# Using analog computation circuits, engineers design cells that can compute logarithms, divide and take square roots

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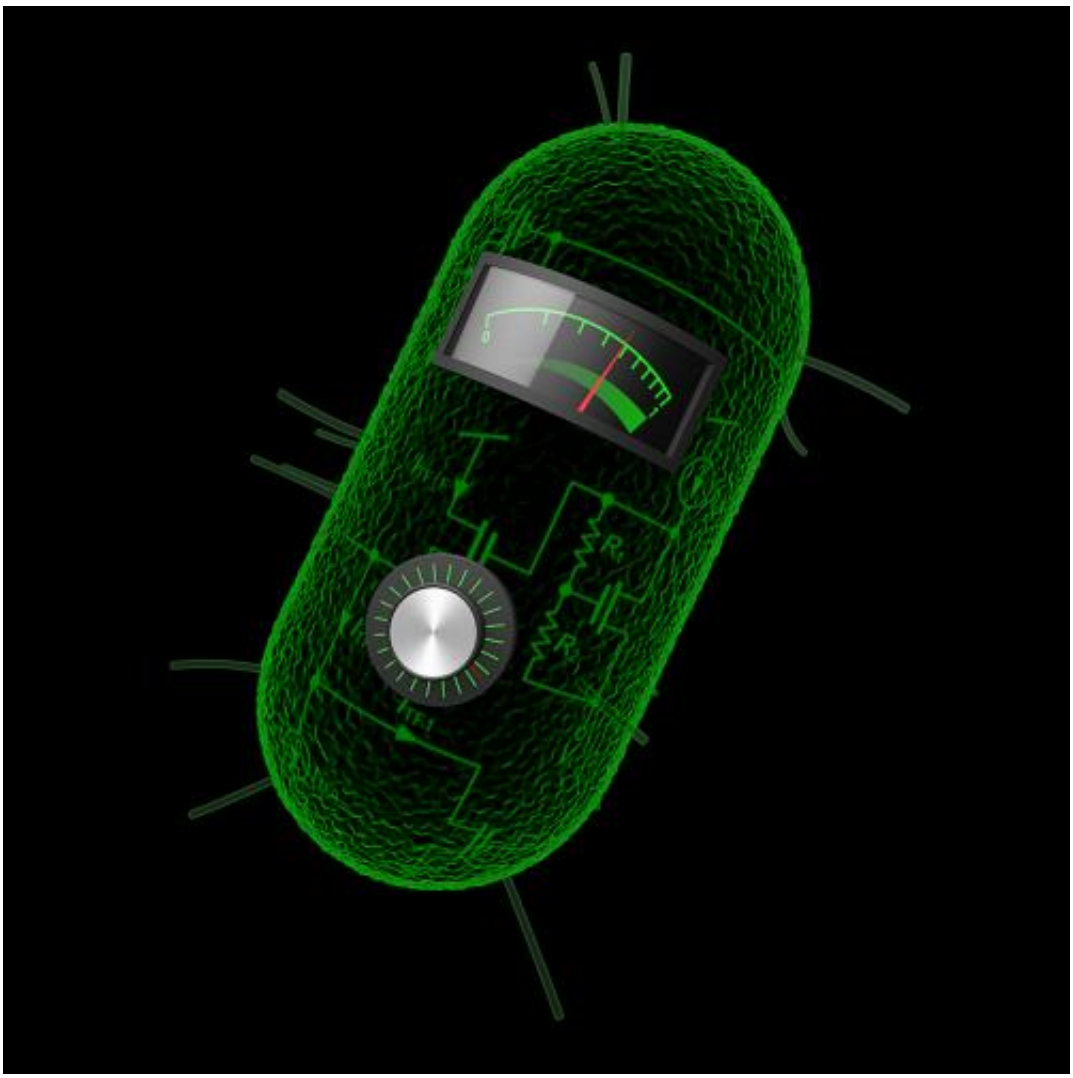

MIT engineers have created synthetic biology circuits that can perform analog computations such as taking logarithms and square roots in living cells.

MIT engineers have transformed bacterial cells into living calculators that can compute logarithms, divide, and take square roots, using three or fewer genetic parts. Inspired by how analog electronic circuits function, the researchers created synthetic computation circuits by combining existing genetic "parts," or engineered genes, in novel ways.

The circuits perform those calculations in an analog fashion by exploiting natural biochemical functions that are already present in the cell rather than by reinventing them with digital logic, thus making them more efficient than the digital circuits pursued by most synthetic biologists, according to Rahul Sarpeshkar and Timothy Lu, the two senior authors on the paper, describing the circuits in the May 15 online edition of *Nature*.

"In analog you compute on a continuous set of numbers, which means it's not just black and white, it's gray as well," says Sarpeshkar, an associate professor of electrical engineering and computer science and the head of the Analog Circuits and Biological Systems group at MIT

Analog computation would be particularly useful for designing cellular sensors for pathogens or other molecules, the researchers say. Analog sensing could also be combined with digital circuits to create cells that can take a specific action triggered by a threshold concentration of certain molecules.

"You could do a lot of upfront sensing with the analog circuits because they're very rich and a relatively small amount of parts can give you a lot of complexity, and have that output go into a circuit that makes a decision—is this true or not?" says Lu, an assistant professor of electrical engineering and computer science and biological engineering.

Lead author of the Nature paper is MIT postdoc Ramiz DanielJacob Rubens, a graduate student in microbiology, is also an author of the paper.

## Analog advantages

Sarpeshkar has previously identified thermodynamic similarities between analog transistor circuits and the chemical circuits that take place inside cells. In 2011, he took advantage of those similarities to model biological interactions between DNA and proteins in an electronic circuit, using only eight transistors.

In the new *Nature* paper, Sarpeshkar, Lu and colleagues have done the reverse—mapping analog electronic circuits onto cells. Sarpeshkar has long advocated analog computing as a more efficient alternative to digital computation at the moderate precision of computation seen in biology. These analog circuits are efficient because they can take in a continuous range of inputs, and they exploit the natural continuous computing functions that are already present in cells. In the case of cells, that continuous input might be the amount of glucose present. In transistors, it's a range of continuous input currents or voltages.

Digital circuits, meanwhile, represent every value as zero or one, ignoring the range of possibilities in between. This can be useful for creating circuits that perform logic functions such as AND, NOT and OR inside cells, which many synthetic biologists have done. These circuits can reveal whether or not a threshold level of a certain molecule is present, but not the exact amount of it.

Digital circuits also require many more parts, which can drain the energy of the cell hosting them. "If you build too many parts to make some function, the cell is not going to have the energy to keep making those proteins," Sarpeshkar says.

## Doing the math

To create an analog adding or multiplying circuit that can calculate the total quantity of two or more compounds in a cell, the researchers combined two circuits, each of which responds to a different input. In one circuit, a sugar called arabinose turns on a transcription factor that activates the gene that codes for green fluorescent protein (GFP). In the second, a signaling molecule known as AHL also turns on a gene that produces GFP. By measuring the total amount of GFP, the total amount of both inputs can be calculated.

To subtract or divide, the researchers swapped one of the activator transcription factors with a repressor, which turns off production of GFP when the input molecule is present. The team also built an analog square root circuit that requires just two parts, while a recently reported digital synthetic circuit for performing square roots had more than 100.

"Analog computation is very efficient," Sarpeshkar says. "To create digital circuits at a comparable level of precision would take many more genetic parts."

Another of the team's circuits can perform division by calculating the ratio of two different molecules. Cells often perform this kind of computation on their own, which is critical for monitoring the relative concentrations of molecules such as NAD and NADH, which are frequently converted from one to the other as they help other cellular reactions take place.

"That ratio is important for controlling a lot of cellular processes, and the cell naturally has enzymes that can recognize those ratios," Lu says. "Cells can already do a lot of these things on their own, but for them to do it over a useful range requires extra engineering."

That extra engineering included modifying the circuits so that they can compute with inputs over a range of 1 to 10,000—much wider than the range of a naturally occurring cell circuit.

"It's nice to see that frameworks from electrical engineering can be concisely and elegantly mapped into synthetic biology," says Eric Klavins, an associate professor of electrical engineering and adjunct associate professor of biological engineering at the University of Washington who was not part of the research team.

The researchers are now trying to create analog circuits in nonbacterial cells, including mammalian cells. They are also working on expanding the library of genetic parts that can be incorporated into the circuits. "Right now we're using three of the most commonly used transcription factors in biology, but we'd like to do this with additional parts and make this a generalizable platform so everyone else can use it," Lu says.

"We have just scratched the surface of what sophisticated analog feedback circuits can do in living cells," says Sarpeshkar, whose lab is working on building further new analog circuits in cells. He believes the new approach of what he terms "analog synthetic biology" will create a new set of fundamental and applied circuits that can dramatically improve the fine control of gene expression, molecular sensing, computation and actuation.

**More information:** "Synthetic analog computation in living cells", www.nature.com/nature/journal/ … ull/nature12148.html

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