

# Water is an active matrix of life for cell and molecular biology

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Szent-Györgi called water the “matrix of life” and claimed that there was no life without it. This statement is true, as far as we know, on our planet, but it is not clear whether it must hold throughout the cosmos. To evaluate that question requires a close consideration of the many varied and subtle roles that water plays in living cells—a consideration that must be free of both an assumed essentialism that gives water an almost mystical life-giving agency and a traditional tendency to see it as a merely passive solvent. Water is a participant in the “life of the cell,” and here I describe some of the features of that active agency. Water’s value for molecular biology comes from both the structural and dynamic characteristics of its status as a complex, structured liquid as well as its nature as a polar, protic, and amphoteric reagent. Any discussion of water as life’s matrix must, however, begin with an acknowledgment that our understanding of it as both a liquid and a solvent is still incomplete.

water | hydration | hydrophobic effect | protein chemistry | solvation chemistry

Liquid water is so central to life on Earth that it conditions the search for the possibility of life elsewhere. The mistaken identification of “canals” on Mars in the late 19th century fueled speculations about life on that planet, including H. G. Wells’ seminal 1897 alien invasion fantasy *The War of the Worlds*. The possible discovery of recent flowing surface water on Mars (1) and the existence of global briny oceans beneath the icy surfaces of Jupiter’s moons Europa, Callisto, and Ganymede have kept those speculations alive. Our experience of terrestrial life has encouraged the assumption that liquid water is almost a *sine qua non*, a notion expressed in the unofficial slogan of NASA’s early astrobiological program to “follow the water.”

Despite this status, water’s roles in sustaining life are still imperfectly understood and have until the past several decades been routinely underestimated (2). The common picture was that of a passive matrix: a solvent that simply acts as a vehicle for the diffusive motions of functional biological macromolecules, such as proteins and nucleic acids. It is now clear that, on the contrary, water plays an active role in the life of the cell over many scales of time and distance (3). Although life on Earth seems unable to exist in any sustained way without it, this dependence is subtle and multifaceted.

In truth, that should not surprise us. Water is a complex fluid in its own right (4, 5), and Darwinian

adaptation to a complex milieu might be expected to generate much the same kind of enmeshing and interplay of the biological and environmental at the molecular scale that we find at higher levels of life’s organizational hierarchy. That, one might add, does not guarantee that water is uniquely suited to be a solvent of life (6). However, it does give aqueous life a rich, varied, and endlessly nuanced character.

Water exhibits diverse structural and dynamical roles in molecular cell biology (3). It conditions and in fact partakes in the motions on which biomolecular interactions depend. It is the source of one of the key forces that dictate macromolecular conformations and associations, namely the hydrophobic attraction. It forms an extraordinary range of structures, most of them transient, that assist chemical and information-transfer processes in the cell. It acts as a reactive nucleophile and proton donor and acceptor, it mediates electrostatic interactions, and it undergoes fluctuations and abrupt phase-transition-like changes that serve biological functions. Is it not rather remarkable that a single and apparently rather simple molecular substance can accomplish all of these things? Looked at this way, there does seem to be something special about water.

These, furthermore, are just the molecular and nanoscopic roles. I will not consider, for example, hydrodynamic processes, although these might not be insignificant even at the nanoscale (7). Control of

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water transport and osmosis, wetting properties, heat management, and other factors is important at scales from the cellular to the organismal, and indeed to entire ecosystems and habitats. Water is never far from the surface of life.

### Water in the Cell

Whereas water in the cell was traditionally regarded as a backdrop—to be conveniently omitted from colorful ribbon diagrams of biomolecular structures—an alternative school of thought awarded water a quasimystical role as an agency of life. The term “biological water” sometimes denoted a putative state allegedly “tamed” and rendered biophilic by cells (8).

There is no meaningful value in the notion of biological water today (9). However, we also cannot assume that water in the cell is the same as pure, bulk liquid water. Aggregate measures of water dynamics, for example, suggest that around 10–25% of water molecules in cells have slower reorientational dynamics, by around an order of magnitude, than those in the bulk (10, 11). It is generally assumed that this “slow water” is in some way engaged in hydrating macromolecules and other cytoplasmic solutes. However, the devil is in the details, and apportioning cell water into fractions labeled “bound” and “free”, or “slow” and “bulk-like”, does little to elucidate the functions that it serves.

Even the nature of bulk liquid water itself has been riven with disputes and controversies. In many ways, these arguments stem from a long-standing tension between the tendency to speak of “water structure” in almost crystallographic terms and the recognition that it is an inherently dynamical entity (12). Liquid water forms a fluctuating network of hydrogen bonds, but each bond has an average lifetime of around a picosecond. The shape of the H<sub>2</sub>O molecule encourages the formation of a tetrahedrally coordinated motif, which itself is the building block of ephemeral five- and six-membered rings (13). Such ring structures create a good deal of empty space within the network, giving ice a lower density than the liquid, in which defects in the network may enable molecules to encroach into the free space. Fundamentally, water structure can be regarded as a compromise between ice-like open networks and liquid-like random close packing. The thermodynamics of solvation in water are generally governed by a balance between the enthalpic water–water and water–solute interactions (hydrogen bonding, electrostatic, and van der Waals) and the entropic consequences of forming and disrupting relatively ordered hydrogen-bonded networks, conditioned by geometric factors of the interfaces and possibly the microenvironment.

In particular, much cell water is, to some degree, confined or constrained. The average distance between macromolecules in the cytoplasm is around 1 nm, corresponding to just three to four molecular layers of water—which, simply on the basis of classical solvation theory, cannot be considered bulk-like. The presence of a solute usually alters the hydrogen bond network. Some small polar solutes, such as urea (14), can be “fitted in” with relatively little solvent rearrangement, whereas small hydrophobic solutes can be enclosed in a cavity around which surrounding water molecules preserve their hydrogen bonding by rearrangement (15). Small, simple ions are typically solvated by two or so layers of hydration water, with no longer-ranged perturbation of bulk structure (16). For larger surfaces, such as those of proteins, truncation of the hydrogen bond network is inevitable. At hydrophilic interfaces, water molecules might engage in hydrogen bonding with surface groups, such as acidic residues in proteins. At hydrophobic surfaces, meanwhile, water can be considered

to form structures that preserve as much hydrogen bonding as possible.

This picture of “water ordering” around a hydrophobic particle was the basis of the classic explanation of hydrophobic interactions advanced by Kauzmann (17). The attraction of hydrophobes in water is well-attested and is one of the key driving forces for protein folding and the formation of functional multiprotein aggregates (18). It also sustains the self-assembly of lipid membranes, and matching of hydrophobic surfaces is often observed in protein–ligand binding. It is no exaggeration to say that hydrophobic interactions are a dominant force in molecular biology.

Kauzmann’s argument (17) was that this force is entropic in origin. If water becomes more orderly—perhaps more “ice-like” (with six-membered rings) or “clathrate-like” (with five-membered rings)—around hydrophobic surfaces, the expulsion of that water when two such surfaces come together incurs an entropic premium. The picture is intuitively very appealing, which is doubtless why one still sees it invoked. However, both computer simulations and direct measurements of water structure and dynamics around hydrophobic solutes have failed to offer support for a more static and orderly hydration environment (19, 20)—in some respects, quite the reverse (21). There is good reason to believe that entropy is indeed the main factor in the hydrophobic interaction (22), but quite how to account for this at the molecular scale—at least in terms of structural pictures of hydrogen bonding—is not clear. Part of the problem here is that there is no unique way to quantify water structure, and different choices are not necessarily consistent with one another (20).

In any event, there is now good reason to suppose that the hydrophobic interaction is not a single phenomenon. Lum et al. (23) proposed that there should be a cross-over between small (<1 nm) hydrophobic solutes, to which water’s hydrogen bond network can adapt itself to some degree, and large hydrophobes (>1 nm), which ought instead to be considered in the context of extended wetting and interfacial free energies (24). For small hydrophobes, such as methane (25), the water molecules may indeed form a clathrate-like structure around the solute, although not in a static sense. Rather, the hydration shell is evidently dynamic, although it is not clear how much so relative to the bulk: some measurements (26) have shown slower relaxation, whereas others (27) have shown enhanced rotational mobility. The two pictures, obtained with different experimental techniques, are not necessarily incompatible (28).

For large hydrophobes, meanwhile, Lum et al. (23) propose that hydrophobic attraction happens via the classical phenomenon of capillary evaporation: an abrupt collective evacuation of water from the intervening space between surfaces at some critical separation, pulling the surfaces together because of the menisci at the edges. This drying transition is driven by pronounced fluctuations in water density (29), which might facilitate a nonclassical nucleation mechanism for vapor cavities with a low free energy barrier (30).

There is reason to expect a drying transition for strongly hydrophobic, smooth surfaces (31); whether it can occur for chemically heterogeneous and nonplanar protein surfaces is less clear (32, 33). Camilloni et al. (34) have even argued, on the basis of modeling of NMR chemical shifts, that water molecules at the protein surface have the same number of hydrogen bonds on average as those in the bulk, and therefore should be considered to be in the “small-hydrophobe” regime in which only rotational entropy is decreased. That extreme view, however, conflicts with evidence of dangling bonds (nonhydrogen-bonded OH groups)

at the surfaces of proteins, especially in planar and concave regions (35). Moreover, enhanced water density fluctuations of the kind thought to drive dewetting (29) are observed at protein surfaces regardless of whether they actually undergo dewetting during aggregation (36, 37). Although the generality of dewetting as a mechanism for the interaction between “large” hydrophobic surfaces or patches in biology therefore remains an open question, it seems entirely plausible that evolutionary “tuning” of the proteins to bring the hydration environment close to a phase transition of this sort offers a way to produce big effects from small changes in the environmental conditions (36).

That kind of delicately poised “life at the edge,” facilitating abrupt drying of an enclosed hydrophobic space, has also been observed in simulations of protein channels and might account for gating of ion transport in mechano- and voltage-sensitive pores (38, 39). Here, emptying of the pore prevents ion transport not sterically but because of the excessive cost of ion dehydration in the dry environment. Emptying of water from buried hydrophobic cavities might also create a driving force for ligand docking in thermophilic proteins (40).

In summary, hydrophobic interactions are central to the cell’s supramolecular chemistry, but their origins are still not fully understood, and in all probability there is no unique mechanism: the chemical nature, size, and geometry of the interacting particles are all important, as are dynamical, collective fluctuations of the intervening water (41).

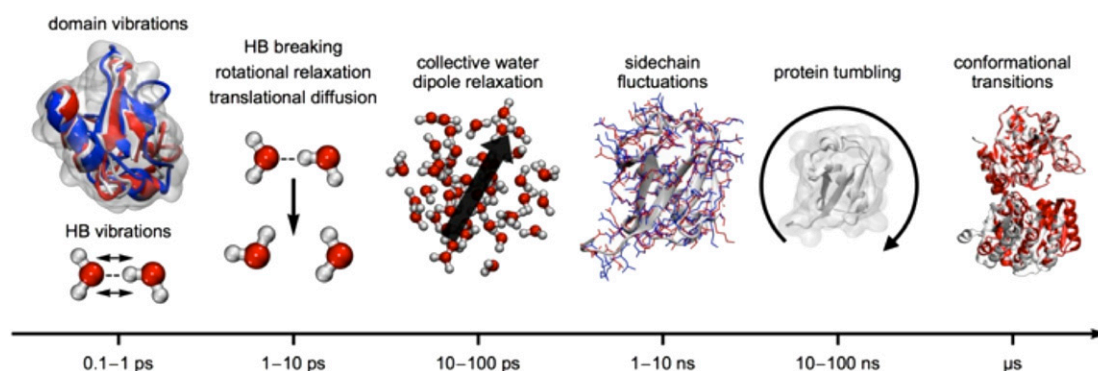
A word of caution is due: there is no obvious reason to think that solvophobic effects, such as drying transitions, are specific to water. The question, still unresolved, is to what extent water’s idiosyncrasies guide and condition them (42). Might the enthalpic and entropic consequences of water’s ability to form relatively structured hydrogen bond networks in small clusters and cavities make it especially sensitive to the geometry of confinement, for instance? Might water’s particularly large surface tension give it an unusually (although not extraordinarily) long evaporation length scale, a measure of its readiness to undergo drying transitions (43)? Or might enhanced density fluctuations be a general property of solvents in small confining geometries between solvophobic blocks, owing to the effects of incipient capillary evaporation on the solvent’s local compressibility (44)? How special, really, is water in its ability to mediate these macromolecular interactions? We might not yet be able to give a definitive answer to that question, but we have a better sense now of where to search for it.

## Hydration Is Dynamic

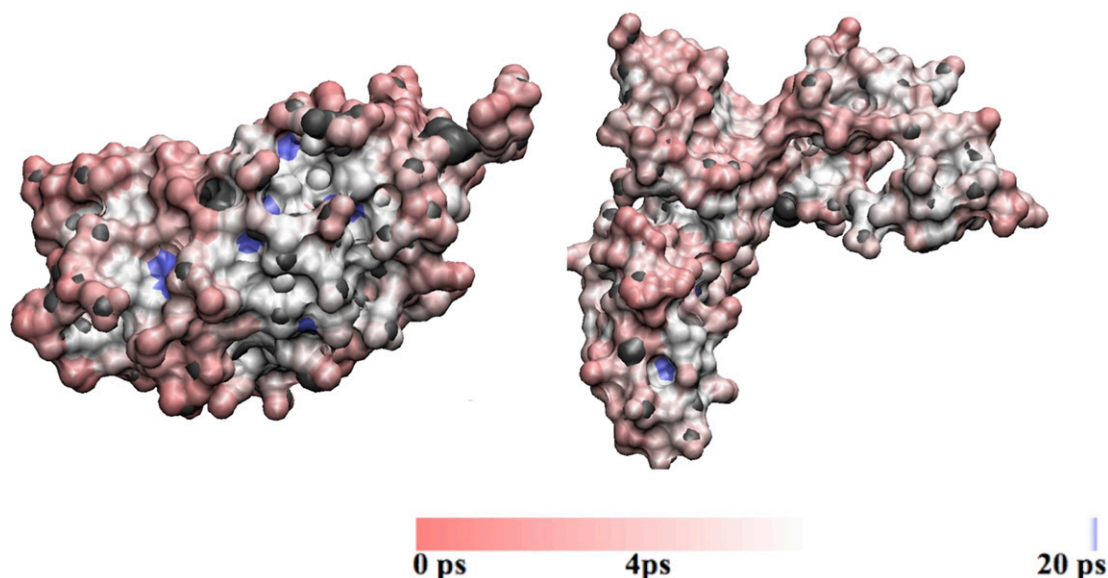
As these instances already make clear, we will understand rather little about water in molecular biology on the basis that biomolecules are surrounded by some vague sheath of hydration water. It is necessary to have a detailed, perhaps atomic-resolution picture of where the water molecules are and how they fit together. This structural information has been obtained for many molecular entities—especially proteins, but also DNA and membranes—from a variety of methods, such as X-ray and neutron scattering, NMR, and second harmonic generation spectroscopies, assisted by molecular dynamics and *ab initio* simulations. Low-frequency, large-amplitude modes in the terahertz range are particularly important in controlling the conformational changes that dominate protein function, and are conveniently probed using terahertz spectroscopy (45, 46). However, there is no simple qualitative account of how protein and solvent dynamics interact. Fluctuations of both take place over a wide range of timescales from milliseconds to picoseconds, influencing several aspects of protein function (Fig. 1). Because no single technique can span so many temporal orders of magnitude, there has been considerable debate about how to reconcile the results of different experimental methods that explore dynamics, such as NMR relaxation, neutron scattering, ultrafast IR, and terahertz spectroscopies (28, 47).

The general picture that emerges, however, is one in which water molecules partake in the hydration environment with a very wide range of residence times and dynamics that may be both faster and slower than the bulk. In general, hydration waters at the solvent-exposed surfaces of proteins have residence times of several picoseconds, but those within deeply concave clefts and internal cavities can be much longer-lived—up to several microseconds—before exchanging with the bulk (48, 49). Molecular dynamics simulations of myoglobin, for example, indicate that, although the residence times of hydration water molecules are mostly rather similar to those in bulk water (<10 ps), there is a long tail of longer residence times, with some waters in cavities and clefts—geometry, rather than surface chemistry, seems to be the dominant factor—reaching up to 450 ps (48).

Orientational relaxation too is often slowed in the hydration shell. For example, a comparison of molecular dynamics simulations with femtosecond IR spectroscopy of the hydration of bovine  $\alpha$ -lactalbumin (50) reveals a continuum of water relaxation times; slow waters have relaxation times >7 ps, and some are as much as 20 ps (Fig. 2). The latter molecules again tend to be located in concavities on the protein surface, and they make fewer hydrogen bonds with surrounding waters than do molecules in the bulk.



**Fig. 1.** The hierarchy of timescales for motions of proteins and their hydration environment. HB, hydrogen bond. Reproduced from ref. 46 with permission from AIP Publishing.



**Fig. 2. Water reorientational decay times seen in simulations of (Left) native and (Right) misfolded bovine  $\alpha$ -lactalbumin. Reproduced from ref. 50 with permission, copyright 2016 American Chemical Society.**

Moreover, waters near hydrophobic groups tend to be slower on average than those near hydrophilic groups.

A study of four diverse proteins by Fogarty and Laage (51) shows that, despite their many differences, all have rather similar hydration shell dynamics. This finding was interpreted as an indication that the dynamics are determined by rather general features of surface chemistry and topology, which induce excluded volume effects and hinder the approach of new hydrogen bond acceptors within the hydration network.

The traditional “lock and key” picture of enzyme action has long been modified to acknowledge the vital importance of conformational freedom (52). In short, dynamics must collaborate with structure to get the job done. There has been somewhat slower but now widespread recognition that the dynamical behavior of biological macromolecules in general, and of proteins in particular, cannot be decoupled from that of its solvent. In one view, dynamical degrees of freedom in the hydration shell supply fluctuations that help proteins to undergo the conformational shifts entailed by their chemical function. For example, X-ray scattering from the collective modes of hydrated lysozyme (53) shows that a weakening of “soft” phonon modes at low hydration is correlated with a decline in enzymatic activity. Frauenfelder et al. (54) have proposed a “unified model” of protein dynamics, in which short-wavelength fluctuations are slaved to those of the hydration layers whereas large-scale protein motions are slaved to bulk fluctuations and dominated by viscosity.

### How Hydration Water Assists Protein Function

Hydration water molecules may adopt crystallographically well-defined positions around a macromolecule, and some of these have functional roles. One might say that the surfaces of the biomolecules are not sharply defined: their sphere of influence extends beyond the van der Waals surface into the solvent, and this coupling can make the hydration shell for all intents and purposes part of the biomolecule itself, imbued with some of the information that it encodes and therefore able to play a role in intramolecular rearrangements and intermolecular recognition processes. Examples of how water molecules and networks at a

protein surface may assist in its recognition and catalytic functions are legion; one might reasonably suspect that proteins treat water as a resource to be exploited whenever convenient. For example, water molecules can mediate interactions between a protein and a substrate either to increase selectivity or to enable recognition of multiple substrates. They can transmit conformational changes from one location to another; they may act as channels for proton conduction or provide proton donor, acceptor, and storage sites. I have outlined some instances in previous articles (3, 55); here, I take the opportunity to indicate some recent ones, while pointing to some of the general strategies that they exemplify.

**Proton Donation and Translocation.** One of the most common uses for bound water in biology is as a channel for proton transport, generally by means of the Grotthuss hopping mechanism that produces anomalously fast proton transport in pure water (56). This hopping process is more complex than once thought, not least because it seems to occur over a wide range of length scales (57).

Hydrogen-bonded chains of water molecules may comprise “water wires” that support proton translocation into and through proteins (58). This transport can happen in passive fashion, but it may also be active, dynamic, and controlled by protein motions. Kaila et al. (59) describe such a process in Complex I, an enzyme involved in the initial step in the mitochondrial and bacterial respiratory process, in which proton pumping is redox driven by coupling to electron transport between NADH and quinones. Here, a transient proton-conducting water channel is formed by the cooperative hydration of three antiporter-like subunits within the membrane domain of the complex. As Kaila et al. (59) conclude, “water-gated transitions may provide a general mechanism for proton-pumping in biological energy conversion enzymes.”

Delicate marshaling of water molecules into positions that control the proton conductivity of a channel is also evident in cytochrome c oxidase, a transmembrane proton pump driven by oxygen reduction. Goyal et al. (60) show how hydration seems to



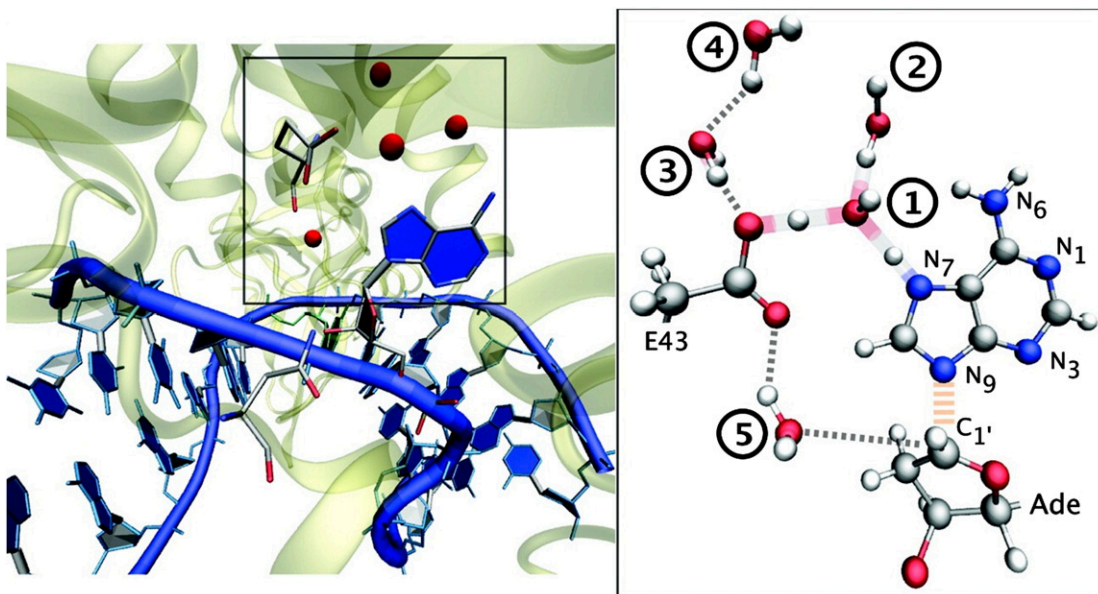


Fig. 4. Water-assisted excision of a damaged adenine in DNA by MutY. (Left) The mispaired adenine is extruded into a cavity. (Right) The catalytic site contains five water molecules. Proton transfer from E43 to N<sub>7</sub> is mediated by W1, supported by neighboring structured water molecules. Reproduced from ref. 66 with permission, copyright 2012 American Chemical Society.

**Antifreeze Proteins.** Spatially extended ordering of bound water is observed in antifreeze proteins, which bind to ice to control crystallite nucleation and growth. For example, the arrangement of hydrogen-bonding moieties on the protein surface may be commensurate with those in the ice lattice, as seen, for example, in wfAFP-1 (71). The involvement of bound water can be more exotic. The fish antifreeze protein Maxi is a four-helix bundle with an interior, mostly hydrophobic channel filled with more than 400 water molecules, crystallographically ordered into a clathrate-like network of predominantly five-membered rings (72). It seems that this ordered network extends outward through the gaps between the helices to create an ordered layer of water molecules on the outer surface that enables Maxi to bind to ice crystals and

hinder their growth, acting as a kind of “molecular Velcro” for ice binding (Fig. 5).

#### Water in Ligand Binding and Drug Design

The structural participation of hydration water in biomolecular recognition recommends it as a potential element in drug design. The difficulty, however, is that it is far from obvious how to generalize such behavior to extract design rules. Until recently, therefore, there has been relatively little effort to make use of the versatility of hydration water in this manner (73–76).

In general, water networks are rearranged and/or displaced by ligand binding—and here, the thermodynamic consequences may be subtle and hostage to fine details. That difficulty was

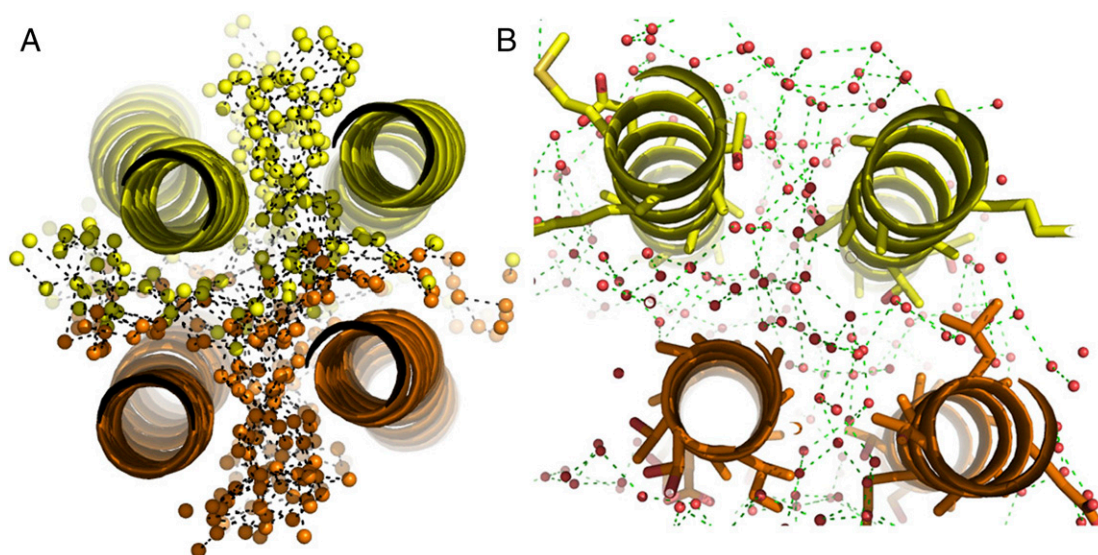


Fig. 5. (A) The network of some 400 interior waters in the antifreeze protein Maxi, with hydrogen bonds indicated by dotted lines. (B) Cross-section showing part of the water network rich in five-membered clathrate-like rings. Reproduced from ref. 72 with permission from AAAS.

made particularly clear in studies by Whitesides and coworkers (77–79) of protein–ligand binding in the human carbonic anhydrase system. A series of ligands modified with various thiazole-based sulfonamides was used to probe the effects of solvent rearrangements within the binding cavity. The changes in the free energy of binding and the contributions from enthalpy and entropy are largely determined by the rearrangements or displacements of water: Breiten et al. (78) conclude that a “water-centric” view of ligand binding cannot be rationalized by the lock and key principle; rather, the molecules of water surrounding the ligand and filling the active site of a protein are as important as the structure of the ligand and the surface of the active site. However, there is nothing obvious about how water molecules function in this capacity. Although it is tempting, for example, to imagine that binding will be governed by the entropic benefit of expelling bound water from the hydrophobic face of the binding pocket, in fact enthalpic effects at the hydrophilic surface seem to predominate in this case.

Despite such complexities, rational design of ligands and drugs that takes water-mediated interactions into account does now seem to be becoming feasible. Consider, for instance, the M2 proton channel of the influenza A virus, a common drug target. Here, a water network seems to gate proton conduction (58, 80). Gianti et al. (81) have studied how the proton channel may be targeted with inhibitory drugs. Known inhibitors seem to bind to the channel and disrupt the proton-transporting water cluster. By calculating the energetics of pore blockers at different sites in M2, they conclude that effective ligand scaffolds mimic the water cluster contour, while also preserving the interactions that the cluster made with the protein.

Krimmer et al. (82) focus instead on the nature of hydration of the final protein–ligand complex. They say that optimizing the water layers covering hydrophobic inhibitors of thermolysin can boost the enthalpic contribution to binding free energy. Their simulations enabled the prediction of high binding affinity for a series of ligands, one of which was subsequently shown experimentally to have 50 times higher binding affinity than the known, patented parent ligand.

Perhaps data-mining and empirical correlations will, in the end, offer more in the way of rules of thumb for ligand design than will studies from first principles. By analyzing over 2,000 crystal structures of hydrated and nonhydrated ligand–receptor complexes, including many drugs, García-Sosa (83) finds, for example, that bridging water molecules are effective targets for achieving tight binding.

There is increasing reason to believe that the efficiency of ligand binding is also influenced by dynamical aspects of hydration. Studies using terahertz spectroscopy have shown that modified dynamics can appear in a protein’s hydration shell up to at least 10 Å from the protein surface (84). On these timescales, the solvent motions involve collective modes of many water molecules. The metalloprotease MT1-MMP establishes a dynamical gradient close to the active site as the substrate approaches, creating a “hydration funnel” that guides the molecular recognition process by reducing the entropic cost of binding (84). Long-range control of water dynamics, extending up to 20 Å from the molecular surface, also seems important for the ice binding function of some antifreeze proteins and glycoproteins (85, 86).

## Conclusion

Insights gleaned over the past two decades or so about the roles of water in molecular and cell biology leave no doubt that it exerts

an active agency in life, extending, modifying, complementing, and enabling the functions of biomolecules. Many questions remain open. How are the dynamics of water and biomolecular solutes related, and how do these dynamics influence function? How are fluctuations on different timescales and spatial scales coupled? How are the properties of water modulated at surfaces, and how do these depend on the chemical and geometric features of the surface? How are these properties modified by the presence of cosolutes, such as salts and small osmolyte molecules? How does hydration affect the behaviors of membranes, nucleic acids, and glycoproteins, which have been afforded rather less attention than proteins? Does hydration play a role in disease (for example, in mediating protein misfolding)? Are there general principles of hydration that can be exploited in ligand and drug design?

Broader questions on which it is, at this stage, perhaps possible to do no more than speculate are whether, where, and by how much the biomolecular uses of hydration in function are evolutionarily adaptive. It could be that—like, for example, examples of quantum mechanical tunneling in biomolecular proton and electron transfer—at least some of these manifestations are an inevitable physicochemical outcome rather than an adaptation. However, whatever the case, the sensitivity of the hydration environment, exploiting the cooperativity of water motions, to small changes in protein conformation offers a sensitive way for macromolecular dynamics to alter behavior. As De Simone et al. (87) have put it: “The sensitivity of the energy surfaces of proteins to minor perturbations supports the view that there is a delicate balance between functionality, stability, and solubility, which is encapsulated by the concept of ‘life on the edge.’”

All of this touches on the astrobiological question mentioned at the outset: should we, like Henderson (88) in 1913, regard water as uniquely “biophilic” and “fit” to act as life’s matrix? The answer remains unclear, although, given that there are several potential alternative astrobiological solvents (6), we would be well-advised not to take it for granted. However, what the current understanding of biological hydration does tell us is that the issues are more subtle than is often supposed, because water’s biological roles are not easily reduced to a handful of properties that follow self-evidently from its molecular nature, or indeed even from the characteristics of the pure bulk liquid. We might say, however, that water does seem rather special in offering a degree of what one may call biological affordance: it offers opportunities for refining and conditioning intermolecular information transfer that seem less readily available from other solvents. [I use “affordance” here in Gibson’s (89) original sense of opportunities provided by the environment.]

It can be hard to keep an appropriate perspective when water is concerned. As a substance of primal significance to human culture, it has a propensity to generate mythology that becomes manifest even at the scale of basic physics and chemistry. Its notorious roles in episodes of pathological science, such as polywater and “water memory,” are the most egregious instances, but there is a whiff of this mythopoeic character in discussions of “vicinal water” (90), biological water, and water structure invoked to explain, *inter alia*, long-ranged hydrophobic (91) and hydrophilic (92) interactions and Hofmeister or ion-specific effects of electrolytes on protein aggregation (93). We should approach water’s biological behavior with this in mind, wary not to claim too much on its behalf. To take just one example, the alluring concept of solvent “structure making and breaking” as an explanatory scheme for the biological effects of ions, denaturants, and other

osmolytes seems now to be a simplistic residue of attempts to use “water structure” to explain puzzling solvation phenomena. Such cosolute effects are better understood by delving into the specific details of direct interactions between solutes and biomolecules (94). This is not to suggest that water structure is in itself an obsolete concept: there seems no doubt that hydration must take account of structural aspects, such as tetrahedrality, coordination number, and dangling bonds. The point is that, first, it is hard to generalize about such things, especially when discussing

biomolecular hydration, and second, dynamical factors often seem to be at least as important as any static structural pictures.

However, if we should abandon notions of some special and well-defined phase called biological water, there does not seem to be any prospect of or virtue in returning water to its humble position of life’s canvas. It is a versatile, responsive medium that blurs the boundaries between mechanism and matrix. It surely is special; we might have to depend on either synthetic biology or observational astrobiology to tell us just how special.

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