*NATURE* | NEWS

# Rewritable memory encoded into DNA

**But 750 rounds of 'debugging' shows that synthetic biology needs better ways to write genetic programs.**

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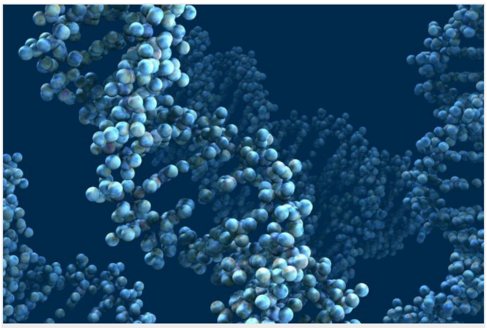
Researchers have encoded a form of rewritable memory into DNA.

The arduous work involved in building the system is almost as notable as the achievement itself, says Drew Endy of Stanford University in California who led the work, which is published today in *Proceedings of the National Academy of Sciences*[1].

Synthetic biologists have long sought to devise biological data-storage systems because they could be useful in a variety of applications, and because data storage will be a fundamental function of the digital circuits that the field hopes to create in cells.

Rewritable biological memory circuits have been made previously, for instance from systems of transcription factors, which can be used to shut gene expression on or off in a cell. In such systems, once the memory state of the circuit is set, it can be erased and encoded with a new memory state, as is done in everyday devices such as personal computers.



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DNA can be programmed to act as a biological data-storage device.

Endy's group attempted to create a rewritable memory system by splicing genetic elements from a bacteriophage — a bacterium-infecting virus — into the DNA of the bacterium *Escherichia coli*.

The system consists of a stretch of DNA flanked by sites that signal to enzymes made by the bacteriophage, instructing them to cut out the DNA and paste it back into the chromosome in the reverse orientation. Endy's group shows that the device can be set and reset repeatedly — up to 16 times. One advantage this system has over those using transcription factors is that it is truly digital, with forward and reverse orientations of the DNA acting like a '0' or a '1' in binary. Also, the cell expends no energy in storing the memory, beyond DNA maintenance, says Endy. He points out that combinations of such elements could be used to track cellular events, such as the series of cell divisions by which a stem cell becomes a differentiated adult cell.

"What Drew's group can do that others haven't demonstrated is the ability to cycle the memory element over and over, kind of like you can write a bit to a hard drive, read it and change it back over and over again," says synthetic biologist Eric Klavins of the University of Washington in Seattle.

### Debugging designs

Endy's group chose a particular bacteriophage element for the work because it seemed to have the potential to reliably change the orientation of DNA. But that didn't turn out to be the case. As a result, Jerome Bonnet, the postdoctoral student who spearheaded the project, spent three years tweaking the system to make it work, ultimately creating 750 different designs in his attempts to troubleshoot various aspects.

"It's a pretty sad criticism of the state of technology in synthetic biology where we're trying to program the expression of half a dozen genes and it takes 750 design attempts to get that working," Endy says. "It's like trying to write a six-line code on a computer that takes 750 debug attempts to work."

Klavins agrees that many experiments in the field must go through extensive testing and tweaking processes before they achieve their goals. But he says that this is changing as the gene-synthesis tools that are needed to make new pieces of genetic circuitry become faster and cheaper.

"The cheaper and easier gene synthesis becomes, the more easily we'll be able to do this kind of thing," Klavins says.

Endy also hopes that initiatives such as the BIOFAB, which he co-directs with Adam Arkin at the University of California, Berkeley, will streamline the process by delivering standardized, reliable biological parts for researchers to use.

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## References

1. Bonnet, J., Subsoontorn, P. & Endy, D. *Proc. Natl Acad. Sci. USA* http://dx.doi.org/10.1073/pnas.1202344109 (2012).