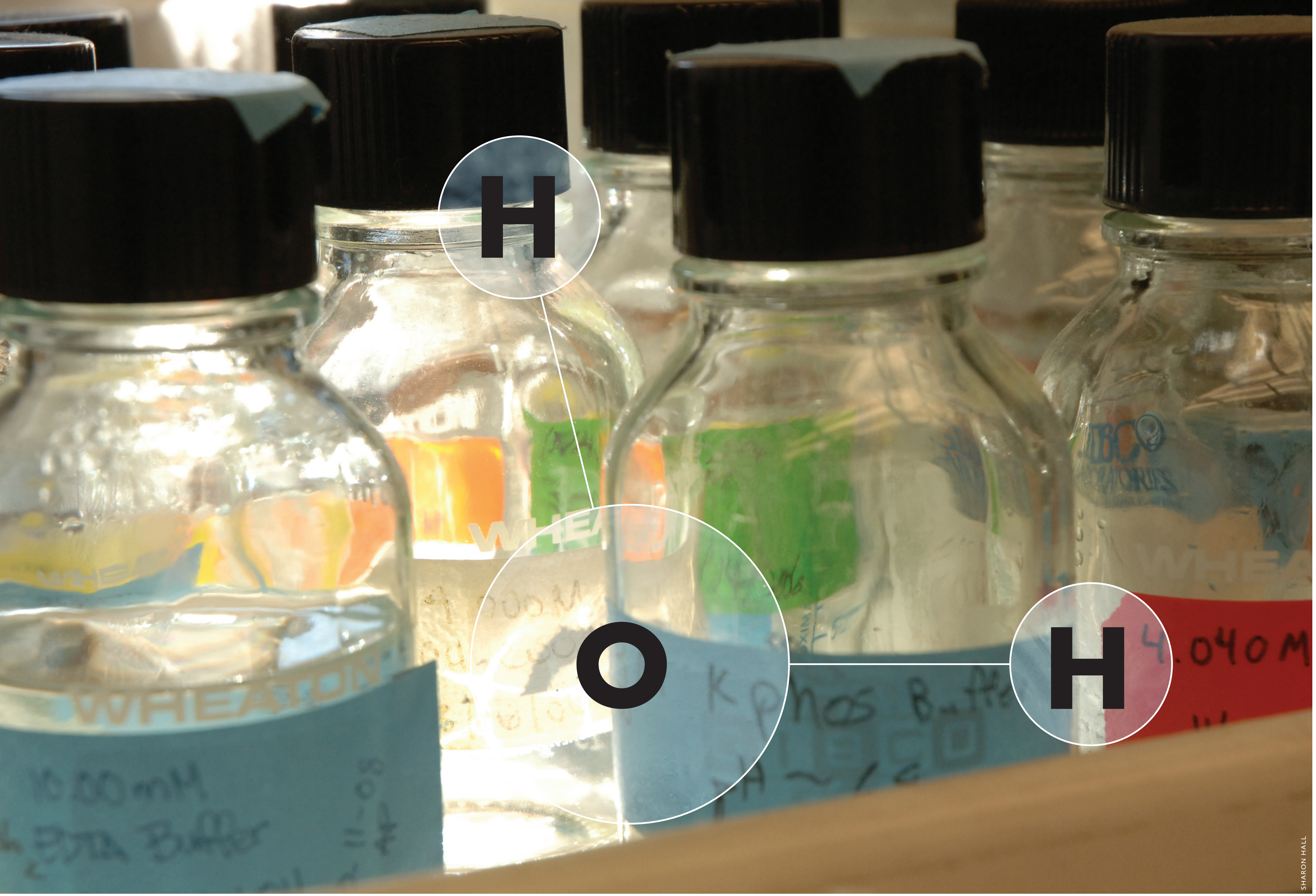


SHARON HALL

A NEW PERSPECTIVE ON WATER

Long neglected by science, H_2O gets a closer look

BY JODY ULATE

IN AN OFFICE ALONG a wide corridor papered with science posters and safety warnings, biochemist Daryl Eggers has water on his mind.

Eggers, an associate professor who shares his office with an impressive collection of SpongeBob SquarePants figurines, says the quirky cartoon sea sponge knows more about water than scientists do. In fact, he says a complete understanding of water is missing from the biochemistry textbooks packed into his ceiling-high bookcase. But he hopes his research will change that.

"Water is an extremely prominent driving force," says Eggers. "Lots of people are trying to understand it, but no one has got it yet."

Eggers thinks scientists often underestimate the importance of water, believing it to be just "filler" that allows other molecules to move around. To better understand water, Eggers is studying its effect on protein folding—the way proteins change shape before carrying out their biochemical functions. Understanding water and its effect on protein folding could have far-reaching impacts—for biochemistry and beyond.

Water is "the fluid in which all reactions that define life take place," says Eggers. When planetary scientists look for life beyond Earth's atmosphere, they're looking for evidence of water. Something about it makes life possible. And part of what makes water unique is its structure. Even the most science-averse can identify a water molecule: two parts hydrogen, one part oxygen.

"What's amazing about water is when you have groups of water molecules next to each other, they interact in a very specific way," Eggers explains. The hydrogen on one water molecule likes to touch the oxygen of its neighbor to form hydrogen bonds. All of those Hs and Os getting together is where Eggers says things get interesting.

"If you take a snapshot of a group of water molecules next to one surface versus another that is chemically different (for example, water in a glass versus a protein in water) you will see that the water's structure—the pattern of its hydrogen bonds—changes."

And the pattern keeps changing. In fact, even describing the patterns is difficult because the structure constantly moves over time, says Eggers. The idea that water's structure varies in different environments is pretty new. And if the structure changes, water can't be "just filler." It has to influence the behavior of the molecules it touches, insists Eggers. He and a team of 12 undergraduate and graduate engineering, biochemistry and biology students are taking a close look at what happens to both the water and the protein during the biochemical process of protein folding.

Proteins at work

A mid-West engineer turned California biochemist, Eggers' experience in industry piqued his interest in protein folding and paved the way for his current research. He got his introduction to proteins and the importance of how they fold at Syntex, a now-defunct Palo Alto biotech company, where one of his projects was to refold proteins. But the proteins wouldn't fold properly. "When a protein isn't folded right, it's not functional," Eggers says.

Long, chain-like molecules, protein "necklaces" are biology's workhorses. They carry out biochemical functions (as enzymes), make up hair, bone and muscle (as structural elements) and support the immune system (as antibodies). Before proteins can get to work, they fold into shapes—roundish globules, accordion-like sheets and helices, for instance.

Although protein function is well understood, scientists around the world continue to puzzle over exactly how proteins fold. What has been firmly established is that diseases like Alzheimer's, Parkinson's and Lou Gehrig's are associated with misfolded proteins.

If you've ever cooked an egg or added lemon juice to milk, you know a bit about how proteins work. Changing a protein's environment changes its folded shape, sometimes irrevocably. In these examples, changing the temperature or acidity results in scrambled eggs and curdled milk. Whether in a frying pan or in a living cell, a protein's environment is one of many factors that affect how it folds.

"In the crowded environment of a cell, there are proteins and water," Eggers explains. "And that water is going to have a different structure next to each one of those proteins' surfaces."

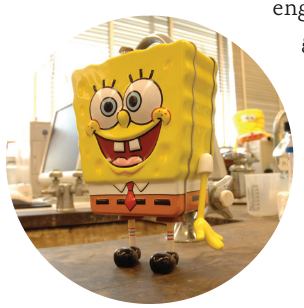
While there are other factors driving a protein to fold, establishing the impact of what Eggers calls "perturbed" water is his current focus. With Eggers' guidance, his student team changes the structure of water with different salts and then experiments with a model protein to see how it responds to the various water solutions.

Through the sol-gel glass

Eggers describes his model protein, apomyoglobin, as his "little reporter." Everywhere it is placed, it "reports" the effect of the water in its environment. A highly sensitive protein similar to oxygen-binding hemoglobin, it has been used widely in protein folding studies—meaning Eggers has plenty of data with which to compare his findings. To mimic the crowded environment of a living cell, Eggers uses a relatively new technique to create a special type of porous glass.

"The sol-gel technique is a means of making a special glass that starts out in a liquid state," explains Eggers. He and his students add apomyoglobin and other ingredients to the mix while it's a liquid, and the solid glass forms in minutes. "When the protein is added to the solution before you make it solid, the protein gets trapped in the pores."

Similar to the structure of Swiss cheese, the glass has interconnected pores that keep the proteins in place but allow the different water solutions to flow in and out. Students in lab coats, like recent engineering graduate Carlos Torres, '09, create the sol-gel glass with apomyoglobin trapped within its structure. They cut it into small rectangular sheets and put the sheets into the different water solutions to see how the apomyoglobin responds. They see firsthand if and how the protein folds and unfolds.



Torres enjoys the idea of being part of the "next big thing."

DARYL EGGERS

water impacts nearly every reaction in biology

SHARON HALL

"What we're doing is providing an alternative view of water," he says. "I like the possibility of being able to explain some of the inconsistencies in protein behavior."

Many proteins inexplicably unfold or improperly fold during experiments, but the special glass should theoretically help to keep proteins stable, Eggers says.

He compares the protein in the environment inside the glass pores to being on a crowded elevator: "You can't yawn and stretch out your arms because there are people all around you." Likewise, proteins should not be able to unfold inside the pores, so crowding should enhance the proteins' stability.

However, during his post-doctoral work at UCLA, where Eggers first experimented with apomyoglobin, he found that the protein was more unfolded inside the glass than it should have been. The water in the pores was responding to the sol-gel glass. "The unfavorable change in water structure influences everything else in the pore, including the protein," explains Eggers.

So began his interest in water structure. Currently the only scientist putting apomyoglobin in sol-gel glass, Eggers says he's taking the first steps toward getting a handle on water. Sitting on the lab's scuffed black countertop, a pair of $90,000 calorimeters (which might easily be mistaken for toaster ovens) will aid in the next step: measuring the thermodynamics, or energy, of the water during the protein folding process. Understanding how the energy changes will have broad applications.

"What I'm learning about water is very important for protein folding, but also for almost everything that goes on in a living cell," says Eggers. "Water bathes and affects all these molecules."

Water, water everywhere

Almost everything in a living cell, which contains this oft-mentioned water, happens when two entities come together and bind, says Eggers. A big protein might bind to a small protein, or a protein might bind to DNA before it's replicated, for example. According to Eggers, when that happens, the watery environment in the cell changes because the water on the surfaces of the two entities that have come together is released.

"There is some change in the energy of the water when two entities come together," he says. "Since these binding interactions are fundamental to everything in cell biology, and therefore everything in life, we need to get a better grasp of water's energetic contribution."

Including water as part of the equation means scientists will be able to better mimic biochemical reactions in a living cell. And being able to more precisely mimic the water of a living cell in a test tube could mean more accurate results in laboratories everywhere.

"A discussion of water is totally missing from textbooks, from literature, everywhere," says Eggers. "My excitement for the future is that I'm going to have a big impact when people begin to understand the importance of water."

When Eggers gives talks on his research, SpongeBob SquarePants often makes an appearance in the slide presentation. Seeing SpongeBob, who lives in water and understands its importance, helps the audience remember Eggers' take-home message: Water structure varies and has consequences for nearly every reaction in biology. In time, Eggers' research will speak for itself.

"I will really feel like I've made it when biochemistry textbooks include a discussion of water," says Eggers of his long-term goal. "There's just something exceptional about water." ❖