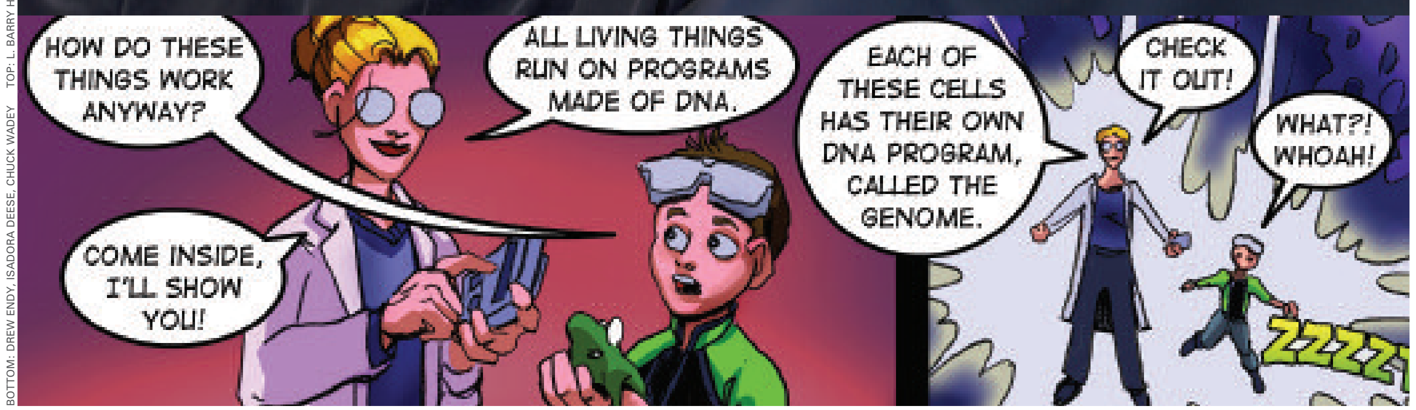
Do-It-Yourself Biology



BOTTOM: DREW ENDY, ISADORA DEESE, CHUCK WADEY   TOP: L. BARRY HETHERINGTON

In Drew Endy's world, things are a little different.

BY DAVID BOCHNER

There, bacteria run relay races, lie down to create a modern version of the Etch A Sketch® toy, and even work as photographic film.

Though it may sound like a weird world, Endy sees big promise in convincing living things to work as machines and perform useful tasks.

Endy, 35, is a synthetic biologist at the Massachusetts Institute of Technology (MIT) in Cambridge.

He and other researchers who work in this emerging area of science blend engineering, biology, and computer programming to find out how life works and how we can make it work for us.

"Biology is often thought of as [a mysterious process], where you don't actually know what's going on…or wet, goopy stuff that doesn't feel like it should be like a clock or something with gears and pistons and rods," he explains.

While biological materials and organisms may well be wet and goopy, to Endy they aren't all that different from engine parts. Not because of what they're made of, he says, but because of what they can do. The sheer capacity for innovation in biology is what makes it so cool to him.

And it's definitely cool to his students, as well: Every one of the bacterial tools mentioned above was dreamed up by a college student participating in the International Genetically Engineered Machines, or iGEM, competition that grew out of Endy's synthetic biology class at MIT.

Building Knowledge

Endy is by all accounts an engineer, in thinking and in training. He earned a bachelor's degree in civil engineering from Lehigh University in Bethlehem, Pennsylvania.

But even then, during a molecular genetics course, Endy's interest turned biological and he became fascinated with the nuts and bolts of living things.

He went on to earn a master's degree in environmental engineering 2 years later, also from Lehigh, and then a Ph.D. in biochemical engineering, this time from Dartmouth College in Hanover, New Hampshire.

Now, the building materials Endy works with are far from steel and concrete. The parts in his lab "shop" are made of DNA: Endy builds genomes.

Genome is the scientific term for all of the genetic material in an organism. By studying how genome organization creates templates for living things as diverse as people, penguins, and petunias, researchers can get clues about how genes affect health and disease.

"Building is a great way to learn."

For his research, Endy decided to focus on the tiny T7 bacteriophage, a virus that infects bacteria. The T7 genome has been intensively studied for years by researchers interested in questions about how information carried in DNA can cause a cell to reprogram itself, generating new products and behaviors.

To analyze any system, engineers begin by identifying all of its parts and then figuring out how they connect together to produce a functioning whole.

For T7, this work had been done. The organization of the T7 phage genome—or the order in which all of its genes string together—was already known. Scientists had figured out that the phage's genome has only 56 genes, which produce 60 proteins that direct various stages and types of infection.

The T7 genes cluster into several distinct classes, each of which is expressed at a specific point during infection. As the virus infects a bacterium, Endy explains, it has to switch from expressing one class of genes to another in order for the infection to continue and be successful.

One approach to understanding T7 would be to look at its genome and try to pry it apart piece by piece, to investigate the function of each individual gene. But Endy had a different idea.

"It's immediately obvious when you encounter [a] DNA sequence that this is a program, and that you could change it," Endy says.

But decoding the T7 phage "program" proved harder than he thought it would be. Endy's engineering background gave him a new strategy.

"The biological systems that we find in nature are not themselves designed by nature to be easy to understand. And so if I wanted to have biology that I understand," Endy recalls thinking, "I'd be better off building it myself."

AARON CHEVALIER (UT AUSTIN), JEFF TABOR (UCSF)

▲ Bacteria can be genetically altered to produce a dark pigment in response to a flash of light. When researchers exposed a plastic dish of these bacteria to the black-and-white text, "Hello World," they created the world's first living photograph.

Bacteriophages are viruses that infect and destroy bacteria. Endy and other scientists study the genome of the T7 bacteriophage, shown in this drawing.

"You might try to understand a car, or a bicycle, by taking it apart and having the pieces all over your lawn," says Endy, "But you're going to have a much *better* understanding of a car or a bicycle if you take the bits and pieces and put them together to build one from scratch."

Programming Life

Synthetic biologists like Endy are driven by their desire to understand life's design rules, because this knowledge would make biological processes much more predictable.

In turn, the hope is, we'll all be better off. Knowing the rules of biology—and how the rules get broken in the early stages of disease—would provide the opportunity to implement health interventions well before symptoms appear, when the chance for cure is highest.

"How do we get to some future where the programming of living systems is as simple, understandable, and reliable as computers are today?" Endy asks.

It also doesn't hurt that Endy has a driving need to solve problems.

"When I don't understand how things work, I'm curious," he explains. "It bothers me."

So he went to work rebuilding the T7 genome from its parts. His goal was to construct a stripped-down, functional version of the genome that would be easy to understand.

The idea is that if he could build a version of T7 that works like the real thing, it would be a great step toward understanding the entire biological machine. And then Endy could simultaneously test each part of his synthetic, model genome.

When Endy thought about how to construct his own T7, he decided to equip it not only with the viral genes it needs to survive, but also with "cut-and-paste" sites in the DNA that would make it easy to change the phage's genetic program. That means scientists could add new DNA sequences, deactivate genes, or measure the activity or expression of any particular gene.

"Building is a great way to learn," says Endy, explaining that failure just means more experiments.

In 2005, Endy succeeded in partially redesigning the T7 phage. His lab creation, called T7.1, could perform just as well as the original.

Part of the effort, Endy explains, involved untangling some overlapping genes. This genetic handiwork, he says, will enable other scientists to manipulate parts of the T7 genome that could never before be separated in the real virus.

But in truth, T7.1 was only a partial redesign, because Endy was unsure of how many changes T7 could tolerate at one time. Following on the success of the first effort, researchers in Endy's lab are working on a new genome, T7.2. This one, he says, will have even more tools to make it user-friendly for other molecular builders.

For all his building enthusiasm and excitement for figuring out biology, Endy has other passions, unrelated to science.

What would he do if he weren't building genomes? To this, Endy simply shrugs.

"[I'd probably be] surfing…writing poetry and surfing. But probably in the other order."

MAUREEN GUNN

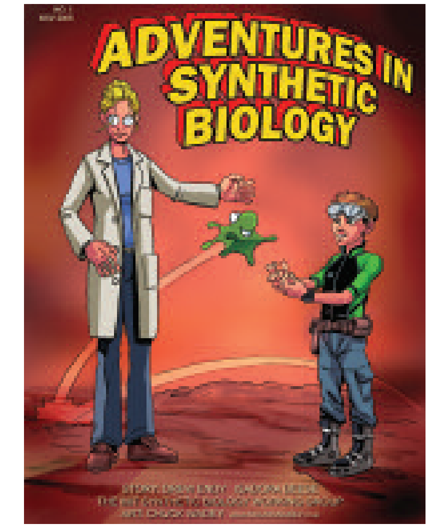
Endy has many adventurous interests outside the lab. In this photo taken in Kahului, Hawaii, Endy (back) kitesurfs with friends.

Communication Breakdown

As Endy continued his work retooling the T7 genome, he grew frustrated that biological engineering didn't seem to be evolving like other engineering disciplines. For example, a mechanical engineer can pick up a screw and know exactly what size and shape it is, he says, but many genetic devices are designed only to work in the research lab in which they were made.

> "I don't see what I'm doing as work."

"It'd be like having an MP3 player that you could only hook up to your computer and your stereo," Endy explains, "whereas what you'd like is to have an MP3 player that could be hooked up to any computer and any stereo."



DREW ENDY, ISADORA DEESE, CHUCK WADEY

Endy created the comic book *Adventures in Synthetic Biology* to help explain his work to students and other scientists. The first page (right) shows "The Dude" scheming about how to get bacteria to work for him.

Through some trial-and-error efforts, Endy and his coworkers did discover a standardized way to get molecular machines to talk the same language. But what proved more difficult, he says, was trying to teach the language to new students.

The solution to this problem turned out to be, of all things, humor.

While attending a meeting in Los Angeles, California, Endy wore a name tag with a picture of one of his genetic gizmos. Out of the blue, one of the other attendees at the conference asked him to explain his image.

It didn't turn out quite as well as Endy might have hoped.

"I tell him the story about how a genetically encoded inverter works," Endy remembers. "I finish my story, and he goes, 'That sucks!'"

The man's harsh words took Endy by surprise until he realized that the guy had a point. The image needed way too much explanation to be understood clearly.

The man went on to suggest that a comic strip might get the message across. Endy laughingly recalls wondering at the time who in the world this person he was talking to might be.

As it turned out, the man who verbally accosted Endy was Larry Gonick, author of *The Cartoon Guide to Genetics*.

When Endy returned to Boston after the meeting, he got to work sketching a draft of the comic strip. But his assistant, who also happens to be a screenwriter, wasn't impressed. In fact, she responded with criticism similar to Gonick's.

"She happened to know the guy who does the storyboards for Spider-Man," remembers Endy, adding that they convinced the artist, Chuck Wadey, to do some drawings.

DREW ENDY

▲ Endy created a database, the Registry of Standard Biological Parts, to store components of biological machines.

The result was the comic book *Adventures in Synthetic Biology*. In the first issue, boy scientist "The Dude" and his wisecracking teacher navigate the tricky terrain of synthetic biology and sum up all of its principles in living color.

On the Same Page

Endy's comic helped establish a way for scientists to talk the same synthetic biology language, but he knew that another key step would be finding a common place to keep all the parts so researchers could easily find and use them. It would not be an actual warehouse, but rather a common framework for organizing all the components of biological machines.

That amounts to a registry, or database, where everyone can find information and detailed descriptions about how to use that information. The Registry of Standard Biological Parts, which Endy helped to establish, keeps track of genetic components the way an engineer might keep track of machine parts or electrical circuit diagrams.

A single genetic "part" could be made up of several related and interacting genes. Endy's hope is that the tools for biological engineering become so advanced that someone with little or no biology background could still build a useful, living organism from off-the-shelf parts.

Endy likens the situation to household appliances.

Imagine if, in order to use a television, you had to know how every wire and tube functioned, and why only certain ones could connect to certain others.

Luckily for us, watching television is no more complicated than switching on the set.

"My motivation is that years from now, anybody who wants to [can] dream up a useful biological system and pull it off, without having to go through this whole big research process to do it," Endy explains.

Others have already begun to use the biological parts in the registry Endy set up: that's how students made the bacterial machines that create living photos and run relay races. Those projects emerged from the iGEM competition, which Endy helped launch in 2004.

In the summer of 2006, 37 different schools from around the world registered teams of undergraduates to engineer biological machines for the iGEM competition held last November. Participating students came not just from U.S. schools, but from all over the world. The contest hosted teams from the United Kingdom, Spain, India, Japan, and Slovenia, the 2006 grand-prize winners.

The Future Is Now

By bringing together undergraduates to engineer biology, the iGEM competition is a community teaching tool. It inspires students to try new combinations and build amazing genetic machines with standard biological parts.

MELISSA LI

▲ Students from 37 countries gathered at MIT for the 2006 iGEM Jamboree.

Endy says what's really neat about the living photographic film, for instance, isn't what it can do, but how it was made.

"[The bacterial film] was doubly cool because [the students] made the system out of some of the components that we already had … a novel combination of off-the-shelf parts."

In a cutting-edge field like synthetic biology, even the professors learn something new with each competition.

Endy continues to teach in innovative ways, and he has won awards for his creative educational approaches. Through his teaching and research, Endy aims to change the way biologists and engineers think about and use biology.

Basically, he wants engineers to see biology as just another way to build things.

"If you ask engineers what they want to do in their hearts, they want to make something," Endy says. He hopes to attract more engineers into synthetic biology by teaching them what they can make and how they can make it.

And as far as Endy's concerned, there's nowhere else he'd rather be.

"I'm doing what I want to be doing, and if I wasn't, I would change it," Endy says. "If at some point in the future, I'd rather be raising pheasants in southern France, or in northern France … or wherever they raise pheasants in France, I presume I would go do that."

"I don't see what I'm doing as work," he declares. ■

David Bochner, a Harvard University junior studying biology, was an intern at the National Institute of General Medical Sciences in summer 2006. He is an aspiring science writer who also writes for Harvard student publications.

Science and Society

Concerns about bioterrorism have led to calls for regulating synthetic biology and making it secure. If a scientist can easily make a virus from off-the-shelf parts, who else could?

MARSHA MILLER (UT AUSTIN)

Synthetic biologist Drew Endy thinks that the potential of biological engineering makes it worth pursuing (see main story), in conjunction with societal conversations about the technology's applications.

"There are lots of things we can imagine," Endy explains, offering examples of genomes designed to be understandable and genomes whose evolution is directed by researchers, as opposed to by nature.

Endy predicts that synthetic biology will evolve sort of like the Internet, through innovation and the widespread distribution of information. To him, spreading knowledge via the BioBricks Foundation, which he helped to establish in an effort to promote the free exchange of data and information, will encourage a revolution in the field of biological engineering. He doesn't see it putting power into the wrong hands.

Living machines are already better than their mechanical counterparts at a lot of tasks, Endy says.

DREW ENDY

"Biological systems are really good at material construction, chemical production, energy production, and information processing," he explains. The challenge is to find ways to make them work for us.

While some might claim that Endy and his colleagues are "playing God," Endy believes that he is simply realizing the human potential for innovation and imagination.

"Instead of just imagining the world as it exists, and as we inherit it from nature, I think it's becoming increasingly important that we understand how to imagine worlds that might be, how we would choose how to design and construct them."—*D.B.*