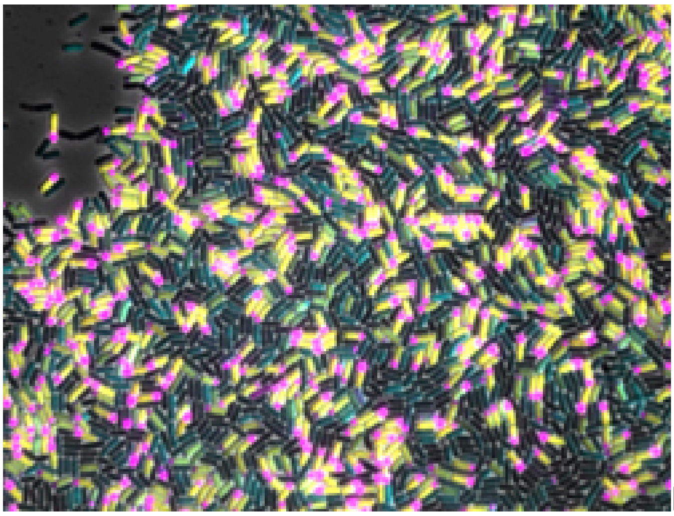
Deciphering bacterial doomsday decisions



Like a homeowner prepping for a hurricane, the bacterium *Bacillus subtilis* uses a long checklist to prepare for survival in hard times. In a new study, scientists at Rice University and the University of Houston uncovered an elaborate mechanism that allows *B. subtilis* to begin preparing for survival, even as it delays the ultimate decision of whether to "hunker down" and withdraw into a hardened spore.

The new study by computational biologists at Rice and experimental biologists at the University of Houston is available online in the *Proceedings of the National Academy of Sciences*.

"The gene-expression program that *B. subtilis* uses to form spores involves hundreds of genes," says Oleg Igoshin, lead scientist on the study and professor of bioengineering at Rice. "Many of these genes are known and have been studied for decades, but the exact mechanism that *B. subtilis* uses to make the decision to form a spore has remained a mystery."

B. subtilis is a common soil bacterium that forms a spore when food runs short. Spore formation involves dramatic changes. The cell first asymmetrically divides within its outer wall, forming one large chamber and one small one. As spore formation progresses, one chamber envelopes the other, which becomes a vault for the organism's DNA and a small set of proteins that can "reboot" the organism when it senses that outside conditions have improved.

B. subtilis is harmless to humans, but some dangerous bacteria like anthrax also form spores. Scientists are keen to better understand the process, both to protect public health and to explore the evolution of complex genetic processes.

During spore formation, scientists know that a bacterium channels its energy into producing proteins that help prepare the cell to become a spore. Many of these spore-forming proteins are required in a specific sequential order, and some are "master regulators," proteins that initiate and control entire subroutines of the spore-forming program.

"Sporulation is a complex and mysterious process," Igoshin says. "For example, some cells choose to become spores and others don't—even if they are exposed to the same conditions. Even more intriguing is the fact that some cells begin the process of converting into spores only to turn back and revert to normal behavior."

To decipher how *B. subtilis* decides to form a spore, Igoshin and Rice graduate student Jatin Narula created a set of sophisticated computer models that recreated the organism's genetic controls. The results from the computer model were compared and refined based on experimental observations by UH's Masaya Fujita and Seram Devi.

"The master regulator Spo0A is responsible for kicking off the process of spore formation, and our initial hypothesis was that this was the key player involved in the decision to become a spore," Igoshin says. "We found that the decision-making process was considerably more complex."

Signal processing in bacteria is complicated because the amount of information that their network can receive and process is related to the number of molecules inside the cells. The tiny size of the bacterial cell therefore leads to very noisy signals. The problem is akin to the challenge a political pollster would face in attempting to predict the outcome of a national election based on interviews with only 50 voters.

"It's a statistical sampling problem," Igoshin says. "Because the bacterial cell is small, master regulator genes have to contend with very noisy signals. One way to overcome the problem is to average the signals over a long period of time. We examined whether *B. subtilis* did this in making the decision to form a spore, but we found that if the cell waited for a clear signal, it may not complete the complicated spore-forming program before it would die."

Instead, the cell kicks off the spore-forming process and begins making preparations, even as it continues to perform its statistical sampling. The paper's authors found that a key to this process is a series of nested "feed forward" loops—network motifs in which one master regulator controls another by directly regulating its amount and indirectly regulating its activity.

"Cells have an ingenious strategy, which allows them to change their mind and process information while they are executing the program," Narula says. "This strategy allows them to make an accurate decision without delaying their decision just to average noisy signals."

Source: Rice University [1]

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