Science Careers From the journal Science

Genetic Engineering on Steroids

By Vijaysree Venkatraman
January 20, 2012

"With our pipettes, gloves, and lab coats, we were an unusual sight in that engineering division." -- Ron Weiss

In 1994, the world was on the verge of the dot-com boom and Ron Weiss, a graduate student in the computer science program at the Massachusetts Institute of Technology (MIT) in Cambridge, had just earned a master's degree for his work on a Web application to manage video streams. Just as Internet technology was heating up, the focus of his adviser's research was starting to shift to a more esoteric topic: DNA-based computers. Weiss, who had not taken a biology class since high school, wasn't entirely happy with the new direction. "Biology is so messy. I don't want to deal with it," he recalls thinking.

Weiss has since revised his opinion of the science of life, but he hasn't entirely abandoned his preference for well-ordered things. Today, as the director of MIT's Synthetic Biology Center, he is working to program cells.

Two advances make this new branch of biological engineering possible: a better understanding of biochemical mechanisms in cells and the ability to make DNA sequences from scratch in the lab. Besides providing further insights into how cells work, this emerging discipline has likely applications in numerous fields, including diagnostics, environmental remediation, and sustainable energy production, among others. "Synthetic biology is like genetic engineering on steroids," Weiss says.

Computer scientists in lab coats

Weiss's entry into synthetic biology was fortuitous. After his master's degree, he wasn't sure what he wanted to do except that he wanted to stay in academia. He continued to take classes to fulfill the course requirements for a computer science Ph.D. One evening, as Weiss was walking down the hallway, Gerald Sussman, a professor in MIT's Department of Electrical Engineering and Computer Science, asked him to pop into his office to look at a proposal. The proposal was on amorphous computing.

The object of amorphous computing is to understand how identical entities in nature work together toward a common purpose, like a swarm of bees building a hive. The idea is to learn tricks nature has perfected over billions of years and use them to build distributed systems, Sussman says. Despite his distaste for biology, Weiss signed on. Sussman became his adviser.

Any living creature is an example of an amorphous computing system. A colony of cells in an embryo self-organizes to form an organism, facilitated by the information-dense code -- the common genetic program -- embedded in each cell. Weiss began his work in amorphous computing by building a model to elucidate the mechanisms by which nature achieves cell differentiation during the development of the embryo.

Communication between neighboring units is necessary, obviously, for coordinated behavior in cells. For his Ph.D. thesis, Weiss developed Microbial Colony Language to build and analyze cell aggregates. Not content with testing simulations, he wanted to direct intercellular interactions in a colony of *Escherichia coli*. So, he designed DNA constructs with synthetic genes derived from the bioluminescent bacteria *Vibrio fischeri*. He outfitted the sending cell with promoters and genes to allow the controlled expression of a chemical called *V. fischeri* auto-inducer. Upon detecting this chemical, the receiving cell would express specific genes. “I didn’t know if this would work, but the potential of programmable DNA constructs was unbelievable,” he says.

Building genetic circuits

Sussman, who is essentially a mathematician, was not keen on the idea of Weiss doing benchwork. He preferred to keep things simple and clean. But his student could not be dissuaded, and, anyway, had already done nearly enough to start writing his dissertation. So, Sussman put Weiss in touch with Tom Knight, Sussman's former graduate student, who is now considered the father of synthetic biology. Knight became Weiss's co-adviser.

In the late 1990s, people on a tour of MIT's artificial intelligence lab would have found Weiss and Knight running wet lab experiments. “With our pipettes, gloves, and lab coats, we were an unusual sight in that engineering division,” Weiss says. Weiss's goal was to build a plasmid, a custom-made DNA sequence that can be replicated easily. Knight, an electrical engineer, aimed to pare down the genome and repurpose the cell to produce things it was not originally designed to make -- plastics, say, or fuels.

It took Weiss 6 months to build his first plasmid. Once it was done, he was in business. Now he could design, build, and test DNA constructs to control the cell’s machinery through standard biochemical operations like transcription, translation, or post-translation processes. Weiss combined elements like promoters, binding sites, and repressors to form modules with a characteristic behavior. Along with Knight, Weiss documented these devices -- roughly analogous to electronic components -- in the Registry of Standard Biological Parts, an open-source toolkit for biological engineers. Weiss calls these systems -- connected networks of components designed using DNA -- "genetic circuits."

Just as engineers use Boolean logic gates to build digital devices, synthetic biologists can encode logic operations in networks of these DNA modules.

In 2000, when Weiss gave talks in MIT's biology department, the weirdness of this biology/engineering synthesis was apparent. “When I spoke of circuits that could turn genes on and off, some probably thought I had fallen out of space,” he says. “Those days, we did not speak the same language. Now we have developed a hybrid vocabulary.”

Upon graduating a year later, Weiss joined the electrical engineering faculty at Princeton University and continued to work on programming cells with grants from the U.S. Defense Advanced Research Projects Agency. For one project, his team programmed cells to detect the presence of bioweapons like anthrax.

Tumor-killing gene circuits

Weiss returned to MIT as an associate professor with two appointments: one in electrical engineering and computer science, the other in biological engineering. “My research interests haven’t changed all that much in 10 years,” he says, but he has moved on to testing genetic circuits in eukaryotes, including yeast and mammalian cells.

Members of the Weiss group devise techniques to engineer stem cells, turning them into tissue that can replace cells lost to injury or disease. Just as the human body differentiates cells into types based on a complex set of rules during embryogenesis, DNA circuits march stem cells through a series of steps to yield a desired tissue. Already, the team has achieved a measure of success in converting mouse stem cells into insulin-producing pancreatic cells. Patrick Guye, a postdoctoral associate in the Weiss group, is investigating whether the system can work in human cells.

In a recent *Science* paper, Zhen Xie, another postdoctoral associate from Weiss’s group, published results on using a genetic circuit to identify HeLa, a model cancer cell. When inserted into cells, this circuit determines the levels of a half dozen biomarkers to determine whether the cell is cancerous. If the final result is positive, it triggers cell death. “Whether it is a specific cancer cell, stem cell, or neuron, each cell state is characterized by a set of biomarkers and it is possible to develop reliable diagnostics for diseases based on that,” Weiss says. “There is a gold mine of information inside the cell.”

Weiss says he cannot predict when such synthetic biology applications will move from the lab to the clinic, but he thinks it won't be long. The team is already collaborating with other groups at MIT to find efficient ways to deliver tumor-killing DNA circuits into living animals.

Biology and complexity

One of the most basic premises of biological engineering is to take something complex -- such as a living cell -- and simplify it by treating it as a series of interchangeable parts. But to make the work pay off, the real challenge is the reverse: to get systems that work well in a lab's relatively simple setting to work in the more complex natural environment. Engineers need to design systems that can evolve and adapt to such contextual differences, Weiss says.

After a decade and a half of programming cells, Weiss believes that “it is possible to simplify biology.” But it's necessary for engineers to learn to respect nature’s complexity, its inherent messiness. “You cannot oversimplify biology,” he says.

Vijaysree Venkatraman is a Boston-based science journalist.