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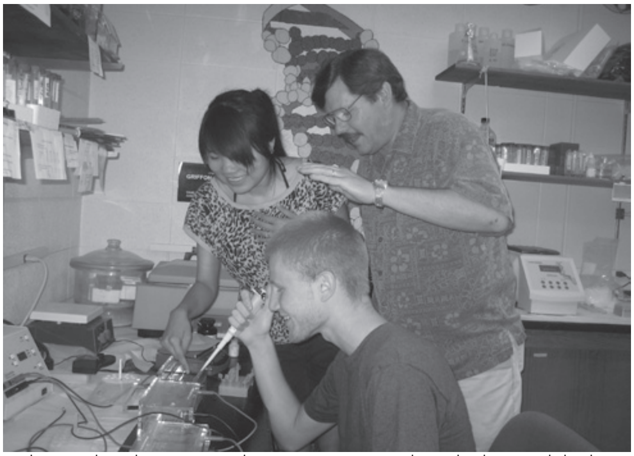
Synthetic Biology as a New Opportunity for Multidisciplinary Undergraduate Research

Many of the most profound discoveries have occurred at the boundaries between traditional scientific disciplines. When chemists talk to physicists, or psychologists work with biologists, or mathematicians confer with engineers, new perspectives arise and lead to scientific breakthroughs. Scientists from these and other disciplines are finding ways to communicate and collaborate, addressing research questions in a multidisciplinary fashion. We should encourage the next generation of scientific researchers, our students, to understand the nature of multidisciplinary research and provide them opportunities to practice it.

BIO2010, a report by the National Research Council on transforming undergraduate biology education, recommends that reformers of undergraduate education "should consider the importance of building a strong foundation in mathematics and the physical and information sciences to prepare students for research that is increasingly interdisciplinary in character" (NRC, 2003). Engaging students in multidisciplinary research is also in accord with the mission of the Council on Undergraduate Research to support and promote student-faculty collaborative research in biology, chemistry, geosciences, mathematics, computer science, physics, astronomy, psychology, social sciences, and the arts and humanities.

Multidisciplinary undergraduate research presents the usual challenges involving availability of funding, instrumentation, laboratory space, student preparation, faculty expertise, and faculty time. But it also brings special challenges, including the fact that it can be hard to find interesting and accessible research questions at the intersections between disciplines. In addition, it is often difficult, especially at primarily undergraduate institutions, to find two or more faculty members with overlapping expertise and research interests. Funding multidisciplinary research is also difficult given the discipline-specific nature of many programs of the National Science Foundation and other funding agencies.

The new field of synthetic biology is particularly well-suited, however, to meet the challenges of engaging undergraduates in multidisciplinary research. It presents a large variety of original multidisciplinary research projects, allows faculty and students from diverse areas of expertise to bring their experience and creativity to bear on important problems, and is accessible to undergraduate students. In this article, we describe synthetic biology as an emerging multidisciplinary field, explain the role that undergraduate researchers can play in its development, and describe iGEM, the international Genetically Engineered Machines competition as a vehicle for conducting undergraduate research. We also use our own experiences in undergraduate research in synthetic biology to illustrate how it can foster connections between disciplines and institutions.



Biology and mathematics students investigate synthetic biology with biology and mathematics faculty mentors.

Synthetic Biology as an Emerging Multidisciplinary Field

Synthetic biology is an exciting new field that uses engineering principles and mathematical modeling to design and construct biological devices with applications in energy, medicine, environmental studies, and technology (Endy, 2005). For example, a high profile success of synthetic biology is the engineering of bacterial and yeast cells to produce an important antimalarial drug. The blurring of traditional lines that occurs in synthetic biology—among biology, computer science, mathematics, and engineering; between institutions in different locations or with different missions; and between education and research, promises to catalyze widespread reform of scientific research.

The foundation of synthetic biology is recombinant DNA technology as it has matured over the past 35 years. Advances in our ability to synthesize DNA, cut and paste it with enzymes, amplify it by the polymerase chain reaction, sequence it, and introduce it into cells have made molecular cloning not only more versatile, but also extremely accessible and increasingly affordable. However, synthetic biology is more than a collection of experimental tools. It is a way of thinking that uses fundamental principles of engineering to promote collaboration and creativity (Chopra and Kamma, 2006).

One such principle is standardization. Those of us who are not engineers take for granted that there are collections of parts, such as nuts and bolts, that are standardized, catalogued, quality-controlled, and have well-defined properties agreed upon by a community (Knight, 2003). Standardization of parts is accompanied by the standardization of the assembly of those parts; nuts and bolts go together in ways that are agreed upon by the entire world. This standardization creates efficiencies and encourages collaboration.

Another important engineering principle is abstraction. According to this principle, parts made from basic materials are assembled into devices, which in turn are combined to produce systems. For example, raw materials of metal, plastic, and silicon are used to make microprocessor parts that are assembled into a hard drive device, which is then integrated into the system of a computer. Abstraction allows engineers to manage complexity, to specialize, and to engage in creative and higher-order thinking.

In synthetic biology, standardization of parts is occurring in much the same way it has in engineering. The community of synthetic biologists is coming to agreement on what properties biological parts should have and how their functions should be measured. The most extensive collection of DNA parts is the Registry of Standard Biological Parts, a catalog of over 3,200 gene-coding sequences, promoters, ribosome-binding sites, transcriptional terminators, and many other useful components of genetic circuits (http://partsregistry.org/Main_Page). The Registry parts are configured as "BioBricks™," enabling their assembly in a standardized fashion using a clever scheme (Knight, 2003). The result of putting two BioBricks™ together produces a new BioBrick composite part, analogous to the assembly of Legos™.

Synthetic biologists also use the engineering principle of abstraction. They use DNA as a raw material to construct biological parts, designing them from scratch or borrowing them from nature. The parts are assembled into devices that are, in turn, used to construct systems. Abstraction simplifies thinking about complex systems and encourages creativity in the process of engineering living cells. Because systems function in ways that cannot always be predicted by the functions of their constituent parts and devices, abstraction is reminiscent of emergent properties in biological systems.

Approaches to synthetic biology most often follow one of two paths. One path is to use the tools and ways of thinking of synthetic biology in a reductionist approach to understanding natural biological systems. By deconstructing complex systems into devices and their component parts, and reassembling them, synthetic biologists can develop and test hypotheses about how natural systems function. They can compare the behavior of their synthetic models to natural systems and devise experiments to learn why differences occur. Another path is to borrow parts and devices from nature or to design and construct synthetic ones, and build systems that enable living cells to carry out new functions not found in nature. In this way, synthetic biologists seek to assemble a collection of components and develop the tools needed to engineer biology.

Early successes in synthetic biology have captured worldwide attention. For example, Chris Voigt and his group at the University of California, San Francisco engineered bacteria to respond to the anaerobic environment produced by cancerous cells by secreting a cytotoxin (Anderson *et al*, 2006). The study is a first step toward arming bacteria that can sense the microenvironment of a tumor and selectively kill it. Michael Elowitz at Caltech constructed the "repressillator," a synthetic oscillatory network consisting of three interacting repressors in a negative feedback loop (Elowitz and Leibler, 2000). At the University of California, Berkeley, Jay Keasling and his group used synthetic biology to re-engineer the metabolism of bacteria and yeast to produce artemisinin, an important antimalarial drug. Keasling was named the 2006 Discover Magazine Scientist of the Year in part because he reduced the cost of malaria medication by a factor of ten. These and other examples of successful synthetic biological applications serve to invigorate the existing community of synthetic biologists and encourage others to join it. They validate the approach of synthetic biology as a means to understand complex natural biological systems and to design artificial ones with important applications.

Left: Synthetic biology research students work closely with a faculty mentor, using tools from a variety of disciplines.
Right: Undergraduates from the 2009 Missouri Western/Davidson iGEM team conduct synthetic biology research with faculty mentors.

Undergraduate Research in Synthetic Biology

In addition to advancing our understanding of living systems and engineering new biological devices, synthetic biology is very accessible to undergraduate researchers. Biology students only need an understanding of the fundamentals of molecular genetics and cell biology, which are reinforced early and often in the course of a research project. Because of the simplicity with which parts can be designed, built, and assembled into devices and systems, students easily learn the experimental methods for conducting projects in synthetic biology. This gives them the freedom to use abstraction to think about the purposes of their research designs and their applications. Mathematics and computer-science students can use the abstractions and not get bogged down in the details of experimental protocols.

Synthetic biology is inexpensive and can be conducted on any campus that has standard molecular biology equipment such as a dry incubator, a shaking incubator, a microcentrifuge, micropipettors, a water bath incubator, and an agarose electrophoresis apparatus. Many original projects can be conceived and conducted using existing parts from the Registry. The basic supplies needed include four different restriction enzymes, DNA ligase, a miniprep plasmid purification kit, a gel purification kit, competent bacterial cells, and the materials to culture bacteria. With the additional equipment of a thermal cycler, the purchase of oligonucleotides, and access to DNA sequencing, new parts can be mined from nature or designed, expanding the number of possible projects.

Undergraduate research in synthetic biology is also accessible to a wide variety of institutions. Major research universities can provide opportunities for undergraduates, working as part of a large research group, to conduct projects in synthetic biology for which they can feel ownership. Students at primarily undergraduate institutions can conduct research projects in synthetic biology with sophistication and outcomes comparable to those conducted at research institutions. Smaller institutions can use the accessibility and affordability of synthetic biology to make new research opportunities available to their students.

iGEM, the international Genetically Engineered Machines Competition

Each year since 2004, undergraduates from around the world have explored the possibilities of research in synthetic biology as part of the international Genetically Engineered Machines competition, or iGEM (http://2009.igem.org/Main_Page). The competition grew out of a course at the Massachusetts Institute of Technology in which students designed genetic circuits for blinking bacteria. MIT faculty members Tom Knight and Drew Endy founded iGEM by asking the questions, "Can simple biological systems be built from standard, interchangeable parts and operated in living cells? Or is biology too complicated to be engineered in this way?"

The founders of iGEM and its director Randy Rettberg believe that undergraduates are well-suited for research in synthetic biology because they are not burdened with assumptions about what cannot be done; they have a healthy enthusiasm for research; and they have a high level of creativity. In addition, undergraduate research projects can carry a risk of failure that is not appropriate for graduate-level research. The high-risk, high-gain approach benefits synthetic biology, since undergraduates will try things that graduate students will not. iGEM is modeled after robot competitions, in which student teams are given collections of parts and challenged to build robots that battle each other. For iGEM, undergraduates form teams, are given access to the Registry of Standard Biological Parts, and use the methods and concepts of synthetic biology to creatively engineer living cells (see review by Katsnelson, 2009). Construction of a team Wiki page is required, so that the designs and results of research projects can be communicated to the iGEM community. In November, teams meet to present their work alongside peers from around the world.

Held at MIT, the annual iGEM "Jamboree" provides a high-profile forum for iGEM teams to present their research with posters and oral presentations (Campbell, 2005). The iGEM Jamboree is nothing short of a celebration—of the enthusiasm, creativity, energy, and accomplishments of undergraduates, and of the multidisciplinary and multi-institutional collaborations of a growing international community. Each year, we celebrate the latest breakthroughs in synthetic biology. The fact that these advances have been made by undergraduates bodes very well for the future of synthetic biology as an increasingly important approach to multidisciplinary research and as a means to revolutionize the engineering of biology. Table 1, available in the Winter 2009 issue of CURQ on the Web at www.cur.org/quarterly/webedition.html, describes the growth of the event and highlights some of the iGEM projects. Further information about these and other projects is available at http://2009.igem.org/Main_Page.

Connections between Disciplines and Institutions

Undergraduates with majors in biology, engineering, chemistry, computer science, exercise physiology, biochemistry, physics, mathematics, and others have joined multidisciplinary iGEM teams. Students learn how to communicate what they know about their respective fields to other team members as they work together to explore the intersections of their disciplines. The practice of multidisciplinary research becomes the strength of iGEM teams, and students realize the benefits of collaboration.

The spirit of collaboration in synthetic-biology research also extends to institutions. For example, the authors' two institutions, Missouri Western State University and Davidson College, have collaborated on synthetic biology and entered joint teams in the iGEM competition for four years. As faculty members at two primarily undergraduate institutions, we appreciate the opportunity to combine the limited resources of faculty time and expertise, access to larger numbers of appropriately prepared students, and greater availability of research equipment and supplies that such collaboration provides. In the context of iGEM, our undergraduate research teams have designed and conducted several projects that illustrate the potential for multidisciplinary synthetic-biology research.

In 2006, for example, we designed a bacterial computer to solve the "burnt pancake" problem. The problem is one of sorting by reversals illustrated by a stack of differently sized pancakes with one burnt side that must be flipped to be arranged from largest to smallest, with all the burnt sides down. This has important applications to parallel-processing computer networks and can serve as a model for genome rearrangements (Haynes *et al*, 2008). The iGEM project our undergraduates conducted in 2007 also shows how synthetic biology allows the exploration of connections between mathematics and biology. Our students were able to program bacterial computers to solve a Hamiltonian path problem, which is the problem of determine a route through the nodes of an ordered graph. This can be likened to a traveler trying to visit each of several cities on a worldwide tour (Baumgardner *et al*, 2009; http://parts.mit.edu/igem07/index.php/Davidson_Missouri_W). For the 2008 iGEM competition, our students designed and built genetic circuits that could implement a "hash" function, capable of using logic gates to process inputs in a manner important for encryption and message validation (http://2008.igem.org/Team:Davidson-Missouri_Western).

We recruit first- and second-year students enrolled in introductory biology and mathematics courses to participate in weekly discussions of research topics that bridge the two disciplines. These BioMath Connections allow our two campuses to engage in electronic collaborations and learning activities. During these meetings, students and faculty also have an opportunity to gauge students' interest in and suitability for multidisciplinary research. In the spring semester, these students and others are encouraged to apply for summer research positions, although more students apply than can be accepted. We especially target students from underrepresented groups through personal contacts and faculty referrals. Students are selected based on academic performance and research potential as indicated by letters of recommendation. We are keen to find students who express an interest in both biology and mathematics, although we know most students are better prepared in one or the other of these two areas. Once selected, all the students work together in the spring to improve their ability to communicate across disciplines and to identify potential research projects. With funding from NSF and other sources, we have hired six to eight students on each campus for full-time summer research.

Undergraduates from the 2009 Missouri Western/Davidson iGEM team conduct synthetic biology research with a faculty mentor.

Research into synthetic biology conducted for iGEM has been an excellent way for us to address several important goals for our undergraduate research programs:

- First, it is a very exciting area of research. Students are interested to hear of the previous projects conducted by our iGEM teams and other teams from around the world; they become very enthusiastic once they realize the possibilities for their own research. And as collaborators with our students, we share their enthusiasm for the research; synthetic-biology research is just plain fun.
- Second, synthetic biology allows us to offer our students opportunities to engage in multidisciplinary research. We have been able to assemble research teams of undergraduates with majors in biology, chemistry, and mathematics. As faculty members with expertise in biology, mathematics, and computer science, we also value the chance to work together.
- Third, we found financial support for work with undergraduates. In addition to garnering funds from programs administered through our respective institutions, we secured funding from the National Science Foundation through a program called Interdisciplinary Training for Undergraduates in Biological and Mathematical Sciences (UBM, http://www.nsf.gov/pubs/2008/nsf08510/nsf08510.htm). Our UBM project uses research in synthetic biology to allow undergraduates to explore connections between biology and mathematics.
- Finally, research conducted as part of iGEM has provided opportunities for our students to contribute to the knowledge base of the nascent field of synthetic biology. Our students have been able to present their work not only at the iGEM Jamboree, but also at local, state, and national conferences. We also have been able to publish the results generated by our undergraduate research teams in national peer-reviewed professional journals (Haynes *et al*, 2007; Haynes *et al*, 2008).

Call for Participation in Undergraduate Research in Synthetic Biology

We encourage faculty members from the various disciplines in the mathematical, natural, and social sciences to consider mentoring an iGEM team of undergraduates for multidisciplinary research in synthetic biology. It can address many of an institution's objectives for undergraduate research and allow students to learn firsthand the value of conducting research in a multidisciplinary manner, working together on a team and contributing to a growing worldwide research community. It can offer faculty from different disciplines a chance to work together and reinvigorate the research agendas of individual faculty members or academic departments. Undergraduate research in synthetic biology can be a public-relations benefit for institutions, illustrating the value of students engaging in applied-learning activities. The results of undergraduate research can be presented by both undergraduates and their faculty mentors at a variety of venues, including disciplinary society meetings, undergraduate research conferences, campus research symposia, or community forums. Publication of the research results is also feasible, as is obtaining funding from institutional and extramural sources.

Registration information for student teams is available on the iGEM Web site (http://2009.igem.org/Main_Page). Currently, there is a $1,250 registration fee that pays for administration of iGEM and maintenance of the Registry of Standard Biological Parts. The fee also covers distribution of the most commonly used parts to registered teams and the opportunity to contribute parts to the growing registry. Meetings are held each spring for faculty members who would like to learn firsthand about mentoring an iGEM team. In summer 2010, Davidson College will host a synthetic-biology workshop, sponsored by the Genome Consortium for Active Teaching (http://www.bio.davidson.edu/GCAT) and funded by the Howard Hughes Medical Institute. We also highly recommend the comprehensive guide "Running a Successful iGEM Team," by Wayne Materi (available at http://www.bio.davidson.edu/GCAT). Technical support is readily available from iGEM headquarters and from the iGEM community. Funding for iGEM teams can be sought from institutional sources, local or national sponsors, or extramural grant programs.

It is unusual for undergraduates to have the opportunity to shape the development of a new field of scientific research, but that is exactly what is happening in synthetic biology. With the accessibility of research in the field to undergraduates and the entry point into the field facilitated by the iGEM competition, undergraduate research is, in fact, a driving force in the establishment of this new discipline. The sense of excitement that comes from moments of discovery during undergraduate research is amplified in synthetic biology because it can impact an emerging worldwide scientific community. Having gained an entry into this multidisciplinary field early in their careers, today's undergraduates can take ownership of synthetic biology. This holds tremendous promise for the future of synthetic biology and for all scientific research, as undergraduates mature into scientists with an appreciation for cutting-edge multidisciplinary research.

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