Microbes & Manufacturing: Moore's Law Meets Biology

Patrick Boyle, Ginkgo Bioworks

Abstract

Biology is the most powerful manufacturing technology we know of. Proof of this is all around us: at the continental scale, the Earth's surface is defined by plant life, and we've harnessed that with agriculture. At the nanoscale, biological systems routinely self organize with a precision that can't be matched by our most advanced silicon chip fabrication methods. Even petrochemicals, the defining building block of 20th century manufacturing, are derived from the decomposition of prehistoric biomass. For over four billion years, biology has been evolving solutions that we are now beginning to understand and adapt. For example, antibiotics, aspirin, and many other drugs were isolated from nature. Today, we can further engineer microbes to produce new drug variants. Similarly, spider silk has been prized for its high strength to weight ratio and its promise as a next-generation material. Today, multiple companies are producing spider silk via engineered microbes. Many petrochemicals can now be produced from sustainable carbon sources via engineered microbes. Traditional petrochemical products are now being enhanced with biological components. For example, modern laundry detergent contains enzymes (again from engineered microbes) that function in cold water and save heating energy. All of these applications are advantaged by the fact that biological systems self-assemble, self-repair, and self-replicate. In effect, a microbrewery can serve as a common manufacturing platform for any number of products, simply by engineering the microbe that is grown in the fermenter. These advances are possible now, because we finally have the tools to

read (“sequence”) and write (“synthesize”) DNA. Both of these technologies have been improving at a rate faster than Moore’s law for nearly 20 years. This exponential improvement in our ability to program DNA is driving a technological revolution that rivals the computer revolution of the 20th century, but impacting manufacturing at a scale not seen since the industrial revolution of the 19th century.

Ginkgo Bioworks is a Boston-based company that leverages software and automation to engineer biology for customers in many different sectors including those traditionally associated with biotechnology, such as agriculture and pharmaceuticals, and those that are being transformed by biology, such as materials, electronics, and nanotechnology. This presentation will provide a brief history of the field and demonstrate how biology as an engineering substrate is a transformative manufacturing technology.

The History of Synthetic Biology

Manufacturing with biology far predates our ability to genetically engineer biology. The domestication of plants and animals for food, clothing, and other materials is synonymous with the emergence of civilization, as these biotechnologies allowed humans to settle in towns and cities with access to cultivated bio-based products. These domestication efforts were considerable engineering feats in their own right: modern corn bears little resemblance to the teosinte grass that served as the starting point for domestication (Doebley, et al., 2006). Similarly, many distinct vegetables such as mustard, broccoli, cauliflower, and even kohlrabi are human-crafted variants of common ancestor species (Dixon, 2017). Dogs, cattle, and other animals were similarly differentiated from their wild ancestors via selective breeding over thousands of years. In the 20th century, the advent of genetic tools, as well as the ability to read and write DNA allowed biologists to consider directly engineering biological organisms for the first time. Many of the earliest examples of genetic engineering have been extraordinarily successful: human insulin produced in microbes, developed by Genentech in the 1980s, allowed a transition away from the use of animal insulins isolated from pig and cow pancreases (Fraser, 2016). In agriculture, genetically modified crops entered use in the United States in the 1990s. Today, more than 90 percent of soybean, cotton, and corn grown in the US is genetically modified (USDA, 2019).

Tom Knight, one of Ginkgo's founders, is also widely considered as one of the founders of the field of Synthetic Biology (Bluestein, 2012). Dr. Knight is an Electrical Engineer by training, having worked on early minicomputers in the 1960s and 1970s, and contributing to projects such as ARPANET. In the 1990s, while teaching semiconductor design at MIT, Dr. Knight became interested in engineering biology, partially as a means to reach the end of Moore's Law for semiconductors. Simply put, biology appeared to be the only technology capable of coordinating atoms with nanometer precision into complex three-dimensional structures. For example, bacterial flagella (tail-like features that propel many bacteria) are self-assembling rotary motors with a diameter of approximately 25 nm which rotate at greater than 100 Hz. A typical *Escherichia coli* cell is about 1 μm in length and will have several flagella (van den Heuvel & Dekker, 2007). Then and now it is hard to imagine how to design machines at the nanometer scale of comparable complexity without biology. Inspired by this, Dr. Knight—along with other

Electrical Engineers, Computer Scientists, and Biologists—began to meet regularly to discuss the application of engineering principals to biology. DARPA worked with this group to convene an ISAT study in 1996 on "Cellular Computing" that laid the groundwork for the field: seeking to develop methods to understand and program DNA for the purposes of engineering biological organisms to produce new products (Knight & Matsudaira, 2016). Synthetic Biology combined efforts from many parallel fields: computer science and electrical engineering abstractions to describe cellular circuitry, metabolic engineering engineer the metabolic pathways of cells, genetics to understand the control elements of gene expression, systems biology to measure and simulate cellular systems, and more. Many of the principals developed in the 1996 ISAT study remain relevant to understanding the approaches and applications of synthetic biology today. In particular, a technology development roadmap from that study predicted the development of progressively better tools and modeling capabilities that predicted much of today's rapidly-developing Synthetic Biology "stack" (Figures 1 and 2) (Canine, 2018).

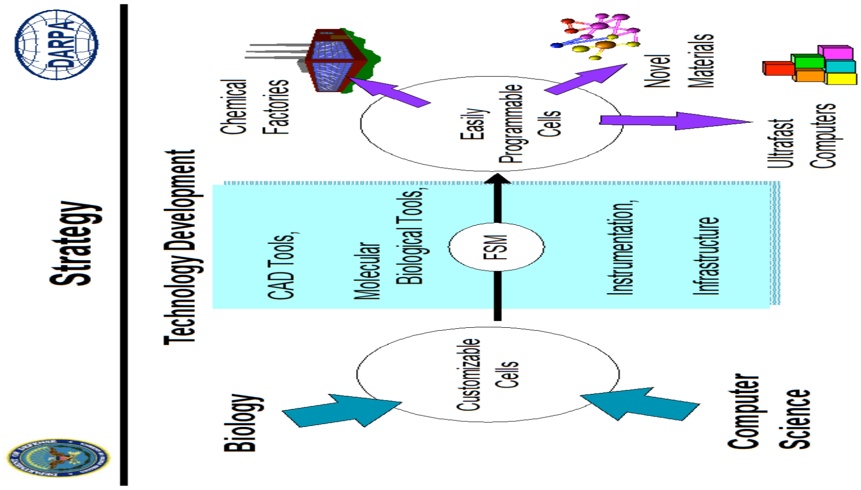

Figure 1. Excerpt from 1996 DARPA ISAT Study on "Cellular Computing" (Knight & Matsudaira, 2016). Image shared under Creative Commons license (CC BY-NC-ND 3.0 US)

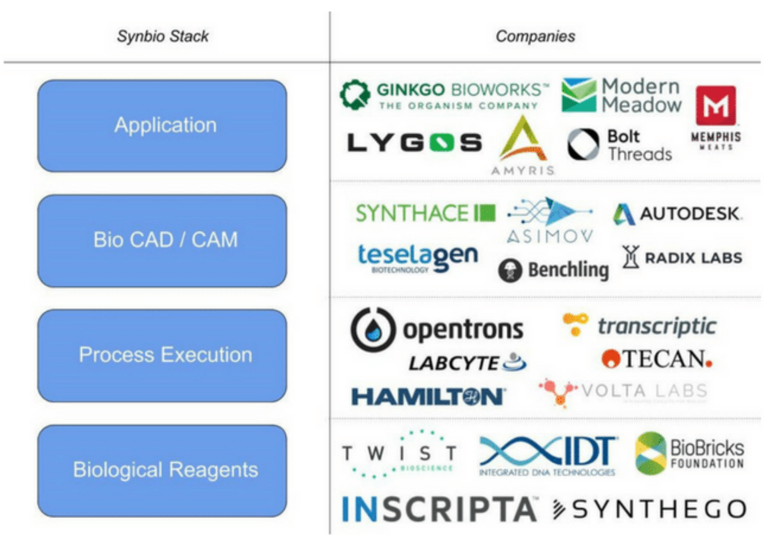

Figure 2. Overview of the Synthetic Biology technology stack from 2018. Figure by Will Canine (Opentrons), reused with permission from Synbiobeta (Canine, 2018)

Design principles for synthetic biology

Two founding design principles of synthetic biology remain especially relevant today: the concept of reusable parts and the engineering design cycle. First, synthetic biologists seek to identify and take advantage of modular subunits of biology as reusable parts, to allow the design of more complex systems. For example, repurposing genetic control switches such as promoters (the DNA elements that control transcription of a gene into messenger RNA), ribosome binding sites (RNA elements that control the translation of messenger RNA into protein), and other genetic parts have been used to construct oscillators, logic gates, and memory circuits in cells (Boyle & Silver, 2009). The engineering design cycle breaks down the process of engineering into three stages: Design, Build, and Test. In contrast to other engineering disciplines, synthetic biologists engineer organisms shaped by evolution, not design. As such, Design-Build-Test in biology requires many more iteration loops than is typical for more mature fields such as mechanical engineering (Petzold, et al., 2015). Many successes in synthetic biology follow hundreds or even thousands of failed designs, and are often only function in a narrow range of conditions, such as a tightly controlled fermentation tank. These challenges have led to a worldwide effort to develop better “foundries,” facilities which leverage automation to enable rapid prototyping of biological designs, often by conducting many experiments in parallel (Hillson, et al., 2019).

Synthetic biology has been an interdisciplinary field since its inception, and a number of trends in design, build, and test technologies have accelerated progress. On the “design” front, systems biology, modeling of cellular systems, and data science have enabled synthetic biologists to develop better design algorithms. As in many other fields, machine and deep learning methods are being applied to large biological datasets to refine biological designs (Camacho, et al., 2018). “Build” technologies in biology have centered around the ability to read and write DNA, as DNA is the core programming substrate for biology. Here improvement has been defined by two technologies improving faster than Moore's law: DNA sequencing and synthesis. Over the past 20 years, the cost to sequence a human genome has fallen more than a million fold, to less than $1000 per genome (National Institutes of Health, 2019). This revolution in sequencing technology has led to exponential growth in the number of sequenced genomes across the tree of life, with these novel genes representing novel functional parts for synthetic biologists. Similarly, the cost of DNA synthesis has steadily decreased to today's price of pennies per base pair (Carlson, 2017). DNA synthesis is impressively cheap considering the chemistry involved, but still represents a key bottleneck to progress: imagine paying $0.07 per bit when writing a software program. "Test" approaches in biology often make use of cheap DNA sequencing as readouts, and new high throughput methods for mass spectrometry are allowing researchers to measure the majority of metabolites and proteins in engineered cells (Petzold, et al., 2015).

Security for Biology

Synthetic biology is the only engineering discipline where the engineers are made of the same substrate that they are engineering. Since the advent of the first DNA engineering technologies in the 1970s, researchers and the broader community have raised concerns about the potential mis-use of engineered biology to cause harm. As early as 1975, researchers convened to consider the hazards of engineering DNA (Berg, et al., 1975). In Cambridge Massachusetts, a series of public hearings were held in 1976 to develop guidelines for using DNA editing technology as a research tool (MIT Infinite History, 2019). These hearings and resulting regulations (such as standard biosafety ratings) have been credited for the emergence of

Cambridge and Boston as leading biotech hubs, as these regulations allowed universities and companies to perform this research in a sanctioned environment. Biology is also the only field of science for which all weapons made within that field are banned by international treaty (Archy, 2018). Despite these precedents, the rapid progress of biological research has led to continual re-assessments of biosecurity (National Research Council, 2004) (National Academies of Sciences, Engineering, and Medicine, 2017) (National Academies of Sciences, Engineering, and Medicine, 2018). Given the lessons learned in other fields of engineering—particularly in computing and the continual challenges of cybersecurity—anticipatory development of safety and security standards, methods of forensics and attribution, and design of biological safety mechanisms must be continually addressed. Some examples of these approaches include the BSL biosafety standard, the development of screening protocols to prevent the synthesis of known harmful sequences (Office of the Assistant Secretary for Preparedness and Response, 2015), and deep learning research to identify engineered DNA in sequencing experiments (Office of the Director of National Intelligence, IARPA, 2019).

Applications of Engineered Biology

Many of the applications of engineered biology today are products of engineered microbes. The fast growth rates, ease of engineering, and the ability to scale up production via fermentation. Many of the early applications for synthetic biology sought to produce sustainable drop-in replacements for products that are typically derived from petrochemicals, such as 1,3-propanediol (used in specialty polymers like Dupont's "Sorona" product), 1,4-butanediol (used in compostable plastics), lactic acid (used to produce poly-lactic acid polymers), and farnesene (both a fuel and bio-rubber monomer) (Gustavsson & Lee, 2016). The commercial viability of commodity petrochemical replacements was challenged by the falling price of oil in the 2000s, leading to a pivot to higher-value products. Today, most companies in the synthetic biology space are focusing on these types of products, like fragrances, higher-value materials, and drugs (Schmidt, 2017). Because fragrances typically command a high price but are produced in low volume, they made a natural starting point for companies seeking to develop and commercialize new bio manufactured products. This focus has parallels with the development of synthetic chemistry as a field, which initially focused on the production of high price low volume synthetic dyes before expanding to other products (Yeh & Lim, 2007). This approach to transfer the production of volume-limited high-value products to more scalable microbial platforms may be best exemplified by the current competition to produce cannabinoids via fermentation, with hundreds of millions of dollars invested in just the last two years (Synbiobeta, 2019).

Beyond drop-in chemical replacements, there are many new applications emerging that are unique to biology. More energy efficient laundry detergents contain enzymes that improve stain removal (Snejbjerg, 2018). Several companies, such as Indigo Ag, Pivot Bio, and (Ginkgo-affiliated) Joyn Bio are developing microbial treatments that enhance plant growth or lower the need for conventional fertilizer (Molteni, 2018). Next-generation materials like fermented spider silk may revolutionize textiles, with both Bolt Threads in California and Spiber in Japan developing clothing made of the product (Feldman, 2018). Spider silk, which is prized for its high strength-to-weight ratio, is also being explored as a product for aerospace use via a partnership between the German company AM Silk and Airbus (Hyde, 2018). Moving the production of silk to microbes means that the proteins that make up silk fibers can be rapidly customized to fit new applications. Similarly, there has been a growing interest in the production of animal proteins in microbes, allowing vegan production of meat and other animal products without harm to animals. Products such as the “Impossible Burger” by Impossible Foods in California use microbially produced leghemoglobin protein as a replacement for the hemoglobin proteins contribute to meat flavor (Wolf, 2019). A range of other companies (including Ginkgo spinout “Motif Foodworks”) are now pursuing the production of a wide variety of animal proteins to produce vegan foods, including dairy products and other animal-derived products like leather. This approach is also seen as a means to provide high-protein diets more sustainably, given the high energy requirements for meat production (Sheikh, 2019).

It is impossible to predict which of the many applications of synthetic biology will come to define the field as it matures. Unlike all other fields of physical engineering, biology is unique in that it depends on a programmable substrate in the form of DNA. As such, rapid progress has been made on the basis of exponentially improving tools for reading, writing, and debugging biological systems. While we may not know exactly where synthetic biology will take us, the stunning diversity of the natural world provides a compelling example of what can be achieved with biology.

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