Water in nanoconfined and biological environments  
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ABSTRACT

We discuss some recent progress in understanding the anomalous behavior of liquid water, by combining information provided by recent experiments and simulations on water in bulk, nanoconfined, and biological environments. We interpret evidence from recent experiments designed to test the hypothesis that liquid water may display “polymorphism” in that it can exist in two different phases — and discuss recent work on water’s transport anomalies as well as the unusual behavior of water in biological environments. Finally, we will discuss how the general concept of liquid polymorphism may prove useful in understanding anomalies in other liquids, such as silicon, silica, and carbon, as well as metallic glasses which have in common that they are characterized by two characteristic length scales in their interactions.

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1. Water: a complex liquid

Water is vital for life [1]. Not surprisingly, then, water though seemingly simple in its chemical formula, is a very complex liquid. In particular, its phase diagram is rich and complex, with more than sixteen crystalline phases [2], and two or more glasses [3–5]. The liquid state also displays complex behavior, such as the density maximum for 1 atm at 4 °C. The volume fluctuations (δV)², entropy fluctuations (δS)², and cross-fluctuations between volume and entropy δVδS, proportional to the magnitude of isothermal compressibility Kₜ, isobaric specific heat Cᵥ, and isobaric thermal expansivity αₜ, respectively, show anomalous increases in magnitude upon cooling [6]. Further, data on all three quantities are consistent with a possible “apparent divergence” for 1 atm at ~45 °C [6], a phenomenon that has attracted many scientists and which hints at interesting phase behavior in the deeply supercooled region.

Microscopically, liquid water’s anomalous behavior is understood as resulting from the tendency of neighboring molecules to form hydrogen bonds (H-bonds) upon cooling, with a decrease of local potential energy, decrease of local entropy, and increase of local volume due to the formation of “open” local structures of bonded molecules. Different models include these H-bond features, but depending on the assumptions and approximations of each model, different conclusions are obtained for the low-T phase behavior. The relevant region of the liquid state cannot readily be probed experimentally, so a great deal of ingenuity has been used to obtain the results we have.

2. Four scenarios for understanding low-temperature water

Due to the difficulty of obtaining experimental evidence, theoretical and numerical analyses are useful. Four different scenarios for the pressure–temperature (P–T) phase diagram have been proposed:

(I) The stability limit (SL) scenario [7] hypothesizes that the superheated liquid–gas spinodal at negative pressure re-enters the positive P region below the temperature Tₛ(P) of homogeneous nucleation of the crystal ice. In this view, the liquid state is delimited by a single continuous locus, Pₛ(T), bounding the superheated, stretched and supercooled states. There is no reference to the phase into which the liquid transforms when P→Pₛ(T). As the spinodal is approached, Kₛ, Cᵥ, and |αₜ|→∞. A thermodynamic consequence of the SL scenario is that the intersection of the retracing spinodal with the liquid–vapor coexistence line must be a critical point [3]. The presence of such a critical point in the liquid–vapor transition, although possible, is not confirmed by any experiment. This fact poses a serious challenge to the SL scenario.

(II) The liquid–liquid critical point (LLCP) scenario [8] hypothesizes a first-order phase transition line between two liquids — a low density liquid (LDL), and a high density liquid (HDL) — which terminates at a liquid–liquid critical point C’. HDL is a dense...
liquid with a highly disordered structure, whereas LDL has a lower density and locally tetrahedral order. The experimentally observable high density amorphous (HDA) and low density amorphous (LDA) solids correspond, in this scenario, to a structurally arrested state of HDL and LDL respectively [9,10]. Starting from C, the locus of maxima of the correlation length \( \xi \) (the Widom line) projects into the one-phase region [11,12]. Asymptotically close to the critical point, response functions can be expressed in terms of \( \xi \), hence, these too will show maxima, e.g., as a function of \( T \) upon isobaric cooling. These maxima will diverge upon approaching \( C \). However along paths that miss the critical point, these functions will display maxima, a phenomenon discussed in the context of water by Sciortino et al. [13]. Furthermore, for \( P>P_c \), the pressure of \( C \), the response functions will diverge by approaching the spinodal converging to \( C \). Specific models suggest [8,14] that \( P_c>0 \), but the possibility \( P_c<0 \) has also been proposed [15,16].

(III) The singularity-free (SF) scenario [17] hypothesizes that the low-\( T \) anticorrelation between volume and entropy is sufficient to cause the response functions to increase upon cooling and display maxima at non-zero \( T \), without reference to any singular behavior [18,19]. Specifically, Saxtry et al. [17] consider the temperature of maximum density (TMD) line, where the density has a maximum as a function of temperature, and prove a general thermodynamic theorem establishing the proportionality between the slope of the TMD, \( (\partial P/\partial T)_{TMD} \) and the temperature derivative of \( K_f \). Thus, since the TMD has negative slope in water, i.e. \( (\partial P/\partial T)_{TMD}<0 \), it follows that \( K_f \) must increase upon cooling, whether there exists a singularity or not.

(IV) The critical-point-free (CPF) scenario [20] hypothesizes an order-disorder transition, with possibly a weakly first-order transition character, separating two liquid phases and extending to \( P=0 \) down to the superheated limit of stability of liquid water. This scenario effectively predicts a continuous locus of stability limit spanning the superheated, stretched [21] and supercooled state, because the spinodal associated with the first-order transition will intersect the liquid-gas spinodal at negative pressure. No critical point is present in this scenario.

These four scenarios predict fundamentally different behavior, though each has been rationalized as a consequence of the same microscopic interaction: the H bond [22–24]. A question that naturally arises is whether the macroscopic thermodynamic descriptions are in fact connected in some way. Previous works have attempted to uncover relations between several of the scenarios, for example between (I) and (II) [14,25] or (II) and (III) [26,27]. Recently, Stokley et al. [28] offered a relation linking all four scenarios showing that (a) all four can be included in one general scheme, and (b) the balance between the energies of two components of the H bond interaction determines which scenario is valid (Fig. 1). Moreover, they argue that current values for these energies support the LLCP scenario.

3. Selected experimental results

Current experiments on this problem are of two sorts. The first is a set of experiments on bulk water inspired by Mishima that involves probing the No Man’s Land by studying the metastable extensions of the melting lines of the various high-pressure polymorphs of ice: ice III, ice V, ice IV, and ice XII [29,30]. Two of these lines clearly display “kinks.” Since the slope of any melting line is the difference of the volume change divided by the entropy change of the two phases that coexist at that line, if there is a change in slope there must be a change in these quantities. Since there is no change in the crystal part, there must be a change in the liquid part. This means the liquid must undergo a jump in either its volume or its entropy or both. That is the definition of a first-order phase transition.

![Fig. 1. Possible scenarios for water for different values of H bond energies \( J \) of the covalent (or directional) component, and \( J_s \) of the cooperative (or many-body) component, obtained from MF calculations [28]. (i) If \( J_s = 0 \) (red line along X-axis), the singularity free (SF) scenario is realized, independent of \( J \). (ii) For large enough \( J_s \), water would possess a first-order liquid-liquid phase transition line terminating at the liquid–gas spinodal—the critical point free (CPF) scenario; the liquid spinodal would retrace at negative pressure, as in the stability limit (SL) scenario (yellow region in top left). (iii) For other combinations of \( J \) and \( J_s \), water would be described by the liquid–liquid critical point (LLCP) scenario. For larger \( J_s \), the LLCP is at negative pressure (orange region in bottom right). Dashed lines separating the three different regions correspond to MF results of the microscopic cell model. The \( P-T \) phase diagram evolves continuously as \( J \) and \( J_s \) change.

A second set of experiments is being carried out on confined water in the MIT group of Chen and the Messina group of Mallamace, which have stimulated many of our recent calculations. Mallamace, Chen, and their collaborators succeeded in locating the Widom line by finding a clearcut maximum in the coefficient of thermal expansion, at \( T_{\text{CP}} \approx 225 K \) [31], which remarkably is the same temperature as the specific heat maximum [32]. Also, private discussions with Jacob Klein reveal a possible reason for why confined water does not freeze at \( -38C \), the bulk homogeneous nucleation temperature: Klein et al. [33] noted that confined water behaves differently than typical liquids in that water does not experience the huge increase in viscosity characteristic of other strongly confined liquids. They interpret this experimental finding as arising from the fact that strong confinement hampers the formation of a hydrogen bonded network, and we know from classic work of Linus Pauling that without the extensive hydrogen bonded network, water’s freezing temperature will be depressed by more than 100 degrees. Thus confinement reduces the extent of the hydrogen bonded network and hence lowers the freezing temperature, but appears to leave the tetrahedral local geometry unchanged.

4. Theoretical predictions and experimental tests of the liquid–liquid critical point and singularity free scenarios

Using Monte Carlo simulations and mean field calculations, a cell model of water proposed by Franzese et al. [12,34–36] can reproduce all four scenarios that have been discussed for water. Kumar et al. [37–39] found that both the LLCP and SF scenarios exhibit a dynamic crossover at the temperature of the maximum isobaric specific heat \( C_p \), which decreases for increasing \( P \). They interpret the dynamic crossover as a consequence of a local breaking and reorientation of the bonds for the formation of new and more tetrahedrally oriented bonds. Above \( T(C_p) \), when \( T \) decreases, the number of hydrogen bonds increases, giving rise to an increasing activation energy \( E_A \) and to a non-Arrhenius dynamics. As \( T \) decreases,
entropy must decrease. A major contributor to entropy is the orientational disorder, that is a function of $p_b$, the probability of forming a hydrogen bond, as described by the mean field expression for the entropy change $\Delta S$ with orientation. They found that, as $T$ decreases, $p_b$ increases. They found that the rate of increase has a maximum at $T(CP^{\beta})$, and as $T$ continues to decrease this rate drops rapidly to zero — meaning that for $T < T(CP^{\beta})$, the local order rapidly becomes temperature-independent and the activation energy $E_A$ also becomes approximately temperature-independent. Corresponding to this fact the dynamics becomes approximately Arrhenius.

They found that the relaxation time at the crossover temperature $T_A$ is approximately independent of the pressure (isochronic crossover) consistent with their calculations of an almost constant number of bonds at $T(CP^{\beta})$. They found also that $E_A$ and $T_A$ decrease upon increasing $P$ in both LLCP and SF scenarios. Instead, the $P$ dependence of the quantity $E_A/(k_BT_A)$ has a different behavior in the two scenarios, although the difference is about 1%. For the LLCP scenario it increases as $P \to P_c$, while it is approximately constant in the SF scenario. They interpret this difference as a consequence of the larger increase of the rate of change of $p_b$ in the LLCP scenario, where $p_b$ diverges at finite $T$, compared to the SF scenario, where $p_b$ can possibly diverge only at $T = 0$. Experiments can detect local changes of water structure from HDL-like to LDL-like, (e.g., [40]). Hence, it is possible to test the predictions on the dynamic consequences of this local change. Franzese et al. [41] found that three of the four predictions made by Kumar et al. in [37,38] are verified in experiments. Indeed, Chen and collaborators verified that the crossover is isochronic, and that $E_A$ and $T_A$ decrease upon increasing $P$. The fourth prediction about the behavior of $E_A/(k_BT_A)$, discriminating between the two possible scenarios, cannot be verified within the precision of the experiment [42].

5. The Widom line emanating from every critical point into the one-phase region

By definition, in a first order phase transitions, thermodynamic state functions such as density $\rho$ and enthalphy $H$ discontinuously change as we cool the system along a path crossing the equilibrium coexistence line [Fig. 2(a), path $\beta$]. In a real experiment, this discontinuous change may not occur at the coexistence line since a substance can remain in a supercooled metastable phase until a limit of stability (a spinodal) is reached [43][Fig. 2(b), path $\beta$]. If the system is cooled isobarically along a path above the liquid-gas critical pressure $P_c$ [Fig. 2(b), path $\alpha$], the state functions continuously change from the values characteristic of a high temperature phase (gas) to those characteristic of a low temperature phase (liquid). The

![Fig. 2](image-url)

(a) Liquid–Gas ("theory")
(b) Liquid–Gas ("experiment")
(c) Water
(d) Jagla Model

Fig. 2. (a) Schematic phase diagram for the critical region associated with a liquid–gas critical point. Shown are the two features displaying mathematical singularities, the critical point (closed circles) and the liquid–gas coexistence (bold dashed curve). (b) Same as (a) with the addition of the gas–liquid spinodal and the Widom line. Along the Widom line, thermodynamic response functions have extrema in their $T$ dependence. The path $\alpha$ denotes a path along which the Widom line is crossed. Path $\beta$ denotes a path meeting the coexistence line. (c) A hypothetical phase diagram for water of possible relevance to the recent neutron scattering experiments by Chen et al. [60,61] on confined water. The liquid–liquid coexistence, which has a negative sloped coexistence line, generates a Widom line which extends below the critical point, suggesting that water may exhibit a dynamic crossover (non-Arrhenius-to-Arrhenius) transition for $P \to P_c$ (path $\alpha$), while no dynamic changes will occur above the critical point (path $\beta$). (d) A sketch of the $P$–$T$ phase diagram for the two-scale Jagla model. For the Jagla potential, as well as for the shouldered potentials [109–112], the liquid-liquid phase transition line has a positive slope. Upon cooling at constant pressure above the critical point (path $\alpha$), the liquid changes from a low density state (characterized by a non-glassy Arrhenius dynamics) to a high density state (characterized by glassy Arrhenius dynamics with much larger activation energy) as the path crosses the Widom line. Upon cooling at constant pressure below the critical point (path $\beta$), the liquid remains in the LDL phase as long as path $\beta$ does not cross the LDL spinodal line. Thus one does not expect any change in the dynamic behavior along the path $\beta$, except upon approaching to glass transition where one can expect the non-Arrhenius behavior characterized by the Vogel–Fulcher–Tamman (VFT) fit.
thermodynamic response functions which are the derivatives of the state functions with respect to temperature [e.g., isobaric heat capacity \( C_P = \left( \frac{\partial H}{\partial T} \right)_p \)] have maxima at temperatures denoted by \( T_{\text{max}}(P) \). Remarkably these maxima are still prominent far above the critical pressure \([11,12,32,44,45]\), and the values of the response functions at \( T_{\text{max}}(P) \) (e.g., \( C_P^{\text{max}} \)) diverge as the critical point is approached. The lines of the maxima for different response functions asymptotically approach one another as the critical point is approached, since all response functions become expressible in terms of the correlation length. This asymptotic line is sometimes called the Widom line, and is often regarded as an extension of the coexistence line into the “one-phase regime” \([11]\).

Water’s anomalies have been hypothesized to be related to the existence of a line of a first order liquid–liquid phase transition terminating at a liquid–liquid critical point \([3,8,29,36,43,46]\), located below the homogeneous nucleation line in the deep supercooled region of the phase diagram — sometimes called the “no-man’s land” because it is difficult to make direct measurements on the bulk liquid phase \([29]\). In supercooled water, the liquid–liquid coexistence line and the Widom line have negative slopes. Thus, if the system is cooled at constant pressure \( P_0 \), computer simulations suggest that for \( P_0 < P_\text{c} \) \([2,29]\), path \( \alpha \) experimentally-measured quantities will change dramatically but continuously in the vicinity of the Widom line (with huge fluctuations as measured by, e.g., \( C_P \)) from those resembling the high density liquid (HDLC) to those resembling the low density liquid (LDLC). For \( P_0 > P_\text{c} \), path \( \beta \), experimentally-measured quantities will change discontinuously if the coexistence line is actually seen. However, the coexistence line can be difficult to detect in a pure system due to metastability, and changes will occur only when the spinodal is approached where the HDLC phase is no longer stable. The changes in behavior may include not only static quantities like response functions but also dynamic quantities like diffusivity \([32,44,45]\). See in particular the very recent work of Ruocco et al. \([47,48]\).

In the case of water, a significant change in dynamical properties has been suggested to take place in deeply supercooled states of bulk \([3,49]\) and confined water \([50–52]\). Unlike other network forming materials, water behaves as a non-Arrhenius liquid in the experimentally accessible window \([3]\). Based on analogies with other network forming liquids and with the thermodynamic properties of the amorphous forms of water, it has been suggested that, at ambient pressure, liquid water should show a dynamic crossover from non-Arrhenius behavior at high \( T \) to Arrhenius behavior at low \( T \) \([11,37,53]\). Using Adam–Gibbs theory \([54]\), the dynamic crossover in water was related to the \( C_P^{\text{max}} \) line \([11,37,49,55]\). Also, a dynamic crossover has been associated with the liquid–liquid phase transition in simulations of silicon and silica \([56–59]\). Recently a dynamic crossover in confined water was studied experimentally \([60–62]\) since nucleation can be avoided in confined geometries.

6. Appearance of a fractional Stokes–Einstein relation in water and a structural interpretation of its onset

The Stokes–Einstein (SE) relation has long been regarded as one of the hallmarks of transport in liquids. It predicts that the self-diffusion constant \( D \) is proportional to \( \left( \frac{T}{\tau} \right)^{-1} \), where \( \tau \) is the structural relaxation time and \( T \) the temperature. Xu et al. \([63]\) recently presented their experimental results on water confined in MCM-41-S nanotubes. They measured the self-diffusion \( D \) by nuclear magnetic resonance (NMR), and they measured the translational relaxation time \( \tau \) by using incoherent, quasi-elastic neutron scattering (QENS) \([64,65]\). Thus, the SE relation,\[ D = \left( \frac{T}{\tau} \right)^{-1}, \]can be tested. Their data \([Fig. 3(a)]\) confirmed Eq. (1) at high temperatures, but showed that, upon cooling below a crossover temperature \( T_c \approx 290K \), the SE relation \([92]\) gave way to a “fractional SE relation” \([65–69]\).

\[ D = \left( \frac{T}{\tau} \right)^{-\zeta}, \]with \( \zeta \approx 0.62 \).

They interpreted the microscopic origin of this crossover by analyzing the OH stretch region of the FTIR spectrum over a wide \( T \) range from 350 K down to 200 K. Simultaneous with the onset of fractional SE behavior, they found that water begins to develop a local structure like that of low-density amorphous solid \( \text{H}_2\text{O} \). These data lead to an interpretation that the fractional SE relation in water arises from a specific change in local water structure. To further test this interpretation, they performed computer simulations of two molecular models, and their simulation results supported their experimental observations.

As a first step to obtain a structural interpretation this fractional SE behavior, they turn to measurements of the infrared spectrum \([64,65,70–72]\). For water this spectrum can be split into two contributions, one resembling the spectrum of HDA solid \( \text{H}_2\text{O} \) and the other resembling the spectrum of LDA solid \( \text{H}_2\text{O} \). They interpret these two contributions as corresponding to water molecules with more HDA-like local structure, or more LDA-like local structure, respectively \([73,74]\). They show in Fig. 3(b) the relative populations of molecules with locally LDA-like structure and molecules with locally HDA-like structure calculated by decomposition of the infrared spectra. With decreasing \( T \), the LDA-like population increases, while the HDA-like population decreases. The fractional SE crossover temperature \( T_c \) appears to roughly coincide with the onset of the increase of the population of molecules with LDA-like local structure (and a corresponding decrease of the population of the molecules with HDA-like local structure), consistent with the possibility that the changes in intramolecular vibrational properties may be connected to the onset of fractional SE behavior.

To more clearly see the change in the relative populations of molecules with LDA-like local structure (and, correspondingly, with HDA-like local structure), they calculate the derivatives of the relative populations with respect to temperature \([Fig. 3(c)]\). The derivatives of the relative populations become noticeably non-zero at the same value of the crossover temperature, \( T_c \approx 290K \). In contrast, we find that the maximal rate of change of the vibrational spectrum occurs at a much lower temperature, \( T_{\text{max}} \approx 245K \), approaching the Widom temperature 225 K for bulk water \([49]\).

Concerning simulations: since experiments on bulk water at \( T < 250K \) are impractical due to crystallization, Yamada et al. perform constant-\( T \) and constant-density molecular dynamics simulations of \( N = 512 \) water molecules interacting with the TIP5P potential \([91]\) at a fixed density \( \rho = 1 \text{ g/cm}^3 \). Additionally, direct access to the molecular coordinates makes it possible to connect the changes in \( D \) to changes in the local molecular structure.

The relaxation time \( \tau \) is defined as the time when the coherent intermediate scattering function decays by a factor of \( e \) for the wave vector \( q \) of the first peak of the static structure factor. Unlike the relaxation time of the incoherent intermediate scattering function, the coherent relaxation time closely tracks the \( T \) dependence of the viscosity (viscosity is used in the original formulation of the SE relation). The diffusion coefficient is computed from the root mean square displacement of the oxygens as a function of temperature. Analogous to the experimental results in Fig. 3(a), we simulated \( D \) for TIP5P water for as a function of \( \frac{T}{\tau} \). We found that below \( T_c \approx 320K \) the SE relation crosses over to a fractional SE relation \([92]\) of Eq. \((2)\) with \( \zeta = 0.77 \), similar to the exponent observed in SPCE water \([92]\).

We observed a gradual increase in LDA-like local structures, and a decrease in HDA-like local structure. The derivatives of the relative populations of the LDA-like and the HDA-like molecules with respect to temperature show that the change does not have a sharp onset at
The change of slope from and HDA-like species.

(c) The derivative of the relative population with respect to temperature for LDA-like species.

**Fig. 3.** Experimental results for water at $P=1\text{ bar}$. (a) Parametric relation of $D$ as a function of $\tau/T$. The onset of the fractional SE relation around $T_m \approx 290 K$ is indicated by the change of slope from $\zeta = 1$ to $\zeta = 0.62$, while $T_{max} \approx 245 K$ is determined from panel (c). (b) The relative population of different species of water molecules in experiment. (c) The derivative of the relative population with respect to temperature for LDA-like and HDA-like species.

For each species (LDA-like and HDA-like), the maximum change defines a temperature $T_{max} \approx 255 K$ for the structural evolution. Like our experimental results, $T_\tau > T_{max}$ for TIP5P, indicating that the change to fractional SE behavior can be connected with the emergence of more highly structured regions of the liquid, rather than the maximal rate of change.

Both our experimental findings and our simulation results are consistent with the possibility that in water the fractional SE relation (2) sets in near the temperature where the relative populations of molecules with LDA-like and HDA-like local structures start to rapidly change. A structural origin for the failure of the SE relation can be understood by recognizing that the SE relation defines an effective hydrodynamic radius. The different species have different hydrodynamic radii, so when their relative populations change, the classical SE relation (based on the assumption of the fixed hydrodynamic radius) breaks down. Moreover, a connection between the local structure of water and its dynamics is expected [92, 94, 95]; molecules with a locally tetrahedral geometry are more “sluggish” than well-networked molecules. This effect also occurs in solutions, where a failure of the scaling between diffusion and relaxation has been interpreted in terms of changes in the local network structure [96, 97]. For these reasons, our structure-based interpretation for the failure of the SE relation is particular to water. An explanation for the failure of the SE relation for liquids in general must involve understanding how the intermittency of the molecular motion couples to diffusion and relaxation mechanisms near the glass transition. For the majority of liquids, the breakdown of SE occurs within 30% of the glass transition temperature, while for water it occurs at almost twice the glass transition temperature. For the case of water, the emergence of such intermittency of the dynamics is inseparable from water’s unusual thermodynamics and corresponding changes in the fluid structure.

7. To what degree are experiments on confined water relevant to understanding bulk water?

Since these experiments examine water confined to cylindrical pores of $\approx 2 \text{ nm}$ diameter, it is natural to question whether the experimental findings might be instructive for understanding bulk water at low $T$. There are many reasons to be concerned about the degree to which experiments on confined water are relevant to “real water”. For example, the fact that confinement suppresses the melting temperature by about 100 K shows that at least one property of confined water differs drastically from the corresponding property of bulk water. This issue is not completely resolved, as there exist currently arguments that are not in agreement.

On the one hand, recent experiments suggest the answer is “no”. The similarities between bulk and water confined in MCM-41-S have been recently challenged by a neutron diffraction work [75]. This has clearly shown that the cross correlation term between water and silica not only is not negligible but it is also temperature dependent, as it reflects the balance between water–water and water silica surface interactions (see Fig. 2 of [74]. In addition, coupling neutron diffraction data with a Monte Carlo simulation, it has been shown that confined water cannot be considered as a homogeneous fluid filling the available pore volume. The microscopic structure of water changes depending on the distance from the pore wall and on temperature. Concerning the interaction between water and silica, see also the recent careful work of Findenegg et al. [76].

There are two reasons that suggest the answer may be “yes”: (i) computer simulations of confined water on a hydrophilic surface [77] show that hydrophilic silica-confined water has similar behavior as bulk water, indicating that the hydrophilic surfaces do not have serious effects on the properties of water, except for significantly lowering the freezing temperature and stabilizing the liquid phase which allows the study of supercooled region made impossible in bulk water due to crystallization; (ii) the presence of hysteresis in a...
temperature cycle (upon cooling/heating) is a signature of an interaction between water and silica. However, for the MCM-41-S confined system, only negligible hysterisis was observed by means of X-ray scattering and calorimetric experiment [78,79].

A different category of potential concern arises from the fact that the comparison of simulation/theory results with experiments thus far is limited to MCM41-S, to three biological systems (lysozyme, DNA, and RNA) and to cement. In any case, it is plausible that the disturbance brought by the confining matrix to water can be considered negligible for larger pore sizes, but the experimental fact is that water freezes for pore sizes larger than about 2 nm.

Recently Gallo et al. [80], building on their wealth of experience studying confined liquids [81–90] have accurately tested the degree to which the experiments on MCM-41 confined water are in agreement with simulations in confined geometries.

8. The tetrahedral entropy and tetrahedral specific heat reflecting space-time correlations in the tetrahedral order parameter

Very recently Kumar et al. [93] introduced the space-dependent correlation function $C_{Q}(r)$ and time-dependent autocorrelation function $C_{Q}(t)$ of the local tetrahedral order parameter $Q = Q(r,t)$ [98]. Using computer simulations of 512 waterlike particles interacting through the TIPSP potential, they investigated $C_{Q}(r)$ in a broad region of the phase diagram. They found that at low temperatures $C_{Q}(r)$ exhibits a two-step time-dependent decay similar to the self intermediate scattering function, and that the corresponding correlation time $\tau_{Q}$ displays a dynamic crossover from non-Arrhenius behavior for $T > T_{W}$ to Arrhenius behavior for $T < T_{W}$, where $T_{W}$ denotes the Widom temperature where the correlation length has a maximum as $T$ is decreased along a constant-pressure path. They defined a tetrahedral entropy $S_{Q}$ associated with the local tetrahedral order of water molecules and find that it produces a major contribution to the specific heat maximum at the Widom line (Fig. 4), and showed that $\tau_{Q}$ can be extracted from $S_{Q}$ using an analog of the Adam–Gibbs relation.

In his previous work, Kumar et al. [37–39] found similar results for a cell model of water, where the local tetrahedral order is defined by the states of discrete orientational bonding variables. They calculated, for both scenarios, the relaxation time $\tau$ of $S_{i} = \sum_{j} \delta_{i,j}/4$, which quantifies the degree of total bond ordering for site $i$, where each molecule $i$ has four bond indices $\delta_{ij} \in \{1, ..., 6\}$, corresponding to the four n.n. cells $j$, each occupied by a water molecule, giving rise to $\epsilon^{4} = 1296$ different molecular orientations. They associated the tetrahedral ordered configuration to the case when the four bond indices are in the same state. They identified $\tau$ as the time for the spin autocorrelation function $C_{\text{aut}}(t) \equiv \langle S_{i}(t)S_{i}(0) \rangle / \langle S_{i}^{2}(0) \rangle$ to decay to the value 1/e. They found that $\tau$ shows a crossover (Fig. 5a) from non-Arrhenius behavior for $T > T_{W}$ to an apparent Arrhenius behavior for $T < T_{W}$, where $T_{W}$ is approximated with the temperature $T(C_{P}^{\infty})$ of the maximum of the isobaric specific heat $C_{P}$.

To prove that the dynamics is regulated by the structural changes, Kumar et al. proposed that $\tau_{1}$, the lowest free energy excitation relevant at $T_{W}(P)$, is associated to the local rearrangement of a bond to assume a more tetrahedral (ordered) configuration. If the proposal is correct, then $\tau_{1}$ should correspond to the $T$-dependent activation energy $E_{A} = k_{B}T \log (\tau_{1}/\tau_{0})$, where $\tau_{0}$ is the unknown relaxation time for $T \to \infty$ and depends only on $P$. The results of their calculation is shown in Fig. 5b as lines, compared to the simulation results of Fig. 5a (symbols), with log $\tau_{0}$ increasing with $P$ as would be expected on the basis of a hard-sphere approximation, valid for $T \to \infty$. Hence, the calculations show that the mechanism to relax from a less structured state (low tetrahedral order) to a more structured state (higher tetrahedral order) corresponds to the breaking of a bond and the simultaneous molecular reorientation for the formation of a new bond.

![Fig. 4.](image-url) Constant pressure specific heat $C_{P}$ and specific heat associated with tetrahedral entropy $C_{Q}$ of water at atmospheric pressure for TIPSP model of water.

![Fig. 5.](image-url) (a) Dynamic crossover (large $\beta$) in the tetrahedral order relaxation time $\tau$ for a range of different pressures, approaching the LLCP critical $P$ from below, with crossover temperature at $T_{W}(P) = T(C_{P}^{\infty})$. The error on $T_{W}(P)$ is approximately equal to symbol size; thick and thin lines represent VFT and Arrhenius fits. Notice that the dynamic crossover occurs at approximately the same value of $\tau$ for all seven values of pressure studied. $P$ is expressed in internal units of the model. Lower panel: nd thin lines represent VFT and Arrhenius fits. (b) The theoretical prediction $E_{A}/k_{B}T + \log \tau_{0}$ (lines) describes well the $\log \tau$ from simulations (symbols) for $P_{0}/e = 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6$. Only for the two largest values of $P$ a deviation is observed at high $T$ (dash and dot-dash lines) and $\log \tau = E_{2}/(k_{B}T) + \log \tau_{0}$ with $E_{2} = -3E_{3}\rho_{\text{Max}} - E_{4}\rho_{\text{Min}}$ and log $\tau_{0}(P)$ given in the legend.
More recently, Mazza et al. [99,100] reached even more insight into this subject, by showing that the $C_{p}^{\infty}$ is determined by the maximum variation of the enthalpy associated to the formation of hydrogen bonds and that another crossover in the time-correlation function and another maximum of $C_{p}$ occur at lower $T$. This lower-$T$ maximum of $C_{p}$ is due to the maximum variation of the enthalpy associated to the local tetrahedral order of water molecules and merges with the higher-$T$ maximum of $C_{p}$ when the pressure increases. These findings compare well with the dielectric spectros-copy experimental results of water molecules adsorbed onto lysozyme powder at low hydration level [100].

9. Selected results for bulk water

Using molecular dynamics (MD) simulations [101], Xu et al. [11] studied three models, each of which appears to have a liquid-liquid critical point. Two of the models (the TIPSP [102] and the ST2 [103]) treat water as a multiple site rigid body, interacting via electrostatic site–site interactions complemented by a Lennard–Jones potential. The third model is the spherical “two-scale” Jagla potential with attractive and repulsive ramps which has been studied in the context of liquid–liquid phase transitions and liquid anomalies [45,53,104,105]. For all three models, Xu et al. evaluated the loci of maxima of the relevant response functions, compressibility and specific heat, which coincide close to the critical point and give rise to the Widom line. They found evidence that, for all three potentials, the dynamic crossover occurs just when the Widom line is crossed.

Still another model has been studied, SPC/E, but the temperature shift is about 40 K since SPC/E is under-structured compared to real water as it collapses the two negatively charged lone pairs into a single negative point charge. Hence at such low temperatures the statistics are not very good for recognizing the critical point [106,107].

Other models, which are particularly tractable, include a family of spherically-symmetric potentials pioneered by Stell and Hemmer which are characterized by two length scales and hence reflect many of the properties of real water: see, e.g., [108–113].

These findings are consistent with the possibility that the observed dynamic crossover along path $a$ of Fig. 2a is related to the behavior of $C_{p}$, suggesting that enthalpy or entropy fluctuations may have a strong influence on the dynamic properties [45,49,59]. Indeed, as the thermodynamic properties change from the high-temperature side of the Widom line to the low-temperature side, $\frac{\partial S}{\partial T}|_{p}=C_{p}/T>0$ implies that the entropy must decrease. The entropy decrease is most pronounced at the Widom line when $C_{p}=C_{p}^{\infty}$. Since the configurational part of the entropy, $S_{conf}$, makes the major contribution to $S$, we expect that $S_{conf}$ also decreases sharply on crossing the Widom line.

According to Adam–Gibbs theory [54], $D=\exp(-A/T_{Sconf})$. Hence, we expect that $D$ sharply decreases upon cooling at the Widom line. If $S_{conf}$ does not change appreciably with $T$, then the Adam–Gibbs equation predicts an Arrhenius behavior of $D$. For both water and the Jagla model, crossing the Widom line is associated with the change in the behavior of the diffusivity. (i) In the case of water, $D$ changes from non-Arrhenius to Arrhenius behavior, while the structural and thermodynamic properties change from those resembling HDL to those resembling LDL due to the negative slope of the Widom line. (ii) For the Jagla potential, $D$ changes from Arrhenius to non-Arrhenius while the structural and thermodynamic properties change from those resembling LDL to those resembling HDL, due to the positive slope of the Widom line.

Thus these results for bulk water are consistent with the experimental observation in confined water of (i) a fragility transition for $P$<-$P_{c}$, [60,61], and (ii) a peak in $C_{p}$ upon cooling water at atmospheric pressure [114], so this work offers a plausible interpretation of the results of Ref. [61] as supporting the existence of a hypothesized liquid–liquid critical point.

10. Glass transition in biomolecules

Next we explore, using MD simulations, the rather novel hypothesis [115] that the observed glass transition in biomolecules [116] is related to the liquid–liquid phase transition. Specifically, Kumar et al. [115] studied the dynamic and thermodynamic behavior of lysozyme and DNA in hydration TIP5P water, by means of the software package GROMACS for (i) an orthorhombic form of hen egg-white lysozyme and (ii) a Dickerson dodecamer DNA at constant pressure $P=1$ atm, several constant temperatures $T$, and constant number of water molecules $N$ (NPT ensemble).

Kumar et al. calculated the mean square fluctuations $\langle x^{2} \rangle$ of the biomolecules from the equilibrated configurations, first for each atom over 1 ns, and then averaged over the total number of atoms in the biomolecule. They find that $\langle x^{2} \rangle$ changes its functional form below $T_{g} \approx 245$K, for both lysozyme and DNA.

Kumar et al. also calculated $C_{p}$ by numerical differentiation of the total enthalpy of the system (protein and water) by fitting the simulation data for enthalpy with a fifth order polynomial, and then taking the derivative with respect to $T$. Fig. 6(a) and (b) show the rate of increase of $Q$ has a maximum at $245 \pm 10$K for lysozyme and DNA hydration water respectively; the same temperatures of the crossover in the behavior of mean square fluctuations.

Upon cooling, the diffusivity of hydration water exhibits a dynamic crossover from non-Arrhenius to Arrhenius behavior at the crossover temperature $T_{c} \approx 245 \pm 10$K [Fig. 6(e)]. The coincidence of $T_{c}$ with $T_{g}$ within the error bars indicates that the behavior of the protein is strongly coupled with the behavior of the surrounding solvent, in agreement with recent experiments [116]. Note that $T_{g}$ is much higher than the glass transition temperature, estimated for TIP5P as $T_{g} = 215$K [120]. Thus this crossover is not likely to be related to the glass transition in water.

The fact that $T_{g} \approx T_{c} \approx T_{W}$ is evidence of the correlation between the changes in protein fluctuations and the hydration water thermodynamics [Fig. 6(a)]. Thus these results are consistent with the possibility that the protein glass transition is related to the Widom line (and hence to the hypothesized liquid–liquid critical point). Crossing the Widom line corresponds to a continuous but rapid transition of the properties of water from those resembling the properties of a local HDL structure for $T>T_{W}(P)$ to those resembling the properties of a local LDL structure for $T<T_{W}(P)$ [11,37–39,61]. A consequence is the expectation that the fluctuations of the protein residues in predominantly LDL-like water (more ordered and more rigid) just below the Widom line should be smaller than the fluctuations in predominantly HDL-like water (less ordered and less rigid) just above the Widom line.

The quantitative agreement of the results for both DNA and lysozyme is consistent with the interesting possibility that it is indeed the changes in the properties of hydration water that are responsible for the changes in dynamics of the protein and DNA biomolecules. Our results are in qualitative agreement with recent experiments on hydrated protein and DNA which found the crossover in side-chain fluctuations at $T_{g} \approx 225$K.

11. Recent experiments using complementary experimental approaches

Complementary experimental approaches have been carried out by the Messina group of F. Mallamace and the MIT group of S.-H. Chen. The Chen et al. work using neutrons is discussed above. In this section
we briefly mention some of the work of the Mallame group, especially using NMR.

Figs. 7 and 8 deal with the equilibrium magnetization, $M_0(T)$ measured in water confined in MCM 41 micropores and the hydration water of the protein lysozyme. $M_0(T)$ is a quantity directly proportional to the magnetic susceptibility $\chi$ of a material under a static magnetic field $H$ ($\chi = M_0 / H$) that, in thermal equilibrium, is sensitive to the average angle between the direction of the atomic magnetic moment $m$ and the applied field $H$. According to the Curie law, $\chi$ is related to the mean square value, per unit volume, of the nuclear magnetic moment and hence is sensitive to the local structural properties of the system. Details about the temperature behavior of $M_0(T)$ in confined supercooled water are reported in the reference [62]. In particular, the observed inflection point has been attributed to the fragile-strong dynamical crossover observed in the $T$ behavior of the self diffusion coefficient $D_S$ and in the average translational relaxation time $\tau$ measured respectively by means of nuclear magnetic resonance and neutron scattering techniques. The inflection point temperature ($T \approx 225K$) is the same temperature below which water dynamics violates the Stokes–Einstein law.

Fig. 7 reports $M_0(T)$ for MCM samples of different nanotube sizes i.e.: 2.4, 1.8 and 1.4nm measured in the cooling (C) and heating (H) experiments. Fig. 8 reports $M_0(T)$ measured in the lysozyme hydration water at the different protein concentrations: $h = 0.3; 0.37$ and 0.48. One sees that the observed crossover temperature of protein hydration water is approximately the same of nanotube confined water.

Also reported in this issue is a demonstration that the fragile-strong crossover (observed with the same experimental approach)
characterizes the supercooled state of many different glasses forming materials such as glycerol, salol and O-Terphenyl [121].

12. Outlook

It is possible that other phenomena that appear to occur on crossing the Widom line are in fact not coincidences, but are related to the changes in local structure that occur when the system changes from the “HDL-like” side to the “LDL-like” side of the Widom line. In this work we concentrated on reviewing the evidence (see, e.g., [122]) for changes in dynamic transport properties in both confined and bulk water—recognizing that the two systems are not identical, for indeed there is a rich literature concerning altogether new phenomena occurring in confined systems, as discussed in recent work of Han and collaborators [123–126] and references cited therein. Additional examples not discussed include: (1) a breakdown of the Stokes–Einstein relation for $T=T_{\text{W}}(P)$ [63,65,67,127–129], and possible relationships between these phenomena and properties of the hydrogen bond network [24] (2) systematic changes in the static structure factor $S(q)$ and the corresponding pair correlation function $g(r)$ revealing that for $T=T_{\text{W}}(P)$ the system more resembles the structure of LDL than HDL (3) appearance for $T=T_{\text{W}}(P)$ of a shoulder in the dynamic structure factor $S(q,\omega)$ at a frequency $\omega \approx 60\text{ cm}^{-1} \approx 2\text{ THz}$ [116], a feature that we are currently studying to test if it may be related to the appearance below the Widom line of a novel vibrational mode (a “Boson peak”), (4) rapid increase in hydrogen bonding degree for $T= T_{\text{W}}(P)$ [37], (5) a minimum in the density at low temperature [75,130], and (6) a scaled equation of state near the critical point [131]. It is important to know how general a given phenomenon is, such as crossing the Widom line which by definition is present whenever there is a critical point. Data on other liquids which have local tetrahedral symmetry, such as silicon and silica, appear to also display a liquid–liquid critical point and hence must possess a Widom line emanating from this point into the one-phase region. For example, Morishita interprets structural changes in silicon as arising from crossing the Widom line [132]. Underway are tests of the effect of the Widom line on simple model systems that display a liquid–liquid critical point, such as two-scale symmetric potentials of the sort recently studied by Xu et al. [45,133]. It is becoming clear that a local tetrahedral symmetry matters because it is associated with two characteristic length scales in the interaction potential. Other systems, such as metallic glasses, also appear to have two scale and there is evidence of polymorphism [134]. Finally, we mention the fact that there are many unsolved problems associated with what occurs when water dissolves a solute, and some of the approaches developed to understand the hypothesized liquid–liquid phase transition may be useful in addressing these problems [135–138].

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