Integrating Synthetic Biology into the Microbiology Curriculum

Teaching labs and research projects that feature synthetic biology steer clear of rote learning and help to motivate students

Malcolm Campbell, Laurie J. Heyer, Todd T. Eckdahl, and Jeffrey L. Poet

College educators face the ongoing challenge of determining what and how much content to cover, knowing that it is impossible to keep up with all the new research findings and trends. And we cannot continue adding new content unless we throw out an equal amount of the old. With genome sequencing, metagenomics, and comparable developments, microbiology is experiencing its greatest expansion since the microscope was invented. No textbook can remain current. Moreover, because students are not smarter than we were as students, it is pointless to throw vast amounts of information at them and expect them to retain it all.

What should we do to be current but not overwhelm our students? Although computers and flash drives readily store massive amounts of data for long periods, students do not. Rather than treating them like data storage devices, we should focus on their creative, analytical, and problem-solving skills, encouraging them to enjoy useful intellectual challenges. For students motivated to solve the global energy problem, detect trace amounts of hazardous compounds in the environment, or cure metabolic diseases such as diabetes, consider introducing them to synthetic biology through your curriculum. Doing so can achieve many important educational goals while providing incentives for students to learn and apply what they learn in novel ways.

Synthetic biology is a relatively new discipline within microbiology. Although its practitioners are not settled on how to define it, many of them agree that it uses engineering principles, molecular cloning methods, and mathematical modeling to design and construct biological parts, devices, and systems with applications in energy, medicine, and technology. Synthetic biologists typically use microbes as part of their synthetic systems.

Many undergraduates participate in synthetic biology research, thanks in large part to the International Genetically Engineered Machine (iGEM) competition (Fig. 1). Started in 2005, iGEM encourages undergraduates from all over the world to apply what they know to solve a biological problem of their choosing and then work on it with students from a variety of disciplines while learning whatever they might need to make progress. This approach mirrors what professional scientists do every day. By popular demand, iGEM now includes high school and "entrepreneurship" teams, and the number of teams increases each year (*Microbe*, January 2012, p. 13).

SUMMARY

- **Synthetic biology, a relatively new discipline within microbiology, is providing a novel approach for teaching undergraduate students and encouraging them to take interdisciplinary approaches.**
- **College and university faculty members have several options for incorporating synthetic biology into microbiology or related scientific teaching curricula.**
- **Student research projects, even when they do not meet anticipated end points, prove useful to students and sometimes yield publishable findings.**
- **Workshops, networks, and materials are among the resources available to faculty members who are interested in incorporating synthetic biology into their courses.**

Incorporating Synthetic Biology into the Microbiology Curriculum

Synthetic biology laboratory projects can be incorporated into several different undergraduate courses. For example, when students learn about gene structure and regulation, they could also

FIGURE 1

iGEM empowers undergraduates to conduct synthetic biology as part of a global community. Teams of undergraduates from North and South America, Asia, Europe, Africa and Australia compete in the annual iGEM competition.

learn how to use synthetic biology tools to study gene promoters and determine the output of a reporter gene such as red fluorescent protein (RFP). Students in more advanced courses such as microbiology, molecular biology, biochemistry, bioengineering, and genetics can learn to construct newer promoters based on recently published results and to test mutations in promoters that they design.

Synthetic biology could also be incorporated into the microbiology curriculum by having students explore research papers published in ASM journals or others such as the *Journal of Biological Engineering* (www.jbioleng.org), *ACS Synthetic Biology* (http://pubs.acs.org/journal/asbcd6), or the more general journal *Interdisciplinary Bio Central* (http://www.ibc7.org/article/journal.php). Those open-access journals and others such as ASM's *mBio* provide free, high-quality PDFs without copyright restrictions or user fees. Many students enjoy learning information that is on the cutting edge.

Undergraduate microbiology students can also conduct independent research projects in synthetic biology. Student-based synthetic biology research is relatively inexpensive, and teaching laboratories may have the equipment needed to manipulate DNA and transform host cells. The newness of synthetic biology and its many topics offer students and their teachers a range of challenges that call upon divergent expertise and interests. We focus on mathematics and microbiology, but other collaborations in synthetic biology include chemists, engineers, and computer scientists.

Feasible Research Projects for Undergraduates

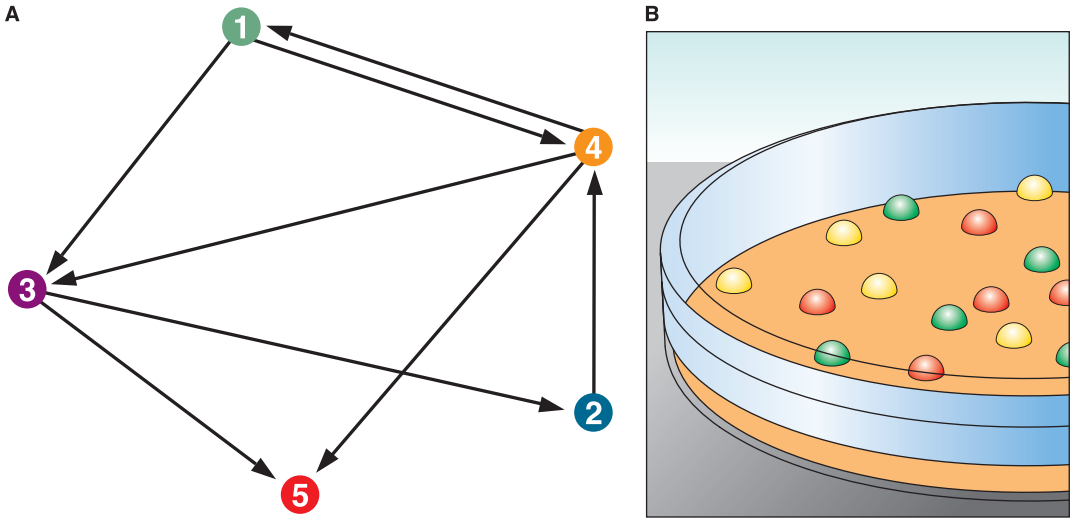
Synthetic biology projects fall under various headings, including environmental biology, biomedical applications, and energy (see http://igem.org/Previous_iGEM_Competitions). One exciting aspect of synthetic biology is the creativity that students bring to their projects. Consider, for example, two projects that our students designed, built, tested, presented, and published.

During the summer of 2007, our two-campus team of undergraduates decided to build a bacterial computer to try to solve the challenging Hamiltonian Path Problem (HPP; Fig. 2). HPP asks whether a directed graph contains a pathway such that every node is visited exactly once and the pathway has designated start and stop nodes.

The HPP project built on the previous year's burnt pancake project by using a DNA recombinase from *Salmonella typhimurium* called Hin and its recognition site called *hix*. Our HPP students pioneered splitting genes such that the half-genes do not function unless they reunite with the appropriate other half gene. The mathematicians in our group modeled the system and guided others who constructed instances to test the capacity of the engineered *Escherichia coli* computers. Our biologists built three versions of the problem. The students then used the bacterial computer to solve small versions of the HPP. Their paper, published in the July 2009 *Journal of Biological Engineering* (JBE), became the JBE "paper of the year" and remains its most accessed report.

In synthetic biology research, like other fields, failures are more common than successes. However, in terms of educational value, having students do research projects in synthetic biology is a win-win proposition. Thus, when projects fail to work as expected, we encourage our students

FIGURE 2



Hamiltonian Path Problems can be solved by bacterial computers designed and built by undergraduates. (A) Example of a directed graph. If the pathway must start at node 1 and finish at node 5, a Hamiltonian path is 1 → 3 → 2 → 4 → 5. (B) Close-up photograph of part of a petri dish with colonies of *E. coli* where yellow indicates a correct solution to the HPP.

to conduct additional research and uncover reasons why. Sometimes this effort leads them to novel findings in biology. For example, in 2008 the Davidson and Missouri Western (DMW) iGEM team set out to build a bacterial hash function, that is, an algorithm that can convert an input of arbitrary length, such as a computer password or document, into an encrypted output with a fixed number of characters.

The DMW team of undergraduates sought to design an unhackable algorithm as their bacterial hash function (Fig. 3). The first requirement was to use DNA to make an XOR logic gate—in this case, producing a reporter gene output if only one of two possible inputs is present. Although other iGEM teams built DNA-based AND-OR logic gates in earlier competitions, no one reported making an XOR logic gate. Another iGEM team told our students "it can't be done—we tried and failed last year." That comment led our students to push even harder.

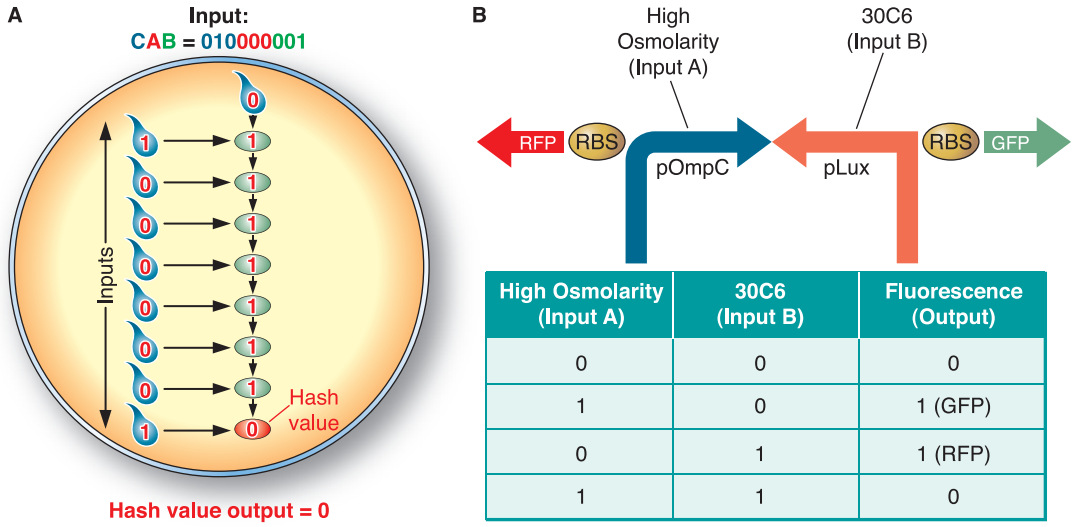
The students chose a pair of inducible promoters facing each other to be the central controller of their experimental XOR logic gate. They chose well-characterized promoters—*ompC* from *E. coli,* which is involved in osmoregulation, and the *luxI* promoter from *Vibrio fischeri,* used in quorum sensing. The design was simple enough that it could be built within one summer. The XOR gate worked well for three of the four input combinations, but gave the wrong output with the fourth combination. After many replicates with identical results, the students designed experiments to determine which promoter was not working the way that they expected and why.

They discovered that the *luxI* promoter can initiate transcription in the opposite direction when the LuxR protein is present and the autoinducer 3OC6 is not. Because this observation was not documented in the literature, the students published the results and thereby contributed to basic biology. Even though the device our students designed failed to work, those efforts plus their follow-up experiments proved to be a win-win in terms of how much they learned from that failure but also how it led to a valid discovery in basic biology.

Support Network Helps Faculty Members Learn about Synthetic Biology

Time is a scarce resource for busy faculty members, making it difficult for them to learn a new discipline and convert that information into teachable content. To help address this issue, the Genome Consortium for Active Teaching

FIGURE 3



High Osmolarity (Input A)	30C6 (Input B)	Fluorescence (Output)
0	0	0
1	0	1 (GFP)
0	1	1 (RFP)
1	1	0

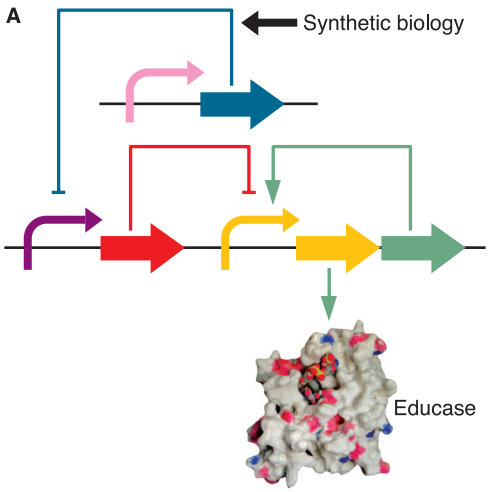
Biological hash function composed of a DNA-based XOR logic gate led to a new discovery about a well-known promoter. (A) Proof-of-concept design in which the word "cab" was converted to binary, and given to a series of bacterial colonies to generate a hash value using successive XOR logic gates. (B) Design of the DNA-based XOR logic gate and the corresponding truth table.

(GCAT; www.bio.davidson.edu/GCAT) obtained funding from the National Science Foundation (NSF) and the Howard Hughes Medical Institute (HHMI) to run summer workshops in 2012, 2013, and 2014 (Fig. 4). These workshops are available free of charge to faculty members at U.S. colleges or universities who teach primarily undergraduates. Faculty apply in teams of two, with one having experience in molecular biology and the other coming from another discipline, including chemistry, mathematics, computer science, and engineering. These workshops provide training that enables participating faculty members to develop courses and plans for engaging undergraduates in synthetic biology research projects.

In addition to attending the three-day workshops, each pair of participating faculty members receives a starter collection of 111 sequence-verified DNA parts for use in student projects. Based on well-characterized parts from the much larger iGEM Registry of Standard Biological Parts, the GCAT Mini-Registry was synthesized by GeneArt. The Mini-Registry is composed of DNA plasmids with inserts that include promoters, ribosomal binding sites, protein coding regions, and devices or systems that are ready to function as soon as they are transformed into *E. coli*. The Mini-Registry is a significant contribution to a distributed network of parts called the GCAT-alog, which is maintained across the country in the freezers of GCAT faculty volunteers.

GCAT faculty members are encouraged to make available their synthetic biology stocks, including newly developed components, through the GCAT-alog online database of parts (http://gcat.davidson.edu/GCATalog/). This free database allows anyone to catalog the precise location (room number, freezer, shelf, box, position in box) of every DNA part in a collection. Keeping track of growing DNA collections is essential as the number of parts accumulate in each lab. We have developed a collaborative process for sharing GCAT-alog parts within our growing community. Any GCAT member can see what DNA parts exist in the national network and can request parts they need. When a GCAT member sends a request, they produce a backup copy of their own stocks that can serve as an emergency source should the original be lost. If a faculty member ships the DNA part, his or her name goes to the bottom of the list when another part is requested. The recipient of the part pays for the shipping and adds the part to his or her GCAT-alog collection, and the sharing cycle continues. GCAT-alog is the only distributed network of

FIGURE 4



B

GCAT SynBio provides a distributed network of faculty who work with undergraduates and each other to develop a failsafe repository of DNA parts. (A) GCAT SynBio circuit logo that leads to the production of an inspirational enzyme termed educase. (B) Group photograph of the first 30 GCAT SynBio workshop participants in 2010.

synthetic biology DNA parts and is freely available to all GCAT SynBio members.

GCAT SynBio also facilitates assessment of learning by students engaged in synthetic biology coursework or independent research. Our online assessment tool (http://checkboxweb.davidson.edu/Survey.aspx?s=a317ef10fb42498dbab5fb3e72d4d36c) is based on student learning outcomes associated with synthetic biology. Faculty can ask their students to take surveys before and after the course or project to measure the degree to which their students made progress. Because funding agencies and accreditation teams require assessment data, GCAT SynBio makes it convenient for faculty to evaluate their own synthetic biology teaching and research initiatives.

GCAT SynBio has developed lab modules for introductory biology. These modules are meant to help first-year students understand gene regulation by letting them test promoters of their own design. Students can either build promoters based on published reports or they can mutate well-known promoters to test how those altered promoters behave. These student-tested promoters are being compiled in a GCAT SynBio Registry of Functional Promoters (RFP; http://gcat.davidson.edu/RFP/index.php) to become a research tool in its own right.

With the combination of GCAT-alog and the RFP, GCAT faculty and their first-year students can produce a world-class collection of characterized promoters for use in research. Through the collaboration of GCAT SynBio members, research conducted in the classroom for educational purposes will enrich basic research conducted by professional scientists. Students will be learning while doing research, finding motivation and building a sense of accomplishment.

Conclusions

As undergraduate students learn about and conduct research in the field of synthetic biology, they will gain a deeper understanding of the big ideas in biology and not get bogged down with memorizing countless facts that they are likely soon to forget. The recent Vision and Change report from NSF outlines how biology faculty at U.S. colleges and universities can better educate their students. GCAT SynBio can help those teachers implement these NSF recommendations in ways that are both convenient and cost effective. The GCAT SynBio workshops, the Mini-Registry collection of sequenced parts, and the GCAT-alog network of distributed parts will put undergraduates and their teachers on the forefront of an exciting discipline that will provide jobs and research opportunities with very little added cost to colleges or universities. What's not to love?

Malcolm Campbell is Professor of Biology and Director, James G. Martin Genomics Program, and Laurie J. Heyer is Associate Professor in the Mathematics Department, Davidson College, Davidson, N.C.; Todd T. Eckdahl is Professor and Chair, Department of Biology, and Jeffrey L. Poet is Associate Professor of Mathematics, Missouri Western State University, St. Joseph, Mo.

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Note: the September 2, 2011 *Science* features several papers in the synthetic biology, http://www.sciencemag.org/content/333/6047.toc#SpecialIssue.