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How bacterial communication 'goes with the flow' in causing infection, blockage

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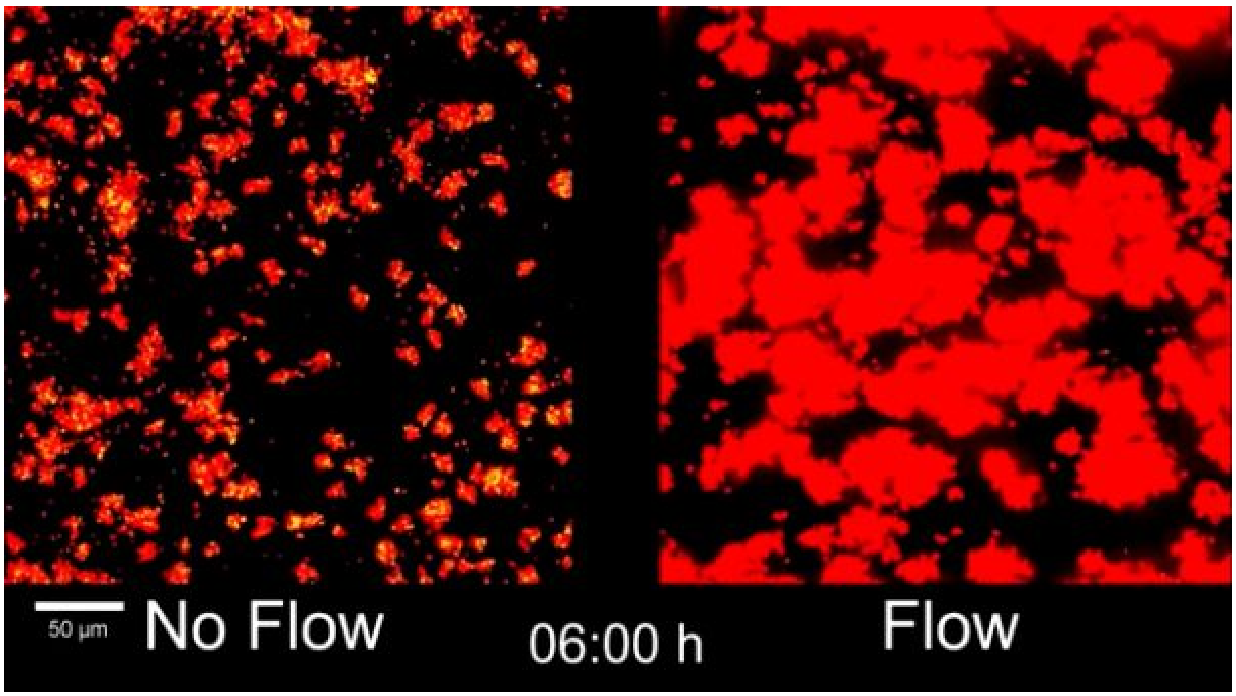

The destructive ability of bacteria to organize an infection or block pathways such as intestines, medical stents and wastewater pipes relies on communication with one another.

New work from Princeton University researchers shows that the effectiveness of [bacteria](#)'s ability to keep in touch is influenced by the physical characteristics and flow of fluid in the environments they're invading. The findings provide a better understanding of where and when in a system scientists can interfere with bacterial communication to help prevent infections and blockages.

The researchers simulated real-life environments in the laboratory and found that the shape of the spaces and the flow of fluids through them affected bacterial growth and the formation of slimy surface layers called biofilms. Published in the journal *Nature Microbiology*, the study also found that fluid flow can determine where and when bacteria begin to act as disease-causing agents.

Bacteria communicate through a chemical process called quorum sensing , in which they release molecules that serve as messages detected by nearby bacteria. Most studies of this process, however, have been done under controlled laboratory conditions, explained co-corresponding author Bonnie Bassler, Princeton's Squibb Professor of Molecular Biology and an investigator with the Howard Hughes Medical Institute. Bassler, a molecular biologist, worked with Princeton colleagues with expertise in engineering and chemistry to explore quorum sensing in settings that more accurately resemble real-world situations.

"We realized that if we are going to learn how to manipulate quorum sensing on demand to find ways to treat disease, we have to know how it works in realistic settings," Bassler said. "The eventual goal of this research is to alter quorum sensing in ways that destroy harmful bacteria, and benefit desirable bacteria."

In these real-world situations, fluid flow can interfere with the delivery of the chemical messengers used in quorum sensing, said co-corresponding author Howard Stone, Princeton's Donald R. Dixon '69 and Elizabeth W. Dixon Professor of Mechanical and Aerospace Engineering. "If you have sufficient flow, it can wash away a chemical before your neighbor knows it is there," Stone said.

First author Minyoung Kevin Kim, a graduate student in Princeton's Department of Chemistry, built experimental devices that mimicked common environments in which bacteria are subjected to the flow of liquids such as wastewater or bodily fluids: the interior surfaces of pipes, the crevices found in the lining of the intestines, and surfaces coated with biofilms, among others. Co-author Francois Ingremeau, a former postdoctoral researcher in mechanical and aerospace engineering at Princeton who is now at the University of Grenoble in France, also conducted significant experimental and modeling work related to quorum-sensing response to fluid flow.

Kim introduced a flow of fluid at speeds comparable to those found in real life. He studied two types of disease-causing bacteria, Vibrio cholerae—the infectious agent behind cholera—and Staphylococcus aureus, which can cause various infections such as abscesses and hospital infections. In each situation, the researchers found that the level and location of quorum sensing depended on the three-dimensional shape of the physical space combined with the flow conditions.

In one experiment, the researchers confirmed previous observations that moving fluids can repress quorum sensing by carrying away messenger molecules. This finding helps explain why robust biofilms form under flow conditions in pipes, the researchers said. What is more, the transported quorum-sensing molecules can find their way to bacteria downstream and establish long-range communication between bacterial cells, the researchers found. This sort of communication may occur in pipes, across colonies of soil bacteria, and in the intestinal tract of animals, potentially aiding the spread of disease.

In addition, quorum-sensing molecules at the base of biofilms are protected from fluid flow and can be detected by neighboring cells, the researchers observed. Cells that receive these quorum-sensing messages can then kick off a gene-expression program that enables bacteria to break free of the biofilm, travel via the flowing fluid to new sites and potentially spread infection to new sites.

The researchers also investigated quorum sensing in crevices, such as pockets in the intestinal lining known as crypts. Sheltered from flow at the bottom of the crypt, quorum-sensing molecules can travel between bacteria, but molecules near the top of the crypt are carried away. This conforms to what is known about how S. aureus causes disease, Kim said.

"Inside crypts, the bacteria engage in quorum sensing and activate the production of a toxin called enterotoxin B, which functions to increase the depth of the crypt," Kim said. "According to our findings, this activity further insulates S. aureus from flow, which is a mechanism that presumably enables quorum-sensing control of pathogenicity, specifically inside crypts."

To explore the health consequences of quorum sensing in the crypts, the researchers introduced into the flow a molecule that acts as an antagonist to turn off quorum sensing in chambers colonized by the well-known scourge of hospitals, methicillin-resistant S. aureus, or MRSA. The researchers' antagonist molecule—synthesized by co-author Aishan Zhao, a graduate student in chemistry—diffused in the crevices and inactivated quorum sensing, which suggested that it could be used as a potential strategy for alleviating MRSA virulence.

The researchers concluded that identical bacterial strains—exposed to flowing liquids and in oddly shaped spaces—can experience widely different levels of quorum sensing, leading to complex patterns of pathogenesis and colonization. "This was one of the surprising findings from the study," Kim said.

More information: The paper, "Local and global consequences of flow on bacterial quorum sensing," was published Jan. 11 in the journal Nature Microbiology.

Provided by Princeton University

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