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What Is the Role of Circuit Design in the Advancement of Synthetic Biology? Part 3

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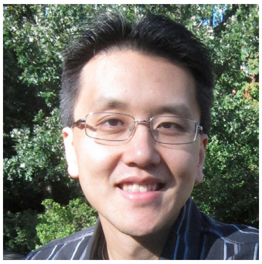
What Is the Role of Circuit Design in the Advancement of Synthetic Biology? Part 3

Different biological substrates dictate design rules and enable new functions.

Biological Design



Wilson Wong
Boston University

A long-standing goal of synthetic biology is to genetically reprogram biological systems to follow a set of user-defined rules. While many tools have been developed to tackle this challenge, increasingly complex genetic circuits with multiple inputs and outputs are required to perform more demanding tasks, such as cell-type classification for animal model development or antigen detection for cancer therapy. However, the engineering of such complex genetic circuits has thus far proven to be challenging. As such, improving circuit design will continue to be a major focus in synthetic biology.

Innovations in circuit design are often fueled by fundamental biological discoveries, which provide genetic parts with novel functionalities that can be repurposed by synthetic biologists. Interestingly, genetic parts with different functionalities may enable alternative circuit designs that can be exploited to simplify or augment existing genetic circuits. For example, sophisticated circuits can be created in a single transcription unit by cleverly arranging recombination sites because DNA recombinases can be co-opted to initiate and inhibit gene expression with equal efficiency in a single genetic layer. In contrast, transcription-factor-based circuits often require multiple interconnected transcription units to achieve the same behavior. As new discoveries enable the development of more complex genetic circuits, synthetic biologists will continue to leverage genetic circuits for achieving difficult biological design objectives and exploring novel design principles.

Beyond ‘Electronic’ Circuits

Cheemeng Tan
University of California, Davis

Through a series of works in the 1960s, Sugita applied the concept of electronic circuits in the analysis of chemical systems in vivo (Sugita, J. Theor. Biol. *1*, 415–430). Since this ground-breaking work, electronic-circuit design has been used as both an analogy and the conceptual framework for the design of synthetic biological systems. However, the two systems are fundamentally different: while an electronic circuit contains parts that are fixed on a board, a biological system contains parts that are transported in nano- to femto-liter compartments.

Despite the glaring contradiction, electronic-circuit design was critical to the initial phase of synthetic biology, leading to elegantly designed cells that perform logical calculations, pattern formation, oscillations, and bistable decision making. To build on this foundation, it may be time to create a new circuit design paradigm that transcends the framework borrowed from electronic circuits. The new paradigm would capture at least three properties of biological circuits that do not exist in electronic circuits.

First, biological circuits exhibit tremendous plasticity in their physical properties and spatial-temporal localization. Second, biological circuits integrate mechanical, optical, chemical, and electromagnetic signals. Third, biological circuits operate across multiple length scales through feedback loops that coordinate dynamics between the length scales. Based on this biologically inspired framework, we may finally design synthetic biological systems that match the sophistication of natural systems.

Biological Breadboard

Kate Adamala
University of Minnesota

Life is a very complex network of genetic circuits, and evolution is, in a way, natural iterative circuit design. Our ability to design artificial circuits in the lab is now approaching the level of complexity found in natural cell circuitry, and technological advancements have enabled a high-throughput approach to circuit design, modeled after the trial-and-error approach of Darwinian evolution.

I find it most fascinating that recent advancements in synthetic biology allow us to re-create natural complexity, not only by building artificial circuits in natural cells, but also by building whole cell-like bioreactors from scratch. With the ability to create artificial circuits matching the complexity of natural pathways, synthetic biology will finally fully live up to the promise of its name: we will build a fully autonomous synthetic cell.

We will learn a great deal about the general principles of life using circuits in a synthetic cell as a biological breadboard. We will study healthy and diseased natural pathways; we will be able to decode those natural circuits and their possible failure modes represented by various diseases. The ability to design complex circuits will amount to a potent tool for biotechnology, enabling novel pathways for biomanufacturing, and doing so completely outside of live cells will allow for greater freedom of design without the need to care for the well-being of the host cell.

Synbio for Advanced Materials

Xiaoxia Xia
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In my view, circuit design has played and will continue to play a fundamental role in synbio. So far, many gene circuits with increasing complexity have been constructed to understand naturally existing gene networks and to rewire endogenous circuits to maintain "healthy" metabolic and cellular homeostasis. It would be desirable to move beyond. Can we reprogram living cells to create novel functional materials and reconstitute organelle-like polymersomes in vivo?

Many biogenic materials, such as spider silk and bacterial flagella, are fascinating. Indeed, I am curious about the genetic circuits that control silk spinning and how to recapitulate the amazing properties of natural materials. My team focuses on the development of synthetic biology tools and systems for the design and sustainable production of silk-based materials. Currently, computational tools are used to recombine silk and other structural and biological building blocks and to make advanced materials with novel properties such as sensing, targeting, and dynamic functions, for wider applications.

It would be more interesting, yet challenging, to construct gene circuits for the creation of artificial microcompartments within living cells from self-assembled nano- to micro-scale materials. The formation of these polymersome- and organelle-like compartments helps achieve spatiotemporal control over cellular processes by promoting metabolic channeling, directing transcription, and translation and by performing novel tasks. By doing so, delivery vehicles and intracellular spaces can be generated to fulfill many biomedical needs.

Dealing with Imperfection

Tobias Erb
Max Planck Institute for Terrestrial Microbiology

How does nature deal with imperfection? Biological systems operate far from thermodynamic equilibrium (better known to us as death), but how do they manage to keep genetic and metabolic circuits running despite many perturbations? Building efficient, robust biological circuits is not only technologically relevant, but also teaches us about the fundamental principles of life.

Constructing metabolic circuits de novo by combining enzymes from different biological backgrounds with no apparent evolutionary relation taught us several valuable lessons. Metabolic circuits not only require that each enzyme of the circuit recognizes its respective substrate, but also notably that it discriminates against all other intermediates in the network. If not, this can lead to deleterious side reactions—"metabolic noise," which will inevitably result in equilibrium formation and bring any metabolic circuit to a halt.

There is an upper limit to reaching perfection on the individual enzyme level, and biological systems use other principles to keep metabolism running smoothly. For instance, reactions and intermediates can be separated in different reaction chambers, compartments, or organelles to isolate incompatible chemistries from each other within a cell. Alternatively, more enzymes and reactions can be added to metabolic circuits so as to remove or recycle deleterious side products, a strategy that we and others now call "metabolic proofreading." Thus, biological imperfection is very often counteracted by increased complexity. Implementing these natural strategies into the design of next-generation circuits will be key to advancing synthetic biology toward achieving life-like features.

A Role for Chemistry

Abhishek Chatterjee
Boston College

Biology is driven by sophisticated molecular circuits that integrate complex signals from the environment and respond with precise functional outcomes over a wide range of timescales. It has inspired synthetic biologists to build non-natural biological circuits that are engineered to make complex decisions in response to specific cues. Such abilities will be at the heart of creating engineered biological systems with useful new properties for applications such as precision therapeutics. Designing such engineered circuits to date has largely depended on regulation at the level of transcription and translation, owing to the relative ease of rationally manipulating these processes.

However, much of the regulatory prowess in biology is derived from molecular processes that operate beyond the central dogma. For example, small-molecule regulators and reversible chemical modifications of specific amino acid residues can be used for versatile and tunable control over the activity of proteins. Developing an orthogonal set of non-natural small-molecule regulators and reversible chemical modifications to control protein function, while challenging, is necessary to create engineered biological circuits with the same regulatory capacity as their natural counterparts. The ability to access a new dimension of functional regulation using such orthogonal chemical entities holds the key to unlock the full functional potential of synthetic biological circuits.