Cellular 'computers' gain a hard drive

DNA-based memory can record multiple inputs from engineered gene circuits.

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A new DNA-based recorder allows bioengineers to create cell cultures that detect information in their environment and store it for later use. Such 'designer' cells might in the future be used to monitor water quality in a village, or measure the amount of sugar a person eats. The technique is described this week in *Science*[1].

In synthetic biology, genes are engineered to regulate each other's expression in such a way that they can perform logic operations similar to those in computer circuits. Memory storage has long been considered one of the key components needed to fulfil the promise of this technology.

“Building gene circuits requires not only computation and logic, but a way to store that information,” says bioengineer Timothy Lu of the Massachusetts Institute of Technology in Cambridge. “DNA provides a very stable form of memory and will allow us to do more complex computing tasks.”

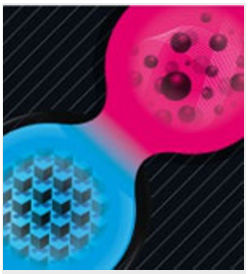
In previous synthetic-biology attempts, data storage has been laborious to create. It also recorded only the presence or absence of one particular sensory input, and could be used only for limited applications. In the latest paper, Lu and his colleague Fahim Farzadfard describe how they can record many types of data simultaneously, and can register the accumulation of the input over time, like a car’s odometer counts kilometres. The stored information can then be read out by sequencing the DNA. They dub their method SCRIBE, for Synthetic Cellular Recorders Integrating Biological Events.

“It’s a nice addition to the toolbox”, which could complement other memory-storage techniques, says Jérôme Bonnet, a bioengineer at the Centre for Structural Biochemistry in Montpellier, France, who was not involved in the research. “There’s room for different types of memory in synthetic biology — as in computing you have the hard drive and the RAM.”

Living memory

The team's work on SCRIBE began three years ago as an attempt to improve gene editing, in which cells are coaxed to incorporate new information into their genomes. One seemingly straightforward approach involves using single-stranded DNA molecules.

Bacterial genomes, like human genomes, are made up of double-stranded DNA molecules. But when single-stranded DNA is floating around in the cell, it is possible to stimulate the bacterium to insert it into its genome, using an enzyme from a virus. However, most bacteria do not readily manufacture a significant number of single-stranded DNAs.



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Farzadfard and Lu found a 1984 paper on a soil bacterium that contained hundreds of copies of single-stranded DNA[2]. This DNA was manufactured by a freely floating strucure made of double-stranded DNA, called a retron.

The natural biological function of these retrons remains mysterious, but Farzadfard and Lu realized that they could reprogram them to produce the single-stranded DNA encoding the information they wanted, and use the viral enzyme to store it in a bacterial genome.

In a proof-of-concept experiment described in their latest paper, the team created a colony of *Escherichia coli* bacteria in which retrons responded to the presence of a chemical, flipping a switch in the *E. coli* genome that made it resistant to an antibiotic. This transformation did not happen to the same extent inside every *E. coli* cell in the colony, however. The higher the concentration of the triggering chemical, the greater was the proportion of cells that ended up antibiotic resistant.

Unlike previous methods that serve as a digital form of memory — turning on or off like a light switch — SCRIBE could work as an 'analog' form of memory that functions more like a dimmer switch. The memory is not contained in a single *E. coli* cell, but in the entire culture. “Distributing memory across this population becomes a powerful way of doing things.”

Farzadfard and Lu also showed that this collective cellular memory can be reversed and rewritten, and that — by inserting photosensitive proteins into the genetic circuit — it can even be triggered by light. Furthermore, the bioengineers were able to use cells to record two variables at once, and think that their technique could be readily scaled up to perform more-complex tasks.

The retron-based gene-editing technique could have impacts beyond the realm of synthetic biology. Danwei Huangfu, a stem-cell biologist at the Memorial Sloan Kettering Institute in New York City, envisages harnessing it to regulate gene expression in transplanted cells that are used for treating diabetes or to make precise genetic changes in, say, pancreatic tissue while leaving liver cells untouched. “That seems very exciting to me,” she says.

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References

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2. Yee, T., Furuichi, T., Inouye, S. & Inouye, M. *Cell* **38**, 203–209 (1984).