Lucky bacteria strike it rich during formation of treatment-resistant colonies

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In biology, we often think of natural selection and survival of the fittest. What about survival of the luckiest? Like pioneers in search of a better life, bacteria on a surface wander around and often organize into highly resilient communities, known as biofilms. It turns out that a lucky few bacteria become the elite cells that start the colonies, and they organize in a rich-get-richer pattern similar to the distribution of wealth in the U.S. economy, according to a new study by researchers at UCLA, Northwestern University and the University of Washington.

The study, to be published online May 8 in the journal *Nature*, is the first to identify the strategy by which bacteria form initial colonies in biofilms. The research may have significant implications for battling stubborn bacterial infections that do not respond to powerful drugs, as well as for other applications.

Biofilms are colonies of bacteria that form on surfaces, including human tissue. Bacteria in biofilms change their gene expression patterns and are far more resistant to antibiotics and the body's immune defenses than individual, free-swimming bacteria, because they mass together and surround themselves with a matrix of proteins, DNA and sugars. This makes seemingly routine infections potentially deadly.

Gerard Wong, a professor in the UCLA bioengineering and chemistry departments; Erik Luijten, an associate professor of applied mathematics and of materials science and engineering at Northwestern University; and Matthew R. Parsek, a professor of microbiology at the

University of Washington, led a team of researchers who elucidated the early formation of biofilms by using algorithms to track the development of different strains of the bacterium *Pseudomonas aeruginosa* and by conducting computer simulations to map the movements. *P. aeruginosa* can cause lethal, difficult-to-treat infections. Examples include infections found in cystic fibrosis and AIDS patients.

Surprisingly, the researchers found that the individual bacteria that start the formation of micro-colonies have no special inherent qualities.

As bacteria move across a surface, they leave trails composed of a specific type of polysaccharide, or long sugar molecules.

"Some of the bacteria remained fixed in position," Parsek said, "but some moved around on the surface, apparently randomly but leaving a trail that influenced the surface behavior of other bacteria that encountered it."

Bacteria arriving later also lay trails, but tend to be guided by the trails from the pioneers. This network of trails creates a process of positive feedback and enables bacteria to organize into micro-colonies that mature into biofilms. By being at the right place at the right time, and by using communally produced polysaccharides, a small number of lucky cells—often ones that come later—become the first to form micro-colonies, which give cells many survival advantages over other bacteria.

Interestingly, these biofilms develop in accordance with Zipf's Law, which is one special form of the rich-get-richer phenomena. A well-known example of this is the distribution of wealth in the United States. Recent statistics indicate that the wealthiest 20 percent of the population have more than 80 percent of the total wealth. Most of the wealth in this elite group is in turn owned by a small elite fraction within the elite, and so on.

"It turns out bacteria do the same thing," Wong said. "By effectively taking a census of bacteria using our recently developed methods, we find that the way they organize into micro-colonies is not random, as was previously thought."

Extending the economic analogy, Wong said the research may provide insight into how to fight antibiotic-resistant bacteria. "Typically, when we want to get rid of bacteria, we just kill them with antibiotics," he said. "As a result, they develop defense mechanisms and grow stronger. Maybe that's not always the best way to treat biofilms. Perhaps we can regulate bacterial communities the way we regulate economies. Our work suggests that new treatment options may use incentives and communications as well as punishment to control bacterial communities."

"A truly beautiful aspect of this work is how it relies on a combination of experiments and computer simulations," Luijten said. "Only through combination of the totally different types of expertise of three different research groups has it been possible to disentangle what is going on, and how polysaccharides influence the organization of bacteria into micro-colonies."

More information: Psl trails guide exploration and microcolony formation in Pseudomonas aeruginosa biofilms, DOI: 10.1038/nature12155

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