Command performances

Controlling organisms withbiological circuits, opens up a world of possibilities and dangers

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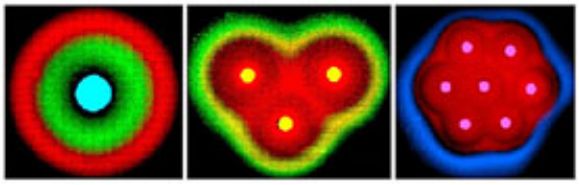
For decades, biologists have modified plants and animals by snipping genes from one organism and popping them into another in a process called genetic engineering. Corn will produce its own pesticide – a toxin harmful to caterpillars – when spiked with a bacterial gene. And copies of the human gene for insulin have been slipped into bacteria, transforming them into biological drug factories and reducing the need to extract the hormone from slaughtered pigs.



RON WEISS / Princeton University

Bacteria exchange signals generated by synthetic circuits to form colorful patterns. The bulls-eye pattern (left) formed around a patch of turquoise cells, which send a chemical message. Surrounding cells turn green near the center, where the message is strong, and red farther away, where the message is weaker. Multiple patches of messenger cells (center and right) create more complex patterns. Similar multi-cell communication circuits could form complex biological structures such as liver or skin.

Until recently, those useful genes had to be found in nature and transferred from one organism to another. Now our ability to manipulate biology to suit our needs has taken a startling new turn. Scientists are using custom-designed DNA, synthesized from scratch, to create novel biological "circuits" they hope will do anything they can program them to do.

Their goal is to plan new biological tasks, such as detecting pathogens and rendering them harmless, with the kind of precision and control exercised by designers of electrical circuits. They call themselves synthetic biologists, and they have set out to engineer life.

Is this a good idea? The goals sound promising: create tiny packets that travel through the bloodstream to find and treat diseased cells, design cells to generate replacement organs or bridge a severed spinal cord, weave high-tech fabrics of proteins from spider silk.

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These possibilities have arisen largely from technical advances over the past few years that have made chemical synthesis of DNA relatively inexpensive. Custom-designed DNA is available by mail and can be ordered through the Internet. Researchers specify the sequence of the gene they desire and pay as little as a dollar per letter of the genetic code.

The problem is that the sequences of dangerous things, such as the virus that caused the 1918 influenza pandemic, are public knowledge. Some worry that a renegade group of synthetic biologists could unleash something horrifying.

"In an overall sense, the security situation is grave," said Roger Brent, president and CEO of Molecular Science Institute in Berkeley. "One can re-synthesize flu. The people who call themselves synthetic biologists didn't bring this situation about, but they bear some measure of the responsibility for keeping us safe."

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Natalie Ostroff prepared to measure a signal from a synthetic circuit she designed and inserted into yeast cells.

Brent isn't concerned about the field's pioneers. "They're the products of long apprenticeships, acculturated to using the technology only for good and never for evil." But he worries about younger people. A self-taught teenager can pore deeply through a computer operating system, he said. At this point, manipulating genes requires more specialized training, but the future may be different.

"Possibly the best protection is promulgation of ethical standards. If people act now, they can stop a hacker culture from the start." Scientists and policy makers have begun discussions, but few existing regulations apply to this new endeavor.

Leaders in the field convened the intercollegiate Genetically Engineered Machine, or iGEM, competition at the Massachusetts Institute of Technology in Cambridge last month. Nine teams fielded by universities and colleges from San Francisco to Zurich presented projects in a prize-less contest.

"We could have made this another 'robot wars' scenario and got the kids all excited about bashing each other's biology," said geneticist George Church, of Harvard University, who helped organize the meeting. "But we specifically discouraged that and instead encouraged a more constructive way of looking at things."

Each team picked a goal, some task for their bacteria to accomplish, then designed a biological circuit to do the job using plug and play components call BioBricks. Each component is a piece of DNA that can do a single simple thing, like make a protein to sense light, relay a signal or fluoresce. The students strung together BioBricks, much like assembling a simple electrical circuit from an electronics kit, and stuck them into cells to see if they would boot up properly. Revisions are always needed.

The UC Berkeley team exploited a bacterial trick called conjugation. Bacteria naturally exchange bits of DNA through tunnels they form when they come into close contact. "One of bacteria's favorite things to do is to spread resistance to antibiotics," said graduate student Jonathan Goler, who helped coach Berkeley's team.

Instead, the students used the channels – by sliding a strip of DNA from cell to cell – to send messages they designed. In this case, the message was the order to make a protein that glows and also an "address" for the next cell to send the message to. The practical use isn't yet clear, but the organizers hailed it as a creative new approach to controlling a group of cells.

Promising directions

Goler's own work addresses a more pressing need. He is part of a team led by professor Jay Keasling that is engineering bacteria to produce a drug to treat malaria. The team is using at least 10 genes from three organisms to forge new machinery within bacterial cells that will manufacture artemesinin. The potent protein is naturally found in the wormwood shrub, but in small amounts. Isolating it from the plant is inefficient and expensive. But if easily grown bacteria can be made to do the job, the drug could be produced in volume, dropping its price and making it more widely available.

Former Keasling lab member Christina Smolke, now at the California Institute of Technology, is working on "smart therapeutics." Her research group is designing DNA-based probes to detect a type of viral infection that transforms a normal cell into a cancerous one. "We're working on small delivery vehicles that could deliver therapy once they detect the errant cells," she said.

Ron Weiss and colleagues at Princeton University have programmed bacteria from the human gut to communicate with each other to produce colorful designs. They have created a "Goldilocks" circuit that lights up when the concentration of a target chemical is just right.

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Glowing green colonies of engineered bacteria cells spotted a Petri dish.

In one experiment, they designed cells to glow green when they sensed a high concentration of a signal

chemical and red when the concentration was low. They placed a different set of cells designed to secrete the signal chemical in a center of a plate of bacteria food. When the chemical bled out through the goo, like a wine stain on a table cloth, the sensor cells responded by forming a bull's-eye pattern – green ringed by red.

If the sensing bacteria could be programmed to detect a contaminant, they could be sprayed over a chemical spill to highlight the most dangerous zones with their color patterns, Weiss said.

Arrays of cells could also form more complex patterns as the basis for generating tissues, even organs. Current attempts encourage cells to arrange themselves on artificial scaffolding. "The way we're doing tissue engineering right now, one could claim, is very unnatural," Weiss said. "Clearly cells make scaffolds themselves. If we're able to program them to do that, we might be able to embed them in the site of injury and have them figure out for themselves what the pattern should be."

Hello world

An early success in the field, reported in 2000, was a three-gene program that made bacteria blink on and off like fireflies. That system mimicked biological clocks that cycle on and off. Most biological rhythms, though, are regularly reset by cues from the outside world, such as daylight. Jeff Hasty's lab at UCSD is designing rhythmic circuits in yeast and mold that synchronize with light cycles.

"I'm trying to design a minimal circuit needed to maintain these cycles," said graduate student Natalie Ostroff, who works with yeast.

Light is a favorite signal for synthetic biologists, perhaps because nature has provided so many examples. For now, most teams have created cells that signal with colored fluorescent proteins found in jellyfish.

A team from UC San Francisco and the University of Texas in Austin hopes to use light detectors tuned to various wave lengths to turn on specific synthetic circuits. For a start, they borrowed a protein from blue-green algae that is activated by red light, linked it to an enzyme that deposits a black pigment and inserted this simple circuit into bacterial cells. When the cells are spread in a thin sheet and exposed to light, they act much like a photographic film.

For their inaugural outing at a meeting last year, the team shined light on their film to form the words "Hello World." Subsequent efforts produced an image of one of their advisers and the name of the journal that published their work.

But these are just demonstrations. At UC San Francisco, Christopher Voight imagines something more useful – creating materials composed of multiple proteins, like those that make up spider silk, each contributing properties of strength and elasticity, each controlled

by a color of light.

Keeping it safe

Much of this work is preliminary: jellyfish lights and cells that make pictures. Getting them to work remains quite a challenge, even for the brightest minds, so the threat of using the process for intentional harm is unlikely for the moment. Everyone interviewed for this article agreed the risk of accident or inadvertent introduction of something harmful was minuscule.

"You have to remember all these experiments are done in a petri dish," Weiss said. "Once you go outside the petri dish, the environment becomes so complex, the engineered cells have a hard time surviving. It's easy to imagine dangerous, but to realize it is much more difficult."

Still, scientists, ethicists and government advisers are meeting now to decide how best to manage and control this new power. They are discussing means of monitoring the genes ordered, codes of conduct and the possibility of licensing scientists.

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One emerging practice is the notion of stamping the work with an identifying mark. "When we synthesize genes, we add a bar code or signature into the DNA that identifies it as something we made. That makes it easy to detect," said Drew Endy, of the Massachusetts Institute of Technology.

The National Science Advisory Board for Biosecurity is currently considering a code of conduct. Less clear is what the consequences of violating the code should be and how a code would stop people who intend to do harm.

Current laws require a permit to work with certain dangerous pathogens such as anthrax. But those pathogens are listed by species, not by specific sequences of DNA. "We would like to see regulations expressed in terms of sequences," said John Mulligan, president and CEO of Blue Heron Biotechnology. He said his company does screen orders and has yet to receive one for a suspicious sequence.

But what should happen if Blue Heron or another company does? "Let's say you're starting up a new company and you're screening and you find something that looks really horrible," Endy said. "Who do you talk to?"

Even the controls are preliminary. Weiss advocates constructing synthetic "self destruct" circuits. "You can actually engineer them to kill themselves after some amount of time. When it counts to 10, the cell dies."

That requires cells to count, which happens to have been one of the projects in the iGEM competition this year.

"We began by talking about counting to infinity," said Robin Künzler, a member of the team from Zurich. But that proved too high a hurdle.

Instead they designed a cell that could count to two.

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