

## Feature

# Meeting Report: Synthetic Biology Jamboree for Undergraduates

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While most of us have been following news in the fields of genomics, proteomics, bioinformatics, and maybe even systems biology, a new field may have escaped our attention. The field of synthetic biology (the name is derived from an analogy to synthetic chemistry) has recognized itself as a “field” only since about 2002. Synthetic biology has gotten some high-profile attention recently (e.g., Ferber, 2004; Hasty *et al.*, 2002; Hopkin, 2004; Nature Staff, 2004a, b; Pennisi, 2003; Zak *et al.*, 2003), but most people are not aware the field even exists. Synthetic biologists apply engineering principles to genomic circuits to construct small biological devices. The Jamboree, as it was affectionately called, was the culmination of a summer of undergraduate research on five campuses across the United States.<sup>1</sup> The participants shared data, frustrations, lessons learned, and plans for the future. The entire weekend was, to some extent, a pyramid turned upside down. Normally, new fields in biology are explored first by postdocs and graduate students under the watchful eyes of their Primary Investigator (PI) mentors. This National Science Foundation (NSF)-supported Jamboree featured undergraduates (some having just completed one year of college) who were pushing the boundaries of a field so new, its name is subject to debate. This report will highlight some of the interesting research conducted by undergraduates during the summer and early fall of 2004.

Teams of undergraduates spent 10 weeks of their summers blending biology with computer science, engineering, and chemistry (Figure 1). As is often true of young students, many were oblivious of the significance of their efforts before the Jamboree. Only after sharing their stories did they begin to appreciate the magnitude of their summer’s efforts. Each group of students had been given a one-phrase directive (design and build a genetically encoded finite state machine), and over the summer, they designed, modeled, built, and tested their constructions. The most interesting presentations were those made by undergraduates. One team had more

senior people present, and you could tell they were less candid and less enthusiastic. When the undergraduates spoke, they had a sheen of freshness and personal investment that was infectious and exhilarating.

The teams were composed of diverse sets of students, with only two self-identified as biology majors with previous lab experience. The educational goals of this NSF-funded program were varied and vague: to introduce students to a new field; to encourage them to stay in this field; to increase excitement about research; and to foster cross-disciplinary education and collaboration. Although these goals are difficult to define and assess, they are exactly what the National Research Council’s publication *Bio2010* stated the future of biomedical research requires to bring success in the future and a more diverse population to biology (National Research Council, 2003).

## BACKGROUND FOR SYNTHETIC BIOLOGY

Any new field evolves from the work of pre-existing fields, but a few seminal papers can be cited as the foundation for synthetic biology. In one such paper, Gardner *et al.* (2000) report the design and construction of a genetic bistable toggle switch in *Escherichia coli* (Figure 2A). The design is simple: two promoters and three genes. When the black gene is active, the gray gene and the reporter gene are silenced. Conversely, when the gray gene is active, so too is the reporter gene, but the black gene is repressed. The gray inducer (IPTG) leads to the production of the reporter protein, green fluorescent protein (GFP), whereas the black inducer (tetracycline) halts production of the reporter GFP (Figure 2B). This simple biological machine might seem like a widget that does nothing in particular, but imagine if the reporter gene were exchanged with a biologically functional gene. Then a production facility could turn the secretion of a biomedical product on and off that otherwise would be toxic to the cells. Or, perhaps the cells could monitor waste sewage from a factory to detect violations of environmental laws.

The “repressilator” by Elowitz and Leibler (2000) set a precedent for naming (fill in the blank-alator) and sophistication. The repressilator is composed of two plasmids (Figure 3A). The larger plasmid contains the oscillatory circuit of three repressors. Each repressor is induced in turn, so the circuit rotates around the plasmid as the previous repressors are degraded by the cell. When TetR is produced, the production of GFP is silenced. Activity of the repressilator

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<sup>1</sup> Participating schools: Massachusetts Institute of Technology, California Institute of Technology (Caltech), Boston University, Princeton, University of Texas at Austin.



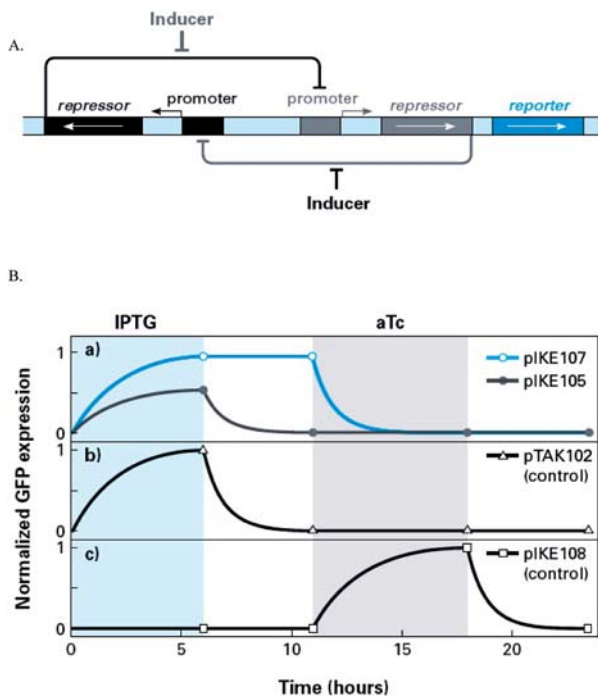
**Figure 1.** Participants and mentors at the 2004 Synthetic Biology Jamboree, held on the grounds of the American Academy of Arts and Sciences in Cambridge, MA.

is monitored by observing GFP, which oscillates at a regular interval (Figure 3B). It is worth noting that the periodicity of the GFP cycle was much longer than the periodicity of cell division by the bacteria, which indicates the signaling mechanism outlived the lifetime of any given cell.

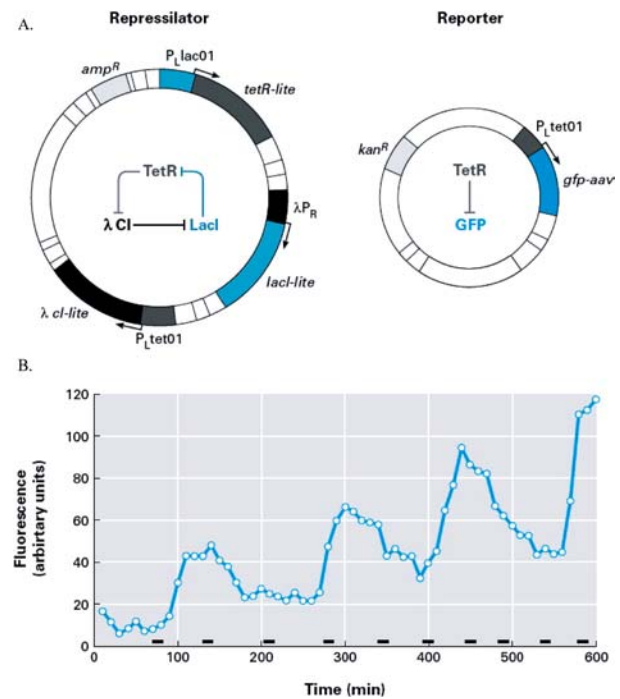
### THEIR AMAZING MACHINES

Now that you have an idea what synthetic biologists do, I want to share two student constructions with you. The first

was produced by a Princeton team that wanted to build a biological equivalent of the children’s game called Simon (see <http://www.begent.net/games/simon/simongame.htm> for an online version). The object of the game is for the user to repeat a pattern of signals that grow in complexity at each successful iteration. What the Princeton team wanted to produce was a set of three bacterial strains that could correctly detect the



**Figure 2.** Bistable toggle switch. A. Generic design of a bistable switch that can be flipped one of two ways depending on which inducer is applied. B. Data produced by the final bistable toggle switch (panel a, blue trace) as well as several control constructs (black traces).



**Figure 3.** Repressilator. A. The repressilator was designed to produce three repressors in succession, each degrading over time and repressing a different promoter. The progress of the cycle was monitored by the production of GFP, encoded on a separate plasmid and repressed by one of the three repressors on the repressilator plasmid. B. Production of GFP was monitored over time. The black bars at the bottom indicate the time of cell division for a collection of *E. coli* cells monitored through a microscope.

input of three environmental stimuli that had to be delivered in a particular sequence. In addition, like the game, their biological Simon had the capacity to be reset at will (Figure 4).

With the use of BioBricks from the MIT database (<http://parts.mit.edu/>), the students designed three strains of cells that had three different circuits. The first cell type accepted the input of anhydrotetracycline (aTc) and secreted a molecule in response. Cell type 2 accepted the input of homoserine lactone (HSL) and the secreted molecule from cell type 1 and responded by secreting a new molecule, which was half of the signal required by cell type 3. When the user applied arabinose to cell type 3, which had been signaled by cell type 2, the third and final cell in the chain responded by producing yellow fluorescent protein (YFP). At any step in the process, the students could reset their biological Simon by applying a heat shock, which would destabilize a temperature-sensitive component (cl<sup>ts</sup>) shared by the last two cell types. The team was not able to build their biological Simon because of problems they had in the construction phase and the YFP gene in particular. The students used parts from the BioBricks library and offered suggestions for ways the BioBricks repository could be improved.

One of the CalTech teams designed and built a strain of yeast that was capable of detecting three concentrations of caffeine. For their design, this team relied on small noncoding RNA switches composed of two domains: an aptamer domain and an antisense domain. Aptamers are nucleic acid molecules that can bind to small ligands with a high degree of specificity. Depending on how the RNA switches were designed, they could activate or inactivate sequence-specific mitochondrial RNAs (mRNAs). The students designed and constructed RNA switches that could detect the ligand caffeine at different concentrations and built two types of switches. One switch destroyed GFP mRNA at high doses of caffeine, whereas the other switch activated YFP mRNA beginning at medium doses of caffeine. The combination of switches produced a cell

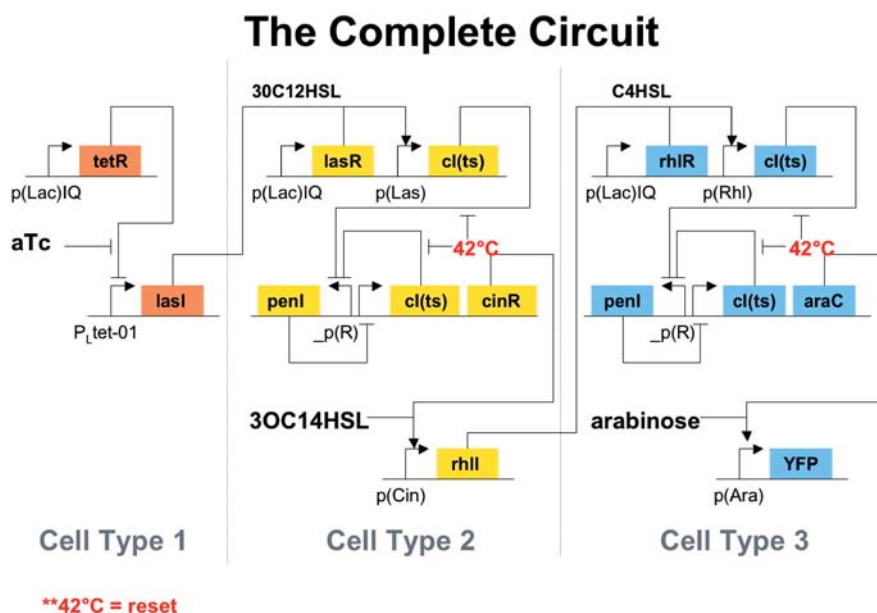
that glowed green in the presence of low caffeine, green and yellow in medium caffeine, and yellow only in high caffeine. Having proven their device worked under laboratory conditions, the students headed out to their favorite campus source of coffee and tested their device on real-world samples (Figure 5). To everyone's delight, their modified yeast could distinguish decaf, regular, and espresso coffees. As one Jamboree participant noted, combining coffee and yeast metabolites is the dream of every student.

There were additional presentations by students. Some emphasized computer modeling of behaviors and others focused on biological output. For example, some cells were designed and modeled to swarm toward a chemoattractant, signal each other, diffuse away, signal each other, and reswarm. Another team produced cells that were photosensitive and produced a color product. The photosensitive results culminated in the world's first biological photograph of the oft used phrase in computer science, "Hello World."

## MEASURING SUCCESS

One goal of the Jamboree was to foster interdisciplinary collaborations. The selection process assured the goal of mixing students from different disciplines. Chemistry and computer science were the two most common majors after engineering. Some of the students had taken a previous course at their home institutions that prepared them for synthetic biology, but this was true for only a small percentage of the summer research students. Therefore, many participants were exposed to a new field during their summer research.

As the summer began, it was uncertain whether the students would enjoy their experience and be influenced to stay in the field of synthetic biology. During the breaks, I talked to several students informally and heard some say how the summer had affected their career interests. A couple of their comments were: "I had some prior research but now I'm more interested



**Figure 4.** Circuitry for Simon 1.0, designed by a team of undergraduates from Princeton University. The three cell types were part of a pattern of inputs that had to be produced in the correct order for the reporter protein, yellow fluorescent protein (YFP), to be produced.



**Figure 5.** The team from Caltech constructed yeast cells that were able to distinguish low, medium, and high levels of caffeine. Two reporter proteins, green fluorescent protein (GFP) and yellow fluorescent protein (YFP), signaled which level of caffeine was detected. Shown here are the four student investigators comparing their skills against the caffeine-sensing fungi. Clockwise, from top left: Travis Bayer, Maung Nyan Win, Brandon Rawlings, and Jack Lee.

in biology, specifically in engineering circuits. I am continuing to do research this semester and am working now to make our machine function.” and “I gained an appreciation for CS [computer science] and will take some CS courses during the last semester of my senior year as a biology major.”

Every one of the summer groups has some students that continue to work on their constructions. This shows real commitment, excitement, and the spark of a researcher in the making. Approximately one-third of all students at the Jamboree were still working on their projects in November. Rather than seeing this as a sign of failed summer work, the students saw continuation on their projects as a challenge worthy of their time. Research is not easy and they know it.

When asked whether the weekend gathering was useful, everyone at my lunch table said absolutely. Before the weekend, they did not realize others were interested in their efforts. They had assumed none of the other groups were having problems and something must be wrong with them for the frustrations and setbacks they faced. Hearing the troubles experience by each group helped individuals gain a better understanding of the expression, “if it were easy, no one would interested.” They enjoyed hearing the diverse plans and outcomes from the other groups.

Some lessons learned include the need for clear and ongoing communication. The participants learned that a community is more productive than an individual, uncoordinated effort. They took pride in their work and enjoyed sharing with their peers. Although an electronic discussion

board was available, it was not used much, which probably says more about the negative side of electronic communication compared with personal contacts.

## CONCLUSION

It is a rare treat to watch the birth of a new island when a volcano rises from the ocean. The Jamboree felt like the intellectual equivalent, with burgeoning students creating fantastic designs and finite state machines. The future of synthetic biology could be very bright. These undergraduates personified the recommendations of *Bio2010* (National Research Council, 2003). They did world-class work, yet their level of training was embryonic. Imagine where they may lead the field in 20 years. I was so impressed with their work that this summer, I too will have my students design, model, and produce simple biological machines. We will begin by reading and designing, but the students will need to settle on a design quickly enough to have time to build their devices.

During the final session of the Jamboree, the group discussed the ethical, legal, and social implications (ELSI) of synthetic biology (see Ferber, 2004; Hopkin, 2004). Considering the ELSI of synthetic biology was new for the undergraduates, although it was a familiar topic for their PIs. The perception of a self-contained, insulated group of scientists is what could put synthetic biology in the same politically charged boat as stem cells, somatic cell cloning, and GMOs; knowledge is trumped by fear every time. All

investigators should link ELSI and education with synthetic biology research if we want it to be funded by the U.S. government.

The Jamboree leaders also need to place a bit more effort in measuring educational outcomes. Educational assessment is awkward and sometimes abhorrent to scientists, but why treat our teaching any less seriously than our science? Would you accept a claim in science without data? If not, then why trust your instinct when data are available? A short survey at the end would provide “summative” data. How many of you will take additional courses in this area? How many of you will take courses in different departments as a result of your experience? How many of you would like to continue your work beyond the summer? How many of you would like to pursue this type of research in graduate school? Would you like to use this as a foundation for an honors thesis? Would you recommend your friends get involved in future summers?

In the end, the students seemed unanimous that the Jamboree should become a national and annual event. It is impressive that students could design cells from BioBricks parts to perform new functions. Perhaps next year, my students can share their results, and more schools will join the fun of the 2005 Jamboree.

## ACKNOWLEDGMENTS

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