Engineered swarmbots rely on peers for survival

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Duke University researchers have engineered microbes that can't run away from home; those that do will quickly die without protective proteins produced by their peers.

Dubbed "swarmbots" for their ability to survive in a crowd, the system could be used as a safeguard to stop genetically modified organisms from escaping into the surrounding environment. The approach could also be used to reliably program colonies of bacteria to respond to changes in their surrounding environment, such as releasing specific molecules on cue.

The system is described online February 29, 2016, in *Molecular Systems Biology*.

"Safety has always been a concern when modifying bacteria for medical applications because of the danger of uncontrolled proliferation," said Lingchong You, the Paul Ruffin Scarborough Associate Professor of Engineering at Duke University.

"Other labs have addressed this issue by making cells rely on unnatural amino acids for survival or by introducing a 'kill switch' that is activated by some chemical," You said. "Ours is the first example that uses collective survival as a way of intrinsically realizing this safeguard."

In the experiment, You and his colleagues engineered a non-pathogenic strain of *E. coli* to produce a chemical called AHL. They also modified

the cells so that, in high enough concentrations, AHL causes them to produce an antidote to antibiotics. When the population of *E. coli* is dense enough, the antidote keeps them alive, even in the presence of antibiotics that would otherwise kill them.

The researchers then confined a sufficiently large number of the bacteria to a capsule and bathed it in antibiotics. As long as the *E. coli* remained inside their container where their density was high, they all survived. But if individual bacteria escaped, they were quickly killed off by the antibiotic.

While this specific example would not work in general environments without the antibiotic present, You says that the experiments are a proof of concept. The concept can be applied to other circuits that can implement collective survival in one or multiple populations.

"In general, this concept does not depend on the use of antibiotics," said You. "There are multiple directions we are hoping to follow with this platform. We're using non-pathogenic *E. coli*, but we hope to demonstrate that the same concept can be established with a probiotic strain of bacteria."

"We can imagine programming probiotics that can respond to changes in their environmental conditions," said Shuqiang Huang, a postdoctoral associate in You's lab. "That response could include delivering proteins or chemicals to modulate the microbiome."

Another way to take advantage of the technology would be to insert a contained population of bacteria that could help the body respond to intruders.

"We want to program cells to respond to signals produced by pathogenic bacteria," said Anna Lee, a graduate student in You's lab, who plans to

pursue this line of research for her doctoral thesis. "We could inhibit their virulence and attack them at the same time."

"This is the foundation," said You. "Once we've established the platform, then we have the freedom to introduce whatever proteins we choose and allow these cells to engage in many different applications."

More information: "Coupling spatial segregation with synthetic circuits to control bacterial survival." Shuqiang Huang, Anna Lee, Ryan Tsoi, Feilun Wu, Ying Zhang, Kam Leong, and Lingchong You. *Molecular Systems Biology*, Online Feb. 29, 2016. DOI: 10.15252/msb.20156567

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