

SYNTHETIC BIOLOGY

Memoirs of a gut bacterium

Engineered bacteria sense and record conditions in the gut.

In the 1966 sci-fi film *Fantastic Voyage*, a group of patriotic adventurers save a comatose scientist from a blood clot by submitting themselves to miniaturization and traveling through his body in a shrunken submarine. After curing the clot, they escape through a teardrop, and the scientist—along with his state secrets—survives. Half a century later, sending in submarines is not yet a realistic option, so Pamela Silver of Harvard University and her colleagues have recruited bacteria instead—this time for adventures in the mouse gut.

The potential to use engineered organisms for therapeutics or as sentinels of disease has been a rich source of fantasy among synthetic biologists. Gut bacteria affect host digestion, immunity and many other aspects of health. And as a staple of laboratory science, they are an ideal starting point to test the potential for

synthetic monitoring and reporting in a complex living system.

Silver and her colleagues chose to test a bistable switch that could sense and remember the presence of anhydrotetracycline (ATC). A classic switch from the bacteriophage λ virus fit their design criteria: naturally high stability before and after switching and very low expression to ensure bacterial fitness. The core circuit consists of two mutually repressive transcription factors, cI and Cro. The group fused a reporter to Cro and integrated the entire switch into the chromosome of a streptomycin-resistant *Escherichia coli* lab strain, where it was locked in the Cro-repressed state. They also engineered a trigger: a very sensitive ATC-responsive promoter to drive Cro and toggle the switch.

Silver's team fed mice the bacteria along with streptomycin-laced water to help establish them in the gut, also giving ATC to a subset of the mice. They found that essentially all

streptomycin-resistant colonies taken from feces had switched within a day of treatment and that these retained the ATC memory for days. In the absence of streptomycin, the lab strain was outcompeted by host bacteria, so the researchers transferred the entire system to an endogenous *E. coli* strain isolated from the mice. It showed the same bistability as the exogenous strain and better gut retention in the absence of streptomycin.

More stable switch designs and complicated circuitry may eventually find a role in diagnostics, environmental sensing or even *in vivo* decision-based therapeutics. The success of sensing bacteria in the mouse brings living probes one step further from fiction.

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RESEARCH PAPERS

Kotula, J.W. *et al.* Programmable bacteria detect and record an environmental signal in the mammalian gut. *Proc. Natl. Acad. Sci. USA* **111**, 4838–4843 (2014).