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Synthetic Biology: evolution or revolution? A co-founder's perspective

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In this article, we relate the story of Synthetic Biology's birth, from the perspective of a co-founder, and consider its original premise — that standardization and abstraction of biological components will unlock the full potential of biological engineering. The standardization ideas of Synthetic Biology emerged in the late 1990s from a convergence of research on cellular computing, and were motivated by an array of applications from tissue regeneration to bio-sensing to mathematical programming. As the definition of Synthetic Biology has grown to be synonymous with Biological Engineering and Biotechnology, the field has lost sight of the fact that its founding premise has not yet been validated. While the value of standardization has been proven in many other engineering disciplines, none of them involve self-replicating systems. The engineering of self-replicating systems will likely benefit from standardization, and also by embracing the forces of evolution that inexorably shape such systems.

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The seeds of Synthetic Biology

As a first year graduate student in 1996, I (Tim) was possessed of the desire to build Luke Skywalker's robotic arm in Star Wars. After a short investigation of nerve/machine interfaces, I concluded that engineers and scientists would grow arms back before they made machines that could interface with nerves with anywhere near the fidelity needed for fully integrated robotic arms. Thus, I set out to figure out how to grow arms back.

Considering that an arm is composed of a myriad of different tissues and cell types, all of which possessed the same DNA instruction set, it was clear that cells were operating as a sort of finite state machine — possessing the ability to progress to and remain in one of many distinct gene expression states [1]. To control the growth and differentiation of tissues, it seemed we would need to build control programs that could manipulate the states of cell differentiation, and direct the progression of cell division through those states [2,3].

I discussed the idea of building finite state machines in cells with Carson Chow, a Research Associate Professor at Boston University working alongside me in Jim Collins' lab. Chow pointed me towards the theory of Hopfield networks — a type of neural network design that could be 'programmed' to store a multitude of complex patterns, or states [4]. Hopfield networks could be constructed from large numbers of switches wired together with programmable weights on the signal transmission between them (Figure 1). Hopfield networks were a paradigm for human memory and, we theorized, could also be applied to encode memory in gene networks.

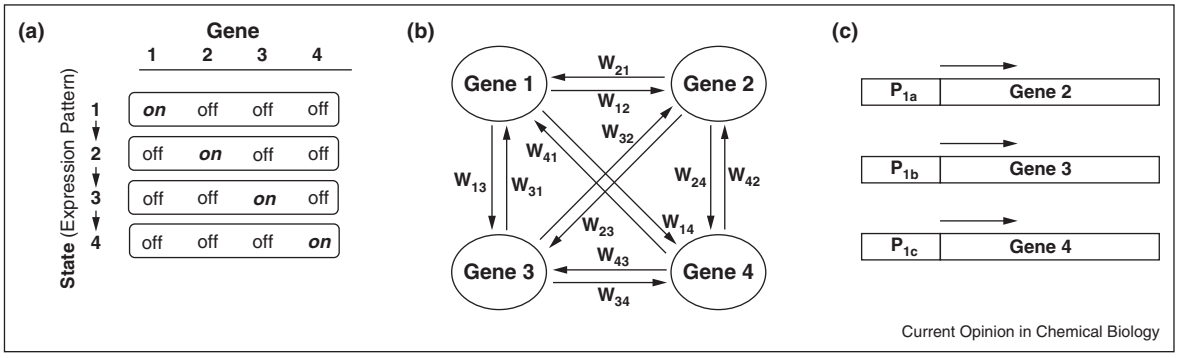
As I pondered the means to implement a Hopfield network in cells in early 1998, I realized a single-bit memory element might be a more practical place to begin building cellular memory. I recalled the transistor-transistor RS Latch from my introductory course in electrical circuits, the design for a single-bit memory element in digital computers. I realized such a device could also be constructed from two cross-repressive promoters. A genetic version of the RS Latch could be useful in regulating gene therapies and might also demonstrate the foundation for more complex programmable logic in cellular components [5•,6]. Sixteen months later this idea was published as the 'genetic toggle switch' [7••], a work that captured the imaginations of the news media looking for the next innovation in computing and biotechnology [8,9], and helped to kick-off the field of Synthetic Biology [10]. This work demonstrated some of the founding ideas of Synthetic Biology — reusable parts, predictive mathematical design and simulation of the circuit properties, and elements of programmable digital logic.

The premise of Synthetic Biology

Ostensibly, we (Tim and Kristy) are practitioners of Synthetic Biology, but we still struggle to use the term to describe what we do. There are two reasons.

First, since the modern re-coining of the term Synthetic Biology in 2001 [11•], the definition of the field has evolved to a breadth so extensive that it has become synonymous with the terms 'Biological Engineering' and 'Biotechnology'. In gaining such breadth it has lost some of the novelty and uniqueness that helped launch it into existence. The retitling of an existing field does not

Figure 1



Figures reproduced from a 1998 Boston University whitepaper submitted by Gardner, Collins and Cantor to the Office of Naval Research. The paper outlines the concept of a finite state machines programmed into gene expression networks called 'genetic applets' [5•]. **(a)** Example of a sequence of expression patterns produced by a four-state gene network. Transitions from one state to the next might be stimulated by a genetic oscillator when one protein reaches a peak level. Each expression state might trigger a sequence of downstream regulatory or metabolic activities in the cell, thereby forming a 'genetic applet.' **(b)** The general architecture of a four-gene network constructed as a Hopfield network. The weights, w_{ij}, determine the sequence of expression patterns stored by the network. A network of N genes can store a maximum of N patterns. **(c)** A simplistic example of how Gene 1 in the could be coupled to Genes 2–4 to form the Hopfield network. Promoter 1 (P1a-c), which is activated by Gene 1, is spliced to Genes 2–4. The strength of the coupling could be altered by varying the promoter strengths or the regulatory activities of Genes 1–4.

constitute an advance of knowledge — rather it more likely creates distractions in the form of uncertainty among the general public and government organizations about what it is and whether it deserves closer regulatory oversight [12,13]. Synthetic Biology can offer more to Biological Engineering when it represents and pursues its distinct founding idea — the standardization and abstraction of biological components.

Second, the founding idea of modern Synthetic Biology has been promoted to a level of significance beyond its demonstrated value [14,15]. While Synthetic Biology has rapidly catapulted itself to the status of a field, it remains fundamentally a proposition originally formulated by Adam Arkin and Drew Endy in a whitepaper submitted in 1999 [16] to help DARPA define its Biocomputing research program [17]:

> ''Without standardization, the qualitative design methods used in other engineering fields are simply inapplicable. [In practice, rational design of biological systems] is usually realized through an expensive stepwise trial and error approach or through mutation and selection. Furthermore, these otherwise practical approaches are limited in terms of the problems they can solve.
>
> To address this deficiency, we propose herein a program to produce a set of well-characterized and systematized biological components that can be generically assembled to create custom biological circuitry.''

Put simply, the central premise of Synthetic Biology is that standardization of reusable biological components is the most efficient and effective way to engineer biology. This is a tantalizing concept, one that has nearly 200 years of evidence from other engineering disciplines to support its value [18], yet one that also remains largely unvalidated in the engineering of biological systems. It is a premise very much worth attempting to substantiate, but until then the 'technosalvational rhetoric promise and peril' [11•] is premature.

From genetic engineering to cellular computing and genetic applets

Synthetic Biology has repeatedly arisen in the past decades with the first explicit references dating back at least to the turn of the 20th century (Figure 2). Luis Campos and Rob Carlson, in their contemporaneously published works [11•,19•], trace the first use of the term to the work of Stéphane Leduc who published his attempts to create artificial life from physio-chemical substrates in 'La Biology Synthétique' in 1912. From 1904 through the 1930s, researchers at Carnegie Institution's Station for Experimental Evolution at Cold Spring Harbor pursued the formation of 'synthetic new species' through the use of mutation and breeding to gain control over evolution and produce new and useful varieties. This work was called 'genetic engineering' (including its eugenical applications) until rebranded in the 1970s with the emergence of recombinant DNA technology. As Campos explains, the concept of re-usable parts for designing biological systems was well-recognized by the pioneers of modern genetic engineering in the 1970s:

> 'The essence of engineering is design,' Robert Sinsheimer wrote in 1975, 'and, thus, the essence of genetic engineering, as distinct from applied genetics, is the introduction of human design into the formulation of new genes and new genetic