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Heads Up, Digital—Make Way for Synthetic Biology

MARCIA STONE

> "Oh, God help us! We're in the hands of engineers." (*Jurassic Park*)

So goes the opening quote in Adam P. Arkin and colleagues' 2011 paper (doi:10.1093/nar/gkr433) on the rational design of bacterial genomes. In fact, it's pretty much what some biologists fear with every astounding bioengineering advance. Why? Because whereas biologists tend to view evolution with something akin to religious devotion, engineers are evolutionary atheists: They don't revere evolution so much as they want to fix it.

The recent creation of a *transcriptor*, the final component needed to build cellular computers, along with the development and distribution of *standardized DNA sequences*, which can be reliably used and reused in novel combinations, show that bioengineers may well have the skills needed to solve many of the world's most pressing problems—"most of which are deeply tied to biological resources," says Arkin, of the University of California, Berkeley, who cites pervasive environmental pollution and insufficient food production as two examples.

Drew Endy and his Stanford University team's transcriptors could be the biological equivalent of digital transistors, which transformed electrical engineering in the 1950s and gave birth to Silicon Valley. Like transistors, transcriptors are on-and-off switches, gatekeepers or "gates" of information input, storage, and output. Transcriptors give cells already programmed to store and transmit information a "brain," a system of logic governing the way they deal with that information.

Endy's research group made their transcriptors out of DNA, put them into *Escherichia coli*, and used traditional computer-based Boolean language to tell the computerized cells what to do. As a proof of concept, the cells were instructed to change color with encoded fluorescent proteins—turn green if both enzyme A and enzyme B were inside the cell or red if either enzyme A or B were present—which they did on command.

It's not that bacteria aren't already little computers; just ask IBM scientists such as Yuhai Tu, who are studying *E. coli* to help them design faster and more efficient computing machines. But instead of following their own instincts, which generally revolve around food, danger, and sex (of a sort), microbes in the employ of bioengineers will be programmed and deployed by the billions to seek out and neutralize toxic waste, arm plants with a nitrogen-fixing capability, synthesize biofuels and medicines, and perhaps even roam our bodies searching for and killing cancer cells.

The Endy team isn't the only group stuffing microbes with synthetic logic and memory circuits; Timothy K. Lu's and Christopher A. Voigt's bioengineering teams—both at the Massachusetts Institute of Technology—are doing the same. However, as of this writing, only the Endy group's transcriptors are "robust enough to make a family of low-power logic gates within single cells and allow the gates to power each other if needed," according to Arkin, who calls their work a "great step forward."

"After years of working with *E. coli*, you'd expect that manipulating its genes would be straightforward, but it's not," says Endy who, along with Arkin, codirects the International Open Facility Advancing Biotechnology (BIOFAB), launched in 2009 and charged with creating standard biological "parts," including DNA sequences that control gene expression, or *promoters*, and ribosome binding sites (RBS).

Until recently, scientists trying to make a protein in *E. coli* had only a 50-percent chance of success. "Such hit-or-miss expression is unacceptable for synthetic biologists who need to engineer circuits involving dozens and eventually even hundreds of genes," says Endy.

"The standard parts we've been using were imprecise and unpredictable and their performance inconsistent in changing genetic contexts. Every project has been a one-off," adds Vivek Mutalik from the Lawrence Berkeley National Laboratory, in California, and BIOFAB team leader.

Mutalik's BIOFAB group came up with an ingenious way to more precisely control *E. coli* gene activity. They adapted a complicated natural genetic architecture for RBS that ensures uniform activity, regardless of the genes with which they're paired. "We were humbled yet excited to find that a more complicated physical architecture—one developed by evolution—encoded the functional simplicity we sought for engineering," according to Mutalik.

For their next act, these researchers developed "an easy-to-deploy mathematical framework that can score the intrinsic activities of various genetic elements—promoters and RBS sequences, for example—and determine [whether] and by how much they vary across changing contexts," says Arkin, who expects individual researchers to share their findings.

Indeed, data sharing is a priority for BIOFAB, whose members have collectively produced thousands of high-quality standardized DNA sequences and made them available free online at *www.biofab.org*. Transcriptors have also been contributed to the public domain (see *www.biobricks.org/bpa*).

Endy assures us that he, Arkin, and Mutalik are not antievolution; rather, they try to "transcend it via an embrace-and-extend approach."

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