteristically quite different from the portion of the plasma lemma not facing any synapse. he post-synaptic membrane is necessarily populated with high densities of channels, receptors and pumps. It may or may not be convenient to populate the synaptic surround with reuptake mechanisms necessary to clean out the messengers to avoid echoes. In any case, the maintenance of synaptic tonicity is likely to be critical to synapse performance in information transfer.

Boutons are known to grow and to alter their shapes with learning. Although this model is upgradable to such phenomena, growth will not be included in this first release. To implement such a feature, the shape would be recalculated, the nodes recalculated, the actors be reassigned to nodes nearest were they were in the previous shape, and otherwise the state actors the same, and particle positions “stretched” to fill the new volumes.

Assuming that the functional role of the bouton is to house the vesicle recycling machinery, we focus on the vesicular release mechanisms of the bouton. The boutons are simulated as a group, in the form of an obtuse cone. Vanes may optionally be installed to effect separate timing and processing via varying ion channel and pump densities.

7.8.4 STALKS

Arborizations are large determinants of neural function. They shape the field of reception. They place the synapses in the loci so as to make connections with neighboring cells. By the lengths and diameters of stalks the time lag to soma for each input signal is determined. By bifurcations of stalks the partial convolutions of inputs may offer opportunities for inhibitory or other information-modifying treatments along the way. Patterns of taper and bifurcation are characteristic of each cell type. A method is provided to map bio-data into radial partitions hat mimic stalk cross sectional areas.

Close up (partial) view of the goblet shape main compartment. Each open circle is an available node for an actor.

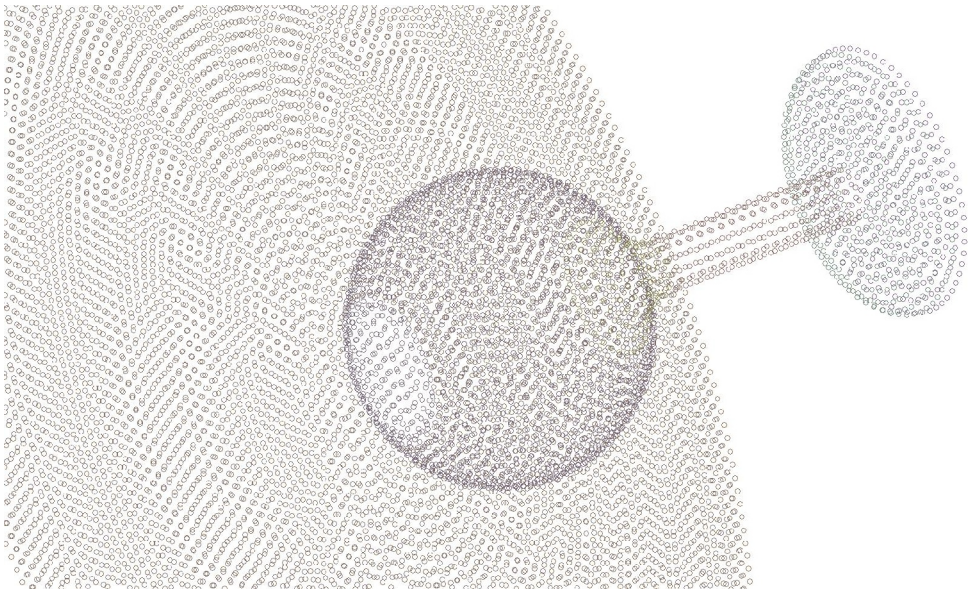


FIGURE 48: ZOOM-IN VIEW OF GOBLET SHAPE ADDRESSABLE NODES

Simulation of the dendritic arbor begins with 1 or more disks. Stalks and bifurcations require radial partitions within these disks. This consideration is addressed below.

7.8.5 MANIFOLDS

3-D shapes may be mapped onto 2-d matrices if there are no sharp corners. There is a significant computational advantage to doing so (2/3 power rule).

7.8.6 COMPARTMENT ORGANIZATION

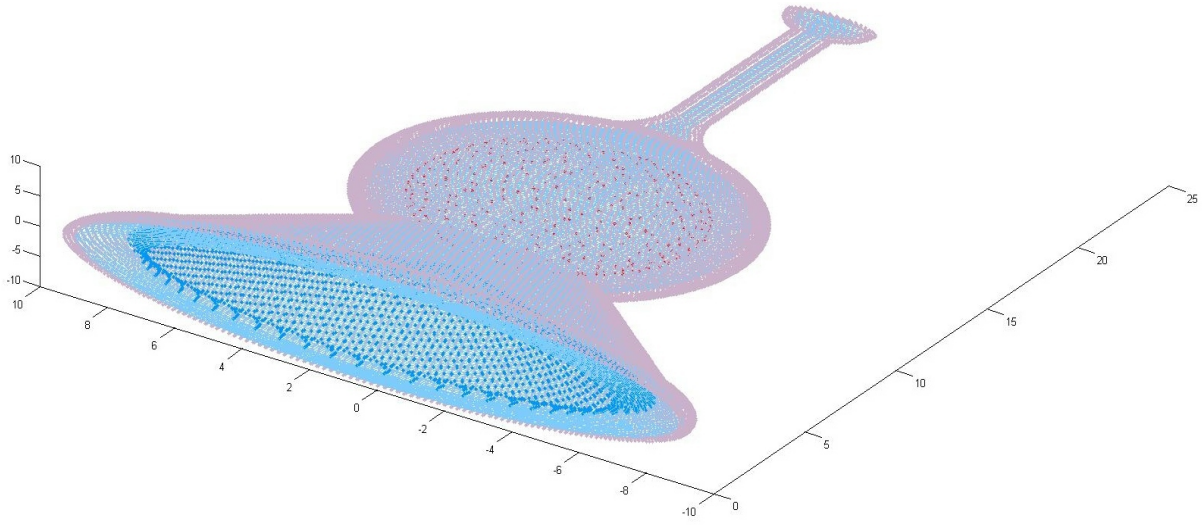


FIGURE 49: WHOLE CELL EXTRACELLULAR COMPARTMENT (LAVENDER)

Once the main neuron shape is established, then an extracellular "wrapper" can be applied. This yields another compartment (of specified thicknesses for each zone).

The extracellular membrane is fully functional, being afforded the same actors as the main membrane. This supports experiments to determine neighbor non-synaptic exchanges glial support exchanges, adaptation to drifting, and depleting concentrations in the extracellular fluid.

Membrane inner and outer surfaces serve as the Ceiling and Floor determination for each particle in motion.

7.8.7 HOMOGENEITY OF THE MEMBRANE

Membranes are closed surfaces with large numbers of addressable nodes. Each possesses two identifiable surfaces, which are generally labeled "inside" (nearest the center of the core) and "outside.

It is critical that all of the addressable nodes be positioned equidistant apart, as this allows the superposition of PDFs on them to position actors without geometric distortions.

Homogeneity is a mathematical issue and in no way limits the placement of actors in non-uniform patterns or distributions. The nodal spacing can be may arbitrarily fine with little computational cost.

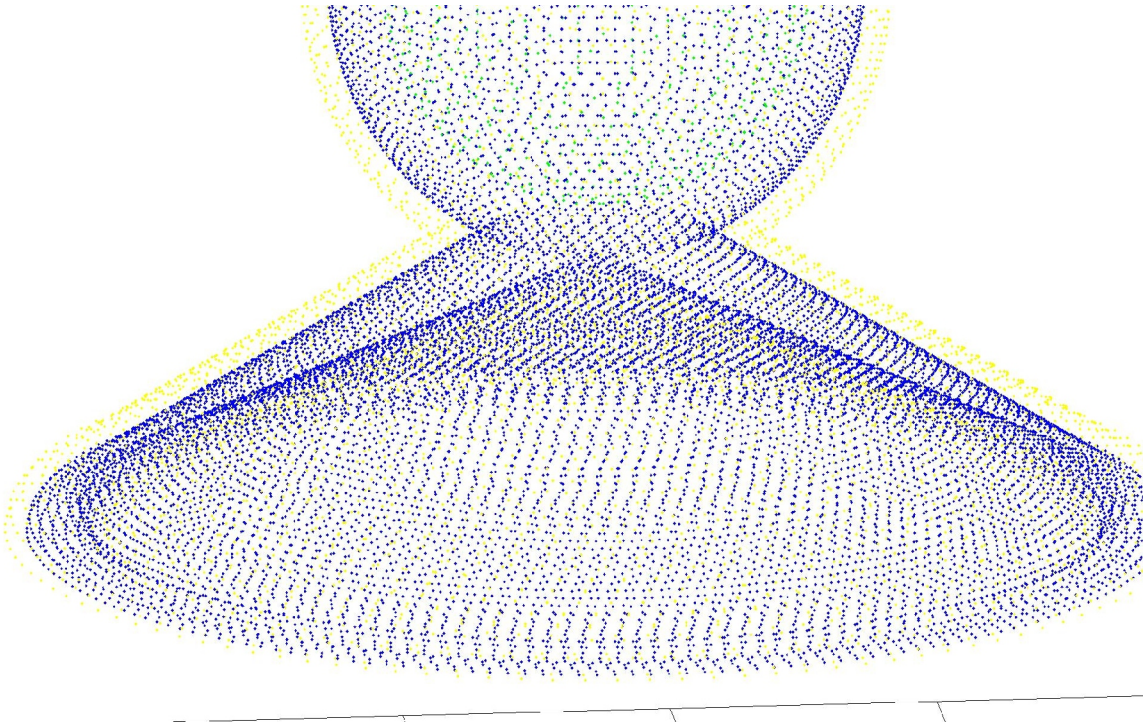


FIGURE 50: ZOOM-IN OF WHOLE CELL HOMOGENEOUS SPACING OF NODES

The generation of homogeneous surfaces consisting of nodes as equidistant apart as whole number divisions of a circumference allow, is valuable in that it supports addressable nodes, which also represent uniform areas of that surface.

7.8.8 ADDRESSABLE NODES

Addressable nodes typically number 10000 to 800000. They are the available sites for actors of any type. No two actors may occupy the same node. (However, a structure of actors in a functional group may be positioned relative to a single node, so as to preserve their distance relationships.) The nodal density sets the limit on actor density. In studies of high channel density, the node count is elevated simply by setting one parameter (*dx*) to a smaller distance. Setting the node count high does not increase the computational load significantly when the actor count remains the same.

7.8.8.1 Bifurcations

The dendritic tree consists of tapered volumes that join in arborizations. This pattern can be simulated by adding radial vanes within a obtuse cone. Although the cross-sectional shapes are rectangular, the cross-sectional areas can reasonably mimic those of neurons. Length variation is not strictly simulated in such a cone, but the positioning of synapses along the length (cone radius) has a very similar effect. The length and the spacing between vanes can be randomized to parametric variance. The fan-in topology of the dendrites have obvious summing function from an information processing perspective.

A similar geometry can be employed to effect multiple axonal outputs. The fan-out topology is not expected to perform significant information processing other than as a lag line. However, with inhibitory, modulator, or

Bifurcations can be simulated by dividing up a radial shape with vanes. These vanes may be randomized in both length and width.

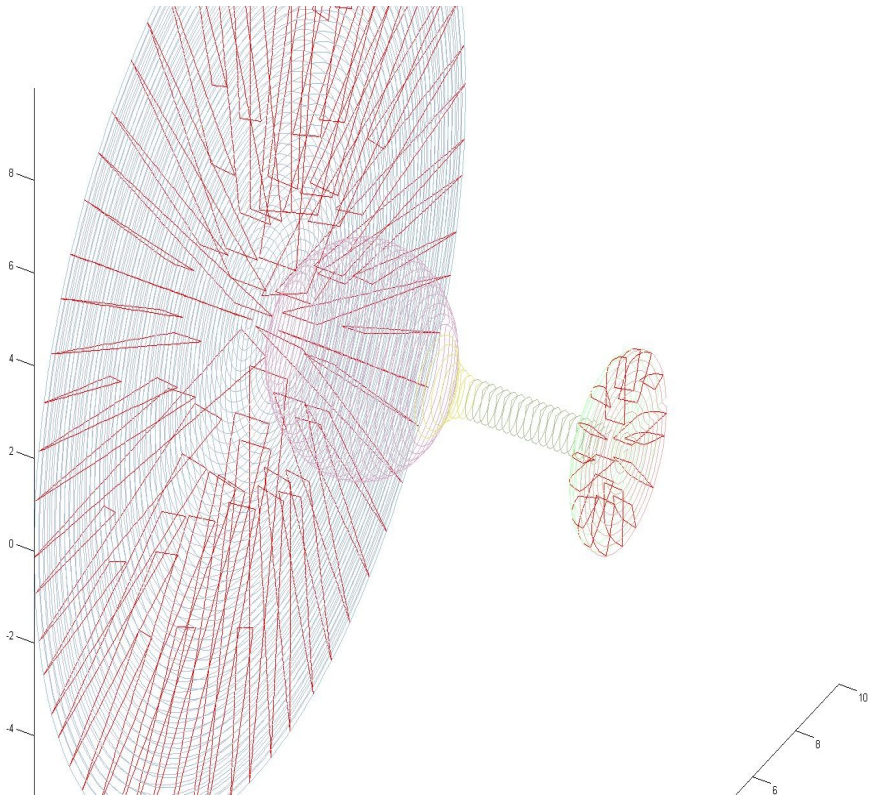


FIGURE 51: WHOLE CELL WITH VANE PARTITIONING OF DENDRITIC TREE

7.8.9 SOMA

Not much is said in the literature about the role of the soma in information processing. The obvious need for cellular machinery to produce and maintain a living cell dictate its presence, and a central location is strategic for protein and nutrient transport. It is seems to be fertile ground for inhibitory connections. The inhibitory processes are not the opposite of excitatory processes. To accomplish excitation, every step of the process must work flawlessly and with some amplification. For inhibition to succeed, one only need break or disrupt any one of the excitatory steps along the process. Inhibition is disruption. Inhibitory inputs impinging on a small diameter cross-section of the dendrites may throttle the entire signal. Inhibitory inputs over the larger somatic surface are not likely to quench a signal. This might imply that a patterned inhibitory effort in both time and space is necessary to quench a signal. We tend to think of "critical mass" of a concentration of excitatory inputs achieving propagation. But with inhibition, such concentration is ineffective, simply allowing wide swaths of alternative paths around the quenched area. It is expected that widely spaced equatorial inputs would quench any coincident signal, whereas the same number of longitudinally spaced inputs would not.

Some neuronal types, e.g. bipolars, push the soma entirely to the side on a small stalk, leaving dendrite-to-axon continuity without a bulge. Is this a hint that a membranal bulge is not completely benign, and that there are some information processing roles where it must be eliminated? Is this merely to shorten the input-to-output length to a minimum, for speed? Hopefully, simulations can suggest possible answers.

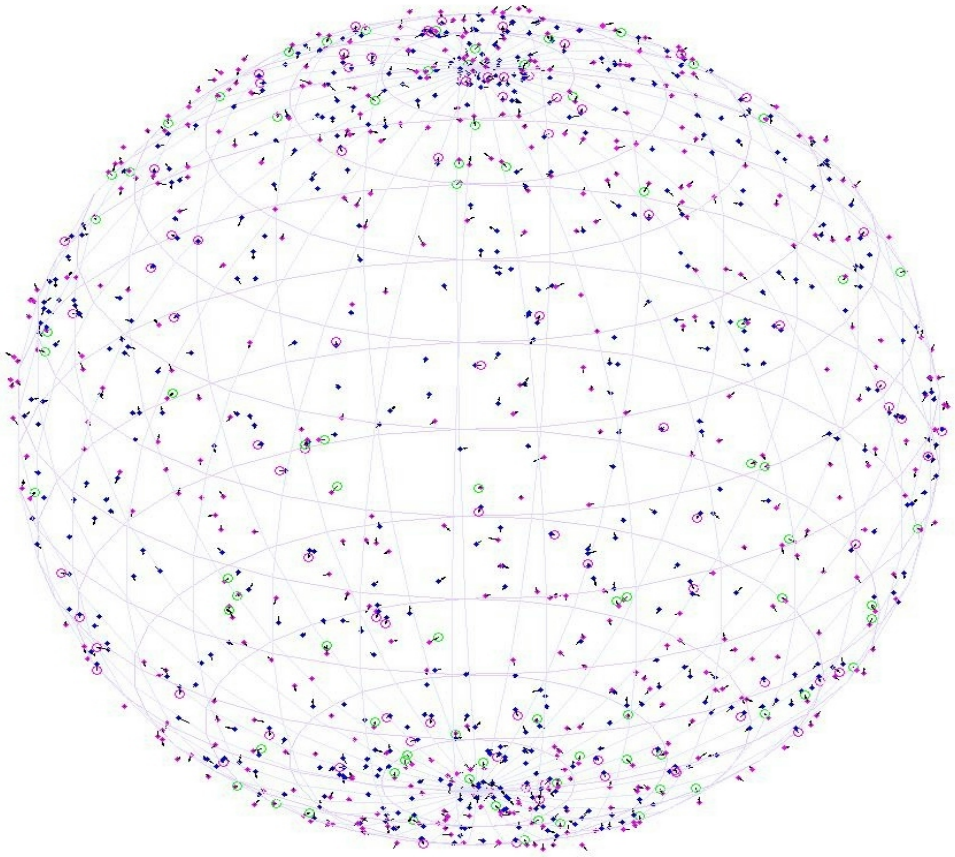


FIGURE 52: CELL MEMBRANE CROSSINGS, DETECTION

The above figure displays a study detecting ions crossing the membrane (zone = soma). Only the particles whose paths crossed the surface of a sphere are shown, and their velocity quivers are also shown. They are classified as to whether crossing inward or crossing outward. The points of penetration are identified.

7.8.10 AXONAL HILLOCK

A distinct change in ion channel types, mix and densities can effect an analog-to-digital conversion of the signal. If the prior signal is a summation of graded excitatory and inhibitory inputs, Q matrices that effect an all-or-nothing response will be making a “decision” on the part of the neuron. There are other ways of accomplishing this effect. If the propagated signal represents a gain of less than one, then the signal will be quenched in just a few ion channels down the line. Therefore analog responses can be “wired” so as to act digitally. Whatever the case, so long and the kinetic schemes are known, these effects can be simulated.

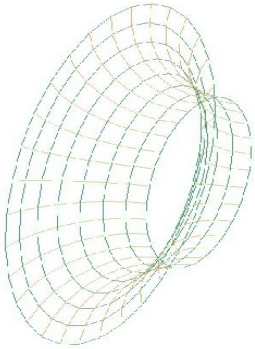


FIGURE 53: AXONAL HILLOCK

The axonal hillock does not require any special algorithms. It is distinguished as a zone of sometimes unique channel distributions. These are related via the channel PDFs.

7.8.11 AXON

It was fortunate for Hodgkin and Huxley that they chose an axon to study, and the particularly simple squid axon at that. Curve fitting the action potential data to fourth order equations was tractable in the 1950's via mechanical adding machines. Most patches of neuron membrane are more complicated than that, and simulations have tended toward 7^{th}, 10^{th}, even 30^{th} order matrices, that need to be inverted or exponentiated. Axons, if homogeneous, can be simulated with an initial characteristic response curve then merely adding a delay to represent down-stream points along its length. This is computationally very efficient but will not pick up any perturbations along that length. A particle system is a rather tedious way to accomplish the same thing. It is therefore computationally prudent to shorten uneventful axons to the minimum, add delay functions when output phase is of interest, but interrupt that

process where ever perturbations are expected along the length f the axon, and there return to the particle system model (as a patch).

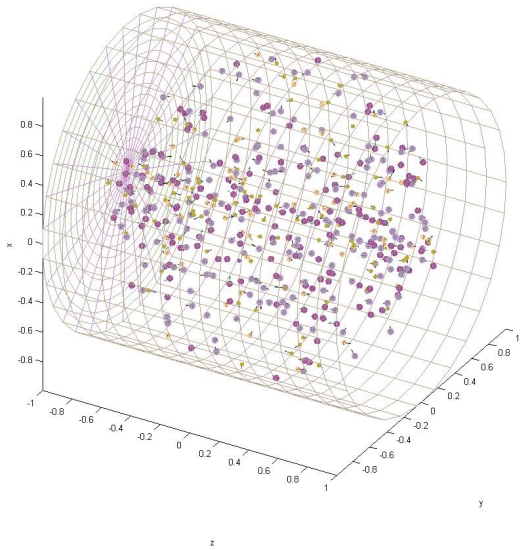


FIGURE 54: DIFFUSION WITHIN A CYLINDER

In a particle system model of axons, longitudinal communication takes place only via diffusion. Action potentials are propagated as a function of membrane capacitance per ion channel and channel kinetics. Channel activation kinetics determine speed, capacitance slows down that speed (as a low pass filter does), and inactivation kinetics prevent antidromic propagation. This is quite slow and inadequate for axons, which have evolved much faster active transport. For directional sensitivity, chloride gradients are established via the placement of chloride pumps at one end only. Is the passive axial diffusion of chloride fast enough to serve this function?

7.8.12 NODES OF RANVIER

Axons may be myelinated or unmyelinated. Unmyelinated display a high capacitance and a rather continuous pattern of sodium and potassium channels. Myelinated display a very low capacitance and absence of ion channel below the myelin. What do the paranode K channels do given that they are smothered in myelin?

The axon zone may be interrupted by any number of Nodes of Ranvier. They are characterized by a sharp change in capacitance.

7.8.13 MEMBRANAL STRUCTURES

Of all the membranal proteins relevant to signal processing by the neuron, those with time constants slower than 100 msec need not be considered in this model, as their effects can be accounted for parametrically. Of those that are fast enough to participate iteratively can be handled in one of two ways: Via an approximating function, or by adding a kinetics model.

7.9 BUILD OF PARTICLES

1. The membranes define the volume of each compartment
2. A center of compartment is defined as an adequate injection point for a bolus of particles
3. The quantities of particles for each compartment are instantiated into a bolus
4. The bolus is injected into the compartment and allowed to diffuse until uniformly diffused

7.10 BUILD OF ACTORS

1. The membrane surfaces are defined
2. Membranes are populated by nodes in quantities in multiples of the total quantity of actors on each membrane.
3. The distributions of actors are instantiated as node assignments for each actor type

7.11 IMPLICIT COMPONENTS

There are no proper elements in this division. Certain measurable variables (observables) of the model are emergent, not having been specified at the design or build phases. They are usually an interesting pattern of position or motion. Positions result in concentrations and voltages. Movements result in flux and currents.

Finite Element Capacitors	Once the positions of all actors on the membrane are known, an algorithm calculated a polygon around each actor. This polygon has and area, and that area has a capacitance as a function of permittivity. The capacitance value is stationary for the RUN.
Finite Element Resistors, Extracellular	The shape and salinity of the extracellular fluid between any 2 Actors can be employed to calculate the resistance between those 2 nodes. This resistance can fluctuate with conc0, but usually is stable.
Finite Element Resistors, Intracellular	The shape and salinity of the intracellular fluid between any 2 Actors can be employed to calculate the resistance between those 2 nodes. This

	resistance can fluctuate with conc1, but usually is stable.
Channel Conductances	The conductance values of each individual channel must be calculated at the finest available dt, as they are extremely dynamic. These G values are the result of gating variables * Gmax values.
Modulators	Modulators may be Ligands, ions, voltage or concentrations. "Modulator" is merely a concept, referring only to whatever serves as the "input" signal to an actor.
diffusion rate	is a consequence of collisions and reflections
flux, horz	is a function of the distance between actor nearest neighbors
Current, ionic	Is the net charge movement due to all flux of charged particles. Currents occur in 3-D volumes of irregular shapes, not in 1-D metallic long cylinders as in solid state circuits. This current has mass, and is therefore slow and has some inertia. It is "smeared" by water collisions.
Current, electronic	Is the instantaneous (speed of light) electrical effects due to electron wave fronts. It is not modeled by particles but rather calculated.
voltage	Pressure on charged particles, to cross a barrier (membrane) due to net charge imbalances. Voltage is calculated by the Nernst EQ.

7.11.1.1 concentrations

Concentration is the quantity of particles of a single type per unit volume, especially voxels.

7.11.1.2 concentration gradient

This is a measure of the pressure to diffuse particles of one type in a given direction due to concentration imbalance. It is the 3- dimensional differential of the voxel concentrations. It constitutes a force that translates to an acceleration of particles of the same type.

7.11.1.3 charge density

Charge density is the net quantity of charges per unit of volume, especially per voxel, or per the standard hemisphere volume around each actor pole. Given that the membrane thickness may be significant to the sectioning of a sphere centered at the node location, it may be necessary to double the computation by finding the particles within a sphere centered at each pole of each actor. For sparse particle densities, where a larger sphere is necessary to get a desired level of confidence, and where the size of the sphere is then large *vis-a-vis* the thickness of the membrane, it may be an acceptable expedient to calculate a single sphere and then sorting by compartment. The size of the sphere is dependent upon the sparsest particle, often Calcium. If calcium must be found for binding purposes, then the sphere

must be large enough that the probability of a calcium is acceptably high. The advantage of the hemisphere approach is that when actors are close, the hemispheres may legitimately overlap, so long as their is a claim conflict resolution routine that allows the first actor to claim a particle causes all other actors to release their claims and choose another.

The charge density is not correlated with ion density. This is because ions of opposite charge can "pair off" into a neutral pair that diffuses away from the contested membrane area. This leave only unpaired charges to be attracted towards the membrane. This charge attraction decays exponentially with distance from the center of the membrane.

There is however a maximum charge packing density. Any two like charges cannot come any closer than the thickness of the membrane. If they did, the repulsive force would over ride the attractive force, and one of the two would be forced away from both the membrane and the opposite charge to a new position at the periphery of the charge field. As a result of such charge interplay, particles tend to organize in layers of ever sparser occupancies. Thermal motion jostles this pattern, but it is none-the-less characteristic of liquid state capacitance.

7.11.1.4 voltage

The ratio of the charge densities on either side of a membrane determine the voltage. However the arbitrary choice of voxel size for this calculation will vary the value somewhat. While in nature the spatially instantaneous voltage at the exposed channel surface will determine the voltage effects upon it, we cannot calculate a surface voltage, only a volume voltage. Ironically, there is a surface effect that impinges upon voltage, and that is capacitance. Because ions are being transported non-homogeneously, the voltage across each ion channel is unique. Because the capacitance effects of the adjacent membrane are practically instantaneous, capacitance is a dominant determinant of voltage in response to flux, on all but the very highest channel packing densities (where the remaining area for capacitive membrane per channel is low).

It is more accurate to calculate the voltage via Coulombs law when only taking into account the unbalanced charges. This is done by counting the unbalanced N charges and identifying those ions of that charge closest to the membrane, ignoring all else both positive and negative. This is because real particles are more organized so as to neutralize than ae computer simulations of particles.

Voltage units are redefined to apply to individual particles: ev = (kelv/valance)*log2(q.out/q.in)

Current units are redefined as charges per msec. Thus Ca++ would carry twice the current as K+.

Nernst Voltage is scaled to eliminate the constants = natural log of ratio of charge densities between 2 (usually adjacent) volumes, especially voxels. So long as the temperature is constant, only the log of the concentration ratio need be in the iterative calculations.

7.11.1.5 voltage gradient

The voltage gradient across the membrane is the measure of the electrostatic force on a charged particle located in that gradient. It is the differential of the 3-d solution to the N-body problem. It constitutes a force that translates to an acceleration of particles of the same type.

However the voltage driving each ion channel is more complicated. The Coulomb membrane voltage plus the concentration gradient plus the specific ion Nernst partial voltage are all major factors that sum to determine the net pressure that moves ions through an open channel. As each ion channel has multiple conductances for each ion type present, this calculation must be performed for each channel x each ion type, per *dt*.

7.11.1.6 capacitor charge

The default value for membrane capacitance is that it is proportional to the membrane area allocated to each actor, divided by the effective thickness of the membrane, times the voltage across the membrane. Any net charge imbalance across a membrane will be strongly attracted to the membrane via the EM force. Capacitance is quantity of charges held per unit of membrane area. The quantity of charges held is proportionate to the voltage across the membrane. Capacitive charge is synonymous with charge imbalance. However capacitors of higher dielectric strength can hold charges in a higher packing density, therefore higher voltage.

Conceptually, capacitance is a 2-dimensional phenomenon, but in liquid state capacitors at normal temperature entail a layer of near-Brownian movement of charges on either side of the dielectric membrane. The charge density tapers off exponentially with distance from the membrane. This charge is referred to as the zeta potential.

In experiments where the membrane capacitance is non-homogeneous, the vector of membranal area elements can be multiplied by an equal length vector of capacitance modifier values from say 0 to 2. Typically such values would be near 1, as the membrane capacitance does not vary much due to variation in mix of lipids and proteins.

7.11.1.7 flux

Flux is defined as the 3-d movement of particles per second. It can be measured in 3-d free space relative to points of interest via grad, div and curl functions common to physicists. As particles may be neutral, charged positive or negative, or multiply charged:

flux * valance = current

7.11.1.8 Salt Water Resistance

Saline acts as an electrical resistor. When a pressure exists to move electrons in at one point and electrons out at another point, then the resistance can easily be measured with an ohmmeter. However, under normal physiological conditions this does not happen. The normal charge carriers are ions, and to a much lesser extent protons (as hydrogen ions modulating pH). Because of the capacitance effects of the membrane, almost all of the unbalanced charges reside very near the membrane. Although it is possible for current to flow through the saline volumes, there is no charge imbalance to drive such. The driven charge flows are between channel and channel; pump and channel; and the repulsion between like charges. Unbalanced unlike charges must be across the membrane from each other; else they would cancel each other out extremely quickly (at the speed of conduction of electricity).

As a result, most or all of the charge flux is along the membrane and acts as an oscillatory mass-spring grid, held near planar by attraction to opposite charges across the membrane.

Whenever a voltage gradient exists across some distance of saline, then there will be some current in the direction of that gradient until such a gradient is neutralized. The resistance of the saline is in parallel to the relatively free flow of charged particles along the capacitance of the membrane. Because the forces at the capacitor are stronger, it is likely that the dominant horizontal current is through the capacitor rather than through the volume of saline above it.

7.11.1.9 Electronic vs Ionic Conduction

Electronic conduction takes place at near the speed of light, whereas Ionic Conduction takes place at the speed of diffusion and drift. In modeling, diffusion is practical to simulate, but electronic conduction is too fast to do so, requiring quite rigid coupling between electrons. Any pure electronic effects must be calculated and applied analytically, not via particle movement. So far it is difficult to conclude that electronic conduction is present in the neuron membrane propagation waves. If it were present, it would short circuit out all the neurons via the extracellular saline conduction, and he result would be epileptic synchrony, not information processing. The ever-present capacitance of lipid membranes severely mutes the electronic conduction that is possible in solid state materials. Although electronic conduction is practically instantaneous, the saline resistance values between ion channels insures varying voltages at each actor, and the capacitance between actors acts as a low pass filter, absorbing all the high frequency signals. Voltages over the membrane are analogous to surface waves upon a lake wit ha shallow rough bottom topography.

7.11.1.10 Channel Conductivity

While an ion channel is in an open state, ions may pass through as a function its ion conductivity profile, voltage gradient, and concentration gradient.

J = S*(V+C)*O, where
J=flux, S=conductivity profile, V=voltage gradient, C=concentration gradient, O = gating state

Ions within a designated radius of the channel are available for such passive transport.

Current equals net charge flux
I = sum(Jx*D) , where
I = current, Jx = ion flux in the axial direction, D = valance of the ions

Current is an implied variable, not physically represented as something separate from flux. However its calculation may be used to determine the voltage gradient. Alternatively, the particle transports alter the unbalanced charge differential across the membrane, and from these alone may be calculated the Coulomb voltage.

7.11.1.11 current

Current is defined as the net 3-dimensional movement of charges per second, across some designated area. Pumps are a current source. Ion channels provide selective current "short circuits" or "loads". If channels are truly resistive, then they should heat up upon opening to experience flux.

7.11.1.12 Circuits

Resistance to nearest neighbors both above and below the membrane.

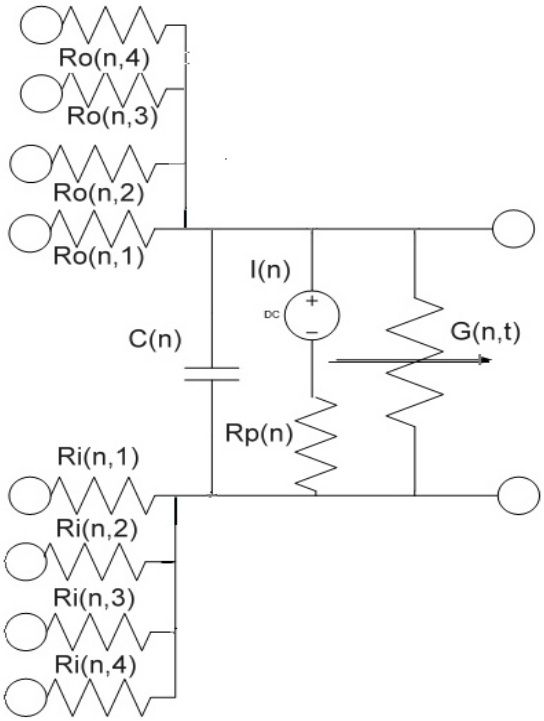


FIGURE 55: STANDARD NODE ELECTRICAL SCHEMATIC

The figure above shows 4 nearest neighbors connected via saline conductance. Though each ion types gets its own variable resistor through the open pore, all ions share the capacitance and voltage associated with the membrane. The pumps then again, are quite specific to ion types. As conventional electronics expects complete circuits (loops of several nodes), it is noteworthy that ion channels flicker open and closed, often spending most of their time closed. This implies statistically that most of the time when a single channel is open its neighbors are probably closed, and thus there may not be a "complete circuit". Instead, the ion flux through an ion channel in response to concentration gradients and/or voltage gradients is absorbed by capacitance. The charges that are captured at the

capacitive membrane surfaces tend to alter the voltage across the membrane because they effectively remove charges from solution that otherwise would contribute to that voltage.

Development of the circuit approach lead to the following extensions:

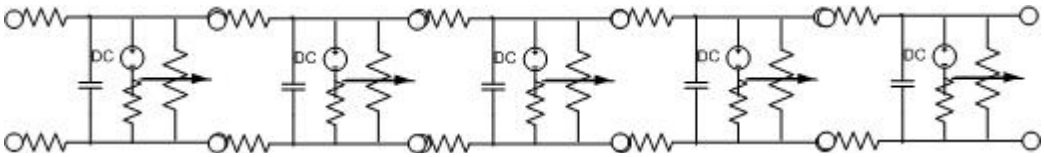


FIGURE 56: 4-PORT LADDER FILTER

A 4-port RC filter rendition of a neural membrane with pumps and channels, with saline above and below. This is the simplest depiction of axonal conduction as an electrical circuit. As with all such representations, discrete capacitance and resistive coupling between channels are required. Such discrete elements are called into question by the facts of continuous capacitive membrane, and the wavelike communication of mid frequency disturbances (approx 1E3 Hz) not as diffusion through the saline, but rather as a wavelike disturbance of the capacitated ions.

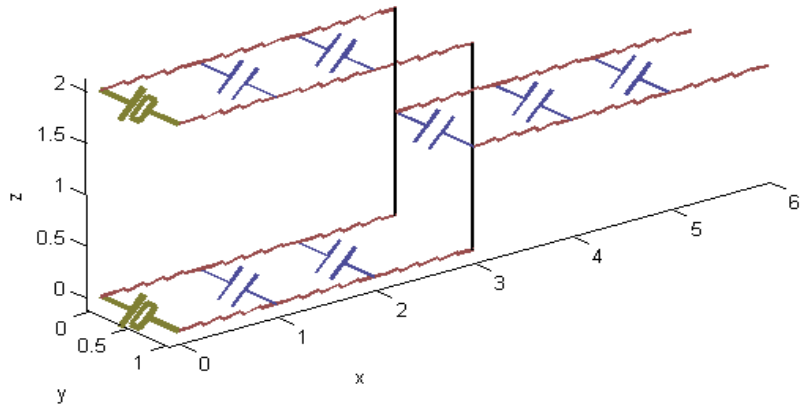


FIGURE 57: Bifurcation circuit

Bifurcation circuit was considered but later abandoned due to the need for channel participation.

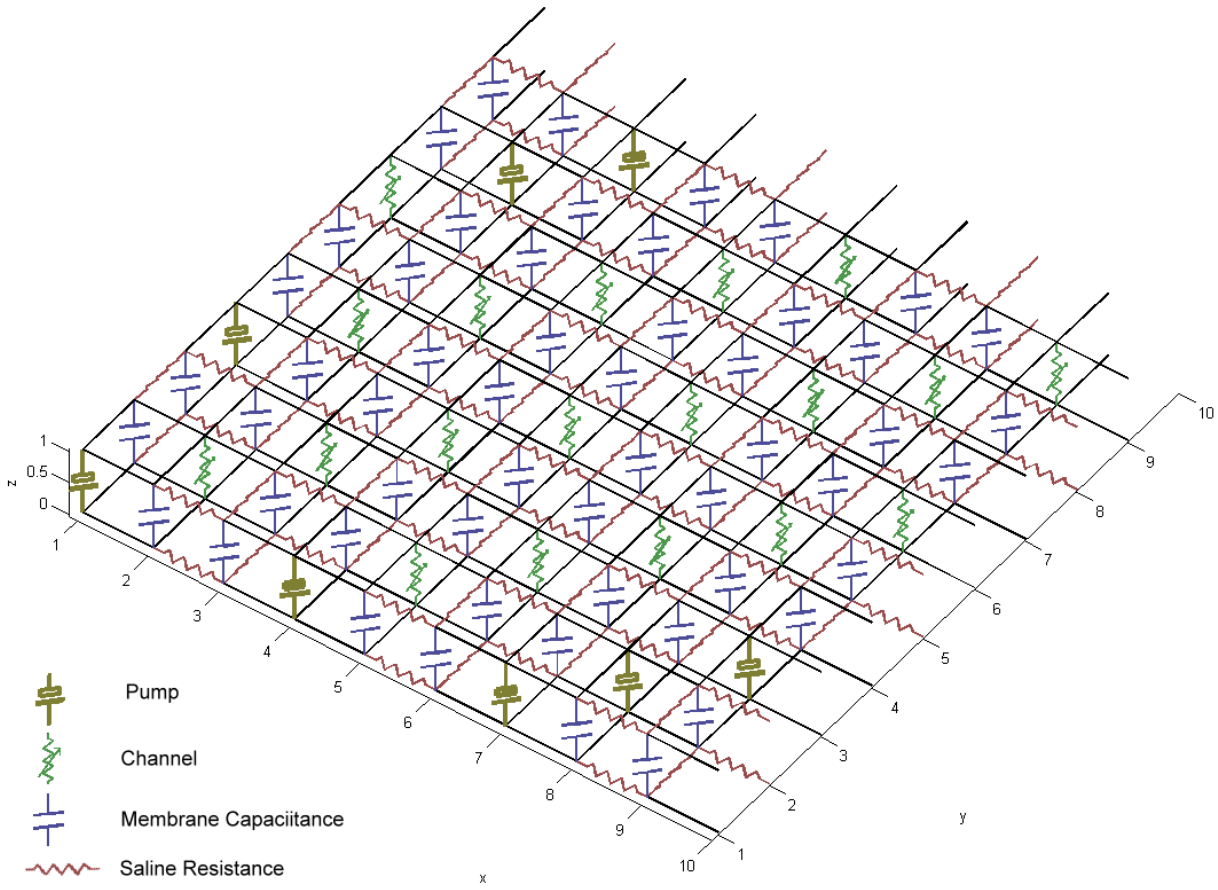


FIGURE 58: RC grid representation of Membrane Patch

And such a mesh of components can be shaped as per cellular portions.

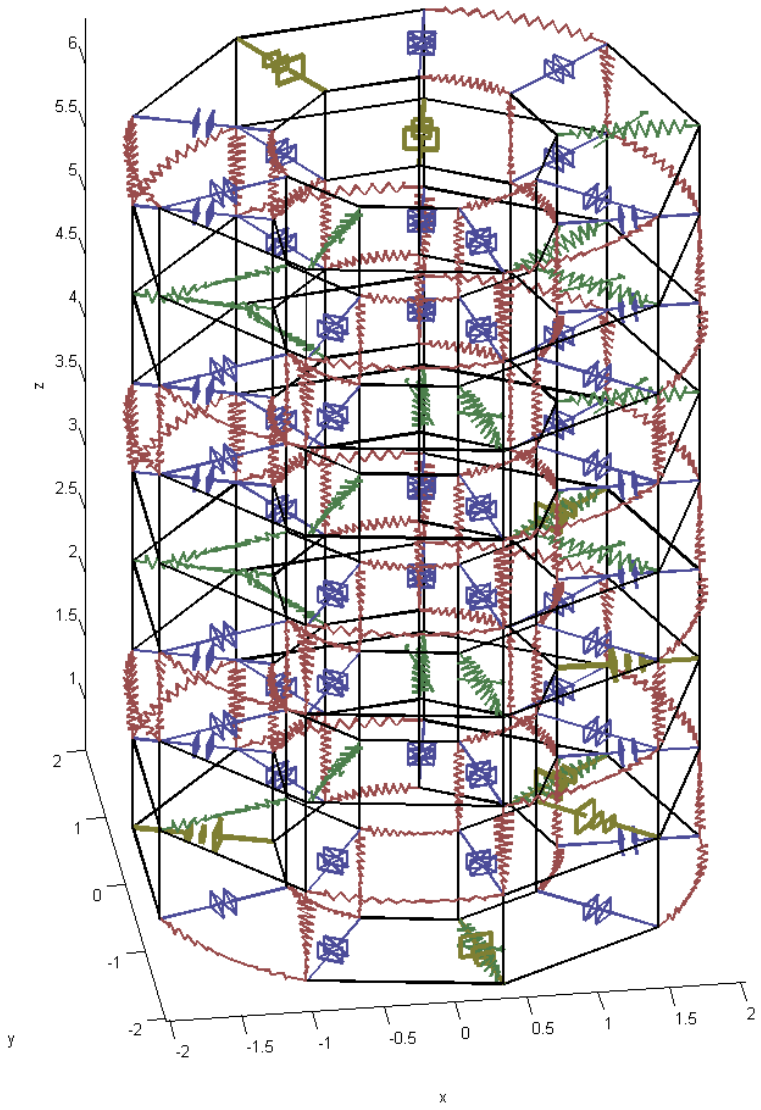


FIGURE 59: Circuit Representation of a Portion of Axon

This cylindrical representative of a portion of axon supports the modeling of a filter approach to he membrane.

7.12 OUTPUT VARIABLES

Concentrations Concentrations change as function of flux = dc. These must be tracked because the Nernst potentials depend on them, and because many actors are sensitive to local concentrations. Because diffusion takes time, it is necessary to track concs on a per voxel, or per node basis. Note that pH is

	also a conc of H+.
voltage	The membrane voltage is highly dynamic and must be tracked both nodally and for each dt. Calculated by the Nernst EQ.
capacitive charge	q, the charge is local and temporal, and has the effect of sequestering many charged particles while the membrane is exposed to a non-zero dV. This is modeled by membrane charge attractors (dielectric effect).

7.12.1 SEQUESTRATION

Regulation of the internal environment of the cell requires more than mere pumping between the extracellular and intracellular compartments. The sequestration of Calcium for example is accomplished by pumping it into intracellular vesicles. A single core compartment can serve the function of providing a place to park ions and ligands which are temporarily removed from solution.

A minor offense of sequestration in the core is the dislocation of particles that may be involved in messaging and other location critical roles. Because there is only provided this single core compartment,m rather than thousands of local compartments, the model translocates particles in and out of core instantaneously, violating physics for this simplicity. Presumably, to the pair of translocations in and out of sequestration cancel out to no impact upon the conservation laws. However, charged particles are a problem, as a sudden and unnatural shift in charge is disruptive. This may require shutting off valance while in sequestration. It is not known whether doing so will lead to model spuriousness.

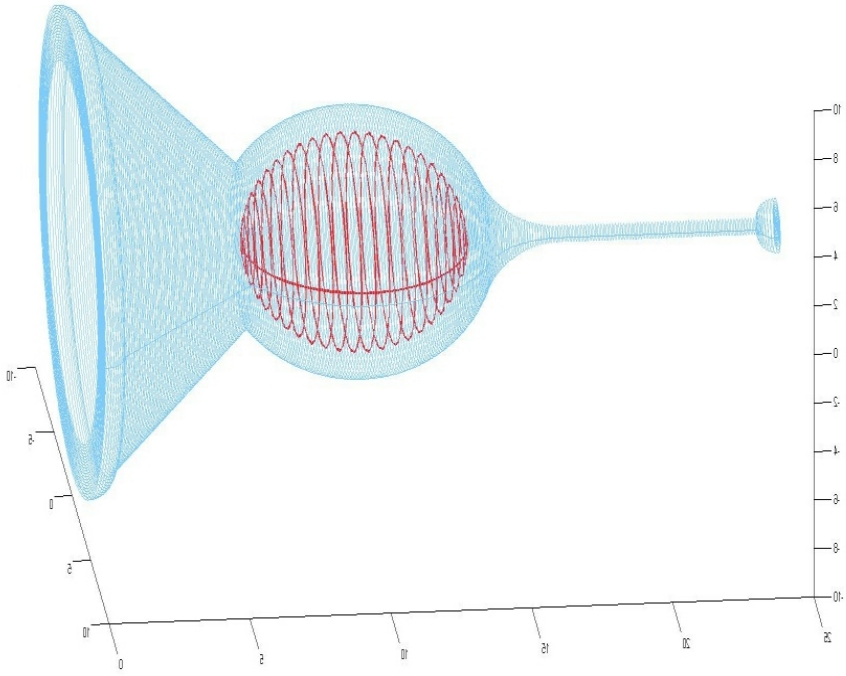


FIGURE 60: SOMA VOLUME REDUCTION

Within the soma, a smaller sphere is placed. It serves as a general compartment to store particles out of circulation (sequestration). The core also serves to block out most of the soma volume where organelles would do the same in biological cells, and thus make the intracellular fluid diffusion active only near the plasma lemma. The core may be used to store particles not is use, but as discussed about, charged particles in large quantities will distort the charge field unnaturally.

7.12.2 TIME SCALING

Generally, there are 4 types of time to be discussed:

1. biological time (that of the empirical data on wet neurons);
2. simulation time (that particular slice of biological time to be modeled)
3. computer time, the quantity of CPU clock cycles consumed to perform a simulation
4. user time, the length of time required to perform certain human tasks and waits to effect a simulation

Most design work is concerned with simulation time. For example, let one second of model simulation playback equal 1 biological millisecond.

Computer time will necessarily be many orders of magnitude slower than biological time. Digitization suffers a total loss of continuity in space and time. This implies a large computational load to recalculate inter-particle distances and forces each *dt*. Forces which occur without computation in nature must be tediously recalculated each dt as an N-body problem. Natural systems are able to exploit the physical forces in ways that silicone computers do not, and thus realize many orders of magnitude advantage in energy consumption and in quantities of computational steps (flops). This leads to the conclusion that biological systems are not at all slow. The massively parallel architecture of neuronal processing, combined with the molecule-sized elements, effect an immense amount of processing in micron-scale space-time. Popular comparisons to computer clocks and bits avoids the fact that a single neuron is doing a lot more than a common computer. By assigning a neuron an arbitrarily simple task, like a "yes or no" decision, we trivialize the work load of a neuron, and then wrongfully declare it to be "slow". Computer time rapidly becomes a limiting factor for practical reasons.

7.12.2.1 Log Scaling of temporal events

For some studies it may be desirable to study the effects of fast processes upon somewhat slower processes. When the ratio between them is too great for the available computer, some compression of time between the two may be done to render the simulation tractable. See chapter Strategies for discussion of this topic.

7.12.3 SPACE SCALING

1. Whole Cell dimensions, in microns
2. Patch dimensions, in nanometers
3. Voxels – volume units within the Whole Cell, for purposes of flux measurements
4. Pixels – surface units at the membrane which correspond to the face of an adjacent voxel
5. Flux – net movement of ions, parallel or perpendicular to the membrane

7.12.3.1 Log Scaling of compartment sizes

Large scale models, such as whole cell models may encompass 8 orders of magnitude from ions at 1e-1 nm to axon lengths at 1e7 nm. This is not tractable with current computing power. The surface area would entail too many actors and the volume would entail to many ions and messengers.

A practical solution is to logarithmically scale distances down to the limits of the available computer. An algorithm found to be of use is:

```
Newsizes = antilog((desiredmaxsize/maxsize) * log(sizes));  % name of operator = scalebylog
```

This particular transformation does not enlarge the lowest values as does the operator:

```
Newsizes = logN(sizes,basis); % where basis is a value in range 1..1.1;
```

The scalebylog.m function receives a list of compartment dimensions, checks to ratio of largest to smallest, makes no change to the smallest, but scales everything else on a log scale so proportioned that the max value has been scaled down to a set desired maximum size .

For EX, let the membrane dimensions of the model be:

```
  Dx   =   [ 5 50 20000 500000 6000000 1.2E8]; and set the model maxdim = 1e4.
[newDx descalar minx] = scalebylog(Dx,1e4);    % generating output
newDx = [5 17.416 447.97 2564 9858.8 50000].
descalar and minx are saved for decompression later.
```

As this is a compression algorithm, accelerations are also compressed and velocities distorted somewhat, resulting in compressed lag times due to velocity. However, such results can be de-scaled back to their original values via a reversing algorithm. A function for decompression is provided.

```
oldDx = descalebylog(newDx,descalar,minx);
```

Note that over-compression will distort diffusion results. Nonlinear behaviors must be verified by comparing compressed against non-compressed results.

7.12.4 QUANTITY SCALING

1. Let one model Actor equal _____ live actors
2. Let one model Interactor equal ____ live interactors
3. Let one model collision equal ____ live water molecules
4. Let one model synapse equal ____ live synapses
5. Let one pixel of model membrane equal _____ picofarads of capacitance

Particle radii relative to the particle density? Because the quantity of particles is reduced, various compensation are indicated. One such compensation is to increase the radius of particles to increase the probability of collisions. However, this requires the enlargement of the ion channel pore sizes.

7.12.4.1.1 Quantity of elements, factors

While modeling on personal computers, it is advisable to restrict particle counts to about 1E5, and the number of actors to 1E3. This is but a tiny fraction of bio-reality for a neuron. The use of super computers can increase these quantities 100-fold, or even 10,000-fold if month-long runs are tolerable. (2,592,000 sec/month)

7.12.4.2 Log Scaling of quantities

See chapter: Strategies for a discussion of log scaling.

7.13 MODEL QUANTIFICATION

A list of parameters will require values to run a model. Follows is a form to assist in collecting those value.

	SAMPLE CASE	
Quantity of membranes	5	
Quantity of compartments	5	
Membrane areas		
Membrane pixelation		
Membrane capacitance		
Compartment volumes		
Compartment voxelation		
Species of ion		
Quantities of each species of ion		
Species of Ligand	[Na Cl K Ca An]	
Quantities of each species of ligand		
State of each ion and ligand, free or bound to ___		
Collision rates for each ion and ligand		
Solvent collision rate for ions and ligands		
Surface collision rates for ions and ligands		
Forces resulting in accelerations for each ion and ligand		
Species of Receptor		
States of each receptor		
Quantities of each species of receptor		
Distribution of each instance of receptor		
Modulators for each receptor		
Affinities and dissociation rates for each receptor		
Species of channel		
Modulators to each species of channel		
Conduction profile for each species of channel		
Phenotype to each species of channel (gating function)		
States of each channel (Q =10x10)		
Modes of each channel (number of Q)		
State transition rates for each channel (determine dt)		
Affinity/binding/dissociation rates for each channel species		
Quantities of each species of channel		
Distribution of each instance of channel		
State stochastics for each instance of channel		
Particles bound/transported for each channel		

Species of Shuttle		
Quantities of each species of shuttle		
Distribution of instances of shuttles		
Links (receptor to channel) for each shuttle		
Second messenger progress for each instance of shuttle		
Species of Pump		
Staging each side of each Pump		
Modulators for each species of pump		
State kinetics of each species of pump (Q = 6x6)		
Starve and Saturate kinetics for each species of Pump (number of Q)		
Affinity/binding/dissociation kinetics for each pump		
Quantities of each species of Pump		
Distribution of each instance of Pump		
Particles bound/transported for each instance of pump		
Species of Vesicle		
States of each Vesicle		
Quantities of each species of Vesicle		
Distribution of each instance of Vesicle		
Modulators for each Vesicle		
Affinities and dissociation rates for each Vesicle		
Contents of each species of Vesicle		
Release kinetics for each vesicle		
Quantity of input plugs		
Contents of each input plug		
Distribution of input plugs		
Quantity of output plugs		

TABLE 17: MODEL QUANTIFICATION

8 DESIGN PROCESSES

The currency of this model is not energy. It is not structure. It is not random processes. It is information.

The elements described in the prior chapter, Design Elements, are each endowed with the static aspects of their type. This chapter addresses the dynamic functions of those elements and their inter-relationships. There is an abundance of modeling approaches in the literature that serve physics, for such purposes as conserving the energy of the system and/or the mass of the system. They meet conservation law requirements by aggregating the particles, forming grouped continuous phenomena. But a study of information does not allow such aggregation. To pursue the information flows of neurons it is necessary to dis-aggregate the analytic EQs, via instantiation. It is necessary to build particle systems that faithfully process information, demonstrably representative of how living neurons perform their functions. Some articles declare as "molecular models" what are analytic equations representing aggregated particles. This model, however, represents particles individually so as to investigate the information carrying and modifying potentials of particles by position, velocity, charge, mass, type, bond tendencies, etc..

The neuron is a system which receives varying chemical concentrations over a portion of its surface, as inputs (via bindings to receptors). It also emits varying chemical quantities from very certain portions of its surface (via vesicles) as outputs. In between these two transduction processes, there is a vast network of ion-processing devices. This ionic system is driven by steadily replenished concentration gradients and voltage gradients (generated by pumps). This system is heavily modulated by many types of chemical messenger molecules. Additionally, the forces of voltage gradients and concentration gradients are not static and are not homogenous. Fluctuations in both voltage and particle concentrations modulate transmembrane ion conductivities as they impinge upon the transmembrane actors. Available energy and channel response patterns give rise to various forms of signal processing along the membrane, e.g. positive feedback, regeneration, and propagation. In complementary fashion, the pumps must restore what the channels "bled" out. That is, the passive channel transport is driven by the active pump transport. The pumps are numerous enough, and fast enough, to participate in signal shaping; and that can only be investigate by mimicking position relationships between channels and pumps.

This model is silent to the processes of genetics, proteomics, energetics and housekeeping functions. It is intended to perform basic neuron functions of graded responses and action potentials as a consequent of stimuli working through actor molecular kinetics. Only those actors of immediate causal significance in the transfer and processing of information need be included. The various nonlinear responses of the actors may result in a wide variety of patterns. Forward compatibility shall support adding features of longer time constant processes such as plasticity and learning.

Channel conductivities are altered dynamically by internal state transitions. These state transitions, in turn, are modulated by external modulators. Modulators may be impinging forces and/or particle bindings.

In this model, particle collisions and actor state changes are energy conserving. Mass is conserved , and may be regrouped in chemical reactions and hydration. Energy is consumed in the transporting of particles against the gradients, but this is recorded as a bookkeeping exercise, not derived from first principle results, and therefore does not account for how this energy is dissipated out of the system. It remains for others to investigate the thermal dynamics of the kinetic schemes proposed herein, so as to determine feasibility of molecule designs proposed.

8.1.1.1.1 Element Processes

a) Actors are any of four protein classes which are found affixed to the membrane at static or nearly static locations. They operate as finite state machines, with states changes resulting from the impacts of thermal motion, voltage pressures, allosteric bindings, and energy-yielding chemical reactions. Some of these states result in actions that impact the outside world. Actors usually have binding sites that may effect modulation, or be involved in transporting particles.

b) Particles are free to move about in aqueous solution unless bound. Particles have traits, at a minimum consisting of mass, radius, charge and mechanical mobility. Ions in aqueous solution diffuse and drift throughout each compartment, and operate as a charged particle system. Their motion is due to thermal energy, concentration gradients and drift forces. Particles may bind and unbind to each other or to actor binding sites.

c) Membranes, serve as the boundaries of compartments, as charge barriers (that cause capacitance), and as sites of actor placements. Membrane processes include reflection, actor placement nodes (addressable), and voltage building due to any accumulation of unbalanced charge.

d) In addition to the explicit elements, there are several implicit aspects of the model. Particle flux, voltage, current

and capacitance are emergent phenomena. The concept of phenostate is also emergent, whereby an actor internal conformation, may in certain environments result in significant impacts upon that environment.

Actor dynamics emerge from their intrinsic traits, collisions of motile particles and temperature. There is a coupling between actor state transition probabilities and actor binding site binding kinetics. This model evaluates actor state transitions for their role in holding and processing information, and for their ultimate impacts upon their immediate environment (also a form of information). This model generates and tracks bindings, unbindings, conformation state changes and phenostates for each individual actor.

Each particle types gives rise to dynamic behaviors emergent from its intrinsic and extrinsic traits. Particles experience velocities and accelerations, collisions and bindings. This model tracks individual particle position, velocity, acceleration, binding, and transport events.

Although the compartments are static structures, they do partake in the critical dynamic of capacitated charge, which this model tracks. In digital simulation, the collisions of particles with the shaped membrane is not a passive phenomenon, but requires significant calculation load.

Actor intrinsic traits: TYPEA.Chan = { bindkinetics, conformerkinetics, phenotable, transportfunction }
Actor extrinsic traits: DIST.A.Chan = { position orientation poles comp# B#bindings O#action }

In similar fashion, the particles (also called interactors) are characterized by their intrinsic and extrinsic traits:

Interactor intrinsic traits: TYPE.B.Ions = { # mass charge radius mobility }
Interactor extrinsic traits: DIST.B.Ions = { comp# position velocity acceleration bind actor# pole#}
There are also TYPE.B.ligands, and DIST.B.ligands, treated in much the same way.

And finally, the compartment membranes are characterized in similar fashion:

Compartment intrinsic traits: TYPE.C.memb = { thickness dielectric_coefficient capacitance }
Compartment extrinsic traits: DIST.C.memb = { shape nearestneighbors voltageacross current_through }

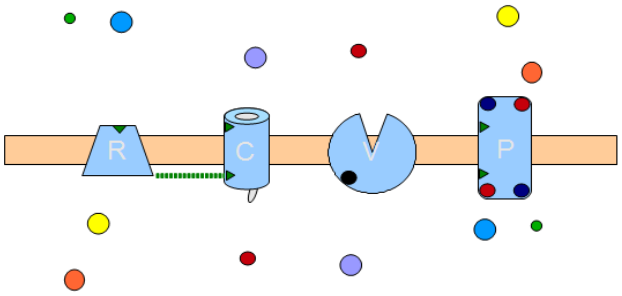
These organizational notions are pervasive in this model.

8.1.2 PROCESS ENGINES

There are three main actions that must be generated by this model: free ranging particle movement; actor state changes; and the electrical phenomenon of signal propagation along the membrane. Each of these subdivides into several specific types and processes. There is generally one class of membrane, two classes of particles, and four classes of actors.

It was discovered in the course of model development that the electrical phenomena of signal propagation is emergent from the charged particle system. The model evolved into representations of 4 major processes: particle movements, actor state changes, particle/actor bindings and unbindings, and actor action functions (e.g. channel openings). A summary of that development follows.

Depicted in the cartoon below is a membrane with four types of actors embedded in it and saline solutions on either side.



Receptor Channel Vesicle Pump

FIGURE 61: ICONIC VIEW OF MODEL ELEMENTS

The four actor types are: R = receptor, C = channel, V = vesicle, and P = pump. The dashed green line is 2-D diffusion shuttle from one receptor to many channels. The vesicle stochastically releases a pre-packaged group of particles. And the pump attempts to restore the original "rest" conditions.

The processes of the model are divided into groups corresponding to the three main elements: membrane, particles and actors.

1. Membranal processes include barriers to forces and capacitance. As a result some unique phenomena occur along the membrane. Membranes support 2-d diffusion and 1-d diffusion, and charge-motivated behaviors. They reflect particles that impact them according to reflection angles about the pixel normals. Each membrane may be tessellated into triangular pixels. Then, each node has a hexagonal (6 pixel) surround which comprise the capacitive area for that actor. These surrounds vary in area as a function of actor densities.

2. Interactors are particles in solution which possess position, mass, radii, charge, position, velocity, and the capacities to collide, reflect, bind and unbind. Momentum is employed to resolve the frequent collisions. Supported is 3-d diffusion, collisions with water molecules, collisions between ions, force accelerations with respect to both free ion charges and fixed charges, and binding to actors and membranes.

   A particle system of diffusive processes must include the electrodynamics of charge fields to account for the significant behaviors of membranal information processing.

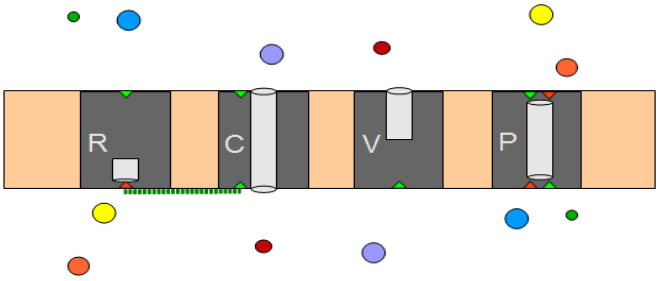


FIGURE 62: DIFFUSION ENGINE VIEW

In the diffusion software engine, the electrical processes and diffusive processes can be merged , treating the actors as black box sources and sinks.

3. Actors are considered to be point processes driven by thermal energy and modulated by messengers and the voltage force. Some actor types (e.g. pumps) require additional energy sources to function properly. Model energy sources, such as ATP, are treated as allosteric modulators. That is, the Gibbs energies are not calculated. The conformational changes executed within the model actors are not energy-aware, although kinetic schemes imply energy relations by their state path probabilities which give them direction. Pump performance is modulated by concentration levels due to the kinetics of binding/unbinding. The channels

are driven by thermal energy and modulated by messenger bindings and impinging local voltage gradients, resulting in changes in conductivities (openings and closings). Collectively, pump and channel functions may be referred to as transport, whereby ions and/or ligands may be moved from one compartment to another compartment. Receptor and vesicle function may be referred to as transduction, converting a signal on one side of the membrane into a different, usually amplified, signal on the other side.

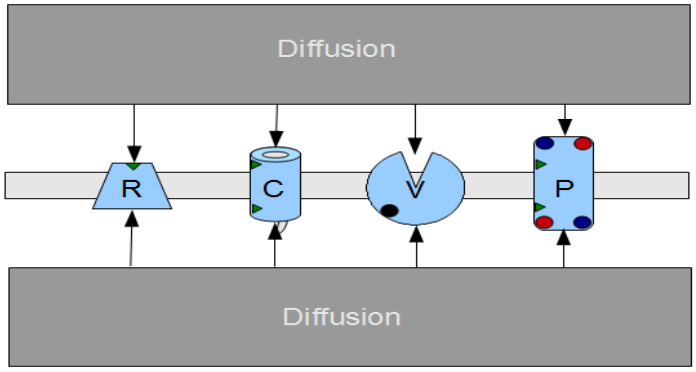


FIGURE 63: KINETIC ENGINE VIEW

In the kinetics software engine, the actor kinetics are separated as stochastic PDEs, and diffusion deliveries are treated as a black box source and sink. The reception of particles delivered by the diffusion/drift process is not certain, and the stochastics of binding and unbinding to actors add an additional uncertainty/variance.

A binding or unbinding event causes an alteration of the internal transition probabilities between possible conformations to be altered, resulting in a phenomenon called modulation. For durations while the modulator binding combination is stable, the internal conformation changes are driven by thermal noise, yet another source of uncertainty. The stochastics of messenger release may be very similar to those of modulator bindings and unbindings. For vesicles, a group of particles (the vesicle contents) are placed within it, according to A4.traits which specify contents profile mean and variations. The timings of recharge and release, lags, speeds and variance are also stochastic.

This project was founded on the project plan to design and implement the three engines above. However, as the model matured, it was found that the particle model increasingly encroached upon the electrical grid model. The particle model was more predictive, solved more problems, and exhibited more useful and emergent behavior. It eventually became clear that the electrical grid was to be completely replaced by the features of the particle model.

8.1.3 TAG MANAGERS

Particles in a digital simulation require some bookkeeping. They are assigned to a compartment and are not allowed to leak out unless by design. If they become bound to an actor, they must be tagged with the actor number and the velocity temporarily set to zero. Tags are changed by the binding and unbinding of a particle, and by the transport to a different compartment. There may be other data necessary to capture for the sake of digital model bookkeeping. The collision of a particle with an actor, is "owned" by the particle. It is individual particle motions that determine collisions, and such collisions are tracked via particle data tables. However, once a collision occurs, it is the actors that "own" the decisions whether or not to bind. The binding/unbinding decision process is a stochastic one that is driven by the bind site probabilities residing within the Actor state machines. Thus, the Actors are *de facto* Tag managers for bind/dissociate actions, and for transport actions. A is mapped onto a partial of B , and then certain functions are applied to B. These functions include chemical reactions, and relocations. They include catalysis, such as the rapid creation of messenger particles by a stimulated receptor, and the conversion of ATP to ADP by some pumps. In order to handle a query about a particle location, velocity or state, the particle must maintain pointers to the actor that captured it. If such queries are intensive (asked every *dt)* then an inverted table needs to be generated each *dt*., mapping B to A The normal relationship would be: given an actor#, return all particle#'s involved with that actor and their status. The converse would be: Where is B?

```
AB = getBindinfoAB (actor# );
AB = [actor# pole# bindingsite# particle# rlevel];   % where rlevel =  { 1 for bound naked, 2 for bound
hydrated, 3 for within binding radius; 5 = within affinity radius, 6 = this actor is nearest actor };

BA = getBindinfoBA(particle#,rmax);                  % where rmax sets maximum rlevel returned
BA = [particle# actor# pole# bindingsite# rlevel];
```

To the extent that particles may incur probabilistic events with membranes, the kinetics of such particle interactions and molecular state transitions have both forward and backward probabilities. Such probabilities can be accommodated whenever the particle is identified as a Kolmogorov entity, in which case an R matrix shall be provided for that Actor across all particle types. The treatment of R matrices is stochastic, similar to the Q matrix of the Actor internal state, except that forward reactions must be multiplied by the local concentrations of particles, based upon first order rate kinetics.

From the software perspective, all collisions and binding state updates can be performed *en bloc*, regardless of ownership by the Actor, Particle or Compartment membrane, as B **x** [A B C]

In the working model, the membrane nodes were given 200 traits. The particles were given 34 type traits and 100 instantiation values. The actors were given a complex of 10 type matrices and 34 traits and 40 instantiation vectors. See chapter “Data Structures” for details.

8.2 RC_GRID

The nodal EQs solve for the currents through the membrane at a single node each *dt.* These currents are dissipated and propagated horizontally to neighboring nodes via the saline conductors between nodes both above and below the membrane.

The RC_Grid is an electric network consisting only of resistors, capacitors, voltage sources and current sources. It is ultimately responsible for the propagation of the action potential and all other graded responses of the neuron. Each actor occupies one node. Each node may be vacant, or occupied by one actor. The effective area of an actor extends half way to its nearest neighbors. (calculated via Voronoi's algorithm).

Membrane capacitance is allocated to each occupied node, not to the edges between the nodes. The nodal capacitance values are per Voronoi polygons of varying sizes and shapes. However, the shape has been standardized to a hexagon wherever possible to assist in CPU speed.

The edges are all comprised of saline resistors, both intracellularly and extracellularly, which connect each node to its nearest neighboring nodes. The nearest neighbors are calculated via the Delaunay algorithm, and may vary from 3 to 12 in quantity, at the choice of the user. The computational load goes up with the NN count, but the richness of coupling is accordingly increased.

8.2.1.1 Channels are variable resistors

The voltage sources across channels are Nernst potentials calculated for each ion type at each actor. Each such partial subtracts from *Vm* to get the net voltage potential driving that type of ion. If there is no conductance for that ion type at that node, then that Nernst potential is undefined (0/0), but is practically zero, in that its term is dropped from the GHK EQ which sums the partial voltages into an aggregate value. Be reminded that channels are gates, with low duty cycles. Although every electrical circuit needs a complete circular path, closed channels disrupt that path. The membrane capacitance must serve as a buffer for currents from pumps and intermittently open channels.

8.2.1.2 Pumps are current sources

Ion pumps are current sources. A node is a pump if it has any negative conductance values. Pumps impact flux, concentrations, current, membrane charge, all on a basis of peculiar ratios between ion species. As a group, pumps create a non-orthogonal basis for charge balance restoration after each channel event, and thus are logically complex when solving for solutions. Co-transporters can be treated as coupled double-barreled, or triple-barreled, transporters with local presence of special 'ligands' (e.g. ATP) that drive some of the ions against their gradients between the compartments. The energetics of “pumping” can be treated as a negative conductivity or as a energy conversion machine. Pumps are generally cycling rather rhythmically, for two reasons. Because they pump only 1 to 5 ions per cycle, and channels can allow the flux of 1E6 ions in a single pore opening, the pumps must work continuously to restore a quantity exceeding what the channels allowed to passively transport. The pumps may be modulated to set their saturation concentrations, but are less likely to be modulated as dynamically fast as the channels because their very few ions in transport cannot have much effect that isn't masked by the channel openings.

The general RC Grid circuit well represents both ion channels and ion pumps. Co-transporters may appear graphically as several separate channels with dotted line coupling between them. They require the additional logic of ratio pumping, which is represented in an electrical circuit as "mechanical linkage". Kinetic representation of the pumps can effect any stoichiometric ratio.

For purposes of pump BUILDs in this model, what ever ions are pumped from compartment A to compartment B are listed in “Bind1” (a table of pump staging required ions, starve concentrations, saturation concentrations); and from compartment B to A as Bind2. From these data are calculated sigmoid performance curves as determinant of ion

binding and unbinding statistics. A third pump table manages: maximum pump rate and energy consumed per pump cycle, the pump position, its pole locations. Pumps may be set up to receive their bind1 ions in sequential order, or in “no order specified”. They may require completing the Bind1 sequence then Bind2 sequence alternately or simultaneously. Such settings depend upon the biological data which characterizes each Type of pump.

Pump RUN data is managed as pump states, via Bind1, Q, and Bind2. Pump functions include: Attractor, Binder, Transporter, Unbinder, Converter (ATP).

8.2.1.3 Saline Resistance

Copper wire and carbon blocks are very predictable in their resistivity, and so might saline be in a cylindrical shape with a metal plate at each end. But saline in the cell is employed as a conductor from point to point, or from point to surrounding surface. It therefore does not produce a resistance linear with respect to distance between source and sink. Ion channels are effectively point sources and sinks, with extremely small “cross-sectional area” of conductance, the lines of current tend to balloon out from the source point into the open liquid space, then shrink back to a sink point at one or more neighboring channel. Most of the resistance is concentrated at the poles. The belly of the path is fat, therefore of low resistance, and so resistance does not vary much with distance. Or is this effect not a volumetric effect, but rather a surface effect?

There is not as much point-to-point conduction as textbook drawings of the neural membrane would suggest. Channel duty cycles as mostly in the closed state. Most of the time, current flow is point source to membrane capacitance. This presents a large planar sink with a cross-sectional area hundreds or thousands times larger than than the ion channel pore (suggesting a cone of resistance, or more accurately, a fountain shape). The dominant variable of resistance is tonicity. Conductance is proportional to the ion density. Divalent ions have twice the EM force applied to them in a field, and thus move about twice as fast. If electrons can be freed by the presence of a charge field, then the ion masses become irrelevant, and the velocity of conduction approaches c. This is a matter of great import to the model. Are there free electrons available for conduction near the membrane (above and below)?

8.2.1.4 Capacitance

Capacitance is essential to simulate an action potential in neurons. The physics says F= q1q2/r^2 for EM force, with a dielectric barrier holding apart dissimilar charges, and voltage applied via ion pumps.

Inter-particle forces result in acceleration. The sum of all forces impinging upon a single particle determine the acceleration of that particle for one *dt*. A plate charged oppositely on each face does not produce a capacitor when elasticity is high. Reflective surfaces bounce the particles back, unless water is present to smear this effect. Elasticity might be reduced, but such reductions in velocity cool the solution. Water as a solvent diffuses the bounce but does not help get particles to stay near the plate, quite the contrary.

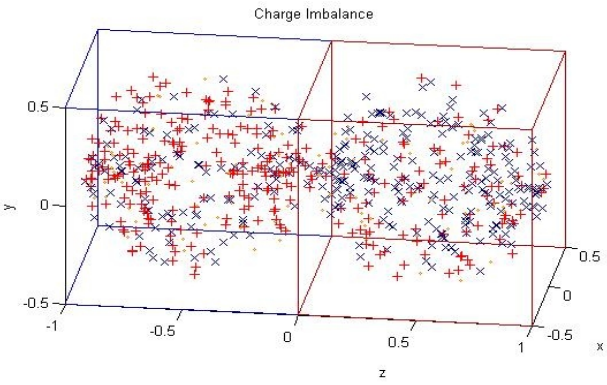


FIGURE 64: INIT USING BOLI, T=0

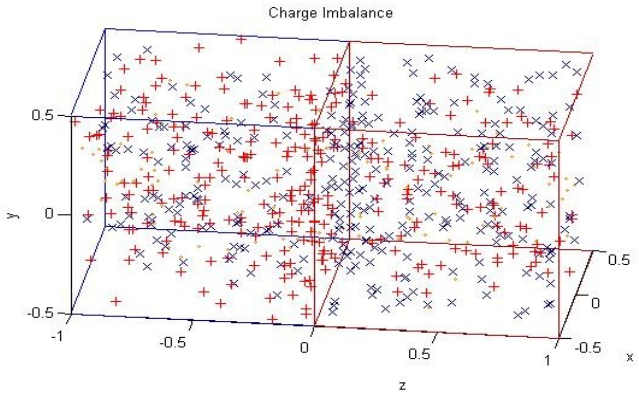


FIGURE 65: UNBALANCED CHARGE, T=25

Note the accumulation of charges at the central membrane by the end of the run of only only 25 *dt*.

Results of a dielectric membrane, and a 5% charge imbalance. Negative charges pile up against the membrane on the side with a surplus of negative charges, and are repelled away from the membrane on the side with a deficit of negative charges. The quantities of charge attracted to the membrane are equal on either side. The "charging curve" continues until the remaining particles (not at the membrane) are net-neutral in charge. The dielectric factor of the membrane can increase the capacitance due to dipole surface effects within the membrane. This is modeled by adjusting the "effective" thickness of the membrane.

There is an equal number of positive and negative charges on either side of the barrier (located at x=10). These form a capacitor within several *dt*. The neutral particles remain randomly distributed.

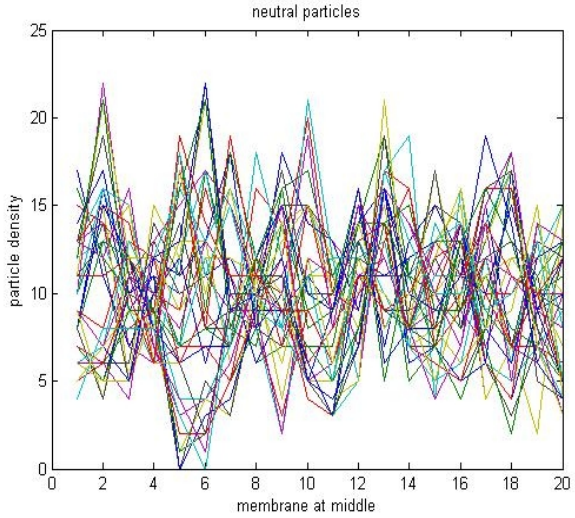


FIGURE 66: DISTRIBUTION OF NEUTRAL PARTICLES

Electro-diffusive equilibrium is temperature sensitive. At equilibrium, the voltage pressure is proportional to the log of

the charge density, per the Nernst EQ. The equilibrium state is derived by Weiss as:[183]

phi(x,inf)-phi(x0,t0) = (gask*kelv)/ (-z*faraday) * ln(conc(x0,t0)/conc(x,inf));
d^2 phi(x)/ dxdx = 2*z*faraday*conc(inf)/permit * sinh(z*faraday*phi(x) / (gask*kelv)); %
d^2 Phi(X)/ dX^2 = sinh(Phi(x)); % removing all constants via normalization, where Phi(x)
debye = sqrt (permit*gask*kelv/ (2*z^2 * faraday^2 * conc(inf)) % The space constant equals the debye length.

phi(x) = phi(0)*exp(-x/debye); % the Debye length is about 1 nm

The charge field along the membrane drops to zero within 3 Debye lengths = 3 nm. The need for a buffer region outside the charged region is not yet determined, and would depend upon the variations in charge on the membrane. Studies by Johnston and Wu concluded that action potentials only deplete about 1e-5 fraction of the total charge on the membrane. [184] This suggests that very little if any additional fluid thickness is necessary to model the membranal system.

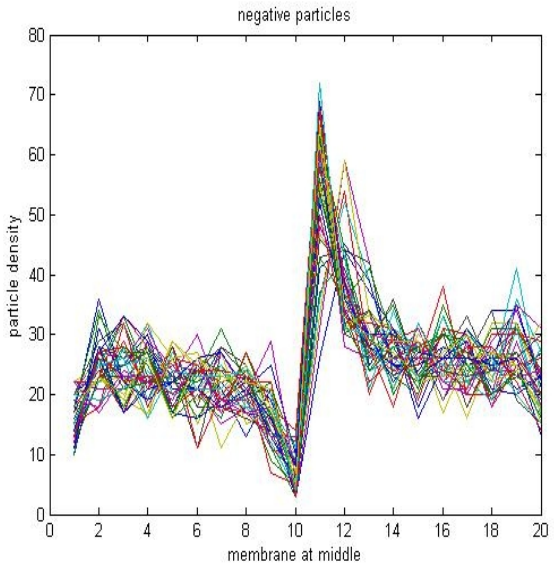


FIGURE 67: DISTRIBUTION OF NEGATIVE CHARGES

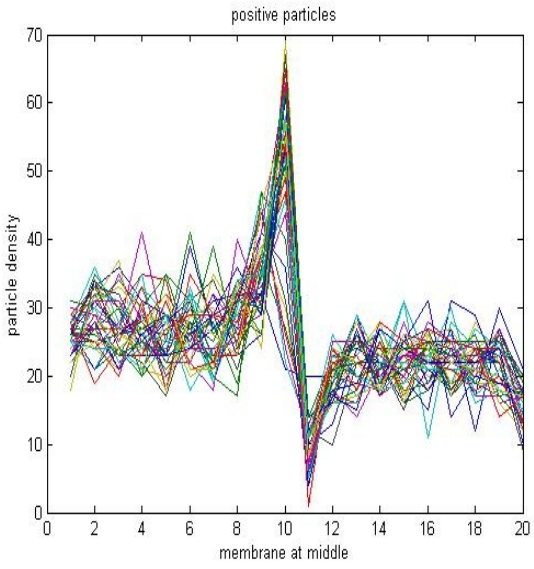


FIGURE 68: DISTRIBUTION OF POSITIVE CHARGES

The above are measures of charged particles at various distances from the membrane. A simulation of particles in equal concentrations of positive ions and negative ions on each side of a membrane. Then a charge imbalance is introduced of 5%. X-axis units are nm. The particles follow a "charging curve" in that the negative are attracted to the right surface of the membrane and are repelled by the left surface. Vice versa for the positive particles. The number of particles captured in capacitance are exactly the number of the charge imbalance. The remainder are therefore experiencing a charge-neutral environment and are completely free to diffuse in random walks.

Particle systems with charge are problematic at the boundaries. A common technique of physicists is to define the model as a cylinder such that the system repeats endlessly with clones of itself rather than meet an actual edge. These are referred to as periodic boundary conditions. However in this model the compartment boundaries are the membranes and that is where the critical action is located on both sides. Periodic boundaries would not support such clearly denoted shapes, inputs and outputs of neurons. The solution turns out to be quite simple. Charge imbalance occurs only very near the membranes, within 3*Debye, where the membrane serves to capacitate the surplus charges. All the rest of the volumes are charge neutral. As elaborated elsewhere, charge-neutral volumes are null areas as far as information processing goes, except in the synaptic cleft, where diffusion is primary. They act as sinks and sources for the membrane system ions, whenever the voltage across the membrane changes.

8.2.1.5 RC Grid Nodal schematic

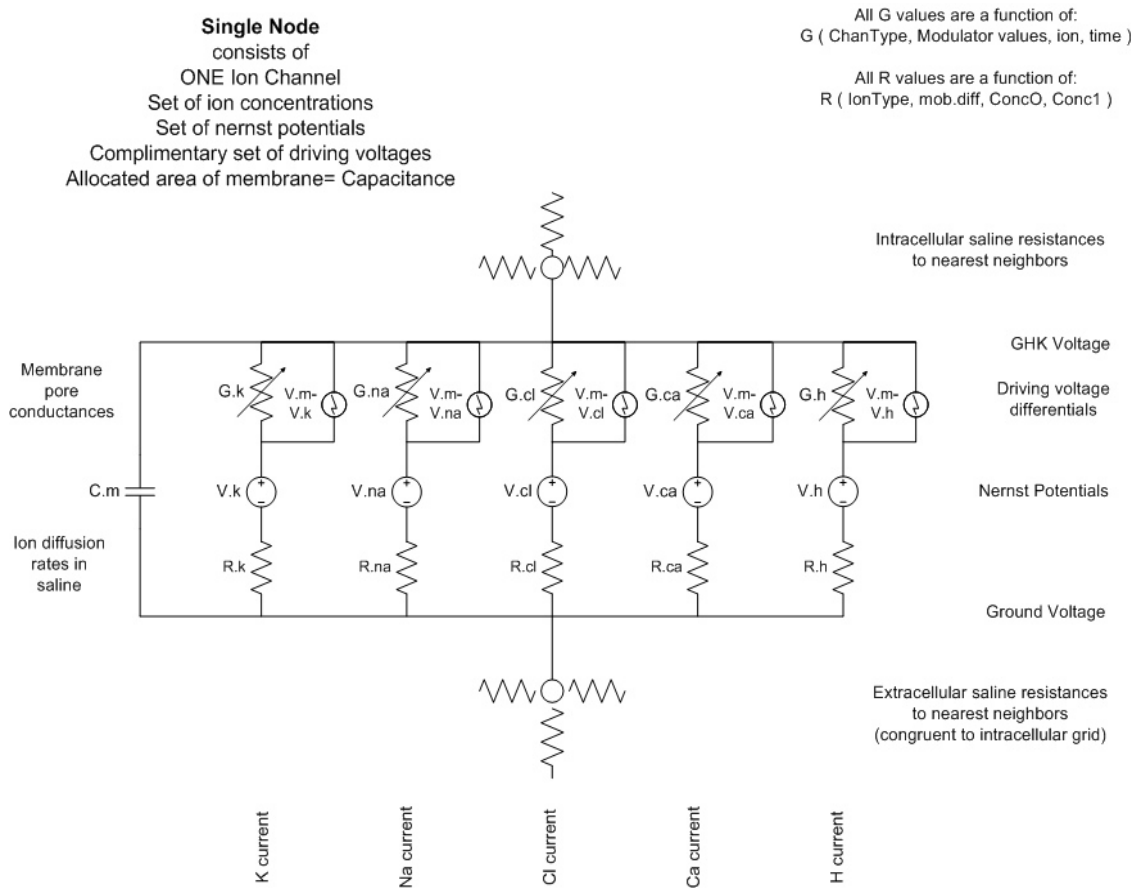


FIGURE 69: ELECTRICAL CIRCUIT FOR A SINGLE NODE IN THE RC-GRID

The RC_GRID is a closed surface network of low pass filter stages. It is sustained by energy consuming current sources, the ion pumps. It is modulated by varying the conductance values (vertical resistors labeled G only). Despite its effectively infinite series of low pass filters it is quite capable of propagating a pulse made up of frequencies as high as 5 k Hz. This presumably is due to the strongly non-linear response characteristics and to the positive feedback loop that drives the action potential.

The RC_GRID is implemented as a modified nodal analysis method matrix representation.

The BUILD includes one matrix for the intracellular saline resistances, one matrix for the capacitance, one matrix for the extracellular saline resistances. This trio is doubled when the closed shape is split sagittally into "left" and

"right" panels. Such a split has the advantage of minimizing distortions of node to node relationships when projecting the 3-D half onto a 2-D matrix.

Solving for voltage changes across the entire membrane, on a node-by-node basis.

$$\dot{V} = \begin{bmatrix} \left(\frac{-1}{r_m C} - \frac{1}{r_i C}\right) & \frac{1}{r_i C} & 0 & \cdots & 0 \\ \frac{1}{r_i C} & \left(\frac{-2}{r_i C} - \frac{1}{r_m C}\right) & \frac{1}{r_i C} & 0 & 0 \\ 0 & \frac{1}{r_i C} & \left(\frac{-2}{r_i C} - \frac{1}{r_m C}\right) & \frac{1}{r_i C} & 0 \\ 0 & 0 & \cdots & \ddots & \vdots \\ 0 & \cdots & & \frac{1}{r_i C} & \left(\frac{-1}{r_i C} - \frac{1}{r_m C} - \frac{1}{r_o C}\right) \end{bmatrix} V + \begin{bmatrix} \frac{Io}{2C} \\ 0 \\ \vdots \\ 0 \\ 0 \end{bmatrix}$$

FIGURE 70: RC GRID MATRIX

General form of the matrix to solve for dV across a tessellated surface. Given N occupied nodes, the the matrix G is an N x N matrix expressing all the relationships of each node to its nearest neighbors.

R values are to nearest neighbors. C values are nodally allocated to local area via a Voronoi-like algorithm.

Element data is stored as ELE = [x1 y1 z1 x2 y2 z2 type value]; It is generated by a spreadsheet driven by input of channel positions, pump positions, radius, thickness, length. In a 10x10 grid there are 200 nodes and 500 elements.

By convention, x is axial, y is radial, z is circumferential. There are 5 axes of resistors: outer-x, outer-z, inner-x, inner-z, and through membrane y. There is 1 axis of capacitance: through membrane y. And 1 axis for pump currents. It is computationally expedient to initialize resistances inverted as conductivities. We then have:

G1x, G1z, G2x, G2z, Cy are static or nearly static values;
Gy(t) and Py(t) are dynamic values, parametrically driven by modulators and internal kinetics.

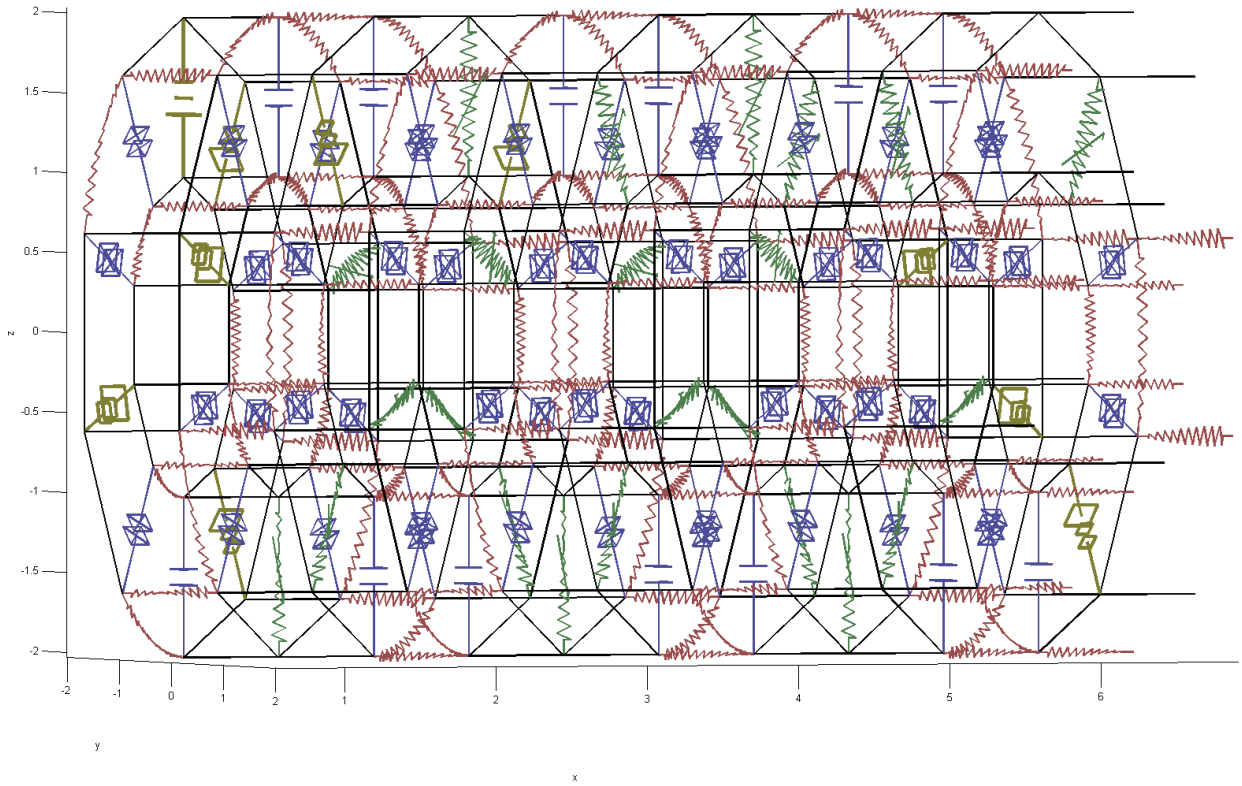


FIGURE 71: CYLINDRICAL RC GRID CIRCUIT

The cylinder above is a 10 x 10 x 2 nodes grid. Element data is stored as ELE = [x1 y1 z1 x2 y2 z2 type value]; It is generated by a spreadsheet driven by input of channel positions, pump positions, radius, thickness, length. In a 10x10 grid there are 200 nodes and 500 elements.

By convention, x is axial, y is radial, z is circumferential. There are 5 axes of resistors: outer-x, outer-z, inner-x, inner-z, and through membrane y. There is 1 axis of capacitance, through membrane y, and 1 axis for pump currents. It is computationally expedient to initialize resistances inverted as conductivities. We then have:

G1x, G1z, G2x, G2z, Cy as static or nearly static values;
Gy(t) and Py(t) as dynamic values, parametrically driven by modulators and internal kinetics.

The use of the words “electronic” or “electric” are misnomers, or misused, when describing the workings of neurons. First of all, they employ ions, not electrons. This would not matter much if it was a one-to-one mapping or

analogy between the two. But ions are chromic, where electrons are not. The pallet of ion types opens up many possibilities that are not possible in electronic circuits. None the less, our point of departure is an electrical circuit.

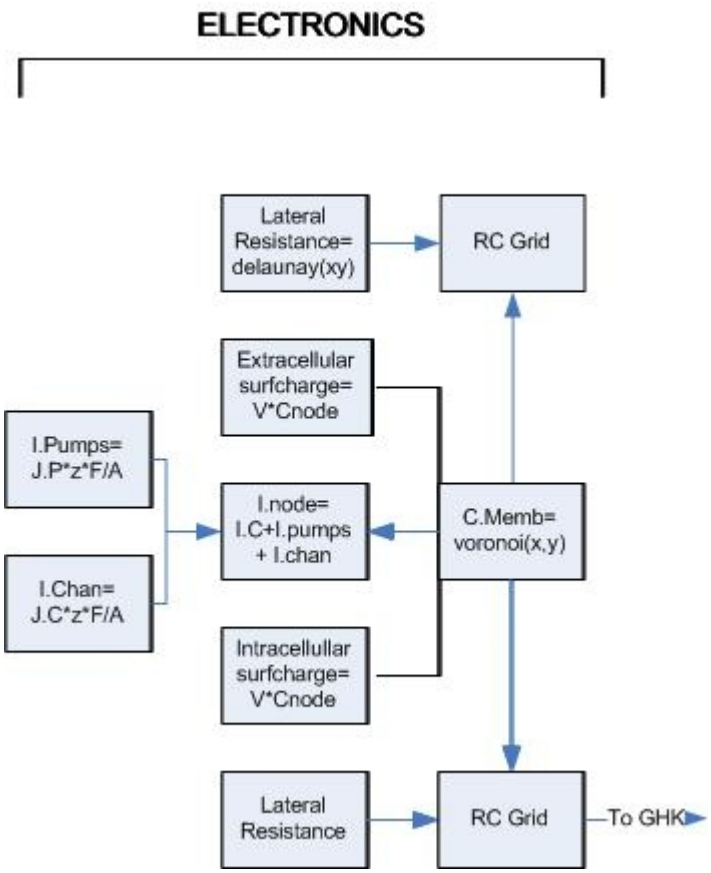


FIGURE 72: ELECTRONIC MODEL EQUATION FLOW

Currents, which are the net electrical effect of ion flux through ion channels, directly effect the local membrane voltage, which dissipates out in the RC grid to nearest neighbors. Membrane local capacitance is essential to determine the membrane voltage.

8.2.1.6 Electrical Networks

FEM grids Resistance-Capacitance are measurements of the state of the system, particularly the particle positions, and the voltages and currents their charges induce. Although this project included the construction of an RC grid in its specific aims statement, it is found through model building that the resistors of such a grid are embodied in the particle system behaviors, and that the capacitors of that grid are also embodied in the particle system behaviors.

And finally, the conducted (transported) ions through the ion channels must be calculated via the Nernst EQs. Newly transported particles immediately participate in the capacitance, either increasing or decreasing it. The challenge is to get the force, size, charge, and velocities to scale proportionate to actuality so as to yield model timing accurate to bio-phenomena.

Implicit Components are:

Finite Element Capacitors	Once the positions of all actors on the membrane are known, an algorithm calculated a polygon around each actor. This polygon has and area, and that area has a capacitance as a function of permittivity. The capacitance value is stationary for the RUN.
Finite Element Resistors Extracellular	The shape and salinity of the extracellular fluid between any 2 Actors can be employed to calculate the resistance between those 2 nodes. This resistance can fluctuate with conc0, but usually is stable.
Finite Element Resistors Intracellular	The shape and salinity of the intracellular fluid between any 2 Actors can be employed to calculate the resistance between those 2 nodes. This resistance can fluctuate with conc1, but usually is stable.
Channel Conductances	The conductance values of each individual channel must be calculated at the finest available *dt*, as they are extremely dynamic. These G values are the result of gating variables * Gmax values.
Modulators	Modulators may be Ligands, ions, voltage or concentrations. "Modulator" is merely a concept, referring only to whatever serves as the "input" signal to an actor.
diffusion rate	is a consequence of collisions and reflections
flux, horz	is a function of the distance between actor nearest neighbors
Current, ionic	Is the net charge movement due to all flux of charged particles. Currents occur in 3-D volumes of irregular shapes, not in 1-D metallic long cylinders as in solid state circuits. This current has mass, and is therefore slow and has some inertia. It is “smeared” by water collisions.
Current, electronic	Is the instantaneous (speed of electricity) electrical effects due to electron wave fronts. It is not modeled by particles but rather calculated.
voltage	Pressure on charged particles, to cross a barrier (membrane) due to net charge imbalances. Voltage is calculated by the Nernst EQ.

8.2.2 ABANDONMENT OF THE RC-GRID

The decision to abandon the RC-grid is based upon the following findings. While the resistors of the RC-grid connect only to nearest neighbors, saline in actuality is “connected” to all points on the closed surface of the neuron. The particle system accurately reflects this fact. While the capacitors of the RC-grid are created as discrete, proportionate in capacitance to the membrane area immediately surrounding each channel and pump, in actuality,

membrane capacitance is continuous over the entire surface of the neuron. This continuity results in markedly different behaviors. This continuity allows the capacitance to act as a conductor over all the surface, thus bypassing the saline resistance. Because the capacitance of unbalanced ion concentrations are infiltrated by balanced saline solution, the capacitance is a mixed component of both capacitance and resistance, distributed all along the surface. This is not easy to model with discrete electronic components. However the particle system model is an accurate representation of such distributed commingled capacitance and resistance. Finally, the nano-geometry of like-charged particles forming a monolayer sheet along the membrane surface can produce some emergent properties, like frictionless transport for the next higher layer of charges. Because the purpose of this model is to seek out the means by which information is transmitted (preserved) from channel to channel, every opportunity must be afforded the particles to reveal the patterns by which information is coded and moved. It is quite possible that due to the mass and charge repulsion of the ions that some wave phenomena are present, as any mass-spring system can oscillate unless critically damped. Because waves transcend the entropy of diffusion, they would be of great interest in the investigation of information transmission.

Additionally, given a continuous saline compartment, and a continuous capacitive membrane, the model is expected to reveal new knowledge concerning the “clearing” of old messages out of the system to make way for new messages. That is, any information moving through the system must have sufficient persistence to move to its destination, but little more. A particle system model is expected to reveal some of the nuances of how this might occur.

8.3 THERMALLY DRIVEN STOCHASTIC SYSTEMS

Biological systems are characterized by large numbers of coupled chemical reactions all, or mostly all poised at their “tipping points” such that they can go either way with little or no energy consumption. This allows complex systems to be driven largely by thermal energy, with the addition of consumable energy forms like ATP to set the direction of dominant flows. Therefore the main metabolic pathways direct and establish the purpose of the system, while thousands of thermally driven side reactions maintain the homeostasis and adaptations of the system. This model avoids most of the cell thermal dynamics by restricting elements to 4 classes of protein defined by state transition probabilities, allowing ions to move in response to diffusion and drift, and leaving the membrane as a

fixed structure. Of the membrane elements, only the pumps consume energy; the rest are either static or driven by ambient temperature (Brownian impacts). Note hat thermal energy is not consumed. Each molecule returns as much as it receives. There is no lower form of energy to degrade to, and this model does not employ explicit endothermic reactions. Energy transfers are irrelevant to information processes except as needed to drive the pumps in their roles of restoring trans-membrane charge gradients and tonicity gradients. Although the pumps are crucial to viability, it is not yet found that pumps are informationally significant in the short time frame of action potentials. They may be said to be informationally significant in that their fatigue alters channel behaviors in ways that diminish the information processing potential of the cell, and may trigger modal shifts to "low-energy mode" reductions in information processing. In this model pumps may fatigue due to ATP shortages.

The stochastic processes of interest are the molecular states and bindings of actors. The actors work as finite state machines, per the kinetics of their chemistry and molecular contortions. Every molecular conformation has a set of possible transformations to alternate conformations. This may be enantiomeric or reactive chemistry. Each of the possible transformations has a probability of occurrence wrt to the most significant parametric factors (modulators). Each transformation has a forward probability and a backward probability. These transition probabilities may have a value of between 0 and 1 for each *dt*. As they are probabilities over time, their values change with the width of the timeslice. If the *dt* is sufficiently short then the probabilities of all possible next states will be <1. But if the probability of occurrence is such that two or more events will likely occur in the time duration of interest, then the probability will calculate to be greater than 1. This violates the definition of probability, but is a necessary concept for repetitive events. To avoid distortions in event frequency, *dt* should be chosen small enough to avoid transition probabilities greater than 1, but there always exist a few outliers. A decision must be made whether to clip these, write a routine to stuff two or more events into a single dt, or shrink the *dt* to reduce the stochastic probabilities to less than 1.

As we are concerned with events per unit time, the probabilities gleaned from the literature are not unit-less, but rather have units of frequency (1/s). In most applications of probability the chance of occurrence is multiplied by some value of that occurrence. However, in stochastic probabilities such multiplication works for all state changes, but it does not work for calculating the probability that no change will occur. All of the state *i* to state *j* transition probabilities scale linearly with *dt*. But the state *i* to state i probability requires special attention. The chances of a state remaining unchanged, of course, is a real number between 0 and 1 for any system, biological or silicon. But

the modeling simulation of that possibility is heavily dependent upon the size of *dt*. As nature enjoys continuous time, large artefactual error is picked up when *dt* is not much smaller (<<) than than the natural period of events. The probability of remaining in the same state = 1 - sum(transitions to other states). A *dt* value of <1/8 the period of the highest frequency in the transition matrix should be chosen to avoid aliasing error.

Transition matrices that are symmetric produce fully reversible processes. At sufficiently short time slices, all relevant processes are reversible. But the very transition itself changes the transition matrix. And this next matrix alters the path preferences. Therefore, *dt* chosen too large may see altered (unrepresentative) limit cycles.

```
% Q collects the event frequencies per second of all possible transitions, and
% therefore establishes the ratio between the transition possibilities,
% but is properly silent on the probability of "no change" (hold state).
% Normally, Q(pivot) = diag(Q)  =   1 - rowsum (all other possibilities)
% but when that sum > 1, then what must be Q(pivot)?
% the solution is to reduce dt such that the sum of all possibilities is smaller than the accuracy desired.
Qdt = Q*dt;                          % Qdt is a vector of the probabilities of transitions within 1 dt
Pdt(pivot)=0;                        %  pivot is the position in the vector that is the diagonal element
Pdt(pivot) = 1-sum(Pdt);             % let dt = 1/8*(1/max(Qfreq)
Pdur = qt*Pdt;                       % qt = duration as quantity of dt's
Pdur(pivot) = Pdt(pivot)^qt;         % Pdur is a vector of transition probabilities in qt*dt = duration
```

Each of the above vectors of probability for a single molecule (or subunit) are stacked to form an S1xS1 matrix of possible conformational state transitions, where qS1 = the quantity of internal states. The challenge is that these probabilities are even more dynamic than the neuron signals being propagated, changing as fast as 1E-6 to 1E-17 s . The fastest of these must be characterized as to their impact upon information processing. Typically, the fastest state transitions are found to be not significant to information processing, as they are classified as flutter. Those short states that are declared to be only noise or flutter are bundled into consecutive groups. For example, a fast buzzing between two states may be blurred into a single hold state with similar net effects.

A similar problem occurs with slow states. If they never occur then why would you model them? One noteworthy exception to the dismissal of slow states is the modal shift or toggle. No matter how rare is a modal shift it is the consequences of that change and the duration of that change that matters. To study these toggled modalities, take them out of the stochastic processor and fix them for the desired duration and run the model. This can easily be done with a state number over ride line of code added right after the state instantiation on target actors. To work

with modal limit cycles, a modified Q matrix can be substituted in, by zeroing out other possibilities. One must be careful to not dismiss any gateway states whose absence would render other states inaccessible.

The state transition matrix must be expanded into the third dimension (at least) according to how many modulator combinations significantly alter the transition probabilities. It is the modulation state (R) that determine which of the pages of the matrix apply each *dt*. Where dc = quantity of bind combinations possible within R. It is the internal conditions at the time which determines the page of the BT x d **x** S matrix that applies (where BT = list of particle types; d = list of binding sites on actor; S = list of actor states). Particle bindings and unbindings determine which R combination applies each *dt*. It is the prior state that determines which row in the S x S x dc matrix applies (dc = binding combinations), and the instantiation of the CDF from that row that determines the new state. Once chosen, the new state number is mapped to its phenostate, which calls functions making impact upon the surround (open channel, transport, release of messengers, etc).

Actors will have some number of configurational states, 2 or more. If an actor had only one state, it would not be an actor. The interactors (particles) have only one state. Configurational states in reality may be in the millions, but the biologists find that only a few of them are significant for their impact upon their environment. Typically 3 to 30 states are represented as a "kinetic scheme", as determined by repeated stimulation trials such as the two step voltage clamps.

Actors usually have one or more modulation site(s). These support allosteric bindings of certain messenger molecules. A modulation site may be either extracellular (at pole 2) or intracellular (at pole 1). In either case, a binding has the effect of altering the values of the kinetic scheme. Furthermore, the conformational state of the actor also tends to alter the binding rates at each allosteric site, influencing the forward and backward reaction rates. Receptors may be conceptualized as either catalysts, or as reservoirs of messenger particles at the ready. When the catalytic rate is faster than *dt*, the quantity of catalyzed second messenger molecules per *dt* must be staged by pre-binding them at the receptor's intracellular pole, ready for release. Particles are not allowed to appear from nowhere, so all must be created at the Build, and merely moved about thereafter. Particles may be stored at the receptor, then released during each *dt* there is binding of a primary extracellular messenger. Once depleted, the restoration mechanisms of affinities and/or pumps should replenish messengers at a realistic rate.

Therefore the kinetics of the extracellular pole are altering the kinetics of the intracellular pole. Although each pole may have any number of distinct binding sites, for purposes of the model there is no advantage to trying to give each a unique position on what is ostensibly a point process. Therefore the two poles of the actor represent by superimposition all the binding sites for purposes of both bindings and releases (stimuli and responses).

Actors may also have transport binding sites. For example, pumps must have one or more (usually 2..5) binding sites for specific ions to be transported. The binding rate must be high on the intake side and low on the output side of the membrane. Conversely the dissociation rate must be low on the load side and high on the unload side. To trigger the actual transport through the membrane, it is the complete staging of ions on one side that alters the conformational kinetics enabling transport. Those altered kinetics are then predisposed to move some arm across the membrane, taking the ion(s) with it. This movement imposes a torsional alteration of the kinetics, such that the ion bindings are weakened, and thus released. Then the exchange ions become highly attractive (high forward rate, low backward rate). Such dissociations again alter the conformational kinetics, predisposing the movable arm to develop and affinity for the binding of the exchange ion types. The successful exchange binding causes kinetics to return back across the membrane. And finally, such movement alters the binding kinetics so as to favor release of the exchange ion(s).

Adding to this complexity, pumps usually have modulator sites, and energy sources as well. Modulators can have effects of : speeding or slowing the pump rate; altering the maximum pressure (concentration + voltage) that can be pumped against; altering the preference for type of ions and ligands that are to be transported; and altering the affinity for low concentration particles. Energy sources are necessarily altered chemically. This is significant to the model because releasing an ATP rather than an ADP is informationally significant, both to pumps as a concentration of available ATP, and as a messenger, because there are ATP modulation binding sites on some actors.

The kinetics of modulation are not qualitatively different from the kinetics of a transport or second messenger catalysis. The concept of modulation exists only at a more macro view. Every binding and every force impinging on a molecule “modulates” it to some degree. That is, binding necessarily alters the state transition probabilities. Therefore, modulators and transport particles may be treated by the same mathematical representations. Only the transported particles must be re-assigned to new compartments. In this model, transport is triggered by the phenostate, not directly by the Q. The phenostate is merely a lookup table that maps state to environment impact

function. Channel phenostates are open and closed. Pump phenostates are binding arm on side 1 or side 2. Receptor phenostates are release mode or replenish mode. Vesicle phenostates are release mode or replenish mode.

The kinetics of an actor may be organized by degrees of freedom. The conformational states comprise one degree of freedom. Each modulator binding site adds another degree of freedom. And each transport binding site adds another. For example, an actor with 5 conformational states, 2 modulator binding sites and 1 transport binding site would have 4 degrees of freedom. If the first modulator site could bind either of 2 ligands, the second could bind 1 type of ligand, and the transport site could bind any of 3 types of cation, then the size of the kinetic scheme would be:

5 x 3 x 2 x 4 = 120 matrix elements (Note that a vacant possibility is added to each binding site)

8.3.1 ACTOR KINETIC SCHEMES

The validity of kinetic schemes has been challenged numerous times.[185] They apparently hold up because they mathematically reflect chemical interactions per the Michaelis-Menton EQ, because they lend themselves to increasing refinement as new information becomes available, and because no other representation has performed as well. There are often several competing Q matrices proposed to represent a single actor type. As each is a simplification of actual kinetics with some arbitrariness on the part of the worker to chose how many states will comprise the model, each scheme may serve a different purpose best to the needs for which it was created.

A founding assumption of all kinetic schemes is that molecules have no memory, aside from their current state, and therefore qualify as Markov processes. This is a simplifying assumption that has held up well for three decades. It is an important one *vis-a-vis* information processing by these molecules. Can a memory-less entity process anything more than a one-to-one mapping?

Kinetics are embodied as infinitesimal transition probabilities, according to Kolmogorov/Chapman/Colquhoun stochastic methods. Actors have multiple conformational states ... which implies they have memory.

Each protein molecule is capable of numerous conformers. Given its environmental parameters, each state has a numeric probability of occurring. In conditions of conformer changes slow enough to detect each transition, it is then possible to calculate state change as a function of the current state (conditional probabilities). In very fast

changing conformers, the probabilities can only be calculated irrespective of the previous state. Generally actors change states faster than can be measured, and thus we use memory-less probabilities (unconditional probabilities). This is admittedly the weaker representation. However, large numbers of actors in aggregate average out, in both space and time (ergodic), to perform quite reliably and predictably, true to the natural processes they represent.

Each kinetic process requires a forward rate and a backward rate. In complex chemical networks, the words "forward" and "backward" lose their meaning, so I reference them to the products themselves. Given conformers A,B,C, there are rate constants for AB, BA, AC, CA, BC, CB. If s = [A B C], then all rate constants can be captured in an s X s matrix, with the diagonal being the "rate" at which the product remains the same.

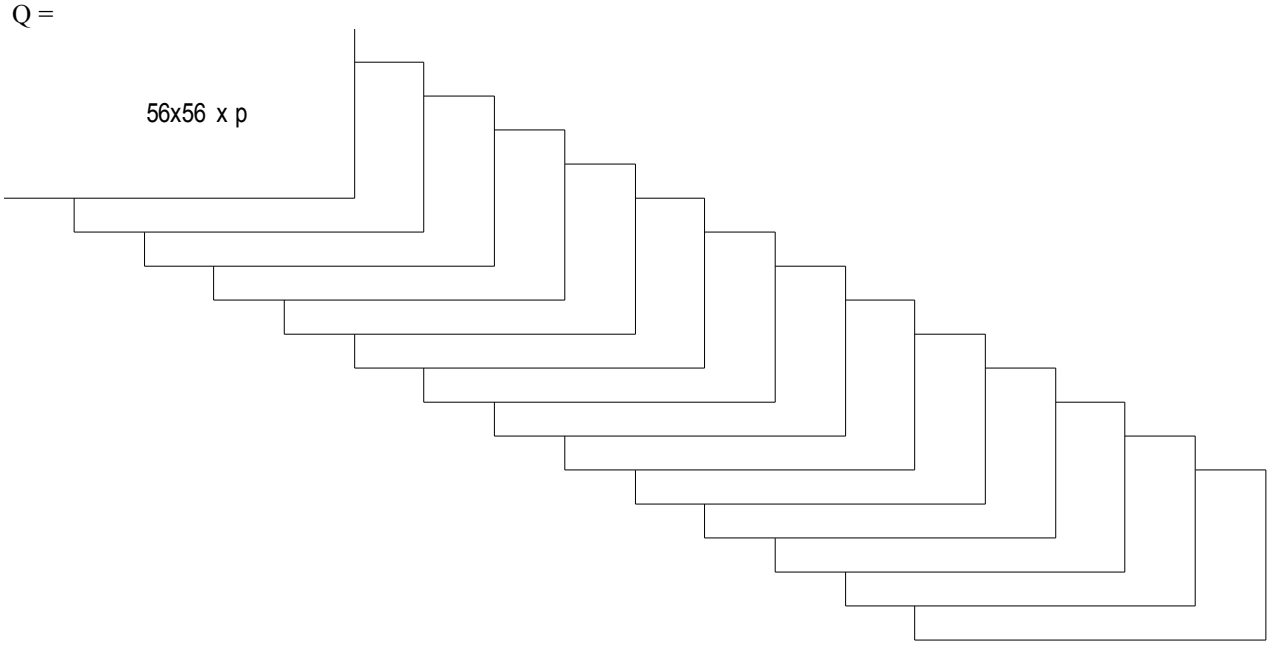
Each protein molecule is capable of numerous conformers. Given its environmental parameters, each state has a numeric probability of occurring. Large numbers of actors in parallel yield a summed behavior that sharpens the duty cycle and averages the noise to near zero. A singular actor will perform over time to much that same sum, therefore exhibiting ergodic behavior. Either way, a stochastic actor can perform quite reliably and predictably, true to the natural processes they represent.

Consider the simple case of one modulator site on a pump that exchanges 2 NA+ for 1K+. With 3 ions being pumped plus 1 modulator site, there are 4 variables (degrees of freedom). In the simplest case each binding site is either vacant or bound to its complimentary B type. 2^4 = 16 combinations. That requires 16 pages of Q matrices. Some compression can be realized if many of the Q pages are nearly the same. If the two Na sites are kinetically equivalent, then there only need be 9 Q pages. However, an extra lookup table is necessary to map the 16 combinations to only 9 choices.

An exchanger has a minimum of 6 states: load1, transport12, unload2, load2, transport21, unload1.

Additionally, when a load state involves more than one binding, more states may be necessary to represent the changes in affinities. Same thing with unloading states. A pump exchanging 3 for 2 would have 14 phenostates, before modulators. With 2 modulator sites, there are 4 modulator combinations and the number of states rises to 14*4 = 56.

Q =



The above Q contains 43904 probabilities. When glycosylation and phosphorylation sites are taken into account, the quantity of bind combinations can be much larger. This does not take into account voltage modulated probabilities. Then there is still the possibility for numerous intermediate and alternate states that are internal, showing themselves as hold states, alternate timing, change in mode, or reversals. A pump could easily have 100 significant states, which may reveal multiple state paths (duty cycles). The various transition probabilities and affinity values must account for pump starvation, pump saturation, pump reversal, pumping reliability, and resetting the saturation point as a function of modulator combinations. All of these are accomplished through the Q and R (only).

ATPases add to the complexity of the state transitions and state paths. But they add the clarity of direction for the duty cycle. Any form of injection of energy into a cycle tends to determine the direction of spin and spin the cycle faster than it would without such energetics. We tend to think of catalysts and enzymes as passive surfaces that are conducive to particular reactions. But in the case of pumps, at least, the ATPase is a nano mechanical device that turns on high affinity receptor sites, then physically moves it through the membrane , then turns off the affinity such that the particles are repulsed out of the pump. This is an interesting form of dynamic enzyme, and the cleaving of ATP to ADP + Pi drives this mechanical action. Because the pump is a stochastic finite state machine, it is not deterministic in its pumping performance.

When pump mis-binds are taken into account (for example, taking a Mg++ for a Ca++), the affinities and transition probabilities can become more complex. An environment of 10 particle types, 3 allosteric bind sites, and 56 internal states would produce an R matrix of 10^3*56 = 56000 probabilities forward, and again that many for the backward reactions. This is a lot more data than can currently be found in the wet lab reports on actors.

The generalized concept of an actor is that each consists of: R, a modulation matrix, which relates bindings to state probabilities; Q, a transition matrix, which is altered by the allosteric bindings, and tends to proceed through a duty cycle; O, a phenostate map, maps the internal state to the external expression; and a G vector which determines the particle effects as a function of the phenostate.

The above depictions {R Q O G} give us a set of structures within which to collect much data on the actors, sufficient to bring them to life as Markov processes. Additional modeling accessories have yet to be added: affinities, energy consumption, and messenger launches {aff erg eff}.

8.3.1.1 Adapting Biologic Q matrices

Physiologists often report the binding of modulators as though each was an internal state change. The problem with this method of representation is that the actual binding of a ligand is an external event, mostly outside of the "control" of the transition matrix, determined by external concentrations and temperature. The transition matrix may embody the actor's affinity for a particular ligand type, but not the concentration nor the velocities of the ligands. A modulator binding is an external event that, once it occurs, alters the transition matrix, often quite dramatically. New transition probabilities need to be determined for the bound state. Indeed for each combination of bound states. Therefore every actor type needs to have one transition matrix for each of its possible ligand combinations. Diffusion will determine which ligands collide with the actor. Forward and backward stochastic rates determine if they bind and when they unbind. The particular combination of bindings determines which transition matrix is is effect for the current *dt*. The transition matrix can be altered as a function, or can be swapped out by a choice from a deck of conditionals.

Here is an example, adapted from Breitinger, 2001[186] for a Kca potassium channel with 2 Ca++ allosteric binding sites, and one open state (OLL). O = open; C = closed; I = inactivated; L = ligand bound.

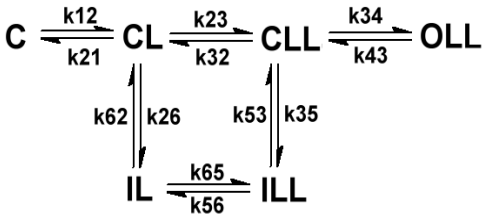


FIGURE 73: KCA CHANNEL KINETIC SCHEME

This scheme, adapted from Breitinger, has only three internal states {C O I}, and two external allosteric binding sites {L1 L2}.

This diagram is a mixture of internal conformers and external bindings. When these are separated out:

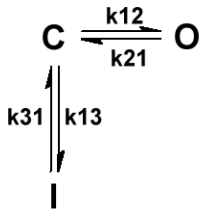


FIGURE 74: KCA CHANNEL CONFORMATIONAL KINETIC SCHEME

Then the bindings are treated separately as the external events at ligand sites, by creating a modulator matrix R:

R =

R	L1	L2	Qpage
1	0	0	1
2	0	1	2
3	1	0	2
4	1	1	3

where

L1 is the occupancy of the first allosteric binding site, L2 is the second. With only one possible type of ligand (Ca++) to bind to either L1 or L2, there are only 4 possible modulation combinations for this actor. R assigns a number to each of these ligand binding combinations (row). RQ is a pointer to which page within the Q matrix applies under these binding conditions, with a default that Qpage = 1. In this case the literature reported that combinations 2 and 3 elicited the same effect upon the conformational kinetics, so did not warrant separate pages in Q.

This Q matrix has only 3 pages because R row 2 and R row 3 are identical. Its element values (transition probabilities) might look something like:

Q.page1

1	0	0
1	0	0
1	0	0

Q.page2

0.9	0	0.1
1	0	0
0.3	0	0.7

Q.page4

0.1	0.6	0.3
0.5	0.5	0
0.1	0	0.9

Q can be interpreted thusly: When no Calcium ions are bound, the actor is in Q.page1, which only allows state 1 (C=closed). When one calcium is bound, Q switches to Q.page2, a new set of transition probabilities , which allows for a recovery from an inactivated state with one calcium, but little else (transitioning from I to C). The binding of the second calcium switches the conformation transition probabilities to Q.page4 which favors the open state for a time, then the return to closed, then a quick shift to Inactivation state. This particular scheme can easily short circuit its own opening by going straight from CLL to ILL, skipping OLL. If that is what the molecule really does, then this scheme is a fine representation. But if the biologic molecule expresses a proclivity to open before going into an inactivation state then a different scheme would be necessary to represent this in the model. An efficient gating scheme that avoids wasted and lost signals, would be more likely the following:

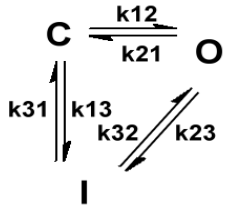


FIGURE 75: K CHANNEL KINETIC SCHEME WITH I-O TRANSITION

Directional preference is accomplished by weighting the clockwise pointing reactions more heavily than the counterclockwise pointing reactions. In general, purposive systems employ cycles predisposed to one direction over the other, rather than mere chance to accomplish a function. One might reasonably expect that a recently loaded closed state might be most favorable to transition to an open; that an open state might linger as open for some useful period of time, and then incur a strong predisposition to enter an inactivation state (refractory period). And after the refractory period has expired, then strong proclivity to return to the closed state (ready for another ligand to arrive) The above scheme is a minimal arrangement to accomplish this if the rates: k12, k23, and k31 are high while

the reverse direction rates k21, k32, and k13 are low. But this says nothing about lingering time in any given state, and this leaves a default time of 1 *dt*. - Not very satisfactory given that *dt* is an arbitrarily set parameter having nothing to do with biology.

So how might one control dwell times stochastically? Adding reaction probabilities for remaining in the same state improves performance.

Given a refractory period longer than a channel opening, one would expect k33 > k22. Alternatively, additional hold states can be added.

Another example showing the RQ matrix of a channel with 3 binding sites (d1<Ca++, d2<Ca++, and d3<NT), 4 internal states, and 1 of these sates results in an open channel phenostate.

RQ =

	m1	m2	m3	m4	m5	m6	m7	m8
Ca++	0	1	0	0	1	1	0	1
Ca++	0	0	1	0	1	0	1	1
NT	0	0	0	1	0	1	1	1

RQ maps all the possible binding combinations back into the state transition matrix, as a pointer to the active page. If the binding of one modulator site alters the affinity of bindings at other allosteric sites then an additional R matrix is required to express this. The actual state change is effected by the particle collisions. It is inappropriate to include these within the Q because R refers to the binding and unbinding rates only, not to internal configuration state changes.

R(S1, forward) =

R	m1	m2	m3	m4	m5	m6	m7	m8
Ca1	0.24	0.11	0.11	0.25	0.07	0.44	0.67	0.98
Ca2	0.53	0.45	0.34	0.16	0.45	0.24	0.65	0.27
NT	0.66	0.87	0.12	0.2	0.78	0.31	0.03	0.94

R typically is of high dimensions because there exists one degree of freedom for each binding site. Each binding site has forward and backward binding/dissociation rates. However, these rates are highly modulated by the state of the molecule. These binding rates are the forward rates employed to determining bindings to the various sites on an actor. There must be a same-sized matrix of complimentary values for the unbinding rates. Each conformation state (S1) is likely to produce different R forward and backward values. There are as many pages in R as there are state

numbers in S1.

Let D be the number of binding sites on an actor, and DC the number of binding combinations. DC can also be thought of as a modulation state. Then, DC = Π(Bj+1); where j = the binding site number, Bj = the particles that can bind to the jth site, the "+1" represents a vacant binding site.

Then the quantity of elements in R = 2*S2 + S1; where S1 = the quantity of internal conformations, and the 2 represents the forward and backward binding rates for each of the possible bind combos.

The bind combo dc is, after all, a collapse in dimensionality of the bind site degrees of freedom, but it is convenient to map directly to specify which page in the Q matrix shall apply.

R	r1	r2	r3	r4	r5	r6	r7	r8
Qpage	1	2	2	4	5	6	6	8

When there are two or more equivalent bindsites, then either one maps to the same Q page. In the above example, values 2 and 3 are the same when the two binding sites for calcium are interchangeable, as are 6 and 7.

Q, as already discussed, is the sate to state transition probabilities, and is corrected for the *dt* in effect in the run in any simulation.

Q =

page1	**1**	**2**	**3**	**4**
1	0.44	0.37	0.11	0.44
2	0.98	0.75	0.7	0.22
3	0.67	0.51	0.23	0.43
4	0.12	0.47	0.77	0.64

page 2	**1**	**2**	**3**	**4**
1	0.17	0.57	0.31	0.45
2	0.98	0.84	0.54	0.28
3	0.04	0.78	1	0.11
4	0.78	0.36	0.57	0.44

page 4	**1**	**2**	**3**	**4**
1	0.3	0.25	0.73	0.82
2	0.87	0.44	0.05	0.31
3	0.66	0.65	0.88	0.01
4	0.34	0.2	0.67	0.85

page 5	1	2	3	4
1	0.98	0.91	0.31	0.43
2	0.96	0.73	0.74	0.13
3	0.91	0.51	0.15	0.7
4	0.67	0.21	0.7	0.01

page 6	1	2	3	4
1	0.83	0.7	0.6	0.57
2	0.38	0.25	0.96	0.7
3	0.97	0.81	0.43	0.29
4	0.5	0.27	0.09	0.67

page 8	1	2	3	4
1	0.96	0.26	0.7	0.01
2	0.8	0.05	0.55	0.45
3	0.52	0.52	0.87	0.36
4	0.02	0.73	0.75	0.09

RQ is a map that inputs the R value combination and outputs the page in Q.

The current internal state, S1(t)), chooses the row in Q.

The instantiator (random number across the CDF of the row) chooses the column, which reports the new state, S1(t+1) .

The new state s(t+1) = Q(s(t), CDFinstantiation,Qpage).

The new state is then read for its phenostate, O(s(t+1)).

O =

1	2	3	4
0	0	0	1

% says that states 1,2,3 are closed, and state 4 is open.

O reports whether a channel is open or closed after receiving input of the new state s.

Some workers seek to reduce the computational load by collapsing a group of conformations into a single state when they are all determined to map to the same phenostate. However, there is the possibility that doing so will lose modalities of behavior that the larger group of states can perform and the reduced set cannot. For example, the shift from a single spike action potential response to a burst of about 50 actions potentials in tight sequence, is a modal shift that can easily be accomplished by switching pages in the Q matrix, provided there is an adequate number of

states. But without the various pages in Q indicated by various modulator combinations, such modality shifts may be impossible to simulate as inherent qualities of the transition probabilities.

The phenostate is often portrayed as binary (open or closed; pumped forward, pumped back), but the complexities of nano environments introduce many variables. It is the domain of Molecular Dynamics (MD) to model such phenomena, and this new field cannot be adequately treated in this project. However, the results of MD can usually be incorporated into this model as a look-up table. For example, if MD workers report ion passage details affected by the presence of Zn++ , then their results can be mapped into a binding site affinity for zinc and consequent alteration of the Q.

As the R and the Q determine the the dynamics of the molecule, it is worth pondering what their mathematical relationships are, and whether or not all of their complexity is to be modeled. Each molecule has degrees of freedom, which define a possibility space. Each dimension is sized depending on how many choices are available for that site, ranging from 2 to qB for binding sites and qS for conformational changes. It may be surprising that the binding sites had such high dimensionality while all of the rest of these complex molecules add merely one. Well, that is an artifact. The molecule has a huge number of degrees of freedom, but they have been collapsed into a kinetic scheme. Similarly, all of the binding site combos can be collapsed into a binding scheme, which have already named (dc).

In pursuit of information, it is prudent to ask what balance might be struck in the degree of "collapsing dimensionality" in the interests of purging everything but the high runners.

Changes in state are expressed as ΔS. $\Delta S = s \mathbf{x} s$, in that a change of state $\Delta S = S1 \rightarrow S2$, which requires an s **x** s table. Changes in bindings are expressed as $\Delta D = D \mathbf{x} B$, in that a change of binding requires an interaction between the binding site D and the particle B, which requires an D **x** B table. However, neither of these two tables are static. They are switched by the conditions of the molecule. The s **x** s table is modulated by the D **x** B conditions, and the D **x** B table is modulated by s.

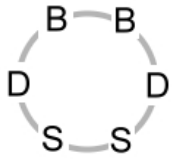
$\Delta S = S \times S (\times D \times B)$, where modulation is in parentheses.
$\Delta D = D \times B (\times D \times S)$, where the second D allows the conditions at one binding site to alter the kinetics of other binding sites.

These two EQs are partial views on the same molecule, and therefore can be assembled to represent the whole.

Let ΔM be defined as any changes in the overall condition of the molecule. Then:

ΔM = B x D x S x S x D x B;

Because the first B above equals the last B, this system of equations is circular: In matrix algebra, there is a circle of multiplications to get to the next event in the cycle. Each step spins off certain effects: state binds, transport, etc..

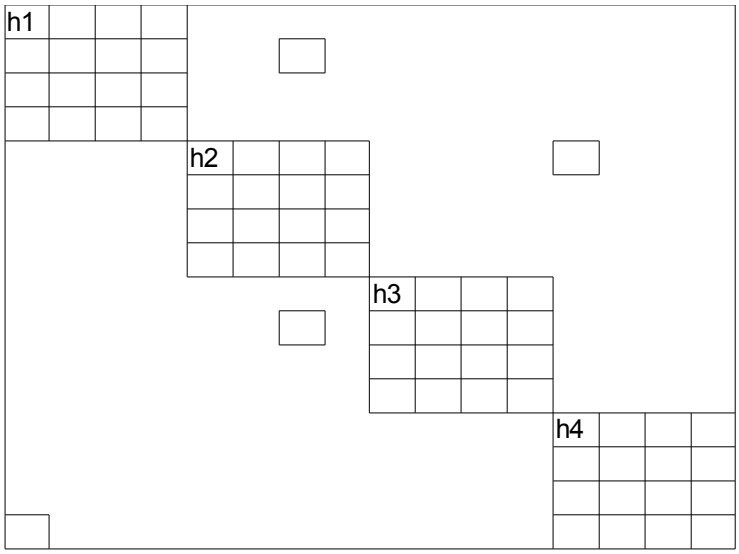


Where B = particle availability; D = bind site occupancy; S = state . Then, B to B is the particle collisions. S to S is the state change. S to D is the effects of state change upon binding kinetics. D to B is the dissociation kinetics instantiating unbindings. B to D is the binding kinetics. D to S is the effects of the binding combo upon the conformational kinetics. Because B can be viewed as representing the "outside world", an alternative graph can separate the internals from externals. It would show an arc from D to D, the effect of the binding combo upon the binding kinetics, with dotted lines to B from both D's. From this modeling perspective, B is part of the system under test (SUT) and so the S S D B D ring shown is chosen.

This ring spirals through time into a helix. The state transitions can be modeled rigorously, as within Molecular Dynamics, or they can be simplified into schemes (reductions in complexity by choosing only the high runner states).

A further complication arises with the presence of subunits, necessary to faithfully comprise a whole actor molecule. There are two possible treatments. The first is to treat each subunit independently, and only at the O matrix of phenostates, "wire" them together in logical series. This works when the subunits perform independently. If the subunits are combined chemically such that the state of one can alter the state of another, then the subunit state spaces must be merged into a single larger matrix. This is done by aligning the subunits along the diagonal, and adding in the coupling element values (off diagonal values).

Q = (channel with 4 subunits)



A Q matrix containing 4 subunits, with miscellaneous coupling between subunits. The extra burdens of this approach include: separating and evaluating 4 states, treating each subunit as a separate entity, and looking up the 4 current state numbers in their respective phenostate tables; and then preforming the inherent logic of the gate positions to determine the final condition of the pore.

In any case, 4 separate stochastic processes determine the states or each subunit. For demonstration, let a subunit have 6 states. Then a stochastic process of one subunit will trace something like:

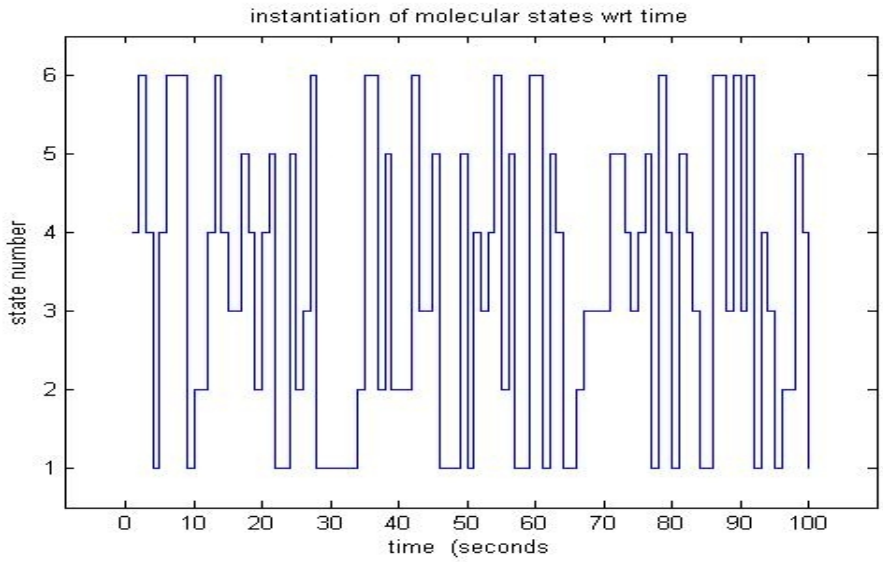


FIGURE 76: INSTANTIATION OF STATE FOR A CHANNEL SUBUNIT

Repeating this process for each of the subunits, then assembling them, with logic, into a whole, results in:

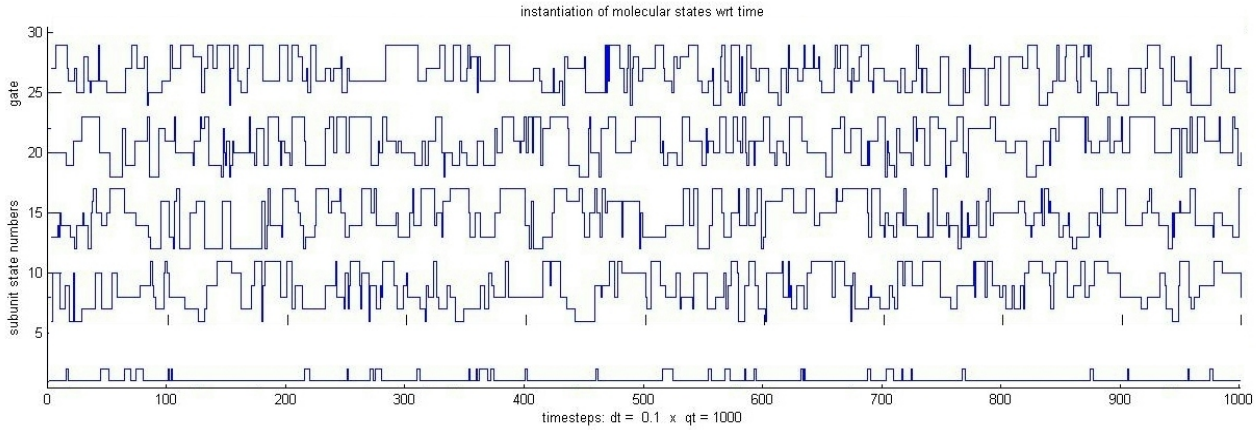


FIGURE 77: SIMULATION OF CHANNEL WITH 4 IDENTICAL SUBUNITS, 6 STATES EACH

The top 4 traces indicate the state number of each subunit. The lowest plot is the net result, showing whether the channel is open or closed. The phenostate trace is not shown. Of the 6 states, 1,4,5,6 are closed states, and 2, 3 are open states for the respective subunit gate.

This enacts four independent subunits, which can be individually swapped with other types of subunit. It is also possible, that despite the assembly of subunits to make a channel, that the subunits do not act independently. The nature of their bonds might shift charge or contour the subunit shape. In this case, the entire channel might best be modeled as a single entity, rather than 4 sub-entities.

Note the low duty cycle of channel openings. Had there been only 1 open state out of 6, the open time as a percentage of the duty cycle would have been much smaller. Real channels must have a duty cycle less than the aggregate pumping capacity. Pumps transport at rates about 1/1000th channel conductivity. When the quantity of pumps is about equal to the quantity of channels, then the duty cycle must be less than 0.1%.

A program has been written that traces the primary and secondary duty cycles through the state space. Quite significantly, the quantity of cycles determines the quantity of modes, and the quantity of branch points around each cycle determines the potential for pattern recognition. Follows is a simple Channel duty cycle, for a channel with two requisite binding sites, a singular opening, followed by a refractory period:

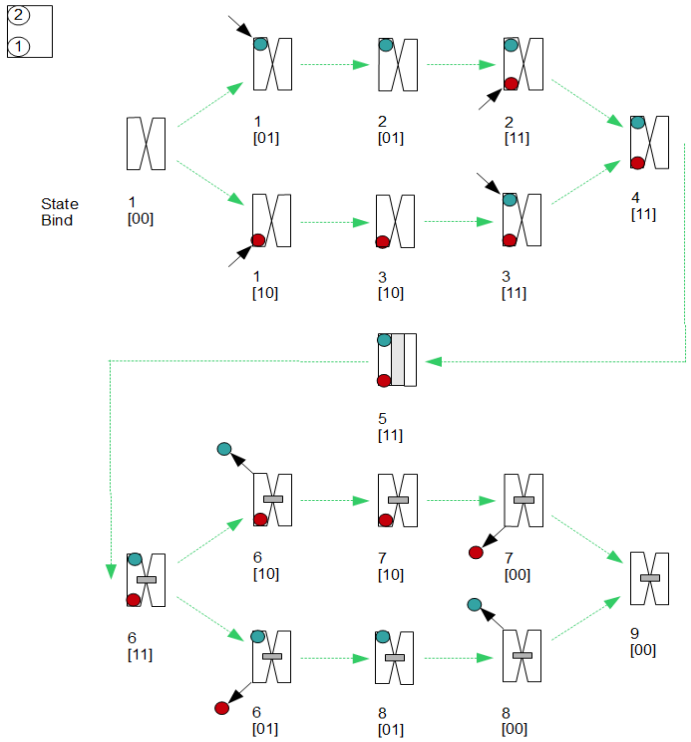


FIGURE 78: Simple Channel Duty Cycle

State 9 then proceeds to state 1 (arrow not shown). The prerequisite of two bindings prior to opening helps to insure the open time will be short compared to the closed time. Also the refractory period extends the closed time such that there is even less opportunity for open time. Perhaps most crucially, state #5 is highly unstable. There is just no way to maintain state 5 more than 1..2 ms. Because a channel stuck open could kill the cell, and there may be a million channels on the plasma lemma, there must be essentially zero chance of lingering in state #5. Therefore state #5 should be the highest energy state, with little energy well to hold it there; perhaps no well at all; just a hill. By this reasoning, state #1 should be the lowest energy state, most relaxed. Then the molecule will linger there in the ready state, receptive to the binding events. Ideally, each binding event would use to collision energy to heighten the Gibbs, helping it get up the energy hill of channel opening. Then all of the refractory states would be downhill wrt energy.

Only state #5 had a phenostate of consequence. It calls for a lookup of the conductivity profile for this channel type, then a count of ion types on the profile and near the channel pore, then a calculation of the Nernst partial voltages for each relevant ion type. These are merged into driving forces via the voltage across the membrane and the concentration gradients. The conduction of ions is: J = duration open * concentration differential * net driving force.

8.3.1.2 Phenostate

When the conformational transitions are represented by state transition probability matrices, and the number of states is greater than the number of expressions (e.g. open, closed), then a means must be provided for mapping the various internal states onto their outward expression. This is not difficult but is necessary.

In living cells, there is no need for the concept of phenostate. Some molecular conformations of ion channels result in an open channel and other conformations result in a closed channel. This is simply a geometric implication of the conformation. But in the digital world, the internal state is only a number; generated as the output of a separate stochastic process. That instantiated state number is mapped, via a table, to a function list, to determine what impacts this new state might have on the molecule's relationships with the surrounding environment. Digital modeling must explicitly transform the intrinsics to the extrinsics. The extrinsic state (open or closed) is called a phenostate because it is the external expression of an internal process. This notion of phenostate is but a ghost of the digital computer. It is the result of breaking into two events what in the wet world is a singular event.

Doing so, however, has some advantages. It forces the modeler to explore the relationship between internal events like state change and external events like collisions. When looked at from the perspective of physics, the problem may be characterized as the engagement of an unbound group with a bound group. But when investigating the information flows, disaggregation is necessary (no groups), so as to follow specific instances of the influence of the intrinsics upon the extrinsics, and *vice versa*. Modulation is conceptualized in the literature, but the phenostate process, much less so, though these are complimentary processes. The phenostate deserves equal bearing with modulation, because these two are in series, participating within the same loop, passing the same quantity of information along the neuron. The weakest link in a series of steps limits the entire neuron. Given evolution's ability to achieve extremely high efficiencies, we should expect the phenostate process to be the equal to the modulation process in regards to information capacity, and also as regards reliability.

Though the actor's internal states are of the essence of the information processing engine, each of these states may or may not have an impact upon their surround. In a digital model, it is the phenostate table that holds this information, which states have external impact, and what function would implement that impact. Thus, transport phenomena occur only at certain state numbers, upon which the phenostate table calls into action the appropriate function to reassign the particles on certain bind sites to a new compartment. This function is triggered by the phenostate,

therefore only indirectly caused by the Q state. Channel phenostates are open and closed, though the Q states may include various flavors of closed, like { rest, refractory period}. Pump phenostates are {binding on side 1, release on side 2, bind on side 2, release on side 1}. Receptor phenostates may be {catalyst off, catalyst on}. Vesicle phenostates may be {release mode, replenish mode, hold, rest}.

A simple look up table can convert each conformation into its outward expression. This allows all of the internal kinetic probabilities to remain preserved in large number, while the simpler outward expression typically has fewer possibilities, and these need be reported to the model for subsequent effects (releasing messengers, opening for flux, exocytosis, pumping, etc.). The internal states shall be referred to as conformations or simply states (*s* as a product of Q). The outward expression *o* is a product of the table O shall be referred to as the phenostate, meaning "states to show forth".

o(t) = S(t) * O; % where S(t) = instantiation of the state at time t; o(t) = 1 if open, 0 if closed;

state	1	2	3	4	5	6	7	8	9	10	11	12
gate	0	0	0	0	0	1	1	0	0	0	0	0

TABLE 18: O MATRIX FOR CHANNEL PHENOSTATE WITH 12 STATES

This is an example of a 12-state channel, that requires a lookup table to convert the state # to the action this actor has with its surround. In this case, 2 of those states, #6 and #7, cause the channel to be open. All other state #s leave the channel closed.

8.3.1.3 Transport

We no longer talk about semipermeable membranes. We now know that the membrane is exceedingly impermeable to ions. Rather, single protein molecules may be embedding into that membrane and serve as point processes for purposes of transport and catalysis. Such actors may be divided into 2 classes: transducers and transporters. Transducers effect horizontal processes, and transporters effect vertical processes.

The horizontal process switches on and off a catalysis of messenger particles. The vertical processes effect the passage of particles moved through an actor from one compartment to another. This may be a electrogenic process,

or merely a physical relocation process. In every instance there is both a concentration gradient and voltage gradient to contend with. Transport in the model may take place via the following mechanisms:

1. 1-d diffusion/drift: adjust pore diameter to align to natural conduction rates (suitable for modest downhill conduction rates in channels).

2. Mechanized transport arm: pump cycling determines rate. Simple non-modulated single-particle pumps conform to: P(C) = Pmax * (2*C/(1+(C/k))), Where P = particle pump rate, C = concentration on the pump intake side, k = pump dissociation constant. As C approaches k, the pump saturates. Suitable for transporting up-gradient, and for ratiometric transport.

3. Energy barrier profile forces: radial energy profiles may reject particle and/or accelerate it. Useful for detailed ion channel dynamics. Charge patterns within the pore of the channel can create a ballistic gauntlet that only a certain ion type can get through. Suitable for more detailed nuance of when particles will pass and not.

4. Super-conducting passage: transport quantity is accomplished by contrived high affinity attraction to actors, and moving these across the membrane so as to match natural transport rates (usually of several actors). Even simple funnels accomplish this effect up to about a 15% bias on ratios between the two sides.

Any actor capable of being modulated mid-duty cycle is responding to a temporal pattern. It acts uniquely to a mid-cycle modulation, then it qualifies as a pattern recognizer. Multiple modulation changes during a duty cycle constitute a temporal pattern. If that pattern is the one most strongly responded to, then such an actor is acting as an input pattern recognizer. Point processes can also act as pattern generators, mapping input patterns to output patterns. This makes feasible such behavior modalities as bursts, rhythmicity, chaotic openings, and patterned openings.

8.3.1.4 Capacity

Channels conduct at about 1000 times the rate of pumps. Therefore:

Pump quantity * pump rate > channel quantity * conductivity * duty cycle* safety factor;

Aqueous ions hydrate with 1 to 3 shells of water molecules, resulting in varying outer diameter and mass. This variance makes for a rather fuzzy definition of what is to be modeled. In this model, ions can be randomly assigned some degree of hydration by variance about a mean, each *dt*. This composite mass determines diffusion and drift rates.

8.3.1.5 Selectivity

Concerning channels, pore diameter is not especially determinant in its selectivity of ion type passage. Selectivity filters are more sophisticated than mere geometry can model. The ion channel inter-pore charges are sufficient to strip off most or all of the water molecules of hydration, in a manner that increases the ion selectivity of that pore. This is accomplished via replacement of very nearly like-charged charge points alone the pore. The ion jumps from charge point to charge point along the pore are very fast, approx. 1E-12 s. Ion channels are often funnel shaped, which act as bio-diodes. They can accomplish approx. 15% differential in concentration gradients with only thermal energy driving the system, according to model simulation results. These complexities are averted by the model employing empirical conductivity data to calculate the flux through a channel opening.

There is often flutter between nearly equivalent configuration probabilities, which is driven by, and proportional to, temperature. Time constants are determined by mass and elasticity, but are made stochastic due to water collisions, and are quantal due to nearby charge attractions that result in ionic bindings.

Active systems are driven by one of several possible potential energy sources: thermal energy, which gives pressure as a function of concentration gradient; the EM force, which gives pressure as a function of the voltage gradient; and chemical reactions (usually ATP to ADP) at allosteric binding sites on actors, which release quanta of potential energy from the chemical bonds.

8.3.2 BINDING AND UNBINDING

The kinetics of binding and unbinding are stochastic, the net result of forward and backward chemical reactions. The forward reaction depends upon ligand or ion availability, which is directly related to collisions. For modeling

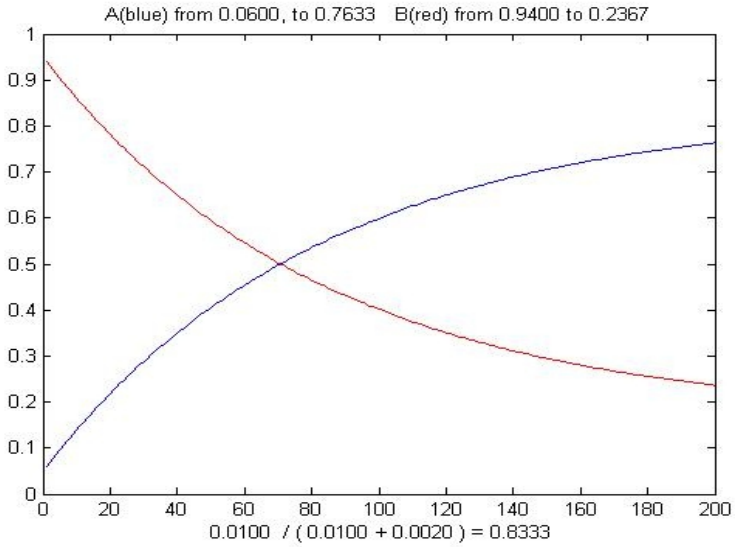


FIGURE 79: RATIO OF BOUND TO UNBOUND APPROACHING EQUILIBRIUM

purposes, a proximal ratio is necessary to determine "availability". This is especially necessary when one model particle represents some multiple of biological molecules. A single model particle representing 10,000 biologic particles cannot possibly experience a realistic collision rate. Therefore, compensating factors must be added. But first, questions must be answered: What is the information value of the collision rate? What is lost when down scaling it?

8.3.3 G-PROTEIN SHUTTLES (SECOND MESSENGERS)

Shuttles provide leverage between a ligand binding and the number of ion channels opened/closed as a result. They consist of a reduced quantity of trajectories to the likely target actor bind sites. Messenger transverse these trajectories at physiological velocities and when arriving at the bind site engage in the normal kinetics of a collision.

For modeling purposes, it is necessary to know the types of ion channels targeted, what the lag time is, and what the variances are. All of the above can be reduced to a straight-line "shuttle" representation that predestines messages to be send from a given receptor to a set of nearby target channels, with a somewhat varying amount of time transpiring to do so. Thus we draw message ways as transverse edges between the receptor and its nearby ion channels as designated in the build of this type of receptor.

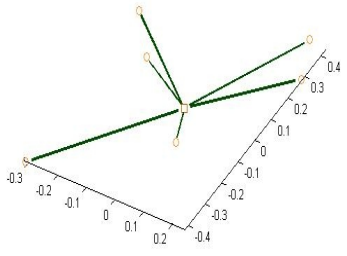


FIGURE 80: RECEPTOR IDLE WITH TARGET ACTORS

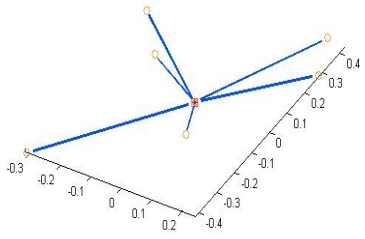


FIGURE 81: LIGAND BINDS TO RECEPTOR

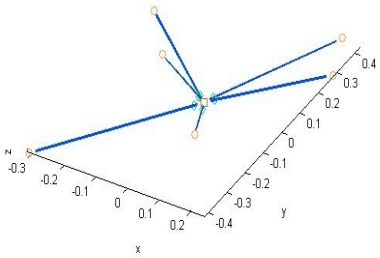


FIGURE 82: INITIATING G-PROTEIN RELEASE

A shuttle system of second messengers is persistent, but inactive until a ligand binds to its receptor. Then second messengers are bound to their "start positions"

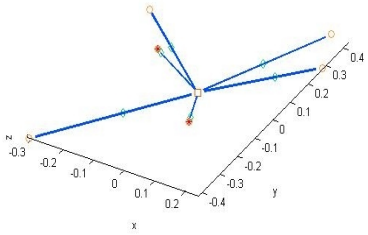


FIGURE 83: MESSENGERS IN TRANSIT

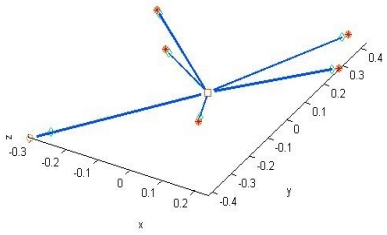


FIGURE 84: MESSENGERS BIND TO TARGETS

Second messengers proceed at mildly randomized velocities, arriving over a programmed time spread to their target channels, as binding modulators. Upon completion, the second messengers remain persistently bound to their target ion channels until the phosphate concentration dies down, and dissociation kinetics unbinds them. The feedback mechanisms are such that phosphate concentrations remain static until the original ligand is dislodged from the receptor.

Note that the entire G-protein/second messenger system is "owned" by the receptor, not the channel.

The model shuttle system representing second messengers is a persistent structure, but inactive until a ligand binds to its receptor. Then second messengers are bound to their "start positions" .

Bio-data shall be processed on Secondary Messenger quantity, speed and variance., cAMP cGMP phosphorylation modulation & its time envelopes; so as to form shuttle Types for library.

8.3.4 MODULATORS

The state transition probabilities of channels and pumps are not static. The elemental values (or formuli of the Q matrices are altered by modulators. These modulators may exert their impact as forces (e.g. voltage or mechanical displacement) or via particle collisions (ligands, protons, ions). Therefore the term “modulator” is one of semantic ambiguity and cannot be effectively used as a software class. We would do better to replace our concept of modulator (a noun) with modulation (a verb). Further mixing inconsistent types, voltage is continuous while particles are of course discrete. To produce a single modulation function, discrete can be added to a continuous number if all arguments are linear in effect. Else, all values can be binned for like effects; and the bins of course are discrete. This latter method is the least computational, because it supports producing the least number of Q matrix pages to represent behavior.

It should be understood however, that in the application from biologic literature, some modulators are Interactors, some are stressors, and some are virtual (like voltage, which as far as the Software is concerned, is the result of a calculated sum of charges divided by another sum of charges). Thus the term “modulator” will not be used within the algorithms.

Q matrix values are calculated by equations that are a function of the relevant modulator levels. When multiple modulators act upon a single actor type, this equation set may represent non-linear, time-dependent interactions between the modulators. Generally, such equations are curve fits to the empirical biodata.

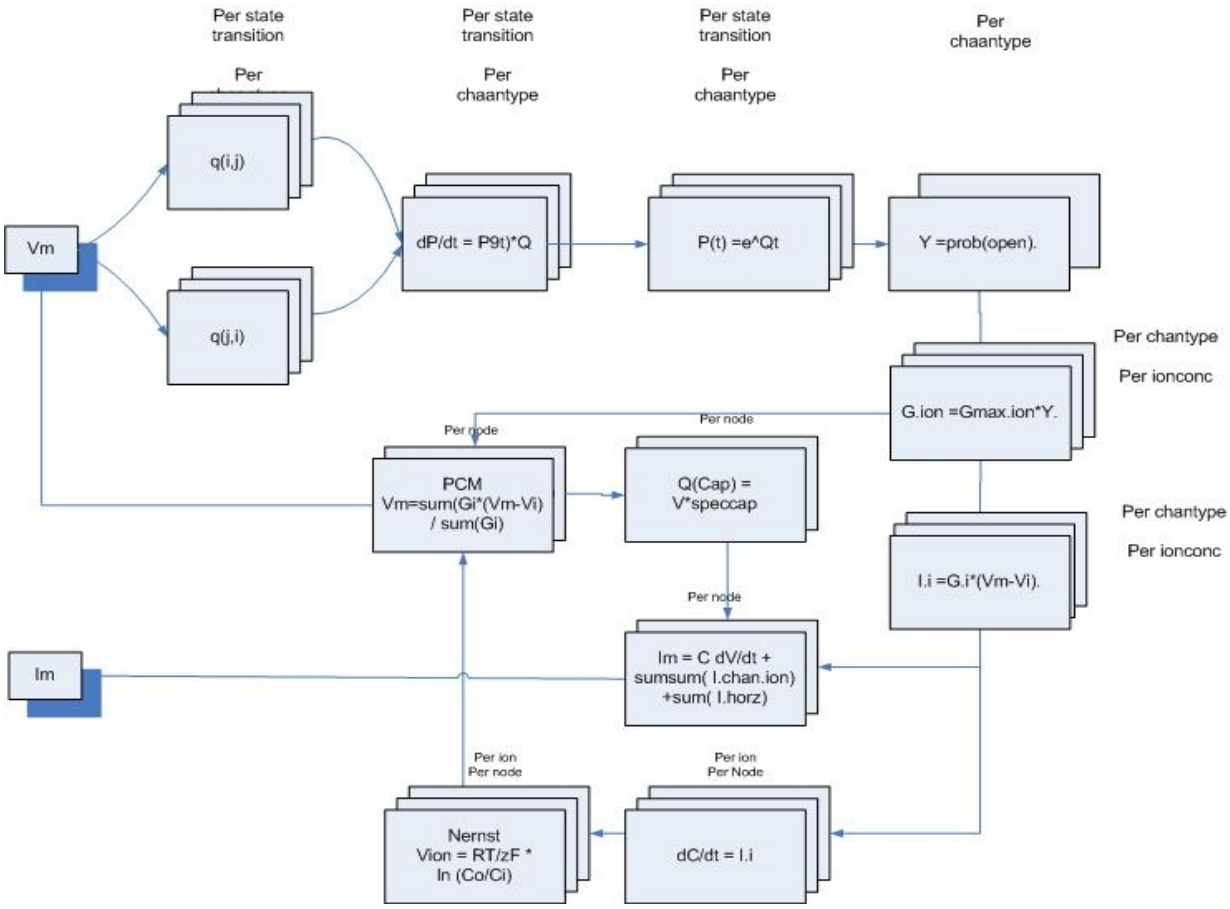


FIGURE 85: CLASSIC VOLTAGE AND CURRENT EQS SYSTEMATIZED

Software architecture, depicting relationships between the HH EQs and the Kolmogorov EQs. Note that there are two feedback loops, the membrane voltage and the ion concentrations.

Each of the InterActors has one or more tags. While a state is an internal conformation, a Tag is an external condition. Tags would not be necessary if digital computers were perfect mimics of space-time. However, the digitalization process is leaky and creates uncertainties about which compartment a particle is in. Tags are merely a concession to the weakness of the digital model, providing a convenient means to keep track of the interactors.

Typical tags mark Interactors as: in a certain compartment, in aqueous or lipid matrix, bound or unbound. Tags are dynamic, therefore they are recalculated every *dt*.

Tag changes are under “change management” to avoid corrupting the operations of particles and actors. That implies access is by limited functions that preserve the data free from corruption, and comply with other rules of

physics and housekeeping. There may be implications in tag changes that require state changes. Certain tag changes may be probabilistic, and produce probabilistic effects. In that case Kolmogorov Q matrices may be called into play to calculate those probabilities. The actors do not own the particles, yet negotiate interactions with particles. If an actor state requires a particle be bound, unbound, transported or converted, there may be a probabilistic process called that does not guarantee that the actor's request will be fulfilled. Conversely, even when the actor state is not calling for any function, certain thermal energy effects may impinge on the actor state, bringing about state changes that do not serve the duty cycle. These are the characteristics of a stochastic processor.

8.3.5 MODALITIES

In 1990, Shrager computer modeled a demyelinated axon.[186] He divided the axon under study into 20 equal length compartments; modeled Calcium effects upon the axon membrane; and produced oscillations as extracellular calcium concentrations were reduced to near zero. Calcium modulated the behavior of sodium channels and potassium channels. His found oscillation required two opposing forces metered by each other so that each limits the other. When potassium current consisted of positive charges outward and sodium current consisted of positive charges moving inward, then these two forces were opposing.

It is understood that the depolarization of the resting potential by sodium influx triggers the potassium channels, after a 1E-3 s delay, to open. If a mechanism is added whereby the action of the potassium channels, after a delay, triggers the opening of the sodium channels, then a sustainable oscillation should occur. Normally sodium channels have a refractory period to prevent this. When modulation of sodium channels has the effect of shortening (or eliminating) the refractory period to where the sodium channel could respond to the voltage changes induced by the potassium channels (about 3E-3 s), then oscillation occurs until some change breaks the cycle.

Bursts are characterized by very distinct on and off events, not gradual and not chaotic. This sharp modal change would require either a sharp voltage range shift (unlikely) or a modulator that could be released near the ion channels to turn on the oscillation, and then somehow sequestered again to turn it off (or *vice versa*, where a modulator is removed from an ion channel to start a burst, and replaced to turn it off). A model can be said to be systemic when one or more feedback loops are present. Without feedback loops, the model is merely a step-by-step process.

Focused, synchronized activity in a dendritic tree will maximize the wave peak at the soma.[187] Many dendritic arbors consist of two zones, the distal and the proximal. The proximal zone acts to suppress the inherent nonlinearities so as to emulate a linear response for all points in the tree. The distal end is variable, modified per learning and plasticity.[188] Workers are variously aware that the modalities of firing patterns cannot be modeling by firing rates or binary open/closed kinetics, but perhaps assumed these phenomena emerged from multicell synaptic structures.[189] They had noticed that the activations and deactivations of sodium channels were often incomplete and chaotic,[154] and this suggested that kinetics play a role more than the Hodgkin Huxley equations would have suggested. They built stochastic models to simulate the kinetics of shifting between the modalities of: single spikes, oscillations, and chaotic firing.[190] [191][192]

Some potassium voltage gated channels have I/V plots that are monotonic and smooth second order curves. A single variable input (V) does not support any significant state conformations. Some reported sodium channels I/V plots appear to be third order (two inflections). But as I/V plots are recorded from aggregate large numbers of like channels, these plots average out the kinetic subtleties. From them, we can only measure the openings and closings of the channel, and will be deprived of the internal state transition kinetics.

Not expressed in the I/V plot are the time lags between stimulus and response. Not expressed is the inactivation function. For these and other reasons, two-dimensional plots are not adequate to model membranal performance. Each allosteric modulation site adds at least 1 degree of freedom (requiring another dimension in the input/output plot. But there are also hidden states, that can be thought of as intermediate conformations to get from modulation effects to phenostate expressions.

Every state transition requires time, and reversible processes make the outcome a bit uncertain. The opposition of the Na and K flux can produce oscillations when the kinetics of one is fast the other slower. [193]

Each of the historic models has been reviewed for its ability to perform modally, that is exhibit multiple modes.[194] The HH, Fitzhugh-Nagumo, Morris-Lear, Hindmarch-Rose, Conner was analyzed mathematically for limit cycles. They can imitate the aggregate, but not the unitary channels.

The mechanisms of neuron and neural tissue behavior take place at smaller scales than previously thought. A single cell has been shown to be capable of a seizure.[195] This implies that the channels are acting among themselves in feedback loops (recurrence).

Protein molecule state transitions are analyzed as first order processes, with an exponential curve wrt time as their solutions. Given complex data, a number of exponential curves can be "peeled" out by subtraction, leaving a remainder from which more exponentials can be peeled out. This can be repeated to some level of accuracy or diminishing returns. Each found exponential is weighted in amplitude and by time constant. The measurable current is then presumed to be:

I(t) = I(inf) + w1*exp(-t/t1) + w2*exp(-t/t2) + ... + wn*exp(-t/tn); % where I(inf) is steady state

This is only a curve fit of exponentials, but is justified by kinetic first order reactions. The problem is that it is not the conformational change that is being measured, but rather the effect that conformational change happens to have on conductivity of the channel. In many cases that would be none, and so those conformations are invisible and ignored.

Another problem arises once terms are added together. Information is lost, more so when the quantity of terms is unknown. Given a sum of 7, what originally comprised it? 1+6, 2+5, 3+2+2, 1+1+1+1+1+1+1 ? Using only integers, there are 14 possibilities, and of course using decimals, there are an infinite number. We receive the sum effects of conformational changes as a measurable current through the open pore. Teasing them apart leads to what are called "kinetic schemes"

The argument is made that to achieve higher frequencies of flux across the membrane, one cannot reduce the mass of the ions, so must have greater forces. Higher voltages were found to support higher frequencies by Buckingham. [158]

The input waveform is the spatiotemporal integration of spikes, and may present as rather sinusoidal (single frequency) or more jagged (mix including high frequencies). It is the high frequency part of the spectrum that can most easily trigger the rate-of-change sensitive ion channels. Therefore the temporal shape of the input wave makes a difference. Some of these effects can be mimicked spatially. With inputs converging from various length dendrites, they assemble in a phase pattern that can shape waves over a wide range of possibilities.[196] To probe

for the temporal shape domain of various dendritic spatial field shapes, various patterns across the field were stimulated[188] And what did they find?

8.3.5.1 Q matrices, stationary stack

Q matrices follow a specific form. Size = N x N, where N = quantity of states. The upper triangle is populated with alpha values = forward transition probabilities between the various states. The lower triangle is populated with beta values = the backward transition probabilities. The diagonal however is not the probability of remaining in the same state. As one has been subtracted from this value. Thus the diagonals are always negative. Q = transition probabilities – eye(N) = the eigenvectors of the Actor. Q easily solves for the eigenvalues of the Actor.

8.3.5.2 Q matrices, variable

The Q matrix is a state transition probabilities table. Q matrices follow a specific form. Size = N x N, where N = quantity of states The upper triangle is populated with alpha values = forward transition probabilities between the various states. The lower triangle is populated with beta values = the backward transition probabilities. The diagonal however is not the probability of remaining in the same state. This is because the Q matrix is pre-processed for solving eigenvalues, by subtract 1 from each diagonal value. Thus the diagonals are always negative. Q = transition probabilities – eye(N) = the eigenvectors of the Actor.

8.3.5.3 Kolmogorov Scaling

Kolmogorov stochastic state transitions are derived for each of the actor types. A stochastic process is one which is not deterministic, but rather requires a substantiation process via a random number generator and a Cumulative Distribution Function (CDF). Such a function implies a mean, a variance and even higher orders of statistical performance. The end result of a stochastic process for an actor is a change in conformational state. These states, if transient, are relevant to information processing by the neuron.

If state transitions were instantaneous, awaiting only the proper conditions, then a finite state machine would be the proper representational model. However, the kinetics of cellular chemistry are stochastic. That is, they are multi-state entities with probabilities in time that that determine which and when a state change occurs (instantiation). They are not instantaneous, but always require some (varying) amount of time to make a transition. Stochastic

transition matrices are called Markov chains if the states are memory-less Most chemical states qualify as Markov processes. The actors in this model are all Markov, which qualifies them for ease of solution via Kolmogorov Q matrix exponentiation. The output of a Kolmogorov Q matrix (s x s) is a vector p, (1 x s), which is a probability distribution (PDF) for all s possible states. If the rate coefficients (alphas for forward rates and betas for backward rates) are stationary, then this calculation need only be preformed once, at Build. If they are transient, then they must be performed each *dt*.

Actor configurations may be of two types: finite modulations, or variable modulation. Finite modulations are effected by ligand bindings. Usually an actor has 0, 1 or 2 such binding sites. Zero binding sites implies that this actor type has a 1 page Q matrix. One binding site which accepts only 1 type of particle implies { vacant occupied } modulation possibilities; therefore a 2 page Q matrices. Which one of the Q's is in use is determined by whether or not the bind site is occupied. An actor with 2 binding sites will have at least 4 pages in the Q matrices, one for each of the possible combinations of bound and unbound sites.

Vesicles may employ a stochastic process in determining the particle contents in each vesicle. When charging up a vesicle, the ratio of particle types is specified as a profile. The variance of each constituent type is also specified. The content of a single vesicle is instantiated as a random selection across int(G), the CDFs of content distributions.

The Hodgkin Huxley EQs were exponential curve fits to aggregate channel current recordings. Chapman applied statistics to the neural data so as to predict the channel openings wrt time, and also gave us analytic EQs to determine the steady state ratios of state dwell time. Chapman adapted Kolmogorov stochastics to quantum mechanics of single channel openings. Though Kolmogorov representation gets a lot closer to first principles, its predictive accuracy is limited by the fact that the protein molecules comprising an ion channel may have billions of possible states, but only a small number of those are of consequence to the conductivity of that channel. The available data, mostly nanoamp readings to measure the conductivity, do not, and cannot, "read" all the states. Thus we remain blind to most of the conformers, and collect a woefully simplified state diagram which is a substitute for, but not a replica of, the actual ion channel states.

$$\frac{dP(t)}{dt} = P(t)Q$$

According to standard probability conventions, P is a vector of unit-less values that sum to one. However stochastic probabilities are in units of frequency, and are divided by time to get the resultant probability of occurrence. This probability of occurrence may be greater than one, if indeed two or more occurrences would have occurred in that unit time. It is prudent to chose *dt* such that all probabilities are less than one, else distortions occur. Certain corrective measures can be made for fast processes. Generally an average state is representative of flutter too fast to be informationally significant in this model.

Q is a matrix of alpha and beta rate coefficients between the various states, forward (upper triangle), and backward (lower triangle).

8.3.6 STATE FLOW DIAGRAMS

Follows are the state transition diagrams for each of the Actors. While in a particular state, the specified function is called every *dt*. To transition to another state, all conditions must be met for that transition. Once all conditions are met, then probabilistic attempts are made to change state. These state transition diagrams are simplified versions of reality, called schemes. Reality often has both forward and backward probabilities along each edge. This model will accommodate forward and backward probabilities whenever the actor is identified as a Kolmogorov entity by providing a Q matrix in the DESIGN load. Else the actors work as finite state machines and change states the instant prerequisites have been met for such (deterministic). A few of the early, simpler state diagrams, motivated only by phenostate requirements, are shown blow.

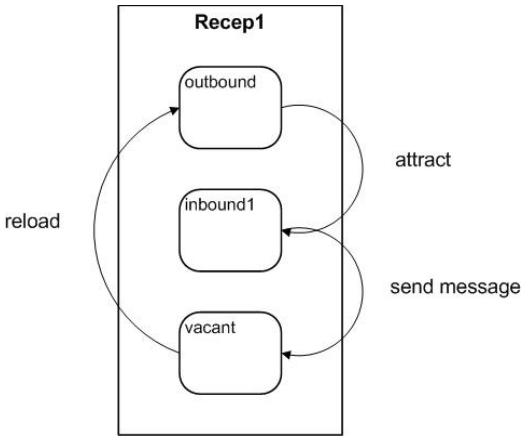


FIGURE 86: STATE DIAGRAM FOR A SIMPLE RECEPTOR

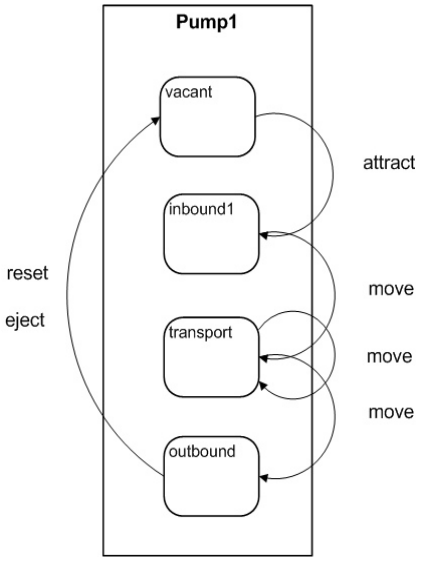


FIGURE 87: STATE DIAGRAM FOR AN ION PUMP WITH 4 STATES

A Recep must be Typed over several aspects:

1. *Vector of interactors attractiveness (set attractors to a* pre-calibrated rate that mimics in vivo)
2. Vector of interactors. binding constants, alpha and beta
3. Response profile to each possible binding (how much message? noisy? delay in sending it?)

The message can be massive or merely electromechanical linkage within an ion chan. Massive messengers require a 3 step process:

1. release;
2. diffusion to the nearest chan;
3. binding to the chan.

Presumably the chan is capable of being modulated by the messenger particles.

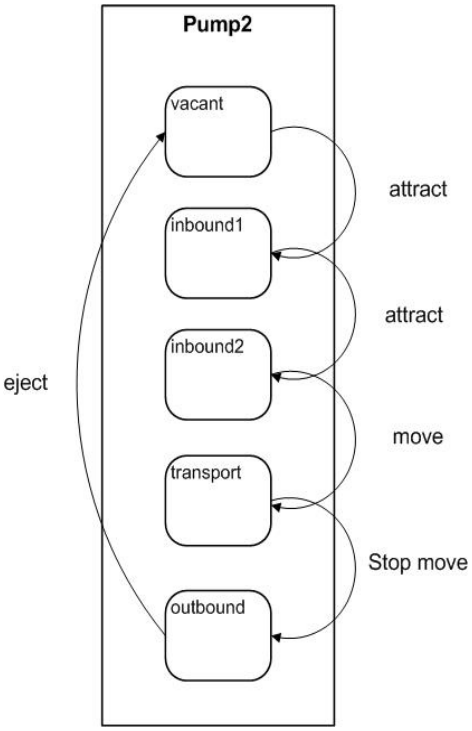


FIGURE 88: STATE DIAGRAM FOR 2-WAY EXCHANGE PUMP WITH 5 STATES

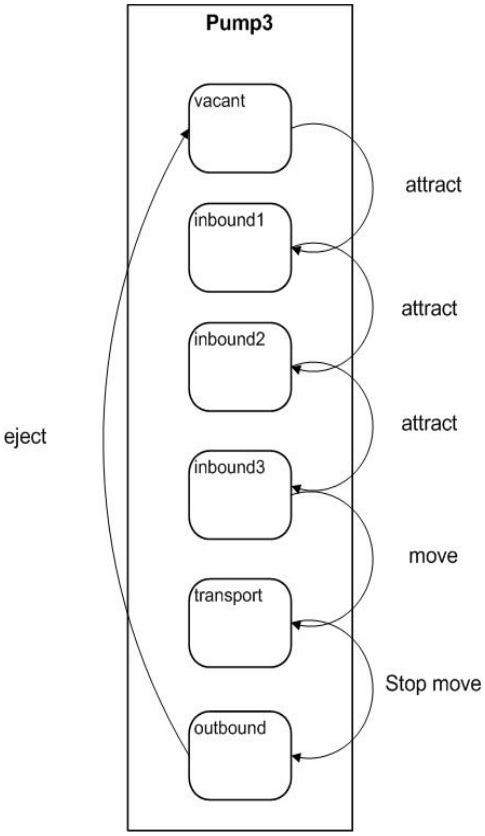


FIGURE 89: STATE DIAGRAM FOR 3-WAY EXCHANGE PUMP

EX Given that interactors = [K Na Cl Ca H An Ach NE GABA]

Type	value	comments
Attracts	Ach	(Modulators may be assigned a serial number)
Attraction Force	0.01	(scaled relative to velocity)
Binding alpha	0.6	
Binding beta	0.3	
messenger	Ca++	
release amount	7	(ions)
noise	0.2	fraction of max signal
release time alpha	0	delay
reset time beta	0	delay

TABLE 19: PUMP WITH 4 STATES

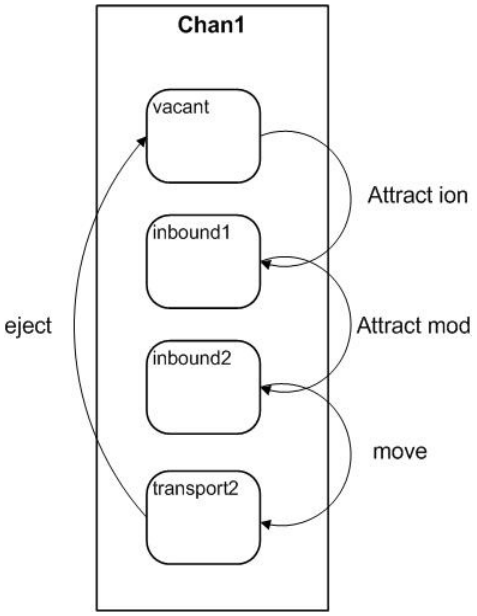


FIGURE 90: STATE DIAGRAM FOR A ION CHANNEL WITH 4 STATES

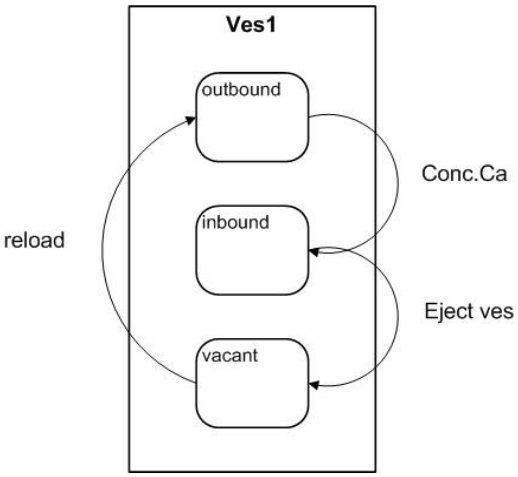


FIGURE 91: STATE DIAGRAM FOR A SIMPLE VESICLE

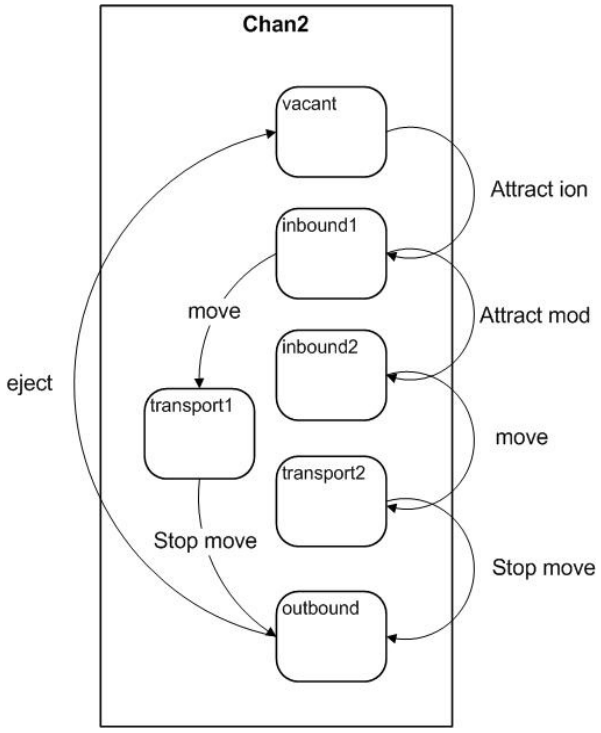


FIGURE 92: STATE DIAGRAM FOR ION CHANNEL WITH 6 STATES

State Diagram for a hypothetical ion Channel with 2conductance values

Each of the above state transition diagrams can be treated as logical calls of certain functions given certain states. However a superior approach is to treat each as a Kolmogorov SDE model, wherein forward and backward probability values are provided. These transition rates may or may not be modulated by any of the available modulators, including voltage and concentration levels.

Note that pH may be a modulator. It is merely an H particle concentration level as far as the digital model is concerned. Voltage is a common modulator to any transmembrane molecule with non-homogeneous charge distributions.

State transition diagrams are populated by empirical data processed by "peeling" exponential curves from a presumed summation of curves. The resultant "Schemes" are simplifications of reality. Therefore, multiple schemes may be produced from the same data. They must compete for the best fit and the most robust behavioral representations of the channel type. From a modeler's point of view, it is worthwhile to run both schemes with experimental designs intending to detect any behavioral difference between the two, . If there are no consequential

differences, then choose the computationally lighter load. If there are interesting differences then keep both in the library.

8.3.6.1 States and Tags for Actor-Particle Interactions

States are those changes in molecular configuration intrinsic to the entity (e.g. mass, charge, radius). Tags are those changes in environmental relationships extrinsic to the entity (e.g. position, velocity, force impinging, compartment assigned to, in capacitance).

Each actor has three types of state. It has its modulator binding state (impact of environment upon the actor), it internal conformational state, and its phenotypical state (its impact upon the environment). The first two are kinetic, represented by probability transition matrices, usually dynamic. The latter is usually a simple lookup table, not requiring stochastics to map internal state to external effect.

When mobile particles become bound to an actor, their positions are set equal to the pole location to which they are bound, and their velocities are set to zero. The actor must know specifically which particles are bound to it. Only by this information could particles be unbound or transported to the other pole.

Optionally, each particle could be tagged as to which compartment it belongs to, and which actor it is bound to if any. Upon transport, its compartment tag would be changed, its position changed to the opposite pole, and the kinetics of its release would be changed.

8.3.7 IDEAL ACTORS

Primary characteristics of actor type:

1. Characterize a singular type and assign it a permanent name or number
2. How many binding sites in this molecule? Are there any other action sites (voltage, pore_opening)?
3. Which side of the membrane is each binding site on?
4. What are the affinities of each binding site, of all the possible particle types?
5. What is the action of each binding sites or other action site?
6. What are the internal configuration states of the molecule? (this is often an abbreviated scheme)

Secondary characteristics of actor type, higher order relationships:

1. How do the B particles relate to the binding sites?
2. How do the binding sites relate to the states?
3. How do the states relate to the actions?
4. How do the actions relate to the B particles?

To these ends has been developed the concept of actor Type data.

```
TA = { BA R RQ Q O G aff erg eff }

% BA is a list of particle types needed, order-sensitive, as tabulated in R
BA_h1 = '[C1 C2]';   % compartment have differing particle concentrations
BA_h2 = '[Na Cl K Ca Gly Glu cGMP ADP ATP]';

% R is the bind and unbind kinetics for each bind site wrt state of the molecule
R_h0 = 'R(state,B,cd,d,fb) dimensionality';
R_h1 = 'states';
R_h2 = '[vacant Na Cl; vacant ADP ATP ]';
R_h3 = 'bindcombo = row of RQ';
R_h4 = 'bindsite';
R_h5 = 'forward or backward rate coefficients';

% Q is the conventional state transition matrix
Q_h1 = 'currently in state';
Q_h2 = 'going to state';
Q_h3 = 'bindcombo = row in RQ';

% RQ maps the R bind combo into the Q page#
RQ_1 = 'occupancy of bind sites = bindcombo';
RQ_2 = 'bind site';

% O maps the Q state into the external action, if any
O_h1 = 'state';
O_h2 = 'external effects = [in thru out convert]';

% G is the conduction profile of channels, the particle contents of vesicles
G_h1 = 'binding site';
G_h2 = 'B type';
G_h3 = 'state';

% aff assists R in receiving the appropriate particles for binding
aff_h1 = 'bind site';
aff_h2 = '[d o B A r4 f1 r6 f2 var]';
aff_h3 = 'B types, when there is more than 1 type binding';

% erg provides reactions that supply energy (e.g. ATP > ADP + Pi), for pumps
erg_h1 = 'reaction number';
erg_h2 = '[reactantA reactantB productA productB]';

% eff assists recep O in transmitting the appropriate messengers to targets
```

```
eff_h1 = 'bind site';
eff_h2 = 'd o B A r4 f1 r6 f2 var';
eff_h3 = 'B types, when there is more than one messenger type';
U = subunit data.  How to divvy up the Q matrix into subunits and the logic of the gates between them.


TA_h = 'cell {1  2  3  4  5  6  7   8   9   10 11}';
          {BA R RQ  Q  O  G aff erg eff  id  U}';
```

% TA is only the type data. There is also needed distribution data DA , and from these two instantiation data IA is generated. IA has static elements and dynamic elements.

```
EX  Recep1 has 1 bind site extra for gly and 1 bind site intra for cGMP
Rq(:,:,1)  = [ 0   0   0   0   0   0   0  10;          % mean
                 0   0   0   0   1   0   0   0];
Rq(:,:,2) = [ 0   0   0   0   0   0   0   1;          % variance
                0   0   0   0   0   0   0   0];

Rcombo =  [ 00 10 11 01];   qRcombo = 4;
R = [bindsite x B x Rcombo x forwardbackward

% recharge state (0 0)
R(:,:,1,1)  =  [ 0   0   0   0   0   0   0   0;          % forward
                  0   0   0   0 .99  0   0   0];
R(:,:,1,2) =   [ 0   0   0   0   0   0   0   1;          % backward
                  0   0   0   0 .01  0   0   0];
% ready state (1 0)
R(:,:,2,1) =  [ 0   0   0   0   0   0   0 .98;          % forward
                  0   0   0   0   1   0   0   0];
R(:,:,2,2) =  [ 0   0   0   0   0   0   0 .01;          % backward
                  0   0   0   0   0   0   0   0];
% stimulated state (1 1)
R(:,:,3,1) =  [ 0   0   0   0   0   0   0 .98;          % forward
                  0   0   0   0 .01   0   0   0];
R(:,:,3,2) =  [ 0   0   0   0   0   0   0 .01;          % backward
                  0   0   0   0 .99   0   0   0];
% release state (0 1)
R(:,:,3,1) =  [ 0   0   0   0   0   0   0 .01;          % forward
                  0   0   0   0 .01   0   0   0];
R(:,:,3,2) =  [ 0   0   0   0   0   0   0 .99;          % backward
                  0   0   0   0 .99   0   0   0];
```

	recharge	ready	release1	release2
00	1	2	3	4
1	0.99	0	0.01	0
2	0.99	0.01	0	0
3	0.99	0.01	0	0
4	0.99	0.01	0	0

	recharge	ready	release1	release2
10	1	2	3	4
1	0.01	0.99	0	0
2	0	0.99	0.01	0
3	0	0.99	0.01	0
4	0	0.99	0.01	0

	recharge	ready	release1	release2
11	1	2	3	4
1	0	0.01	0.99	0
2	0	0.01	0.99	0
3	0.01	0	0.99	0
4	0.01	0	0.99	0

	recharge	ready	release1	release2
01	1	2	3	4
1	0	0.01	0	0.99
2	0	0.01	0	0.99
3	0	0.01	0	0.99
4	0	0.01	0	0.99

where each page represents a certain bind combination. [pole1 pole2] = { 0 0; 1 0; 1 1; 0 1}; Note that the binding conditions are the primary determinant of the next state. This is characteristic of a transducer, as opposed to an information processor. Vesicles have a very similar ideal form; with pole1 and pole2. reversed.

8.3.7.1 General Form for Actors

R: All actors are capable of binding and unbinding certain types of particles
Q: All actors are capable of changing conformation (state-to-state transitions)

O: Pumps are capable of moving binding sites from one side to the other side of the membrane
O: Channels are capable of opening up a pore through the membrane
G: Channels have conductivity profiles (selectivity through the pore)

aff: All actors have certain affinity profiles for particles to bind to their binding sites
eff: Receptors have certain ability to broadcast particles via G-protein systems
erg: Pumps may consume energy by converting one particle type into another type

R		(un)binding B to actor
Q		internal state of actor
O		internal motion of actor
G		conductivity of channel
	A	actor types
	S	actor states
	D	allosteric binding sites
	P	page = combo(DxB+)
	W	[pole1 pore_open pole2]
	B	particle types
	B+	B + null + voltage
	Fi(B)	driving force partials
	Fe(B)	driving force partials
aff		affinity of B to D
	r4	distance reach of affinity
	r3	distance reach of bind
erg		energy consumed per cycle
	in1 in2 .. inn	energy source reactants
	out1 out2 ..outn	energy byproducts
eff		emitted B from A
	qB	quantity of B released
	vel	messenger mean velocity
	var	variance on velocity
	-vel	return velocity (reset)

ACTOR TRAITS	R	Q	O	G	aff	erg	eff
action	E-I kinetics	I-I kinetics	I-motion	selectivity	E-motion inbound	Energy converted	E-motion outbound
matrix	SxPx(DxB+)	SxPx(S)	SxW	Wx(BxFi(B))	[B r4 Fe(B) r3]	[in1 in2 out1 out2]	[B qB A vel var -vel]
Recep	☒	☒			☒		☒
Chan	☒	☒	☒	☒	☒		
Ves	☒	☒			☒	?	
Pump	☒	☒	☒		☒	☒	
clas							

In summary:
The R matrix is the modifier of Q.
The Q matrix is the modifier of R.
Q expresses via O.
R expresses via Bind combinations
aff Bindings are facilitated by aff
erg Pumps consume energy according to erg; or any chemical conversion intrinsic to the duty cycle
eff Dissociations are guided by eff

8.3.7.2 Recep General Function

A generic receptor scheme requires 4 states. There is typically one Bind and Unbind processes for a ligand. This changes the state of the receptor so as to release a messenger (ligand or ion).

EX: Recep for Ach, nicotinic type

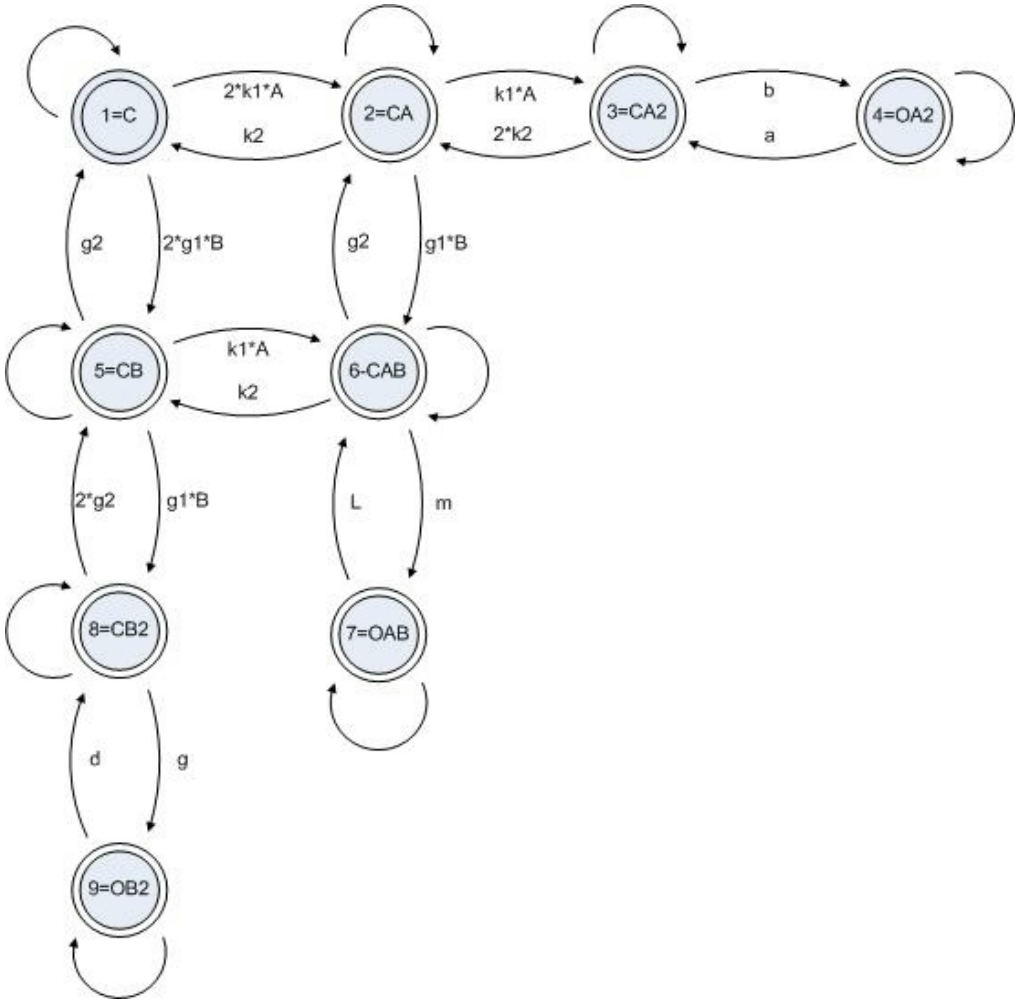


FIGURE 93: KINETIC SCHEME FOR ACH-N RECEPTOR

Above is an example of a kinetic scheme for a Ach nicotinic type receptor, adapted from Salamone, 1999.

A = k2/k1; B = g2/g1; T = a/b; R = g/d; Q = sqrt(T*R) = m/L;
A = 10e-6 M; B = 100e-6 M; T = 100; R = 0.2; Q = 0.935 ;

Notice all hold states have residual values, and for others there are missing values. For any given *dt,* and the probabilities of transitioning to another state are calculated and summed. The residual time equals the hold state probability.

Receptors are presumed to be transducers, a switched catalyst that converts an extracellular NT binding event into an intracellular stream of second messengers until the NT dissociates. This constitutes a mathematical integration. Whenever a receptor behaves in a more complicated fashion than simple on/off, then there must be greater kinetics internal to the molecule. A Q matrix can be designed to mimic various lags, variance, volume control via modulation, as real receptors may display. A pure is receptor is optimized by a faithful one-to-one between detected signal and delivered message. However, in biology, things are rarely simple, and multiple functions may be present.

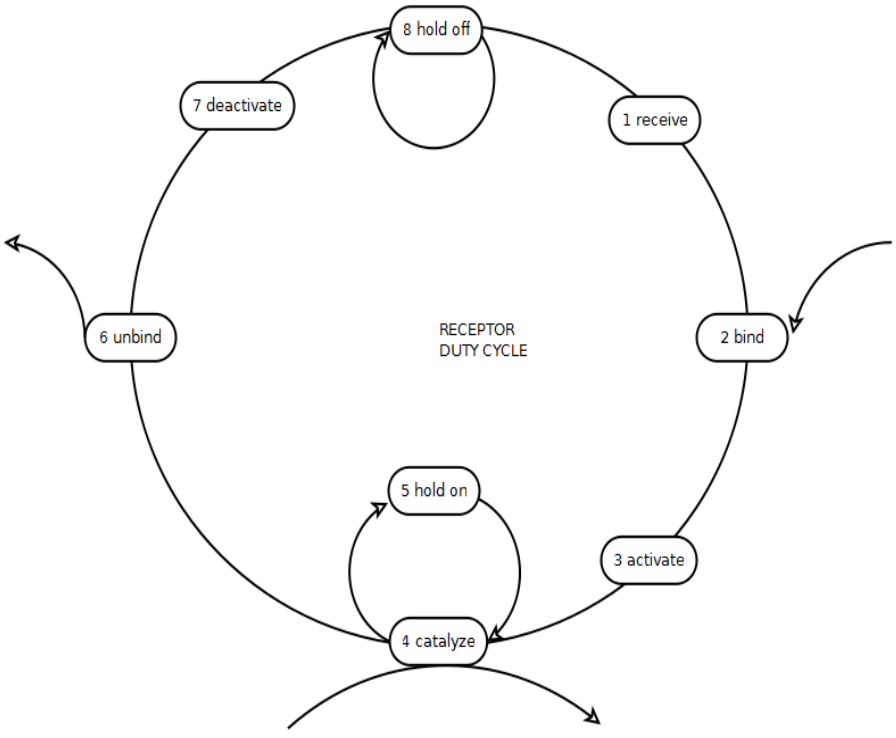


FIGURE 94: Receptor Duty Cycle

8.3.7.3 Receptors, ionotropic and metabotropic

Binding sites located on ion channels are ionotropic, and induce immediate modulation of the Q matrix element values of that ion channel. Remote receptors that employ G-protein messenger shuttles to modulate one or more ion channels per receptor are metabotropic. The latter requires additional iconic structures to enact the communication linkages between receptor and a set of channels.

Receptors broadcast information to a set of channels. From an information perspective, the issues are timing, leverage, and modulation. If there is no intervening modulation between the the receptor's release of messenger particles and the channels' receipt of such messenger particles, then the problem is reduced to timing and quantity. These can be handled is a straight forward manner as a state transition probabilities table for the timing, and straight line links (serving as shuttles) to move the particles to their targets.

The axial poles (round) are loci for ion transport. The eccentric poles (asterisks) are the binding sites for modulating ligands. Z=0 is the membrane plane. X,Y=0 is the axis of the actor.

8.3.7.4 Ion Channel state transitions

A library of channel types is maintained. Each is characterized by an ion conductivity profile, an instantaneous state transition matrix, and a P vector for state to gate mapping. The Q- matrix is one of 2 types, variable or discrete. A discrete Q is a set of several Q matrices consisting of fixed element values, chosen according to modulator bindings, if any. A continuous Q-matrix is a single matrix consisting of elements that are functions of a modulator value, such as voltage. The discrete corresponds to metabotropic and the continuous to ionotropic channels. For discrete Q's there is an R function which translates the modulator state into a choice of Q matrices each *dt*. For continuous Q's the variables within it are re-evaluated each *dt*. Ion channels open and close stochastically as a function of state transitions within the Q-matrix

O = P*S*Q(R), where
R = receptor binding or modulator value
Q = infinitesimal transition matrix (as determined by R)
S = current molecular conformation
P = functional expression of any given conformer
O = open/close status of the ion channel
So = stochastically determined initial state of each channel

Practically, ion channels consist of 4 to 6 subunits which are protein molecules changing conformation somewhat independently. It requires less computation to treat each subunit separately and then take the product of their conformers, than it does to process a single large joint matrix representing the whole channel.

Ion channels can be fitted with energy barrier profiles which will influence which velocity ions get through.

Ion channels consist of 3 to 10 subunits, each of which may or may not be active in gating or inactivating that channel. Subunits are generally regarded as independent finite state machines, but theoretically may be coupled. If dependent, then the Q-matrices of the subunits would be represented as sub-matrices within a greater channel Q-matrix.

Let us begin with the Hotchkin-Huxley model of ion channels. One type of sodium channel was deemed to be present. It consisted of identical 4 subunits, referred to as 'n'. There was also one more channel type present, the Potassium channel. It consisted of 3 identical subunits referred to as 'm' and a fourth subunit referred to as 'h'. All subunits were deemed to possess gates, any one of which could obstruct the channel. Therefore the probability that the sodium channel was open was n^4, and the probability that the potassium channel was open was h*m^3. The opening and closing rates are measured as the forward and backward “rate constants”alpha and beta, which unfortunately are not at all constant. So let us call them rate coefficients.

In the circumstance of opening and closing, a complete cycle consists of one alpha and one beta. Thus the period = alpha+beta; and accordingly the frequency = 1/(alpha+beta). In solving a first order differential to get the aggregate response, the time constant tau = 1/(alpha+beta). This is best thought of as a frequency – how many open-close cycles occur per second.

Because h,m, and n refer to subunit gate openings, a more general form is sought that would accommodate any subunit and any number of subunits per ion channel, and any mix of subunit types per ion channel.

We can call each subunit h, and number then h1, h2 ... hn. A library of subunits can be used to mix and match to create new ion channel types, or merely refer to existing types by listing their subunits. As it is expected to be tedious to always construct an ion channel from an existing library of subunit types, it is allowed to define a new channel and its subunit types simultaneously.

The general form of the Hodgkin Huxley EQ for one of the channel subunits:

$$h1(t) = h1_{\infty} + (h1_0 - h1_{\infty})e^{-t/\tau_{h1}}$$

For a channel with 4 identical subunits the gating function would be h1^4.

The source of tau in the above EQ is the reciprocal of the sum of the forward and backward rate coefficients. The exponential response of one subunit changing forward and backward rate coefficients in response to its modulators

$$h = h_{\infty} - (h_{\infty} - h_0)e^{-(\alpha+\beta)t}$$

is:

The forward and backward rate coefficients originate, in the case of certain voltage modulated subunits as:

$$\alpha_h(V) = \alpha_h^0 e^{\delta zFV/RT} \qquad \beta_h(V) = \beta_h^0 e^{-(1-\delta)zFV/RT}$$

Kolmogorov's contribution to channelology was that he provided the methods to generalize all subunits of ion channels as finite state machines with stochastic transition probability frequencies :

$$\frac{dp(t)}{dt} = p(t) * Q$$

Q is the instantaneous transition probabilities matrix for all relevant states (configurations) of the subunit and P is the vector of all states with the probability of being in each state at that moment in time. The upper triangle of Q is the forward coefficients and the lower triangle is the backward coefficients. Q can be any size from 2x2 (for a single alpha and beta, to NxN where N = the number of relevant states. P can be treated as a PDF, and instantiated to a particular state for any instant in time.

Q is in units of frequency,(events/sec), and must be adjusted to the span of *dt* to be valid in discrete time.

$$Qdt = e^{Q*dt}$$

None-the-less any conversions to discrete time are fraught with potential errors when the span of Q-matrix values is great, or when all values are many orders of magnitude away from one.

EX: a Q matrix for a Kv Chan type:

The simplest 4 subunit channel would have kinetics similar to:

SIMPLE CHAN
consisting of 4 subunits

sub1			sub2			sub3			sub4			phenostate
bind	closed	open	bind	closed	open	bind	closed	open	bind	closed	open	
0	0.99	0.01	0	0.99	0.01	0	0.99	0.01	0	0.99	0.01	
1	0.01	0.99	1	0.01	0.99	1	0.01	0.99	1	0.01	0.99	

sub1	sub2	sub3	sub4	
bind	bind	bind	bind	open
0	0	0	0	0
1	0	0	0	0
0	1	0	0	0
0	0	1	0	0
0	0	0	1	0
1	1	0	0	0
1	0	1	0	0
1	0	0	1	0
0	1	1	0	0
0	1	0	1	0
0	0	1	1	0
1	1	1	0	0
1	1	0	1	0
1	0	1	1	0
0	1	1	1	0
1	1	1	1	1

TABLE 20: CHANNEL WITH SUBUNITS, PHENOSTATE LOGIC

In the above case, each subunit is either open or closed. When all 4 subunits show open, then the actual channel is open. Other logical relationships between subunits are possible. There are reasons why channels are all vastly more complex than this value set. The homeostatic characteristics of living forms is in large part dependent upon ion channels that modulate in accordance with changes in their environment.

This example is a voltage sensitive potassium channel.

Q yields a probability density function for a given prior state. This PDF (the vector from Q chosen by the prior state) can be instantiated by converting the PDF into a CDF , then applying a random number generator to choose the next state. Once a P has been instantiated to a state s for a given *dt*, it must be interpreted for its external expression (open or closed). When more than one subunit is gating, then there are several P's and several

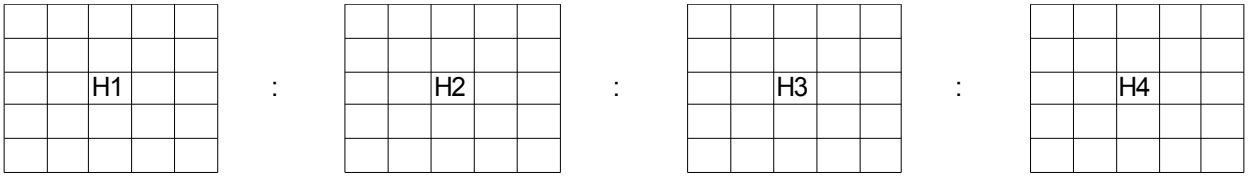
instantiated states. A logical gate function must then be applied to interpret the particular combination of subunit states for the over all channel opening/closing expression.

Two kinds of Q matrices are possible, the variable Q and the discrete Q. The variable Q is most often responding to voltage, but may be responding to other continuous parameters such as pH or temperature. The discrete Q's, which are a stack of possible Q's, one of which is chosen by the particular combination of bindings of modulator ligands on the subunits is present.

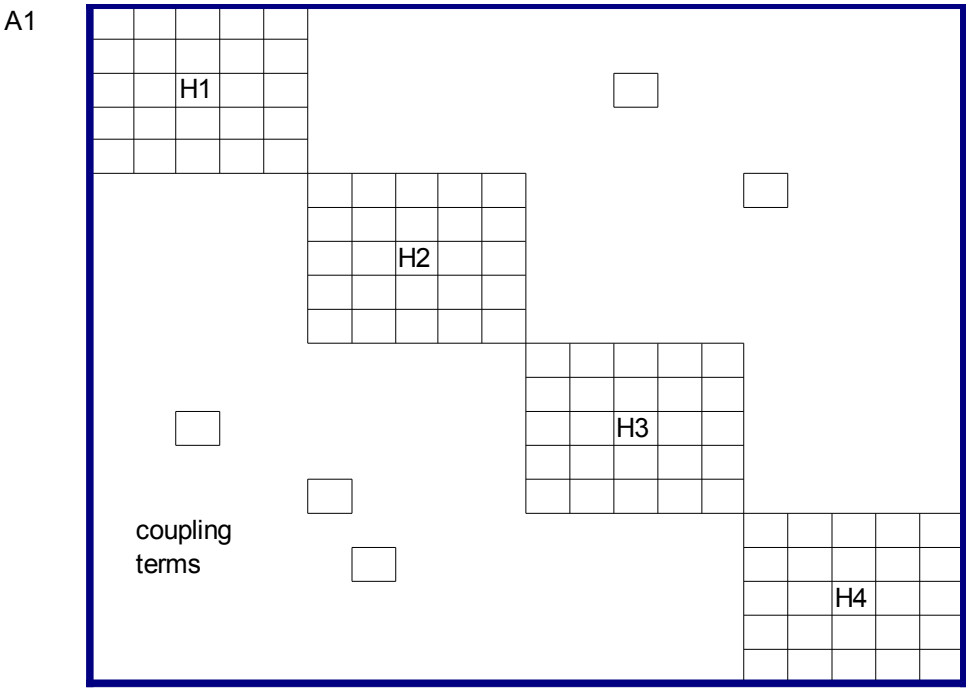
It is computationally desirable to convert the continuous forms to discrete, because this allows all of the Q-matrix calculations to be performed in the BUILD, rather than the RUN. The sacrifice is that continuous values must be made discrete (binned into the most significant domains, which need not be of equal width. By this means the given continuous variable(s) are looked-up on a bin table which yields a pointer to which Q-matrix to use for that *dt*. The look-up table will have a dimension of N when N equal the number of input variables, be they discrete or continuous.

8.3.7.4.1 Actor Subunits

Some actors are know to consist of 2 or more subunits that are assembled and inserted into the membrane to become functional. There is a question as to whether there is any advantage to modeling the actor as a single entity, ignoring the subunits , or alternatively treating actors as “mix-and-match” assemblies from a library of subunits. The major consideration is computational load. Each actor subunit has its own Q matrix. If the values within the matrix are not significantly altered by the coupling (binding) of say 4 subunits into a single ion channel, then treating each subunit as a separate entity is computationally efficient. However, if the binding of subunits involves stressing the molecule so as to change their Q matrices, then each channel type (as a combination of various types of subunits) will be unique. This nullifies the utility of subunit Q matrices, because none survives the association anyway. The resultant singular Q representing all 4 subunits as a single entity is necessarily more complex. Four 5x5 matrices involve a lot less computational load than one 20x20. But the 20x20 would be necessary to reflect the kinematic coupling between the subunits as they become one. The pivotal question is: Is the intensity of coupling between subunits sufficient to necessitate merging the 4 subunit Q matrices into a single Q matrix so as to accurately represent the state transitions?



Given 4 subunits each with 5 significant states, they could be treated separately as four small computations to determine the phenostate of each. In the case of an ion channel, a simple AND function would determine the general phenostate of open or closed for the whole channel.



In a similar situation, but if the subunits bind in such a way that their state changes are coupled to each other, then the subunits must be represented as a single larger matrix that provides the coupling terms at various locations outside of the four subunit blocks. This simply acknowledges that the actor has become a larger entity with 20 significant states.

8.3.7.5 Vesicle General Function

For purposes of information flows, the vesicle is modeled as an inverted receptor.

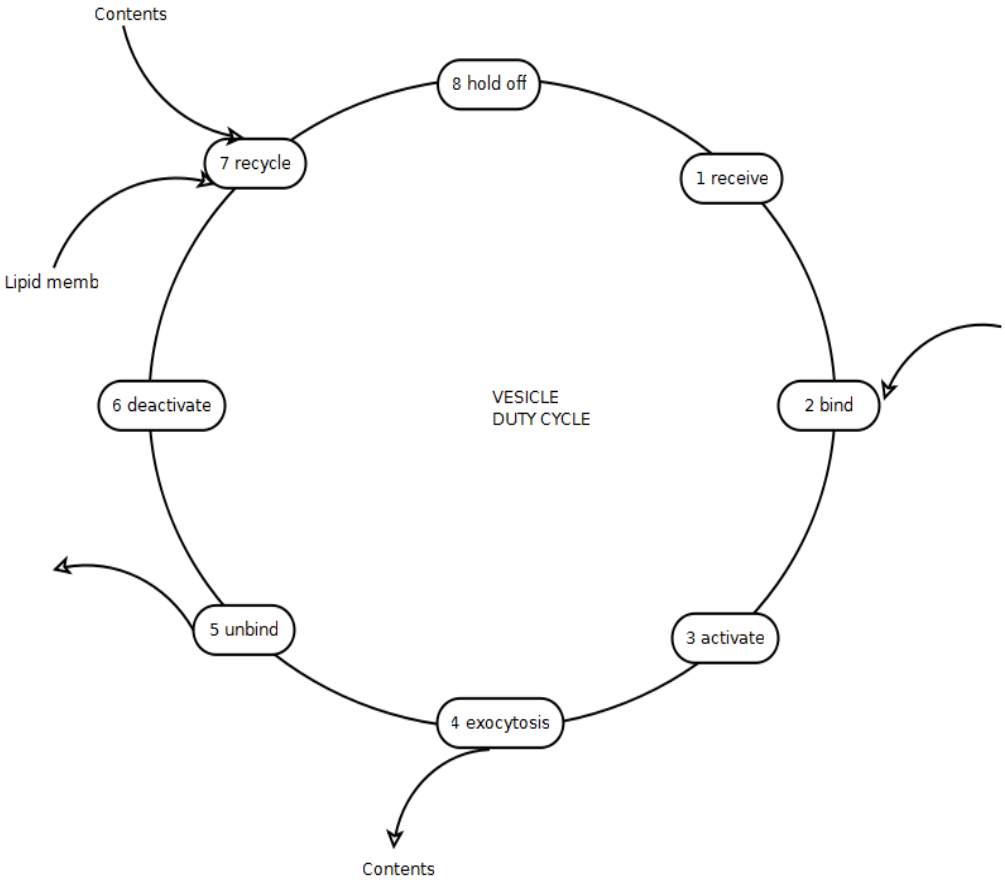


FIGURE 95: Vesicle Duty Cycle

8.3.7.6 Pump General Function

Ion pumps are indispensable in many modeling queries.

1. They determine what the steady state is regarding tonicities. Therefore they determine the resting potential. One definition of clinical death is the cessation of ion pump activity, so critical is their contribution.

2. Pumps are logical devices, whenever they co-transport. Rather than merely pump one or another ion to desired levels, they force ratio-based movements, more apt to preserve the ratio between species of ion than set the absolute concentrations. Further complexity arises by the interplay of various types of pumps, each with its own idiosyncratic ratio. Tonicities can be shifted to different concentration profiles by re-weighting pump type activities. This can play a role in shifting the functional role of the cell across several "moods", by altering tonicities along viable paths to modulate the Q-matrices of ion channels (and other actors).

3. Pumps fatigue, presumably due to energy shortages. This effect is certainly relevant to neuron behavior. Pump fatigue can be simulated by giving them receptors which modulate pumping rate, and may become

starved for ligand. Thus ligand concentration controls pump rate. If modulators alter or switch pumping curves, then ligands can alter the steady state conditions as well.

4. Pump distribution can set up significant effects for information processing. A cluster of ion pumps at one end sets up an ion current down the entire length of a process. For example, such currents are instrumental in motion detection.

A library of Ion Pump types is maintained.

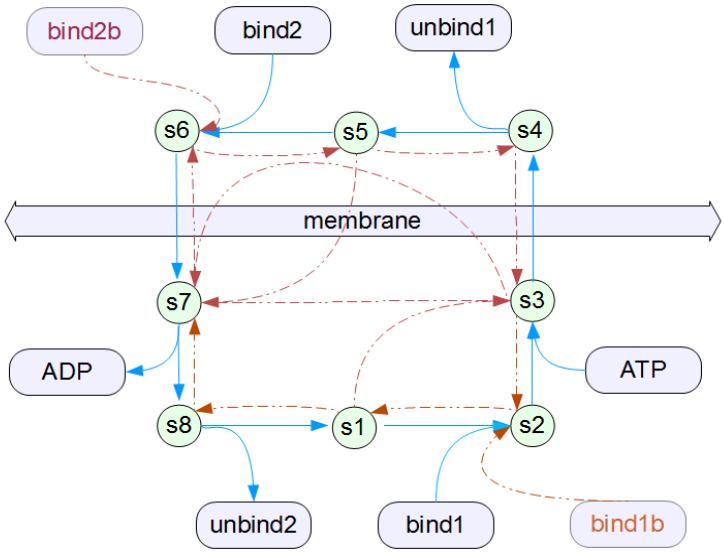


FIGURE 96: PUMP STATE FLOW DIAGRAM

The rest states s1 and s5 are optional. The red arrows show alternative and mis-step transitions that show up in the transition probabilities matrix. It is helpful to add in the actions that take place between states. Either the prior state triggers the action, or some external event triggers the change in state.

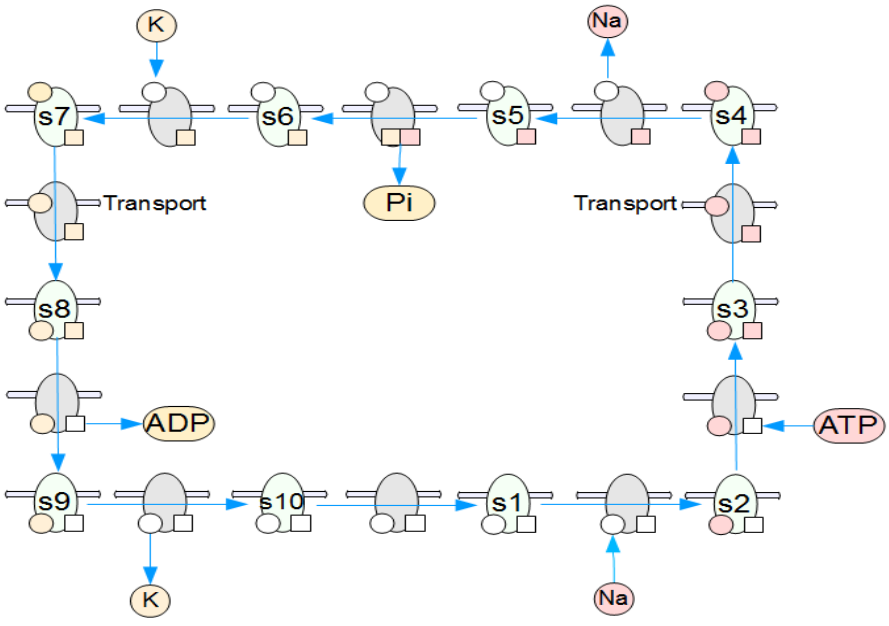


FIGURE 97: Ideal pump with 10 states and actions

For pumps that require binding dissimilar ion types, it is more accurate to add a position for each possible binding event, including extras for binding in alternative orders. Below is the Q matrix for a 16 state pump.

Q =

0.52	5.93E-007	0.97	6.81E-007	0.02	8.79E-007	9.71E-007	2.86E-007	0.02	2.69E-007	7.87E-008	6.28E-007	1.83E-007	2.55E-007	7.81E-007	0.04
3.16E-007	0.64	0.06	8.35E-007	1.79E-007	1.05	6.03E-007	8.33E-007	8.70E-008	0.01	8.68E-007	7.86E-007	3.21E-007	9.12E-007	2.90E-007	0.06
0.03	0.94	0.34	8.96E-007	2.49E-007	3.57E-007	0.01	7.70E-007	3.18E-007	9.54E-007	0	7.49E-007	2.56E-007	3.68E-007	5.51E-007	2.52E-007
8.86E-007	4.13E-007	1.94E-007	0.65	0.01	0.04	8.63E-007	2.01E-007	4.53E-007	1.18E-007	7.97E-007	0.01	9.41E-007	3.80E-008	5.75E-007	1.01
0.01	7.70E-007	9.13E-007	0.01	0.36	8.06E-007	0	7.65E-007	1.61E-007	2.49E-008	7.86E-007	1.83E-007	0.01	6.51E-007	2.04E-007	3.99E-008
8.63E-007	0.05	6.84E-007	0.96	9.21E-007	0.85	0.01	6.16E-007	5.99E-008	4.22E-007	3.31E-007	8.44E-007	9.88E-007	0.02	5.55E-007	6.24E-007
2.45E-007	6.08E-007	0	3.10E-007	0.01	0.01	0.54	9.64E-007	4.45E-007	6.44E-008	9.50E-007	7.16E-007	9.52E-007	8.38E-008	0.01	3.87E-007
4.34E-007	7.95E-008	7.13E-007	4.47E-007	9.03E-007	9.47E-007	6.95E-007	0.67	0.01	0.01	8.28E-007	0.01	8.74E-007	1.15E-008	5.49E-007	0.11
0	4.15E-007	4.85E-007	9.64E-007	1.90E-007	9.51E-007	8.41E-007	0.01	0.26	9.24E-008	0.01	6.13E-007	0.01	3.66E-007	6.98E-008	3.32E-007
2.16E-007	0.01	8.33E-007	4.62E-007	9.93E-007	3.21E-008	6.76E-007	0.01	5.10E-007	0.12	0	8.74E-007	1.47E-007	0.01	8.60E-007	9.32E-007
7.75E-007	8.43E-007	0.01	4.96E-007	3.26E-007	2.76E-007	7.01E-007	9.80E-007	0.01	0.01	0.04	7.93E-007	6.50E-007	4.16E-007	0.02	4.68E-007
8.72E-008	5.24E-008	2.55E-008	0.02	2.28E-007	6.78E-008	8.95E-007	0.01	8.30E-007	6.10E-007	9.89E-007	0.89	0.01	0.01	2.39E-007	7.10E-011
4.00E-007	7.28E-007	3.36E-007	1.92E-007	0.01	8.27E-007	5.87E-007	2.61E-007	0.01	3.95E-007	3.44E-007	0.01	0.75	4.66E-007	0	7.26E-007
5.90E-007	1.15E-007	4.87E-007	8.98E-007	8.11E-007	0.01	3.25E-007	5.90E-007	4.27E-007	0	2.40E-007	0.01	2.45E-007	0.8	0	3.99E-007
1.97E-007	4.85E-007	2.25E-007	3.89E-007	9.24E-007	5.81E-007	0.01	7.45E-007	7.33E-007	9.61E-007	0.02	6.24E-007	0	0	0.44	2.29E-008
0.96	0.06	5.55E-007	0.01	7.19E-007	3.44E-007	2.08E-007	0.11	5.27E-007	7.50E-007	9.09E-007	3.53E-007	2.33E-007	5.08E-007	3.19E-007	0.08

.

A generic pump scheme requires minimum of 6 states. But these are only the internal transformations. There are also the possible external events of binding and dissociation.

Each of the Bind and Unbind processes may be assigned {0 : many} particles to be pumped. A particle may be an ion or a ligand. Energy may be implicit (as when driven down the sodium gradient), or explicit (as with converting ATP to ADP). Chemical energy sources are presumed to be available intracellularly, not extracellularly.

This scheme requires that all of the particles bound at Bind1 be unbound at Unbind1, and all of the particles bound at Bind2 be unbound at Unbind2.

For purposes of transport, pumps and channels are assigned 2 poles. Each pole is assigned to a compartment at Build, according to physical placement in a particular membrane. Each of the state transitions is purported to consist of one (or several) first order kinetic interactions.

1. S1 state 1 empty, Attractor1 binds “Bind1” particles
2. S2 state 2 loaded, Attractor1 off
3. S3 state 3 transporting towards Pole2, note consumption of energy
4. S4 state 1 release all Bind1 particles

5. S5 state 2 empty, Attractor2 binds Bind2 particles

6. S6 state 3 transporting towards Pole1, note consumption of energy

```
Bind1 =  [ atomic weights ID the ions to be bound at pole 1;
             Starvation concentration parameter for each;          % units are particles/cumicron
             Saturation concentration parameter for each ];        % units are particles/cumicron

Bind2 =  [ atomic weights ID the ions to be bound at pole 2;
             Starvation concentration parameter for each;          % units are particles/cumicron
             Saturation concentration parameter for each ];        % units are particles/cumicron

%%   BUILD:
posA = BuildPump ( TypePump, TypeAttract, DistPump )   % maps types of pumps to locations
TypePump (Shape, Bind1, Bind2, PumpRate)
   % a pump type is defined by an icon, poles, binding functions, and pump rate
TypeAttract ( MW, R, F, r )   % parametrizes each attractor, draw radius, force, bind radius
   *  MW = molecular weight of ion to be attracted and pumped
[ PosPump, PolAttract ] = DistPump ( pdfPump, posC )   % posC = node locations on comp
Bind1 = [ AW, starve, saturate]    % creates a sigmoid probability curve for bindings
PumpRate =  max pump cycles / msec
 %%   RUN:
Function  [NewPos, NewTag] = pump ( DistPump, Pos, Tag)   % completes 1 pump cycle
```

IDEAL PUMP	001	101	100	000	010	011

load1	load1	transport12	unload2	load2	transport21	unload1
001	1	2	3	4	5	6
1	0.98	0.01	0	0	0	0.01
2	0.98	0.01	0	0	0	0.01
3	0.98	0.01	0	0	0	0.01
4	0.98	0.01	0	0	0	0.01
5	0.98	0.01	0	0	0	0.01
6	0.98	0.01	0	0	0	0.01

transport12	load1	transport12	unload2	load2	transport21	unload1
101	1	2	3	4	5	6
1	0	0.99	0	0	0	0.01
2	0	0.99	0	0	0	0.01
3	0	0.99	0	0	0	0.01
4	0	0.99	0	0	0	0.01
5	0	0.99	0	0	0	0.01
6	0	0.99	0	0	0	0.01

unload2	load1	transport12	unload2	load2	transport21	unload1
100	1	2	3	4	5	6
1	0	0.01	0.98	0.01	0	0
2	0	0.01	0.98	0.01	0	0
3	0	0.01	0.98	0.01	0	0
4	0	0.01	0.98	0.01	0	0
5	0	0.01	0.98	0.01	0	0
6	0	0.01	0.98	0.01	0	0

load2	load1	transport12	unload2	load2	transport21	unload1
000	1	2	3	4	5	6
1	0	0	0.01	0.98	0.01	0
2	0	0	0.01	0.98	0.01	0
3	0	0	0.01	0.98	0.01	0
4	0	0	0.01	0.98	0.01	0
5	0	0	0.01	0.98	0.01	0
6	0	0	0.01	0.98	0.01	0

transport21	load1	transport12	unload2	load2	transport21	unload1
010	1	2	3	4	5	6
1	0	0	0.01	0	0.99	0
2	0	0	0.01	0	0.99	0
3	0	0	0.01	0	0.99	0
4	0	0	0.01	0	0.99	0
5	0	0	0.01	0	0.99	0
6	0	0	0.01	0	0.99	0

unload1	load1	transport12	unload2	load2	transport21	unload1
011	1	2	3	4	5	6
1	0	0.01	0	0	0	0.99
2	0	0.01	0	0	0	0.99
3	0	0.01	0	0	0	0.99
4	0	0.01	0	0	0	0.99
5	0	0.01	0	0	0	0.99
6	0	0.01	0	0	0	0.99

A generic pump scheme requires 6 states. Each of the Bind and Unbind processes may be assigned {0 …many} particles to be pumped. A particle may be an ion or a ligand. Energy may be implicit (as when driven down the sodium gradient), or explicit (as with converting ATP to ADP).

Due the the combinatorial expansion of space and the permutation exploding in time, the quantity of elements in the multidimensional matrices representing just one actor can be huge (3600 in a very simple pump). Fortunately, such matrices are sparse, and approaches can be developed that trace out the duty cycle, then populate one-bit errors as alternative paths, then two-bit errors, and on until some point of diminishing returns. Beyond that background noise can fill in the rest of the fields for greater authenticity, albeit at heavier computational load.

Ideally, molecular dynamics will soon be able to generate all the probabilities for a given molecule in a given environment, so there need not be interpolation, guesswork and background fill. With such data, runs can be made to determine the truly significant bits, and the rest can be purged for leanness in the systemic studies.

8.4 EM DRIVEN STOCHASTIC SYSTEMS

8.4.1 VOLTAGE AS POTENTIAL ENERGY

Trans-membrane voltage is a force upon each charged particle. It is a modulator to many actor types. It is a driver determining the quantity of charges driven through open channels. It directly determines how many ions are contained in membrane capacitance. Voltage can be calculated for each pixel of membrane, or for each actor vicinity (r5).

Many neurophysiology texts begin the consideration of voltage with the Donnan's Equilibrium, which expresses the tendency for each ion type to achieve the same charge ratio between adjacent compartments with permeability between them, except that multiple charge ions tend towards the ratio of the square roots for valance =2 and cubed roots for valance =3 .

$$\left(\frac{K^{+}_{out}}{K^{+}_{in}}\right)^{\frac{1}{z.k}} = \left(\frac{Na^{+}_{out}}{Na^{+}_{in}}\right)^{\frac{1}{z.na}} = \left(\frac{Ca^{++}_{out}}{Ca^{++}_{in}}\right)^{\frac{1}{z.ca}} = \left(\frac{Cl^{-}_{out}}{Cl^{-}_{in}}\right)^{\frac{1}{z.cl}} = \left(\frac{An^{-}_{out}}{An^{-}_{in}}\right)^{\frac{1}{z.an}}$$ ... one term for each ion type

Donnan's, of course, expresses the relationship between the ions at their steady state, given the EM force due to voltage differentials. This EQ does not determine which one or which combination of ions determine the voltage

that all must align to, to achieve equilibrium. It only represents the tendency through pores. The GHK EQ helps to establish which of the ions will dominate in determining the membrane voltage, in the steady state.

Generalized GHK Voltage EQ, which employs a Nernst approach to calculating Voltage. It is intended to measure the voltage through a man-made voltmeter with probes in each solution, as it measures the ability to inject electrons on one side of the membrane and receive electrons on the other side to complete the circuit.

$$V_{rest} = \log 2\left(\frac{\sum_{i}^{N}(g_{B_i} * B_i^{+}.out) + \sum_{j}^{M}(g_{B_j} * B_j^{-}.in)}{\sum_{i}^{N}(g_{B_i} * B_i^{+}.in) + \sum_{j}^{M}(g_{B_j} * B_j^{-}.out)}\right) * kelv * R / K * 2.3026 / 3.3219;$$

where kelv, R, K, 2.3026, and 3.3219 are constants that may be kept outside the dynamic equations. The log has been changed from natural to base 2 in the discrete problem to facilitate particle counts and particle ratios.

V.steadystate = kelv * log2 ((sum(G.i*conc2.i) + sum(G.j*conc1.j)) / (sum(G.j*conc2.j) + sum(G.i*conc1.i)));

where *i* is a list of all cations and *j* is a list of all anions
conc1 is the concentration extracellularly, and conc2 is the concentration intracellularly
G.i is the permeability of the cations, and G.j is permeability of the anions.
Permeability is to flux as conductivity is to current.

Because this EQ is completely dependent upon channel selective conductances, it can only apply where those conductances are valid. That is, the values must be local to a specific channel constellation in a particular state of openings. Because the openings are extremely transient, so to is the applicability of this equation. The EQ is most often labeled as the voltage across the membrane, but in fact calculates the pressure through a given channel set, not across the membrane by and of itself. The concept has been extended across a local cluster of channel types, but at some risk, as the charge densities vary dynamically around each channel opening and therefore are not uniform over an area large enough to include several channels. Further complexity arises from the membrane charge times, which in conjunction with slow conduction velocities result in lag conditions between actors.

There is reason to challenge the validity of the Nernst EQ in true vivo conditions without man-made instrumentation hooked up to it. The basis of challenge concerns the behavior of electron flow through artificial instrumentation vs the behavior of ion flux circuits in the living cell in the absence of that instrumentation. Any electrical instrument involving a voltage pumps electrons into a living system that otherwise would not have such free electrons added and removed. Electrons travel extremely fast through saline, compared to ions, and therefore yield results that are

unrealistic to the natural cell. Measurements of electron flow suggests that the extracellular saline short circuits all extracellular entities. And yet voltage sensitive dyes reveal that the extracellular saline is not isotonic. Why the discrepancy? Because ions do not flow as fast as electrons. In an ionic system, the mass and size of the electrons slow the action down such that a tortuous topology of voltages are found over the membrane, all acting in a complex of dynamic waves, analogous to the ocean's surface.

The Nernst EQ calculation of partial voltages remains as a reliable indicator of selective conductance through a single unit channel, as it represents the chemical interaction of ions with pore charges so as to effect transport. In those situations where the conduction of an ion type is dependent upon chemical processes (bindings and dissociations, electron transfers, etc.), then electrochemistry applies, as a function of temperature, charge, and the log of ratios between reactants.

Meanwhile, the voltage across the membrane is strictly a matter of charge density on either side, and that charge density is necessarily within an exponential envelope wrt distance from the centerline of the membrane.

$V_{memb} = \frac{thk * q}{\varepsilon_0 * A};$ where q/A = surface charge density (coulombs/m^2), thk = effective thickness of membrane (meters)

At the point where the quantity of unbalanced charges is large enough to start forming a second layer, then that equation becomes a summation of the layers:

$V_{memb} = \frac{1}{\varepsilon_0 * A} \sum thk_i * q_i$ where the *i*th layer is calculated separately, and then all layers are summed.

When thermal noise is present, these layers do not achieve orderly stacks, but their equivalents can be surmised by beginning with absolute zero and increasing temperature while noting the resultant voltage reduction due to scatter. This voltage is not temperature dependent, nor ion species dependent, and so the reconciliation between the Nernst voltage and the Coulomb voltage is not trivial.

For a final word on voltage we call upon the Coulomb's law, which is one of the most rigorously verified equations in physics, as it serves as the basis for Maxwell's EQs and Einstein's relativity.

$$V_{memb} = \frac{1}{4 * pi * \varepsilon_0} \sum (q_i * q_j) / r_{ij}\text{^}2$$

In a particle system, Coulomb's law is the most reliable and accurate calculation of the voltage field, especially regarding membrane capacitance. It serves not only to calculate the voltage, but also to drive the acceleration of each individual charged particle with a composite EM force. It first calculates the net force on each particle. Then, as superposition is valid for Coulomb's law, all the forces of the particles on one side of the membrane can be summed, and all the forces on the particles of the other side of the membrane summed, which their net opposition force equal to the force against the membrane.

It is concluded that the model particle system should be driven by Coulomb's law, and the channel fluxes calculated using the Nernst EQ. The distinction is due to filters. The raw voltage at large (all along the membrane) is Coulombic; while the voltage pressure within the pore of a specific channel type is highly filtered by the phenomenon called selectivity. The Nernst EQ is derived from first order chemical kinetics, implying an interaction rate, not a force.

In man-made systems, voltage is often regards as the sole information content of the system. Following this habit, many studies of the neuron also hold o presume that voltage is the single significant measure of information. This is especially tempting given the successful studies and models of the action potential. However, neurons are not single charge species systems. They certainly employ Na, K, Cl, Ca, Mg and other ion types. Those ions present in lower concentration, e.g. Ca++ and Mg++ are known to serve as messenger molecules in minute quantities, about 6 orders of magnitude smaller than the recorded action potential formed by the sum effects of the Na partial voltage and the K partial voltage and Chloride partial voltage. They have masses at least 42000 times greater than that of the electron. Such mass and size makes the movement of ions a much slower process. than that of electrons. If the charge movement around a neuron could be electronic, then all conduction velocities would be at the speed of electricity, rendering each cell essentially isotonic, and all cells sharing continuity via extracellular fluid isotonic. But we do not see such phenomena at all. Conduction velocities are always measured much lower, and this fact rules out electronic conduction.

It is therefore prudent to consider what information is being carried that is not showing up distinctly on the electrician's volt meter. Indeed every messenger molecule, of which there are many types, is not represented in the

voltage reading. Certainly, neutral particles are silent in the voltage readings. Is this analogous to taking a readout from the computer by putting an amp meter on its power cord, completely missing all the nuances of those little bits? Well, its not that bad, but certainly misses the nuances of the many signals being generated.

Voltage is merely an emergent property of two charge concentrations somehow held apart. It is analogous to the force between two magnets as they are allowed to come closer together. Therefore, the mathematical construct of partial voltages does not exist in actuality, except that some selectivity filters may approximate a partial voltage effect.

Strictly, voltage represents a loss of information, as the concentrations of the dominant ions are summed via their charges into voltage. Which contains more information, [2 4 1 9] or [16] ? Any time several data are merged there is loss of information unless there is an obvious way to reverse the process back into the constituent parts. Therefore it makes sense that the output of the neuron is not voltage, but Ca++ driven chemical releases. A single Ca++ contains more information than a singular voltage spike, and a vesicle release contains much more information than a Ca++ ion. Voltage is a crude measure of information being processed in a neuron, for it is blind to the many species of ion acting independently of each other, and is blind to the many non-charged messenger molecules.

The primary role of voltage is to serve just as gravity does, as a ubiquitous force. As gravity makes surface waves possible on the ocean, so does voltage make surface wave possible on the membrane. The information is in the waves, and the height of these waves we happen to call voltage. But this leads to a bit of confusion between the force and the results of the force. Consider that we do not confuse the height of the ocean waves with gravity. We may consider any ocean wave height as being defiant of gravity. A horizontal force (wind) acts upon lose mass in a force field to yield potential "pile ups" of P.E. embodied as wave crests. But we must consider that gravity is essential to the phenomena of waves, though it runs perpendicular to the motion of waves. This analogy holds with the membrane phenomenon: opposite charge attraction provides the "gravity", the ions have sufficient mass to "pile up" into wave crests whenever there is a disturbance (channel pulses).

A further point is worth mentioning. For the most part, voltage readings on living cells are taken with a glass probe. This is a single sampling point in an immensely complex grid of dynamic fluctuations. Such a probe is analogous to sampling a TV screen by watching only one color dot, or the ocean by the bobbing height of a single buoy. Yes, it

may give some insights as to how the system works, but it certainly does not convey the content of the visual scene and how it is transformed. More recent voltage sensitive dyes are breaking out of this limitation, and allow the visualization of the surface the dye is sprayed onto. Even more detailed Ca+ sensitive dyes support the visualization of just one ion type (and an important messenger at that). MRI technologies are moving towards the specific visualization by atom types (Na, K, Cl,Ca) . However the resolution is limited and not likely ever to be fine enough to study nano-scale events. It remains to be calculated what would be a minimal quantity of wave height sensors to determine the where and when of distant disturbances.

8.5 PATCH MODEL

Patch models consist of a small number of voxels with a maximum of one actor per voxel. Distortions arise from a simplification of ions into quantal "groups" of a million ions each, and scaling the conductivities of ion channels up 1 million times to accommodate these, a recalibration of membrane capacitance, receptor bindings, and pump function.

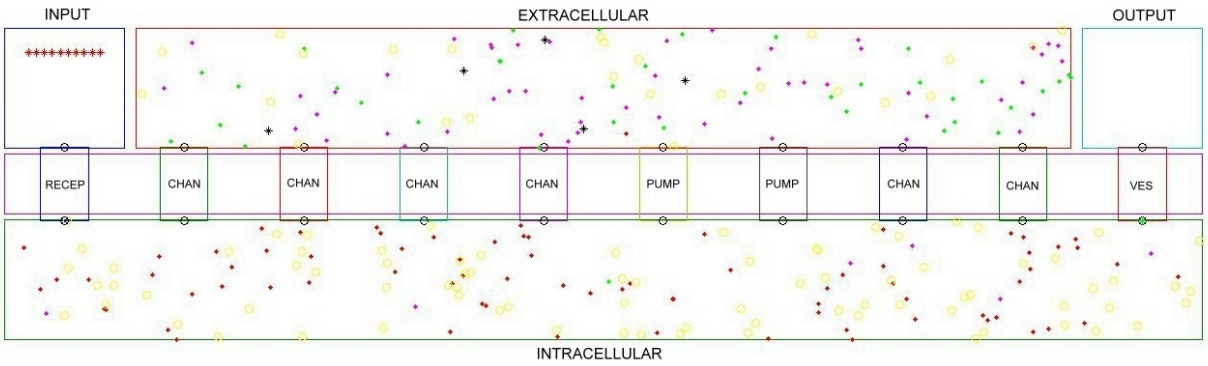


FIGURE 98: PATCH MODEL WITH PRE-SYNAPSE AND POST-SYNAPSE COMPARTMENTS

8.5.1 DIFFUSION IN 3-D PARTICLE SYSTEM

Particle systems for fluids are easily implemented within cubical containers, as reflections are simply a matter of changing sign on velocities. Positions can be initialized randomly, with uniform distribution. Velocities are

randomized spherically, with magnitudes determined by the Boltzmann distribution as a function of temperature and mass. Particles can be attributed (scaled) radii and masses, and accurate valence values. Any number of species of particle can be mixed in. Diffusion will achieve steady state in the absence of active processes. However, irregular shapes quickly increase the computational load.

EM force is implemented with the inverse square law of attraction/repulsion (optionally any exponent). This requires an NxN matrix size to measure the inter-particle distances each *dt*. For moderate quantities of particles (say 1E6), numerical methods for minimizing computational load are necessary for both forces and collisions.

Point forces, line forces and plate forces are all similar, by merely reducing the dimensionality of the force. Compared to point forces, line forces are 2/3 the computation and plate force is 1/3.

Generally, the motion EQs are.
Anew = sum(force/mass);
Vnew = Vold + Anew;
Pnew = Pold + Vnew;
where A = acceleration, V = velocity, and P = position

8.5.1.1 Positions

Initial positions of particles need not be distributed evenly in their respective compartments. They may be deposited as a bullion, and allowed time to dissolve in the water. All that is necessary is that the bullion is placed firmly within the correct compartment. Ligands are often initialized as bound and then released later. Bound particles are assigned to their positions and their velocities effectively set to zero, and tagged as to which element they are bound to. Generally, any bound particle may remember its former velocity, as the tag indicating it is bound causes a multiplication of any velocity by zero, until unbound. An unbound particle may have a remembered velocity direction that when released drives it right back into the binding site or membrane. Its compartment tag identifies it as trying to escape out of its assigned compartment and causes a reflection.

8.5.1.2 Velocities

Physics models prefer working with momentum rather than explicit velocity. When particles are aggregated and the system is required to conserve momentum, this makes sense. But when position is information, ad each particle is instantiated for its positions every *dt*, then staying in the momentum equations is not an option.

Velocities can be modeled easily with the aid of the Boltzmann Cumulative Distribution Functions (CDFs), and spherical instantiations. The result is satisfactory in that it maintains its velocity profile characteristic over any number of iterations. However, one must use spherical coordinates for all velocity re-directions (collisions, reflections, and bound releases), else a cuboidal distortion of velocity values results.

Each mass has its own velocity probability curve for a given temperature.

Shown are the velocity probabilities for protons, Na, Cl K, Ca, Protein with M.W = 500.

Boltzmann distributions are used to initialize particles, and to create random collisions with water molecules.

8.5.1.3 Accelerations

Initial accelerations are set to zero. All charged particles exert force on one another. This is the N-body problem. The sum total of all attractive forces minus all repulsive forces determine the net force upon a particle. That force divided by its mass determines its acceleration.

8.5.1.3.1 Particle-Actor Forces

EM Repulsion applies Coulomb's law to each particle, and sums all impinging forces on each. EM Attraction is simply repulsive force with a negative sign.

8.5.1.4 Solvents

Charged particles in a container with a point or line force produce orbiting particles. As this is not at all realistic to bio-cells, the presence of water is essential. Water as a solvent produces a collision about every 10 angstroms. More accurately, each mass at a given temperature has a mean free path. This implies that within each *dt*, a random portion k of the particles will have collided with water. When they do they will emerge with an aggregate conservation of momentum, temperature and Boltzmann distribution of velocities.

8.5.1.5 Particle-Membrane Forces

EM Charge-Imbalance across membrane

Of all of these, the Concentration Gradient is an emergent phenomenon from collisions, and needs no further analysis. It is calibrated to reality via the mean free path and mechanical mobility.

All of the EM forces require computational evaluation. The general scaling factor for this force must be calibrated to reality as a ratio to electrical mobility.

8.5.1.6 Membrane Lipid Molecules

The neuronal membrane consists of self organizing molecules, but interestingly, there are many dozens of types of such molecules present in any membrane, some of which alter the thickness and the capacitance of the membrane. They are not stationary, but apparently adaptive changes are made in response to temperature, hydration, pH and other factors. The dielectric strength of the polar heads of the membranal lipids alter the electrical capacitance. There may be "rafts" of inhomogeneities floating around in the lipids. The membrane also provides various forms of tethering for the proteins active in NIP.

As with water, the quantities of molecules in a neuronal membrane are too great to model individually. Treating the membrane lipids in aggregate is justified in that neither their movement nor their state changes have been reported significant to the generation of an action potential. Specifically, they have not been reported to contain, process, nor pass information.

Verification of the proposed model of reduced quantities shall be accomplished by modeling membrane patches small enough that the number of particles is tractable to current technologies. These patches may then be extrapolated in size and complexity, in stages, such that verification work for each stage can be performed by comparing the performance of the reduced quantity model to the performance of the full quantity model.

The roles of the membrane from a NIP perspective is to define compartment shape, to reflect particles that collide with it, to provide positional "addresses" for each membranal protein, to define the sidedness of the compartment (e.g. inside vs outside) so as to orient pumps and receptor sites, and to act as a capacitor for any charge imbalance across the membrane. Implied by any closed surface is the volume which it contains. To fulfill all of these roles requires a surface location system, an equivalent membrane thickness that determines capacitance, and the ability to divvy up the surface into small areas suitable for finite element methods nodes. It also must allow penetration by the various protein actors embedded in it. The inhomogeneities of constituent molecule types can still be represented by pixel-wise variations in thickness and capacitance.

8.5.1.7 Membrane capacitance

The mere fact of a barrier impenetrable to ions within a charged field will result in ions accumulating at or near the membrane to the extent of any charge imbalance between the two sides of the membrane. Charges are pumped across the membrane, relatively slowly, with the effect of "building up" a charge imbalance that acts as a potential energy source. The pumps usually do not pump more than 15% beyond what would have been the Donnan's equilibrium anyway, and often only 5 to 10%. This suggests that pumps merely restore what was already there, rather than pump the natural state up to some unnatural pressure. The presence of negatively charged large protein molecules in the intracellular compartment biases the membranal system to keep chloride outside. With chloride outside, then so must a cation remain outside to charge balance. Which cation will balance the chloride is statistically a function of what's available; in seawater, Na is the dominant cation. The cation will match the concentrations of seawater, all to maintain charge balance with the chloride, and the concentration ratios. That leaves room for several cations to move inward to balance the protein anions. Next to Na, the most available in seawater is Potassium, then Magnesium and Calcium. Potassium influx is enforced by the selective permeability of the membrane to it. The so called leak current is really partially open potassium channels. It is this steady influx of potassium that allows it to dominate the mix in determining the rest potential. Furthermore, in many cell types the chloride may move passively across the membrane and in so doing maintains charge balance. Allowing chloride to move freely means the pumps will not need to do much work to move ions, as they will no be pumping up an charge imbalance. Even without pumps there will be such asymmetries of ion distributions across the membrane that contains large anion molecules within. However, charge imbalance is a method of storing up potential energy, and so the chloride passive flux is usually restricted somewhat, so as to allow a certain amount of charge build up (resulting in (0.100..0.500) V at steady state. Such passive leak currents can be regulated so as to effect some homeostasis, or be modulated in response to changing environmental conditions.

To serve as a capacitor, the membrane need only be intact as a closed surface and have the ability to withstand (not arc through) at any of the physiologic voltage values. It is not yet known how charges move alone the membrane after being ejected out of an ion channel. Because of the inverse square law we can expect unbalanced charges to be tightly held near the membrane, but the lateral movement will be some resultant of repulsive forces, impacts from above, inertia, collisions with neighbors, and reflections off the membrane surface. There may also be some membrane lipid polar head attractions.

There is much work to do towards understanding the behaviors of charged particles about the membrane when perturbed by a channel opening. Because the goal of this project is to determine the information quality of ion movements, a distinction is made between the balanced charge pairs and the unbalanced charge pairs. Every charge-balanced pair, by their neutrality, opt's out of the force field. Such pairs are free to wander in random collisions of diffuse into white noise along the Gaussian gradients. By this, they become null in their information value. But the patterns of unbalanced ions around ion channels is of particular interest. The charge-imbalance pairs remain as players, and do not participate in diffusion, which would dissipate their information value. They cannot diffuse because the EM force over rides any such tendencies. They slam into the membrane by the force of attraction coming from the other side, and are then capacitated in a thermally active zone. Perhaps ions diffuse laterally (2-dimensional diffusion). Perhaps they bounce along the membrane, jumping over repulsive charges. Perhaps they move in waves, as radiating rings on water after a pebble is dropped in. Because ions are far more massive than electrons (20000x), and are constrained within a pool of repulsive like-charged particles, they act as mechanical oscillators. This implies a second order system, which elevates the analytic descriptor from diffusion equation to the wave equation. It is expected that the pulse of ion flux through a channel results in a wave radiating out from the channel. If so, a great advantage is bestowed upon the cell, for a wave preserves information, while diffusion loses it. Simulations shall be conducted in attempts to determine the nature of such ion movements.

8.5.2 PROCEDURE TO SIMULATE AN ACTION POTENTIAL

By action potential is meant one trip across the neuronal membrane with an informationally significant cascade of ionic and proteomic events. The classic Hodgkin Huxley action potential is but one example of this, and certain types of neurons only traverse with a graded response. For lack of a better term, action potential generation is used to connote all such sorties.

1. ion tonicities initialized to steady state concs in each compartment (tonicity profile)
2. ion diffusion and drift in water, in each compartment – with charge, acceleration and collisions
3. ligands concs initialized to steady-state concs in each compartment, especially those bound to actors
4. ligand particles are released into synaptic clefts per input signals from pre-synaptic cells (SigGen)
5. ligands diffuse in water, in each compartment (3-d diffusion)
6. actor affinity profiles activated (for modulation and transport)

7. local voltage readings modulate all voltage-gated proteins
8. ligands bind to receptors via forward/backward rates
9. actor Q-matrix page selection based upon modulator combo, switching Q-modes, which in turn alter state paths
10. instantiate actor state changes, per *dt*, acting upon a Qdt matrix (which is Q adjusted to *dt* probabilities)
11. read actor phenostate = gating function, transport function, messenger release, vesicle release
12. ligand unbindings from actors as a func of kinetics and concs
13. ligand "reuptake" pumps restore ligands to original positions, kinetically, per concs
14. receptors release second messengers in response to ligand bindings (1:5 ... 1:20 leverage ratio)
15. second messengers migrate along membrane (2-d diffusion or 1-d shuttles)
16. second messengers bind to cyclases kinetically, as a func of concs
17. cyclases enzymatically produce phosphates (rate = hundreds /msec)
18. phosphates diffuse in water (3-d diffusion)
19. phosphates may bind to ion channels (phosphorylation) as func of kinetics and concs
20. modulation combos (including voltage) map to Q-matrix page change in Ion Channels
21. channel Qdt is instantiated as state change, every *dt*, although statistically may remain in same state
22. map state to phenostate, to determine impact on environment
23. when chan phenostate is open, read conductivity profile of chan type: Flux = phenostate* G*F
24. F = (dV -Nernst potential) + concentration potential drive flux: F = (Vmemb - Nernst(iontype) +k*dC)
25. ligand affinities to ion channels vary with gating function
26. ions are transported through chan, reassigned to new compartments, released with conservation of momentum
27. transports alter local charge density and ion concs
28. ions spew out of ion channels and encounter a strong EM force. Many go to the membrane per I = C*dV/dt
29. change in concs results in change in Nernst voltages
30. change in concs results in change in Vm, as Coulomb's Law, F = k0*q1*q2/r^2
31. change in quantity of charges across the membrane results in change in voltage and capacitance charge
32. new voltages and charges result in altered drive through the membrane leak channels
33. changes in saline tonicity changes electrical resistances between voxels, which changes ion currents: I12 = (V2-V1)*(1/R12)
34. horz flux also shifts Nernst voltages and capacitance charges at a velocity of ionic drift

35. vesicles bind Ca++ as a modulator, a a func of kinetics and conc
36. vesicles change state per their Qdt as a func of mod combo
37. vesicles release ligands kinetically into synaptic cleft (contents and frac_discharge may vary about the mean)
38. vesicles and receptors restore their contents via kinetic sequence and pumps (recycling sequence)
39. pump cycle kinetically to load1 via affinity profile for side 1
40. pump completes bind1 staging, kinetically
41. pump bind1 state alters Q-mode, also mods and concs may alter Q-mode
42. pump state change kinetically, may transport across membrane (forward) or unbind (backward)
43. pump offload at side2 after transport
44. pump load side 2 via affinity profile for side 2
45. pump completes bind2 staging, kinetically
46. pump bind2 state alters Q-mode, also mods and concs may alter Q-mode
47. pump state change kinetically, may transport across membrane (forward) or unbind (backward)
48. pump offloads side2 after transport

Several of the above steps involved more detailed processes. Specifically, ions move due to thermal and electromagnetic forces. These must be calculated as a whole system effect each *dt*. Then container walls must reflect all particles that collide with them. All actors are represented as the point processes of stochastic Markov chains. These state transitions require multi-dimensional arrays that capture both the internal state transition probabilities and the external binding event combinations. These are instantiated each *dt*.

9 ALGORITHMS

To design and implement a software application of this size requires an organized break down into linked modules. Each module may consist of objects and/or actions. As each object (element) and each action (process) is typically called thousands of times per simulated time slice (*dt*), coordinated use of arrays is advised. In pursuit of such an organization, the following steps were followed.

1. Enablement maps each element and process to available resources as necessary to give each a place to live.
2. Primitives are defined as the mutually consistent building blocks for the construction of elements
3. Algorithms define the potential actions and limits of action for each element.
4. Feeders insure the algorithm receives all that it required as input and context, in qualified formats and units.
5. Usage checks insure that elements do not corrupt the data nor attempt to do physically impossible tasks.
6. Behaviors are broken down into specific functions and sub-functions, as objects for efficient re-use.
7. Data structures support all function inputs, states, outputs, and transition rules. (see following chapter)
8. Data structure integrity functions (data base management) constrains operations to insure a sane database.
9. Command structure calls the functions in a realistic series (quasi causality).
10. Harvesting of useful data and metrics from all that is generated; and archiving it in an orderly fashion.
11. Organizing gleaned information into human friendly reports, visual graphics, comparables, and reusables.

9.1 ENABLEMENT

Unless otherwise noted, enablement is now handled by the operating system.

9.2 PRIMITIVES

In many software projects the primitives are previously defined for general use and made available generally. In this case, the open source available primitives were found to be not compatible with the requirement of a homogenous membrane and particle system dynamics. Matters as simple as an integer or a sphere needed to be re-written to insure interoperability in the massive arrays to be implemented for the dynamic equations.

9.2.1 MATH

9.2.1.1 Geometry

Geometric techniques are necessary for computer modeling of particle systems, because in a genuine neuron shape intractable amounts of computing power would be consumed in shape-related particle reflections. Topology manifolds establish the basis for shape simplification by demonstrating (and proving) that a tortuous surface can be represented as a plane or a set of planes, so long as the representative planes where sufficiently small. This is quite convenient for neuron modeling, because a lot of the valuable data comes from electrode patch clamp studies. The patch is the physical embodiment of the abstract manifold plane.

As the long axis of the neuron provides the major direction of information traffic flows, models absolutely require at least one dimension (not merely a point process) to represent the whole cell. Early experiments with 1-dimensional models resulted in: a) little or no propagation, due to missing collateral sympathy in wave generation; and b) unrealistic diffusion, in that ions could not get by each other and behave in patterns characteristic of a 3-d world. Admittedly, 2-d models provide qualitative improvement over 1-d performance, as they capture many of the salient features of 3-d representations. However what they gain in Cartesian simplicity they lose in incurring artefactual boundary conditions problems, the absence of circumferential movement, loss of wave fronts, and an improper relationship between surface and volume. Although circumferential information flows are rarely discussed in the literature, and are certainly less likely to be crucial than axial information flows, 3-d models do solve the problems of accurate representation of propagation and diffusion. In addition 3-d models exemplify more realistic membrane behavior in that they permit the study of capacitation and support for actor rafts (local structural dimensioning between actor types).

Tessellated surfaces are popular within the CG community, but computationally heavy for reflecting particles. They necessarily impose cuts and edges where there are none in biological cells, and these create significant differentiation errors which require compensating algorithms. I have chosen to put that effort, instead, into a 3-d model response to the needs of texture, in search for whatever effects and behaviors might emerge therefrom. After various trials, shape simplification finally settled around contours of revolution. The load of particle instantiation, reflection, drift, diffusion and bindings is such that a 3-d model is justified. However, the tortuosity of dendritic arbors is not yet tractable on small computers.

All contours of revolution in digital representations can be further simplified into primitives of cones, cylinders, spheres and tori. The use of primitives greatly reduces shape-related calculations. They easily interact as intersections and/or unions. In any case, the surfaces of all employed shapes must be amenable to a homogenous set of addressable nodes. It is at the loci of these nodes that various actors are placed. While the static features of shape need only be calculated once, the dynamics of ion motion between nearest neighbors and the capacitated ions along the membrane must be calculated each *dt*.

In particle systems, the simplifications of compartment shape (e.g. whole cell shape) may be justified by the equivalence of reflection angle distributions. However, the computational loads of particle motions, collisions, and bindings are still computationally complicated. Compartment shape simplification need not be reduced to much less than this unavoidable particle load, as beyond that, much may be lost with little gained.

The model build process begins with defining membranes. It is useful to consider compartmental membranes (C) as warped 2-d structures. The Actors (A) are positioned only as embedded in those membranes, so also require 2-d positioning. The actors are assigned to addressable nodes on those membranes. The volumes for the B particles exist between membranes. Only the particles (B) fill 3-d volumes. By convention, each volume shall be named according to the membrane that is its ceiling. The core volume is that which is under the core membrane. The intracellular volume is that which is above the core membrane and under the plasma lemma. The extracellular volume is that which is under the extracellular membrane but above the plasma lemma. The plugs are a special case, because they represent all three of the above volumes. A plug is defined as a stack of 3 cylindrical compartments. The core is the largest of these and is merely a storage compartment for sequestered messenger particles. The middle active volume contains the staged particles ready for release. And the extracellular volume is the synaptic cleft. The synaptic cleft may be defined separate from the general extracellular fluid, or may be defined as a separate compartment.

9.2.1.2 Geometric Primitives

The following conventions have been adopted. It is rare to deal with singular instances of any type of entity in this program. Each type is therefore defined in the plural to facilitate the matrix handling of groups.

9.2.1.2.1 Points ::: [x y z], n x 3

9.2.1.2.2 Line segments ::: [x y z x y z], n x 6 (2 points)

9.2.1.2.3 Vectors ::: [dx dy dz], n x 3, magnitude = |r|

9.2.1.2.4 Lines ::: [x y z dx dy dz], n x 6, typically expressed as: [x y z]+t*[dx dy dz], -inf<t<inf

9.2.1.2.5 Rays ::: [x y z dx dy dz], n x 6, typically expressed as: [x y z]+t*[dx dy dz], 0<t<inf

9.2.1.2.6 Planes ::: [x y z nx ny nz], n x 6, [point normal form]

9.2.1.2.7 ContourSurface ::: [x r], n x 2, [axial location radius]

9.2.1.2.8 ConicSurface ::: [x0 y0 r0] = swing point & arm, for spheres and tori

9.2.1.2.9 TesselSurface ::: [p1 p2 p3] = T = triangles of nearest neighbors on a surface

9.2.1.2.10 Disks ::: [x y z nx ny nz r], n x 7, centroid, normal, extents

9.2.1.2.11 Polygons (planar shape) ::: [x y z], n x 3 (checked for coplanar points)

9.2.1.2.12 Cube ::: [x y z nx ny nz x y z] , centroid, normal, extents

9.2.1.2.13 Cylinder ::: [x y z nx ny nz x y z] , centroid, normal, extents

9.2.1.2.14 Cone ::: [x y z nx ny nz x y z] , vortex, normal, extents

9.2.1.2.15 Sphere ::: [x y z x y z nx ny nz x y z] , centroid, normal, extents

9.2.1.2.16 Torus ::: [x y z x y z nx ny nz], extents, centroid, normal

9.2.1.2.17 Intersection of Shapes ::: (algorithm)

9.2.1.2.18 Union of Shapes ::: (algorithm)

9.2.1.2.19 Subtraction of Shapes ::: (algorithm)

9.2.1.2.20 Perforations ::: disk subtracted from a larger surface (algorithm)

9.2.1.2.21 Transform ::: homogeneous 4 x 4, h=[sizx 0 0 1; 0 sizy 0 1; 0 0 sizz 1; movx movy movz 1]

n ::: quantity of a type in any grouping

9.3 GENERAL REQUIREMENTS

Having established a 3 layer model, a sandwich of perhaps 20 nm, 8 nm, 20 nm, (representing extracell, membrane, intracell, respectively), the model suggests a planar approach, using a topology that projects 3-d shapes onto 2-d surfaces. The essence of information processing is connectivity. Any projections which disrupt the nearest neighbor relationship will have broken that connectivity. Many forms of analysis for 3-d surfaces involve cut lines

or other forms of discontinuities. For purposes of tracking information processing, it is advisable to avoid such techniques.

The compromise is to construct a genuine 3-d model which, in every way practicable, simplifies the dynamic equations to the equivalent of 2-d math. By employing a contour of revolution, the distance to the surface is always a radius, and the conversion to polar coordinates essentially converts a 3-d problem to 2 dimensions.

9.3.1.1 Shape creation

1. Choose primitives for concatenation, scale to mate end rings. Then add end seals if needed.
2. Repeat for each membrane in system
3. position for connectivity
4. generate floor/ceiling EQs for each compartment wrt x-axis
5. smooth each contour so as to be differentiable
6. Rings are seeded as evenly spaced points along the contour
7. Nodes are generated as evenly spaced along each ring
8. Nearest Neighbors are sought out after the population of some nodes with actors

9.3.1.2 Particle population

1. Identify safe locations within each volume to inject boli without violating membranes
2. Calculate volumes of each compartment
3. Calculate particle quantities necessary to attain desired concentrations in each compartment
4. Create and position mixed type boli with random positions within an ellipsoid, assigned Boltzmann velocities
5. Init particles that are bound to actor binding sites, stochastically

9.3.1.3 Run Particles

1. Calculate ABC distances
2. Detect collisions on trajectories
3. Choose earliest collision on path
4. If BB collision, resolve with 3-d elastic momentum transfer
5. If BC collision, resolve with reflection

6. If BA collision, resolve with instantiation of binding and dissociation events at each allosteric binding site.

9.3.1.4 Actor Population

14. Get actor distribution functions by A type, per cell type to be modeled
15. Map distribution onto model cell shape, interpolating across zones
16. Instantiate actor placements onto homogeneous grid of surface nodes
17. Initialize each actor according to rest state probabilities

9.3.1.5 Modulus of the model

At the smaller scale is the matter of voxels. A uniform voxel size would create a monstrous bookkeeping load as particles crossed the voxel boundaries. An uneven voxel size (b-tree divisions, with the smallest in the most critical regions) improves on this problem, but does not accommodate the various shapes of neurons. That is, the voxels will intersect the angles of the membrane in random ways, requiring additional computation to address the mismatch between the voxel grid and the membrane shape. This problem can be averted via tetrahedral shaped voxels, following the finite element method. This supports adapting the voxel shapes so as to align to membrane surfaces, and around actors in useful ways. Unfortunately, it implies every voxel has unique coordinates, unique surface areas, and unique volumes. It is computationally the worst of the considered options. A superior solution would be to create the volumes according to the "grain" of model details, or only as needed, and shaped specific to that need. Free ranging particles can easily be modeled without voxels until they happen near to an actor. Within a certain distance of actors, chemical affinities dictate that certain interaction types may occur: bindings, transport, unbindings. A useful shape, therefore, is the hemisphere. Placing 1 hemisphere above the membrane and 1 below the membrane, at each actor, both with a radius set equal to the chemical affinity radius, provides a terse voxel list, exactly 2 times the quantity of actors. Any particles within the hemisphere contribute to local concentrations, partial pressures, and voltage impinging on the actor. However, as the membrane is not flat, the geometric definition of a flat bottom hemisphere will not quite do. Some allowance is made for the membrane curvature by defining a hemisphere as all particles belonging to 1 compartment within distance r6 of a given actor pole. At the smallest diameter shapes, e.g. near dendritic boutons, the volume of the outer "hemisphere" will be considerably larger than the volume of the inner "hemisphere". When calculating concentrations, a correct factor is indicated for this distortion. The algorithm is:

Get all actors.
Get the pole locations for each actor
Get the compartment assignment for each pole
Get all particles in each compartment
Note that all bound particles are subtracted from compartment assignment lists
Get all poles in each compartment
Find distance between all particles and poles in each compartment
Get all particles with distance less than r6. (creates hemisphere)
Count all found particles by type within each hemisphere.
Calculate volume of hemisphere if membrane shape is sufficiently non-planar
Get charge valance of each particle type
Sum positive charges. Sum negative charges. Subtract for net charge.
Align matching hemispheres on opposite sides of the membrane at each actor
Calculate Coulombic transmembrane voltage between hemispheres.
Calculate Nernst partial voltages at each actor
Calculate partial concentrations for each particle type, for each hemisphere
Calculate the concentration gradients across the membrane for each particle type

This yields the concentrations and partial voltages impinging upon each actor, within local hemispheres above and below. Note that r6 is defined as the draw radius (affinity), and r5 as the bind radius. Depending on how tightly these are set, and if the ion densities are high, perhaps r5 can be used for the hemispheres that determine concentrations. The particle counts must be high enough to yield useful ratios, yet local enough to represent the conditions at the actor poles, not far away.

As the EM force decays with the square of the distance, the effects of increasing the radius adds linearly. That is, the outer shell with its much large area, carries equal weight in the concentration calculation to an inner shell with far less area. It is practical to write an algorithm that weighs distant particle with reduced EM effects inversely proportionate to distance. Charge of the pole times charge of each particle, divided by dX, where dX = positions of particles within actor hemisphere minus position of the actor pole at the center of that hemisphere.

F = sum(z(Apole)*z(Bi) / (pos(A) -pos(Bi))); % non-coulombic distance increases the effect of distant e-
% this can be trialed experimentally to access the effects upon binding rates within the hemispheres

9.3.1.6 Algebra

9.3.1.6.1 Basis changes:

Required for 3-d momentum-conserving collision resolution, are basis changes, one each per colliding-particle-pair. This is computationally very costly. As such intense computation is likely to only be crucial very near the membrane, if the model must be reduced due to machine limitations, one approach might be to reduce the thickness of water modeled on each side of the membrane. As one gets into the charged area, these two water layers must be identical in thickness, else severe EM force distortions will occur. It is prudent to model water thicknesses as thicker

than the layer of unbalanced charge. The thickness of the charged layer is temperature dependent, so the modeling thickness may be determined after the max temperature to be modeled is known. It is also prudent to model equal or near equal thicknesses of water above and below the membrane. At 293 kelv the charge layer thickness is about 3 nm on each side. Setting the model thickness of saline on each side of the membrane to twice this charge layer thickness is deemed adequate for modeling information flow along membranes, as this leaves a generous reserve of neutral particle pairs available for ionization in response to voltage changes. The increase in veracity, if any, when using thicker layers of saline is not yet tested. However, the computational load increases linearly, with diminishing returns.

9.3.1.6.2 Linear Systems

Properly designed matrix representations of dynamical systems will appear as tightly interfacing dimensions and units between matrices. State to state transitions will require an (s x s) matrix. With the new state determined, that state may "express" upon its environment, in particular, upon the particles. Therefore an (s x o) matrix is executed next, where o represents the phenostate. This is followed by an (o x b) matrix which determines the effect of the phenostate upon the particles (as conductivity or transport ratios). This matrix may need to be multiplied by a driving force, e.g. voltage or concentration. Then a (b x b) matrix to determines the effects of the particles upon particles (diffusion, drift and collisions). These 3 effects are tranched for separate mathematical treatment. Meanwhile, the new molecular state **s** also alters the binding characteristics of the molecule's binding sites. This requires an (s x d) matrix. The binding sites **d** must release bound particles via a (d x b) matrix. And finally, the free particles may come to bind with available binding sites via a (b x d) matrix. The (bxd) represents the forward reactions, and the (d x b) the backward reactions. The treatments of these 2 are distinct because the forward reactions are proportional to B concentrations, whereas dissociation is not.

9.3.1.6.3 Eigenvalues:

Eigenvalues are typically used to find the steady state conditions, and natural resonances of the sytem. In a particle model, they serve as metrics for determining the early model simulations, as to how long it takes to achieve a steady state in the warm up. In realistic simulation, there really is not such a thing as resonance modes (as one would often find in mechanical systems). Biologics are of higher orders, producing not sinusoids, but rather complex modalities expressing limit cycles. As a result the eigenvalues yield far less information than the simulations themselves, and are limited to use as "sanity checks" at various "quiet periods" where there is no dynamic input. The more

stochastic and nonlinear is the system, the less eigenvalues can capture the behavior of that system. With increasingly complex behavior patterns (higher order), composite frequencies become less useful in evaluating those behavior patterns. How much would telling you which notes will be struck during the course of a musical piece help you to grasp the experience of listening to that piece? Very little indeed.

Matrix inversions: solve first order differential equations. The model is intended to populate as few and as large of matrices as is practicable. That is, better to invert one large sparse matrix than many small ones. This is counter-intuitive because large matrices are well known to be very tedious to invert. In this project, each matrix is constructed from a variety of sources, often involving disk calls. Furthermore, the matrices are sparse and and only portions of them active in any given *dt*. As the largest of the matrices are stochastic, the applicable probabilities of the matrix are selected out according to conditions of state and chemistry, and this greatly culls the quantity of elements involved. The setting up of the matrix for processing takes 1E1..1E3 times as long (because of disk calls) than the execution of the code. Therefore, it is prudent to size model matrices so as to bring in a full RAM's worth of processing with each matrix.

9.3.1.6.4Determinants:

Used to check for stability of numerical methods, and for feeding shortcuts to the next chosen operation. Use the standard linear algebra technique.

9.3.1.6.5Conditioning the Q and R matrices

The published data is usually in units of frequency, i.e. events per second (eps). This is sometimes converted to the instantaneous frequency. The model minimizes computational load by performing all possible calculations prior to the RUN; that is pulling all constants out of the interative EQs. This entails multiplying eps algorithm is:

```
Normalize all transition probabilities to eps (events per second)
Qdt = Q*dt;
set the diagonal = 0
ptest = sum the rows of Qdt;
if all row sums < 1, then  diag = 1 - rowsum;   % diag = the hold state probability
if rowsum > 1, send warning:  'Need smaller dt value to avoid missed events';
Qcdf = cumsum(Qdt,1);    % convert PDF into CDF via integration

Normalize all binding and dissociation rates to eps
Rdt = R*dt;
Rcdf = cumsum(Rdt,1);   % convert CDF into CDF via integration
```

The *dt* must be set sufficiently small so as to not distort the probabilities into significant aliasing error. Typically, the *dt* must be set to less than $1/8^{th}$ of the highest frequency event in the transition matrix, although up to ½ the highest frequency is tolerable for crude work.

9.3.1.6.6 Instantiation of actor states:

The modulation conditions and current conformation determine which transition probabilities will determine the next state. The R matrix yields the current binding combination, which determines the applicable Q matrix page; the page which contains a complete set of transition probabilities for the molecule's current modulation conditions. Of course, the Q diagonal provides the probability of remaining in the same state. The current state determines which row in the state transition matrix shall apply. The algorithm is:

```
Get all actors.  Each actor type has a unique R matrix for binding rates, and Q matrix, for state transitions
Get each actor's current state number s
Get each actor's current particle B occupancies on its binding sites d
For each actor, map d into a modulation combo number dc[19]
use the modulation combo number as a pointer to a page number in Qcdf
on that page get the row number equal to the current state number s.
that row is the CDF for instantiating the next state
generate random number Aran, of uniform distribution, 0..1.
map Aran onto CDF to get new state s for the following dt
```

9.3.1.6.7 Instantiation of actor bindings:

There are 2 R matrices, for the forward and backward (Rf and Rb) rates for particle bindings. Rf contains the binding affinities, and Rb contains the dissociation rates, for each binding site d on actor A. Rf is multiplied by the local B concentrations; and Rb is not. The new state **s** serves as a pointer, to determine the page in each R that applies during the current *dt*. The algorithm is:

```
Get all actors.  Each actor returns its 2 pole locations; each pole returns its compartment assignment.
Get each actor's current B bindings across all binding sites d.  All vacant d = 0.
For each compartment, get the actor poles in that compartment
For each compartment, get dX the distances of all particles B to each actor pole in that compartment
Identify all particles within distance r6 of each pole.
Count particles B of each type within r6.
Divide by the volume of the hemisphere created by r6 to determine the partial concentrations concBA.
Sort all bind sites d into 2 groups: d_vacant and d_occupied.
d0(new) = instantiate(d_vacant*Rf(:,:,s)*concBA, rand);
d1(new) = instantiate(d_occupied*Rb(:,:,s), rand);
d(new) = union(d0,d1);
```

[19] In its pure mathematical form, each degree of freedom requires a dimension in R and in Q. In such an arrangement there would be no need for the intermediate mapping of RQ that lists the possible binding combinations. However, this often leads to excessively large quantities of Q and R elements. Reasonable compression is accomplished via mapping similar pages into a merged form via the RQ lookup table.

9.3.2 PHYSICS

It was the initial impetus and intent that all operations shall be consistent with the known applicable laws of physics regarding: mass, radius, charge, momenta, thermal movement, EM force, acceleration, collisions, surface reflections, absorption, binding/unbinding, and water/lipid partition coefficients. Omitted was angular momentum, quantum effects, magnetism, light and thermodynamics of chemistry. The conservation of mass shall be observed, and the conservation of energy shall be conserved in limited ways. Mass is conserved in that particles are fixed in number for the simulation run, although they may be sequestered so as to add and remove them from the region of interest as appropriate to biological processes. Similarly, particles may bind together into new mass configurations, such as with hydration shells or anabolism of ATP to yield ADP + Pi.. The thermodynamics of chemical binding and dissociation are not accounted for, and indeed the model is consciously built so as to minimize the need for thermodynamic calculations. Some of the thermodynamic consequences are implied by the state transition probabilities, which themselves are abstractions of the Gibbs energy in general, and of the bond energies in specifics. Energy may be explicitly injected into the system if appropriate to biological processes, e.g. temperature changes or bond denaturing. Energy may be removed as waste heat (dissipated).

Early particle system experiments revealed that the effects of magnetism were 1E-11 to 1E-14 the size of the electrical effects. This justified abandonment of all magnetism, cutting the EM calculations in half. Thereby, particle dynamics can be accurately calculated with only electrostatic equations.

The limitations of current machines for simulation will not support a full physics model of anything much larger than a membranal patch. There are 2 software engines of great computational load. The particle system and the actor stochastics. Only1 channel, in full molecular dynamic representation, consumes the resources of a super computer. Similarly, the quantity of water molecules above and below a patch is of sufficient size to require a super computer. Therefore only the smallest of patches can be modeled in full rigor. Arguing from the point of view of massive particle redundancy, the quantities of particles can be scaled down to make much larger patches tractable. Arguing from the point of view of the published kinetics schemes of actors, reasonable abstractions of the dynamic models of molecules are justified. Therefore, the quantities of states and state transitions can be scaled down, perhaps to the point of making even whole cell models tractable and of predictive value.

Much is written on scaling throughout this paper, but it is appropriate here to confess the ways in which such scaling sacrifices strict adherence to principles of physics. The prime expediencies of this model is to base all motion on Coulomb's law for the EM force and upon Boltzmann's velocities for thermal energy. The minimum quantities that can still represent the behaviors of ion motion in saline are then determined empirically. Similarly, the minimum number of states per actor are determined so as to effect robust information processing by actors. Both may be adjusted to meet required levels of confidence.

To this end, the relevant physical traits will be discussed.

9.3.2.1.1 Mass

The mass of a particle type is introduced as its trait, and used consistently throughout. A library of particle traits for possible use in simulations is accumulated. Because particles may assemble water shells of varying quantities of water molecules, particle dynamics must take into account this varying mass and viscosity. A statistically varying sum of the solvation shell water masses, and an equivalent radius of the outer shell, are calculated regularly. The hydrated ion constitutes a “new” particle type, persistent until one or more water molecules are added or removed from this ensemble. What effects the changing masses of hydrated ions has upon the neuron's information processing potential is yet to be determined. The effects of the hydrophobic and hydrophilic forces upon information transfers are yet to be determined. Though the radial distributions of solvation have been measured, the temporal aspects of shearing off water molecules wrt to the acceleration of drift forces has not been reported. Drift force can bring about an autocatalysis in the following manner. As an ion accelerates it tends to shear off the outermost of its solvation molecules. Doing so reduces the effective mass of the ion. A lowered mass results in greater velocity, according to $a = f/m$. The greater velocity results in increased shear force to remove further water molecule from the shell. Knowing the mass of the solvated ion wrt velocity through its medium would be of great value in predicting the communication of ionic waves between actors.

Mass is used in velocity determinations, and momentum transfers are factors during collisions. For reference, the mass of a proton = 1836.15 times that of an electron, and the mass of a neutron = 1838.68 times that of an electron.

9.3.2.1.2 Radius

There are at least five measurements and calculation of the radii of monatomic ions. It has not been determined which, if any, is the best for use in particle system models. It is hoped that, due to the limited impact of radii in

digital models, that this is an insensitive parameter. The scalability of the model will support varying the radii used, for sensitivity analyses.

Polyatomic particles are assigned an equivalent radius based upon the quantity of atoms and how they might fill a sphere. Although a sphere is not representative of carbon chains, the equivalent radius can be adjusted so that the diffusion rate matches that of the real molecule in water. Larger radii also collide more frequently, and thus experience apparently greater viscosity. Radius is used in collision detection and in collision resolution. It is also available for ion pore selectivity equations, but is not necessary, as channel selectivity data is taken directly from the literature to determine flux through channels. That is, transport is empirical, not simulated as a physical process.

In addition the the physicists many measures of atomic radii, there are several modeling considerations that evokes several more radii to carry as particle traits.

r1 = radius of the naked particle in collision
r2 = dipole distance between charges in a mobile particle
r3 = radius of minimum solvated particle
r4 = radius of maximum solvated particle
r5 = affinity binding radius
r6 = affinity draw radius
r7 = raft size
r8 = maximum nearest neighbor
r9 = maximum shuttle radius

In the case of solvated ions, the radius is a direct function of mass (quantity of water molecules attached). There are relevant traits of water that affect model performance. Water is not at all spherical in shape. It does not pack densely (equilibrium of binding forces produced a certain degree of sparsity). The effect of solvation is to “smear the ion's charge over a greater volume. Over these concerns, the model awaits empirical data as to the radial distribution function of solvation for a given ion type wrt its velocity due to drift.

9.3.2.1.3 Charge

The valance of a particle type is introduced as its trait, and used consistently throughout. The value may be any real number. The valance is changed only by exchanging one particle type for another particle type, e.g. Fe+2 for Fe+3; or through binding events, which may nullify the particle's charge. All charges in the system are employed in the unified EM field calculation each *dt*. That produces/implies charge gradients Charge is used in EM force, particle acceleration, capacitance and membrane voltage calculations. Particles may have zero charge, and therefore are not

driven by a drift force. However, the affinity function may treat an uncharged particle as though it was being attracted by an EM force. This is artefactual, used only to compensate for an under represented collision rate.

9.3.2.1.4Momentum

Linear momentum is conserved via:

18. Velocity information passed to each successive *dt* calculation.

19. EM force generates Acceleration on every charged particle, but this acceleration is muted by viscosity

20. Particle-particle collisions are calculated so as to transfer momentum along the collision axis.

21. Reflections with surfaces are elastic. This is necessary to maintain temperature.

22. Binding events reduce the velocity to zero. For modeling purposes the arrival velocity is remembered, such that at the unbinding event, that velocity is resumed, either as reflected (if released ipsilateral to membrane) or continued at it was (if released contra-lateral to membrane). This is to conserve energy.

The static elements, including membrane and actors, are not considered in momenta calculations.

Angular momentum of particles will not be considered unless it is reported in the literature that spin is a carrier of information.

9.3.2.2 EM force

This model's particle system consists of a maximum of 1024 types of charged particles and uncharged particles, supporting a great span of masses and radii. The membrane is embedded with stationary actors, which may have fixed charges that serve to bind and unbind certain particle types. The membrane thickness is such as would achieve the equivalent dielectric strength and capacitance.

The EM force is calculated each *dt* for the complete set of charges in the system, as a single group. Though the distal effects be miniscule, this N-body problem cannot be divided into sub-regions without losing the charge flux and partitioning effects near the membranes, especially achieving the correct amount of capacitance. Situations of charge imbalances are quite sensitive to missing particles in the calculation. Errors in the charge imbalance will then strongly effect the calculations of flux through open ion channels.

$F = 1/(4*pi*\varepsilon_0) * (q1*q2/(pos1-pos2)^2)$;
F is in Newtons, q in Coulombs,
(pos1-pos2-r), r in meters
e_0 = 8.85E-12 F/m.

EX Find the force of 1 Na+ and 1 Cl- held apart by a membrane of thickness 9.714 nm. Dielectric = 3. Radius of Na = 0.186 nm, radius of Cl = 0.100 nm.

m(Na+) = 23 / 6.02E23 grams = 23/6.02E26 kg
m(Cl-) = 35.45 / 6.02E23 grams = 35.45/6.02E26 kg
a = F/m. m is in kilograms, a is in m/s^2.
dX = Center to center distance = 10 nm = 1e-8 m.
q = 1.6E-19 Coulombs.
F = 7.25E-12 N * 3 = 2.175E-11 N

The packing density of capacitated ions near the membrane is limited by the thickness of the membrane. The center to center distance of ipsilateral like charges must be greater than the contralateral distance between unlike charges. Al though it is the barrier effect of the membrane that enables capacitance, the thickness of the membrane creates geometric limitations on the packing density of like charges.

9.3.2.3 Acceleration

The initial source of energy for a particle system is thermal. The Boltzmann velocity distribution equation predicts the PDF of velocity for each particle type, as a function of mass and temperature. Inevitable collisions between the particles, as elastic spheres, are interpreted as the phenomenon of viscosity at the macro scale. However, acceleration is induced by EM charge field. A =F/M; yields accelerating motion, which is interrupted at each collision.

A = E/mass, where E = k0*q1*q2/r^2 for the set of all charged particle pairs;
k0 = 1/(4*pi*e0*eW) ; eW = relative permittivity of water

For a substance to be incompressible, there must be fixed geometric relationships between adjacent molecules, atoms and ions, such that the average distance between them is constant. Therefore the movement of water molecules and dissolved ions must be rather serpentine, weaving between neighbors while maintaining fixed distances apart until a substitution of neighbors is made. These substitution events are roughly the liquid equivalent of gaseous collisions. The important consideration for the model is that the resulting diffusion patterns of the model ions correspond to those of ions in water. It is argued that because the statistical positions of particles after diffusion, whether in liquid and gas, are mathematically equivalent, then the gaseous model of free path and collisions is a reasonable, simpler representation of the serpentine travel of ions in liquid state. Due to Van der Waals, charge distribution, and hydrogen bonds, viscosity is more than mere elastic collisions. However, because these effects are homogenous relative to the net distance traveled, they are considered as implied within the velocity distribution curves. In any event, they are found to not contribute information to the system, so their effects will

cancel out to zero. Regardless of the multiple factors of viscosity, the net effect is to convert an accelerating force into a terminal net velocity through the medium, randomizing its direction, and distributing its velocity according to the Boltzmann velocity distribution. This is accomplished by adding a friction term, which subtracts a drag proportional to the velocity. The particle can then only increase in speed when the EM force is greater than the drag force.

Unlike in man-made systems, in biological systems the drift forces are almost always local (electric eel excepted). Collisions reflect and dissipate drift due to EM. Given all possible reflected directions, the net effect of drift forces across the system must average to zero, as half will slow down what the others speed up. None-the-less drift is a significant, even critical, force creating capacitance and driving flux through the ion channels.

The collision rate in liquids is so high that all acceleration is subverted into terminal velocities. Therefore, unlike mechanical systems, accelerations are not cumulative. While the standard EQ pair for motion is:

```
V2 = V1 + A2;
X2 = X1 + V2; |
```

In a viscous system this becomes :

```
X2 = X1+V1 + mobm*A2;
```

9.3.2.4 Collisions

Momentum must be conserved, least there accumulate temperature anomalies. Such errors effect the diffusion rates of the ions and messengers, which can cost a loss of phase phenomena. Therefore, collisions are calculated as 3-d momentum transfers.

9.3.2.5 Particle - Compartment Surface reflections

Membranes are the containment surfaces which must reflect elastically to avoid cooling of the particles. Although considered to be “soft matter”, for purposes of particle reflection membranes may be treated as hard surfaces. The modeling of soft matter is more complex, but the net result must still be a conservation of energy. To date, no significant effects of soft matter are noted that would alter the processing and transmission of information. Therefore simple reflection is deemed sufficient. Because many of the surfaces are curved, the normals to the

surface are maintained or calculated to assure a proper reflection. This is necessary to avoid a cumulative directional bias amongst the particle velocity vectors. The algorithm for particle reflections is:

Get particle positions and velocities
Calculate velocity normals and magnitudes
Get compartment surfaces, as nodes and surface normals
Measure distances of particles to surfaces
Where distance is less than velocity, calculate collision points
find node closest to collision point
calculate reflection angle from velocity normal and collision node normal
calculate time of collision
subtract remaining time in dt
calculate final position at end of dt from remaining time * new velocity vector

9.3.2.6 Chemistry

In saline, particle drift comprises is the analog aspect of the system. Particle collisions comprise the digital aspect. The interior of the membranal proteins have a similar dualism: Each molecule is held together by a flexible hydrocarbon backbone, but each amino acid has a radical with a polar termini. These frequent charge foci along the outer surface of the molecule give it a tendency to "click" from configuration to configuration. This bestows upon the molecule a digital nature. Each configuration is a state, and each state may transition to other states by probabilities that vary with various external conditions.

The genius of the Hodgkin Huxley's work on the axon is that they conceived of the large protein molecules as reacting chemically with themselves to produce conformational changes. This justified use of already established reaction kinetics, especially of first order reactions, which see exponential approaches to equilibrium. Hodgkin and Huxley were then able to use exponential curve fitting approach to derive the ion channel subunit opening and closing kinetics.

Binding and unbinding not only follow standard chemical laws and equations, but serve as modulators on actor function.

Upon binding of B to A, record velocity of particle.
check for chemistry at this A bind site d. This is catalytic potential, as "erg" values in actor type traits
If erg is non-zero, then get concentrations of implicated B types within r6
CDF = int(PDF);
prob = CDF*concs;
instance = rand(prob);
d(new) = instantiate(CDF,rand);
Follow up bookkeeping: Replace current reactants with products on replacement table in erg.

9.3.2.7 Particle - Particle collisions

Three-dimensional collisions between unlike radii and unlike mass requires detection algorithms, and then a unique basis change and reversion per collision pair. The detection algorithm picks up all scheduled collisions along the particle path within 1 *dt*. But only the earliest in time of these actually occurs. Therefore, a culling must take place after the first path intersection algorithm reports. The collision resolve algorithm is:

sum radii of all particle pairs
get all particles for each compartment
measure distances between all particle pairs within a compartment
find all such distances less than the sum of the radii % this indicates that a collision must have occurred.
calculate time of hit for these collision pairs
cull out all but earliest hit for each particle. This must be done chronologically to avoid non-causal results.
calculate axis of collision
calculate new basis based upon axis of collision
calculate transfer of momentum
revert back to global basis
calculate new velocity and final position at end of dt
check for surface violations
if surface violation, send to surface collision routine.

9.3.2.8 Particle - Actor Binding/Unbinding

Binding and unbinding events are considered for each particle collision within a designated binding site. Binding sites are typically on actors, but may also be on particles and membranes. Only actors can change state as a result of a binding event. Binding is supported for water shells around ions. Binding is supported for particles that modulate actors. Binding is supported for purposes of transport and for messenger release.

Although the conformational kinetics of actors are well represented in the literature as “kinetic schemes”, these are often commingled with some of the kinetics of binding modulator particles. Without a proper function of concentration of the particle in the local volume, these can be valid only as steady state equilibrium calculations. For the dynamic case, critical to this model, the internal conformational kinetics must be treated separately from the external binding kinetics. The matrix that captures the transition probabilities of particle-actor bindings is:

d = binding sites of 1 instantiated actor. There are 2 sets of d, 1 set at each of the actor's 2 poles.
d contains aff(BT) values % where d is the list of binding sites on a particular actor type, instantiated
aff(BT) = profile of affinities, for a given binding site in a given actor state, across all particle types BT,
within the binding radius r6 of each of the poles, defining hemispheres of saline;
conc finds densities of each B type within the hemispheres
d0(new) = instantiate(Rf(s)*conc(pos,BT)) % where pos = the position of the actor pole

```
d1(new) = instantiate(Rb(s), d1(old))  % Unbinding does not require the multiplication by conc.
d(new) = union(d0,d1);  % vacancies were treated separately from occupancies
s = state of the actor hosting d
```

In their complete forms, binding is a function of actor#, actor bindsites, compartment#s, pole#s, actor position, particle assignments, particle#s, particle traits, particle positions, actor traits, actor state, actor bindings, particle concentrations, and *dt* size. Optionally, there may be other modulators, e.g. voltage, pH, that factor into the determination of which binding rates in R apply.

9.3.2.8.1 Particle - Water Collisions

Ions are variously hydrated at 0 to 45 water molecules, via a PDF of quantity H2O:1 ion. The quantity of attached water molecules is determined by instantiation. The quantity of solvation molecules translates to a radial distribution, also to a mass distribution, and also to an equivalent radius of the shell. The latter is useful for collision detection and viscosity effects. The mass is needed for acceleration determination. Algorithm is:

```
get all ions
subtract bound ions
qW = instantiate(B,CDF(PDF_hydration),velocity(B));
mass.ion_solvated = mass.ion+18*qW;
radius.ion_solvated = cubedroot (sum(radius.B(water))) * packingfactor;
```

Water collisions determine the equivalent mean free path. In the liquid state, there are no free paths, but there is an equivalent phenomenon. Ions move in serpentine fashion between the water molecules until a change of trajectory takes place, presumably because of a blocked path. This is calculated to occur about once every nm. Abiding by this would place a computational burden far greater than any other process. Therefore, a compromise must be made that greatly reduces the quantity of water collisions. One form of justification is diffusion equivalence. If a liquid requires a million collisions to result in a diffusion pattern that a gas takes only a thousand collisions to effect, then can we substitute the mathematics of a gas to represent water? If the net distributions of particle positions are the same, then the answer is yes.

Water also provides viscosity, resistance, and charge dissipation. These factors are ideally received from wet lab studies. In their absence, modeling efforts must proceed empirically, adjusting downward the water calculations until further reduction causes unacceptable error rates.

```
sfw = scaling factor for particle-water collision rate.
qB = total quantity of particles in system
qBD = total quantity of particle bound to an actor;
```

```
qBF = qB-qBD;   % free particles engaged in thermal motion.
randomly choose sfw*qBF particles
reassign their velocities from the randBoltz PDF.
% this causes the water temperature to temper the ion temperature
```

Note that the above algorithm is not strictly momentum conserving, as it assigns random new velocities to particles. However, this is what would occur in nature as the particle collided with water. Statistically, the velocities are correct, and over time they average to yield momentum conservation. To hold the velocity magnitude constant would conserve momentum, but would not be true to the natural process, and might lead to misleading velocity patterns (biases) concerning the transmission of information coded as velocity.

9.4 SOFTWARE FEATURES

9.4.1.1 Shape (compartment algorithms) features

1. morphometric data is converted to canonical shape parameters
2. shape parameters include: membrane working points, curvature, node spacing, relative positions
3. special shapes: plugs, vanes, extracellular envelope
4. contour generation via a parameter driven CAD routine
5. contours are revolved into closed surfaces
6. closed surfaces proscribe volumes within
7. surface areas are calculated
8. compartment volumes are calculated
9. node positions and orientations are assigned to actors according to PDFs
10. piecemeal equation set along x-axis provides reflection angles for surfaces
11. plugs are created and positioned (as input and output ports)

9.4.1.2 Particle features

1. convert molarity to quantities of each particle type
2. create boli, for injecting particles into volumes
3. initialize particle velocities via Boltzmann's velocity distribution
4. diffusion is emulated via particle velocities, particle accelerations and particle collisions

5. particle forces are calculated as drift according to Coulomb's law
6. particle acceleration convert forces according to Newton's law
7. particle-particle collisions are detected
8. particle-particle collisions are resolved
9. particle-container reflection angles are calculated and momentum is preserved
10. particle-actor collisions stochastically result in bindings and dissociations
11. particle-actor affinities give preference to which B types will bind
12. particle-actor affinities are variable, as a function of actor state
13. particle-actor binding is a function of affinity times concentration times dt
14. particle-actor binding accounting requires A#, B#, pole#, pole position, C#, velocity memory
15. particle-actor dissociations
16. particle transport accounting requires A#, B#, pole#s, pole positions, C#s, velocity memory
17. particle partition coefficients support penetration of the lipids per water/lipid transition stochastics
18. execute move particles
19. every particle that is released must have a reuptake mechanism: special high affinity pumps

9.4.1.3 Actor features

1. Actor density data converted to positional PDFs (Actor placements)
2. PDF_Aposition are instantiated and each actor type mapped to available nodes
3. PDF_Ainitstates used to set Actor Initial states in a realistic manner
4. Actor links set by type: recep, chan, shuttles, vesicles, pumps
5. init shuttles (Actor states)
6. init actor state, load messenger particles
7. define R kinetics to instantiation of bindings/dissociation
8. Actor modulation management (R matrix processes)
9. dissociations per R PDFs
10. get shuttle messenger positions
11. index shuttle messenger positions
12. execute bindings per the PDFs from Rf, times the B concs

13. execute the dissociations per the PDFs from Rb
14. define Q matrix as a function of all possible modulation conditions
15. read d (actor modulation bind combinations) into Q page
16. read actor voltage modulation into Q page
17. instantiate conformational state changes via Q(s,:,mod)
18. read phenostate table to get o from s
19. if phenostate calls for it, read conductivity of actor type
20. calculate actor vicinity Nernst voltages driving each B type through the conductivity profile
21. calculate total voltage impinging on actor internal charges via Coulomb's law
22. When phenostate calls for transport, execute reassignment of B to opposite pole position and opposite C#

9.4.1.4 SigGen

1. Release/Uptake of Ligand according to an acoustic signal
2. Readout of axonal plugs
3. After each signal burst, the reuptake pumps for the released Ligand types must be sufficiently quick to avoid lingering messengers, echos, or blockage of receptors. Such pumps must be sufficiently local to the release sights that messenger travel does not trigger unwanted reactions along the paths.

9.4.2 CONTOURS OF REVOLUTION

The working points are typically downloaded from a spreadsheet.

```
[ s0                    ] = Design_Core(L1,r18);    % inner compartment roughly representing nucleus+ reticulum
[ s1 s2 s3 s4 Zone_header ] = Design_Main(L1,L2,r1,r3,r4,r5,r6,r7,r8);    % plasma lemma
[ s5 s6 s7 s8           ] = Design_Extra(s1,s2,r28,thk1,thk5,thk6,thk8);      % boundary for extracellular fluid
[ s9         Plug_header ] = Design_Plug(g1,g2,gr);                          % input and output synapses
% in these 4 EQs, s is a list of working points, zone assigns each point to a zone#
%%  contours to be rotated to form of the five membranes

load DistComp          %  contains point spacing, and plug placement data
% plugs may be cloned and placed anywhere, not overlapping, on any platen
% there are at least 2 types of plugs, input and output, though a plug may have both recep and ves

% extract the geometric shapes from the working points
% it is better to begin with shape definitions, concatenate them, and derive working points from the composite
SH = WP2SH([s0;s1;s2;s3;s4;s5;s6;s7;s8;s9],sf);

% generate the x and r values for each contour point, then count quantity
[pxr0 slice0] = ContourPoints(s0,dx0,0);   % (X,R, NumPts) = core(params)
[pxr1 slice1] = ContourPoints(s1,dx1,0);   % upper main
[pxr2 slice2] = ContourPoints(s2,dx1,0);   % lower main
```

```
[pxr3 slice3] = ContourPoints(s3,dx2,0);   % dend syn
[pxr4 slice4] = ContourPoints(s4,dx2,0);   % axon syn
[pxr5 slice5] = ContourPoints(s5,dx5,0);   % upper extra
[pxr6 slice6] = ContourPoints(s6,dx6,0);   % lower extra
[pxr7 slice7] = ContourPoints(s7,dx7,0);   % dend syn
[pxr8 slice8] = ContourPoints(s8,dx8,0);   % axon syn
[pxr9 slice9] = ContourPoints(s9,dx9,0);   % plugs
% pxr gives equally spaced points along a contour, tracking which zone each point belongs to
% each contour point is given a ring#, because it will be revolved into a ring

% clone and position plugs
pxr10(:,1) = L1+L2+0.2 - pxr9(:,1);  % places a plug contour at axonal end
pxr10(:,2) = pxr9(:,2); % this algorithm not consistent with XX4,YY4,ZZ4, which contains all
pxr9 (:,1) = pxr9(:,1) - 0.2;  % temporary gap between parts to display inter-surfaces
pxr = merge_pxr(pxr0,pxr1,pxr2,pxr3,pxr4,pxr5,pxr6,pxr7,pxr8,pxr9,pxr10);

%%  Organize into Rlims slice by slice
% note that the ceiling point is unlikely to have the same x value as the floor point, therefore interpolate
twice
%%  Convert segs into homogeneous surface points

[C0 zone0] = RotateContour(pxr0,dc0); % core
[C1 zone1] = RotateContour(pxr1,dc1); % main neuron
[C2 zone2] = RotateContour(pxr2,dc2); % main lower
[C3 zone3] = RotateContour(pxr3,dc3); % dend synapses
[C4 zone4] = RotateContour(pxr4,dc4); % axon synapse
[C5 zone5] = RotateContour(pxr5,dc5); % extracell mains
[C6 zone6] = RotateContour(pxr6,dc6); % extracell lower
[C7 zone7] = RotateContour(pxr7,dc7); % dend endcaps
[C8 zone8] = RotateContour(pxr8,dc8); % axon endcaps
[C9 zone9] = RotateContour(pxr9,dc9); % axonal plug (not plotted in this pos)
[C10      ]    = positionPlug(C9,r1,A4,L1,L2);  % dendrite plugs
```

Vanes create bifurcation trees in dendritic and/or axonal cones.

Statistical parameters for vane generation =
[segstart segstop xstart xstop rstart rstop Lvar Wvar Lsec2 Lsec4 Lsec8 Lsec16 Lsec32 Lsec64 Lsec128]

where
segstart = left zone #; segstop = right zone #; xstart = left x-axis limit;   xstop = right x-axis limit;
rstart = lower radius limit; rstop = upper radius limit; Lvar = length variance; Wvar = width variance;
Lsec2 = average length of vanes near 180 and 360 degrees;
Lsec4 = average length of vanes near 90 and 270 degrees;
Lsec8 = average length of vanes near 45, 135, 225 and 315 degrees;
etc.

Plugs may be created at each of the platen, in varying numbers and sizes. It is tedious to install a plug (synapse) onto a non planar surface, maintain a synaptic cleft distance, and control diffusion at the margins. For computational efficiency, the whole cell models provide two or more planar surfaces near where synapses would normally be found on the cell.

```
plug_statparam = ...
[  sh platen funcflip gap xpos ypos zpos Apos rpos qR diam Dmax Dmin Rmax Rmin auto ];
```

% where
sh = plug type; platen = location of plug along x-axis; funct = function #; flip = orientation;
gap = synaptic cleft; [xpos ypos zpos] = Cartesian coordinates; [Apos rpos] = cylindrical coordinates;
qR = quantity of plugs; diam = avg diameter; Dmax = maximum diameter; Dmin = minimum diameter;
Rmax = outer boundary of platen; Rmin = inner boundary of platen; auto = 0 manual, 1= automatic;
Plugs : col 1:9 =defined positions for individual plug: suitable for low quantities and test conditions
Plugs: col 10:15 =statistic placement of plugs: suitable for large quantities and bio-realistic arrangements
% if xpos and ypos are given, auto = 0;
% if Apos and Rpos are given, auto = 1;
% if Rmax and Rmin are given, auto = 2

All the above features are supported by source libraries, state data structures, and report matrices.

9.5 SOFTWARE SEQUENCE

It is not trivial to say that the purpose of the Design is to realize the Build, The purpose of the Build is to realize the Run; and The purpose of the Run is to generate the Report. Thus, the Design does not concern itself with the Run nor Report. Neither does the report look back any earlier than the Run. The Run should be an emergent property of the Build. All of this is to say that the software should avoid links that skip over a step. Each phase should present a complete package to the next step, as necessary and sufficient to complete its task.

9.5.1.1 Surface Action

1. read membrane capacitance
2. read local tonicities
3. compute local partial Nernst voltages
4. read local Coulombic transmembrane voltage at each actor node

9.5.1.2 Transport metrics

1. Chan flux accounting = vertical motion through the membrane (1-d constrained)
2. Sol flux accounting = horizontal motions parallel to the membrane (2.5-d unconstrained)

The value of 2.5 indicates that particles are free to move in 2 dimensions and partially free to move in the third dimension. Charged particles may only move away from the membrane if they form a neutral pair.

9.5.1.3 Recycling of particles

In addition to the reuptake pumps described above,

1. reset receptors via completion of state path to rest state
2. reset shuttles via rapid reversal of messenger paths
3. reset vesicles via recycling of particles and reassemblies with contents

9.6 MODELING INFORMATION FLOW

Model entities include: Elements, States, Forces, Inputs, Functions, and Outputs. These are dynamic, implying they are driven through time. Mobile elements are also driven through space. Stationary elements are driven through configurations, called state space, a sort of internal space. The problem is, there is no continuous time, nor continuous space, within the software of a digital computer.

The modeling process is meta to the model *per se*. This is the work done by the human experimentalist. In the process of constructing a model, one passes through phases: Library, Experimental Design, Build, Run, Report, Feedback. That is, beginning with archived sources and prior experiments, one defines the experiment to be simulated, generally by setting parametric values. These values then drive the construction rules for the model, to the point of instantiating all the elements in a static initial form. Then the dynamic processes are launched and iterated some number of steps until the simulation run is complete. The run generates copious amounts of data, and a selection is made as to which is to be captured for future viewing and analysis. Of the essence are particle positions and actor states, from which most other measures can be generated. This data is formed into reports, which may be data arrays, plots or animations. A key feature of the modeling process, is that it is not intended for single runs, but rather repeatedly with improvements in each run. Therefore thoughtful analysis of the results are required so as to determine ways to improve the quality of the simulation. These conclusions can be added to the library as an experimental design, so they are readily available for the next run. Modeling itself is an organic, evolving process.

As already discussed, the information flow through a neuron has been determined to involve a membrane bathed in saline, with receptors, channels, vesicles and pumps embedded in that membrane at rather specific locations. The processes of diffusion, drift, and kinetic state changes are the processes by which these elements are brought into dynamic performance.

This chapter attempts to advance the design elements and design processes to specific instructions for digital computers. The continuities of time and space must somehow be represented as discrete values. Although simple in concept, this conversion is fraught with error generation. A mechanism must be provided for measuring the values of such errors and provision made for parametric adjustment of *dt* and *dx* so as to reduce such error to within acceptable limits.

1. compartments determine nearest neighbors, and thereby the implied coupling/connectivity between them
2. particle radius determine collision rate,
3. particle mass determines momentum transfers
4. particle charge determines capacitance, voltage pressure, and modulation of actors
5. position determines concentrations and proximity
6. velocity determines impact force, impact rate, and temperature
7. net force impinging determines bonding rate
8. bonding determines modulation
9. actor atomic complexity determines state paths
10. modulation determines state path to be taken
11. state path determines modalities of the actor
12. modalities determine information processing of signal
13. nearest neighbors determine the passing of the signal, which are to be the next stage of signal processing
14. the sequence of processing steps is the essence of the function of the cell

To facilitate all of this , certain supporting operations are necessary, including the means to:

1. detect particle collisions, with actors, surfaces and other particles
2. change assignment of particles: to compartment or actor pole
3. to dissociate after bindings: particle release dynamics
4. to adjust affinities: especially so as to compensate for quantity reductions,
5. to effect bind kinetics, and dissociation kinetics, dynamically as a function of actor state
6. to effect actor conformational kinetics,
7. to distribute actors stochastically to addressable positions and orientations,
8. to maintain membrane thickness, water thickness, and dielectric constants of membrane,

9. to effect particle conversions, chemistry reactions

At a deeper level of detail, each actor type requires specific traits and functions that enable it to participate in NIP in a realistic fashion.

9.6.1.1 Every receptor needs:

1. load profile
2. variable binding quantities and mixes on the output side (treated kinetically as one)
3. catalysis chemistry PDF
4. shuttle maps to nearest neighbor targets
5. shuttle kinetics
6. shuttle move

9.6.1.2 Every channel needs:

8. binding site list, with affinities as a function of state
9. transition probabilities, as a function of binding site occupancies
10. phenostates (reads state to indicate channel openings)
11. conductivity profiles
12. transport equation

9.6.1.3 Every vesicle needs:

1. load profile (average contents)
2. binding site list, with affinities
3. variable exocytosis dynamics and reliability
4. cooperation with pumps to effect reloads

9.6.1.4 Every pump needs:

1. duty cycle implied within Q matrix
2. means of directing the state flow (irreversibility)
3. bind/unbind probabilities as a function of state
4. state as a function of bind site occupancies

5. transport phenostates
6. reassignment of particles to new compartments
7. chemistry PDF for energy consumed, (ATP particles, down gradient exchanges, etc)

9.6.2 PROCESSES OF A NEURON SIMULATION

The necessary and sufficient processes for conveying a neural action across the cell.

1. Diffusion, as water collisions
2. Drift, as the N-body Coulomb's Equation (whole system, not portioned)
3. Particle-particle Collisions
4. Particle-Compartment Collisions
5. Particle- Actor Collisions
6. Actor-Particle affinities
7. Binding/dissociation kinetics per state + current bindings + voltage
8. Binding/Unbinding and implied assignments
9. Actor combo modulation (select page in Q-matrix)
10. Conformational kinetics
11. Active transport (pump phenostates)
12. Passive transport (channel conductivity* pressures* concs)
13. Second messenger 2-d diffusion (or shuttle transport)
14. Enzymatic production of third messengers, triggered by second messengers
15. Messenger / target pairings
16. Nernst partial voltages, local to each actor
17. Voltage composites from partial voltages impinging upon each actor
18. Voltage effects upon membrane lipids
19. Voltage effects upon membrane proteins
20. calculate Voltage gradient force
21. calculate Concentration gradient force
22. move particles by diffusion
23. calculate N-body charge forces

24. move particles by drift (force> acceleration> viscosity)
25. membrane dielectric coefficient > capacitance on the polar heads of fatty acids
26. membrane stiction of the closest layer of ions
27. record charging curves in electrolytic solutions (time an space constants must be realistic)
28. Saline resistance to electrical and ionic activity (ionic flux resistance)
29. Ion channel conductivity flutter
30. Ion channel conductivity profile consequences
31. Wave fronts, free in direction, and free in shape of the front
32. Inactivation fronts, the spatial effect of fields of channels going into refraction
33. Escapements release energy conditionally (Wave front + Inactivation front)
34. Propagation (Chain reaction of Escapements)
35. Exocytosis of vesicles
36. Vesicle release of ligands
37. Re-uptake of ligands and particles
38. Returning of ligands to initial positions (recycling of particles for next action potential)

Where ever the operation of division is performed, there is the danger of dividing by zero and generating an infinity as a result. This will carry through all subsequent steps rendering all down stream values mute. This is in fact a common occurrence in Nernst Voltage calculations where the ratio of concentration outside over inside the membrane is taken millions of times in a single run. If there happens to be no ions of a certain type within the local vicinity, an infinite voltage results. This is admitted by the chemists to be an incorrect result, as the equation fails at extremely low concentrations. Such equations must be conditionalized so as to catch extreme values and limit them to what the model can withstand. Where available, corrective equations from the literature should be incorporated.

9.6.2.1 Dimensionality of Processes

As concerns digital computation, the mathematical dimensionality of a function is a heavy indicator as to how much CPU resource it will consume. Regardless of the physical dimensionality of the problem , it is the informational dimensionality, as expressed in the mathematical resolution, that is most relevant. A zero-dimensional physical process can turn out to be a very high-dimensional information process.

Information interactions have a rather curious relationship to physicality. In the greater volume of XYZ, interactions decrease as the distance apart grows. Given an object of size radius = 1, then informational exchanges are maximal very near that radius of 1. Below that, they are in fact inside the object. Proceeding above 1, they are leaving and fading away. Thus we may speak of external events (>1) and internal events. (<1) as possessing a kind of symmetry. The interior acts in reciprocal fashion to the exterior, tending towards zero rather than infinity, with distance and therefore with diminished interaction. Thus we may conceptualize that internal events may transpire deep in the interior (near zero) or be near the surface (near 1) where they may impact the outside world . Typically the actions of greatest interest are the ones that cross the line r=1, indicating a transaction between exterior and interior events. In one view of information processing, a maximum information value is located at this threshold, while information diminishes either above or below 1. The log scale possesses some of these qualities, and indeed information is measured as the log2 of the possibility space. However, creating a new scale by leaving the values below 1 untouched, and inverting the above 1 values comes closer to this metric of information value.

iv = (r/R)^2, when r<R; iv = (R/r)^2, when r>R;

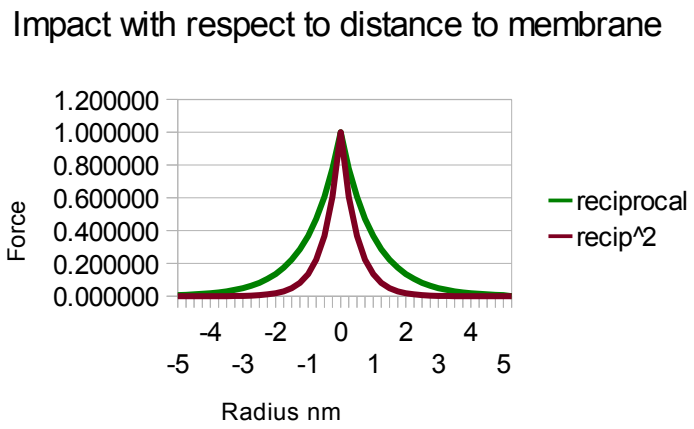


FIGURE 99: Methods of weighting interactions near the membrane

This is similar to the attractive force from opposite the membrane. This force determines the maximum repulsive force amongst the like-kind ions pulled into close proximity by the attractive force. The repulsive force determines maximum velocities, and any change in this force determines the driving force of horizontal waves. The maximum velocity determines both the speed of the wave and the impact force of collisions, both valuable in the transmission of information.

9.6.2.2 0-dimensional processes

The concept of a point process is useful in that it allows action where no outwardly observable physical motion is observed. The process may be located as a stationary point in an otherwise dynamic setting. However, the complexity of the "process" being executed "inside" is indicative of dimensions and distances of that internal space described above, and these may be large. Although physically a process is often represented as merely a point, it is recommended that the point process be conceptualized as the internal space, the reciprocal of external space. Whereas external events take place in Cartesian space, internal events take place in state space. Each has its own dimensionality per its degrees of freedom. A nominally zero-dimensional physical process may be a high-dimensional informational process.

Point processes are fictions that occur due to the graininess of the model. Events taking place smaller than the resolution of the observer are said to appear as mere points. But with sufficient magnification, of course, there is a lot of subatomic action. Molecular intra-kinetics are analogous to external motion except that the chemical bonds act a leases and so constrain the movement. And various charges set up strong attractors which result in snap actions rather than ballistic ones. Internal motions usually do not register outside the molecule, but when they do, we call those phenostates (e.g. a channel pore opening). Point processes in this model include:

1. Molecular conformational changes. Point processes in this model include Markov chains. State changes are instantiated as random processes, calculated without visible motion.
2. Chemical binding. Deemed to occur on one of the actor poles without dimension nor orientation.
3. Point charges. Particles are given a radius for purposes of collision detection but such radii do not factor into the Coulombs force equations. For that all charges are treated as points.
4. 2-point charge neutralization. When a charged particle binds to an oppositely charged actor site, then these two charges neutralize . In actuality they might form a dipole, but in the model they are reassigned charges of zero, so no dipole is represented. When they unbind, their original charges are reassigned back to them. Also when a charged particle binds to an oppositely charged particle, then these two charges neutralize. They may separate at any time by a sufficient force of random collisions.

What may be named as a point process in Cartesian space may be of arbitrarily high dimensionality in information-space. The kinetic schemes of actors are point processes of significant information dimensionality, corresponding to the molecule's internal degrees of freedom. In particular, the R and Q matrices and the stochastic instantiation of states from them are point processes.

9.6.2.3 1-dimensional processes

All 1-dimensional processes require a directional vector called a normal. A magnitude is usually calculated and this is multiplied by the normal to result in directional motion or force. One dimensional processes in this model include:

1. point-charge to point-charge force vector. Every possible combination between pairs of charge particles creates a Coulombic force between them.
2. velocity vectors. Every particle in motion has a position and a velocity vector, and optionally an acceleration vector. The acceleration may be zero (for ballistic motion) and the velocity may be zero (for bindings)
3. accelerating force. F = m* a; therefore A = F/m; In this model F is usually the EM force: F = k0*q1*q2/r^2;
4. voltage across a barrier. The body of charges on one side of the membrane is attracted to an equal quantity of opposite charges on the other side. The net direction of force is perpendicular to the membrane.
5. molecular shuttles: as an expedient for second messenger mechanisms, links between a receptor and a set of target channels may be defined by their normals. Velocities can then be set from a velocity distribution. The lengths of each link must be known so as to detect the arrivals at targets.
6. energy barriers through channels: out of scope for this model in its early releases, but it is feasible for those experiments that are investigating the effects of energy barriers over varying environmental conditions. The axis through the channel is perpendicular to the membrane surface. The energy profile is a contour over the length of the axis of the pore. It may be positive (repulsive) or negative (attractive) at any points along its length. Its shape has interesting effects upon selecting certain velocity and mass particles for transport.
7. pumping across membranes (transport): Although the molecular pumping arms may sweep a curvacious path, for purposes of this model, ions are pumped by moving straight across the membrane along the actor axis.
8. net current: the turbulence and colors of current may be collapsed into a net average change in position of charged particles.

9.6.2.4 2-dimensional processes

Two-dimensional processes are surface effects. The 2-dimensional processes in this model include:

1. Membrane capacitance. Nominally 2-dimensional, but in actuality and in the model, capacitated charge has some thickness, due to like particle repulsion. The thickness of the charge layer is about 5 times as thick as the membrane.
2. Membrane associated diffusion. charged particles still are driven to diffusion by the thermal energy, but they are constrained by the EN force to very near the membrane. As a result they diffuse 2-dimensionally along the membrane.
3. Containment barriers: the edge of every volume is a surface. The differential of the compartment is its surfaces.

4. Nearest neighbors on a surface Nearest neighbors between actors (NN) may be found by sweeping an increasing radius from the center node until the desired number of neighbors are found. If this search is performed 3-dimensionally it will yield false results whenever two membrane come close or touch, or a single membrane folds back on itself.

9.6.2.5 3-dimensional processes

Spatial interactions in this model include:

1. Diffusion: diffusion is the consequence of thermal energy in a fluid. It also is the process of creating white noise, and therefore destroying information.
2. EM fields: calculated by applying Coulomb's law to a particle system.
3. Flux: in a system of free ranging particles, flux is a fluid dynamics problem
4. Particle-particle collisions: linear momentum must be conserved 3-dimensionally to keep the system sane
5. Particle-surface collisions: reflections are about the surface normals, complete elasticity preserves temperature
6. Adjacent voxels: Tetrahedral tessellation allows a systematic subdivision of a volume of any shape. Easy to visualize, but of large computational load to implement and maintain.

9.7 DESIGN

9.7.1 PHYSICAL CONSTANTS

TYPE:

physics: mass, radius, charge, temperature, viscosity, collisions, capacitance, resistance, conductivity

chemistry: conformations, kinetics, bindings, states, phenostates, modulators

biology: signaling, sequestering, re-uptake, second messengers, shape, nearest neighbors

9.7.2 COMPARTMENTS

1. Shape of each surface shall be a contour of rotation about a single axis,
2. Shape shall be a closed surface, with no edge boundary conditions.

9.7.2.1 Type

1. thickness
2. capacitance
3. shape primitives

9.7.2.2 Dist

1. shape concatenations
2. membrane closed surfaces
3. multi-membrane juxtapositions

9.7.2.3 Neuron Compartments

1. Shape shall be oblong, such that one end can be designated as "input"
2. The opposite end shall be designated as the "output" end .
3. Platens shall be provided in the areas where synapses are to be connected
4. Bifurcations into arbors shall be accomplished via vanes of varying lengths and radial positions
5. An inner core compartment shall block the center volume of the soma in a manner realistic to ion paths
6. The extracellular saline shall be bounded by a membrane that establishes the thickness of the extracellular space
7. The synaptic clefts may be contiguous with the extracellular saline, or else may be treated as separate compartments.

9.7.2.4 Extracellular space and the membrane that defines it

1. There shall be an outer membrane similar to, but larger than, the Neuron shape, establishing fluid thickness.
2. The outer membrane shall not touch the neuron nor cross the neuron at any point.
3. Shall conform to biological data so as to tend to reasonable tonicities of extracellular space around the neuron.
4. The outer membrane may have actors and zones to bind and release particles.
5. May have a specialized area or additional compartments at the input and/or output ends of the neuron.
6. The outer membrane may not support a voltage as there are no particle on the far side of this membrane.
7. There may be receptors, vesicles, and bind/release sites, but no pumps and no channels.

9.7.2.5 Membrane

The boundary between two fluid volumes shall be designated as membrane. Membrane shall be mathematically defined such that coordinated or random locations on this surface shall have addresses so as to locate the actors in their correct zones according to PDFs. It shall be mathematically defined such that interactors that might collide with the membrane can easily be detected as having an eminent collision and can be reflected from this surface within a tolerance of the interactor's radius, via the surface normals. Interactors shall not "leak out" of the membrane unless specifically directed to do so by an actor, or absorptivity kinetic.

The basic design for the membrane is a 1-D arbitrary cell shape profile line rotated cylindrically. Ideally the model would include 1:10 dendrites. It is acceptable that the dendrites arrange in a double-planar configuration. (think of 2 pieces of fabric sewn together to make a glove), for easy of splitting into front and back panels. The front and back panels will organize the R grids into 2-d matrices. The Design must be careful to avoid boundary value problems when mapping the closed surface of the membrane into a matrix. Any number of compartments is possible.

If channels are to commute interactors between two compartments then those two compartments must share a common membrane and such actors placed within this common membrane. Each actor has 2 poles, 1 in each compartment. A pole is a binding site for ligands, ions, transport. The poles also define an central axis for the actor, assisting in its orientation perpendicular to the membrane.

9.7.2.6 Lipid Capacitance

Capacitance permeability (betas). While charged particle systems exhibit capacitance as an emergent phenomenon where ever there is a barrier and and a charge imbalance, the amount of capacitance must be calibrated to dielectric strength of the membrane.

A specific capacitance value per unit area shall be settable within physiological range for the thickness of the membrane.

Although in vivo membranes are not homogeneous, mathematically modeling rafts is out of scope at this time. As lipids have polar heads which induce charge distortions into a portion of the membrane thickness, there is an

equivalent thickness that brings the ions closer together to effect the increased capacitance that results. A dielectric factor of 3 implies a reduction in the thickness of 1/3, as the attraction increases with the square of the distance.

C = diel*e0*area/thk; % where C is in Coulombs, area in square meters, thk in meters.

9.7.3 PARTICLE TYPES

9.7.3.1 ions

TYPE = [K Na CL Ca H An] where An is a bogus filler ion for charge balancing purposes.
TRAITS = { name mass size charge }
N total number of each ion species in the system
DistIon = initial velocity distribution of the ions per Boltzmann and temperature

9.7.3.2 ligands

TYPE = { GLU Ach 5HT ATP GABA GLY NE G1 G2 G3 }
TRAITS = { name mass charge size hydration mobility }

DistLigand records found distributions of ligand release points and recovery points in the neuron

Libraries of ligands and their traits are kept for modeling convenience. All ligands are are numbered by their molecular weight + 100. This is to allow them sharing the same list with the monatomic ions. Because several of the ligands and polyatomic ions share the same molecular weight, some numbering "stretch" is needed; it is important to at least preserve the molecular weight, as this will determine the diffusion speed and electrophoresis speed, compared to other species. Which species arrives first in an electric field could be significant is some bio-processes.

The relevant traits are: concentration, binding and unbinding kinetics to leave the receptor, delay to reach ion channels, which types of chan, fan-out leverage to number of ion channels, binding and unbinding kinetics at the ion channel,

Typical effects include:

Ligand	Receptor	Ion G's	
GLU	AMPA, NMDA	Na K Ca	
Ach	nicotinic	Na K Ca	
5HT	5ht3	Na K	
ATP	purineP1	Na K	
GABA	AMPA, NMDA	Cl	
GLY	Gly	Cl	
NE	Beta, Alpha2	G-protein	
PIP2	Kg chan	K	
G-protein1	chans	K down	Ca up
G-protein2	chans	Ca down	
G-protein3	chans	K up	

TABLE 21: RECEPTOR LIGANDS

9.7.4 PARTICLE ACTIONS

tag = { comp# bound2A#P# }
if in a comp state, then particle will diffuse
if in a bound state then particle is under control of a specific actor, subject to its operators.

Diffusion is of major importance in the model. All Interactors diffuse, except while bound. At the Design and Built stages, bindings are recorded as Tags on the position and velocity. Because interactors may move between compartments, tagging them is an efficient means to know which compartment they are assigned to and therefore which rules apply.

To maintain mass balance, ions are not created nor destroyed at any time during a Run. Re-uptake of ligands needs to be handled by special self-regulating pumps if they are to be recycled in a sustainable manner. All pumps must be self-regulating if a steady resting state is to be possible.

Diffusion requires considerable verification work to ascertain the proper space and time scales that mimic biologic phenomena.

The randomization of velocity cannot be Cartesian, as in [dx dy dz] = k*rand(3,1), because that results in cuboidal diffusion patterns.

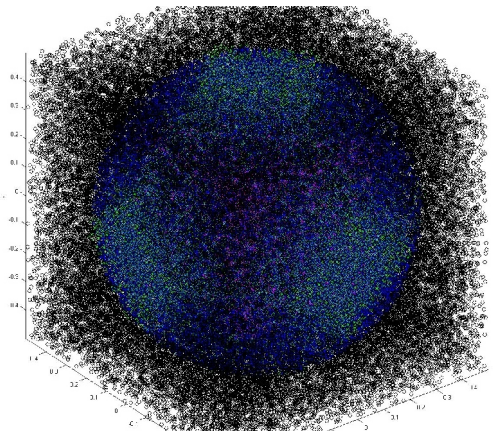


FIGURE 100: CARTESIAN DIFFUSION VS SPHERICAL DIFFUSION

The black particles are the immediate effect of using rand(N,3) to generate velocities. The positional effects tend to cancel out over time, but the velocity effects remain. The diagonals are 3^0.5 hotter than the face centers. If one randomizes the x-component, y-component and z-component partials of a velocity independently, then ion movement potential fills a cube-shaped volume each *dt*: p(x2,y2,z2) = p(x1,y1,z1) + (dx,dy,dz); This allows a maximal translation distance of 1 unit straight up, but a maximal diagonal distance of 1.732 units. This is a digital distortion that in the intensely iterative simulations necessary, produce huge cumulative error, which can quickly render all particles only moving up and down the diagonals, perhaps only due to round off error. Therefore, motion must be generated in spherical coordinates, which adds two basis changes per *dt*. Ballistic motion takes place in a single Cartesian world, but collisions occur in a set of small spherical worlds. The full equation set for 3-d collisions between varying masses, radii and charge require spherical coordinates.

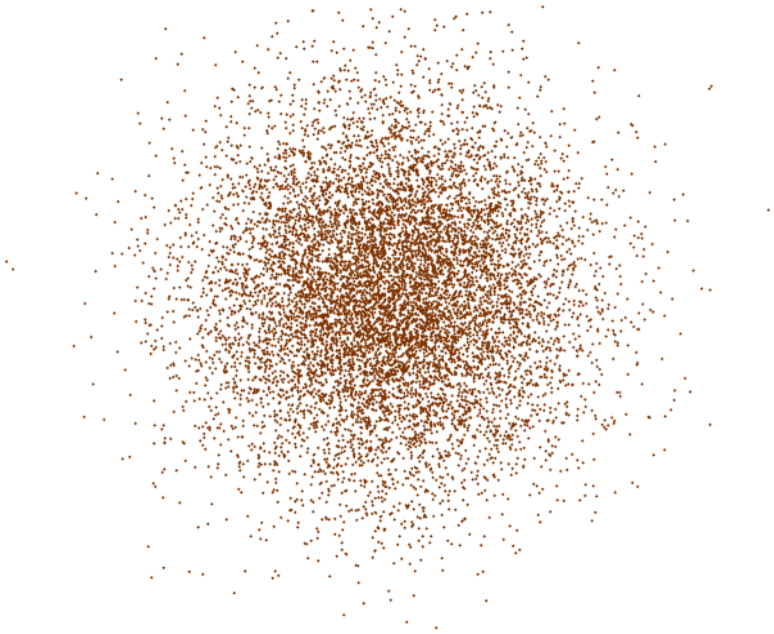


FIGURE 101: POINT SOURCE SPHERICAL DIFFUSION VIA BOLTZMANN'S EQ

The spherical diffusion above is generated by a Boltzmann velocity distribution driving the magnitude of random angles in spherical coordinates.

```
                                                    % mag2vels in spherical coordinates
r = rand(qB(i),3);                                  % r = [ a1 a2 r ];
A1 = 2*pi*r(:,1) - pi;                              % A1 = scale for spherical angle phi
A2 = 2*pi*r(:,2) - pi;                              % A2 = scale for spherical angle theta
                                                    % r(:,3) is not used as the radius, but rather as
                                                    % the random selector along PDF of possible radii.
for j = 1:qB(i);  ix(j) = find(CDF(i,:)'>=r(j,3),1);  end   % mag for each particle via readings of CDF
                                                    % Vaar(:,3) = 1E6/(1E4*1E3)* vrange(P);
                                                    % micron/meter, vel water/vacuum, sec/msec
mag = sfV*vrange(ix);                               % sfV = scales velocity, vacuum to water viscosity
[vx vy vz] = sph2cart(A1,A2,mag);                   % convert from spherical coordinates
                                                    %   Vxyz = [dx dy dz];   wrt time      % Cartesian vel
                                                    %   Vaar = [angle1 angle2 radius];   % Spherical vel
```

Most simulation techniques in digital computers require some form of compromise. For example, the Boltzmann velocity distribution has a tail that proceeds to infinity. Extremely fast particles as outliers cause many problems, including forcing the *dt* down to infinitesimally small steps, making collision detection very tedious (missing many legitimate collisions is the more common outcome), bestowing energy levels that would damage the things it hits, like making a hole in the membrane, and numerous “escapees” from compartments. As a result, the practical solution is to filter them out or clip the velocity at high limit. Too many particles clustered at the high velocity limit creates a Boltzmann anomaly and can distort other aspects of model performance. But clipping the tail (of high

runners) is also a distortion that will tend to cool the system temperature. The particle-water collisions may be simulated by assigning new velocities from that particle's Boltzmann velocity distribution; which will restore the temperature. For accurate temperature studies, a small amount of extra heat (higher Boltzmann temperature) must be steadily injected to compensate for high velocity particle clipping.

The Boltzmann velocity distribution is calculated as a function of statistical spread of velocities after a large number of collisions.

```
pdf = 4*pi*v^2 *(m/(2*pi*boltz*kelv)).^(3/2)*e^(-m*v^2/(2*boltz*kelv));  % where boltz = 1.381E-23;
m = the mass of the particle in kg = mass in amu / avogadro's number.
```

9.7.4.1 diffusion in water

Water is modeled as random collisions similar to the mean free path of ions in water. Spherical angles are randomly chosen, and a random velocity chosen from the Boltzmann CDF for that particle species mass and temperature.

9.7.4.2 diffusion through a pore

Although it is a straightforward geometry task to create a pore through a barrier and allow particles to diffuse through it, biological systems do not work this way for any of the ions. The movement of each species of ion is independently controlled via specific types of transporter, both channels and pumps. The finesse of pore selectivity is complex and still under investigation. The models of just one pore in isolation are immense undertakings. Therefore this model will only address the resultant conductivity profiles. These may be dynamic as a function of actor parameters, especially state.

9.7.4.3 Drift

A charged particle is accelerated by the net EM force impinging on it, as a function of density of the particles in the immediate vicinity, solvation, and hydrogen bonding. These 3 factors determine the viscosity of the medium. As the EM force is the strongest force in the system, it can dominate in determining the direction of ion motion, resulting in currents and distinctive flux patterns.

9.7.4.4 passive transport

Channels provide the passive transport through the membrane. Each type of channel has a conduction profile across all ion species present in the model system.

9.7.4.5 active transport

Pumps provide the active transport of ions across a membrane. Each type of pump binds a specific number of ions of specific types. This is referred to as the bind1 profile on the intracellular side and bind2 on the other side (extracellular or core). Pumps transport at least one species of ion against their concentration gradient, and therefore require an energy source. This source may either be another ion gradient (often Na) or chemical potential energy (usually ATP binding, then splitting into ADP + Pi). Whenever the effort to transport an ion or ions across the membrane is greater than the available energy then the pump will do one of the following: run backwards, stop working, or become chaotic in its actions (leaky, inefficient and mis-binding the wrong species of particle).

9.7.4.6 Affinity

Affinity is accomplished by identifying the closest particle(s) of interest. This would usually be done by measuring the Pythagorean distance over a hemisphere volume. However, such calculations involve both squares and square roots. Several opportunities to reduce the computational load present themselves. Using only the square of the distance, rather than the square root of the sums - saves a step, with no loss in accuracy. Using city block distance saves 2 steps but is less accurate.

```
dX = sqrt((x2-x1)^2+(y2-y1)^2+(z2-z1)^2);
dX1 = abs(x2-x1) + abs(y2-y1) + abs(z2-z1);
dX2 = (x2-x1)^2+(y2-y1)^2+(z2-z1)^2;
```

Using the square of the distance (sparing the square root step in computation) preserves the rank order of who is closest to furthest, so is fully justified. Using the city block distance makes the diagonals appear further than they really are and can accumulated distortions in the distributions of particles. If the city block calculations are less frequent than the water collision calculations by 2 orders of magnitude, then city block effects are quickly washed out of the system. City-block distances do not preserve the nearest to farthest rank positions so may not be justified unless the need for computational load reduction overcomes the reduction in confidence in the particle system modeled behavior. A benefit of using the city block distance is that it favors those particles closer to the axis of the

actor. That is likely to be an effect shared by natural systems which are more likely to accept a straight shot rather than an oblique shot to the pore.

9.7.4.7 Binding_to / unbinding_from actor allosteric bind sites

Each actor has a binding profile for each of its states. Generally only a few states accept modulator or ion bindings. Each binding has a probability of success between 0 and 1. There may also be a probability of mis-binding of the "wrong" ion or ligand. Therefore, the frequencies of binding are multiplied by the dt to yield the probability of binding per *dt*.

The unbindings after transport may not be a significant factor in actor performance, but because most actors are reversible, the symmetry of binding and unbinding is maintained.

9.7.4.8 Capacitation

Ions often become charge-bound along the membrane surface in numbers precisely equal to the charge imbalance across that membrane. Such charges do not diffuse 3-dimensionally into the saline solutions, but rather "bounce" along the membrane in a 2-d diffusion. This greatly increases their "local" concentrations and directs them towards neighboring actors. It is also these particles which comprise the voltage across the membrane.

Capacitance is an emergent property of an unbalanced charge among ions with a barrier to stop their neutralizing that unbalance. No functions are required to bring this about. However, all static notions of capacitance as a uniform voltage over a surface are in error. Like the surface of the ocean, all is in flux at all times.

9.7.4.9 Sequestration

Messenger particles must be tightly controlled in their locations, concentrations, and removal rates. This may be accomplished by sequestration pumps that move particles to the core compartment. This is especially employed for maintenance of Ca++ concentrations, and second messengers. It may also be employed as a place to store the contents that will later be installed within vesicles.

9.7.5 ACTORS = { RECEP PUMP CHAN VES }

Biological systems of molecular interactions and regulations within the cytoplasm are beyond the scope of this model. To the extent that they are significant in the neural signaling, they must be modeled elsewhere and the results injected into this model as to release time/place, and reuptake time/place.

Many of the actors consist of protein subunits. Subunits may be cataloged as such and "assembled" to comprise specific types of actor. Each subunit in a channel may determine a gating characteristic, and in a pump may determine the ion binding distributions. Therefore subunit behaviors are key to the overall actor performance. The model library provides a list of subunits and their characteristics, which actor types they are found is. A table of ensemble performance is also provided. However, the chemistry of conversion and recombination of these subunits is beyond the scope of this model. If such events are relevant to the experiment, then the systems biology will need to be worked elsewhere and injected into this model with Q-matrix, R-matrix and O-table representation of each.

In general, actor types are defined intrinsically by 10 characteristics:

R matrix = affinities across all B types modulate them: modulator response profile vector
Q = state transition probabilities table
RQ = mapping from R instantiated to d bindings into which page in Q applied to that combo
O = phenostate expression of internal state s upon the actor's environment
G = conductivity profile across all B types, for channels and catalysts

aff = pseudo force to draw B particles in the vicinity close enough to bind.
erg = transformations of certain B types after binding, usually ATP converted to ADP + Pi
eff = directed release of B particles towards target receptors, usually per G-protein mechanisms

TYPE = class#.type#
ID = instantiation #
% These are the 10 traits of the A TYPE trait data

In addition, actors require the tracking of several transient traits:

s = the current state, the molecular conformation as affects bindings and transports
d = bindings, which B are bound to each binding site of an instantiated actor

And finally, there are several external traits of the immediate environment:

Vm = the Coulombic voltage across the membrane as surrounds an actor
Vn = the Ernst partial voltages for each B type, between the poles of an actor
U = concentration gradients of each B type within the affinity radius of an actor

9.7.6 ACTOR POSITIONING

Individual Actors are positioned as follows. The biological distributions are converted to CDFs.

Individual positions are "read" randomly chosen from this distribution.

9.7.6.1 Recep1

Recep1 is a modulator binding site on an individual ion channel. It shall bind its received modulator particle according to alpha and beta rate kinetics. During the time of binding, the Recep shall cause its associated ion channel to switch Q matrices to the “modulated” set of transition probabilities as indicated by a linkage table.

Recep and Ligands must be matched, else rendered useless.

Recep1 connects directly to a specific and singular Chan. Thus a ligand modulates the chan Q matrix directly.

TYPE = { AMPA NMDA nicotinic 5HT3 PurineP1 GABA-A GLY-R NEbeta }
DIST locations define the input region of the cell, via shape function indices
MODs
STATES
Qindex

EX
given that Interactors = { ions ligands }
= { k na cl ca h an GLU Ach 5HT ATP GABA GLY NE G1 G2 G3 }
Then a GABA receptor :
IN = [0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0] * conc
U = 0.5 + 0.5*tanh(IN-1); % where 1 is a threshold concentration of modulator
a= U; b=1-U;
R provides the kinetic probabilities of binding and unbinding = [1-a a; b 1-b] ;
Qindex associates the bound state to an alternate Q matrix for the associated ion channel. There may be more than one bound states, and therefore more than 2 Q matrices.
P(t+1) = P(t) +P(t)*Q;
Y = P*(phenotype); phenotype interprets states for effect upon the external world
messenger = OUT = e.g. 7 molecules of messenger released

9.7.6.2 Recep2

Recep2 receives a modulator particle which causes it to release a second messenger particle. The second messenger is an interactor and must diffuse, 2-d, to its target ion channel(s) in the near vicinity.

TYPE
DIST
MODs
STATES
Q
s

s(t+1) = P(t) +P(t)*Q;
Y = P*(phenotype); phenotype interprets states for effect upon the external world
messenger = OUT = e.g. 7 molecules of messenger released

Otherwise similar to Recep1 above.

9.7.6.3 Chan

TYPE = { chan01 chan02 chan03 chan04 chan05 chan06 chan 07 chan08 }
Note Chans are not named by their ion conducted because they often conduct many ion types

DIST = distribution of Chan will determine the information processing characteristics, including decay, graded response, delays, gain, action potential, propagation (or not), summation, subtraction, lateral inhibition, temporal and/or spatial integration or differentiation, and many filtering possibilities. DIST is of the essence!

EX
given that Interactors = { ions ligands }
= { k na cl ca h an GLU Ach 5HT ATP GABA GLY NE G1 G2 G3 }
Then a Na type Chan :
IN = [.03 4 0 .3 0 0 0 0 0 0 1 0 0 0 0 0] * sum(F), where
F = GRADconc (ion) + z*GRADvolt + Attractor(x,y,z)
U = 0.5 + 0.5*tanh(IN-1); % where 1 is a threshold concentration of modulator
a= U; b=1-U;
Q = bind/unbind rates = [1-a a; b 1-b] ;
P(t+1) = P(t) +P(t)*Q;
Y = P*(phenotype); phenotype interprets states for effect upon the external world
messenger = OUT = e.g. 7 molecules of messenger released

NOTE that the Y function is the Hodgkin Huxley EQs, and the P function is the Kolmogorov EQ. They have been merged by allowing for the possible coupling between internal states of the ion channel proteins. The alphas and betas need to be generalized into Q matrices.

Each channel type consists 3 to 10 subunits. Each subunit has at least one kinetic scheme, and multiple schemes if modulated. The modulators determine which Q applies, each dt. The Q's are instantiated to a single state and that state is “expressed” via a gate function, which contains AND and OR logic to determine channel openings.

EX
```
Q_CaV(-90)  = [   -2.8201     2.8201      0
                423.6046 -425.0146      1.4101
                  0         847.2091 -847.2091];
Q_CaV(0)    = [  -248.8200  248.8200       0
                    0.7705 -125.1805  124.4100
                    0             1.5410   -1.5410];
```

where state 3 is open, and states 1 and 2 are closed.

9.7.6.4 Ves

Vesicles are stimulated by Ca, which causes them to be drawn toward the membrane and puncture the membrane, releasing neurotransmitter into the synaptic cleft. A vesicle usually has only one type of neurotransmitter inside, but may also contain a peptide and ATP. The vesicle shall be represented by a small circular compartment containing ligand particles inside. The vesicle shall have a Ca binding site and attractor.

TYPE = Interactors = { ions ligands }
= { k na cl ca h an GLU Ach 5HT ATP GABA GLY NE G1 G2 G3 }
actually only a small number of these will be found in vesicles, but it is generic to use this vector

DIST locate vesicles at random points near the "output end" of the neuron.

Re-uptake need also be considered on all but the shortest of RUNS. This is accomplished by designing a pump for the purpose. Although, it would also be possible to use a simple attractor to "vacuum up the area", this is not recommended, as it distorts the mass balance of the system. As vesicles communicate to antecedent neurons, compartments must be constructed to mimic synaptic clefts for diffusion across to the antecedent receptors.

EX
given that Interactors = { ions ligands }
= { k na cl ca h an GLU Ach 5HT ATP GABA GLY NE G1 G2 G3 }
Then a GABA Vesicle responding to Ca :
IN = [0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0] * conc
U = G/V curve for Ca chan
a= U; b=1-U; for Ca binding rates
Q = bind/unbind rates = [1-a a; b 1-b] ;
P(t+1) = P(t) +P(t)*Q;
Y = P*(phenotype); phenotype interprets states for # of vesicles released
OUT = vesicles released e.g. 2 vesicles of GABA released
Note: once a vesicle has released a quantity of ligand into a compartment, it will diffuse and "pollute" the entire compartment unless there is a re-uptake mechanism.

9.7.6.5 Pump1

Pumps a single ion species against the gradient. Self regulating to pre-set conc ratios
TYPE = { ATP/Ca ATP/Na ATP/K ATP/Cl }
DIST positioning of the pumps will set up ion flux over distances along the membrane
These flux, in turn, will result in ion gradients along the processes.
Such gradients can have profound effects upon the information processing of the neuron.

9.7.6.6 Pump2

Pumps 2 species of interactor, with or against the gradient, with or without energy consumption,
TYPE = { K/Na Na/Ca Na/Cl K/Cl }

DIST positioning of the pumps will set up ion flux over distances along the membrane
These flux, in turn, will result in ion gradients along the processes.
Such gradients can have profound effects upon the information processing of the neuron.

Pumps are quite important in the modeling of diffusion, because everything that is created must be removed, to maintain a steady state. This is especially true for neurotransmitters and Ca.

EX
given that Interactors = { ions ligands }
= { k na cl ca h an GLU Ach 5HT ATP GABA GLY NE G1 G2 G3 }
Then a 2K/3Na pump :
IN = [2 -3 0 0 0 0 0 0 0 0 0 0 0 0 0] * conc
U = 0.5 + 0.5*tanh(IN-1); % where 1 is a threshold concentration to start pumping
a= U; b=1-U;
Q = bind/unbind rates = [1-a1 a1 0; b1 1-a2-b1 a2; 0 b2 1-b2] ;
P(t+1) = P(t) +P(t)*Q; % determine pumping rates as a function of multiple concs
Y = P*(phenotype); phenotype interprets states for effect upon the external world
OUT = [2 -3 0 0 0 0 0 0 0 0 0 0 0 0 0] molecules pumped this dt (success)

Note conventions: positive number indicates inward pumping, negative number = outward

9.7.6.7 Pump3

TYPE = { 2K/3Na 3Na/1Ca ATP/Ca Na,HCO3/Cl Na,K/2Cl }
DIST positioning of the pumps will set up ion flux over distances along the membrane
These flux, in turn, will result in ion gradients along the processes.
Such gradients can have profound effects upon the information processing of the neuron.
Pumps3 contains realistic pumps, but the ratios make it somewhat difficult to set up so as to mimic reality.

9.7.7 IMPLEMENTATION CONSTRAINTS

An experimental design consists of a combination of newly defined entities (if any), library choices (Design), Input signals, and choice of Output variables to be recorded. In modeling an entity with the complexity of a neuron, many simplifications must be made.

Virtual Time	time is represented arbitrarily as dt, which computationally is not linked to any real time process, and thus may vary considerably. However real time computing hardware is ideal for neural simulations, because the many safeguards built into them work very well to protect the model runs from interruptions and crashes. They also have good parallel processing administration. The model run is not displayed as a video. This is to allow more efficient processing of data. That data is collected into a matrix which can be played as a movie AFTER the run is completed. This "batch" mode was found to greatly speed up the computational time, and supported more complex models to run.
Real Time	This is not a real time program. As it is a simulation, it can benefit from many of the real time processor features. As it is computationally quite demanding, it can benefit from the parallel processing clusters often employed in real time problems.
Time scale	Although there are significant events within the neuron that occur over time scales from 1E-9 seconds (molecular state changes) to 1E9 seconds (long term potentiation), we are only interested in he timeframe of the action potential;

	and so strive to account for all processes of time constants 1E-4 to 1E-1 seconds; those that impact the shape of action potentials and graded responses.
Space	space is arbitrarily scaled to present nicely on computer screens. As a typical neuron might be 10 to 100 microns long, we could scale 1 micron to be 1 cm on the screen
Dimensionality	We can model in 2-D or 3-D. As the number of assumptions and conversions necessary in collapsing 3-d to 2-d is high, it is often best to model in 3-d. A noteworthy exception is the membrane itself, which is inherently planar. Thus, we "peel" the neuron of its membrane and attempt to lay it "flat" into a 2-d matrix, or matrices. This is justified by the fact that it yields more accurate results than leaving it in 3-d. (Which is prone to numerous errors in knowledge of which side of the membrane a protein or ion is actually on.)
Concentration	As the number of atoms in a neuron of volume 100 cu microns = 1e16, we must model concentration at a reduction of about 1e-13 to get less than 1000 particles.
Water	The medium of all compartments not membrane is assumed to be water. As a liquid f=m*a is muted to f=m*v, and the velocities are about 1e-5 of what they would be in a vacuum, or as a gas.
Proteins	Most proteins are completely ignored, even though they play many crucial roles for the cell.
Ligands	We do very little with non-proteins, except for those which are active messengers in the information processing of the neuron. Phosphorylation, gylcosylation, neurotransmitters, peptides can be handled as modulators to the actors.
Number of channels, pumps, receptors, and vesicles	as there are about 1e6 ion channels per cell, these quantities are scaled down about 1E-5. As there are repeating patterns of channel combinations and mixes, or there are gentle gradients of ion chan distributions from end to end, the behavior of the cell type can often be surmised and duplicated even though the representative sample size is many orders of magnitude smaller.
Turn over	Real neurons experience continual protein turnover (and other constituents as well) Protein may be floating in the lipid membrane or be tethered to some stable structure. None of this is being accounted for in the model. The reason is: anything happening on a time constant of greater than 1 second is too slow to appear in the generation of an action potential. Such long time constant processes must be modeled by doing repetitive runs at useful sample points in time reflecting the changing constellation of proteins.
Particle collisions	Water molecules are not taken into account when detecting particle collisions. So long as the collisions result in random new directions, and conserve momentum, the energy profiles will remain true to natural conditions. So the addition of water collisions is superfluous, and a major computational burden, without benefit.
Membrane collisions	Interactors may collide with membranes. Usually this results in a reflection according to the orthonormal. However, if beta values are present, then there is a probability that an interactor may penetrate into the lipid. If such an event occurs, a tag is set to mark the interactor as in lipid, and different mobility applies. A similar process occurs if an interactor collides with the aqueous face of that lipid.
Actor collisions	Interactors may collide with Actors. In such an event binding kinetics apply. If a binding occurs a tag is set to mark the interactor as bound and its velocity is set to zero.

9.7.7.1 Space Digitization

Organizing the membrane into addressable nodes can be accomplished via several different algorithms. The Delaunay algorithm will generate nodes on convex shapes, but fails on typical neuron shapes due to concavities. Once node locations are established, a certain area must be allocated to each node for purposes of calculating capacitance. The Voronoi algorithm can be used for this purpose.[197] The compartmentalization of the cell create artifacts when crossing their boundaries, so it is ideal to avoid sectioning of the naturally contiguous volumes. One challenge is the dendritic spines, which are indeed semi-compartmentalized from their host stem. The presence of spines forces the loss of simple cylindrical coordinates for particle collisions with membrane and actors.[198] Many workers strive to degrade the fine structure of the dendrite so as to minimize computational load, although doing so always sacrifices some information content.[199][200]

Quenet surveyed the consequences of modeling in higher dimensionality. He added multidimensional synapses and multistate neurons so as to generate the spatiotemporal patterns that reproduce the experimental recordings by reverse engineering.[201] He continued to use Hodgkin Huxley EQs to represent the ion channels, however.

9.7.7.2 Time Digitization

The response time of pyramidal cells is often less than 1 msec. But to generate these responses in simulation requires some very nonlinear differential EQs.[202] Once the dt is down around 1E-5 s then the dynamic EQ become quite accurate. But when dt > 2.5E-5 s, then the strong nonlinearities of channel openings begin to pick up significant error. [198] This presents a serious challenge for modeling. While the computational load is tractable when the dt = 1e-3 s, getting to 1e-5 requires 100 times larger computer.

The very nature of the nonlinear sensitivities suggests that information could easily be coded in phase timing. Buonomano in 2000 found instances of such.[203] Phase sensitivities can operate at far smaller time slices than 1E-3 s. Two action potentials that require 1E-2 s to execute can be 1E-4 s out of phase - and that difference can be quite significant. This is the case in detection of sound localization.

The discretization of continuous space into digital particle systems also has its challenges. Trajectories are no longer differentiable, and that makes boundary crossing detection problematic. Digitization of fast events subjects them to extreme artifacts in sampling phase, thus necessitating very fine dt's. Furthermore, biological events are

asynchronous, vs. the silicon-based computer synchronous clock-driven events. Thus, there will always be aliasing error. It cannot be tuned out. There are well established strategies for mapping asynchronous events into a digital world, but they are only effective for few particles on long trajectories (ballistic) with occasional collisions. In saline solution, ions are hugely numerous (1e7), mean free paths are very short, because collisions occur about 1e12 /sec/particle. This makes for impossible utilization of event-driven algorithms. See also[204][205] for an attempt at this by Destexhe. In 1997, Schaff attempted 27000 elements (particles plus actors), with only 3 nonlinear EQs each, no electrostatics. Two seconds of sim time required a run of 2 days.[206]

9.7.8 LOAD FUNCTION

LOAD shall be provided which moves all .mat files created per the above, into a standardized structured work space as necessary for an automatic BUILD.

9.8 BUILD

The essence of the BUILD is to place all design data into a Matlab ™.mat file in such a standardized form that it can be automatically read within the model. The challenge is to be formal enough that there are no ambiguities in data matrix formats, but yet flexible via open-ended lists to allow for a great variety of Experimental Designs.

9.8.1 COMPARTMENTS

1. Each compartment C type is instantiated via SH, a shape generator
2. Shapes consist of any number of functionally significant Zones
3. for example C.Main.zones = { dendrite soma axon bouton }
4. each Zone consists of any number of line Segments which determine their shape
5. each Segment consists of a number of Rings (slices), quantity determined by node spacing
6. each Ring consists of a prescribed number of Nodes, so as to maintain homogeneous spacing
7. each Node may be vacant or occupied by any instantiated Actor
8. In addition to providing Nodes, a compartment also provides a surface capable of particle reflection and holding an electrical charge (capacitance).

9.8.1.1 Membrane

DIST the perimeter should be fully populated with points in a 3-D matrix, for speed of detecting a reflection or absorption.

There shall be 2 positioning functions: posB and posA.

posB positions or repositions interactors within a compartment (including the treatment of the membrane as a compartment). This function uses collision detectors and orthonormals to define the point of collision and calculate a response.

posA positions actors as stationary objects embedded in the membrane, and protruding through it. This function uses the compartment definitional nodes, per their indices.

9.8.1.2 Lipids

capacitance: is calculated on a nodal basis as the charge concentration within a designated radius of an actor. The choice of radius is critically time dependent. The opening of a channel allows a pulse of particles to pass. These fall back to the membrane and spread radially at a propagation speed dependent upon charge concentration, charge gradient, and viscosity. A meaningful radius will be drawn at the leading edge of this wave, each *dt*, over the period of interest. The result does not have much validity if it knows nothing about where the wave front is at the time. Capacitated charge is an extremely dynamic phenomenon in neurons, and therefore meaningful mensuration requiring this kind of tracking.

It is possible to incorporate inhomogeneous lipids in the membrane on a per node basis , at the time of membrane design. Merely calculate the equivalent thickness for its effects upon capacitance for that nodal-region. Using membrane thickness to limit the closest distance ions are allowed will cause them automatically to redistribute, lowering capacitance for thicker membranes., increasing capacitance for thinner ones.

9.8.2 PARTICLES

1. Each B type (interactor) is instantiated from a Molar Concentration per compartment via a Boltzmann velocity Distribution.

9.8.2.1 Synapse

There is no synapse function, *per se*, as synapses are constructed from constituent parts: compartment, membrane, actors, vesicles, ligands, diffusion, and pumps.

There may be some advantage to formalizing those structural combinations which are used repeatedly. When modeling advances to multicell communication, there are often large numbers of very similar or identical parts. Provision shall be made to support such assemblies as callable functions. Thus, several canonical synapses could be made available by a function call.

9.8.2.2 RC Grid

Use Euclidean Magnitude calculate the distance of each node to its nearest neighbors.

Calculate nodal specific resistance to nearest neighbors as a function of concs and thickness of extracellular space.

Calculate the resistance of each of the edges using the Euclidean magnitude multiplied by specific resistance.

Output the resistance vector ordered by Di Sort for the resistance grid matrix by Nei.

Delaunay function produces 2 R matrices
Voronoi function produces 1 C matrix

9.8.2.3 Charge

Nodal capacitance is calculated as follows:

1. Given the location of each node on the membrane, call Voronoi to determine a polygon around the node.
2. Call poly-area to determine the area of that polygon
3. Calculate the nodal capacitance by multiplying the area times the specific capacitance from TYPEC
4. The net charge imbalance is sufficient to calculate the unbalanced charge on the membrane, but the distribution of that charge requires a FEM approach.

9.8.3 ACTORS

1. Each A type is instantiated via a Spatial Distribution on C and a State Initializer.
2. Spatial Distributions are PDFs specific to a neuron type, neuron zone and specific to an A type.

3. Actors are stochastically-driven finite state machines that probabilistically receive inputs and modifiers via AR, probabilistically change states via infinitesimal probability matrices AQ, which map to effect some external condition via AE.

4. For example, Acetylcholine may bind to an ion channel receptor according to the AR matrix for that channel type, which causes the instantiated channel AQ values to change, which begins a probabilistic drift in molecular states over time, which eventually changes the ion channel from closed to open, according to AE.

5. Actors and capacitors may act as force generators (affinities and EM force fields, respectively).

6. Actors shall be able to call Attractor, whenever they cycle from the Vacant to the Staged state.

7. ACTORS_IC Because Actors have transitional states, they must have ICs. Those ICs are best determined by their natural steady state values. Each Kolmogorov Q matrix has a P of steady state values. This Pss should be calculated as a first step in a RUN, to insure that Actors are not arbitrarily in some awkward, non-biologic state, which will produce artefactual behavior. This is especially critical for the highly non-linear behavior of ion channels.

ATTRACTOR: Each actor shall have the capacity to attract particles for binding

1. Attractor represents a force which incrementally adds to the velocities of interactors. Attractors may be defined as located virtually in the Actor inlet, or may be twinned (more realistically) on either side of an inlet.

2. Attractor calls DistMat which determines the distance to every particle, and operates only on particles in its vicinity, as determined by AttractRadius.

3. ATTRACT_RADIUS a constant which sets the max distance between Attractor and a specified Interactor species, that Attractor can add to their velocity vectors.

4. ATTRACT_SPECIES a constant which specifies which species of Interactor the Attractor is to operate on.

MODULATORS: Each particle binding onto an actor shall have the capacity to modulate that actor.

MODS = { B_bindings force_variables } Actors can be modulated by any particle or force that impinges on it. Therefore, the possibilities are concatenated as a Mod vector, such that voltage, pH, temperature, and Na conc are all available as possible modulators. The challenge is to make all of these LOCAL via Finite Element Methods. Any modulation event is mapped into the RQ matrix, which inputs binding site combinations and indicates which page in Q shall apply.

9.8.4 PUMP LIMITATIONS

PUMPMODULATORS = vector { interactors variables} concatenation
PUMPINTERACTORS = vector of all interactors. positive value indicates pumping inward
PUMPMAXRATE constants for each ion species to be pumped
PUMPSATURATIONCONC constants for each ion species to be pumped
PUMPSTARVECONC constants for each ion species to be pumped
PUMPQ kinetics matrix

PUMP0 steady state initial conditions
PUMPSTATE { 1 2 3 4 …} see state transition diagrams
MICHAELIS-MENTEN_EQ = Rate = conc.s1*conc.s2*RateMax / (Half + conc.s1*conc.s2)
where Half = the solute conc at which Rate = 0.5*RateMax.

9.8.5 CHAN LIMITATIONS

CHANMODULATORS = vector of all modulators
CHANMAXG constants for each ion species conducted
CHANSATURATIONCONC constants for each ion species conducted
CHANSTARVECONC constants for each ion species conducted
CHANP0 steady state initial conditions
STATE = rand(P) see state transition diagrams

9.8.6 VES LIMITATIONS

HOWMANYVESICLES = rand(P)
HOWMUCHNT = rand(DIST_NE)
state = { 1 2 3 4 …} see state transition diagrams
attract = on or off, dependent upon state. Attract params separate

9.8.6.1 Staging

1. Set point for target quantity of vesicles ready to fire
2. production rate of vesicles, dependent upon availability of B types
3. recycling programs

9.8.6.2 Transport

Prior to transport, particles must become bound to the actor stochastically, per the R matrix. The transport event is determined stochastically by the actor Q matrix and its phenostate O table.

Each particle, upon transport to a new compartment , must be re-assigned to that compartment. This is necessary for the reflection and leak algorithms

9.8.7 MARKOV PROCESSES

Two state Markov models can only represent a firing rate and a variance. They cannot do patterns nor modal shifts. [207] In 1989, arguments were proffered on the merits of discrete vs continuous quantities for states of the kinetic schemes of the ion channels.[208] Ball, in 1994 provided theory for a semi-Markov framework for channel kinetic schemes.[209][210]) By 2001, Wagner reviewed a list of Markov chain models of ion channels.[211] Biological

noise is philosophically different from silicon circuit noise. Commercial artificial chips are designed to minimize noise as far as possible. In biological systems noise is the energy source for fluidics and state changes. It is harnessed exquisitely, and the neuron could not work at all without it. Therefore, design objectives must be rewritten for liquid state processors. Noise continues to weaken the signals of man's instrumentation, however.[212][213][214][215][216][217]

9.8.7.1 Kolmogorov molecular stochastics

Bind R is a B x d x S matrix that determines forward and backward probabilities of allosteric bindings and unbindings. Each binding combination in turn affected the R and Q values.

State Q is a S x S x R matrix that determines forward and backward state changes determining molecular conformations. Each conformation in turn affected the R and Q values.

Release Receptors and Vesicles may release batches of particles. The direction, velocity and timing of those releases, following the time of triggering, are determined be their capture velocity. Alternatively, velocity is mapped from the Boltzmann velocity dist.

9.8.8 ASSEMBLY OF PARTS, MINIMAL MODEL

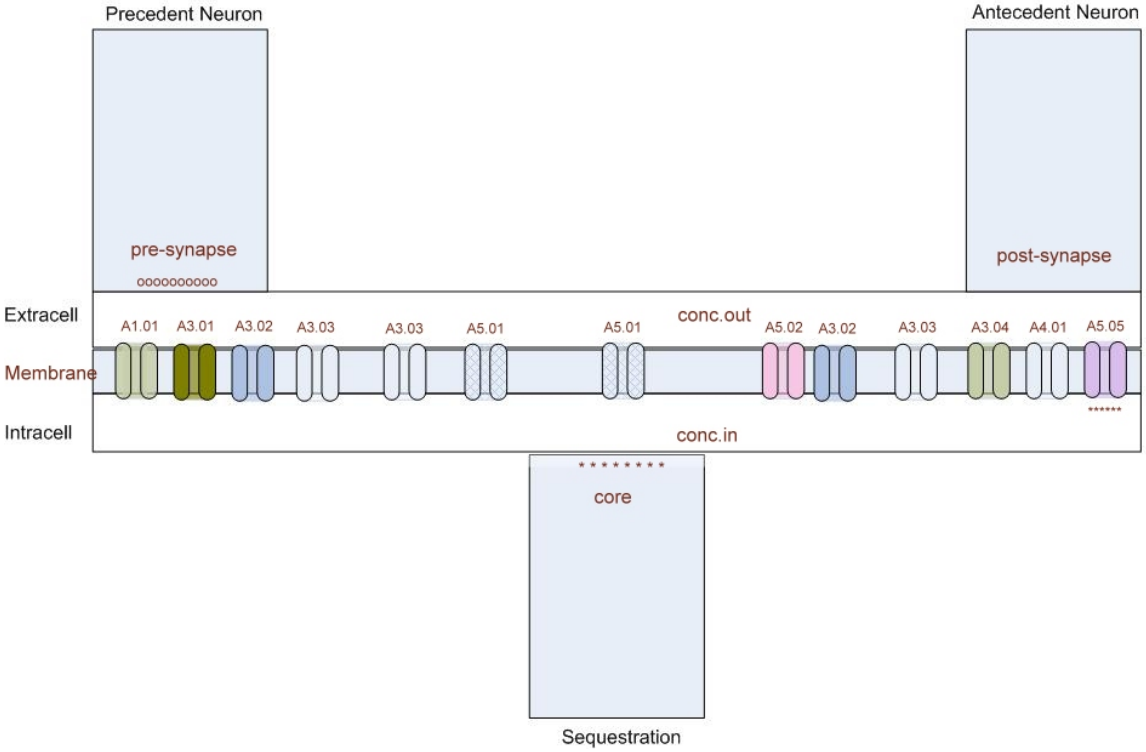


FIGURE 102: A MINIMAL INSTANTIATION OF A NEURON

Instantiation model consisting of the available actors as defined herein

1. A precedent neuron may release a neurotransmitter, say NE into the extracellular space.
2. It will diffuse rapidly (0.5 msec) across the fluid towards the receptor for NE.
3. At the receptor it binds, causing a Na chan to open via Kolmogorov state transitions.
4. Na fluxes into the intracellular space causing a voltage disturbance across the membrane.
5. This triggers the K chan to begin opening which allows K flux outward.
6. These two disturbances set forth a "wave" of propagation to other Na and K channels.
7. The second to last chan at the right is a Ca channel.
8. It releases Ca into the intracellular compartment very near to a vesicle.
9. The last element is a vesicle, which releases GABA into the extracellular space.
10. This diffuses to the antecedent neuron's receptors.
11. Sequestration maintains the low levels of Ca in the intracellular compartment.

9.9 SIGNALING

1. Modulators, including Ligands and Neurotransmitters
2. Synapses, via specialized small compartments, called plugs
3. SigGen, a signal generator may be used to drive the neurotransmitter release patterns
4. Output Reports, as graphs, movies and raw data on particle positions and actor states wrt time

As with most models, there are signal input ports, environmental fluctuations, internal state monitor points (read as signals), and the formal output ports. Signals are deemed present in this model as follows:

1. Input Signal Generators and output signal capture devices: plugs are designed as excised, intelligent boutons
2. Information throughput metrics: mutual information is honest only when the complete set of messages are known.
3. Information processing metrics: The system has a quantity of states, each with a quantity of possible values. These set the upper limit on processing capacity. The patterns recognized and patterns generated determine the processing operators.

9.9.1 SIGNAL GENERATOR

Input signals shall be provided to represent the output of the precedent neuron, so as to drive the neuron model.

It shall provide Pulses, Steps, sawtooth waves, ramps, sine waves, Additive combinations. and Multiplicative combinations.

It shall be "clonable" so as to provide as many channels as there are receptors. These clones may be coupled via a root signal, variable wrt amplitude, inversion, phasing, and noise levels. The root channel may be any signal reasonable to neural networks: visual, auditory, touch, smell, chemical, proprioception, temperature, pain, or memory recall.

Additionally, standard engineering signals, and arbitrary signal streams shall be possible over as many channels as there are receptors. These include step, pulses, ramps, sigmoids, sines, sawtooth, and trig functions e.g. parabolas and hyperbolas; Gaussian envelopes, white noise, pink noise, and additions from among these. Additionally, effort shall be made to mimic natural signals to the neuron, in time and place. An A2D converter will sample analog signals at 10 kHz and decide whether to fire an action potential or not. The action potential will have a canonical shape, and may have varying amplitude.

These signals shall be available in virtual time (not necessarily real time).

9.10 RUN

A run is an iterative process by which particles move, and the finite state machines call relevant functions to effect collisions, bindings, transport, capacitance, voltage and current. Data is collected raw. The RUN portion of the program execution consumes, by wide margin, the most computational load. It is therefore the most demanding of attention to numerical methods.

INTEGRATION methods considered include:

1. explicit euler
2. implicit euler
3. midpoint leapfrog
4. crank-nicholson
5. runge-kutta
6. adams-bashforth
7. adams-moulton

All of the variable-length *dt* methods would require some synchrony across the elements, or else some very fast switching between the calculations of elements. CPU time tests often found that the overhead of managing variable strategies was effective when the elements were few and complex. However, in this model, the elements are numerous and only moderately varying in form. In such large scale models, CPU time is best arranged to handle the greatest number of particles at a time. Doing so requires a fixed *dt* and fixed matrix sizes for the kinetics. Standardization of the form leads to greater computational efficiency than does heuristics.

There is some possibility of “skip step” techniques whereby uneventful trajectories are skipped over on the fine *dt* but calculated on the large *dt* setting. This only realizes a gain to the extent of the total list of particles exceeding the CPU capacity for a single clock cycle. Reducing the load within a clock cycle offers no benefit and costs extra steps to identify and mark the “skips”.

A converse strategy, “back time”, employs large *dt* steps until some violation of space occurs, then time is backed up by a small dt to resolve the details. Although theoretically effective, the cost to detect them and then calculate such events *separately* quickly eats up the gain. It only works within narrows windows of ratios of events to the whole. The exact ration depends upon the number of calculations per particle per *dt* in the back time algorithm.

Although a straight *dt* is cumbersome, it offers straightforward debugging and collecting of metrics. It also frees up time that would need to be spent of numerical methods, for higher priorities concerning the functions of the model. Therefore, in early releases of this model, straight dt calculations will be made, adjusting the value of *dt* increasingly larger until an unacceptable error rate is incurred.

9.10.1.1 Causality

Causality in a digital machines is established by chonological order, and by the output of one or more causal functions feeding the input of another function. Causality is weakened by stochastic processes which inject some degree of randomness into the system.

The run, because it is digitized, processes a sequence of events as separate and serialized, even though in the analog world they are parallel and concurrent. Functions which do not receive temporally sensitive information (i.e. do not receive inputs from a causal group), may be regarded as parallel processes, and therefore insensitive to the order of execution. These will be placed so as to optimize numerical methods. To the extent practical, order of execution is chosen for causality, but also for the convenience of the conditional EQs, so as to minimize redundant calls. It can easily be tested that altering the sequence has little effect upon the results.

In a digital universe, things might pass right through each other without a collision. There is a strobe light effect when sampling each *dt*. This is a type of error, of discontinuity. Perhaps some percentage of particle collisions may be missed without altering the experimental result. But collisions with the membrane are far more significant. A missed membrane collision become a leak. In digital software, the collisions with the membrane containers are performed last, because this minimizes the need to detect leaks more than once per *dt*.

The set of EQs represent physical and chemical phenomena of 1 molecule type. The physics of actor proteins is sufficiently complex that the state space is usually collapsed into a simplification called a “kinetic scheme”.

The major mathematical processes of the run are mapped below.

9.10.1.2 Mathematics Flow

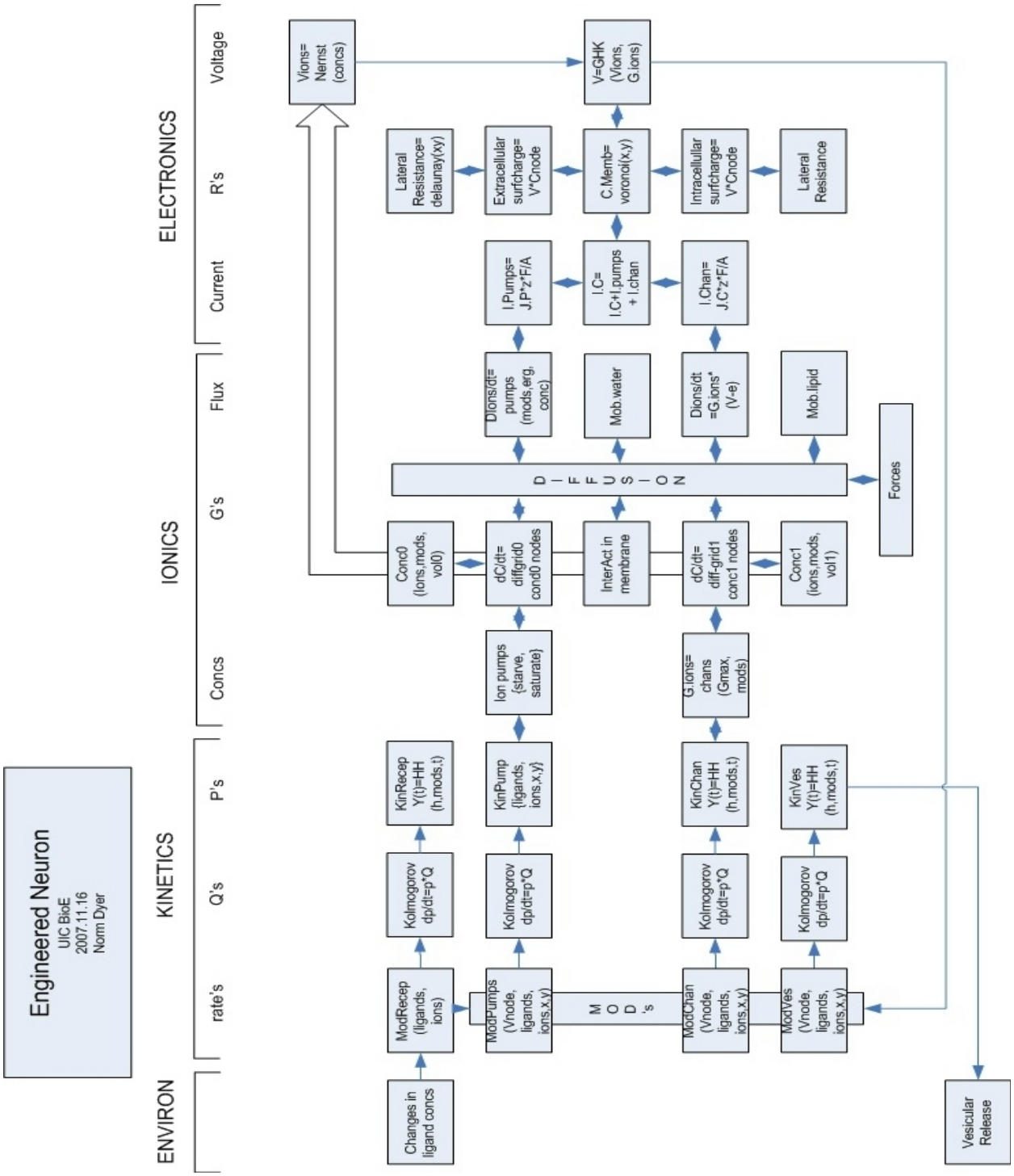


FIGURE 103: Mathematics Flow

Implied in the Diffusion block are limits to diffusion, namely reflections. Note also that the distinction between ionics and electronics is fuzzy. It will later be found that these two are best merged into a charge system, with the "electronics" of interest emergent to the particle system.

9.10.2 DIFFUSION

Diffusion applies to all neutral, unbound particles. It is accomplished by simply adding its current velocity to its position.; and then detecting any collisions and resolving them with 3-d momentum conservation. Diffusion into barriers results in reflection or absorption, statistically determined. Velocity distributions are periodically checked against the Boltzmann velocity distribution curves. Variance from these curves indicates a failure to conserve linear momentum.

Bindings must remember their former velocity while setting current velocity to zero while bound. Upon dissociation the velocity must be "reflected" in a reasonable manner, and the old velocity resumed.

Frequent water collisions reset velocities from the Boltzmann distribution.

```
boltz = 1.381E-23;
e= exp(1);
avogadro = 6.022E23;                                    % avogadro's number
m = 0.001*mass(:) / avogadro; m=m(:);                   % required by Boltzmann's formula
v2=repmat((vrange(:)').^2,[Lm,1]);
vel = 4*pi*v^2 *((1/pi) * m /(2*boltz*kelv)).^(3/2)*e^(-v^2 * m /(2*boltz*kelv))          % Boltzmann's EQ
```

9.10.3 DRIFT

Drift applies to all charged, unbound particles. This must be calculated as a whole system, not divided into one compartment at a time. The N-body net EM force of each particle is added to its Boltzmann velocity, the sum of which is added to its position. Any collisions are detected and resolved with 3-d momentum conservation. Drift into barriers results in reflection, absorption or capacitation.

Drift is a force of acceleration. A = F/mass; F = k0*q1* sum(q2*normV(p1-pi)/ |p1-pi|^2); % where i = 1:qB

9.10.4 CONC

ConcNodal A hemispherical volume above and below each node, and the particles of each type counted within those nodal volumes, divided by the volume.

9.10.5 CHARGE

dVnode voltage across the membrane at each node, drives current in and out of the nodal capacitance

IcNodal current in and out of a nodal capacitance; counts net change in charge per dt

9.10.6 NERNST

Vions function to calculate nodal Nernst potentials for each ion type. = k*log2(conc2)/log2(conc1)

9.10.7 FLUX

The volume of each compartment is divided into voxels defined parametrically at BUILD. The number of each type of interactor may be counted in each voxel, each dt. This allows an accurate monitoring of flux as the change in concentrations from voxel to voxel. Each ion has a serial number, which points to much data about that individual, both Type and Dist info. Ion position tracking can serve to track nano currents and even radio tracer equivalents.

Gradients are continuously available as differentials in density. The distance between nearest neighbors in the inverse of density.

Divergence is always relative to a chosen point position. Points chosen are usually the actor poles. Divergence is done on a Btype basis. The divergence function is also applied to charge fields.

Curl is always relative to a chosen point position. Points chosen are along a suspected ion flux circuit. Curl is applied to Btypes and the charge field.

9.10.8 CURRENT

CurrentEval dimensional charge net charge movement

9.10.9 RC GRID

The RC Grid is a major component of the RUN. It calculates, via modified nodal analysis, the electrical relationships between all nodes. It inputs the nodal capacitance, the nearest neighbor resistances, and the nodal dV.

Propagation Voltage variations at one node translate into differential voltages between neighboring nodes. These differentials translate to horizontal currents between the nodes. These horizontal currents translate to modulators of the neighboring actors.

9.11 FEEDBACK

Model error metrics must be set up so as to improve the model with each run. In high-dimensionality spaces, it is useful to plot topological hill climbing towards desired performance, with the terrain being filled in as it is explored. This can help alert the user to opportunities to change direction towards more fruitful results, and conversely to discontinue paths that are not yielding improvements in performance.

The thorough user will ponder the output error gaps and hypothesize their cause. These can be tested via adjusted parameter sets, serving as subsequent experimental designs.

		Design	Build	Run	Report
1	physical constants				
2	surfaces	TypeC	DistC	reflectB	
3	lipids	TypeC	DistC	capacitance	
4	ions	TypeB	DistB	Coulombs law	position x time
5	receptors	TypeA	DistA	bind/unbind	bind,state x time
6	channels	TypeA	DistA	modcombo	bind,state x time
7	shuttles	TypeA	DistA	indexShuttles	
8	vesicles	TypeA	DistA	bind/unbind	bind,state x time

		Design	Build	Run	Report
9	ligands	TypeB	DistB	ligand setup	position x time
10	pumps	TypeA	DistA	instantiateState	bind,state x time
11	diffusion			watercollisions	
12	drift			Bacc	
13	nernst			calcNernst	
14	affinities	TypeA	DistA	calcAff	
15	bind/dissociate	TypeA	init A	getbind kinetics	
16	configuration state	TypeA	init A	instantiateState	
17	phenostate	TypeA		dophenostate	
18	conductivity	TypeA		calcflux	
19	transport	TypeA		transC, transP	
20	voltage			calcV	voltage x time

TABLE 22: SOFTWARE DESIGN

9.11.1 ARCHIVAL PROCESS

Each experiment is defined a a set of values for :

- Compartment Types
- Particle Types
- Actor Types
- Physical Constants and Scaling Factor
- Compartment Distributions (arrangements of shapes)
- Particle Distributions (concentrations per compartment and binding site)
- Actor Distributions
- Assemblies of the above (structures)
- Connectivity relationships (for signals in and signals out)

The longer is the RUN time, the more valued are the results. Simulations that require weeks to complete are not often repeated. Thus, a proper and thorough capture of results is prudent.

9.12 SOFTWARE ENGINES

This MODEL has Three ENGINES

1. Diffusion and Drift

2. Kinetics and Bindings
3. Electrical Grid, capacitance and resistance

... deemed to be the necessary and sufficient processes for capturing the behavior of neurons with respect to their information processing function

9.12.1.1 Model Aspects

1. Topographic problems of sectioning, transitioning, movement in non-convex shapes

Solution: Employ only point to point distances and point to surface distances, sort by distance threshold

2. Tessellation of arbitrary shapes (whole cell neurons)

Solution: organize by rings and nodes. Tessellate actor to actor, not arbitrarily

3. Handling of physics: force resolution, resistivity in solutes

Solution: Forces are all N-body problems, solved simultaneously. acc = k/(m*(r2-r1)^b); m=mass; b=2; k= force coefficient to units

4. Numeric methods to reduce computational load on particle collisions

Solution: only recalculate those processes at high risk of change. But the detection algorithms are worse than the ballistics.

5. Impulse-based simulation of particle systems

Solution: abandoned due to overhead load

6. Dynamics = motion with mass and forces

Solution: charge systems respond to all forces simultaneously

7. Fluid phenomena

Solution: viscosity at macro scale is collision rate at nano scale

8. Patch I/O:

Solution: Cloning and stitching patches together in an information theoretic manner. Each patch is collapsed to a lookup table. Table values are interpolated between key nodes.

9. Converting morphometric data into model parameters

Solution: Create PDF for each actor, stretched to zone delineations

10. Collision detection:

If hyperbolic orbits are not used, then interference center to center distances detect collisions

11. Collision resolution:

Hyperbolic orbits: result in asymptotic trajectories to the elastic spheres, but require a much finer dt to negotiate.

Elastic spheres: calculate exact time of collision; calculate axis of collision; create basis, calculate momentum transfer, return to original basis.

```
dx = distanceBB(Bpos,BC);  calculates  ||p1-p2||
rr = r1+r2;
if dx < rr,  then collision occurred
```

12. The directrix

Hyperbolas can be used to avoid collision detection algorithms, and thus provide continuity rather than discrete events. However they require much smaller dt steps and therefore consume far more computer resource. It is found that collision detection, though itself computationally costly, is still several orders of magnitude faster than running hyperbolas.

13. Electrical circuit - 5-layer 2-D grid: saline imbalanced membrane imbalanced saline

Solution: found to be unnecessary

14. Random matrix theory: initial velocity, state transitions, temporal releases of particles

Stochastic processes are extensively applied. Each random process is instantiated via a PDF integrated into a CDF, and then a uniform random number selected across the CDF. In most cases, multidimensional probability matrices will be pared down each *dt* to current conditions, yielding a single row vector to use as the PDF.

9.12.2 ENGINE ONE: INTERACTOR DIFFUSION

9.12.2.1 Diffusion is embodied via a 3-dimensional particle system

Particle systems for fluids are easily implemented within cubical containers, as reflections are simply a matter of changing sign on velocities. Positions can be initialized randomly, with uniform distribution. Velocities are randomized spherically, with magnitudes determined by the Boltzmann distribution as a function of temperature and mass. Particles can be attributed (scaled) radii and masses, and accurate valence values. Any number of species of particle can be mixed in. Diffusion will achieve steady state in the absence of active processes. However, irregular shapes quickly increase the computational load.

EM force is implemented with the inverse square law of attraction/repulsion (optionally any exponent). This requires an NxN matrix size to measure the inter-particle distances each dt. For moderate quantities of particles (say 1E6), numerical methods for minimizing computational load are necessary for both forces and collisions.

Point forces, line forces and plate forces are all similar, by merely reducing the dimensionality of the force. Compared to point forces, line forces are 2/3 the computation and plate force is 1/3.

Generally, the motion EQs are:

```
Anew = sum(force/mass);
Vnew = Vold + Anew;
Pnew = Pold + Vnew;
where  A = acceleration,  V = velocity,  and  P = position
```

9.12.2.2 Positions

Initial positions of particles need not be distributed evenly in their respective compartments. They may be deposited as a bullion, and allowed time to dissolve in the water. All that is necessary is that the bullion is placed firmly within the correct compartment. Ligands are often initialized as bound and then released later. Bound

particles are assigned to their positions and their velocities effectively set to zero, and tagged as to which element they are bound to. Generally, any bound particle may remember its former velocity, as the tag indicating it is bound causes a multiplication of any velocity by zero, until unbound. An unbound particle may have a remembered velocity direction that when released drives it right back into the binding site or membrane. Its compartment tag identifies it as trying to escape out of its assigned compartment and causes a reflection.

9.12.2.3 Velocities

Velocities can be modeled easily with the aid of the Boltzmann Cumulative Distribution Functions (CDFs), and spherical instantiations. The result is satisfactory in that it maintains its characteristics over any number of iterations.

Each mass has its own velocity probability curve for a given temperature.

Shown are the velocity probabilities for protons, Na, Cl K, Ca, Protein with M.W = 500.

Boltzmann distributions are used to initialize particles, and to create random collisions with water molecules.

9.12.2.4 Accelerations

Initial accelerations are set to zero. All charged particles exert force on one another. This is the N-body problem. The sum total of all attractive forces minus all repulsive forces determine the net force upon a particle. That force divided by its mass determines its acceleration.

9.12.2.4.1 Particle-Particle Forces

1. EMF
2. Concentration Gradient

9.12.2.4.2 Particle-Actor Forces

1. EM Attraction
2. EM Repulsion

9.12.2.5 Core motion equations

$x(t+1) = x(t) + v(t)*dt$

v(t+1) = v(t) + a(t)*dt
x(t+1) = x(t);
a = F/mass
F = sum(f(P-p)) ; distance often determines strength of a force
adhesion, friction, viscosity, cohesion,
uni-directional force, like gravity
F = k * (m1*m2)./ dp^2 * n, where n = (p2-p1) / |p2-p1|
omni-directional force, like viscosity
F = 0.5*rho*|v|^2 * c * a * n, where n = -v/|v| a = area xsect n = opposite of v
unidirectional force of repulsion or attraction   (springs)
F = -k*p*n = -k * (p2-p1)-length   * (p2-p1) / |p2-p1|
convertion of directed flow into random flow (friction to heat)
F = -k*v *n = -k * (v2*n – v1*n) * (p2-p1) / |p2-p1|
force fields, such as voltage , there are gradients
F = E/length * n, where n imparts directionality of the field
collision laws, algebraic or incremental

IMPACTS
impules = j
j = int(f*dt) = dW   (change in momentum)
v(t+1) = v(t) + (1/m) * (f dt + j)
p(t+1) = p(t) + v(t+1)*dt
v.close = v*n.plane   or v*n.touch
j = -(1+e) * m * v.close * n
Japproach = - Jdeparture
dV = J/m
% dt = dtb+dta;   is divided into 2 intervals (pre-collision and post-collision)
dtb = hitT; % the portion of dt prior to the collision is hitT
dta = dt-dtb; % the portion of dt after the collision is he remainder
the final positions at the end of dt are
P1contact + dta*V1new;
P2contact + dta*V2new;
e = coeficient of restitution = 1 for elastic collisions; =0 for plastic collisions
j = impulse = (e+1)*dV*(m1*m2/(m1+m2);
V1new = V1old - j/m1;   % j is built from dV, which points from v1 to v2
V2new = V2old + j/m2;
V1new = V1old * ((m1 – e * m2) / (m1+m2))   +   V2old * (e+1) * (m2 / (m1+m2));
V2new = V2old * ((m2 – e * m1) / (m1+m2))   +   V1old * (e+1) * (m1 / (m1+m2));
INTEGRATION
to speed things up, the double integration of velocity and position are combined
p(t+1) = p(t) + v(t)*dt + a(t)*dt^2
verlet integration:
x(t+1) = 2*x(t) - x(t-1) + a(t)*dt^2
x(t-1) = x(t)
dot product constraints create joint limits: (x2-x0) dot (x1-x0) < a
area of a triangle
area = 0.5* |(p3-p1) X (p3-p2)|
NORMAL
triangle has a normal
n = (p3-p1) X (p3-p2) / |(p3-p1) X (p3-p2)|
projection of a flow onto a triangle
area.projection = area * (v dot n) / |v|
When a particle is destroyed, the last particle in the list is copied into its place
(cost: 1 integer decrement & 1 particle copy)
Creation rules apply to ll instantiations
system momentum = sum(m* |v|)
center of mas of the system = weighted su m = mass*position

velocity of the center of mass, for moving bodies
angular velocity about the center of mass for rigid bodies
dw/dt = sum(F(p(i))
moments = position * momentum
torque = radius * perp(force)

9.12.2.6 Particle-Membrane Forces

EM Charge-Imbalance across membrane

Of all of these, the Concentration Gradient is an emergent phenomenon from collisions, and needs no further analysis. It is calibrated to reality via the mean free path and mechanical mobility.

All of the EM forces require computational evaluation. The general scaling factor for this force must be calibrated to reality as a ratio to electrical mobility.

9.12.2.7 Solvents

Charged particles in a container with a point or line force produce orbiting particles. As this is not at all realistic to bio-cells, the presence of water is essential. Water as a solvent produces a collision about every 10 angstroms. More accurately, each mass at a given temperature has a mean free path. This implies that within each dt, a random portion k of the particles will have collided with water. When they do they will emerge with an aggregate conservation of momentum, temperature and Boltzmann distribution of velocities.

9.12.2.8 Particle-Particle Collisions

Given that cytosol consists of ions of many velocities, 5 different radii and masses, the computational load of collision detection is significant.

Analysis of a two body collision, conserving momentum. Note that even when the exact trajectories is known, that doesn't tell you anything about the reflected velocity vectors after impact. Only after the exact point of contact is determined can they be known.

An impulse of energy is transferred between the particles along the axis of collision. Temperature is conserved when momentum is conserved. Thus any absorption or other loss of momenta will result in model “cooling” of the particle system.

9.12.2.9 Particle-Container Collisions

Particle-Container collisions are straight-forward and of relatively low computational cost. They occur proportional to surface area, rather than to volume. And they do not require a basis creation and change, only a reflected angle calculation off the surface normal.

9.12.2.10 Particle-Actor Collisions

Certain types of Particle-Actor collisions are managed by the affinity function. This is because they must usually be accelerated towards the actor to simulate a realistic reaction rate. They frequently bind to allosteric sites according to forward reaction rates, and unbind according to backward reaction rates. All particle types not on the binding profile of the actor causes all collisions to be treated as though the actor is not there, and a mere Particle-Container collisions is executed.

9.12.2.11 Diffusion SubModel

The Interactors experience movement according to the sum of impinging forces on each and thermal Brownian motion. A diffusion model is inherently a spatial model, and must address hundreds or thousands of moving particles individually. Critical is the arrival times of diffusing molecules (Interactors) to the Actors' binding sites or channels. Interactor impinging forces include: thermal, voltage gradients, concentration gradients, charge attraction, viscosity and energy barriers.

Concentrations must be measured per voxel, as altered by ion and ligand flux. The ion concentrations, are determinant of partial voltages on a per species basis, transmembrane voltage, and of course create concentration gradients that drive flux.

DIFFUSION MODEL: Receives its INIT inputs from the DESIGN data, It receives its IITERATIVE inputs from the KOLMOGOROV Model, which processes the stochastics. The diffusion model is a physical model that can easily accommodate and interpret the typical molecular events quantified in the physiologic literature.

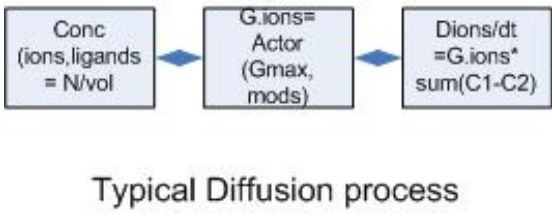


FIGURE 104: TYPICAL DIFFUSION PROCESS MODEL

9.12.3 ENGINE TWO: ACTOR KINETICS

Kinetics is embodied via a Kolmogorov/Chapman/Colquhoun conformation transition probabilities for actors

Actors have multiple conformational states ... which implies they have memory. However they have no memory beyond their current state, and therefore qualify as Markov processes.

9.12.3.1 Actor Kinetic Schemes

Each protein molecule is capable of numerous conformers. Given its environmental parameters, each state has a numeric probability of occurring. In conditions of conformer changes slow enough to detect each transition, it is then possible to calculate state change as a function of the current state (conditional probabilities). In very fast changing conformers, the probabilities can only be calculated irrespective of the previous state. Generally actors change states faster than can be measured, and thus we use memory-less probabilities (unconditional probabilities). This is admittedly the weaker representation. However, large numbers of actors in aggregate average out, in both space and time (ergodic), to perform quite reliably and predictably, true to the natural processes they represent.

Each kinetic process requires a forward rate and a backward rate. In complex chemical networks, the words "forward" and "backward" lose their meaning, so I reference them to the products themselves. Given conformers A,B,C, there are rate constants AB,BA,AC,CA,BC,CB. If X = [A B C], then all rate constants can be captured in an X x X matrix, with the diagonal being the "rate" at which the product remains the same.

9.12.3.2 Binding/Unbinding

The kinetics of binding and unbinding are stochastic, the net result of forward and backward chemical reactions. The forward reaction depends upon ligand or ion availability, which is directly related to collisions. For modeling purposes, a proximal ratio is necessary to determine "availability". This is especially necessary when one model particle represents some multiple of biological molecules. A single particle representing 10,000 biologics cannot possibly experience a realistic collision rate.

9.12.3.3 G-Protein / Second Messengers systems

Second messenger systems provide leverage between a ligand binding and the number of ion channels opened/closed as a result. The biological process is a two-step combination of releases for about 15 G-proteins along the membrane inner surface (2-dimensional diffusion) gliding along the negatively charged "heads" of the fatty acids until these bind with a Cyclades. This, in turn , stimulates the enzymatic production of phosphates which diffuse in 3-d until they bind to ion channels in the neighborhood (and other targets as well). Unless the intermediate Cyclades step is modulatable by other means, the overall effect of this system is to leverage a single extracellular ligand binding into the modulation of thousands of nearby ion channels via their intracellular phosphorylation sites. The effect is activated and disengaged for an amount of time quite closely following the amount of time that the ligand remains bound to the receptor. However, there is a lag of about 1E-1 s.

9.12.3.4 Pumps

A library of Ion Pump types is maintained. Ion pumps are indispensable in many modeling queries. Firstly, they determine what the steady state is regarding tonicities. Therefore they determine the resting potential. One definition of clinical death is the cessation of ion pump activity, so critical is their contribution.

Secondly, pumps are logical devices, whenever they co-transport. Rather than merely pump one or another ion to desired levels, they force ratio-based movements, more apt to preserve the ratio between species of ion than set the absolute concentrations. Further complexity arises by the interplay of various types of pumps, each with its own idiosyncratic ratio. Tonicities can be shifted to different concentration profiles by re-weighting pump type activities. This can play a role in shifting the functional role of the cell across several "moods", by altering tonicities along viable paths to modulate the Q-matrices of ion channels (and other actors).

Thirdly, pumps fatigue, presumably due to energy shortages. This effect is certainly relevant to neuron behavior. Pump fatigue can be simulated by giving them receptors which modulate pumping rate, and may become starved for ligand. Thus ligand concentration controls pump rate. If modulators alter or switch pumping curves, then ligands can alter the steady state conditions as well.

Fourthly, pump distribution can set up significant effects for information processing. A cluster of ion pumps at one end sets up an ion current down the entire length of a process. Such currents are instrumental in motion detection for example.

9.12.3.5 Stochastic Kolmogorov SubModel

The actors are stationary but the most dynamic component of the neuron. While the membrane is a passive stable lipid, the Actors embedded in that membrane are all proteins. The thermal noise and other forces which impinge on them, have the effect of changing their shape (over various conformers) in random ways (due to collisions and charge effects). Each transition between conformers can be treated as a kinetic transition, with both forward and backward transition rates. It is found that these rates are not constants (as the old name "rate constant" would suggest). Instead they are often modulatable. Modulation of rate coefficients (chemical kinetics familiar as alpha and beta values), is best handled by Kolmogorov stochastic partial differential equations. These can be solved as a single system of simultaneous EQs. Computationally this involves the inversion of a single matrix per individual actor.

KOLMOGOROV model: Receives its inputs from 2 sources: the environment, via concentrations of modulating ligands and ions; and from the ITERATION with the RC_GRID model provides some outputs that also are modulating the stochastic processes. The STOCHASTIC processes are intrinsic to the Actors. The DESIGN data contains Q matrices, which LOAD into the Kolmogorov model as state transition rate coefficients. These serve as stochastic engines which respond to a variety of modulatory signals (both external and internal).

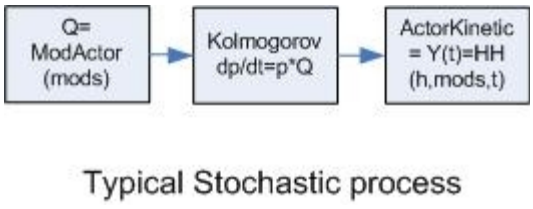


FIGURE 105: TYPICAL STOCHASTIC PROCESS

9.12.4 ENGINE THREE: MEMBRANE R-C ELECTRICAL GRID

9.12.4.1 Capacitance

Capacitance is essential to simulate an action potential in neurons. The physics says F= q1q2/r^2 for EM force, with a dielectric barrier holding apart dissimilar charges, and voltage applied via ion pumps. Capacitance absorbs the charge imbalances resulting from selective channel transport driven by Nernst potentials. Without such absorption, ions would be pushing against a very hard resistance to charge imbalance in 3-space. In modeling, getting the capacitance to the right value is critical. Fortunately, particle systems automatically "charge" membranes exactly to the amount of charge imbalance. How long they take to do this is sensitive to dt, so some compensation might be necessary to yield results that mimic continuous charging time of bio-systems.

9.12.4.2 Saline Resistance

Copper wire and carbon blocks are very predictable in their resistivity, but saline is does not produce a resistance linear with respect to distance. As ion channels are effectively point sources and sinks, with extremely small "cross-sectional area" of conductance, the lines of current tend to balloon out from the source point into the open liquid space, then shrink back to a sink point at one or more neighboring channel, resistance does not vary much with distance. Most of the resistance is concentrated at the point source and point sink. Is there empirical data on this curve, or a theoretically sound formula?

Furthermore, such point-to-point conduction is quite intermittent and rare. For most spikes, which are themselves brief and sparse, it is point to membrane capacitance. So most of the time it is capacitor to capacitor charge leveling, and ionic flux horizontal leveling. The point to capacitive surface flows present a large planar sink with a cross-

sectional area hundreds or thousands times larger than than the ion channel source (a cone of resistance). The dominant argument to saline resistance is tonicity. Conductance is proportional to the charge density. Tonicity is merely the summation of the several ion concentrations.

Convert the above to useful EQs

Divalent ions are handled thusly: [ ] in calculating point to point resistance in a liquid.

9.12.4.3 RC Grid SubModel

The net result of charged Interactor movements is electrical current. Charged particles in 3-D space are not limited to unidirectional movement as might be the electrons in a copper wire. Furthermore, rather than one species of electron, we must track many species of charge carriers, measure the net particle flux parallel to directions of interest and multiply particle quantities by their respective valances. Non-parallel flux may also have effect upon model behavior, so we track all 3 dimensions via voxel to voxel movements. For convenience, currents through the membrane are referred to as “vertical” and movements parallel to the membrane are referred to as “horizontal”.

An RC Grid model calculates, via linear algebra, the stored charges, horizontal and vertical currents, and voltages across the membrane at each node of the mesh circuit. This mesh circuit approximates a low pass RC ladder filter in 2-D. The mesh is derived employing the general strategies of the Finite Element Method (FEM) As common solid state electrical circuits consist of the quintessential finite elements, its worth considering what is implied by imposing FEM upon biologic membranes. While the membrane is a continuous surface at any higher perspective than molecular, the ion channels and pumps act as nodes. The extracellular and intracellular fluids between nodes serve as edges. FEM provides a uniform strategy for divvying up the membrane into capacitive areas and interpreting 3-D saline into discrete resistors.

The pumps are current sources and the ion channels are variable resistors. An additional challenge is to accommodate the many species of charge carriers. The circuit is actually multiplied by the number of types of ion species, and each of them must be calculated each dt. Then they are summed via the GHK voltage equation to yield a net voltage per node.

The net voltage per node will determine the number of charges to enter into membrane capacitance, and that capacitance, in turn has a significant impact upon the free charges remaining. Those free charges determine partial voltages via the Nernst equation.

RC GRID Model: Receives its inputs from the DIFFUSION model. Metrics are applied to the physical behavior of molecules to derive electrical values. For example all the ion fluxes can be collapsed into a net current across the membrane; and the various charged particles held tight to the membrane by EM fields from the other side collapse into a single q value. Furthermore, the incidental locations of the actors can be used to calculate nodal capacitance and resistances to nearest neighbors.

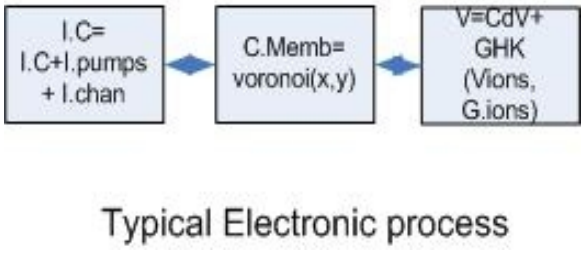


FIGURE 106: TYPICAL ELECTRONIC PROCESS

9.12.5 SUBMODELS IN FEEDBACK LOOPS

The electronic loop passes through membrane voltage which then modulates the Actor states. The Kolmogorov states determine the conductance values for fluxes in the diffusion model. Such fluxes translate to current, voltages, and capacitive charge in the RC grid. And the RC grid generates the voltages which modify Kolmogorov protein states.

The mass transport loop is slower because it relies upon diffusion in the various compartments to alter concentrations. Changing concentrations alter the Nernst Voltages, which in turn alter the flux through ion channels.

The two feedback loops interact with each other multiplication, via ohm's law.

The LOOP: Kolmogorov model generates Conductance values (G) for each of the Actors in the diffusion model. The DIFFUSION model generates flux values for the various ions at various locations. These fluxes are translated

into currents via the nodes within the RC GRID model, and therefore for each of the nodes in the RC grid model. As the kinetic states cannot change instantly, but instead exhibit characteristic time courses, they have the peculiar effect of giving the system a "pseudo inertia". Such a phenomenon allows for the possibility of oscillations, which would not be possible in a strictly first order system.

Note that each neuron is a closed surface. There are no ports for current or voltage inputs. There are no current or voltage outputs. There are only chemical modulator inputs (as concentration values), whose only effects are to alter Kolmogorov states in the actors. These in turn alter only conductance values. Thus each neuron is an information processing system that is driven by clusters of potentiometer settings!

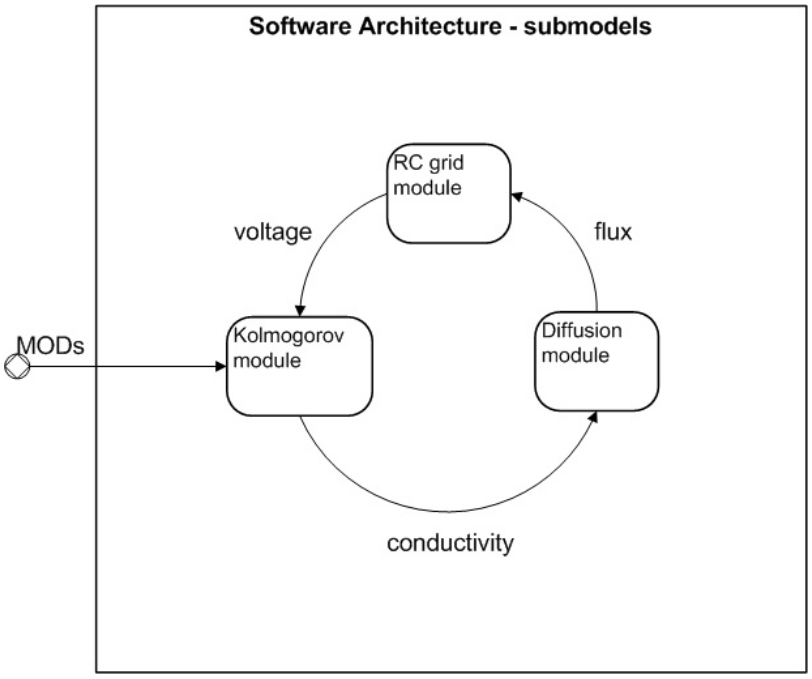


FIGURE 107: SOFTWARE ARCHITECTURE SUBMODELS

Architecture Diagram for the main three Modules, noting that the sole input to the system is via the external modulators arriving via diffusion, and acting so as to chemically bind to actors, and thereby modifying the Kolmogorov transition coefficients of those actors.

9.12.5.1 SubModel Functions

From Figures above, we can conclude that the software should be partitioned accordingly:

SW org	Design	Build	Run	Report
	TypePhysic			
RC Grid	TypeComp	DistC	RCgrid_engine	v,i Plots
	TypeMemb			
Stochastics	TypeRecep TypeChan TypeShuttle TypeVes TypePump	DistRecep DistChan DistShuttle DistVes DistPump	State_engine	State reports
Diffusion	TypeIon TypeIon2 TypeLigand	DistB	Dif_engine	Movie

TABLE 23: SOFTWARE MODULES

As the project developed, it was found that particle drift attended to matters of capacitance and current without programming. It was further discovered that the ions do not pass through saline resistance volumes but rather go immediately to the membrane capacitance and travel (make current) by pushing along the membrane. This made the calculations of resistance through saline irrelevant. The channel conductances remained as specialized functions driven by Nernst EQ partial voltages. The pumps are not calculated *per se*, but rather run their kinetics and in the process transport ions via binding and unbinding. All of these conspire to eliminate the RC Grid engine.

Meanwhile, the Kolmogorov kinetics was necessarily split into 2 separate engines, one for the internal state changes, and the other for the external events of bindings and unbindings. The latter was adapted to modulate the internal kinetics, and was augmented to handle voltage modulation.

Follows is the second version of the Software Architect SubModels.

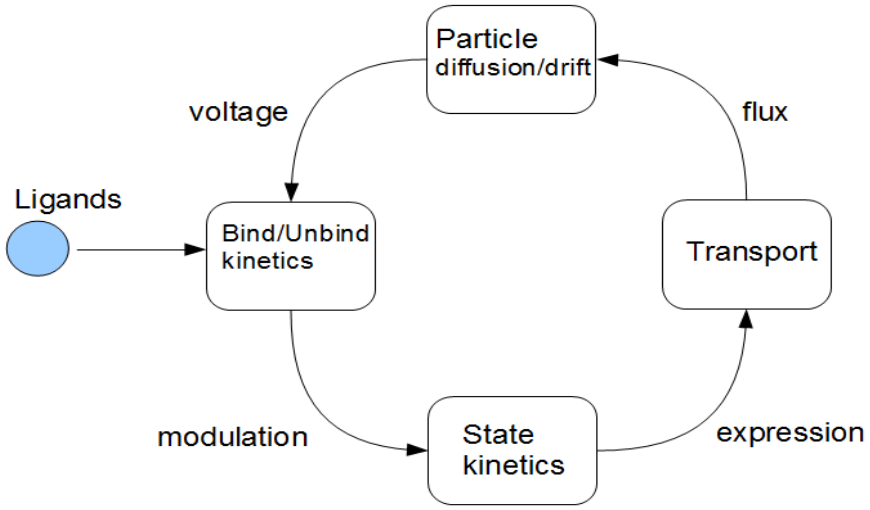


FIGURE 108: SOFTWARE ARCHITECTURE FOUR SUBMODELS

The settled schematic for a NIP model serving actor kinetics and particle dynamics is:

9.13 REPORT

Membrane	shall be represented by an arbitrary axis line, the (variable) radius of a cylinder, and the scaling factors from neuronal proportions to computational and presentational practicalities of screen size. A continuous line, triangular mesh grid, or solid rendering are acceptable.
Interactors	shall be represented by color coded dots which move per their velocity values.
Actors	shall be represented by iconic shapes and colors that distinguish each type, with a size just large enough to easily distinguish.
Concs	are implied, but are also counted nodally and recorded for analysis.

Voltages and currents are represented in separate plots. A color dot at each node would optionally help to visualize voltage activities. With the prismatic color spectrum keyed as: black brown red orange yellow green blue purple for min to max voltages.

RUNS shall be stored in such a way that multiple run results can be superimposed as families of curves for parametric sweeps or other variations in input pattern.

9.13.1 NEURONAL EVENTS SIMULATED

Follows is a list of the specific series of events that are instrumental in the passage of one pulse of information along the length of a neuron. It is not the only possible path and sequence, but will serve as a canon for design.

1. ions concs initialized to steady state concs in each compartment (tonicity profile)
2. ion diffusion in water, in each compartment – with charge, acceleration and collisions
3. actor affinity profiles activated, for ligands and other modulators (e.g. voltage)
4. actor state change, per dt
5. actor binding changes, per dt
6. ligands concs initialized to steady-state concs in each compartment (modulation "rest" profile)
7. ligands are released into synaptic clefts per input signals from pre-synaptic cells (signal)
8. ligands diffuse in water, in each compartment (3-d diffusion)
9. ligand bindings to receptors, kinetics as func of concs and Q-modes
10. actor Q-matrix modality changes mode per modulator combo
11. actor state changes, per dt
12. actor phenostate = gating function, transport function, messenger release, vesicle release
13. ligand unbindings from actors kinetically per concs
14. ligand "reuptake" pumps restore ligands to original positions, kinetically, per concs
15. receptors release second messengers upon ligand bindings (1:5 ... 1:20 leverage ratio)
16. second messengers migrate along membrane (2-d diffusion)
17. second messengers bind to cyclases kinetically, as a func of concs
18. cyclases enzymatically produce tertiary messenger (phosphate rate = by the hundreds /msec)
19. tertiary messengers diffuse in water (3-d diffusion)
20. tertiary messengers may bind to ion channels (e.g. phosphorylation) kinetically per concs
21. modulation combos (including voltage) > Q-matrix modality change, Ion Channels
22. instantaneous conductivity of ion channel G = channel gating function * conductivity profile
23. Nernst potential + concentration potential drive flux: $I = (E+C)*G$
24. ion affinities to ion channels vary with gating function
25. ions transported through channels per I
26. ions released and diffuse out of ion channels

27. change in local ion concs (and by implication, change in local charge density)
28. change in Nernst voltages
29. change in Vm as weighted sum of Nernst voltages; and as Coulomb's Law
30. dV > change in capacitance charge > current in and out of capacitance I = C*dV/dt
31. saline resistances between voxels result in ion currents: I12 = (V2-V1)*(1/R12)
32. horz flux changes Nernst voltages and capacitance charges laterally, radially
33. vesicles bind Ca++ as a modulator, kinetically, per conc
34. vesicles change state per mods
35. vesicles release ligands kinetically into synaptic cleft
36. vesicles reset their state (recycling sequence)
37. pump affinity1 profiles, per mode
38. pump bind1 staging, kinetically
39. pump bind1 state alters Q-mode, also mods and concs may alter Q-mode
40. pump state change kinetically, may transport across membrane (forward) or unbind (backward)
41. pump offload at side2 after transport
42. pump affinity2 profiles, per mode
43. pump bind2 staging, kinetically
44. pump bind2 state alters Q-mode, also mods and concs may alter Q-mode
45. pump state change kinetically, may transport across membrane (forward) or unbind (backward)
46. pump offloads side2 after transport

9.13.2 IONS

Pos	[x y z]
Vel	[dx dy dz] velocities are necessary for carry forward inertia
Acc	[ddx ddy ddz] acceleration provides only a convenient place for force calculations, discarded each dt
Assign	assignment to compartment or to [actor# pol#]
VelStop	{0 or 1} multiplier on velocity for { bound free }

From pos alone it can be known:

1. which compartment a particular particle is in.
2. concentrations, both nodal and compartmental
3. Nernst potentials
4. horizontal net flux, and horizontal net current since last dt

9.13.3 LIGANDS

Pos	[x y z]
Vel	[dx dy dz] velocities are necessary for carry forward inertia
Acc	[ddx ddy ddz] acceleration provides only a convenient place for force calculations, discarded each dt
Assign	assignment to compartment or to [actor# pol#]
VelStop	{0 or 1} multiplier on velocity for { bound free }

(same as ions, sans charge field)

9.13.4 RECEP

input signal	is recorded on psuedo receptor, as function of messenger local concentration
bind combo	modulator bindings are recorded each dt
state	state instantiation is recorded each dt
release	particles released are recorded each dt

Track which receptors received inputs, and which did not. (distribution). Track delays between inputs and outputs to receptors. Note std deviation.

9.13.5 PUMP

Pumps modify conc ratios across the membrane on a per node basis. Only a portion of all nodes have pumps, depending upon PDFs. No two pumps can occupy the same node. Particles are released from pumps with small "upward" (away from membrane), random spray angle velocities. This is adjusted to approx. match the inertial effects of channel efflux and pump rejection at the release points. Optionally, particles could wait for collisions to dislodged them. However the real collisions rates are so many orders of magnitude higher than the modeling rates that for practical purposes they are best "launched".

Energy spent on running pumps is expressed as kinetics. ATP may be bound, and ADP unbound, but the actual energetic value is only implied by the effects such binding have upon the probabilities of state change. There is an ATP cycle, consisting of ATP bound, ADP unbound, ADP pump retrieved, Adt converted to ATP for release. The count of particles through this cycle is a reasonable accounting of energy consumed to drive the system.

Setup: Note difference between the concs with pumps off, and then running until steady state is acheived.

9.13.6 CHAN

on flux thru chan	vertical flux and vertical currents are recorded
	chan activity patterns and correlates
open dwell histogram	closed dwell histogram

9.13.7 VES

output signal

How much neurotransmitter does it cost the cell to operate a communications line?

What are the patterns? Noise? Reliability? Repeatability? Information carrying capacity?

NOTE modulators are released from Vesicles. They do not spontaneously appear. Good practice would be to define an attractor to return the ligand back to the vesicle, in an amount of time proportional to the biologic process of re-uptake.

9.13.8 DIFFUSION

lateral flux	Detect net lateral movement of charge, above and below membrane
grad	Differential of systemic charge
div	Must choose points of interest as foci
curl	Must choose points of interest as foci
Vertical flux	Net current across membrane per dt

Do they affect propagation? How to they change thresholds? How do they filter information?

9.13.9 DWELL TIMES

open dwell histograms	Unitary chan recordings vs aggregate recordings
closed dwell histograms	Compliment to open
Steady state probabilities	Finds eigenvalues

9.13.10 PLOT ROUTINES

Plots shall be 3-D whenever 3-D data is available.

2-D data shall be plotted as 3-D with all z values = 0, so that both 3-D and 2-D data can be plotted on the same frame.

9.13.10.1 Computer graphics considerations

Computer graphics consideration include envelopes, collisions, reflections, adhesions, transports and state changes.

Geometry of motion: triple coordinate systems are maintained:

1. XYZ (Cuboidal) for ballistics
2. ARX (Cylindrical) for reflections of particles off container walls
3. AAR (Spherical) for particle distances and collisions
4. AAR (Hemi-spherical) for attractions to actor bind sites; also useful in collision detection

Contour of revolution is represented as meridians and circles of latitude (ribs ad rims, respectively)

Determinant of basis: if positive then right-handed and outside; if negative, then left-handed and inside (Isomorphism = orientation preserving).

The Simplices are: point, seg, triangle, and tetrahedron. However, the triangle and tetrahedron have largely been abandoned, except when working with nearest neighbors amongst the actors. The essence of continuity is to not divide up the space, as the finite element method does.

9.13.11 POSTING USER SPECIFIED TRACES AND VALUES

The plots shall provide screen locations for posting certain variables and certain traces during a run.

Often an experimental design will be seeking to watch closely a particular variable, e.g. K current. A menu of all generated variables shall be made available from which to choose up to 20 simultaneous traces, each color coded uniquely.

The user may set threshold levels for any variable. If that variable crosses the set threshold any time during a RUN, then event markers shall be provided to clearly announce those facts, which are persistent after the run is complete.

9.13.12 RUN TIME METRICS

The program shall incorporate a CPU-timer that measures run time in seconds, and reports such values immediately after each run.

Run time can be limited by assigning a value in seconds to toc_max prior to the RUN. If CPU time exceeds this setting, control is returned to the keyboard. If the execution of the program was in a for loop, then the index value (how many times through the loop) will be preserved.

An abort command keyboard control key sequence shall be defined such that the user may choose to abort overly-long runs. Such abort kills program processes and returns control to the keyboard.

9.14 INFORMATION THEORY METRICS

Information theory is relevant to the overall mission of modeling information flow and processing in a cell. First, how much information is being received? Second, how much of the input information is loss along the length of the cell? Third, how is this information altered or transformed? Fourth, what new information is being generated? Fifth, how much of this generated information is lost along the length of the cell? Sixth, how do the received information and the generated information interact and merge? Seventh, what is the mutual information between the input and output? Eighth, how is the output information significant to the organism? There are also geometric issues of interest. How is channel capacity affected by fan-in and fan-out architectures? How much antidromic information flow is there, and under what conditions? Are there regenerative cycles of information within certain cell types? How are the multitude of inputs at the thousands of synapses merged into a single output signal? Is such a merge constitute a loss of information?

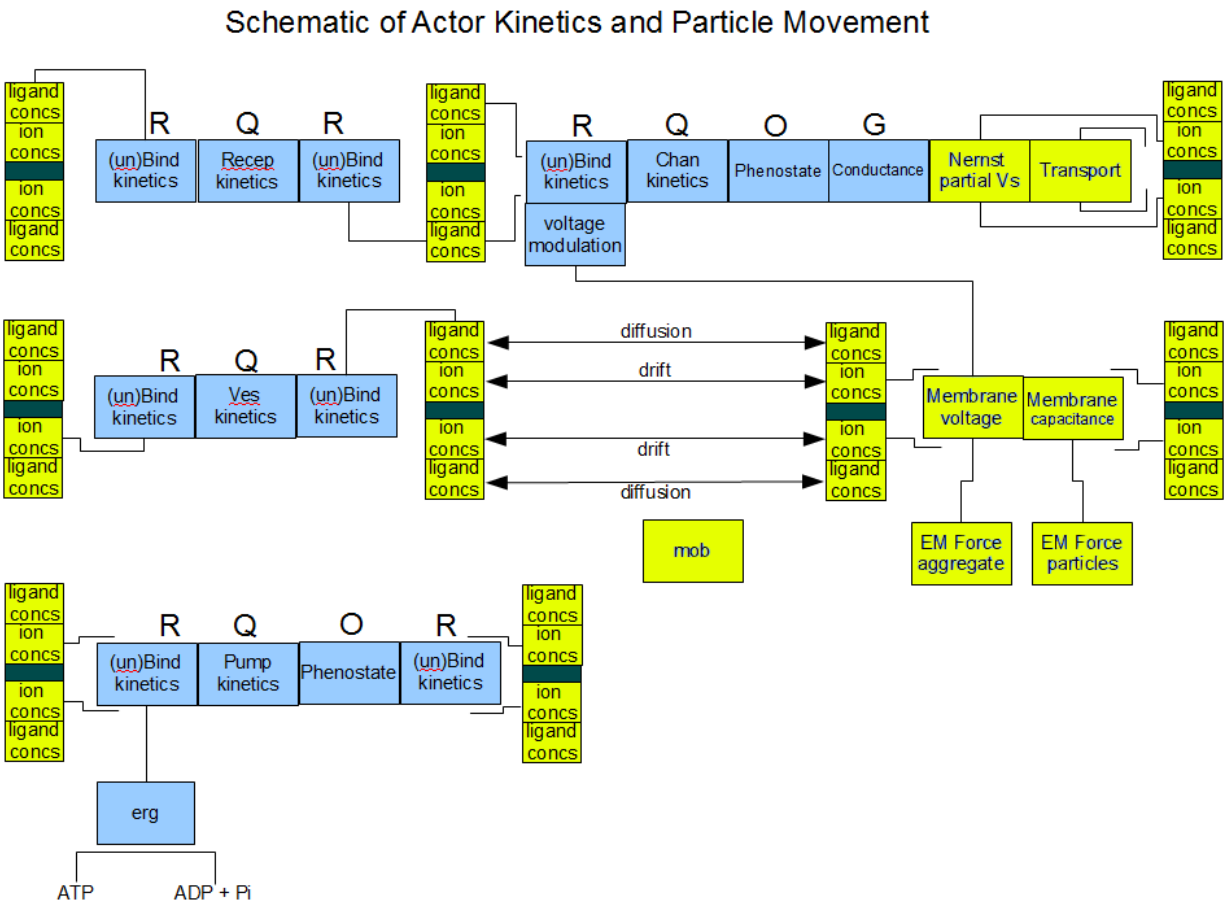


FIGURE 109: Matrices and Information Flow for Actor Processes

Blue = stochastic processes. Green = particle system.

9.14.1 CONVOLUTIONAL CODES

A convolution code converts the entire input pattern, regardless of size, into a single output "word". The effects of convolutional coding is not compression *per se*, but rather to transform inputs with high error rates into rather consistent outputs. They correct errors by realigning to canonical patterns. Convolutional codes are additive as many can be merged into one. Markov processes are noisy but powerful in their ability to recognize and generate patterns. The input data arrives as a wave of particles washing over the actors. The actors convolve with the particle wave to alter that wave. This process eventually ends up as one of the patterns which the actors are capable of generating, regardless of whether the input pattern matched it or not. Thus the convolution serves to sort inputs into "recognizable" types. Outputs may be yes or no (pulse or no pulse); but also may be firing patterns or graded patterns. Because of the active processes of the actors, the original input signal is transformed into a standard "word". It will take a discovery process to determine how many words a neuron is capable of. We may think of these words as modalities (firing patterns like burstiness, rhythmic, or chaotic). Variations in actor plaiding must result in altered "word" patterns, or at least alter the thresholds above which a pattern is transmitted.

Convolution processes are strongly implied by the physical relationship between the statically positioned actors and the dynamically flowing interactors. A wave of particles passes over and under the actors, and the actors respond by altering the particle flows. An incoming wave is altered by the actors into an outgoing wave, a product of actor types and positions. This is the physical embodiment of the very essence of a convolution. In fact it is a double convolution, as there are 2 output streams: the particles are continuously altered; and the actor states are continuously altered.

It is not necessary to employ analytic techniques to resolve this effect. The model instantiates it as an emergent property.

9.14.2 LOGIC

Operators: AND, OR, NOR, NAND, XOR, ALL, ANY, CUM, DIF, EXP, ABS, EuclidDistance, CityDistance are in common use within the Computational Theory community. Alan Turing demonstrated that NAND gates could be wired to emulate all the others, and so they are often chosen to serve as the general processor. Indeed, if a rigorous

model can perform just the first 5 of these, then the computational potential of synthetic neurons will have been firmly established thereby. Such conventional logic serves as system performance tests, to determine the operators that the membranal system can execute. Within the model however, the prevalent logic concerns conditions. IF certain conditions exist at this moment, THEN certain actions will follow. This is a result of the modality of complex systems, and the discretization of chemical systems. In an analog world these modalities emerge from the continua of space, time and nonlinear relationships between the elements. In digital models, hyperbolic orbits are simplified into conditional events. Admittedly, the analog representations are the more accurate and true to that which is being simulated. Logic is therefore a rather weak substitute prone to introducing "round off" error. Meanwhile, continuous functions can approximate digital events like step functions via higher order polynomials, to arbitrary accuracy.

Logic does however, have a strong function to play in computation. The distinguishing feature between a calculator and a computer, in modern parlance, is logical flow control ... specifically, conditional switching within the program algorithms. These are the IF THEN statements, the DO loops, FOR loops, WHILE loops, and SWITCH CASES. All are forms of flow control, and all imply switching. There is a strong implication of this sort of functioning going on in the nervous system, but not yet established at the molecular level. To receive 2 million channels of visual information via the pair of optic nerves, and use that information to decide what to do next, requires some form of switching between optional behaviors. The common drawings in neurophysiology texts may lead the reader to think that most neurons have many inputs but only one output. This suggests no switching is going on, only filtering. If there were neuron types with 2 distinct axons, and these 2 did not both fire at once, but rather in either independent or complimentary fashion, then that arrangement would imply switching within the neuron, and implicate the ion channels in the execution thereof.

However, the absence of independent multiple axons does not rule out flow control by the neuron. There is a commonly encountered phenomenon in neural nets called "winner takes all". This has many analogies, from radio tuning in stations to lottery winners selected from a box of flying ping pong balls. In neural nets it is a result of nonlinear inhibitory surrounds. Overlapping competitive signals will always have some one strongest signal, which by virtue of the strongest inhibitory surround squelches out all lesser signals, delivering forward only the one strongest signal. This is definitely a form of switching, and a particularly useful one. It allows competing options to be developed, and then a decision made to go with the peak performer of these options. That is management

decision-making in its essence. The dendritic tree is appropriately structured for such kind of functioning. The asynchronous refractory periods are prone to patterned responses due to channel densities and conduction velocity. Might branches of the arbor be competing to “win” for their pattern, thus excluding that others vying for that position? If so, then how can such a pattern “feed back” antidromically to let the system know of a successful pattern? Can the refractory period be read as “holes”, as is done in the solid state devices?

The pursuit of logic within the workings of NIP must await the growth of this model through stages of justification and verification. Then a build out of a library of phenomena at the molecular level of significance to NIP. Once the subcellular mechanisms are established ans successfully built up into whole cell performance, then it is time to look for the opportunities to effect logical flow control along the course of the membrane.

It may be hypothesized that modulation may serve to control the flow of information via shutting off one actor group while turning on another actor group. Another possibility is that modulating a group one way elicits one output pattern when stimulated, and modulating differently the same actor group may elicit a different output pattern to the same stimulus. That also would constitute flow control if the difference in pattern was significant in its downstream effects.

Logical function may be pursued methodically running whole cell models, and upon patches large enough for multiple actor types to influence each other via modulation. The reason this matter must be contemplate is that actors cannot be designed so as to disallow any of these potential phenomena. That would cripple the model's predictive abilities from the onset.

9.15 METHOD SIMPLIFICATION

9.15.1 TESSELLATION

Capacitance is distributed according to known spacing between ion transporters (channels and pumps)

9.15.2 TIME SCALE, FACTORS

There are numerous time scales in play. Pure voltage effects travel at the speed of light. Ionic collisions and protein conformational changes occur on about the nanosecond scale. The events most relevant to the action potential transpire on about the millisecond scale. The non stationarity of learning and adaptation occur in seconds to weeks. It is prudent to collapse all the nanosecond phenomena down to mean values, and to ignore the long term (>= 1 s) phenomena all together, within any run. Despite these 2 simplifications, the mechanics of getting the 3 sub-models of diffusion, kinetics and electronics to achieve both optimization and cooperation, remains a tedious undertaking.

9.15.3 SPATIAL SAMPLING

Regarding the larger scale phenomena, such as the bifurcation of a propagating wave, it is possible to "pre-calculate" the behavior of the variety of voxels along the routes. Once calculated for a given parametric set, they can be stored in a lookup table, for efficient computation of large scale behavior. Care must be taken to not "assume" across any gaps of uncertain nodal behavior, and it is algorithmically tractable to leave certain "uncharacterized" nodes in full computational mode while having most others in collapsed "lookup" mode, both types in a single run. It is the very nature of manifolds that the calculation of the relationships to nearest neighbors is sufficient to fully characterize a node's range of response. However, it is a challenge to the modeler to avoid over simplifying these results so as to thwart the emergent behavior of the membranal system that is ultimately being sought. In similar fashion, both over simplification and any distortions of ill-chosen simplifications can give rise to emergent behavior that has no counterpart in biologic systems. Perhaps this is junk,; perhaps it is a novel and useful pattern of behavior. By "emergent" is meant any instantiation of the domain of neuronal information processing capacities. Special interest goes to those not yet discovered. And it thus behooves us to build models that do not preclude the expression of such - a creative challenge indeed.

9.15.4 TEMPORAL REPRESENTATIONS

There are a number of straight forward numerical methods to adjust dt dynamically to the rates of change of the second, third, fourth and even fifth order of an EQ. However, such efficiency guarantees temporal misalignment to other threads in any parallel processing scheme. Thus binary time scales are enforced, such that for a necessary

detail to maintain accuracy, dt may be halved, quartered etc., but not float continuously. Thus ensuring synchronicity when this process returns to the fold, without the need for an additional step of interpolation.

9.15.5 NORMALIZING THE BIO-DATA

For purposes of creating a coherent and representative model, normalization of the available bio-data is critical. There are many factors that distort measured data from the actual *in vivo* performance of cellular components. Electron micrographs dehydrate the sample and so distort the extracellular space (to smaller than actual). This in turn may cause us to mis-calculate extracellular volume and resistances. Tissue excised for purposes of inserting micro-electrodes and patch clamps distort the electrical relationships between the cells and may trigger any number of mode changes in proteins, both outside and inside the cell.

In non-linear systems, such distortions are not easily predicted, not easily understood, and not easily compensated for. It is therefore valuable to develop multiple sources, multiple experiments and multiple analyses. All of these should be allowed to form consensus, vectoring towards the likely “truth” of the matter. Iterations help discover the variance and robustness of the phenomenon. Modeling a sweep over the suspected parametric range may help to identify a stable “middle”, which in turn may be the bio-configuration.

9.15.6 ABSENCE OF DEVELOPMENT AND PLASTICITY

The process by which a channel naturally arrives in the membrane is complex and individualized (all channels do not appear in the membrane at the same time and in the same state). So to do that in a simulation is to create an artifact of synchrony. Although natural development processes are not being modeled here, some of the artifact of false development can be avoided by taking the step to distribute the states of all actors of a type across their PDF. This preserves the ergodic quality of both spatial and temporal distribution.

9.15.7 THE LIMITS OF PARSIMONY

A system of simple elastic collisions does not require Avogadro's number of ions to accurately predicting the behavior of the aggregate. Therefore the number of particles can be scaled down. Chi-square test for levels of

confidence with respect to degrees of freedom shall be employed to determine the limit of such down-scaling. Similarly, the huge complexity of protein conformations comprising a modulated ion channel can be substantially reduced to a small number (about 10) which predict channel openings within the set level of confidence. Complex heterogeneous ion channel distribution patterns might also be simplified without loss of veracity, but the determination of to what degree of down scaling is permissible must be determined empirically via sensitivity runs. Of course, when large numbers of each type of involved ion channel are required to elicit accurate aggregate behavior predictions, then the computational load on simulation computers may become burdensome or even intractable.

It is not the purpose of this model to prescribe what quantities of each actor and interactor type are appropriate to the veracity of the model, but rather to build a model capable of performing sensitivity analyses so as to determine optimal numbers of actors and interactors for any given predictive purpose.

Statistics predicts that within such a model far greater reductions in the quantities of interactors may be justified than reductions in the quantities of actors.

There is a copious surplus of the simple particles, e.g. ions, while the complex ones are several orders of magnitude less in quantity. The irony for modelers is that the simple ions can consume the greatest computational load in their collisions and reflections, yet yield very little relevant information to the model outputs. It is for this reason that the quantity of ions is scaled down disproportionately to the channels. The collider algorithm may be turned off and results compared to when it is turned on.

9.15.8 PARAMETRIC SCALING

Scaling within the model is of great import. There are several aspects that need be distinguished:

Presentational Time scaling: because real-time speed of ion collisions and diffusion in solution cannot be modeled, some conversion is selected. Typically microseconds of nano-scale events are expanded to seconds in presentations, and milliseconds of micron-scale events are expanded to seconds in presentations. These are arbitrary and of little consequent because they do not alter the mathematical consequences.

Presentational Space scaling: a voxel is typically 10 nanometers ^3 and this is scaled to ~ a centimeter in visual presentations.

Size scaling: Of far greater impact is scaling nonlinear events to take place slower and fewer in number. This is analogous to making a picture more grainy by reducing the resolution. In a complex system of non-linear equations, such a "simplification" is fraught with dangers. Each such move must be verified by comparing the 'pre' to the 'post', and stopping whenever the inherent nonlinearities render the simplification invalid. 100 1E-8m^2 patches of axon can be replaced by a single patch scaled such that the action potential retains the same shape and the propagation time across the length is 10 times as long. Each particle would represent 10 ions, and each post-channel would have a flux of 10 times the amperage of the pre-channel. There are implications for radius, mass, charge, and delay functions.

N by 1E-6. This would result in Nmanaged = 3.6E5, a tractable number on today's PC's. We must carefully consider the consequences of such a reduction. The many impacts include:

1. channel flux becomes highly quantized, and incapable of passing less than 500,000 particles in an action potential, or other gating phenomenon.
2. shot noise is greatly increased and distorted, in magnitude and altered frequency
3. Membrane capacitance is zero for less than 1 million particles, and
4. very "chunky" thereafter.
5. Diffusion to nearest neighbor may be altered in speed and delay.
6. The effects of water upon such chunky ions needs to be re-evaluated.
7. Thus, a lot of verification and recalibration work are needed to justify a model with its quantal nature rescaled 1E6 times.
8. If the ion channels are to be scaled accordingly, what should be their relationships to the modulators?

Another approach is to assume some degree of radial symmetry. Although not valid for the dendritic field, once a signal is summed in the soma, then a single wave front proceeds down the axon. For most of the length of the neuron, radial heterogeneity effects are minimal, although not zero.

9.15.9 COMPUTATIONAL COMPRESSION

The incentive is to eliminate redundant calculations. Size scaling is analogous to voice compression by clipping out the repeating patterns, and pasting copies of the unique patterns back in at the end to reconstitute the original signal. It is anticipated that the molecular pattern redundancies in the neuron are large, and thus must computational compression may be realized.

9.15.10 RUN DYNAMIC SIMULATIONS

In this model, large numbers of collisions occur asynchronously. If variable dt numerical methods were employed, the dt sequence would be unique to each particle pair. The bookkeeping overhead of such an arrangement outweighs the benefit. The dynamic equations are therefore executed with a fixed dt such that all particles can be processed as one matrix, and all actors as one matrix.

The relationship between the particles and actors is tabulated below.

Transition Map:

entities	conc (dist)	profile (filter)	affinity (force)	un(bind) kinetics (prob)	un(bind) instantiation (state)	bind state determines			transport process (force)
messengers	1	2	3	4	5	6			
actors						7	8	9	
ions	10	11	12	13	14	15			16
						conformer kinetics (prob)	conformer instantiation (state)	phenostate (mapping)	

TABLE 24: ACTOR PROCESS SEQUENCE

Each of the numbered cells represents a process critical to the model. Causality is implied by the necessity of time-wise ordering the execution of code functions. However, in reality, causality is much more diffuse over a network of coupled interactions. The sequence chosen above is intended to maximally capture the flow of information through the membranal system. Nearby particle concentrations are selected by actor profiles for affinity to allosteric binding sites. Once collided, bind/unbind kinetics determine the probabilities of binding. Instantiation converts probabilities into actuality. The resultant combination of modulators at binding sites determines which kinetic scheme for the internal conformation shall be in effect. The determined conformer kinetic scheme is instantiated to determine the next conformer state. This state is mapped, via a lookup table, to its external impact upon its surround. for example, an ion channel may 12 states, e 9 of which are closed states and 3 of which are open states. The instantiation may be to any state 1 to 12. This resultant state number is looked up in the phenostate table to determine whether it is open or closed. Meanwhile, the surrounding ions exist in some concentration. Based upon the actor's conductivity profile the actor will have affinity for certain of these ions. Those that bind or enter the actor via the probabilities of bind kinetics will be staged for transport. The state of the actor will determine if and when transport takes place. The actual flux through an actor may be determined by external concentration and voltage forces times the conductivity profile, times the phenostate (open or closed gating function).

9.15.11 ITERATIONS

All functions within a time loop are difference equations. The stability of iterations concerns avoiding cumulative error, and avoiding exponential growths. Many physical systems, and all biological systems, saturate and thereby limit themselves. The model must be designed to include such limit functions. These are usually sigmoid in shape. In a system of functions, behavior may emerge which is not inherent to any one of the component functions. Although Lyapunov stability analysis can be performed on the obvious cases, there are such a multitude of function series permutations that it is easier to place limit switches into the software, set to abort when the values are clearly off what is physically possible. The greater danger is those errors which produce results within physiologic ranges. They require verification procedures to detect.

9.16 NUMERIC METHODS

There are numerous and significant opportunities for producing incorrect results due to the vagaries of digitization. In particular, the inversion of matrices can produce wildly wrong answers when near-zero elements are processed. Because the near-zero values are most often the noise of the system, it is essential to filter them out and replace with zeros prior to inversion, least they become large dominant numbers masking all the significant elements. Unfortunately, this problem can present itself every step during matrix manipulations, and a single “cleaning” step is not enough. Ill-formed matrices cannot be eliminated by design , but rather must be detected on the fly. Each matrix may be rated by its condition index, with those out of tolerance changed to a basis resulting in less ill-formed elements. This requires tracking the matrix until it can be un-transformed. But to the extent that this matrix is blended with others, such a reversal may no longer be mathematically justified.

9.16.1.1 Digitization Challenges

The many characterizations of nature at nano-scale are easily and often distorted in man's attempts at representing them in digital machines. Justification is necessary at every step, every function, every assembly, and every aggregate to check for bias, drift, accumulative error. Particles moving in digitized space-time may tend toward the 45-degree lines, slow down, clump together, escape from compartments, pass through other particles, misread the charge forces from neighboring particles and surfaces, and many other such distortions. Given the necessary and sufficient elements and processes for following information flow along the length of a neuronal membrane, how might these be digitized?

9.16.1.2 Precision

It is noteworthy that double precision is not necessary for most computations. Due to ever present thermal noise, the massively parallel nature of the model, and its inherent biologic robustness, random error down at 5 or 6 decimal places has no effect on the outcomes. This allows a single 64-bit processor step to actually solve 4 computational steps simultaneously. This is unusual, in that most differential equation models are hypersensitive to error and require double precision or better. This is not to be confused with aliasing error, which is cumulative and does indeed result in serious (fatal) distortions

9.16.2 WATER

Temperature, consists of velocity distribution across each particle type. Temperature therefore is expressed as a pattern of changes in position of the particles. Temperature of the actors is expressed as a general rate of state changes, but this may become quite nonlinear with temperature-caused denaturing.

Water density determines particle collision rates. In doing so, it breaks up mean free paths and orbits (that are possible in gases). As water is felt by its collisions, there will need to be some means of collision detection. In analog space this is trivial, but in digital space it is an immense problem. There are no collisions in digital space, because there is no physical movement, so they must be carefully calculated.

Water solvates ions. Variable quantities of water molecules form solvation shells around ions. This has the effect of preventing positive and negative charges forming neutral bond pairs, which they would do without the presence of water. This requires that ions change mass and radius from time to time, and that somehow these larger globs do not bind to their oppositely charged counterparts because the charge is “smeared” across so many “molecules”. The cation would head towards the anion, except that the water has some of the anion's charge and the water is closer. These are very transient relationships.

Momentum is conserved when two particles combine and the new velocity is the sum of the two momenta. Momentum is conserved when particle collisions are resolved with 3-d momentum transfer equations.

9.16.3 IONS:

Ions may be monatomic or polyatomic. The monatomic particles have a true radius, although different mensuration methods yield different numbers. Polyatomic ions are modeled as spheres of an equivalent radius chosen that model collision rates are very close to the *in vitro* collision rates. With very small particles like ions, a timestep in digital space that allows an ion to move just 2 angstroms could have completely missed a collision that would have certainly occurred in analog space. This makes collision detection computationally very expensive. Not merely the detection algorithm, but the fact that it requires *dt* and **dx** to be finer than the smallest particle at the fastest speed. The collisions are more than statistical random walks. The ions are the carriers of information between channels, and the collisions transfer this information from particle to particle and/or from particle to actor. Therefore, in a particle system representing information processing, accurate collisions are of the essence.

Because the smallest particles are indeed going the fastest, the smallest particle in the simulation constrains the entire model to rather tedious computations, that the larger molecules do not require. Omitting free electrons avoids a 1844 fold decrease in mass and a 354861 fold decrease in radius, when compared to hydrogen. These are multiplicative effects. A model without hydrogen avoids a 22 fold decrease in mass. These are items of dramatic impact upon digital computational load, though they may be trivial matters in analog space.

Ions experience drift within charge fields, unless bound. If they should meet a barrier across the path towards their attractor, then they do not stop dead, but rather churn in thermal energy so as to "spread out" along the membrane surface (due to like charge repulsion). They can comprise some degree of charge thickness on either side of the barrier, but the charge density decays exponentially from mid-thickness of the barrier (not from the surfaces). As temperature rises, this thickness increases. Temperature also fluidizes the drift, facilitating its progress by reducing friction.

```
Given a matrix qBxqB, its diagonal is zeroed because the EM force of a particle with itself = inf
Force.drift.i = k0*sum( (normal(pos.Bj - pos.Bi) * (charge.Bj * charge.Bi ) / (magnitude(pos.Bj - pos.Bi))) );
for j=1:qB;   normal(p2-p1) = (p2-p1)/magnitude(p2-p1);   magnitude(p2-p1) = (sum((p2-p1)^2))^0.5;
```

Volumes of saline cannot maintain charge imbalance. This is referred to in textbooks as "space charge neutrality". Any charge imbalance must move under the forces of drift to the surface that forms the barrier between the positive and negative charges. Therefore, charge accumulation is a surface effect, not a volume effect. Thus the model must be capable of such phenomena whenever there is drift and a barrier to that drift. All movement must be sensitive to such barriers and ions reflect off them. Drift is an acceleration factor calculated via A = F/m; The acceleration is degraded to terminal velocity by the collisions rate. In a digital framework,

```
F(t-1) = k0*q1*q2/r(t=1)^2;
A(t=2) = F(t=1)/m;                  % frictionless acceleration
W(t=2)= V(t=1)+A(t=2);              % frictionless new velocity
V (t=2) = W(t=2) - k1*V(t=2);       % subtract friction term
V(t=2) = W(t=2) / (1+k1);           % soln to line above
P(t=2)= P(t=1)+V(t=2);
```

The charges are reported to accumulate within 3 nm of the membrane at room temperature, 293 K. It is calculated herein that 81% of all charges are essentially flat against the membrane, and that successively sparse layers of ions reside at even multiples of the membrane thickness away from the membrane. Thermal noise tends to make these layers fuzzy.

Ions may bind to actors. This is accomplished by:

1. Identify particles within some defined attraction radius of the actor. As each actor has two poles, one on each side of the membrane, there are 2 hemispherical attraction volumes per actor.
2. allow particle to collide with the actor pole, with a collision defined as entering into within some smaller distance from the pole.
3. consult the bind profile of the actor's binding site (probabilities of binding by type of particle)
4. create PDF from bind profile by including the probability of a vacancy, then integrate a CDF from the PDF
5. instantiate the binding (or absence thereof) via a uniform distribution random number across the CDF
6. any "winning" particles have their velocity set = 0; their assignment tag switched from the compartment number to the actor number with pole number; and any solvation water molecules are stripped off. If the actor binding site has an opposite charge, then the two will cancel out, so both charges are turned off to avoid participation in the drift algorithm.

Ions may unbind from actors. This is accomplished by:

1. particle identities are known to the actor, and to which binding site and pole the particle is bound.
2. each binding site has a dissociation frequency for each particle type. That becomes the probability of release.
3. the dissociation probability for only the type of particle actually bound is used to calculate the probability of remaining bound this *dt*. From these two numbers as PDF is formed; and from that a CDF.
4. instantiate the unbinding (or remaining bound) via a uniform distribution random number across the CDF
5. any released particles have their velocity set back to their original velocity at the time of binding; their assignment tag is switched from the actor number to the compartment number; charges are turned back on; and the solvation algorithm is turned back on.

Ions may be transported. This is accomplished by:

1. reassigning a bound particle from one pole to the other pole of the actor.
2. transport is triggered by a stochastic process that determines the conformational changes within the actor.
3. when released from this pole, the particle is reassigned to the new compartment (see unbinding above)

9.16.4 LIGANDS:

Ligands are particles that serve as modulators, messengers and/or neurotransmitters. They modulate actors by binding allosterically. See Allosteric Binding sites below for details. Ligands may or may not have charge. Ligands and ions share many processes, especially diffusion and drift. The radius of a ligand is of lesser utility, in that ligand

shape is instrumental in its binding. However is not necessary, nor even feasible to represent ligand shape for purposes of modeling information flows.

The heavier mass particles, like ATP necessarily move slower, both in response to thermal energy and to drift.

The distinction between ions and ligands is weak and not distinct. Ions may serve as ligands when they bind merely to modulate. Ligands may be transported in the process of returning them to their original locations for the purpose of completing duty cycles. Use of the term ligand is more for the benefit of the user than for the modeling effort *per se.* For strictly modeling considerations, all moving entities are particles. They each have mass, and an effective radius. They may have charge or the charge value may be zero. The binding sites of each actor have various affinities for various particle types. These affinities are determined empirically in the wet lab. Any particle type might bind and unbind to an actor. Any particle can be transported by a pump. Any particle may be chemically modified into one or two other particle types (e.g. ATP > ADP + Pi). All particle types can undergo diffusion driven by concentration gradients and thermal energy. Only charged particles participate in drift, capacitance, current and voltage. The effects of diffusion and drift are additive.

Functions for Ligands: same functions and usage as functions for ions. Only the charge of zero nulls out EM force effects.

9.16.5 MEMBRANES:

Membranes are expressed as closed surfaces. Membranes necessarily have thickness, else particles on ether side could come infinitesimally close, resulting in forces approaching infinity. The lipid constituents are expressed only as thickness and dielectric constant. Optionally, the water/lipid partition factor will vary with inhomogeneous lipid distributions.

Membranes are generated as contours of revolution. Each contour consists of a series of points, the distance apart of which determines the dx value. Then each point on the contour is rotated into a ring. Each ring is populated by as many nodes as result in consistent dc values. (dc = the dx value curved along the circumference) Each ring therefore has a diameter and a thickness. From these a ring volume can be calculated:

volume.i = thk.i*pi^r.i^2;

And the entire shape volume is the integration of all the rings:

volume = sum(volume.i); i = 1:qR;

Membranes may be juxtaposed and/or nested. Nesting, of course, affects volumes. Compartments are defined volumetrically as the volume contained by its outer surface minus the volume contained by its inner surface. If there is no inner surface, then the default volume =0;

By virtue of assigning each actor to a membrane node, the nearest neighbor relationships between actors are easily established and measured. Nearest neighbors are identified at the time of nodal assignments because the construction rules relate only to adjacent rings. If at a later time simple distance was used to identify nearest neighbors, then two different membranes that happen to come close to each other or touch would produce false "nearest neighbors" across the two membranes. A similar error would occur when a membrane folds back on itself. This would lead to spurious conductances, poles, circuits and driving forces, so is to be avoided.

Every node in a membrane has a Cartesian (and cylindrical) position in 3-space. Every node also has a normal to the surface which serves to orient the actor poles. Because every node has orientation and thickness, there must be 2 points along the nodal normal where the normal meets the inner and outer surface of the membrane. From these surface nodes can be constructed two separate surfaces, their distance apart of course, equaling the thickness of the membrane. It is these two surfaces that reflect particles, not the center-line nodes of original construction.

The role of membranes in the dynamic simulation is primarily its capacitance. However the membrane, *per se*, makes no calculations for this. Capacitance is merely an emergent property of the EM force acting on the particles, which may or may not bounce off the obstacle of membranes. The thickness of the membrane is passively used in the particle EQs.

9.16.6 PARTICLE COLLISIONS WITH MEMBRANES

Each membrane has a thickness and each particle has a radius. The inner and outer membrane surfaces have their nodes calculated at the build, and each particle collision occurs when the center point of the particle gets within a distance of the membrane surface equal to the particle radius. Because the normals to the membrane surface are known, the distance between particle and surface is measured along the surface normal from the closer of the two

membrane surfaces to the center of the particle minus the particle's radius. If this is a negative number, then a collision has already occurred. The particle is then backed up in time to the point of intersection, and a reflection angle is calculated. The point in time of collision is also calculated, as a fraction of the *dt*. The remainder of the *dt* is then ascribed to the reflection angle and the particle is repositioned out to the end of that trajectory. This is an accurate calculation for a reflection, regardless of the size of *dt*, and so avoids aliasing error. It is as accurate as the analog, but at a cost of intense computation. Note that this approach requires a double calculation, the first in pseudo time that allows the particle to penetrate the membrane. Then a back-up in time and rerunning of the scenario, only this time cognizant of the surface and calculating a realistic approach, collision, and reflection. The reason for two is that the first is concerned with collision detection, and the second with collision resolution. In the digital realm these two are necessarily separate.

9.16.7 RECEPTORS:

All receptors in this model are metabotropic, and include a second messenger mechanisms which shuttles messenger particles to a set of channels. The model easily portrays ionotropic receptors as well, but they are covered as channels. Receptors have allosteric binding sites, as described above. For a chemical binding to serve as a signal, it must have several qualities: a) it must be fast enough to serve in a timely fashion; b) it must stay bound long enough to effect the appropriate state transition of the receptor, but no longer. A lingering binding will act as a blocker to subsequent signals, may block the rest mechanisms, and may continue sending spurious signals beyond the useful period. This could flood the system with messengers, rendering communication in a congested state; and c) the messenger must be promptly removed , disabled, denatured, or sequestered, so as to stop its functioning as a stimulus for receptors. Lose and wandering messengers can create echoes and noise the degrade the messenger system. This requirement is quite severe for the ligands that arrive at receptors and for the second messengers that receptors release. Therefore:

1. All messenger particle releases must be positioned for speedy delivery to the target actors. A shortage of particles must be such that it represents a legitimate depletion of cellular resources.

2. When diffusion alone does not serve reliably in this capacity, mechanisms which narrow the path of messengers may be needed. These are called shuttles. Alternatively, high affinity binding sites can be created which expedite motion towards a binding site in a similar manner to the EM attractive force.

3. The binding kinetics must be appropriate to the communications needs. Typically this involves a high affinity for a messenger particle when in the "ready" state; a fast kinetic change upon binding that results in the release of second messengers (either directly or by catalysis);

4. The kinetics of messenger release leaves vacated sites which in turn cause further kinetic changes in the receptor molecule. The original trigger site must be vacated to ready for the next triggering event. The second messenger mechanism must be "reset" such that a new set of second messengers are staged and made ready for the next release. The reset sequence involves a refractory period where there are not yet any second messenger particles ready for release. They must be attracted and bound. The final binding (staging) of the second messenger particles causes yet another kinetic change which readies the receptor site for the trigger particle.

Some receptor sites act only as a catalyst, and as such need only turn on and turn off that catalytic property. In a model, this process is akin to the challenge of the vesicle which must manufacture all the contents of a single vesicle (presumably by catalysis) and then get everything in the proper position and set all the mechanisms that can very quickly push the entire package out into the synapse. The practical solution for vesicles was to get all of this work done prior to the release stimulus, because then the response can be much faster. The model has the same challenge: how to get all of these necessary steps accomplished fast enough to be truly useful as a receptor. If the dt is reduced down to millionths of a second then it is feasible to represent all of these steps individually, in sequence driven by chemistry. But there is a great need to get the dt up to about 1E-4 seconds so as to focus on NIP. This suggests taking a cue from the vesicles and setting up the receptors in advance, loaded with a package of second messengers, then delivering them efficiently to their target channels at a rate of speed similar to the timing of such signaling *in vivo*. Every abstraction of the physical processes into some such "short-cut" is a compromise to the physics, and thereby deprives the modeler of a genuine first principles model that can generate emergent properties. As larger computing machines become available, fewer such compromises are necessary. The modeler must make the decisions at the time of experimental design as to which processes are priority, and which can be simplified by

abstraction because they are not NIP significant. If the receptor is truly serving as a transducer, not as an information processor, then simplifying the receptor to a kinetic release mechanism is justified.

A catalytic receptor would need accomplish a series of steps all within the time known for a receptor to trigger nearby channels (about 1e-4 s). The sequence must include:

1. Affinity for the reactant particles in quantities sufficient to its second messenger role, at least as many as there are target channels. This requires identifying the quantity of reactant particles within an affinity distance not so great that it would steal from other receptors. All of these then must be moved to the receptor.

2. A kinetically triggered chemical conversion of the reactant particle into the second messenger particle. This would be fast and voluminous to provide all needed second messenger particles.

3. The second messenger particles must arrive at their target actors very quickly and precisely. Simple diffusion is likely to have a very high miss rate. If only 1% of the created particles collided with a target actor in a timely fashion, then 100 times as many particles must be created.

4a. Second messenger systems are known to operate by a sort of 2-dimensional diffusion, whereby the messenger molecules trolley along the membrane surface, free to move in the X and Y directions, but not Z (away from the membrane). This cuts down the number of particles to the 2/3 power. But it still relies upon random collisions to communicate with the target channels. The biological membrane is such a busy place with so many proteins and structures that it is quite likely those X and Y directions are not so free, but rather are constrained so as to hit the target channels reliably. To the extent this is true, the simple concept of a 1-dimensional shuttle may be justified. When the experimenter is not concerned with the intricacies of the second messenger system, a straight shuttle mechanism may be the most computationally efficient mechanism to communicate between receptor and channels.

4b. Some forms of G-protein second messenger systems employ intermediate stages of catalysis. In particular, the cyclases receive second messengers via 2-dimensional diffusion, and then produce copious amounts of third messengers, such as phosphates. The third messengers apparently diffuse 3-dimensionally and hit multiple types of targets, many more than channels, and much that is out of scope for this model. Such two-step multipliers can achieve great fan out leverage, up to 30000:1. For very sensitive detectors, such as the eye in near darkness, this leverage enables “seeing” a single photon. Because this model can do both diffusion and shuttles, these systems can

be modeled. For experiments where this is not of interest, computational load can be conserved by collapsing the second messenger system to a shuttle that delivers in time envelops mimicking the *in vivo* performance.

5. A shuttle is a set of links, each between a single receptor, and one of the prescribed set target channels. A receptor triggering event releases all the messenger particles within a time envelope, and each proceeds down its link at a velocity of mean plus variance. The length of the link determines arrival times. The kinetics of binding at the target determines the success rate of communications. The particles then return down the link to reset for the next communication event.

Theoretically, a receptor can be made to preform its intended function even when its kinetics are fully reversible. A messenger must bind on one side, which causes a messenger on the other side to unbind. When the far side resets (binds again, the first side must unbind to reset. The 2 sides are complimentary. A rather simple kinetics can accomplish this, and it needs no energy source other than thermal. It is only modulation that necessitates greater kinetic complexity.

9.16.8 CHANNELS:

Channels have allosteric binding sites as described above and are thereby modulated stochastically. In addition, channels typically consist of 4 or 6 subunits which operate almost independently. They can be treated as 4 (or 6) smaller stochastic devices, or merged into one larger stochastic device. Which one is used depends upon the degree of coupling between the subunits. Significant coupling indicates the merged state transition matrix. The digital instantiation of the subunits and their state changes yield only state numbers, not pores that open up. The state number has consequences only when it is fed into a lookup table (called the phenostate table) which lists which executable functions to call in response to each state number. In the case of channels, most states have a closed pore, so there is nothing to do. However those few states which result in an open pore require a digital process that culminates in particles moved across the membrane to a new compartment.

When a pore is indicated to be open, the affinity hemispheres on both sides of the channel are consulted. They return all particle types within the hemispheres. From these counts several calculations are preformed. The local concentration gradients are calculated. The local voltage gradient is calculated. the individual Nernst partial voltages are calculated. Then the driving force for each ion type is determined as membrane voltage minus partial

voltage ; and the concentration gradient force is calculated. These two forces are summed to a single driving force. This set of forces, one for each particle type, is multiplied with the conductivity profile of the channel type. This yields the flow rate of all particle types through the open pore under those local conditions. These flows are then multiplied with the open duration time. The solution is rounded off to whole numbers. This yields the exact number of each particle type that was transported by that channel during that opening event. The conductivity profile may reveal the channel to be highly selective, or quite unselective. No matter, the calculation steps are the same. This sequence works equally well for fast channels and for leak channels. The only difference is that for any duration of opening longer than 1 *dt*, then the duration = 1 *dt*, repeated as many times as necessary. This is to move particles in a timely fashion, avoiding bunching them all up at the end of the duration.

Channel gating may be determined to last some time duration less than the model dt. That is OK, because the calculated duration time (from the stochastic process) multiplies with the flow rates to transport the correct quantities of particles. Where such fast events trigger downstream events within that same *dt*, the model will become sluggish to *in vivo* performance unless the *dt* is shortened . A distinction is made between short intervals which merely downsize the quantities of particles transported and a fast series of causal events.

Although channels have been extensively characterized by others with regard to the open times and modulator types, little has been said thus far about the patterns of openings. We know with certainty that channels can change modes, i.e. change opening patterns (e.g. bursts, rhythmic, chaotic), but to date no framework for investigating these patterns has been proffered. It is the intent of this model to support such investigations. This requires robust kinetic schemes that are instantiated and run at length so as to capture, average and characterize the patterns that emerge under various modulation conditions. The kinetic schemes are crucial to this objective. That some of the kinetic schemes are admittedly arbitrary works against this objective. When several different kinetic schemes are available for the same actor type, they can each be run, characterized and then comparisons made to determine which behaves closest to the biological entity. This is a new area of investigation so little can be cited as peer reviewed fact. But it is a promising direction, because it is these kinetic schemes that are key to biocomputation. As biologic methods improve, the kinetics yielded will be less “schemes” and more real kinetics. It is expected that the new field of MD will assist in this quest.

Adding to the complexity of the investigation of actor kinetics is that the possible combinations of modulation site bindings can grow to very large numbers. It is not the quantity of modulation sites that determines the number of state transition matrices, but the quantity of combinations of modulation. For example, given 3 binding sites; the first which can bind Ca++ or Mg++, the second which can bind 5HT, and the third which can bind Na+ or K+; then there are 18 binding combinations, including the possibilities of vacant sites. Then, if the actor has 10 states in its kinetic scheme, there must be 18 separate pages of 10x10 probabilities. This comes to 1800 data values for one actor type. It is suspected that some actors will have upwards of 30 states and a dozen allosteric binding sites (many are known to have more). And we are already over 900*2^12 data values for one actor type. (That's 3686400 probability values). It is admittedly unlikely to come from wet lab work. But conceivably may be generated by molecular dynamics simulations.

Channels do not require an energy source other than thermal. Their kinetics may be simple and reversible and still accomplish the gating function. Complexities in the kinetics are implied by modulation, by pattern recognition, and by pattern generation.

```
Given:   t,  s(A01,t),  Q(A01),  r(A01,t),  R(A01);
pdf(A01,t) = Q(A01(s(t),:,mod(A01,t)) ;                                  % transition probs at t+1
s(A01,t+1) = randI(CDF(pdf(A01,t))));                                    %  state of channel at t+1
o(A01,t+1) = O(A01,s(t+1));                                              %  opening/closing of
channel
g(A01,t+1) = G(A01)*o(A02,t+1);                                          %  conduction of channel at
t+1
Vm(pos(A01),t) = CoulombMemb(pos(B,t),BT,BC);                            % EM force across
membrane
Ev(Ao1,t+1) = Nernst( concin(pos(A01),t), concout(pos(A01),t), z(BT(i,:)),kelv(t));    % force due to half cell
Ec(A01,t+1) = ConcGrad(concin(pos(A01),t+1), concout(pos(A01),t+1);       % force due to
concentrations
E(BT(i,:),pos(A01),t+1) =  Ev(Ao1,t+1) + Ec(A01,t+1);                    %  sum 2 gradients , for ea
ion
J(BT,pos(A01),t+1) =  (Vm(pos(A01,t) - E(BT,pos(A01,t+1)) * g(A01,t+1) ;  % full - partial = net for ea
ion
concin(pos(A01),t+1) =  concin(pos(A01),t) + J(BT,pos(A01),t+1) ;         % net gain of ions to concin
concout(pos(A01),t+1) = concout(pos(A01),t) - J(BT,pos(A01),t+1) ;        % net loss of ions to
concout
```

9.16.9 VESICLES:

The modeling of a single vesicle replete with its many subunits and intricate mechanisms would of itself be a major project. It is simply not tractable to this project to replicate a physics based model of vesicles. Compromise is not optional; its necessary. The great risk of simplification is that some modulation mechanisms are inherent in the

design, and would be lost when simplified. In answer to this concern, if and when modulation functions are they can be added into the stochastic representations in a straight forward manner, with little if any design work required. Because this model is set up to accommodate any size state transition matrix, a very wide variety of modulation mechanisms can be captured by such. Ultimately, some one or more input patterns sets into motion certain kinetics that culminates in the release of ligands into the synaptic cleft. The release mean, variance, and lag are studied and published. It is not difficult to create a kinetic table to replicate the timing performances, and to enact a set of links to insure that messengers arrive at targets in a timely fashion. Such links are not authentic, but rather a shortcut to avoid computation of a much larger number of particles, most of which are unsuccessful at reaching targets.

The vectorial directions from the receptor to each of its target channels is calculated.
Upon release, the messengers are set upon these vectors at velocities that vary per in vivo results.

When messenger particles eventually arrive at the target actors, they are treated as any other allosteric binding. If, however, there is found to be modulation of these individual messengers after they are released, then an intermediate type of actor must be created to effect that modulation. It would act as yet another receptor type, in series. The logic of the cell dictates the wiring of the actors. Shuttles are merely devices to make that wiring explicit, rather than as implicit in the case of diffusion.

It is worth noting that charged messengers necessarily cling to the membrane. There is no choice in that. The EM force is too strong, and nothing else the cell offers can override it to break charged particles away from that membrane. Therefore the trolley like mechanisms of G-proteins might be nothing more than the effects of charge. The more nuanced effect is that they are so effective at finding their targets in such a obstacle-ridden environment. Perhaps we must suspect that those obstacles are really acting as curbs to guide the direction of the messenger towards their targets.

Vesicles represented as transducers may be built of simple kinetics that require no energy source other than thermal. They may even be reversible processes, though pumps are required to retrieve the exocytized particles.

9.16.10 PUMPS:

Pumps are specific transporters of ion and ligands, performed ratio-metrically. The pumping rates are modulatable, and are dependent upon some source of energy. Pumping rates may vary in response to concentration pressures, especially at levels of starvation on the input side, and saturation on the output side. and for steady state and recycling

Pumps always require some source of energy to drive them, unless they are allowed to run backwards and "bleed" the concentrations gradients down. The effects of energy injection, such as with the conversion of ATP into ADP+Pi, are 2-fold. First, to overcome the concentration gradient and the voltage gradient to move particles "up-hill" metaphorically speaking. The second is to give the state graph directionality. Pumps must have a state path cycle, and traverse that cycle only forwards. To run backwards means death for the cell, so this is a critical feature. So how do pumps ensure the directionality of their duty cycles? Though this is ultimately a thermodynamics question, you can see it in the state transition probabilities. We can run a little program that identifies the duty cycle by following the probabilities for each subsequent state change, and pumps will always go forward except for one of the transitions in the cycle. That one step is the one that requires ATP (or other energy source). The metaphor is a staircase. Each transition is a step down, until you get to the bottom. Then ATP is required to boost back up to the top of the stairs. If the geometry between the atoms is such that ATP can only degrade to ADP in a reaction that simultaneously resets the Gibbs energy of the pump molecule to the top level - then you have directionality in state flow.

Therefore, the kinetics of pumps are limited in the sense that there must be at least one step that injects energy into the molecular conformation, and that the sequence through the subsequent steps each gradually release this energy. Unlike the other classes of actors, directionality of pump state paths is required.

Pumps can be made to run backwards. They will do this only when the voltage gradient plus concentration gradient forces sum to something greater than what the ATP (or other source) injects. In that case the pump is making ATP out of ADP, and the work is not lost, but merely stored in a different form. This is somewhat like driving an electric motor against its driven direction. This will result in forcing the motor to become a generator. Such reversals are brought about not by the conformer kinetics (internal states) but by the bind kinetics. This requires a certain

intelligence in the software to recognize untenable thermodynamics, and allow the kinetics to run backwards under those conditions.

When the ATP's of the system are overworked, then there will be a shortage of ATP and a surplus of ADP. This will result in a low binding frequency of ATP, but a high frequency of ADP bindings to that site. This predicament sets the pump up to run backwards. The probabilities of backward transitions may be low but they are not zero. When there are no forward cycles, then the pump is stalled in precisely those states likely to initiate backward cycles, i.e. ADP binding sites. Even the thermal energy might help bump the pump into backward transitions, and occasionally, and ATP is born.

9.16.11 ALLOSTERIC BINDING SITES ON ACTORS

All actors have allosteric binding sites for particles which may modulate actor behaviors. All actors have 2 poles, one on either side of the membrane. The poles are found along the surface normal of the node, out some distance equal to or slightly greater than the half thickness of the membrane. Each pole may have any number of separate binding sites. Each binding site is exposed to every type of particle in the compartment, and the binding algorithm acknowledges this fact.

The particular combination of bindings on a single actor molecule determine the kinetics table (state transition probabilities) in effect for the actor at that time. The state number that the actor is in at each dt determines the bind/unbind kinetics in effect. The total number of matrix elements necessary to describe a single actor is a summation of the internal events and the external events:

qS1*qS1*CqS2 + qS2*(qB+1)*qS1; where qS1 = quantity of states; qS2 = quantity of binding sites on actor;
qB = quantity of types of particle; CqS2 = quantity of possible binding combinations;

In each of these triple products, the first two terms comprise the possible transactions and the third defines the conditions of those transactions. Note that they impinge on each other, that is, are heavily coupled. That is the whole point; that external events can modulate internal events, which in turn effect other external events. This is of the essence of neuronal information processing, so will be given a lot of attention throughout this modeling effort.

To populate all of these states and their transition probabilities requires considerably more data than is collected by biologists when they study the kinetics of an actor. It may be that it simply is not feasible to measure all of these possibilities on a single molecule. Reasonable approximations for the missing bits are necessary for modeling their behavior. Of course, as data becomes available, the accuracy of the kinetics improves.

Code for Hill's EQ:

```
a = -7:.2:-2;         % spans log space
c = 10.^a;            % log scale
k = c;                % dissociation constant
h = (1:0.1:2.0);      % hill's coefficient

figure(1),
N=length(k);          % number of plots
col = linspace(0,1,N)';    % span of colors
col3 = 1-col;
col2 = 1-abs(col3-col);
color = [col col2 col3];   % rainbow
for i = 1:N,
y(:,i) = c.^h(5) ./ (c.^h(5) + k(i)^h(5));
semilogx(c,y(:,i),'color',color(i,:)),hold on,
end
title('varying the dissociation constant'),
xlabel('concentration of the ligand'),
ylabel('fraction of ligand bound to receptors')
hold off

figure(2),
mid = round(N/2);
N2=length(h);     % number of plots
kol = linspace(0,1,N2)';              % span of colors
kolor = [kol 0.3*ones(N2,1) 1-kol];   % rainbow
for i = 1:N2,
y(:,i) = c.^h(i) ./ (c.^h(i) + k(mid)^h(i));
semilogx(c,y(:,i),'color',kolor(i,:)),hold on,
title('varying Hills coefficient'),
xlabel('concentration of the ligand'),
ylabel('fraction of ligand bound to receptors')
end
hold off
```

9.16.12 KINETICS OF BINDING AND UNBINDING

The kinetics capture in the binding and unbinding rates at each allosteric binding site on the actor, and at each transport binding site as well. The challenge is that .

Bound and unbound states are identified by tags.

The challenge is to relate the mathematical outcomes to the actual collision rates and visual events of the diffusion model. See Kolmogorov below.

9.16.12.1 Kolmogorov representation of Kinetics

Q matrix transition rate constants in Q matrix form system.

P(t) utilize the probabilities as input into the gating equation

Y(t) gating function as input into conductance equation

G(t) maximum conductance determines dynamic conductance

I(t) determined by ohm's law and Nernst, conductance through a unit channel

Pss Steady State values are initialized to establish system sanity, and initialize that matrix of Nernst dV's.

9.16.13 KINETICS OF MODULATION

Functions are offered in the literature for voltage gated channels. They make worthy study cases for how one might simulate modulated channels. Given a set of formulas for determining the element values in the Q matrix, how is the behavior of that type to be characterized?

```
EX   a 10 x 10 Q matrix scheme for a Kv channel (voltage modulated)
Q = zeros(10);
Q(1,2) = 0.007*e^(V/91);
Q(2,1) = 0.002*e^(-V/65);
Q(2,3) = 0.122*e^(V/81);
Q(3,2) = 5.00*e^(-V/112);
Q(3,4) = 0.212*e^(V/91);
Q(4,3) = 1.65*e^(-V/38);
Q(3,6) = 3.28;
Q(6,3) = 5.06;
Q(4,5) = 0.246*e^(V/73);
Q(5,4) = 5.61*e^(-V/70);
Q(4,7) = 1.06;
Q(7,4) = 4.38;
Q(5,8) = 8.37;
Q(8,5) = 2.44;
Q(6,7) = 0.027*e^(V/93);
Q(7,6) = 0.561*e^(-V/39);
Q(7,8) = 0.012*e^(V/72);
Q(8,7) = 0.019*e^(-V/68);
Q(7,9) = 0.07*e^(V/88);
Q(9,7) = 0.6;
Q(8,10) = V/130;
Q(10,8) = 0.08;
```

If one knows the physiologic voltage domain and the critical voltages, then one can run this "matrix" over a series of voltages and study the dominant state path circuits in each one. If they were all the same, then at most voltage would merely be speeding up or slowing down the circuit. However, if the circuit changes above or below certain voltages, then we have modalities.

V = [-100 -80 -60 -40 -20 0 20] ; generates the following Q from the EQs above.

val(:,:,1) =

-0.0023	0.0023	0	0	0	0	0	0	0	0
0.0093	-0.0448	0.0355	0	0	0	0	0	0	0
0	12.2105	-15.5611	0.0706	0	3.2800	0	0	0	0
0	0	22.9279	-24.0504	0.0625	0	1.0600	0	0	0
0	0	0	23.4090	-31.7790	0	0	8.3700	0	0
0	0	5.0600	0	0	-5.0692	0.0092	0	0	0
0	0	0	4.3800	0	7.2868	-11.6923	0.0030	0.0225	0
0	0	0	0	2.4400	0	0.0827	-1.7535	0	-0.7692
0	0	0	0	0	0	0.6000	0	-0.6000	0
0	0	0	0	0	0	0	0.0800	0	-0.0800

val(:,:,2) =

-0.0029	0.0029	0	0	0	0	0	0	0	0
0.0068	-0.0523	0.0454	0	0	0	0	0	0	0
0	10.2136	-13.5816	0.0880	0	3.2800	0	0	0	0
0	0	13.5453	-14.6875	0.0822	0	1.0600	0	0	0
0	0	0	17.5914	-25.9614	0	0	8.3700	0	0
0	0	5.0600	0	0	-5.0714	0.0114	0	0	0
0	0	0	4.3800	0	4.3634	-8.7755	0.0040	0.0282	0
0	0	0	0	2.4400	0	0.0616	-1.8862	0	-0.6154
0	0	0	0	0	0	0.6000	0	-0.6000	0
0	0	0	0	0	0	0	0.0800	0	-0.0800

val(:,:,3) =

-0.0036	0.0036	0	0	0	0	0	0	0	0
0.0050	-0.0632	0.0582	0	0	0	0	0	0	0
0	8.5433	-11.9330	0.1096	0	3.2800	0	0	0	0
0	0	8.0022	-9.1704	0.1081	0	1.0600	0	0	0
0	0	0	13.2195	-21.5895	0	0	8.3700	0	0
0	0	5.0600	0	0	-5.0742	0.0142	0	0	0
0	0	0	4.3800	0	2.6128	-7.0334	0.0052	0.0354	0
0	0	0	0	2.4400	0	0.0459	-2.0244	0	-0.4615
0	0	0	0	0	0	0.6000	0	-0.6000	0
0	0	0	0	0	0	0	0.0800	0	-0.0800

val(:,:,4) =

```
  -0.0045    0.0045         0         0         0         0         0         0         0         0
   0.0037   -0.0782    0.0745         0         0         0         0         0         0         0
        0    7.1462  -10.5628    0.1366         0    3.2800         0         0         0         0
        0         0    4.7275   -5.9298    0.1422         0    1.0600         0         0         0
        0         0         0    9.9342  -18.3042         0         0    8.3700         0         0
        0         0    5.0600         0         0   -5.0776    0.0176         0         0         0
        0         0         0    4.3800         0    1.5646   -5.9959    0.0069    0.0444         0
        0         0         0         0    2.4400         0    0.0342   -2.1665         0   -0.3077
        0         0         0         0         0         0    0.6000         0   -0.6000         0
        0         0         0         0         0         0         0    0.0800         0   -0.0800
```

val(:,:,5) =

```
  -0.0056    0.0056         0         0         0         0         0         0         0         0
   0.0027   -0.0980    0.0953         0         0         0         0         0         0         0
        0    5.9775   -9.4277    0.1702         0    3.2800         0         0         0         0
        0         0    2.7929   -4.0400    0.1870         0    1.0600         0         0         0
        0         0         0    7.4653  -15.8353         0         0    8.3700         0         0
        0         0    5.0600         0         0   -5.0818    0.0218         0         0         0
        0         0         0    4.3800         0    0.9369   -5.3817    0.0091    0.0558         0
        0         0         0         0    2.4400         0    0.0255   -2.3117         0   -0.1538
        0         0         0         0         0         0    0.6000         0   -0.6000         0
        0         0         0         0         0         0         0    0.0800         0   -0.0800
```

val(:,:,6) =

```
  -0.0070    0.0070         0         0         0         0         0         0         0         0
   0.0020   -0.1240    0.1220         0         0         0         0         0         0         0
        0    5.0000   -8.4920    0.2120         0    3.2800         0         0         0         0
        0         0    1.6500   -2.9560    0.2460         0    1.0600         0         0         0
        0         0         0    5.6100  -13.9800         0         0    8.3700         0         0
        0         0    5.0600         0         0   -5.0870    0.0270         0         0         0
        0         0         0    4.3800         0    0.5610   -5.0230    0.0120    0.0700         0
        0         0         0         0    2.4400         0    0.0190   -2.4590         0         0
        0         0         0         0         0         0    0.6000         0   -0.6000         0
        0         0         0         0         0         0         0    0.0800         0   -0.0800
```

val(:,:,7) =

```
  -0.0087    0.0087         0         0         0         0         0         0         0         0
   0.0015   -0.1576    0.1562         0         0         0         0         0         0         0
        0    4.1823   -7.7264    0.2641         0    3.2800         0         0         0         0
        0         0    0.9748   -2.3583    0.3235         0    1.0600         0         0         0
        0         0         0    4.2158  -12.5858         0         0    8.3700         0         0
        0         0    5.0600         0         0   -5.0935    0.0335         0         0         0
        0         0         0    4.3800         0    0.3359   -4.8196    0.0158    0.0879         0
        0         0         0         0    2.4400         0    0.0142   -2.6080         0    0.1538
        0         0         0         0         0         0    0.6000         0   -0.6000         0
        0         0         0         0         0         0         0    0.0800         0   -0.0800
```

By taking the eigenvalue conditions we hope to identify the state of greatest occurrence, to use as a start state for our searches. A state tracking algorithm begins at each state as a start node yields the following state path cycles.

V(1) V(2) V(3) V(4) v(5) v(6) v(7)

[1;2;3;2]	[1;2;3;2]	[1;2;3;2]	[1;2;3;2]	[1;2;3;2]	[1;2;3;2]	[1;2;3;2]
[2;3;2]	[2;3;2]	[2;3;2]	[2;3;2]	[2;3;2]	[2;3;2]	[2;3;2]
[3;2;3]	[3;2;3]	[3;2;3]	[3;2;3]	[3;2;3]	[3;2;3]	[3;2;3]
[4;3;2;3]	[4;3;2;3]	[4;3;2;3]	[4;3;2;3]	[4;3;2;3]	[4;3;2;3]	[4;7;4]
[5;4;3;2;3]	[5;4;3;2;3]	[5;4;3;2;3]	[5;4;3;2;3]	[5;8;5]	[5;8;5]	[5;8;5]
[6;3;2;3]	[6;3;2;3]	[6;3;2;3]	[6;3;2;3]	[6;3;2;3]	[6;3;2;3]	[6;3;2;3]
[7;6;3;2;3]	[7;4;3;2;3]	[7;4;3;2;3]	[7;4;3;2;3]	[7;4;3;2;3]	[7;4;3;2;3]	[7;4;7]
[8;5;4;3;2;3]	[8;5;4;3;2;3]	[8;5;4;3;2;3]	[8;5;4;3;2;3]	[8;5;8]	[8;5;8]	[8;5;8]
[9;7;6;3;2;3]	[9;7;4;3;2;3]	[9;7;4;3;2;3]	[9;7;4;3;2;3]	[9;7;4;3;2;3]	[9;7;4;3;2;3]	[9;7;4;7]
[10;8;5;4;3;2;3]	[10;8;5;4;3;2;3]	[10;8;5;4;3;2;3]	[10;8;5;4;3;2;3]	[10;8;5;8]	[10;8;5;8]	[10;8;5;8]

We can see from these cycles that modal changes occur between voltage 4 and voltage 5, that is between -40 and -20 mv. This is as expected. This channel type spends most of its life oscillating between states 2 and 3, but in depolarized conditions experiences the other states, especially a state 5 to state 8 oscillation.

By exploration of state graph alternatives, the modalities can be characterized.

In this EX 16 state Q matrix, we can find the modalities.

% columns 1:8

5.20E-01	5.93E-07	9.70E-01	6.81E-07	1.80E-02	8.79E-07	9.71E-07	2.86E-07
3.16E-07	6.41E-01	6.00E-02	8.35E-07	1.79E-07	1.05E+00	6.03E-07	8.33E-07
3.00E-02	9.40E-01	3.41E-01	8.96E-07	2.49E-07	3.57E-07	9.20E-03	7.70E-07
8.86E-07	4.13E-07	1.94E-07	6.48E-01	5.20E-03	4.40E-02	8.63E-07	2.01E-07
5.00E-03	7.70E-07	9.13E-07	1.34E-02	3.55E-01	8.06E-07	3.20E-03	7.65E-07
8.63E-07	4.60E-02	6.84E-07	9.56E-01	9.21E-07	8.50E-01	1.12E-02	6.16E-07
2.45E-07	6.08E-07	3.00E-03	3.10E-07	5.20E-03	6.60E-03	5.43E-01	9.64E-07
4.34E-07	7.95E-08	7.13E-07	4.47E-07	9.03E-07	9.47E-07	6.95E-07	6.73E-01
2.60E-03	4.15E-07	4.85E-07	9.64E-07	1.90E-07	9.51E-07	8.41E-07	6.20E-03
2.16E-07	1.30E-02	8.33E-07	4.62E-07	9.93E-07	3.21E-08	6.76E-07	1.46E-02
7.75E-07	8.43E-07	1.26E-02	4.96E-07	3.26E-07	2.76E-07	7.01E-07	9.80E-07
8.72E-08	5.24E-08	2.55E-08	1.68E-02	2.28E-07	6.78E-08	8.95E-07	1.02E-02
4.00E-07	7.28E-07	3.36E-07	1.92E-07	1.40E-02	8.27E-07	5.87E-07	2.61E-07
5.90E-07	1.15E-07	4.87E-07	8.98E-07	8.11E-07	6.40E-03	3.25E-07	5.90E-07
1.97E-07	4.85E-07	2.25E-07	3.89E-07	9.24E-07	5.81E-07	1.08E-02	7.45E-07
9.56E-01	6.20E-02	5.55E-07	1.20E-02	7.19E-07	3.44E-07	2.08E-07	1.12E-001

% columns 9:16

1.56E-02	2.69E-07	7.87E-08	6.28E-07	1.83E-07	2.55E-07	7.81E-07	4.40E-02
8.70E-08	1.00E-02	8.68E-07	7.86E-07	3.21E-07	9.12E-07	2.90E-07	6.20E-02
3.18E-07	9.54E-07	3.40E-03	7.49E-07	2.56E-07	3.68E-07	5.51E-07	2.52E-07
4.53E-07	1.18E-07	7.97E-07	1.22E-02	9.41E-07	3.80E-08	5.75E-07	1.01E+00
1.61E-07	2.49E-08	7.86E-07	1.83E-07	1.40E-02	6.51E-07	2.04E-07	3.99E-08
5.99E-08	4.22E-07	3.31E-07	8.44E-07	9.88E-07	1.92E-02	5.55E-07	6.24E-07
4.45E-07	6.44E-08	9.50E-07	7.16E-07	9.52E-07	8.38E-08	1.08E-02	3.87E-07
1.26E-02	1.00E-02	8.28E-07	1.16E-02	8.74E-07	1.15E-08	5.49E-07	1.12E-01
2.57E-01	9.24E-08	1.30E-02	6.13E-07	7.80E-03	3.66E-07	6.98E-08	3.32E-07
5.10E-07	1.21E-01	4.40E-03	8.74E-07	1.47E-07	1.10E-02	8.60E-07	9.32E-07
1.08E-02	6.80E-03	4.06E-02	7.93E-07	6.50E-07	4.16E-07	1.58E-02	4.68E-07

8.30E-07	6.10E-07	9.89E-07	8.88E-01	1.24E-02	1.36E-02	2.39E-07	7.10E-11
7.80E-03	3.95E-07	3.44E-07	1.24E-02	7.53E-01	4.66E-07	5.80E-04	7.26E-07
4.27E-07	4.60E-03	2.40E-07	1.12E-02	2.45E-07	8.02E-01	2.20E-03	3.99E-07
7.33E-07	9.61E-07	1.58E-02	6.24E-07	1.48E-03	2.20E-03	4.41E-01	2.29E-08
5.27E-07	7.50E-07	9.09E-07	3.53E-07	2.33E-07	5.08E-07	3.19E-07	7.52E-02

A method for detecting the dominant limits cycles is developed here:

```
for k = 1:p,                                    % where p = number of pages in Q
Q = diagzero(QQ(:,:,k));                        % zero out the diagonals
for j = 1:length(s0),                           % for each starting state
    elx = [];                                   % init
    elx(1) = s0(j);                             % capture first state
    rowx = Q(elx(1),:);                         % go to state probability row
    if max(rowx)~=0,                            % all zeros means dead end
        [junk elx(2)] = max(rowx);              % find column# of highest prob
        i=2;                                    % cannot use for loop, len
unknown
        while ~ismember(elx(i),elx(1:(i-1))), % keep going to a previous state
            rowx = Q(elx(i),:);
            if max(rowx)==0, break;  end
            [junk elx(i+1)] = max(rowx);
            i=i+1;
            if i>100, break;  end               % safety break extremely long
paths
        end  %  while
    end  %  if
    series{j,k} = elx(:);                       % columnize
end  %  for j
end  %  for k
```

This Q matrix results in the following dominant limit cycles, starting at each of the state numbers:

[1;3;2;6;4;16;1]
[2;6;4;16;1;3;2]
[3;2;6;4;16;1;3]
[4;16;1;3;2;6;4]
[5;13;5]
[6;4;16;1;3;2;6]
[7;15;11;15]
[8;16;1;3;2;6;4;16]
[9;11;15;11]
[10;8;16;1;3;2;6;4;16]
[11;15;11]
[12;4;16;1;3;2;6;4]
[13;5;13]
[14;12;4;16;1;3;2;6;4]
[15;11;15]
[16;1;3;2;6;4;16]

Revealing three modalities:

1,3,2,6,4,16
5,13
11,15

Only the first of these three can do work, because a minimum of 3 states are required to impart directionality. As interesting as this might be, it is only the beginning of investigation. Each modulation combo produces another Q matrix, and each of those Q matrices produce a set of limit cycles. Having determined the complete 3-dimensional Q-space, then limit cycles may be investigated as to their dynamic possibilities. Though many of the possibilities be found worthless, it is those occasional few that perform useful work that will be selected for.

A huge new fascinating area is the pursuit of dynamic duty cycles that can be brought about by fast modulation patterns.

9.16.14 ENERGY BARRIER PROFILES FOR ION CHANNELS

Each type of ion channel has a complex charge/shape interaction with any ion passing through it. Because ions are of varying size, mass and charge, the energy barrier profile will be different for each ion type. This is critical because it determines the selectivity of the channel. Furthermore, this energy profile will change as a function of any force which strains the shape of the proteins comprising the channel, e.g. voltage. To the extent that the energy profiles can be accurately measured across it parametric domain for each type of ion present in the system, a model incorporating this data should have high predictive value regarding the quantity of ions passing in both directions under any given set of conditions.

However, the literature rarely produces such completeness. As of this date, it is usually the case that only one ion type, the dominant one, is studied quantitatively. Others may be referred to qualitatively, or as assumed or approximated ratios in conductivity.

Such paucity of data is not fatal IF:

a) the conductance of other ions is several orders of magnitude smaller than that of the dominant ion;

b) the conductance ratios between ion types are nearly constant.

9.16.15 GATING MECHANISMS

Gating phenomena can be effected via a variety of mechanisms. In essence:

there must be some obstructive arrangement via: lever, plug, twist, charge, reflection, deflection, binding, wedge, misalignment, loss of pressure, freezing, viscosity, etc.

This obstruction must be modifiable via changes in its conformation, position, charge, temperature, etc.

The gating mechanism thereby "opens" to allow the passage of some commodity.

At some later time a different type of event occurs that effectively closes the gate. This may be a totally separate obstructive mechanism, moving the same obstructive mechanism by different means, or by the same obstructive mechanism closed by a reversal of the original opening force.

The forces that open and close gates may be thermal, charge, mechanical.

There may additionally be "hidden" states that effect the opening and closing behavior of gates. For example if there are four gates, any one of which obstructs a channel, then when only on closed, the states of the other three are unknown (and do not immediately matter for purposes of mensuration, but do matter for correct stochastic behaviors).

9.16.16 CONDUCTION

Most references to ion channel conduction in the literature refer to ohm's law $I = V*G$, as the determinant of exactly how many ions are conducted per unit time. This imported concept from the realm of linear electronics in the solid state is too simplified for biological prediction. Ion channels are not acting a passive resistors, but rather extremely dynamic (thermally) with complex resonances, that have great effect upon which types of ions pass through and how many of each. Therefore, it must be recognized from the onset that an ion channel might conduct far more than ohm's law would predict. Some report up to 100 times as much. Although we may talk of the effective diameter of a channel to compensate for this phenomena, doing so cannot explain why then most types of ions cannot pass. Another compensation scheme might be to consider negative resistance, whereby some pumping might take place against the gradient. This too has its shortfalls because it would then predict flows against the gradient all the time.

Another approach might be to consider superconductivity as in play. There is merit to this in that those ions with matching resonances to the interior of the channel might be greatly facilitated in passage.

9.16.17 DIRECTIONALITY

Given that ion channels are cylindrical in shape and positioned perpendicular to the membrane, how is it that the neural membrane can propagate any action potential in a single direction from dendrites to axonal boutons? There is no algorithm for directionality. It is an emergent property of the channel refractory period.

9.17 PROGRAMMING LANGUAGES

When I first looked at the computer simulation program Neuron, written in C, the documentation described an ion channel as being an I/V curve (current over voltage lookup table). This implies no time function, no multi-configuration molecules, no probabilistic state changes, patterns, rhythms, modes, reversals, multiple modulator binding kinetics. This was woefully inadequate to my stated goals, and so I pursued Neuron no further. The criteria I use for deciding which feature should be included in the model is"What contribution does this phenomenon make to the information processing of neuronal throughput?" Rank ordering phenomena by their impact upon information sets the modeling priorities. And when the impact is low enough to be masked by natural noise, then the model may be deemed complete. To this end , a model of primarily Stochastic Differential Equations (in massive quantities) can meet the need.

Matlab enjoys a short learning curve thanks to its ready made plotting routines and Fortran like simplicity in notation, making it tempting for most non- Computer science majors. However, in the course of this project several downsides to Matlab have been revealed . They include:

1. There is lacking a coherent library of geometry functions.
2. The few canned plotting routines had to be rewritten to receive the outputs directly from this project.
3. Numerically intense simulations absolutely require efficient algorithms, but Matlab functions are often written with multiple features to accommodate a variety of fields. The logical tests within these (installed to receive various input formats) must be stripped out to achieve speed.
4. Ultimately the programmer must "bit manage" to get each routine lean and powerful, but Matlab is not conducive to low level manipulations, as it protects its files from read/write privileges.

5. All of the benefits that entice the newbie to use Matlab fade into insignificance in the face of the deep mechanics of accurately representing the continuities of space-time and physical principles in a digital machine.

6. Matlab has errors, but are not always easy to discover nor correct, due to its packaging and proprietary encoding.

7. The proprietary nature of Matlab puts economic distortions into research efforts that were not present with Fortran or C++. Buying toolboxes, renewing licenses, and embedding routines in other languages often caused delays and slows progress where open source domains can support unencumbered progress in these respects.

8. It is not easy to collaborate in Matlab, as it does not animate over the web without tedious efforts, and may trip on proprietary restrictions for those who have not paid a Matlab license. Note that Octave is an open source application that will run mat lab functions (albeit with careful editing for coding exceptions).

In retrospect, this project probably would be better off written in Java. Java is as algebraically complete as C++ and is immediately post-able on the web for animation, sharing and collaboration. My greatest surprise in tackling this project is how little has been done, and therefore the immense amount of work that remains to be done, to create a library of routines that constitute a platform (library, toolbox) of useful, mutually compatible functions in physics and geometry, upon which to build and tackle ever more complex phenomena, such as chemistry and biology. Accepting that so large of a library is a challenge beyond one person's ability, it is imperative that global collaboration be facilitated, encouraged, and captured in public databases. One of the huge benefits from the open source movement is that it has enabled the participation of millions of people who previously could not afford to participate.

The development of computer languages in many ways has paralleled the production of scientific literature. Historically, science has been written in many languages, using many units systems and employing distinctive mathematical symbolisms. Over time English has become dominant, and the SI units have been tightened and become dominant. Computer languages are in a much earlier phase, one of exploding numbers of languages. This is a great exploration of the semantic space, but is also an implicit admission that we do not yet understand the theory of languages well enough to create a general computer language for science. This is a tough time to be modeling, forced to express one's “science” in some transitory language experiment, doomed to go extinct soon.

Human thinking relies heavily upon assuming, bundling, naming, and associating - in a discrete, subjective fashion. These are of the essence in human information processing and decision making. But the underlying mechanisms of these “thoughts” are stochastics within the neurons, and that is where probabilistic mathematics performs admirably.

When we maintain a basis in drift[20] and kinetics, we gain both the ability to predict and the benefit of emergent properties and behaviors. Ones that mimic the naturally emergent higher phenomena. This is a strong case against the distilled shadows of mathematics that we call logic and procedure, which are endlessly fraught with inadequacy and poor predictions when applied to the real world. No amount of man-made law can predict the next exception to the rules. But stochastics can predict them probabilistically.

The concepts that embody science are merely facades unless they obviously disassemble into their constituent first principles. Yes, even the emergent phenomena. A teaching aid for demonstrating simulations requires a Graphical User Interface (GUI) over either a physics model or over a concepts library. The concepts library is simpler, cheaper and less prone to trouble. A research simulating program must be based upon first principles, else it will be blind to important phenomena, will be more a model of man's prejudices than of real science, and will hit the "brick wall" every time one ventures outside the tried and true. Once the research project has stabilized to the point of parametrizing the input domains, then it may be economical to add the GUI and "release" it for teachers and students. Noteworthy, is that it is often a different person or group who adds the GUI, and the motivations and talents are different from the original creators

In my experience domain specific languages always lead to the "brick wall" experience. All fields at some point interface with other fields, and require their incorporation, while field-specific applications lack this wisdom. Just as disappointing, any "general purpose language" consisting of a library of "concepts" derived from years of teaching, will likely be built up of menu selections of useful but shallow formulas. The history of education is but a mighty collection of well digested heuristics, far divorced from the tools and mental agonies of original experimentation. Concepts are not the end game. Concepts are static snapshots brought home from a vacation visiting an aboriginal tribe. The snapshots are not life, nor can they be "drilled down" to arrive at life. They are shallow indeed. They predict the deterministic, but are wrung clean of the variance and emergent behaviors. Therefore they only predict the simple things. Concepts are a weak intermediate form of knowledge, the projections of science upon the billboards, convenient for visitor though they may be. The end game is prediction. Science is the observation of nature, and allowing its current state to grow new behaviors, patterns, and future states. These subsequent states and patterns we may choose to call concepts, or not. They will be too numerous to name. The

[20] Drift is a weak term for naming the important ionic wave transmission. We need a new term. How about lasma?

more complex behaviors are usually beyond our ability to assign a “concept” name to each, but rather a series of them is seen as a “performance”, no two quite alike.

Thus, it is not concepts we wish to store in our languages, but rather capacities, potentials, traits, natural patterns and probabilities (spatial, temporal, and others). New nomenclature will undoubtedly evolve to give names to observed patterns that do not fit into our old concepts. It is the patterns themselves which the computer must embody, not as individual entities (concepts), but as a network of coupled interactions, all growing from the underlying first principles. So called “emergent behaviors” are simply the addition of layers of complexity built up of patterns meta to the previous patterns.

A frequent complaint about the quest for a universal computing machine, or a theory of everything, is that it is crazy to insist that anyone employing a computer to do, say, graphic art, needs to drill all the way down to the molecule and built up from there. Certainly, it would seem computationally impractical to do so. Yet, that is precisely what each computer “application” does in the every day work place. It takes user interface data (keystrokes), runs them through the “highest” levels of software (e.g. PhotoShop), which calls lower level functions (e.g. Windows), which calls still lower levels (Drivers), down to “machine code”(e.g. AMD instruction set), which in turn is constrained by a “hardwired” set of chipset constraints and procedures. For those “drill downs” which are too cumbersome to repeat and are reliably consistent, prior runs may be “saved” as lookup data. Whenever there is an exception (query exceeds bounds of domain), then a drill down must be executed to expand that domain. This is the essence of multiscale modeling. To make all of this work for science we need only replace “machine code” with first principles of physics. It is quite feasible. We only need a new hardware architecture. The rest is consequent.

Not an expert in the philosophy of language, there are none-the-less some aspects of it relevant to this work. A universal language must be capable of mimicking physics, and of assembling first principles into aggregate behaviors of chemistry, biology, ecology, society, art and politics. Where ever there is continuity in time and/or space, then the continuous number line of mathematics (not digital bits) is an appropriate representation. It is not until we build up complexity to the level of human sociology, particularly symbol-manipulating societies, that nominalism and logic emerge. And there we discover that man's rendition of things (giving names to perceived entities and applying logic to their various potentials) is a gross simplification of reality. Counting numbers are a

gross simplification of the whole of mathematics. So also is the digitization of scientific processes. The surprise is that we have gotten so far with such a handicapping view of things.

The digital computer is one creation of such handicapped thinking. By imagining that logic was somehow valid outside of contrived simple games, we declared the scientific method ("All other things remaining equal, A causes B."). We have held the concept of causality in high esteem and are simulating rather complex physical phenomena based upon it. But we do so painfully, having to compensate for both the digital discontinuities at every "step" and the very large quantities of "causal" combinations. Digital representations distort ("butcher" would be more accurate) the behavior of most natural phenomena. It is like trying to discover fractions where only whole numbers are allowed. Where continuity is absolutely not allowed, how can one emulate and study continuity? What is sorely needed is development of HAD machines (hybrid analog digital).

9.17.1.1 Universal simulation language characteristics

A representation of continuity in N-space implies a native adjacency, not a calculated one. This, in turn, implies what is usually called an analog computer.

A representation of physical particles, with size, mass, charge, movement, transmutations, etc. This implies a native sense of discreteness, entities that can move and collide.

A library of aggregate phenomena, stored as patterns of lower level interactions. These may be "simplified" (collapsed) into lookup tables of previously recorded results when used consistently.

These three will get us from atoms to astronomy, but may not well serve the whimsical, the arbitrary, symbolic or science fiction based projects. And that brings us to a critical decision. Do we really want to incorporate impossible fiction into our modeling language, or would we be better off with a reality-based modeling program that checks unrealistic "models" and labels a hypothetical as such?

For better or worse, we now live in an arbitrary context of such artifices as persuasive logic, legal systems, and digital computers. Postmodernity is defined, among other things, as going beyond reality-based semantics. Science however would be best served by developing a strictly reality based software environment, such that fiction would require conscious effort to "violate" its general domain. Admittedly, arguments are sure to continue as to the nature

of claimed reality domains, as refinements. The man/machine interface is a mapping between how nature works and how humans like to think they work.

Matlab uses scripts, functions, external calls and data. Python is very good at external calls, fetching pieces from various data bases, fetching routines from a variety of languages and scripting them together to execute a task. It also offers a certain terse style of database manipulations. It allows opening the lower level code accessible to bit management. All of these are strong pluses. Unfortunately, because Python is a top down effort, it is way at the other end of the spectrum from natural phenomena. Python works at the most abstract end of the spectrum in its handling of arbitrary human data deposits. It provides great man/machine interface, but interface to what? That is left wide open (nice) and unconstrained (no reality checks). What is most needed by scientists is a fundamental and complete basis for representing (and indeed building) nature. And that is what we usually call physics. Physics supports every manner of complexity "above" it, so "bottom up" modeling works. But the higher forms of complexity, such a sociology and politics, do not support "top down" modeling of physics (certainly not in their current forms, anyway). That is because they stop cold at their conceptual definitions. Concepts that do not disassemble into physics. The unification of the body of scientific knowledge requires the spectrum from physics to politics be continuous. This is certainly possible, but not yet implemented.

Any general simulation language, to have staying power, will need GUI's that mimic the way humans learn a new field. Closely enough that learning the language and learning the field are one and the same thing, not two separate undertakings. This is the essence of "user friendly". Python is a step in this direction, but surely not yet looking like the way scientific fields are taught. A general simulation language will also be graceful in its transitions and interfaces between fields of study. It will also require ll constructs to be built up from a library of true physical phenomena expressed in natural units, not abstract thinking, not a *carte blanche*. This is likely to be accomplished within a mathematics program, like Matlab, Mathematica, Maple, or Octave, cleaned up so as to be driven by such a library. Growth will be via evolution and accretion, expressed as patterns. Each new entity will record its basis, exercise its domain, and then offered a collapsed image of itself for convenience, with a "clickable" portal into its inner workings and subcomponents. The relationship between the traditional library of books and the library of computer routines is the precise relationship between statics and dynamics. A successful language will support the gradual translation of all paper library holdings into a form that brings them to life via the natural dynamic processes inherent to each, of which the paper records were mere snapshots. We are in transition from sketches to animations.

The argument has frequently been made that there is no perfect language, that special purpose languages are much more efficient, and allow the user to learn his field without the encumbrances of learning all fields. The fallacy of this argument is revealed by the statement "One does not have to learn every word in the dictionary before speaking English." A single mathematics, although not unique (see Godel's proof), may be adequate to represent the whole of physical phenomena. One can then focus on a specific field or project by employing those bundled phenomena that are relevant. Special purpose routines, if not based in the underlying phenomena, are built of shallow representations (facades) and therefore of limited value. The reductionist and anti-reductionist arguments have fallen on their logical over-simplifications. Both the analysis to reduce, and the synthesis to induce are true and real, thanks to the highly coupled nature of all components of the universe and their ability to assemble in ever more complex patterns. Nature supports both the analysis of science and the synthesis of engineering. Therefore we must not recoil at the thought of using physical phenomena as a basis of all that is knowable. The key is in how we aggregate lower level phenomena into ever higher complexity. That is, the calculus of complexity, in essence, the language of aggregate phenomena, that extends physics through biology and beyond. But can it do poetry? Yes, it can do poetry in the style of any author you wish, and invent new styles as well.

A noteworthy technical development in the entertainment industry employs Computer Graphics (CG) workers within Dreamworks, Pixar, etc. to master the modeling of many natural phenomena: 3-d space, inertia, acceleration, gravity, force fields, collisions, material deformations and fractures, texture, water, flows, wind, fabrics, skin, human organs, hair, skeletons, muscles, eyes. Such modeling has understandably evolved from fiction and over simplifications towards ever more realistic and detailed models of reality. Their contributions are soon to impact science by their development of the tools of representation, prediction, presentation, and the effective utilization of ever larger computing machines. They may even drive the development of new hardware, e.g. machines not based on step-by-step logic.

Be reminded that at the present we are hardware bound, with the vast majority of machines architected as step-by-step logic only. A machine that efficiently mimics natural phenomena will surely not be step-by-step. That single change throws out almost all of the computer languages in current use. Although the quantum computer has met with multiple, formidable snags on its quest to become a practical machine, it does embody both the continuity and the discreteness inherent in natural phenomena. It will take something like this to break away from our current digital shortcomings.

In an important sense, two languages are needed. One to address real phenomena. This is essentially the mathematics and stochastics of physics and its emergent phenomena. The second to address the arbitrary ruminations of human queries, arbitrary databases, arbitrary industries, arbitrary labs and arbitrary funding agencies. Humans entertain hypotheticals, attend to urgencies, love art, and make decisions as to which to attend to. Python might be very good at these (via semantics), but we still have to develop the sound basis (science).

Though the plethora of computer languages currently being invented represents progress in the understanding of representations of knowledge, modeling real phenomena, and human/machine interface, it is not good for the communication of science nor the collaboration now urgent in the tackling of large problems. If you imagine science as being written in 200 different languages, with translations between them difficult, slow and uncertain - that would cast the current situation of computer languages in perspective. There will be a shake out, and a very short list of surviving “winners”. Like English they will not be perfect, but rather good enough to carry us another decade or so. Like mathematics, each must be algebraically complete, continuous, and support all manner of dynamics. The resistance to this conversion will be substantial, for the same reason that the digitization of the library of congress is a monumental undertaking – its an economic burden most organizations cannot afford. But science needs a universal language which couples all into a single body, coupled dynamically, rather than statically as in the present and past. The more this new language looks like textbook mathematics the easier the transition. In any case, it will be quickly bundled and built into more familiar routines, like colors, shapes, flowers and poems.

9.18 MASTER ALGORITHMS

Follows is a summary account in English of the main features of this model. The mathematical accounts for the patch and whole cell are below.

An experiment is initialized via the Whole Cell Experimental setup, which entails creation of membrane shapes, particle populations, actor placements, and actor initialization. Membranes are defined both as a group of nodes homogenously spaced over the membrane, and as piecemeal algebraic equations that define the contours. Particles, initialized as boli, are then allowed to diffuse and equilibriate throughout each compartment. The transmembrane voltage is measured via Coulomb's law, at all occupied nodes. The Nernst partial voltages driving ion types through

open channels are calculated via log2 of the ratio of particle concentrations in small hemispheres above and below each actor.

Actor traits include: Q represents the state transition probabilities; and R represents the forward and backward bind affinities to the allosteric binding sites of the actor. Both are stochastic processes. R and Q matrices are conditioned to events per second, scaled to *dt*, and converted to CDFs.

Actor states are instantiated thusly: For each actor, the particle bindings at the allosteric binding sites d are mapped into a modulation combo number dc. This number is a pointer to the page in Qcdf. The current state s is a pointer to the row in Qcdf. The diagonal of Q indicates the probabilities of remaining in the same state. The indicated row contains the CDF for instantiating the next state. A random number 0..1 is generated from a uniform distribution. The resulting number is projected onto the CDF to yield the new state.

Actor binding events are instantiated thusly: For each actor, the current state s points to the page in R that contains the current binding affinities. R contains a forward table for bindings and a backward table for dissociations. The row is the current bind combo number. The indicated row contains the CDF for instantiating the next particle bindings to the allosteric sites. This CDF is dot-multiplied across the particle concentrations near the site. That is, each binding site is assigned to one of two actor poles, and each pole is assigned to a compartment. A random number 0..1 is generated from a uniform distribution. The resulting number is projected onto the CDF*conc to yield a new binding for each of the binding sites in d.

The state s maps to a phenostate which indicates the transport activities of the actor, if any. An open pore returns o=1, which is dot-multiplied across the actor type's particle conductivity profile, and then dot-multiplied across the concentration deltas of each of the particle types, multiplied times the duration of *dt*. This determines the quantities of particles to pass in a channel opening event. The process is similar for receptors and pumps, replacing conductivity with catalysis rates, and transport ratios, respectively.

Particles, upon being transported and dissociated, are reassigned to a new compartment, and assigned new velocities consistent with Boltzmann velocity distributions. Most particles are in constant motion due to thermal inertia. The EM forces from all charged particles, calculated each *dt* for the whole system simultaneously, results in summed drift acceleration (muted by viscosity) on each charged particle.

Particles may collide with other particles, with the membranes, or with actors. Collisions are detected via center to center distances less than the sum of the two radii. Particle-particle collisions are resolved via 3-d momentum transfers, using basis creation and reversion, along the axis of collision. These are carefully executed so as to preserve the information carried by any patterns of motion other than white noise. Actor collisions are described above.

Most significant behaviors of the model are emergent from these basic processes. An emergent result of the EM forces is the capacitation of all unbalanced charges, while balanced pairs are free to roam. The strength of the EM force dominates over the thermal noise, propagating signals between actors.

English account of the general model:

1. Establish actor traits: Q R O G aff erg eff = state transitions bindings openings conductivities affinities energy and messages
2. Q represents the state transition probabilities, as frequency of events per second;
3. R represents the forward and backward bind rates to the allosteric binding sites of the actor afo concentrations.
4. Condition R and Q matrices to units for uniform digital representation (some log compression is useful)
5. Rdt = R*dt; Qdt = Q*dt, with diagonal calculated as residuals
6. Rcdf = cumsum(Rdt,2); Qcdf = cumsum(Qdt,2); Integrals are useful for instantiation
7. Create: membrane 3-d shapes, particle populations, actor placements on surfaces as homogeneous nodal maps.
8. Each binding site is assigned to one of two actor poles, and each pole is assigned to a compartment.
9. Identify unbound particles. (Bound particles have their velocity frozen at zero.)
10. F = sum(k0*q1*q2/dx^2); Drift = sum across all charged particles in system.
11. A = F/m; Acceleration per Newton
12. Va = mob*A; Acceleration is converted to velocity by viscosity

13. V = V + Va; Current velocity plus drift = new velocity Most particles are in constant motion due to thermal inertia.

14. P = P + V; Current position plus new velocity = new position

15. Allow stabilization time for particles in motion to diffuse and equilibriate throughout the compartments.

16. Measure transmembrane voltage via Coulomb's law.

17. Measure Nernst partial voltages within small hemispheres above and below each actor, via log2 of ratio of particle concs.

18. PB – PA = dxAB; Positions of particles - Positions of actors = distance apart

19. If dxAB < affinity distance, then possible bindings

20. Actors are given initial states per stat distributions (or eigenvalues on Q)

21. For each actor, the particle bindings at the allosteric binding sites **d** are mapped into a modulation combo number **dc**.

22. This number serves as a pointer to the page in Qcdf. The current state ***s*** is a pointer to the row in Qcdf.

23. The indicated row contains the CDF for instantiating the next state ***s***.

24. A random number (0..1) is generated from a uniform distribution.

25. The resulting number is projected onto the CDF to yield the new state. Both are stochastic processes.

26. For each actor, the current state ***s*** points to the page in R that contains the current binding affinities.

27. For each actor, the current state s also points to the O table to determine the phenostate (openings, transport, etc.)

28. R_forward* local concs yields probabilities of bindings to particles in immediate vicinity

29. R_backward yield probabilities of dissociations.

30. A row in R is selected to match the current bind combo number ***dc***.

31. The indicated row contains the CDF for instantiating the next particle bindings to the allosteric sites.

32. This CDF is dot-multiplied across the particle concentrations near the site.

33. A set of random numbers (0..1) are generated from a uniform distribution for the binding sites.

34. The resulting numbers are projected onto the CDF*conc of each **d** to yield a new binding for each.

35. The phenostate **o** of chan indicate open pores. **O** =1 is dot-multiplied across the actor type's particle conductivity profile G

36. then dot-multiplied across the transmembrane concentration gradients of each of the particle types,

37. then multiplied times the duration of *dt*.

38. This determines the quantities of particles **nB** to pass in a channel opening event. The nearest **n** particles are chosen.

39. The process is similar for receptors and pumps, replacing conductivity with catalysis rates and transport ratios, respectively.

40. Particles, upon being transported and dissociated, are moved to the opposite pole and reassigned to a new compartment.

41. Such particles are assigned new velocities consistent with Boltzmann velocity distributions (as a function of temperature).

42. If distance between particle centers < sum of radii of the two particles, then a collision has occurred.

43. Particles may collide with other particles, with the membranes, or with actors.

44. Collisions with actors are detected via center to center distances less than the sum of the two radii.

45. Particle-particle collisions are resolved via 3-d momentum transfers, using basis creation and reversion, along collision axis

46. Each collision is momentum conserving to preserve the information carried by any patterns of motion other than white noise.

47. Particles impacting membrane are reflected off without loss of momentum.

48. Particle may be absorbed into and out of the membrane via stochastic treatment of partition coefficients.

49. Certain experiments may require higher level dynamics, such as moving actors, changing shape, changing tonicities.

Most significant behaviors of the model are emergent from these basic processes. An emergent result of the EM forces is the capacitation of all unbalanced charges, while balanced pairs are free to roam. The strength of the EM force dominates over the thermal noise, propagating signals between actors.

9.18.1 PATCH PROCEDURE

```
Script:  patch01
  particles in adjacent boxes with a dielectric membrane in between
  pump to build a charge differential across membrane
  units are [nm ms amu e-]

BEGIN DESIGN %  % BEGIN DESIGN %  % BEGIN DESIGN %  % BEGIN DESIGN %

cd C:\Users\Norm\Documents\dissertation\RSD21\Matlab
cd C:\Users\dyer1\Documents\ndyer1\dissertation\Matlab
load TypeP, load TypeA, load TypeB, load TypeC,
load DistP, load DistA, load DistB, load DistC,

P
dt    = 1E-5;          % seconds
qt    = 1E4;           % duration of run equal qt*dt
kelv  = 300;           % temperature, kelvin

C dist
Cchoose selects SH rows, or else a new row must be created in SH_master.
SH_h1 = {'Sh#','quad','qx','qc','xmin','xmax','ymin','zmin','ymax','zmax'};
SH_h2 = {'0=start point' '1=box' '2=cone' '3=cylinder' '4=disk' '5=perforation' '6=sphere' '7=torus' '8=vane'
'9=arbitrary'}';
SH   = [1,0,4,8,-43,-3,-50,-50,50,50;     % compartment dim's in nm
       1,0,4,8, 3, 43,-50,-50,50,50];    % membrane thickness = 6 nm

a membrane is the differential of the compartmental volumes. M = derv(C1,C2);
or a compartment is the integral between two membranes C = int(M1,M2)
how many membranes there are is determined by the juxtapositioning of the compartments
it would be more elegant to define the membranes and let the compartments
be the integrals between them, but for today, this method is expedient.
```

```
MC = [2 1];  % assign a membrane# to each compartment-compartment interface
1 row says there is only 1 membrane, lying between compartments C2 and C1
  MC creates membranes into which A can be embedded
  Membranes are subdivided lengthwise into zones (along x axis),
  Zones are subdivided into rings (similar SH rims, but spaced at dx)
ZON = [1]; % the 1st zone goes from 0 to ZON(1); 2nd zone is from ZON(1) to ZON(2),etc.
in this model there is only one membrane and it has only one zone.
EX:   2 membranes 3 zones ea:  ZON = [.2 .6 1; .1 .3 1];
you can name the zones with ZON_h8 ={...};
by convention h8 indicates the units of the values of the matrix elements



B type
TB          = getspreadsheet(pathB,'20datastructures.xls','211','F11:AK1034');
[junk TB_h1] = getspreadsheet(pathB,'20datastructures.xls','211','E11:E1034');
[junk TB_h2] = getspreadsheet(pathB,'20datastructures.xls','211','F8:AK8');
Bchoose chooses which particles from TB will comprise the shortlist BT
BT_h1_ =
{'Na','Mg','Cl','K','Ca','Gly','GABA','Ach','Glu','His','NE','Ser','Epi','caf','dop','cAMP','cGMP','IP3','ADP','ATP','
An','NU'}';
Bchoose_ = [11  12  17 19 20 475 503  531 547 553 566 572 580 593 594 746 762 817 827 903 1021
1022]';
Bq0_     = [95  0  105  0  0  0   0    0   0   0   0   0   0   0   0   0   0   0   0   0   100;
          105  0   95  0  0  0   0    0   0   0   0   0   0   0   0   0   0   0   0   0   100]';   % quantities of each
ion type in each compartment

BT_h2_ = {'mass','valance','radius','mob','red','green','blue','sh','sz','clas'};
Uchoose  =  [ 2     3       4       9     27    28      29    30   31    32];
%new assign [ 1     2       3       4     5     6       7     8    9     10]



A type
%         1 2  3 4 5   6   7 8   9 10
TA = cell {B R RQ Q O aff eff G erg id} library of actor type traits
for convenience actors are stored separately by clas:  TA1 TA3 TA4 TA5
  clas#=1 recp;  clas#=3 chan;  clas#=4 ves;  clas#=5 pumps;
Achoose selects actors from TA to create the shortlist AT
Achoose = [5 1];   % [clas# type#] list to be used in this experiment; populates AT from TA


A dist
AD = [2 3; 2 1; 2 4; 2 5];  % =[intra extra; intra core; intra dendroplug; intra axoplug] is standard
convention is to put intracellular compartment in first position if possible
AD = Atype x [pole1 pole2] x membrane#;  3-d
AD1 = 1;  % membrane#'s that the receptors are on.  See MEM for pole to compartment mapping
AD3 = 1;  % membrane#'s that the channels are on
AD4 = 1;  % membrane#'s that the vesicles are on
AD5 = 1;  % membrane#'s that the pumps are on
the only surface for actors in this design is between compartments 2 and 1
this ordering implies compartment 2 is intracell and 1 is core;
AD_h1 = 'actor#';
AD_h2 = '[pole1 pole2]';
the only surface for actors in this design is between compartments 1 and 2
this ordering has defaults: compartment 1 is intracell and 2 is extracell
```

```
all pdfs must be same length and same units: units are actors/nm^2
Apdf = Atype x pdf x membrane#;  3-d
each row in AT1..AT5 requires one row of pdf for each membrane
Apdf1 = [0 0 0 0 0 0 0];
Apdf3 = [0 0 0 0 0 0 0];
Apdf4 = [0 0 0 0 0 0 0];
Apdf5 = [0 0 0 700 0 0 0];  % (AT x pdf x qM)   q elements in pdf should be a 1/multiple of qrings
Apdf is the lengthwise density distribution for each actor type along a membrane.
when there are more than 1 membrane, a third dimension, or cell struct is needed

spatial pattern (length by width)
Apdfx = [0 0 0 1 0 0 0];      %  actortype x distribution of actors
lengthwise density distribution for each actor type in a membrane.
Apdfc = [0 0 0 7 0 0 0];     %  radial distribution of actors on ring
sum(Apdfc)== length(Apdfc;  This is to normalize the effects of Apdfx
circumferential density distribution function for each actor type

in this model there is only 1 actor, so 1 row
    Apdf = qAT x length(pdf) x qAM
each row in AM requires a page of pdf's in Apdf, 1 row for each actor type in AT

A check should be performed that A pole to pole distance > Mthk


 ABC
designtitle = '2 cubes with membrane between, 1 Na pump at ctr';
disp(designtitle);


P dist                PARAMS, MODEL scaling and limits
sfA   = 0.0000000001;    % acceleration scaling factor
sfB   = 01.0000;         % particle size factor
sfC   = 1.00000;         % scaling factor for size of C compartments
sfD   = 00.0500;         % set water collision fraction equal to
sfE   = 01.0000;         % collision elasticity
sfF   = 01.0000;         % Force scaling factor, EM
sfG   = 01.0000;         % Force scaling factor, affinity
sfH   = 1.00000;         % downscale quantities of A actors by
sfI   = 3.0;            % actor icon scaling factor (original=[-.5 .5])
sfJ   = 0.00001;         % downscale particle quantities by factor of
sfK   = 1 ;             % temperature downscaled by factor of
sfL   = 1.00001;         % log scaling C compartments (compression)
sfM   = 1.00001;         % log scale quantities of B particles
sfN   = 1.00001;         % log scale quantities of A actors
sfO   = 1.0;            % radius of bolus
sfP   = 1;              % pump rates
sfQ   = 1;              % channel conductivity
sfR   = 1E-6;            % channel density units /micron^2 to /nm^2
sfS   = 1.0;            % nodes per pdf value (use 2,4,8 for finer grain)
sfT   = 0.0;            %
sfU   = 00.0010;         % water viscosity
sfV   = 1;              % velocity scaling factor
sfW   = 0.01000;         % downscale quantities of D water by
sfX   = 1;              %
sfY   = 00.0600;         % clipA = limit acceleration/dt (to avoid escapees)
sfZ   = 00.0600;         % clipV = limit velocity per dt (to avoid escapees)
```

```
swAaff = 1;   % switch on/off particle actor attraction
swBaff = 0;   % switch on/off particle particle attraction
swCaff = 0;   % switch on/off particle container attraction
swDaff = 0;   % switch on/off particle water attraction

swAr = 1;   % switch on/off particle actor bind/unbind kinetics
swBr = 0;   % switch on/off particle particle bind/unbind kinetics
swCr = 0;   % switch on/off particle container bind/unbind kinetics
swDr = 0;   % switch on/off particle water bind/unbind kinetics

swAq = 1;   % switch on/off particle actor kinetics
swBv = 1;   % switch on/off particle particle velocity collisions
swCv = 1;   % switch on/off particle container velocity reflections
swDv = 1;   % switch on/off particle water collisions

swAo = 1;   % switch on/off actor phenostates
swBo = 1;   % switch on/off particle phenostate effects
swDo = 0;   % switch on/off water phenostate effects
swAeff =1;  % switch on/off shuttles
swAerg =1;  % switch on/off energy consumption reactions


particle switches:  (qCxqB, (C#,Btype) )
BT_h1_ = {Na Mg Cl K Ca Gly GABA Ach Glu His NE Ser Epi caf dop cAMP cGMP IP3 ADP ATP An NU};
Bchoose_=[11 12 17 19 20 475 503 531 547 553 566 572 580 593 594 746 762 817 827 903 1021 1022];
swB     =    [ 1   1   1  1  1   1    1   1   1   1   1   1   1   1   1    1    1   1   1   1    1    1;
               1   1   1  1  1   1    1   1   1   1   1   1   1   1   1    1    1   1   1   1    1    1];
Bchoose  = [ 1   0   1  0  0   0    0   0   0   0   0   0   0   0   0    0    0   0   0   0    0    1];

% actor switches  (qCxqA, (C#,Atype) )
switch on/off recep shut chan ves pump];   1 row for each compartment;
swA     =  [ 1    1    1    1    1;
             1    1    1    1    1 ];

% END DESIGN %  % END DESIGN %  % END DESIGN %  % END DESIGN %

% BEGIN BUILD %  % BEGIN BUILD %  % BEGIN BUILD %  % BEGIN BUILD %

 0. load data set (TP TA TB TC DP DA DB DC)
 1. create compartments (SH)
  1a. CB  SH piecemeal boundary equations (segs)
        CAD working points + spacings (arcs)
          contour of rotation
          point fill (dx)
  1b. CR rings
          point fill (dc)
  1c. CN nodes
        pos, orientation, polarity
        nearest neighbors
        Cceilings
        Creflectors
        Careas
        Cvolumes
        Volume subtractions for nested shapes
        bolus injection sites (Cinj)
  1d. Cvanes
  1d. Cplugs, create and locate boli within
```

1e. position all compartments relative to each other
2. create actors
2a. AC assign to nodes via dists: poles, orientation
2b. AT copy in actor trait subset:
2b1 affinities, aff function for A bindsites
2b2 bind/unbind probabilities, R function for A bindsites
2b3 conformational transition probabilities, Q function
2b4 phenostate map, O function
2b5 conductivity profile, G function
2b6 transport equations,
2b6 aff function
2b7 erg function
2b8 eff function

3. BT create particles
3a BC per concs, volumes: center bolus and sequestered
3b BV per temp, mass: assign Boltzmann velocities
3c RUNB until particles at SS (random positions)

4. RUNC sequence
4a AS initialize states of actors
4b B reflections, BC
4c B collisions, BB
4d B bindings/unbindings BA, R
4e turn on pumps A5: aff R Q O erg; document approach to SS
4f turn on channels A3 and vesicles A4: aff R Q O G (G gives conductivity rates)
4d turn on receptors A1 and input signal: aff R Q O G eff (G gives catalytic rates)

```
% C Build
qC = length(SH(:,1));                          % quantity of compartments
Mthk = abs(SH(2,5) - SH(1,6));                 % thickness of membrane
Mmid = (SH(2,5) + SH(1,6)) /2;                 % location of middle of membrane
Mpoles = [ Mmid-0.6*Mthk  Mmid+0.6*Mthk ];  % ideal location for actor poles
Mx = SH(1,9) - SH(1,7);                        % awkward, but expresses the 'length' of patch
Mc = SH(1,10)- SH(1,8);                        % awkward, but expresses circumference of patch
Msz = [Mx Mc];
Marea = prod(Msz);
fluidabove = abs(SH(2,6)-SH(2,5));             % thickness of extracell or core saline
fluidbelow = abs(SH(1,6)-SH(1,5));             % thickness of intracell saline

% NOTE: although nodes belong to C, they are best calculated with A


[Crib Crim Cnor Ccg] = buildCwireframe(SH,Cax,0);   %row1=leftcomp; row2=rightcomp;

qSH = length(SH(:,1));                     % count how many compartments there are
qC = qSH;
for i=1:qSH, SHctr(i,:) = Ccg{i}; end    % merely converts a cell list to a matrix



% B build
Bchoose chooses which particles will comprise the shortlist BT
then eliminate Btypes with zero quantities to further shrink BT
BT_h1_ = TB_h1(Bchoose_);    % ion types chosen for this model
BT_h2 = TB_h2(Uchoose);       % ion traits needed for this model
```

```
BT_ = TB(Bchoose_,Uchoose);  % Shrink TB to the needs of the model
% e.g. BT column headings: mass=2; valance=3; radius=4; color=5:7; shape=8; size=9; type=10;

[Bq0 BT BT_h1 Bchoose] = compress0(2,Bq0_,BT_,BT_h1_,Bchoose_);
% note flags on long forms
% note that [ Bq0 BT h1 Bchoose ] have been truncated to remove zero entries
Bq0 = qB x Cix = tonicities of each compartment
qBT = length(BT(:,1));

sfO = bolus size;
sfV = velocity scaling
[CDF vrange] = CDFboltz(BT(:,1),kelv*sfK,0:1:3000,1);  % make cdf's for Bvel
[BP BU LB LC] = buildB(BT,Bq0,CDF,vrange,SHctr,sfO,sfV);
BP = [ positions velocities acceleration ];       % Bpos
BU = [ atomicnum mass radius valance ... ];  % Btrait
LB = qBxqBT =                                     % logicals for Btypes;
LC = qBxqC =                                      % logicals for Comps;

BBr = BU2rr(BU);                                  % table of radius additions = r1+r2
[qBT qC] = size(Bq0);                             % quantity of Btypes and of Ccompartments
qB = length(BP(:,1));                             % quantity of particles in system


% A build
qAT = length(Achoose(:,1));
[AT1 AT3 AT4 AT5] =  peelA(Achoose,TA1,TA3,TA4,TA5);
AT = shortlist from TA by clas of each actor type traits in this experiment
AT1 = cell receptor traits, short list
AT3 = cell channel traits, shortlist
AT4 = cell vesicle traits, shortlist
AT5 = cell pump traits, shortlist
Hereafter, actor type will be only referred as the row# in AT

easiest way to determine node count is via pdf's.
change units of pdf's from A/micron^2 to A/nm^2
Apd1 = sfR*Apdf1;
Apd3 = sfR*Apdf3;
Apd4 = sfR*Apdf4;
Apd5 = sfR*Apdf5;
Apdc = Apdfc;                % Apdc = sfR*Apdfc? No, its units were never /micron^2
if pdfs are too grainy, interpolate them to greater node counts of choice
lenpd = length(Apd1(1,:,1));   % quantity of nodes along length of patch
widpd = length(Apdc(1,:,1));   % quantity of nodes along width of patch
Nsz = [lenpd widpd];          % size of nodegrid = [len wid]
qN = lenpd*widpd;             % total quantity of nodes according to pdfs

check for required actor density.  See if node grid can handle them all.
Apdq = sum([Apd1;Apd3;Apd4;Apd5],1); % sum pdf's to get total density
qApd = Marea*Apdq;               % mem area * actor density/nm^2 = lineal q
Apdxc = Apdc'*Apdq;              % grid of nodes with density values, according to pdfs
qN = sfS*numel(Apdxc);           % sfS is 1/grain
qA = sum(qApd);                % q nodes should be at least 8 times this
Narea = Marea/qN;                % area/node
Npeakload = max(max(Apdxc))*Narea;% find greatest channel density per node
                          % You can only put 1 actor in a node
sfS=1;                         % default grid size = pdf size
if Npeakload > 1, sfS = ceil(sqrt(Npeakload)); end  % surface area
```

```
NOTE: if there is 1 anomaly of very high actor density, ...
% this will drive up the node count to extremely high quantity.
Nlen = sfS*lenpd;
Nwid = sfS*widpd;
Nsz = [Nlen Nwid];
qN = Nlen*Nwid;
Narea = Marea/qN;
if sfS~=1,              % then all pdf's must be interpolated to fit Nsz
 Apd1 = interpoNor(Apd1,1:Nlen);
 Apd3 = interpoNor(Apd3,1:Nlen);
 Apd4 = interpoNor(Apd4,1:Nlen);
 Apd5 = interpoNor(Apd5,1:Nlen);
 Apdc = interpoNor(Apdc,1:Nwid);
end

NODES  = NODES4patch(x,y,pdfxc,grain)
NODES  = NODES4patch([SH(1,7) SH(1,9)],[SH(1,8) SH(1,10)],Nsz,Mmid,1);


Apos = placeActors(Acdf,SH);
[AN AU LA LM sf] = buildA2(NODES,Apd1,Apd3,Apd4,Apd5,Apdc,Msz);
NODES = (length x [xyz] x width)
Apd = pdfs for 1 actor clas; row = type
Apdfc = pdf for circumference
qA = quantity of actors
AN = actor# to node# assignments (see NA for node# to actor# assignments)
AU = [class type ] = extension of AT wastes RAM; so use only pointers to AT
LA = logical for actor columns = [recep chan ves pump]
LM = logical for actor assignments columns = [mem zon rin]
Apos = NODES(AN,:);
qA = length(Apos(:,1));
get pdfs for Apos and position icons
CellIcons = iconGen(Aicoparam,sfI,Aax);
% this function will crash if header column is in Aicoparam
CellIcons = {ico1 ico2 ico3 ico4};
ico1 is a cell of 5 icon rims;  ico2 is a cell of 5 icon ribs;
icon3 is a cell of 5 icon poles; ico4 is a cell of 5 icon names;

Atype = 5;   % 5=pump
for i = 1:qA;          % ico1,2,3,4,5 are cells for 5 icons
ico1{i} = RowAdd(CellIcons{Atype,1},Apos(i,:));   % ico1 is a cell of rims
ico2{i} = RowAdd(CellIcons{Atype,2},Apos(i,:));   % ico2 is a cell of ribs
ico0{i} = RowAdd(CellIcons{Atype,3},Apos(i,:));   % ico0 is a cell of poles
ico3{i} = RowAdd(CellIcons{Atype,4},Apos(i,:));   % ico3 = cell of bind sites
icoN{i} = RowAdd(CellIcons{Atype,5},Apos(i,:));   % icoN = cell of joysticks
end

 P build
Activity Switches, set to defaults, then manually alter to suit
swAp = ones(1,qAT);   % switch on/off actor position assignments, length = qAT
swBp = ones(1,qBT);   % switch on/off particle initial assignments, length = qBT
swCp = ones(1,qC);    % switch on/off compartments, length = qC
swDp = ones(1,qC);    % switch on/off water positions in each compartment manually set to off as desired



% STATIC Plot
```

```
 concatenate all points within plot axes
figure(2),
bord  = border(0.2,1,Crib,Crim);

C
for j=1:qC  % loop, for each compartment
   plotC(sC,Ccol,bord,varargin)
   plotC(1,Ccol(j:(j+1),:),1,0,Crib{j},Crim{j}), hold on;
end % j
plotNode(si,col,sz,NODES),

plotNode(9,[.7 .7 .7],12,node),

A
qA=1;
for k=1:qA,
    plotA(Asi,Acol,Alw,p1,p2,p0,p3,cn)
    plotA(Aico_si,Aico_col{k},Aico_lw,0,ico1,ico2,ico0,ico3,icoN);
end

B
for j=1:qC,   % for compartments
   for i=1:qBT    % for particle types
      plotB(sC,FaceB,EdgeB,SizeB,bord,varargin)
      plotB(Bico(i),Bcol(i,:),rand(1,3),Bsiz(i,:),0,BP(LB(:,i),:)),
   end % i
end % j
 title(designtitle),
 xlabel('x'), ylabel('y'), zlabel('z'),
 axis equal, view(20,20), axis(bord),

END BUILD %  % END BUILD %  % END BUILD %  % END BUILD %  % END BUILD %
BEGIN RUN %  % BEGIN RUN %  % BEGIN RUN %  % BEGIN RUN %  % BEGIN RUN %


 %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%



  TIME LOOP
for t=1:qt,
tic;

   logicals
   BinC1 = BP(LC(:,1),:);  % to get all the particles B in compartment C
   BinC2 = BP(LC(:,2),:);
   Required: re-assignment of compartment for each particle transported


    %%  %%  ACCELERATION  EFFECTS DUE TO FORCES %%  %%  %%

    BA  acceleration   Actor Affinities
   if swAa == 1,
     [Blist] = ABprofile(TA,TB);
     [Bconcs Bacc] = Abaffinity(TA,TB,r6,Blist);
```

```
   [A B] = ABbinding(A,B,Bconcs);

      get local concs at actor poles
   Mconc = getAconc(AP,AT,Apoles,Aprof,Aaffin,Cnum,Bconc);
   % identify all profiled particles for affinity within capture radius
   BAacc = affin2acc(AP,Apoles,Aaffin,Mconc,sfMa);
   BAacc = BAz2Bacc(BP,BU,AP,AU,expon,sfBa);
   % determine reaction rate wrt current modulation and effects upon state

  else BAacc = zeros(qB,3);
  end

 % BB  acceleration   Charge forces
  if swBa == 1,
   BBacc = BBz2Bacc(BP,BU,expon,sfBa);

  else BBacc = zeros(qB,3);
  end

 % BC  acceleration   Charge forces
  one side of plate is positive, other negative
  Be aware of impact on temperature of velocity increases.
  if swCa == 1,
     BCacc =  BCz2Bacc(BP,BU,CP,CU,expon,sfCa);

  else BCacc = zeros(qB,3);
  end

 % BD  deceleration   Water forces
   water is a dampener on velocity, but slowing velocity cools liquid
  if swDa == 1,
     BDacc = BDz2Bacc(BP,BU,DP,DU,BBacc,expon,sfDa);
  else BDacc = zeros(qB,3);
  end

 %  SUM Acceleration
  Bacc = BAacc + BBacc + BCacc + BDacc;



   %%  %%  VELOCITY EFFECTS  %%  %%  %%

  % BD  Detect Water Collisions
  [V qHits] = colliderWater(V,LB,CDF,vrange,sfW,sfV)
  if swDv==1,
     BP(:,:,t) = WaterViscosity(BP(:,:,t),LB,CDF,vrange,sfW,sfV);

  % BD  Resolve Water Collisions  ( handled within colliderWater)
    end

 % BB  Particle Collisions
        %  BB  Detect Collisions
  if swBv == 1,
     [BBd2 BBd] = B2ABCdistance(BP(:,:,t),BP(:,:,t));
     BBhitlog  = BBcollisionDetection(BBd,BBr,sfR);

       %  BB  Resolve Collisions
```

```
  [BP2 BP3] = BBcollisionResponse(BP,BU,BBhitlog);

  end


  BA  Actor Bindings
  if swAv ==1,
   BA  Detect Collisions
     [BAd2 BAd] = B2ABCdistance(BP,BA);
     BAhitlog = BBcollisionDetection(BAd,sfR);

   BA  Resolve Collisions as bind/unbind
   BAbindings = BAinstantiate(AS,AMkinet,ABkinet,BAhitlog);
   [AMbound BP] = BAbind(AMbound,BP,AS,AR,AMkinet);
  end



 % BC  Container Reflections

 %  BC  Detect Collisions
  if swCv==1,
      BP   =  collisionBox(BP,box,sfE)
     [BCd2 BCd] = B2ABCdistance(BP,BC);
     [inbound outbound in out log] = collideBox(BP,BV,Sh);
     BP(LC(:,1),1:6,t)   =  collisionBox(BP(LC(:,1),1:6,t),Sh(1,:),sfE);
     BP(LC(:,2),1:6,t)   =  Ccollision(BP(LC(:,2),1:6,t),Sh(2,:),sfE);

   BC  Resolve Collisions
     BP(LC(:,1),1:3,t) = noLeaks(BP(LC(:,1),1:3,t),BU(LC(:,1),3),Sh(1,:));
     BP(LC(:,2),1:3,t) = noLeaks(BP(LC(:,2),1:3,t),BU(LC(:,2),3),Sh(2,:));
  end


    %%  %%  POSITION EFFECTS  %%  %%  %%

  BD  Water shells,  solvation
if swDv==1,
     BP(:,:,t) = WaterShells(BP(:,:,t),LB,CDF,vrange,sfW,sfV);

    BD  Resolve Water Collisions  (covered above)
  end

  [A B d] = bindBA(A,B,s,d)
  get AMcombos
  get Bbound

  %%   ACTOR STOCHASTICS
 %   Certain blocks omitted per proprietary protection requirements
  %   ACTORS  % organize data extracted from TA to cell of short list
    Each Actor type has associated with it kinetics: AR, AQ, AO, and AL
    AR = binding site kinetics:  ARf for bindings, ARb for dissociations
    AQ = conformation kinetics  = kolmogorov Q
    AO = lookup table from state to phenostate (effects transport)
    AL = subunit interlogic

 %   Actor modulation
```

```
   ARf = modulator kinetics perform stochastic bindings
   Arb = modulator kinetics perform stochastic dissociations
   ARQ = lookup table maps D into a page number for Q
   ADbinds = current bind state of each actor (vacancies+Boccupancies)
   ABaff = draws B into binding range to match empirical
  ABerg = conversion of bound ATP-like particles into less energetic forms
  ABtrans = stochastic transport of bound B to other pole
  Dcombo = Actor:B bindings:   allosteric bind state + transport bind state


 Actor state
   AQ = state transition matrix
   AS = list of all actor current states as time series
   D = list of all actor vacancies and bindings, as time series

 Actor phenostate
   AL = lookup table for logical relationships between subunits
   AO = instantiated phenostate

 BA Transport
  receptors, none
  pumps, only by kinetic schemes
  vesicles, none
  channels, as function of partial pressures
  shuttles, as function of kinetic schemes

 %  BA unbindings


%  Add VELOCITY to POSITION
  BP(:,4:6,t+1) = BP(:,4:6,t) + clipit(BP(:,7:9,t),clipA);   % acceleration
  BP(:,1:3,t+1) = BP(:,1:3,t) + clipit(BP(:,4:6,t),clipV);   % velocity

  %  check BB Collision Detection
  %  check BB Collision Response

end  % time loop
```

9.18.2 WHOLE CELL PROCEDURE

Assemble the concepts into a computer program that executes compartments, actors and particles dynamically and captures their behaviors for replay.

```
 BUILD SCRIPT for Goblet-shaped neuron
_extracts design data from Spreadsheet

   INPUTS
  Main = [neu mem zon p2x p2y h thk memnane ];  where
  p1 = [ x1 y1 ] = first p1.   starter point = [0 0]
  h = arc height above line between P1 and P2 (this is recalculated into [r0 x0 y0].
  neu = which neuron cell this is: type, serial #
  mem = { main extra core plugin plugout }
  zon = { synin stalk soma hillock axon ranvier bouton synout }  (others may be defined)
  thk = thickness of fluid spaces, to calculate adjacent membrane working points
```

```
 dxdc = { internode spacing on this membrane }

   OUTPUTS  (calculated values)
 wall = B layers that particles perceive as their floor and ceiling (calculated)
 segm_sorted = seg numbers ordered to align to pdfs

    VERSION    ndyer1    20090311
Copyright    Norman Jay Dyer    20090311


   NOTES
shapes = {0=startpt 1=box 2=cone 3=cyl 4=disk 5=perf 6=sphere 7=torus 8=vane 9=arb 10=spindle)
ss = {'-';'--';'-.';':';'.';'*';'+';'x';'o';'v';'^';'>';'<';'d';'s';'p';'h'};
      1   2    3    4   5   6   7   8   9  10  11  12  13  14  15  16  17

SEGM = nx200 block of line segment traits for contours of revolution
       columns 1:50 = geometry
       columns 51:100 = types
       columns 101:150 = adjacencies
       columns 151:200 = externalities

  SEGMS,RINGS,NODES have the following columns
P=position D=derivatives T=types S=serial Q=quantity N=nearest F=pdf C=color

P          1           2           3           4           5
         'x1',       'y1',       'z1',       'a1x',      'a1z',

           6           7           8           9          10
         'x2',       'y2',       'z2',       'a2x',      'a2z',

          11          12          13          14          15
         'x0',       'y0',       'z0',       'r0',       'h',

D         16          17          18          19          20
    'bisectx',   'bisecty',   'bisectz',    'intLen',       'sh#',

          21          22          23          24          25
    'midarcx',   'midarcy',   'midarcz', 'thk under',  'thk over',

          26          27          28          29          30
       'norx',     'nory',     'norz',       'dx',       'dc',

          31          32          33          34          35
      'perpx',    'perpy',    'perpz',    'circum',    'redund',

          36          37          38          39          40
     ' r2r x',    'r2r y',    'r2r z',      'r2r',   'ar surf',

          41          42          43          44          45
      'wallR',    'wallL',    'vane+',    'vane-',        '  ',

          46          47          48          49          50
    'compart',  ' compart',   'compart',   'compart'         '  ',

T         51          52          53          54          55
    'neutype',   'memtype',   'loctype',   'radtype',   'functype',
```

```
         56          57          58          59          60
    'zontype',   'segtype',   'rintype',  ' nodtype',   'acttype',

S        61          62          63          64          65
       'neu#',     'mem#',     'loc#',     'rad#',     'func#',

         66          67          68          69          70
       'zon#',     'seg#',     'rin#',     'nod#',     'act#',

         71          72          73          74          75
      'plotG',    'plotN',    'xposSN',    'rposSN',    'funcSN',

         76          77          78          79          80
      'zonSN',    'segSN',    'ringSN',    'nodeSN',    'actSM',

Q        81          82          83          84          85
       'qneu',     'qobj',     'qloc',     'qmem',     'qrad',

         86          87          88          89          90
       'qzon',     'qseg',     'qrin',     'qnod',     'qact',

N       101         102         103         104         105
 'NN1 before', 'NN2 after', 'NN3 left1', 'NN4 left2','NN5 right1',

        106         107         108         109         110
 'NN6 right2', 'NN7 above', 'NN8 below', 'NN9 Rwall', 'NN0 Lwall',

        111         112         113         114         115,
 'dx Abefore', 'dx Aafter',  'dx left1',  'dx left2', 'dx right1',

        116         117         118         119         120
  'dx right2',  'dx above',  'dx below',  'dx Rwall',  'dx Lwall',

        121         122         123         124         125
    'aR xA', 'aR xRbelow','aR xRabove','aR RAbelow','aR RAabove',

        126         127         128         129         130
    'aN xA', 'aN xRbelow','aN xRabove','aN RAbelow','aN RAabove',

        131         132         133         134         135
  'vol over', 'vol under',  'ring vol'  'vaneunder',  'vaneover',

F       156         157         158         159         160
    'pdf zon',   'pdf seg',   'pdf rin',   'pdf nod',   'pdf act',

        171         172         173         174         175
      'loadx',    'loady',    'loadz',      '  '        '  ';

C       191         192         193         194         195
       'red1',    'green1',    'blue1',     'sym1',       ' ',

        196         197         198         199         200
       'red2',    'green2',    'blue2',     'sym2',       ' ',
```

PEEL from master table of points a structure can work for keeping track of a hierarchy of pieces
neuron.membrane.zone.segments.rings.nodes
disadvantage is that the zone is best defined after the segs are all assembled

```
 and to merely cross from one seg to the next in a new zone requires going up and down the hierarchy

 calculate: pivot, radius, start angle, stop angle,
          bisectors, midarcs, normals, perpendiculars, intLen, shape
 note: negative radius on arcs indicates counterclockwise sweep from start point
 cones DO have p0,r0 values; sign(r0)= - indicates expansion to the left

 LOAD
clr, pause,
filename = 'DistC05';   %% CHANGE THIS TO SPREADSHEET NAME of DESIRED SHAPE

% load DistA06
cd C:\Users\Norm\Documents\matlab_work\474\WholeCell
path='C:\Users\Norm\Documents\matlab_work\474\WholeCell';
sheetname = {'Mem','Van','Plu','Act','Com' };
header = {'Mem_h', 'Van_h','Plu_h','Act_h','Com_h' };

Mem data = [ neu      mem      zon      x2      y2      h       thk1 thk2 dx dc ];
[Mem Mem_h] = getspreadsheet(path,filename,'Mem');
Vane data: 'xstart' 'xstop' 'Lvar'  'Wvar' 'Lsec2' 'Lsec4' 'Lsec8' 'Lsec16' Lsec32' Lsec64' Lsec128'
[Van Van_h] = getspreadsheet(path,filename,'Van');
Plug data: xpos   rpos  Apos  flip  gap  type  xpos  Dmax  Rmax  qR  Dmin    Rmin
[Plu Plu_h] = getspreadsheet(path,filename,'Plu');
% Actor data: pdf chan densities over length of neuron divied into 100 values
[Act Act_h] = getspreadsheet(path,filename,'Act');
Act = Act';   % transpose such that a pdf is horz = [1 x 100]
% Compartment data:
[Com Com_h] = getspreadsheet(path,filename,'Com');

%% PARAMS

graphit = 1;
maxcol = 200;   % sets quant of columns for SEGMS,RINGS, NODES
log = 1;        % 1 = asks for log plots on pdfs 0 = linear plots
sf = 0.3;       % scaling factor, depends upon node density, lower densities require lower sf
cols = [ 51 52 53 55 56 62 63 64 66];        % search columns

memM=1;    memE=2;    memC=3;    memV=4;    memP=5;   % membrane numbers for ref

%% find out what we've received in the package
typeneu = unique1(Mem(:,1));     % get all types of neuron
qneu = length(typeneu);          % how many neurons are there?

% for neuN = 1:qneu,             % so far this script only processes one neuron
neuN = 1;                        % set which neuron you want to process
Mem = Mem(Mem(:,1)==neuN,:);     % reduce Mem data down to one neuron as a time

memT = unique1(Mem(:,2));        % get all types of membrane
qmem = length(memT);             % how many membranes are there?

iplu = Mem(:,2)==5;              % get all plugs
plum = unique1(Mem(:,3));        % how many plug types are there?

%%  peel out text: column and row headers and NAMES of things
NamesActor = Act_h(end,2:(end-1));  NamesActor = NamesActor(:);  % columnize
NamespdfZone = Act_h(1:(end-1),end); NamespdfZone = removeemptycells(NamespdfZone);
```

```
NamesMembrane = Mem_h(:,end); NamesMembrane = removeemptycells(NamesMembrane);
NamesMemTrait = Mem_h(end,1:(end-1));  NamesActor = NamesActor(:);  % columnize

NamesPlug = Plu_h(1:(end-1),end); NamesPlug = removeemptycells(NamesPlug);
NamesPluTrait = Plu_h(end,1:(end-1));

NamesVane = Van_h(1:(end-1),end); NamesVane = removeemptycells(NamesVane);
NamesVanTrait = Van_h(end,1:(end-1));

% NamesCompartment = Com_h(1:(end-1),end); NamesCompartment =
removeemptycells(NamesCompartment);
% NamesComTrait = Com_h(end,1:(end-1));

% calls multiple membranes at once
mems5=[memM; memE; memC; memP];
mems6=[memM; memE; memC; memV; memP];

%% generate SEGMS
                        % sets data block size for: SEGMS,RINGS,NODES
[SEGMS SEGa Extr Main] = Mem2SEGMS(Mem,maxcol);     % diagnostics
pause(.1),

Van = zeropad(Van,15);                      % clip off dummies or pad with zeros to insure std block size
SEGMSv = Van2SEGMSv(SEGMS,Van);    % create vane segments, borrowed from SEGMS
% SEGMS = [ SEGMS; SEGMSv];             % vert cat

%%  Define RINGS
RINGS  = SEGMS2RINGS(SEGMS);        % genRINGS
RINGSv = SEGMS2RINGS(SEGMSv);      % genVaneRINGS

plotRings(RINGS,cols),
plotRings(RINGSv,cols)
RINGS = [RINGS; RINGSv];
%% define Floors, Ceilings, Walls

%% Final Ring sort
RINGSz = sortZones(RINGS,mems5,0);       % mems is vane-less at this point

%%  Define NODES
% from [neuron#, membrane#, zone#]
NODES  = RINGS2NODES(RINGS,0);        % this function consumes minutes

% from vane params
NODEX(:,64)=0;                                % clean slate for vanes
NODESv = VanePlacer(RINGSv,Van);          % col52=4 to retrieve all vanes

% from plug params
NODEX(:,63)=0;                                % clean slate for plugs
Plu2 = Plu2many(Plu,gcf+2);                 % clone plugs already in RING
NODESp = PlugPlacer(NODES(NODES(:,52)==5,:),Plu2,0); % col52=5 to retrieve all plugs

NODES(NODES(:,52)==5,:)=[];                % delete base plugs to replace with multi plugs
NODEX = [ NODES; NODESv; NODESp ];    % vertcat positioned multi plugs
plotRings(NODEX,cols), pause(.1),

%% Final Nodes sort
NODEX = sortZones(NODEX,mems6,0);       % resorts all nodes for pdf's
```

```
                                                % mems6 includes vanes & plugs
%%  Nearest Neighbors

%%  load actors
NODEX(:,60)=0;                                  % clean slate for placing actors
zonebreak = displayDistA(Act,NamespdfZone,1);           % finds zones in pdf's
RINGSpdf = Act2pdfA(RINGSz,Act,memM,13);                % scales pdf's into actor counts per ring
NODEX   = ActorPlacer(NODEX,RINGSpdf,memM,sf,0);    % 60=type; 70 = SN 80=quantity

%% static plot
si =    [ 9    9    9    1    2    6];
siz =    [ 5    3    3    2    1    8];

swit = [0 0 0 0 0 1];
plotNODES(si,col,swit,NODEX,gcf+1),                     % plot: zones, core, extra, vane, plug, actors

Act1 = NODEX(NODEX(:,60)==1,6:8);
Act2 = NODEX(NODEX(:,60)==2,6:8);
Act3 = NODEX(NODEX(:,60)==3,6:8);
Act4 = NODEX(NODEX(:,60)==4,6:8);
plotP(6,[1 0 1],8,0,Act1),
plotP(6,[0 1 0],8,0,Act2),
plotP(6,[1 .2 0],8,0,Act3),
plotP(6,[0 1 1],8,0,Act4),

%% motivate particles

 TIME LOOP
for t=1:qt,
tic;

  logicals
  BinC1 = BP(LC(:,1),:);  % to get all the particles B in compartment C
  BinC2 = BP(LC(:,2),:);
  Required: re-assignment of compartment for each particle transported


   %%  %%  ACCELERATION  EFFECTS DUE TO FORCES %%  %%  %%

%  BA  acceleration   Actor Affinities
  if swAa == 1,
    ABprofile
    ABaffinity
    ABbinding


%         get local concs at actor poles
    Mconc = getAconc(AP,AT,Apoles,Aprof,Aaffin,Cnum,Bconc);
    identify all profiled particles for affinity within capture radius
    BAacc = affin2acc(AP,Apoles,Aaffin,Mconc,sfMa);
    BAacc = BAz2Bacc(BP,BU,AP,AU,expon,sfBa);
    determine reaction rate wrt current modulation and effects upon state


  else BAacc = zeros(qB,3);
  end
```

```
 BB  acceleration   Charge forces
if swBa == 1,
 BBacc = BBz2Bacc(BP,BU,expon,sfBa);

else BBacc = zeros(qB,3);
end

 BC  acceleration   Charge forces
one side of plate is positive, other negative
Be aware of impact on temperature of velocity increases.
if swCa == 1,
   BCacc =  BCz2Bacc(BP,BU,CP,CU,expon,sfCa);

else BCacc = zeros(qB,3);
end

 BD  deceleration   Water forces
%   water is a dampener on velocity, but slowing velocity cools liquid
if swDa == 1,
   BDacc = BDz2Bacc(BP,BU,DP,DU,BBacc,expon,sfDa);
else BDacc = zeros(qB,3);
end

 SUM Acceleration
Bacc = BAacc + BBacc + BCacc + BDacc;



 %%  %%  VELOCITY EFFECTS  %%  %%  %%

 BD  Detect Water Collisions
[V qHits] = colliderWater(V,LB,CDF,vrange,sfW,sfV)
if swDv==1,
   BP(:,:,t) = WaterViscosity(BP(:,:,t),LB,CDF,vrange,sfW,sfV);

  BD  Resolve Water Collisions

end


%   BB  Particle Collisions
%   BB  Detect Collisions
if swBv == 1,
   [BBd2 BBd] = B2ABCdistance(BP(:,:,t),BP(:,:,t));
   BBhitlog  = BBcollisionDetection(BBd,BBr,sfR);


%    BB  Resolve Collisions
[BP2 BP3] = BBcollisionResponse(BP,BU,BBhitlog);

end


%  BA  Actor Bindings
if swAv ==1,
%   BA  Detect Collisions
   [BAd2 BAd] = B2ABCdistance(BP,BA);
```

```
    BAhitlog = BBcollisionDetection(BAd,sfR);

%   BA  Resolve Collisions as bind/unbind
  BAbindings = BAinstantiate(AS,AMkinet,ABkinet,BAhitlog);
  [AMbound BP] = BAbind(AMbound,BP,AS,AR,AMkinet);
 end



%   BC  Container Reflections

%  BC  Detect Collisions
 if swCv==1,
     BP   =  collisionBox(BP,box,sfE)
    [BCd2 BCd] = B2ABCdistance(BP,BC);
    [inbound outbound in out log] = collideBox(BP,BV,Sh);
    BP(LC(:,1),1:6,t)   =  collisionBox(BP(LC(:,1),1:6,t),Sh(1,:),sfE);
    BP(LC(:,2),1:6,t)   =  collisionBox(BP(LC(:,2),1:6,t),Sh(2,:),sfE);

%   BC  Resolve Collisions
    BP(LC(:,1),1:3,t) = noLeaksBox(BP(LC(:,1),1:3,t),BU(LC(:,1),3),Sh(1,:));
    BP(LC(:,2),1:3,t) = noLeaksBox(BP(LC(:,2),1:3,t),BU(LC(:,2),3),Sh(2,:));
 end


   %%  %%  POSITION EFFECTS  %%  %%  %%

%  BD  Water shells,  solvation
if swDv==1,
    BP(:,:,t) = WaterShells(BP(:,:,t),LB,CDF,vrange,sfW,sfV);

%    BD  Resolve Water Collisions
 end


%  BA bindings
 get AMcombos
 get Bbound


%  ACTORS
% Certain blocks omitted to meet proprietary protection requirements
   Each Actor type has associated with it kinetics: AM, AQ, and AL
   AR = binding site kinetics  = AM1 for modulators;  AM2 for ions that modulate
   AQ = conformation kinetics  = kolmogorov Q
   AO = lookup table from state to phenostate (effects transport)


%   Actor modulation
    AR = modulator kinetics
    AMbind
    AB = transport particle kinetics
    ABbind
    AcomboBM


%  Actor state
```

```
    AQ transition matrix
    AS instantiated state


 %  Actor phenostate
    AL  lookup table
 %  AO  instantiated phenostate

   BA Transport
    receptors, none
    pumps, only by kinetic schemes
    vesicles, none
    channels, as function of partial pressures
    shuttles, as function of kinetic schemes

   BA unbindings


    Add VELOCITY to POSITION
   BP(:,4:6,t+1) = BP(:,4:6,t) + clipit(BP(:,7:9,t),clipA);   % acceleration
   BP(:,1:3,t+1) = BP(:,1:3,t) + clipit(BP(:,4:6,t),clipV);   % velocity

   % check BB Collision Detection
   % check BB Collision Response
end  % time loop
```

10 DATA STRUCTURES

Every function must receive data from an array or structure, and deliver its output to an array or structure. As the digital model works primarily by applying functions to matrices and lists of data, formality is essential to achieving consistent usage and predictable results. Each function requires one or more input arguments and generates one or more outputs arguments. Most function arguments are constants, lists or matrices. Standardization is achieved by defining the columns of each matrix, in fixed order, but allowing the quantity of rows to float with the instantiation count of the moment, and allowing some columns to remain blank if not applying to the specific row type. Follows is the set of forms as employed in this model, with rationale as to what the options were, and what the selection criterion was, that determined data structure choices.

10.1.1 DATA CAPTURE & REPOSITORIES

A significant part of the work in getting the model experimental design to RUN benefits from pre-existing libraries of TYPEs. From the physics of ions to the neuronal cell types, the discovery, translation and formatting of such data is a valuable resource to the modeler. Conversely, there is always more such foraging to be done, and so it must be convenient and appreciated that all interested parties contribute what they find in the biological literature to the base info within this model.

Beyond the elemental types, there are the DISTs that can also be preserved in the library. DISTs are the PDFs of elemental placements within the neuron. They include ion concentrations, membrane shapes, actor placements and initial states. At a slightly higher order of capture. A set of Types and DISTs may constitute an “neuron type” or “neuron type instance”.

Furthermore, this model is evolving new functionality. The available set of functions is also part of the “library”of choices that enables a user to tackle increasingly complex phenomena. A readme.txt file shall be maintained, the first section of which announces new functionality since the last release.

10.1.2 RE-USE POTENTIALS

All algorithms shall be written across the most general usage space except when doing so incurs computational inefficiencies detrimental to the model. In such cases, the commentary within such functions shall clearly indicate the compromises made in the interest of speed, and document the code (as comments) that would serve a more general case. Where both the specific heavy use case and a lighter use more general case would both be used, then two functions shall be written; the general one by the standard name, and the specific one written with the same name but tagged "_fast".

Those functions and variables which serve to operate and maintain the database and data structures shall be set up as globals. Most other functions shall be set up as local operators, to avoid the accidental overwrite of far off variables that happen to have the same name.

10.2 DATABASE MANAGEMENT

As data is received from various sources, with occasional new data superseding old data, the database grows in awkward ways. Judgment is required to discard one bit to replace with another, especially problematic when data groups overlap, and neither completely meets the needs of the model. Ideally, a peer review committee would review proposed additions, with an eye to what it would be replacing, and to its overall compatibility to the model.

Once a new entity is deemed worthy of inclusion in the model library, then the matters of units, normalization and completeness of traits are addressed.

Critical are the methods by which data is read, added and modified. Defending the integrity of the database is a heavy liability because it is so easy to destroy blocks of data, even very large blocks. Slight errors in the pointers in copy and paste maneuvers can easily result in devastating damage and/or corruption to data. Then there results two problems. The first is to detect such damage; and the second is to be directed to the best copy for replacement. It is easy to call in old data and overwrite the one best and correct copy. It is much more secure to lock the user out from touching the original data. And only allowing images to be copied from that original database.

10.2.1 DATA BLOCKS

Data Structures are necessary for:

1. libraries of Actor TYPE's: Binding kinetics, Conformational kinetics, Phenostates, Conductivity, aff, erg, eff
2. libraries of Actor DIST patterns for each actor type: PDF (along axis), PDC (around circumference), per cell
3. TA = Actor types cell structure for binding/unbinding, state, modulation, transport, energetic, shuttles
4. TA.B = of Actor matrix particles of interaction list
5. TA.G = receptor catalytic rates, channel conductivity profiles, vesicle contents, pump pumping rates
6. TA.R = Actor binding site lists and their forward/backward rate kinetics with Btypes as probabilities
7. TA.Q = state transition probabilities
8. TA.RQ = maps bindsite states from R into internal states in Q
9. TA.O = actor phenostates (outward expressions of impact upon environment, e.g. channel openings)
10. TA.aff = actor affinities for both modulators and transport particles
11. TA.eff = actor release of messenger particles, identifying target types
12. TA.erg = actor requirements for energy inputs, e.g. ATP must bind and be converted to ADP+Pi
13. TB = library of Particle TYPE's, with trait values as may be useful to modeling molecular phenomena
14. TC = library of Compartmental Shapes, as primitive shapes
15. DA = Actor distribution patterns, CDFs across the length of the neuron
16. DB = init concentrations, particle counts, and particle bolus init params
17. DC = compartment extent, positions, contiguous shapes
18. MEMBS = Cbuild, matrix for cell membrane components
19. SEGMS = Cbuild, matrix for shape SEGMENTS, manages reflective surfaces
20. RINGS = Cbuild, matrix for shape RINGS, manages nearest neighbor events
21. NODES = Cbuild, matrix for shape NODES, manages particle bindings and transport
22. CONNEX = Cbuild, library of connectivity matrices, for multi-neuron models
23. INPUT = library of commonly used, or repetitively used, input signals
24. HIER = A diagrammatic relationship tree; depicting organization of elements
25. DESIGN = library of experimental DESIGNS; sets chosen from the above
26. CT, CU, BT, BU, AT, AU = BUILD sequences instantiate every element

27. RUNparam = library of simulation RUN parameters; set of scaling factors, switch settings, constants,
28. BP = matrix of PARTICLE DYNAMICS during run: [pos vel acc comp binds act pol]
29. As = matrix of instantiated Actor STATES during run: [state modulation transport pheno]
30. Bs = matrix of particle assignments (compartments, bindings, transport processes, etc.)
31. Bf = matrix of instantiated FORCES during a run
32. Bx = matrix of particle collisions: BA, BB, BC, BW and their impact upon momentum and velocity
33. Bbinds = matrix of instantiated BINDINGS during a run mapping B to A and A to B
34. Btrans = matrix of instantiated TRANSPORTS during a run (transport events, what was transported)
35. Of = process support arrays with links from phenostate to functions (process conditions map)
36. Evar = calculate concentrations, voltages, flux, and currents during a run, on a per voxel basis
37. Bwave = track wave fronts during a run, as tags generated by detection algorithm
38. W = system OUTPUTS
39. Werror = capture error measures and out-of-tolerance events
40. Wcorrect = record corrective measures to out-of-tolerance events [adjustments results]
41. REPORTtypes = library of data visualization customizations, display preferences for data captured
42. REPORTformats = library of REPORT formats [print preferences]
43. REPORTcapture = capture of streaming REPORT data from runs
44. REPORTgraphics = REPORT's and plots generated shall be archived

10.3 DATA DESIGN

Input data for each of the components is largely organized around two principles: intrinsic qualities and extrinsic qualities. Intrinsics are referred to as traits, and extrinsics as distributions. Instantiations require both of these.

Libraries are maintained for convenience, such that to construct an experimental design the user need only select which particle and actor types and at what concentrations they are to be present in each compartment or zone. New entities can be created or adapted by modifying pre-existing ones. This is usually accomplished by choosing row numbers in list of options. Therefore, whenever practicable rows are entities, and columns are the traits of those entities.

10.3.1 INDEX SETS

Given that dynamic data will be held in large matrices, and will be operated on unevenly by a variety of functions, database integrity is a challenge. For example the Compartment nodes are held in a matrix about 100000 rows x 300 columns. Particle instantiations are held in a matrix about 10000 rows x 40 columns. The chosen strategy is avoid doing sorts, finds, or other means of extracting subsets. But rather to utilize the bit-efficient and non-disturbing method of index sets. Any subset of matrix M can be specified either by its dimensional array addressing as a subscript, M(i,j,k), or by counting the cell number as an index, M(n). The effect of this method is to leave the master array unscathed except for time-wise updates, while all other uses employ projections from that array. That is, all subsets are stored only as pointers to the original data, not as copies of parts of it.

MAP1 **Data Structure**

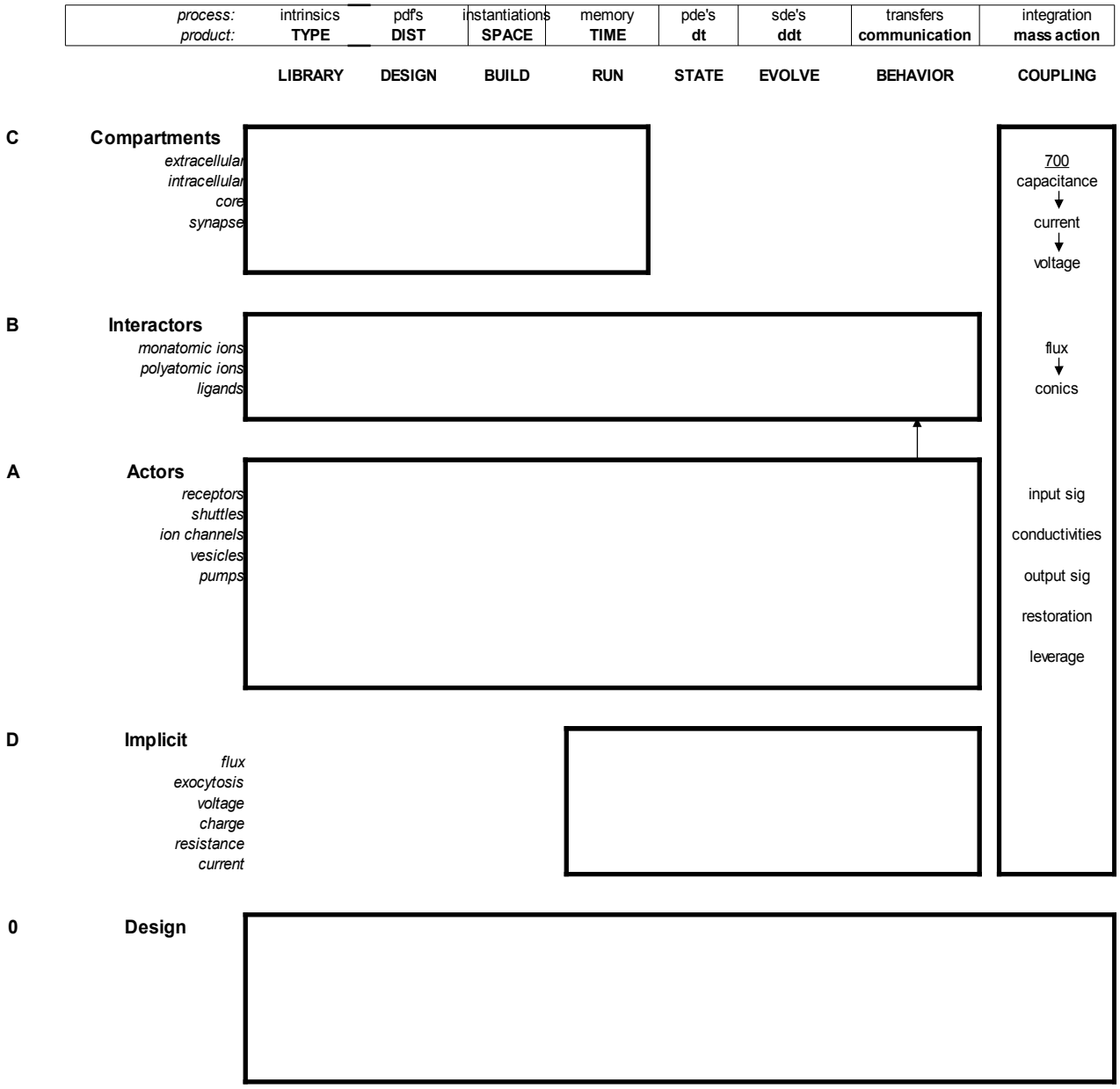


FIGURE 110: GLOBAL DATA STRUCTURE SCHEME

In its most general an abstracted form, the data of the model is organized into :

23. persistent forms, types, intrinsics, libraries
24. variable forms, distributions, designs, parametric values
25. instantiations, that occupy space, that are built
26. runs, that occupy continuous time, that require memory

27. changes in state, changes in discrete time, nonlinear events

28. systemic evolution, stochastics, modulation, behavior

29. interaction, communication, transfers

30. integration, merging, higher levels of order

Expanding that scheme to address the divisions, classes and types of the model, let's first consider the volumetric compartments of the cell, each enclosed by membrane.

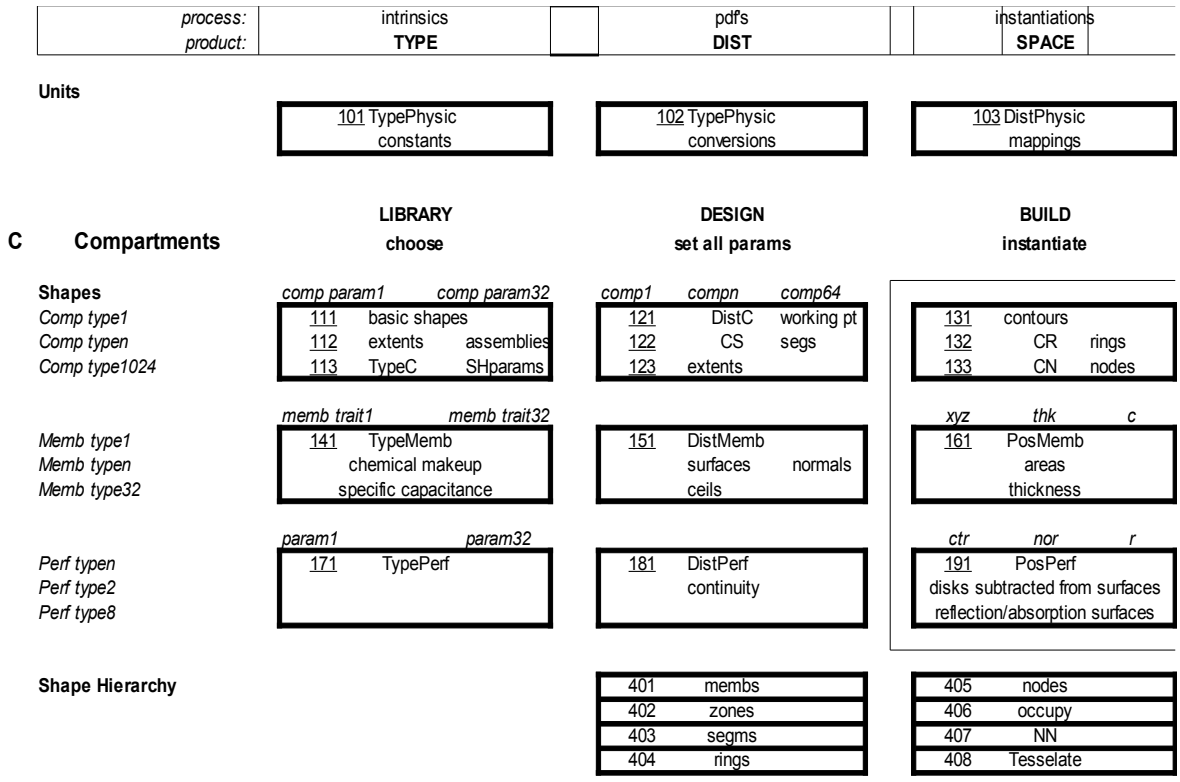


FIGURE 111: DATA STRUCTURE SCHEME FOR COMPARTMENTS, PART 1

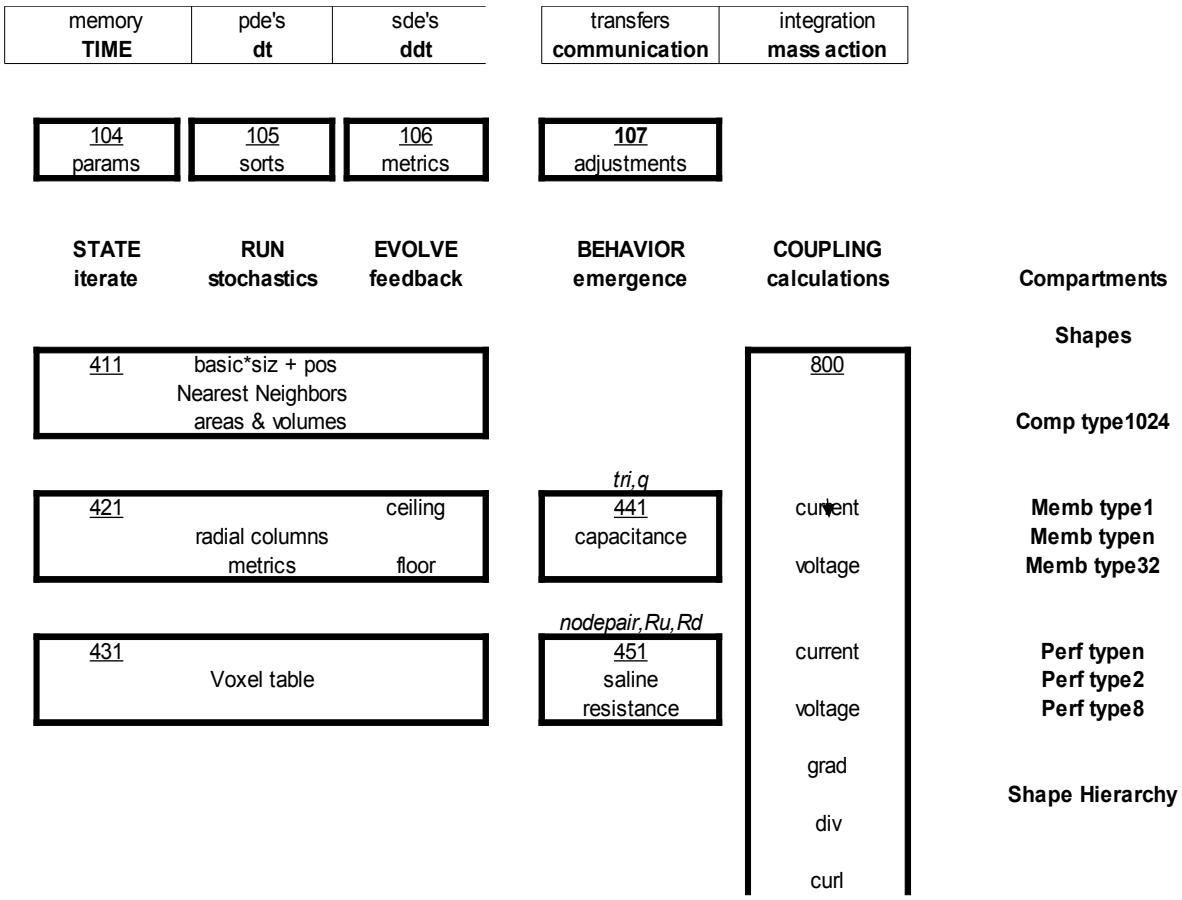


FIGURE 112: Data Structure for Compartments, part 2

Part 2 is a continuation to the right of part 1. The box entitle coupling extends downward through all of C,B,A,D

Then the core data for the particles is expanded.

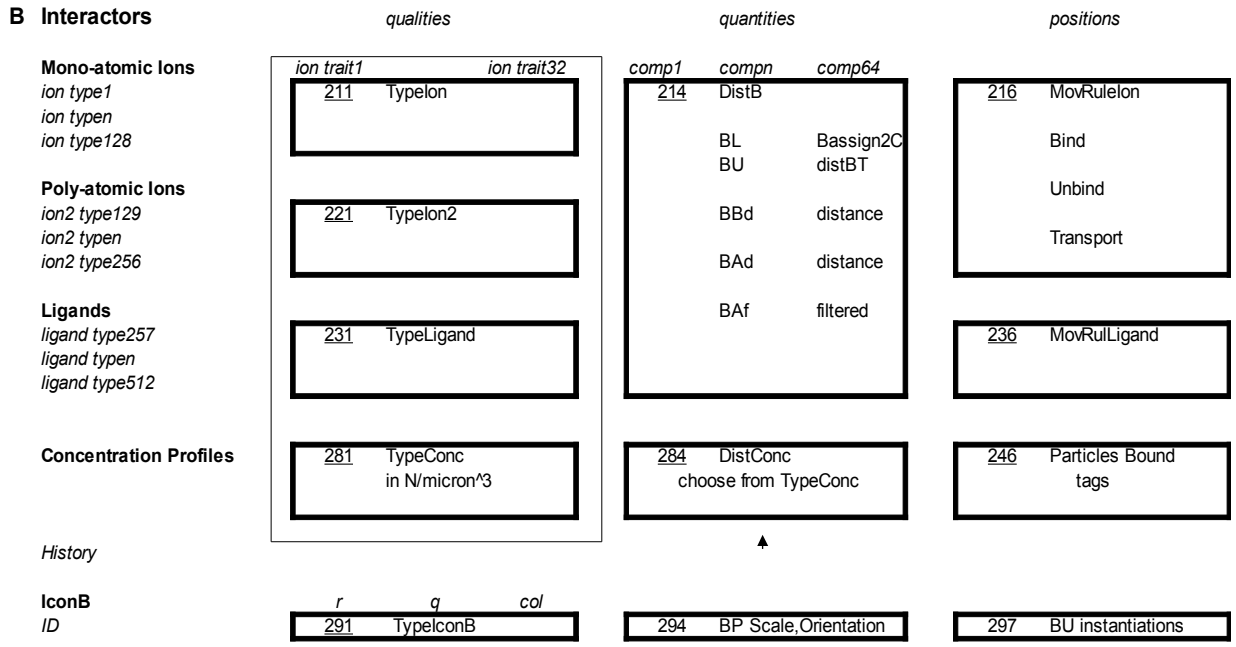


FIGURE 113: DATA STRUCTURE SCHEME FOR PARTICLES, PART 1

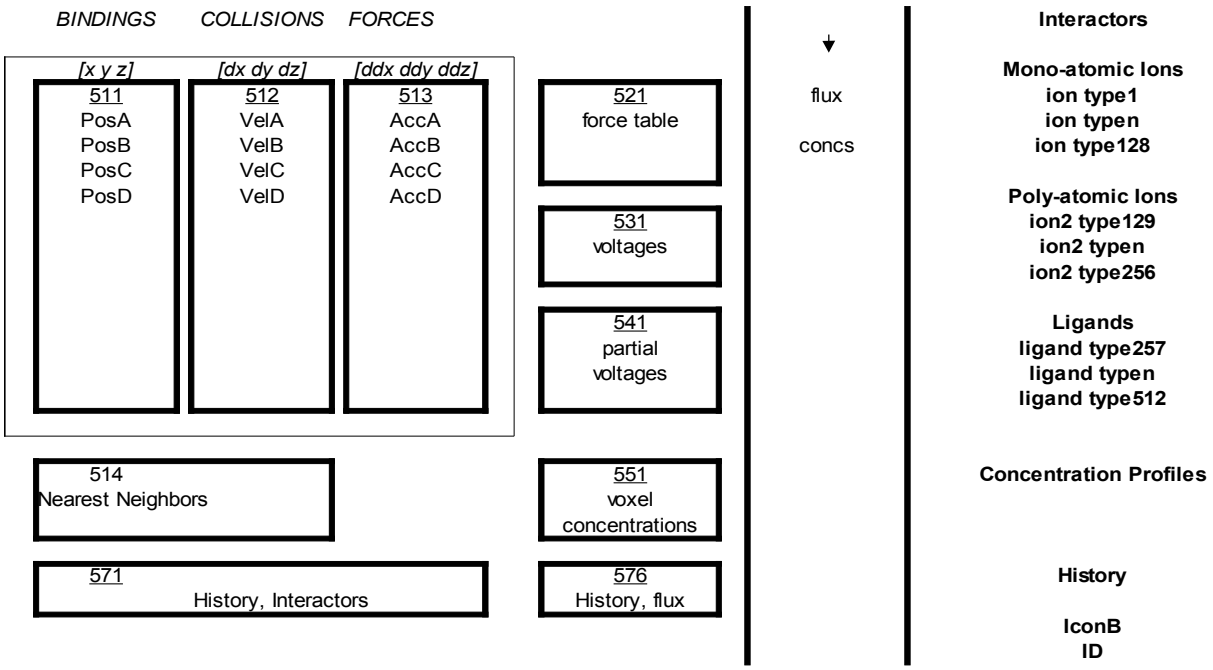


FIGURE 114: Data Structure Scheme for Particles, part 2

Particles require tracking of position, velocity, acceleration, type, serial number, compartment assignment, floor and ceiling membranes (implied by compartment assignment), binding events, actor bound to, pole of actor bound to. The the case of a binding, the velocity goes to zero, but the old velocity is remembered so as to release (unbind) at a reflection of that velocity. These are formalized into a 30 column standard matrix. When a transport event occurs, the particle is reassigned to the opposite pole of the actor, and to its new compartment.

Next is expanded the scheme for the actors (receptors, channels, vesicles, pumps)

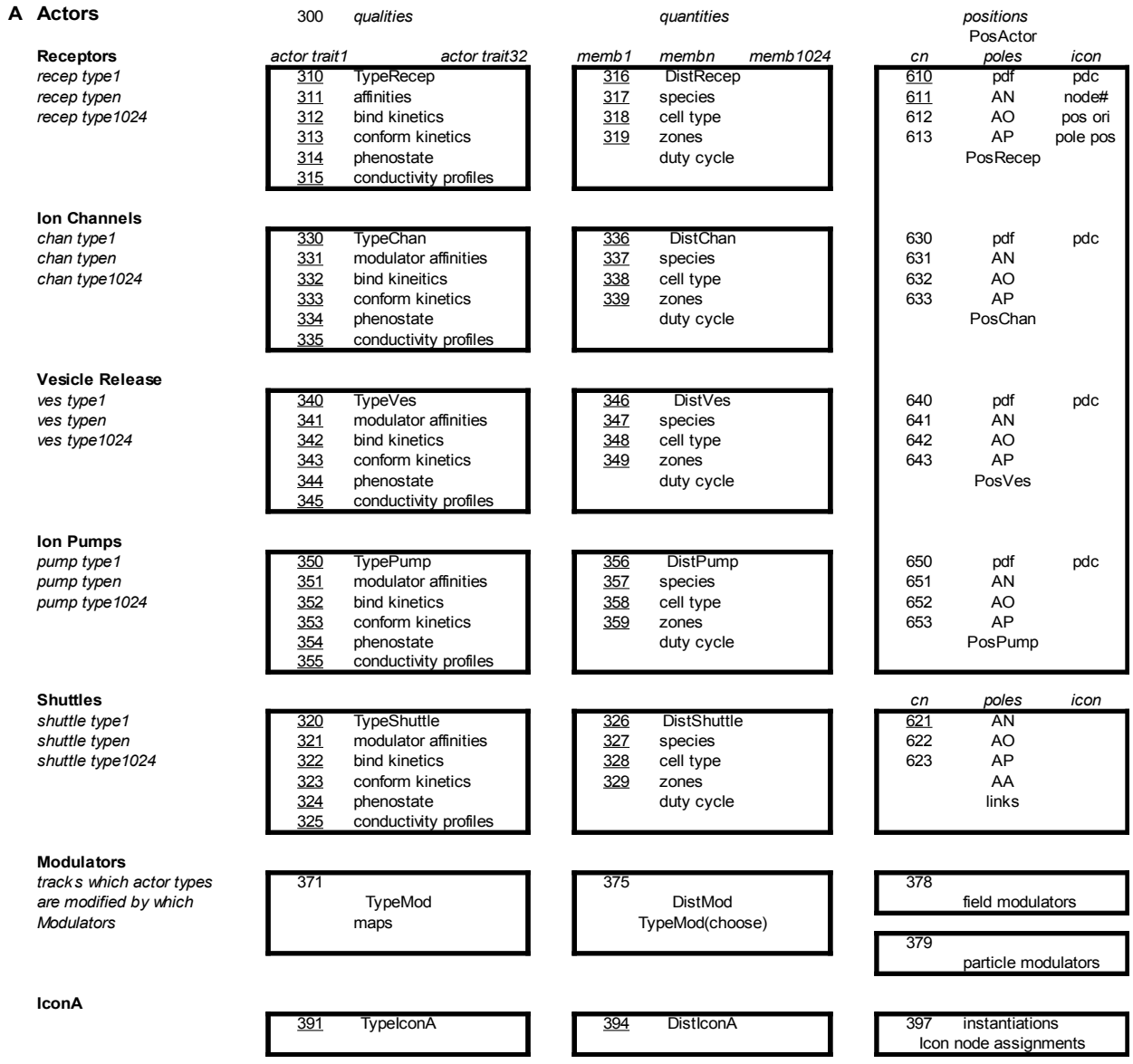


FIGURE 115: DATA STRUCTURE SCHEME FOR ACTORS, PART 1

Each of the numbers in the boxes corresponds to a spreadsheet sheet number in Appendix C, which contains design information and other details for that matrix form. Figure 4 continues to the right; see figure 5 for additional matrices.

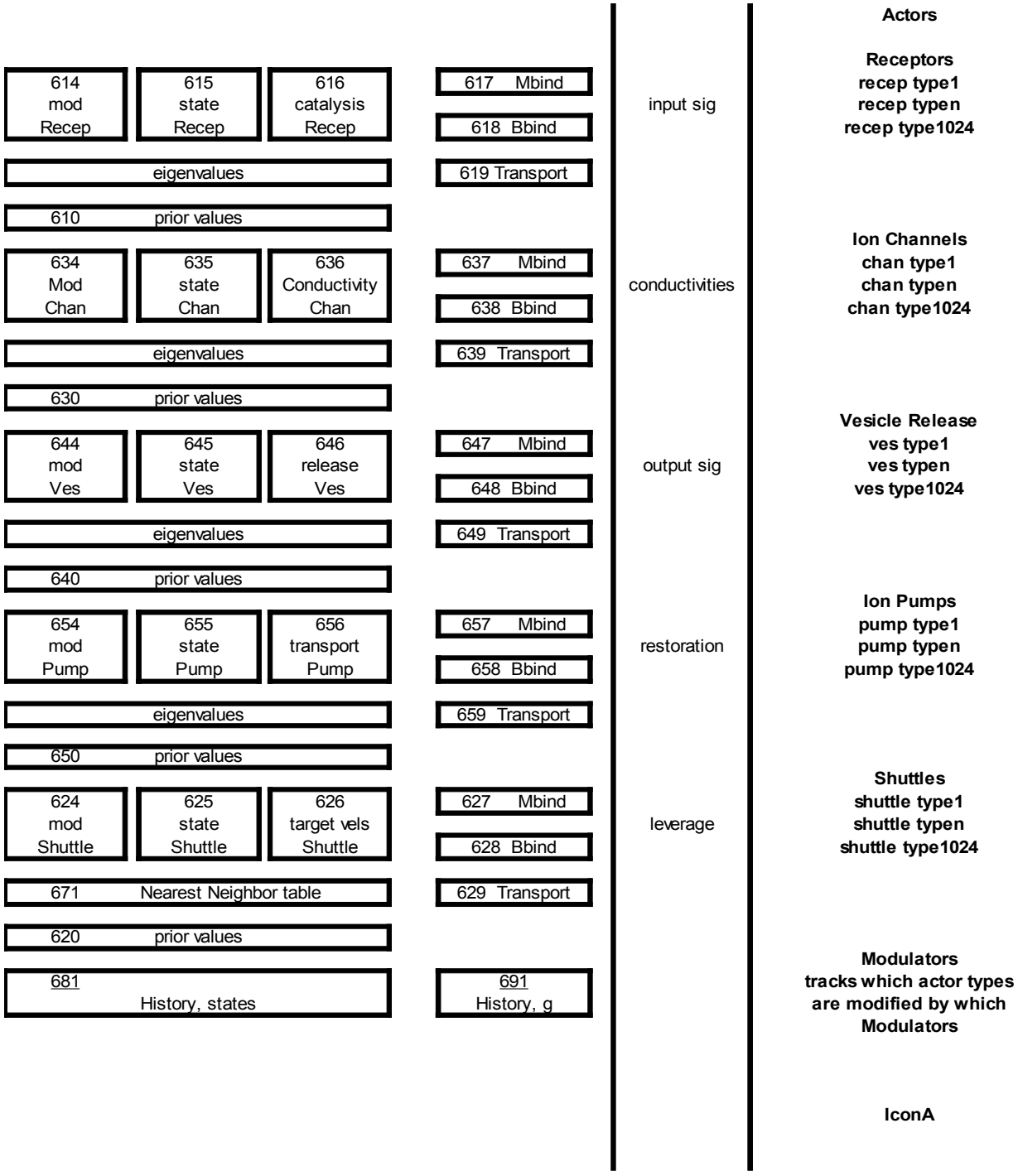


FIGURE 116: DATA STRUCTURE SCHEME FOR ACTORS, PART 2

Actors are all complex and highly individualistic. This posed a challenge for general treatment within digital computers. If a general treatment could not be abstracted, then each new actor type to come along would require a computer programmer to fathom how it should be represented within this model. Follows is an attempt to reframe what actors do into a general structure. The strategy is to find a union of all actor processes, and then allow some of these processes to fall silent, as would best characterize each actor type. There are 3 rows in the table below, the first for inputs, the second for state, and the third for outputs.

D Implicit Variables

			instant equations		
flux	720	Physical metrics	721	flux	
			722	grad	
			723	div	
curl			724	curl	
un/binding	730	Chemical metrics	731	BAd	distance
			732	BAf	affinity
			733	collisions	
			734	binding	unbinding
energy transfers			738	energy	
voltage	740	Electrical Metrics	741	volts	
capacitance			742	cap charge	
resistance			743	resistance	
current			744	current	
exocytosis	750	Biological metrics	751	exocytosis	
channel capacity	760	Systemic metrics	761	info capacity	
mutual information			762	mutual information	
			765	pattern depth	

0 Design Actors

Receptors	810	811	812	813	814	815	816
with recycling	automated design of transducers	affinity	un)bind	modulate	duty cycle	s1	contents
with Shuttles	retrieval and recharge mechanisms	821	822	823			
	broadcasting mechanisms	setup	targets	transport			
Ion Channels	830	831	832	833	834	835	836
with Subunits	automated design of ion channels	affinity	un)bind	modulate	duty cycle	s1	s2
	as pattern recognizers						
	as pattern generators						
Vesicle Release	840	841	842	843	844	845	846
with recycling	automated design of transducers	affinity	un)bind	modulate	duty cycle	s1	contents
	retrieval and recharge mechanisms						
Ion Pumps	850	851	852	853	854	855	856
with energy source	automated design of pumps	affinity	un)bind	modulate	duty cycle	s1	s2

FIGURE 117: Data Structure Scheme for Implicit Variables, part 1

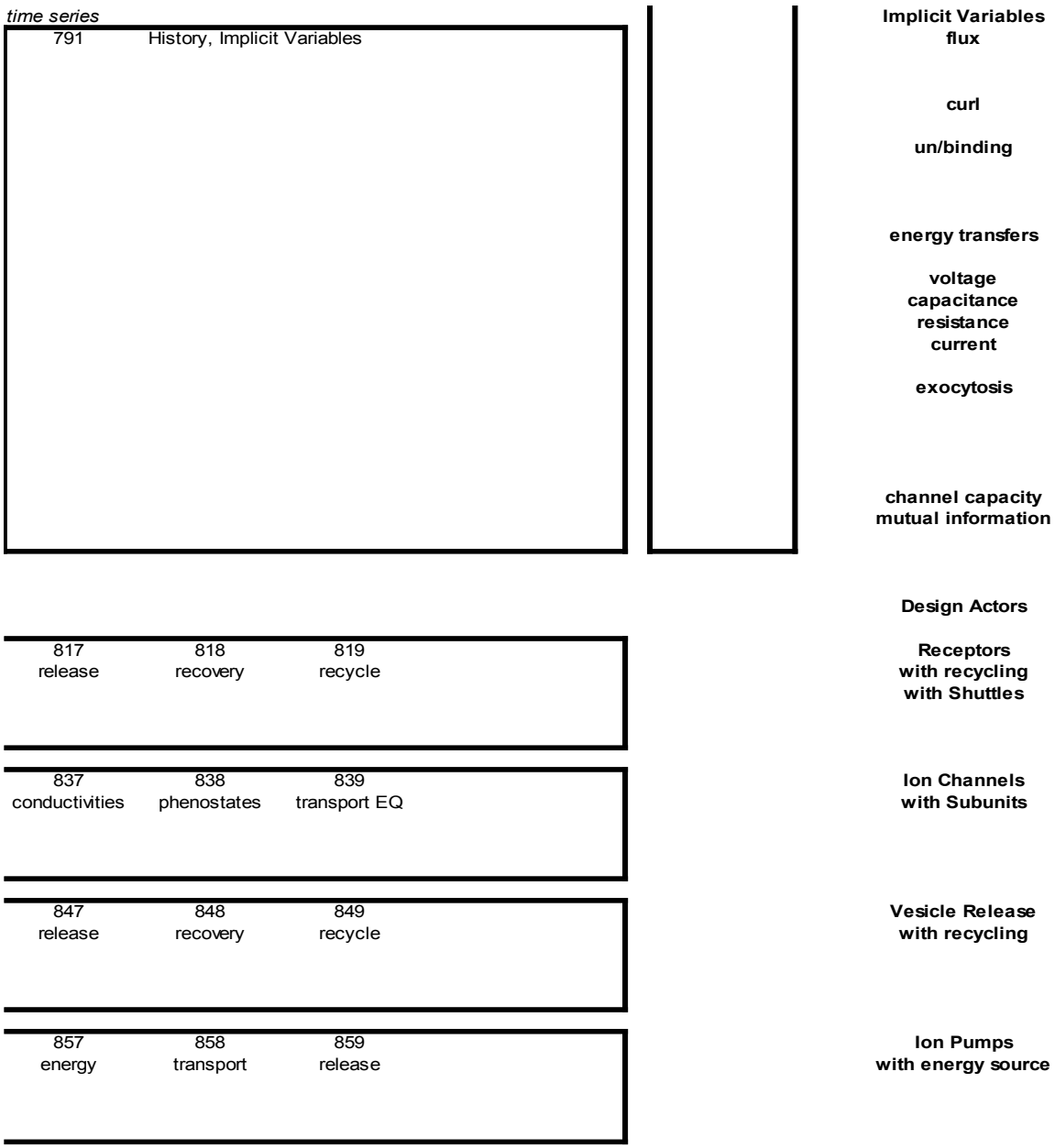


FIGURE 118: Data Structure Scheme for Implicit Variables, part 2

Universal process scheme for all actors

Transition Flow Map

entities	conc	(dist)	profile	(filter)	affinity (force)	un(bind) kinetics (prob)	un(bind) instantiation (state)	bind state determines			transport process (force)
messengers	1		2		3	4	5	6			
actors								7	8	9	
ions	10		11		12	13	14	15			16
								conformer kinetics (prob)	conformer instantiation (state)	phenostate (mapping)	

Function Map

entities	conc	(dist)	profile	(filter)	affinity (force)	un(bind) kinetics (prob)	un(bind) instantiation (state)	bind state determines			transport process (force)
messengers	Mmove		AMprofile		AMattractor	chooseAMkin	instAMbind	MB2Astate			
actors								Qrow	Qelement	lookupAR	
ions	Bmove		ABprofile		ABattractor	chooseABkin	instABbind	MB2Astate			transport
								conformer kinetics (prob)	conformer instantiation (state)	phenostate (mapping)	

Data Structures

entities	conc	(dist)	profile	(filter)	affinity (force)	un(bind) kinetics (prob)	un(bind) instantiation (state)	bind state determines			transport process (force)
messengers	Mconc		Gmod		AMaffinity	AMkinet	AMbind	AMcombo			
actors								AQ(M,B)	AS	AR	
ions	Bconc		G		ABaffinity	ABkinet	ABbind	ABcombo			flux
								conformer kinetics (prob)	conformer instantiation (state)	phenostate (mapping)	

TABLE 25: DATA STRUCTURE SCHEME FOR ACTOR PROCESS

The columns, in order, track the environmental availability of interactors, the attraction and conductivity profiles of each interactor type, the bind/unbind kinetics, the impact of bindings upon state kinetics, the state transitions, the expression of state upon the environment, and any transport processes that are executed. Only the receptors release messengers, only the channels have conductivity profiles. Only the pumps and (optionally) vesicles consume energy. The receptors do not effect transport processes.

Defining an actor type adequate to modeling needs requires copious amounts of data, especially to capture their stochastic behaviors. Modulation is a process of attraction of certain types of particles, leading to stochastic binding (and unbinding) to certain intracellular and/or extracellular sites on the actor. The interactions between the various possible binding combinations across multiple sites expresses as a complex relation to the molecular state

transitions. Transport phenomena are also captured as numeric values. Although a set of these substructures define an actor, they do not lend themselves to populating a single matrix due to their widely varying dimensionality. They are therefore assembled into a structure (within Matlab, called a “cell”):

10.4 TYPES

Type is an input format that contains data intrinsic to each Actor and Interactor. It can be thought of as trait constants. Traits are usually persistent throughout the RUN, but may be altered between runs for hypothetical studies. All Types are stationary, and therefore only calculated once, in the BUILD.

EX: For each particle, certain traits are relevant to the RUN

BU = `{'mass''valance''radius''mob''red''green''blue''sh''siz''clas''typ''ID'};`
These constitute the columns of BU, a complete list of particles in the system and their traits, repeated per their type. Columns 5..10 are artificial attributes for plotting the icn of this particle type. BU may easily be extended when the model run requires additional traits. The full list of particle traits is embodied in TB, the master library of particle types.

columns 1 2 3 4 5 6 7 8

TB_h2 = 'Atomic #' 'mass, amu' 'valance' 'radius calculated nm' 'radius Atomic nm' 'radius Pauling nm' 'mobE'

9 10 11 12 13 14 15 16

'mobM' 'beta H20:lipid' 'electronegativity' 'gram atomic vol' 'sphere volume' 'density' 'melting pt' 'boiling pt'

17 18 19 20 21 22 23

'ionization pot' 'ionization pot2' 'ionization pot3' 'ElectroAfinity Ev' 'Electroresistivity' 'Electro pot half' 'Oxidation pot'

24 25 26 27 28 29 30 31 32

'diffusion coef' 'solubility' 'ppm earth' 'color_R' 'color_G' 'color_B' 'icon shape' 'icon size' 'Class'

Actor Traits are somewhat more complicated, involving variously sized matrices. They therefore cannot be aligned as values in a matrix, but rather require organization within a cellular structure. Actors have states, and therefore require transition matrices. Actors can bind and unbind, therefore have probabilistic kinetics for each allosteric bind site across all particle types in the system.

TA = cell {1.B 2.R 3.Q 4.RQ 5.O 6.aff 7.eff 8.G 9.erg 10.id}, where
B = list of particle types of any relevance to this actor
R = forward and backward reaction rates for each bind site, across all particle types, one set of R for each state
Q = state transition probabilities, one set of Q for each bind combo.
RQ = maps current bind conditions into a particular set of Q
O = maps state into the actor's outward expression.
aff = [d o B A r4 f1 r5 f2 var]; affinity of each bind site for each particle type given the current state
eff = [d o B A r8 f1 r9 f2 var]; release of one or more particles as messengers
erg = [b1a b2a, b1b b2b, ...]
id = serial number for each actor type = class.type

Taking the Actors as 4 classes, then taking a union of their traits, generates the following:

W	[pole1 pore_open pole2]
B	particle types
B+	qB + empty_site + voltage_mod
f1	driving force partials, inward
f2	driving force partials, outward
aff	affinity of B to D
r5	distance reach of affinity
r4	distance reach of bind
erg	energy consumed per cycle
ba1	energy source reactants
ba2	energy byproducts
eff	emitted B from A
qB	quantity of B released
vel	messenger mean velocity
var	variance on velocity
-vel	return velocity (reset)
r8	mean messenger target range
r9	max messenger target range
d	bind site
o	position of bind site (for pumps)

10.4.1.1 Cell Structures for Types

ACTOR TRAITS	R	Q	O	G	aff	erg	eff
action	E-I kinetics	I-I kinetics	I-motion	selectivity	E-motion inbound	Energy converted	E-motion outbound
matrix	SxPx(DxB+)	SxPx(S)	SxW	Wx(BxFi(B))	[d o A B r3 F r4]	[in1 in2 out1 out2]	[B qB A vel var -vel]
Recep	☒	☒			☒		☒
Chan	☒	☒	☒	☒	☒		
Ves	☒	☒			☒	?	
Pump	☒	☒	☒		☒	☒	

R and Q matrices are required for every actor, because by definition every actor has states and has relationships with the environment. Note that their dimensionality expresses their intent. They start with a definition of the actor mathematically: SxP; where S = the conformer state, P = the bind combination at present. Each bind combination becomes a page in the state transition matrix. Then the 'self' (SxP) crosses the possible states (S) to effect a state change (Q = SxPx(S)). The 'self' crosses the environment to effect a binding change (SxPx(DxB+); where D = the binding sites on the actor. B = all the types of particles in the system. B+ is that list augmented with a “hole” to indicate a vacant binding site, and a series of voltage steps so that voltage can also act as a modulator.

The matrices R, Q, O, and G manage the internal traits of the actors. But some effects of actors are more like functions than states. They requires operations to be performed upon B (particle types) in the vicinity.

'aff' = the parameter set for the affinity function. This function draws particles to the binding sites at a rate consistent with empirical data.

'erg' = the parametric set for the energy_consumption function for an actor. Mostly this is so pumps can consume ATP, become fatigued when ATP is depleted, and even run backwards when there is a high ADP concentration.

'eff' = in some sense the opposite of 'aff' in that it radiates out particles. In this model it serves the specific function of providing second messengers between receptors and certain channel types. So 'eff' provides the parametric set for a G-protein system.

Channels and Pumps actually have parts that move ions around. Three things can happen: 1) some part of the molecule moves from compartment 1 to compartment 2; 2) a pore opens up connecting compartment1 and compartment 2; or 3) something moves from side 2 to side 1. Moving actor parts are represented by the O matrix.

Finally, the G matrix provides the ion conductivities for each channel type.

10.4.1.2 Type Comp

The main compartment of the cell is its plasma lemma. Other relevant compartments may be generated automatically around this shape. For example the extracellular compartment may be specified by its "thickness", i.e. distance away from the plasma lemma.

Compartment types include a library of shapes that may be specific to a neuron type, an animal species, or even a individual cell from which the morphometrics were collected. In most cases, a single main compartment type will have associated to it several companion compartments, e.g. the extracellular compartment and the core compartment. However any number of shapes may be associated with the main when together they form the various compartments of interest comprising a neuron.

For single cell studies, the synapses are modeled by synaptic plugs, each of which has two compartments.

When local circuits are studied, and several neurons are present in the model, the synaptic plugs may be replaced with interneuron synaptic links.

10.4.1.3 Type Ion

TypeIon, a fixed length vector of choices for types of ions to place in solution in each compartment. Data is based upon the chemist's periodic table = { number, mass, radius, charge, electronegativity, mob.water, mob.lipid }

10.4.1.4 Type Ligand

TypeLigand, neurotransmitters, cellular messengers and other signaling molecules, data held in a fixed-length vector based upon assembly of its constituent atoms, data from the chemist's periodic table.

data ={ number, mass, radius, charge, electronegativity, mob.water, mob.lipid }

10.4.1.5 Type Recep

TypeActor = periodic table data = { number, mass, radius, charge, electronegativity, mob.water }

10.4.1.6 Type Chan

TypeActor = tabular data = { number, mass, radius, charge, electronegativity, mob.water }

10.4.1.7 Type Shuttle

TypeActor = tabular data = { number, mass, radius, charge, electronegativity, mob.water }

10.4.1.8 Type Ves

TypeActor = tabular data = { number, mass, radius, charge, electronegativity, mob.water }

10.4.1.9 Type Pump

TypeActor = tabular data = { number, mass, radius, charge, electronegativity, mob.water }

10.5 DISTRIBUTIONS

DIST contains positional data for each actor. Any stationary input parameter which contains variety, variance, a contour, or variations over the length of the neuron can be represented in Dist. Approaching spans of data as distributions (pdf's) provides a highly generalized scheme for the generic handling of most parametric ranges. Stationary Distributions, such as Membrane shape and Actor locations, are only calculated once, in the BUILD. Distributions can be in 1-space, 2-space, 3-space or 4-space.

The storage of DIST data per membrane consists of qAT x 100, where qAT is the quantity of actor types in the model. There are usually more than one membrane; e.g. the boutons, the core and the extracellular envelope.

The extracellular envelop usually parallels the main plasma lemma quite closely, so these two may be of the same length and the same zone designations . The boutons are much shorter and simpler so need not consume a length of 100. A membrane length of 10 per bouton is found sufficient, as it begins in the center and radiates outward, so as to address the conditions of the wrap away from the synapse. The core is usually simple, with few zones, and a length of 10% is usually sufficient. All of the membranes of one experiment may be concatenated horizontally. For EX, an experiment consisting of membranes: main, extracellular envelope, a core, five dendritic boutons and one axonal bouton; and with 5 actor types, would be housed in a matrix of qAT x (100+100+10+50+10) = 5 x 270 elements.

It is convenient to designate zones along the course of the PDF's. For EX, the main membrane may consist of a dendritic bouton, dendritic stalk, soma, hillock, axon, and axonal bouton. Its allocation of 100 values may be allocated thusly:

Dzon.main = [10 30 60 70 90 100]; for DIST zones on the main membrane, and

Dzon = [10 30 60 70 90 100 110 130 160 170 190 200 210 220 230 240 250 260 270]; for the set of membranes,

zon_h2 = { 'db1' 'ds1' ' soma1' ' is1' 'axon1' 'ab1' 'db2' 'ds2' ' soma2' ' is2' 'axo21' 'ab2' 'core' 'dplu1' ... 'aplu' }

Repeated boutons of same actor densities need not be represented in the DIST more than once. Similarly, when a series of nodes of Ranvier are present, the node need only be represented once (as a zone). The length of each zone is not related to actual size in the living cell, but rather to detail and variations within it. A physically lengthy zone of absolutely homogenous distributions needs only a PDF length of 1. The arbitrary lengths of zones are managed by calling them through the vector Dzon, onto the actor distributions, and interpolated each onto corresponding zones of the shape nodes as built in C BUILD. That is, Dzon maps onto Czon.

Approaching spans of data as distributions (pdf's) provides a highly generalized scheme for the generic handling of most parametric ranges. Distributions can be in 1-space, 2-Space, 3-space or 4-space. DISTmod data is regarded as transitory, and calculated iteratively each dt throughout the RUN.

10.5.1 SPATIAL DISTRIBUTIONS

Although most particles are initialized as freely roaming within an assigned compartment, messenger molecules may be held (bound) a specific locations. To initialize stationary particles, tags are set to 'bound', velocity set to 0, and position set to poles of actors to which they are bound. Where the actor affinity for such particles is high, then ligands need only be released near the actors, in the usual free sense, and the actors will soon pick them all up and bind them.

10.5.1.1 Shape

The general hierarchy of shape:

EXPER: experiment defined
CELLS: lists the cell types, quantities and positions of an EXPERIMENT
MEMBS: lists the membranes and their positions from CELLS [given]
ZONES: list the types and positions of zones of each membrane [given]
SEGMS: list the line segments comprising each zone [given as Sh]

RINGS: list the rings comprising each seg [ContourMake]
NODES: list the nodes comprising each ring [ContourRotate]
ACTRS: list the actors occupying the nodes [PlaceActors]

Note: 5-letter code refers to the hierarchical data tables above. Please avoid other 5-letter names unless they are consistent with this scheme.

Most commonly:
MEMBS = { 'main'; 'extr'; 'core'; 'plug' }
ZONES = {'isyn'; 'stlk'; 'soma'; 'hill'; 'axon'; 'node'; 'bout'; 'osyn' }
SEGMS = {'cone'; 'cyln'; 'disk'; 'sphr'; 'tors'}

Primitive Shape format, generated as contours of revolution

Sh = [Sh# 0 qx qc x0 r0 x1 r1 x2 r2];
Sh# = {1=boxs 2=cone 3=cyln 4=disk 5=perf 6=sphr 7=tors 8=vane 9=arbi }
quad = 0
qx = quant spaces longitude; calculates dx
qc = quant spaces circumferential; calculates dc
x0 = vertex
r0 = swing radius from vertex (not used in cylinder)
x1 = start
r1 = start
x2 = stop
r2 = stop

The Sh data drives the creation of the Line Segments comprising the contour.

%% SEGMS is populated Sh and generated by Sh2SEGMS

y1_ = SEGMS(:,2); = start point of seg (given)
a1_ = SEGMS(:,3); = start angle
x2_ = SEGMS(:,4); = stop point of seg (given)
y2_ = SEGMS(:,5); = stop point of seg (given)
a2_ = SEGMS(:,6); = stop angle
x0_ = SEGMS(:,7); = center point horz position
y0_ = SEGMS(:,8); = center point vert position
r0_ = SEGMS(:,9); = swing radii for each segment (used to calc reflections)
h__ = SEGMS(:,10); = arc height, of curve off secant (given)
mem = SEGMS(:,11); = membrane# this segment is part of, (given)
zon = SEGMS(:,12); = zone# this segment is part of, (given)
seg = SEGMS(:,13); = seg#, KEY (given)
rin = SEGMS(:,14); = last ring# in this segment
nod = SEGMS(:,15); = last node# in this segment (later, from Rotate)
act = SEGMS(:,16); = last actor# in this segment (later, from PlaceActors)
Ls_ = SEGMS(:,17); = integrated length of segment
are = SEGMS(:,18); = area contained by segment
vol = SEGMS(:,19); = volume contained by segment
typ = SEGMS(:,20); = shape type = {2cone 3cyl 4disk 7sphere 8torus}
NN1 = SEGMS(:,21); = Nearest Neighbor = seg# left
NN2 = SEGMS(:,22); = Nearest Neighbor = seg# left under

```
NN3 = SEGMS(:,23); = Nearest Neighbor = seg# right under
NN4 = SEGMS(:,24); = Nearest Neighbor = seg# left over
NN5 = SEGMS(:,25); = Nearest Neighbor = seg# right over
NN6 = SEGMS(:,26); = Nearest Neighbor = seg# right
onz = SEGMS(:,27); = orthonorm to secant z
ony = SEGMS(:,28); = orthonorm to secant y
htu = SEGMS(:,29); = height under
hto = SEGMS(:,30); = height over
qm_ = SEGMS(:,31); = which membrane in this model       (given)
qz_ = SEGMS(:,32); = which zone number in this membrane (given)
qs_ = SEGMS(:,33); = which segment number in this zone  (given)
qr_ = SEGMS(:,34); = quant of rings in this segment
qn_ = SEGMS(:,35); = quant of nodes in this segment
qa_ = SEGMS(:,36); = quant of actors in this segment
aru = SEGMS(:,37); = area under the segment (vane)
aro = SEGMS(:,38); = area over the segment  (vane)
dr_ = SEGMS(:,39); = differential euclidean spacing of points
sn_ = SEGMS(:,40); = serial#  (for sorts)
```

Note: 3 letter code allows calling a column value by name. Underline characters must be included in the name. These names are declared as global variables.

```
%% RINGS  is populated via SEGMS data and generated by ContourMake
 x1  = RINGS(:,1);  = posx
 r1  = RINGS(:,2);  = posy
 h   = RINGS(:,3);  = posz
 x2  = RINGS(:,4);  = Z2      magnitude
 r2  = RINGS(:,5);  = R2      radius
 a2  = RINGS(:,6);  = A2      angle
 nx  = RINGS(:,7);  = nx      normal to the point
 ny  = RINGS(:,8);  = ny      normal to the point
 nz  = RINGS(:,9);  = nz      normal to the point
 cla = RINGS(:,10); = class
 mem = RINGS(:,11); = membrane# this ring is part of, (given)
 zon = RINGS(:,12); = zone# this ring is part of,     (given)
 seg = RINGS(:,13); = seg#, this ring is a part of,   (given)
 rin = RINGS(:,14); = ring#   KEY
 nod = RINGS(:,15); = last node# in this segment (later, from Rotate)
 act = RINGS(:,16); = last actor# in this segment (later, from PlaceActors)
 len = RINGS(:,17); = circumference
 are = RINGS(:,18); = ring area
 vol = RINGS(:,19); = ring volume within (ignoring the presence of others)
 typ = RINGS(:,20); = type = {2cone 3cyl 4disk 7sphere 8torus}
 NN1 = RINGS(:,21); = Nearest Neighbor = ring left
 NN2 = RINGS(:,22); = Nearest Neighbor = ring# left under
 NN3 = RINGS(:,23); = Nearest Neighbor = ring# right under
 NN4 = RINGS(:,24); = Nearest Neighbor = ring# left over
 NN5 = RINGS(:,25); = Nearest Neighbor = ring# right over
 NN6 = RINGS(:,26); = Nearest Neighbor = ring# right
 dx  = RINGS(:,27); = width (to left) of ring (z-axis projection)
 dy  = RINGS(:,28); = height (to left) of ring (radial projection)
 htu = RINGS(:,29); = height under to next ring
 hto = RINGS(:,30); = height over to next ring
 qm  = RINGS(:,31); = membrane # in this model
 qz  = RINGS(:,32); = zone # in this membrane
 qs  = RINGS(:,33); = segment number in this zone
 qr  = RINGS(:,34); = ring number in this segment
```

```
 qn  = RINGS(:,35); = quant of nodes in this ring
 qa  = RINGS(:,36); = quant of actors in this ring
 vau = RINGS(:,37); = vane area under to next ring
 vao = RINGS(:,38); = vane area over to next ring
 O   = RINGS(:,39); =
 sn  = RINGS(:,40); = serial number (for sorts)


%% NODES  is populated with RINGS data and generated by RINGS2NODES
 x1_ = NODES(:,1);  = posx
 r1_ = NODES(:,2);  = posy
 h__ = NODES(:,3);  = posz
 x2_ = NODES(:,4);  = Z2      magnitude
 r2_ = NODES(:,5);  = R2      radius
 a2_ = NODES(:,6);  = A2      angle
 nx_ = NODES(:,7);  = nx      normal to the point
 ny_ = NODES(:,8);  = ny      normal to the point
 nz_ = NODES(:,9);  = nz      normal to the point
 cla = NODES(:,10); = class
 mem = NODES(:,11); = membrane# this node is part of, (given)
 zon = NODES(:,12); = zone# this node is part of,     (given)
 seg = NODES(:,13); = seg#, this node is a part of,   (given)
 rin = NODES(:,14); = ring#, this node is a part of,
 nod = NODES(:,15); = node#   KEY
 act = NODES(:,16); = actor# on this node, if any
 vu_ = NODES(:,17); = node volume under
% aro = NODES(:,18); = node area
 vo_ = NODES(:,19); = node volume over
 typ = NODES(:,20); = type = {2cone 3cyl 4disk 7sphere 8torus}
 NN1 = NODES(:,21); = Nearest Neighbor = node# left under
 NN2 = NODES(:,22); = Nearest Neighbor = node# left over
 NN3 = NODES(:,23); = Nearest Neighbor = node# under
 NN4 = NODES(:,24); = Nearest Neighbor = node# over
 NN5 = NODES(:,25); = Nearest Neighbor = node# right under
 NN6 = NODES(:,26); = Nearest Neighbor = node# right over
 dx_ = NODES(:,27); = width (to left) of node (z-axis projection)
 dy_ = NODES(:,28); = height (to left) of node (radial projection)
 htu = NODES(:,29); = height under to next node
 hto = NODES(:,30); = height over to next node
 qm_ = NODES(:,31); = which membrane in this model
 qz_ = NODES(:,32); = which zone number
 qs_ = NODES(:,33); = which segment number
 qr_ = NODES(:,34); = which ring number
 qn_ = NODES(:,35); = node number
 qa_ = NODES(:,36); = quant of actors in this node
 vau = NODES(:,37); = vane area under to next ring
 vao = NODES(:,38); = vane area over to next ring
 dc_ = NODES(:,39); = dc
 sn_ = NODES(:,40); = serial number (for sorts)
```

BUILD Compartments

```
SH = [sh# sect; qx qc; -z  z; -x  -y; x  y ]    %  compartment shape
parameters
```

Ccg = compartment center of gravity or load point

Crib = compartment ribs

Crim = compartment rims

% each row is a compartment

BUILD Particles

TB = Type Particles: table of particle 66 traits

BS = quantities of each particle type by compartment

BT = TB(unique(BS),:) = subset of TB as employed in this model

BU = BT expanded over the instantiation of particles

Ba = particle atomic numbers, a column within BU

Be = particle valance, a column within BU

Bm = particle mass, a column within BU

Br = particle radii, a column within BU

Bv = atomic volume, a column within BU

10.5.2 TEMPORAL DISTRIBUTIONS

The vesicle release patterns require instantiation of a temporal distribution. They determine stochastically when each vesicle will exocytize, how many, and what percentage discharge of contents. The opening of a vesicle will produce a time distribution of released particles. If these events are 2 or more orders of magnitude faster than the diffusion time across the synaptic cleft, then perhaps they can be ignored and treated as instantaneous.

10.5.3 TYPE DISTRIBUTIONS

In matters of choice, the options are usually weighted unevenly. There must be a type distribution for each binding site on an actor. This can be represented as a binding probability for each particle type. But it is not static. Such distributions are altered both by discrete events (bindings on other binding sites and transport events) and continuous events (e.g. voltage).

10.5.3.1.1 Conductivity profiles

Proper interpretation of Q requires multiplication by a O vector, which is a 1-D DIST type row vector, to indicate which of the states represent an open channel (=1), and which states represent a closed channel (=0).

For the above, O = [0 0 0 0 0 1 1 1 0 0]; because only states 6, 7 and 8 are open states.

Note: Q matrix elemental values may be modified any or every *dt*.

10.5.4 FORM DISTRIBUTIONS

There are three cases for Q, each requiring rather unique treatment and associated functions. a Static Q is the type most commonly presented in the literature. By holding all modulation effects constant in the lab, a 2-d Q matrix can represent the all the measurable state transitions found. However, there are at least two ways to modulate actors. The first is discrete. A chemical binding event usually alters the values throughout the Q matrix. When there are more than one binding site on the actor, each possible binding combination will yield a unique set of transition probabilities. Therefore, the Q takes on a third dimension, one page for each bind combination. Because all considerations are discrete, a digital computer makes efficient execution of this case. The third case is one of continuous modulation. The classic example is voltage gated channels. Other continuous variables may apply: temperature, pH, pressure. In the continuous case, the entire Q matrix must be recalculated each *dt*. This is likely to consume much more computational effort than a mere page look-up, especially as the EQs usually involve exponentials and reciprocals. It is noteworthy that the continuous case may be degenerated into the discrete case by choosing physiologically significant ranges, and treating any value within that range as a discrete (precalculated) page in the Q matrix. Similar to above, but its values are not stationary. They may be modified any or every *dt*.

10.5.4.1 Static Q

The state transition probability Q matrices contain values in units of 1/s. When all values are constants, Q matrices can be held as data, rather than as functions. The latter being computationally more expensive. Within the Q, the states should be numbered so as to follow the most common state path that performs the actor's biological function, referred to as the 'duty cycle'. The rest state may be the last state or the first state. Off the diagonal, the upper triangle is populated by alpha values (forward rate coefficients) and the lower triangle is populated by beta values

(backward rate coefficients). The Q element values are regarded as persistent throughout the RUN, and therefore are only calculated in the BUILD. Values are scaled to the chosen *dt* value of the run, and should not exceed 1.0. Probabilities of 2 or more events within a single *dt* will lead to distortions and possibly errors. Static Q applies to all actor kinetics not modulated during the RUN. Generally, unmodulated actors play support roles. They cannot directly play a role of information processing, though they can do transduction, ratiometric exchanges, and resets.

Unmodulated Q matrices are s **x** s in size.

EX Q matrix for a unmodulated pump

For a 16-state pump, the Q =

0.52	5.93E-007	0.97	6.81E-007	0.02	8.79E-007	9.71E-007	2.86E-007	0.02	2.69E-007	7.87E-008	6.28E-007	1.83E-007	2.55E-007	7.81E-007	0.04
3.16E-007	0.64	0.06	8.35E-007	1.79E-007	1.05	6.03E-007	8.33E-007	8.70E-008	0.01	8.68E-007	7.86E-007	3.21E-007	9.12E-007	2.90E-007	0.06
0.03	0.94	0.34	8.96E-007	2.49E-007	3.57E-007	0.01	7.70E-007	3.18E-007	9.54E-007	0	7.49E-007	2.56E-007	3.68E-007	5.51E-007	2.52E-007
8.86E-007	4.13E-007	1.94E-007	0.65	0.01	0.04	8.63E-007	2.01E-007	4.53E-007	1.18E-007	7.97E-007	0.01	9.41E-007	3.80E-008	5.75E-007	1.01
0.01	7.70E-007	9.13E-007	0.01	0.36	8.06E-007	0	7.65E-007	1.61E-007	2.49E-008	7.86E-007	1.83E-007	0.01	6.51E-007	2.04E-007	3.99E-008
8.63E-007	0.05	6.84E-007	0.96	9.21E-007	0.85	0.01	6.16E-007	5.99E-008	4.22E-007	3.31E-007	8.44E-007	9.88E-007	0.02	5.55E-007	6.24E-007
2.45E-007	6.08E-007	0	3.10E-007	0.01	0.01	0.54	9.64E-007	4.45E-007	6.44E-008	9.50E-007	7.16E-007	9.52E-007	8.38E-008	0.01	3.87E-007
4.34E-007	7.95E-008	7.13E-007	4.47E-007	9.03E-007	9.47E-007	6.95E-007	0.67	0.01	0.01	8.28E-007	0.01	8.74E-007	1.15E-008	5.49E-007	0.11
0	4.15E-007	4.85E-007	9.64E-007	1.90E-007	9.51E-007	8.41E-007	0.01	0.26	9.24E-008	0.01	6.13E-007	0.01	3.66E-007	6.98E-008	3.32E-007
2.16E-007	0.01	8.33E-007	4.62E-007	9.93E-007	3.21E-008	6.76E-007	0.01	5.10E-007	0.12	0	8.74E-007	1.47E-007	0.01	8.60E-007	9.32E-007
7.75E-007	8.43E-007	0.01	4.96E-007	3.26E-007	2.76E-007	7.01E-007	9.80E-007	0.01	0.01	0.04	7.93E-007	6.50E-007	4.16E-007	0.02	4.68E-007
8.72E-008	5.24E-008	2.55E-008	0.02	2.28E-007	6.78E-008	8.95E-007	0.01	8.30E-007	6.10E-007	9.89E-007	0.89	0.01	0.01	2.39E-007	7.10E-011
4.00E-007	7.28E-007	3.36E-007	1.92E-007	0.01	8.27E-007	5.87E-007	2.61E-007	0.01	3.95E-007	3.44E-007	0.01	0.75	4.66E-007	0	7.26E-007
5.90E-007	1.15E-007	4.87E-007	8.98E-007	8.11E-007	0.01	3.25E-007	5.90E-007	4.27E-007	0	2.40E-007	0.01	2.45E-007	0.8	0	3.99E-007
1.97E-007	4.85E-007	2.25E-007	3.89E-007	9.24E-007	5.81E-007	0.01	7.45E-007	7.33E-007	9.61E-007	0.02	6.24E-007	0	0	0.44	2.29E-008
0.96	0.06	5.55E-007	0.01	7.19E-007	3.44E-007	2.08E-007	0.11	5.27E-007	7.50E-007	9.09E-007	3.53E-007	2.33E-007	5.08E-007	3.19E-007	0.08

10.5.4.2 Discrete Q

Actors that possess allosteric binding sites are subject to alterations in their state transition probabilities. Qmod is the same as Q except that the matrix elemental values are subject to modulation and must be recalculated each dt throughout the RUN.

Qdt = e^(Q*dt);

It should be noted that Qdt creates a DIST-type output, and must be instantiated for a specific molecular state.

Whenever the computational cost of the variable Qmod 's (see below) is too great, they may be represented as a series of static Q matrices. The modulator values are then used to choose which of these Q series is to be applied, and the previous state is used to select the row applied. This reduces computation to the inequality of binning the mod values into a lookup table.

10.5.4.2.1 Ligand Modulation of Q Matrices

A number of variables may serve as modulators to the actors. Each actor has two voxels associated with it, one above and one below. Within each of these voxels, all modulators may be measured. A single standard vector for all modulator values is used to make portable these values to all actors in a uniform manner. Mods includes kelv, voltage, pH, concentrations of all ions and ligands

10.5.4.3 Continuous Q

When ever EQs are provided for transition probabilities (often a function of voltage and or concentration), then the Q must be reconstructed each *dt*. Typically, the forward state paths to the transport event are dependent, and the return state path back to the rest state is not dependent. Using the variables with reconstruction can eliminate some of the pages in Q, but the computational load is always increased none-the-less in the evaluation of probabilities.

Qmod's are those Q matrices with variables embedded in the matrix. Often this is voltage, but also may be other continuous variables like pH, temperature, concentrations, etc.. This applies to all kinetics which may be subject to modulation of transition rates during the RUN.

Qmod are functions, not data, and therefore require different coding algorithms. Maintaining a library of such functions that can be called as though data may require passing one function to another function for evaluation. This can be accomplished via function handles or anonymous functions. Qmod functions are therefore created differently than common functions: Qmods = { @Qmod1 @Qmod2 ... }

EX Variable Qdt matrix that is a function of voltage. (Kv channel)

		c0	c1	c2	c3	c4	o2	o3	o4	b4	b5
		1	2	3	4	5	6	7	8	9	10
c0	1	0	.007*e^(v/91)	0	0	0	0	0	0	0	0
c1	2	.002*e^-(v/65)	0	.112*e^(v/81)	0	0	0	0	0	0	0
c2	3	0	5.0*e^-(v/112)	0	.212*e^(V/91)	0	3.28	0	0	0	0
c3	4	0	0	1.65*e^-(v/38)	0	.246*e^(v/73)	0	1.06	0	0	0
c4	5	0	0	0	5.61*e^-(v/70)	0	0	0	8.37	0	0
o2	6	0	0	5.06	0	0	0	0.027*e^(v/93)	0	0	0
o3	7	0	0	0	4.38	0	0.561*e^(v/39)	0	0.012*e^(v/72)	0.07*e^(v/88)	0
o4	8	0	0	0	0	2.44	0	0.019*e^-(v/68)	0	0	.00003*e^(v/130)
b4	9	0	0	0	0	0	0	0.6	0	0	0
b5	10	0	0	0	0	0	0	0	0.08	0	0

A consolidation technique is to identify a small number of voltage ranges that are functionally distinct, such as: hyperpolarized, rest, depolarized, deep depolarization. This discretizes a continuous input variable. Then one page in Q is assigned to each range. The only computation then is to determine which if these ranges the current voltage value falls into. The treatment is similar for variables other than voltage.

The cleanest way of treating the continuous modulators is to support N-dimensional Q and R, where N = the degrees of freedom. Each allosteric bind site, plus each continuous variable, gets a dimension. Instantiation is a walk down each dimension to reach its new value, then a right turn is taken onto the next dimension. The entire Q is not evaluated, but rather only one value for each dimension. This leads to a single vector of values, which become the probability distribution for instantiation of the next state. The process for R is always simpler, because the R page is selected only on the basis of the new state number from Q.

10.5.4.4 Ion Distributions

DistInteractor = list of x,y,z positions of all ions in the SUT

10.5.4.5 Ligand Distributions

DistInteractor = list of x,y,z positions of all ions in the SUT

10.5.4.6 Actor Distributions

DistActor= list of x,y,z positions of all ions in the SUT

10.5.4.6.1 Dynamic Actor Distributions

DistActordt = list of x,y,z positions of all ions in the SUT

Most, if not all, Actors are modulatable. Modulation changes the Q matrices. There are two methods of altering the Q matrices. The first is to maintain a stack of possible Q matrices, then the presence of a bound modulator merely

serves to select which of the stack shall be active at any given time. The second method is to define the Q as a function of the modulator(s), such that it must be recalculated each dt. The former is much faster in real time processing, but may require a large number of Q matrices in the stack, particularly when an Actor possesses multiple modulator sites. The former is desirable for chemical modulators, but is rather crude for force modulators, e.g. voltage. It must be determined empirically as to the optimal trade off between cpu time and graininess of Q-matrix switch offs.

10.6 DYNAMIC DATA FOR PARTICLE ACTOR INTERACTIONS

DATA structures
for Particles and Actors

			Time			BT data				
			t start	t event	t stop	num	mass	z	r	mobm
						1	2	3	4	5
	init values from previous									
AE	BB force	1	0.00		0.01			from		
AE	BA force	1	0.00		0.01			from		
PE	ABaffinity	1	0.00		0.01					
AE	B force	2	0.00		0.01					
AE	B acc	3	0.01		0.02		from			
AE	B vel	4	0.02		0.03					from
VE	compartments	5	0.03		0.03					
VE	BB collisions	5	0.03	0.04	0.05					
VE	BA collisions	6	0.05	0.06	0.07					
SE	get actor states	7	0.07		0.07					
SE	bind probabilities	7	0.07		0.08					
PE	BA bindings	8	0.08		0.09					
PE	A assignment	9	0.09		0.09					
SE	bind combos	10	0.09		0.10					
SE	state probabilities	11	0.10		0.11					
SE	phenotypes	12	0.11		0.12					
OE	gating	12	0.11		0.12					
SE	conductivities	13	0.12		0.13					
OE	receptor transduction	14	0.13		0.14					
PE	BA transport	15	0.14		0.15					
OE	vesicle transduction	16	0.15		0.16					
PE	C assignment	17	0.16		0.17					
OE	receptor catalysis	18	0.17		0.18					
PE	A catalysis	19	0.18		0.19					
OE	g-protein catalysis	19	0.18		0.19					
OE	pumping	20	0.19		0.20					
OE	vesicle packets	21	0.20		0.21					
PE	BA unbindings	22	0.21		0.22					
PE	BA release vel	23	0.22		0.23					
ME	free chemistry	24	0.23		0.24		from/to		from/to	
ME	hydration	25	0.24		0.25		from/to		from/to	
OE	shuttle pathways	26	0.25		0.26					
VE	BW collisions	27	0.26		0.27					
VE	BC collisions	28	0.27		0.28					
VE	limits	29	0.28		0.29					
VE	*velocity effects (collisions)*	*BY COMP*								
PE	*position effects (bind & transport)*	*BY COMP*								
AE	*acceleration effects (forces)*	*WHOLE*								
ME	mass effects (hydration & chemistry)	WHOLE								
SE	*state effects*	WHOLE								
OE	operators	WHOLE								

FIGURE 119: Data Structure, Particle Actor Interactions, part 1

BP data

	pos	vel	acc	Btype	c1,c2	m1,m2	n1,n2	a1,a2	p1:p2	vela	velb	velc	magV	acca	accb	accc	magA	Fa	Fb	Fnor	magF
	1:3	4:6	7:9	10	11:12	13:14	15:16	17:18	19:20	21:23	24:26	27:29	30	31:33	34:36	37:39	40	41:43	44:46	47:49	50
AE	from	from								to	to										
AE	from																		to		
PE	from																	to			
AE	from																	to			
AE																	to	from	from	to	
AE												to					from			from	
AE												from									
VE					from	from															
VE	from	from																			
VE	from	from																			
SE																					
SE	from				from			from	from												
PE					from		to	to	to		from										
PE	from						to	to	to												
SE																					
SE																					
SE																					
OE					from	from		from	from												
SE	from												to								
OE					from	from		from	from												
PE									from												
OE					from	from		from	from												
PE					from/to																
OE					from	from		from	from												
PE	from			from/to										from		from					
OE					from	from		from	from												
OE					from	from		from	from												
OE					from	from		from	from	to											
PE		to																			
PE																					
ME																					
ME																					
OE					from	from		from	from												
VE		from																			
VE	from	from				from															
VE					from					from	from	from									
VE																					
PE																					
AE																					
ME																					
SE																					
OE																					

FIGURE 120: Data Structure, Particle Actor Interactions, part 2

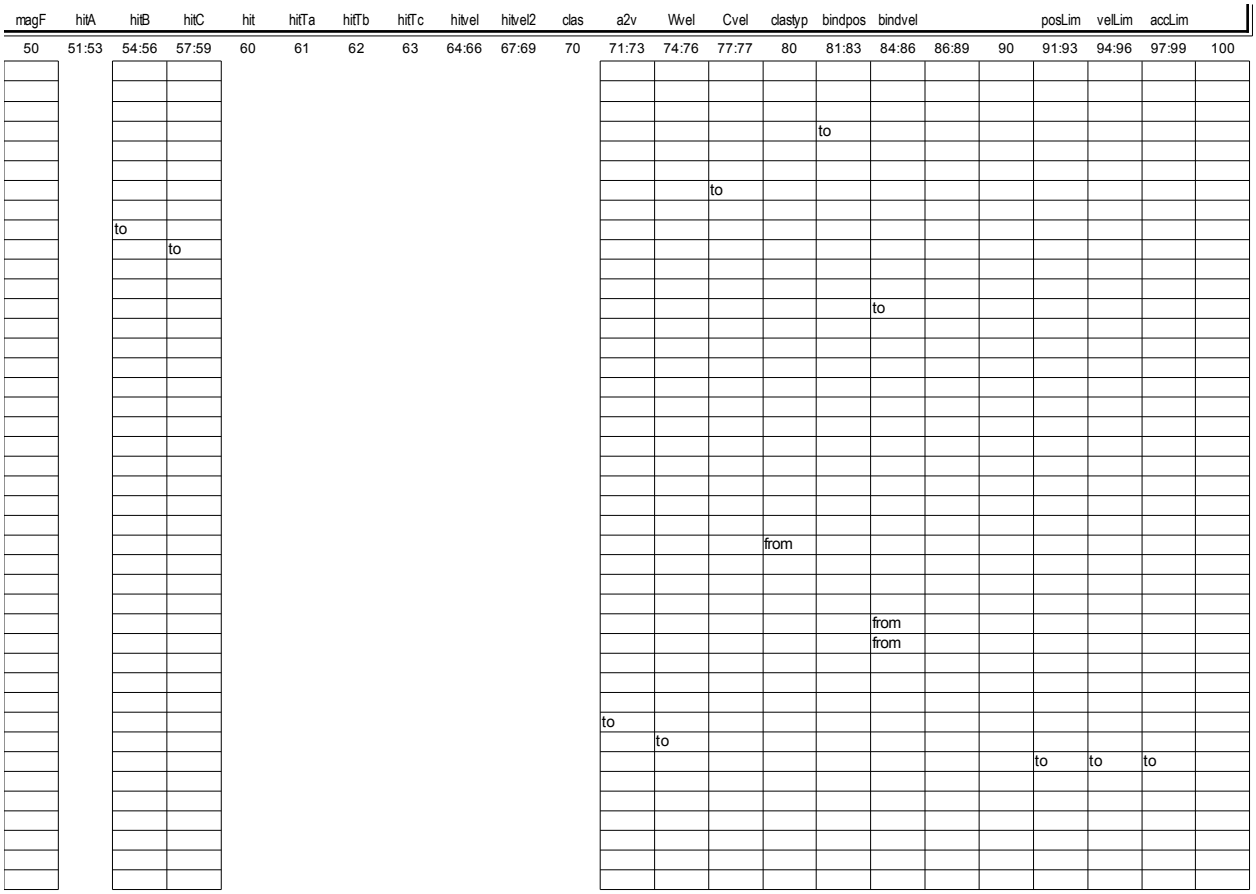


FIGURE 121: Data Structure, Particle Actor Interactions, part 3

AT data

num	mass	z	r4	r5	h	Faff	dc	s	o	Rrowf	Srow	Rrowb	Beff	Feff	G#
1	2	3	4	5	6	7	8	9	10	11:15	16:20	21:25	26:29	30	
						from									
							to			from	from				
								from/to							
								from	to						
									from						
									from						
													from	from	
									from						

FIGURE 122: Data Structure, Particle Actor Interactions, part 4

AP data

pos	ori	p1	type	p2	d1	d2	SN	c1,c2	m1,m2	n1,n2	a1,a2	p1:p2	Aclas	clastyp	func	bindvel	Fa	Fmag
1:3	4:6	7:9	10	11:13	14:16	17:19	20	21:22	23:24	25:26	27:28	29:30	31	32	33	34:36	37:39	40
					from	from												
from																		
		from		from				from/to										
					from	from												

FIGURE 123: Data Structure, Particle Actor Interactions, part 5

Fnor	velB	velA	magV	velW	velC	velAcc	Btype	occup1	occup2
41:43	44:46	47:49	50	51:53	54:56	57:59	60	61:65	66:70
								from	from
								from	from
								from	from
								from	from
								from	from

FIGURE 124: Data Structure, Particle Actor Interactions, part 6

10.7 DATA SET FOR MODEL RUN

Neuron Design Dimensions	units	min	max	norm	var
derived contour of revolution of neuron shape, to scale (microns)					
Dendrogram for dendritic arbor (with diameter data)					
Synaptic types defined by ves, recep, pump (types/dists)					
Synapse locations/size on dendritic arbor, soma, axons (by type)					
Thickness contour of extracellular fluid					
Thickness contour of intracellular fluid					
Thickness of synaptic clefts					
other compartments?					
Membrane thickness profile					
Membrane capacitance profile					
texture of membrane, microstructure, caveoli, mossy					
bifurcation radii					
calculated Surface area of plasma lemma					
calculated volume contained by plasma lemma					
initial Tonicity of intracellular					
initial Tonicity of extracellular					
initial Tonicity of synaptic clefts					
receptor distributions, by type, across membrane contour, polarity					
channel distributions, by type, across membrane contour, polarity					
vesicle distributions, by type, across membrane contour, polarity					
pump distributions, by type, across membrane contour polarity					
define receptor types					
binding sites (pole1, pole2)					
binding affinity profiles (pole1, pole2, quantities per release)					
binding kinetics (s2xs2xs1)					
conform kinetics (s1xs1xs2)					
define channel types					
binding sites (pole1, pole2)					
binding affinity profiles, per site					
binding kinetics (s2xs2xs1)					
conform kinetics (s1xs1xs2)					
phenostate table					
Conductance profile					
transport equation					
define vesicle types					
binding sites (pole1, pole2)					

binding affinity profiles (pole1, pole2, quantities per vesicle)					
binding kinetics (s2xs2xs1)					
conform kinetics (s1xs1xs2)					
transport profile					
transport statistics (probabilities of events, fractions, timing)					
define pump types					
binding sites (pole1, pole2)					
binding affinity profiles, per site					
binding kinetics (s2xs2xs1)					
conform kinetics (s1xs1xs2)					
transport profile, per seat					
energy source/sink per cycle					
s = conformational kinetic states					
d = bind/unbind kinetic combinations					

TABLE 26: FORM FOR COLLECTING DATA FOR A MODEL RUN

10.8 DATA STRUCTURE TERMS

type	all intrinsic traits of an actor necessary for the model. For particles: mass, radius, charge, hydration shells. For actors, see below.
dist	pdf of density distribution across the axial length of each membrane. Any membrane may have actors occupying its nodes. This is useful in maintaining neighboring cell interactions across the extracellular fluid. Implied is actor polarity, which end is inside/outside, and therefore which two compartments are assigned.
contour	a constant sampled at various points along the axial length of the neuron (e.g. diameter, or thickness of the extracellular fluid) A contour domain is 100 values from 0 to 1, where 1 represents the total length of the neuron (from dendritic end to axon end). Contour range depends upon that which is being measured.
profile	a profile domain is a vector of all particle types within the model. Its range might be affinity to a type of allosteric site, conductivity of an ion channel type, transport statistics of a pump type, binding probabilities under certain modulation conditions) Rather than talk of say a Calcium binding site, the model entertains that any particle might collide with that site, but that Ca++ has the highest probability of binding and staying bound there.
Derived contour of revolution of neuron shape, to scale (microns)	Shape of neuron is mapped into an equivalent contour of revolution. Any form of morphological data that captures lengths, surface area, and volume will suffice. Desirable would be designated zones, e.g. boutons, dendritic stalks, soma, initial segment, axon, nodes, boutons, but these may be inferred from the actor distribution data.
Dendrogram for dendritic arbor (w/ diameter data, synapse pos)	Bifurcation patterns, diameter tapers, radius of bifurcation. Typically read off morphometrics.
Synaptic types defined by ves, recep, pump (type/dist)	Multiple types of synapses are supported, defined by the actor types/dists present + cleft thickness
Synapse locations/size on dendritic arbor, soma, axons (by type)	May have been included in dendrogram, but would like data on size of synapse
Thickness contour of extracellular fluid	EM micrographs may show thickness of extracellular space. Need variations along entire length. A fixed thickness is used unless, the variations in extracellular fluid thickness is specified. This data is converted to a axial vector of thicknesses from dendrite to axon.

Thickness contour of intracellular fluid	It is desirable to limit the distance above and below the membrane that is modeled molecularly. With the extracellular this is often measurable, but more vague for the intracellular where the reticulum is complicated. Aside from Ca++ sequestration and ATP supplies, the model regards the membranal sandwich as autonomous: a known thickness of extracellular fluid above and a reasonable cut-off on modeled fluid below. Because the EM force holds most ionic activity quite close to the membrane, varying the intracellular thickness doesn't affect model performance much, but can significantly increase computational load if thicker than needed for consistent results.
Thickness of synaptic clefts	A question arises: Is the circumferential edge of each synaptic bouton open to the extracellular fluid, or some how restricted/obstructed?
additional compartments are created by adding membranes	The model easily accommodates any number of compartments, e.g. endolymph, perilymph, by adding more membranes, e.g. reticular lamina. Each membrane declares two surfaces, assigned respectively to two compartments, used in orienting actors.
Membrane thickness profile	Membrane is assumed to be of uniform thickness, unless variations are specified over axial length.
Membrane capacitance profile	Membrane capacitance is assumed to be of uniform value, unless either proportional to thickness, or specified as axial variations along the length of the neuron. Rafts of differential thickness/capacitance are possible, but require some additional coding.
texture of membrane, microstructure, caveoli, mossy	At current build state, the model does not implement specific textures, except as corrugations to increase surface area. Specific shapes and structures,e.g. caveoli, will require additional coding.
bifurcation radii	Sharp vs rounded have some effect on antidromic conduction
initial Tonicity of intracellular	includes all mobile particle types, including basal levels of messenger molecules (hormones, ATP, etc.)
initial Tonicity of extracellular	ditto
initial Tonicity of synaptic clefts	ditto
receptor distributions, by type, across membrane contour, polarity	receptor densities, by type, per sq micron, samples taken at each significant zone, any gradients noted
channel distributions, by type, across membrane contour, polarity	channel densities per sq micron, samples taken at each significant zone, any gradients noted
vesicle distributions, by type, across membrane contour, polarity	vesicle densities per sq micron, samples taken at each significant zone, any gradients noted

pump distributions, by type, across membrane contour polarity

pump densities, by type, per sq micron, samples taken at each significant zone, any gradients noted

define receptor types

binding sites (pole1, pole2)

how many allosteric binding sites intra-, how many extra-? How are second messenger particles to be released accumulated? (just one at a time, or how many, or catalyzed?). The existence of these binding sites is implied in the affinity profiles

binding affinity profiles (pole1, pole2, quantities per release)

the collision rate of modulator particles to their target sites (may be implied in the binding data, but needs to be separated out)

binding kinetics (s2xs2xs1)

Matrix of forward and backward rates for all binding sites, both allosteric and transport particles, per conformer state

conform kinetics (s1xs1xs2)

Matrix of forward and backward rates between all state transitions, per modulation combo

define channel types

binding sites (pole1, pole2)

binding affinity profiles, per site

binding kinetics (s2xs2xs1)

conform kinetics (s1xs1xs2)

phenostate table

identifies which state numbers have environs impacts, e.g. channel open, channel closed

Conductance profile

selectivity profile as a vector across all particle types present, including messengers. Default value =0

transport equation

Nernst per ion type + concentration pressure per ion type

define vesicle types

binding sites (pole1, pole2)

binding affinity profiles (pole1, pole2, quantities per vesicle)

binding kinetics (s2xs2xs1)

conform kinetics (s1xs1xs2)

transport profile

contents of each vesicle, vector across all possible particle types, variance

transport statistics (probabilities of events, fractions, timing)	probability of performance, probability distribution of fraction of contents emptied, variation in timing of response.
define pump types	
binding sites (pole1, pole2)	stage1, stage2, and modulator sites
binding affinity profiles, per site	
binding kinetics (s2xs2xs1)	
conform kinetics (s1xs1xs2)	
phenostate	state number maps to transport functions
energy source/sink per cycle	e.g. transformation from ATP to ADP; or concentration driver equations
reuptake mechanisms and locations for each type of messenger particle	The model can only be stabilized when adequate reuptake of all messenger types, either by affinities or by pumps.
calculated Surface area of plasma lemma	any means of determining surface area and total membrane capacitance
calculated volume contained by plasma lemma	any means of adequately determining volume
s1 = conformational kinetic states	kinetic states “with bindings” (as sometimes indicated by asterisks) must be separated out as s2 states.
s2 = bind/unbind kinetics, as combinations	s2 states modulate s1 transition probabilities and s1 states modulate s2 bind/unbind probabilities

11 DISCOVERY

11.1 PROBLEM REDUCTION

The initial stance was that this project would consist of a hybrid model of diffusion, Kolmogorov stochastics and electrical circuit representations, as necessary to capture the information flows through the neuron. Subsequent findings have altered that set considerably. Diffusion provides the back ground white noise of liquid state interactions, and drift provides the informationally significant motion. Although the method of eigenvectors can calculate steady state conditions of a transition matrix, it is the dominant state paths (and the near dominant alternates) that are informationally significant. And it is the ability of a state path to map to a temporal pattern that is its most significant functionality.

Although circuit representations of ion channel action have been in use for more than half a century, they fall short of capturing the information flows and processes. The charged particle model implemented herein transcends the circuit representation via several strong reasons.

31. Ions generate flux in 3 dimensions, whereas circuits restrict flow to 1-dimensional flows. Membrane capacitance is continuous over the entire cell surface.

32. A circuit analysis would treat that either as 1 monotonic capacitor, instantaneously responding *en bloc* to any voltage changes, or as a series of discrete capacitors, severing the continuous membrane with artefactual barriers.

33. The circuit interface required a number of compromises to convert calculated currents into a set of individual particles being transported. In the final analysis, the electrical circuit analogy over-constrains the representation of biological systems that possess and require greater degrees of freedom to perform their tasks.

34. A charged particle model acknowledges that an ion has mass, acceleration, and radius. These conspire to slow down the charge time along to the membrane, which in turn supports widely varying topology of charge over the surface of the membrane.

35. The particle system exhibits emergent behavior without programming to induce it. Capacitance, resistance, complex 3-dimensional flux patterns, waves of charge disturbance radiating outward from ion channels upon openings, the zeta potential of exponential charge densities wrt distance from the membrane - are all emergent behaviors of the model. The impacts of ion channel shape and pore locations upon conductivity and selectivity - are all emergent from particle system dynamics.

As a result the entire circuit representation effort of several years had to be abandoned to make way for a charged particle system of diffusion and drift that completely supplanted what the circuits promised to deliver. The particle system was superior in performance and predictive potentials, and it integrated into the stochastic system of the actors seamlessly, on a one-to-one basis (particle colliding with actor). The particle/actor combination provided a match of types (atomic scale to atomic scale), a match of space (sharing the same 3-dimensional volumes) and a match of time (no conversions necessary to communication in either direction).

11.2 MODELING WITH WET LAB DATA

11.2.1 K DR CHANNEL (DELAYED RECTIFIER)

A kinetic scheme for the K delayed Rectifier channel was provided in 1998 by Klemic KG, Durand DM, Jones SW [221]. Given their kinetic scheme of 5 closed channels in ladder formation with 5 open channels, what can be deduced from the resultant Q matrix? This simple scheme offers all the transition rates at two voltages. These project directly into the formation of a 2 page Q matrix.

The states which are open are captured in the matrix O:

O=	c0	c1	c2	c3	c4	o0	o1	o2	o3	o4
	0	0	0	0	0	1	1	1	1	1

When this channel is instantiated, there are 2 voltage conditions to run: rest at 0.060 v, and excited, at 0.020 v.

orig		c0	c1	c2	c3	c4	o0	o1	o2	o3	o4
Q(:,:,1)	c0	0	134	0	0	0	0.0064	0	0	0	0
-0.060 v	c1	566	0	1405	0	0	0	0.077	0	0	0
	c2	0	177	0	936	0	0	0	0.924	0	0
	c3	0	0	266	0	468	0	0	0	1.1	0
	c4	0	0	0	355	0	0	0	0	0	1.33
	o0	725760	0	0	0	0	0	1604	0	0	0
	o1	0	60480	0	0	0	47.2	0	16856	0	0
	o2	0	0	5040	0	0	0	14.8	0	802	0
	o3	0	0	0	420	0	0	0	141	0	401
	o4	0	0	0	0	35	0	0	0	189	0
Q(:,:,2)	c0	0	1873	0	0	0	0.0064	0	0	0	0
+0.020 v	c1	88.7	0	1405	0	0	0	0.077	0	0	0
	c2	0	177	0	936	0	0	0	0.924	0	0
	c3	0	0	266	0	468	0	0	0	11.1	0
	c4	0	0	0	355	0	0	0	0	0	133
	o0	725760	0	0	0	0	0	22475	0	0	0
	o1	0	60480	0	0	0	7.39	0	16856	0	0
	o2	0	0	5040	0	0	0	14.8	0	11237	0
	o3	0	0	0	420	0	0	0	22.2	0	5619
	o4	0	0	0	0	35	0	0	0	29.6	0

This maps the original biodata into a Q matrix of state transition probabilities. This raw Q is then conditioned to a uniform scale suitable for an iteratively generated stochastic time series.

komp

Q(:,:,1)

0	219.081	0	0	0	10	0	0	0	0
169.151	0	392.88	0	0	0	18.5458	0	0	0
0	126.742	0	184.441	0	0	0	34.3726	0	0
0	0	140.232	0	155.278	0	0	0	17.4319	0
0	0	0	150.65	0	0	0	0	0	34.4279
1000	0	0	0	0	10	0	0	0	0
0	539.553	0	0	0	0	18.5458	0	0	0
0	0	291.117	0	0	0	0	34.3726	0	0
0	0	0	157.073	0	0	0	0	63.7228	0
0	0	0	0	84.7493	0	0	0	0	118.059

Q(:,:,2)

0	118.279	0	0	0	0	421.973	0	0	0
169.151	0	211.992	0	0	57.6003	0	392.88	0	0
0	126.742	0	191.654	0	0	68.4413	0	355.249	0
0	0	140.232	0	161.351	0	0	75.6907	0	299.085
0	0	0	150.65	0	0	0	0	81.2953	0
1000	0	0	0	0	0	219.081	0	0	0
0	539.553	0	0	0	91.2818	0	392.88	0	0
0	0	291.117	0	0	0	68.4413	0	184.441	0
0	0	0	157.073	0	0	0	119.784	0	155.278
0	0	0	0	84.7493	0	0	0	128.823	0

The data is mildly compressed on a log scale so as to avoid computationally burdensome small *dt*'s. That is, frequencies higher than, say, 10000 Hz are treated as 10000 Hz, effectively instant in a digital time model.

Then a maximum *dt* is calculated. Then Q is proportioned to the *dt* itself, with residuals calculated.

dt

Q(:,:,1)

0.98804	0.01188	0	0	0	8.49e-5	0	0	0	0
0.02429	0.93727	0.03815	0	0	0	0.00029	0	0	0
0	0.01364	0.95418	0.03118	0	0	0	0.001	0	0
0	0	0.01669	0.95776	0.0221	0	0	0	0.00345	0
0	0	0	0.01927	0.9689	0	0	0	0	0.01183
0.84885	0	0	0	0	0.11041	0.04074	0	0	0
0	0.24712	0	0	0	0.00707	0.61479	0.13102	0	0
0	0	0.07194	0	0	0	0.00398	0.89521	0.02888	0
0	0	0	0.02094	0	0	0	0.01218	0.94641	0.02047
0	0	0	0	0.0061	0	0	0	0.01409	0.97982

Q(:,:,2)

0.95591	0.044	0	0	0	8.488522	0	0	0	0
0.00968	0.95188	0.03815	0	0	0	0.00029	0	0	0
0	0.01364	0.95418	0.03118	0	0	0	0.001	0	0
0	0	0.01669	0.95776	0.0221	0	0	0	0.00345	0
0	0	0	0.01927	0.9689	0	0	0	0	0.01183
0.84885	0	0	0	0	0	0.15115	0	0	0
0	0.24712	0	0	0	0.00282	0.61904	0.13102	0	0
0	0	0.07194	0	0	0	0.00398	0.81696	0.10713	0
0	0	0	0.02094	0	0	0	0.00486	0.89826	0.07593
0	0	0	0	0.0061	0	0	0	0.00561	0.98829

These values are then converted to a CDF via integration.

CDF

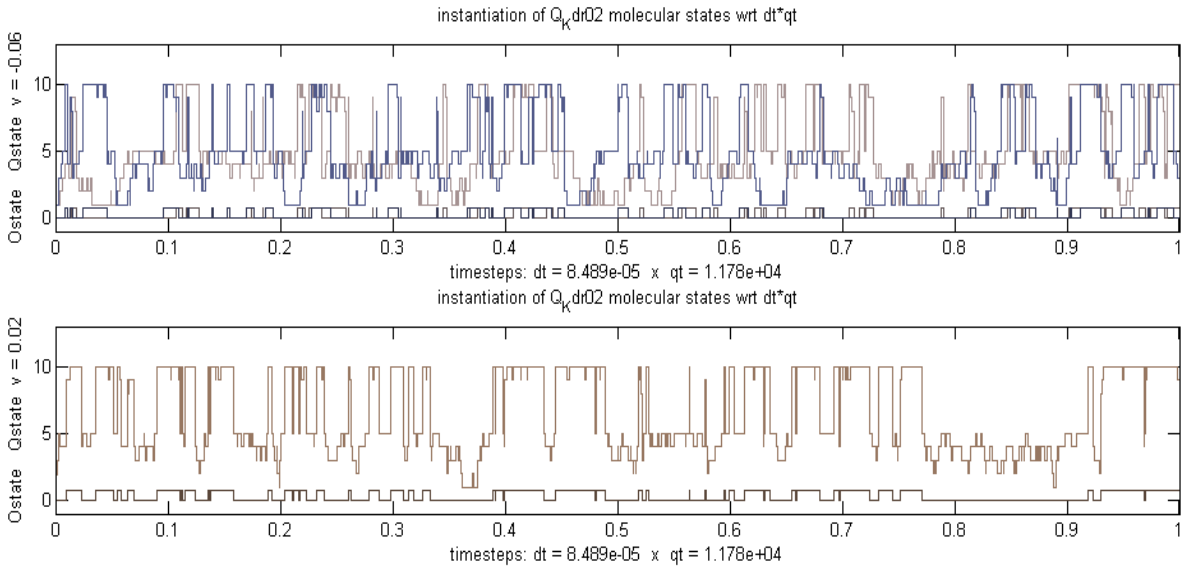
Q(:,:,1)

0.98804	0.999915	0.999915	0.999915	0.999915	1	1	1	1	1
0.024287	0.96156	0.999708	0.999708	0.999708	0.999708	1	1	1	1
0	0.013635	0.967818	0.998997	0.998997	0.998997	0.998997	1	1	1
0	0	0.016693	0.974454	0.996553	0.996553	0.996553	0.996553	1	1
0	0	0	0.019265	0.988169	0.988169	0.988169	0.988169	0.988169	1
0.848852	0.848852	0.848852	0.848852	0.848852	0.959258	1	1	1	1
0	0.247116	0.247116	0.247116	0.247116	0.254189	0.868975	1	1	1
0	0	0.07194	0.07194	0.07194	0.07194	0.075916	0.971123	1	1
0	0	0	0.020943	0.020943	0.020943	0.020943	0.033122	0.979533	1
0	0	0	0	0.006097	0.006097	0.006097	0.006097	0.020184	1
0	0	0	0	0	0	0	0	0	0

Q(:,:,2)

0.955912	0.999915	0.999915	0.999915	0.999915	1	1	1	1	1
0.009675	0.96156	0.999708	0.999708	0.999708	0.999708	1	1	1	1
0	0.013635	0.967818	0.998997	0.998997	0.998997	0.998997	1	1	1
0	0	0.016693	0.974454	0.996553	0.996553	0.996553	0.996553	1	1
0	0	0	0.019265	0.988169	0.988169	0.988169	0.988169	0.988169	1
0.848852	0.848852	0.848852	0.848852	0.848852	0.848852	1	1	1	1
0	0.247116	0.247116	0.247116	0.247116	0.249932	0.868975	1	1	1
0	0	0.07194	0.07194	0.07194	0.07194	0.075916	0.892873	1	1
0	0	0	0.020943	0.020943	0.020943	0.020943	0.025806	0.924068	1
0	0	0	0	0.006097	0.006097	0.006097	0.006097	0.011707	1

The CDF can then be instantiated, yielding a time series of states. The state number can then be mapped through O to yield the openings and closings. The results of biodata simulation follow. The upper trace pair is at rest voltage and the lower trace pair is at depolarization voltage.



The x-axis is time in seconds. There are 2 y-axis; the lower trace is the phenostate (openings/closings), and the upper trace is the internal conformational state. This result indicates that the "resting state is 0.2569 fraction of the time open; and the depolarized states is 0.4362 fraction open. Multiple runs yielded quite similar numbers, so these are indeed characteristic of the Q. While directionally correct, if true to the biology this would be a metabolically expensive type of channel. Much more likely is that the resting state is closed all but 1 or 2% of the time.

Note the dominant pathways through the state space.

Q1		c0	c1	c2	c3	c4	o0	o1	o2	o3	o4
-0.060 v	c0	0	134	0	0	0	0.0064	0	0	0	0
	c1	566	0	1405	0	0	0	0.077	0	0	0
	c2	0	177	0	936	0	0	0	0.924	0	0
	c3	0	0	266	0	468	0	0	0	11.1	0
	c4	0	0	0	355	0	0	0	0	0	133
	o0	725760	0	0	0	0	0	1604	0	0	0
	o1	0	60480	0	0	0	47.2	0	16856	0	0
	o2	0	0	5040	0	0	0	14.8	0	802	0
	o3	0	0	0	420	0	0	0	141	0	401
	o4	0	0	0	0	35	0	0	0	189	0

dominant state paths

c0	c1	c2	c3	c4	c3	
	c0	c1	c2	o4	o3	c3
					c4	o4
o0	c0					
	o1	c1				
		o2	c2			
			o3	c3		
				o4	o3	
					c4	

Q2		c0	c1	c2	c3	c4	o0	o1	o2	o3	o4
+0.020 v	c0	0	1873	0	0	0	0.0064	0	0	0	0
	c1	88.7	0	1405	0	0	0	0.077	0	0	0
	c2	0	177	0	936	0	0	0	0.924	0	0
	c3	0	0	266	0	468	0	0	0	11.1	0
	c4	0	0	0	355	0	0	0	0	0	133
	o0	725760	0	0	0	0	0	22475	0	0	0
	o1	0	60480	0	0	0	7.39	0	16856	0	0
	o2	0	0	5040	0	0	0	14.8	0	11237	0
	o3	0	0	0	420	0	0	0	22.2	0	5619
	o4	0	0	0	0	35	0	0	0	29.6	0

dominant state paths

c0	c1	c2	c3	c4	c3	
					o4	c4
						o3 o4
o0	c1					
	o1	c1				
		o2	o3	o4	c4	
			c2		o3	o4

O	c0	c1	c2	c3	c4	o0	o1	o2	o3	o4
	0	0	0	0	0	1	1	1	1	1

The high probability paths lead to the attractors of the state space. In all cases leading to a nest consisting of {c3,c4,o3,o4}. This is not healthy, because it results in too much open time for a quiescent channel. As channel openings are metabolically expensive, most, if not all, neuron types can be expected to perform physiologically with less than 25% open time while busy, and less than 1% or 2% while “at rest”. Ranges of greater than 25% open would put the organism into emergency or panic conditions. That is, while optimal coding hoovers around 50% opening time, the energy cost biases that mean downward.

There is much more analysis to do. The time envelops, as they may change wrt voltage should reveal the delayed rectifier behaviors. This is future work.

This particular Kdr scheme has an equal number of closed and open states, which conveniently allows us to split the Q into quadrants.

BLOCK02 – color coded

c0	c1	c2	c3	c4	o0	o1	o2	o3	o4
0	134	0	0	0	0.0064	0	0	0	0
566	0	1405	0	0	0	0.077	0	0	0
0	177	0	936	0	0	0	0.924	0	0
0	0	266	0	468	0	0	0	0.06	0
0	0	0	355	0	0	0	0	0	0.93
725760	0	0	0	0	0	1604	0	0	0
0	60480	0	0	0	47.2	0	16856	0	0
0	0	5040	0	0	0	14.8	0	802	0
0	0	0	420	0	0	0	141	0	401
0	0	0	0	35	0	0	0	189	0

0	1873	0	0	0	0.0064	0	0	0	0
88.7	0	1405	0	0	0	0.077	0	0	0
0	177	0	936	0	0	0	0.924	0	0
0	0	266	0	468	0	0	0	11.1	0
0	0	0	355	0	0	0	0	0	133
725760	0	0	0	0	0	22475	0	0	0
0	60480	0	0	0	7.39	0	16856	0	0
0	0	5040	0	0	0	14.8	0	11237	0
0	0	0	420	0	0	0	22.2	0	5619
0	0	0	0	35	0	0	0	29.6	0

	volts	-0.06	0.02
grey	closed to closed	high	mid
green	closed to open	low	high
orange	open to open	low	mod
yellow	open to closed	high	high

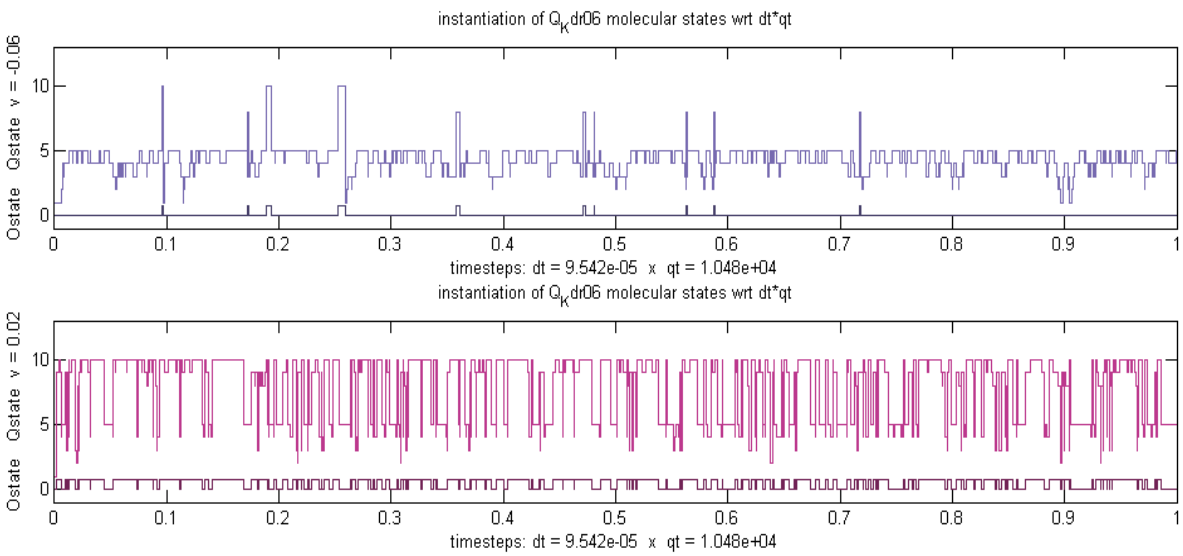
Conventional channel behavior would require quadrant weightings similar to above. To generate behavior typical of channels, that is, low firing rates at membrane rest voltages, and moderate to high firing rates during depolarization voltages, the quadrants would look something like:

BLOCK03 – quadrants exchanged, color coded

-0.06	0	1604	0	0	0	0.0064	0	0	0	0
	566	0	16856	0	0	0	0.077	0	0	0
	0	177	0	802	0	0	0	0.924	0	0
	0	0	266	0	401	0	0	0	0.06	0
	0	0	0	355	0	0	0	0	0	0.93
	725760	0	0	0	0	0	0.0064	0	0	0
	0	60480	0	0	0	47.2	0	0.077	0	0
	0	0	5040	0	0	0	14.8	0	0.924	0
	0	0	0	420	0	0	0	141	0	11.1
	0	0	0	0	189	133	0	0	35	0

0.02	0	134	0	0	0	0	22475	0	0	0
	566	0	1405	0	0	7.39	0	16856	0	0
	0	177	0	936	0	0	14.8	0	11237	0
	0	0	266	0	468	0	0	22.2	0	5619
	0	0	0	355	0	0	0	0	29.6	0
	725760	0	0	0	0	0	1604	0	0	0
	0	60480	0	0	0	47.2	0	16856	0	0
	0	0	5040	0	0	0	14.8	0	802	0
	0	0	0	420	0	0	0	141	0	401
	0	0	0	0	35	0	0	0	189	0

These fields of values will generate ion channel behaviors such that rest voltage results in low firing rates and depolarization voltage results in rapid firing rates.



This demonstrates open fraction times of 0.0184 while the at rest voltage (-0.060), and 0.6325 while under depolarizing voltage (0.020). The key considerations are what modulates these behaviors, and how complex may be the responses to such modulation.

11.2.2 KV SHAKER CHANNEL MODEL ATTEMPT

Three papers by Zogotta [173] in 1994 gathered wet lab data on the potassium channel Kv 1.1 (shaker). The See also PMID's: 8189206, 8189207, 8189208. The data provided yielded a state transition matrix:

```
% Q construction
a0 =   1010 ;    %  alpha0    k alpha  values at V = 0 mv
b0 =   6.25 ;    %  beta0  k beta
g0 =   3400 ;    %  gamma0    k gamma
s0 =   8.5  ;    %  sigma0    k sigma
d0 =   600  ;    %  OC  k OC
e0 =   3800 ;    %  CO  k CO
h0 =   2.00 ;    %  eta
t0 =   11.8 ;    %  theta

a1 =   0.32 ;    %  z alpha
b1 =   2.5  ;    %  z beta
g1 =   0.32 ;    %  z gamma
s1 =   1.1  ;    %  z sigma
d1 =   0 ;       %  z OC
e1 =   0.17 ;    %  z CO

a3 =   a1+b1;    %  zx
b3 =   g1+s1;    %  zy

a4 =    a0*exp(a1*FRT*V/1000);     %   alpha    % 1000 may be removed for mv
b4 =    b0*exp(b1*FRT*V/1000);     %   beta     % leave it in for units in volts
g4 =    g0*exp(g1*FRT*V/1000);     %   gamma
s4 =    s0*exp(s1*FRT*V/1000);     %   sigma

a5 =    exp(-a1*a3*h0*FRT);     %   x alpha
b5 =    exp(b1*a3*h0*FRT);      %   x beta
g5 =    exp(-g1*a3*h0*FRT);     %   x gamma
s5 =    exp(s1*a3*h0*FRT);      %   x sigma

a6 =    exp(-a1*b3*h0*FRT);     %   y alpha
b6 =    exp(b1*b3*h0*FRT);      %   y beta
g6 =    exp(-g1*b3*h0*FRT);     %   y gamma
s6 =    exp(s1*b3*h0*FRT);      %   y sigma


% Init Q
Q = zeros(qs);

% forward reaction rates, per second
% horz links
Q(1,2) = 4*a4*a5^0;
Q(2,3) = 3*a4*a5^1;
Q(3,4) = 2*a4*a5^2;
Q(4,5) = 1*a4*a5^3;

Q(6,7) = 3*a4*a5^1*a6;
Q(7,8) = 2*a4*a5^2*a6;
Q(8,9) = 1*a4*a5^3*a6;

Q(10,11) =  2*a4*a5^2*a6^2;
```

```
Q(11,12) =  1*a4*a5^3*a6^2;

Q(13,14) =  1*a4*a5^3*a6^3;

% vert links
Q(2,6) =    1*g4*g5^0*g6^0;
Q(3,7) =    2*g4*g5^1*g6^0;
Q(4,8) =    3*g4*g5^2*g6^0;
Q(5,9) =    4*g4*g5^3*g6^0;

Q(7,10) =   1*g4*g5^1*g6^1;
Q(8,11) =   2*g4*g5^2*g6^1;
Q(9,12) =   3*g4*g5^3*g6^1;

Q(11,13) =  1*g4*g5^2*g6^2;
Q(12,14) =  1*g4*g5^3*g6^2;

Q(14,15) =  1*g4*g5^3*g6^3;
Q(15,16) =  d0;

%           backward reaction rates, per second
% horz  back links
Q(2,1) = 1*b4*b5^0;
Q(3,2) = 2*b4*b5^1;
Q(4,3) = 3*b4*b5^2;
Q(5,4) = 4*b4^b5^3;

Q(7,6) =    1*b4*b5^1*b6;
Q(8,7) =    2*b4*b5^2*b6;
Q(9,8) =    3*b4*b5^3*b6;

Q(11,10) =  1*b4*b5^2*b6^2;
Q(12,11) =  2*b4*b5^3*b6^2;

Q(14,13) =  (1/t0) *b4*b5^3*b6^3;

% vert back links
Q(6,2) =    1*s4*s5^0*s6^0;
Q(7,3) =    1*s4*s5^1*s6^0;
Q(8,4) =    1*s4*s5^2*s6^0;
Q(9,5) =    1*s4*s5^3*s6^0;

Q(10,7) =   2*s4*s5^1*s6^1;
Q(11,8) =   2*s4*s5^2*s6^1;
Q(12,9) =   2*s4*s5^3*s6^1;

Q(13,11) =  3*s4^s5^2*s6^2;
Q(14,12) =  3*s4*s5^3*s6^2;

Q(15,14) =  4*s4*s5^3*s6^3;
Q(16,15) =  e0;

V = 0.060;  % volts = rest potential
Q(v) = [ ...
  x1  4480   0  0       0           0    0       0          0          0          0          0          0          0          0
373         x2   3360     0         0          2800       0          0          0          0          0          0          0          0          0
            0;
0           746         x3     2240 0          0          5600       0          0          0          0          0          0          0          0
            0;
0           0           1119        x4     1120 0          0          8400       0          0          0          0          0          0          0
            0;
0           0           0           1492        x5     0    0          0          11200      0  0       0          0          0          0          0;
0           2800        0           0           0          x6     3360    0          0          0          0          0          0          0          0
            0;
0           0           21.2        0           0          373         x7         2240       0          42.2       0          0          0          0
            0           0'
0           0           0           21.2        0          0           746        x8         1120       0          5600       0          0          0
            0           0;
0           0           0           0           21.2       0           0          1119       x9     0   0          8400       0          0          0
            0;
0           0           0           0           0          0           42.2       0          0      x10 2240       0          0          0          0
```

```
        0;
0       0       0       0       0       0       0       42.2    0       373     x11     1120    2800    0
        0       0;
0       0       0       0       0       0       0       0       42.2    0       746     x12     0       5600    0
        0;
0       0       0       0       0       0       0       0       0       0       63.6    0       x13     1120    0
        0;
0       0       0       0       0       0       0       0       0       0       0       63.6    373
        x14     2800;   0
0       0       0       0       0       0       0       0       0       0       0       0       0
        84.8    x15     600;
0       0       0       0       0       0       0       0       0       0       0       0       0       0
        3800    x16     ];
```

R = [ ]; % R is unnecessary in an analog voltage Q, because modulation does not require bindings.
O = [0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0]; % state 15 is the open state; all others are closed.

The results of instantiating this Q for 1000 *dt* iterations is:

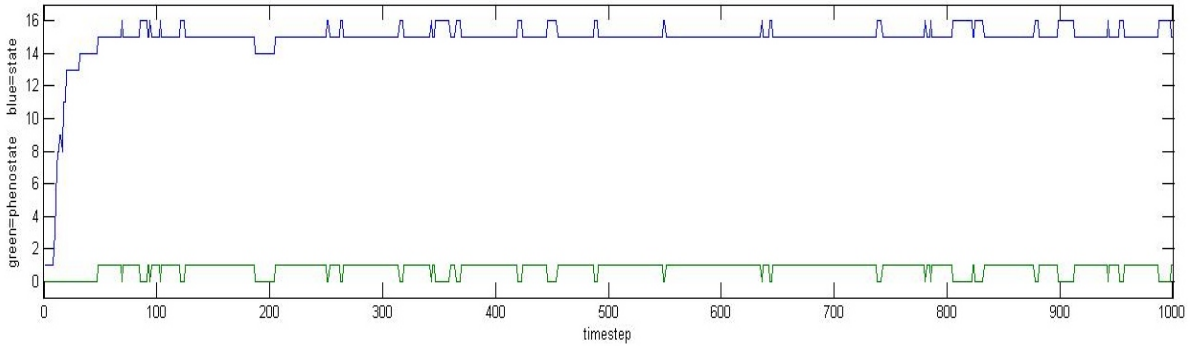


FIGURE 125: Kv1.1 Channel simulation

Repeated trials, of which this plot is typical indicates that no matter what state the actor starts in, the Q will tend toward state 15, followed by a flutter between 15 and 16. At first glance this appears undesirable, similar to a poison state – proceeding to just one state and staying there forever. But this data was collected, indeed can only be collected by getting the channel to open. Thus modulation conditions must be produced in the lab for channel openings. Regardless of how it was accomplished (voltage, neurotransmitters, blocks). What this represents then is 1 page of the Q; not the entire Q.

A minimum of 3 more pages in Q must be constructed: Hyperpolarized, mildly depolarized, deeply depolarized, as a function of voltage modulation. However, following the formuli provided by Zagotta, the values for Q were not suitable for a state transition matrix. Although one can estimate and speculate what a working Q matrix might requires in terms of values, the purpose of this exercise was to locate a most complete set of state transition rates and "run" them to disclose their inherent behavior. This set was not quite viable to do so.

The necessary characteristics of channel behavior are that they remain largely closed during their “rest” conditions, and then respond rather quickly to stimuli such as voltage or neurotransmitter bindings, but never engaging in prolonged openings, as this would deplete the cell's membrane potential (usually regarded as lethal). Variations on this theme include delayed responses, and prolonged closed times (refractory periods). While a depolarizing voltage should open the channel, the Q-matrix state transitions should also be such that the channel cannot be held open indefinitely during a sustained depolarizing voltage. State transitions must take place that not only close the channel but also delay its opening. One of the characteristics of the shaker channel is that the refractory period is either missing, short or erratic; and the “shake” is the result. But the above performance of holding open indefinitely may not be physiologic, due, again, to its danger to cell viability.

The larger problem with the published data is that the second block of voltage dependent equations do not produce a Q matrix consistent with the first block of constants, provided by the same paper.

11.2.3 NAK-ATPASE PUMP MODELING ATTEMPT

In 1994, Heyse [219] published an extensive set of state graphs and transition probabilities on the NaK-ATPase pump. The state graph provided can be rearranged to order which side of the membrane the bind/release sites are active one:

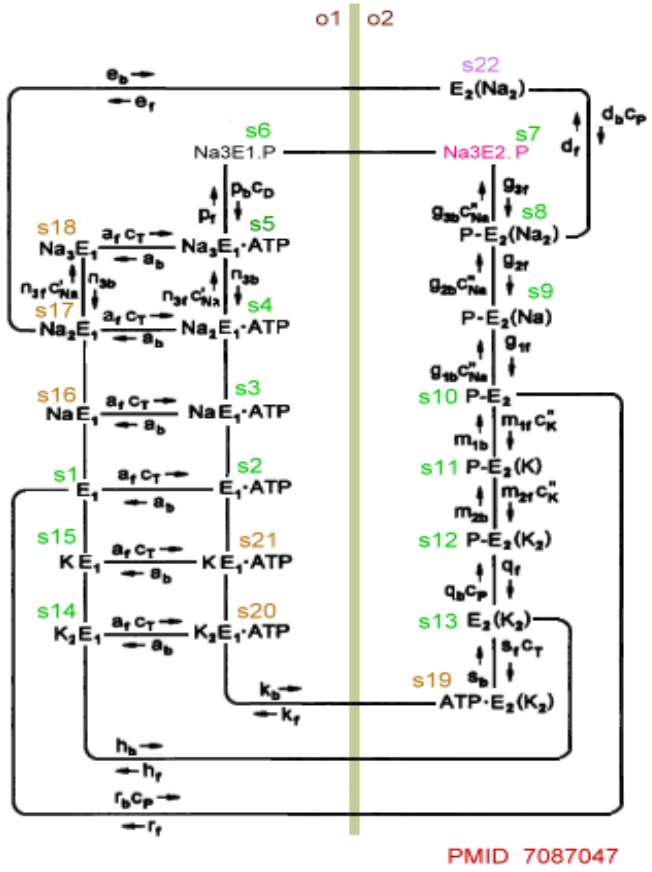


FIGURE 126: State Graph of NaK-ATPase pump

Such a state graph can then be depicted as a duty cycle, with an educated guess as to which would be the dominate path. This exercise reveals a missing state (s7 in red), or rather a complex transition that is better broken down into two simple transitions. State s6 transports across the membrane, but cannot lose a bound Na along the way. It must complete the transport, as one step, and then dissociate the first of three Na's bound to it.

The numbering and positioning of the states is driven by the highest probabilities of occurrence and the need to complete the pumping cycle so as to pump across the membrane many thousands of times per second. If, in modeling it should be come apparent that the choice of state numbers was not accurate to the actual behavior, then these can be re-ordered, for convenience. Those outside the main loop. But none-the-less, participating as alternative paths can be drawn in (as brown links). And pumps are found to have the occasional “skips” or shortcuts, whereby only a partial number of particles are transported per cycle, or a cycle is completed without an energy source (ATP lysis), perhaps while being driven backwards during unusual concentration reversals. These are represented as lavender links.

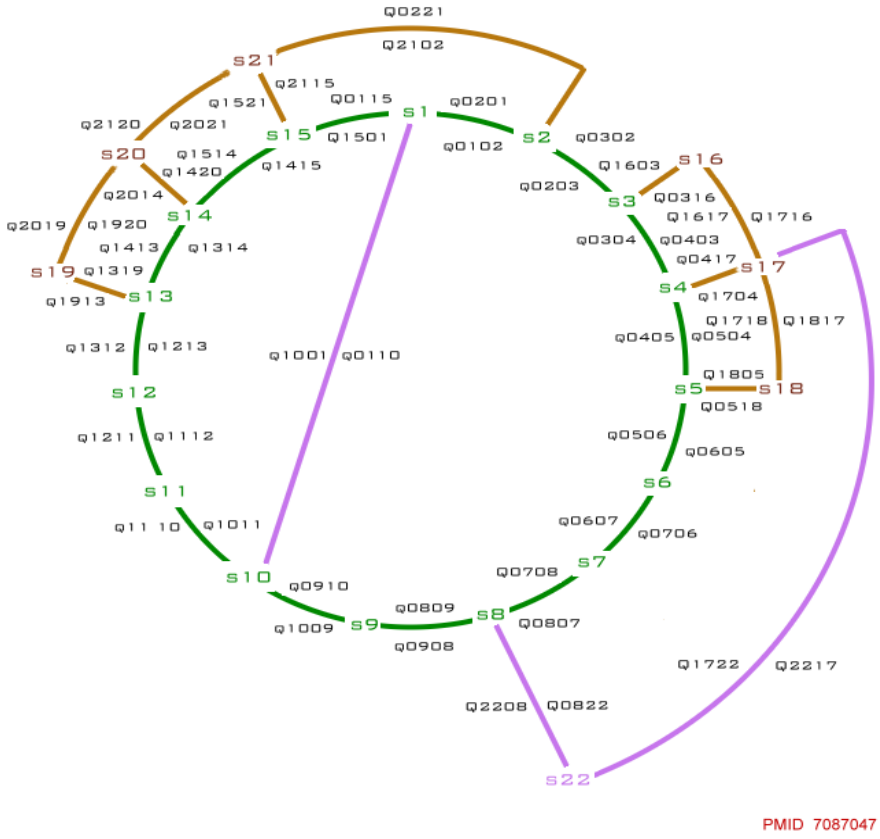


FIGURE 127: Duty Cycle of NaK-ATPase pump

This is a combined conformation and bind event depiction, mapping to the following state transition matrix.

Q State	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1	X	q0102								q0110					q0115	q0116						
2	q0201	X	q0203																		q0221	
3		q0302	X	q0304												q0316						
4			q0403	X	q0405												q0417					
5				q0504	X	q0506												q0518				
6					q0605	X	q0607															
7						q0706	X	q0708														
8							q0807	X	q0809													q0822
9								q0908	X	q0910												
10	q1001								q1009	X	q1011											
11										q1110	X	q1112										
12											q1211	X	q1213									
13												q1312	X	q1314					q1319			
14													q1413	X	q1415					q1420		
15	q1501													q1514	X						q1521	
16			q1603													X	q1617					
17				q1704												q1716	X	q1718				q1722
18					q1805												q1817	X				
19													q1913						X	q1920		
20														q2014					q2019	X	q2021	
21		q2102													q2115					q2120	X	
22								q2208									q2217					X

Many of the rate coefficients were provided by Heyse.

GREEN forward loop duty cycle
KHAKI alternative forward loop
PURPLE free paths, short cuts, forward bypass
BROWN backward
RUDDY portals to backward motion

Rate Coeff	interpretation	Value	Units	Range of Confidence	Units for Range of Confidence
af			15000000 M-1*s-1	10000000 .. 100000000	M-1*s-1
ab			1.64 s-1	ab / af = 50 .. 200	nM
df			10 s-1	3 .. 30	s-1
db			25200 M-1*s-1		
ef			50 s-1	> 10 (or equal to)	s-1
eb			0.1 s-1	< 1 (or equal to)	s-1
gf		< 1E4	1.00E+004 s-1	5000 .. ?	s-1
gb			1000000 M-1*s-1	gf / gb = 0.05 .. 0.2	M
g2f		< 5E3	5.00E+003 s-1	3000 .. ?	s-1
g2b			2680 M-1*s-1	g2f / g2b = 1 .. 2.5	M
g3f			22 s-1	18 .. 30, & g3f / g3b = 0.12M	s-1
g3b			180 M-1*s-1	60 .. 600	M-1*s-1
hf			0.1 s-1	0.005 .. 0.5	s-1
hb			100 s-1	50 .. 500	s-1
kf			22 s-1	15 .. 30	s-1
kb			400 s-1	100 .. 1000	s-1
mf			34000 M-1*s-1	20000 .. 50000	M-1*s-1
mb			10 s-1	5 .. 20	s-1
m2f			5000000 M-1*s-1	> 1000	M-1*s-1
m2b			2000 s-1	M2b / m2f = 1 .. 100	Ụm – mM
n3f			2000 M-1*s-1	> 1000	M-1*s-1
n3b			800 s-1	n3b / n3f = 4	mM
of			1000000 M-1*s-1	1000000 .. 4000000	s-1
ob			0.01 s-1	0.005 .. 0.002	s-1
pf			200 s-1	150 .. 300	s-1
pb			3700 M-1*s-1	1000 .. 1000000	M-1*s-1
qf			100000 s-1	>= 1000	s-1
qb			5000000 M-1*s-1	>= 1000	M-1*s-1
rf			0.8 s-1	0.3 .. 1	s-1
rb			3300 M-1*s-1	100 .. 50000	M-1*s-1
sf			500000 M-1*s-1	250000 .. 1000000	M-1*s-1
sb			400 s-1	Sb / sf = 4 .. 10	Ụm

Concentration	interpretation	Value	Units	symbol as used herein
Cna	conc_in.Na	0.0104	M	ci.Na
	conc_out.Na	0.1090		co.Na
Ck	conc_in.K	0.1240	M	ci.K
	conc_out.K	0.0023		co.K
cT	conc.ATP	0.0100	M	ci.ATP
cp	conc.ADP	0.0010	M	ci.ADP
cd	conc.Pi	0.0020	M	ci.Pi

TABLE 27: NAK-ATPASE REACTION RATES

According to the Heyse scheme, 59 transition probabilities are needed. But only 42 were provided, leaving 17 absent, yet necessary to complete the duty cycle.

Map coefficients to scheme links

		affin	* conc	affin	conc	prod
1	q0102	af	ci.atp	15000000	0.01	150000
2	q0110	rb	ci.adp	3300	0	3.3
3	q0115	-			1	0
4	q0116	-			1	0
5	q0201	ab	1/af	10	0.61	6.097560976
6	q0203	-			1	0
7	q0221	-			1	0
8	q0302	-			1	0
9	q0304	-			1	0
10	q0316	ab		10	1	10
11	q0403	-			1	0
12	q0405	n3f	Cna	800	0.11	87.2
13	q0417	ab		10	1	10
14	q0504	n3b		1000000	1	1000000
15	q0506	pf		3700	1	3700
16	q0518	ab		10	1	10
17	q0605	pb	ci.adp	100000	0	200
18	q0607	-			1	0
19	q0706	-			1	0
20	q0708	g3f		180	1	180
21	q0807	g3b	co.na	0.1	0.12	0.01
22	q0809	g2f		2680	1	2680
23	q0822	df		25200	1	25200
24	q0908	g2b	co.na	22	0.12	2.73
25	q0910	g1f		1000000	1	1000000
26	q1001	rf		3300	1	3300
27	q1009	g1b	co.na	5.00E+003	0.12	620
28	q1011	m1f	co.k	10	0.01	0.1
29	q1110	m1b		5000000	1	5000000
30	q1112	m2f	co.k	2000	0.01	20
31	q1211	m2b		2000	1	2000
32	q1213	qf		1000000	1	1000000
33	q1312	qb	ci.adp	5.00E+003	0	10
34	q1314	hf		100	1	100
35	q1319	sf	ci.atp	400	0	0.4
36	q1413	hb			1	0
37	q1415	-			1	0
38	q1420	af	ci.atp	1.64	0	0
39	q1501	-			1	0
40	q1514	-			1	0
41	q1521	af	ci.atp	1.64	0	0
42	q1603	af	ci.atp	1.64	0	0
43	q1617	-			1	0
44	q1704	af	ci.atp	1.64	0	0
45	q1716	-			1	0
46	q1718	n3f	ci.na	800	0.11	87.2
47	q1722	eb		1.00E+004	1	10000
48	q1805	af	ci.atp	1.64	0	0
49	q1817	n3b		1000000	1	1000000
50	q1913	ab		10	1	10
51	q1920	kf		400	1	400
52	q2014	ab		10	1	10
53	q2019	kb		34000	1	34000
54	q2021	-			1	0
55	q2102	-			1	0
56	q2115	ab		10	1	10
57	q2120	-			1	0
58	q2208	db	ci.adp	50		0
59	q2217	ef		0.1	1	0.1

TABLE 28: EXTENSION OF REACTION RATES TO STATE TRANSITION PROBABILITIES

events/s
econd

Q State	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1	X	150000								3.3					0	0						
2	0	X	6.1																		0	
3		0	X	0												0						
4			10	X	0												87.2					
5				10	X	1000000												3700				
6					10	X	200															
7						0	X	0														
8							180	X	0.01													2680
9								25200	X	2.73												
10	1000000								3300	X	620											
11										0.1	X	5000000										
12											20	X	2000									
13												1000000	X	10					100			
14													0.4	X	0					0		
15	0													0	X						0	
16			0													X	0					
17				0												0	X	0				87.2
18					10000												0	X				
19													1000000						X	10		
20														400					10	X	34000	
21		0													0					10	X	
22								0									0					X

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
	10	1	16	17	18	5	8	9	10	9	12	11	12				18		13	14	15	
									8			13							20			
1	2			5	4		8	9	10	9	12	13	19	20	21	3	4	5	20	19		17
					6				8	11		11	12									

TABLE 29: KV CHANNEL Q MATRIX VALUES AND COMPLETIONS

Out of the 22 state provided in the Heyse scheme, only two of them, 5 and 17 are viable, in that they have adequate in feed and out feed rates. The rest display either a lack of input sources or a lack of output sinks. For a pump to complete 10000 cycle per second, and for this pump in particular to execute a minimum of 15 states per cycle – then there must be 150 000 states traversed each second. This implies an average rate of >15000 per state on the dominant cycle. Each and every state on this cycle should be capable of a speed of 150000 input events and 150000 output events per second. More exactly, the sum of the time durations of each of the 15 steps around the cycle must add up to less than 1/10000th of a second. The provided data does not even provide for a single cycle, given any length of time. Ergo, there is missing data.

Only 2 out of the 22 states are viable, in that they have a significant input and significant output. However, they do not complete a duty cycle. There must be additional transition probabilities to complete a cycle. Because each of the binding combinations is likely to result in a unique Q page, there is missing data. The above Q should be representative of only one binding combination, but may be a mix of several. In either case there remains work to do: To ad, and maybe to separate. In one sense the Q above is correct: any given bind state only represents a

portion of the cycle; never the entirety. If we look at the duty cycle as a series of phases, then we can "solve" each phase independently, then stitch them together.

Presuming the pump to begin in a rest state with no bound Na, K, nor ATP, then:

Phase 1 spans from the rest state to 1Na bound on the king site.
Phase 2 spans the loading of 2 more Na
Phase 3 binds an ATP
Phase 4 is transport across the membrane, while lysing an ATP, leaving only Pi bound
Phase 5 unbinds 1,2,3 Na
Phase 6 binds K and sites 2 and 3
Phase 7 return transports the K's across the membrane
Phase 8 releases 2,3 K
Phase 9 releases the Pi

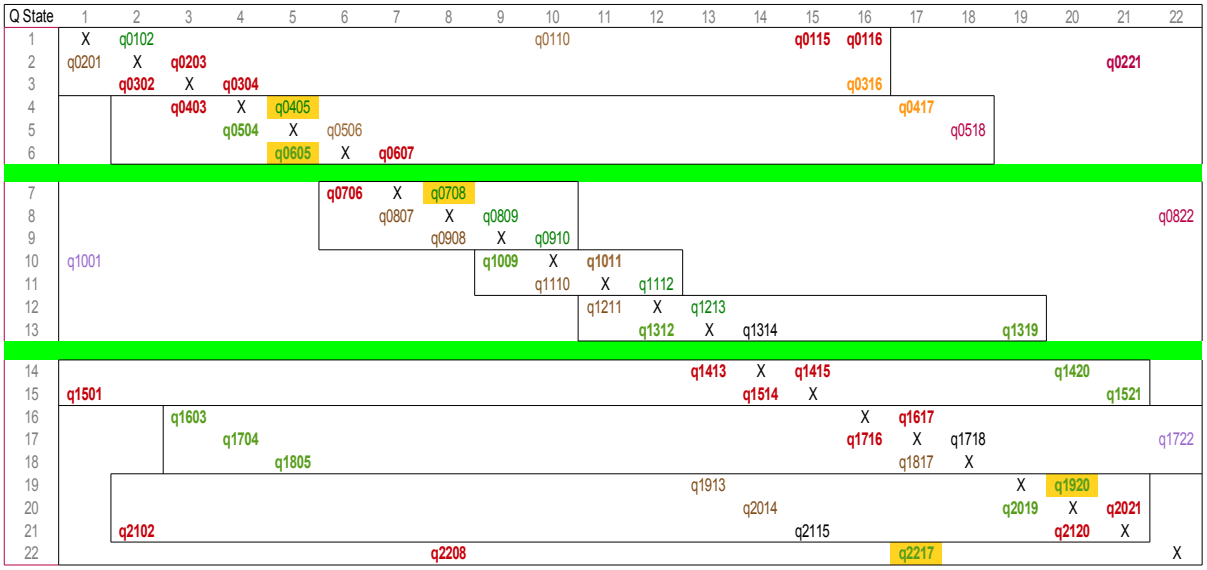


TABLE 30: NAK-ATPASE PUMP CHART OF TRANSITIONS AND EVENTS

The green bars symbolize transport events. The lowest two blocks contain alternative paths, which probably run concurrently with the dominant path.

This matrix can be separated into a Q matrix of 6 to 9 states, and the rest of the transactions (bindings and dissociations) belong to the R matrix. How many possible permutations to the bind sites *d* are there?

State Name by Heyse	Rationalized state name	D =[Na Na Na K K ATP]	page in Q	O	Q
E1	N0K0P0E1	[0 0 0 0 0 0]	1	1	1
E1*ATP	N0K0P1E1	[0 0 0 0 0 4]	2	1	2
NaE1*ATP	N1K0P1E1	[1 0 0 0 0 4]	3	1	3
Na2E1*ATP	N2K0P1E1	[1 1 0 0 0 4]	4	1	4
Na3E1*ATP	N3K0P2E1	[1 1 1 0 0 4]	5	1	5
(Na3)E1—P	N3K0P1E1	[1 1 1 0 0 3]	6	1	6
missing	N3K0P1E2	[1 1 1 0 0 3]	6	2	7
P—E2(Na2)	N2K0P1E2	[1 1 0 0 0 3]	7	2	8
P—E2(Na)	N1K0P1E2	[1 0 0 0 0 3]	8	2	9
P—E2	N0K0P1E2	[0 0 0 0 0 3]	9	2	10
P—E2(K)	N0K1P2E2	[0 0 0 2 0 3]	10	2	11
P—E2(K2)	N0K2P2E2	[0 0 0 2 2 3]	11	2	12
E2K2	N0K2P0E2	[0 0 0 2 2 0]	12	2	13
K2E1	N0K2P0E1	[0 0 0 2 2 0]	12	1	14
KE1	N0K1P0E1	[0 0 0 2 0 0]	13	1	15
NaE1	N1K0P0E1	[1 0 0 0 0 0]	14	1	16
Na2E1	N2K0P0E1	[1 1 0 0 0 0]	15	1	17
Na3E1	N3K0P0E1	[1 1 1 0 0 0]	16	1	18
K2E2*ATP	N0K2P1E2	[0 0 0 2 2 4]	17	2	19
K2E1*ATP	N0K2P1E1	[0 0 0 2 2 4]	17	1	20
KE1*ATP	N0K1P1E1	[0 0 0 2 0 4]	18	1	21
missing	N1K0P0E2	[1 0 0 0 0 0]	14	2	22
(Na2)E2	N2K0P0E2	[1 1 0 0 0 0]	15	2	23
not used	N3K0P0E2	[1 1 1 0 0 0]	16	2	24

TABLE 31: NAK-ATPASE PUMP LIST OF BINDING COMBINATIONS

There are in fact 192 permutations, though all may not occur in nature. Part of the modeling process is to sort out the high runners from the rare-to-never events, which might be purged to conserve computational resources.

The R matrix is then extracted from the general state graph above. In this scheme there must be a minimum of 16 bind combinations (dc=16), which in turn defines the quantity of pages in Q. The actor must have a minimum of 4 bind sites (qd=4) . There must be 3 Na sites and 1 ATP site. The ATP site doubles as a P binding site, and 2 of the 3 Na sites double as K binding sites. Obviously, the binding kinetics must change drastically to first bind NA, then discharge NA, then bind K, then discharge K. There must be a minimum of 6 states (qs>=6) to accommodate the necessary changes in bind kinetics and move the pump mechanisms to and fro. The alternative path blocks run in parallel to the normal blocks, and may or may not require additional affinity sets.

This exercise may be continued, but would move into the realm of conjecture without additional wet lab data to guide its choices, and affinity values. The objective is to produce an R with all the bind and dissociate kinetics for each state of the molecule, as would effect the necessary dynamics of the pumping cycle.

In the cases of individual actors, and also in the case of an assembly of actors into a model for nervous system behavior, it was found that of the wet lab data, though great effort was made by others to derive the transition probabilities, none yet has been found with a quantity of states and bindings sufficient to drive a viable duty cycle. Evidently, while some states are outwardly measurable, (e.g. via current measurements), there are other states of the cycle that are not so easily measured. They are “the dark side of the moon”, in that they are not visible, with no easy way to find a point of observation that can “see” them.. Although I earlier coined the term phenostates for those states made obvious by their impacts upon the surround, I neglected to address a converse type of state, the unexpressed, hidden states. States that are not measurable by today's methods will deprive us of the wet lab data needed to simulate complete duty cycles, iterating so as to enact the behavioral repertoire of the actor type. Models require information to complete the duty cycles, else no iterative action can take place. Wet lab timing studies may serve “bridge over” or provide “place holder” states that estimate transition probabilities to be inserted to complete those cycles for modeling purposes. These estimates are expected to represent the merge of whatever states happen internally during the missing “dark” interval. Such a strategy breaks down when those internal states are sufficiently logical to vary their behaviors with varying conditions, e.g. shift modes. Then System Identification work will need to be performed so as to extract statistically probable internal “mechanisms” so as to explain the observed behaviors. It will probably be through the efforts of future Molecular Modeling projects that the inner workings of molecular order and its cycles within actors will be revealed. Modeling offers the advantage of rendering every internal nuance as observable.

It is not within my skills, nor this project's scope, to tackle instrumentation and methods for deriving single unit recordings. So any comments by me as to what can only be conjecture or quoting earlier workers. Suffice it to say, that membranal proteins definitely work in duty cycles, capable of repeating their function hundreds, and sometimes thousands, of cycles per second. The issue is not “can they do it?”, or indeed “do they do it?”. The issue is the feasibility of mensuration of intra-molecular events. If it should prove impossible to to measure such events without distorting the thing being measured; then science must rely upon modeling from first principles to derive the mechanisms of biomolecular function.

It is possible to make reasonable assumptions across missing data. However the quantities of missing data are not tiny. They represent greater than half of any of the duty cycles to be modeled. The fiction of making up numbers to fill in the missing matrix cells with values only constitutes a hypothetical case, several of which have already been

done within the dissertation. Therefore, continuing to create new such cases does not add anything to the argument of the thesis: That the state transitions of membranal proteins are germane to creating functional behaviors, and hold the potential for information processing. Beyond the estimating across missing bits we enter into the realm of engineering new molecules, and new behaviors for definite functions, as would be needed in liquid state computational devices. This is an interesting aspect of the work, but does not fulfill the request to demonstrate a biological case.

Though not feasible at this time to map biological data to the complete inner workings of the molecule, this work will continue, both from the biological perspective of understanding channel function, and from the computational perspective of determining the feasibility of single molecule pattern recognizers.

11.3 OBJECTIVES MET

Much of the work of this project has been synthetic, the building of a model to represent the key elements of an information processing system representative of neuronal molecular processes. The grand objective has been to provide a tool useful in the exploration of channelopathies and their therapies. But to get there a considerable list of issues must be resolved. The main contribution of this project is intended to be the laying of the ground work for this greater endeavor via a careful breadth-first search for the perspectives, philosophies, options and strategies that map out a sound and reasonable path. A path to a successful and near-optimal investment of efforts towards understanding neuronal function at the molecular level, to such depth and detail as to create predictive models of computational function as result from particular actor constellations. The laying of ground work does not include as much analytic science as it does the canvasing of the philosophy of science for applicable ground rules. It concerns characterization of the concept space. It concerns what is to be measured and how such measurements are to be utilized. And for practical reasons, it involves the means of representation.

Fortunately, all of the elemental objectives were successfully modeled so as to abide by the known applicable physics as relevant to information flows. As the bio-data does not arrive complete and exhaustive on any given cell type, there remain a great quantity of biological unknowns. This ofrces the modeler to engage in a significant amount of “reasonable interpolation”merely to complete state transition tables sufficient to be “run”. The missing bits force a contemplation of both the biology and the modeling process. If its working correctly it will suggest

fruitful experiments to the biologist as to what data would complete a predictive model of the cytological process of interest . Once dynamic models are behaving reasonably, then they are amenable to incremental improvements as new data become available from the wet lab work and MD work.

11.4 MODELS ARE NOT SCIENTIFIC EXPERIMENTS

Models live in a limbo between doing laboratory research and data interpretation. The art of drawing conclusions about the data gleaned from the lab is more akin to hypothesis generation than to analysis. That is, models are more closely aligned to interpretation of the data than they are to the procurement of data. But models do both, somewhat, and do neither completely. A simulation can generate data that looks like wet lab data, and it can demonstrate the current level of understanding of the biology under study. The model itself is a new beast, in competition with the biological specimen it mimics. It requires someone to collect its data, analyze it and interpret it. This puts an interpretation on top of an interpretation - a scientifically risky stack to be sure. If models are allowed to displace the wet lab work, then science is at risk of honoring fiction, rather than fact.

In this particular modeling effort, there was no basis to be found upon which to build. If there had been a geometry of shapes with homogeneous skins, a database manager suitable for cytology, a CAD program for constructing contour of revolution shapes, including nested shapes; if there had been a particle system toolbox; if stochastic representations of large bio-molecules like proteins and DNA had been available; Then all investment of time would have gone into deriving applicable scientific data, and applying that data to engineering design. As it turned out, the very few usable functions done by others took longer to find, than it takes to write them from scratch. And once found there remained large compatibility issues to recode around. As a result at least 70% of hours put into this project went into platform development. That is, most of what needed to be done was neither science nor engineering. It was the enablement of science and engineering via a set of mutually compatible tools and methods.

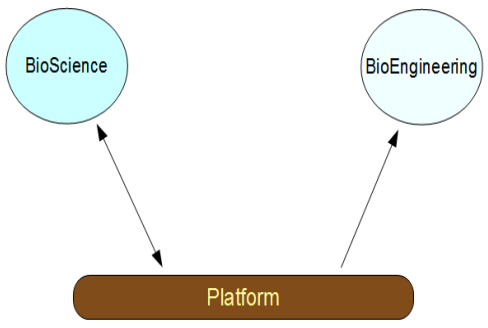


FIGURE 128: Project effort on Platform exceeded Science and Engineering

.A cursory view of the Octave/Matlab code that was written reveals a majority of functions to build up a platform and toolbox with which to assimilate scientific data, and re-conform it to engineered product. Such modeling would not be cost effective unless it serves well in re-use. If it can reach wide spread use, then of course, the effort was worth whiled.

The attraction of models are as follows.

1. The underlying physics can be made explicit and harnessed as science has claimed it could be. Building up from first principles allows one to check and verify how various aspects fit together, work together, and the limits of such cooperation.

2. Scientific findings can be demonstrated. To claim something as fact leaves one's work in the form of static ink in journal articles. But to build a dynamic model based upon those findings represents a form of proof of concept. It also makes obvious a set of behaviors such that the audience is invited to consider of what utility these may be.

3. As no model is perfect, the gap between the model behavior and the biological behavior is highly suggestive of where the model is deficient. If it should further be found that such deficiencies trace back to missing biological information, then the biologists are perhaps incentivized to probe deeper in experimentation to uncover and/or resolve such "missing" observations.

4. Modeling may go where no living thing is allowed to go. Simulated and hypothetical constructs can explore many aspects that to not pay the cost of killing subjects or spreading disease, or other malady. Thus, modeling is a "safe playground" for exploring some aspect of life in preparation for more delicate handling of live specimens.

5. Modeling supports the hypothetical case. Modeling often provides a platform for divergence from what is known into some new arena previously unknown and unexplored. New fields may better be discovered through modeling, because the highest risk aspects can be simulated, and eventually optimized so as to reduce risk.

6. Modeling can to some things much faster than the equivalent wet lab work. Once a model has been verified authentic to biology, then thousands or even millions of experiments can be run, designed by algorithmically indexing the parameters, so as to cover the possibilities in a much more thorough manner than would be practicable in the wet lab.

11.4.1.1 Model Assumptions

The models herein and their results are predicated on the following assumptions

1. Every particle is a sphere. Angular momentum and the complexities of shape factors in binding are dismissed, on the grounds that spin does not convey information about when an action potential should occur. Each sphere is modeled with hard body molecular dynamics, dismissing molecular deformation, internal bonds, and external force fields such as Debye force, the Keesom force, or the instantaneously induced dispersion force.

2. Particle-particle collision is detected by interference, then backed up in time to the hard sphere minimum center to center distance, to avoid unrealistic force calculations.

3. Three body interactions are avoided by keeping the *dt* small enough that they break down into two two-body collisions.

4. This model will only represent whole charges, not partial charges, per molecule. There may be Coulombic interactions of partial charges on fixed and hydrated molecules. This is a complex problem, having much to do with the effects of water as a solvent.

5. Dipoles are not explicitly modeled. While they produce many fascinating effects, a rationale has not yet been found as to their necessary influence of information transmission and processing. However, dipoles are an emergent phenomena in the model. Charge neutralization occurs without programmers intent between oppositely charged particles, and pair cling together until coming into and unbalanced charge region.

6. Heat gradients are not expected to be a factor in action potentials and other membranal functions. However, temperature does affect diffusion velocities, Nernst voltages, and stochastic conformational change rates, and eventually denatures critical proteins. For specific queries as to the effects of temperature, additional features may need be incorporated to mimic denaturing.

7. The effects of water can be summarized as molecular collisions with the particles. As a polar solvent brings about a dissolution of opposite charge attraction so they are free to diffuse. The total mass of the water represents a thermal sink, and thus mediates temperature changes.

8. A further effect of water is to variably increase the mass and radius of ions via solvation. Solvation can be re-evaluated each *dt* to statistically alter the quantity of water molecules attached to each ion, according to a probability density function.

9. The kinetic schemes reported in the literature are physiologically representative of the probabilities of state changes in the molecule. This assumption is occasionally undone by newer claims that an alternative scheme better fits the known function of the actor.

10. The quantities of actors and particles can be gradually scaled down while gauging the loss in confidence in so doing; and then setting such down-scaling so as to hold desired levels of confidence.

Some of these assumptions can be replaced with biological facts as they become available. Some of these assumptions can be eliminated with super computers which do not require heavy scaling or heuristics.

Godel's proof is apropos here. A good model is an axiomatic system, but it is incomplete until each axiom is proven to be based solidly in reality. The model only applies the logic of the axioms to generate the many theorems which fill the space of possibilities (state space). Only natural facts provide the axioms, and validates the model. A dynamical model extends the notion of a set of theorems into characteristic behaviors. If such model-generated behaviors are predictive of biological behaviors, then the model is said to have utility. If the model is methodically swept across its parametric space and found to be fully consistent with physics and known biology, then the model is said to be validated over its intended span.

11.5 INFORMATIONAL CONTENT OF ELEMENTS

To communicate information between any 2 or more actors the information must necessarily be carried by the mobile particles. The two phenomena of particle motion and actor state changes are in series; therefore it is required that each have the potential to carry 100% of the information throughput, and do so in a timely manner. Although actor states can fairly easily be rationalized as information, little discussion is found concerning the ions as carriers of information.

11.5.1 INFORMATIONAL CONTENT OF ACTORS

Information, by definition, is a change in state. Accordingly, actor state transitions constitute information. The fact that kinetic schemes represent actors with 3 to 30 states is evidence that actors are significant information handlers. The quantity of internal states is greater than the quantity of external expressions of state. This is typical of information processors. It remains to be investigated as to the significance of this information.

11.5.1.1 Information of Energy Content

There is a total amount of energy in the system. This energy is distributed discretely amongst the particles, as a division of unity at any given time slice. Therefore, any particle, as regards energy, may be regarded as a chard of the whole, and is therefore, in small part, representative of the whole. To the extent that energy is not homogeneously distributed, the system has some pattern of distribution of energy.

A large portion of the energy of the system is packetized, as ATP, as chemical potential, and bond torsions in certain configurations. This discrete energy usually is served as a driving force from a few common sources, like glucose and ambient light. Common sources, almost be definition, are of low energy. They have only one state: how much fuel is available. Therefore, the energy value of a common energy source concerns depletion rate and depletion time.

Another large portion of energy is on the lose, such as embodied in ion concentrations. Charge concentration represents the differential of position, because it is the primary mover of ions (drift, PE being continuously converted into KE). The voltage topography plus the channel openings are determinant of which way the particles

will move next. Are the patterns of energy moving around the system as the information of the system? This is not likely.

The detection of these patterns generally need not involve carrier oscillations which are fittingly a quality of the energy source. Studies of metabolism find the living cell to be exceptionally efficient in use of energy. Biological energy is typically cascaded down the chemical train, each reaction "peeling" a very small portion of the total available. Such energy usage, aligned to the cascade, would then be independent of any other sequence or set of relationships. Some of the significant information processing steps operate on free thermal energy, which do not show up at all in the metabolic cascade maps. Evolution evidently selects for utilization for what is readily available, not for some alignment between energy and information. The information flows may be completely orthogonal to or independent of the points of energy consumption. An information model may therefore dispense with energy bookkeeping, but not at the expense of state transitions and particle positions.

11.5.2 INFORMATIONAL CONTENT OF PARTICLES

Because monatomic particles are not believed to have multiple conformations for any purpose of communicating between actor molecules[21], several other traits are under consideration for their information carrying potential: voltage, concentration, position, velocity, binding location patterns.

Information quantities are supposed to stay constant for the duration of transit time down a propagation line. But such constancy does not apply to an information processor. Information is often compressed in the process or evaluation and making decisions. Information is often expanded when short commands are issued that require complex behaviors to implement. We must accept that both compression and expansion may occur in a liquid state processor. However, for purposes of tracing information through such a processors, it is convenient to treat all information as remaining constant in quantity at all points along the flow path. This arrangement merely serves the purpose of noting loses and gains as errors. As with strobe photography, one can trace the flows of information from tip to tip, noting its shape and quantity as each sampling time. Here is a series of such snapshots. Each item answers the question:

Where's the information? Answers, over time: All of the information is in the:

[21] Atoms and ions may be "energized" by high frequency bombardment which knocks electron orbits to a higher level for a while, but this phenomenon is not found to be present in neural information processing.

1. Messenger particles in the synapse (or a set of synapses)
2. Receptor states
3. Second messenger particles
4. Channel modulation combinations
5. Channel states
6. Channel expressions (phenostates)
7. Ion flux through channels
8. Ion radiation waves out from channel openings
9. Ionic voltages impinging on neighboring channels
10. Voltage contortion of (channels and pumps)
11. Calcium channel openings (near the vesicles)
12. Calcium bolus hitting vesicle receptors
13. Vesicle contents release patterns

There are minor variations on this series. The 4 through 10 step may repeat any number of times to effect propagation. Sometimes step 3 is skipped. The pumps may play a role in complement to the channels in signal shaping. But the point remains. Each one of these much carry all of the information that the cell is to process, as they are in series. There is some parallelism, and therefore, some redundancy, in the particles that never impinge upon any actor so as to modulate it. Do they merely dissipate their information, or are there other ways to harness it?

One of the more surprising findings concerns the wavelike behavior of ions in aqueous solution. As the model does not take into the considerable complexities of water as a solvent , it remains for physics to verify empirically ionic wave phenomena, robustness and factors, as might determine the extent of dominance of waves over diffusion. Water is a complicated solvent, and research continues to be done by others on the characteristics of water. The theory and results presented herein modeling ionic waves do not constitute a scientific proof of how ionic waves communicate between actors. They do provide an intellectually satisfying explanation of how information can pass through a medium believed to have offered only diffusion as the means. Apparently, there is significant information contained within ions moving through water due to thermal activity and drift. This information is passed on via

collisions, both particle to particle, and particle to actor. I hope the field of physics will some day soon verify or refute my findings.

11.5.2.1 Information of positions and velocities

In order to convey information from point A to point B a carrier must, of course, preserve that information about as long as it takes to traverse the actor-to-actor distance. Once arrived at the target this same information must then somehow be dissolved so as to avoid that message echoing on through the system in unwanted ways. In a gas system, both direction and velocity are candidates for information carriers, because these two qualities are preserved for fairly long distances. But in a liquid, the collision rate is sufficiently high that the distances between collisions is much shorter than the actor to actor distances. This frustrates any reliable information transfers by position or velocity coding. The Brownian motion of particles in a liquid, by definition, defeats information with entropy. Brownian motion is white noise, and white noise is defined as zero information.

None-the-less, because the actors are stationary (in time scales relative to action potentials), the particles must be carrying information between those actors. The two aspects of particles that actors are known to be sensitive to are concentrations and voltages.

A concentration code suggests the simplest of coding schemes: one particle = one bit of information. Certainly the specificity of the various receptor sites suggests that particle types are the message. Higher hits rates might conceivably cross an actor threshold, or at least increase the probability of actor action. Particles without charge and with charge, particles small and large, trigger or catalyze chemical events all over the cell. How are these particles moved to their targets? A derivative of position code is arrival code. It is fairly obvious that it is the arrivals of messengers that carry information, valuable when delivered to the right place and the right time. The timing is going to be “as fast is practicable”; but how to address destinies?

The specificity of binding sites is one effective method to determine a specific subset of addresses. This is a rather fixed arrangement, not a form of dynamic addressing as is common in a digital computer. There are as many target sub groups as there are messenger-specific binding sites, but these are not necessarily “on” at all times. Because actors proceed along state paths they may greatly influence the binding affinity at each of their binding sites with each change in state. This grants the downstream actor flow control, but does not necessarily grant the upstream

actor any flow control. To accomplish that, a pre-message would need be sent that biases the downstream actor states. We can think of this as setting up the modalities prior to the execution of a problem solution. This is consistent with intuitive sense concerning problem solving. When one switches from the hungry mode to the sleepy mode, one switches the types of problems to be solved from “what's left in the fridge?” to “go brush your teeth”. The dominant reticular neurotransmitters are known to predispose the neurons of the brain towards characteristic problems types: noradrenergics, serotonergics, dopaminergics, cholinergics and histaminergics. They alone, and in combinations, set the modalities of the neurons, which by implication alter the interpretation of inputs and/or how signals with be altered, and/or how signals will be routed.

A question to be investigated is: How fine of a level does modality control operate? Given the fact that those neurotransmitter bind to receptors and ion channels, it certainly is reasonable to hypothesize that such modal shifts may be effected at the molecular level of the actors. If so, how many modes can 1 actor possess? There is an equivalence between 1 actor that can switch between 3 different modes in response to which of 3 input signals is being received; and 3 actors each of which only have only 1 mode, but switch on only when 1 of 3 possible input signals is received.

11.5.2.2 Role of Diffusion in information transmission

Various historical conceptualization of diffusion as the mechanism of messenger delivery is weak when the distance to be traversed is more than a few nm. Fast communication (say 1 ms) The assumption of diffusion is a weak one for several reasons: Firstly, diffusion is slow. It can be calculated using Fick's law of diffusion that for common ions to diffuse the length of a meter long neuron (in the human leg) it could take months. Secondly, in any contest between thermal forces and EM forces, EM wins. Both forces are clearly present in neurons. Any charged particle relying on diffusion to arrive at its target is hugely vulnerable to any charge field or charge stations on radical groups passed near, sure to divert it off its path. Capacitance, on the other hand, attracts and holds charged particles within its grasp by significant attractive force. This renders most or all unbalanced charges unavailable to other binding opportunities, to diffusion loss, or to interference from any structures away from the membrane.

Diffusion is a very distant second place performer where ever a strong charge field is available for ions to surf on. Besides its slowness, diffusion is the absolute worst choice for conveying information. Of all the possible choices,

diffusion is the one that tends toward white noise via the Gaussian envelope. Diffusion is in the business of destroying information, not of delivering it. Conclusion: Diffusion is only a valid communication mechanism over very short distances, e.g. the synaptic cleft, or receptor-to-channel messaging within structured protein distances.

Within the neuron, the second messenger systems are known to be extensively used for receptor to channel communication. They provide a speedy amplification mechanism which generally constrains the messenger flow paths to very near the membrane. Apparently, charge effects are utilized to cause the messenger particles to "trolley" along the membrane. Again, the particle removal system must be just a quick and just as sure as the particle release mechanism. The absence of a particle is information just as is the presence of a particle (just as 0's and 1's). Speed of the path multiplies the information carrying capacity. Note also that once a messenger has arrived at target (or passed beyond target), speedy removal mechanism must be close to avoid polluting the reception field. Such recovery is also part of the economy of the system, for to lose messengers requires replacement synthesis.

Because the EM force over-rides all the other available forces in the neuron, it is prudent to investigate the various behaviors of particles near the membrane and how they arrive at actors and depart from actors. This model, as a particle system, might be used to investigate the behaviors of particles about the actors, so as to determine the transfer of information from particles to actors, and from actors to particles.

11.5.2.3 Information Content of Voltage

Electronic technicians are well accustomed to taking voltage readings for diagnostic purposes when attending to solid state devices. In the neuron, voltage spikes must occur which each channel opening so long as their is a net gradient across the membrane at that point to produce flux. The pumps are current sources, and their relatively steady pump rates are regarded as maintaining the steady state rather than as creating signals. To the extent that pumps are modulatable, and that those modulation signals are fast changing (say, within 1 ms) then it is possible for a group of pumps running in parallel to compete with ion channels in creating significant voltage changes. However, being many in quantity means that they will not produce a focal spike, but rather a tsunami like swell.

Returning to channel pulses, the flux through channels necessarily feeds into the surrounding capacitance of the membrane. Each pulse results in a disturbance to the unbalanced charges held to the membrane by opposite charges

on the other side, yet spaced widely by the repulsion of like charges. The channel pulse forces a redistribution of charges on both sides of the membrane. This disturbance follows second order dynamics, resulting in an outwardly radiating wave. Theoretically, such a wave could be critically damped by sufficient thermal forces. However the EM force is by far the strongest force available, and dominates the action.

Therefore, voltage, which can be defined as charge pressure, drives the communication between actors via charge waves over the capacitance surfaces. In such an arrangement, voltage is the integral of charge flux and current is the differential of voltage.

11.5.2.4 Information content of Charge

The role of charge in an information system must be considered. The EM is the strongest force available to the cell, and it is harnessed for duties in both power and communications. Charge force dissolves salt into its constituent ions in water. Charge is what gives large molecules a rather fixed number of somewhat stable conformations. Charge is what drives unbalanced pairs into capacitance right near the membrane that holds them apart. Charge is what neutralized pairs of opposite charges and thereby removes them from any significance in wave transmission between actors. Charge does the double duty of causing particles across the membrane to attract, and particles on the same side of the membrane to repel.

For true independence of motion and state, neutrality is essential, as all charges are coupled together by Coulomb's law. Independence increases the information value of a particle, because coupling implies redundancy. But neutrality limits transportation to diffusion and active pumping.; neutral particles cannot surf the charge field gradients. Neutral particles met the criteria for carriers of high information content, but they are underpowered for the job of carrier. This begs the question of how to track and evaluate all the neutral messenger particles for information value. They work best diffusing across very short gaps, like synaptic clefts.

Charge fields provide the energy for much faster transmission (75 m/s vs 1 m/month). The repulsion of like charges sets up a tense grid such that a disturbance a one end will initiate a traveling wave. The wave front can travel much faster than the individual ion does. The energy of the wave is being transposed via momentum transfers at collisions. In an incompressible medium, momentum transfer is fast.

In membranal systems, charge possesses the unusual character that when it moves vertically through channels it is split into partials according to ion type (per the Nernst EQ). But when it moves horizontally along the charged membrane, all charges are treated alike (per Coulomb's law), and variations in mass are small enough that a disturbance proceeds without much distinction between particle types. The discrepancies in treatment of the same particle group give rise to some logistical issues of representation in a model:

1. By what physics does water molecules enable the capacitance of unbalanced charge across the membrane? And in what ways do they hinder it?
2. In what ways does solvation hinder the wave phenomena? Can it serve to enable it?
3. In what ways does variations in mass within the same repulsion grid affect wave formation in response to disturbances?
4. Given unequal massed particles in opposition across a capacitance membrane (say Na+ and Cl-), how can the wave disturbance on one side reconcile with its compliment on the other? Given near equal coupling strength between attraction and repulsion forces, both must act in an FEM way, as masses and springs.
5. What realistic scenarios would be able to critically damp the disturbance wave of a liquid sate capacitance? How much of a disrupter is thermal motion?
6. Does the charge proceed as a wave front and lead the actors, with the actor response to the charge stimulus lagging behind?
7. At what speed of actor duty cycles could the actors initiate and therefore lead the wave front, driving and pushing it along (propagation by actors, not by particles)?
8. Does increasing the transmembrane voltage increase the horizontal propagation speed of the wave front?
9. What is the damping rate of radiating signals given that all channels and pumps are generating them in interference or construction, and given that the membrane is usually of cylindrical topology (allowing spiral waves)?
10. Given the orthogonality of horizontal particle movements to the verticality of channel gating and modulation thereof, the modulation signal may read as a differential of the flow rate of particles above, or as a one-to-one read on the concentration of particles above. Does this imply a fractional calculus to define a functional relationship between particle flow and actor modulation?
11. If genuine signal transformation is to take place, must a transforming channel type be present in complete rings around the neural process to intercede all incoming signal, and generate all outgoing signal?

11.5.3 INFORMATION TRANSFER IN ACTOR-PARTICLE INTERACTION

It is easy to imagine that receptors emit chemicals that stimulate channels that initiate a wave of charged particles. But it is less easy to imagine how the subsequent downstream actors can become awash in this wave and respond in

such a way as to propagate the wave. Wouldn't their response be generated too late? How can such a lag do any leading? The answer might be found not in time but in amplitude.

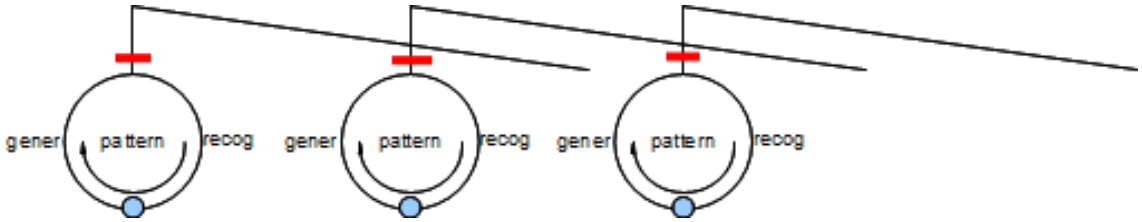


FIGURE 129: Relationship of actor cycles to particle wave amplitude

The signal traffic is shown moving from left to right. A channel generates a pulse of ions. Vertical height signifies amplitude of signal. The red tic marks indicate the threshold of responding to an input signal. If the decay of the signal is not so great as to fall below the threshold, then propagation transpires. The actor output pule radiates outward in concentric rings, decaying linearly as it goes. If upon reaching its nearest neighbors, its amplitude is greater than the response threshold of that channel, then the channel proceeds through a duty cycle or recognizing the input pattern and generating an output pattern. Thus, it responds with a pulse formation of its own. There is a matter of speed of each actor in cycling through its state space. Is it fast enough to participate in the furtherance of the incoming signal? Or does is lag so far behind that the actor is merely creating another (echo) signal? There is an issue of lag between the stimulus to a wave disturbance and the response pattern. Empirical measures will be needed to determine the phase relationships between actor input and output, type by type. The actors none-the-less serve to boost the amplitude of the wave that was on a linear decay track. The incoming, older stimulating wave is integrated into the new, outgoing wave create by the gate opening. The old provides the leading ramp, and a quickly generated new boosts the amplitude without much lag. The new wave, however, has its own center of focus, and it therefore cannot sum cleanly into a composite wave. It must create an interference pattern. The new wave being the strongest, propagates on to wash over the nearest neighbor actors.

The integrity of the composite wave is determined by the relative speed of the channel opening. Because channels effectively are digital, either open or closed, with an extremely fast flip time (faster than the 10 MHz op amp instrumentation that attempts to measure how fast), once opened, a channel will restore the wave front to as crisp a leading edge as is possible.

A significant variable is the time between the stimulus crossing actor threshold to opening. As the wave propagation speed is driven by straight forward physics of a mass-spring grid, the ratio between propagation speed and actor response speed will determine the continuity of the wave, and also the shape of the leading edge of the wave.

The situation is more complicated when the actor type changes along the signal's course. The various actor types selectively gate different ion types under different time envelopes. A simple exchange of one ion type for another ion type might contain no information. A patterned field of responders that allow some directions of signal to go unchanged and other directions become blocked or altered would constitute a logical switch. That is switching can be temporal and/or spatial. The ability to set up new wave fronts and terminate portions of old wave fronts creates multiple concurrent waves. These must interact with interference patterns, a form of information processing. New peaks and troughs will appear from such interactions, and these may be exploited for information values, ans the min/max solutions to complex equations. This would be particularly powerful if minimums and maximums occurred near axonal branches from the soma, thus selecting which branches would send signal and which would be blocked.

Every interactor and every actor is tracked individually for its activities, position, velocity, state, modulation. The differentials on this data provide the clues to information flows and information processing essential to the functional role of neurons. Because the interactors and actors are in series, there must be analogous forms of information between them, near equal in quantity, and some means of mapping one into the other. All the information must flow through these two blocks alternately:

Interactors	Actors
position	state
velocity	state transition probabilities
acceleration	modulation
binding	transporting
gating	modulating
integration	differentiation

TABLE 32: ACTOR PARTICLE COMPLEMENTARITY

The Actor Particle Complementarity wrt information, as portrayed in the table above, attempts to draw analogies between the motile stateless particles and the stationary stateful actors. Please contemplate the analogies between the columns. The internal world of the molecule in some abstract sense acts as the reciprocal of the outside environment. Position of particle outside is analogous to position of atoms inside the molecule (conformation). Velocity external to the actor is of course motion. Motion internal to the actor is constrained by chemical bonds, and results in changing conformations. Forces outside result in accelerations of particles. Modulation of an actor results in altered state change speed. A particle impacting an actor may result in a binding. Actors impact particles by effecting a transport. That particles are gated by actors is analogous to actors being modulated by particles (binding). And finally, particles act as an integrated group, fungible, with no one particle being distinguishable from others of its type. They flow together to form flux and currents.

Looked at mathematically, when a channel gate opens, the flow is the integral of the gate position (open time). When binding and unbinding events occur on an actor they are the differential of the concentrations of particles, and more accurately, the differential of the flow of ions washing over the top of the actor.

These many symmetries suggest that it is possible that the particles can carry what the actors can generate. Particle are cheap (an ocean of salt water; but actors are expensive (DNA coding, ribosomal decoding, amino acid assembly, folding and shape control, subunit assemblies, insertion, placement, recalls, turnover, and more.). There must exist some balance between the quantities of particles and the quantities of certain actors such that the information handling capacity is near equal between the two, with a bias toward the cheaper elements.. It is the challenge for the modeler to establish by experimentation the details and limits how this alternating series process might work and be optimized.

11.5.3.1 Pattern Recognition Potential

Let the reader consider what would constitute a proper test for information processing by any one of the actors. Exceedingly rare in the literature are patch clamp data seeking the information processing potential of the ensemble of channels on the patch. The conventional mathematical operators (addition, subtraction, differentiation, integration, lag, and convolution) are man-made abstractions intended for step by step algorithms. Searching for actor performance to duplicate them may be inappropriate criteria for information processing function in living

neurons. In asynchronous stochastic processing systems, a more generic information processing function would be pattern mapping, such that various natural input patterns are “recognized” via distinguishable output patterns (two or more). As concerns living cell examples, types most likely to be information rich are those encountering the greatest variety of input patterns. Candidates within the mammalian central nervous system might be neocortex local circuits (small granule, stellate and granule cell types). When the channel types and their distributions are known for each such cell type, and rigorous kinetic schemes for each channel type are compiled, this model might explore the information processing potential of these cells.

While the spatial aspects of information can be processed by mere connectivity patterns alone, temporal processing requires mechanism. While space affords three dimensions for connectivity, time restricts to one. As point processes are denied space, this restriction can add a severe constraint on information processing potential. Touring-machine-like algorithms are required to parse a temporal pattern, but still state spaces are required for storage while processing. An alternative might be frequency domain processing, if indeed the input consists of frequencies (e.g. music or bird calls). Stochastic processing of temporal information still requires some form of memory or states. Within the processor, a present value is compared to, and appended onto, a past value. A times series of values only comprises a pattern to the processor that can hold the entire set at once, or some function of that set. Else some portion of the pattern is missed or discarded.

Such state space handling of temporal patterns is not a learning process. Learning processes require seconds, minutes, hours, days. They usually involve structural changes at a much more macro level that the actor molecule. The molecular sized temporal processor must be processing “real time” on a millisecond basis, or finer.

A temporal pattern arriving at a molecule is analogous to a melody. How does one recognize a melody after only say 4 notes? There must be some form of pattern “receiver”, such that each feature of the temporal pattern moves it further along the process of recognition. One receiver processes one pattern at a time. Each feature is “tested” for a match as it arrives. Any failures along the way stop the progress of recognition, and the receiver is reset. Each match moves the receiver into the next state, which anticipates the next feature. In an analog world, tolerance is an important consideration. Too fast, too slow, pitch too high or low, can cause failure of recognition.

The recognition need not be absolute either. Graded recognitions are useful. When many different pattern recognition types are in competition, and the highest responder wins, this makes for a very useful device. Complex

receivers may be modulatable so as to switch between several patterns. This is useful when two or more completely different input signals trigger the same output signal. There is also the possibility of pattern generation. When one pattern as input triggers a different pattern as output, that is genuine information processing. In a complex receiver, various input patterns are able to trigger a unique output pattern. That we might begin to call a computer. The ability to map input patterns to output patterns can mimic a lot of mathematical functions.

Music provides a well established and formalized space for considering temporal patterns. Consider the practical problem of scalability in time, where a melody is recognized whether it is played fast or slow, or in different keys. What sort of processor could be so flexible and robust? The tempo challenge can theoretically be handled logically, with a first note match proceeding to a second note test match, regardless of lag. But such a mechanism would not capture the rhythm at all. Again theoretically, the frequency scaling of key changes could be neutralized by only recording/recognizing the frequency ratios between the notes. This has several challenges to it. How does one record the first note? What marks the start and stop of a melody? Must rhythm be captured by a completely separate mechanism? If so, how do they get back together again, without misalignment? Frequency can be mapped into a place code, but as with notes on sheet music, there must also be sequence and duration information for each frequency in the sequence. In a one-to-one mapping, as with an A2D converter, all three are preserved in unity. But the Fourier transform from time domain to frequency domain is not conducive to preserving all the information unless there is some time to space mapping to keep the order of things straight. As channels and pumps have not yet been considered for their pattern recognition potential, this is an open field for exploration.

11.5.3.2 Oscillations

Oscillations are possible and likely in any real particle system. In gaseous models, e,g, flutes and organ pipes, the shape of the container has a resonance frequency,. Physics views particle systems as a set of oscillators. That invites frequency analysis. But in a particle system with collisions, most or all of the oscillations are disrupted. There are still frequencies of events, but the randomness spreads them out into a power spectra rather than a short set of harmonics. Those oscillations that may persist through collisions are not yet found to be relevant to to the information imparted from particle to particle. For example, a constant ambient temperature (molecular vibrations), by definition, is not information. A basal periodicity may be resetting some downstream receiver to “zero” or a “ready” state, (sometimes called a “heartbeat”), but is not sending a message to be parsed and trigger downstream

events. In most cases a quiescent state can be defined as zero information, such that any other possibility has surprise value, and therefore constitutes information.

Charged particles will go into orbit around a fixed charge if there are no collisions along the orbit path. While oscillations may be relevant to the conveyance of energy, they must be less relevant to the conveyance of information. In the field of radio broadcasting, oscillations are regarded as the "carrier" of the signal. The carrier is periodic and therefore deterministic, with no information. The signal modulating the carrier is arbitrary and chaotic, and therefore has high information content potential. It is concluded that for purposes of processing information in an aqueous medium, oscillations may play little or no significant role.

In liquid models, oscillations may occur only if some means of protecting them from the thermal impacts is provided. This might occur very near the membrane where like-charge concentrations become high enough to over-ride the thermal forces and literally squeeze them out of the way. This might be capable of producing a frictionless layer, or near-frictionless conditions. Such a layer could serve as a carrier for wavelike phenomena.

There are other forms of carriers. Consider a rope in tension. It may "carry" a traveling wave, or be induced into a standing wave. Thus, a tension element may serve as a carrier. It remains for the model to ascertain whether such behaviors are physiologic to the neuron.

Conformational transformations may be slow, soft and continuous in molecules with no charge concentrations, as with pure hydrocarbons. Intramolecular dynamics theoretically could support oscillations if there were no such charge concentrations, because it is the charges that drive the very quick staccato conformational transformations. The presence of various charge foci within protein molecules, however, put them in a class of discrete conformational transitions. And thus the state transition probability matrices. These are often found to contain values indicating very high speed transitions, faster than 1E-10 s. This is the behavior of a finite state machine, not an oscillator. Thus the protein actors are state machines, and the lipid membranes are not.

From a mathematical perspective, the information of the membranal system flows along in the ions, then undergoes a differentiation when a few of these ions become bound or otherwise modulate the channels. The channels then reprocess this differential, and implement channel openings. Such openings are integrated into flux, which rejoins the ionic flows, but with significant reshaping of that flow.

In summary we have: differentiation, stochastic conversion, integration. It is quite reminiscent of the linear algebra concept of basis change operators: $s(t+1) = sRQR^{-1}$. Beyond that, it is a matter of what conversions you want to execute. The physical placement of ion channel types determines the order of operators.

Note that the differentiation function is not the usual deterministic one. As a stochastic process, it lives in the fractional calculus world of some where between first order and zeroth order differentiation.

11.5.3.3 Particle Systems

Models only capture a very limited set of aspects of reality. Chosen for inclusion are mass, radii, charge and mobility. Not included in this model are: angular momentum, nuclear spin, atomic vibration, and quantum effects. These have not (yet) been found to be of consequent to the mechanism of information processing by neurons. Deemed significant are the phenomena of: the EM force, thermally driven molecular velocities, particle collisions, particle momentum, particle capacitance, particle bindings.

Processes chosen are those well established in the literature. As the movement of ions is fundamental to the model, the various applicable EQs are mapped to show how they fit together as a framework suggestive of how a particle system might be built that is analogous to these EQs. The exercise of constructing the flowchart is to insure that the group output of one is indeed the complete and sufficient input for another. The exercise of the model is to de-aggregate the group treatments down to individual particles and to employ the physics first principles to move those particles about. Consider, for example the mapping of Ohm's law as it calculates current into a particle flow rate driven by the EM force and mixed with thermal chaos. The model particle behaviors must be calibrated to the known aggregate behaviors.

11.5.3.4 Ionics flowchart

The distance between pumps for ion type *i* and the channels which conduct ion type i determine ion flow circuits. These flows may be significant determinants in the receptivity of the neuron, as they are current biases that must be overcome.

On the chart below, the right most column lists the transport operations through the membrane. The resultant concentrations of ion types are fed into the Nernst EQ to yield the partial voltage of each. These are combined into

the GHK EQ for the Vm. That voltage then becomes the modulation value for the voltage gated channels back in the right column.

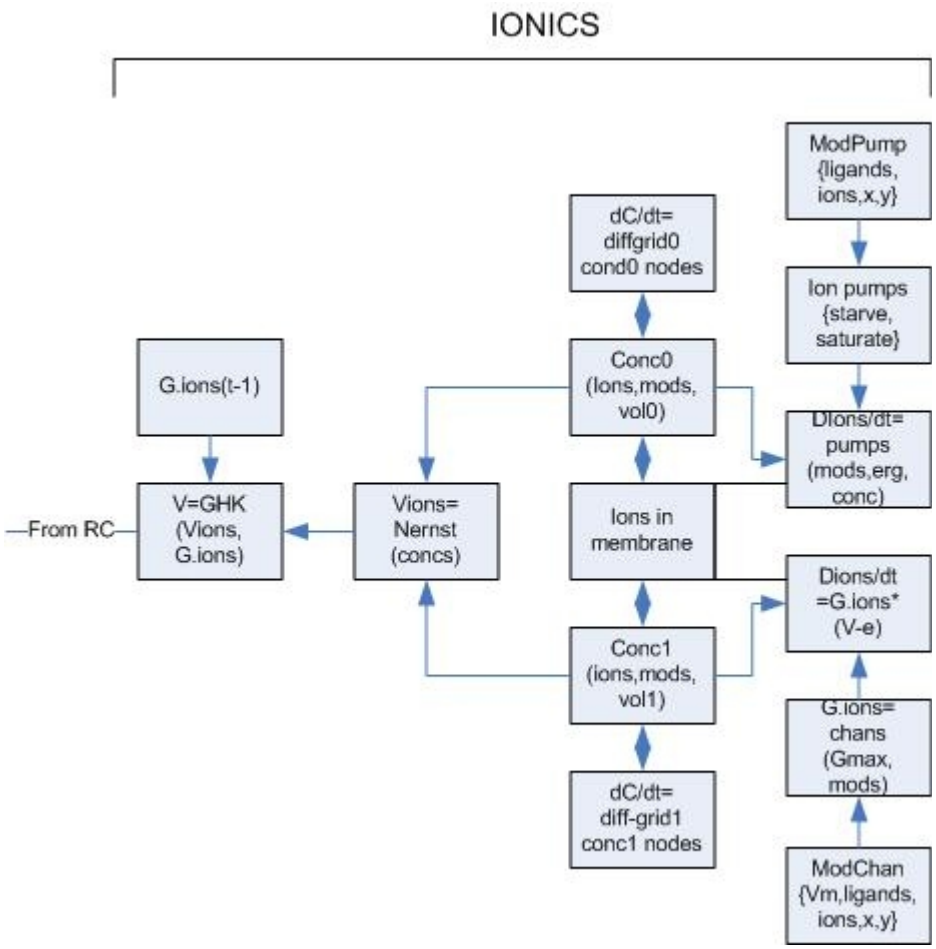


FIGURE 130: DIFFUSION MODEL EQUATION FLOW

Figure above depicts relationships between the EQs of the Diffusion model. All arrows pointing to right feed to the Electronic Model. This is the Dyer 2007 model of the ion cycle.

11.5.4 PARTICLE-PARTICLE COLLISIONS

There are at least two ways of modeling particle collisions. The first method is to negotiate collisions as continuous forces that will strongly repel at very close distances. This is the effect of overlapping electron orbits when particles "collide". The hyperbolic orbit equation will handle these interactions as smooth continua. This can be set up to closely mimic the natural paths of atomic particles. The asymptotes of the hyperbola are equal to the straight line trajectories of an elastic reflection. This method is elegant in that every particle trajectory is continuous, and no

collision detection algorithm is needed. It simply sums the forces to yield net accelerations, and those forces are greatest when electronic orbits start overlapping. The down side of this approach is that it requires extremely fine resolution to be accurate. Three to six orders of magnitude smaller *dt*'s than the traditional collision method below. It is intractable for any particle system of more than say 10 particles. Compromises on the *dt* or the *dx* result in wildly incorrect results. No matter what shortcuts or heuristics are employed, it will requires hundreds to thousands of more flops than the collision calculation.

The second method is to regard a collision as a nonlinear, singular event. In which case there must be a logical collision detection algorithm followed by a physical collision resolution algorithm. Because only those particle pairs identified by the collision detector are "pulled" for the collision resolution calculator, this is a discontinuous process, operating digitally, quite unlike nature's way of doing it. Momentum conserving collisions must carefully determine the axes of collisions, reflection angles and impulse transfers. This approach is computationally very expensive, but still much less so than the hyperbolas. A large scale model may not be able to afford even these simpler collisions as a regular feature for each and every particle, each and every *dt*. To avoid errors of omission, which result in a large percentage of missed eminent collisions, the *dt* must be set such that the fastest particle moves less than one half of the distance of the smallest particle radius per *dt*. Such rigor is always advisable for short runs, for patch-sized models, and for justification runs of the larger scale heuristics and general algorithms.

It is collisions at or near the membrane that are most informationally significant. In particular it is unbalanced charges that have proved to be critical to the model objectives. Accordingly, collisions occurring away from the membrane surface, among charge-neutral pairs, can optionally be simplified statistically to reduce the computational load. Various methods will be discussed below.

Particles may collide with each other, with the membrane, with actors, or with water. Rank ordered by their informational significance they are BA, BC, BB, BW. where B = interactors (ions); A = actors (e.g. channels); C = compartment walls; W = water molecules. Water-ion collisions are the least significant of the four, but determine temperature, mean free path, the diffusion patterns and times, and the disbursed charge effects. Ion-container collisions are more important than water-ion collisions because they present opportunities for capacitance, and impacting ion channels, receptor bindings etc.. The membranal surfaces are reflective (fully elastic) so as to maintain temperature. Both ion channel transport and pump transport are highly significant to the model.

Specifically, the ligand bindings to receptors are the most significant, because of the high leverage effects. However, there remain many significant collisions that require tracking details of the instantiation to capture the informational processes.

Every *dt*, there is a need to detect particle collisions: collisions with other particles, collisions with container walls, and collisions with actors (actors are stationary).

Given that cytosol consists of ions of many 3-dimensional velocities, 5 different radii and masses, the computational load of collision detection is significant.

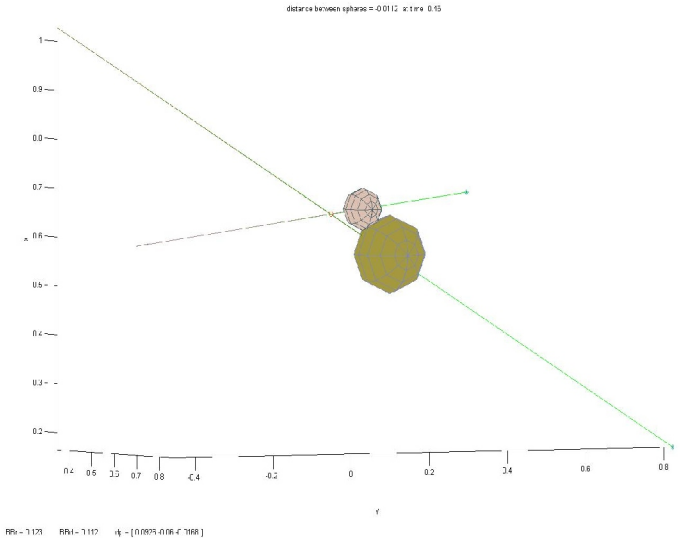


FIGURE 131: 3-D COLLISION BETWEEN DISSIMILAR RADII, MASSES AND VELOCITIES

Analysis of a two body collision, conserving momentum. Note that even when the exact trajectories are known, that doesn't tell you anything about the reflected velocity vectors after impact. Only with the addition of the exact timing (phase) can the exact point of contact be determined. From that the axis of momentum, from that the transfer of momentum, and from that the directions and velocities of the resolve can be calculated.

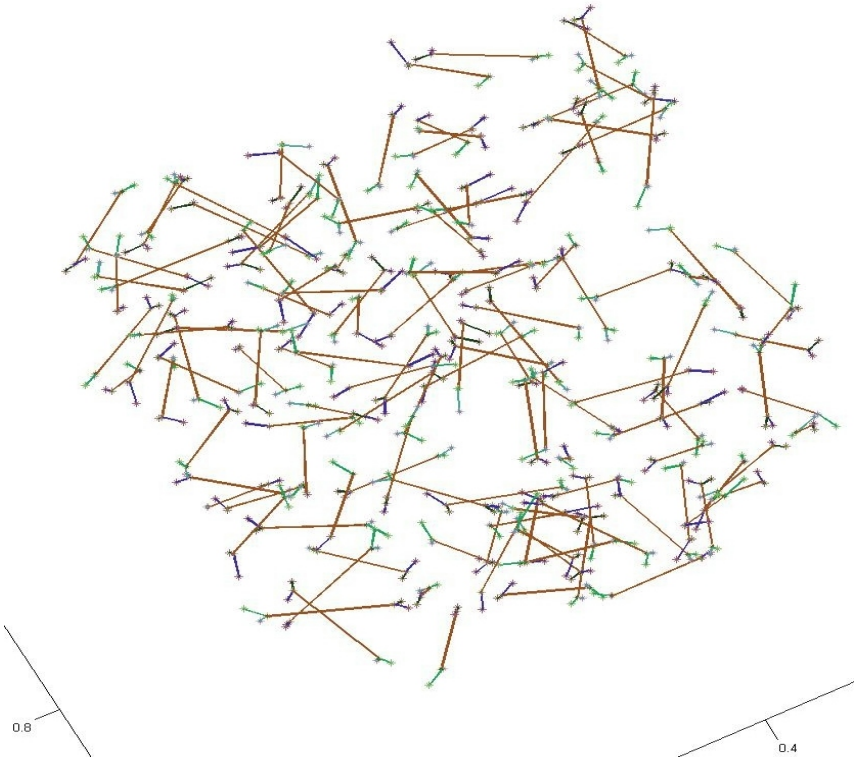


FIGURE 132: PARTICLE SYSTEM COLLISIONS WITH AXES OF MOMENTUM TRANSFER

In a particle system of 5000 particles of varying mass, radii and velocity, 268 (134 pairs) were found to be in impact within a single *dt*. Their momentum-conserving collisions are calculated, and the CPU load is measured as the number of particles increases. The brown segments are the axes of collision. They are long (= r1+r2) relative to the particle movements (green = v1**dt* and purple=v2**dt*) because *dt* was set short to avoid collision detection failures.

Once a collision has been detected, the exact timing and positions of the collision can be determined. Then a collision response may be calculated, including the time remaining on the new paths before the *dt* expires. 3-D collisions require two bases changes, including creation of that basis on the fly. An impulse of energy is transferred between the particles along the axis of collision. Temperature is conserved when momentum is conserved in this system with no molecular spin nor vibration.

The role of collisions within the model has risen over time as they have come to be appreciated for information transfers between critical information carriers. They are the read/write operations of a stochastic system.

11.5.5 PARTICLE-MEMBRANE COLLISIONS

To preserve momentum, particles must reflect off the membrane elastically. But the lipid membrane has a polar surface which must interact with the ions that collide with it. This creates stiction between fluid flow and the stationary membrane, thus adding a friction term to the wave equation of ion disturbances, resulting in resistance to shear, resulting in a type of "laminar flow". If the collision resulted in a binding that increased the potential energy, and released precisely that energy upon unbinding, then momentum would be preserved. Nature does not work this way, but for modeling purposes, mathematical sanity is preserved when the collision velocity is stored, and later released upon unbinding, as a reflection of the initial collision.

A further issue regarding particle-membrane collisions regards the potential to propagate waves through the ion-dense regions nearest the membrane. There is a question as to how much the lipid polar heads might damp out ionic waves passing by, critically or not?

11.5.6 SEQUESTRATION

Regulation of the internal environment of the cell requires more than mere pumping between the extracellular and intracellular compartments. The sequestration of Calcium for example is accomplished by pumping it into intracellular vesicles. A single core compartment can serve the function of providing a place to park ions and ligands which are temporarily removed from solution.

The speedy removal of all messenger molecules after accomplishing their informational mission is essential to avoid a system of all noise and no signal. Particles can be recycled by any of three ways:

1. they disintegrate into some other substance. For example, ATP becomes ADP.
2. they experience high affinity back to their original points of release. This is the simplest, but may not be realistic.
3. they may be pumped into sequestration, some other compartment.

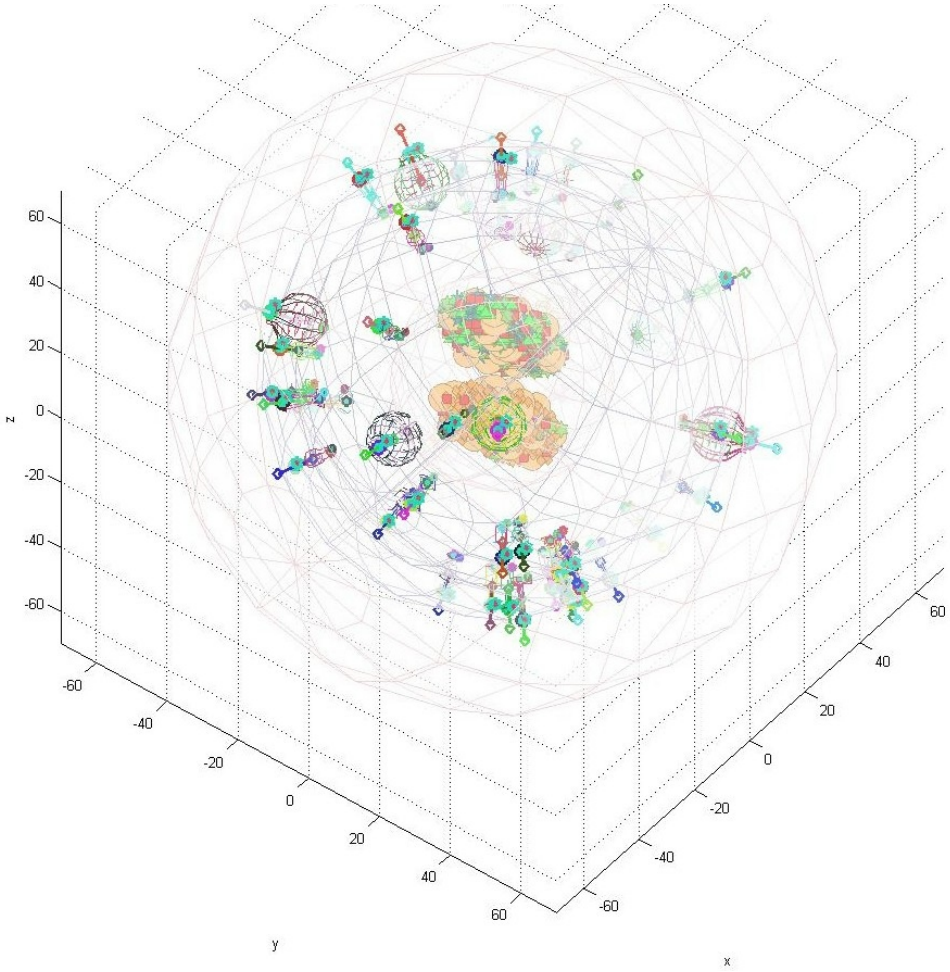


FIGURE 133: CORE COMPARTMENT SEQUESTRATION

Within the soma, a smaller sphere is placed. It serves as a general compartment to store particles out of circulation. The core also serves to block out most of the soma volume for organelles, and thus make the intracellular fluid diffusion active only near the plasma lemma. The core size can be adjusted for the desired thickness of intracellular saline. It is expected, due to modeling results, that substantially all of the informationally significant particle interactions occur within saline thicknesses of about 5 times the membrane lipid thickness. This is consistent with Weiss calculations that charge imbalance falls to zero within "several" times the space constant of 1 nm.[183]

Forces	When ions do flow through channels, it is the result of the summation of all forces impinging on the particle. All of the impinging gradients are summed to determine the flux. (mechanical, thermal, concentration, voltage). Note that voltage gradients may push in the opposite direction

as the concentration gradient $F = \Sigma(\text{voltage+conc+heat+mech})$

Attractors

As opposite charged particles exert attractive EM forces, ligands also are described by chemists as though they have "affinities" for certain bind sites. Affinity is a fiction that is actually the result of high collisions rates with favorable geometry for binding. However, in the process of simplifying diffusion models, the number of particles is reduced by as much as 1E-10. This reduces the number of collisions and subsequent bindings correspondingly. To avoid very long wait times for bindings, attractors are allowed to bias the model toward a collision. This bias is adjustable as a function of attractor strength (affinity), but does not contrive a collision where there could not have been one *in vivo*, as particles presence, its momentum and random direction are still in play.

Attractors are particle-type specific. That is, each binding site has an affinity profile across all particle types. Most values are expected to be zero, but any number of types could conceivably have some chance of binding. The risk of attractors is that they can speed up the velocities of particles in the vicinity. This warms the liquid temperature. This must be compensated for.

The attractors are one aspect of the actor which they serve. But because their action is rather distinct and requires its own bookkeeping, it exists in code as a separate function.

The opposite of attraction is the release of a bound particle. This does not require a repulsion, but does need a velocity assignment in the hemisphere on one side of the membrane. This velocity must be assigned the reflection of the approach velocity, or else be reassigned a new Boltzmann velocity.

11.6 PATTERNS ARE A HIGHER ORDER OF INFORMATION

Pattern is the name we give to behaviors and or results of behaviors of higher than second order systems. First order system we characterize by exponential trajectories. Second order system we characterize by sine waves, plus exponentials. Orders higher than 2 exceed the realm of physics, which holds that all things are made of second order oscillators. Meta to physics is order. Chemistry exploits the order of atoms The complexity of the possibility space increases dimensionality with the quantity of type of atoms involved. The jargon of chemistry that talks of secondary and tertiary structure is grappling with the challenges of higher order patterns. It names the most commonly encountered shapes. Biology adds dynamics to chemistry. By organizing cascades of energetic processes, very small signals can trigger very elaborate responses. Therefore, the understanding of the information processing by biological entities requires an accounting for the order of grouped atoms so as to elicit emergent properties of the group that were not at all obvious nor inherent to any of its elements.

While we enjoy very crisp mathematical definitions of sines, patterns have not yet been methodically defined.

The processing of information can be cast 3 processes: constructive wave interactions; pattern mappings; and a convolution between these two. The particles must be responsible for the processing of spatial information because the actors are ignorant of space, and ignorant of direction. Having established the significance of spatial considerations via particle movement and interaction, the temporal pattern is next to be processed, by the actors. Only actors can map input patterns to output patterns arbitrarily. Thus, the evolution of actors and the mechanisms which place them, determine which input patterns will be parsed, and what the response to each such input will be.

Heretofore, pattern recognition was supposed to be accomplished at the poly-cell level of organization. The neuron was often referred to as the transistor of the brain, implying the entire cell was only a simple gate, providing a yes or no response to a simple input summed value. This would implicate dozens if not hundreds of neurons in performing each pattern recognition problem. It also implies that the up to 1 million actors per cell were redundant. That they are spending significant metabolic energy to perform what a single molecule could have done. Although this arrangement of things is possible, it would be highly out of character for living cells, which are known to be exquisitely efficient and frugal with resources. It is far more likely that each genetically produced protein has a useful role to play, else it would be selected out of existence over time. This places the burden on the researcher to discover what specific functions of each actor type might be, in constellation with the others. The varying distributions of actors exhibit patterns that suggest varying function along the path of information from dendrite to axon. It is hypothesized here that actor constellations serve to filter and process the various possible input patterns, so as to generate a unique or nearly unique output pattern in response to each one. From an informational point of view, a silent response is significant and sometimes useful. At the least, it demonstrates a filtering function being performed.

It is established within this project that pattern recognition can transpire at much smaller scales than the neuron. Any molecule that has a sufficient quantity of conformations to express a duty cycle; and can be modified so as to alter that duty cycle, has the potential for pattern recognition. In some sense the actor is better disposed to perform pattern recognition than is the whole cell. This is so because the inner life of the molecule may be delicately balanced to tip effortlessly in response to input signals. The intra-molecular atomic relationships are well established, optimized, stable and reliable.

Meanwhile, the greater cell requires a large effort to effect the mechanism that maintain viability. This requires the cell to perform the role of resource management (production, maintenance, repair, replacement). It is at the cellular level of organization that metrics of channel performance can be used to decide whether there should be more or less of each channel type, and where to place them. Also, the ratio of pumps to channels must be gauged and maintained. Perhaps most critically, learning is predominantly a function of cell growth, though the triggers for specialized growth often originate extra-cellularly.

11.7 ONE MOLECULE CAN RECOGNIZE & GENERATE PATTERNS

It is of the essence that patterns are frequencies of a higher order. As the Fourier transform proved, any signal (time series of information) can be deconstructed into finite set of frequencies. Humans are not generally accustomed to thinking of patterns as frequencies, but it is a fruitful exercise. Every repeating event can be thought of as having one or more frequencies. A molecule sufficiently complex to express many configurations experiences many internal events, each with it characteristic frequency. Frequencies directly translate to probabilities, and *vice versa*. Therefore, a molecule of many possible events, each with corresponding probabilities, is expressing patterns of behavior, albeit internally. The question is whether there is some coupling between the external and these internal "behaviors".

When these internal events are set up in delicate balance such that the slightest perturbation from outside cause a jump in conformation, then we may say that the molecule receives inputs. Conversely, when the outside world is placed into delicately balanced relationships to the actor, such as lightly bound particles, then an internal change in conformation can result in a change in these relationships, which are detectable remotely. Thus an internal pattern expresses itself externally. In principle, these facts and observations establish that single molecules may act as pattern recognizers and/or as pattern generators.

How would such a delicate balance be built? A delicate balance of numerous configurations would require many subunits that are identical save the slightest variation between them. They would each need to be equidistant to, or at least close to, the stimulus. This suggests a spherical arrangement, or cylindrical arrangement of "sensors" . The repeating backbone with variable ornamentation seems to fit this requirement. Proteins and nucleic acid are rich in

information because they provide a steady reliable backbone with variable ornamentation. The more closely matched are the radicals, the less energy required to transfer between them and shift conformations.

11.7.1 MODALITY REQUIRES PATTERN RECOGNITION

Variations in voltage and concentrations may be deemed as signals if they in any way alter the actor state transition probabilities. Using the action potential as a benchmark of convenience, one may distinguish between those effects upon actors which are of lower frequency than the action potential and those which are of equal or higher frequency than the action potential. Lower frequency effects we may properly call modulators. They may switch the actor to various modes. Each mode is a fixed, inherent quality of the actor. These modal changes may be quite pronounced as between random spikes, bursts, and periodic spikes, but the modulatory only gets to switch between them, not participate in the construction of a novel response. The higher frequency effects, e.g. voltage and second messenger arrivals, because they are faster, may and do modify the response during the response cycle; not merely switching modes, but actually participating in the generation of the output pattern. Fast signals are not modulators - they are the signal. We should not dismiss allosteric bindings as merely modulation effects whenever their frequencies are the equal of the action potential. Any actor that is receiving two (or more) “high frequency” signals is acting as a binary (or n-ary) operator, in the mathematical sense. This strongly implies information processing. And as the actors are not capable of directional sensitivity nor spatial pattern generation, all information processing by actors must be done temporally. It is therefore promising to pursue the intricacies of such temporal processing.

The strong potential for pattern recognition emerges from the measured state transition probabilities, replete with allosteric and voltage modulation of those probabilities. The detail of information required to completely specify a biological actor type is typically greater than wet lab work can currently deliver. For example, with each different combination of allosteric bindings and transport bindings, the entire transition probability matrix is expected to be altered. However, once garnered, demonstrating its potential pattern recognizer requires only a finite state machine rendition of its kinetic scheme. To further this line of thinking, several plausible state transition tables are developed fully and they easily demonstrate pattern recognition.

When ever the changes in modulation of a molecule take place at rates of change slower (of lower frequency) than the ionic traffic patterns which the actor both responds to and produces, then necessarily, modulation does not

participate in switching or shaping those patterns. When ever the modulation frequencies, especially voltage modulation, take place at high enough frequencies to alter the kinetics during a reception pattern or generation pattern, then, of course, there is ample opportunity for that modulation to alter, and shape, that pattern. Second messengers are already known to be of sufficient frequency to directly cause action potentials through their modulatory effects upon actors, and so are as likely as voltage to participate in switching and shaping actor output patterns.

For example, let us consider a channel type with 2 binding sites for neurotransmitters on the extracellular side, 1 allosteric modulator site and 5 phosphorylation sites on the intracellular side, and ten found states in the derived kinetic scheme. There are at least 2^8 binding combinations, but there are likely more, as one binding site occasionally binds more than one type of ligand (such as Mg substituting for Ca). In the simple case of only 1 type of ligand per site there needs to be 2^8 * 10 state transition vectors for each possible state and binding combination (which require 2560 vectors, each ten elements long = 25600 measurements).

The wet lab work would necessarily be much greater than the 25600 because of the uncertainly of how many ligand types can bind to each site or be transported. Furthermore, the often numerous glycosylation and phosphorylation sites accelerate the quantity of binding combinations to be measured. Mensuration is further complicated by the need to catch the molecule in particular states to determine the changes in binding site affinity. When state life is short, sometimes only nanoseconds, measuring affinities, binding and dissociation constants to repeatable accuracy is daunting. Only simulations done as Molecular Dynamics experiments can hope to provide such intimate detail of molecular behaviors.

Actors may be custom designed to specified needs. If a specific medical or computational need were characterized, then the kinetics developed to meet that need, then a search through available membranal protein types might (or might not) come close enough to fill that need. Biochemistry may be able to modify available proteins to achieve an ever closer match.

Because of the large extant family of proteins, they may serve as a pool of possibilities. It remains for the biologists and chemists to determine which types of channels (and pumps, receptors, vesicles) in nature qualify, if any, for temporal pattern recognition functions demonstrated below.

11.7.1.1 Test for Pattern Recognition

Suppose there exists a channel that opens only when the impinging voltage sequence is: -60,-40,-60,-20,-60, over a period of 5E-3 s. This is an arbitrary pattern for demonstration purposes. Any such pattern will suffice. Real patterns will vary both the cadence and amplitude.

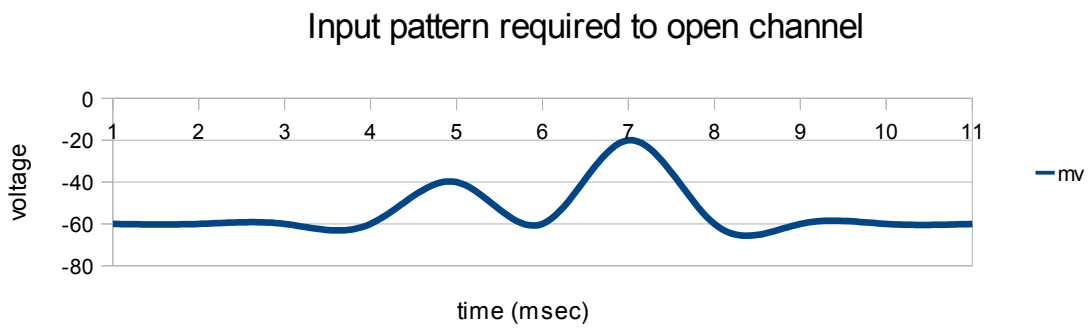


FIGURE 134: INPUT PATTERN HYPOTHESIZED TO OPEN CHANNEL

What would be the necessary kinetics to accomplish this?

We need only consider three voltages: -60, -40, -20 mv, although finer steps would result in less grainy results. If the only modulator is voltage, then 3 pages in the transition matrix are necessary, one for the modulation state resulting from each of these voltages, expressed as ranges: -100..-50; -49..-30; -29..0

For purposes of determining what actor transition probabilities would be necessary to recognize this pattern, the voltage signal is converted into a state-wise procedure. We start with a generic actor duty cycle. If the actor is a channel, then there is a rest state, a modulation trigger, and opening, a closing, a refractory period, and then back to rest state. In order to respond to a pattern "match", we add a 5 msec time slot into the duty cycle of the actor prior to opening. Within this 5 msec, there must be a series of states that serves as receptive to one input pattern but not to others. Also during this period of reception, the output of the actor should be silent, as it has not yet been determined whether the input pattern or lack thereof indicates a silent output, nor what pattern the output will be.

Given a minimum of 5 states, and replace 1 of those states (the modulation trigger) with the 5-step series of input pattern recognition, we have a requirement of a minimum of 9 states.

Notice in the sparse matrix below, that the rest state of -60 mv holds the actor in state 1, and that depolarization to -20 mv also holds it in state one. Only the -40 mv reading causes the actor to advance forward to state 2.

1 While in state 1 if v=60, then state=2									t=1	
60	1	2	3	4	5	6	7	8	9	OPEN
1	1									
2										
3										
4										
5										
6										
7										
8										
9										

40	1	2	3	4	5	6	7	8	9	OPEN
1		1								
2										
3										
4										
5										
6										
7										
8										
9										

20	1	2	3	4	5	6	7	8	9	OPEN
1	1									
2										
3										
4										
5										
6										
7										
8										
9										

36. While in state 1 if v=-60, then state=2
37. While in state 2 if v=-20, then state=3
38. While in state 3 if v=-60, then state=4
39. While in state 4 if v=-40, then state=5
40. While in state 5 if v=-60, then state=6
41. While in state 6 then OPEN
42. If state=6, then OPEN and goto state 7
43. If state=7, then OPEN and goto state 8
44. If state=8, then OPEN and goto state 9

45. If state=9, then OPEN and goto state1

The populated state transition matrices then look like:

60	601	1	2	2	3	3	4	4	**5**	6	6	7	7	8	8	9	9	OPEN	OPEN
1	1		1	1															
2	21	1																	
3	3						1	1											
4	41	1																	
5	51	1																	
6	6									0	0	5	5	0.5	0.5			1	1
7	7											0.5	0.5	0.5	0.5			1	1
8	8													0.5	0.5	0.5	0.5	1	1
9	91	1																1	1

40	401	1	2	2	3	3	4	4	**5**	6	6	7	7	8	8	9	9	OPEN	OPEN
1	11	1																	
2	21	1																	
3	31	1																	
4	4								**1**										
5	51	1																	
6	6									0	0	5	5	0.5	0.5			1	1
7	7											0.5	0.5	0.5	0.5			1	1
8	8													0.5	0.5	0.5	0.5	1	1
9	91	1																1	1

20	201	1	2	2	3	3	4	4	**5**	6	6	7	7	8	8	9	9	OPEN	OPEN
1	11	1																	
2	2				1	1													
3	31	1																	
4	41	1																	
5	51	1																	
6	6									0	0	5	5	0.5	0.5			1	1
7	7											0.5	0.5	0.5	0.5			1	1
8	8													0.5	0.5	0.5	0.5	1	1
9	91	1																1	1

First, biological systems do not employ synchronized clocks which would divide time up into even timesteps, like *dt*. The choice of even msec steps is only for digital computer convenience; as varying timesteps would be more realistic.

Second, in biological molecules, transitions never enjoy a probability =1, nor 0. Thermal noise continuously jostles the molecule, and these bombardments arrive from random directions, each tending to bias the next state transition. Although wet lab data is strongly preferred, in its absence we can add some white noise as a first approximation of this effect. QQ=

-60	1	2	3	4	5	6	7	8	9	
1	0.07	0.69	0.03	0.03	0.01	0.07	0.02	0.02	0.06	
2	0.76	0.05	0.01	0.01	0.06	0.07	0.01	0.03	0.01	
3	0.04	0.06	0.04	0.68	0.04	0.01	0.07	0.06	0	
4	0.72	0	0.01	0.01	0.04	0.02	0.06	0.06	0.07	
5	0.64	0.04	0.05	0.06	0.05	0.02	0.07	0.02	0.04	
6	0.06	0.05	0.06	0.06	0.01	0.31	0.32	0.05	0.06	
7	0.05	0.03	0.01	0.02	0.06	0.05	0.37	0.34	0.07	
8	0.06	0.07	0.02	0.02	0.02	0.01	0	0.4	0.4	check
9	0.67	0.03	0.06	0.06	0.06	0.05	0.04	0.02	0.03	1

-40	1	2	3	4	5	6	7	8	9	
1	0.73	0.07	0.01	0.05	0.06	0.03	0.03	0.01	0.02	
2	0.65	0.02	0.04	0.06	0.01	0.05	0.06	0.06	0.04	
3	0.76	0.01	0.05	0.01	0	0.07	0.03	0	0.05	
4	0.04	0.05	0.07	0	0.71	0.01	0.06	0.01	0.04	
5	0.73	0.02	0.08	0	0	0.01	0.08	0.04	0.03	
6	0.06	0	0.08	0	0.08	0.39	0.33	0.03	0.03	
7	0.04	0.02	0.07	0.07	0.01	0.01	0.43	0.36	0.01	
8	0.05	0.06	0.01	0.07	0.04	0.01	0.04	0.37	0.35	check
9	0.75	0.06	0	0.04	0.02	0	0.03	0.02	0.07	1

-20	1	2	3	4	5	6	7	8	9	
1	0.74	0.07	0.06	0.02	0.02	0.02	0.01	0.02	0.04	
2	0.01	0.03	0.73	0.06	0.02	0.02	0.07	0.04	0.02	
3	0.66	0.03	0.05	0.06	0.01	0.04	0.06	0.06	0.04	
4	0.68	0.06	0.07	0.03	0	0.03	0.01	0.05	0.06	
5	0.69	0.06	0.05	0.05	0.03	0.03	0.03	0.01	0.05	
6	0	0.02	0.08	0.07	0.05	0.36	0.34	0.03	0.06	
7	0.06	0.08	0	0.03	0.04	0.05	0.35	0.34	0.03	
8	0	0.01	0.05	0.04	0.06	0.06	0.07	0.35	0.36	check
9	0.72	0.03	0.02	0.01	0	0.07	0.07	0.01	0.07	1

Column = current state, row = next state, page = current voltage.

A function is provided, page = volt2page(currentvoltage,pagevoltranges), which reads the current voltage and determines which page of the transition matrix shall apply for this timestep. The current state plus the current voltage determine which probability vector shall determine the next state. For the above, each page must have a range of voltages for which it applies.

```
pagevoltranges = [-70 -50; -50 -30; -30 -10];     % where row number indicates page number
EX   If currentvoltage = -37 and currentstate = 1,
then page = 2;
Q = QQ(:,:,page);
P = Q(currentstate,:);
P(1,-37)  =  [0.73 0.07 0.01 0.05 0.06 0.03 0.03 0.01 0.002];
```

indicating a 73% chance of remaining in state=1.

```
EX   suppose the voltage had been -61 mv, then
page =1;
P(1,-61) = [0.07 0.69 0.03 0.03 0.01 0.07 0.02 0.02 0.06];
```

indicating a 69 % chance of moving to state=2.

By means of voltage, steering the transition probabilities, a course through the state space is defined. Such a course may be difficult, rare or impossible to traverse without the voltage temporal pattern to drive it through a cycle. It is therefore reasonable that voltage-gated channels may be involved in pattern driven duty cycles. This notion supports the often discussed "phase information" of the neural signal. The only requirement for pattern-driven duty cycles is that the pattern be presented at a speed faster than the length of the duty cycle. Obviously, a duty cycle of 1 msec, with a pattern recognition portion of that cycle being s fraction thereof, say 0.5 msec, and a pattern of 5 significantly distinct levels in series, would require a pattern generation frequency of at least 10000 cps. I use units of cps rather than Hz because Hz refers to sine wave cycles, and I am referring to pattern steps. A realistic pattern frequency would necessarily be higher because biological patterns do not follow strict metronome timesteps but rather vary in the duration of each step. The shortest step would determine the minimum frequency.

Because ion channels and ion pumps are not one-time-use devices, they must complete cycles through the state graph, repeating them millions of times during the service life before they are enzymatically subjected to "turn-over". The state of lowest Gibbs energy (most relaxed) is deemed to be the "rest state" in the cycle, whether it spends a lot of time in that state or not. Every other state requires some amount of energy increase and therefore a little nudge to get it there. This energy is usually provided by thermal energy. But for the one greatest energetic hill climb, the molecule may receive a boost from an ATP binding (or other energy-transferring molecule) and subsequent release of chemical energy. It is conceivable that a molecule spends more time in a high energy state than in its rest state if the escape walls are steep enough. If the release of such energy awaits some external triggering event (think of the duty cycle of a mouse trap), then such energy storage may be put to practical use. For information processing, the most straightforward strategy is likely to be a rest state, followed by an energetic "trigger" state that lifts the molecule to its highest Gibbs potential, and then all states thereafter are a gentle downhill run all the way back to the rest state. And along the way, they happen to perform useful services to the cell. The "trigger" could be an energetic impact, or a chemical reaction. Modulation is expected to distort the energetics topography s as to enable the initiation of the sequence. Or else alter the state path by switching at a probable bifurcation point.

Most (or all) of the steps in a duty cycle may be driven by thermal energy, a free ambient source. Usually, only one step (or none) in a duty cycle requires metabolic energy. Such a boost is necessary in pumps for two reasons: First, to cause the cycle to be directed. That is, a pump cannot be effective if allowed to run both forward and backward. It needs a directed state path to be an effective pump, not undoing its work by running backwards; Second, a pump does work, to overcome the forces of concentration gradients and charge gradients against which it "pushes".

In the case of channels it is possible, and indeed common, to operate the entire mechanism on thermal energy alone, while concentration and charge gradients provide the energy of transport through the open pore. Because the pores are ion-species selective, an opening event is not a pure entropic event. Rather gradients are harnessed to drive a long list of molecular operations, including exchangers, cotransporters, and other metabolic processes. This allows a single type of pump, the Na pump (an ATPase), to drive a lengthy cascade of processes, which independently transport K+, Cl-, Na+, and others across the membrane (in either direction).

For any given Q matrix, from each state certain other states are most reachable, most likely to serve as the next state in the cycle. Cycles are not fixed, but rather are probabilistic. There are alternative paths, partial reverse paths, holding pattern paths, and rare disruptive paths. With so many possibilities, how can an actor fulfill its role without wasting energy or being unreliable? Despite the statistical nature of membranal molecules, a small group of like channels (say, eight) can sharpen the processing cycle, average out the noise, and steepen up the nonlinearities - so a to perform reliable service. Where reliability standards are established, and redundancy factors calculated, then a "minimal cell" may be determined as to actor types, quantities and placements. Any gap between these calculations and the biodata begs the question: what more is the cell doing than we are taking into account?

The next concern is: What happens after the pattern has been matched? Presumably the channel opens. This is not an instantaneous event, but rather must have some duration to be effective. How are hold states accomplished? They may consist of a single state with a high probability of remaining in the same state, or the the state path may cascade through several states in a rather predictable manner. A series of states, cascading down the Gibbs curve, can produce a more reliable open duration than can a single state.

The standard mathematical treatment of transition probabilities through time is:

```
P = P0*Q^t;   % where P0 = initial state;  t = the quantity of time steps.
```

This is handy for when the timesteps are smaller than the modulation events spacings. However the instantiation of the state requires that P be resolved into *s* each *dt*.

A cascade of steps is superior to a single hold step in a stochastic system because of the sharpening effect of multiple steps, as opposed to a single longer step. Referring to the above state transition matrix QQ, we note that once the pattern as been parsed successfully, the following states 6,7,8,9 probabilities do not vary from page to page. This indicates that they are voltage invariant. While the pattern recognition states are necessarily sensitive to the outside environment (to "read" it), the molecular output function, that which characterizes the actor type, must be robust, and therefore not sensitive. This is the refractive period of the actor. During the time of its output performance, and perhaps somewhat beyond, the actor does not respond to incoming signals in the physiologic range. This makes sense if the actor is a pattern recognizer, as there must be an end to the recognized pattern, after which the actor shifts to some action to be performed. After that action is completed, the molecule returns to the rest state where it becomes receptive to the next input pattern.

Follows is a table of probabilities for a sequence of 3 open states. A single open state with the composite probability will not perform the same as the 3, as a single state is more chaotic. Multiple states can tame the chaos via averaging.

OPEN 6	OPEN 7	OPEN 8	OPEN 9	**CLOSED 1**
0.50000	0.50000			
0.25000	0.25000			
	0.25000	0.25000		
0.25000	0.50000	0.25000		
0.12500	0.12500			
	0.25000	0.25000		
		0.12500	0.12500	
0.12500	0.37500	0.37500	0.12500	
0.06250	0.06250			
	0.18750	0.18750		
		0.18750	0.18750	
			0.00000	**0.00000**
0.06250	0.25000	0.37500	0.18750	**0.00000**
0.03125	0.03125			
	0.12500	0.12500		
		0.18750	0.18750	
			0.00000	**0.00000**
				0.00000
0.03125	0.15625	0.31250	0.18750	**0.00000**
0.01563	0.01563			
	0.07813	0.07813		
		0.15625	0.15625	
			0.00000	**0.18750**
				0.00000
0.01563	0.09375	0.23438	0.15625	**0.18750**
0.00781	0.00781			
	0.04688	0.04688		
		0.11719	0.11719	
			0.00000	**0.18750**
				0.18750
0.00781	0.05469	0.16406	0.11719	**0.37500**
0.00391	0.00391			
	0.02734	0.02734		
		0.08203	0.08203	
			0.00000	**0.15625**
				0.37500
0.00391	0.03125	0.10938	0.08203	**0.53125**
0.00195	0.00195			
	0.01563	0.01563		
		0.05469	0.05469	
			0.00000	**0.11719**
				0.53125
0.00195	0.01758	0.07031	0.05469	**0.64844**
0.00098	0.00098			
	0.00879	0.00879		
		0.03516	0.03516	
			0.00000	**0.08203**
				0.64844

This results in the following state probabilities wrt time. The time sequence from through the open states 6..10 proceeds as follows:

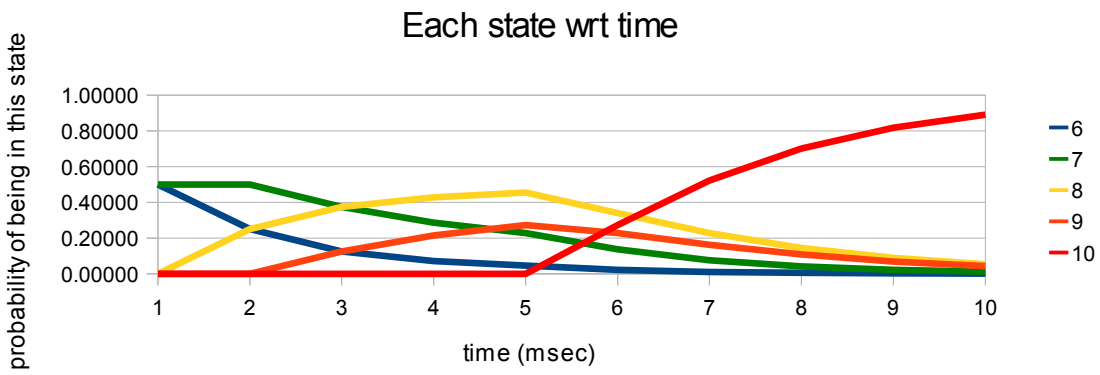


FIGURE 135: STATE DURATION PROBABILITIES

There is a cascade of time windows for each state in the dominant sequence. The above open states sum to:

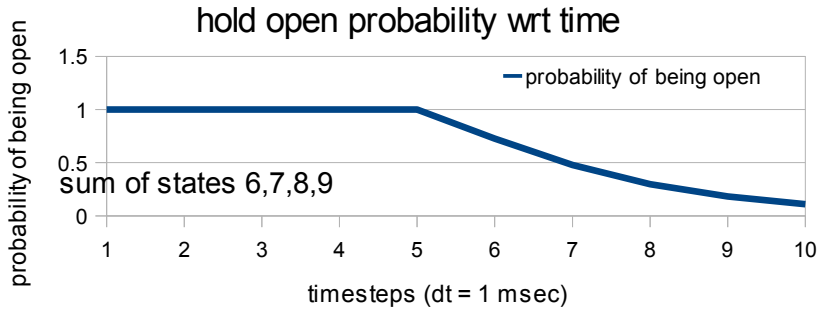


FIGURE 136: HOLD-OPEN TIME PROBABILITY FOR 1 SUBUNIT

This provides a means of causing a phenostate hold state, either open or closed, in the case of channels. Due to the rather gradual probability slope, its reliability is rather poor. Note the length of time open can vary from 5..10 msec. This can be sharpened via sequence of shorter states.

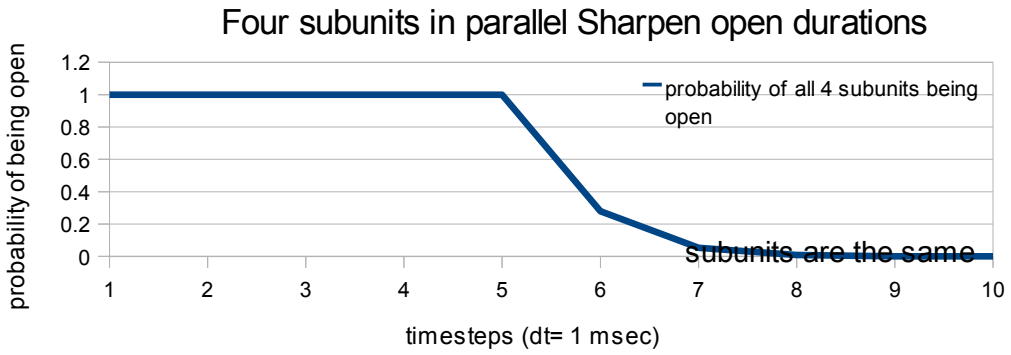


FIGURE 137: HOLD-ON TIME PROBABILITY FOR MULTIPLE SUBUNITS

The sequence of 3 states reduces the duration to 5..7 msec. More intermediate state could sharpen the response time (make it more deterministic).

One can see that a small cluster of such actors say 10, would constitute a reliable 5 msec opening in response to a voltage temporal pattern of -60 -40 -60 -20 -60 mv.

Although the EX presumed 1 msec steps in the voltage pattern for the sake of a digital simulation, a true voltage pattern match would align to the modal probabilities of each state's duration, which, of course, do not keep cadence but vary over continuous time. This in no way limits the precision of the pattern. Thus, a voltage pattern of any tempo, rhythm or chromatics is feasible; to the extent of the various kinetic probabilities (frequencies) of transitions between possible molecular configurations.

Limit cycles are always implied in the actor transition probabilities. Transition probabilities offer opportunities for extremely large quantities of state paths through the 3-dimensional table. Such complexity infers a pattern space. It is not yet known what variety actors traverse *in vivo*. Usually, there is more than one circuit possible. Each different limit cycle may be a different modality of response. These have utility if they can each be elicited by a unique modulation combination. Each of these limit cycles may be altered by external pressures like voltage, pH, concentration., and the torsional effects of bindings, e.g. phosphorylation and glycosylation. As the rate of change of modulation signals speeds up it may reach a point where it participates in creating a uniquely-shaped response. At that point, the actor is serving as an information processor.

The case above demonstrated the feasibility of employing stochastic processors in parallel to generate reliable computation. Hundreds of trials suggest that with certain Q matrices, a redundancy (parallelism) of 8 identical ion channels will yield 99% accuracy over widely varying conditions. It my be engineered that for a desired duty function, the tolerance of the transition probabilities may be plotted against the resultant reliability of the actor. Because of the phenostate mapping to exterior impact, and some impacts being more desirable than others, each type must be investigated for reliability as a separate case.

11.7.2 PATTERN GENERATION

Characteristic of an information processor is that some portion of it responds to the input conditions with changes in state, and some portion responds to the internal state conditions with a generated output. Whatever a membranal protein does to process its inputs, the successful input triggers a characteristic response of that actor type. Indeed each actor type is functionally distinguished by its input to output map. Systems engineers will recognize this necessity immediately. A dead system, a mere function, requires only 1 matrix to represent it. This is the o/i matrix. It is a zeroth order system in the sense that it has no states (to be mathematically precise: it has only 1 state). But the introduction of actors with kinetic schemes implies 2 or more states in each. These comprise first order stochastic systems, in the sense that the transition probabilities are the differentials of the state probabilities. When ever these transition probabilities are modulatable by say, hormone bindings, then such actors comprise second order stochastic systems. Modulation alters the transition probabilities, which in turn alter the states. Thus, modulation acts as an acceleration factor, a second order effect. As the states, via phenostates, alter particle flux via gating, the modulatable actor particle system is necessarily a third order stochastic system. This places us out of the reach of Fourier analysis; and we must therefore embrace pattern processing to appreciated the functioning of the membranal system. The input-state-output process is represented by two matrices: state/input, and output/state.

So far, it has not been reported that a single molecule can perform pattern recognition and pattern generation concurrently, as though 2 parallel processes within the molecule. Doing so is theoretically possible if the molecule were large enough to carry on 2 mostly isolated processes, yet supported the signaling of the pattern recognition portion over to the pattern generation portion. Further complications include the possible asynchronicity between the 2 processes. In the digital world, this problem is solved with buffer memory, but it is already established that the molecule has no memory other than its present state. Therefore, parallel processing is much more difficult than

serial processing. Within a single molecule, serial processing makes a lot of sense and solves most or all problems of functional logic. Indeed, a duty cycle, almost by definition, is a serial process. However, there remains the matter of subunits. If they act independently, with minimal coupling of their state transition probabilities, then the problems of design and modeling are straight forward. With coupling, a long list of asynchronicity problems arise. This greatly increases the state space, which may expand the pattern recognition and generation capabilities, add a lot of noise to the system, or impede the ability of the actor to perform its function. Most likely, the subunits are minimally coupled wrt information, as the biodata, all the way back to Hodgkin and Huxley experiments of 1951, is consistent with independence. Had they been coupled, the n^4 term and h*n^3 term of the HH EQs would have resulted in fractional exponents.

The question has been raised as to whether an actor type is capable of more than one characteristic response. If each actor type produced one response type, then merely shutting one type off and turning another on would accomplish shifts in cell performance without expecting molecules to do such herculean tasks as multiple pattern mappings; so the argument goes. Well, there must be multiple response types, or else we would not be able to talk of modulation. Messenger molecules can only work on actors one-on-one. Coordinating 1 actor type to up regulate, and another type to down-regulate in response to the same messenger is feasible and reported. But the simulation of the Q matrices demonstrate that there are always more than one possible paths through the state space, each with a characteristic probability of occurrence, and each with those probabilities is typically altered by modulation. Modulation, by definition, alters the relationship between inputs and outputs. If it could only turn on and turn off, then it would be called “blocking”, not modulation (more completely: antagonist or agonist). Conceivably, modulation could switch effective input triggers for the actor, but it could just as easily be that modulation alters which output will be elicited from the same input. Kinetically speaking, these are both much the same thing, and have quite equal chances of mutating into existence in nature. The question then becomes: is there a selective advantage to actors that recognize multiple temporal input patterns and generate multiple temporal output patterns?

Much literature on ion channel gating concerns itself with channel openings as % open time, or dwell open times, but so far, no literature has been found seeking to detect temporal output patterns. The strong tendency of kinetic schemes to generate characteristic patterns, emergent directly as a result of the state paths, suggests that temporal patterns are likely present *in vivo*. And if they are present, what functions may they serve?

In artificial finite state machines (FSMs) by design the duty cycle is customarily placed along the upper first diagonal band of the state transitional matrix This defines state 1 as being the highest energy state, that state=1 most often transitions to state=2, then state=2 most often transitions to state=3, and so forth. State N then is the rest state as it has no where left to go. State N may be escaped from when energy is added to the system. It can bump state N back up to state 1 via the probability in the lower left hand corner of the matrix. If there are 2 or more open pore states, and if these open states are separated by 1 or more closed states, then necessarily a temporal pattern emerges along the course of the most probable state path.

11.7.3 PATTERN RECOGNITION

The following QQ matrix recognizes an input pattern and then generates a temporal output pattern.

```
 fsm02(:,:,1) = ...
 [ 0.0200   0.9576   0.0210   0.0096   0.0014   0.0027   0.0041   0.0027   0.0041
   0.0500   0.9400   0.0013   0.0040   0.0066   0.0066   0.0026   0.0026   0.0066
   0.0027   0.0053   0.0040   0.9626   0.0013   0.0040   0.0094   0.0094   0.0013
   0.9595   0.0068   0.0041   0.0014   0.0054   0.0054   0.0068   0.0054   0.0054
   0.0025   0.0076   0.0063   0.0038   0.0013   0.9722   0.0038   0.0025        0
   0.0300   0.0600   0.0500   0.0600   0.0400   0.3900   0.3100   0.0200   0.0400
   0.0600   0.0800   0.0100   0.0500   0.0300   0.0100   0.3800   0.3800        0
   0.0300   0.0400   0.0700   0.0600   0.0300   0.0600   0.0500   0.3500   0.3100
   0.9375   0.0094   0.0078   0.0094   0.0063   0.0078   0.0078   0.0047   0.0094 ];

fsm02(:,:,2) = ...
 [ 0.9551   0.0070   0.0084   0.0042   0.0028   0.0070   0.0028   0.0070   0.0056
   0.9648   0.0026   0.0026   0.0052   0.0065   0.0026   0.0052   0.0091   0.0013
   0.9544   0.0071   0.0043   0.0043   0.0100   0.0014   0.0085   0.0028   0.0071
   0.0013   0.0026   0.0064   0.0013   0.9665   0.0077   0.0039   0.0064   0.0039
   0.9643        0   0.0013   0.0066   0.0092   0.0066   0.0026   0.0026   0.0066
   0.0500   0.0400   0.0700   0.0200   0.0600   0.3000   0.3400   0.0600   0.0600
   0.0396   0.0792        0   0.0396   0.0099   0.0297   0.3861   0.3465   0.0693
        0   0.0500   0.0100   0.0200   0.0500   0.0500   0.0100   0.4000   0.4100
   0.9544   0.0071   0.0071   0.0100   0.0014   0.0028   0.0071   0.0071   0.0028 ];

fsm02(:,:,3) = ...
 [  0.0210   0.0084   0.0014   0.0070   0.0028   0.0084   0.0084   0.0056   0.0042
   0.0043   0.0085   0.9517   0.0099   0.0071   0.0014   0.0028   0.0085   0.0057
   0.9690   0.0065   0.0078   0.0013   0.0039   0.0052   0.0013   0.0013   0.0039
   0.9597   0.0083   0.0056   0.0014   0.0070   0.0014   0.0083   0.0070   0.0014
   0.9489   0.0029   0.0088        0   0.0102   0.0015   0.0102   0.0088   0.0088
   0.0300   0.0400   0.0700   0.0100        0   0.3800   0.3800   0.0700   0.0200
   0.0198   0.0792   0.0297   0.0099   0.0297   0.0792   0.3663   0.3861        0
   0.0303   0.0202   0.0707   0.0202        0   0.0505   0.0505   0.4141   0.3434
   0.9489   0.0044   0.0073   0.0058   0.0088   0.0058   0.0015   0.0088   0.0088 ];
```

This is a state transition probabilities matrix that does pattern recognition, because any failures to match the required input pattern result in energetic blocking of the duty cycle, and the state path reverses back to rest state without completion.

Stimulated with a voltage pattern = [-60 -20 -60 -40 -60]; % mv the following time line results

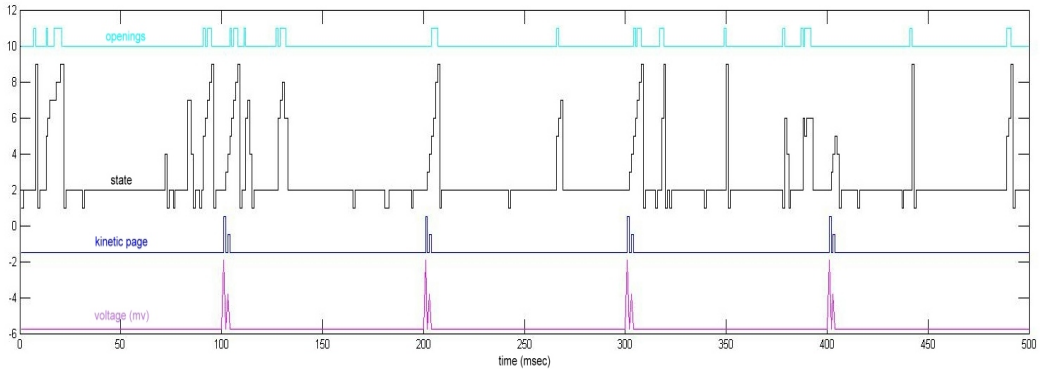


FIGURE 138: At 0% noise, 1 unit detected the Pattern poorly

The traces from bottom to top: input signal; modulation effect within actor (Q page); concurrent plots of actor states; composite phenostates; threshold line above which propagation takes place. If upon each input stimuli, the molecule responds with a particular state sequence (appears like a staircase), then the molecule is responding to a pattern. Being a stochastic processor, the output for a solo actor may not be very impressive. In the plot above, there is no noise in the input signal, but internal thermal noise continues to drive the molecule through its states. This may be chaotic, but most often follows a characteristic state path.

11.7.3.1 Signal Noise

The noise level of a signal may be measured as the root mean square of the series of sample values. A uniform distribution of 1 million random numbers from 0 .. 1 has an rms = 0.5773 (= sqrt(1/3); But how is the test pattern to be measured for rms? A pattern of [0.0 0.5 0.0 1.0 0.0] has an rms of 0.5. But this value changes markedly with the quantity of zero padding, arbitrary though it be. One could argue that given a uniform distribution from 0..1 with its rms = 0.5773, and given any pattern created by ordering a sequence of samples taken from that distribution, then the rms of both the white noise and the pattern are equal. And from there, the noise could be scaled up or down to effect a known signal to noise ratio. This does not quite hold up, however, because if one of those patterns to be recognized happened to be comprised of a series of small values, then the noise would be proportionately larger

despite that the rms values were supposed to be the same. One solution is to select the complete family of patterns to be recognized, and to solve for the rms of them as a group. This would not take into account that some patterns may be heavily used while others are seldom or never used. This problem can be corrected via a weighted concatenation of patterns, each repeated proportionate to usage.

Confusion may arise from interchanging signal strength with information value. Demonstrations of patterns recognized despite a back ground of noise of various amplitudes, stands as a verification of pattern recognition capacity. From an information perspective, one can define a physiological range of signal values, above which some denaturing occurs. Then that range can be divvied up into some maximal quantity of distinguishable values. For example, suppose there are found to be 21 voltage values for which differences in consequent state transition probabilities can be discerned. Then, using only those 21 values, there are a finite number of patterns that are feasible for a given series length. A few of these patterns are declared significant stimuli, and the rest are defined as "noise". The information value of low numbers within the pattern may be equal to or greater than the value of high numbers, irrespective of the noise level.

The rms is merely a convenient metric on the noise and signal levels; it more heavily weights the high values, which may not be appropriate in information coding. The choice of using the squares was motivated by the need to treat negative and imaginary components on equal footing. However, taking the squares of bits (information) is probably inappropriate. Noise could be measured as a ratio between the rms of the noise signal and the rms of the maximum signal that is physiologically sustainable. The noise level of neuronal inputs can be measured as a fraction of the physiological range. Due to the nonlinearities of the living system, this approach may be complicated by unequal responses to various frequencies, and to frequency combinations. Accordingly, frequency response curves may be plotted, and a signal expressed as a plot under the maximal response curve.

While the rms may be of interest to those concerned with power and energetics, the pattern recognition function is concerned with reliability given certain conditions. Various encountered conditions (patterns) may be cataloged and the reliability of useful patterns measured and noted. For demonstration purposes, the maximum value of the test pattern is compared to the maximum value of 100% noise, given that the noise is generated as a uniform distribution of values 0..1, then scaled to the physiological range. It is somewhat more realistic to create a uniform distribution of frequencies, then perform a Fourier transform to the time domain to get white noise. However, given the

constraints and aliasing of digital sampling, this method of generating randomness matters little to a molecule that only responses to a few certain patterns. The larger concern is that within the noise signal must be a few patterns capable of causing the molecule to change state. This is reminiscent of the 2-step voltage clamp, wherein the purpose of the first value was to change molecular state prior to the test voltage. Prior perturbations may be useful or detrimental, and their uncertainty contributes to the stochastic nature of the molecular mechanisms. They are "filtered out" via signal averaging across parallel actors.

11.7.3.2 Stochastic Noise Filters

Let us consider if there were 8 stochastic actors operating in parallel, responding to the same stimulus (in phase).

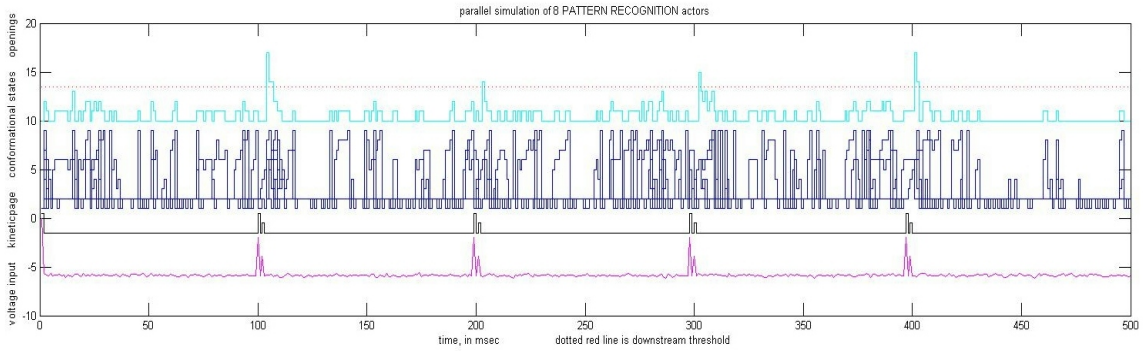


FIGURE 139: At 5% noise levels, 4 units detected the pattern 88% of trials

In this case, despite the noise, the output spikes correlated to the 4 stimulus events. In this case, the threshold is established by the downstream neighbors which, as Hodgkin and Huxley determined, propagate a signal only when channel thresholds are exceeded.

When the output appears one-to-one with the stimulus, the actor does not constitute much of an information processor, as this is mere transduction/transmission. So lets make it more challenging. What about high noise environments; wouldn't the chaos of thermal state transitions disrupt the pattern recognition function?

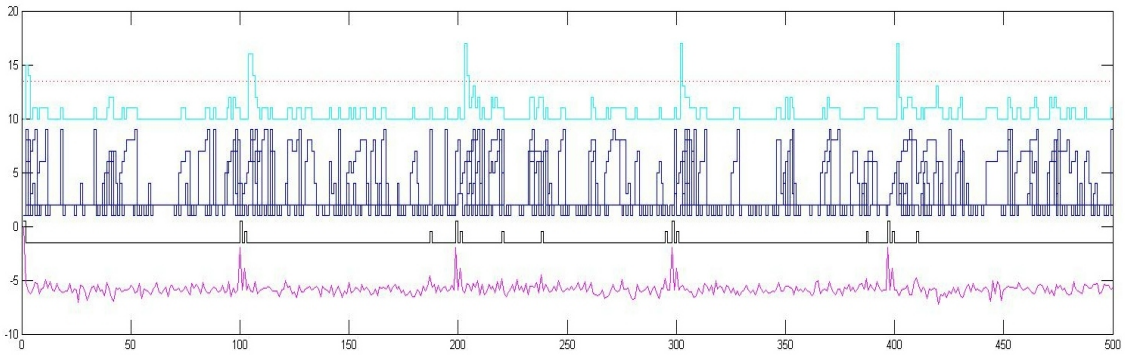


FIGURE 140: At 25% Noise levels, 4 units detected the pattern 79% of trials

What if the stimulus were modified to a similar but different pattern? Would not other stimuli elicit the same response? The stimulus voltage pattern is modified to [-60 -40 -60 -20 -60]; % mv , whereby the 2 voltage dips are reversed in order. The result is that there is no correlation between stimulus and output, as the pattern did not match. No threshold crossings occurred. This establishes that it is the temporal pattern that matters, not the energy of the stimulus.

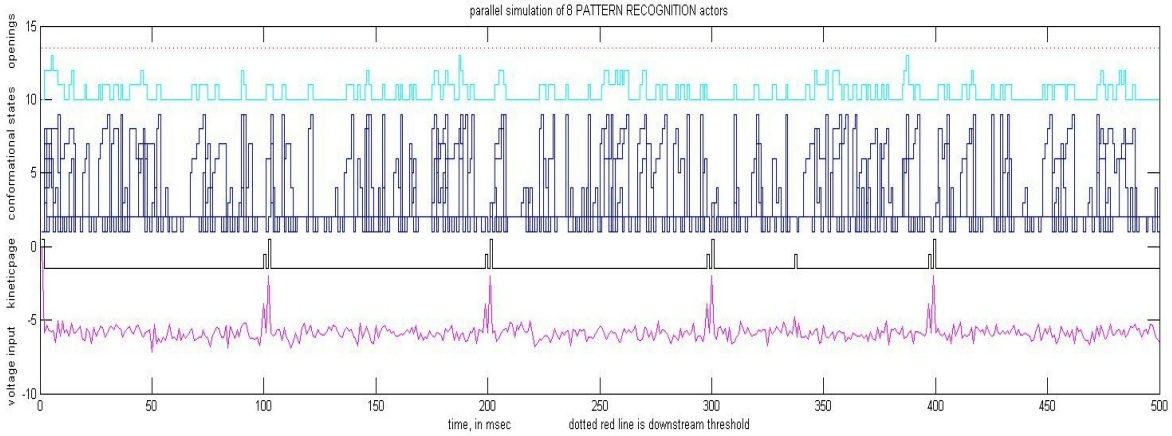


FIGURE 141: same as above, but reversed input pattern

And finally, let's resume the original pattern and increase the noise to be of equal amplitude to the signal pattern itself.

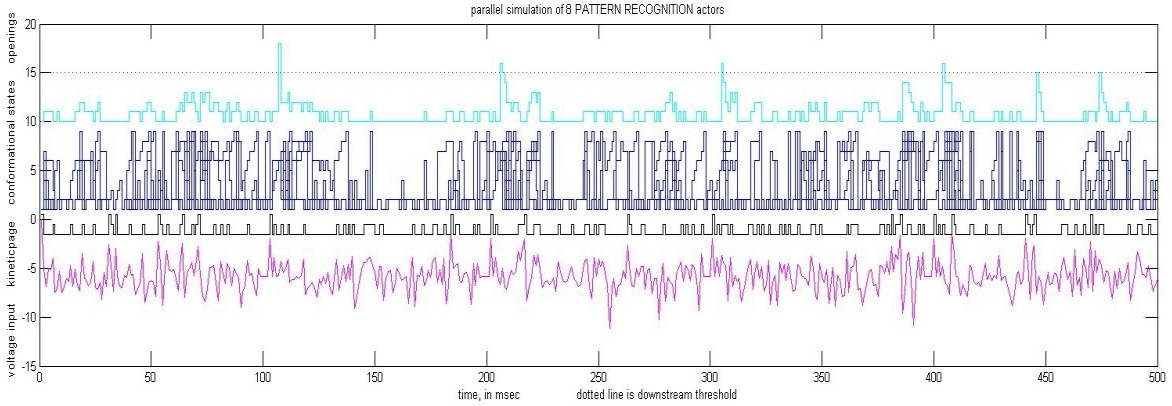


FIGURE 142: Stimulating 8 Q matrices with pattern + 100% noise

Even under such noisy conditions as 1:1 signal to noise ratio, given 4 identical input patterns embedded in back ground noise, there results 4 threshold crossings as output; aligned perfectly in time to the patterned stimulus. Repeated trials (in simulation) attest that arbitrary precision may be obtained via a) particular kinetic rate values in

the Q, or b) multiple units operating in parallel. The Q matrix becomes more deterministic as alternative paths are zeroed out. Such kinetic rate values increase reliability as the probability of subsequent states approach 1 along the duty cycle. This is not the easy solution, because soft matter molecules are stochastic, not deterministic. The biological solution to reliability needs is increasing the quantity of actors in parallel.

The next challenge undertaken is to cause the actor molecule to respond with its characteristic output pattern. Can these be made reliable in small parallel groups, as above? Pattern generation has the characteristic of being unresponsive to the environment. Regardless of modulation or voltage, once the pattern commences, it ideally continues to completion. Thus all the Q pages are identical, or nearly identical, in the regions of pattern generation. The second trait is that during this sequence there must be some expression to the outside world. This could be a channel opening, a trans-membrane transport, a release of messengers, activation of a catalyst, etc.. I call this expression the phenostate. In the case of channels, the phenostate map is a list of those conformational states which result in an open channel. In the case of pumps, the phenostate maps lists those states which result in a transport event from side A to side B, and those states which result in a transport from side B to side A. In the case of receptors, the phenostate map is a list of states which result in the release of messengers, and how many. In the case of vesicles, the phenostate map is a list of states that result in a partial or full discharge of contents into the synaptic cleft.

Returning to biological actors, they almost always are modulated by one or more environmental variables. As the modulation points increase, the size of the state transition matrix increases geometrically. Modulation may alter the dominant limit cycle by speeding up some steps and slowing others down. This constitutes a change in the pattern of response. You can hear it in the rhythm of the openings. It is the nonlinearities of state transitions that may cause a slight change in modulation to result in a switch to an alternative state pathway, with a completely different temporal sequence expressing itself. Modulation may increase uncertainty by bringing two or more paths into nearly equal probabilities, or conversely decrease uncertainty by reducing the probabilities of alternatives to near zero. Modulation might result in skipping a step, by short circuiting to a subsequent step. Modulation might allow running backwards, to some extent. Modulation might also increase or decrease the selectivity of particles to be transported, or alter the affinity at other modulation sites. This latter effect should properly be referred to as meta-modulation or second order modulation, as it modulates the modulator. This adds yet another order to our membranal system, bringing it to minimum of being a forth order stochastic system.

This project defines several primitive tools for exploring these phenomena. There remains much work to be done to characterize the biological uses of such potential and to develop artificial applications for the information processing potentials of these molecules.

11.8 COMPUTATION WITH PATTERN PROCESSORS

The discipline of computation is biased towards step by step procedures, a/k/a logic. Much of this originates with Alan Turing, who defined the computer as a digital step-by-step procedural processor. Though he explicitly addressed analog computers in several of his papers, digital machines act logically, while analog act via continuous functions. Some work in formalizing what analog systems can compute is written, but mostly as a conversion of the theories from the digital realm. Stochastic processors are distinctly different in that they do not require programming, as do all digital computers. Stochastic processors begin naive but are self motivated to derive information from the environment and develop patterns that resonate with it. They derive operating energy from both the thermal surround and from specialized molecules like ATP. A network of paths is possible through the state graph, and which path is taken is a function of modulating particles which may impinge on it.

What is often interpreted as “uncertainty” in stochastic processors is in reality an extensive exploration of the possibility space so as to maximize harmony (viability) with the many variables of the environment. It is also the means of deriving energy from the thermal surround. Rather than being severely constrained - as digital computers are intentionally designed - organic systems presumably evolved with wide responsivity to relevant variables of the environment. For example, each living cell must adjust to temperature, pH, tonicities, light, and available energy sources - and still serve in its role to the greater organism. This implies that the living cell possesses far more intelligence than the inorganic transistor. Indeed it gives a single membranal protein molecule far more intelligence than the transistor.

Is it reasonable to impose man's notion of computation upon neurons as a metric of their information processing potential? Are not addition, subtraction, multiplication, division, integration differentiation, lag and convolution creatures of step-by-step procedures? Yes they are, and as such may not apply to stochastic systems. However some aspects of them do carry over.

Consistent to conventions of 1 page per input combination, the AND, OR, XOR, NAND and NOR gates have the following QQs, each having their size = 2x2x4:

AND

page				page				page				page			
input1	0				1				0				1		
input2	0				0				1				1		
states	0	1		state	0	1		state	0	1		state	0	1	
0	1	0		0	1	0		0	1	0		0	0	1	
1	1	0		1	1	0		1	1	0		1	0	1	

OR

page				page				page				page			
input1	0				1				0				1		
input2	0				0				1				1		
states	0	1		state	0	1		state	0	1		state	0	1	
0	1	0		0	0	1		0	0	1		0	0	1	
1	1	0		1	0	1		1	0	1		1	0	1	

XOR

page				page				page				page			
input1	0				1				0				1		
input2	0				0				1				1		
states	0	1		state	0	1		state	0	1		state	0	1	
0	1	0		0	0	1		0	0	1		0	1	0	
1	1	0		1	0	1		1	0	1		1	1	0	

NAND

page				page				page				page			
input1	0				1				0				1		
input2	0				0				1				1		
states	0	1		state	0	1		state	0	1		state	0	1	
0	0	1		0	1	0		0	1	0		0	1	0	
1	0	1		1	1	0		1	1	0		1	1	0	

NOR

page				page				page				page			
input1	0				1				0				1		
input2	0				0				1				1		
states	0	1		state	0	1		state	0	1		state	0	1	
0	0	1		0	0	1		0	0	1		0	1	0	
1	0	1		1	0	1		1	0	1		1	1	0	

From these data, it is obvious that transistors do not have true transition probabilities. They are deterministic, as the state is solely determined by the two current inputs. They are not Markov processes because they do not change state as a function of the current state. Although Markov processes are regarded as the simplest of stochastic processes because they “have no memory” beyond the current state, transistors don't even have that. Concerning systems with memory, transistors are zeroth order and Markov processes are first order. It is the state memory that enables actors to process temporal information. Without it they could not be pattern recognizers. A second order process would retain memory of its prior and current states (as is necessary for differentiation and for integration). In silicon computational systems, the capacitors provide memory of the prior state. In neural systems, the ion positions (and resultant charge densities) provide memory of the prior state. Much of this memory resides in the capacitance of the membrane. Some of it resides in sequestered messenger particles, staged for triggered release.

Silicon transistors are binary operators, in that they receive two inputs to determine one output. Membranal proteins are N-ary operators, where N = quantity of allosteric binding sites + voltage + state. As the state transition response to inputs is the essence of computation, it is reasonable to conclude that membranal proteins perform greater computation than do transistors. The question confronting investigators is: What are the operators?

In all cases of state transitions in response to various inputs (including prior state), what characterizes a given type of processor is the pattern of responses. In response to the same set of input patterns: [0 0; 0 1; 1 0; 1 1]; the above types of transistor respond with characteristic patterns in the next state (taken as output): 1112, 1222, 1221, 2111, 2221. This short list of patterns is responsible for everything that a digital computer can do, attesting to the power of primitives in combination. Two such gates in series may determine or recognize a two-step temporal pattern, and N gates in series may determine an N-step temporal pattern. That membranal proteins can easily determine 2- and 3-step patterns is manifest in the kinetic schemes observed. The practical question is how might patterns deeper than 2-steps be harnessed in an aqueous environment, presumably where “cross-talk” between channels is rife.

A mathematician may be concerned as to whether or not the set of patterns available within a neuron constitute an “algebraically complete” set of operators. But in living forms, the question is only whether or not a sufficient set of operators is available to attain viability. A methodical pursuit of the question of viability are expected to suggest which patterns will be present. For example, homeostasis will require patterns that contribute to negative feedback loops, and “startle” will require patterns that participate in positive feedback loops.

Excitation and inhibition receive a lot of attention. Differentiation is also essential for such operations as acoustic source location determination. Integration is implied in the “integrate and fire” behavior of some neurons. The presence of both inhibitory and excitatory neurotransmitters is a single dendritic arbor suggests that the presence of some inputs AND the absence of certain other inputs is necessary to generate a signal. This combination constitutes are spatial pattern. Similarly, distal excitation must get started earlier than proximal excitation if the two are to sum to an above- threshold response. This constitutes a temporal pattern. Inhibitory surround is prevalent both spatially and temporally, suggesting the need to isolate the dominant signal from the background clatter. A vague input pattern is often sharpened into one or another canonical output pattern, as a form of “classification” of inputs. Such sharpening can be accomplished by a single ion channel, and successive stages of the same type of channel can result in increasing that sharpness. In this sense, signal filtering is merely a subset of pattern recognition. Pattern

recognition can perform blocking, filtering, smoothing, sharpening, amplifying, addition, subtraction, AND, OR, NAND, NOR, XOR, comparison, classification, and decision.

There are two fruitful approaches to discover the computational potential of membranal proteins. The first is to perform molecular dynamics simulation experiments until the complete state transition data set is exercised and valued. The second is to write requirements for biocomputation and then engineer kinetics that will fulfill those requirements. Chemists are then tasked with scanning the molecular possibilities to choose from the extent molecule of the closest matches to needs. A third method might be direct observation of *in vitro* ion channels, but instrumentation is not yet available to complete the task. The first approach is useful for understanding biology and the second for engineering new forms of liquid state computers.

It has become apparent that large protein molecules are capable of pattern handling, and that addition and subtraction may be too simple for them, in that the Q matrices must be shrunk down to a small number of states to do such tasks. One ion channel has a lot more computational horsepower than a solid state transistor.

A great challenge in harnessing the pattern processing power of molecules concerns reversible processes. Energy-less systems are almost always reversible processes; while systems with energy injected are usually directed processes that proceed only 1 way around the duty cycle. It is possible however to design stochastic ratchets. On ambient temperature alone, a timed sequence of state changes and modulation changes can effect a directed flow. Channels must somehow enforce directed flow around their duty cycles for all patterns except palindromes.

11.8.1 PATTERN CONVERGENCE FOR CLASSIFICATION AND DECISIONS

Each of the possible state paths can be mapped into input implications and output implications. The input is expressed as that modulation pattern(s) which will have this state path as its highest probability. The output is defined as the transport pattern that results from this state path. This sets up a mapping between input pattern and output pattern.

It is expected that an actor will either express as one-to-one mapping of input pattern to output pattern, or a several-to-one. There is utility for a processing device that can take several different inputs and classify them into a reduced

set of output possibilities. The goal of many computational problems is to digest a lot of data down to a decision. This requires a successive reduction in data via several-to-one mappings.

After all, actors are parametrically swept for patterns recognized, then a grand library of input patterns can list which actors recognize it and what their responses are. This information can be organized into a conversion table, working much like logical tables do.

11.8.2 COMPUTATIONAL FLOW CONTROL

The distinction between an adding machine and a computer is the capability of conditional branching. A calculator follows instructions set forth before the initiation of the calculation steps. But if during the course of those calculations conditions can be detected that would cause (dynamically) a switch to a different sequence of steps, then we call that a programmable computer. Observing the human players in any fast sports, such as soccer or basketball, makes it obvious that humans can respond quite dynamically to changing conditions, even mid-maneuver. The question is, at what level of nervous system organization does flow control effect switching to alternative actions? For purposes of this model, the question is reduced to: Can a constellation of ion channels implement flow control, so as to switch the modality or the path of streaming data to alternate processing?

As a starter, we know modalities exist, down to the level of individual channel molecules (expressed as bursts, rhythmic pulsing, chaotic firing). What remains to be investigated are the pathways of information that trigger those modal shifts. Are the triggers patterns of input? Or is there feedback from some down stream point that gauges the output? In the former case, we have channels that are definitely pattern recognizers. In the latter case, whatever is generating the feedback signal must be the pattern recognizer. We must find it.

Feedback is certainly plausible, as antidromic communication can take place across synapses, and messenger molecules are not bound to diffuse only dromically. While the charged particle waves are energetic, forceful and fast, the neutral particles may serve as supplemental messengers diffusion in the gray zones, the non charged volumes 5+ nm away from the membrane. Is it possible that some may surf the charged particle waves?

11.9 AQUEOUS ION WAVE TRANSMISSION

The force that creates such waves is the EM force, the strongest available to the cell. Therefore it has the potential to over ride all other forces, including diffusion, inertia, and water molecules acting as a solvent. However, it remains for physics to verify the degree of dominance and ascertain the facts of the phenomenon.

First is considered the static charge case for capacitation by a membrane given unbalanced charges across that membrane. The packing density on either side of the membrane is not well represented by a square grid, but rather by an equilateral triangular grid.

A significant consideration is that Coulomb's law of forces due to inhomogeneous charge densities does not support independent action by the various ion types. According to Coulomb's law, charge is fungible. The channel pore selectivity of charge is a chemical feat, not a physical one. Which ever ion types are caught up in the charge attractions across the membrane are also going to participate in disturbance waves. Variations in mass, especially due to hydration, are expected to leave some ions more sluggish than others, due both to inertia and viscosity increases. It remains to be studied by physicists what might be the effects of mixed mass particle systems in radiating surface waves. It remains to be studied whether some one species of ion has advantage over the others and is able to crowd other types out into neutral zones via the surrender of oppositely charged particles. It is contemplated that the lightest mass is the fastest to occupy near-membrane positions. That would be Na+, or possibly H+ if sufficient quantities were available. The effects of dynamic hydration are not yet adequately taken into account. If there is any competitive effects between the ion types for capacitation, then that would tend to render the charge fields more homogeneous, and therefore more prone to waves than chaotic dampening.

Another effect in need of further study is the differential in mass between the ions on one side of the membrane verses the other side. With Na+ at 23 Dalton and Cl- at 34.5 Dalton, and with near even matches in quantities, the two wave-like movements are coupled by great force and may act as one body. To what degree does such a mass differential hinder a smooth sinusoidal wave? Are there two resonance frequencies, or are they joined into one? Is the coupling between them sufficiently strong to cause them to reach a compromise action; or do they each tend to smear the other type's movements?

The packing density of charges on either side of a charge barrier results in the capacitation of the unbalanced charges. The first layer is against the membrane. The closest like charges can come to each other is equal to the the thickness of the membrane. If they come any closer than that the repulsive forces will exceed the attractive forces from across the membrane, with the result that one of the overpacked particle will be expelled into the outer regions, at least a membrane thickness away. The repulsive forces equilibriate in layers, each one sparser than layers closer to the membrane. The first layer contains 81.77% of all charge of the capacitor. Thus the contributions of subsequent layers diminish rapidly, with the fifth layer contributing only 1%. The fifth layer is located 9*thk away from its counterpart layer on the other side of the membrane.

B2C B2B

lay	d	D	spaces	force	N	N cum	frac	cfrac	%	cum %	density	cdens
1	1	100	1000000.0	1.00	1.00E+012	1000000000000	1.00000	1.00	0.81771	0.8177	100000000	100000000
2	3	300	333333.3	0.33	1.11E+011	1111111111111	0.11111	1.11	0.09086	0.9086	11111111	111111111
3	5	500	200000.0	0.20	4.00E+010	1151111111111	0.04000	1.15	0.03271	0.9413	4000000	115111111
4	7	700	142857.1	0.14	2.04E+010	1171519274376	0.02041	1.17	0.01669	0.9580	2040816	117151927
5	9	900	111111.1	0.11	1.23E+010	1183864953389	0.01235	1.18	0.01010	0.9681	1234568	118386495
6	11	1100	90909.1	0.09	8.26E+009	1192129416199	0.00826	1.19	0.00676	0.9748	826446	119212942
7	13	1300	76923.1	0.08	5.92E+009	1198046575962	0.00592	1.20	0.00484	0.9797	591716	119804658
8	15	1500	66666.7	0.07	4.44E+009	1202491020406	0.00444	1.20	0.00363	0.9833	444444	120249102
9	17	1700	58823.5	0.06	3.46E+009	1205951228019	0.00346	1.21	0.00283	0.9861	346021	120595123
10	19	1900	52631.6	0.05	2.77E+009	1208721311121	0.00277	1.21	0.00227	0.9884	277008	120872131
11	21	2100	47619.0	0.05	2.27E+009	1210988884818	0.00227	1.21	0.00185	0.9902	226757	121098888
12	23	2300	43478.3	0.04	1.89E+009	1212879243986	0.00189	1.21	0.00155	0.9918	189036	121287924
13	25	2500	40000.0	0.04	1.60E+009	1214479243986	0.00160	1.21	0.00131	0.9931	160000	121447924
14	27	2700	37037.0	0.04	1.37E+009	1215850986098	0.00137	1.22	0.00112	0.9942	137174	121585099
15	29	2900	34482.8	0.03	1.19E+009	1217040046740	0.00119	1.22	0.00097	0.9952	118906	121704005
16	31	3100	32258.1	0.03	1.04E+009	1218080629467	0.00104	1.22	0.00085	0.9960	104058	121808063
17	33	3300	30303.0	0.03	9.18E+008	1218998903112	0.00092	1.22	0.00075	0.9968	91827	121899890
18	35	3500	28571.4	0.03	8.16E+008	1219815229643	0.00082	1.22	0.00067	0.9975	81633	121981523
19	37	3700	27027.0	0.03	7.30E+008	1220545689833	0.00073	1.22	0.00060	0.9980	73046	122054569
20	39	3900	25641.0	0.03	6.57E+008	1221203152029	0.00066	1.22	0.00054	0.9986	65746	122120315
21	41	4100	24390.2	0.02	5.95E+008	1221798036026	0.00059	1.22	0.00049	0.9991	59488	122179804
22	43	4300	23255.8	0.02	5.41E+008	1222338868909	0.00054	1.22	0.00044	0.9995	54083	122233887
23	45	4500	22222.2	0.02	4.94E+008	1222832696069	0.00049	1.22	0.00040	0.9999	49383	122283270
50	101	10100	9901.0	0.01	9.80E+007	1222930725674	0.00010	1.22	0.00008	1.0000	9803	122293073
500	1001	100100	999.0	0.00	9.98E+005	1222931723677	0.00000	1.22	0.00000	1.0000	100	122293172
	100001	10000100	10.0	0.00	1.00E+002	1222931723777	0.00000	1.22	0.00000	1.0000	0	122293172
	10000001	1000000100	0.1	0.00	1.00E-002	1222931723777	0.00000	1.22	0.00000	1.0000	0	122293172

TABLE 33: MAXIMUM CHARGE DENSITY WRT MEMBRANE THICKNESS

lay = layer; d = multiple of membrane thickness; D = angstroms apart; N = quantity B in the layer; frac = fraction of the first layer capacity that this layer contributes; % = percentage of the whole; density = charge density of this layer; cdens = cumulative density.

These stratifications only appear at kelv=0; As temperature rises, the layer boundaries grow fuzzy. At full destratification, the charge density is are found to follow an exponential decay curve away from the membrane, with 95% of the charge located within 3 membrane thicknesses.

This implies that substantially all of the charge effects, including disturbance waves, are taking place within 25 nm of an 8 nm thick membrane.

11.9.1 INFORMATION IS DESTROYED BY DIFFUSION

As previously discussed, earlier models of communication between ion channels via diffusion is quite unlikely. The EM force will not allow it. Diffusion is defined mathematically by the Gaussian curve. The Gaussian curve is found to be synonymous with the distribution of white noise. White noise is defined as zero information. This is corroborated by the Fourier transform, which only passed the Gaussian curve unscathed, as zero. That is, the zero point shared by both the time domain and the frequency domain is white noise. Events are information. Events per unit time is information per unit time. Events per unit time is frequency. Therefore frequency is information. This is an informal proof that diffusion is not a carrier of information.

In contrast, all information transmitted though space is accomplished via waves, or by transport of solid objects with information marked upon them. That is, information is sent via radio or the letter carrier. The physical arrival of a messenger molecule is analogous to the letter carrier, and the disturbance waves of the capacitated ions is analogous to the radio waves.

Diffusion does have utility as an echo cancellation mechanism. The many disturbance waves meld into back ground ripples of too low an amplitude to trigger ion channel action. Motions that diffuse join into the background noise, which may be tapped as energy, but not as information.

The information value of diffusion is its likely delivery times between actors via random walks. All other effects need not be calculated, though the patterns of spread may be of academic interest.

11.9.2 THE EM FORCE AND ION MASS INTERACT TO FORM WAVES

Physics defines a second order mechanical system as having inertia and spring. Electrical analogs have capacitance and inductance. In general, oscillation requires two forces opposing each other in a non-linear fashion. Saline, *per se*, does not lend itself to oscillations or waves. It is resistive and diffusive. These are first order effects that lead directly to Gaussian distributions, and end in white noise - the total lack of information.

11.9.3 INFORMATION IS PRESERVED AND MADE PORTABLE BY WAVES

One of the quirks of waves is their strong temporal asymmetry. They radiate outward from point sources, but are never seen to radiate inwardly to point sinks. Because waves are not so reversible, they impose a directionality upon the information they transmit. This can be a great asset in the milieu of saline as a conduction medium. Ion channel intercommunication is more analogous to a nation of radio stations than it is to a nation of telephones with copper wires conducting between them. That does not imply radio frequencies at all. Frequencies are determined by a) what is available to resonate, and b) which frequencies the medium is most transparent to.

11.10 POSITIONAL ORGANIZATION FOR COMPUTATION

The membrane, as the static 3-d structure, imposes an organizational layout upon the actors. This spatial pattern structures the connectivity relationships between the actors. These are informal, as there are no “wires” acting as definite conductors. As an open forum, ions must gather into waves to communicate between actors, and always tend to radiate outward in concentric circles from the points of perturbation. Despite such perfect radial symmetry, the neuron manages to process information directionally, as though channels had distinct input and output ports and distinct directionality of signal propagation.

11.10.1 OPEN SALINE CONNECTIVITY

Given a pool of saline above the membrane and another complimentary pool below, how can some hundreds of actors communicate with each other without it being simply a mass effect or a muddle. The fact that there are multiple types of ions present helps the actors act independently, due to selective conductivities, and selective allosteric binding sites. But once the ions are on the lose in the saline, their role is determined by charge. The

waves of disturbance are determined by Coulomb's law, which is agnostic to types of ion. They all contribute to a single voltage wave that radiates outward from each point of channel flux. They may sum or subtract from each other as interference patterns when they cross.

The issue is not so much which actors the wave will strike, as it will strike all within reach. The issue is which actors will respond to each wave. And the answer to that is dependent upon the shape of the wave. The wave is a signal, and the signal expresses a temporal pattern, and each actor type responds to only certain patterns. It is therefore possible that in a field of actors, only a certain few will respond at all to a given wave, while a different set will respond to a different pattern. Thus, a singular input signal can stimulate completely different sets of actors, merely based upon the pattern of that signal.

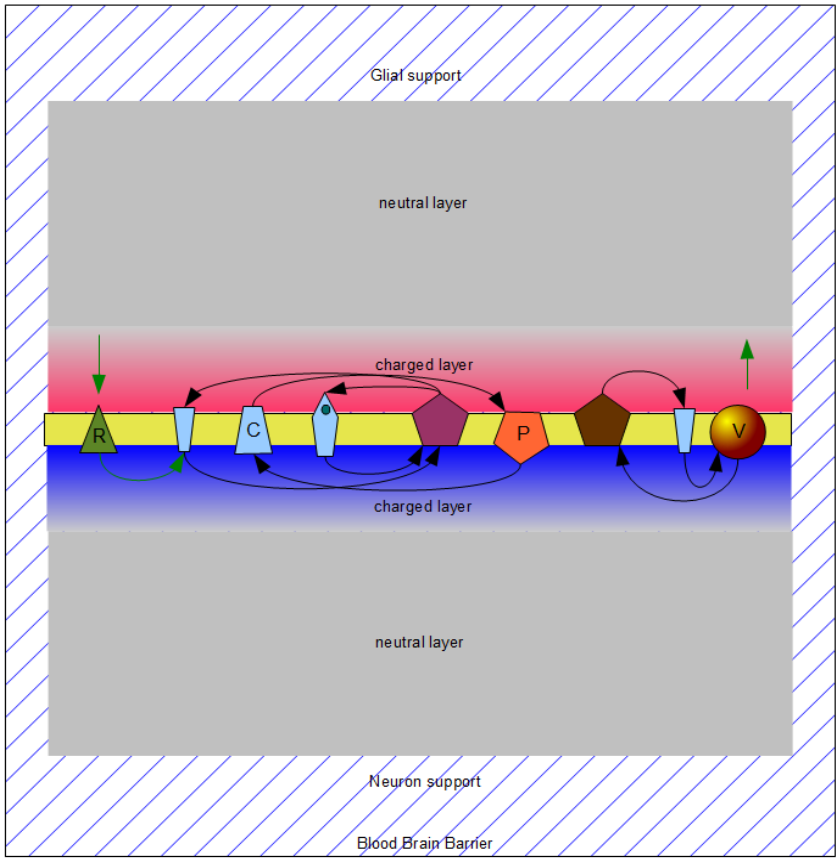


FIGURE 143: Membrane charge and communication between actors

The membranal system is only about 56 nm thick, is equally busy on both sides, and is the essential 'works' of the neuron. There is so much fragile activity on the outside of the cell, that support is needed; thus the critical glial cells, and the blood brain barrier.

11.10.2 SPATIAL ORGANIZATION MAPS TO TEMPORAL INFORMATION

1. particles move by diffusion
2. there is an N-body charge force accelerating each charged particle
3. there is water viscosity which sublimes acceleration into mere velocity
4. the membrane dielectric coefficient determines the capacitance involving the polar heads of fatty acids
5. such immobile charges result in membrane stiction of the closest layer of ions
6. stiction and ion mass determine the charging curves in electrolytic solutions
7. all of the above determine the rates of ionic waves spreading across the field of actors
8. actor fields are characterized by actor types, densities, type interactions, and membrane capacitance
9. lose actor field densities can process sequential steps of information
10. tight actor field densities tend to act *en masse* to reinforce and amplify a characteristic output signal
11. Wave fronts may be passive (when channels do not modify it) or active (when channels modify or amplify it)
12. Channels produce Inactivation Fronts, the spatial effect of fields of channels going into refraction (dark bands)
13. Channels imply Escapement mechanisms, that release energy conditionally (Wave front + Inactivation front)
14. Escapements organize random data into wavefronts (Propagation = Chain reaction of Escapements)
15. the Temporal separation of waves by Escapements keeps information from overlapping into ambiguities

11.10.3 FAN IN AND FAN OUT IMPLICATIONS

Most neural networks are architected for a fan out during the first half and a fan in during the second half. Indeed, biological neural nets follow this organizational pattern. Studies of the retina find that the earliest of layers are sorting out features. The raw data is filtered in edges, motion, direction, differentials, etc. Presumably, evolutionary selection favored detection of certain features over others. Though not proven, most attempts at processing information involve a separation process, such as solving for eigenvectors, an uncoupling process. Indeed the whole of systems theory is based upon this action. Such uncoupling yields a set of independent, or near independent variables, which can then be manipulated.

The manipulation is based upon 3 large factors. First, is the incoming signal itself. Second, memory serves to suggest what previous outcomes were, and becomes a gauge for suggesting which action is appropriate in this

instance. Third, it must be geared toward mapping into available resources, like arms and legs. That is, urges to act must be based upon what is feasible.

The fan in half implies convergence. It implies parsimony. It implies decisions. After the raw data has been exploited for every useful feature, these features are interpreted in light of recorded history, then a progressive set of classifications and decisions are made until a linear stream of action is chosen and committed to.

Data can be sorted into several features very fast: temporal differential, temporal acceleration, spatial differential, spatial acceleration, comparisons, integration, selective integration, temporal frequencies, spatial frequencies. There are third and fourth order extensions of these as well.

11.10.4 HIGHER ORDERS OF ORGANIZATION

After each actor type is well characterized, and understood as to the stimulus set and the response set, and the sufficient set of redundancies to achieve the desired levels of confidence, then the raw computation of each of these processes becomes redundant. For purposes of modeling larger scales of elements, especially for modeling multiple whole cells, the standard actor behaviors can be stored in lookup tables.

We begin by characterizing patches. Given a list of the actors present and their pattern transforms, we can organize this list into a lookup table. It does not matter what the pattern is. It only matters which actor types recognize a particular pattern and how they respond to it.

EX Given a set of 5 processor types, with the following pattern recognition and pattern generation capabilities.

pattern in	pattern out	actor type
A	C	1
B	D	1
A	G	2
B	D	2
C	E	3
D	F	3
E	G	3
F	H	4
G	H	5
H	H	5

In the system above with possible input patterns IN = { A B C D }. What constellations serve any purpose? (Most constellation dead end. It is a sparse map). What are the possible output patterns? There are usually fewer output patterns than input patterns. Classifications are reductive. Decisions are reductive.

Digest, input interface

A	1	C
B	1	D
A	2	G
B	2	D
C	3	E
D	3	F

Digest, secondary patterns

C	3	E
D	3	F
E	3	G
F	4	H
G	5	H

Digest, tertiary patterns

E	3	G
F	4	H
G	5	H
H	5	H

Digest, quaternary patterns

G	5	H
H	5	H

This is all the system possibilities up to through the fourth stage. It shows that there is only 1 output pattern (H) after the fourth stage, although it is possible to produce { C D E F G} after the first stage; { E F G H } after second; and {G H } after third. A successive classification process takes place.

A 1 C 3 E 3 G 5 H
2 G 5 H

B 1 D 3 F 4 H

C 3 E 3 G 5 H

D 3 F 4 H

For completeness, H 5 H can serve in amplification.

Each of these conversions is dependent upon the availability of the appropriate actor type near by. Each molecule is a pattern recognizer, but the order in which they are placed is critical to the membranal system behaviors. This biological arrangement of pattern processors is immensely more complex than an artificial parser machine handling the same data stream. Selective tuning takes place in an environment rich in overlapping patterns, and therefore, multiplexing is possible. Communication between channels takes place analogous to radio stations sharing the airwaves, rather than as a solid state transistors employ a conductive copper wires to direct signals. Using tunable waves is more flexible than hard wiring, and thus allows modal shifts without physical switching.

These Turing machine like rules may be combined thusly:

	A	B	C	D	E	F	G	H	
SET 1	1	2	3	4	5	6	7	8	input#
1	3	4							
2	7	4							
3			5	6	7				
4						8			
5							8	8	
actor#									

This would allow the timely superposition of output patterns as a function of propagation time to each actor. One could set up a "wiring diagram" to determine the arrival times between actors, and from that build a patch transfer function (nonlinear). It would be made more realistic by considering the actor refractory periods and the phase relationships which predispose the prior states. A multi-dimensional model could be made to address the various degrees of freedom of the input set.

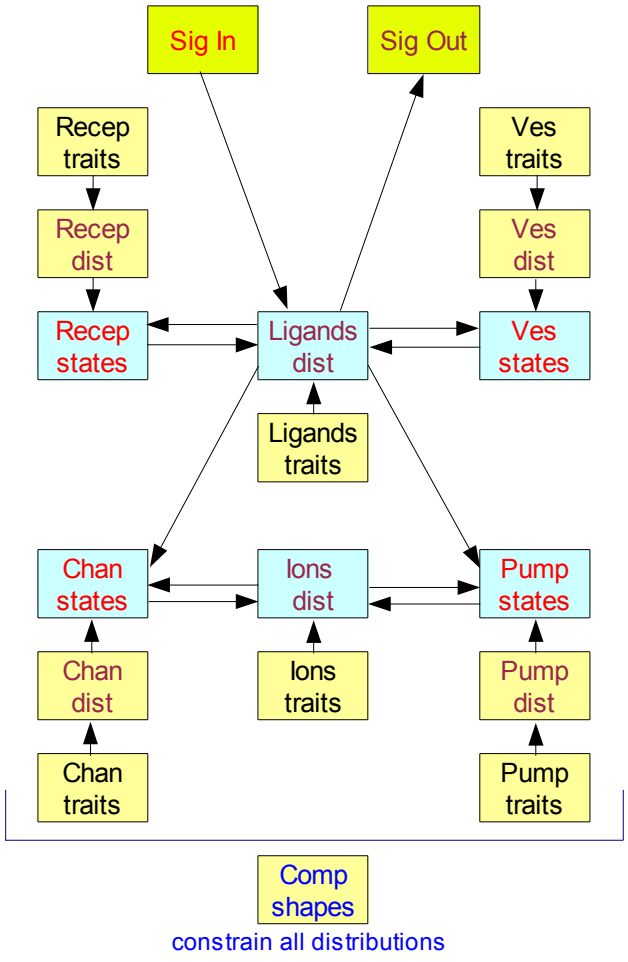


FIGURE 144: Information Types and interactions in Neurons

Signals arrive as ligands and impact receptors. Receptor states impact channels via messengers. This is a flow map for information, but does not depict what the processing is. The upper half of the flowchart serves as the I/O unit (input output handler). The bottom half of the flowchart is the engine, driven by the EM force, and conducting multiple convolutions.

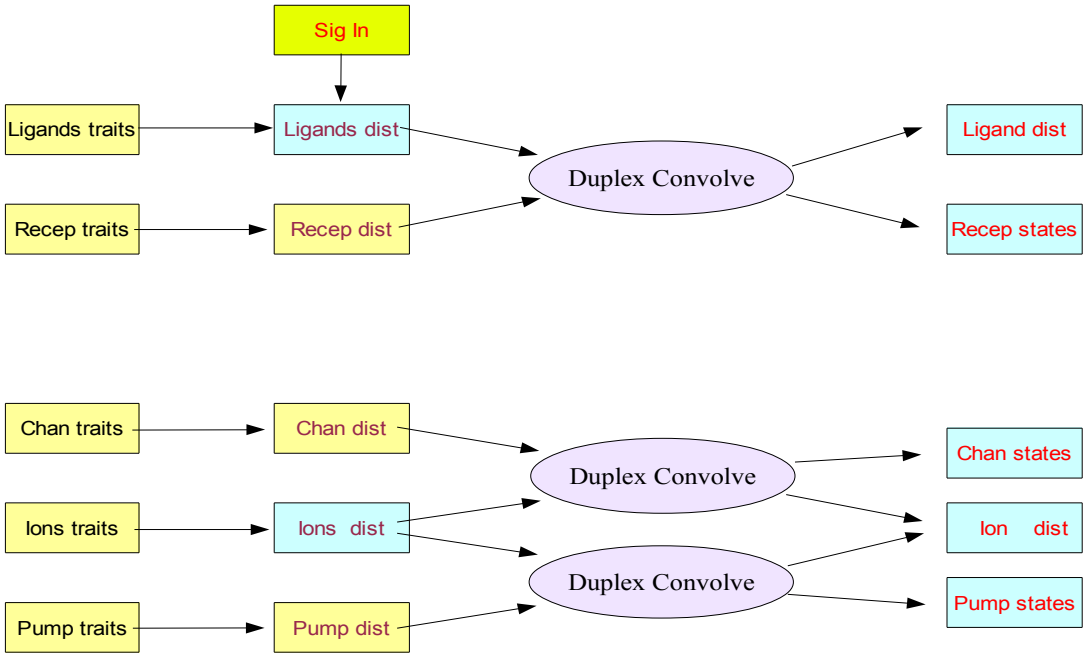


FIGURE 145: Duplex Convolution in Neurons

The primary processing function that occurs in the transfers between particles and actors is a convolution. A convolution is defined as one function integrated into a second function to yield a third function. But in this case, both function are convolved by the other, yielding two new functions. These convolutions are streaming data, so not capsulized unless artificially snipped by the recording mechanism.

There are yet two other forms of information processing transpiring. The second is the pattern to pattern mapping of the actor state transitions. And the third is the summing of wave functions of the charge layer disturbances,similar to the commingling of ocean patterns.

11.10.4.1 Actors as Finite State Machines

Actors are proteins. Proteins have hydrocarbon backbones with charged radical groups at each monomer along that backbone. The side chains may be uncharged hydrocarbons, or charged termini (e.g. serine, glutamine, lysine, arginine). Each is prone to attractions and repulsions with its immediate charged neighbors. Some of these attractions predispose the shape of the molecule, endowing it with secondary and tertiary structure. Some are prone

to attach subunits, which add to the molecular mass and order. To the extent that neighboring charges are similar they are exchangeable. The more similar they are, the more probable that ambient thermal energy is sufficient to loosen one and set another. Thermal energy alone is often sufficient to cause protein molecules to change configurations many hundreds or thousand of times per second. Because of the strength of the EM force, a broken bond results in the making of a new bond in extremely fast time frames, usually less than 1E-15 s. Relative to the millisecond action potential, such speed appears as instantaneous. There are no practical processes taking place within these brief transition times, and so they may be treated as discrete state transitions. That is, the protein acts through finite states without intermediary positions. The significance of each state depends upon its interaction with the outside world, or its interaction with subsequent states that will interact with the outside world. For example, states that result in the opening of a pore through the membrane tend to be of high impact when ever there is a gradient across that membrane to drive particles through that pore. Finite state machines are of great potential with regard to information processing. The Channels can act as finite state machines that recognize temporal input patterns and can generate specific temporal output patterns in response to specific input patterns. Pattern mappings can always be arranged so as to provide useful computational services. This concept was originally embodied as the "Turing machine".

Actors can be custom engineered for specific input patterns and specific output patterns (arbitrarily different from each other).

Define:

Inpat (sic) = input pattern to be recognized.

Outpat (sic) = output pattern to be generated.

EX Suppose a hypothetical channel to which the following is its strongest input pattern :

inpat = [0 1 1 0 0 0 1 0] ;

a more faithful analog version of such a pattern would accompany the above with a list of duration times; And better still with a third vector of duration tolerance times.

EX

```
inpat = [ 0       1       1       0           0           0           1          0 ;
1.23E-3  0.93E-3  0.66E-3  0.09E-3  1.01E-3  0.29E-3  0.95E-3  0.81E-3 ;
0.02E-3  0.043E-3  0.1E-3  0.06E-3  0.07E-3  0.02E-3  0.05E-3  0.032E-3]
* [ open  s  ds ]';
```

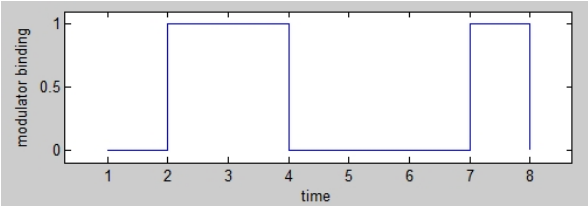


FIGURE 146: Input Pattern Required for Chan04

(this pattern in time is the triggering input)

This input pattern represents the binding/unbinding pattern of a modulator site on the channel molecule.

Our hypothetical channel type, when receiving inpat, generates this output pattern:

outpat = [0 1 0 0 0 1 1 1 0] :

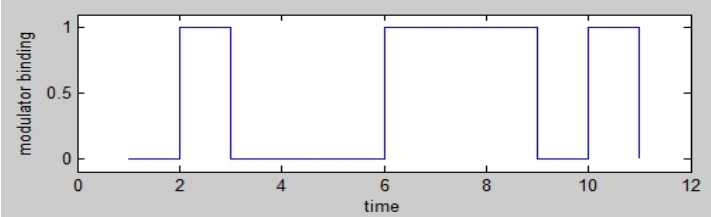


FIGURE 147: Resultant Output Pattern from Chan04

(what state graph would generate this pattern?)

Then it is a straight forward design problem to graph states that would accomplish this.

To test the Q matrix we need to ascertain that the channel can pick out inpat from a wide variety of other patterns. A realistic scenario would be a random pulse train of back ground activity. Then certain sections replaced with the desired pattern to be recognized.

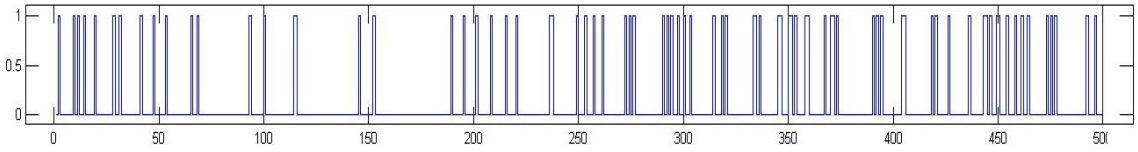


FIGURE 148: Random Pulses (duty cycle = 0.2)

A test for the ability of a neuron to extract a signal from random back ground spikes requires an input signal of random spikes with a selected pattern imposed.

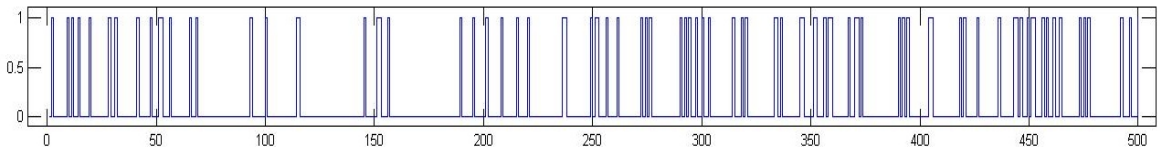


FIGURE 149: Random Pulses with Pattern Imposed at t = 50,150,250,350,450

The second plot looks almost identical but has the sought-after pattern inserted 5 times, at 50,150,250,350,450. Automatically constructed inputs such as this one can be used to test the ability of a given Q matrix to detect a pattern out of back ground noise. With such a test set, one can begin to reverse engineer molecules with the desired behaviors.

The results of parallel pattern recognizers, in these two trials, only 4 actors in parallel, are shown below. The function Qgen proceeds by defining the input pattern states in sequence, followed by the desired out put states in sequence. Added to this are alternative paths, back paths, an hold states. Then the transition probabilities are calculated as a function of hold probabilities. Often the thermal dynamics are such that the Gibbs is building during the input pattern and relaxing during the output pattern. This expresses as gradients in the transition probabilities. Extremely unlikely transitions may be zeroed out, and non-zero probabilities may be filled in with appropriately sized noise.

Q matrices from the biodata need only be reordered along the most frequent paths. In some cases the duty cycle is incomplete or else unlikely. This indicates missing data within the kinetic schemes published. Most often what is lacking is adequate transition probabilities under modulation conditions. The fact that modulation is quite dynamic, complete transition tables are needed for each possible modulation state. The total quantity of modulation states equals the total combinations of bindings to the binding sites. That would included all particle types that may bind

there and the vacancy condition as well. It would also include all significantly distinct voltage ranges. Voltage could be imposed upon the Q matrix as a function, but may not be necessary to do more than 3 to 6 discrete range segments, each prescribing a page within Q.

11.11 FUTURE WORK

The project of defining and developing liquid state information processors has grown to far beyond what one student can complete in the course of school years. It will continue for the equivalent of many lifetimes across many people's efforts to bring to fruition liquid state computers. The difficult decision was where to cut it, to make it of dissertation length. The current state is such that each of the software pieces has been prototyped and tested against design function. Many new concepts and phenomena have been produced for review and scrutiny. The validation via wet lab experimentation is future work for others.

In particular, there are two phenomena that beg wet lab verification. It is hoped that one or more physicists will take an interest is ionic waves along saline bathed capacitance membranes, and measure the trade-offs between diffusion and drift motion at various temperatures, degrees of solvation, etc. It is hoped that one or more biochemists will pass judgment on the feasibility of working from various kinetic state graphs back molecules that come close to implementing those graphs. Of all possible state graphs that can be designed, some will be feasible and others not. Atomic interference, and limited action of the various bond types will rule out kinetics that may look good on paper. An investigation, perhaps with the aid of Molecular Dynamics principles, might identify the boundary within which lie the feasible set of synthetic actors.

11.11.1.1 Designing new channel types

One begins with an ideal duty cycle. What conditions indicate actions? This is the modulation setting. How many distinct settings are detectable? What changes in function should each setting indicate? This determines the number of duty cycles, and what each one of them should do, step by step. The number of steps determines the minimum quantity of states. Additional states may come into existence as a result of the chemist attempting to build such a molecule.

Next is the timing of each state and the transitions between states. As transitions are determined by thermal energy, which is largely random, a distribution of momenta allows the prediction of events by how much energy is required to effect a state transition.

1. convert the Boltzmann velocity distribution curve to momentum by multiplying by mass.

2. as one slides a vertical bar along the Boltzmann momentum distribution curve, the area under the curve to the right of the bar equals the probability of transition. Stronger bonds, of course, reduce the probability.

3. the timing of each of the states is prolonged either by a hold pattern, looping around a few nonsense states, or by strengthening the bond that awaits the rarer high energy impact sufficient to dislodge it.

4. each act of binding or unbinding necessarily alters the state transition probabilities. Use this to advantage. Each such event switches pages in the Q matrix, so that page must be designed to pick up where the last page left off and continue the cycle.

5. modulators may be slower than the duty cycle, or faster than the duty cycle. The slow ones set the modality. The fast ones are data patterns to which the actor must respond mid cycle.

6. in most cases, there is a rest state, where the actor is in its most relaxed conformation. This should be designed as the "stand by" state, positioning the actor ready to be stimulated into action.

7. the first action state is the trigger which initiates a complete cycle. To accomplish this one of two things must happen. Either the first state absorbs an inordinately high energy from impact, putting the molecule into its highest Gibbs energy, and running downhill through all the remaining states. Or, the cycle must pick up an energy booster, such as through ATP cleavage, so as to give the cycle impetus and direction.

8. there may be a number of auxiliary states, such as the refractory period. This does not benefit the duty cycle directly, but rather benefits the waves of particles so as to thwart antidromic conduction. Thus reminding the designer, to consider the impact of actor actions upon the surround in the design of the duty cycle.

9. it is the nature of stochastic systems to provide multiple paths. The designer must decide if these paths are to be equivalent and parallel, or in some way complimentary, adding timbre to the melody of the cycle. A transporter might be performing an extra service if every 10^{th} ion was a Mg++ instead of a Ca++. Or that some channels linger open a little longer to reshape the aggregate curve. Or that a small percentage respond more sensitively and earlier, on the chance that if the stimulus is a "go" then a little head start is provided.

10. next is analyzing the performance of stochastic processors. The reliability of each unit can be calculated by traversing the probabilities along each state path. This yields a distribution of performances. The desired performance will show up somewhere between 60% and 99.99% of the time. If the number is too low, then parallel actors must be run to determine the sharpening effects of multiples. Generally, a small number, like 8, actors in parallel can perform with very high reliability. Thus such parallelism is commonplace in nature.

11. the interactions between subunits may be simple, as when all subunits are identical, or complex, as when each subunit performs a unique task. The interplay between the subunits must be cooperative across the permutations. There can be no poison states that would lock up the works. We call this denatured. Molecules must be robust by resistance to deviations from the duty cycle, and a strong tendency to complete each duty cycle commenced.

12. switched catalysis is a valuable function. The binding of a modulator on one side of the membrane that causes the unveiling of a catalyst on the other side serve both as a transducer and a broadcaster.

13. mechanical actions are perhaps the more difficult of features to implement. They require getting molecules to do what are normally thought of as macro machine tasks. Pumping ions across a membrane, one by one is perhaps the most sophisticated action of a single molecule.

14. pumping logic, whereby ratiometric transport is the norm, and single species transport is rare, suggests some interesting aspects of ion concentration maintenance. Are these designs necessary, or merely convenient? Do they convey any information, or are they merely tricks to arrive at target ion concentrations? Are they fast enough and voluminous enough to play as peers to the ion channels in determining ion waves? When answered, then the design process can begin. Before then, it is not clear what our design criteria for pumps is, except to imitate.

15. finally, a careful assessment must be made of tragedies. Channels that get stuck open, pumps that quit, receptors that lock the catalytic function wide open, vesicles that burst inside the cell - are examples are catastrophic design. Probabilities are an asset when designs carefully set the probabilities of such events to near zero. Certainly evolved nature actors have such qualities. Both the inherent design, and the rigorous testing, are necessary to avoid life threatening failures.

The ideal channel possesses several rest states, because holding a single state in a noisy thermal environment required too much stiction. However, getting knocked out of the rest state ensemble requires a relatively high thermal energy or a catalytic effect facilitated by modulation. This begins the sequence of recognition. There will be an ensemble of states involved in input pattern recognition, but only the correct order will allow the state path to exit this ensemble. Having completed a pattern match, a new threshold is passed, usually at high energy state, and a cascade of states are negotiated which express as phenostates. The sequence of phenostates may exhibit a temporal pattern.

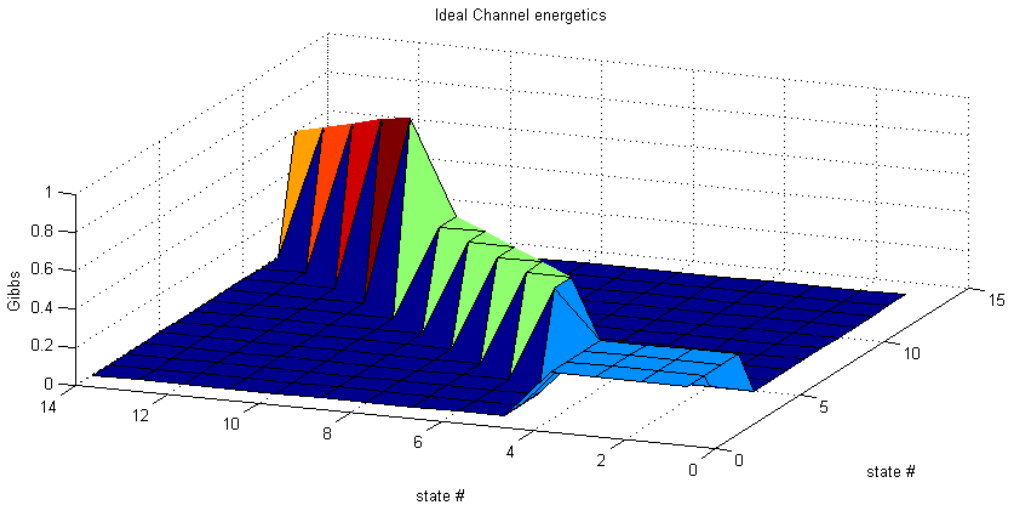


FIGURE 150: Idealized Channel state transition probabilities

The figure above depicts a low platform of rest states (aqua colored). The only reason the path lie straight down the diagonal is the states were renumbered so as to force that arrangement, just for convenience and clarity. Escape from the rest states requires sufficient energy (voltage, modulator binding, or rare thermal event) to initiate

attempts at pattern matching by jumping from state 1 to state 14 (to the yellow orange red sequence). This long jump is an artifact of state ordering within the matrix. If the match fails, the state returns to the rest state ensemble. If it succeeds, it has achieved maximal Gibbs energy, sufficient to launch the pattern cascade as a downhill run (the green sequence). Traversing the output sequence results in a time series through phenostates that express as an opening/closing pattern. The downhill outcome always tends towards the rest state ensemble. The probability of a particular state occurrence is inversely proportionate to the energy required to achieve that state from its adjacent state levels of energy. Therefore, it is possible to climb incrementally what is not at all likely as one jump (a single transition from a low state to a high state).

During the pattern recognition phase, it is feasible to be driving up the energy hill, processing along a plateau, running downhill, or some combination of these. For practical reasons, an ambient thermal processor must accumulate sufficient energy to insure a regular pattern of output. The more strictly timed, and the more intricately patterned, the more energy must be expended to enforce it. A critical output pattern would show as a steeper slope, while a short variable timed pattern needs only a shallow sequence. The flatter the ensemble, the greater the chances of back stepping, which is not desirable when a pattern is to be generated. Even though forwardly directed, the duration of each open and each close interval increases variance with the leveling of energy differentials. This cumulative variance can render pattern generation too sloppy for any practical utility. A build up of Gibbs energy over the first half of the cycle is desirable, and is possible incrementally.

In the simplest of mechanisms, a build up of Gibbs energy would require a sequence of increasingly energetic pulses to make it to “the top”. But a latching mechanism, whereby little force is require to restrain and later to release, a molecule could accumulate energy disproportionately large in comparison to the energy of the collisions it receives. Consider a cascade of mousetraps arranged so that the release of one would trigger the release of the next, incurring a chain reaction. Therefore the slight trigger energy could release many times the energy of one trap spring. Yet, no one trap would require any more energy to set than any other. Given the hydrocarbon backbone of proteins, it is possible to imagine repeating mechanisms where a charged arm is shifted to a higher energy state, to be released by a disturbance from its neighboring monomer. Then a series of like monomers might result in a similar chain reaction.

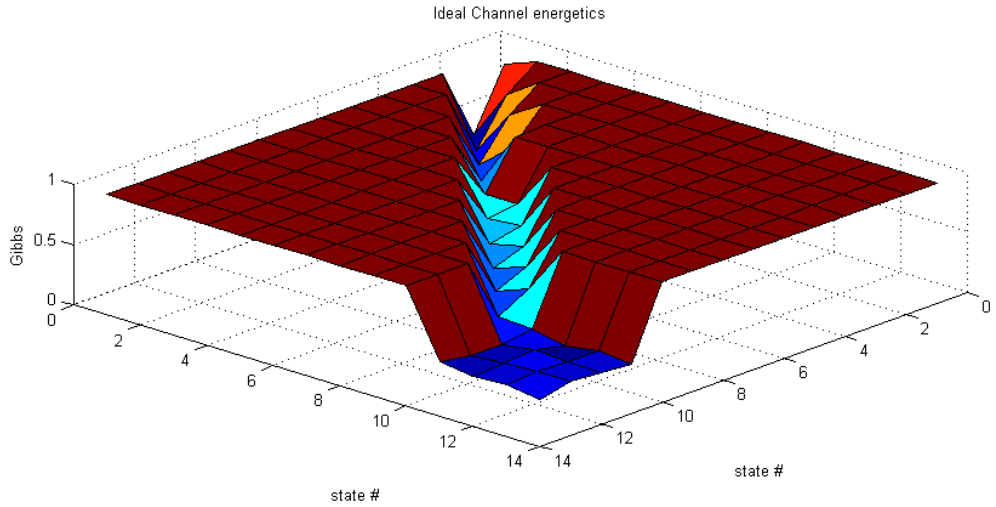


FIGURE 151: Energy Well depiction of a single purpose Channel

Single purpose is defined as a maximum of one pattern recognition, followed by a maximum of one pattern generation. There is a Gibbs boost to initiate the cycle which is entangled with pattern recognition steps (orange yellow), and then a subsequent down hill run through the output pattern (cyan) to the rest state (blue). The high plateau covers all unreachable state transitions. Energy barrier = 1/exp(int(probability)). What is not accurately depicted is that state 14 and state 1 are contiguous.

```
 - log( Gibbs energy) = k*probability(reaction);   %  other sources/sinks of energy holding equal
Energy barrier = 1/exp(int(probability));   % integration across a kinetic scheme is not valid
                                            % because it skips many states
```

A multi-pattern channel would have multiple valleys. In a state graph they would radiate out from the rest state, and in a transition matrix they appear as separate sub-matrices along the diagonal of a larger matrix.

Future research efforts will include mapping hypothetical Q matrices back to known and feasible chemistry. It is expected that a portion of hypothetical cases are physically impossible, and that those resembling the kinetics of known molecules are achievable by selection from extant molecules. Not yet determined is whether one can predict new molecules based upon a hypothetical kinetics scheme, mapped back to implied kinetics, mapped back to atomic configurations.

Given that ions most directly harness the electromotive force via Coulomb's law, and the EM force is the strongest force available to the neuron, and that this force is being applied to the smallest particles in the neuron (ions), it is

ionic movement that represents the fastest information path through the neuron. The known actors that participate in this path are the receptors, channels, vessels and pumps, with optional catalytic boost from the G-protein systems. The particle systems embodies both drift (information) and thermal diffusion (noise). The actor kinetics also also embody both modulation (information) and thermal conformational changes (noise). This suggests that the representation is informationally complete, in that having drilled all the way down to white noise, there is no more information that can be gleaned from the system. We cans say it is depth-complete, though the breadth of variety and variability be wide and yet unexplored. It is possible that this modeling approach will be found to be complete, in that it offers a straight forward method of capturing all neuronal membrane information processing. It does not include off-membrane processes, such as learning, which would require additional mechanisms.

11.11.2 MANUFACTURING

The task remains to assemble all software routines into a software application that will gracefully accept patch or whole cell experimental designs and run multiple CPU's for as long as it takes to simulate all the actions implicated in the experiment. Much progress has bee made towards this end , about 4 man years worth, but it will take approximately 2 more man years to complete a user friendly package. There also remains the continuation of the large task of taking in thousands of scholarly articles of raw data, and normalizing it to model standards, so as to build a library of ready-to-use parametric values for cell types, actor types and realistic physiological conditions.

As theory establishes feasibility of constructing liquid state processors, then follows is the development of production techniques. Each of the elements must be manufactured in economic quantity and tested for longevity in the environment of their duty. As elements are to be installed in particular micro-array lipid-embedded configurations, there is work to be done in assembly, materials compatibility, stability and “learning mechanisms”. An exploration of variety of types will discover which are optimal to certain utilities: membrane shape, actor placement, interfacing planes, sealing liquid compartments, and unit protection. Some of the specific tasks are:

1. Lipid Membrane synthesis
2. Pattern recognizing Ion gate synthesis
3. Ion pump synthesis, novel power sources
4. Switchable catalysts, to serve as receptor/transducers, synthesis

5. Microarray technologies employed to embed actors into membrane
6. synthetic hormone pumps
7. synthetic neurotransmitter pumps
8. actor location fixatives
9. peroxide driven pumps, light driven pumps, ATP driven pumps
10. ADP phosphorylator
11. quick release mechanisms for output particles
12. quick recovery of output particles
13. staging mechanisms for particles to be released
14. programming stochastic processors
15. learning mechanisms for stochastic processors
16. membrane edge interfaces and intercoupling
17. protein lifespan studies and longevity enhancers

Ultimately, product architecture is made significant by the ordering of tasks and priorities it yields. In particular, such ordering of actors that effect flow control. However, all chemical relationships within the cell contribute to order, and only a systems approach will optimize the designs.

The human nervous system is thus engaged in producing yet another nervous system. Solving problems in an environment of streaming data channels forces the consideration of abandoning batch processing and its subroutine calls, for "continuous flow" computation. Real time designs have advanced toward this goal, as has parallel processing. The HAD computers are necessary to carry "continuous flow" processing to fruition. And, of course, the Liquid State Information Processor is a molecular-scaled HAD.

The Liquid State Information Processor receives secondary information relayed in from sensors, processes the flows of such information; intermingles these flows with other flows being generated by "neurons" exhibiting "memory" of past patterns; and by convolving these two streams to generate a third stream of information that feeds to motor, chemical and/or electrical outputs. These outputs may conspire to build houses, bridges and space ships.

Information processing may be encapsulated as the conversion of available sensible input data into such actions determined to be of benefit. Determining what is to be deemed beneficial is a task meta to the processor and may prove to be the more difficult design challenge.

One of the essentials of biology is the nano-management of resources, organized to the end of striving and thriving. The promise of biomimetics is to reach near-ultimate finesse of the process in the middle; between the "read" on the environment and the "write" on the environment, with a happy individual in the middle.

12 CONCLUSIONS

12.1.1 NEURONS ARE HADs (reaffirming earlier conclusions by others)

In contrast to the analog nature of the particle positions and velocities, particle bindings to actors are discrete events and therefore constitute asynchronous digital operations. The conformational changes in membranal proteins take place when the charged termini of the arms of radical groups of amino acids jump from one neighboring opposing charge to another nearby opposite charge. This occurs many orders of magnitude faster than the neuron generates action potentials, and so may be considered as instantaneous for purposes of modeling information. These very discrete-state objects none-the-less open channels which allow the flux of ions through them, varying in quantity as a function of concentration gradient and charge gradient. Thus the digital device yields an analog output. This output directly alters the analog nature of particle positions and velocities, which brings us full circle. All of this implies that membranal systems are Hybrid Analog Digital (HAD) systems.

Note that the actors carry systemic information in its differential form, and the particles carry that information in the integral form. The channel opens a valve (a discrete process) which allows the passage of ions through its pore. The amount of ions passing is not determined by the channel, but by the sum of two pressures: local voltage gradient and local concentration gradient, the sum of these two times the open time. One may argue that the change in voltage gradient is determined by a discrete number of charges passing through the ion channel, but their positions are continuously changing, and their acceleration is continuously changing. A faithful representation of the information flow, once again, requires the HAD perspective.

The analog portion presents the options, and the digital portion makes the decisions. Recall that decision means "to cut down". Iteratively paring down large numbers of input streams into fewer and fewer decisions, typically leads to a singular decision of the cell, i.e. the presence and timing of the action potential.

12.1.2 ACTOR STATES CONTAIN COMPLETE INFORMATION OF THE SYSTEM

Actors include Receptors, Channels, Vesicles and Pumps. The set of conformation States across the entire Pool of Actors, stationary to the membrane, is the Full Information of the system. The particle positional system and the actor state system are in series. The entire information of the system throughput must pass from free moving particles to the actors. Therefore whatever passes through one must pass through the other. It if does not, the information dissipates and is lost into the background noise. There may be losses along the way, but such losses cannot be considered as part of the throughput. There may be redundancies along the way, but redundancies neither add to, nor subtract from, the information of the system. (That certain parallel elements increase precision and reliability, and therefore are not truly redundant, is acknowledged.) Therefore, the throughput information passed by the particles is equal to that passed by the actors. This is especially true during propagation. It is less so for pre-axonal processing, where each iteration may filter, or otherwise condition, the information. A more general statement is: Given an iterative series of steps, consisting of alternate particle movements and actor state changes, each prior step must contain an equal or greater amount of information than its next downstream step. The modification to this rule would be at the merge points, where two streams of information are processed into one: The set of prior steps must contain an equal or greater amount of information than the subsequent step.

12.1.3 PARTICLE POSITIONS CONTAIN COMPLETE INFORMATION OF THE SYSTEM

The Positional Pattern of the Pool of Free-Moving Particles in the System is the Full Information of the System. To capture a snapshot in time of the neuron information processing system might predispose one to argue that the sum of the actor states, plus the sum of the particle states, equals the total information of the system. However, the information of the particles is in series with the information processing role of the actors. All of the information of the particles must be transduced into the conformational state of the actors, or else be lost in dissipation. Thus one is redundant to the other.

Three-dimensional closed compartments can be simulated to contain any quantity of particles with mass, radii, and charge. They may be initialized with random positions and realistic velocity distribution. They may collide with each other and with the container walls. Momentum-conserving collisions self-maintain the Boltzmann velocity distributions if care is taken to eliminate the aliasing error of digitization. Particles may be caused to become bound

and unbound stochastically. They may be transported from one compartment to another. The positional patterns of all of the particles at any one instant in time is the informational state of the particle system. This information is crucial to the neuronal information processing function.

There are two types of particle information relevant to this model: Concentration and charge field. Accurate renditions of conditions local to each channel and pump determine the requisite model resolution. The charge information is nullified for the vast majority of particles located away from the membrane, beyond the zeta distance in the volumetric regions of "space charge neutrality". There, they may still contribute information of value on concentration levels, albeit at frequencies lower than relevant to action potentials, and they may also participate as a buffer to absorb excess particles and provide particles in shortage, as they come about resulting from membranal processes. The vast majority of charge information, if not all of it, lies within the zeta potential zone on either side of the membrane. Therefore the critical ionic information may be modeled by merely identifying the charged particles within zeta distance of the membrane.

Because ions have mass but no internal state changes, position plus velocity constitute the informational state. Charge and mass determine the accelerations. Radius and density determine the collisions rates. As these latter four values are constants, they may characterize systemic behavior, but they are not information.

Particles, *de facto*, represent an image, internal to the cell, of the space-time continuity of the external world. To act as an analog to the environment, there need only be a one-to-one mapping of external events to internal events. Take for example, the retina receiving light that is arranged by a lens as a one-to-one mapping from environment to internal states. The particle release pattern, created as a space-time image, then flows along membranes between actors. This movement is an analog process in the sequence of information flow, determining lag time and strength of signal to ever more distant actors. Ion flux may be considered as an analog process in its creation of voltage and concentration pressures, and as a digital process upon any ions binds to or dissociates from an actor. The particular directions and confluences of ion flux are determined by sources, shapes and sinks. Although this is antithetic to the thermodynamics of the cell, the sources of information are typically the channels, and the sinks are the pumps. Ion channel flux rates may vary from 1E1 to 1E8 ions transported per opening. At the small end, the analog nature of the flux may quite distinctly grainy, but the fact of their immediate commingling with the ion pool within the lasma[22]

[22] lasma = defined as a state of matter, liquid except acting as a plasma, with a flux of like-charged particles that due to their repulsion and mass, produce wave-like phenomenon rather than diffusion. Lasma is only known to

reinforces their analog nature. Particle pools integrate information, while the actors differentiate it. It is the nature of pools of particles to act integratively to the addition and subtraction of particles.

Because of the temporal nature of the information, and because analog time is mapped in space over the length of the neuron, there is no convenient way to get a "snapshot" in time, that captures an input pattern going to resolution. The perspective of "solving a problem to get an answer" understates what neurons do, as the accommodate a continuous flow of input streams from thousands of neighbors and process it into a single decision stream that gets distributed, albeit somewhat out of phase, to thousands of neighbors.

The use of the word "complete" is weak in the following sense: In a serial process all of the information in one stage must have been passed on to it from the previous stage. But there may be loss, modification, and/or creation of new information within each stage. To the extend of these changes, each stage is not a true and complete representation of each of the stages upstream of it. However, to the extent that there are no parallel alternative paths for information to pass that support the splitting of information into partials, then that stage is receiving as complete of information as is possible within the constraints of function of the cell.

12.1.4 PARTICLE SYSTEMS EXHIBIT EMERGENT BEHAVIORS

Free-moving Charged Particles will exhibit Emergent Behaviors. A particle system can accurately represent diffusion patterns and rates, flow through channels, capacitance along the membrane and "resistance" due to ion collisions with water. When particles possess charge, capacitance is emergent from the N-body electrostatic problem about any charge barrier. Because charged particles drift within a diffusing solvent, 3-dimensional current and flux are emergent.

The original intent of this project was to create a hybrid model of diffusion, actor kinetics and the electrical grid of the capacitance and resistance effects of membrane and saline. However, development of the model has resulted in the diffusion portion of the model subsuming the electrical grid aspects as emergent properties, with no computer programming to induce them. The electrical grid concept is useful in verification work, but no longer necessary to the models ability to replicate the information processing capabilities of living cells.

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exist in symmetry on either side of a charge barrier membrane, and thus is a surface effect, not volumetric.

Furthermore the lasma state of matter (capacitated ions in solution behaving as a plasma) has subsumed all of the charged particle diffusion, as the EM force does not allow unbalanced ions to diffuse. Only charge-balanced ions in Space Charge Neutrality can diffuse. Unbalanced ions accelerate towards the charge barrier, then organize into a mass-spring grid that behaves as a second order system. The interactions between the EM force and thermal force depend upon charge concentrations, with higher concentrations tending towards lasma and away from diffusion. Increases in temperature make the lasma layer thicker but weaker, tending towards diffusion. However, be reminded that the EM force is immensely greater than the thermal forces, and will dominate charged particles.

Wave propagation around the channel openings is emergent due to the EM force and charged particle mass, which together produce an oscillatory system. Because of these effects, signal propagation, *per se*, is emergent. Such signals will decay per the standard RC filtering effects unless active processes along the path renew the signal strength. Certain ion channel and pump distributions serve to accomplish such signal boosting, and may also reinforce the directionality of signal propagation (e.g. dromic opposed to antidromic action potentials). In such a system the primary determinant of signal propagation velocity is the ion mass. The lightest ions available, sodium, will propagate the fastest. This poses a phase problem for the chloride ions on the opposite side of the membrane. As chloride has twice the mass, they will lag the sodium. This will result in a lateral "stretch" of the distances between the charge pairs which in turn can weaken their organization.

Voltage gradients are emergent as the differential in charge densities across a barrier, and express as a net force of acceleration on all charged particles. Current is emergent as the net velocity of charge. Resistance is emergent as particle collisions which disrupt drift. Flux is emergent as average particle movements per type. Ion species move in spatial-cycles (loops). These are emergent as a function of ions being moved against their gradient by pumps, then moving down gradient along the membrane until arriving at channels, which sporadically open and allow down gradient flux across the membrane, followed by further down gradient lateral motion along the membrane from channels to pumps. Ionic loops are sustainable so long as the model is constrained to conserve mass and the pumps are within their physiologic range of operation.

"Space Charge Neutrality" within liquid volumes is emergent. Completing electrical circuits is accomplished piecemeal by the various sporadic channel openings, the relatively steady transport by pumps, and by the many temporal discontinuities being buffered by membrane capacitance. In electrical circuits, we speak of "completing

the circuit", failing which no electrons flow. Without the capacitance of the membrane, the pumps could not pump except during the sporadic nature of channel openings, and the quantity of ions through the channel would be limited to the precise number pumped during that interval. Such is the mandate of "completing the circuit". Thus, capacitance is crucial as a source and sink for channels and pumps alike, allowing each to function out of synch with the other. This same membranal capacitance buffers the timing information of channel openings such that very little if any of it is "observable" by the pumps. This suggests that the pumps may not be participating in the fast time constant information processing of the channels.

The ionic valance values that express as acceleration in the N-body problem, do not justify the treating of the EM force acting upon the K+ ion any differently from the EM force acting upon the Na+ ion. The origins of the voltage effects on channel flux lie in the drift velocities of certain ion types. The concentration effects on channel flux lie in the higher probability of being at or near the pore when the gate opens.

Molecular Dynamics is the natural compliment to Particle Systems, in that its conformations are as specific as the Particle System positions and velocities are specific. However, the computational load of Molecular Dynamics in a model of this compass in this model would be enormously intractable. The choice to represent actors as kinetic schemes is an abstraction that is not capable of emergent behaviors. If actors were modeled in Molecular Dynamics, then emergent behaviors could be revealed. Indeed Because to the simplifying of internal molecular states to kinetic schemes in this model, the instantiated state number must be mapped through a phenostate table to determine its impact upon its surround. Phenostates are artifacts of this particular method of abstraction of molecules. The current complexities of channel pore energy barriers and elaborate ion selectivity mechanisms imply that the kinetic modeler will not be able to do Molecular Dynamics sufficient to see flux through ion channel pores as emergent. Rather, a compromise is struck that calculates the ion flux through the pore via conductivity tables times the sum of the two forces (concentration and voltage). Partial voltages are not emergent, and so must be calculated. Although channel current could be emergent as a perforation, it must be filtered by ion type according to the conductivity profile, and so in this model it is not emergent. The selectivity filters in the channel pores are executed via the conductance profiles. This insures that the proper number of the proper types of ions pass through an open channel. Then the local concentrations above and below that channel, taken one type and a time, are employed to calculate the Nernst voltages. Taking into account particle velocities, particularly gradients, may help to see voltage as emergent, via the drift it induces.

In summary, emergent properties are pronounced and clear in a particle system model. Without any programming to elicit such, all of the above phenomena occur. The only forces are thermal and EM, particles only move, and actors only change state.

12.1.5 CAPACITANCE IS CONTINUOUS BUT NOT MONOTONIC

Modelers that tessellate the membrane capacitance into discrete units disrupt the wave signals between channels. The capacitance must be left as a continuous sheet enclosing the neuron to support the mass-spring grid effects of concentrated like charges near the membrane.

The original modeling plan included an RC-grid to handle the electrical aspects of the neuronal function. To accomplish this the membrane was to be divided up into areas surrounding each channel and pump, similar to a Voronoi tessellation. The electrical conductors were to connect each actor to its nearest neighbors via saline above and below, represented by resistors determined by tonicity and distance. Thus, the capacitors and resistors were discreet, consistent with a finite element approach. Finite Element Method approaches are superior to the aggregate analytical equations, but fragment the continuity of capacitance that is crucial to its wave transmission role.

The modeled particle system displayed behaviors that suggested the above plan incorrectly represented what particles in solution actually do. Neither the capacitance of the membrane, nor the conductivity of the saline behave as electron conductors. Ions a more massive, and much larger. These two traits conspire to slow down ionic drift to a much more chaotic and local phenomenon. Very little if any current commuted via the saline. The saline only acted as a store for spare ions whenever they were needed. The current actually commuted along the membrane as capacitated ion. The repulsion between like charges is the force that drives a wave of ions along the membrane, radiating outward from the source very much like those resulting from a stone dropped into still water. There is a certain amount of thermal noise concurrent to this activity, and at distance the various ripples tend to cancel each other out and blend into the background chaos.

All charge imbalances were strongly driven by the EM force towards a membrane, or through a pore towards opposite charges. Thermal noise was sufficient to produce a layer of bouncing charges with an exponential decay of charge density with distance from the membrane. As there was no charge imbalance within the saline, there was no

force to move current through it. Whenever like charges pile up more than one layer deep in capacitance, there is a strong EM force squeezing some charges laterally outward, just as a swell on water would do.

The inertial effects of ion mass are significant. Combined with the repulsive forces between them and the attractive forces from across the membrane, the ions form a mass-spring grid. This grid then oscillates when perturbed, tending to produce rather sharp wave fronts (steep rise followed quickly be a steep fall) which expand radially. The particle collisions that are not contributing to the wave front tend to randomize the wave components. At some distance, depending upon voltage, charge quantity, and temperature, the wave will dissipate into the thermal noise. The key to a successful propagation is that the signal shall arrive at nearest neighbors with sufficient strength to trigger them to act. There are a number of ways to prevent this from happening. Weak initial strength; high noise levels; multiple competing waves out of synch the sum of which lose the sharp rise and fall necessary to trigger certain channels; destructive waves from other sources that cancel the wave of interest; increasing the distance between available actors so that the signal is too weak by then; arranging the neighbors to be in refractory periods just prior to the wave transmission; chemical modulators at the receiving channels which reduce their receptivity; etc. are some of the ways to thwart propagation.

Models which interpret the conductivity between channels as resistance of the saline baths may be incorrect. Models which treat capacitance as discrete electronic capacitors, one per ion channel, may be incorrect. Models which ignore the mass of ions, treating them the same as though electrons may be incorrect. Models which assume that the means of communication of ions from channel to channel is by diffusion may be incorrect.

Capacitance is the conductor from channel to channel. The saline is not. Capacitated ions make a unique conductor, in that they are not resistive and dissipative, but rather act as a loss-less wave transmission medium.

12.1.6 IONIC WAVES, NOT DIFFUSION, COMMUNICATE BETWEEN ACTORS

Ions Communicate Between Channels via Waves. Consider that a function in most computer programs consists of input arguments, internal command functions, then output results. We write: [args_out] = function_name(args_in); In such a command syntax what is inside the function is hidden. To observe that we must “open up” the code. This arrangement is suggestive of concepts of “self”, wherein there is boundary, inside of which is self and outside of which is other (or environment). It can be argued that to make a decision, some nonlinearity must be employed.

There are nonlinearities in space (e.g. cell membranes) and nonlinearities in time (e.g. action potentials). A nonlinearity, by definition, is a disruption from the smooth flow of continuous space and time. Although there are many forms of, and uses of, nonlinearities, for purposes of making a decision, it is usually a pulse or a step.

The neuron easily fits the pattern depicted above for a function. It has input args (receptor bindings of neurotransmitter particles). It has an internal set of operations that are enclosed within an object (the channel/membrane/pump ensemble). It has output args (vesicular release of neurotransmitter particles). Of course, any system could be framed by such a simple scheme. The main concern is: what processing operators are active within the function? We want to open up the code.

Let's take that concept and drop down in scale to the individual actor. So far we know that receptors often feed signal into some amplification mechanism. The amplified signal modulates some number of channels of a particular type. These channels, so modulated, change their open/close patterns. Although the channel conformational changes are internal to the molecules, they may have a phenotypical effect upon their surroundings, depending upon the available energy potentials adjacent to the channels. If a channel moves to the OPEN state AND there is a pressure differential across the channel pore such that the channel can allow particles to pass through, THEN the passing of particles is an INTEGRATION of the channel OPEN time. Thus time was converted to quantity, just as an hourglass sand clock does. These new quantities are information, because their movement alters the pressure across the membrane. Such altered pressures can be “read” as modulator function values by other types of channels. Modulation implies that those altered pressures will alter the open/close patterns of certain other channel types. If there is a non-zero pressure gradient across the channels, once again there will result in flows of particles through the pore of these channels. Quantities flowed are the integral of channel open time. Perhaps more subtle, the peeling off from the pool of particles of a single particle to bind and modulate an ion channel is an act of differentiation. There is a symmetry involved. That which is integrated must be differentiated to complete the cycle. The differentiation here is a peculiar one. Out of a pool of particles, one is selected to bind. This binding removes it from the pool of many types. What information does it contain? It contains two types of information. First it is the answer to the question: What is the difference between the pool before binding and the pool after binding? Second it is a sample from the probability distribution function of the pool. If repeated (and indeed it is repeated voluminously), then the samples construct an accurate and complete probability distribution function of the pool.

Then there is the matter of integration. In simple integration, information is lost. An individual known entity is added to and mixed into the bucket of other entities. The many become the one. Information is diluted and diminished. If the particles spewing out of an ion channel simply diffused three-dimensionally then this would constitute an integration resulting in lost information. The neuron cannot afford this. It is clear that the ion concentrations above and below the membrane contain crucial information that is in series with the channel responses to that information. Therefore it would be inefficient in the extreme to allow that information to diffuse away and become lost.

What actually happens at the membrane is that ions proceed like a fountain to spew outward from the membrane surface then immediately become drawn back to the membrane by the EM force, where their opposite charges are capacitated. Then opposite charges are neutralized by those recent admits. Once neutralized, indeed three-dimensional diffusion takes place, and in so doing serves to remove them from the membrane. But the information remains as the "hole" or absence of a charged particle that was previously capacitated. Information is preserved as the remaining voltage across the membrane.

Next there is a matter of spatial information. If ions had no inertia, then the change in charge distribution would be a Gaussian distribution around the ion channel, as calculated by Green's function. It can be set up to proceed from a cylindrical pulse through a series of progressively flattening two-dimensional Gaussian "hills". However, ions do have significant mass, 23,000 to 40,000 times that of an electron for the main monatomic ones. Unlike modeling electrons, a model of ions must account for mass effects. When mass is added the response is not an exponential in time, nor a Gaussian in space. Rather, the response follows the wave equation, like dropping a pebble onto a still pond. The charge effects covering the surface of the membrane are disturbed, and a wave radiates outward in concentric rings, eventually "washing" across its neighboring channels. The information is contained in a temporal pulse, much like a radio transmitter radiating out a signal. Though the information is being radiated outward, information is not being diffused. Most of its temporal significance is preserved. The shape is preserved though the energy is being spread over an increasing circumference, thus reducing the amplitude in space and time. The decay curve is linear for the wave equation, not exponential.

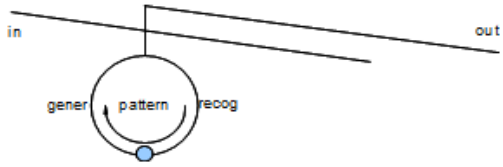

FIGURE 152: INFORMATION FLOW THROUGH AN ACTOR

The strength of the ion signal degrades linearly with distance (not an exponential decay). Ion channels have nonlinear response curves to these waves. There are regions where there is little response and other regions where the response is strong. As numerous signals radiate and commingle with each other, the net result is a mid-range, low amplitude "noise" to which most channels do not respond. It is only those strong signal amplitudes from nearby processes that elicit a response, and therefore informationally significant. Thus, the system acts as a filter, such that single distant channels can have no effect upon a given channel, but multiple synchronized distant channels that sum to a higher amplitude wave will radiate a taller crest reaching further actors with significant events. This ergodicity comprises a type of analog computer, where heavy weighting will influence other operations over a longer distance (radius). It should also be noted that the more distant responders are both weaker in amplitude and later in time. They cannot serve in the leading edge of the signal wave front. They only serve to bolster, widen and prolong the signal.

We can now assemble several of these operators into mechanisms that propagate an action potential or other signal through a neuron.

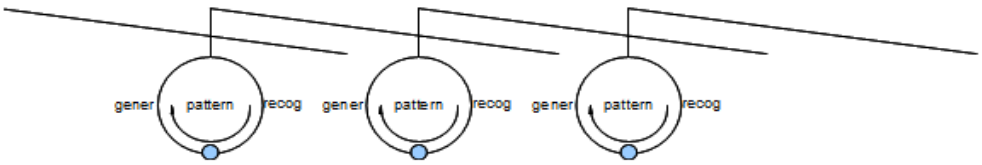

FIGURE 153: CHANNELS SPACED FOR ITERATIVE PROCESSING

The x-axis is intended to convey time, not space. Spatial signal propagation would be shaped as (looking from above) concentric circles radiating outward around each channel. There is a delay in the iteration process as the channel undergoes a sequence of conformational changes. If the iteration time is greater than the radiation time, then a neighboring channel will respond to the more distant channel that signaled at and earlier time, rather than the

nearest neighbor. In a highly repetitive arrangement, the sequence of events is iterative. This may effect such phenomena as oscillations, spiral trajectories, or tuning of the input signal into one of several possible output forms.

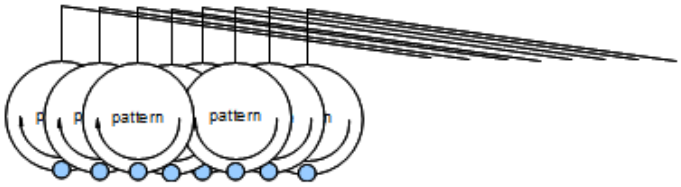

FIGURE 154: DENSELY CLUSTERED CHANNELS OF SAME TYPE

Under these conditions, it is expected that dense clusters of channels would need to be all of the same type, (or a few types so tightly coupled they act as one type) else the characteristic patterns of signal processing would be muddied by the overlaps. In such a homogenous group, they act more as one large channel, though the signal may be somewhat smeared spatially and temporally. It has leading thresholds the energize its forward movement, and lagging refractory periods that close up the rear.

Integrating for a composite wave front is trivial, but how are we to access its information value? If we accept one wave front as one bit, then we have returned to the simple solution of the early integrate and fire models. But the fact that a neuron must on average have as many outputs as inputs, and that these outputs cannot be in perfect synchrony nor co-located the same spatially, indicate there must be a spatial-temporal output pattern for each neuron. Apparently this pattern is not fixed, but may vary with the mechanisms by which the signal was initiated and modulated along the way. The ability to direct which regions of the output field are sent a signal is a strong form of information processing. It differs from digital machines in that every synapse would not be individually addressable.

At its essence, a placement pattern of actors embodies information 2-dimensionally, as a spatial pattern, and as an implicit temporal pattern, the response curves of each of these actors. These actors comprise the fixed set. Then there is the dynamic set, the ions. The interaction between these two is a spatiotemporal convolution. We then may speak of convolutional coding in regards to the information processing function.

Spatially, the ion concentration ratios by type across the membrane leverage channel opening flux. Temporally, they will stimulate, compete with, and ultimately respond to the response grid of the fixed structure as they wash over.

The interactive result must be a new pattern. If the responses were only positive (excitatory) then two patterns convolving would produce a smoothed version. However, if the patterns are mixed positive and negative, then the convolved pattern may be arbitrarily different from either of the originals, perhaps without loss of detail (no smoothing). To generalize, one spatial-temporal pattern convolves with another spatial-temporal pattern and in so doing creates a third spatial-temporal pattern. This certainly qualifies as computation.

The membranal system is a “neural network” in the small; a sub-neural network. To sharpen or otherwise process the input signal, both positive and negative effects must be present. This predicts the presence of complimentary pairs of actor types (e.g. Na and K channels). This also explains the ubiquitous presence of the sharp excitatory response followed by the duller, elongated negative response, both temporally (e.g. action potential) and spatially (e.g. surround inhibition), in the neurophysiological literature.

12.1.7 PARTICLES PROFILE THEIR SURROUND VIA RAPID COLLISIONS

Particles develop relationships with their environment equivalent to decision making. Particles in the liquids of a living cell are moving sufficiently fast to negotiate billions of collisions per second. Each collision is an opportunity to do some chemistry. In a rich environment of biologic systems, there may be thousands, or even hundreds of thousands of types of molecules accessible for collisions. At these high collision rates, a probability distribution emerges which will display the large number of types interacted with proportionate to time spent there. All those collisions that were nothing more than elastic will show as zero values on the probability distribution. Of all the possibilities, some collisions are more prone to binding than others, and each binding has a life span. Therefore, the particle will have a life history of fractions of time spent with one or another binding relationship. When all of the data is recorded, a given particle type will have a “preference” profile as to how it spends its time in a given environment. Metaphysical though it may sound, the particle's ability to sample and move on to sample all the others is in some way equivalent to “deciding” where to spend one's time, or setting one's priorities. This is not to elevate the particle to some high state of intelligence, but rather to question whether or not the supposed higher intelligence of the mammalian nervous system might not be acting out what is merely lower level mechanisms of particle explorations and bindings. So long as there is a one-to-one mapping between outside entities and internal entities, outside movement and inside movement, then nervous tissue can simulate reality, run scenarios, and choose among them. The one-to-one mapping need not be perfect. The mapping arrangement may be chaotic looking. But

so long as the linkages come to be weighted in a fashion that reflects useful aspects of reality, then such an arrangement can display intelligent behavior.

12.1.8 PARTICLES HAVE "SCHEMES" TOO

Just as the actors (large stationary molecules with significant conformational states) can be abstracted into so called "kinetic schemes" so to can the modalities of particle flux patterns of movement between actors be characterized into common patterns of heavy re-use. Just as actor conformational state paths form duty cycles, so to each particle type has its duty cycles. A particle typically goes through cycles of drift below, transport, drift above and re-transport. If particles should become sequestered or otherwise bound or delayed along the route, then those constitute additional states in the path. Because most of the observable actions of particles have been in the analog mode (diffusion and drift), it is likely that any information processing being performed is literally analog processing. presumably because there are too many variables, and because the needed mensuration is not yet developed. Contrast this with the actor state changes which are known to be very much digital events. The requirements for such include that the ionic system be of a type, stable in form and predictable in behavior. The kinetic scheme of actors is justified by the extremely fast jumps from conformation to conformation, allowing these events to be treated as digital. The initiation of such transitions is the result of thermal collisions, breaking bonds which are defining the current conformation. The speed of conformational change is driven by intra-molecular charges, which exert superordinate force until a new configuration is achieved. This allows the molecule to be treated as being in only one of the several possible states (as found experimentally). There are presumably many conformations which are either improbable or insignificant that can be ignored in the model, so as to conserve computational load.

With ions in solution, there are no such jumps to discrete formations. Rather, flux is continuous in time and space. However, there are recurrent patterns of ionic flux, some more probable than others, and others quite improbable. This is a form of logical fluidics, with switching effected by actor behaviors. From these patterns it must be possible to calculate the likely outcomes and assign probabilities across the set of particles. The system of particles is driven by digital events, and the resultant behavior (flux) is deterministic (Ohm's Law). Therefore it is reasonable to characterize the resultant flux patterns for any given neuron type as a discrete set with one-to-one correspondence with the actor state set. This is complicated by the presence of more than one actor type, and by the plaiding pattern

of actor distribution, but the concept holds. There is a further matter of time constants to respond to actor events, but thanks to the strength of the EM force, this is adequately fast to treat particle modes as discrete.

Although the ionic flows are continuous, the actual binding events at the actors are discrete. Each actor may be modulated or transport a fixed number of particles each event (e.g. pump cycle, or channel opening). One ionic flux pattern will result (statistically) in certain (discrete) actor impacts. These impacts are justifiably the phenostate of the discrete "kinetic state" of the particles. Each such abstraction is only valid for a particular neuron type, shape, actor placements and tonicity-pair. Accordingly, particle kinetic schemes would not be as portable as actor kinetic schemes. However, they do offer the potential for a great reduction in computational load if they can be pre-calculated at build time, then simulated as a lookup table or PDF instantiation during the run.

In the realm of digital modeling, types are a given. With a concrete quantity of types, there must be a finite number of modalities which particle systems will exhibit when exercised across their parametric domain. Each of these modes is originally created by the full simulation of ballistic particles and their interactions (collisions and binding). For each type of neuron, within a range of shape variations, these modes should be abstractable for their information value in the same way that only a few high runner conformations are abstracted as significant for the actors. Getting all aspects into the same data structure and functional procedure realizes even greater computational efficiency by avoiding the conversions of bases between Newtonian and Kolmogorov representations. Then the model can be computed in bulk so as to fully utilize the computational horsepower of super computers vastly reduced administrative swapping of tasks and major portions of the logical fabric in wait states.

Such an approach realizes a huge reduction in computational load for the repetitive aspects of modeling intra-neuron events. It furthermore brings the model to a condition of higher consistency, whereby all elements are abstracted to the same level (state transition matrices), rather than the hybridization of several levels. This has the advantage of allowing a given computer to simulate a much larger (more complex) neuron than otherwise it would be capable of. It also has the advantage of rendering the complete model as a singular manner of representing physical phenomena.

Metrics for the utility of such an approach are yet to be developed.

12.1.9 CHANNELS QUENCH AN INSTABILITY WITH ANOTHER INSTABILITY

Dangerous Positive Feedback Loops may be Managed with Instabilities. The ability of a neuron to "make decisions", to integrate many inputs into a single output pulse train, the ability to effect signal repeater stations (e.g. the nodes of Ranvier), and the ability to create refractory periods after each pulse, all employ positive feedback loops. Positive feedback loops that allow the in-rush or out-rush of ions are potentially lethal to any living cell. That they should evolve at all is both awesome and scary. How can any living cell insure against the mistake of leaving an ion channel open too long, enough to bleed to death? A mechanism of instability (internal conformational instability) is the cure for external instability (explosive influx of Na into the cell). No engineer was ever trained to cure an instability problem by adding yet another instability! From the point of view of engineering, setting up such processes is as awkward as trying to propel a boat forward by opening leak holes below the water line through the hull at the front of the boat! Theoretically, at least, this would convert the force due to gravity into some small lateral motion due to inertia of the water rushing in. The small lateral gain would seem to be far out-weighed by the large loss of gradually sinking the boat. And so pumps must be added to bail the dredge overboard. The neuron is doing something just as peculiar when it punches holes in its hull to allow leaks, just to gain some horizontal movement of the ions along the membrane. Pumps are definitely required to avoid death by such "leaks". The ion pumps are known to cycle up to 1000 times per second. The highest known capacity pump moves 3 Na+ and 2 K+, giving us up to 5000 ions per second transport. But ion channels are known to admit millions of ions in a single brief (0.1 second) opening. Thus, either the pumps must outnumber the channels thousands to one, or else the ion channels must be restricted to very low duty cycles, less than 0.1% open time. This may explain the evolution of the refractory period, which prevents the channel from opening for several tenths of a second. Preventing the channels from prolonged openings is an absolute prerequisite to staying alive.

Nonlinearities are essential for making "decisions". Perhaps the ancient Greeks understood this because the word means "to down cut" (or in English syntax "to cut down"). Cutting is certainly a form of nonlinearity; an act of reducing many possibilities down to fewer (or one) possibilities. It is a "management" activity, a type of information processing function. Nonlinearities may be achieved by many different mechanisms, but neurons create them via positive feedback loops involving voltage. A voltage sensitive sodium channel (as is typical in the Hodgkin Huxley model) may become perturbed enough to begin opening the channel. But such openings allow the in-rush of Na ions into the cell, which alter the voltage across the channel, which in turn further perturb the channel

to open even more. This must be stopped. And how is this dangerous instability terminated in a 100% reliable manner, this crucial closing of the leak? By adding yet another instability! The inherent stochastics of the actor conformational changes that open the channel are very unstable. Statistically, they can only stay open for several milliseconds before the molecule transitions into a more stable state. The solution, therefore, has been to design the open state as a very unstable state, and the closed state as very stable. This implies that biology has "invented" a cure for instability: by added yet another instability - in series. The extrinsic particle inrush which creates an instability for the whole cell is checked by the intrinsic instability of the actor conformations that cannot maintain the open state more than a millisecond or so.

12.1.10 ACTORS RECOGNIZE PATTERNS AND GENERATE PATTERNS

Single molecules of protein are capable of Temporal Pattern Recognizers and Temporal Pattern Generators. The stochastic nature of the various kinetic schemes being submitted to modelers as abstractions of the *in vivo* actors lead inevitably to the conclusion that channels and pumps are not merely exponential response curves due to first order differential equations. The Hodgkin Huxley approach of fitting one exponential curve fit per channel subunit, for a number of reasons, falls significantly short of capturing the information processing capacity of the channel.

1) the Hodgkin Huxley equations only represent aggregates of large quantities of channels. They cannot imitate a single channel. This is roughly analogous to insisting on representing a silicon CPU chip by averaging all the transistor flips into one smooth response curve. Surely the information processing has been sacrificed in order to collapse the response via integration into the much simpler calculation of an average activity. Quantitatively, 200,000,000 bits corresponding to 200,000,000 transistors (gates) are collapsed to say a 100 point response curve. That is but a tiny portion of the original information (0.00000050). This ratio of information collapse depends upon the quantity of types of channels, the ratios in quantities of each type, and the number of states in the kinetic schemes for each type. It may well be that living neurons employ a high degree of redundancy in channel function, especially in transmission, where signal propagation and preservation are presumed paramount. But we cannot say the same for the upstream soma and dendritic arbor are processing information. Please be reminded that transmission, by definition, means that no information processing may take place. That is, no modification of the signal.

2) the Hodgkin Huxley equations are silent on the conformational states that are not expressed as changes in gate position. The kinetic schemes, culminating from two-step voltage clamps, reveal that there may be many closed states, several open states, and several refractory states. The distinction between these is significant because they each have distinct frequencies resulting from their transition probabilities. These transition probabilities determine the response patterns of the actor to varying conditions. Multiple states imply multiple responses.

3) The Hodgkin Huxley equations are deterministic. They do not support, nor allow, any variability in response. Therefore, they reduce the nerve to an automaton. It is known, however, that the actors are not deterministic, and that stochastic processes are necessary to mimic the behaviors of individual actors. Actors are necessarily stochastic because of the thermal energy bombardments to which they are continuously exposed. Stochastic behavior is informationally significant for a number of reasons. It allows actors to exploit timing patterns and group gradations that would not be possible using deterministic processes.

4) It is the nature of the kinetic schemes of actors (and indeed the biological actors) to exhibit patterned behaviors that serve the cell and the organism in some useful function. To provide a service, the kinetics may not be reversible. A simple reversible process would simply undo what it did each cycle, with a net zero progress. To provide a service, there must be some directional bias to the state transitions. Transition probabilities can be found that predispose the actor toward progressing through states in a cycle.

5) Thermodynamics requires that to repeat actor cycles in a non-reversible manner some energy or escapement must be provided that "resets" the Gibbs free energy of the actor from its entropic resting state back to energized starting plateau. Then the sequence of states thereafter can be a cascade down in energy content. This energy source may, however, arrive as an ATP, a thermal collision or some other extrinsic event. It is also possible that energy be injected into the cycle at more than one node around the loop. These energetics are expressed in the kinetic schemes as probabilities to go down hill are far larger than the probabilities to go up hill (energetically speaking).

6) state transition cycles need not be fixed in their nodal makeup. There may be alternative pathways, back slippage, hold states and other forms of path variance.

7) The totality of a set of transitions that constitute a irreversible cycle implies that the first half of a cycle is by a path through states different from the second half of that cycle. This is significant., because it implies that the first half of the cycle will have some optimal resonance pattern; and that the second half will have some different optimal resonance pattern. This is profound for three reasons. First, it implies that every actor is a pattern recognition device. This is so because there is some optimal input pattern which maximizes its response, state transition by state transition. Second, it implies that the "second half" of the cycle always generates a pattern in time. The transitioning from state to state according to probabilities also determines the likely speed of transition. A series of various intervals constitutes a rhythm. They will not precisely repeat, but there is a dominant theme. And the summation of a few such dominant themes can present arbitrarily precise and repeatable results.

We have already established that for each actor there exists a phenostate table which maps the states to their impact on the surround. The existence of any one or more dominant patterns of state change sequences (rhythms) implies that the series of phenostates will be driven by that rhythm, and therefore also have a rhythm, though usually simpler. Thus actors are pattern generators.

Thirdly, because the input resonance is on a different state transition path from the output resonance, each actor is a pattern processor (mapping device). While most people are familiar with the phenomena of resonance, fewer are comfortable with higher order resonances, which might be easier conceptualized as pattern matches. It is significant to the capacity of bio-computation that individual molecules can respond to one or more input patterns by emitting one or more corresponding output patterns. Such pattern conversion constitutes information processing of a fairly high order. Each actor, therefore, is unto itself a computer. It is measured that state transition probabilities may change with changing environmental conditions. This may serve useful in mechanisms of homeostasis. The question is: for each actor type, how many distinct input:output pairs are there within physiological range?

If a 3-note pattern is found in a naturally occurring actor type, it would be comparable to a minimum of 200 transistors and 200 memory bits to match that digitally (in practice quite a bit more, as this number only allows distinguishing 5 input values over 10 timesteps in and 10 timesteps out, with 2 possible modes, when in continuous time many more are possible). That constitutes an IC chip within a single molecule!

12.1.11 SYMMETRY IS FOUND BETWEEN ACTOR EXTRINSICS AND INTRINSICS

The many complexities of biology can cause an investigator to “loose sight of the forest for all the trees”. Attempts at systematizing biological chemistry quickly grow to include hundreds of species of molecules and elaborate conversion and transport mechanisms. To model these many-fold phenomena within a singular model often results in a “spaghetti bowl” of relationships that require large-scale bookkeeping actions that may rise in quantity as the square of the number of elements.

It therefore came as some surprise that the many concepts of the model, after years of attempts to organize their various relationships, led to a simple symmetry between the actions of freely moving monatomic particles (e.g. ions) and stationary complex molecules (e.g. channels and pumps).

While there are many downsides to the forced digitization of phenomenon that occur in continuous space and time, there is also one distinct upside. Every thing done within a digital computer is information. Information is defined as a change in state. Every possible action in a digital computer requires to move/set one or more bits (change their states). In continuous space-time, a ballistic motion can be thought of as one state. Momentum holds the velocity constant until impinged upon by an outside force. Throwing a ball in continuous space time is easy because there is only one state to initiate (velocity). But throwing a ball in a digital computer requires a lot of calculations. Every dt and dx is truly a change in state and each one must be calculated. All of this is information, which we use as a substitute for simple momentum effects. Digitization is equivalent to making observations of the real ball every dt, collecting information on it as a data series. Observations are equivalent to collisions. For example, you cannot see anything until you collide some photons off of the objects to be “seen”. Such collisions digitize otherwise ballistic trajectories.

In the case of modeling the information flow through neurons, at the onset it was not at all obvious what constitutes information in continuous space-time. Lots of things are happening, but some may be noise or not of consequent to the output signal. However, the very effect of digitizing it forces everything to be converted into information. The very act of digitization requires pondering which information is relevant to the model and which is not. Most information is discarded in favor of those necessary and sufficient bits that allow construction of a predictive model. Whether intended or not, digitization results in an (imperfect) extraction (parsimony) of information from a continuous physical / energetic / informational system.

When working with strictly the information content, rather than the physicality of the neuron, new and interesting relationships may emerge. Certainly those relationships that persist through both physics and information require differing perspectives to extract the desired aspects. Generally, the informative perspective will be the differential of the physical perspective. Follows is a novel perspective on the informational aspects of particles impacting actors and actors impacting particles. The fact that these relationships constitute a closed loop infer the opportunity and indeed the probability that an iterative cycle may be effected. Cutland in 1980 reduced all computation to recursive functions.(9999226) This loop might be thought of as a limit cycle, except that information is inherently novel, and such novelty will alter the shape of the cycle in unpredictable ways.

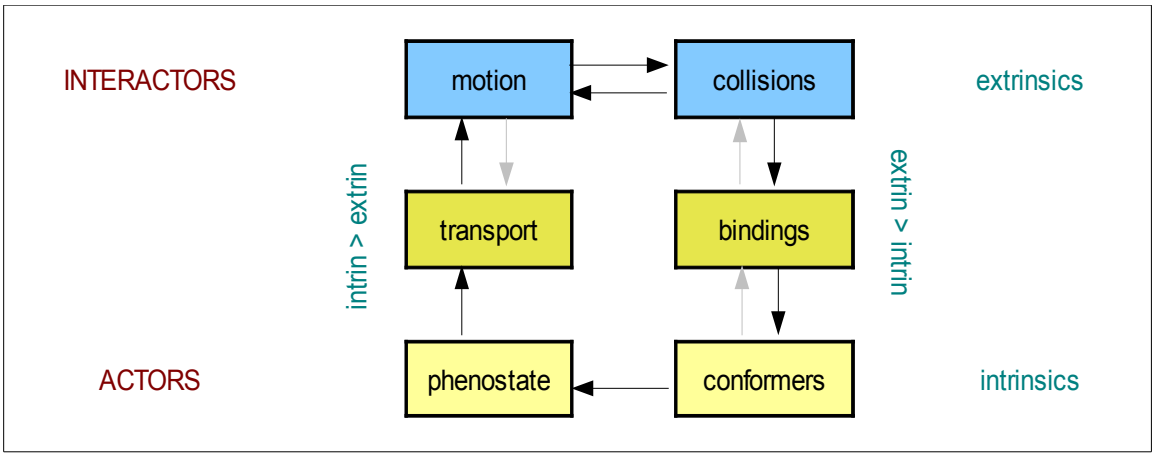

FIGURE 155: EXTRINSIC-INTRINSIC SYMMETRY, PRODUCING INFORMATION ITERATION

As for sources of each of the above processes, motion and collisions were developed in physics; transport and bindings are covered in physical chemistry, cytology and pharmacology ; and conformers and their expressions are covered in neurophysiology, and molecular dynamics. However, collisions were elaborated upon in their own right by computer graphics. Bindings are elaborated upon in pharmacology. Phenostates are developed in genetics, as "phenotypes"

Proceeding clockwise:

1) To calculate collisions requires conservation of momentum in three dimensions. But to detect collisions in a digital computer where there is no continuity of space and time requires heuristics. And it was the field of computer graphics that is tackling those heuristics for purposes of physics based animations. While physicists usually treat collisions as elastic scatter, in aggregate, or as hyperbolic orbits, it was the computer graphics people that took each

collision as a whole art unto itself, and explored the nuances of detection and resolution. One must by their processes consider that collisions were transformative and imparted information.

2) Granting that bindings are inherently a process of chemistry, the pharmacologists were enamored with the fact that a singular molecular binding can effect a fan-out cascade of changes, dynamically complex, that can have very large effects upon the whole biologic system. Witness the power of hormones.

Granting that conformers and enantiomers are a major concern among biochemists, it is the new field of molecular dynamics that allows us to see a large molecule go through its motions in a probabilistic fashion over its degrees of freedom. The MD simulations present as movies with molecules "dancing". Their movement sequences imply that real information is being conveyed or somehow processed as temporal patterns. Information is altered by various ligand bindings, which bring about different patterns.

3) The modeled molecule requires a set of calculations for its internal state (conformation) and another separate set of calculations for it effects upon its surround. That is, in the information realm, as opposed to the physical realm, these two processes are separate: reaction with self and reaction with others. Components of self are fixed in number and therefore comprise a matrix of fixed size to represent the atoms and bonds of a given molecular types. But when the molecule interacts with its environment, there is no fixed size for the possibilities, as it must respond to what ever impacts it from the outside. The former is a closed system and the latter an open system. This distinction is well exercised in genetics, where the genotype is an intrinsic trait and phenotype is its extrinsic expression in its normal environment. Varying environments may well alter the "expression". Just such a concept was needed for the digital representation of the actors, where first the internal state must be determined, and then the consequences of that state, if any, upon the external environment can be determined. For this secondary effect was coined the name "phenostate" .

4) In this subtle progression from conformational changes to the effects of those conformational changes upon the environment, the stationary molecule becomes a change agent on the environment. Obviously, an ion channel opening can result in a significant shift of concentration and charge on both sides of the membrane. Transport is most intensively studied in kidney, eggs, neurons, muscle, and lungs, though present in every living cell type. Cytology was first to tackle the interplay between structure, function and chemistry of cells. It eventually branched off Cell Physiology which continued the investigation of transport mechanisms. The contribution here is that

cytological transport is not like a mechanical pump or shovel merely moving commodity. It is specific to timing, ratios, and responsive to conditions. Such transport is serving more of an informational role than a materiel role. For example, one type of pump requires 3Na bound inside 2K bound outside and 1 ATP to provide the energy, to perform one pump cycle. Then there is another pump type that requires 1Ca bound inside and 3Na bound outside. If these two cycle alternately, then 2K move inward and 1Ca moves outward each cycle. Different combinations juggle the ratios of the various ion types. Ion pumps are as much logical devices as they are physical pumps. There is information in the requisite ratios, and how their comparative speeds result in different tonicities. Such transports are the intrinsics of the large stationary molecules impinging upon the extrinsic of the small mobile particles. For the brief time of transport, there is a marriage between the large molecule and the small particle. There is a transduction of information in this process.

5) When the conformation changes (due to thermal energy), there may or may not be an expression of that change externally. For example, if an ion channel changes conformation, it may or may not result in the pore opening. If the external effects of the protein are engaged, then the small mobile particles are forced to change states (change compartments). They then resume their motion, albeit in a new location.

6) For the particles, a change in state is a move to a new compartment. For the stationary molecules, a change in state is a different combination of modulators. For the particles, motion is the result system energy levels, and collisions are the use of that energy to “communicate” to the inside world. For the stationary molecules, conformational changes are the result of system energy levels, and phenostates “communicate” to the outside world.

Therefore, the symmetries are:

1) Extrinsic motion of the small particles is symmetric to the intrinsic motion of large molecule conformational changes. Both are driven by thermal energy. Both are modified by charge effects (particles accelerated and actors discretized).

2) Small moving particles colliding with the large static molecules are attempting to influence the large static molecules. We can think of this as an “observation” by the stationary molecule about its surround. Collisions then are an “expression” of particle movement. Without collisions the small particle movements would go undetected and remain unto themselves. The symmetry is that the large stationary molecules “express” themselves by

impinging upon the particles. Without this effect the conformational changes would go undetected and remain unto the molecules themselves.

Particle motions are ballistic until they make themselves known by colliding with something. These “detections” may result in a change in status or not (binding, unbinding). In a sense, the particles are acting as change agents upon the stationary molecules. When they bind with a static large protein, there is for a time a marriage between the extrinsic motion of ions in solution with the intrinsic “motion” of conformational changes inside the large molecules. For the duration of the binding while the two become one, there is a transfer of information of the particle spatial patterns into the large molecule internal states. Strictly speaking this is a place code, because the location of the particle determines which actor it would bind to. Then that actor is modified marking the place of the particle. As a marker, it preserves this place code, persisting a while even after the particle may unbind. Such bindings usually cause conformational changes, and also bias the probabilities of various conformational changes. Obviously, where actors are widely spaced, the resolution of the place code is low. But it is more than a place code. The type of particle determines the type of modulation that will be imparted to the actor. This also is a transduction of information. So we have a place code and a type code for the particle, captured within the actor.

3) A particle collision with an actor (stationary molecule) may result in a binding to that actor. Such bindings usually effect a conformational change in the actor, and as such have a modulating action. Notice that such bindings are initiated by the particle, by virtue of its individual motion. The symmetry is the that the actors may act to bind and transport certain particles, and in so doing effect a state change for the particle. Notice that such bindings are controlled by the actor, by virtue of its mechanism of pumping or channel opening. Both sides of the symmetry appear as bindings, but from an informational point of view, the controller and controllee are swapped.

4) We may also note that a) the particle ballistic motions and collisions make up the extrinsic operations; b) the conformations and expressions (phenostates) make up the intrinsic operations; and c) the modulator bindings and particle transport make up the interfaces (conversions) between intrinsic and extrinsic operations. An operational symmetry is present between the differentiation of the moving particles by the stationary molecules, and the integration of the stationary molecule modulation states into the flows of particles being transported.

5) Implicated in this loop is that there is an “inhalation” process, when the extrinsic particle motions are transduced into an internal conformational state, followed by an “exhalation” process, when the phenostate is transduced into an external change in state for the particles. This is perhaps a novel perspective of iteratively processed information.

Referring back to the figure above, there are 6 operations that are the necessary and sufficient set to support an iteration cycle through them all, to effect a relationship between inside and outside, between self and environment. By relationship is meant an ongoing viable “conversation” during which each is being changed by the other. With the potential of iterative sequences, relatively simple processes can effect or create extremely complex patterns in space and time. In this sense, these elements effect a fractal mathematics. They constitute a generative function.

It may come to fruition that this approach offers a clean, easier way to teach, and to model, the complexities of cellular information processing. Hopefully, such an approach is conducive to perceiving and demonstrating the information reception potential, and information generating potential, of membranal systems.

The essential aspect of neuronal information processing is a highly iterative loop through a differentiation, then a pattern recognition, then a pattern generation, then an integration. This loop, spiral, or network cascade (depending on your preferred metaphor) cycle rate may be calculated. Where the action potential is initiated by voltage sensitive Na channels, then the time to propagate along the shortest contiguous path from origin until axonal termination, divided by quantity of Na channels along that path, yields the effective cycle time. The concept of cycle time is different for the nodes of Ranvier which employ high concentrations of Na channels in the nodes, and are very sparse in between. In such cases, many of the channels are acting more like a single large unit, rather than as a cascade or network of units. It must be appreciated that to some extent this is also true for other areas of membrane where there are high channel densities. The cycles are present, but in high, overlapping packing densities, the propagation wave tends to ride over the actor cycles, the way a school child rides over the rollers in that certain kind of play ground “slide” constructed of closely placed rollers all the way down.

Is it possible then that the outputs of close-packed cycles are too slow to alter the leading wave of the propagated signal? Usually not. The wave speed is directly dependent upon the reaction time of the Na channels to open plus the diffusion time to the next channel. That implies full cycle between neighboring channels unless diffusion is faster than channel opening. In that case, the down stream channel is actually responding to the upstream channel, with the middle channel only serving to “fortify” the signal. In transmission lines, where no change in the signal

pattern is desired, over-packing the channel density does not change the shape of the action potential. It simply lengthens the stretch of myelinated axon that is feasible by putting out a higher current. But in graded response areas, pattern overlaps might be problematic. Wherever pattern recognition is desired, channel density needs to be low enough and refractory periods long enough to avoid the creation of muddy signals. Temporal patterns require sufficiently long durations of quietude upon which to overlay their signal without distortion. Therefore refractory periods and cross inhibition are desirable features of such an arrangement.

12.1.12 ACTOR CONSTELLATIONS IMPLY SPATIAL FUNCTIONS

Channels and Pumps can be positioned into patterns over the neuron membrane so as to effect specific mathematical functions. Whether one wishes to add, subtract, multiply, divide, exponentiation, integration, differentiation, lag, perform second order fits, third order fits, and so forth - merely the positioning of two types of ion channel are sufficient to perform any one of these. It is deemed to be novel that by rearranging the existent set of channels, one might be able to cause the neuron to change its function, mathematically and biologically. The motion of ions in aqueous solution over the statically positioned channels and pumps constitutes a convolution process.

There are, other ways of accomplishing various mathematical functions. Shape is highly determinant of the way a spatiotemporal input signal will be interpreted.

Perhaps the easiest way to intuit how this might be so is to consider the slide rule. One set of relative positions is slid over another set of fixed positions. The convolution of the two positional patterns yields a third pattern, as a binary mathematical operator might do. The speed of the ionic wash is in play against the speed of the actor state changes. There will be synchrony or asynchrony, depending on the spatial pattern match and the phase match. Synchrony can build and sustain the signal, while asynchrony can serve to filter this signal out. Iterative treatments can tune for and select narrow signal patterns, and filter out “almost matching” signals.

The slide rule analogy applies more closely if we treat the center slide as stationary and the two stator bars as the moving part. Then tic patterns above and below are analogous to the dynamic ion positional patterns, and the center bar is analogous to the membrane with actors embedded. The tics on it are equivalent to the fixed actor positional pattern, but they do not capture the actor internal states. Different scales solve different problems, and accordingly, different ion patterns can present different problems to be solved. Merely by moving the tics around we can solve

the sin, the log, base conversion, hyperbolic tangent. square roots, etc. Each scale essentially represents an input to output map of values. And by this means any input curve can be mapped to a different output curve.

Three pieces of bamboo, with some black marks sprinkled along their lengths were sufficient to do all the calculations to deliver men to the moon and back. And this is a much simpler more limited arrangement of things than the patterns of actors and ions, and the dynamics of their intra-actions and interactions.

The neuron has a much larger dimensionality of processing potential than a slide rule. It has greater computational width and greater computational depth. Rather than a single line that determines the pattern, there is a wrap around the circumference of the dendrite, soma and axon, that also constitutes a pattern, be it homogenous or otherwise.

The ion channels read the ions by binding them. Depending on the surplus of similarly moving ions, the signal is absorbed at this reading (effecting an end of calculation, a transduction of information). The n-th ion channel "writes" a message in code as a temporal sequence, similar to Morse code, via channel openings. This sets ions off on a new wave pattern, on down the line to the n+1th receptive channel. Thus the computation is iterative. Iterations most commonly result in tuning. For example, a mix of frequencies may be iterated into a pure sine of the most dominant frequency. The digital nature of channel openings allows them to simulate any arbitrary wave shape merely by the timing sequence.

The depth of the processing power concerns what order of differential that the actor state transition paths can uniquely respond to. If the arrival of a particular particle initiates a state transition path, and at a certain point along that path another modulator arrives to alter the progress of that path, then that actor is responding to a first order temporal pattern. Similarly, if the path then continues to a different state which is especially modulated by a third timely binding, then that actor is a second order processor of temporal information. It is not yet known to what depth biological actors can process temporal patterns. It is established herein, however, that such pattern recognition is possible at the molecular level in a straight-forward manner.

With neurons, there must be an interaction between a sheet of ions washing over the actors, a response from the actors that eventually forces the ions into a new pattern, which is the "answer" as it washes on against the vesicle release mechanisms. It is far more likely , and necessary, for the neural membrane to work iteratively. As with a continuous audio signal passing through a digital amplifier, the calculations never end. They are cascading real-time

through the system, along prescribed paths. And as with the audio amplifier, it may not be necessary to effect radial changes in the signal, only some conditioning and removal of extraneous bits. The purpose may be to tune and amplify the signal, or to route the signal to the appropriate port.

With the variety of ion types we have several colors of charge carriers making their own individual patterns. Although this fact suggests large informational potential, we known that these signals are not orthogonal. Some pairs are complimentary, as K is to Na. Some act as the parity bit stream, as passive Cl is to Na and K net flux. It may be that the ion colors are sufficiently coupled that there is only one signal after all (one eigenvalue).

This neural signal is at least 2-dimensional. It is distinctly more than 2-dimensional in the dendritic arbor, where each branch is independent enough of the other branches to necessitate it being treated as a separate degree of freedom.

Continuing the slide rule metaphor to its elastic limit, the ions can be said to be "reading" the ion channels when the ion channels open. This necessarily alters the ion positions and patterns. Whenever there is a refractory period within the channels, then there is an enforced directionality to the wave being propagated. An "answer" is produced whenever a wave makes it all the way to the vesicles, which proceed to release an output signal to the synaptic cleft.

If we insist on looking at one spike at a time, then we can only find one bit of information. That would be like reading a book by focusing only on one letter at a time, with no intention whatsoever to "see" a series of letters as a word. To get the information out we must process long temporal patterns (whole words, whole sentences, whole paragraphs, whole chapters.) Each of these adds an order of depth. Information is organized thusly, in many layers of meaning, built up over time. A intact paragraph has a much higher information value than a random series of letters of the same length because of the nature of the code book. The uniqueness or surprise value of an entire paragraphs can be much higher than the sum of the surprises of guessing what the next letter will be. This is because S, the set of all possibilities, is far greater for the intact paragraph than it is for letter guessing. This is an extrinsic quality, not the intrinsic measure of channel capacity.

In the slide rule, the slider is a set of fixed relationships between tics. They all move as a unit. Not so with the ions. Every moment they comprise a different pattern. In fact their current pattern is the problem to be solved by the ion

channels. They all respond according to this pattern, interacting with their previous state, a kind of memory of its history. In this important sense, the ion channels are processing a temporal problem.

The ions, too, are responding to their previous state, reacting as a function of repulsive forces between like charges, inertial effects of mass and attractive forces from across the membrane. This would amount to straightforward wave phenomenon, preserving information as it radiated outward - but for the disruptions going on as channels open. Thus ions carry forward the memory of their past, but alter that memory somewhat with every channel opening. The channels may serve to strengthen the original signal (as in action potential propagation); may serve to diminish or quench it; or may serve to alter it into an entirely different spatiotemporal curve. Whenever one curve convolves with a second curve to create a third curve - well, that is certainly computation. An it is reasonable to pursue convolutional coding as a method for analyzing the results.

All the channels are simultaneously sampling the messenger and ion pool above and below; and reciprocally, all the ions are receiving pulses from the channels. This is analogous to solving simultaneous equations. Given that the fluid of ions and and the membrane of channels are both 2-d sheets, not 1-d bars, then it is solving a family of simultaneous equation sets at once. It is only the refractory periods which prevent such a system from degrading into a noisy feedback whistle saturating everything out. Such iteration can serve several purposes: tuning (sharpening), integrating (as additional branches join in along the line; amplifying (as the risk of some spatiotemporal smear; or serial processing step (where the channel mix changes along the line).

Ion channels are moving, gradually, all the time along the surface of the membrane. They are also being “pulled” and replaced regularly. The new ones are placed, but optionally may be placed slightly differently than the set before. Positional placements do vary over the cell's life cycle phases. But mightn't they also change with life experiences?

Changes in the placement patterns changes the function of convolution with the ions. The positional pattern determines what kind of math the neuron is doing (trig, logs, etc.). The rearranging of the pattern of ion channels can change the computational operation from add to subtract, multiply, integrate, differential, log10, log2, sine, etc. This is true even if nothing else is changed. It is not required to change the shape, nor the types of channels.

The upper and lower ion layers are sliders, and tend to be compliments of each other (resulting from through-the-membrane transport phenomena). Because of the complementarity, these two may be acting as a single mathematics function. A stator exists between them, the membrane with a pattern of actors. The Stator and the slider interact in a convolutional manner. The result is that both are altered by the interaction, but only the slider carries information spatially to the next processing station.

12.1.13 GENERAL ACTOR FORMS FOR MODELING PURPOSES ARE FEASIBLE

Previously, each species of membranal protein required an amount of custom modeling work. The great variety of biological moieties makes standardization of digital representations a challenge. Provided herein is a method for mapping biological information as parametric values in general software representations. Actors may be Classified into Classes, and Classes sub-classified into Types. (For example, Actors are divided into the classes of Receptors, Channels, Vesicles and Pumps. Pumps are divided into 8 Types of pump.) Each type is distinguished by a unique set of affinities, bind/unbind kinetics, conformational kinetics, conductivity profile, and transport equations. A small number of actor forms may populate shaped surfaces so as to mimic thousands of neuron types. Bindings are embodied as stochastic processes, and the binding combinations determine the instantaneous transition probability matrices for the conformational kinetics. Typically, these probabilities are dynamically altered by modulators. Transport is in turn determined as a stochastic process as a function of actor state transitions.

For example, a singular scheme for representing ion pumps, co-transporters and exchangers is presented, which can accommodate all of the bio-pumps found described in the literature to date. The great variations between pump types are accommodated by providing for binding and transport poles on each side of the membrane, then binding and transport profiles for each pole, including the binding of ATP and release as ADP. Modulation, as a function of binding combinations, which page of kinetics are in effect each dt. Effects of such modulation include reducing/increasing the efficiency of the pump, reversing the flow direction, resetting saturation limit, resetting its starvation concentrations, changing the error rate (alternate ion type pumped, pump runs backwards, or the pump pumps empty).

In similar fashion, a thorough stochastic treatment of receptors, channels, and the mechanisms of vesicle release, yields actor simulations which can be tuned to closely mimic the behaviors of their biological counterparts, over

multi-dimensional domains of numerous modulator combinations and high numbers of conformational states. They are not deterministic, so do not repeat same responses to identical stimulus. Each actor is instantiated in space and state individually, at model build time, and the state of each individual actor is re-instantiated each dt.

These Forms include binding probabilities across all the particle types present in the system. They express differently for each modulator combination, by altering the internal state transition probabilities. In complimentary fashion, they allow for the particular state of the moment to alter the binding kinetics of the modulator sites. They include a means of tracking which particles in particular are bound, and where. They include a means of tracking which particles are being transported and which pole they are at, therefore assigning particles to new compartments. They include a means of assigning each actor to a node on a membranal surface, including orientation. They include a means of instantiating each new state as a function of the prior state and the current modulation combination. They include a means to interpret the resulting state for its effect upon the immediate environment (herein called the "phenostate". They include a means of releasing messengers according to known quantity, ratio and temporal patterns and their variances.

With an appropriately sized dt, this method adequately captures the information content of each actor, but not the physicality. (Molecular dynamics simulations do capture the physicality.) The effects of varying the value of dt are accounted for, noting that increasing the dt in non linear systems at some point results in serious artifacts at wide variance from biological performance they portent to represent. The dt value can be optimized by sensitivity analyses on parametric value sweeps.

Note that the actors, by their bindings, select out only a representative few of the particles from the pools of particles above and below them. This is a differentiating function. The integrated pools of particles are differentiated to act as modulators upon the actors. This process is inherently one of information processing. And it is reversed when the channels open the "valves" to allow ion flux through them. The valve position is a differential to the flux. And thus the flux is an integration of the channel state.

12.1.14 DIGITAL GENERALIZATION OF ACTORS REQUIRES PHENOSTATES

Both the Internal and External State of an Actor may be Represented by a Unified Kinetic Scheme. Though many kinetics schemes in the literature are rather mixed internal states and binding states, the modeling of such requires

explicit and different treatments for each. The dimensionality of the internal states is found to be s1xs1xs2, where s1 = internal states and s2 = the possible combinations of allosteric binding (external state). Meanwhile the allosteric binding forward and backward reaction rates are altered by changes in the internal conformations. The external state space is found to be s2xs2xs1. It is therefor possible to join these by an s1xs2 interface into a single matrix of the size s1xs2x(s1+s2).

Whenever the states of an actor are abstracted into nominals, then the effects of such state numbers are arbitrarily ascribed by assignment, as pointers to the next function to be executed. Therefore, the outward impact upon the environment, (the output of a point process) is represented digitally not by the state, but by an additional table that maps that state into some outward effect. This secondary table is herein named the phenostate of the actor.

12.1.15 NEURON SHAPES REDUCED TO CONTOURS OF ROTATION

A method is provided for neuronal shapes to be simplified to contours of revolution while preserving the nearest neighbor relationships between actors, and maintaining cross sectional area profiles relevant to the neuronal processes. Radial vanes may be inserted so as to partition the dendritic cone(s) into sectors, creating an effective arborization of dendritic bifurcations and branches. Any bifurcation pattern may be accomplished by this means, with some compromise concerning the 3-dimensional pattern of attachment points on the soma (and elsewhere). Multiple dendritic cones alleviate this limitation somewhat. Vane surfaces within the dendritic cone are necessarily dead zones with respect to actor placement and transport, unless alternate interstitial spaces are provided that are contiguous with the extracellular compartment. For convenience, planar surfaces are provided to facilitate synaptic connections without the need for reshaping the mating surfaces.

12.1.16 ACTOR POSITIONS MAPPED ONTO ARBITRARY SHAPES

The plaiding patterns of channels and pumps may be explored and modeled using the 3-dimensional shape generators provided herein, which include a homogenous surface of loci for actor placements. The bio-data may be classified into functional zones, such that the distribution data is stored as a contour from the identified start zone through to end zone (typically from dendritic synapses to axonal synapses). This supports the “stretching” of the PDF (probability density function) to fit any arbitrary shape so long as that shape specifies equivalent zones. Each

actor type has its own PDF for a given neuron type. Therefore, a neuron type is defined, in part, by a set of actor PDFs. Once occupancies are instantiated, then measurements can be made to determine nearest neighbors, area of membrane serving a capacitance role per actor, equivalent saline resistance to each of the neighboring actors. It is possible to add, subtract or replace actors during the course of a simulation run, according to conditional events or to a development schedule.

Each PDF set corresponds to a (possibly unique) transfer function (nonlinear) for the neuron. It lays out the stationary pattern over which the ionic waves will wash and convolve. It is possible to reverse engineer a PDF set into its mathematical function,; or to engineer a desired mathematical function into a PDF set.

12.1.17 DESIGN OF ARTIFICIAL AND THERAPEUTIC ACTORS

Channels and Pumps may be Custom Designed to fill specific mathematical operations. The state transition probability matrices may be manipulated to accomplish any number of input patterns mapping to any number of output patterns, as stipulated by any combination of modulator bindings. Any number of internal states may be mapped to any form of external expression by those states. Therefore, in theory, channels, pumps, receptors and vesicles can be designed to serve in completely arbitrary custom roles. In practice the limitation of atom types and their fixed physical traits implying limited patterns in chemistry may not always provide for combinations that can realize the molecules with the hypothesized transition probabilities. It is yet to be determined whether nature has already exploited the combinatorial possibilities, and that humans will add little else to this list; or whether there are many not yet realized computational potentials that can be constructed of liposomes, synthetic channels and pumps, and induced synaptic connections between them. Given that the ocean tonicity was heavily determinant as to what was possible in evolving life forms, and that the periodic table offers 92 elements with which to build actors and artificial tonicities, that there must surely be untold realizable computing molecules and tonicity profiles for their surrounds.

While actors may be engineered at the kinetic scheme level, it will take molecular dynamics to determine which ones are feasible, or how close realizable molecules can come to matching the desired states and rates. A further challenge is to map the internal state behaviors to external functional role, such as pumping, catalyzing, releasing or gating. While the digital representations treat the genostates separate from the phenostates, real world

implementations make no such distinction. There, the phenostate is merely emergent from the genostate. Anticipating such emergent behaviors by design would require molecular dynamics modeling at a higher level, including the surrounding environment as a dynamic (information rich) space.

12.1.18 LIQUID STATE PROCESSORS ARE FEASIBLE

This Model provides a molecular basis for Liquid State Processors, and finds them feasible as Artificial Computational Devices. Liquid state processors operate by entirely different procedures and processes than those of solid state digital processors. A new investigation of computation is needed to characterize the potentials, limits and "programming methods" of such a distinctly different way of computation. The western world so takes for granted its Aristotelian logic, that it does not have a word for any alternatives.

In an important sense, the solid state lends itself to digital logic. Positions are fixed and the clock rate is usually fixed and synchronized across the gates. Logic is usually at its weakest when it forces the breaking up of continuous gamuts in a finite number classifications. But in digital machines everything must be made discrete.

By contrast, liquid state machines as characterized herein employ both continuous space-time and kinetic discrete time. The particle system is an analog space-time processor and the actors are kinetic discrete processors. Thus, liquid state processors are indeed hybrid analog/digital computers. As such they have the potential to solve problem types that digital computers fail at.

Liquid state computers can operate the analog space-time continuity portion of the computer for free. That is, it is driven by thermal energy acting in elastic collisions that consume no energy. The result is diffusion and drift. Similarly, the discrete portion of the computer is accomplished by conformational changes in the actors, and these changes are also driven by free thermal energy, with state changes precipitated by elastic collisions. However the directionality of those state changes imply certain energy injection. This comes via ATP or concentration gradients. Biological systems are found to be exquisitely efficient in their use of such energy sources and usually cascade the original transfer of energy into a long series of steps back down to ambient levels.

The liquid state is conducive to relativistic calculations rather than absolute. All particles are coupled in a liquid. In solid state processors, it is of the essence to decouple every transistor from every other. Hardware designers would

consider any such coupling to be “cross-talk” and a source of error. In a completely coupled system, however, it is the patterned response that is the information, and it is the solution to the problem. All that is necessary is to arrange things so as to mimic some aspect of the outside world for which problem solving of this type provides a useful service to the organism.

In the solid state, due to the complete uncoupling of each bit, any single bit can be arbitrarily more valuable and more powerful than other bits. Precision is created by generating one number to many decimal places of accuracy. The bit representing the largest decimal place in the “answer” is in most circumstances a lot more valuable than the bit representing the smallest decimal place. Even stronger contrast can be attained. The bit that turns the machine on an off is a lot more powerful than the bit of one dim pixel in a worthless little advertizement that the user doesn't want at all anyway. Errors therefore can be arbitrarily large, caused by arbitrarily small events, even a single bit change.

The liquid state is not bit-sensitive. In the liquid state, particles are far more democratic. Errors are within the variance of the normal operating range. Precision is created by narrowing the bell curve of responses ever tighter; accomplished by repetitive feedback.

A digital machine is discrete in time, and this carries over to the way it “learns”. It receives a concise set of instructions and executes them as perfectly as the machine is capable of, on the first time. It does so without reference to the prior problem and has no innate preferences in how the problem should be solved. The liquid state machine cannot do that. It begins with poor performance, and more likely reenacts the answer to the prior problem more than it does in getting the new problem correct. Repetitions are necessary to improve performance. Feedback is necessary to determine just what is desired in the response.

The liquid state is inherently recursive in its design. The process of signal propagation may be likened to a spiral of ion flux down the axon. What needs to be investigated is the relationship between dendritic signal flow, the spiraling of ion flux in the process, and the opportunities from genuine information processing along the way. Such information processing always implied because that ion spiral passes through the kinetics of the actors, which as discussed earlier, differentiates, pattern resonates, pattern generates, and integrates back into particle flux. This is a long way from the passive cable equation that is so often referred to as represented what dendrites do.

This project has not (yet) incorporated learning as described above, into the model. Learning can be easily added as a model feature, but should not be until all of the verification work for the main diffusion and kinetics engines prove out. Model building requires successful testing at the lowest levels first, progressively working up the complexity scale. This is necessary because if their is any doubt about the based functions, then error at higher levels of complexity become nightmares to isolate. This is that same curve of arbitrary bit power in digital computers. However learning can be accomplished by adding algorithms which capture messengers after use so as to count them. They could be captured only as coincidence pairs for Hebbian learning. The quantities could, via a lookup table, translate into changes in the number of actor types at each synapse according to use. Synaptic plug sizes could be made to grow and shrink. Pumps could be modulated to alter tonicities to support more active areas. Pumps could be moved farther away from the ion channels to induce axial flux. Various messenger particles could be released that alter the kinetics of certain channel types, including shortening their refractory time. Different subunit combinations could be caused to present themselves. The neuron could grow larger somas, lengthier dendrites and axons, form new connections to neighbors. Each of these is not difficult to add as a feature, to this model.

It is intended that such a modeling approach as this paper presents will support the deep investigation of this computational potential of neurons and of liquid state processors in general.

12.1.19 MULTISCALING FROM ION TO WHOLE CELL IS EFFECTIVE

Multiscaling is effective in reducing Computational Load. Particle systems that represent a real world cellular compartments entail quantities approaching 1E17. By iterative reduction in particle quantities, and in each step comparing the results to the prior larger quantity model, the total quantity of each particle type may be reduced to optimal levels for the desired error tolerance. However, for whole cell models this still may require 1E9 particle quantities.

In order to employ these whole cell models in connected networks of say, 100 cells, further reduction in the computational load is needed. The criteria of this project is that the information processing potential must be preserved. And this forbids many if not all of the prior simplification strategies.

One solution is to excise representative patches of membrane which contain such ratios and spacings of actors that if the patch were cloned and tiled across large expanses of neural membrane, that they would perform similar to the original membrane of the same size and location. This is not merely a problem of actor density; it requires that the patterns within the densities be accounted for. At the extents where such a tiling exercise fails to duplicate original behavior then another canonical patch must be introduced.

Because strict cloning of one patch type results in clone fields stitched together with sharp transitions at their boundaries, unrealistic artifacts are thereby created. This is remedied by creating gradient clones, by a method similar to point-to-point interpolation. Interpolating between patterns is not trivial, however, and the criteria of gradations must be chosen in advance. For example, for some cell types the distance between one channel type and another channel type may be fixed. They may be rafted together as diads or triads. A gradation pattern would therefore adjust the raft densities, but not alter the spacing within the rafts. This can be formalized by grouping the constituent entities of a raft into a single new entity, an ensemble. In any case verification of the interpolation fields across the parametric space via sensitivity analysis is deemed prudent.

The patch interpolation fields assemble into zones. Zones are the functionally distinct areas of the neuronal membrane. Zones of course share boundaries, and again, care must be taken not to create artificially sharp transitions when they are not biologically present.

Using two canonical patch types to generate of gradient of patches in between is also at high risk of creating unintended non linearities. In any nonlinear system, stability analysis is prudent to insure against creating nuisance artifacts merely for the convenience of short cuts.

If the excised patch is to provide a benefit it needs to yield results in isolation that can significantly reduce repeating those computations when large numbers of such patches are in situ in the whole cell model. This can be accomplished by three methods.

1) To the extent that radial symmetry proves to be redundant around the ring, then only one patch of each ring need be calculated.

2) Exercising each patch down to some minimum number of particles that preserves the information processing function of course reduces computation.

3) The main objective of multiscaling is to exercise each patch across its parametric space (which includes all possible input signals). This allows the entire patch to be collapsed into a look up table. In other words the calculations are pre-performed and the results stored for future reference as look up tables. If each canonical patch is parametrically swept and the results stored, then it becomes possible for the whole cell model to be reduced from a computational engine to a grid of look-ups. Caveats include that conditions going outside of the known response domain must trigger yet another intensive patch study; and that interpolations must only be attempted between canonical patches sufficiently similar that the interpolation gradients yield realistic outputs.

12.2 NEGATIVE RESULTS

12.2.1 EVENT BASED ALGORITHMS ARE INEFFICIENT

Event based *dt*'s are found by many modelers to conserve computational load when collisions are occasional. It was found in large scale particle systems that the overhead to detect events and rank order them in time was equal to or greater than the computational cost of a simple fixed *dt* simulation sufficiently fine to avoid ghosts. While variable *dt* and *dx* algorithms, as are common in PDE algorithms and FEM calculations, are certainly more efficient and accurate for individual equation calculations, such an approach has so far been found unwieldy for asynchronous equations across >1E6 particles and actors. The older conventional difference equations are not quick and are not small, but support processing almost everything within a few very large matrices. Doing so allows the internal algorithms of the compiler to optimize silicon resources. The models prescribed in this paper are first and foremost exploratory, not intended to be commercially efficient.

Real efficiency will not arrive until hybrid analog/digital processors become available (if ever they do). A major challenge for the future of computation is develop machines that neatly represent the continuity of space-time, as well as discrete decision processes. HAD computers could provide the single greatest improvement is simulation performance.

12.2.2 RESISTANCE-CAPACITANCE GRID REPRESENTATIONS THWART NEURONAL FUNCTION

The conventional circuits approach which lays out an R-C grid as a ladder filter proved to misrepresent neuronal function, because such configurations over-constrain the flows of ions (from 3-dimensional radiation to 1-dimensional signals). Though adequate for predicting axonal transmission, this approach disallows radial transmission and resultant wave forms. In also discounts the mass of the ions, which is a major determinant in transmission speed and in the dynamics of capacitance. It also reforms the capacitance such that the channel pulses do not spread evenly around the channel.

12.2.3 INCOMPLETE STATE TRANSITION TABLES

Though the biological literature is rich in actor kinetics and state transition data, it has proven to bee very difficult, as of 2011, to find a set of transition probabilities compete enough to model actor duty cycles without resorting to estimating over missing pieces. Evidently, the actors possess both phenostates and hidden states. The hidden states much be measured or otherwise derived before the veracity of this model can be established.

12.3 VALIDITY OF THE MODEL

There are two concepts to prove. First, that ions in capacitance along a lipid membrane can be disturbed by channel opening ion flux in such a way as to initiate a wave that carries information to other actors. Second, that single molecules of protein can detect temporal patterns in such a way as to elicit a distinct output pattern of ion gating.

The existence of charged particle waves radiating out from point disturbances may be proven by instrumentation that reflects photons off the surface of the charged layer during a disturbance. The pattern of reflection, projected upon a photon detector grid (e.g. CCD), will reveal the shape of the response to disturbance. The response found may be a Gaussian slump, as predicted by Green's function for processes of diffusion (a first order effect similar to the heat equation). It may be a radiating concentric ring, constituting a traveling wave (a second order effect capable of carrying information). It may be something other than these standard first and second order responses. Provided that the photonic wavelength is short enough (hard x-rays with wavelength less than 0.1 nm) set at a shallow angle of incidence for good reflectance, and provided that the grid resolution is fine enough to distinguish a wave pattern,

the reflected image will distinguish between these three possible responses. The challenge is to remove the saline overburden so as to yield a reflective surface near the charged layer of about 3 nm thick on each side of the membrane. Most of the saline might be replaced with oil to create such a surface. The difficulty lies with the charge density profile that decays exponentially from (0.0..3.0) nm away from the lipid membrane. For bare ions, most of the wave action will necessarily take place within the nearest 0.1 nm to the membrane. Only the tortuosity of the lipids, if any, will cause moving ions to "bounce" outward away from the membrane towards the reflective surface. Another consideration concerns the size of solvated ions. With a maximum of five layers of water molecules, their size approaches a radius of 0.55 nm. There is also the matter of undercurrents resulting in surface disturbances. How thick can the saline be, and still reveal a detectable disturbance on the surface in response to movement along the bottom 1 nm of that saline?

Indirect methods of determining radiating waves include signal analysis received at remote points. If, say six receptors surrounding the source point can detect a pulse following the stimulus of the source point, then we garner information on the speed of transmission, and the envelope of the wave (content of second order and first order terms). A planar grid of FET detectors could conceivably map the spread of any disturbances down to the resolution of the grid. As the waves are predicted to travel several microns, that infers an equal radius of the circular wave being propagated. Current technologies should be able to distinguish a radiating wave at some expansion point. Of course, the FET response times must be faster than the pulse rise and decay. Although the electrons in plasmons were clocked at infrared frequencies, solvated ions, due to mass values 100,000 times larger, must exhibit frequencies of less than 10 megaHz.

An alternative approach to consider would be a substrate of voltage sensitive dyes, which might detect a growing ring of voltage disturbance. There are trade-offs between spatial and temporal resolution in such dyes. A dye that is temporally fast enough to detect an ionic wave is likely to be spatially too course. Current fluorescent frequencies are at 530 and 630 nm, far too long of wavelengths to resolve ion channel activities. Even if the wave were detected along a propagation path of several microns, the image would be crude and unconvincing.

X-rays are too energetic to illuminate the delicate plasmon wave without severe disruption. However, a series of strobe shots can be executed, so as to take one picture per wave, but in a sequence of staggered timing so as to reconstruct the sequence of the entire wave.

Diaconescu B, Pohl K, Vattuone L, Savio L, Hofmann P, Silkin VM, Pitarke JM, Chulkov EV, Echenique PM, Farias D, and Rocca M, in Nature v 448, 2007.07.05 presented a proof that the existence of plasmon waves. They claimed that charges on surfaces behave like water on a lake's surface, and that these waves propagate up to a few microns. When a stone is dropped into a still lake, waves spread radially as growing rings. A similar wave can be created by the electrons on a metal surface when they are disturbed. Plasmons are proven to exist on solid surfaces but not yet on liquid surfaces because the experiment was performed under high vacuum. Plasmons have been regarded as a viable means of transmitting information, due to the fact that they can support high frequencies where other means are very lossy (diffusion degrades signal). The extension of this effect from electrons on a solid surface to ions on a liquid surface requires continuity of principles of dense matter (commonality between liquids and solids) and scaling to the mass and size of an ion, which will greatly slow down the velocity and frequency of the wave, but provide greater inertia to travel further. Mass and like charge repulsion predict such waves as a second order phenomenon, whenever a grid of like charges is disturbed. Soft matter physics addresses the superconducting quality of such wave phenomena. The work done to create the initial pulse is finite, yet the propagation effect continues nearly infinitely (the more regular the substrate, the greater the propagation distance). This effect is at the very least a quite efficient process, and some describe it as superconducting.

The second issue, protein kinetics, is founded upon the work of Colquhoun D, and Hawkes AG in the 1990's. They established the validity of kinetic schemes as the best available (at the time) representations of protein conformational changes, as relevant to channel and pump functions. The application of standard chemical kinetics to large molecules capable of reacting with self, predicts that there will be some quantity of significant conformations, usually 5 to 30 in ion channels, that determine the behavior of the actor type in its cytological role. As the field of Molecular Dynamics matures, its ability to model every atom and bond comprising an ion channel or pump will reveal the conformational processions in response to ambient thermal impingements, and in response to modulation events (voltage, bindings, etc.).

At this time, MD simulation runs are only for a few nanoseconds, despite that exercise of protein duty cycles will require milliseconds (a million-fold increase in computational power). The environment of the molecule being simulated is critical to the results. Workers report that molecular conditions, down to excruciating detail, can completely change the behavior of ion channels. Unfortunately, there is not much wet lab data available on the

immediate environment of each protein molecule *in vivo*. MD will need the support of such wet lab work to verify its assumptions in physics.

Of great interest would be experiments by Molecular Dynamicists that establish: the feasibility of molecular designs that require certain temporal patterns of modulation to initiate a duty cycle; the elucidation of molecular mechanisms of such protein molecules to generate a temporal output pattern (e.g. channel openings rhythm); and the extent to which channels can effect non-reversibility of its duty cycle without the injection of energy to drive its directionality.

In summary, it will be Molecular Dynamics, with the assistance of super computers, that demonstrate the internal workings of the ion channel molecules - given the constraints of the dense net of chemical bonds, given the impinging aqueous surround, and to the extent to which such phenomena can be engendered, articulated, and harnessed. This model's potentialities will either be found consistent with, or else disproved, by the physics of intramolecular order.

12.4 CONCLUDING DISCIPLINES

The evolution of the model led to certain of the initial efforts to dominate while others were found wanting, and eventually dismissed. In this model the complexities of the lipid mix within the membrane was simplified to membrane thickness. The vesicles were overly complicated in structure for their mission of information transduction. The RC circuit grid was overly constrained for representing a charged particle system, and was totally replaced by free roaming charged particles in 3-space. Without such structure the finite element approach was no longer needed. Three specialties were recognized as out of scope but useful for reference and sources: Computer Graphics for collisions detection; the chemistry of self-assemblying molecules for molecular order; and Molecular Dynamics for verification of the kinetic schemes. The very strong winners stochastic instantiations of actor states and binding; and Coulombic forces driving charged particle systems.

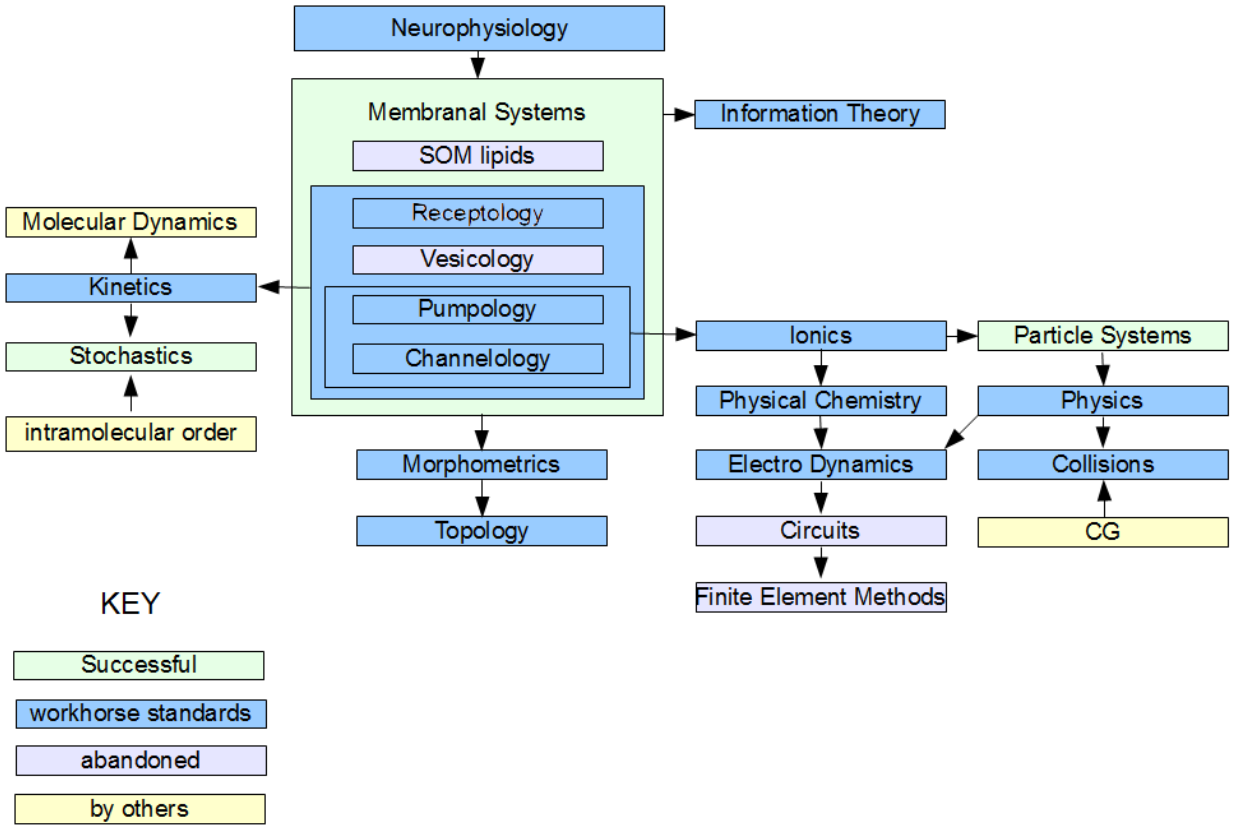

FIGURE 156: Disciplinary Map as built

12.5 FUTURE DIRECTIONS

12.5.1 COMPLEXITY OF PATTERNS

Neuronal ionic signal patterns could be observed to determine the extent they are generated by, varied by, and made complex by, actors. This would clarify the extent to which the stochastic conformational changes are exploited for their potential to recognize patterns and generate patterns. Are neurons processing these patterns at zeroth order, first order, second order, third order or more? Are there subtleties such that as an alternative to resonating patterns, actors can also block some patterns (via dissonance)? How well tuned are these pattern recognizers? Do they respond to anything close to a match or can they be very selective in the pattern they respond to? (equivalent to the Q-factor of electronic tuners) What are the implications for biology if it were quite possible to evolve deep complex pattern responders with in single molecules, but in fact none but simple first order

responders are found in nature? What are the common-place natural patterns to which neurons would have necessarily evolved to detect?

12.5.2 VALIDITY OF THE MODEL

There are two concepts to prove. First, that ions in capacitance along a lipid membrane can be disturbed by channel opening ion flux in such a way as to initiate a wave that carries information to other actors. Second, that single molecules of protein can detect temporal patterns in such a way as to elicit a distinct output pattern of ion gating.

12.5.2.1 Particle System representation

The existence of charged particle waves radiating out from point disturbances may be proven by instrumentation that reflects photons off the surface of the charged layer during a disturbance. The pattern of reflection, projected upon a photon detector grid (e.g. CCD), will reveal the shape of the response to disturbance. The response found may be a Gaussian slump, as predicted by Green's function for processes of diffusion (a first order effect similar to the heat equation). It may be a radiating concentric ring, constituting a traveling wave (a second order effect capable of carrying information). It may be something other than these standard first and second order responses. Provided that the photonic wavelength is short enough (hard x-rays with wavelength less than 0.1 nm) set at a shallow angle of incidence for good reflectance, and provided that the grid resolution is fine enough to distinguish a wave pattern, the reflected image will distinguish between these three possible responses. The challenge is to remove the saline overburden so as to yield a reflective surface near the charged layer of about 3 nm thick on each side of the membrane. Most of the saline might be replaced with oil to create such a surface. The difficulty lies with the charge density profile that decays exponentially from (0.0..3.0) nm away from the lipid membrane. For bare ions, most of the wave action will necessarily take place within the nearest 0.1 nm to the membrane. Only the tortuosity of the lipids, if any, will cause moving ions to “bounce” outward away from the membrane towards the reflective surface. Another consideration concerns the size of solvated ions. With a maximum of five layers of water molecules, their size approaches a radius of 0.55 nm. There is also the matter of undercurrents resulting in surface disturbances. How thick can the saline be, and still reveal a detectable disturbance on the surface in response to movement along the bottom 1 nm of that saline?

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Diaconescu, in 2007 presented a proof of the existence of plasmon waves on the surfaces of dense matter coated with a charge field, and perturbed with a moving point charge. [220] They claimed that charges on surfaces behave like water on a lake's surface, and that these waves propagate up to a few microns. When a stone is dropped into a still lake, waves spread radially as growing rings. A similar wave can be created through a field of electrostatic charges on a surface, via a point disturbance. Plasmons are proven to exist on solid surfaces but not yet on liquid surfaces because the experiment was performed under high vacuum. Plasmons have been regarded as a viable means of transmitting information, due to the fact that they can support high frequencies where other means are very lossy (diffusion degrades signal). The extension of this effect from electrons on a solid surface to ions on a liquid surface requires continuity of principles of dense matter (commonality between liquids and solids) and scaling to the mass and size of an ion, which will greatly slow down the velocity and frequency of the wave, but provide greater inertia to travel further. Mass and like charge repulsion predict such waves as a second order phenomenon, whenever a grid of like charges is disturbed. Soft matter physics addresses the superconducting quality of such wave phenomena. The work done to create the initial pulse is finite, yet the propagation effect continues nearly

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12.5.2.2 Stochastic Actor representation

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12.5.3 DEVELOPMENT OF LIQUID STATE PROCESSORS

Solid state electronics is reaching developmental limits with regard to miniaturization, clock speed, and heat dissipation. Further advancement in hardware will require a new approach. The miniaturization limitations are breached by exploitation of intramolecular order. The clock speed limitation is breached by asynchronous massively parallel processes. Heat dissipation is solved by avoiding energy consumptive processes, rather powering them by ambient thermal energy. Liquid state information processors combine all of these benefits.

First needed is membrane material suitable for micro-arrays of actors. The construction of liposomes is a known craft, performed by universities and pharmaceutical companies. The placement of specific types of large proteins, e.g. channels, has been accomplished in liposomes. Is it feasible to tether certain types of actors together so to determine inter-actor distances? Or can they be anchored to fixed structures within the saline? Where ever fixed distances are critical to function, or locational restrictions to certain zones desirable, stationary structure is needed nearby. Expected feasible is the continuous perfusion of ATP so as to drive the system energy cascade initiated by Na pump ATPases. Removal of the ADT is possible by micro-dialysis. For artificial systems, it may be advantageous to move the ATP circuit to the outside of the cell, similar to a battery or fuel cell.

It is expected to be more challenging to maintain the shape of the extracellular compartments and to establish the “proper” relationships between neighboring cells. It is expected to be difficult to cause liposomes to grow processes in some tropic manner so as to develop scheduled synapses according to prescribed connectivity patterns. Perhaps living neurons will need to be enlisted to generate such intricate and specific shapes and connections. Furthermore, each connection will need to be populated with vesicles, receptors and re-uptake pumps.

If living cells are to be harnessed for computation services, then a very lengthy list of housekeeping and developmental processes are involved. If artificial non-living compartments are to be used, then the initial construction will be challenging and the life span of components is yet to be investigated.

A theory of processing and programming is needed for this "new" type of processor. Similar to the challenge of quantum computers, there is an analog component and a digital component. It remains to be investigated if these two types of computing machine are in anyway equivalent.

A theory of programming an integro/analog/differentio/stochastic finite state machine has yet to be developed. Until such a theory is developed, programming such machines may necessarily be by machine training sessions.

The liquid state has several significant advantages over solid state processing. The essence of a liquid is that it possesses sufficient thermal energy to break all crystalline bonds (melt) yet maintain sufficient hydrogen bonds to render the fluid incompressible. This constant thermal motion is frictionless. Else it would cool down even if in a perfectly insulated chamber. This implies energy is only lent, not consumed. Thus the heat problem of computation is solved. These processors generate no heat.

For statistical reasons, not every molecule in a thermal mass possesses the same energy. The momenta are distributed widely and dynamically, with each collisions resulting in momenta changes. This combination of free energy and a mix of fast and slow movers allows any molecule the opportunity to filter its collisions, taking the fast ones to add more energy, and the slow ones to dissipate energy. This range of gauging energy in and out of the molecule supports the possibility of sequencing state changes up and down an energy "hill". Doing so can be arranged to give the duty cycle directionality. That is, a random process can be harnessed to drive a directed graph, if the geometry of its constituent transitions acts like a ratchet. This is possible even if only one of the steps acts as a ratchet while all other steps are reversible.

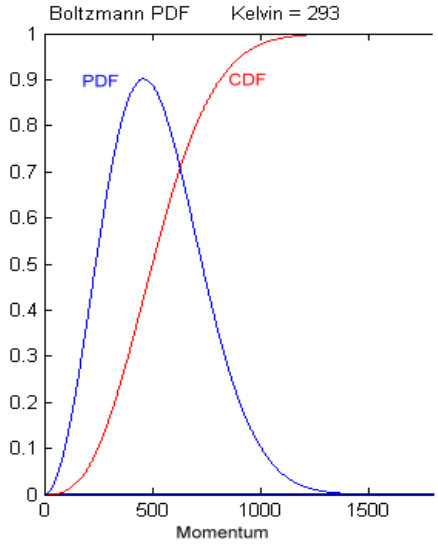

FIGURE 157: Boltzmann distribution

The impact force of a particle collision with an actor can easily vary from 0.1 to 0.9 of the energy range. The order of the atoms and bonds within the actor determine what will become of the energy impacts at the various momenta. Obviously, a state transition with a high energy requirement must wait, as such rarities arrive less frequently. Thus, the higher the energy requirements of the duty cycle, the slower the average cycle time will be.

Large molecules are also known to be stores of chemical potential energy (the Gibbs energy). This can be accumulated more easily (and faster) in a series of several small packets, rather than waiting for that 1 large packet.

Adding another layer of complexity, the outside world may participate in the the molecule's directed graph. Well timed modulation events can shift the state path to another route which may be more or less favorable to completion of the duty cycle. All of this is running on the free energy of the ambient thermal motion. Duty cycles, pattern recognizers, and pattern generators all may be designed to run on ambient thermal energy. Generally, information processing may be made to run on non-consuming ambient exchanges, but work requires energy.

Wait states are very common in digital processors because they are intrinsic to the process of central command. But in stochastic processors, all actors are running all the time. Such stochastic engines need no clock. They run asynchronously and constantly. The fact that they are not perfectly uniform nor deterministic grants them the ability to statistically fill in a graded response curve . The Hodgkin Huxley curves were smooth exponentials generated by a group of on-off gates. It is only the statistics of their state changes that ergodically generates the smooth response curves, quite accurately.

The fact that all actors are processing streaming inputs in parallel means that the information throughput is high despite the relatively slow cycle times (kiloHz rather than gigaHz).

Finally, the miniaturization barrier is breached by abandoning the fight against randomness, and rather embrace it. The Humberto Fernandez Moran 11 nm size limit, where all conductors go unreliable will never be reached by digital computers, because the error rate is already becoming intolerable at 25 nm. Yet, once the stochastic nature of molecules is understood and harnessed, very complicated pattern recognition devices can be built at resolutions below 10 nm. The entire machinery of a pattern recognizer and pattern generator lives in the 10 nm space that would not even make a servicable conductor in the silicon device. The price paid for such efficient use of space is redundancy. The stochastic pattern recognizing cochlea of the ear suggests that a redundancy of 8 is adequate, as it uses about 8 cells in parallel per tunable frequency. This is not a sacred number - redundancy varies with the tightness of the kinetic scheme and the system requirements for accuracy.

The graded response of entities that live in the space-time continuum possess some of the processing promise of quantum computing. Quantum computers are being built of 25 nm quantum dots sitting on solid pedestals. But they leak away their information and require elaborate error correction algorithms that cannot fix all errors. The biological approach is to take an active stance, to treat all data as flows. Errors are compensated for by adjusting the flows. There are multiple opportunities to adjust the data values along the course of the neuron.

12.5.4 LEARNING MECHANISMS, LIQUID STATE INFORMATION PROCESSORS

Learning mechanisms, though beyond the scope of this project, are the next logical step in model development. The current model can assist in significant ways towards this end by developing a successful static model of the pre-trained condition, then developing a successful static model of the post-trained condition. It is the difference between these two that requires a dynamic conversion mechanism. Such physical conversion may be accomplished by any of a number of methods: chronic modulation; relocation of pumps, relocation of channels, addition of more channels of certain types, replacement of one channel type with a different type, or removal of certain channels.

12.5.5 SYSTEMIC MODELS FOR CHANNELOPATHY THERAPIES

The nuances of channel function are sometimes detected by their absence in diseases. Channelopathies are numerous and responsible for many serious diseases. Huber in 2002 listed 49 such diseases.[218] These provide motivation to develop channel therapies, and provide insight into how channels work by the process of elimination.

As the specific kinetics the the R and Q matrices become filled in either by wet lab work or by Molecular Modeling, this model may serve to simulate tests of modifications and substitutions to channels and other actors for purposes of disease therapies.

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15 APPENDIX A: CODE

A. LIBRARY

1. TypeP: Physics.data
2. TypeA: all actor types and their traits: receptor+shuttles, channels, vesicles, pumps
3. TypeB: all ion types and their traits: monotomic, polyatomic, ligands, messengers
4. TypeC: all shape types: box, cones, cylinders, disks, perforations, spheres, tori, vanes, contours of revolution
5. TypeP: physics constants and conversions
6. DistA: pdf's for actor placements
7. DistB: particle velocity distributions; commonly found concentrations
8. DistC: commonly used shapes and their relationships
9. DistP: physical param sets for experiments , dt,qt,kelv,clip,sf, Fexpon, spreadsheetpointers
10. paths, filenames, sheetnames
11. get spreadsheet functions, spreadsheet pointers
12. TC: Import compartment types (may be as spreadsheet: Mem,Van,Plu,Act,Com)
13. Switch between cylindrical and cuboidal, (How about polygon x-sect of N sides?)
    Cuboid specified by [y z x1 x2 … xn], where odd #s = saline thk, even #s = lipid thk
14. TB: Import particle types from spreadsheet
15. TA: Create a cell structure from all actor type data: Affinity, bind/unbind, conformers, phenostate,conductivity, transport equations
16. TCico: Import icon data for compartments
17. TBico: Import icon data for particles
18. TAico: Import icon data for actors
19. plot params
20. hardware params

B. DESIGN

21. CT: select compartment types to be used; get Cdimension.data; based upon neuron type
22. BT: select particle types to be used. determine which traits are needed
23. AT: select actor types to be used. determine which traits are needed
24. DCinit: specify dimensions of compartments, with scaling factors
25. DBinit: Import particle concs from spreadsheet > N per unit volume
26. DAinit: Import actor distributions > N per unit area
27. ScalingFactor.data
28. Switch.data
29. SigGen: signal to be run during simulation
30. DFscaled: time, space, quantity, charge, particle radius, affinities,
31. DCscaled: final size and shape of compartments, envelopes, plugs
32. DBscaled: final quantities, radii, and charges on each particle, locations of start boli
33. DAscaled: final densities of each actor type, kinetic rates, affinities
34. Shape concatenation
35. Metrics, checks: volts, currents, gradients, divergence, curl
36. Experimental Design Package: lists all sources, choices and param values

C. BUILD

37. BuildC: from primitives: membranes, compartments, surfaces, volumes
38. BuildA: place actors, instantiate receps, channels, shuttles, vesicles, pumps
39. BuildB: place particles, free, bound, sequestered
40. CB: Create compartments boundary EQs from piecemeal boundaries: DC > CB.
41. CN: Create nodal grid on membrane surfaces from boundary EQs: CB > CA

42. BT: Create user choice short list of particles from menu TB > BT.
43. B1: Instantiate ions and messengers from menu, position and velocity as boli: TB > B.
44. AT: Create user choice of actors from menu TA > AT. Cell structure of:
    { Affinities, Bind kinetics, Conformation kinetics, Phenostates, Conductivities, transport EQ}
45. AC: Position actors on membrane via DIST using randomizer to density, with orientation
46. Ainit: initialize all actor states as a function of environment
47. B2: Instantiate B types that begin as bound to actors (neurotransmitters, hormones, ATP, etc)
48. BAinit: Position all fixed particles, as function of affinities and concentrations
49. BCinit: create boli of all particles
50. Aicons
51. Bicons
52. Aaff: affinity matrices
53. AR: actor binding matrices
54. AQ: set up actor state transition matrices
55. AO: state to phenostate mapping
56. Aerg actor energetics
57. Aeff actor messenger emissions
58. Ax actor transport rules
59. growth structures and functions

D. RUN

D1. accelerations

60. BBd = distances between particles and particles/actors/compartments
61. BBf = forces between particles and particles/actors/compartments
62. Bacc = accelerations
63. Bvisc = viscosity effects

D2. velocities

64. BB: Method of colliding particles, tracks paired hits, momentum xfer, reflection angles
65. BC: Method for reflecting particles, as table of hits, reflection angles
66. BW: particles to water collisions

D3. bind/unbind

67. AB: Actors affinity hemisphere occupants, bindings and transport
68. BA: Method of binding and unbinding particles to actors, as paired hits and releases

D4. modulation

69. RUN dB, particles for steady state to establish realistic concentrations
70. AS2: Actor binding sites to individual particles
71. ASinit: Initialize the states of the actors

D5. state transitions

72. AQ: Actor transition probabilities
73. AS1: Actor conformational state

D6. transport

74. AO: Actor phenostate opening and transport function
75. BF: force calculations yield: Bacc, V, V gradients, conc gradients
76. AX: Method for processing transport EQ

D7. Param Change

77. temperature functions, growth functions

D8. time loop

78. RUN dB, dA1: particles and pumps
79. RUN dB, dA2: particles, pumps, channels
80. RUN dB, dA3: particles, pumps, channels, receptors, vesicles, SigGen
81. RUN dB, dA4: particles, channels, receptors, SigGen, NO pumps

D9. SigGen

82. input signal series. patterns, musics, visual, spatiotemporal

E. REPORT

83. Capture data: Bpos, Astates, V, A
84. Plot routines (get icons, pos data)

85. Play Movie
86. Generate Report

FUNCTIONS

Functionalized process steps are as follows:

Ion tonicities are initialized to steady state concs in each compartment (tonicity profile), via:

```
Ccreate;        % create the shapes and position them
Cvolumes;       % calculate surfaces, volumes, and addressable nodes
Bquant;         % convert particle concentrations to specific quantities for each compartment and bind site
Ccenter;        % identify bolus injection sites free from membranes
Bplace;         % instantiate particles at boli, with velocities
```

ion diffusion in water, in each compartment – with charge, acceleration and collisions

```
Bmove;          % pos + vel
Bcollide;       % detect collisions   B x ABC
Breflect;       % execute detected collisions via basis change and momentum transfers
```

ligands concs initialized to steady-state concs in each compartment (modulation profile)

```
Bquant;
Ccenter;
Bplace;
```

ligands are released into synaptic clefts per input signals from pre-synaptic cells (or SigGen)

```
SigGen;         % converts temporal multi-channel signal so as to drive vesicle releases at synapses
SynLink1;       % maps outputs of neuron units to inputs of other neuron units
VesRelease;     % stochastic process to release vesicle contents per empirical distributions
```

ligands diffuse in water, in each compartment (3-d diffusion)

```
Bmove;
Bcollide;
Breflect;
```

actor affinity profiles activated, for ligands and other modulators (e.g. voltage)

```
Cnodes;         % takes metrics on nodes to determine if sufficient to implement actor densities in sum
Adist;          % maps general densities onto specific shapes
Aplace;         % instantiates actor placements to available nodes, including orientation
Ann;            % finds nearest neighbors to each actor
Acap;           % determines fair share capacitance around a channel or pump, via voronoi areas
Ares;           % determines equivalent electrical resistance to each nearest neighbor
```

ligand bindings to receptors, kinetics as func of concs and Q-modes

```
Aaffinity;      % as a function of actor state, was is each binding site's affinity for each particle type?
Abinding;       % D x B has a forward reaction rate as a function of actor state
```

actor Q-matrix changes mode per modulator combo

Volt2mod % certain voltage ranges switch the page in the Q matrix
Amod; % the present combination of binding site occupancies determines the page in the Q matrix
Asubstantiate; % actor state changes, per dt

phenostate type = {GatingFunction TransportFunction MessengerRelease VesicleRelease }

Aphenostate; A transport;

ligand unbindings from actors kinetically per concs

Aunbinding; % D (binding sites) have backward dissociation rates as a function of actor state

ligand “reuptake” pumps restore ligands to original positions, kinetically, per concs

Aaffinity;
Abinding;
Amod;
Ainstantiate;
Aphenostate;
Atransport;

receptors release second messengers upon ligand bindings (1:1 ... 1:200 leverage ratio)

Aload;
Arelease; (same as: Abind; Aunbind; Bbind;)

second messengers migrate along membrane (2-d diffusion)

ShuttleMove; % indexes shuttle through cycle

second messengers bind to cyclases kinetically, as a func of concs

ShuttleBind;
ShuttleReset;

cyclases enzymatically produce phosphates (rate = by the hundreds /msec)

ShuttleRelease;

phosphates diffuse in water (3-d diffusion)

Bmove;
Bcollision;
Breflect;

phosphates may bind to ion channels (phosphorylation) kinetically per concs

Aaffinity;
Abinding;
Bbinding;

modulation combos (including voltage) > Q-matrix change, Ion Channels

Amod;

actor state change, per dt

Asubstantiate;

instantaneous conductivity of ion channel G = channel gating function * conductivity profile

Agenotype;
Atransport;

Nernst potential + concentration potential drive flux: I = (E+C)*G

Nearnst1; % partial voltage of one ion type as it impinges on an individual actor
Nearnst2;

ion affinities to ion channels vary with gating function

Aaffinity;
Abinding; %
Bbinding; % bookkeeping for particles being bound, store old velocity, set new velocity to zero
Amod; %

ions transported through channels per I

Atransport; %
Aflux; %
Bcurrent; %
Bcapacitance; %

ions diffuse out of ion channels

Bunbind; %
Bmove; %

change in local ion concs (and by implication, change in local charge density)

Bflux; % metrics on grad, div, curl of each particle type

change in Nernst voltages

Bvoltage; %

change in Vm as weighted sum of Nernst voltages

GHKboltage; % GHK voltage is of limited use due to its steady state validity in a very dynamic environment
CoulombicVoltage % use this whenever possible, valid in dynamic case, and is temperature invariant

dV > change in capacitance charge > current in and out of capacitance I = C*dV/dt

CapCurrentV; % calculate or observe how many ions went in and out of capacitance, per unit area
CapCurrentH; % measure how many charges moved horizontally; depict as a topology

saline resistances between voxels result in ion currents: I12 = (V2-V1)*(1/R12)

SalineCurrent; % extracted from drift data

horz flux changes Nernst voltages and capacitance charges

NodalSums; %

vesicles bind Ca++ as a modulator, kinetically, per conc

Aaffinity; Abind; Bbind; Amod;

vesicles change state per mods

Asubstantiate;

vesicles release ligands kinetically into synaptic cleft

Bunbind;

vesicles reset their state (recycling sequence)

pump affinity1 profiles, per mode

Aaffinity;

pump bind1 staging, kinetically

Abind;

pump bind1 state alters Q-mode, also mods and concs may alter Q-mode

Amod;

pump state change kinetically, may transport across membrane (forward) or unbind (backward)

Atransport;

pump offload at side2 after transport

Aunbind;

pump affinity2 profiles, per mode

Aaffinity;

pump bind2 staging, kinetically

Abind;

pump bind2 state alters Q-mode, also mods and concs may alter Q-mode

Amod;

pump state change kinetically, may transport across membrane (forward) or unbind (backward)

Atransport;

pump offloads side2 after transport

Aunbind; Bunbind; Bconvert;

Over 1300 functions have been written for this project. Some are prototypes designed to exercise a concept. Some are test routines. Some are generalized forms. Others are fast lean specialized work horses. Follows is a few of the more interesting algorithms in code.

Code is available upon approval for use.

Support Functions:

DESIGN	standard functions
Load TypeShuttle TypePhysic	physics and chemistry basics
Load TypeComp	shape-family library
Load TypeRecep	defines each type of receptor, ligands, kinetics,
Load	defines each type of G-protein shuttle, by ligand, speed, mods
Load TypeChan	defines each type of channel by G profile, mods, kinetics
Load TypePump	defines each pump type by action, states, kinetics, poles, attractor
Load TypeVes	defines each vesicle type by sizes, contents, modulators
Load TypeIon	Types of monatomic ions: atomic number, mass, radius, charge, …
Load TypeIon2	Types of polyatomic ions
Load TypeLigand	Types of ligands, neurotransmitters, messengers, etc

BUILD	standard functions
Load DistPhysic	physics and chemistry parametric values for this run
Load DistComp	compartment dimensions specified for this run
Load DistRecep	locations of each Receptor by type by PDFs
Load DistShuttle	locations of specific shuttle types, pole to pole
Load DistChan	locations of each type of channel by PDFs
Load DistPump	locations of each type of pump by PDFs
Load DistVes	locations of each type of vesicle
Load DistIon	initial positions and velocities of each type of monatomic ions
Load DistIon2	initial positions and velocities of each type of polyatomic ions
Load DistLigand	initial positions and velocities of each type of ligand
DisplayBuild	Check all data syntax, then Display results of Build (static 3-D model)

RUN	standard functions
RunTime	sets up dx, dt and time loop, with data capture
SigGen	temporal release/reuptake of presynaptic Ligands (Neurotransmitters)
Attractor	adds acceleration factors to Vel per actor poles
Forcer	adds acceleration factors to Vel per voltage and concentration gradients
Mover	adds new velocity values to PosIL, then tests for collisions
TagMgr	manager tags each particle according to its compartment and binding
Collider	performs momentum conserving particle collisions
Reflector	performs elastic bounces off membranes, or probabilistic absorptions
Binder	performs probabilistic-binding of particles to poles
Modulator	checks mod concentrations near poles and alters kinetics accordingly
StateTrans	checks for Actor state change conditions, changes stat probabilistically
Releaser	probabilistically releases bound particles after transport, assigns vel
Transporter	indexes shuttles, pumps, channels, vesicles along parametrized paths
Conductor	reads Q matrix and instantiates openings and closings
ConcUpdate	after all particles moved and transported, eval voxel concs
NernstUpdate	altered concs cause altered Na nernst, per voxel
ChargeUpdate	Na flux causes eval of charge imbalance, per voxel
ChargeForce	Calculate forces due to charge balance for Forcer, per particle
ConcForce	Calculate forces of diffusion due to conc gradients for Forcer, particle
CapCharger	altered Vm changes charge to nodal capacitor, per Voronoi
Resistor	altered Vm causes saline resistance grid to alter neighboring Vms
CurrentSummer	Na flux plus changes in capacitive charge = current
VoltageUpdate	calculate nodal Vm as a func of I , G and Cm
ModUpdate	eval new mod locations and values
VesInventory	sets probabilities of available ves as a func of replenishment rate
CaptureFrame	capture all position and state data

REPORT	
group1	set report options
group2	PLAY movie
group3	plot implicit variables wrt time

VITA

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