Novel synthetic biology technique could lead to breakthroughs in disease treatment

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Eduardo Sontag poses for a portrait on March 27, 2018. Credit: Adam Glanzman/Northeastern University

Synthetic biology offers a vision for the future of medicine, where cells could be re-engineered to fight diseases such as cancer and diabetes. For this to happen, scientists use viruses to infect and transfer new properties to cells so they behave in a certain way. But there hasn't been a reliable method to ensure all cells behave in the same way, even if they are not infected uniformly—until now.

In a paper published last week in the journal *Nature Biotechnology*, University Distinguished Professor Eduardo Sontag at Northeastern and his colleagues describe a novel synthetic biology technique they developed to give researchers more control over the process than ever before.

"This brings us closer to the goal of designing reliable, robust interventions using synthetic biology and genetic engineering," said Sontag, who holds joint appointments in the Department of Electrical and Computer Engineering and Department of Bioengineering. He co-authored the paper with Christopher Voigt and Thomas Segall-Shapiro of the Synthetic Biology Center at the Massachusetts Institute of Technology.

Scientists are interested in using synthetic biology to develop treatments for a variety of diseases. For example, Type 1 diabetes is caused by an autoimmune disorder in which the body mistakenly destroys beta cells, which produce insulin. What if we could engineer cells to keep track of themselves and divide to produce more cells when they sense the population is dwindling?

This is a theoretical example, Sontag said, but it illustrates the potential power of synthetic biology. Before these interventions can be realized, scientists must master the control circuits they insert into cells.

"It's just like a thermostat," Sontag said. "If the room is too hot, it may turn on the air conditioner. If it's too cold, it may turn on the heating. There is a feedback mechanism that regulates the temperature. In the same way, you build circuits to try to regulate things in the cell."

To insert a control circuit into cells, scientists use viruses as a vector. The problem is that cells become infected in a highly variable manner, making their resulting gene expression very unpredictable.

"If you're planting seeds and you don't want too many plants in one place, you'd like to have everything be uniformly distributed," Sontag said. That's precisely what his new method allows for. When the virus is inserted into cells, genes within the cell measure up to one another and self-regulate so the resulting behavior is the same, as if the infection had spread more evenly.

This work represents a significant development in synthetic biology, according to Wilson Wong, a biomedical engineering researcher at Boston University who was not involved in this research. Wong focuses on cellular immunotherapy—the use of the body's own immune system to target and fight disease. "It enables exceptional control of gene expression irrespective of copy number variation," Wong explained, referring to the distribution of infection in the cells. "This level of control is quite remarkable. I look forward to trying this type of design in human T cells."

As it happens, Sontag's current research is now focusing on the interactions between T cells and tumors, in which the same control circuits are known to play a central role.

More information: Thomas H Segall-Shapiro et al. Engineered promoters enable constant gene expression at any copy number in bacteria, *Nature Biotechnology* (2018). DOI: 10.1038/nbt.4111

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