

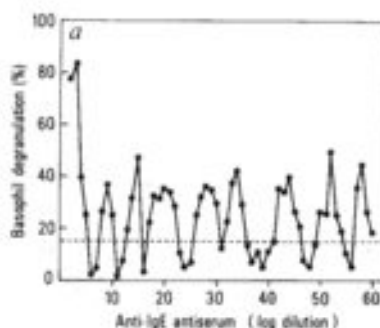
## Why Water Is Weird

A talk presented at the Royal Society of Chemistry

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Philip Ball

When I was asked to join *Nature*'s editorial team in 1988, I didn't expect the doctoral thesis that I'd just completed on liquid-state physics to have much relevance to the science I'd be encountering there. I was proved wrong even before I arrived in London to start work. Because just weeks earlier, *Nature* published a paper that is now infamous, which claimed that water has a memory. The authors of this paper, the French immunologist Jacques Benveniste and his collaborators, reported that they found biological activity in solutions of antibodies diluted to the point where no dissolved molecules should remain. Stranger still, this activity seemed to appear and disappear periodically as the diluting progressed. At face value, this phenomenon seems to have no plausible explanation according to the known principles of chemistry: if you don't have any molecules, they can't have any effect.



The 'cyclical' revitalization of an antibody solution during extreme dilution, as reported by Jacques Benveniste and colleagues in 1988.

But Benveniste and his colleagues did have an explanation. They said this:

Water could act as a 'template' for the molecule, for example by an infinite hydrogen-bonded network or electric and magnetic fields.

What on earth does that mean? Well, it will become clear shortly what they thought it might mean, but let me confess right now that this is actually one of the least meaningful sentences I suspect *Nature* has ever published. Or rather, the meaning is not so much in the words, but what lies behind them. Benveniste and co. had found a way of alluding to the peculiar chemical character of the liquid state of water in a way that sounded plausible and scientific enough to pass beneath the radar screen of the referees, who I doubt had any real knowledge of liquid-state theory. What they had done is to capitalize on the unquestionable weirdness of water.

They were neither the first nor the last to do so, but let me just remind you how this particular story played out. As you can doubtless see, Benveniste's paper seemed to offer

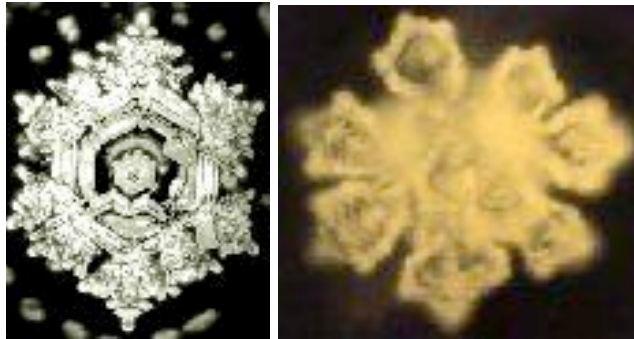
support for the claims of homeopathy: that solutions diluted beyond the point at which any active ingredient remains can nonetheless have physiological effects. For this reason the paper became not just controversial but highly politicized. After *Nature* published it – incidentally in a category of contributions never used before or since – the editor John Maddox led a team on a visit to Benveniste’s labs, where they watched over an attempted replication of the results. The researchers proved unable to demonstrate the same rise and fall of biological activity as a function of increasing dilution, and Maddox’s investigative team pronounced the previous findings a delusion. Benveniste called this a witch-hunt and persisted with his high-dilution work, which culminated in what he called digital biology, whereby he claimed to be able to use electromagnetic signals to send biological activity down a telephone line, programming it into pure water which acts as a vehicle for this information. He pursued this work until his death in 2004. There are still those today who swear that something like a memory of water can cause high-dilution activity or something like it, among them the Nobel laureate immunologist Luc Montagnier.

This was not an isolated episode of strange claims about the properties of water. Most famously, there was the polywater scandal of the late 1960s, in which Soviet scientists claimed to have isolated a new form of water in narrow glass capillary tubes, which had the consistency of soft wax. It was even suggested at that time that this might turn out to be the most stable form of water at everyday temperatures and pressures, and so the fear was raised that a globule of polywater dropped into the oceans might cause them all to gum up, rather as the fictitious ice-nine froze all the world’s seas in Kurt Vonnegut’s novel *Cat’s Cradle*. Yet it turned out that polywater was another delusion: the waxy stuff was a concentrate of impurities, most probably silicates leached from the glass. Incidentally, Vonnegut’s ice-nine was discovered by a scientist named Felix Hoenikker, who was modelled on the American scientist Irving Langmuir who coined the term now used to describe both polywater and the memory of water: pathological science.

Well, water has a remarkable ability to attract pathological science. Sometimes this leaks out into the pages of the regular scientific literature. On other occasions it remains very much at the fringes, where science meets mysticism, as for example in the extraordinary story of the Austrian forest-warden Viktor Schauberger and his ideas about ‘living water’ energized by vortices: ideas that the Nazis allegedly tried to harness by forcing Schauberger to develop a secret weapon based on the implosions that his vortices were supposed to induce. This is an area where New Age mysticism blends into technological reality. I’ve heard serious scientists swear that magnets really can descale kettles, and that specially treated metal rods can alter the taste and viscosity of water with a little gentle stirring. And I’ve discovered that if you tell non-scientists that you’re interested in the properties of water, it isn’t long before someone will mention the work of Masaru Emoto, who changes the shape of snowflakes with prayer.



This is a sample of frozen water from the lake at Fujiwara Dam, in Japan. It's described by Emoto as "dark and amorphous, with no crystalline formations." But then the Reverend Kato Hoki, chief priest of the Jyuhouin Temple, prayed for one hour prayer beside the dam, new samples were withdrawn, and they formed crystals like this:



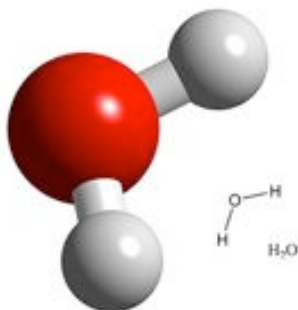
Apparently music makes its influence felt too: when water was crystallized after being exposed to Elvis Presley's *Heartbreak Hotel*, the crystals are reported to have broken spontaneously into two.

Now, what is going on here? Why does water attract such weirdness? One reason, which I think scientists rarely appreciate, is that studying water is not like studying any other substance. It is not a neutral subject. All of us bring to it a wealth of cultural associations that are probably impossible to put aside. Water *is* an element—not, of course, in the chemical sense, but in the mythical and poetic sense, and that is not irrelevant. I'd recommend to you the book by the French philosopher Gaston Bachelard called *Water and Dreams*, which explores various poetic incarnations of water with deep roots in culture, myth and legend. I believe that some such ideas—of water as purifier, water as saviour—lay unconsciously behind some of the pathological episodes of water science.

But there's more to water's propensity to spawn pathological science than its centrality in culture. Because the fact is that water really is weird.

What I mean by that is that water is not like other liquids, or at least not like the sorts of liquids one tends to study as a liquid-state physicist. It would seem very perverse to an outsider that I spent most of my PhD considering liquids such as liquid argon and nitrogen, which most people will never see and which don't exist at all under ambient conditions on Earth. But the fact is that these liquids are easy to understand and to make simple models of: you can think of them as a mass of weakly attracting hard spherical atoms. Water is different. You can tell it is different right away, for example by

comparing it with other chemical compounds of similar constitution. Water is the hydride of oxygen, each molecule an oxygen atom with two hydrogens attached:



But compare it to the hydrides of other elements around oxygen in the periodic table. All the others are gases at room temperature and pressure: methane, ammonia, hydrogen sulphide, hydrogen chloride, and – only just, in summer at least – hydrogen fluoride. Water seems in comparison to these to have an unusual resistance to evaporating. Something is holding those molecules together as a liquid, which doesn't seem to be the case, or less strongly, for these other hydrides.

Then there's ice. Ice floats, which is so familiar a fact that it's easy to forget that almost every other substance gets denser when it freezes. Ice, in contrast, expands, which is why frozen pipes burst and why the *Titanic* sank. But it's even stranger than that, because ice doesn't just suddenly expand when it freezes. It actually begins to expand as it cools below 4 °C, although the decrease in density is much more pronounced and sudden on freezing. So whereas most substances contract as they cool, liquid water first contracts and then expands again. For this reason, the bottom of a lake in winter is a little warmer than the top, and so lakes freeze from the top down. This prevents some of them from freezing solid, since the surface cap of ice insulates the water below.

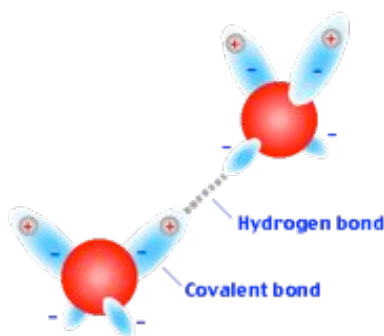


Water's weirdness: it is less dense in solid form than in liquid form (left), and the liquid is most dense at 4°C above the freezing point – which is why lakes freeze from the top down (right).

These are just some of the most obvious and easily understood of a whole list of so-called anomalies of water. Happily, just about all of them can be explained with a single fact, which is what distinguishes water from simple liquids like liquid argon. And this is that

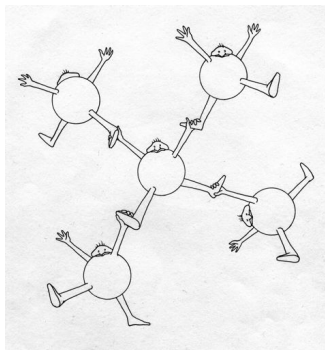
the water molecules have a certain stickiness for one another, because they can form weak chemical bonds called hydrogen bonds.

The conventional explanation for hydrogen bonds goes like this. The oxygen atom tends to draw towards itself the electron cloud that binds it to the hydrogen atoms, giving the hydrogens a slight positive charge. What's more, the oxygen atoms have lone pairs of electrons which don't take part in chemical bonding but which create lobes of negative charge on the back of the V-shaped molecule. The hydrogen atoms are electrostatically attracted to these lone pairs, and this attraction creates the hydrogen bond. Now, this is too simplistic a picture, and in fact a committee for the International Union of Pure and Applied Chemistry (IUPAC) is currently working on a new definition of the hydrogen bond that will take into account all we have learnt about it in recent years. But it will do as a crude description.



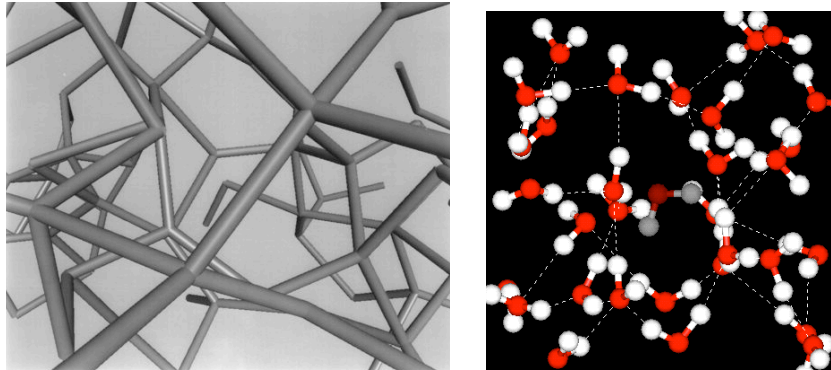
In a simplistic picture of hydrogen bonding, this weak interaction is basically electrostatic.

Hydrogen-bonding isn't unique to water. In fact, several other simple hydrides form hydrogen bonds, including ammonia and hydrogen fluoride, which explains their relatively high boiling points too. But in water, every molecule can form no fewer than four hydrogen bonds to its neighbours: two via the two hydrogen atoms, and two more for each lone pair on the oxygen. What's more, these bonds point in particular directions in space. You can think of the water molecule as a being with two hands, representing the hydrogen atoms, that can grasp the ankles of another, representing lone pairs. So when the molecules link up, it creates a tetrahedral arrangement:



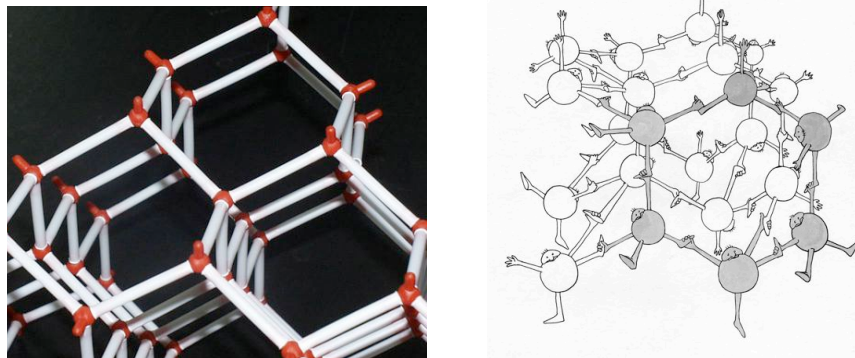
Water molecules, represented here with hands for hydrogen atoms and feet for lone pairs, clasp one another on a tetrahedral arrangement.

And this is a three-dimensional structure: as it repeats again and again, it creates an extended network throughout space:



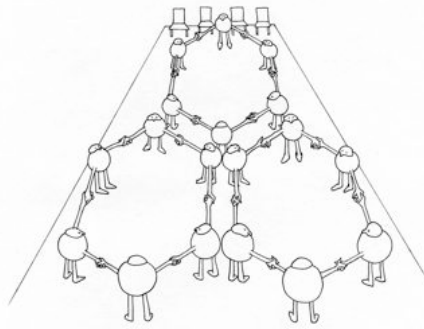
Two representations of the hydrogen-bond network of liquid water.

Because of this network, there is a tension between the usual tendency for the molecules in liquids to jostle close together and the requirement for the water molecules to be kept ‘at arms’ length’, as it were, in order to form the hydrogen bonds. These bonds can bend and deform a little, but too much and they’ll break. The key to water’s oddness lies in this delicate balance between dense, random packing of the molecules and the more open, orderly arrangement of the tetrahedral network. In ice, the regularity of the network is rigidly imposed, so there is plenty of open space.

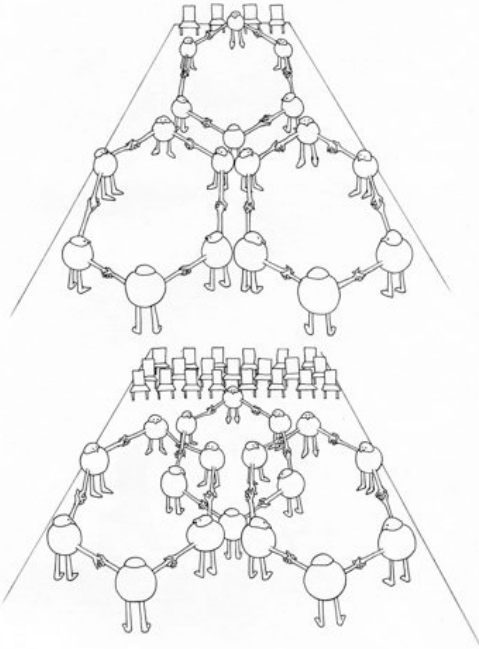


In ice, water molecules hydrogen-bond into six-membered rings, leaving plenty of empty space inside.

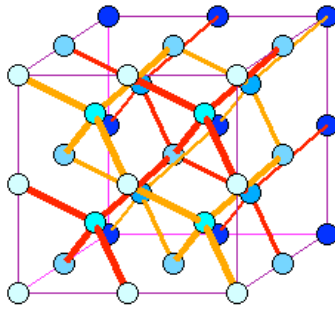
This explains why there are so many different forms of crystalline ice – about 12 at the last count, which appear as ice is squeezed at different temperatures. With all that space, the molecules can find different ways of packing. In particular, they can pack more closely together by forming a second network in the gaps. Here’s a picture representing ordinary ice – it isn’t exactly the true arrangement in ordinary ice, but it’s a two-dimensional structure with six-membered rings like those in real ice:



Now imagine this structure gets squeezed – we put out more chairs at the ends of this dance hall, so that the same number of dancers have to squeeze into a smaller space. Here’s how they can do it, by interweaving the rings. And that’s what happens in some of the denser forms of ice, made under high pressure, where there are two separate hydrogen-bonded networks woven into each other:



So there really is an ice-nine, although it’s not like the one Vonnegut imagined. And there are forms of ice that, like the fictional ice-nine, remain solid above zero degrees centigrade, but only so long as they are kept under high pressure. Here’s one of them, Ice-VII, with the two hydrogen-bonded networks marked in red and orange:



The crystal structure of Ice-VII, with two interlocking networks of hydrogen-bonded molecules.

When ice melts, some of these bonds are broken and the molecules can come closer together, increasing the density. The hydrogen-bonded network in the liquid is therefore highly imperfect and disorderly, and also dynamic: hydrogen bonds between the molecules are constantly being made and broken, so that each of them lasts on average just a picosecond or so – that is, a trillionth of a second. Physicists and chemists working on water have long struggled to find the best way of describing this network, with its intimate blend of order and disorder. It seems clear that each water molecule has a roughly tetrahedral hydrogen-bonded coordination, but because of all the broken bonds, they have an average of less than four bonds each. And whereas in ice the hydrogen bonds link them into six-membered rings, in liquid water it is more common to find five-membered rings instead. What's more, some water molecules actually have more than four hydrogen bonds, because they can form so-called bifurcated bonds in which one hydrogen atom links to lone pairs on two different oxygen atoms.

I should mention that not even this average structure of ordinary liquid water is fully settled. Some scientists have recently claimed that the water molecules can be linked into long chain-like structures rather than the three-dimensional network, or that there are two sub-populations of water molecules, some in chains and others more densely packed. Another proposal is that the structure is more like a mixture of patches of an ice-like orderly network interspersed among a dense jumble of molecules that are barely hydrogen-bonded at all. I should say that neither of these proposals looks at all likely, but the mere fact that they are still being proposed shows how hard it is to pin down exactly what water's structure looks like. And it *does* seem more likely that there are genuinely two forms of liquid water at high pressure and low temperature, in the region where ice is the most stable state. This is a hard idea to test experimentally, because it involves sustaining the liquid state under conditions where it wouldn't normally exist. There are ways of doing that, but to reach the region where the liquid is expected to separate into two forms is tremendously difficult, so all we have so far is rather indirect evidence. All the same, it seems likely that this tension between a more open and orderly network structure and a denser, more disorderly structure does ultimately resolve itself into the appearance of two distinct liquids with different densities. It is possible that the density maximum at 4 °C is an echo of this.



It's because of both these complexities and these uncertainties about the liquid-state structure of water that it remains so easy and tempting to invoke explanations for weird and perhaps pathological properties of water that involve water structure. That's precisely what Jacques Benveniste was trying to do. Because water was known to form this three-dimensional hydrogen-bonded network, he wanted to imply that perhaps a part of the network could freeze around a biological molecule and retain an imprint of its shape – a shape that might hold the key to its biological activity. But sadly, this idea makes no sense. For one thing, it's hard to see why a mould should behave like the object it is moulded around – it's a kind of negative imprint, not a replica. But in any case, we know that the network is just too dynamic to make that possible. If bonds are lasting only a picosecond before they break and reform, how on earth is the shape going to be maintained? Nevertheless, 'water structure' remains a kind of *deus ex machina* for explaining various unusual physical and biological phenomena, almost always with a certain air of desperation.

### *Water in the cell*

This kind of idea is particularly notorious in biology, and specifically in the question of what water behaves like inside living cells. This has been, and remains, a hugely contentious area. On the one hand, many biochemistry textbooks tend to regard water as just the backdrop to the life of the cell. They acknowledge that water is crucial – without it, protein molecules might not retain their shapes or their flexibility, and life grinds to a halt – but they portray it as just a uniform solvent, describing the three-dimensional hydrogen-bonded network of ordinary water and then just leaving it at that. Biological molecules are frequently depicted as though in a vacuum, which might be necessary for clarity but tends to encourage the notion that this is how they'd look whether there was water around or not. At best, the cell is treated as though it is a bag of highly dilute dissolved substances.



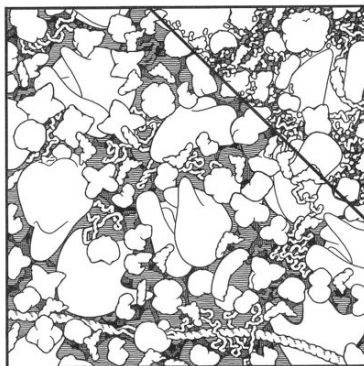
A protein structure – but where's the water?

On the other hand, it has been suggested that water in cells is fundamentally different from that in a cup of water, and that this difference is essential for the health of the cell. There have been claims that cell water is more sluggish, and that it becomes more like ordinary water in diseased cells such as cancer cells. The notion here is that the cell

somehow ‘tames’ ordinary water by altering its structure and rendering it ‘biophilic’. This idea goes back a long way. The Nobel laureate biologist Albert Szent-Gyorgyi, who coined the phrase ‘the matrix of life’ to describe water, talked about the structuring of cell water in the 1950s, and the biologist Gilbert Ling proposed in the 1960s that cell water forms organized, layered structures on the surface of proteins.

Now, the fact is that neither of these ideas – that cell water is like any other water, or that cell water is somehow fundamentally altered throughout the cell – seems to be right. The truth is considerably more complicated, but also much more interesting. It seems that the structure and properties of water in the cell are altered in many small, subtle and exquisite ways by biomolecules, as well as by other components of the cytoplasm such as salts – but that this happens only locally, over short distances. In this way, water seems to adjust itself to the presence of biomolecules and vice versa, and it is the delicate interplay between them that makes life possible. I want to give you a little glimpse at some of the ways in which this happens.

First of all, let’s have a look inside the cell. Here’s what it’s like:

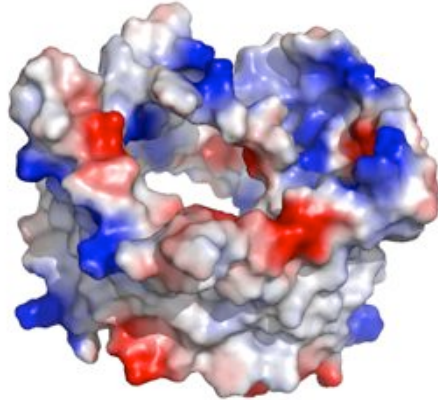


From David Goodsell, *The Machinery of Life* (1993)

This is a scale drawing of a typical bit of the cytoplasm, the watery environment of the cell with all its biomolecules swimming around. And one thing strikes you straight away: this is a crowded place. It’s actually even worse than this, because this picture mostly doesn’t show all the small dissolved substances like sugars and salts that are also in here. On average, the big molecules are separated from one another by typically a distance of around 1 nm (a millionth of a millimetre), which allows room for no more than 3-4 layers of water. So just about all the cell water ‘feels’ the effect of the dissolved biomolecules. The question is what that feeling does to the water.

There’s no single or simple answer to that. But one of the key questions is what the water close to the surfaces of big molecules like proteins looks like. These surfaces are chemically diverse. Some bits are covered in water-soluble chemical groups, such as ones that can engage in hydrogen bonding, as sugars can, or which have electrical charge, as salts do. These are called hydrophilic, or water-loving. Other parts have fatty or oily chemical groups attached, and so are not soluble in water. These are called hydrophobic,

or water-fearing. Here is an image of a typical protein with the hydrophilic and hydrophobic parts marked in blue and red respectively. The deeper the colour, the more hydrophilic or hydrophobic they are; the white bits are neutral in this respect:



Hydrophilic (blue) and hydrophobic (red) regions on a protein surface.

The question, then, is if and how water's structure is altered next to hydrophilic and hydrophobic surfaces – and also, if there is such alteration of structure, how far does it extend into the liquid. This question is still being debated.

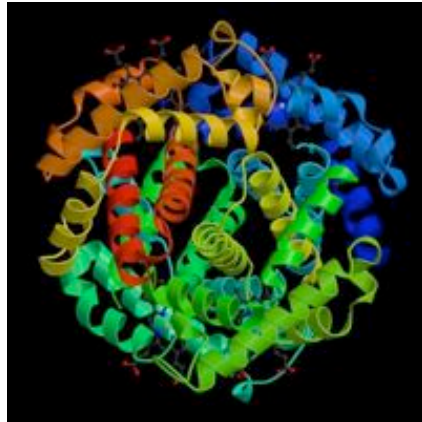
One thing is clear, however: there's something about water that encouraged hydrophobic parts of molecules to stick together. In effect, this means that globules of fatty or oily material in water will stick together. This happens at large scales too, and very recently it's been discovered that fire ants exploit the effect by clustering together on the surface of water to make hydrophobic rafts, which allow them to float and thus to escape being killed by floods.



A 'hydrophobic raft' of fire ants.

At the scale of protein molecules, the attraction of hydrophobic surfaces in water helps proteins aggregate into complex functional assemblies of several molecules. It also enables individual proteins to acquire and hold the very particular three-dimensional shapes that they need in order to work as enzymes. Proteins are made from chains of

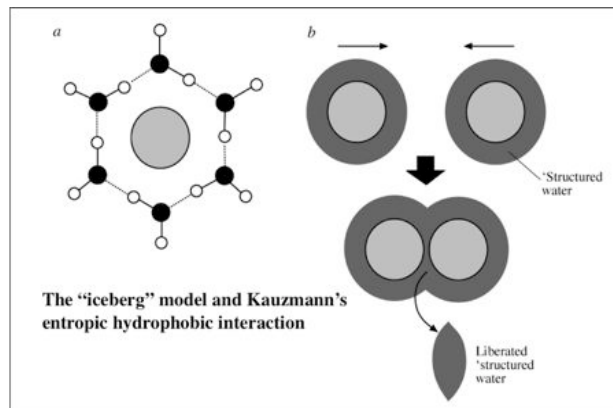
amino acids that fold up into particular shapes, and typically these contain more hydrophobic amino acids in the interior, protected from water.



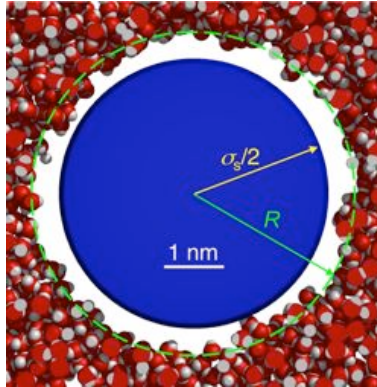
The folded-up chain of a protein. Typically, the 'dry' interior contains many hydrophobic amino acid groups.

Now, it makes intuitive sense that a protein would tend to bury its hydrophobic, water-fearing parts. But what actually drives this apparent attraction between hydrophobic surfaces? The textbook answer draws on an idea proposed in 1945, which says that the structure of water actually becomes more orderly next to a hydrophobic surface. It becomes, in other words, more like ice. This enables the water to arrange itself in a way that minimizes the loss of hydrogen bonds where the water ends and the hydrophobic surface begins. The idea, then, was that water builds a little iceberg around dissolved hydrophobic particles.

In 1959 the biochemist Walter Kauzmann suggested how this sort of picture could lead to an attraction between hydrophobic particles in water. As two particles come together, their coatings of ordered water overlap, and some of this 'structured' water is set free. This means it can become disorderly again, and so there is a gain in entropy, which makes the process favourable. So according to this explanation, the hydrophobic attraction is driven by entropy.

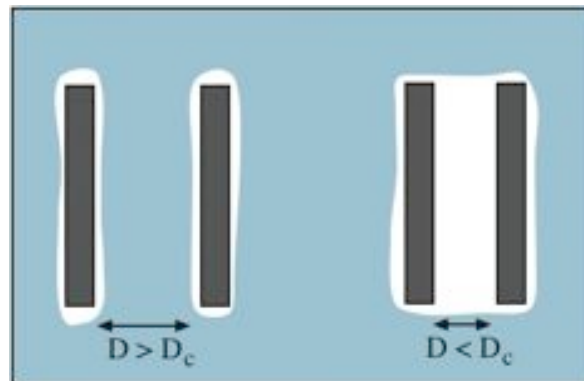


The problem with Kauzmann's model is that there now seems to be no good evidence that it is right, and pretty good reason to believe that it's wrong. That's because it seems very unlikely that water is more orderly around hydrophobic surfaces after all. It may well have a different structure from the one in bulk water, and probably does. But it's not like a layer of ice. It seems likely that in fact there is a very thin layer right next to a hydrophobic surface that contains hardly any water at all – it is a gas-like layer:



Water near a hydrophobic particle.  
From Mittal & Hummer, *PNAS* 2008.

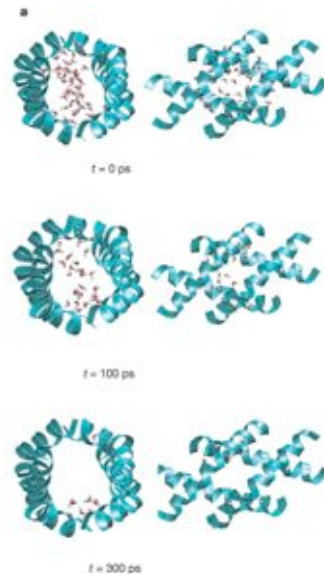
And one new explanation for hydrophobic attraction is that, when two such surfaces come close together, there comes a point where the water remaining between these gas-like layers simply evaporates. This effect, called capillary evaporation, is well known in principle – it means that, in effect, the boiling point of the liquid between the two surfaces is altered just in this little space, and so the gas forms there instead. If this were to happen, then the meniscus at the edges of the space would pull the two surfaces into contact. For obvious reasons, this is called a dewetting transition, and one theory predicts that it might be common between two hydrophobic surfaces when they are just a nanometre or so across.



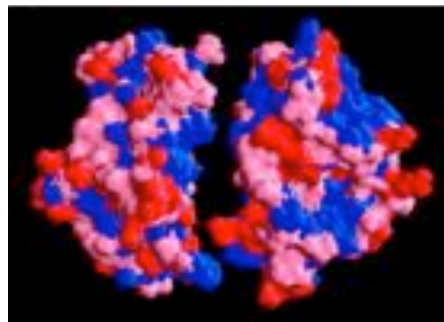
The dewetting mechanism of hydrophobic attraction.

The idea is that this also happens as a protein folds: dewetting snaps the hydrophobic parts of the chain together. Computer simulations of flat hydrophobic plates do show an abrupt dewetting transition.

But it now looks as though dewetting is probably rather rare as a way of getting hydrophobic surfaces to stick together. Computer simulations of a small protein called melittin that is a component of bee venom seem to show a dewetting transition in the clustering together of the four parts to form a tube-like space:



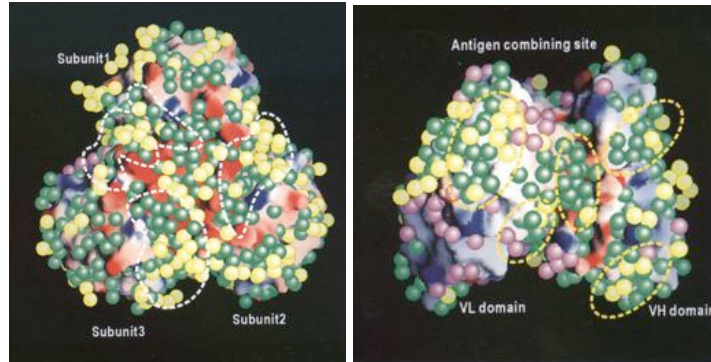
But the two roughly flat portions of an enzyme called BphC seem to come together without sudden dewetting – the water between the two surfaces is only squeezed out gradually, molecule by molecule:



In general, it seems that protein surface just aren't hydrophobic enough to make dewetting happen. So their attraction must have some other origin.

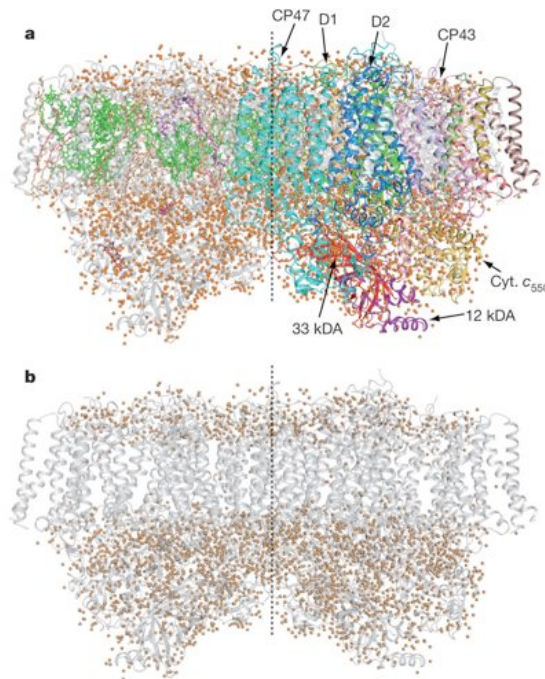
As well as helping proteins hold their shape, water seems to act as a kind of plasticizer, giving the protein molecule enough flexibility to do its job. If proteins are made too dry, or if they are taken out of water and placed in other solvents, they can either fall apart or become too rigid to work. But proteins always seem to have some water stuck firmly to their surfaces, often by hydrogen bonding. This bound water remains in place when the

protein is crystallized, and typically makes up 30-50% of the mass of ‘dry’ protein powders. These water molecules are like limpets attached to the macromolecule, and their positions are generally related to the protein’s own atomic structure, so that the waters can be precisely located in X-ray crystallography. Here are a couple of examples, where the yellow, green and purple spheres show bound water in different layers:



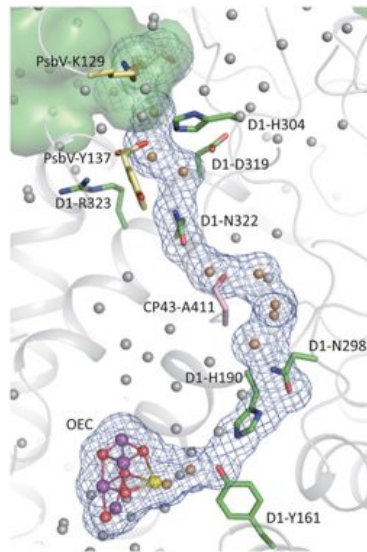
Hydration water of DFV fragment of anti-dansyl immunoglobulin G (left) and scytalone dehydratase (right).

Using X-ray crystallography, it’s now possible to trace out this halo of water molecules around really rather large biomolecule assemblies. Here’s a very recent and rather beautiful example:



The hydration ‘halo’ of photosystem II (a). The waters are shown more clearly as orange spheres in b. From Umena *et al.*, *Nature* 2011.

This is the crystal structure of the entire photosystem II, the molecular assembly responsible for converting sunlight into chemical energy in photosynthesis. It was reported by a group in Japan, and shows the locations of around 1,300 water molecules in the hydration shell – they're shown more clearly in this lower image. At first glance this might look like just a fairly random jumble of water molecules, but in fact they are in several places organized into rather particular hydrogen-bonded assemblies that seems to offer channels for guiding hydrogen ions, other water molecules and oxygen molecules to and from the place where the key reactions take place. Here, for example, is one of these channels shown explicitly, consisting of a chain of hydrogen-bonded groups that include bits of the protein assembly and water molecules coloured orange:



A hydrogen-bonded channel (blue) consisting of water molecules (orange) and protein groups in photosystem II. From Umena *et al.*, 2011.

In other words, this cloud of waters should really be considered to be an integral part of the biological structure itself: the waters are like orchestrated by the proteins and other molecules in the photosystem to perform a host of specialized functions.

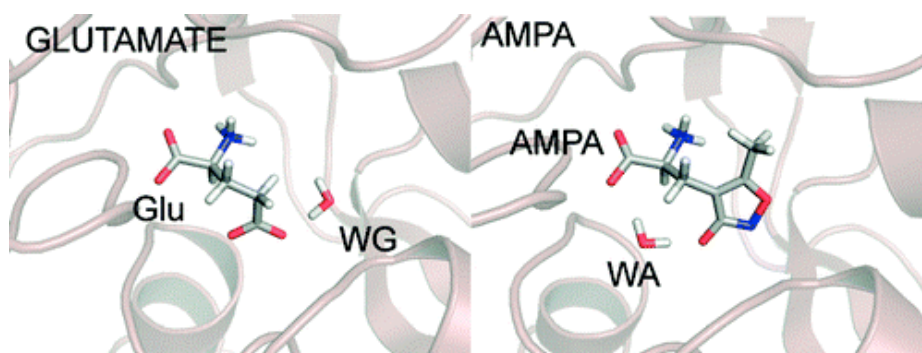
In general, one of these roles that assists the action of protein enzymes is to help them to bind the small molecules that they act on. For example, water molecules can act as a removable filler to make a protein somewhat promiscuous about which molecules it will bind to. Take the so-called oligopeptide binding protein OppA, which will grab hold of very small (2-5 residue) peptides with more or less any amino-acid sequence. This is possible because its binding pocket has a lot of water in it that can be expelled or admitted to fill up any empty space. The water molecules here are a little like bricks that can be inserted or removed around guest molecules of different shape.





A schematic depiction of how the binding site in the protein Opp A can accommodate a range of different substrates, by using water to ‘fill the gaps’.

On the other hand, water molecules in well-defined sites in a protein structure can bridge the gap between the protein surface and the molecule it binds, so as to make the binding very selective for a particular shape. Here is an example chosen simply because it is very recent:



From Sahai & Biggin, *J. Phys. Chem. B*, 2011.

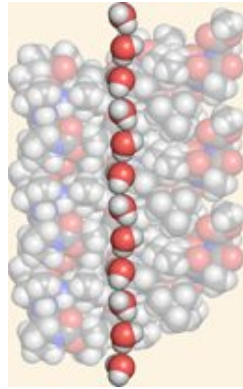
What you see here is (part of) a protein called an ionotropic glutamate receptor, which is found in neurons in the brain and binds the neurotransmitter glutamate. On the left you see it binding glutamate, and on the right, binding an artificial mimic of glutamate called AMPA, which also stimulates the same neural signal. In both cases, there is a single water molecule (WG and WA respectively) that bridges the receptor’s surface and the bound molecule. But the water molecule is in different positions in each case, and it’s the position of this water that makes the receptor receptive to either glutamate or AMPA. Understanding this difference could, then, be important for designing other synthetic molecules that can affect and interfere with this important biochemical process in brain function.

### *Water wires*

As you can see, water molecules can be thought of as being a little like Lego bricks that can be fitted together in certain ways. Some of those ways are found in liquid water and various types of ice, but they just scratch the surface of the possibilities. Biological molecules mould this Lego-like water into new configurations, by for example confining it in spaces with particular shapes or with particular arrangements of water-loving and water-hating, greasy patches on the surface.

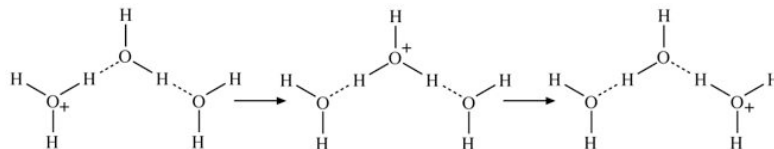
And in fact narrow channels like this produce some of the most versatile and widespread of new water structures in biology. In particular, a channel wide enough to admit just one

water molecule at a time can be threaded by a chain of waters hydrogen-bonded together in what is often called a water wire:



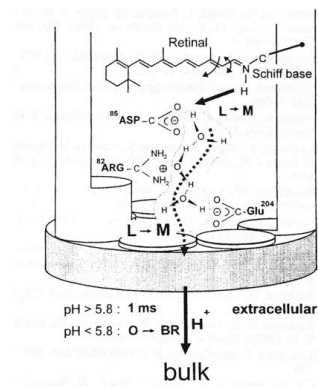
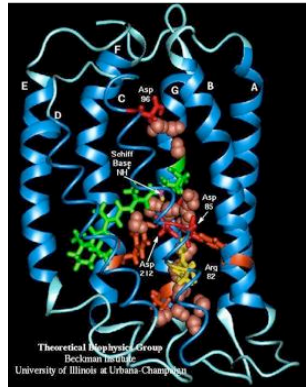
A water wire threading a peptide pore.

The reason it is called that is not only because it is long and thin but also because, like a copper wire, it conducts electrical charge. However, it does this in a very different way from copper. Specifically, these wires can transport positively charged hydrogen ions, which are just bare protons. A proton can pass very rapidly down a water wire, because it can effectively be shunted along just by successive water molecules flipping their arrangement of hydrogen bonds:



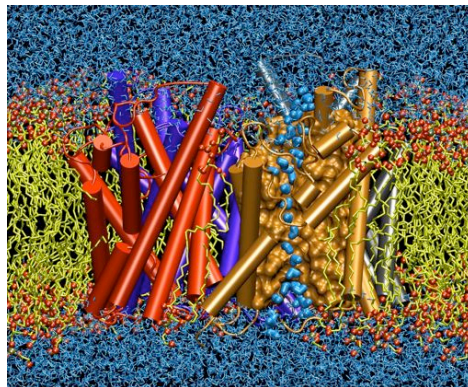
The protons don't actually have to move at all, but only the ultra-light electrons in the bonds. It's rather like the way a Newton's cradle works, a ball striking at one end making one pop off at the other. This is called the Grotthuss mechanism, and it happens in pure water too, where there are long chains like this that make up part of the usual three-dimensional hydrogen-bonded network. For this reason, hydrogen ions can move around unusually fast in water.

But hydrogen ions are often needed in biochemical reactions carried out by enzymes. Several such enzymes use water wires to shuttle the ions from the solution outside, through the protein and into the active site where the reaction takes place. That happens, for example, in cytochrome enzymes that. It also happens in bacteriorhodopsin, which is a protein found in some ancient single-celled photosynthetic organisms called Archaea. Bacteriorhodopsin is a proton pump powered by light, which drives protons across a membrane to convert light energy into chemical energy. It is threaded by a water wire from the light-sensitive core to the inside of the membrane.



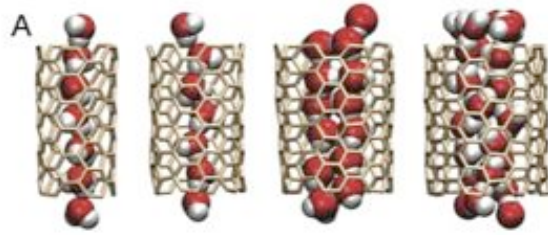
Two views of the water wire connecting the light-sensitive region of bacteriorhodopsin to the exterior of the cell.

Another important class of proteins that contain water channels are the aquaporins, which regulate the flow of water in and out of cells. They will let water through but not salts or other dissolved substances, and as such, they molecular water filters. Aquaporins help our kidneys to process about 180 litres of fluid every day. Because of the way they prevent salt from passing across the membrane with water, aquaporins are being explored as possible systems for biologically based desalination.



The membrane protein aquaporin admits water through a narrow channel.

But it looks as though we can use the same filtration principle without having to rely on aquaporins themselves, which like most biological molecules are a little delicate and not easy to extract intact from cells. One of the most promising approaches uses carbon nanotubes, which are pores of uniform diameter made from pure carbon. These are extremely strong, and we're getting increasingly good at making them from raw carbon sources with only a very narrow range of different diameters. The idea is to embed carbon nanotubes in robust membranes and drive water through them under pressure to remove the salt.

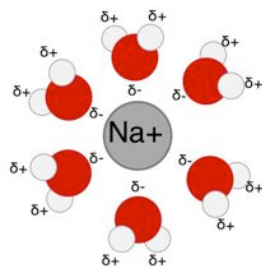


Water in carbon nanotubes. If the nanotube is narrow enough, the water molecules can only pass in single file.

If the nanotubes are narrow enough – less than a nanometre in diameter – then they may be threaded by a single chain of water molecules. But the insides of nanotubes are rather water-repellent, and so the water chain is a precarious thing that can be easily snapped. This, however, can actually make the flow easier: the chain of water molecules experiences virtually no friction at all with the tube walls, no matter how long the nanotubes are, and so the flow rate is very high. Water shoots along the tubes as though their sides are ‘greased’ – which is really just what they are.

What’s more, salt ions couldn’t get through these pores at all. In principle, the nanotubes are perfectly wide enough to let salt ions through – but it seems they can’t make it when the water is restricted to single file.

The trouble is that they are surrounded by a cage of water molecules, held there by the ion’s electrical charge. This makes the effective size of the ion too big to make it through the pore, unless all of the waters are first removed. It’s rather like Nicole Kidman trying to get through a doorway. I believe that Nicole can fit through most doorways easily enough in principle, but it can be tough in practice because she is surrounded by a shell of all these acolytes and fans and paparazzi, and they all have to be stripped away – at a considerable cost in energy, no doubt – before she can fit through.

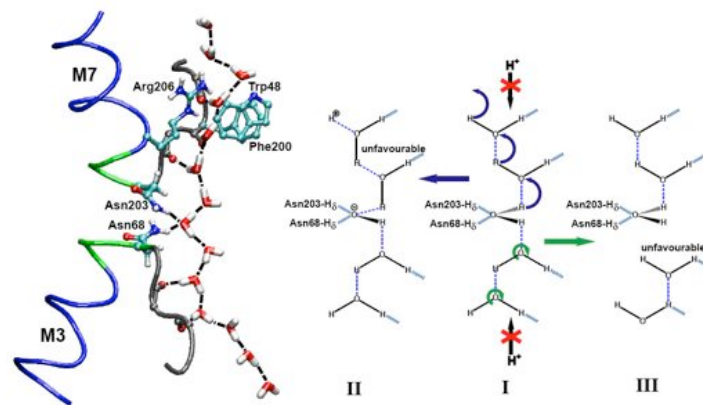


Ions in water are surrounded by a ‘hydration shell’ of water molecules, like celebrities surrounded by admirers, minders and the press.

Computer simulations of this process show that 8-Å nanotubes remove all the salt, and 9.3-Å tubes exclude 95 percent of it, which is good enough to make drinking water from sea water. Driving salty water through a membrane of tubes packed shoulder to shoulder at pressures typical of today’s desalination processes should provide pure water at least a

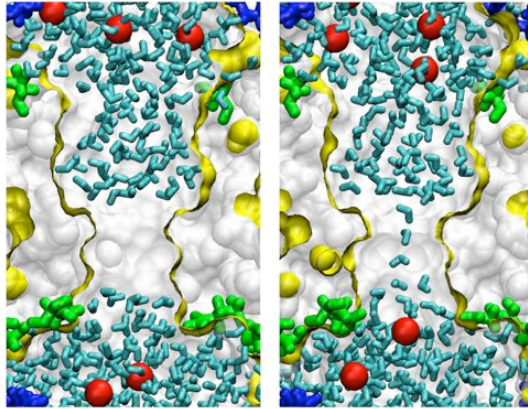
thousand times faster than the reverse-osmosis membranes currently used in desalination. For 9.3-Å nanotubes, a membrane one square metre in area could theoretically produce 1.2 billion litres of fresh water a day. Membranes not very different from this have already been made. For example, a team at the Lawrence Livermore National Laboratory in California made nanotube membranes with inner diameters of just 13-20 Å, embedded in a strong ceramic matrix of silicon nitride, which can prevent up to 98% of ions from passing through.

Like narrow nanotubes, aquaporin lets water through but not salt. But aquaporin is even more clever than that, because it has to block not only salt but also hydrogen ions – otherwise, they will upset the acidity of cells. But I showed just now how hydrogen ions move around very fast in water, and can easily pass down a water wire. So how does aquaporin let water pass but not protons? It seems that the string of waters is cleverly arranged to break the wire for protons. The chemical groups on the walls of the pore force the water molecules to meet in the wrong orientation to form hydrogen bonds at one point in the chain. And there is an electrically charged region in this part of the pore that repels a positively charged proton.



The structure of the hydrogen-bonded chain of water molecules in aquaporin, with a 'defect' in the middle that hinders proton flow. It seems likely, however, that protons are mostly prevented from passing through the channel by an electrically charged region in this central neck that repels them.

Nature has other smart tricks for controlling flow through pores. In the membrane protein MscS, which controls ion transport in bacteria, a hydrophobic water channel about 7-15 Å wide can be opened and closed by stretching of the cell membrane in which the protein sits. This distorts the protein, constricting its pore at a narrow neck, and it seems that this pushes the channel over the brink from one that can hold water to one that cannot: the slight decrease in width induces capillary evaporation, emptying the pore so that neither water nor ions can pass.



The channel of the protein MscS, which can be switched between ‘dry’ (left) and ‘wet’ (right) by only a slight change in the conformation of the peptide chain lining the central pore.

Now researchers are starting to wonder whether behaviour of this sort can be mimicked in smart water-filtration membranes, say by adding chemical groups to carbon nanotubes to act as gates, switches and valves.

### *Water and life*

So I hope you can start to see why water is not life’s matrix in the sense of being a passive backdrop on which the tapestry of life unfolds. Rather, it is a biomolecule in its own right, albeit an extremely complex one that can engage in many different processes and form almost a kind of versatile ‘loose macromolecule’ that interacts with proteins, nucleic acids and membranes.

This image casts a new light on the question of whether water is essential for life, an issue explored in a recent book (*Water and Life*, eds. R. M. Lynden-Bell, S. C. Morris, J. D. Barrow, J. L. Finney & C. L. Harper; Taylor & Francis, 2010). If we assume that all chemical processes complex enough to qualify as life will require the same kind of characteristics we see in protein interactions, then it is hard to identify any other solvent that seems likely to support such things. Many of these properties do seem to depend, to a greater or lesser degree, on the ‘special’ attributes of the H<sub>2</sub>O molecule, in particular its ability to engage in directional, weak bonding in a way that allows for reorientation and reconfiguration of discrete and identifiable three-dimensional structures. Thus, while it seems entirely likely that *some* of water’s functions in biology are those of a generic polar solvent rather than being unique to water itself, it is very hard to imagine any other solvent that could fulfil all of its roles.

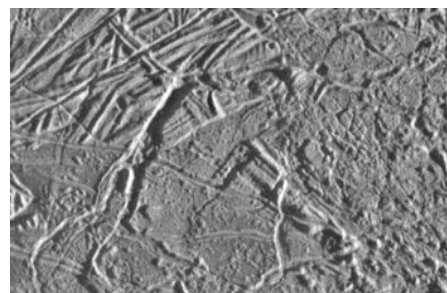
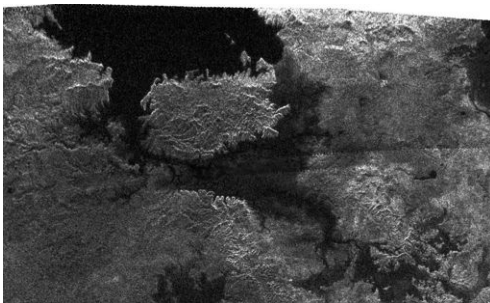
That, however, is not the same as saying that all life must be aqueous. It’s not obvious that any one of the functions of water in biology is an irreducible aspect of a ‘living system’. It is certainly possible to imagine, and even to make, artificial chemical systems that engage in some form of information transfer – indispensable for inheritance and Darwinian evolution – in non-aqueous liquids.

And life in water has some drawbacks too. Perhaps most notably, it's quite a reactive solvent, with a tendency to split apart the building blocks of life's molecules, such as proteins and carbohydrates.

So while NASA has chosen to look for habitability in extraterrestrial worlds by 'following the water', the astrobiologist Chris Chyba has rightly warned that we should 'beware the hydrocentric' —that we should be wary of some arguments for water's indispensability for life. There are plenty of other candidate solvents, as long as we aren't too parochial in insisting that life has to be made from proteins and nucleic acids. How about liquid ammonia, or formamide ( $\text{CHONH}_2$ ), or an oily solvent like liquid methane, or supercritical hydrogen on Jupiter? The basic problem of course, is that we don't know how to delimit what is life, or even if that's a meaningful scientific question.

But in thinking about non-aqueous astrobiological solvents, a review of water's roles in terrestrial biochemistry surely raises one key consideration straight away: it is not sufficient, in this context, to imagine a clear separation between the 'molecular machinery' and the solvent. There is a two-way exchange of behaviours between them, and this literally erases any dividing line between the 'biological components' and their environment. Water is an extraordinarily responsive and sympathetic solvent, as well as being far more than merely a solvent. If living systems depend on that kind of exchange, for example so that molecular information can be transmitted beyond the boundaries of the molecules that embody them, it is tempting to conclude that it would need to make use of water.

At the moment these are strictly hypothetical questions. There are two ways in which they may become more than that. One is, of course, that we are beginning to explore in detail the surfaces of some of these exotic worlds – the Cassini-Huygens mission reached Saturn in 2004 and took stunning images of Titan's surface, leading to this perhaps rather fanciful reconstruction of its putative hydrocarbon lakes.



Saturn's moon Titan is thought to have lakes of liquid hydrocarbons (left; the dark patches may be liquid). And Jupiter's moon Europa seems to have an ocean of salty water beneath its frozen crust (right).

And a joint NASA/ESA mission to Jupiter and its icy moons, such as Europa, which is believed to have a liquid ocean under the ice, is slated for 2020. And we have now accumulated a list of over 500 possible extrasolar planets – planets around other stars –

which are giving us some notion of just what an extraordinarily wide variety of worlds might exist in the universe.

But the other option is that, with the advent of synthetic biology, we might begin to imagine constructing life-like entities in the lab that can live in solvents other than water. Personally I'm agnostic about whether life could be feasible without water. But we can at least say for sure that every life form that we currently know of has reason to be thankful for water's weirdness.