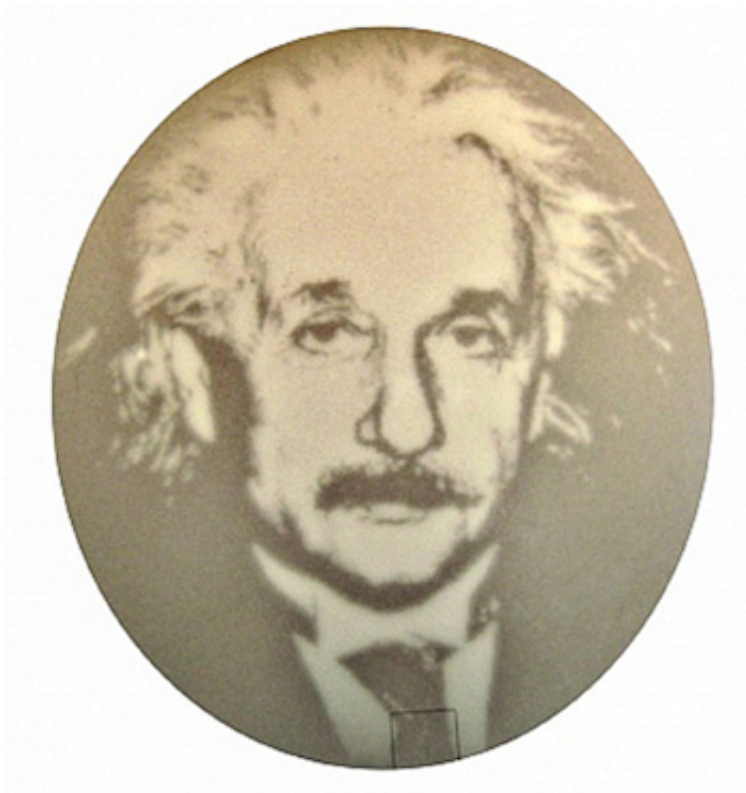


Bioengineers invent 'light tube array,' 'bioscilloscope' to test, debug genetic circuits

March 10 2014, by Jade Boyd



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(Phys.org) —In a significant advance for the growing field of synthetic biology, Rice University bioengineers have created a toolkit of genes and hardware that uses colored lights and engineered bacteria to bring both mathematical predictability and cut-and-paste simplicity to the world of

genetic circuit design.

"Life is controlled by DNA-based circuits, and these are similar to the circuits found in electronic devices like smartphones and computers," said Rice bioengineer Jeffrey Tabor, the lead researcher on the project. "A major difference is that [electrical engineers](#) measure the signals flowing into and out of electronic circuits as voltage, whereas bioengineers measure genetic circuit signals as genes turning on and off."

In a new paper appearing online today in the journal *Nature Methods*, Tabor and colleagues, including graduate student and lead author Evan Olson, describe a new, ultra high-precision method for creating and measuring [gene expression](#) signals in bacteria by combining light-sensing proteins from photosynthetic algae with a simple array of red and green LED lights and standard fluorescent reporter genes. By varying the timing and intensity of the lights, the researchers were able to control exactly when and how much different genes were expressed.

"Light provides us a powerful new method for reliably measuring genetic circuit activity," said Tabor, an assistant professor of bioengineering who also teaches in Rice's Ph.D. program in systems, synthetic and physical biology. "Our work was inspired by the methods that are used to study [electronic circuits](#). Electrical engineers have tools like oscilloscopes and function generators that allow them to measure how voltage signals flow through electrical circuits. Those measurements are essential for making multiple circuits work together properly, so that more complex devices can be built. We have used our light-based tools as a biological function generator and oscilloscope in order to similarly analyze genetic circuits."

Electronic circuits—like those in computers, smartphones and other devices—are made up of components like transistors, capacitors and

diodes that are connected with wires. As information—in the form of voltage—flows through the circuit, the components act upon it. By putting the correct components in the correct order, engineers can build circuits that perform computations and carry out complex information processing.

Genetic circuits also process information. Their components are segments of DNA that control whether or not a gene is expressed. Gene expression is the process in which DNA is read and converted to produce a product—such as a protein—that serves a particular purpose in the cell. If a gene is not "expressed," it is turned off, and its product is not produced. The bacteria used in Tabor's study have about 4,000 genes, while humans have about 20,000. The processes of life are coordinated by different combinations and timings of genes turning on and off.

Each component of a genetic circuit acts on the input it receives—which may be one or more gene-expression products from other components—and produces its own gene-expression product as an output. By linking the right genetic components together, synthetic biologists like Tabor and his students construct genetic circuits that program cells to carry out complex functions, such as counting, having memory, growing into tissues, or diagnosing the signatures of disease in the body.

For example, in previous research, Tabor and colleagues designed [genetic circuits](#) that allowed bacteria to change their color based on incoming light. The technique allowed the team to create bacterial colonies in Petri dishes that could behave like photo paper and reproduce black and white images.

In the new study, Tabor and Olson realized that light could be used to create time-varying gene-expression signals that rise and fall, similar to

those used in electronic engineering.

"In electronics, two of the key tools are function generators and oscilloscopes," said Olson, a graduate student in applied physics. "The function generator sends a known signal into the circuit being characterized. The oscilloscope is a device with a screen that the engineer uses to see the circuit output. By twisting the knobs on the function generator and viewing the corresponding output on the oscilloscope, the engineer can infer what various parts of the circuit are doing.

"The system of fluorescent reporter genes is our version of the oscilloscope," he said. "It lets us view both the circuit's input and output, and because it uses light to report on what's happening, it provides a very clean signal."

With their "bioscilloscope" in hand, the team needed a corresponding function generator. Olson, the lead author of the Nature Methods paper, put his electronics skills to work in late 2011 and invented the "light tube array," a programmable, eight-by-eight set of LED lights that will fit under a standard 64-well tray of test tubes. With the addition of some light-blocking foam around each test tube, the team had a way to send individually programmed light signals into each test tube in the array. By varying the signals and measuring the corresponding outputs with their bioscilloscope, the team was able to determine exactly how its test circuit performed.



Jeffrey Tabor (left) and Evan Olson with their 64-well "light tube array," a programmable platform for controlling and measuring gene expression in living cells via a combination of light and light-sensing proteins. Credit: Jeff Fitlow/Rice University

"The precision of light allows us to create exceptionally clean gene expression signals, which we can use to extract far more information about gene circuits than was possible before," Tabor said.

"We found there was a seven-minute delay between the gene expression going into and coming out of the genetic circuit," Olson said. "We also found we could program the circuit to follow specific patterns. For example, to rise by a specific amount over a set amount of time, stop and stay at another level for a predetermined length of time and then drop down to a third level for another interval of time."

Olson said the light tube array and bioscilliscope will be useful tools for biologists to probe how nature's cells work, as well as for synthetic

biologists who want to build and analyze their own circuits and networks.

"It's really about having a clean input signal, a clean output signal and the tools required to measure them," Olson said.

Tabor added, "You just never see data this clean in biology. It's remarkable."

More information: "Characterizing bacterial gene circuit dynamics with optically programmed gene expression signals." Evan J Olson, et al. *Nature Methods* (2014) [DOI: 10.1038/nmeth.2884](https://doi.org/10.1038/nmeth.2884). Received 15 August 2013 Accepted 23 January 2014 Published online 09 March 2014

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