David Gillum

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Professor Marty Anderies

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Synthetic Biology: The Registry of Standard Biological Parts

Introduction

At its simplest level, synthetic biology involves the manipulation of information: specifically, the manipulation of genetic information. All living organisms contain a specific genetic code, which will define the inherent characteristics of an organism (e.g., what will it look like, how will it function). Scientists are able to modify the genetic code of organisms, such as plants and animals, through selective breeding, or by using physical (e.g., radiation), chemical (e.g., mutagenesis), and biological (e.g., recombination) techniques. More recently, scientists have had the ability to create entirely new genetic codes or add whole suites of synthetic genes that do not exist in nature into organisms. This latest venture is falls into the realm of synthetic biology.

This paper discusses a biological commons dilemma by examining the Registry of Standard Biological Parts that is available on the Internet for everyone to view and to the DNA in that registry. Specifically, the commons dilemma revolves around property rights (intellectual property, generally in the form of patents), ethical concerns regarding the widening gap between those individuals and societies with access to synthetic biology and those without access, and the management of future risks and benefits from synthetic biology development.

A Brief History of Synthetic Biology

Synthetic biology is a relatively young concept. The term has been around since at least 1912, when Stéphane Leduc wrote his book titled, "La Biologie Synthetique." In his manuscript, he theorized about the synthesis of living organisms. Leduc wrote, "besides the method of analysis, fact compilation and classification, there also existed in science a synthetic method that attempts to reproduce observed phenomena in a rule-governed and reproducible manner" (LeDuc, 1912). The term synthetic biology was reintroduced in 1974 when Waclaw Szybalski was writing about genetic transcription, "up to now we are working on the descriptive phase of molecular biology...But the real challenge will start when we enter the synthetic biology phase of research in our field" (Waclaw, 1974).

In 1978, Waclaw and Anna Skalka observed additional opportunities for synthetic biology in an article in the journal *Gene*. "The work on restriction nucleases not only permits us easily to construct recombinant DNA molecules and to analyze individual genes but also has led us into the new era of synthetic biology where not only existing genes are described and analyzed but also new gene arrangements can be constructed and evaluated" (Waclaw and Skalka, 1978). Soon thereafter, the term synthetic biology became a catchphrase for a new technology to re-engineer biological systems.

In 1987, in a way to introduce ethics into the conversation, Steven Benner used the term synthetic biology with reference to efforts to redesign life (Benner, 1987). Benner later acknowledged that his "'grand challenge" was to synthesize unnatural chemical systems that do genetics, catalysis, and the higher order functions in life, including reproduction, adaptation, and evolution" (Benner et al., 2009). In 2000, Eric Kool and other speakers at the American

Chemical Society used the term synthetic biology to describe the "synthetic capability of organic and biological chemistry to design nonnatural, synthetic molecules that nevertheless function in biological systems" (Rawls, 2000).

Since 2000, the size and scope of the synthetic biology field has continued to experience significant growth since (Cameron et al., 2014). It is now a rich, complex interdisciplinary field. Yet, with the fast rate of growth in the past decade, and the fact that so many different types of researchers are working in the field, it has been difficult to develop a precise, formally accepted definition of synthetic biology. One of the more commonly referenced explanations is found on a website (http://syntheticbiology.org/) that was developed by researchers from MIT and Harvard (SCBD, 2015). The creators of the website provide the following definition: "Synthetic biology is a) the design and construction of new biological parts, devices and systems and b) the re-design of existing natural biological systems for useful purposes." Inherent in this definition is the fact that genetic information is being manipulated to create new parts, devices, and systems or to redesign existing systems.

Genetic Code as Information

In many ways, the nucleobases of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) could be thought about like the ones and zeros used to describe the mathematics of computers. These two digits represent two states in a circuit: on (1) or off (0). They also represent memory, or stored information. The nucleobases of DNA are adenine (A), cytosine (C), guanine (G), and thymine (T). From a chemistry point of view, A bonds with T and G bonds with C to form the base pairs in DNA. The base pairs are diagrammatically represented by A--T and G--C. From a theoretical perspective, the A--T could be represented as 1 and G--C as 0 (or

vice versa). These four bases (and base pairs) convey extraordinary amounts of information. In the context of DNA, each base is connected to a sugar (deoxyribose) and a phosphate group to form a nucleotide, a building block of DNA.

Instead of programming a computer, it is now possible to program life using synthetic biology. “In the same way that electrical engineers rely on standard capacitors and resistors, or computer programmers rely on modular blocks of code, synthetic biologists wish to create an array of modular biological parts that can be readily synthesized and mixed together in different combinations” (Rai and Boyle, 2007).

Scientists are now able to sequence large and continually growing numbers of complete genomes. There are companies that specialize in the creation of novel nucleic acid sequences that are sold direct to customers. The cost of sequencing has decreased from tens of dollars per base in the 1980s to a fraction of a cent per base today. There are also several libraries of synthetic biological parts that are making it easier to program biological systems. While most of these libraries are private, the Registry of Standard Biological Parts, which is discussed in greater detail in the next section, is considered to be an open access, public library of synthetic biological parts.

Synthetic Biology and the Commons

According to Anderies and Janssen (2013), the commons (or common pool resources) are “a resource, or collection of resources over which private property rights have not been established.” While much of synthetic biology has seen an increase in property rights for genetic material, there is one example that remains open. This is the Registry of Standard Biological Parts and its use of a common, standardized biological programming language called Biobricks (Rai and Boyle, 2007).

The Registry of Standard Biological Parts was founded in 2003 at the Massachusetts Institute of Technology (MIT). The registry was developed to be an open library of synthetically nucleic acid sequences (i.e., parts) that can be mixed and matched to build novel biological devices and systems. The registry was spun off from MIT on January 1, 2012 to the International Genetically Engineered Machine (iGEM) Foundation. The iGEM Foundation is a non-profit organization located in Cambridge, Massachusetts that is "dedicated to education and competition, advancement of synthetic biology, and the development of open community and collaboration" (PR Newsire, 2015).

As noted on the iGEM website, the registry is the "world's largest open-source community collection of standard parts" (iGEM Labs Program, 2015). These parts are maintained using an open access, standardized model system, better known as BioBricks. Having a standard system "ensures compatibility between parts, allowing them to be assembled together creating new longer and more complex parts, while still maintaining the structural elements of the standard" (iGEM Help: Parts, 2015). The goal is also to have "a set of standard and reliable engineering mechanisms to remove much of the tedium and surprise during assembly of genetic components into larger systems" (Shetty, 2008). There are more than 20,000 different types of Biobrick parts that are available in the iGEM registry. These parts include promoters, ribosome binding sites, protein domains, protein coding sequences, translation units, terminators, DNA, plasmid backbones, plasmids, primers, and composite parts (i.e., combinations of two or more parts).

The Biobricks Foundation (BBF) is a non-profit organization that is very interested in ensuring the open access to knowledge regarding synthetic biology. "The BBF felt that an ownership, sharing and innovation framework based on patents (the property rights mechanisms

most commonly used in biotech) had substantial limitations in the context of an engineering process based on the reuse of thousands of different components across many different systems. Specifically, the cost and time to define and obtain patent-based protection is too great to support the engineering of many-component, integrated, genetic operating systems" (Smolke, 2009). According to Rai and Boyle (2007), a large goal of the BBF is to "serve to coordinate a synthetic biology 'commons.'"

Access to the Registry

"The physical infrastructure of molecular biology is becoming more sophisticated and less expensive every day" (Carson, 2004). Complicated functions that took months, or even years, in a laboratory, are being performed in seconds. Extremely costly equipment is becoming much cheaper, and accessible to more and more laboratories around the world. So, while the Registry of Standard Biological Parts still contains physical DNA, the "developers believe that, as DNA synthesis technology becomes increasingly inexpensive, the registry will be composed largely of information and specifications that can be executed in synthesizers just as semiconductor chip designs are executed by fabrication firms" (Rai and Boyle, 2007).

The DNA in the registry is only accessible to participants of the iGEM Giant Jamboree, a synthetic biology competition held each year in Boston, Massachusetts, and select academic research laboratories from accredited university that have been approved by the iGEM Foundation. In 2015, there were nearly 300 teams participating in the iGEM Giant Jamboree, from five continents: Africa, Asia, Europe, South America, and North America. According to PRNewswire (2015), "over 4,600 participants on 280 teams registered to take part in the 2015 competition."

The cost of sending a team to the iGEM Giant Jamboree can be very expensive. In 2015, the team registration fee was $4,000 (in U.S. dollars) and it was an additional $695 for each individual team member who wished to attend (iGEM: Starting a Team, 2015). Andrew Hessel estimates that a team of seven students and three advisors would costs about $39,200 to attend the competition, although this does not cover "funds for DNA sequencing, synthesis, and basic lab reagents" (iGEM: Funding, 2008). Although the entire team is welcome to attend, it is not a requirement. Perhaps it is not surprising, "the geographical distribution of iGEM participants remains biased toward North America, Eastern Asia and Europe. Every year each of these regions account for around 25% of the participating teams" (Vilanova and Porcar, 2014).

Thus, from the viewpoint of accessibility, it is clear that participation in the competition is limiting simply because of costs. Those individuals or teams with sufficient funds are able to participate. Each team receives a kit of synthetic DNA parts from the iGEM headquarters. Because the DNA from the Registry of Standard Biological Parts is limited to those teams participating in iGEM competitions, those who cannot afford to participate are further limited access to this common pool resource. However, the information in the library is freely available to anyone with a computer, Internet connection, and knowledge and understanding of the materials in the library.

From the perspective of the iGEM Registry of Standard Biological Parts, there are those with access to the DNA from the library and those that are not. According to the European Commission's "Final Opinion on Synthetic Biology II: Risk assessment methodologies and safety aspects," there are four primary ethical issues for synthetic biology. These areas include: 1) blurring the lines between life and non-life, 2) interacting or interfering with nature, 3) expanding the gap between those who "have" and those who "have not," and 4) misusing the

technology, intentionally or unintentionally, which could lead to serious threats to society and the environment (European Commission, 2015). The issue of access to the registry seems to fit in with item number three of the European Commission's report.

Governance

The 1986 Coordinated Framework for Regulation of Biotechnology directed the Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and the Department of Agriculture (USDA) to work together and use existing regulatory frameworks to govern biotechnology. The core premise was that the legal authorities (which remain largely unchanged today) "provide federal regulators sufficient authority to manage any health or environmental risk the products of biotechnology may pose" (Wilson Center, 2015a). Thus, in accordance with the 1986 Coordinated Framework for Regulation of Biotechnology:

- The Animal and Plant Health Inspection Service (APHIS) regulates field trials of genetically engineered crops and plants under general authority to regulate plant pests. APHIS also reviews requests to "deregulate" the crop or plant in order for it to be grown without a permit at a commercial scale.
- The Environmental Protection Agency regulates genetically engineered microbes as "new chemical substances" under the Toxic Substances Control Act (TSCA). EPA also regulates genetically engineered pesticides (including biopesticides and pesticides incorporated into plants) under its authority to regulate pesticides.
- The Food and Drug Administration regulates food, food additives, human and animal drugs, and certain other products, including those that have been produced through genetic engineering.

Intellectual Property

Although the Supreme Court of the United States ruled in *Association for Molecular Pathology et al. v. Myriad Genetics* that DNA is not patentable, synthetic DNA, or cDNA, is patent eligible because it does not occur naturally (SCOTUS, 2013). This harbors potential problems for the iGEM registry, which is described as a common pool resource.

Individuals participating in the iGEM Giant Jamboree are sent a standard collection of synthetic biology parts to use in their research. As participants create new parts, they are added to the library, thus growing the registry year after year. However, since the parts in the registry are synthetic DNA, they could in theory be patentable. Yet, there is also the potential that the material already in the registry is public domain and therefore free for all to use. This is one area that will likely need to be further assessed in the future.

To help ensure the Registry of Standard Biological Parts maintains its status as an open, publicly available library, iGEM participants and other users of Biobricks must adhere to the Biobrick™ Public Agreement. This document is a contract between developers and users of synthetic biological parts. It keeps the parts freely available to share and be used to build new biological devices and systems.

The BBF has a public relations tagline that reads, "Biotechnology in the Public Interest." "We envision a world in which scientists and engineers work together using freely available standardized biological parts that are safe, ethical, cost effective and publicly accessible to create solutions to the problems facing humanity. We envision synthetic biology as a force for good in the world" (Biobricks Foundation, 2015).

Conclusion

The introduction of synthetic biology has brought about many changes in the biological engineering world. Products created using synthetic biology technology are now coming to the marketplace. The Synthetic Biology Project, funded by the Woodrow Wilson Center, is working to catalog existing and future synthetic biology products (Wilson Center, 2015b). However, there is also an attempt to maintain the Registry of Standard Biological Parts, a common pool resource, so that it is free for others to use in the future. There are many hurdles and challenges to ensuring that the library survives, such as ensuring the content in the library is accurate and that users continue to contribute. However, the potential good—such as cures for cancer and other serious diseases, biofuels, synthetic vanilla and coffee, and so on—that could come from using the parts in the library is awe inspiring. The question is, how do we keep the library open and available for current populations and future generations to use?

References

Anderies, J. and Janssen, M. 2013. Sustaining the Commons. Center for the Study of Institutional Diversity, Arizona State University." *International Journal of the Commons* 8.1 (2014): 259-60.

Benner, S. 1987. "Redesigning the molecules of life." Springer, Berlin.

Benner, Steven A., Zunyi Yang, and Fei Chen. "Synthetic Biology, Tinkering Biology, and Artificial Biology. What are we Learning?" *Comptes rendus - Chimie* 14.4 (2011): 372-87.

Biobricks Foundation. 2015. "Frequently asked questions." https://biobricks.org/bpa/faq/.

Cameron, D. Ewen, Caleb J. Bashor, and James J. Collins. "A Brief History of Synthetic Biology." *Nature reviews. Microbiology* 12.5 (2014): 381.

Robert Carlson. Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science. September 2003, 1(3): 203-214.

European Commission. 2014. "Intellectual Property in Biotechnology." European IPR Helpdesk. Web. https://www.iprhelpdesk.eu/sites/default/files/newsdocuments/IP_in_Biotechnology.pdf

European Commission. 2015. Final Opinion on Synthetic Biology II - Risk assessment methodologies and safety aspects. Web. http://ec.europa.eu/health/scientific_committees/consultations/public_consultations/sceni hr_consultation_26_en.htm

International Genetically Engineered Machine (iGEM) Foundation. 2008. "Funding." Web. http://2008.igem.org/Funding.

International Genetically Engineered Machine (iGEM) Foundation. 2015. “Labs Program.” Web. http://igem.org/Labs_Program.

International Genetically Engineered Machine (iGEM) Foundation. 2015. “Registry of Standard Biological Parts.” Web. http://parts.igem.org/Help:Parts.

International Genetically Engineered Machine (iGEM) Foundation. 2015. “Starting a Team.” Web. http://2015.igem.org/Starting_a_Team.

Leduc S. 1912. “La biologie synthétique.” A Poinat, Paris.

PR Newswire. 2015. “Synthetic Biology Students Compete in iGEM 2015 Giant Jamboree.” http://www.prnewswire.com/news-releases/synthetic-biology-students-compete-in-igem-2015-giant-jamboree-300123862.html

Rai A., Boyle J. 2007. Synthetic Biology: Caught between Property Rights, the Public Domain, and the Commons. PLoS Biol 5(3): e58. Web. http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.0050058.

Rawls, R. 2000. 'Synthetic biology' makes its debut. *Chem Eng News* 78, 49-53.

Secretariat of the Convention on Biological Diversity (SCBD). 2015. Synthetic biology. Technical Series No. 82. Montreal.

Shetty, Reshma P., Drew Endy, and Jr Knight Thomas F. “Engineering BioBrick Vectors from BioBrick Parts.” *Journal of biological engineering* 2.5 (2008).

Szybalski W, Skalka A. Nobel prizes and restriction enzymes. *Gene* 1978;4: 18 L -182.

Supreme Court of the United States (SCOTUS). Association for Molecular Pathology v. Myriad Genetics. 13 Jun 2013. Web. http://www.supremecourt.gov/opinions/12pdf/12-398_1b7d.pdf

Vilanova, Cristina, and Manuel Porcar. "iGEM 2.0--Refoundations for Engineering Biology." *Nature biotechnology* 32.5 (2014): 420-4. Web.

Waclaw Szybalski, 1974. "In vivo and in vitro initiation of transcription," in A. Kohn and A. Shatkay (Eds.), *Control of Gene Expression*, pp. 23-24, and Discussion pp. 404-405. New York: Plenum Press.

Wilson Center. 2015a. "The DNA of the U.S. Regulatory System: Are We Getting It Right for Synthetic Biology?" *Synthetic Biology Project.* Web. http://www.synbioproject.org/site/assets/files/1388/synbio_reg_report_final.pdf

Wilson Center. 2015b. "Synthetic Biology Products and Applications Inventory." *Synthetic Biology Project.* Web. http://www.synbioproject.org/cpi/.