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HOW BLUE WATERS IS AIDING THE FIGHT AGAINST SEPSIS

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EXECUTIVE SUMMARY

Owing to their high occurrence in ever more common hospital-acquired infections, studying the mechanisms of infection by *Staphylococcus epidermidis* and *Staphylococcus aureus* is of broad interest. These pathogens can frequently form biofilms on implants and medical devices and are commonly involved in sepsis—the human body's often deadly response to infections.

Central to the formation of biofilms is very close interaction between microbial surface proteins called adhesins and components of the extracellular matrix of the host. The research team uses Blue Waters to explore how the bond between staphylococcal adhesin and its human target can withstand forces that so far have only been seen in covalent bonds. The team uses a synergistic combination of computational and experimental methods. This approach is essential to elucidating the mechanism by which an intricate network of hydrogen bonds makes the staphylococcal adhesion ultrastable, revealing possible routes for the development of antimicrobial strategies.

RESEARCH CHALLENGE

Antibiotics are increasingly powerless against a growing number of "super bacteria" that have evolved to survive humankind's pharmacological offensive. The shortage of new medicines to treat what the U.S. Centers for Disease Control calls "nightmare bacteria" is evident. Public health agencies across the world have begun warning of the consequences of a postantibiotic era in which a common infection could, once again, become a death sentence.

The fight against sepsis, the human body's often deadly response to bacterial infections, has become the topic of nationwide campaigns in the United States. Exploring the mechanism by which bacteria initiate infections is, therefore, key to developing new antimicrobial therapies. Investigations at the molecular level of the mechanism of adhesion between *Staphylococcus epidermidis* and *Staphylococcus aureus* and the extracellular matrix of their human hosts could lead to a detailed understanding of adhesion, one of the first steps of staph infections. This understanding may, in turn, allow researchers to develop possible competitors for their interaction with humans, stopping infection at its early stages.

METHODS & CODES

The research uses single-molecule force spectroscopy along with all-atom steered molecular dynamics (SMD) simulations to investigate with exquisite precision the mechanics of interaction between SdrG and Fgβ. SdrG is an SD-repeat protein G and is one of the adhesin proteins of *Staphylococcus epidermidis*. Fgβ is the human fibrinogen β and is a short peptide that is part of the human extracellular matrix.

For SMD molecular dynamics simulations, the team uses Blue Waters' GPU nodes (XK) and the GPU-accelerated NAMD package. In a wide-sampling strategy, the team carried out hundreds of SMD runs for a total of over 50 microseconds of simulation. To characterize the coupling between the bacterial SdrG protein and the Fgβ peptide, the team conducts SMD simulations with constant velocity stretching at multiple pulling speeds. The SMD procedure is inspired by experimental approaches and is equivalent to attaching one end of a harmonic spring to the end of a SdrG protein and pulling on the Fgβ peptide. To quantify the strength of interaction between the two molecules, the force applied to the harmonic spring is recorded at regular intervals.

RESULTS & IMPACT

The steered molecular dynamics simulations performed on Blue Waters revealed, and single-molecule force spectroscopy experiments confirmed, the mechanism by which this complex withstands forces previously only associated with the strength of a covalent bond. The target human peptide (Fgβ), confined in a screwlike manner in the binding pocket of the bacterial adhesin protein (SdrG), distributes forces mainly toward the peptide backbone through an intricate hydrogen bond network. This behavior allows SdrG to attach to Fgβ with exceptionally resilient mechanostability, virtually independent of the peptide's side chains.

This unexpected mechanism expands the understanding of why pathogen adhesion is so resilient, which may open new ways to inhibit staphylococcal invasion. The development of anti-adhesion therapy could block the first steps of biofilm formation by staph bacteria, facilitating bacterial clearance. Understanding the mechanism of staph infection at the atomic level may also open new avenues for an intelligent design of antimicrobial therapies.

The research team's initial findings were published in *Science* in 2018 [1]. Currently, the team is working on developing a new protocol for finding peptides with a higher affinity for staphylococcal adhesins. The initial results are promising, and a peptide sequence with a slightly higher affinity has already been identified.

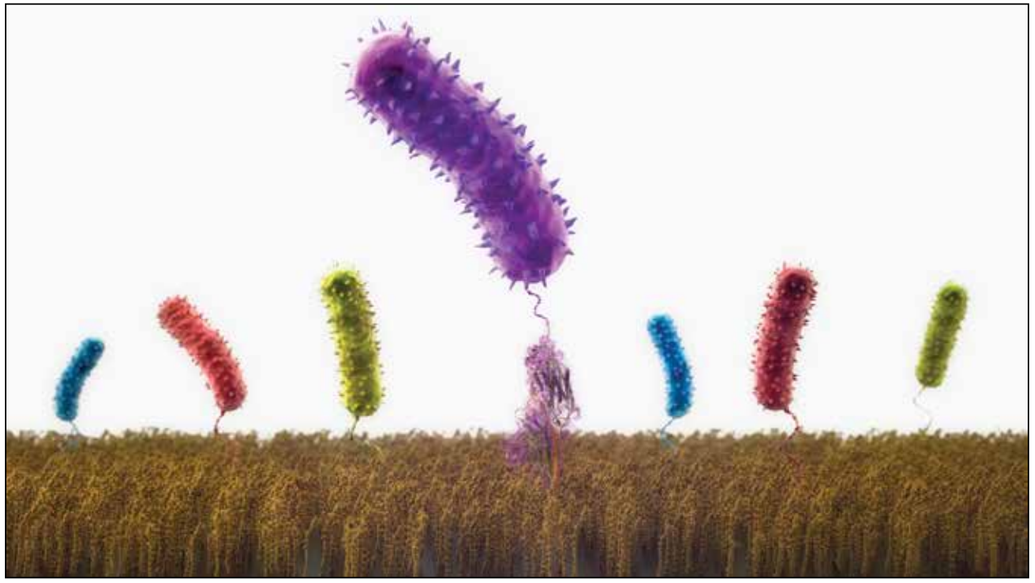

Figure 1: Staph bacteria (shown as colorful rods) adhere to their human hosts (surface at the bottom) with exceptional mechanical resilience. By combining experimental and computational approaches, the research team is deciphering the physical mechanisms that underlie the persistent stickiness of these bacterial adhesins (translucent purple structures), a major step in combating such invaders.

WHY BLUE WATERS

The research group's work depends on obtaining multiple simulation replicas with a fast turnaround time. This approach allows the team to quickly test any and all hypotheses both computationally and experimentally. For this work, the team uses Blue Waters GPU (XK) nodes and CUDA-accelerated molecular dynamics software NAMD.