Simulations guide rapid engineering of new functions in mammalian cells

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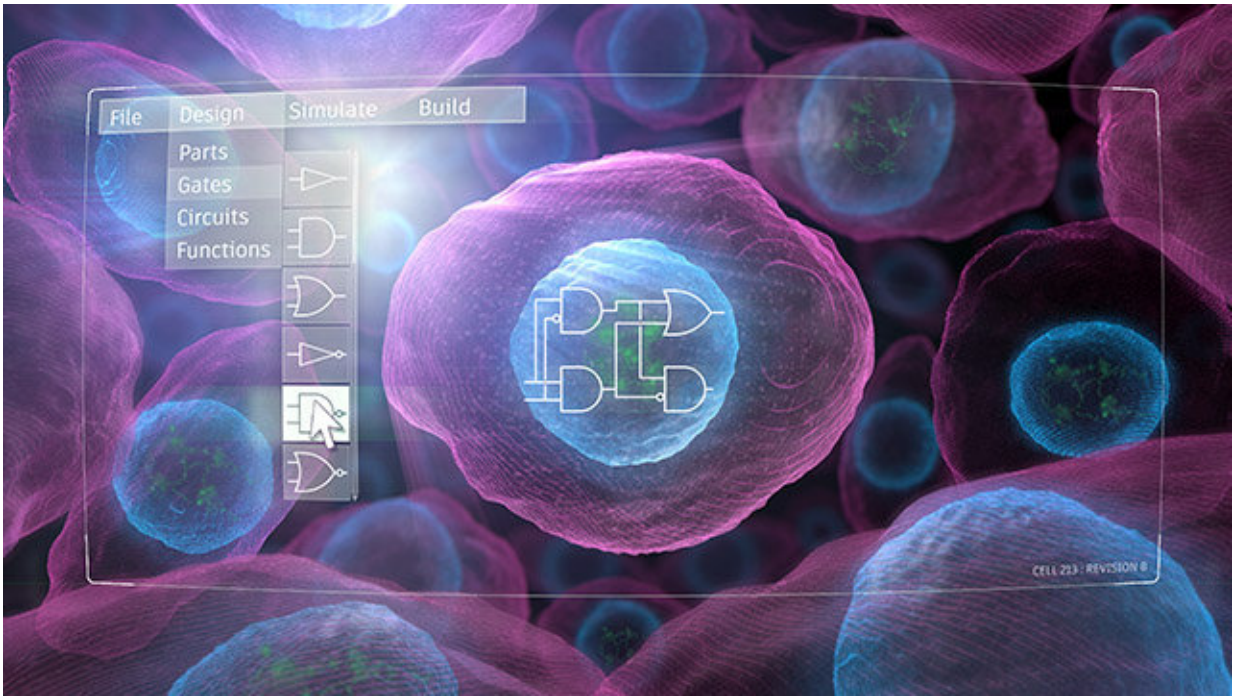

Bioengineers used computer models to build genetic circuits that can be introduced into cells to fight or prevent disease. Credit: Justin Muir

A change of instructions in a computer program directs the computer to execute a different command. Similarly, synthetic biologists are learning the rules for how to direct the activities of human cells.

"Cells are intricate machines that have evolved many interacting

circuits—sets of genes that coordinate functions like migration, metabolism, and cell division," explains David Rampulla, Ph.D., director of the Division of Discovery Science and Technology at the National Institute of Biomedical Imaging and Bioengineering. "Synthetic biologists aim to build genetic circuits that provide cells with new functions, which in the future could be used to monitor and treat diseases."

A challenge in the field, however, is that often there are many iterations of trial and error that go into making a circuit that operates as intended. Now, NIBIB-funded synthetic biologists and computational modelers have teamed up to use computer simulations to circumvent the laborious process of redesigning and retesting each genetic circuit.

One of the team members is engineer Josh Leonard, Ph.D., associate professor of chemical and biological engineering in the McCormick School of Engineering at Northwestern University. The computational modeler is Neda Bagheri, Ph.D., associate professor of biology and chemical engineering and a Washington Research Foundation Investigator at the University of Washington, Seattle. Together with their respective research teams, they are working to build genetic programs more quickly and reliably and to develop tools that help other researchers do the same.

"Engineering a cell comes down to building a piece of DNA, which encodes a set of genes whose products interact in a way that we call a circuit or program. When that DNA is introduced into a cell, the cell is instructed to perform a desired function. Normally, it is difficult to know whether a circuit will work until we test it," says Leonard. "This exceptional collaboration aspires to build genetic programs that do what we want them to do the first time, every time, because the computational models effectively take care of the trial and error for us in advance."

The team used customized simulations to analyze dozens of genetic circuits with different types of functions, such as turning genes on or off in response to various input signals. The most promising constructs were built and tested to see if they functioned as predicted. The research team was a bit stunned to find that nearly all of the circuits designed in this way closely matched model predictions.

"In my experience, almost nothing works like that in science; nothing works the first time," said Leonard. He explained that the usual process is to test lots of options, study the results, and debug to eventually identify a design that works.

Accelerated testing in computational models allowed the team to build and test operational circuits that performed increasingly more complex tasks. For example, programming the cell to evaluate multiple environmental features, such as the overproduction of a harmful protein or metabolite, and determine whether to deliver a therapeutic payload.

"We're now at a point where we have both a reliable set of tools and a formal design process for constructing gene regulatory functions," said Joseph Muldoon, a recent doctoral student and the first author of the study. "Next it will be exciting to see whether these capabilities help address the unmet needs in biomedicine that motivated this work."

The work is a significant step toward the efficient design of a genetic "toolkit" that can be used by the broader biomedical engineering community to meet various application-specific needs. The team believes the new tools combined with computational modeling will enable bioengineers to build customized cellular functions for applications ranging from fundamental research to new medical treatments.

The findings were reported in *Science Advances*.

More information: J. J. Muldoon et al, Model-guided design of mammalian genetic programs, *Science Advances* (2021). DOI: 10.1126/sciadv.abe9375