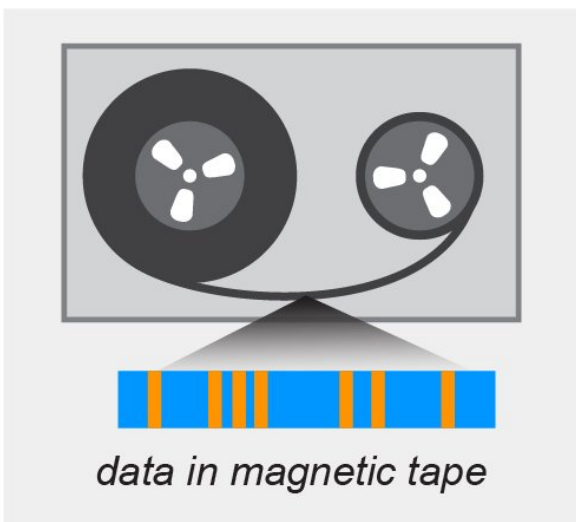


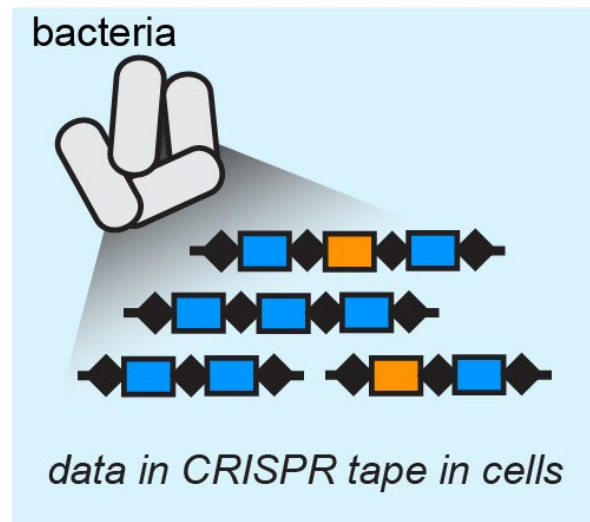
World's smallest tape recorder is built from microbes

November 23 2017

audio tape



CRISPR tape



Audio signals can be stored in a magnetic tape medium; similarly the microscopic data recorder stores biological signals into a CRISPR tape in bacteria. Credit: Wang Lab/Columbia University Medical Center

Through a few clever molecular hacks, researchers at Columbia University Medical Center have converted a natural bacterial immune system into a microscopic data recorder, laying the groundwork for a new class of technologies that use bacterial cells for everything from disease diagnosis to environmental monitoring.

The researchers modified an ordinary laboratory strain of the ubiquitous human gut microbe *Escherichia coli*, enabling the bacteria to not only record their interactions with the environment but also time-stamp the events.

"Such bacteria, swallowed by a patient, might be able to record the changes they experience through the whole digestive tract, yielding an unprecedented view of previously inaccessible phenomena," says Harris Wang, assistant professor in the Department of Pathology and Cell Biology and Systems Biology at CUMC and senior author on the new work, described in today's issue of *Science*. Other applications could include environmental sensing and basic studies in ecology and microbiology, where bacteria could monitor otherwise invisible changes without disrupting their surroundings.

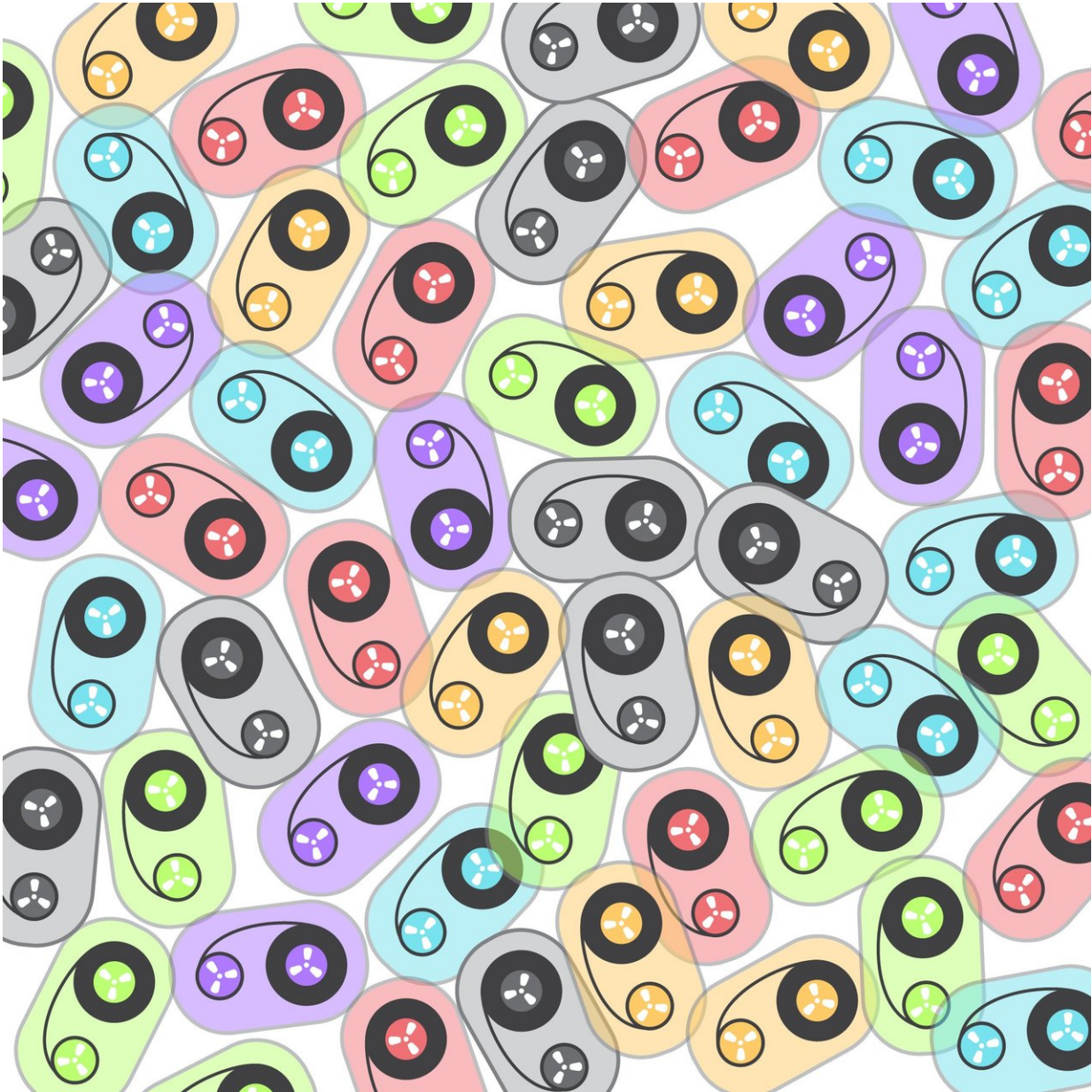
Wang and members of his laboratory created the microscopic data recorder by taking advantage of CRISPR-Cas, an immune system in many species of bacteria. CRISPR-Cas copies snippets of DNA from invading viruses so that subsequent generations of bacteria can repel these pathogens more effectively. As a result, the CRISPR locus of the bacterial genome accumulates a chronological record of the bacterial viruses that it and its ancestors have survived. When those same viruses try to infect again, the CRISPR-Cas system can recognize and eliminate them.

"The CRISPR-Cas system is a natural biological memory device," says Wang. "From an engineering perspective that's actually quite nice, because it's already a system that has been honed through evolution to be really great at storing information."

CRISPR-Cas normally uses its recorded sequences to detect and cut the DNA of incoming phages. The specificity of this DNA cutting activity has made CRISPR-Cas the darling of gene therapy researchers, who

have modified it to make precise changes in the genomes of cultured cells, laboratory animals, and even humans. Indeed, over a dozen clinical trials are now underway to treat various diseases through CRISPR-Cas gene therapy.

But Ravi Sheth, a graduate student in Wang's laboratory, saw unrealized potential in CRISPR-Cas's recording function. "When you think about recording temporally changing signals with electronics, or an audio recording ... that's a very powerful technology, but we were thinking how can you scale this to living cells themselves?" says Sheth.



Conceptual rendition of the CRISPR tape recording system. Credit: Wang lab/Columbia University Medical Center

To build their microscopic recorder, Sheth and other members of the Wang lab modified a piece of DNA called a plasmid, giving it the ability to create more copies of itself in the bacterial cell in response to an

external signal. A separate recording plasmid, which drives the recorder and marks time, expresses components of the CRISPR-Cas system. In the absence of an external signal, only the recording plasmid is active, and the cell adds copies of a spacer sequence to the CRISPR locus in its genome. When an external signal is detected by the cell, the other plasmid is also activated, leading to insertion of its sequences instead. The result is a mixture of background sequences that record time and signal sequences that change depending on the cell's environment. The researchers can then examine the bacterial CRISPR locus and use computational tools to read the recording and its timing.

The current paper proves the system can handle at least three simultaneous signals and record for days.

"Now we're planning to look at various markers that might be altered under changes in natural or disease states, in the gastrointestinal system or elsewhere," says Dr. Wang.

Synthetic biologists have previously used CRISPR to store poems, books, and images in DNA, but this is the first time CRISPR has been used to record cellular activity and the timing of those events.

The *Science* paper is titled, "Multiplex recording of cellular events over 1 time into a CRISPR biological tape."

More information: R.U. Sheth et al., "Multiplex recording of cellular events over time into a CRISPR biological tape," *Science* (2017).
[science.sciencemag.org/lookup/.../1126/science.aao0958](https://www.sciencemag.org/lookup/.../1126/science.aao0958)

Provided by Columbia University Medical Center

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