

## Water as the Fabric of Life

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**Abstract.** Many share the feeling that we are at in the midst of a shift in our perception of water – a shift from the current molecular-level based approach (which focuses on the behaviour of individual or small numbers of molecules) towards a new, systemic view of water. In this new picture, water is perceived as an active substance that responds adaptively to external and internal constraints and signals. These responses can have profound effects on substances immersed in water, and in particular on the functioning of biological constituents, from molecules to living cells. This special volume presents some existing and possible future directions in this trend towards a systemic view of water as an active substance, which plays many essential roles in sustaining life. The work reported here suggests that the notion of water as “life’s solvent” should give way to the new realisation of water as an active “fabric of life”, continuously engaging and interacting with biomolecules in complex and subtle ways.

Three decades ago, in an article entitled “Water Revisited”, Frank Stillinger said:

A comprehensive molecular theory for water is needed for two reasons: First, this substance is a major chemical constituent of our planet’s surface and as such it may have been indispensable for the genesis of life. Second, it exhibits a fascinating array of unusual properties both in pure form and as a solvent. Physical scientists have attempted to respond to this need for nearly a century, but a satisfactory molecular theory has only begun to emerge in the last decade [1].

Stillinger referred to the progress made in the 1970s in understanding the nature and geometry of non-covalent interactions between water molecules via hydrogen bonding. His article focused on the spontaneous creation and annihilation of local clusters of several water molecules, characterised by strong hydrogen bonds and nearly tetrahedral angles. The article presented a molecular-level view of water’s structure, saying that “All the properties of water and aqueous solutions ultimately must be explained in terms of intermolecular forces that are present”. It expressed a sense of optimism that a general theory of water was at hand.

Two and a half decades later, in a monograph entitled “Water? What’s so special about it?”, John Finney commented that:

Although we pay lip service to the biological importance of water, we do not understand what it is about the molecule that makes it a particularly “fit” molecule to form the “matrix of life” [2].

Finney proposed that water's anomalous properties (such as its density maximum and singularities in its thermodynamic response functions) should not be perceived as "mysteries", as they can be explained on the basis of water-molecule interactions at the molecular level. He claimed that "Some demystification of water might help us to understand more clearly its role in the molecular-level processes that are important for maintaining life". The focus in this important article was also on the developments in understanding the role of tetrahedral geometry in governing the local order of water, and the central role of this understanding in explaining water's anomalies. However, at the same time Finney suggested that such understanding "may be incidental to the molecular-level biological fitness of water", admitting that the molecular-level picture falls short of providing a comprehensive theory of water's role in the genesis of life [2].

A decade ago, there was a common view among physical chemists that a satisfactory theory of water was established except for a few details. (We would suggest that among molecular biologists, meanwhile, there was barely any awareness of significant outstanding questions about water at all.) While many scientists still hold this notion, it has been questioned. Six years ago, one of us (P.B.) pronounced it an "embarrassment" that "the stuff that covers two-thirds of our planet is still a mystery... the more we look, the more the problems accumulate: new techniques probing deeper into the molecular architecture of liquid water are throwing up more puzzles" [3]. Although some of those puzzles – such as questions about the tetrahedral coordination of bulk water [4,5] – seem now to be within reach of a resolution, other important questions, such as the nature of hydrophobic hydration [6,7] and the existence of a second critical point in supercooled water [8,9], remain unanswered.

More pertinent than the fact that some basic properties of water and hydration are still not understood, however, is the fact that many facets of water's behaviour can now be seen to be inadequately accounted for by any picture that regards the liquid state as being the sum of its parts. That is to say, the phase, solvation and wetting behaviours of the liquid are not determined in a transparent way from the properties of the individual water molecules, but emerge from their collective interaction, over many length scales, in ways that can be highly context-dependent. To take one striking example, water might be expected to wet a hydrophilic surface like that of platinum metal, but in fact droplets have a finite contact angle because of the formation of an initial monolayer that then acts as a "hydrophobic coating" [10,11]. Hydration and drying transitions are highly sensitive to local geometry (for example, concave or convex surfaces), which are "felt" by the three-dimensional hydrogen-bonded network. In addition, the nature of hydration is dependent on the size of the solute particles [12] or the proximity of an air-water interface [13]. In short, one has to regard the properties of water even on the molecular scale as ones that are emergent and interdependent, in a manner that is analogous to the way in which particle masses in fundamental physics are now seen to be an emergent consequence of their interactions. This means that, for an understanding of water's properties, it is often insufficient to think only in terms of local interactions; one must take a systemic view, considering the ways in which water modifies its own tendencies in response to its environment. Such a picture might be needed to explain several of the phenomena described in this volume. In some cases, the phenomena themselves are empirical, and a theoretical understanding is still speculative or preliminary at best.

This special issue collects together six papers that touch on these topics. Three of the contributions focus on related issues in an area of biomolecular science that has excited much debate: the nature of hydrophobic interactions, and the role of the solvent more generally, in protein folding and substrate binding. Snyder *et al.* interrogate the popular view that some substrates bind to hydrophobic cavities of proteins by a matching of hydrophobic surfaces, producing an entropic driving force through

the expulsion of bound water. They conclude that such “hydrophobic effects” in fact involve a much more subtle balance of entropic and enthalpic factors about which it is hard to generalise – in short, that there is no unique mechanism of the “hydrophobic interaction”. The article by Ben-Naim offers another challenge to the simplistic notions of hydrophobic attractions, which are commonly held to be a, perhaps even the, major factor behind the collapse and folding of globular proteins. On the contrary, Ben-Naim argues, the folding process is dominated by water-mediated interactions between hydrophilic groups on proteins. And the article by McMahon *et al.* offers a unified view of protein dynamics and function that incorporates the role of hydration structure and dynamics into the energy landscape.

In addition to the familiar short-ranged hydrophobic interaction (whatever its precise nature and origin), it has long been recognised that there may exist a longer range attraction between hydrophobic surfaces in water. One popular theory is that the attraction derives from the formation of nanoscale bubbles of dissolved gases, which bridge the surfaces and pull them together through surface tension. At any rate, the existence of such nanobubbles on individual hydrophobic surfaces is now well attested, but has posed a theoretical puzzle because the standard picture of gas-liquid equilibria implies that they should be thermodynamically unstable. Several possible explanations for the stability of nanobubbles have been advanced, some of which draw on non-equilibrium dynamical processes. The article by Attard proposes an alternative view in which nanobubbles may be thermodynamically stable provided that one adopts a more sophisticated description of the interfacial tension.

The final two papers describe puzzling experimental results on the meso- and macroscale behaviour of water for which theoretical explanations remain considerably speculative. Yu *et al.* describe the spontaneous appearance of directional water flow through hydrophilic channels in the absence of an applied driving force. They suggest that this may be related to the formation of a micron-scale layer of “interfacial water” adjacent to the channel surfaces. Fuchs *et al.* examine a phenomenon first attested in the late nineteenth century, whereby the application of a high voltage across two vessels brimming with water can lead to the formation of a “water bridge” between them. They review the phenomenology of these water bridges and suggest an explanation in terms of electrohydrodynamic flow induced by the steep electric field gradient.

With these papers, we hope to trigger debate about the possibility that the common view of liquid water as a substance that simply and universally adopts local tetrahedral configurations through hydrogen bonding is too limited and even wrong in some cases. That debate could revisit the fundamental assumptions that, firstly, at room temperature water can be assumed to be close to equilibrium; and secondly, water is in a homogeneous state with no long-range correlations, dissolved substances are homogeneously distributed, and molecules dissolved in water are subject to non-correlated noise. These notions disregard a systemic view which posits (among other things) the following. 1. Water at room temperature under ordinary conditions (open to the atmosphere) is a non-equilibrium open system that exchanges heat and gases with the environment and absorbs electromagnetic radiation and acoustic signals. 2. Consequently, water is usually in a dynamic state of continuous self-organisation, manifested by the formation of complex organisation on all scales. 3. Immersed nanoparticles and nanobubbles, as well as the presence of hydrophobic surfaces, can change the organisation of water from the nanoscale (local arrangements of tens of molecules) up to a scale of microns. 4. The complex organisation of water can lead to local variations in pH, chemical affinity, density and so on.

Some of these papers also support an emerging view in which water actively engages and interacts with biomolecules in complex, subtle, and essential ways. There is now good reason to regard the “active volume” of molecules such as proteins as

extending beyond their formal boundary by virtue of the way they shape and manipulate the shell of water that surrounds them. Moreover, the structure and dynamics of this hydration shell seem to feed back onto those aspects of the proteins themselves so that biological function depends on a delicate interplay between what are currently regarded as distinct entities: the molecule and its environment. Many proteins make use of bound water molecules as functional units, like snap-on tools, to mediate interactions with other proteins or with substrate molecules or to transport protons rapidly to locations deep inside the protein.

For such reasons, the prevailing notion of water as a passive solvent that does little more than temper or moderate the basic physicochemical interactions responsible for molecular biology is a too simplistic and even a misleading view of water's role in the chemistry of life.

The distinction between the systemic and the molecular-level views of water brings to mind Philip Anderson's seminal article on emergent complexity, "More is different" [14]. Here Anderson promoted the notion of "constructivism" as a way to understand complex systems, and argued that new fundamental principles are needed to explain their higher-level (systemic) properties. He proposed that, even if we accept that the rules that govern the dynamics at a higher level *in principle* emerge (according to reductionism) from the lower-level rules, since *in practice* they are not derivable we should treat them as being equally fundamental as the rules at the lower level. The way water adaptively responds to external and internal constraints, cues and signals by generation of complex organisation on all scales is reminiscent of the adaptive response of living systems. Could it be, then, that the notion that "More is different" (on all levels) fits the systemic view of water as the fabric of life?

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