cellular tasks and phenomena. In such bottom-up approaches to biological function, there is no need to be constrained to bio-derived molecules. If a synthetic polymer or a piece of DNA origami can do a specific task as well as a lipid or protein module, why not construct bottom-up systems as a molecular "Borg," with biological, bioderived, and nonbiological elements combined for higher efficiency and robustness? Polymersomes made of block copolymers have already been shown to support protein activity in adenosine triphosphate–producing "artificial organelles" (*15*). And, multidimensional RNA structures were successfully designed as scaffolds in vivo to engineer the spatial organization of bacterial metabolism (*16*).

Synthetic biology is benefiting from and contributing to an increasing understanding of biology. The fascination is no longer limited to life scientists but has drawn in polymer chemists, physicists, and lately also engineers. In this exciting time, crossing traditional disciplines may lead us to new bioderived technology and an even deeper admiration of the power of living systems.

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POLICY FORUM

Synthetic Biology: Regulating Industry Uses of New Biotechnologies

Brent Erickson, Rina Singh,* Paul Winters

In our view, synthetic biology is an extension of the continuum of genetic science that has been used safely for more than 40 years by the biotechnology industry in the development of commercial products. Examples of synthetic biology use by biotechnology companies illustrate the potential to substantially reduce research and development time and to increase speed to market. Improvements in the speed and cost of DNA synthesis are enabling scientists to design modified bacterial chromosomes that can be used in the production of renewable chemicals, biofuels, bioproducts, renewable specialty chemicals, pharmaceutical intermediates, fine chemicals, food ingredients, and health care products. Regulatory options should support innovation and commercial development of new products while protecting the public from potential harms.

The emergence of synthetic biology into the public's perception has raised some concerns analogous to those expressed at the introduction of genetic engineering in the 1970s, particularly focusing on the potential for developing biological weapons, possible unforeseen negative impacts on human health, the morality of creating artificial life forms, and any potential environmental impact (*1*). Although some nongovernmental organizations have called for "an immediate moratorium on the release and commercial use of all synthetic organisms" or for regulation of the tools used in synthetic biology research, the President's Bioethics Commission "found no reason to endorse additional federal regulations or a moratorium on work in this field at this time" (*2*–*4*). The biotechnology community recognizes that synthetic biology, like other areas of biotechnology, can have both positive uses and negative impacts, and it has responded with guidelines for ethical, self-regulated research (*5*). Beyond that, the current framework for regulation of laboratory research and development of commercial biotechnology products can serve as a basis for regulation of synthetic biology.

Biotechnology Industry Organization (BIO), Washington, DC 20024, USA.

*To whom correspondence should be addressed. E-mail: rsingh@bio.org

What Is Synthetic Biology?

In our view, synthetic biology is an extension of the continuum of genetic science that has been used safely for more than 40 years by the biotechnology industry in development of commercial products (Fig. 1). For instance, gains in the speed and efficiency of DNA synthesis, sequencing, and recombinant DNA technology combined with cataloging of genomic data permit advanced methods for predictable biological production of commercial proteins and chemicals. Gene shuffling and directed evolution, based on the rapid iteration and sequencing of recombinant proteins, are other outgrowths of the increased efficiency of standard biotechnology techniques and have been safely used for many years. Metabolic engineering—the optimization of microbial fermentation pathways, cellular processes and enzymatic activity for biochemical production—is an outgrowth of the increased knowledge of genomics.

Synthetic biology encompasses a set of emerging tools, including applied protein and genome design, the standardization of genomic "parts" or oligonucleotides, and synthesis of full genomes, that are important to the continued evolution of biotechnology. The continued refinement and capability of metabolic engineering techniques, combined with digitized proteomic and genomic data, are expected to enable increasingly complex, multistep fermentation of organic chemicals and longer gene synthesis. Novel proteins and biological functions are envisioned as tools for advanced metabolic engineering. The BioBricks Foundation is creating a catalog of oligonucleotides that they believe can be certified to perform standardized biological functions when inserted into a microbial system (*6*). Similarly, the Massachusetts Institute of Technology has established a Registry of Standard Biological Parts (http://partsregistry.org/) and the International Genetically Engineered Machine (iGEM) competition (http://igem.org). The J. Craig Venter Institute has achieved initial steps in the design and construction of a simplified genome for a natural, self-replicating bacterium (*7*, *8*).

As often occurs with the introduction of new technology, metaphors that exploit effective, yet still imperfect, similarities in more familiar technologies are used to help illustrate the potential offered in the new field. The BioBricks Foundation, for instance, has consciously sought to leverage "time-honored engineering principles of abstraction and standardization" "to reduce the complexity and cost of producing synthetic living organisms" (*9*). The foundation has established four standards—for assembly, measurement, compatibility and exchange of data—taken directly from the field of mechanical engineering, as requirements for BioBricks listed in its catalog. Metaphors utilized for synthetic biology have often been based on electronic toolkits—i.e., systems that are modular and open to reconfiguration. However, these metaphors can mislead public perception of biotechnology because living organisms are not directly analogous to modular electronics, and therefore, law, policy, and research and development in synthetic biology probably should not be modeled after law, policy, and research and development in the fields of computer science and electronics.

Another popular metaphor is the development of computers. Much as earlier developments in somatic cell nuclear transfer were described with terms such as "reprogramming," synthetic biology has been described with terms such as "booting up" of genetic code. J. Craig Venter, in announcing achievement of the first self-replicating cell from a chemically synthesized genome, stated, "This is the first self-replicating cell we've had on the planet whose parent is a computer" (*10*). In looking at the rate of productivity of DNA sequencing and synthesizing technologies to project the potential economic impact, one report notes that productivity is doubling every 24 months and invokes Moore's law (*11*). A recent academic paper described a method for massive parallel replacement of codons within a genome as treating "the chromosome as both an editable and an evolvable template" and was in turn described in the popular press as a method to "seize control of the microbe's genetic code and reprogram it" (*12*, *13*).

The biotechnology industry has used the metaphor of husbandry and hybridization to contextualize its history of technology developments. Breeding genetic traits in animals and plants that are conducive to human interests should be familiar to individuals and societies around the world, even as modern breeding techniques incorporate precise screening, analysis, and long-distance shipment of genetic material—and even reproductive cloning. Use of microbes for production of useful foods and chemicals—such as beer, wine, bread, and yogurt—also has a long history among many cultures around the globe. Biotechnology, the direct manipulation of the genes of microbes, plants, and animals, therefore can be understood as a more precise, predictable, and speedy method for "breeding" useful traits for the benefit of mankind. Synthetic biology, based on the increased speed and precision of standard biotechnology tools, can be understood as a new set of laboratory tools and techniques that now enable biotech researchers and product developers to more rapidly design and build microbial systems, rather than finding and extracting them from nature and modifying their genomes or metabolic pathways.

Innovations from Biotechnology

Innovation for any industry is based on increased speed, efficiency, performance, and cost-effectiveness within product development. The addition of synthetic biology tools to the field of metabolic engineering can enable further innovation in biotech product development in the chemical, pharmaceutical, and food industries (*14*). For example, polyhydroxyalkanoates (PHAs), a broad family of biopolymers, are produced naturally in many microorganisms. However, the cost and range of PHA compositions required for commercial polymers and plastics dictated that PHA pathways had to be assembled in a robust organism that does not naturally produce the product. Metabolic pathway engineering was used to accomplish this task, including DNA sequencing and synthetic construction of genes encoding the same amino acid sequence as the donor strain, but optimized for expression in the engineered industrial host. These technologies provided rapid development and optimization of robust industrial production strains that would not have been feasible by using classical techniques relying on isolation and transfer of DNA from one species to the other.

More than 200 U.S. firms and universities are engaged in synthetic biology research, development, and product commercialization (*15*). Although synthetic biology research is an emerging science that has yet to reach its full potential, there are several products based on synthesized genetic sequences and computer-aided design of metabolic pathways that are at a precommercial stage, with a few already on the market. One of the pioneers of synthetic biology is the life sciences and materials company DSM. The company utilized synthetic biology to improve an existing process for the commercial production of cephalexin, a synthetic antibiotic. Starting with a penicillin-producing microbial strain, DSM introduced and optimized two heterologous genes encoding acyl transferase and expandase, respectively, for a one-step direct fermentation of a dipoyl-7-aminodesacetoxycephalosporanic acid (dipoyl-7-ADCA). This product was then converted into cephalexin via two enzymatic steps, which replaced a process requiring 13 chemical steps. The new process resulted in significant cost and energy savings. DSM has gone on to build a business in antibiotics, vitamins, enzymes, organic acids, and performance materials (*14*).

Several biotechnology companies have used synthetic biology techniques to speed research and development cycles for biological production of specific chemicals. Adipic acid, a building block chemical for Spandex and other polymers with an annual market of ~$5.2 billion, is not naturally produced. Verdezyne used synthetic gene libraries to design a recombinant yeast microorganism capable of expressing a precursor to adipic acid. The bio-based production method could reduce cost by 20% or more compared with petrochemical methods (*16*). Sitagliptin, a dipeptidyl peptidase-4 inhibitor, is a treatment for type II diabetes that also is not naturally produced. Codexis developed a highly active, stable transaminase enzyme capable of producing this substance with a higher degree of selectivity for the specific therapeutic enantiomer than an existing process using metal catalysts (*17*). OPXBIO comprehensively redesigned a natural microbe to optimize its metabolism for low-cost production of acrylic acid from renewable resources. OPXBIO is already producing BioAcrylic at pilot scale and is now in joint development with Dow Chemical.

Isoprene is an important commodity chemical used in a variety of applications, including the production of synthetic rubber. Isoprene is naturally produced by nearly all living things (including humans, plants, and bacteria), but the gene encoding isoprene synthase has only been identified in plants such as rubber trees. Although plant enzymes can be expressed in microorganisms through gene transfer, it is a long and cumbersome process. Genencor, a Danisco Division, has used synthetic biology to construct a gene that encodes the same amino acid sequence as the plant enzyme but is optimized for expression in an engineered *Escherichia coli*. This microorganism is capable of channeling carbon through the mevalonic acid biosynthetic pathway to deliver isoprene at titers exceeding 60 g/liter. Unlike other bio-based systems to produce renewable chemicals, BioIsoprene is produced as a gas-phase product that is released as soon as it is produced into the vapor phase of the reactor. Polymer-grade BioIsoprene is recovered from the integrated process. The production of BioIsoprene from renewable raw material is under development by Genencor and the Goodyear Tire & Rubber Company, and it is considered a major achievement for industrial biotechnology because it has the potential to enable a low-cost monomer as a large-volume

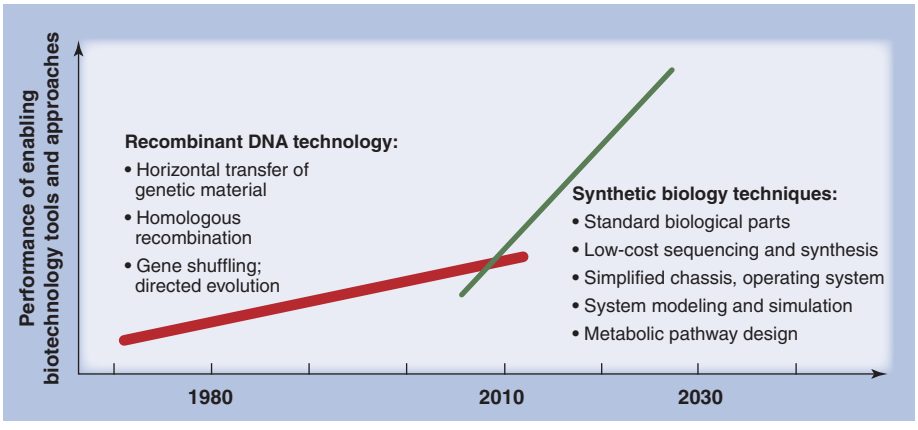

Fig. 1. Evolution of innovation. [Modified from (*11*), ©2007 by Bio Economic Research Associates, www.bio-era.net]

alternative to *Hevea* natural rubber and petroleum-derived isoprene (*18*).

In response to recent oil spills where large volumes of toxic chemical dispersants were used, Modular Genetics, Inc., of Cambridge, Mass., used a computer library of genetic code to generate iterations of a previously engineered microorganism, each producing a different biodispersant for testing. Modular Genetics's work was part of a consortium with three universities working under a National Science Foundation RAPID Response Grant to develop less toxic biodispersants (http://nsf.gov/awardsearch/showAward.do?AwardNumber=1059174).

Options for Governance

Regulatory options should support innovation and commercial development of new products while protecting the public from potential harms. One of the key needs for regulation identified by the biotechnology community is to inculcate the biomedical culture of safety in engineers, chemists, material scientists, computer modelers, and others drawn into synthetic biology by its interdisciplinary nature (*3*, *4*). The community also recognizes that synthetic biology has dual-use implications, in that the speed in creation of novel genetically engineered organisms and the sharing of this information via computer or mail order apply equally to beneficial uses and nefarious purposes.

Because synthetic biology is not constrained to use readily available genetic material, the directed synthesis of polynucleotides has great potential to generate novel organisms or to regenerate ones that no longer exist, including pathogens. To reduce the risk that individuals with ill intent may exploit nucleic acid synthesis technology to access genetic material derived from or encoding select agents or toxins, the U.S. government has developed recommendations for a framework for synthetic nucleic acid screening (*19*). This document for voluntary use is intended to provide guidance and to encourage best practices among producers of synthetic genomic products so that they screen and fill orders in compliance with current U.S. regulations. Voluntary guidelines for sharing synthesized genetic sequences should help providers meet their responsibilities of knowing who is receiving their product and if the sequence they are providing contains "in part or in whole" a "sequence of concern." In light of public concern, NIH established guidelines in 1976 that are mandatory for investigators at institutions that receive NIH funds doing research involving recombinant DNA (*20*). The guidelines encompass synthetic biology and are followed voluntarily by scientists and organizations, both public and private.

At the dawn of the era of recombinant DNA technology, researchers in the field agreed to develop similar guidelines to ensure the safe practice of the technology. The Asilomar Conference on Recombinant DNA Molecules held in 1975 proposed the outlines for a system of regulating biotechnology research, commercial development, and commercial production in which levels of containment of biohazards were balanced against potential risks. As the biotechnology industry grew and spread to other countries, the culture of safety that prompted the Asilomar Conference strengthened.

The President's Bioethics Commission, charged with reviewing the field of synthetic biology and identifying appropriate ethical boundaries, in response to the announced creation of a self-replicating cell from a chemically synthesized genome, put forward 18 recommendations not only for regulating the science, but also for educating the public and regulators about the science. The key five principles established by the commission were public beneficence, responsible stewardship, intellectual freedom and responsibility, democratic deliberation, and justice and fairness. The report advocates prudent vigilance—which balances responsible stewardship of the technology with intellectual freedom for continued investigation—and regulatory parsimony—establishing only as much oversight as is necessary to ensure public safety and public benefits from the technology. A key recommendation is to ensure regulators have adequate information to conduct risk analysis and harmonization of regulatory standards.

Many groups worldwide, including government organizations, nonprofits, academia, and the amateur synthetic biology community have been discussing the implications of synthetic biology, and a complete listing is beyond the scope of this article. There have been meetings of members of the U.S. National Academies, U.K. Royal Academy, and Chinese Academy of Sciences and Engineering (*21*), and there are ongoing conversations in many countries. Synthetic biology has also been included as a topic in the Science and Technology assessments prepared by the U.S. National Academies and the Chinese Academy of Sciences for the Seventh Review Conference of the Biological Weapons Convention to be held at the United Nations Office in Geneva later this year (*22*). Industry groups have also proposed codes of conduct. Through the International Association Synthetic Biology, the International Consortium for Polynucleotide Synthetics published a potential oversight framework for the development and implementation of sequence screening tools and mechanisms for reporting and resolving concerns about orders of potentially dangerous sequences (*23*).

At this early stage of development, synthetic biology does not pose novel threats that are fundamentally different from those faced by the current biotechnology industry. The regulatory framework that has been shaping continually evolving recombinant DNA technology for the past 40 years is generally applicable and relevant, and we recommend that academic researchers and industry continue to develop synthetic biology technology and derive products under the framework. In the future, as the technology matures and if scientific consensus warrants it, the need may exist to develop a regulatory framework as overarching federal policy, based on the existing voluntary regulatory guidelines.

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