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Viewpoint

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Engineering for the 21st Century: Synthetic Biology

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ABSTRACT: For years, scientists have hoped that biology would find its engineering counterpart − a series of principles that could be used as reliably as chemical engineering is for chemistry. Thanks to major advances in synthetic biology, those hopes may soon be realized.

As long as there have been efforts to understand biology and how organisms and particular biological mechanisms function, there have been parallel efforts to alter biology to better suit a specific need. Even before these organisms were understood on a genetic level, people were breeding animals to make stronger oxen or faster horses, mixing crop strains for higher yield or better flavor, or crossing flowers to create new colors.

But the tremendous complexity of biology has, in some ways, kept these approaches more art than science. The goal of using engineering principles to allow scientists to perturb known biological systems and either alter them slightly or even design completely new biological systems still remains a fundamental need in order to cure disease, produce biofuels, and improve crop yield.

Today, synthetic biology shows more promise than any previous attempt at creating a biobased engineering discipline. In the past 15 years, the nascent field of synthetic biology has made tremendous advances, beginning with the very first custom-built biological components and gradually progressing to a fully functioning synthetic genome. One of the latest achievements in this scientific field is a new approach to producing synthetic DNA at much higher capacity and far lower cost than current standards, which offers the opportunity for even more innovation.

Thanks to synthetic biology initiatives such as the International Genetically Engineered Machines (iGEM) competition, young researchers coming out of academic programs today are the first generation to grow up with a portfolio of biological building blocks at their disposal, making them the first to truly look at biology as a field to which standard engineering principles can be applied.

Synthetic bio is more than just an academic endeavor; by expert estimates, the opportunity for biosynthesizable approaches in the chemical development industry is $50 billion, while the same category in biofuels is expected to be a $500 billion market. Considering the potential for synthetic genes to revolutionize these and many other industries, the business opportunities for synthetic biology-based solutions go well into the trillion-dollar-plus realm.

In this Viewpoint, we will look at the significant accomplishments that have shaped today's synthetic biology landscape and consider what may be possible in the coming years based on recent innovations.

MILESTONES AND HIGHLIGHTS

In the past decade or so, scientists have made real progress in the push to develop a solid engineering foundation for biology. These leaps forward have come in three general categories: basic engineering tools, whole-genome approaches, and non-endemic fields such as electronics.

Within the basic engineering category, the first major accomplishments were two contemporaneous advances. In 2000, scientists built the first biological parts that could be used as basic elements for tuning any biological system. One team, led by Michael Elowitz and Stanislas Leibler at Princeton University, developed an oscillator that used three linked genes to turn off or on the production of certain proteins depending on the presence or absence of other proteins.[1] The other team, led by Boston University's Jim Collins, paired two genes to form a toggle switch, with each gene predisposed to turning off the other gene.[2]

From an engineer's perspective, the oscillator and toggle switch are among the most rudimentary of tools, but from a biologist's point of view, these were the very first reliable means to perturb a biological system in a predictable way. These tools and others that followed became the bedrock of the BioBricks Foundation and the Registry for Standard Biological Parts.

As more of these biological parts were developed, leaders in the synthetic biology field realized it was important to have a central repository where anyone could share their parts and access others. In 2003, the Registry of Standard Biological Parts was founded at the Massachusetts Institute of Technology (MIT) to facilitate this exchange; in 2006, MIT's Tom Knight and collaborators started the BioBricks Foundation, which added to that mission by trying to ensure that biological engineering would be conducted safely, openly, and for public benefit. Today, the registry houses more than 7,000 available parts.

To encourage the production of new biological parts and their use to perform the first real biological engineering projects, some of the pioneers of this emerging field launched a competition. Beginning as a month-long session at MIT taught by Drew Endy, Randy Rettberg, and Tom Knight, the program morphed into an annual competition drawing five teams in 2004 and 190 teams from colleges around the world by 2012.

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With its predominantly undergraduate participants, iGEM has spurred arguably some of the best synthetic biology innovations to date. As an added boon to the field, all new parts developed in the iGEM competition are submitted to the Registry of Standard Biological Parts. Examples of contestants' iGEM entries include BactoBlood, a substitute for red blood cells produced by engineered *E. coli*; a bacterial biosensor that changes pH in response to the presence of arsenic in drinking water; bacteria scented with banana or wintergreen; and bacteria that can produce a rainbow of colors in response to different levels of a particular inducer, such as light or a certain element.

Thanks to iGEM, which recently started a division for high school teams, a new generation is joining the scientific ranks, and it is a generation that has never known about biology without its engineering counterpart. As these young researchers complete their doctorates and start their own laboratories, it is a safe bet that they will contribute even more to the rapidly advancing realms of synthetic biology and biological engineering.

Meanwhile, as progress in building biological parts marches forward, an entirely different approach to synthetic biology has been gaining ground as well. Some scientists have been focused not on the parts, but on the whole, attempting to re-engineer entire genomes.

In 2010, scientists led by Craig Venter reported for the first time that they had synthesized a genome, inserted it into a stripped-out host cell, and created a functioning organism with the new genome. The team used two closely related bacterial species, *Mycoplasma mycoides* and *Mycoplasma capricolum*, as their synthesizing and host targets. The synthesized genome is very similar to the natural genome of *M. mycoides*, with a few genes deleted and some inserted errors to let scientists tell the difference. The genome was assembled inside a yeast cell; once finished, it was transplanted into a cell from *M. capricolum* that had its natural DNA removed. When that cell divided, the team confirmed that offspring cells included the synthetic, rather than the original, genome.[3]

This advance does not have the immediate applications of, say, the arsenic biosensor designed in iGEM, but scientists agree that it is a major step and might be helpful in understanding the origins of life, or the chemical history of bacterial strains.

There is another category of improvements in synthetic biology, and these often do not seem to have anything to do with biology at all. They can best be described as non-endemic innovations and are likely to have significant implications for other fields.

For example, just last year, George Church's lab at Harvard used synthetic biology to encode an entire book in DNA.[4] The scientists stored 70 billion copies of the book in DNA strands, all in the tip of a test tube. Using binary code, the team managed to preserve not just the text of the book but also its images and formatting. They demonstrated the ability to encode 1 million gigabits of information in just a cubic millimeter of DNA, which could be revolutionary to the electronics industry. At that rate, it would take just 4 g of DNA to store as much digital information as people create in a year.

Other non-endemic fields in which synthetic biology holds promise include DNA-based computing, in which DNA strands replace silicon microprocessors, and alternative energy sources, for which engineered plants or bacteria could produce biofuels more efficiently than native strains.

THE COMING REVOLUTION

Despite these remarkable success stories, the synthetic biology field continues to be limited by the ability to create new DNA at the scale required to support a new engineering discipline. This disparity between capacity to innovate with synthetic DNA and capacity to generate high-quality, low-cost synthetic DNA threatens to impede the progress being made in the field.

When it comes to building new DNA, improvements must be made in accuracy, cost, turnaround time, and reliability. Current approaches to oligo synthesis sacrifice accuracy for length, with cost soaring as longer oligos are produced. Today's standard of stitching together oligos to make longer constructs remains a tedious manual process, prone to error and taking far too much time to be scalable.

A new approach, developed by leading academic scientists in the synthetic biology field, has become the foundation for next-generation gene synthesis and addresses many of the current limitations. Based on work from Joseph Jacobson at MIT, Drew Endy at Stanford, and George Church at Harvard, this new technology uses synthetic biology as a novel means of building DNA constructs.[5] The work has been commercialized by Cambridge, Massachusetts-based Gen9, which has built the first gene synthesis fabrication platform based on silicon chips and today offers longer, more accurate constructs at lower cost. The technology relies on highly multiplexed gene synthesis and an error correction pipeline to produce synthetic DNA at far greater scale than is possible with other tools. Known as the BioFab platform, the technology can generate tens of thousands of DNA constructs per year and allows capacity additions on an exponential scale.

This year, Gen9 expects its BioFab platform to be able to produce as much synthetic DNA in a single lab as can be produced by the rest of the world. This improvement will revolutionize the types of experiments, as well as the scale of those experiments, that will be possible in academic laboratories, research institutes, and industrial organizations. Rather than studying a handful of genes, for example, scientists will be able to study whole pathways or even whole genomes in a single project.

Such an ability will fundamentally change the landscape of what is possible in bioengineering for agbio, enzyme design, biofuels, pharmaceutical development, and more. These are all industries that could benefit from synthetic biology but have yet to fully invest in the field because of its high cost and low throughput. With the lower costs, higher accuracy, and longer constructs associated with next-gen gene synthesis, these industries and many others will rapidly deploy resources to see what they can accomplish through synthetic biology.

CONCLUSION

After the slow start characteristic of any new field, synthetic biology has clearly reached a critical mass. The rapid improvements we see today are limited only by our imagination and capacity to create new DNA constructs to enable this new generation of biological engineers to fashion the genes, proteins, and genomes they need for such compelling projects. As next-generation gene synthesis begins to fuel synthetic biology, scientists can expect faster progress at an even more impressive scale.

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Notes

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