

Synthetic Biology: Engineering Life to Examine It

Jalees Rehman

Correspondence to:

Jalees Rehman, M.D.
University of Illinois at Chicago, College of Medicine
Departments of Medicine and Pharmacology
835 South Wolcott Ave, Room E403, Chicago, IL 60612, USA

Email: [jalees.rehman\[at\]gmail\[dot\]com](mailto:jalees.rehman[at]gmail[dot]com)

Twitter: @jalees_rehman

Scientific Blog: The Next Regeneration http://www.scilogs.com/next_regeneration/

Personal Blog: Fragments of Truth <http://www.fragments-of-truth.blogspot.com/>

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Synthetic Biology: Engineering Life to Examine It

Two scientific papers that were published in the journal *Nature* in the year 2000 marked the beginning of engineering biological circuits in cells. The paper [*Construction of a genetic toggle switch in Escherichia coli*](#) (1) by Timothy Gardner, Charles Cantor, and James Collins created a genetic toggle switch by simultaneously introducing an artificial DNA plasmid into a bacterial cell. This DNA plasmid contained two promoters (DNA sequences that regulate the expression of genes) and two repressors (genes that encode for proteins that suppress the expression of genes), as well as a gene encoding for green fluorescent protein that served as a read-out for the system. The repressors used were sensitive to either selected chemicals or temperature. In one of the experiments, the system was turned ON by adding the chemical IPTG (a modified sugar), and nearly all the cells became green fluorescent within five to six hours. Upon raising the temperature to activate the temperature-sensitive repressor, the cells began losing their green fluorescence within an hour and returned to the OFF state. Many labs had used chemical or temperature switches to turn gene expression on in the past, but this paper was the first to assemble multiple genes together and construct a switch that allowed switching cells back and forth between stable ON and OFF states.

The same issue of *Nature* contained a second landmark paper that also described the engineering of gene circuits. The researchers Michael Elowitz and Stanislas Leibler describe the generation of an engineered gene oscillator in their article [*A synthetic oscillatory network of transcriptional regulators*](#). (2) By introducing three repressor genes, which constituted a negative feedback loop and a green fluorescent protein as a marker of the oscillation, the researchers created a molecular clock in bacteria with an oscillation period of roughly 150 minutes. The genes and proteins encoded by the genes were not part of any natural biological clock, and none of them would have oscillated if they had been introduced into the bacteria on their own. The beauty of the design lay in the combination of three serially repressing genes, and the periodicity of this engineered clock reflected the half-life of the protein encoded by each gene as well as the time it took for the protein to act on the subsequent member of the gene loop.

Both papers described the introduction of plasmids encoding for multiple genes into bacteria, but this itself was not novel. In fact, this has been a routine practice since the 1970s for many molecular biology laboratories. The panache of the work lay in the construction of functional biological modules consisting of multiple genes that interacted with each other in a controlled and predictable manner. Since the publication of these two articles, hundreds of scientific papers have been published that describe even more intricate engineered gene circuits. These newer studies take advantage of the large number of molecular tools that have become available to query the genome as well as newer DNA plasmids that encode for novel biosensors and regulators.

Synthetic biology is an area of science devoted to engineering novel biological circuits, devices, systems, genomes, or even whole organisms. This rather broad description of what “synthetic biology” encompasses reflects the multidisciplinary nature of this field, which integrates ideas derived from biology, engineering, chemistry, and mathematical modeling as well as a vast arsenal of experimental tools developed in each of these disciplines. Specific examples of “synthetic biology” include the engineering of microbial organisms

that are able to mass produce fuels or other valuable raw materials, synthesizing large chunks of DNA to replace whole chromosomes or even the complete genome in certain cells, assembling synthetic cells or introducing groups of genes into cells so that these genes can form functional circuits by interacting with each other. *Synthesis* in the context of synthetic biology can signify the engineering of artificial genes or biological systems that do not exist in nature (i.e. synthetic = artificial or unnatural), but *synthesis* can also stand for integration and composition, a meaning that is closer to the Greek origin of the word. It is this latter aspect of synthetic biology that makes it an attractive area for basic scientists who are trying to understand the complexity of biological organisms. Instead of the traditional molecular biology focus on studying just one single gene and its function, synthetic biology is engineering biological composites that consist of multiple genes and regulatory elements of each gene. This enables scientists to interrogate the interactions of these genes, their regulatory elements, and the proteins encoded by the genes with each other. Synthesis serves as a path to analysis.

One goal of synthetic biologists is to create complex circuits in cells to facilitate biocomputing, building biological computers that are as powerful or even more powerful than traditional computers. While such gene circuits and cells that have been engineered have some degree of memory and computing power, they are no match for the comparatively gigantic computing power of even small digital computers. Nevertheless, we have to keep in mind that the field is very young, and advances are progressing at a rapid pace.

One of the major recent advances in synthetic biology occurred in 2013 when an MIT research team led by Rahul Sarpeshkar and Timothy Lu at MIT [created analog computing circuits in cells](#). (3) Most synthetic biology groups that engineer gene circuits in cells to create biological computers have taken their cues from contemporary computer technology. Nearly all of the computers we use are digital computers, which process data using discrete values such as 0s and 1s. Analog data processing, on the other hand, uses a continuous range of values instead of 0s and 1s. Digital computers have supplanted analog computing in nearly all areas of life because they are easy to program, highly efficient, and process analog signals by converting them into digital data. Nature, on the other hand, processes data and information using both analog and digital approaches. Some biological states are indeed discrete, such as heart cells that are electrically depolarized and then repolarized in periodical intervals in order to keep the heart beating. Such discrete states of cells (polarized/depolarized) can be modeled using the ON and OFF states in the biological circuit described earlier. However, many biological processes, such as inflammation, occur on a continuous scale. Cells do not just exist in uninflamed and inflamed states; instead there is a continuum of inflammation from minimal inflammatory activation of cells to massive inflammation. Environmental signals that are critical for cell behavior, such as temperature, tension, or shear stress, occur on a continuous scale, and there is little evidence to indicate that cells convert these analog signals into digital data.

Most of the attempts to create synthetic gene circuits and study information processing in cells have been based on a digital computing paradigm. Sarpeshkar and Lu instead wondered whether one could construct analog computation circuits and take advantage of

the analog information processing systems that may be intrinsic to cells. The researchers created an analog synthetic gene circuit using only three proteins that regulate gene expression and the fluorescent protein mCherry as a read-out. This synthetic circuit was able to perform additions or ratiometric calculations in which the cumulative fluorescence of the mCherry was either the sum or the ratio of selected chemical input concentrations. Constructing a digital circuit with similar computational power would have required a much larger number of components.

The design of analog gene circuits represents a major turning point in synthetic biology and will likely spark a wave of new research, which combines analog and digital computing when trying to engineer biological computers. In our day-to-day lives, analog computers have become more-or-less obsolete. However, the recent call for unconventional computing research by the U.S. Defense Advanced Research Projects Agency (DARPA) is seen by some as one indicator of a [possible paradigm shift toward re-examining the value of analog computing](#). (4) If other synthetic biology groups can replicate the work of Sarpeshkar and Lu and construct even more powerful analog or analog-digital hybrid circuits, then the renaissance of analog computing could be driven by biology. It is difficult to make any predictions regarding the construction of biological computing machines that rival or surpass the computing power of contemporary digital computers. What we can say is that synthetic biology is becoming one of the most exciting areas of research that will provide amazing insights into the complexity of biological systems and may provide a path to revolutionize biotechnology.

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