Synthetic biologists redesign the way bacteria 'talk' to each other

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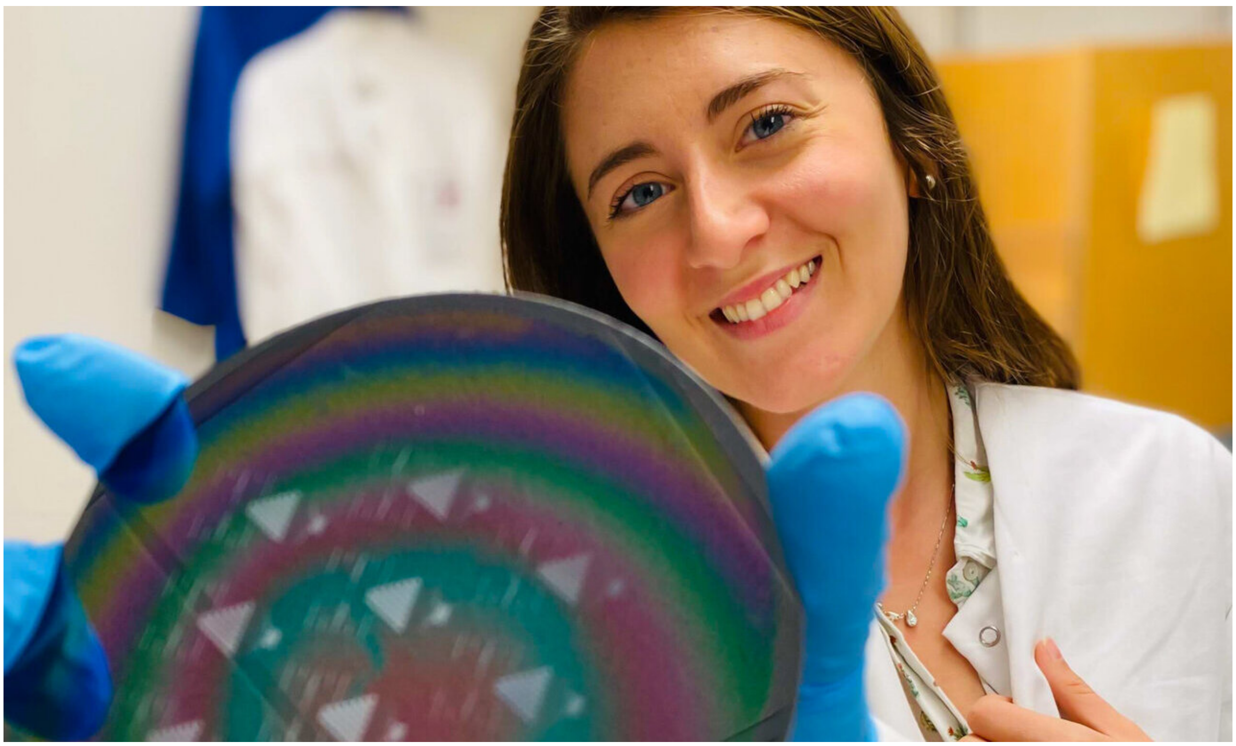

Arianna Miano, a UC San Diego bioengineering PhD student and the first author on the *Nature Communications* paper. She is posing with a silicon wafer used to make the microfluidic devices used in the study. This project is from the lab of UC San Diego professor Jeff Hasty. Credit: Arianna Miano / UC San Diego

Bioengineers at the University of California San Diego have redesigned how harmless *E. coli* bacteria "talk" to each other. The new genetic circuit could become a useful new tool for synthetic biologists who, as a field, are looking for ways to better control the bacteria they engineer to perform all sorts of tasks, including drug delivery, bioproduction of valuable compounds, and environmental sensing.

What's new about the UC San Diego control strategy of the *E. coli* that serve as workhorses of synthetic biology? The bacterial cells within a population are engineered to be unable to communicate with each other through chemical signals unless one particular external molecule is present.

This work is published in the March 4, 2020 issue of the journal *Nature Communications*.

"We hope that this system can increase control and safety of synthetic genetic circuits, and therefore facilitate their transition to real life applications," said Arianna Miano, a UC San Diego bioengineering Ph.D. student and the first author on the *Nature Communications* paper.

This work is from the UC San Diego lab led by Jeff Hasty, who is a professor of bioengineering at the Jacobs School of Engineering, and of biology in the Division of Biological Sciences.

Traditionally, synthetic biologists use native bacterial communication systems, known as quorum sensing, to control the bacterial communities they use for tasks such as targeted drug delivery.

Quorum sensing in bacteria is based on the production, diffusion and reception of small signaling molecules between bacterial cells within a population. The majority of these systems rely on the internal resources of each cell for the production of the signaling molecule.

One of the challenges of quorum sensing systems is that they are hard to externally regulate. To address this issue, the UC San Diego researchers created an "inducible quorum sensing system." It is designed to give synthetic biologists better control of bacterial communication systems—and thus better control of the useful tasks these bacterial communities are performing.

Inspired by a genetic circuit found in the photosynthetic bacterium Rhodopseudomonas palustris and first described in the academic literature in 2008, the UC San Diego researchers created a quorum sensing system that only functions when the bacterial are provided with a plant-derived compound called p-coumaric acid. This compound is found in most fruits and vegetables.

"The bacteria coordinate differently according to how much of the p-coumaric acid we provide in the media," said Miano. "If we give no p-coumaric acid, the bacteria can't communicate with each other, but when we provide them with medium concentrations they are able to signal and share information on the size of their colony."

"If we give them too much, they over-produce signaling molecules which tricks them into behaving as if they were always part of a large population," said Miano.

The UC San Diego bioengineers demonstrated their inducible quorum sensing circuit, which can control bacterial cell coordination in time and space, by co-expressing it with a lysis gene.

The choice to demonstrate via a lysis gene builds on previous projects from the Hasty lab at UC San Diego, including research demonstrating how bacteria lysis could be used to deliver cancer-killing drugs around a tumor.

In the new work, the UC San Diego researchers demonstrated how the inducible quorum sensing could greatly expand control over this cargo delivery platform, compared to currently available native quorum sensing systems.

In particular, the researchers used low and medium concentrations of p-coumaric acid to cause populations of bacteria with both the new inducible quorum sensing circuit and the lysis gene to switch between no delivery and steady oscillations of cargo delivery.

Using a lysis gene and traditional quorum sensing system, the cargo would only be delivered when the bacteria reached a high enough concentration.

"We have just scratched the surface of the potential of this communication system. We are excited to see the applications that will follow by coupling it to the expression of different genes," said Miano.

The researchers also demonstrated that subjecting bacteria to high concentrations of p-coumaric acid wiped out all the cells by forcing them to constantly produce the lysis proteins, independent of population size. (See video)

More information: Arianna Miano et al, Inducible cell-to-cell signaling for tunable dynamics in microbial communities, *Nature Communications* (2020). DOI: 10.1038/s41467-020-15056-8

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