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UCSB professor lands DARPA award to develop mini DNA factories

The Defense Advanced Research Projects Agency (DARPA) has tasked scientists with developing a system that can receive instructions and synthesize a sequence of DNA or RNA without any chemical input. Think wireless DNA printer.

The agency chose UC Santa Barbara's Max Wilson to lead the winning proposal. His team, LUXCODE, includes researchers at four universities, and DARPA has committed $1.7 million to launch the initiative over the first nine months, with potentially tens of millions more based on the team's progress. They aim to develop a nucleic acid compiler, or NAC, in a living cell.

Lean, agile, bespoke and so much more

Scientists can now design tailor-made proteins with unprecedented specificity and success. "A first-year grad student can now carry out processes that, just a few months ago, were restricted to the most specialized labs in the world," remarked Wilson, an associate professor of molecular, cellular and developmental biology. But design is just the first step, researchers still have to make them somehow.

The bioengineering pipeline often involves synthesizing DNA, producing proteins, evaluating, tweaking and repeating. This currently requires sending the instructions for the gene you want to a company to produce and send back. A few firms

specialize in this, taking advantage of economies of scale to produce DNA and RNA sequences on machines one base at a time, like an inkjet printer.

“Synthesizing DNA and nucleic acids and putting them into cells is always the slowest step in this process,” Wilson said. And this bottleneck has become more pronounced as protein design surges forward due to AI and advanced measurement systems.

Wilson envisions a setup where researchers can beam instructions to a cell in the lab, synthesize their DNA, produce and test their protein, then use the results to refine their machine learning system. “It would reduce something that takes a couple months down to a couple hours,” he said.

The ramifications are tremendous: investigating therapeutics in days, testing out antibodies in a work week, designing enzymes for environmental cleanups right after a disaster occurs. What’s more, synthesizing DNA in a living cell may overcome many of the limitations of printing them out biochemically. For instance, organisms have sophisticated error-detection and DNA-repair processes that machines lack.

Humanity’s old friend

Ultimately, DARPA wants to be able to email instructions to a remote location and produce proteins on-site at, say, a military base, a space station or a wilderness area. No post-office deliveries, no eight-week timelines. These NACs need to be small, shelf-stable, packageable, easy to manufacture and self-replicating.

That’s why the LUXCODE team is designing them from yeast.

Humans domesticated yeast at the dawn of civilization, and it’s been an asset ever since. “Yeast is one of the oldest substrates for bioengineering,” Wilson said. In addition to foods and beverages, yeast is used to manufacture a variety of chemicals and enzymes.

The task: Engineer a strain of yeast to produce polymerase enzymes responsive to specific wavelengths of light. That way you can build up a specific nucleic acid sequence with a specific sequence of flashing lights. The technique requires four different light-activated polymerase enzymes — the proteins that build DNA and RNA

— each engineered to respond to both a unique color of light as well as one shared color to synchronize the process.

If all this works, then a researcher will be able to flash a five-color strobe light at this yeast cell and have it synthesize a snippet of RNA or DNA pretty much in real time. Add an enzyme that can splice the sequence into the yeast's own genome, and the cell becomes not just the compiler, but also the model organism.

A powerful tool

Wilson is leading the LUXCODE team, which includes scientists from three other universities. Megan McLean at University of Wisconsin, Madison is developing robotic systems to interface between the optics and the biology. Meanwhile, Sijia Dong at Northeastern University, is addressing the quantum mechanics of protein design and fabrication. Also joining the team is Jim Collins at the Massachusetts Institute of Technology, whom Wilson calls "the godfather of synthetic biology." It's a prestigious crew.

In addition to the technical challenges, the team is seriously considering the biosecurity impacts their project may have. "Really good tools can do really, really bad things in the wrong hands," Wilson said. A functioning NAC could synthesize any protein with just a set of instructions and five LEDs.

Fortunately, this yeast strain will grow much more slowly than its wild and domestic counterparts, making it difficult for a bad actor to cultivate. The scientists are also considering different failsafes that could kill the cell if it synthesizes something toxic or infectious. The LUXCODE team includes a biosecurity expert who will help predict and address the issues that may arise from lowering the barrier to protein synthesis.

First steps to potential spinoffs

Right now, Wilson's lab has to design and produce every light-activated protein it uses from scratch. So the LUXCODE team's first task is to acquire an extensive library of photo-switchable proteins and the genes that code for them. They will then train a neural network to learn how to incorporate these proteins as a remote control on the polymerase enzymes. This system will revolutionize the team's work. Instead

of making parts one at a time like a blacksmith, they'll be producing components on an industrial assembly line.

But this tool should enable them to make any protein light-activated, not just polymerase enzymes. A universal tool for photo-switchable proteins. That's a windfall for bioengineering, and dovetails with Wilson's other research like antiviral therapeutics and stress-signaling in cells. Taking it a step further allows scientists to design proteins with logic built right into their structures: "if-then" proteins, "Or" proteins, "And" proteins.

"It's a very interesting time to be a bioengineer," Wilson said. "The tools continue to mature at quite a rapid clip. It makes the project seem more and more feasible every week."

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