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Author(s): Todd T. Eckdahl, A. Malcolm Campbell, Laurie J. Heyer, Jeffrey L. Poet

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Synthetic biology and the international genetically engineered machines competition

Todd T. Eckdahl[1], A. Malcolm Campbell[2], Laurie J. Heyer[3], Jeffrey L. Poet[4]

[1]Missouri Western State University, Department of Biology, St. Joseph, MO 64507, USA, [2]Davidson College, Department of Biology, Davidson, NC 28036, USA, [3]Davidson College, Department of Mathematics, Davidson, NC 28036, USA, [4]Missouri Western State University, Department of Computer Science, Math and Physics, St. Joseph, MO 64507, USA

Introduction

We are excited to share an exciting new area of biological research that will be of great interest to many TriBeta students and faculty mentors. As biology and mathematics faculty mentors ourselves with a long-standing commitment to undergraduate research, we have advised students working on a variety of research topics, including cell biology, molecular phylogenetics, cancer biology, microarray analysis, graph theory, and computer programming. Each of these areas provided interesting projects for our students, enabling them to learn how to conduct research and disseminate their results through presentations and publications. However, about four years ago, our active undergraduate research programs transitioned to a new research field called synthetic biology. Synthetic biology is exciting, interdisciplinary, relatively inexpensive and appropriate for undergraduate research. Synthetic biology has also enabled us to establish multidisciplinary research groups composed of biology and mathematics professors and students and to work together as a collaborative team from our two institutions, Missouri Western State University and Davidson College. Our students have used their research experience to get jobs and enter graduate school at a time when global interest in synthetic biology is growing rapidly. In this article, we describe the emerging field of synthetic biology, provide examples of the impact it is having on the understanding of biology and the ability to engineer biological systems, and explain how undergraduates are making important contributions to its development. We will also describe the international Genetically Engineered Machines (iGEM) competition as an entry point for undergraduate students to begin synthetic biology research.

Correspondence to: Todd Eckdahl, Missouri Western State University, Department of Biology, St. Joseph, MO 64507; phone: (816) 271-5873; e-mail: eckdahl@missouriwestern.edu

What is synthetic biology?

Synthetic biology is a new research approach that uses engineering principles, mathematical modeling, and the tools of molecular biology to design and construct biological devices that allow the exploration of complex biological systems. Research in synthetic biology has important applications in medicine, technology, energy, and environmental science (Chopra, 2006). Synthetic biologists take an engineering approach

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by building models of complex natural systems in order to better understand how their biological designs might perform. Based on the laboratory results, investigators either validate their models or more often, identify false assumptions in basic biology and thus contribute to our understanding of how cells and organisms work. In short, synthetic biology presents a win-win research paradigm which enhances its potential to facilitate student learning.

Synthetic biology is made possible by advances in recombinant DNA technologies. Improvements in our ability to synthesize DNA, cut and paste it with enzymes, amplify it by PCR, sequence it, and use it to transform cells have made molecular cloning not only more versatile, but more accessible and affordable. However, much more than a set of tools, synthetic biology stimulates a new way of thinking that uses engineering principles to clarify research goals and manage complexity (Endy, 2005). One engineering principle is the standardization of parts and their assembly. In electrical engineering, standardized parts such as resistors and capacitors have known properties, are available from catalogs, and can be assembled in standardized ways thanks to universally agreed upon physical parameters. In synthetic biology, DNA parts such as genes, promoters, ribosome binding sites, and transcriptional terminators are being functionally characterized and contributed to a growing catalog called the Registry of Standard Biological Parts (http://partsregistry.org/Main_Page). The Registry contains over 3200 DNA parts, each of which is configured as a "BioBrick," allowing for standardized assembly (Figure 1). Assembling two BioBricks together results in a composite BioBrick due to the use of compatible restriction enzyme sites (Knight, 2003). This standardization of assembly means any two parts in the Registry can be connected in a consistent and reliable manner. Another engineering principle used in synthetic biology is abstraction. In abstraction, parts are made from raw materials and assembled into devices, which are in turn combined to produce systems. For example, stringing capacitors and resistors together can result in a circuit that functions as a switch. Combining different devices can result in more complex electronic systems such as computers. Synthetic biologists use DNA as a raw material to construct biological parts, designing them from scratch or borrowing them from nature. The parts with BioBrick ends can be assembled into devices that are in turn used to build systems. Abstraction allows investigators to understand and manage the complexity of living systems and encourages creativity in the process of engineering biology without getting bogged down in the details. Students from diverse academic backgrounds do not necessarily need to think about all the parts in order to design new devices or systems and model their expected behavior.

Early successes in synthetic biology have captured worldwide attention. For example, Jay Keasling at UC Berkeley and his group created new biochemical pathways in bacteria and yeast

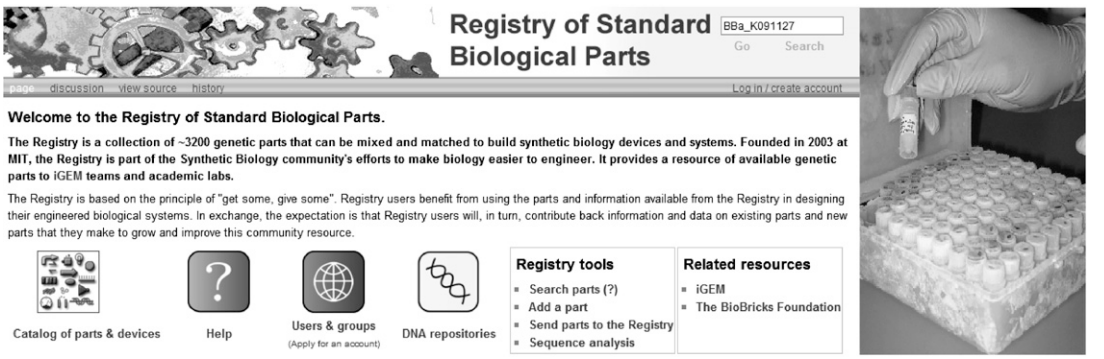

Figure 1. The Registry of Standard Biological Parts is an online catalog of DNA parts, devices, and systems that is made available as frozen bacterial clones to iGEM teams.

that generate an anti-malarial drug for less than 10% of the traditional cost (Martin, 2003). Keasling was named *Discover Magazine* 2006 Scientist of the Year, in part for this work. Researchers at the J. Craig Venter Institute not only transplanted the genome of one bacterium into another, but synthesized the entire genome of the bacterium, taking steps toward the creation of a fully synthetic organism (Lartigue, 2007). Michael Elowitz at Caltech constructed the Repressillator, a synthetic oscillatory network consisting of three interacting repressors in a negative feedback loop (Elowitz, 2000). A primarily undergraduate research team from the University of Edinburgh designed a biosensor to detect levels of arsenic in water and emit a color signal in response (Aleksic, 2007). A team of undergraduates from the University of Texas, Austin, working with researchers at UCSF, designed a genetic circuit that enables bacteria to respond to red light by switching off production of a pigment and published their work in *Nature* (Levskaya, 2005). The resulting biological photographic film was shown to be high resolution, capable of about 100 megapixels per square inch. Synthetic biology is also being used to address global energy concerns. Currently, millions of dollars are being invested in synthetic biology approaches to the development of alternative energy sources. These and other examples validate synthetic biology as a new approach to the investigation of natural living systems and to the design and construction of artificial ones with important applications.

Undergraduate research in synthetic biology

Synthetic biology is poised at the forefront of biological investigation and is an attractive area for undergraduate research. Its use of fundamental molecular cloning techniques and engineering principles simplifies the design and construction of biological devices. Because of the simplicity with which parts can be designed, built, and assembled into devices and systems, students can easily learn the experimental methods needed to build a genetic device and use it to program cellular activities. Even first year students who have basic laboratory skills and an understanding of molecular and cellular biology can quickly master the skills and move to higher levels of thought and analysis. Using the principle of abstraction, students rapidly manage the complexity of system design, and develop creative ways to engineer living systems. We and others have seen firsthand the ease with which undergraduate students adapt to synthetic biology research. It is feasible for students to conceive, design, and conduct a synthetic biology research project over the course of a single academic year or a summer.

Synthetic biology research is also accessible to undergraduate students because of its affordability. All that is needed is the equipment for basic molecular cloning, such as a dry incubator, a shaking incubator, a microcentrifuge, micropipettors, a water bath incubator, and agarose electrophoresis equipment. The supplies needed include four restriction enzymes, DNA ligase, a miniprep plasmid purification kit, a gel purification kit, competent cells, and the materials to grow them. A virtually unlimited number of original projects can be conceived and conducted using existing Registry parts. With the additional equipment of a thermal cycler, the purchase of oligonucleotides, and access to DNA sequencing, new parts can be cloned from natural sources or designed from scratch.

Undergraduate research in synthetic biology is feasible in settings that already exist at diverse types of institutions. Research universities can provide opportunities for groups of undergraduate students to conduct research for which they feel a great deal of ownership. Instead of making contributions to an ongoing research project that involves graduate students and postdoctoral fellows, they can design and execute their own project. Students at primarily undergraduate institutions can conduct original synthetic biology research that makes legitimate contributions to the growing field. Smaller institutions can take advantage of the accessibility and affordability of synthetic biology to make research opportunities available to their students and can establish institutional collaborations to pool resources.

An example of an undergraduate synthetic biology project is described in this issue of *BIOS*. Conducted by three of our research students at Davidson College and Missouri Western State University, the study illustrates several important aspects of undergraduate synthetic biology research. First, it shows how the synthetic biology approach to research enables the development of improved parts for engineering biological systems. The students were able to use information from the literature to redesign the widely used lactose promoter and its repressor, standardize them into BioBrick parts, and characterize their functions (Figure 2). Some of the new parts exhibited improved functions and others surprised all of us. Second, since the parts constructed and tested by the students have become available to the worldwide synthetic biology research community through the Registry of Standard Biological Parts, the project illustrates how the work of undergraduates can contribute to the efforts of others. Third, the paper serves as an example of the accessibility of synthetic biology research to undergraduate students and their faculty mentors. The project was straightforward in design and required only standard experimental methods. Finally, the study shows how undergraduate students can make important contributions to the advancement of biology.

There are many ways to generate ideas for undergraduate research projects. One way is to think about how synthetic biology provides opportunities to examine basic assumptions and hypotheses about the functions of well-studied genetic components. This occurs because of the synthetic biology approach of isolating and characterizing parts. In conducting synthetic biology research, undergraduates gain an understanding that what they learn in their classes, in their textbooks, and from the scientific literature is not always entirely so, and can even be wrong. This is an important insight and one that, in our experience, is exciting for undergraduate researchers to discover. For example, our students learned firsthand that transcriptional terminators do not function as absolute stop signs, but with varying levels of efficiency that cause us to call them yield signs. They also learned that regulatory systems such as repression and activation are not absolute. Our group made the original discovery that DNA containing the lactose promoter can cause transcription initiation upstream in addition to its normal downstream activity. This is especially interesting in light of recent

Figure 2. Students from Davidson College and Missouri Western State University collaborated as iGEM teammates on synthetic biology research in 2008.

evidence of similar divergent transcription from promoters in the human genome (Core, 2008). Each of these observations and many others of this type can form the basis for interesting and important undergraduate research projects.

iGEM, the international genetically engineered machines competition

A major reason undergraduates are able to contribute to synthetic biology is the iGEM competition (Katsnelson, 2009). The founding organizers of iGEM asked, "Can simple biological systems be built from standard, interchangeable parts and operated in living cells? Or is biology simply too complicated to be engineered in this way?" They were compelled to engage undergraduates in synthetic biology research by their belief that undergraduates are highly creative and yet are not burdened with the knowledge of what cannot be done. Teams competing in iGEM have access to the Registry of Standard Biological Parts and use the principles and practices of synthetic biology to creatively engineer biological systems. Construction of a team Wiki page is required, so that research project designs and results can be communicated to the iGEM community. The competition culminates in the annual iGEM Jamboree. Held at MIT each November, the Jamboree provides a high profile forum for iGEM teams to present their work with posters and oral presentations (Campbell, 2005).

The iGEM competition grew from five U.S. teams in 2004 to 112 teams from 26 different countries in 2009. In that time, a wide diversity of creative research projects have been designed, modeled, tested, published, and even patented. For the 2005 iGEM competition, the team from ETH Zurich designed a genetic circuit that allows bacteria to count, and made strides toward programming sequential instructions into cells. Undergraduates from Penn State used quorum sensing to engineer bacteria to engage in a relay race that year while the Toronto team designed a "Bacterial Etch-a-Sketch" based on the Lac operon. Many attendees at the 2006 iGEM Jamboree will not likely forget when a member of the MIT iGEM team walked up to them with three tubes of *E. coli,* asking for a sniff test. The students were conducting field tests to measure the success of their project to rewrite the metabolic program of the stinky bacteria to instead smell of wintergreen or bananas. The result was striking, demonstrating the power of synthetic biology and the creativity of undergraduate students. A project to engineer bacteria to be a cost-effective replacement for red blood cells was called "Bactoblood" by the 2007 iGEM team from the University of California Berkeley. Students from Taipei, Taiwan designed a "Bactokidney" system that would enable bacteria to attach to the small intestine, clear metabolic waste, and detach. The 2008 Rice University iGEM team engineered yeast to produce the cancer preventative resveratrol, with the idea of producing health-promoting beer and wine. In 2009, the Cambridge iGEM team developed a palette of visible reporters for use in biosensing.

The iGEM Jamboree is an amazing showcase of undergraduate achievement in synthetic biology. As the largest concentration of synthetic biology research presentations in the world, it makes a significant contribution to the continued development of the field. It offers a glimpse of what is possible, through the creative work of its future practitioners. Information is available on the iGEM website for registering a new student team (http://2009.igem.org/Main_Page). In 2009, there was a $1250 registration fee that paid for administration of iGEM and maintenance of the Registry of Standard Biological Parts. The fee also covers distribution of the most used parts to registered teams and the opportunity to contribute parts to the growing Registry. The cost of attending the Jamboree is $175 for undergraduate students and $375 for all other attendees. In summer, 2010, there will be a synthetic biology faculty workshop at Davidson College, sponsored by the Genome Consortium for Active Teaching (Campbell, 2006) and HHMI. Technical support is readily available from iGEM headquarters, and from the iGEM community. Funding for iGEM teams can be sought from institutional sources, from local or national sponsors, or from extramural grant programs, including the Tri-Beta Research Scholarship program.

Beta Beta Beta and synthetic biology research

TriBeta has a rich history of supporting students engaging in scholarship, service, and research. Its three purposes of promoting scholarship in the biological sciences, promoting the dissemination of biological knowledge, and encouraging research have spurred many students to explore careers and discover unknown passions for science. In addition to striving to do their best in coursework, being active in their local Tri- Beta chapters, and attending district and national Tri-Beta conventions, successful Tri-Beta students seek out undergraduate research projects. Synthetic biology and the iGEM competition present new opportunities for Tri-Beta students to engage in exciting and important research. In so doing, they will contribute to an emerging discipline while learning important lessons about conducting original multidisciplinary research, meeting the challenges of research at the forefront of scientific progress, and collaborating as part of a worldwide research community.

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