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> ONE MONTH, ONE PROTEIN <

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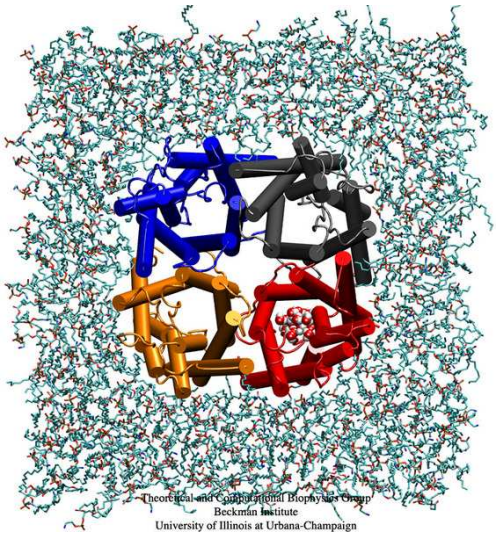
# Liquid states

**Vivienne Baillie Gerritsen**

**Though we appear to be quite solid, we are in fact quite liquid. Like all living organisms, the best part of us – roughly 70% - is water. And it needs to flow into us, out of us and inside us. We sweat water, we cry water, we digest with water, we think thanks to water and we pee water. Hundreds of litres of water go through a human kidney daily. How? Water molecules can cross cell membranes unassisted. However, such a form of transit cannot account for the huge amounts which are processed in a kidney. There must be another system. In the 1990s such a system was discovered: aquaporin. Aquaporins are proteins which are embedded within cellular or intracellular membranes and are high-tech channels specific to water molecules. And they are spread not only throughout the animal and the plant kingdom but also in bacteria.**




Top view image of aquaporin, Dr Emad Tajkhorshid

Courtesy of the NIH Resource for Macromolecular Modeling and Bioinformatics

In the 1950s, scientists were already pondering on how such huge amounts of water could diffuse through membrane lipid bilayers. Membrane diffusion is effective but slow, and could not account for it. There must exist some kind of water pore. It took a further thirty years before the very first aquaporin was discovered…and quite by chance. Scientists had been rummaging around red blood cells on the lookout for a specific Rhesus factor molecule when they stumbled upon an odd protein lodged in the plasma membrane. It turned out that this protein was a pore which let water in and out of the cell. Aquaporin has since been called the Holy Grail of fluid-transport physiology….

What does it look like? A dumbbell. Or, more precisely, an assembly of four dumbbells. One aquaporin channel is made up of four aquaporin monomers, each of which acts as a specific water pore. An aquaporin monomer has a diameter of about 30Å and a height of about 60Å. The four monomers are tightly bound and form a stable complex in the plasma membrane. Were you to unravel one, you would find six long alpha helices and two short ones. Imagine a cylinder. Take six tubes and place them vertically around the cylinder. That is the way the six helices wrap themselves around the centre. Now tie a ribbon around the centre of the pore. The ribbon forms a constriction – of about 8Å in diameter – around the middle of the structure, giving the dumbbell shape to the aquaporin monomers. In reality, there is no ribbon but molecular forces working away. The two short helices tuck themselves into the very middle of the pore and form a barrier to molecules other than water, thus making aquaporin what it is, i.e. a pore for water molecules only.

The passage of water molecules through the pores has been described as a molecular ballet. Nothing complicated. No back-breaking arabesques or hurried ‘pas de deux’. Just a smooth glide followed by a graceful pirouette. The aqueous ballerinas drift into an aquaporin

one by one and face down, i.e. the oxygen molecule faces the inside of the pore. Though perhaps 'drift' is not quite the word since one billion molecules cross a membrane…per second! Once they reach the middle of the channel, the water molecules are grabbed by side chains which line the interior of the pore and swung around so that they exit the pore, bottom down, i.e. hydrogen molecules first.

The system is ingenious and all has to do with protons. Aquaporins not only let water through but they also inhibit the transit of protons, which is a very wise move. Why? Protons are needed to charge cells; if cells lose their protons, they lose their energy. Protons usually hitch a ride on the backs of water molecules, so that a line of water molecules forms what is known as a proton wire, i.e. a path on which protons can move from one place to another. If this path is disrupted, the protons have only one choice but to go back to where they came from. And this is what happens in an aquaporin – thanks to the two short helices mentioned above. It is at this point that the incoming water molecules perform a pirouette and disrupt the proton wire. The protons return to where they came from while the water molecules continue their way. There is also a second major mechanism that stops other molecules from passing through: the constriction, which only lets molecules the size of water molecules through.

Aquaporins must be at the heart of a number of diseases. That is why it is crucial to get to know aquaporins on a very intimate level, with a view to develop new therapeutics. Corneal transparency – i.e. vision – requires a precise regulation of water content, for instance. Water probably has a role in keeping the diameter and spacing of collagen regular, which in turn confers transparency to the lens. Cataracts are known to be a direct consequence of aquaporin malfunction. Nephrogenic diabetes insipidus is a disorder in which patients' kidneys cannot reabsorb water correctly; patients have to go to the bathroom frequently and end up dehydrated. Defective aquaporins are no doubt at the heart of this disease. Aquaporin malfunctions in salivary and lachrymatory glands result in a disorder known as Sjogrens syndrome, or dry mouth. Besides aquaporin malfunction, its overexpression can also be indicative of congestive heart failure or – less worrying – pregnancy.

Within the next decade, a growing number of clinical disorders will no doubt be pointing their finger at aquaporin – its malfunction or overexpression. One interesting biotechnological development would be to incorporate aquaporins into certain materials which could then filter ions – such as salt – from seawater, to produce fresh water in countries where it is so scarce.

## Cross-references to Swiss-Prot

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Aquaporin AQPcic, *Cicadella viridis* (Green leafhopper) : Q23808

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