Living Machines: Some Assembly Required

Kit-based competitions challenge teams of students to learn microbiology and design principles in the context of synthetic biology

Natalie Kuldell

If you were a new student arriving at Massachusetts Institute of Technology (MIT) in Cambridge during the early 1970s with an expressed interest in mechanical engineering, you would have been advised to enroll in a class called "Introduction to Design." Students in this class were provided components such as wooden spools and metal rods, and were told to build a useful device from these parts.

A teaching assistant from that era noted that students taking that class spent little time engineering their machines because it took them so long to decide what to build. When that teaching assistant, Woodie Flowers, became an MIT professor and took over teaching that class, he made two big changes that had a major impact on the students. The first was to assign all the teams a common task, challenging them, for example, to "design a machine that puts a round peg into a square hole" or to "build a mechanical device that can roll down a 30° incline plane in 3 minutes." With an explicit design challenge to meet, students no longer spent so much time wondering what to build and, instead, could concentrate on designing and engineering specific types of machines. The second change was to make each of these engineering assignments competitive. Student teams engaged in sports-like battles to determine which team's machine could perform with the greatest accuracy, consistency, and precision. Not surprisingly, MIT students enjoyed measuring their success against others.

A generation later, other disciplines are embracing the notion of teaching through kit-based design competitions. A prime example is the annual FIRST Robotics Competition, which was founded by Flowers of MIT and inventor Dean Kamen, president of DEKA Research & Development Corporation in Manchester, N.H. Last year, for example, more than 350 high school teams from five countries worked with kits having the same parts, each group striving to build the "best" robots within six weeks. Their efforts are judged regionally, with the local winners advancing to the finals, where the teams match their robots against one another in a competitive atmosphere that rivals what happens at the Super Bowl or World Cup. This design competition engenders not only palpable enthusiasm but lasting learning among the students who participate. Moreover, the event continues to grow, attracting more teams and younger students.

Summary

- The impetus for a popular annual contest for students learning synthetic biology traces to an introductory course in engineering and design at MIT.
- The first chapter of iGEM involved a group of 16 undergraduate students at MIT in 2003 trying to make bacterial cells into a "living lighthouse" using standardized DNA "parts."
- The annual iGEM contest now includes students from four continents who compete regionally, with those winners gathering in November for a Jamboree.
- Formal educational modules at BioBuilder harness the iGEM approach for teaching engineering in the context of high school and college biology, an approach that may be adapted for teaching other scientific disciplines.

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Tapping into Competitive Spirits to Teach Biology

Biology is the new frontier where kit-based design competitions are generating keen enthusiasm. Specifically, those contests are playing out in the field of biological engineering called synthetic biology.

Here, too, the impetus traces to MIT. In 2003, several faculty members and researchers there, including Drew Endy, now at Stanford University, Tom Knight, now at Ginkgo BioWorks, Gerald Sussman, and Randy Rettburg challenged a group of 16 students to build "a living lighthouse" from *Escherichia coli* bacteria, stipulating that their goal was to make bacteria that emit light predictably and reliably.

During January at MIT, classes are suspended for several weeks for a session called IAP, Independent Activities Period. During the 2003 independent session, that group of 16 students struggled to complete the living lighthouse project, working with a limited budget against a tight deadline. Seeking shortcuts or other ploys that would accelerate their progress, they figured out a scheme to make the sharing of useful snippets of DNA more efficient. They found that, by standardizing DNA segments into "parts," it became easier to assemble them into increasingly more complex genetic programs.

That winter session project from 2003 later was turned into an annual contest, called the International Genetically Engineered Machines (iGEM) competition. Held each summer, the main goal of iGEM is to build "biological systems from standardized (DNA) parts."

Unlike the MIT Introduction to Design class or the FIRST Robotics Competition, however, no single design challenge unifies the work of the iGEM teams, and they do not pit their biological machines against one another. Instead, students from the participating schools work on their own campuses during the summer months, and then come to MIT in the fall to celebrate their engineered cells at a "Jamboree." Projects are compared based on their ability to "impress the judges"—a subjective measure, but one that spurs the teams to work diligently on their projects.

The iGEM Synthetic Biology Competitions Keep Growing

By 2004, five U.S. teams were invited to participate in the iGEM synthetic biology competition. The project judged most impressive that year was from the University of Texas (UT) at Austin. The UT team designed and built a strain of *E. coli* that could serve as the pixels in a photograph.

To reach this goal, the UT students fused a light-responsive sensor protein from cyanobacteria to the transmembrane protein from a two-component signaling pathway (EnvZ/OmpR) that is native to *E. coli*. They transformed the gene for this fusion protein into a strain harboring an OmpR-regulated promoter that directed transcription of a reporter gene, β-galactosidase, thereby assembling what they called their "coliroid" strain. When grown in the dark, the coliroid cells transcribe more of the *lacZ* gene, turning an indicator in the media black. In the light, LacZ transcription drops, allowing the yellow media to show. The students displayed a photograph in which the cells spell out "hello world" at the 2004 Jamboree. A report describing their experiments appeared the next year in *Nature*.

The iGEM program continues to grow each year. In 2010, 130 teams from 26 countries participated. In 2011, iGEM grew further, holding three preliminary competitions to determine which teams from the Americas, Europe, and Asia would progress to the final Jamboree, held in November. Other plans call for extending this competition to teams from high schools. Thus, iGEM increasingly resembles FIRST Robotics, with both programs encouraging teams from colleges and high schools to design machines from kits and for those teams to compete against one another.

Kits for Making Robots Differ from Those for Engineering Cells

Although the outlines of the iGEM and FIRST Robotics competition are alike, there are critical differences between the kits used for building robots and those used to engineer living cells. For instance, a student in mechanical engineering has no trouble distinguishing wooden spools from metal rods, even if those parts are mixed together in a single package. By contrast, iGEM students typically work with identical-looking flecks of freeze-dried DNA, making it trivially easy to begin a summer-long project with the wrong stock of DNA.

Kuldell: Hands-on Teaching of Synthetic Biology, and a Stint as a Professional Dancer

Natalie Kuldell worked summers at the National Institutes of Health (NIH) while in high school, and it proved transformative. "It seemed so great to be able to head into the lab every day," she says, crediting her mentors, NIH biochemists Alan Peterkofsky and Marshall Nirenberg, for inspiring her. "I was hooked, and I knew at age 16 that their job was the one I wanted. Since they studied chemistry in college, rather than biology, that's what I did, knowing full well that I'd go to graduate school in the life sciences, as they did."

The experience also helped her to realize the importance of hands-on learning, an approach she now takes when teaching. "I learned early on that part of what makes science exciting is when you can puzzle through some confusing or surprising data," she says. "But when I got to my science classes at school, very few of the experiments we ever ran in class captured this investigative part of science. So I've tried to bring that excitement of doing real science to my students. I take what's current in research, and transform those questions into teachable modules. The laboratory classes I teach at MIT definitely benefit from this philosophy, and lately I've been trying to expand the approach to other schools through the BioBuilder .org web site."

Kuldell, 46, is an instructor in biological engineering at the Massachusetts Institute of Technology (MIT) in Cambridge and a visiting scientist at nearby Harvard Medical School. Her research focuses on understanding the control of gene expression in eukaryotic cells. Working with Fred Winston at Harvard, she examines artificial gene expression systems in cells of *Saccharomyces cerevisiae*.

Kuldell also serves as associate director of education and training at SynBERC, a multi-university program in synthetic biology, and directs BioBuilder.org, an interactive website that features synthetic biology learning materials, some of them animated narratives. She also set up an educational foundation whose goal is to make current topics in research available as synthetic biology curricula for college and high school teachers.

As a youngster in Manhattan, Kuldell attended a bilingual French/English school, but soon moved with her family to Maryland, where she attended middle and high school. Her father, a physician, worked for the Food and Drug Administration, while her mother worked as a nurse. Both are retired. "Neither was disappointed that I didn't choose medicine since they know I get faint when I see blood," she says. After high school, she attended Cornell University, where she earned her B.A. in chemistry in 1987, then moved to the Boston area to complete her doctorate in cell and developmental biology at Harvard University in 1994. She was a postdoctoral fellow at Harvard Medical School from 1994 to 1997.

Kuldell spent a year between college and graduate school as a professional dancer in Boston, performing with several companies, including the Performing Arts Ensemble and the Kelly Donovan Dancers. "I continued to dance, but in a diminished role in the company, through graduate school, through becoming a mom, and through my academic transitions," she says. "I still dance every week. I continue to feel connected to the wonderful dance community here in Boston, even though I no longer perform." Despite this history as a performer, she keeps a low profile. "I've often said that my goal is to be the person who does the most good that no one ever heard of," she says.

Kuldell began dating her husband Scott Kuldell when they both were in high school. "We went to different colleges—me to Cornell, him to Dartmouth—but we managed to work things out, and landed in Boston," she says. "We've been here ever since." They have two children, 15 and 12. "They are, no doubt, the greatest contributions I've made to this world," she says.

Marlene Cimons
Marlene Cimons lives and writes in Bethesda, Md.

For iGEM contestants, the confusion in retrieving parts can be compounded by uncertainties over how to use them. Each summer, iGEM teams contribute materials that make up the latest kit. This "give-and-get" approach keeps the iGEM kit growing. However, it also means that each successive team deals with many parts that are incompletely documented and poorly understood. For example, standardizing junctions between DNA parts should allow the same cloning scheme to be useful for any assembly. However, because not all parts in the kit conform to the original standard, students find themselves frustrated when parts cannot be cloned, when cloned parts do not transform well, and when transformed parts do not generate expected behaviors once in cells.

The complexity of systems that students design can exceed the capacity of the cells to support those systems. Although a mechanical engineer can drop a souped-up engine into a humble car chassis and know what to expect, a biological engineer taking on the equivalent task may find that inserting a highly demanding—or souped-up—genetic program into cells instead leads them to die or mutate.

These limitations, however, can provide educational opportunities. Although they are not a formal part of the iGEM mission, failure analysis could be one of the most important ways iGEM educates its student participants. This approach, if taken up more broadly by academic and industrial partners, could advance the technical standards of the whole field of genetic engineering. It also provides a valuable investigative framework for teaching engineering in the context of biology. The teaching materials available at BioBuilder.org are part of an early effort along these lines (http://www.biobuilder.org/).

BioBuilder Content Includes Failure Analysis and Cartoons, and Appeals to the Senses

BioBuilder content begins with the unreliable behavior and unexpected results from iGEM team efforts and other academic research projects. It converts "glitches" from those projects into teachable modules suitable for advanced high school and early college settings.

Leveraging the success of the publication "Adventures in Synthetic Biology," which is presented in comic book style by Drew Endy of Stanford University, each BioBuilder module begins with open-access animations and comic-strip narratives. Regular characters in these illustrated episodes include "Systems Sally," a laboratory scientist, "Izzy," a veteran of the iGEM program, and "Device Dude," a curious young student who is new to the program.

These three imaginary characters work through ongoing challenges in biological engineering while they hang out in the lab or walk across the bridge linking Boston and Cambridge. In their conversations, these three characters explore foundational ideas about engineering like abstraction and biological processes such as bacterial gene expression. The animated cartoons and the comic strips are freely accessible on the BioBuilder website. Although they may be viewed in any order, they are organized in a way that makes them useful for guiding student activities in classrooms and laboratories.

One recent BioBuilder activity included a project that started with the bacterial photography system that the UT Austin student team developed in 2004. Other laboratory activities explore both engineering and biology challenges. For example, students are asked to compare two different genetic approaches for making bacteria smell like bananas during log-phase growth. One approach depends on a constitutively active sigma-70 promoter to express the ATF1 gene of the yeast *S. cerevisiae* during log phase. The other program connects a stationary-phase promoter to a transcriptional inverter device that directs transcription of ATF1. This BioBuilder activity extended an engaging project that was developed by the MIT iGEM team in 2006. Moreover, it encourages students to delve into system design questions while learning a variety of microbiological and measurement techniques as they track the scent intensity and growth curves of the strains that they engineer.

After completing each BioBuilder activity, students are asked to share their findings through an online forum. This feature is in keeping with the "give and get" philosophy of iGEM. It also instills in students the notion that, in this developing field, their contributions matter.

BioBuilder began as a collaboration between the MIT Department of Biological Engineering and several nearby secondary school teachers, especially Jim Dixon from Sharon High School. Hence, the activities address the needs of high school teachers and take into consideration formal standards for engineering curricula. Indeed, some activities offer an alternative approach to current lessons—enabling teachers to substitute BioBuilder activities for some of the standard classroom exercises. For example, the winning iGEM project from the University of Cambridge team in 2009 included genetic programs that turned *E. coli* a rainbow of colors. In documenting their project, members of that team noted how the intensity of the colors varied in cells with different genetic backgrounds. This observation has been recast into a BioBuilder laboratory activity in which students can transform two color-generating plasmids into two cell types, namely *E. coli* B and K12 strains, to learn how those two cell types affect system performance. This project provides the same technical training as a standard lab project now available for advanced placement biology students. Additionally, the BioBuilder project provides students with stronger incentives for carrying out the procedures, and it also forces them to ask more questions. Moreover, it provides an online forum to support teachers who would like to adopt these activities in their classrooms, connecting them to other teachers who already are following the BioBuilder approach.

Teachers Comment on Current BioBuilder Outlook

In the summer of 2011, a group of 27 U.S. high school and college teachers visited MIT to learn about BioBuilder and to immerse themselves in the vocabulary that engineers use for designing and building systems. Midway through the week, the teachers were asked to describe their own visions of perfect teaching days. Their collective focus was on their students, whom they said they want to "engage" to keep "classrooms buzzing with excitement." The teachers also envision their students "doing things" and "making connections and contributions."

Kit-based design competitions have a strong track record eliciting just these kinds of sought-after student behaviors. The materials available at BioBuilder.org are one additional part of this effort to move this experimental design framework into the formal teaching of biology and biotechnology. There is no reason to think that other subjects such as chemistry, physics, and mathematics would not also benefit from having similar curricula. The central idea is demanding—and empowering—students of biology to think as engineers, defining problems and then designing and implementing solutions.

SUGGESTED READING

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