What Have the Principles of Engineering Taught Us about Biological Systems?

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Engineering combines math and physics to create something that is not existent in nature and also useful for society. In this process, engineering has been uncovering a large number of design principles that are general enough to be relevant to many applications. When approaching biology, critical analysis of natural motifs through an engineering lens has often improved our understanding of cellular functions.

The functioning of many biological clocks can be explained by the design principles of oscillators in electrical engineering, i.e., they are negative feedback systems with lag or hysteretic systems with negative feedback. The core mechanism of cellular chemotaxis can be reduced to an integral control action that is approximately implemented by a protein modification cycle operating in saturation regimes. Cascades of protein modification can function like electronic isolation amplifiers, mitigating the undesirable effects of loads applied by their gene targets.

These and similar discoveries require mutual learning: the engineer needs to acquire biological knowledge and the biologist needs to understand engineering principles. The activation energy of both learning processes is, in general, very high. Therefore, true progress in both using engineering to understand biology and making synthetic biology an engineering discipline will likely require the creation of new education curricula. The recipient of this new education would be someone with a primary expertise (engineering or biology) and a sufficiently deep knowledge in the complementary expertise to significantly lower the activation energy required for mutual learning in an interdisciplinary research project.

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Engineering requires the ability to be replicated. Engineering therefore relies on well-understood principles, communicated concisely, that allow other individuals to create in the absence of the original designer. While biological systems appear to be ad hoc in many ways, the more we begin to understand them, the more we begin to see engineering principles of abstraction, modularity, redundancy, self-diagnosis, and hierarchy. Engineering has taught us to look for these aspects in nature and to try to understand them as such.

By viewing seemingly random biological design "decisions" through an engineering lens, we have found powerful patterns, intricate mechanical mechanisms, and evolved modularity. Engineering has taught us how to take those elements, isolate them, and then introduce them into new designs to leverage their function. Engineering has shown us that biological systems can be composed systematically to be more than the sum of their parts. Above all, engineering has given us a sense of empowerment to try to improve on biological systems to fight disease, improve manufacturing, and provide sustainable energy solutions.

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"Would you like to try turning a printer into an iPad by pulling out a few transistors and maybe adding a few, or prefer to design an iPad from scratch?" We all agree that the first proposition is rather absurd, and yet much of cellular engineering proceeds by deleting (and sometimes adding) genes. Often, educated guesses are made about the qualitative functions of genes to be deleted or added. As a result, some successes exist.

One might even argue that the "turning printer into iPad" approach to cells has garnered more practical successes than the alternative approach—rational design, or as I define it, synthetic biology. To design biological circuits truly rationally, we need to understand the properties and context of biological molecules quantitatively. Here's why: Can you reasonably aspire to build a robust electronic circuit by stringing together resistors of unknown resistance values, without knowing Ohm's law and with little understanding of how these components drift under temperature fluctuations? Of course not.

One of the great contributions of synthetic biology is its sobering effect, clearly indicating to us that our extensive qualitative knowledge of biology is far from sufficient for building circuits that work predictably and robustly. Filling this knowledge gap will require experiments that can pinpoint quantitative parameters and facilitate general theoretical understanding. Crucially, the research community has to value such experiments that do not necessarily discover new genes or mechanisms but that might be setting the stage for a future in which we can engineer biological circuits with a CAD software.

Donald Ingber
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Insights from mechanical engineering have transformed the way biologists approach questions relating to cell fate switching, morphogenesis, and disease development, which has led to the emergence of the field of mechanobiology. Microsystems engineering has been applied to produce new lab-on-a-chip approaches, such as microfluidic culture systems for studying complex cell behaviors, ranging from cell migration to tumor angiogenesis, under more physiological conditions. Synthetic biology approaches being used to gain deeper insight into gene regulation also would not exist without understanding of electrical engineering principles of circuit design.

However, biology is also transforming engineering, as evidenced by the new discipline of Biologically Inspired Engineering, which seeks to leverage biological principles to develop new engineering innovations. Examples of bioinspired technologies that have emerged from this recent melding of disciplines include mechanotherapeutics that become activated by local mechanical cues; microfluidic human ''organs-on-chips'' as replacements for animal testing; self-assembling molecules that form into cancer-seeking nanotechnologies; and engineered biological circuits that can be used to reprogram cells to produce therapeutics, heal tissues, manufacture biofuels, or generate electricity. Thus, while the merging of biology and engineering has already begun to transform biology and medicine, the potential for the future appears to be even greater.

Ahmad S. Khalil
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Engineering and biology are intimately linked through the concept of function: biological systems are selected for functional properties, while engineered ones are designed for them (Hartwell et al., Nature *402*, C47–C52). In biology, we now appreciate that these properties arise from systems of interacting molecules. Engineering gives us a framework to make sense of this.

One way is by infusing a philosophy of building. We now routinely build functional modules in cells from constituent molecular parts. Building is an effective way of exploring potential solutions to reveal design principles, e.g. building molecular oscillators reveals that negative feedback loops are minimally sufficient while positive feedback provides robustness and tunability. Building also offers a rigorous test of modularity, and has helped to define these functional modules as fundamental units of organization in biology.

Engineering has also taught us that quantitative description is essential, especially the use of phenomenological models that abstract beyond molecular detail. A truly elegant example concerns mammalian limb development. Researchers exploring how digits form found that progressive deletion of Hox genes resulted in progressively more digits formed (Sheth et al., Science *338*, 1476–1480). This surprising result was only made intuitive when viewed through the lens of a mathematical model of wave pattern formation developed over 50 years ago by Alan Turing, not coincidentally a pioneer of math and engineering.

Sri Kosuri
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Engineering is the application of math and sciences towards useful ends. In this context, engineering broadly enables biology through the development of methods and instruments to measure, build, and interface with biological systems. For example, new sequencing technology has revolutionized genetics and biochemistry. Imaging technologies such as super-resolution and cryo-electron microscopy give us clearer pictures on the inner workings of cells. Finally, machine learning and statistics enable powerful methods for making sense of the massive datasets coming from these new tools.

Alternatively, we can ask: what are the principles of engineering biology, and how might they help us understand biological systems? Historically, the principles of selective breeding for plant and animal domestication provided deep insights into genetics. The more recent engineering of proteins and organisms has produced stunning successes such as GMOs for increased crop yields and molecular tools such as polymerases and CRISPRs.

However, thus far, the engineering of these biological products have more borrowed from rather than contributed directly to our understanding of biology. I believe this will change in time. The renewed focus, especially amongst the protein engineering and synthetic biology communities, on discovering the principles of reliable engineering of novel biological functions will likely help us better understand the mechanisms, design principles, and limits of natural systems.

Arthur D. Lander
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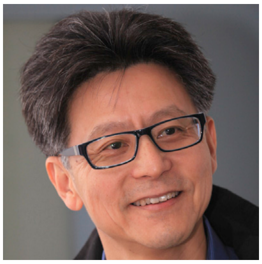
After years of physics-envy, biologists are coming around to the idea that the beauty and complexity of the living world has less to do with emergent consequences of physical laws than with the engineering constraints of operating in a world that is messy and unpredictable. Products of engineering—cars, airplanes, computers, the internet—nicely illustrate how the need for robust performance naturally selects for highly networked systems full of feedback and redundancy. Such examples help explain the daunting—and otherwise seemingly unnecessary—complexity of biological networks.

In particular, control theory, the formal theory of how performance can be guided in the face of disturbances, has been remarkably useful to biologists, transforming our understanding of metabolism, signaling, chemotaxis, sensorimotor coordination, tissue growth, and many other phenomena. Where before we saw only linear pathways, now we see feedback and feed-forward motifs, proportional and integral controllers, switches, and timers. We accept that engineering objectives like robustness, and not just phenotypes, are the object of natural selection.

Moreover, the conduit between engineering and biology is starting to run both ways, as we appreciate that biological systems may solve some control problems by exploiting phenomena that engineers usually try to circumvent, such as stochasticity, strong non-linearity, and spatial dynamics. In the long run, biology may foster the development of new engineering theory as much as engineering helps biology.



Chao Tang
Peking University

There is a convergence between man-made and naturally evolved systems. Dragonflies, geese, and Boeing-777 all follow the laws of aerodynamics so that their cruise speed scales with the 1/6 power of weight. Recent EM imaging revealed that the shape of the endoplasmic reticulum in the cell is strikingly similar to a spiral parking structure, both of which are the consequence of maximizing connected surface area in a confined space. Engineering principles such as integral control and robustness were found to be implemented in diverse biological systems. The intimate relation between function and form often dictates a system, biological or man-made, to evolve to adopt the design principle best suited for the function.

On the other hand, I think there are profound limitations on how far we can go in applying current engineering principles to biological systems. Man-made and natural systems differ in many aspects, such as physical and chemical constraints, internal and external environments, complexity, energy scales, and the spectrum of functions. For example, it is not clear that our brain uses the same principle to process information as in a computer. Furthermore, nature has so far proved to be a superior inventor and innovator over us. While it is fruitful to comprehend biological complexity in terms of engineering principles, perhaps a fascinating question in the near future would be "what can biological systems teach us about engineering (and physics and mathematics)?"