Scientists synthesize memory in yeast cells

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Harvard Medical School researchers have successfully synthesized a DNA-based memory loop in yeast cells, findings that mark a significant step forward in the emerging field of synthetic biology.

After constructing genes from random bits of DNA, researchers in the lab of Professor Pamela Silver, a faculty member in Harvard Medical School's Department of Systems Biology, not only reconstructed the dynamics of memory, but also created a mathematical model that predicted how such a memory "device" might work.

"Synthetic biology is an incredibly exciting field, with more possibilities than many of us can imagine," says Silver, lead author of the paper to be published in the September 15 issue of the journal *Genes and Development*. "While this proof-of-concept experiment is simply one step forward, we've established a foundational technology that just might set the standard of what we should expect in subsequent work."

Like many emerging fields, there's still a bit of uncertainty over what, exactly, synthetic biology is. Ask any three scientists for a definition, and you'll probably get four answers.

Some see it as a means to boost the production of biotech products, such as proteins for pharmaceutical uses or other kinds of molecules for, say, environmental clean-up. Others see it as a means to creating computer platforms that may bypass many of the onerous stages of clinical trials. In such a scenario, a scientist would type the chemical structure of a drug candidate into a computer, and a program containing models of cellular

metabolism could generate information on how people would react to that compound.

Either way, at it's core, synthetic biology boils down to gleaning insights into how biological systems work by reconstructing them. If you can build it, it forces you to understand it.

A team in Silver's Harvard Medical School lab led by Caroline Ajo-Franklin, now at Lawrence Berkeley National Laboratory, and postdoctoral scientist David Drubin decided to demonstrate that not only could they construct circuits out of genetic material, but they could also develop mathematical models whose predictive abilities match those of any electrical engineering system.

"That's the litmus test," says Drubin, "namely, building a biological device that does precisely what you predicted it would do."

The components of this memory loop were simple: two genes that coded for proteins called transcription factors.

Transcription factors regulate gene activity. Like a hand on a faucet, the transcription factor will grab onto a specific gene and control how much, or how little, of a particular protein the gene should make.

The researchers placed two of these newly synthesized, transcription factor-coding genes into a yeast cell, and then exposed the cell to galactose (a kind of sugar). The first gene, which was designed to switch on when exposed to galactose, created a transcription factor that grabbed on to, and thus activated, the second gene.

It was at this point that the feedback loop began.

The second gene also created a transcription factor. But this transcription

factor, like a boomerang, swung back around and bound to that same gene from which it had originated, reactivating it. This caused the gene to once again create that very same transcription factor, which once again looped back and reactivated the gene.

In other words, the second gene continually switched itself on via the very transcription factor it created when it was switched on.

The researchers then eliminated the galactose, causing the first synthetic gene, the one that had initiated this whole process, to shut off. Even with this gene gone, the feedback loop continued.

“Essentially what happened is that the cell remembered that it had been exposed to galactose, and continued to pass this memory on to its descendents,” says Ajo-Franklin. “So after many cell divisions, the feedback loop remained intact without galactose or any other sort of molecular trigger.”

Most important, the entire construction of the device was guided by the mathematical model that the researchers developed.

“Think of how engineers build bridges,” says Silver. “They design quantitative models to help them understand what sorts of pressure and weight the bridge can withstand, and then use these equations to improve the actual physical model. We really did the same thing. In fact, our mathematical model not only predicted exactly how our memory loop would work, but it informed how we synthesized the genes.”

For synthetic biology, this kind of specificity is crucial. “If we ever want to create biological black boxes, that is, gene-based circuits like this one that you can plug into a cell and have it perform a specified task, we need levels of mathematical precision as exact as the kind that go into creating computer chips,” she adds.

The researchers are now working to scale-up the memory device into a larger, more complex circuit, one that can, for example, respond to DNA damage in cells.

“One day we’d like to have a comprehensive library of these so-called black boxes,” says Drubin. “In the same way you take a component off the shelf and plug it into a circuit and get a predicted reaction, that’s what we’d one day like to do in cells.”

Source: Harvard Medical School