Researchers study code that allows bacteria to either bet on the present or travel in time

April 22 2013, by Jade Boyd

(Phys.org)—Individual freedom and social responsibility may sound like humanistic concepts, but an investigation of the genetic circuitry of bacteria suggests that even the simplest creatures can make difficult choices that strike a balance between selflessness and selfishness.

In a study published online this week in the journal *Scientific Reports*, researchers from Rice University's Center for Theoretical Biological Physics (CTBP) and colleagues from Tel Aviv University and Harvard Medical School show how sophisticated genetic circuits allow an individual bacterium within a colony to act on its own while also ensuring that the colony pulls together in hard times.

"Our findings suggest new principles for collective decisions that allow both random behavior by individuals and nonrandom outcomes for the population as a whole," said study co-author Eshel Ben-Jacob, a senior investigator at CTBP and adjunct professor of biochemistry and cell biology at Rice. "These new principles could be broadly applicable, from the study of cancer metastasis to the study of collective decisions by humans during times of stress."

Some species of bacteria live in complex colonies that can contain millions of individual cells. An increasing body of research on bacterial colonies has found that members often cooperate—even to the point of sacrificing their lives—for the survival of their colony. For example, in response to extreme stress, such as starvation, most of the individual cells in a colony of the bacteria Bacillus subtilis will form spores. Spore formation is a drastic choice because it requires the cell to kill itself to encase a copy of its genetic code in a tough, impervious shell. Though the living cell dies, the spore acts as a kind of time capsule that allows the organism to re-emerge into the world of the living when conditions improve.

"This time-travel strategy of waiting and safeguarding a copy of the DNA in the spore ensures the survival of the colony," Ben-Jacob said. "But there are other, less desperate options that B. subtilis can take to respond to stress. Some of these cells turn into highly mobile food seekers. Others turn cannibalistic, and about 10 percent enter a state called 'competence' in which they bide their time and bet on present conditions to improve."

Scientists have long been curious about how bacteria decide which of these paths to pursue. Years of studies have determined that each individual constantly senses its environment and continuously sends out chemical signals to communicate with its neighbors about the choices it is making. Experimental studies have revealed dozens of regulatory genes, signaling proteins and other genetic tools that cells use to gather information and communicate with one another.

"Bacteria don't hide their intentions from their peers in the colony," said study co-author José Onuchic, co-director of CTBP, Rice's Harry C. and Olga K. Wiess Professor of Physics and Astronomy and professor of chemistry and biochemistry and cell biology. "They don't evade or lie, but rather communicate their intentions by sending chemical messages among themselves."

Individual bacteria weigh their decisions carefully, taking into account the stress they are facing, the situation of their peers, the statistics of how many cells are sporulating and how many are choosing competence, Onuchic said. Each bacterium in the colony communicates via chemical "tweets" and performs a sophisticated decision-making process using a specialized complex gene network comprised of many genes connected via complex circuitry. Taking a physics approach, Onuchic, Ben-Jacob and study co-authors Mingyang Lu, Daniel Schultz and Trevor Stavropoulos investigated the interplay between two components of the circuitry—a timer that determines when sporulation occurs and a two-way switch that causes the cell to choose competence over sporulation.

"We found that the sporulation timer and the competence switch work in a coordinated fashion, but the interplay is complex because the two circuits are affected very differently by noise," said Schultz, a postdoctoral fellow at Harvard Medical School and a former graduate student at CTBP.

Noise results from random fluctuations in a signal; every circuit—whether genetic or electronic—responds to noise in its own way. In the case of B. subtilis, noise is undesirable in the sporulation timer but is a necessity for the proper function of the competence switch, the researchers said.

"Our study explains how the two opposite noise requirements can be satisfied in the decision circuitry in B. subtilis," Onuchic said. "The circuits have a special capacity for noise management that allows each individual bacterium to determine its fate by 'playing dice with controlled odds.'"

Ben-Jacob said the timer has an internal clock that is controlled by cell stress. The noise-intolerant timer typically keeps the competence switch closed, but when the cell is exposed to stress over a long period of time, the timer activates a decision gate that opens brief "windows of opportunity" in which the competence switch can be flipped.

Thanks to its architecture, the gate oscillates during the window of opportunity, he said. At each oscillation, the switch opens for a short time and grants the cell a short window in which it can use noise as a "roll of the dice" to decide whether to escape into competence.

"The ingenuity is that at each oscillation the cell also sends 'chemical tweets' to inform the other cells about its stress and attempt to escape," said Ben-Jacob, the Maguy-Glass Professor in Physics of Complex Systems and professor of physics and astronomy at Tel Aviv University. "The tweets sent by others help regulate the circuits of their neighbors and guarantee that no more than a specific fraction of cells within the colony will enter into competence."

Onuchic said the decision-making principles revealed in the study could have implications for synthetic biologists who wish to incorporate sophisticated decision systems as well as for cancer researchers who are interested in exploring the decision-making processes that cancer cells use in choosing to become dormant or to metastasize.

"This represents a real fusion of ideas from statistical physics and biology," he said.

More information: A copy of the *Scientific Reports* article is available at: www.nature.com/srep/2013/13041 … /full/srep01668.html

Provided by Rice University

provided for information purposes only.