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Build life to understand it

Michael Elowitz and
Division of Biology, California Institute of Technology, Pasadena, California 91125, USA

Wendell A. Lim
Department of Cellular and Molecular Pharmacology, University of California, San Francisco, California 94158, USA

Michael Elowitz: melowitz@caltech.edu; Wendell A. Lim: lim@cmp.ucsf.edu

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This year's publicity about Craig Venter 'creating' life[1], and this week's report on the promise and perils of synthetic biology from US President Barack Obama's commission on bioethics, threaten to obscure the most important impact of this field. Synthetic biology is redefining the discipline of biology and helping people reach a deeper understanding of how life works.

Conventionally, biologists have sought to understand life as it exists. Increasingly, however, from stem-cell reprogramming[2] to microbial factories[3], researchers are describing what is and exploring what could be. An analogous shift occurred in physics and chemistry, especially in the nineteenth century. Like biology, these fields once focused on explaining observed natural processes or material, such as planetary motion or 'organic' molecules. Now they study physical and chemical principles that govern what can or cannot be, in natural and artificial systems, such as semiconductors and synthetic organic molecules[4].

The expansion of biology from a discipline that focuses on natural organisms to one that includes potential organisms (see 'Beyond the natural') will have three long-term effects. First, it will enlarge the community of biologists to include researchers with different assumptions and goals, such as engineers. Second, it will alter the way in which scientists address the fundamental problem of how biological systems work. Integrating reverse and forward engineering approaches will free biologists to uncover fundamental principles that explain, unify and extrapolate beyond mechanisms observed in specific model systems. Third, it will provide a new conceptual basis for teaching biology — one founded on stimulating inquiry from students as to how biological components and modules could be used to implement complex functions.

Although traditional disciplinary boundaries are dissolving, the cultural differences between scientists and engineers remain strong. For biologists, genetic modification is a tool to understand natural systems, not an end in itself. Thus, making biological systems 'engineerable' — a goal of engineers in the field of synthetic biology — can seem pointless. Many biologists wonder why engineers fail to appreciate the intricate, beautiful and sophisticated designs that occur naturally. Engineers are often equally perplexed by biologists. Why are they so obsessed about the details of one particular system? Why don't they appreciate the value of replacing a complex and idiosyncratic system with a simpler, more modular and more predictable alternative? These misunderstandings can make for fascinating conversations, but they can also prevent mutually beneficial synergies.

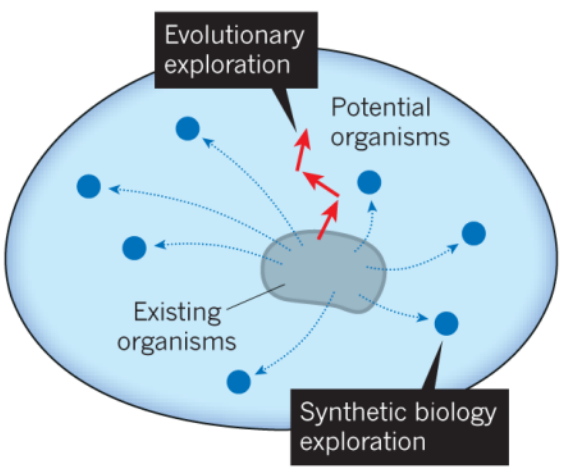
Biologists and engineers need to appreciate the complementarity of their approaches. Below the surface, these two communities have common interests and goals that can, and must, be addressed from both directions — forward and reverse engineering.

SAME CHALLENGES

Traditional biologists seek to reverse engineer natural biological systems — to understand how their molecular circuitry, composed of interacting genes and proteins, gives rise to observed behaviour. Synthetic biologists seem to do the opposite. They forward engineer new behaviour using well-understood genetic components and as simple a design as possible. Both communities face the same daunting challenge: how to relate the architecture of a gene circuit to its behaviour in a cell or tissue.

Synthetic circuits can provide insights into natural circuit-design principles that would be difficult or impossible to obtain using conventional perturbations of natural systems alone. Consider signalling. Biologists have discovered that a handful of canonical pathways are used repeatedly across species, tissues and stages of development. What is it about this set of pathways that makes it sufficient for the development and physiological function of a complex organism? To address this question requires an understanding of what each pathway can do. Synthetic biologists can systematically engineer a diverse range of signalling-pathway architectures and analyse them in relative isolation from any particular set of downstream processes[5,6]. These architectures may include natural, as well as new, configurations. The results could provide a higher-level view of signalling in which one could associate each pathway and architecture with a specific functional repertoire, instead of thinking about them primarily in terms of their molecular interactions.

A second example of where synthetic biology can provide a complementary approach is metabolic networks — one of the most active frontiers in the field. Biology has conventionally focused on understanding the metabolic pathways in particular organisms. Synthetic biology enables researchers to consider what types of metabolic networks are possible by combining enzymes from all species. Such work has focused on engineering novel metabolic pathways that produce specific molecules for medicine and industry. These efforts can also address fundamental biological questions. For example, what trade-offs exist between metabolic efficiency and flexibility? Are there fundamental principles for how cells set up their metabolic economy and synthesize and distribute key chemical precursors[7,8]? These questions could be important for understanding the diversity of metabolic networks in natural microbes as well as in biomedically important systems such as cancer, in which cells alter their metabolism[9].



Synthetic-biology approaches may also provide insights in developmental biology. They could be used to tackle fundamental questions of what types of multicellular patterning processes are possible, and what types of circuits — combining signalling, regulation, differentiation and morphological change — would be sufficient to program the formation of organisms.

Using well-characterized signalling pathways, transcription factors and regulators of cell morphology and division, it should become possible to explore a range of natural and non-natural developmental circuit architectures. This would start with very simple patterns that could be generated in relative isolation from other developmental processes in the simplest systems. Eventually, synthetic developmental systems should yield a deeper understanding of morphological programming, provide insights into natural developmental systems and possibly enable applications in tissue engineering.

The convergence of engineering and biology could bring exciting new ways of teaching biology. Conventional biology, focused on understanding the structure, mechanism and origins of extant beings, tends to involve memorizing nomenclature and facts. In some cases, this approach can obscure unifying principles and concepts.

Instead, teachers could start by challenging students with the question: ‘how might you build a biological system that performs a particular function?’ Students could be asked to deduce underlying design principles — for example, to identify the general types of circuit modules necessary or sufficient to implement a given behaviour in cells. Students thus equipped with organizing concepts could better navigate the sea of confusing nomenclature in natural living systems. Inconsistencies between idealized designs and actual examples would raise important questions about assumed functions, and about constraints inherent to the evolutionary process. In physics and engineering, this kind of approach is commonplace and can be effective at engaging and motivating students.

Such concepts could be introduced to teenage students who are just starting to think more deeply about the mechanisms underlying plants and animals. Requiring theory, computation and experiment would better equip students for multidisciplinary research. It would also expose them, at an earlier stage, to the conceptual and creative aspects of the scientific process, potentially attracting a broader range of people to biology.

Many technical and fundamental obstacles remain before the design and construction of synthetic biological systems can become routine. And as discussed in the commission report, the societal challenges may be equally formidable. Bringing together the energies and expertise of diverse communities that think about biological problems in different terms is a good first step towards taking full advantage of the many opportunities that lie ahead.

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