FROM BIRTH TO DEATH AND BENCH TO CLINIC

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CHAPTER 35

Synthetic Biology

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synthetic biology

by Michele S. Garfinkel, Drew Endy, Gerald L. Epstein, and Robert M. Friedman

Framing the Issue

Using a number of technologies and intellectual approaches, synthetic biology solves biological engineering problems by designing and reconstructing new biological parts, or systematically redesigning existing, natural biological systems. Implicit in this process are some as-yet unresolved issues for policymakers. For example, some applications of synthetic biology that benefit society could also be applied in ways that can harm it, or that could be unintentionally dangerous; the use of such technologies in the development of a biological weapon, such as a virus, is an obvious concern. But also of concern is that scientists who are carrying out legitimate experiments could without malice construct an organism with disease-causing potential.

The issue of safety is further complicated because applications of synthetic biology that are considered beneficial by some may be perceived as harmful or dangerous by others. Perhaps the best-studied example of this sort of disagreement is that of the introduction of genetically engineered (often referred to as "genetically modified") food crops. Use of these crops may bring benefits, such as the possibility of using less pesticide, yet many consider any such modification to be inherently harmful in the absence of compelling evidence to the contrary.

Discussion and debate regarding these issues need to engage practitioners (including students), policymakers, research administrators, and commercial providers of raw materials for the research, both among themselves and in conjunction with a diverse range of interested citizens and civil organizations.

Background and Science

The concept of synthetic biology as an approach to biological engineering dates to the mid-1970s when the advent of readily available enzymes and other materials allowed pieces of DNA to be easily swapped between organisms. The last 10 years have been a time of tremendous improvement in the ease of specific techniques associated with synthetic biology, and this, along with rapidly falling costs and the dispersion of experimental approaches once thought to be the domain of elite biologists, has resulted in the dissemination of synthetic biology widely (among sectors and academic approaches) and deeply (from Nobel Prize winners

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HIGHLIGHTS

- Synthetic biology helps solve biological engineering problems by adapting engineering concepts to design and reconstruct new biological parts, or redesign existing, natural biological systems.
- Synthetic biology also allows scientists to quickly construct new genetic designs that directly test their hypotheses.
- Synthetic biology revisits safety and security concerns first identified with the invention of recombinant DNA technology. Similarly, synthetic biology raises both familiar and new social and ethical questions.
- Some beneficial applications of synthetic biology could also be used in harmful or unintentionally dangerous ways.
- The construction of minimal organisms raises distinct ethical questions, such as how or whether such work changes the concept of what life is.
- Research suggests that synthetic biology may soon be a technology of choice for a nation or bioterrorist hoping to develop or acquire a pathogen for use as a weapon.
- Other issues include the potential impact of organisms created by synthetic biology on the environment, the ownership of technologies, and distribution of the benefits of such research and its products.

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to high school students). Recent results of such experiments include:

- The construction of an infectious poliovirus genome from oligonucleotides (short fragments of DNA that are strung together in the laboratory)
- The reconstruction of bacteriophage T7 to simplify its genome (demonstrating that naturally occurring genomes can be systematically redesigned and rebuilt for further research or for specific applications)
- The synthesis of a 582,970-base-pair genome of Mycoplasma genitalium (showing that the full genome of a replicating organism can be constructed in the laboratory)
- Practical applications, including an attempt to produce artemisinin, the precursor to the malarial drug artemisin, that are very close to succeeding.

Although other biotechnologies could in many cases be applied to essentially the same purposes, the combination of easy access to synthesized DNA, powerful computers to aid design, and the distribution of these technologies to users beyond the "traditional biologist" have raised unique safety and security concerns about synthetic biology. Further, the idea of using these technologies to construct living organisms has sparked discussions about whether the use of these technologies is ethical and, beyond that, what "creating life" means. Ensuring that this field develops in a responsible manner, respectful of society's desires and beliefs, will require some combination of training, oversight, and community external or self-regulation, constructed to allow the science and engineering to advance without compromising safety, security, or society's values.

Ethics, Society, and Synthetic Biology

We discuss here five major areas of concern with respect to the societal impacts of research in and applications of synthetic biology. These include biosafety and biosecurity; the environment; ownership; philosophical and theological issues; and the professional conduct of researchers. Some of these issues have been very well analyzed; for others analysis is just beginning. Each is outlined below.

Biosafety and biosecurity. A key set of technologies for synthetic biology is the construction of DNA in the laboratory from its constituent chemicals. Often referred to as "DNA synthesis," "gene synthesis," and "synthetic genomics," this set of technologies makes it possible to build DNA of any specified sequence and length, up to the size of a whole genome. The biosafety and biosecurity implications have been explored by the authors and others in some detail (in "Resources" box, see Garfinkel et al., National Science Advisory Board for Biosecurity, and Tucker and Zilinskas).

For our 2007 study, a working group of experts in the technologies of DNA synthesis, research applications of DNA synthesis, engineering, policy, law, ethics, and sociology conducted a technology assessment of synthetic genomics. Over 20 months, we systematically explored the potential risks and benefits of synthetic genomics; the technologies that currently exist for carrying out the research; and the technologies that may be available in five to ten years. The analyses aimed to identify the benefits and risks that were specific to synthetic genomics as opposed to biotechnology generally.

We found that, with very few exceptions, synthetic genomics would not now be the technology of choice for a bioterrorist or nation-state hoping to develop a virus for use as a weapon. Within five to ten years, however, it may very well be the case that synthesis will be easier than other means of obtaining a virus.

Based on these qualitative analyses, we constructed a list of 17 possible options for governance, focusing on the commercial suppliers of DNA; the machines and reagents that can be used to synthesize DNA in laboratories; and the legitimate users of these technologies, including their associated organizations, such as universities. These options range from requiring that firms screen every order for potential malicious intent to extending the mandate of institutional biosafety committees to consider the potential security implications of experiments.

Commercial firms that make and sell synthetic DNA have in fact already recognized that they have a role in assuring the safety of researchers and communities nearby and the security of all. Several firms have together formed the International Consortium for Polynucleotide Synthetics (ICPS). ICPS members and others have 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.

The U.S. government is also examining the risks from synthetic biology, particularly from the biosecurity perspective. The National Science Advisory Board for Biosecurity (NSABB) recently released recommendations for dealing with the synthesis of select agents. Various agencies are participating in the U.S. government review of these recommendations, and the NSABB and others are continuing work on assessing whether the mechanisms of prior review of experiments by local institutional biosafety committees will need to be modified to accommodate security and safety concerns associated with synthetic genomics.

Other countries have noted concerns about this technology, as well. In Europe the concerns are generally more directed toward biosafety, particularly as related to accidental releases of synthesized organisms.

Environment. Synthesized microbes might be intentionally or unintentionally released to the environment. Concerns about the potential environmental impacts of the accidental release of engineered synthetic microorganisms are closely related to concerns about biosafety and the impact of an accidental release on communities immediately surrounding laboratories. The accidental release of a truly novel organism is worrisome, as there would be, by definition, no prior experience with how it would act in a specific environment. However, highly modified microorganisms are unlikely to survive in a natural environment.

With respect to planned releases, synthesized organisms would be subject to the same regulations as any other genetically modified organism. For example, in the United States, the Environmental Protection Agency, Food and Drug Administration, and the Department of Agriculture all regulate the introduction of various foods, drugs, pesticides, herbicides, etc., including those that are genetically modified. The question is whether organisms should be subject to a greater degree of scrutiny simply by virtue of having genomes that had been modified using synthetic DNA, rather than DNA extracted from another organism.

Ownership: access, sharing, intellectual property, and innovation. Synthetic biology may pose special problems for those seeking ownership of, or access to, what might become vast arrays of new technologies. Both patent thickets (the need to receive licenses from multiple patent-holders) and the "anticommons" (many patent owners blocking each other) are potential roadblocks to the use and distribution of these technologies. This is an area that will need significant attention as the field develops. It is being studied by several groups within the academic legal community, such as the Center for the Public Domain at Duke Law School and the Samuelson Clinic at the University of California Berkeley School of Law (see Chapter 20: Intellectual Property and Biomedicine).

Philosophical and theological issues. One application of synthetic genomics is to build a microorganism containing a "minimal genome," defined as the smallest set of genes that would permit an organism to live and reproduce in a specific environment. The idea is to construct the minimal genome of a particular bacterium, insert that genome into a cell, and show that the resulting organism can replicate. Such a microorganism would help scientists to better understand the basic functioning of cells, or perhaps be a platform for biotechnology applications.

This potential application led to one of the first robust ethics analyses of the field, which was published in 1999 by Cho and colleagues (see box: "Resources") and preceded any actual work on constructing an organism with a minimal genome. The analysis took into account issues of religion, commercialization, and the potential benefits of the

Governing Genetic Engineering: The Asilomar Model

The power of manipulating DNA was recognized early on. The most famous consideration of the potential dangers of genetic engineering—primarily in terms of laboratory and environmental safety—was at the 1975 **Asilomar** Conference, attended by scientists, along with some lawyers, physicians, and journalists. The conclusions from that meeting were that although genetic engineering research and applications posed risks, those risks could be managed largely through a self-governance process involving funders and practitioners, and that formal oversight and regulatory procedures could be minimal (although not nil). However, Asilomar (and, until recently, most other such discussions) did not specifically consider the possibility of purposeful malicious applications of genetic engineering. Although synthetic biology is not unique in its "dual-use" nature, leaders of the field have been aware of the dual-use problem and have been open in speaking about it and ways to potentially mitigate malicious uses, starting as early as the first international meeting of its practitioners at **Synthetic Biology 1.0,** which was held in Cambridge, Massachusetts, in 2004.

RESOURCES

Web sites

- http://polysynth.info – The International Consortium for Polynucleotide Synthesis. Includes links to participating international synthetic biology companies and some resources.
- http://www.synberc.org – The Synthetic Biology Engineering Research Center. Includes educational, training, and outreach materials.
- http://synbiosafe.eu – Synbiosafe. This European Union–funded project aims to proactively stimulate a debate on issues in synthetic biology; includes project products and an online discussion forum.
- http://syntheticbiology.org – Synthetic Biology. Includes links, resources, and event information.
- http://pbd.lbl.gov/sbconf – Synthetic Biology 2.0. The conference site for the Second International Meeting on Synthetic Biology, held in Berkeley in 2005, includes a webcast of the conference and discussion forums.
- http://www.syntheticbiology3.ethz.ch – Synthetic Biology 3.0. The conference site for the Third International Meeting on Synthetic Biology, held in Zurich in 2007, includes videos of the talks and proceedings available for download.

Recent news

- John Harris, "Who's Afraid of a Synthetic Human?" *The Times*, May 17, 2008.
- Colin Nickerson, "A Quest to Create Life Out of Synthetics," *Boston Globe*, April 2, 2008.
- Wendy Orent, "Crying Wolf Over Bioterror," *Los Angeles Times*, March 2, 2008.
- Erik Parens, "Making Cells Like Computers," *Boston Globe*, February 18, 2008.
- Natalie Angier, "Pursuing Synthetic Life, Dazzled by Reality," *New York Times*, February 5, 2008.

Further reading

- Mildred K. Cho, David Magnus, Arthur L. Caplan, Daniel McGee, and the Ethics of Genomics Group, "Ethical Considerations in Synthesizing a Minimal Genome," *Science*, December 10, 1999.
- Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology, *Biotechnology Research in an Age of Bioterrorism,* National Academies Press, 2004.
- Huib de Vriend, "Constructing Life: Early Social Reflections on the Emerging Field of Synthetic Biology," working document 97, Rathenau Institute, The Hague. Report available at www.lisconsult.nl.
- Drew Endy, "Reconstruction of the Genomes," *Science*, February 29, 2008.
- Michele S. Garfinkel, Drew Endy, Gerald L. Epstein, and Robert M. Friedman, "Synthetic Genomics: Options for Governance," J. Craig Venter Institute, Center for Strategic and International Studies, and Massachusetts Institute of Technology, October 2007. Report available at www.jcvi.org.
- National Science Advisory Board for Biosecurity, "Addressing Biosecurity Concerns Related to the Synthesis of Select Agents," December 2006. Report available at www.biosecurityboard.gov.
- Jonathan B. Tucker and Raymond A. Zilinskas, "The Promise and Perils of Synthetic Biology," *The New Atlantis,* Spring 2006.

research. It also looked at concerns about reductionism—that is, the view that a cell or an organism is only the sum of its parts—in this case, genes. This view is particularly problematic for those individuals—be they scientists, philosophers, or theologians—who think about the interaction of cells or organisms with the surrounding environment. Construction of a minimal genome thus can raise distinct questions as to whether and how such work can contribute to or change the definition of life, and whether policies are needed to assure an equitable distribution of benefits from such research. At the time, those researchers concluded that constructing a minimal (or even new) genome does not violate any moral principles. Others have disagreed with this assessment, and little additional rigorous analysis has been done in the last nine years.

However, there is a clear need for ethicists, theologians, scientists, engineers, policymakers, and the public to understand each others' views on these issues, and such examinations are ongoing. The Venter Institute is continuing its efforts in this area. The Hastings Center has recently embarked on such a project, called *Ethical Issues in Synthetic Biology: Toward Clearer Understanding and Better Policy,* funded by the Alfred P. Sloan Foundation.

Professional conduct of researchers. Codes of conduct, ethics or practice have been considered for biological science in general, and synthetic biology in particular, but none have yet been adopted. Engineers have long worked under various codes of conduct. Training students on aspects of professional responsibility and ethical conduct is a critical feature of the process leading to adherence to these codes and has long been a part of engineering curricula. Devising standards of practice might eventually be a task for any professional society developed for synthetic biology (see Endy in "Resources" box). But whether or not synthetic biology as a discipline articulates a full code of conduct, such codes have been and likely will continue to be communicated to students and researchers in the field at forums such as the International Genetically Engineered Machine Competition, where the participants are mainly undergraduates from various disciplines and national origins, and the series of annual international synthetic biology meetings, where a wide variety of students and researchers gather.

In 1971, in describing the content of a talk in a conference he was organizing, Sidney Fox wrote, "As such processes [of synthetic biology] are brought under control in the laboratory, they have increasing implications for society and its philosophy." This is perhaps even truer today, as the full implications of the science and engineering are only now being appreciated.

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(4) 2. Similar to synthetic biology, biological engineering exploits new developments other biological fields however biological engineering applies these breakthroughs to understand living systems with the goal of solving natural problems with these systems. (4) 3. Systems biology is focuses on the study on natural systems, often with some long term medical significance 4. But the work is fundamentally an engineering application of biological science, rather than an attempt to do more science. (5). The Controversy. Synthetic biology raises risk of new bioweapons, US report warns. Swift progress in our ability to manufacture viruses is making us vulnerable to biological attacks. Published: 19 Jun 2018. Synthetic biology raises risk of new bioweapons, US report warns. September 2017. Unpalatable truths about laboratory-grown food.Â A meeting on synthesising the human genome, convened behind closed doors at Harvard, has caused a stir. Synthetic biology is an interdisciplinary field, best defined as engineered solutions inspired by biology to create renewable, biodegradable, and safe materials. Synthetic biology has found applications in several areas, including healthcare, agriculture, and biomanufacturing of textiles, ink, and other consumer products. Advancements in precise genome engineering tools such as CRISPR have further boosted the scope of this field.