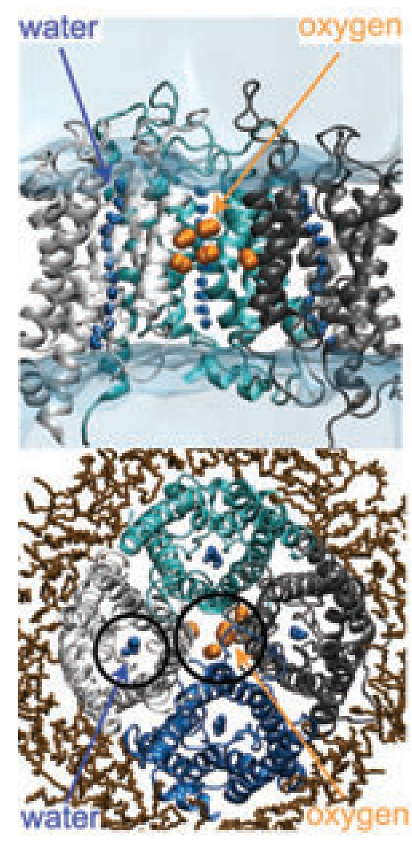
# NewsBytes




***Simulations of the aquaporin tetramer found that carbon dioxide and oxygen are exchanged through the central pore—a site of previously unknown function. Image courtesy of Emad Tajkhorshid, a faculty associate of the NIH Resource for Macromolecular Modeling and Bioinformatics, and his UIUC colleagues Klaus Schulten, Yi Wang, and Jordi Cohen.***

## Aquaporin Simulations De-Bunk Gas Exchange Assumptions

Biologists have long taken gas exchange for granted, assuming that gases simply seep through the cell's lipid membrane. Since 1998, however, evidence has been building that gases might also be exchanged through pores created by specialized proteins.

Now molecular dynamics simulations of aquaporins have weighed in on the question. The result: "It's now well established that these proteins can conduct gas molecules," says **Emad Tajkhorshid, PhD**, co-author of the work and assistant professor of biochemistry, pharmacology and biophysics at the University of Illinois at Urbana-Champaign. But, he says, some uncertainty remains: "Whether or not it's important in the human body, that's the controversial part." The work was published in the March 2007 issue of the *Journal of Structural Biology*.

Fifteen to twenty years ago, scientists believed that water permeation through lipid bilayers was enough for water transport into and out of cells. Gradually, though, researchers realized that some cells need to control water permeability, and other cells have lipid bilayers that aren't very permeable to water. Aquaporins, it turned out, carry water in and out in a controllable fashion. "I think the same might be true for gas permeability," says Tajkhorshid. "Gas permeability of a lipid bilayer is like an open free highway where everything can go through. With a protein, you can have a gating mechanism and some regulation."

One of Tajkhorshid's collaborators, **Walter Boron, MD, PhD**, professor of cellular and molecular physiology at Yale University, has been working on gas exchange experimentally for about ten years. To him, aquaporins are a likely suspect for gas conduction because they exist in places where oxygen must go in and carbon dioxide must come out. For example they are plentiful in cells that line the lung, in red blood cells, and in astrocytes—cells at the blood-brain barrier. But it's very hard to measure small changes in oxygen concentration at the surface of a membrane experimentally.

So Tajkhorshid's team pitched in with molecular dynamics simulations. Aquaporins occur in groups of four (tetramers), with four pores that conduct water (one through each aquaporin molecule) and one central pore where the molecules meet. The latter, until now, had no known function. When simulated using two complementary methods—explicit sampling with full gas permeation and implicit ligand sampling—the team found both oxygen and carbon dioxide were exchanged through that central pore. Carbon dioxide was also transmitted through the four water pores, while oxygen passed through those pores only rarely. The research also found, however, that a plain lipid bilayer conducts two and a half times as much gas as one embedded with aquaporin tetramers. "The question is whether this pathway is significant and makes any difference in terms of total permeability of the membrane," says Tajkhorshid.

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The researchers hypothesize that, as with water permeability, aquaporins may be physiologically relevant to gas exchange when cells have dense, rigid lipid bilayers or when aquaporins occupy a major fraction of the membrane.

Tajkhorshid plans to introduce point mutations inside the central pore and manipulate the behavior of a gating loop to see how that changes the conducting properties of the central pore. Meanwhile, Boron's group is looking for a system in which gas conduction through aquaporins is a major pathway. Says Tajkhorshid: "Even if it's 30 percent of total gas permeability, it becomes physiologically relevant because then you can control it."

According to **Nazih Nakhoul, PhD**, research associate professor in biochemistry at Tulane University, "This idea of gas transport through membrane proteins is really gaining support. It's interesting to see molecular dynamics simulations confirm some of the earliest findings."

***—By Katharine Miller***