The Road to La-La Land

General anesthesia is one of the wonders of medicine. The ability to induce a deeply unconscious, immobile state makes possible life-saving procedures no one could have imagined 150 years ago, when surgeons were “saw-bones” and tooth extraction or amputation of a limb was excruciating beyond description. An estimated 15 million Americans undergo general anesthesia annually. Despite advances in pharmacology and wide use, however, no one can tell you how anesthetics do what they do.

“General anesthesia is one of the most important tools of medicine, and yet it remains mysterious,” says Pei Tang, a physical chemist and assistant professor of anesthesiology and pharmacology at the University of Pittsburgh School of Medicine (UPSM). “Despite years of research, we still don’t understand the molecular mechanism.”

It’s an alluring mystery. Understanding the molecular details would likely lead to better anesthetics, with fewer side effects, but perhaps even more importantly it should tell us something about consciousness itself, one of the grandly intriguing questions in science.

Tang is part of a UPSM team that uses a range of techniques to investigate how anesthetics work. In collaboration with Pittsburgh Supercomputing Center scientists Marcela Madrid and Troy Wymore, she has used computational methods to simulate how the drugs interact with the cellular membranes where they have their effect. The results of these studies challenge accepted thinking and offer support for an emerging new hypothesis.

A TALE OF TWO THEORIES

In the normal, undrugged state of consciousness, sense perceptions trigger a chain of events that releases electrical signals in the form of ion flow — sodium, calcium, potassium and other ions — through channels in the cell walls, better known to biologists as membranes. General anesthetics appear to exert their effect by changing ion flow through these membrane channels, either slowing it down or speeding it up. Thinking about how this happens falls generally into two schools: the lipid theory and the protein theory.

The lipid theory, the older point of view, says that general anesthetics work by their ability to dissolve in lipids, the fat that forms the cell membrane and seals it against the watery environs inside and outside the cell. Some experiments suggest that anesthetics make the lipid more fluid, a structural loosening that relaxes and changes the shape of the channels that control ion flow.

The protein theory is more recent and says, on the other hand, that general anesthetics interact directly with the channels, which are complex proteins, rather than indirectly through the lipids. Experiments have shown that a range of anesthetics have the ability to radically slow down flashes of light from a protein called luciferase, which makes the tails of fireflies glow. Luciferase doesn’t exist in cell membranes, so in this case at least, the effect is direct. Still the question is how.

In experiments with membranes, as opposed to isolated proteins, it’s extremely difficult to test the protein theory because it’s nearly impossible to disentangle direct from indirect action. For that, computational simulations, which track the atom-by-atom details of the drug-membrane-channel interactions, have the potential to break through the theoretical logjam. “Only new techniques like large-scale simulations,” says Tang, “that permit analysis at or near atomic resolution can test these theories.”

LIPIDS, DRUGS & PROTEIN IN A WATER SANDWICH

Cellular membranes are complex molecular assemblies involving tens of thousands of atoms, and only in recent years has computational capability evolved to make it feasible to simulate these structures. Starting in 1999, as the first step in a staged process, Tang used PSC’s CRAY T3E to construct and test a computational model of a cellular membrane called DMPC. The results gave structural parameters that agreed well with experimental data. For the next step, she computed the structural details and electronic properties of two frequently used general anesthetics, halothane and sevoflurane.

With this groundwork in place, Tang simulated 10 halothane molecules inside the DMPC membrane, which itself included a protein molecule, gramicidin, as an ion channel through the lipid bilayer. This very large-scale computation included 38,724 atoms and tracked the molecular movements for two nanoseconds (a billionth of a second) with a freeze-frame picture of the system every femtosecond (a millionth of a billionth of a second).

After about 240 hours of processing (on 128 CRAY T3E processors), the results show, contrary to accepted understanding, that halothane in the center of the lipid moves away from this hydrophobic environment toward the water. This result supports an emerging
hypothesis that bridges between the two competing theories and suggests that general anesthetics act at the channel-water interface.

To further test the interface hypothesis, Tang looks forward to PSC’s Terascale Computing System. She’d like to simulate other anesthetics and extend simulation time into the millisecond range. She also plans to simulate compounds structurally very similar to anesthetics but that produce no anesthetic effect. These studies, she expects, will help pinpoint the molecular events that lead to general anesthesia.

“With these simulations,” says Tang, “I believe we’ll be able to draw some conclusions that will lead us closer to solving this mystery.”

More information: http://www.psc.edu/science/tang.html

RESEARCH IN GENERAL ANESTHESIA WILL HELP IN UNDERSTANDING THE BIOCHEMICAL NATURE OF SELF AWARENESS, MAYBE THE ESSENTIAL TRAIT OF BEING HUMAN.