Researchers resolve structure of a key component of bacterial decision-making

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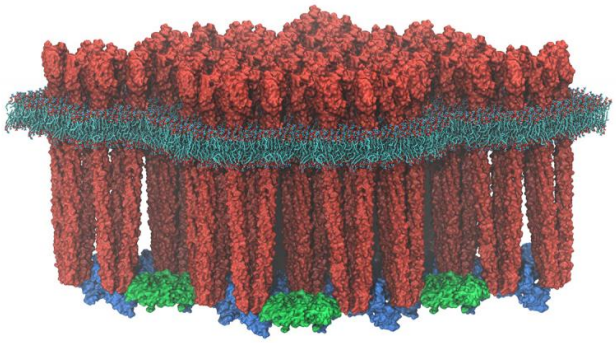

Bacterial chemotaxis, the process by which a bacterium changes direction in response to environmental cues, involves a complex array of chemical receptors (red, elongated molecules) and other sensory proteins (blue and green molecules), which work together to process sensory information. A new study offers high-resolution details of the structure and function of the chemosensory array, researchers report. Credit: C. Keith Cassidy

For bacteria that swim, determining whether to stay the course or head in a new direction is vital to survival. A new study offers atomic-level details of the molecular machinery that allows swimming bacteria to sense their environment and change direction when needed.

The study, reported in the journal *eLife*, represents a major step in understanding the "bacterial brain," said University of Illinois physics professor Klaus Schulten, who led the new research.

"On its surface, a bacterium has thousands of receptors that scan the environment and then tell it what to do," he said. This is very much like the sensory input that all animals must process. Of course, bacteria are single-celled organisms and don't have brains, he said. But they nonetheless manage to organize and "remember" sensory signals long enough to respond to them in a way that aids their own survival.

The receptors on the surface of a bacterial cell detect light, chemicals, edible things and poisonous things, and transmit that information to a deeper layer of proteins, called kinases, which interpret this data and translate it into a simple choice: "Keep going" or "Change direction!"

If the latter decision is made, a kinase hands off a potent chemical signal - a phosphate - to a second kinase, called CheY (KEY why), which then detaches, finds its way to the flagella and activates a process that causes the flagella to reverse their spin.

"That makes the bacterium tumble and go in a new, random direction, which may be better than the previous direction," Schulten said.

Previous studies have yielded key insights into the structure of the molecular machine that orchestrates this feat, the chemosensory array. Electron microscopy of the inner and outer surfaces of bacterial cells gives some clues, and crystallography - a process that involves stacking purified proteins into crystals so that their three-dimensional characteristics can be measured - provides others. But the fuzzy resolution of the EM snapshots leaves a lot of room for interpretation, and the crystals can resolve only small portions of the array's constituent proteins.

Study co-author, experimentalist Peijun Zhang of the University of Pittsburgh, aided this effort by developing a technique to purify the key proteins in the array and combine them in just the right proportions so that they assemble themselves in thin layers - allowing clearer 3-D EM snapshots of their structural conformations and interactions with each other. This vastly improved the resolution of the data.

To resolve the picture of the chemosensory array, Schulten and his colleagues used molecular dynamic flexible fitting, a computer modeling approach Schulten's lab developed at Illinois. MDFF simulates the chemical interactions of every atom in a system and makes use of what is known about the structure from EM, crystallography and other experimental data. Such large-scale modeling and simulation requires the heft of a supercomputer, and for this effort the team used Blue Waters at the National Center for Supercomputing Applications at the U. of I.

The new study revealed key chemical interactions between the proteins that make up the chemosensory array, and offered new insights into the behavior of these proteins. For example, it revealed for the first time that one region of a kinase called CheA (KEY aye), changes its orientation in relation to the other proteins, in a motion the researchers call "dipping." Further experiments revealed that this part of the kinase is essential to the process that allows a bacterium to respond to its environment and change direction.

"A big question in the field is: How does the signal pass from the receptors to the kinases? What is actually happening?" Schulten said. "It has to be a motion. It can't be anything else. But what kind of motion?"

More work is needed to determine the relationships and behavior of all of the components of the system, but the new study represents a major gain in comprehension, Schulten said. He compares the process of discovery to that of someone encountering a mechanical clock for the first time.

"To know how this mechanical system works, we need to know the structure," he said. "Once we open the clock, see how the gears fit together, then we can start thinking about how the clock actually works. The gears of the bacterial brain are now in place."

More information: C Keith Cassidy et al. CryoEM and computer simulations reveal a novel kinase conformational switch in bacterial chemotaxis signaling, *eLife* (2015). DOI: 10.7554/eLife.08419

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