Position paper:
Biomedical systems research - new perspectives opened by quantitative medical imaging.

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Abstract.

Recent advances in quantitative imaging allow unprecedented views into cellular chemistry of whole organisms *in vivo*. These novel imaging modalities enable the quantitative investigation of spatio-temporal reaction and transport phenomena in the living animal or the human body. This article will highlight the significant role that rigorous systems engineering methods can play for interpreting the wealth of in-vivo measurements. A methodology to integrate medical imaging modalities with rigorous computational fluid dynamics entitled image-based computational fluid dynamics (*iCFD*) will be introduced. The quantitative analysis of biological systems with rigorous mathematical methods is expected to accelerate the introduction of novel drugs by providing a rational foundation for the systematic development of new medical therapies. Rigorous engineering methods not only advance biomedical research, but also aid the translation of laboratory research results into the bedside practice.

Keywords: *biomedical engineering; quantitative medical imaging; image-based computational fluid mechanics; parameter estimation in distributed systems; pharmacokinetics.*

1. Motivation

Recent scientific discoveries have advanced systems biology - a new research field at the interface of biochemistry, molecular biology, and genetics at the cellular level (Bailey, 2001; Doyle and Stelling, 2006; Westerhoff and Palsson, 2004). The engineering community has so far paid less attention to revolutionary developments in *medical imaging* that capture the biological processes for an *entire organism*. During the past decades, new *quantitative medical imaging techniques* have opened a window to the detailed anatomy as well as quantified the biochemical and physical transport phenomena inside living organisms. Medical imaging techniques can today measure key metabolic functions *in-vivo* in three spatial dimensions and as functions of time such as oxygen consumption in organ tissues, expressions of proteins, and amount and species

concentration inside single cells, specialized cell clusters or entire organs. Also, blood flow or dispersion of tracer molecules can be tracked non-invasively. These new *medical imaging* techniques offer unprecedented observations about the physical and biochemical functions in the living organism.

Specifically, medical images provide detailed *anatomical* information about the geometric shape of cells, tissues, and organs up to the entire organism. In addition, *quantitative* imaging renders precise measurements such as drug concentrations, fluid flows or drug bioaccumulations. Anatomical and quantitative information provided by medical imaging allows the creation of computer models that capture faithfully the anatomical complexity of biological systems as well as their biochemical and transport mechanisms. The integration and interpretation of medical imaging data with rigorous computational fluid dynamics analysis is the object of the *image-based computational fluid dynamics* (*iCFD*). The *iCFD* process allows modeling patient-specific geometry and biochemical kinetics.

The wealth of novel information acquired by medical imaging enables the systematic identification of the fundamental reaction and transport phenomena as well as the precise determination of their model parameters such as rate laws, reaction or binding constants or diffusion coefficients. Medical images provide precisely the data needed to establish mathematical models with methods already developed by the chemical systems engineering community for studying chemical process systems. These first principles models enforce rigorous mass, species and momentum balances and incorporate constitutive relations for drug dispersion and action in the biological system. Accordingly, organs and their interaction are treated similar to reactors and separators in a chemical plant. Well-established systems engineering methods for flowsheet analysis, design and optimization are also suitable for unraveling pharmacokinetics and pharmacodynamics of new drugs. The integration of medical images into *complex systems analysis* will accelerate the introduction of new drugs, deepen the understanding about diseases and possible remedies, and more readily transfer scientific knowledge between disciplines engaged in biomedical research. System engineering may also offer

the toolset and methodologies needed to achieve transformative changes to designing and optimizing novel therapies for individual patients (Bogle et al., 2009; Dua and Pistikopoulos, 2005). Systems methods are the key for implementing personalized medicine.

To better put into perspective current trends for the introduction of systems engineering methods into biomedicine, this paper will first highlight recent developments in quantitative medical imaging. Systems engineering will play a substantial role in closing the wide gap between fundamental research and translational clinical applications. These possibilities will be illustrated by describing examples drawn from interdisciplinary research collaborations over the past decade.

The paper is organized as follows. In Section 2, a brief overview of novel quantitative imaging modalities is presented. Section 3 introduces *iCFD* as process to seamlessly integrate patient-specific imaging with rigorous engineering analysis. Section 4 demonstrates biomedical case studies highlighting new methods and processes in which systems engineering methods played an essential role in advancing fundamental knowledge about the human brain. The discussion in Section 5 summarizes key areas of systems approaches in biomedical engineering and offers our perspective on future educational and research needs. The paper closes with conclusions and an outlook to future research.

2. Overview imaging

The revolution in medical imaging began with CT scanning. For the first time high resolution three-dimensional information became available and this knowledge has transformed medical diagnosis and treatment. Physicians could not only see the location of pathology — a tumor for example — but also observe its relationship with other internal structures and its precise location for biopsy, removal, or radiation treatment. Furthermore, the pathological condition could be followed over time to help determine how medical treatments were working.

MRI technology has expanded these capabilities — without the need for X-rays — by increasing the sensitivity for soft tissues (Tofts, 2003). A variety of pulse sequences can be used to emphasize different tissue properties such as grey matter and white matter in the brain. Timed examinations can be performed to measure blood flow and cerebrospinal fluid (CSF) pulsations. All these types of images provide three-dimensional, patient-specific information. The capabilities of MRI scanning have been expanded to display the complex architecture of entire organs like the brain. Anisotropic and heterogeneous soft tissue properties like molecular diffusivity, hydraulic and electric conductivity can be correlated to *in vivo* MRI Diffusion Tensor imaging (DTI) measurements. Tensor fields measured with DTI for specific patients can be drawn to account for more realistic soft tissue models needed in realistic bio-transport calculations.

3. Image-based computational fluid mechanics (iCFD)

Before modern imaging techniques became widely available, biological systems analysis was hampered by their complex anatomical shape. Early engineering models of biological systems were constructed with simplified geometries of idealized shapes. For more realistic modeling of flow and reaction phenomena, *image reconstruction of patient-specific medical image data* helps create computational models that precisely matches anatomical dimensions and shapes. The procedure of converting medical image data into realistic computational representations that preserve anatomical and physiological detail is termed *geometric image reconstruction*. The accurate mapping between biological and computational domain is also crucial for validating simulations with experimental data. It is a prerequisite for realistic computer simulations in an emerging field known as *image-based Computational Fluid Dynamics (iCFD)*.

Geometric image reconstruction involves the assembly of three-dimensional imaging data into computational meshes usually unstructured grids. Computational *surface meshes* delineate system boundaries like an organ or the contrast between different tissue types like fluid-filled spaces versus soft tissues. Geometric image reconstruction also involves smoothing, contrast enhancement and automatic edge detection. The computational surface meshes are further divided into a finite number of volumes, typically

tetrahedrons. Grid generation algorithms perform mesh regularization to optimally divide the domain into finite balance envelopes with suitable aspect ratios to form a *volumetric mesh*. Advanced semi-automated meshing software can be employed for rapid generation of multi-block structured or unstructured volume meshes. A sample of reconstructed CSF filled spaces in the brain and the effect of surface smoothing are displayed in Figure 1.

Figure 1:

A great aide in converting pixilated imaging data into physiologically consistent surfaces and domains is offered by automatic image reconstruction software. Several free tools available for spatial image reconstruction such as ImageJ, ITK-Snap, and VTK substantially accelerate the generation of computational maps (Ibanez et al., 2003; Schroeder et al., 2006). Commercial tools such as Mimics (Materialise Inc, 2011) have excellent features for contrast enhancement, automatic boundary detection and surface smoothing. A list of software for *iCFD* is listed in Table 1. Most software tools provide several file output formats for reconstructed surface or volume meshes. These file export formats are essential for importing reconstructed meshes obtained from imaging data into state-of-the-art CFD software such as ANSYS Fluent (ANSYS, 2011) or Adina (ADINA, 2010).

Table 1. List of image reconstruction tools and CFD software for iCFD

Tools	Applications	Source
Image Reconstruction Software		
Image J	Graphics software that defines point and line data; primarily useful for two-dimensional model construction. Reads TIFF, PNG, GIF, JPEG, BMP file formats.	Open(Rasband, 2011)
ITK-SNAP	Software application used to reconstruct medical images into computational maps.	Open(Yushkevich et al., 2006)
VTK	Software library for visualization and reconstruction of medical images.	Open(Schroeder et al., 2006)
Mimics	Medical image reconstruction software; 3D prototyping of complex biological shapes.	Materialise, Corp. Belguim (Materialise Inc, 2011)
Analyze	Biomedical imaging software for	AnalyzeDirect,

	reconstruction of medical images.	Inc. (AnalyzeDirect, 2010)
Mesh generation software		
ICEM CFD	A semi-automated meshing module which provides rapid generation of multi-block structured or unstructured volume meshes	ANSYS, Inc.(ANSYS, 2011)
Gambit	Geometry creation and mesh generation with structured and unstructured volumes.	Fluent, Inc.(Gambit, 2006)
Rigorous CFD Simulation Software		
Elmer	Finite element software for the solution of multi-physical problems.	Open (Elmer, 2011)
FOAM CFD	Finite element software with fluid-structure interaction modules.	Open (OpenFOAM, 2011)
STAR CD	Flow, thermal, and stress simulation software for performing powerful multi-physics simulations.	CD-adapco (CD-adapco, 2010)
COMSOL	Multi-physics simulation and finite element software; fluid-structure interaction capability; also solves thermal and electromagnetic problems.	COMSOL, Inc. (COMSOL, 2011)
ADINA	Finite element analysis software for structural, thermal, fluid-structure interaction analysis; robust for 3d simulations of complex geometry.	ADINA R&D, Inc. (ADINA, 2010)
ANSYS FLUENT	Finite volume and flow modeling software; fluid-structure interaction capability.	ANSYS, Inc. (ANSYS, 2011)

The next section will demonstrate *iCFD* capabilities for designing novel therapies. To illustrate the current capabilities of systems approaches in biomedical engineering, two case studies will be provided. These examples also emphasize the need for interdisciplinary cooperation. An overview of active research areas in which chemical systems engineers may play a critical role will be given in the discussion section.

4. Case studies

4.1. Rigorous prediction of drug transport in the brain

The first case study illustrates the rational design of novel drug administration therapies based on *patient-specific medical imaging information*. Rather than optimizing infusion parameters by expensive trial-and-error animal experimentation, *iCFD* allows to accurately predict expected drug dispersion *in-silico*. Optimal infusion parameters can be found with fast and inexpensive computer simulations; only the best design solutions need to be verified with fewer validation experiments than the current purely empirical practice.

Convection-enhanced delivery (CED) is an invasive drug administration technique in which drugs are infused directly into the brain via a catheter. It is used to overcome the blood-brain-barrier, which prevents many potentially therapeutic drugs from reaching brain cells. In addition, the infusate propels these drugs deeper inside the porous tissue by convective flow. This promising new treatment option has a wide range of applications including Parkinson's disease, brain tumor and gene therapy. However, clinical trials employing CED have failed to meet clinical end points, because current infusion techniques have not covered desired target areas and there is a wide variability between experiments and from patient to patient (Sampson et al., 2010) .

An *iCFD* workflow procedure with four stages is developed (Somayaji et al., 2008). In step 1, *MR imaging* techniques accurately delineate the patients' individual brain geometry. In step 2, *image reconstruction* is used to convert the patient-specific MR data into accurate three-dimensional surfaces and volume representation. In step 3, *mesh generation,* the volume is partitioned into a finite number of small non-overlapping tetrahedrons. In step 4, the equations of fluid motion and species transport defined over the volume mesh are solved numerically.

The distribution of a nerve growth factor (NGF) administered invasively from an infusion catheter was predicted with *iCFD*. NGF promotes the survival and differentiation of sensory and sympathetic neurons in the brain. It has been used for preventing nerve loss in patients suffering from Alzheimer's disease. The aim of the therapy design was to

maximize achievable treatment volumes by optimal choices of infusion parameters such as catheter position, bulk flow rate and drug concentration in the infusate. By applying the iCFD procedures, an accurate anatomical model of the patient's brain was recreated on the computer with physiological brain structures including clear gray and white matter boundaries, tissue permeability and anisotropy, and realistic transport properties. This iCFD model enables patient-specific infusion design by predicting drug transport and biodistribution after infusion via a catheter.

First, the geometry of the patient's brain was captured with MRI. In addition, the prediction of drug biodistribution after infusion requires an anatomically consistent model of anisotropic and heterogeneous brain tissue. Brain tissue anisotropy is taken into account by incorporating information derived from diffusion tensor imaging (DTI). Drug infusion and transport in the brain was simulated with *image-based computational fluid dynamics*. The bulk infusate–an aqueous solution–obeys the laws of incompressible fluid motion in a porous medium as in eq. (1) and (2). The momentum balances of bulk fluid flow inside the anisotropic extracellular space can be expressed by Darcy's law with interstitial fluid pressure, p, and the hydraulic conductivity tensor, K. Species transport of drug molecules is due to *convection* with the bulk as well as *diffusion* according to concentration gradients. The convective-diffusive drug dispersion can be calculated according to the species transport equation given in eq (3). Drug dispersion by convection is given by $v \overset{u}{\nabla} C$. The diffusion flux, $\mathsf{D}_e \overset{u}{\nabla} C$, is a vector equal to the product of the effective molecular diffusion tensor, D_e, with the with gradient of the interstitial species concentration, $C(\overset{r}{x},t)$. In anisotropic media the diffusion flux is not necessarily collinear with the concentration gradient. Drugs are more likely to diffuse radially along axonal white matter tracts than perpendicular to the fibers. This preferential direction of the diffusive transport in each point of the white matter can be quantified with an anisotropic molecular diffusion tensor field. Anisotropic transport properties can be estimated using tensor fields acquired with diffusion tensor imaging (DTI). Figure 2 shows an example for capturing anisotropic material properties exhibiting strong directionality of fibrous white matter tracts in a 38 year old normal subject.

Figure 2.

The reaction term, $R\left(C, \vec{x}\right)$, represents enzymatic drug decomposition, possible metabolic interactions of the drugs with neurons or other pharmacokinetic reactions. In addition, drug-receptor binding $\dfrac{\partial B}{\partial t}$, or drug internalization, $S\left(C, \vec{x}\right)$, for can be accounted for with additional sink terms. The solution of the fundamental conservation laws of mass, momentum and species transport gives the desired drug distribution, $C\left(\vec{x}, t\right)$, the interstitial velocity, $\vec{v}\left(\vec{x}, t\right)$, as well as the pressure fields, $p\left(\vec{x}, t\right)$ as functions of space, $\vec{x}$, and time, t.

Continuity:
$$\vec{\nabla} \cdot \vec{v} = 0 \tag{1}$$

CSF fluid seepage through the porous extracellular space of the brain:
$$\rho \left(\frac{\partial \vec{v}}{\partial t} + \vec{v} \cdot \vec{\nabla} \vec{v} \right) = -\vec{\nabla} p + \mu \vec{\nabla}^2 \vec{v} - K^{-1} \vec{v} \tag{2}$$

Drug transport for convection-enhanced delivery:
$$\varepsilon \frac{\partial C}{\partial t} + \vec{v} \cdot \vec{\nabla} C = \vec{\nabla} \cdot \left(D_e \vec{\nabla} C \right) + R\left(C, \vec{x}\right) + S\left(C, \vec{x}\right) - \frac{\partial B}{\partial t} \tag{3}$$

In step 3, the brain tissue and the infusion catheter were meshed using boundary conditions depicted in Figure 3. The computational grid for a two-dimensional axial human brain segment had more than 20,000 volumes. Achievable treatment volumes were calculated using the finite volume method for the injection of a nerve growth factor (NGF) with convection enhancement. A detailed discussion of the finite volume discretization procedure can be found elsewhere (Somayaji et al., 2008). In step 4, drug distribution was computed numerically.

Figure 3.

Typical simulation results for intra-parenchymal drug infusion are shown in Figure 4. A comparison of predicted steady state drug dispersion in a homogenous ideal porous

medium versus a non-homogenous anisotropic tissue model obtained from real patient DTI data depicted in frames A and B respectively. These simulation experiments predicted irregular drug dispersion due to tissue anisotropy. The anisotropic drug dispersion patterns are more realistic and better approximate NGF distribution in real anisotropic brain tissues. After the injection of a drug, the final drug distribution volume determines the efficacy of the expected therapeutic outcome. In clinical trials, many infusion therapies fail to meet treatment objectives because drug molecules fail to reach the desired target cells or only ineffective sub-therapeutic drug concentrations area realized in the target zone. Optimizing infusion parameters a-priori with iCFD ensures that the drug reaches the desired brain tissue in therapeutically effective concentrations. Simulations such as the result shown in Figure 4B assists physicians in determining whether infusion parameters are adequately chosen to achieve the desired treatment objectives. The case study illustrates the potential of *iCFD* for the systematic design of novel drug therapies.

Figure 4.

4.2. Discovery of cerebral transport and metabolic reaction properties

Image-based computational fluid dynamics (iCFD) not only predicts patient-specific drug distribution with known drug kinetic parameters, but also enables the discovery of unknown drug kinetic parameters. The following case study combines iCFD with parameter estimation to create mechanistic models of drug transport and reaction chemistry in distributed systems. Non-linear optimization (mathematical programming) offer powerful techniques to estimate reaction and transport properties from distributed imaging data. The key advantage with *iCFD* techniques is the possibility to incorporate large datasets about unknown reaction and transport phenomena acquired in spatial dimensions and at different time intervals. The wealth of data available should dramatically improve the quality of the parameter estimation.

Somayaji et al. used *in vivo* medical image data to determine both transport and metabolic reaction parameters for therapeutic agents (Somayaji, 2008; Zhang et al., 2007). A brief outline of the concept using the levodopa treatment for Parkinson's as an example follows.

Figure 5.

In this example, a simplified diffusion-clearance model aims at quantifying the transport and clearance of *F-dopa* in the brain tissue with a distributed parameter estimation technique. First, previously published positron emission tomography (PET) data for infusion of radio-labeled *F-dopa* into the brain were collected. The color intensity of the PET image corresponds to the *F-dopa* distribution in the basal ganglion depicted in Figure 5a in a horizontal cut of the human brain. The pixel color intensities in the PET scan were converted to infer the concentration profiles obtained *in vivo*, $\hat{C}$. Using the iCFD workflow, a model of the patient's brain was reconstructed from the PET image and used to estimate kinetic parameters of *F-dopa* in the brain. The aim of the inversion problem is to estimate the rate of tissue-to-blood clearance, k_2, of *F-dopa* and blood-to-tissue clearance parameter, K_1, of *methyl-F-dopa*. In addition, diffusivities of both species, *D*, were determined. The steady state extravascular concentrations of *F-dopa* and *methyl-F-dopa* in the brain tissue are given in eq (5). The mathematical program in (4)-(5) has a quadratic objective with partial differential equation constraints, with *F* being the covariance matrix of the experimental measurements. It allows for the estimation of diffusion-clearance parameters in the *F-dopa* model. Eq (5) constitutes steady state diffusion with reactions, with *R* denoting the reaction kinetic model for blood-tissue clearance for *F-dopa* and *methyl-F-dopa*.

$$\min_{D,K_1,k_2,C} \psi(D,K_1,k_2) = \left[C(x)-\hat{C}(x)\right]^T F^{-1}\left[C(x)-\hat{C}(x)\right] \tag{4}$$

s.t.

$$\nabla(D_D \nabla C_D) = R(C_D, K_1, k_2) \qquad C = \text{(F-dopa, methyl-F-dopa)} \tag{5}$$

An anatomically consistent computational grid was constructed from the PET image depicted in Figure 5a through the image reconstruction technique described in step 2 of

the iCFD workflow. The reconstructed domain was converted into an unstructured computational grid shown in Figure 5b through the mesh generation technique described in step 3. Finally, the solution of parameter estimation problem gives the values of the unknown parameters that best align the predictions with the image data. Figure 5c depicts the predicted F-dopa concentration field for the optimal parameter set.

The construction of an iCFD model from medical images enables kinetic parameter estimation of a drug from distributed imaging data such as PET scans. Matching the imaged with simulated concentration profiles allows the determination of unknown parameters to describe the transport and reaction mechanisms taking place in vivo. While this case study used a simplified reaction network with only two-dimensional data, it demonstrated the enormous potential of discovering metabolic and transport phenomena from medical images. The *simultaneous identification of metabolic and transport properties from medical images* is a novel capability for biomedical engineering.

5. Discussion

The case studies demonstrate quantitative analysis of complex transport and reaction phenomena using *in vivo* observations from medical imaging. In the examples, *iCFD* produced quantitative results such as spatio-temporal drug concentration in the porous brain parenchyma. Despite the large data set necessary to accurately represent the patients' brain geometry, the first principle fluid mechanics approach only requires a small number of physical parameters such as density, viscosity or frictional coefficients. These computer predictions can be compared to Cine MRI measurements. When simulations and measurements are in good qualitative and quantitative agreement, it is reasonable to assume that mathematical model captures main phenomena occurring *in vivo*. In this sense, *iCFD* analysis should not be considered merely a tool to reproduce transport phenomena, but as an investigative process to explain dynamic forces that cause fluid motion in the living organism. Thus, *iCFD* supports biomedical discovery. Open questions and future research activities are suggested in the subsequent section.

Interstitial transport at the nanoscale. Many biomedical applications require a molecular description of interstitial transport. Several research groups with chemical engineering background have made progress in experimentally describing transport phenomena at the nanoscale (Neeves et al., 2007; Saltzman and Olbricht, 2002; Stephanopoulos, 2005). Yet, the theoretical models explaining transport of large molecular weight drugs or functionalized nanoparticles through the extracellular space are in their infancy. It appears that continuous convection-diffusion models are not sufficient to describe hindered diffusion or particulate transport inside the tortuous extracellular space. Discrete particle simulations may offer the flexibility to incorporate molecular forces, charge interactions and steric diffusive impedance of the molecular species transport in the nano-pore space of the interstitium with relative ease.

Drug transport dynamics in pulsating media. Natural fluid flow such as the pulsatile CSF flow pattern in the central nervous system (CNS) critically affects mass transfer of therapeutic species in intrathecal and intraventricular delivery modalities. For example, the apparent transport speed of proteins infused into the CSF of the lumbar region – a modality known as *intrathecal drug delivery* (IT) - is far greater than can be explained by molecular diffusion alone. In the future, detailed three-dimensional simulations may explain the mystery of accelerated transport phenomena in IT drug delivery providing invaluable insights for anesthesiology or the design of gene therapies for the CNS.

Inversion methods for distributed system optimization. The transport and kinetic inversion problems discussed for dopamine therapy demonstrated the feasibility of estimating unknown transport and reaction kinetic parameters from distributed image data. The solution of parameter estimation problems leads to mathematical programming formulations with quadratic objectives; but partial differential equation constraints defined over three dimensional domains and as functions of time. Advances in optimization techniques for distributed partial differential equation systems, avoiding the repeated solution of the entire set up transport equations to obtain the required sensitivity information would need to be developed. Some techniques such as the *In Situ Adaptive Tabulation (ISAT)*, already successfully developed for large scale chemical kinetic

inversion problems, are also promising for the inversion of distributed image data (Hedengren and Edgar, 2005; Pope, 1997). Another active area of investigation for systems area is to address the solution multiplicity in parameter estimation problems in distributed domains (Lucia and Feng, 2003). The presence of measurement errors introduces multiple extrema in the residual error surface. Global optimization methods to systematically identify *all local solutions* are needed. Currently, few methods such as *niche algorithms* or *hybrid niche methods* have been used for distributed systems optimization (Moon and Linninger, 2009). Selecting the physically meaningful extremum among the many local solutions is another open point of interest. Lucia argues convincingly that the global minimum is not necessarily the desired solution in all cases (Lucia et al., 2008). Engineering insight has to be incorporated into the parameter estimation routine (Biegler and Grossmann, 2004). Yet few researchers have tackled these open issues in the literature.

Implications for software development and modeling needs. The ad-hoc generation of physiological models requires frequent adjustments of the mathematical models. However, it is impractical to maintain large, rapidly changing projects by hand. State-of-the-art modeling tools such as the excellent equation-oriented gProms language (gPROMS, 2010) support version management via object-oriented software engineering techniques. Yet, in distributed systems coupling of mass and momentum equations affects even the choice of solution algorithms. An evolving technique for computer-aided problem formulation is entitled *model generation*. Model generation is a graphically-driven modeling paradigm, which separates automatic or semi-automatic model formulation from its numerical solution procedure. In *model formulation*, the physical domain is represented graphically by a network. Network models are typically assembled by the user with the help of image-reconstruction software. Once the network of spatial domain is drawn, the phenomenological modeling elements are added to the geometry context. This task means that the user selects relevant transport and reaction mechanisms. Given the user choices of physical phenomena, the model generation software instantiates fully automatically the fundamental conservation balances defined over the geometry context given by the domain mesh. In practice, these model

generation steps can automatically synthesize species and momentum conservation equations. These equations are created symbolically in the syntax of a user's preference such as Matlab, C or Fortran code. The symbolic code generated in the model formulation phase can be exported to any target language or platform. Especially for parallel supercomputer applications, the code export may be an indispensible feature in large-scale biological systems modeling. In addition, systems theoretical methods can check model consistency. Automatic model generation based on *physical conservation principles*, in addition to the common mathematical consistency, is an interesting concept proposed recently (Preisig, 2006).

Implications for education. The new trends in biomedical engineering research create opportunities for young chemical systems engineers. Is there further a need to adjust the curriculum for a better preparation of our graduates? In the author's opinion, engineering fundamentals in core courses like reaction engineering, transport and dynamics or control should not be sacrificed in favor of qualitative introductory courses on biomedical *hot* topics. A useful adjustment to existing courses could be the introduction of biomedical case studies as projects into core courses. One example from the author's experience includes a basic mass and energy balance course in which undergraduate student teams constructed whole-body vasculature models of common test animals and humans (Linninger, 2011). This project allowed students to practice large scale linear algebra, yet required students to research blood flow circulation and to investigate suitable material properties like flow resistances in common test animals. The senior design course also offers chemical engineering students ample opportunity to strengthen their interdisciplinary capabilities. Instead of redesigning a standard chemical plant, medical device design projects foster undergraduate experiences in product design. Students were encouraged to use of CFD software such as Ansys, or Comsol for their projects. Design projects with CFD tools engage students in the application of fundamental principles (conservation laws, constitutive equations), introduce state-of-the-art CFD software, yet get students excited about putting their newly acquired rigorous engineering knowledge into the service of life sciences. Versatility with advanced CFD tool is becoming a special

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bonus for graduates seeking assignments in interdisciplinary corporate research and development teams.

At the graduate level, there also appears to be trend towards the use of CFD software applications in life science applications. While CFD tools accelerate problem formulation and solution of biological models, the coupling of mass transfer with species and momentum transfer makes a fundamental understanding of the mathematical principles of transport more important then ever. Courses taught in computational fluid dynamics methods emphasize on the principles of partial differential equation discretization such as the finite volume method, degree-of-freedom analysis as well as detailed discussion of boundary condition selection in distributed systems. Class projects included coding assignments such as the finite volume discretization of convection diffusion equations with Matlab, with validation by commercial CFD tools.

Finally, medical faculty should be brought in to teach about the patho-physiology of specific diseases that relate to student case studies. Engineers need to be exposed to the language of biology and medicine. The excitement of translational projects that use engineering to solve medical problems needs to be illustrated with specific examples. The goal of contributing to patient care should always be a principal motivating factor.

6. Conclusions

Systems engineering which deals with complex interacting chemical processes along with medical imaging technologies are in the ideal position to make biomedical discoveries. While enormous biological progress has been made identifying specific tissues, fluids, and structures, an understanding of how these systems function as a whole will require different skills and approach. Medical imaging provides an overwhelming amount of spatial and tissue information which has not been exploited fully to answer important functional questions. These questions are very significant to medical interventions in numerous diseases. For example, MR images of the patient's brain only offers qualitative insight into the anatomical structure, but from these images, transport rate and final distribution volume cannot be deciphered. Coupled with *iCFD*, these images are

converted into three-dimensional models where infusion can be tested quantitatively. Current empirical attempts and pure trial-and-error animal testing have failed. This is the time and place for engineers to take up these clinical problems. Their strong analytical skills provide the framework to design new tools for solving these problems. For this to interdisciplinary field to advance, a partnership with clinicians is necessary. Physicians and systems engineers use very different languages and methods. However, the goal-oriented, problem solving in complex and not completely understood situations is common. The key to any effective cooperation is for engineers and physicians to recognize their similar interests as problem solvers and to identify medical problems amenable to quantitative engineering analysis. Engineers need to learn a great deal of biology and use their knowledge to formulate proper data gathering from patients. The mutual education is best implemented in small groups. A sufficient time is necessary to learn about each other's strengths, but the potential gains for patients are great.

Abbreviations

CED	Convection-enhanced delivery
CSF	Cerebrospinal fluid
CNS	Central nervous system
CT	Computed tomography
DTI	Diffusion tensor imaging
iCFD	Image-based Computational fluid dynamics
F-dopa	3,4-Dihydroxy-6-fluoro-DL-phenylananine Monohydrate
MRI	Magnetic resonance imaging
NGF	Nerve growth factor
PET	Positron emission tomography

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