Advances in Computational Studies of the Liquid-Liquid Transition in Water and Water-Like Models

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Abstract

There has been uninterrupted interest in supercooled water ever since the pioneering experiments of Speedy and Angell revealed sharp increases in this substance's response functions upon supercooling. One intriguing hypothesis that was formulated to explain this behavior involves the existence of a metastable liquid-liquid transition (LLT) at deeply supercooled conditions. The preponderance of experimental evidence is consistent with this hypothesis, although no definitive proof exists to date. Computational studies have played an important role in this area, because ice nucleation can in principle be controlled *in silico*. It has been claimed, controversially, that the LLT is a misinterpreted liquid-solid transition in all models of water. Recent studies disprove this viewpoint by providing unambiguous counter-examples of distinct liquid-liquid and liquid-crystal transitions in tetrahedral models. In one, state-of-the-art sampling methods were used to compute the free energy surface of a molecular model of water, and revealed the existence of two liquid phases in metastable equilibrium with each other, and a stable crystal phase, at the same, deeply supercooled thermodynamic conditions. Further studies showed that by tuning the potential parameters of a model tetrahedral system, it is possible to make the LLT evolve continuously from metastability to being thermodynamically stable with respect to crystallization. Most recently, it has been shown that the simulation code used to challenge the hypothesis of an LLT contains conceptual errors that invalidate the results on which the challenge was based, definitively resolving the controversy. The debate has vastly expanded the range of fundamental questions being pursued about phase transitions in metastable systems, and ushered the use of increasingly sophisticated computational methods to explore the possible existence of LLTs in model systems.

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1 Introduction

Water is ubiquitous and yet also unusual. It is central to life, climate, agriculture, and industry, and an understanding of its properties is key in essentially all the disciplines of the natural sciences and engineering. At the same time, and despite its apparent molecular simplicity, water is a highly unusual substance, possessing bulk properties that differ greatly, and often qualitatively, from those of other compounds. As a consequence, water has long been the subject of intense scientific scrutiny[1, 2].

In this review, we describe the development and current status of the proposal that a liquid-liquid transition (LLT) occurs in deeply supercooled water. The focus of this review is on computational work, but we also summarize the relevant experimental and theoretical background. Since first proposed in 1992[3], this hypothesis has generated considerable interest and debate. In particular, in the last few years several works have challenged the evidence obtained from computer simulations of the ST2 model of water that support in principle the existence of an LLT, proposing instead that what was previously interpreted as an LLT is in fact ice crystallization[4, 5]. This challenge to the LLT hypothesis has stimulated a significant amount of new work aimed at resolving the controversy, and to better understand the nature of an LLT in water-like computer models. Unambiguously resolving this debate, it has been shown recently that the code used in the studies that most sharply challenge the LLT hypothesis contains a serious conceptual error that prevented the authors from properly characterizing the phase behavior of the ST2 water model[6]. Nonetheless, the burst of renewed activity focusing on simulations of an LLT in water has yielded considerable new insights. Here, we review this recent work, which clearly demonstrates that an LLT is a well-defined and readily observed phenomenon in computer simulations of water-like models, and is unambiguously distinguished from the crystal-liquid phase transition[7, 8].

1.1 Probing Cold Metastable Water Experimentally

One does not have to explore exotic conditions to observe liquid water's unusual properties[9]. At atmospheric pressure, the density maximum of liquid water occurs at 4 °C, below which the liquid expands as temperature T decreases. Minima in the T dependence of the isothermal compressibility κ_T and isobaric specific heat C_P are found at 46 °C and 35 °C, respectively[9-12]. Below these minima, κ_T and C_P increase as T decreases[9, 11-13]. Water's most basic thermodynamic properties are thus changing in the opposite direction from what is found for almost all other liquids as T decreases towards the crystal-liquid coexistence temperature T_m. The transport properties of liquid water are similarly unusual. For example, upon the application of pressure P, the self-diffusion coefficient of cold water initially increases, despite the fact that the liquid necessarily becomes denser as P increases[9, 14-16].

Below the melting temperature T_m, most liquids continue to be observable in the metastable supercooled state[17]. The ultimate fate of a supercooled liquid on cooling is to either crystallize or form a glass. The properties of a supercooled liquid are well defined and can be measured so long as the time scale for internal structural relaxation of the liquid state remains shorter than the time scale for formation of the crystalline phase, and shorter than the time scale of the observation itself. Violation of the former condition results in the measurement

being preempted by crystal nucleation; violation of the latter corresponds to loss of ergodicity at the glass transition. In experiments in which bulk supercooled water is progressively cooled below T_m, it is ice nucleation that intervenes first. Measurement of the properties of bulk samples of supercooled water cease to be possible below the homogeneous ice nucleation temperature, which is approximately 232 K at ambient P[18]. However, recent ultrafast X-ray studies of water droplets (discussed below) show that this limit may be breached using new techniques[19, 20].

In pioneering work that pushed the measurement of the thermodynamic properties of water deep into the supercooled range, Angell and coworkers revealed that the increase of κ_T and C_P as T decreases accelerates for $T < T_m$ [11,21,12, 13, 22]. Analysis of the T dependence of these response functions, as well as of dynamic properties [11], showed that the data could be fit by power laws with extrapolated divergences in the vicinity of 228 K, suggesting the presence of some type of critical phenomenon. These seminal results were the trigger for an enormous body of work related to supercooled water. The development of a thermodynamically self-consistent picture of the behavior of the deeply supercooled liquid that correctly predicts these experimental observations remains at the center of research on supercooled water. While a number of competing scenarios have been advanced over the years, the fact that consensus continues to be elusive demonstrates the complexity of the theoretical problem, and the difficulty of the experiments required to distinguish between scenarios.

One of the first of these scenarios, Speedy's "stability limit conjecture" (SLC)[23], exemplifies the challenge. As formulated by Speedy, and comprehensively analyzed by Debenedetti and D'Antonio[24-26], the SLC proposes that water's line of density maxima in the $P - T$ plane intersects the liquid-vapor spinodal at negative pressure. At such an intersection, thermodynamics requires that the spinodal pass through a minimum, and reappear in the positive pressure region under deeply supercooled conditions. Interestingly, this scenario has recently been observed in a numerical study of model colloidal particles[27]. The apparent power law behavior of water's response functions is predicted by the SLC in terms of the approach to the line of thermodynamic singularities found at the spinodal. Although the SLC has recently been shown to be thermodynamically incompatible with other features of the supercooled water phase diagram[9, 20, 28], it played a key role in the development of new scenarios. The SLC also pointed out the importance of considering the behavior of "stretched" water at negative pressure, a regime in which the liquid is metastable with respect to the nucleation of bubbles of the vapor phase. The properties of stretched water have been probed directly in several innovative experiments[28-32] which continue to generate results that may help discriminate among the competing scenarios that have been formulated to explain the thermodynamic behavior of supercooled water.

As described above, crystallization has prevented all but the most recent studies from observing bulk supercooled liquid water below 232 K at atmospheric pressure. The properties of amorphous solid water, however, provide a rich additional source of behavior that has greatly influenced thinking about the liquid phase. Samples of bulk liquid water can be quenched into an amorphous solid without crystallizing if the quench rate is very fast, e.g. on the order of 10^7K/s for micron-sized droplets[33]. More commonly, amorphous solid water is prepared by vapor deposition onto a substrate cooled by liquid nitrogen, producing a material called low-density amorphous (LDA) ice, having a density similar to that of crystalline ice Ih[34]. In

the 1980s, the startling discovery was made that when compressed, LDA ice would transform suddenly and at a well-defined pressure to a much denser but still amorphous solid, called high-density amorphous (HDA) ice[35]. This transformation, although it connects two highly non-equilibrium glass states, bears many similarities to a first-order phase transition. The experimental phenomenology of amorphous solid water is now quite rich, with numerous additional complexities being reported and characterized[9, 36].

Of particular interest in studies of amorphous solid water have been attempts to determine if the solid passes through a glass transition on warming. All forms of amorphous ice crystallize on warming in the vicinity of 150 K at ambient pressure[37]. However, as we will see below, experimental work to identify the glass transition behavior of the amorphous solid states of water has yielded important insights into the behavior of the deeply supercooled liquid (e.g., Ref.[36]). The range of temperatures lying between the highest T to which amorphous ice can be heated before crystallizing, and the lowest T to which bulk supercooled water can be cooled before crystallizing represents a so-called "no-man's land" for experiments on the liquid phase[38]. Given the complexity of liquid water above the "no man's land", and of the amorphous ices found below it, the challenge has been to develop a unified understanding of both regimes within a single conceptual framework.

In this Section we have briefly summarized experimental approaches to the investigation of the properties of deeply supercooled water. The focus of this review being computational, it is not the aim of this Section to be comprehensive; rather, we have tried to illustrate, through selected examples, the challenges of metastability and the efforts that have been made in the laboratory to overcome them. Additional experiments aimed specifically at verifying or falsifying the LLT hypothesis are discussed in Section 2.1.

1.2 Computer Simulations

As has been the case throughout liquid state physics, computer simulations have played an important role in exploring the properties of liquid water. Relative to the other phases of matter, the theoretical treatment of the bulk liquid state is notoriously challenging. Liquids are dense, strongly interacting, disordered systems, for which only the most idealized models can be solved exactly[39].

Fortunately, molecular dynamics (MD) and Monte Carlo (MC) computer simulations allow for the numerical estimation of bulk thermodynamic and transport properties, starting only from a model of the molecular-scale interactions[40]. The development and exploitation of intermolecular potentials for water for use in computer simulations began in the 1960s[41] and continues to this day[42-47]. Simulations are particularly valuable for clarifying the connection between bulk properties and molecular-level behavior. In the case of water, a long-standing theme of simulation results is the demonstration that this substance's unusual properties can be understood in terms of the local tetrahedral topology of hydrogen bonding in the liquid phase, and the response of this bonding network to changes in P and T[48].

For studying metastable states, such as supercooled or stretched water, simulations also provide important advantages. As described above, the ability to study metastable states depends on a separation of time scales for liquid-state relaxation and for the appearance of the stable phase. For most water simulation models, this intermediate time regime is readily

accessible over a range of metastability larger than that probed in most experiments. The fundamental time step in molecular dynamics simulations is typically on the order of ~1 fs, and so long as the liquid relaxation time is much shorter than the total simulation time, equilibrium liquid properties can be evaluated on a very short time scale (ns − μs) compared to many experiments (~1 − 100 s). Compounding this advantage, simulated water is by construction both chemically pure and unaffected by explicit surface effects, through the use of periodic boundary conditions. Thus, heterogeneous nucleation of the stable phase, almost always a faster process than homogeneous nucleation, is ruled out. Finally, the small size of simulated systems, relative to experiments, also assists in the examination of metastable states. The time scale for the nucleation of a stable phase from a metastable state is inversely proportional to the system volume V. Typical water simulations contain $10^2 - 10^5$ molecules, greatly increasing nucleation times relative to bulk samples in experiment. Combined, these factors have allowed simulations to penetrate deeply into the metastable range of water, both with respect to supercooling and stretching. Indeed, as we will see, the ability to study water models under conditions where the liquid is simultaneously stretched and supercooled has provided crucial insights.

At the same time, relative to experiments, simulations in other respects suffer from the small system sizes and short total observation times accessible using current computers. For example, different approximations associated with the treatment of long range forces and boundary conditions can induce qualitatively different simulation outcomes; see e.g. Ref. [49]. Most significantly, the longest time scales accessible to current simulations are in the range of μs, and are nowhere close to the time scales required to study viscous, slowly relaxing liquids approaching the laboratory glass transition temperature. As we will see, this issue is of central concern in simulations of deeply supercooled water, as many of the phenomena that have been the focus of studies described here occur at T where the equilibration times are such that most simulations require weeks or months of computer time. Careful assessment of the ability of simulations to attain equilibrium and evaluate equilibrium properties is therefore a necessity, especially when the liquid relaxation time varies strongly with T and P.

The focus of this review is the role that simulations have played in the investigation of the proposal that an LLT occurs in supercooled water. Techniques for locating and characterizing first and second order phase transitions in simulations of condensed matter systems have a long history, and have evolved significantly over the past few decades, due to advances in both methodology and computing power. In the following, we will distinguish between two broad classes of methods that aim to identify phase transitions. The first class consists of phenomenological methods in which a simulation is used to seek a particular behavior consistent with a phase transition. Examples include simulations to evaluate an equation of state [e.g. $P(V, T)$], in which discontinuous jumps and/or hysteresis loops will occur across a first-order phase transition; or approaches that test for two-phase coexistence in a simulation conducted in a fixed volume[50]. The second class uses methods that explicitly evaluate the free energy of the system as a function of an order parameter that distinguishes between the phases involved in the transition[40, 51]. Relative to phenomenological approaches, free energy methods are preferable in that they provide unambiguous evidence of a phase transition; can accurately locate the critical point of a second order phase transition and

identify its universality class; and can locate the coexistence conditions between the phases involved in a first order phase transition; see e.g. Ref.[52].

It is important to state clearly at this point that a significant limitation of classical MD and MC studies, such as the ones we describe in this review, is that the force fields used in these investigations are at best approximate representations of water's true potential energy surface. No present classical force field can reproduce water's physical properties with quantitative accuracy and across broad ranges of thermodynamic conditions, important progress notwithstanding (e.g., Ref. [53]). Hence the usefulness of simulations in the context of this review is not to provide an unambiguous answer as to whether an LLT exists (or not) in real water: this is a question that only experiments can settle definitively. Rather, well-performed simulations provide valuable insights into the factors that enable or hinder such a transition (e.g., force field details and how they determine relaxation and nucleation times), and the range of conditions and sample sizes over which an LLT can be observed. Ultimately, the accumulation of knowledge emerging from such studies can serve to constrain the experimental conditions at which an LLT may occur in water or in other substances.

2 The LLT Proposal and Computational Studies

2.1 LLT

LLTs in binary and multicomponent liquids, where phases of distinct chemical composition separate below (or, in some associating mixtures, above) a critical temperature T_c, are commonplace[54, 55]. LLTs in chemically pure liquids are also well known, e.g. in the case of liquid crystals[56], and in quantum liquids such as He[57], where the transition is between a normal liquid and superfluid state. Thermodynamics also allows for the possibility that a purely classical, isotropic liquid can undergo bulk separation into two phases of differing density, and yet it is curious that confirmed instances of this class of LLT are still relatively rare, and have only been the focus of study in the last few decades. For example, experimental evidence for such LLTs exists for liquid phosphorous, melts of yttrium-alumina[58], and cerium[59]. It has also been proposed, and there is a growing body of indirect experimental evidence consistent with this proposal, that they may occur generally in liquids in which tetrahedral bonding dominates the local molecular structure, e.g. Si, Ge, and of course, water.

Long predating the proposal of an LLT in water, there has been discussion of "two-state" models of water, in which two distinct local bonding arrangements, one open and ice-like, the other denser and less ordered, compete to produce the observed bulk properties of water. This idea originated in Röntgen's attempt to explain water's density maximum[60], and debate continues to this day on the evidence for and utility of this approach; see e.g. Ref.[61-63]. Notably, theoretical studies discussing the possibility that these two local states could form the basis for bulk liquid-liquid phase separation in water (and other liquids) can be found in work published in the 1960s[64, 65] and 1980s[66, 67].

In its current form, the proposal of an LLT in supercooled water emerged from computer simulation studies of the ST2 model of water[3, 68-71]. This work exploited the ability of simulations to explore both the supercooled and negative pressure regions of the equation of

state of the metastable liquid. The ST2 model was known to reproduce many water anomalies, including the density maximum, and minima in κ_T and C_P. When the negative pressure regime was explored, however, the behavior required to explain these anomalies within the framework of the SLC was not observed. Specifically, the line of density maxima and the liquid spinodal did not intersect, precluding the reentrance of the spinodal line to positive pressure. Instead, another source for the anomalies was observed in the equation of state: the emergence of an inflection in the isotherms of P versus V. As shown in Fig. 1, this inflection first appears in the ST2 equation of state near 300 K, and becomes progressively more prominent as T decreases. In the vicinity of 245 K, the inflection becomes flat, consistent with the occurrence of a critical point. At lower T, the isotherms have a non-monotonic shape reminiscent of a "van der Waals loop". This behavior of the equation of state suggested the occurrence of an LLT in supercooled water, in which two thermodynamically distinct liquids, a low-density liquid (LDL) and a high-density liquid (HDL) appear in the metastable phase diagram below a critical temperature T_C.

A more complete description of the LLT in ST2 water was subsequently developed from phenomenological simulation studies focused mainly on detailed exploration of the liquid equation of state[72, 73]. The picture that emerges of the LLT in ST2 water involves the occurrence of an interrelated set of thermodynamic features. These features are illustrated in the plane of T and P in Fig. 2. A coexistence line with negative Clapeyron slope separates the LDL and HDL phases. This coexistence line ends at a liquid-liquid critical point (LLCP) at $T = T_C$. On either side of the coexistence line two metastability limits (or spinodals) are found, one for the LDL phase and one for the HDL phase. These spinodals meet at the critical point. In the region beyond the critical point (i.e. $T > T_C$), thermodynamic response functions such as κ_T and C_P exhibit maxima that diverge as $T \rightarrow T_C$. In the $T - P$ plane, the lines of these maxima occur in the vicinity of the so-called Widom line[74], the line of maximum correlation length, and all converge at the critical point. These lines of maxima in response functions thus present a set of thermodynamic precursors leading directly to the LLCP. Near the Widom line, the liquid transforms continuously from an HDL-like liquid to an LDL-like liquid as T decreases. This transformation becomes discontinuous below T_C.

The strength of the LLT proposal is that it provides a unified explanation of the properties of both supercooled liquid water and the amorphous ices. Firstly, the unusual and increasingly divergent behavior of thermodynamic and dynamical properties of liquid water as temperature decreases into the supercooled region arises as the liquid approaches the critical point of the LLT, and its associated metastability limits. Secondly, the coexistence line of the LLT explains the occurrence of two distinct glass forms of water, LDA and HDA ice, in that these amorphous solids are just the sub-glass-transition manifestations of the LDL and HDL phases.
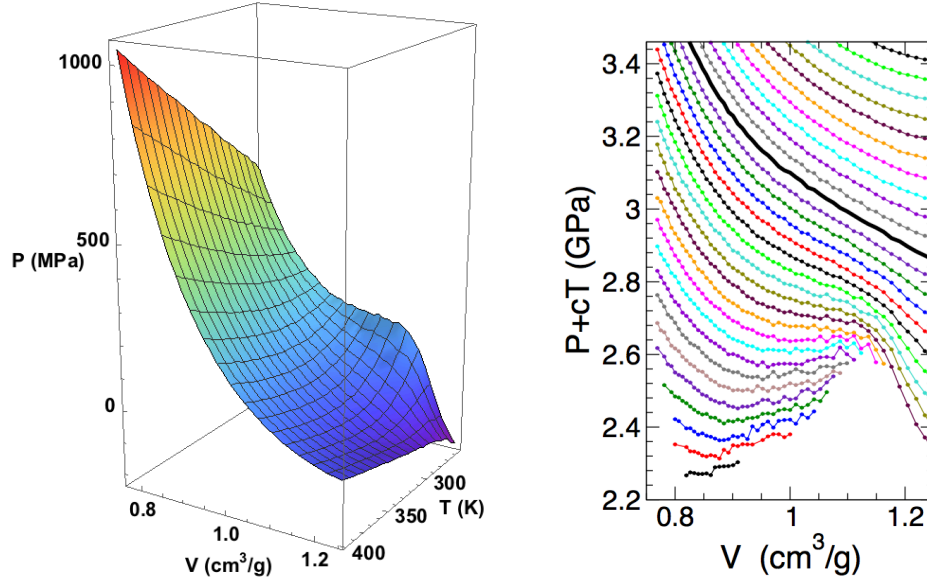
Fig. 1. (left) $P(V,T)$ equation of state surface for N=1728 ST2 water molecules, obtained from the MD simulations[42c,46b] in which the reaction field method was used to handle long-range electrostatic interactions. The surface is shown for T in the range from 255 to 400 K. (right) P as a function of V along isotherms. Isotherms are shown from T = 200 to 350 K, in 5 K steps, from bottom to top. The T=300 K isotherm is the thick black line; below 300 K, the isotherms begin to inflect. Each isotherm is shifted by cT, with c = 10 MPa/K, to facilitate comparison of the curves.
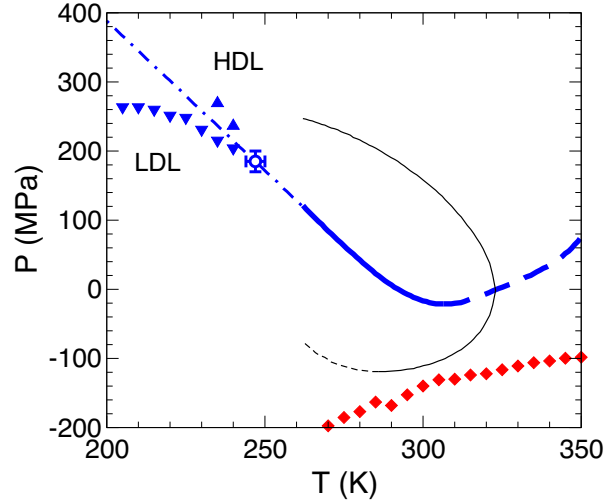

Fig. 2. Phase behavior of the ST2 model predicted from MD simulations[42c,46b] of N=1728 molecules in which the reaction field method was used to handle long-range electrostatic interactions. Shown are the estimated locations of the LLCP (circle with error bars); the HDL spinodal (down-triangles) and the LDL spinodal (up-triangles); the line of κ_T maxima (thick solid line) and minima (thick dashed line); the line of density maxima (thin solid line) and minima (thin dashed line); and the metastability limit of the liquid at negative pressure (diamonds). The dot-dashed line is a line having the estimated slope of the liquid-liquid coexistence curve at the critical point.

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In experiments on deeply supercooled water, the rapid formation of crystalline ice has so far prevented the direct observation of the properties of the bulk liquid under the conditions where the LLT is predicted to occur[9]. However, an increasing number of experimental studies find behavior consistent with the LLT proposal. These works include studies of the melting lines of metastable ice crystal phases[75], the properties of the amorphous ices[36, 76], thermodynamic and transport properties of liquid water confined in nanoporous materials[77, 78] and, very recently, the measurement of a maximum in the T dependence of K_T at negative[28] and ambient pressure[20]. We point out that the interpretation of experiments on water in nanoporous materials remains a subject of debate[79-81], both on account of the extreme confinement, which renders connection with bulk water not straightforward, and due to the incomplete control over the thermodynamic conditions (T, P). We highlight some recent experimental studies in particular, as they illustrate both the challenges faced, and the new opportunities that are emerging, in the pursuit of conclusive evidence for the presence or absence of an LLT in supercooled water.

The first is the work of Sellberg et al.[19], in which high intensity femtosecond X-ray laser pulses were used to obtain scattering patterns and structure factors $S(q)$ for small but still macroscopic water droplets, from 9 to 37 µm in diameter. These water droplets were ejected by a nozzle and cooled rapidly by evaporation as they traveled through vacuum, reaching temperatures as low as 227 K. The intensity of the X-ray pulses allowed the scattering pattern for each individual droplet to be resolved. As a result, droplets that had begun to crystallize, as revealed by Bragg peaks in the scattering pattern, could be distinguished from those that remained liquid. This analysis revealed that most droplets began to crystallize below 233 K. However, by studying thousands of droplets, more than 100 were identified that remained in the liquid state at 227 K on a millisecond time scale. The $S(q)$ data for these liquid droplets showed that the local tetrahedral structure of the liquid continues to strengthen as T decreases, and is approaching the local structure of the limiting cases of LDA ice and ice Ih. In an even more recent contribution[20], the low-q behavior of $S(q)$ was investigated to extract the temperature dependence of the isothermal compressibility. Both for water and heavy water a maximum in K_T was observed, providing the first direct experimental evidence consistent with the existence of a Widom line in supercooled water. This result and the analogous observation reported for a negative pressure isobar[28] are of profound importance. First, by providing high-resolution data on the structure of liquid water 5 K below the historically accepted supercooling limit of 232 K, these studies demonstrate that the no man's land is not impenetrable. Second, these results distinguish between competing scenarios for explaining the behavior of supercooled water. Both the re-entrant spinodal[11] and the critical-point free scenarios[82] are now proven to be inconsistent with the experimental evidence. Very recently, the results of Ref.[20] have been the subject of debate[83, 84].

We also highlight the study of Amann-Winkel, et al.[36] As mentioned earlier, amorphous ices crystallize when warmed above approximately 150 K. However, the possibility of a glass transition in water, in which the glass transition temperature T_g occurs prior to crystallization, has been studied and debated for several decades. If such a glass transition exists, then the liquid state would be observable in a (perhaps narrow) temperature window lying below the no-man's land. After much careful experimental effort, in particular by Loerting and coworkers[85], there is now a consensus that at ambient pressure LDA ice undergoes a well-

defined glass transition at $T_{g,LDA} = 136$ K prior to crystallization, providing access to an ultra-viscous form of supercooled water in the range $136 - 150$ K. The glass transition of LDA ice has an unusually weak calorimetric signature, which accounts for why it took so long to be unambiguously identified. Relative to Angell's strong-fragile classification of glass-forming liquids, the liquid found above $T_{g,LDA}$ is the strongest case known[36]. Remarkably, the work of Amann-Winkel et al. identifies a second, distinct glass transition that occurs in carefully annealed HDA ice samples recovered at ambient pressure, so-called "eHDA ice". On warming, eHDA ice undergoes a glass transition with a much stronger calorimetric signature than for LDA ice, and that occurs at a different temperature of $T_{g,HDA} = 116$ K. The liquid above $T_{g,HDA}$ is also strong, but less so than the liquid above $T_{g,LDA}$. These experimental results are consistent with the LLT proposal: two distinct glass transitions imply two distinct liquids. In this interpretation, warming eHDA ice produces HDL, which at ambient pressure is metastable with respect to the LDL phase formed by warming LDA ice. Analysis of relaxation times obtained from dielectric spectroscopy confirm the liquid-like nature the HDL phase, and show that it relaxes about 100 times faster than LDL at the same T. Following this line of investigation, more recent experiments[86] reported temperature-resolved measurements of the amorphous ice structure along the HDA-LDA transition that indisputably show the cross-over from the typical spectral shape of eHDA to that of LDA. Small-angle X-ray photon correlation spectroscopy shows that a collective fast process starts to be detectable when the sample is still in eHDA form and it is still present when the sample has converted to LDA. The presence of a relaxation process strongly supports the possibility that both liquid forms have been directly observed. While these studies[36, 86] do not directly observe the equilibrium coexistence of HDL and LDL, or an equilibrium phase transition from one to the other (which is predicted to occur only well above ambient pressure), their results are perhaps the strongest evidence to date that LDL and HDL exist as distinct liquid phases, and that both can be prepared and studied experimentally.

We also mention several other recent experiments aimed at exploring the possibility of a LLT in water. Xu et al.[87] estimated the diffusion coefficient of supercooled water to temperatures as low as 126 K from measurements of the growth rate of crystalline ice. Their results are consistent with the possibility that supercooled water becomes an unusually strong liquid in no man's land. In addition, the lack of discontinuities in their data suggests that the LLT, if it exists, occurs at pressures higher than ambient. Lin et al.[88] used rapid decompression, combined with *in-situ* X-ray diffraction, to detect a low-density, non-crystalline phase which the authors identified as LDL. Woutersen et al.[89] used infrared spectroscopy and calorimetry to characterize a low-temperature liquid-liquid transition in a binary mixture of hydrazinium trifluoroacetate in water[90]. The thermodynamic near-ideality of this water-rich mixture was used by these authors as an argument for relating the liquid-liquid transition in the mixture to the HDL-LDL transition in pure water.

2.2 Modeling the LLT

Due to the difficulties presented by crystal nucleation, it is mainly through computer simulations that the nature of LLTs has been directly explored. As described above, the ST2

model of water is one of the most extensively studied cases. Numerous ST2 simulation studies have shown that it is possible to evaluate the equilibrium properties of the deeply supercooled liquid on a time scale that is short compared to the crystal nucleation time, thus exposing the physics of the LLT and its associated anomalies to direct observation[91-96]. ST2 is one of the oldest water models still under study, and it exhibits a number of quantitative deviations from the properties of real water. For example, the density maximum at ambient pressure is 46 K above the experimental value[73]. These differences are a consequence of ST2 exhibiting a hydrogen bond network in the liquid phase that is over-structured relative to real water at the same T. However, for examining an LLT, this defect is an advantage, as it draws the behavior of the highly structured, deeply supercooled liquid to higher T, where it is more readily studied.

Other water models show a range of behavior. The SPC/E[97] and TIP4P[98] models exhibit some of the precursor anomalies associated with the Widom line, but an LLT has not been directly observed in either model in the T range accessible using current computing resources[71, 97]. For the SPC/E case, a potential energy landscape analysis suggests that the critical point is very close to the ideal glass transition line, implying that the observation of an LLCP in this model is hampered by the extremely sluggish glassy dynamics[99]. Evidence for an LLT in the TIP4P/2005 model has been presented[100-104] although this has been questioned in some work[105]. For TIP4P/2005, a Gaussian potential energy landscape analysis predicts an LLCP at T and P consistent with MD results[106]. The case of the mW model[107] is particularly interesting. This water potential is unusual in the sense that ice formation is readily observed on computationally accessible time scales[108]. Indeed, the supercooled liquid in mW water seems to become thermodynamically unstable with respect to crystal formation as T decreases, elucidating the scenario in which the observability of the liquid state simply terminates, rendering moot the question of a possible LLT at lower T.

The microscopic origins of the LLT proposed for water lie in the tetrahedral geometry of local bonding environments in the liquid phase. One of the thermodynamic consequences of tetrahedral bonding is that volume and entropy fluctuations are anticorrelated: the larger local volume that is required to create a well-formed tetrahedral network also corresponds to a decrease in local disorder[9, 48]. This behavior has been captured in a range of idealized lattice models and mean-field theories of water. These have proven useful for clarifying the possible topologies of phase diagrams in which an LLT can occur, as well as elucidating the interrelationship of thermodynamic anomalies associated with an LLT; see e.g. Refs. [109-111].

Many other substances also form "tetrahedral liquids" similar in local structure to water. As in some water models, models of silica[112, 113] and BeF$_2$[114] exhibit precursors of an LLT, but a fully exposed transition has not been observed. Ionic models of silica, for example, exhibit water-like density anomalies and increasing entropy and volume fluctuations upon cooling, which are consistent with the LLCP scenario[112, 113, 115]. Unfortunately, the LLT is predicted to lie at conditions where sluggish relaxation processes frustrate equilibration of the liquid with available computational methods[112, 113, 115]. Lascaris[116] has recently demonstrated, however, that an LLT may be observable in a modified version of the ionic silica model of Woodcock, Angell and Cheeseman (WAC)[117], in which the point charges on the Si and O ions are scaled to reduce their magnitude. The original WAC model of silica exhibits increasing maxima in response functions such as κ_T and C_P upon cooling, but no LLT is observed in the computationally accessible region of its phase diagram. Reduction of the Si and O charges

increases tetrahedral ordering in the liquid and alters the phase behavior of the model such that phenomenological signatures of an LLT can be observed in its equation of state. Recent free energy studies, such as those described in Sec II. C have further scrutinized the behavior of this model and confirmed the existence of an LLT[118]. There has also been debate regarding the existence of an LLT in the Stillinger-Weber model of silicon[119]. Equation of state calculations for this model exhibit signatures that are consistent with the existence of an LLT[120]. Finally, models of DNA tetramers[121, 122], DNA-tetrahedra with sticky corners[123] (a model for recently synthesized particles exploiting DNA-origami nanotechnology[124]), and tetra-functional patchy colloids[125] have been shown to exhibit clear LLTs. As discussed in Section 3.2, the systematic study of the influence of intermolecular potential parameters on the relative locations of liquid-liquid and crystal-liquid phase boundaries in such models has yielded critical insights into the fundamental origin of LLTs, and their observability relative to crystal formation[8].

Finally, we note that simulations of LDA and HDA ice, while necessarily conducted in a regime where the disordered system never attains equilibrium, have nonetheless provided important insights into the nature of the LLT proposed to occur at higher T. The ability of the ST2 model to qualitatively reproduce the sudden phase-transition-like collapse of LDA to HDA ice upon compression was noted in the same work that proposed the LLT hypothesis[3]. More recent simulations of the amorphous ices have established how the hysteresis of the LDA-HDA ice transformation upon compression and decompression may relate to the spinodals of the equilibrium LLT[126]. Simulations of LDA and HDA ice also predicted the existence of two distinct glass transitions in advance of their experimental observation[127]. Analysis of the behavior of simulated amorphous ices in terms of the potential energy landscape has also provided insights into the origins of an LLT in the supercooled liquid[128, 129], while at the same time helping to explain the variability observed in the behavior of the amorphous ices in experiments[130].

2.3 Free Energy Methods and Challenges to the LLT Proposal

Although there exist well-developed free energy methods to study first-order phase transitions computationally[40], it was not until 2009 that this approach was used to investigate the possible existence of an LLT in water-like models. In that year, Liu *et al.*[131] published their study of the metastable phase behavior of supercooled ST2 water. Using grand-canonical Monte Carlo, and treating long-range Coulombic interactions with Ewald summation[40] and vacuum boundary conditions, these authors found clear evidence of a liquid-liquid transition[131], with a critical point located at $T_C = 237 \pm 4$ K, $\rho_C = 0.99 \pm 0.02$ g/cc, and $P_c = 167 \pm 24$ MPa. The original motivation of this work was to assess previous claims of multiple LLTs in ST2 water[132, 133]. Such claims did not withstand the rigorous critical scrutiny provided by free energy methods.

Sciortino *et al.* also found clear evidence of an LLT in supercooled ST2 water[134], using successive umbrella sampling (SUS) in the grand-canonical ensemble, with reaction field[135, 136] treatment of long-ranged electrostatics. SUS is a modification of conventional umbrella sampling in which the relevant range of density to be explored is divided into multiple narrow and overlapping windows, within which parallel independent and unbiased simulations are performed. This leads to a more efficient calculation of the density probability distribution. Notable features of this study, especially in light of the debate that followed, are the careful

microscopic characterization of the coexisting liquid phases, which found no traces of crystallization, the explicit demonstration that the computed density distribution converges to a well-defined time-invariant value, and the verification that the relevant correlation functions decay to zero in every sampled window in a number of steps comfortably smaller than the simulation length[134].

In an important methodological advance, and a direct challenge to the LLT proposal, Limmer and Chandler argued, correctly in principle, that simulations aimed at investigating the possibility of a liquid-liquid transition under conditions of metastability with respect to crystallization ought to sample the free energy not just with respect to density (as had been done in the studies of Liu *et al.*[131] and of Sciortino *et al.*[134]), but also with respect to an order parameter sensitive to long-range crystalline order[4]. Accordingly, they used umbrella sampling in the NPT ensemble to compute free energy surfaces as a function of density and a suitable bond-orientational order parameter[137] (Q_6) that distinguishes crystalline from amorphous configurations. Limmer and Chandler used a hybrid Monte Carlo (HMC) approach[138], in which MD bursts are used to propagate the system under its unbiased Hamiltonian, and the resulting configurations are accepted or rejected via the Metropolis criterion, taking into account the values of the order parameters (density and a suitable bond orientational order parameter) and of the quadratic biasing potential used to force the system to sample relevant regions of order parameter space. Free energy surfaces were generated from the biased histograms using Bennett's multi-state acceptance ratio method (MBAR)[139].

Limmer and Chandler applied this approach to the coarse-grained mW model of Molinero and coworkers[107], and to ST2 water. The mW calculations confirmed MD-based predictions by Moore and Molinero[108] as to the absence of an LLT in this model, endowing this conclusion with the added rigor provided by explicit free energy calculations showing only one (high-density) liquid basin: there is broad agreement that the mW model does not in fact show liquid polyamorphism.

The ST2 calculations used the Ewald summation with conducting boundary conditions. This model is referred to as mST2 in the 2011 Limmer and Chandler paper[4]. Calculations were performed at 235K and 2.2 kbar, and reweighted to two higher pressures. The resulting free energy surfaces showed only one high-density liquid phase and one (low-density) crystal phase (cubic ice). Producing a free energy surface that includes disordered (liquid) as well as long-range-ordered (crystalline) phases, ensuring reversible sampling of the transition region separating these phases, was a remarkable computational accomplishment.

The absence of a low-density liquid basin in the free energy surface computed by Limmer and Chandler for ST2, plus the fact that the density of the stable ice phase is the same as that of the low-density liquid phase reported by Liu *et al.*[131] and by Sciortino *et al.*[134], led Limmer and Chandler to conclude that the LLT had been mistakenly interpreted by previous investigators who reported its existence, and is in reality a liquid-crystal transition. Limmer and Chandler's conclusion that the "putative" LLT is indeed a misinterpreted crystallization transition in "atomistic models" of water inspired a considerable body of work aimed at its verification or falsification. As will be documented below, no subsequent independent free energy calculation has been able to reproduce the Limmer-Chandler ST2 results; all such studies have in fact found an LLT in this model. This points to the need to distinguish the formulation of

an important methodological advance from its actual implementation, which in the case of the Limmer-Chandler studies of ST2, was subsequently shown to be flawed[6].

In a subsequent paper[5], Limmer and Chandler extended their original calculations by considering additional models including TIP4P/2005[140] and the Stillinger-Weber model[119] of silicon. They also considered three variants of ST2 that differ in their treatment of long-range electrostatic interactions: ST2a (Ewald treatment of long-range electrostatics, conducting boundary conditions), ST2b (Ewald, vacuum boundary conditions) and ST2c (reaction field). For all models considered in this study, the free energy surfaces show a single liquid phase and a crystal phase. Limmer and Chandler also developed a "theory of artificial polyamorphism" to explain the discrepancy between their free energy calculations and those reported by Liu *et al.*[131] and by Sciortino *et al.*[134] for the ST2 model. According to this theory, there is only a single metastable liquid, which crystallizes through a sluggish coarsening process under deeply supercooled conditions[30,31]. As coarsening proceeds, large fluctuations drive the system's density back and forth between that of the metastable liquid and crystal phase[5]. This process occurs on time scales that are short compared to the characteristic crystallization time due to a purported separation of relaxation time scales in the metastable liquid, in which density fluctuations relax orders of magnitude faster than those associated with bond-orientational order[5]. The LDL phase is therefore hypothesized to be a transient manifestation of the burgeoning ice phase that has equilibrated its density, but not its bond-orientational order.

Limmer and Chandler's theory suggests that the LDL phase is a robust, non-equilibrium artifact associated with improper equilibration of bond-orientational fluctuations. Accordingly, it should be straightforward to reproduce such behavior directly with simulation. In fact, however, Limmer and Chandler only demonstrated "artificial polyamorphism" indirectly using a theory which assumes that fluctuations in density relax *instantaneously* compared to those associated with bond-orientational order. Invoking this unphysical assumption, Limmer and Chandler modeled the evolution of the non-equilibrium bond-orientational probability distribution using a one-dimensional Fokker-Planck equation. This distribution was then convoluted with simulation data to produce non-equilibrium free energy surfaces displaying a transient low-density liquid phase that slowly vanishes over time. Consequently, Limmer and Chandler argued that this analysis demonstrated that the LLT reported in previous studies is a transient, non-equilibrium artifact. As was the case in their first paper[4], Limmer and Chandler controversially dismissed all previous LLT reports as misinterpreted crystallization transitions.

The basic assumption underlying the "theory of artificial polyamorphism", namely that density relaxes much faster than bond orientational order, was subsequently shown to be incorrect[7, 141], invalidating Limmer and Chandler's argument. In particular, Palmer et al.[7, 141] (see Section 3.1) used standard MD simulations and the same HMC scheme employed by Limmer and Chandler to demonstrate that at no conditions relevant to the LLT in ST2 do density fluctuations decay orders of magnitude faster than those associated with bond-orientational order, as incorrectly assumed by Limmer and Chandler. Likewise, the Limmer-Chandler claims about improper equilibration in others' calculations has also been categorically disproved in subsequent work, as will be documented in the following section. Finally, and focusing on ST2 in light of the diametrically opposite conclusions reached by Limmer and Chandler and all other independent calculations involving this model, it is important to point out that the ST2b and ST2c free energy surfaces reported in the 2013 Limmer-Chandler paper were not the result of

independent free energy simulations, but instead were obtained by applying perturbation theory to the original ST2a results[5].

Shortly after publication of Limmer and Chandler's 2011 paper, three free energy studies obtained results that directly contradict these authors' conclusions. Liu *et al*.[49] used umbrella sampling in density and bond orientational order, and the weighted histogram analysis method (WHAM)[142], and obtained clear evidence of two liquid basins in supercooled ST2 water (Ewald and vacuum boundary conditions). These authors did not sample the high-Q_6 [137]region and hence did not address the relationship between LDL and the stable crystal phase. Poole *et al*.[143] also performed umbrella sampling in density and bond orientational order in conjunction with Bennett's multistage acceptance ratio method (MBAR)[139] to obtain the free energy surface of supercooled ST2 with reaction field treatment of long-range electrostatic interactions. These authors also found two liquid basins, in direct contradiction of Limmer and Chandler's claims. Like Liu *et al*.[49], Poole *et al*.[143] did not investigate the high-Q_6 crystalline region. Shortly thereafter, Palmer *et al*.[144] again obtained two distinct liquid basins in supercooled ST2 (Ewald, vacuum boundary conditions) using two different free energy techniques: umbrella sampling Monte Carlo and well-tempered metadynamics[145]. Like Liu *et al*.[49] and Poole *et al*. [143], this study did not explore the high-Q_6 region of order parameter space. Taken together, these three studies[49, 143, 144] provided a strong challenge to Limmer and Chandler's assertion that the LLT is a misinterpreted crystallization transition. However, because the stable crystal phase was not investigated, it was not until three definitive studies published in 2014 and 2015, which clarified the relationship between the LLT and the crystal phase, that Limmer and Chandler's claims were finally and unambiguously laid to rest. Finally, a recent study published in 2018 identified the origin of the discrepancy as a fundamental flaw in Limmer and Chandler's HMC simulation algorithm[6]. These four studies will be described in Section 3.

2.4 Recent "Phenomenological" Studies

Several recent molecular dynamics studies have been aimed at confirming or disproving the existence of an LLT in light of the influential Limmer-Chandler challenge. Although free energy methods are needed to ascertain rigorously the presence of a phase transition, more traditional, molecular dynamics-based approaches can also provide useful information, and we refer to such approaches as "phenomenological" not in a spirit of criticism, but to indicate that free energy calculations were not involved.

Overduin and Patey[105] studied the TIP4P/2005[140] model with Ewald treatment of long-ranged Coulombic interactions, in the vicinity of the metastable critical point previously estimated by Abascal and Vega[100], 193K, 1.35 kbar, 1.012 g/cm^3. Their approach was based on the analysis of density and concentration fluctuations in the deeply supercooled region. The latter arise from the treatment of water as a binary "mixture", with the two components defined on the basis of their local tetrahedrality[146]. Overduin and Patey computed the total and partial structure factors (the latter arising from the three possible pair correlations in a binary "mixture"), and, using a Bhatia-Thornton analysis[147], calculated the structure factors arising from concentration-concentration and density-concentration correlations, the density-density quantity being the regular (total) structure factor. Correlation lengths were then extracted via

the Ornstein-Zernike equation. Overduin and Patey found that the correlation lengths associated with density and concentration fluctuations increased upon approaching the estimated critical point along the estimated critical isochore, but with an exponent $\nu = 0.19$ (density) or 0.26 (concentration) well below the expected 3D Ising universality class value $\nu = 0.63$. Furthermore, they were unable to see converged bimodal density distributions at conditions where such behavior should be expected based on Abascal and Vega's estimate for the location of the critical point[100]. Overduin and Patey concluded that they were unable to confirm the existence of an LLT in TIP4P/2005. A notable feature of this insightful work is the care taken by the authors to allow for the very long relaxation times that characterize the behavior of deeply supercooled water, as well as their methodical investigation of size effects and simulation ensembles (isobaric vs isochoric). Subsequent long molecular dynamics of TIP4P/2005 and a two-state thermodynamic analysis[103] locate the metastable critical point at a considerably lower temperature and higher pressure (182K, 1.70 kbar) than the above-quoted Abascal and Vega estimates[100]. Similar estimates of the critical pressure and temperature have also recently been reported in Refs [102, 148]. The Overduin and Patey results are thus not inconsistent with the latest computational evidence.

English *et al.*[149] attempted to investigate the mechanical stability of LDL-HDL interfaces in the ST2, TIP4P[98] and SPC/E[150] models. They used canonical (N, V, T) ensemble molecular dynamics of initially inhomogeneous systems consisting of HDL and LDL regions separated by a flat interface, with an overall density close to the estimated critical density for each model, and at sub-critical temperatures. They observed rapid density equalization and concluded that the LLT does not exist because their LDL-HDL interface is mechanically unstable. However, as reported by English et al., the pressures in each of the phases were very different at the outset, by as much as 5 kbar. Due to this large pressure difference between the HDL and LDL regions within the simulation cell, the subsequent isochoric equilibration of this artificially-prepared and far-from-equilibrium initial condition is entirely consistent with expectation, and does not test the mechanical stability of an equilibrium HDL-LDL interface at coexistence, as claimed by the authors. English et al. also attempted to simulate an ST2 system in "nominal mechanical equilibrium", that is to say with conditions chosen so that the initial pressures of the HDL and LDL regions are "approximately equal". However, the chosen conditions (0.94 and 1.17 g/cm^3 at 215K) are not close to the coexistence densities for HDL and LDL at this temperature[131], with the LDL phase being very close to its limit of mechanical stability (see Figure 4 in ref. [131]). As discussed below, we note that other work has successfully demonstrated the occurrence of a stable interface between coexisting LDL and HDL phases in appropriately equilibrated ST2 simulations[7, 92].

Kesselring et al. investigated the ST2 model with reaction field treatment of long-ranged Coulombic forces, focusing on the dynamics of spontaneous "flipping" between the HDL and LDL phases at fixed temperature and pressure[93], and on the application of finite-size scaling analysis to locate the LLCP[94]. Using μs-long molecular dynamics simulations they showed that the LDL phase can exist without crystallizing for times comfortably in excess of the relaxation time. These authors' careful finite-size scaling analysis is especially interesting, as it enabled not only the location of the (metastable) critical point (246 ± 1K, 206 ± 3 MPa) in very good agreement with the free energy calculations of Poole *et al.*[143], but also, by invoking the Challa-Landau-Binder cumulant[151], it provided evidence that the liquid-liquid transition survives in the

thermodynamic limit for this model. Also noteworthy is the extensive characterization of the two liquid phases via structural order parameters.

Li *et al.*[152] performed long molecular dynamics simulations (of the order of μs) of the WAIL potential[45] at supercooled conditions. This potential was obtained by parameter fitting to a coupled-cluster-quality potential energy surface for water[153]. The resulting equation of state is consistent with a critical point at 207K and 50 MPa[152].

Yagasaki *et al*[92] used (N, V, T) MD simulations of the ST2 model with reaction-field treatment of long-ranged electrostatics to demonstrate the spontaneous formation of a long-lived interface between HDL and LDL. These authors started with a homogeneous system at a density intermediate between that of HDL and LDL, which was rapidly quenched from supercritical to sub-critical conditions. Using an anisotropic simulation box (L_z/L_x = 4, L_y/L_x = 1, which favors the formation of an interface normal to the z-axis), Yagasaki et al. observed fast, spontaneous formation of an LDL-HDL interface (~1 ns), and subsequent, much slower nucleation of ice (~100 ns).

Yagasaki *et al.*[92] observed liquid-liquid separation in relatively small systems containing 4,000 to 16,000 ST2 molecules. By contrast, English *et al.*[149] found no evidence of an LLT in systems ranging from 9,000 to 585,225 molecules in size. Palmer and co-workers[154] recently conducted a similar study, in which they observed clear liquid-liquid separation in simulations performed with up to 256,000 water molecules (Fig. 3). They found no evidence to suggest that ST2's LLT vanishes in large systems. This result is another clear demonstration that the ST2 model, when properly simulated, displays a metastable LLT, and is a clear and direct refutation of the conclusions reached by English *et al.*[149]
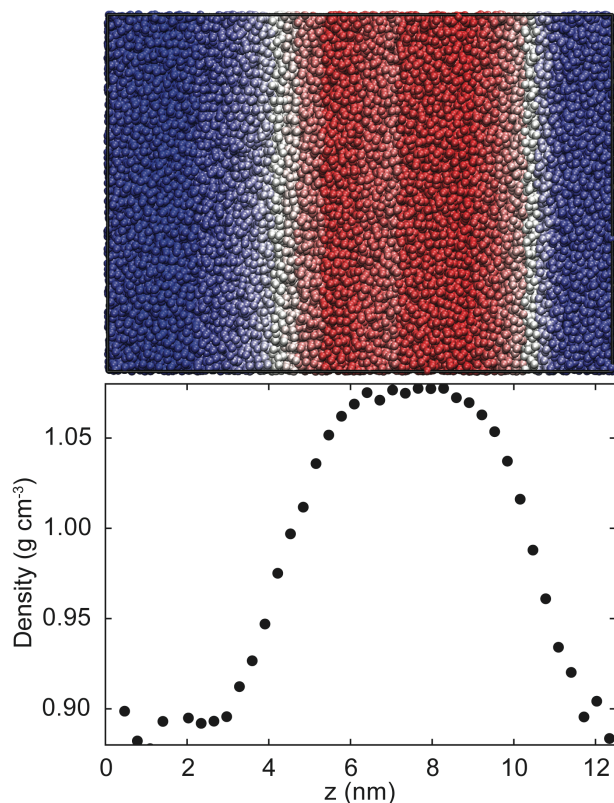
Fig. 3. Liquid-liquid coexistence in ST2 water observed at $T = 235$K and $\rho = 0.98\,\mathrm{g/cm^3}$ in a $N = 32{,}000$ molecule MD simulation[154] in which the reaction field method was used for treating long-range electrostatic interactions. (top) Snapshot of the 8.83 nm × 8.83 nm × 12.49 nm simulation cell with oxygen atoms colored by the local density computed along the z-direction (red = high density, blue = low density). (bottom) Density profile along the z-direction of the simulation cell.

An interesting group of studies[63, 101, 103, 104, 155, 156] has combined MD with so-called two-state theories. The resulting complement of theory and simulation allows smooth interpolation of simulation data, modest extrapolation to supercooled states where long equilibration makes simulations challenging, estimates of the location of the liquid-liquid critical point, and provides microscopic interpretation of simulation results. Theory, in other words, provides here a sound basis for exercises that would otherwise amount to data fitting and regression. As mentioned in Section 2.1, two-state or "mixture" models of water have a long history[60]. They view the liquid as a mixture of two species differing in local structure: one possesses low density, low entropy, and low energy, and is often referred to as "ice-like"; the other species possesses high density, high entropy, and high energy, and is often referred to as "disordered" or "high-density." The usefulness of such descriptions for water at ambient conditions, which is a homogeneous liquid, is a matter of debate[61, 62]. However, the experimentally observed increase in water's response functions and the underlying enhanced fluctuations that these measurements signal have motivated renewed interest in mixture models (e.g., Ref. [157]), in which LDL-like and HDL-like domains play the role of "ice-like" and "disordered" species, respectively. One can then write an expression for the Gibbs free energy of the liquid,

$$G = xG^L + (1-x)G^H + RT[x\ln x + (1-x)\ln(1-x)] + \omega x(1-x) \qquad (1)$$

In the above equation, x is the fraction of LDL molecules, G^L and G^H are the molar Gibbs free energies of the pure LDL and HDL phases, and ω characterizes the non-ideality of mixing. The simple, regular solution form of Eq. (1) has been frequently used, but the underlying ideas do not of course hinge upon this specific choice. What distinguishes Eq. (1) from the usual Gibbs free energy expression for a true mixture is the fact that x is not fixed, but is, instead, determined by minimizing G at any given T and P. In other words, "species" can interconvert.

Computationally, one supplements a conventional MD simulation with the determination of x as a function of T and P. This analysis requires the introduction of an order parameter that classifies a given molecule as being instantaneously LDL- or HDL-like. The thermal average of such a classification yields x. Cuthbertson and Poole[63], Holten et al.[156] and Singh et al.[103] used the distance to the fifth-nearest-neighbor, d_5, as a convenient order parameter: molecules with $d_5 > 3.5$ Å are (instantaneously) classified as LDL-like, whereas those with $d_5 < 3.5$Å are classified as HDL-like. Russo and Tanaka[101] used a different order parameter, namely the difference between the distance from generic molecule i to the closest neighbor to which i is not hydrogen-bonded and the distance from i to the farthest neighbor to which i is hydrogen-bonded. The thermal average of order parameter histograms yields a distribution, which Russo and Tanaka decomposed into two Gaussians, weighted by x and $(1 - x)$, respectively.

Application of Eq. (1) to simulation data requires knowledge of four parameters: ΔE, ΔS, ΔV, and ω, where $G^L - G^H = \Delta E + P\Delta V - T\Delta S$. These parameters are obtained from a combination of criticality conditions and the slope of the locus $x = 1/2$ (Widom line) (see, e.g., Ref.[63] for details). Use of the model sufficiently away from liquid-liquid criticality requires, in addition, knowledge of $G^H(T, P)$. Cuthbertson and Poole[63] set $G^H = 0$, since they were specifically interested in the close proximity of liquid-liquid criticality. Holten et al.[156] and Singh et al.[103], on the other hand, fitted the coefficients of a temperature and pressure expansion of G^H to simulation data. A particularly interesting aspect of the work of Holten et al.[156] and Singh et al.[103] is the inclusion of a crossover procedure to allow for critical fluctuations, in accord with the modern theory of critical phenomena[158].

The above-outlined approach has been used to investigate liquid-liquid criticality and equation of state behavior of ST2[63, 156], TIP4P/2005[101, 103, 104] and TIP5P[101]. It has also been fruitfully applied to supercooled models that do not show liquid-liquid criticality[155]. Finally, it should be added that, in addition to its use in conjunction with simulation data, as explained above, Eq. (1) forms the basis of the most recent formulation of an engineering equation of state for supercooled water up to 4 kbar[159].

Ni and Skinner[160] used MD to calculate the response functions of the E3B3 model of water, which includes explicit three-body interactions[44], along selected isobars ($P \leq 2.5$ kbar) at supercooled conditions. At each pressure they computed the isothermal compressibility and the thermal expansion coefficient as a function of temperature. The resulting isobaric extrema of the response functions with respect to temperature define (P, T) loci that converge at high enough pressure, thereby defining the model's LLCP, which Ni and Skinner estimated to be located at 180K and 2.1 kbar. Corroborating evidence of this estimate was provided by the behavior of the height of the second peak of the radial distribution function, which showed a steep change between 180 and 185K at 2 kbar, consistent with the transition between LDL (which possesses a well-defined second-neighbor shell) and HDL (in which the second-neighbor shell is collapsed).

In subsequent work, Ni and Skinner[161] simulated the IR spectra of the E3B3 model along several isobars at supercooled conditions. At each pressure, the temperature range was chosen so as to span the value corresponding to the maximum in the compressibility, and over this range, the computed IR spectra exhibited a maximum with respect to wavenumber. Ni and Skinner plotted the height of this peak as a function of temperature along each of their simulated isobars. The observed rise with decreasing temperature became progressively sharper at higher pressures, eventually becoming almost discontinuous at 2.25 kbar in the approximate narrow interval $175 \leq T \leq 177.5$K [161]. On the assumption that the E3B3 model is a good representation of real water, this finding suggests that the IR spectra are inconsistent with proposed locations of the LLCP below 500 bar [162, 163], but consistent with the proposed location at 168K and 1.95 kbar. The latter value was proposed by Ni and Skinner for real water[160] based on the convergence of the experimental (and extrapolated) loci of compressibility and NMR relaxation time extrema. An interesting aspect of the Ni and Skinner IR spectra calculations and their thermodynamic interpretation comes from the fact that the approach was inspired by corresponding low-pressure measurements on nm-sized water droplets undergoing supersonic expansion at deeply supercooled conditions[164].

Pathak *et al.*[165] performed a comparative MD study of ST2[119], SPC/E[150], TIP4P/2005[140], mW[107], and the polarizable iAMOEBA potential[46], one of the most accurate models for water, to study their properties in the supercooled regime. Local tetrahedral order in the liquid was characterized by analyzing the second peak in the radial distribution function. Rather than using the height of the second peak, they employed a new order parameter A_2, defined as the integral over a ca. 1 Å interval centered on the maximum, which is less sensitive to peak shape and thus a more robust metric for comparing structural changes in different models. Predictions from the models were compared against experimental data at ambient pressure, including isothermal compressibility measurements[10] (ca. $253 \leq T \leq 375$ K) and A_2 extracted from the X-ray scattering analysis of Sellberg et al.[19] (ca. $227 \leq T \leq 320$ K). Although both iAMOEBA and TIP4P/2005 provided good predictions of these properties over the range of temperatures investigated experimentally, sluggish relaxations in TIP4P/2005 frustrated sampling at deeper supercoolings. Simulations of iAMOEBA at lower temperatures ($180 \leq T \leq 227$ K) and higher pressures ($1.4 \leq P \leq 1.8$ kbar), however, revealed a sharp increase in A_2 upon cooling, similar to that observed in ST2 near its LLCP. Thus the nearly discontinuous behavior of A_2 in iAMOEBA was found to be consistent with analysis of the model's isobaric heat capacity and isothermal compressibility, suggesting the existence of an LLCP in this model at ca. 184 ± 3 K and 1.75 ± 0.1 kbar. Moreover, by aligning the iAMOEBA data to improve agreement with experiment, they estimated that real water exhibits an LLCP at 190 ± 6 K and 1.50 ± 0.25 kbar.

3 Resolution of Controversies

3.1 Palmer et al.

Despite employing similar computational approaches, the independent studies discussed in Section 2.3 yielded conflicting results regarding the phase behavior of the ST2 water model in the vicinity of its hypothesized LLT. This disagreement fueled vigorous debate over the existence of an LLT and the nature of the purported LDL phase in ST2. The preponderance of numerical evidence from phenomenological[3, 63, 72-74, 91-93, 156] and free energy calculations[49, 131, 134, 143, 144] indicates that LDL is a well-defined metastable phase, which can be brought into coexistence with HDL. This view was challenged, however, by Limmer and Chandler[4, 5], who posited that LDL is a non-equilibrium artifact associated with crystallization[30,31]. This lack of consensus highlights the challenging nature of simulating liquids in the deeply supercooled regime, where the equilibration time scales are comparable to those currently accessible with standard molecular simulation methods. To distinguish a reversible phase transition from transient behavior, simulations must be equilibrated for a duration that is significantly longer than time scale of the slowest relaxation mode in the system. Accessing such time scales with molecular dynamics can be problematic because the system evolves by natural physical processes, such as diffusion, that become increasingly sluggish as T decreases. The hydrogen bond network relaxation time, for example, has been estimated to be 40 ns in the vicinity of ST2's purported LLCP[92]. Time scales on the order of 10 relaxations are therefore accessible with μs-long MD simulations. This duration may be sufficient to equilibrate the system, but

significantly longer sampling times are needed to clearly discern between reversible and non-equilibrium behavior.

Monte Carlo methods offer some advantages over MD in exploring the phase behavior of supercooled liquids. Cleverly designed MC moves can artificially accelerate or even bypass sluggish physical processes, significantly reducing the computational effort expended to relax the system[51]. They are also easily combined with advanced free energy methods that allow phase transition processes to be controlled in a reversible fashion. Regardless of the sampling method, however, ensuring that free energy calculations are devoid of artifacts is challenging[166], particularly in the supercooled regime where slow relaxation processes frustrate equilibration and sampling. Fortunately, there are a number of stringent tests that can be performed to verify the accuracy of free energy calculations[166]. Because free energy is by definition an equilibrium state function, it is independent of time and the reversible path used to perform the calculation. Free energies, when properly computed with molecular simulation, should therefore not depend on any aspect of the sampling protocol; they should be independent of the simulation technique, sampling duration, and the reversible path used to connect the states of interest[166]. Consequently, each of these aspects can be diligently scrutinized to check for non-equilibrium artifacts and verify the veracity of free energy calculations.

In a study published in *Nature*, Palmer et al.[7] applied these stringent tests to finally resolve the long-standing debate over the LLT in the ST2 water model. Using six state-of-the-art MC-based free energy methods[51], they demonstrated unambiguous numerical evidence of an LLT in ST2 water. Figure 4 shows the $\rho - Q_6$ free energy surface from their study computed at a state point of liquid-liquid coexistence using umbrella sampling MC simulations[167] with Hamiltonian exchange[168] and collective, smart MC moves[169]. It can be seen that two disordered (low Q_6) phases of different density are in equilibrium (same free energy) with each other, and that both of the liquids are metastable with respect to the crystal phase (ice Ic, $Q_6 \approx 0.5$), which has a much lower free energy. This key result marked the first time that two metastable liquid phases in equilibrium with each other and a third, stable crystalline phase have been identified in a pure substance at the same temperature and pressure in a computer simulation.
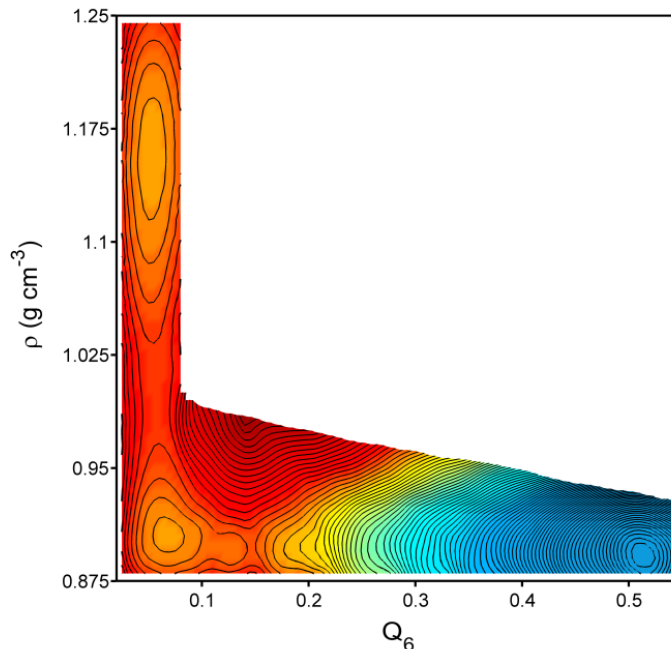
Fig. 4. Reversible free energy surface from parameterized by density, ρ, and the crystalline order parameter, Q_6, for 192 ST2 water molecules at a point of liquid-liquid coexistence (228.6 K and 2.4 kbar). The simulations were performed using the Ewald method with vacuum boundary conditions to treat long-range electrostatic interactions. The high-density ($\rho \approx 1.15$ g cm^{-3}) and low-density ($\rho \approx 0.90$ g cm^{-3}) liquid basins located at $Q_6 \approx 0.05$ are separated by a ~ 4 $k_B T$ free energy barrier and are metastable with respect to cubic ice ($Q_6 \approx 0.5, \rho \approx 0.90$ g cm^{-3}) by ~ 0.75 $k_B T$ (0.76 kJ/mol) at this temperature and pressure. The average uncertainty in the free energy surface is less than 1 $k_B T$. Contours are 1 $k_B T$ apart. Reprinted by permission from Springer Nature: Ref.[7]. Copyright 2014.

To check for spurious path dependence, the free energy surface in Fig. 4 was constructed by using two independent sets of simulations to perform bi-directional sampling. In the first set, a sampling path going from the liquid region to the crystal was constructed by seeding each simulation with initial configurations extracted from the LDL basin. In a similar fashion, the second set of simulations was seeded using configurations from the crystal basin to construct the reverse path along Q_6 from the crystal to liquid region. The free energy surface was found to be independent of the sampling path, demonstrating that reversible sampling was achieved.

The reversibility of the paths connecting the liquid and ice regions definitively excludes the possibility that the LDL basin is a non-equilibrium artifact associated with crystallization. Nevertheless, additional checks were performed to ensure that the computed free energy surface was independent of time and simulation method[7]. The liquid region of the free energy surface was re-computed using five additional sampling techniques, including state-of-the-art methods such as parallel tempering MC[170], well-tempered metadynamics[145], and hybrid MC[138]. These methods allowed for sampling to be performed for durations ranging from 20 to $\sim 10^4$

times the relaxation time of the LDL phase[7]. The free energy surfaces from these calculations were found to be statistically indistinguishable from the liquid region (two basins, low Q_6) shown in Fig. 4[7].

Palmer et al.[7] also demonstrated that the LLT in ST2 water is consistent with thermodynamic criteria expected for a first-order phase transition. At coexistence, the free energy barrier separating the liquids should grow with system size[4, 5, 171], scaling as $N^{2/3}$, where N is the number of molecules in the system. This scaling is a consequence of the surface free energy increasing as the interface between the liquids grows with system size[171]. Free energy calculations performed with systems containing N = 192, 300, 400, and 600 molecules were used to demonstrate consistency with this scaling law, thereby providing strong evidence of behavior consistent with expectations for an equilibrium first-order phase transition.

Finally, in addition to demonstrating that the reversible signatures of the LDL are independent of sampling method, duration, and path, Palmer et al.[7] also computed autocorrelation functions for ρ and Q_6 in the LDL region at liquid-liquid coexistence. These calculations revealed that fluctuations in ρ and Q_6 decay on similar time scales in the LDL, challenging the assumption underlying Limmer and Chandler's "theory of artificial polyamorphism"[5]. Limmer and Chandler[172] rejected this evidence, however, by claiming that their theory is based on the analysis of relaxation processes at higher densities, near the HDL region shown in Fig. 4. Consequently, Palmer et al.[141] revisited this topic to examine ρ and Q_6 relaxations at higher densities. Figure 5 shows the ρ and Q_6 autocorrelation functions from their study[141] computed from MD simulations performed in the HDL region at the same thermodynamic conditions reported in Fig. 4. Although there is indeed a separation of time scales between ρ and Q_6 relaxations, Fig. 5 shows that bond-orientational relaxations occur much faster than those associated with density. This behavior is the exact opposite of that predicted by Limmer and Chandler[5]. Further, Palmer et al.[141] also showed that density is the slowly relaxing variable in the HDL at all conditions where liquid-liquid coexistence has been reported in the ST2 model[141]. In sharp contrast with Limmer and Chandler's "theory of artificial polyamorphism"[5], the studies of Palmer et al.[7, 141] thus collectively demonstrate that at no conditions relevant to the LLT in ST2 do fluctuations in density relax significantly faster than bond-orientational order fluctuations.
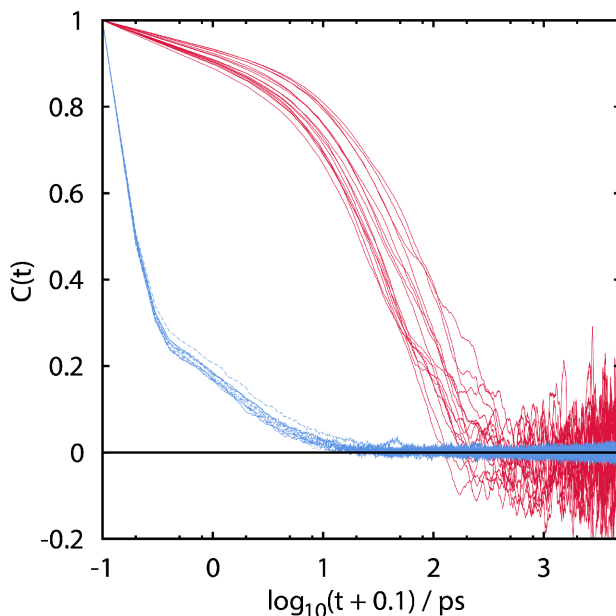
Fig. 5. Autocorrelation functions for ρ (red) and Q_6 (blue) from 18 representative unrestrained NPT MD trajectories in the HDL basin at 228.6 K and 2.4 kbar[141]. The simulations were performed for a system of N=216 ST2 molecules, using the Ewald method and vacuum boundary conditions to treat the long-range electrostatic interactions. Adapted from Ref.[141], reprinted by permission of the publisher (Taylor & Francis Ltd., http://www.tandfonline.com), Copyright 2016.

3.2 Smallenburg et al.

As discussed above, the debate on the existence of an LLT in supercooled liquids is not limited to water. The mechanism underlying such a transition is expected to be a generic feature shared by all atoms or molecules promoting tetrahedral order at the atomic or molecular level. The phenomenon should also affect the collective behavior of particles dissolved in a solvent (colloids) when the effective interparticle interaction similarly promotes tetrahedrality. In recent years, significant developments have taken place in colloidal physics. It has been possible to reproduce features of the atomic world by synthesizing particles which behave as large (sometimes micron-sized) atoms. Models of repulsive and attractive spherical particles are commonly used to investigate (via microscopy) the glass transition[173], crystallization[174], crystal-to-crystal transitions[175], and crystal defect growth[176]. The larger particle size and the associated larger time scale (compared to atoms) allows for a particle-level detection of the investigated processes. Very recently, colloids interacting with highly directional forces have been synthesized, which can serve as models for molecules[177-179]. Among them, particles with four attractive patches located at the surface of an otherwise repulsive colloidal sphere are good candidates for reproducing, at the colloidal level, atomic network-forming liquids and possibly water[180]. The driving force behind the synthesis of bulk quantities of tetrahedrally-interacting colloidal particles stems from a well-defined technological demand: a cheap methodology to produce a diamond colloidal crystal, a lattice with a band structure particularly relevant for photonic applications. The diamond lattice is indeed crucial for inhibition of spontaneous

emission, enhancement of semiconductor lasers, and integration and miniaturization of optical components[181].

The quest for a self-assembling route to diamond nucleation in colloidal systems has stimulated a significant amount of theoretical and numerical studies, which, not unexpectedly, have posed the same questions that have been debated with respect to the relative stability of water and ice. More specifically, the questions that have been raised include: (i) the features of the interaction potential controlling the propensity to crystallize into open crystals; (ii) the possibility to select the thermodynamically stable structure among all possible polymorphs[182]; (iii) the possibility to stabilize the liquid state to suppress crystallization and generate the ultimate glass-former; and, finally (iv) the possibility of generating a liquid- liquid transition and its interplay with the crystal phase.

Colloidal particles are commonly described via primitive models, e.g. models in which the inter-particle repulsion is approximated by a hard-core potential and the patch-patch attractive interactions are modeled via square-well potentials. Indeed, even the first models of water, which were able to capture the tetrahedral coordination and the relevance of the directionality of the interaction[183-186], envisioned a water molecule as a hard sphere (HS) whose surface is decorated by four short-ranged sticky spots, arranged according to a tetrahedral geometry, two of which mimic the protons and two the electron lone-pairs. Primitive models are even more accurate for colloids, where attractions are usually short-ranged and repulsive interactions can be properly modeled as hard-core repulsions. In these primitive models, it becomes easier to control specific features (strength of interaction, range of interaction, bond flexibility, softness) by simply tuning the model. For example, formation of a bond between two adjacent patches depends explicitly on the range and angular width of the selected square-well potential. In this respect bonding properties are clearly connected to geometric features.

Most of the early numerical studies of primitive models of tetrahedral patchy particles with intrinsic tetrahedral symmetry[180, 186-191] (with the exception of Ref.[192]) failed to report crystallization to an open crystal structure (e.g. diamond), despite the fact that the tetrahedrality that characterizes the crystal phase was encoded by design in the tetrahedral arrangement of the patches on the particle surface. Only recently has it become clear that open crystal structures (cubic and hexagonal diamond and their stacking hybrids) spontaneously form (*in silico*) only if bonds are rather directional[193] (e.g. angular width allowing for bonding smaller than about 30°). For larger angles, crystallization is pre-empted by dynamic arrest into a network glass. It has been shown that the chemical potential difference between a network-forming liquid and the open crystal phase is strongly affected by the flexibility of the bonds[193]. As a result, on cooling, particles with highly directional interactions (water, silicon) easily crystallize, while particles with more flexible bonding (silica, tetravalent DNA-constructs[194]) form arrested networks (gels)[195].

Colloidal particles offer the opportunity to extend the range of physical values characteristic of the bond flexibility in atoms and molecules. The recently studied DNA constructs[194, 196] (or even polymerizable monomers with fixed functionality[197]) constitute an example of particles that can form a fixed number of highly flexible bonds. When bonds are highly flexible, the liquid free energy remains lower than the crystal free energy down to vanishing temperature, providing examples of liquids that never crystallize[198]. Thus, on cooling, the liquid phase of particles with a limited number of flexible bonds smoothly forms a fully

bonded disordered network, without the intervention of any phase transition toward an ordered structure. The configurational entropy (particularly large in the case of flexible bonds, being a measure of the number of distinct network realizations) is instrumental in stabilizing the liquid phase with respect to the crystal[198].

The ability to control crystallization in tetrahedral interacting particles via tuning of the bond directionality suggests that perhaps it is possible to design a model of tetrahedral particles in which the LLT appears in full glory (or "naked"[199]) being located in a thermodynamic region where the crystal phase is less stable than the two liquids. This scenaior has been achieved in a recent numerical study[125] where bond flexibility has been tuned from values typical of water and silicon (for which the LLT is located in the "no-man's land", e.g. in the region of the phase diagram in which the diamond phase is stable, Fig. 6(a)); to values where the LLCP emerges and becomes thermodynamically stable (Fig. 6(b)); to the case in which the crystal phase is now completely unstable down to vanishing temperatures (Fig. 6(c)), such that the LLT can be safely explored at all temperatures; to the final case in which the flexibility of the bonds has reached such extreme values that even the liquid- liquid transition disappears (Fig. 6(d)). Interestingly, the possibility to observe a genuine phase separation into two thermodynamically stable liquid phases, with no interference of crystallization at any temperature, becomes possible only because bond flexibility destabilizes the crystal state more rapidly than the liquid-liquid transition (Fig. 7).

The same study[125] has shown that observation of a liquid-liquid transition in primitive models based on tetrahedral bonding geometry requires a minimum amount of interparticle interpenetration (or softness). It appears that the ability to interpenetrate[121] (e.g. the ability to form bonded structures of interpenetrating disordered networks) is crucial for the existence of a liquid-liquid transition. Not surprisingly, water has such an ability, which is made manifest by the thermodynamic stability, at higher pressure, of ice I_{VII} a proton-disordered structure composed of two interpenetrating (but not connected via hydrogen bonds) I_c lattices.

In colloidal physics, the ability to modify the surface chemistry of the particles or the chemical/physical properties of the solvent makes it in principle possible to control both the softness of the interparticle interaction (interpenetration) and the directionality of the interparticle bonding (flexibility), and to rationally design the interaction potential between colloidal particles. Hence, we may expect that the theoretical predictions previously discussed will be subject to experimental test. Meanwhile, numerical simulations of models more realistic than primitive ones can provide support to the results reported in Ref.[125]. In the case of DNA constructs with four double-stranded arms ending with a short single-strand sticking sequence — a model for which the existence of an LLT favored by the ability to interpenetrate was established previously[121] — simulations in which only the flexibility of the DNA arms has been varied have confirmed the possibility of tuning the relative stability of the LLT and of crystallization[122].
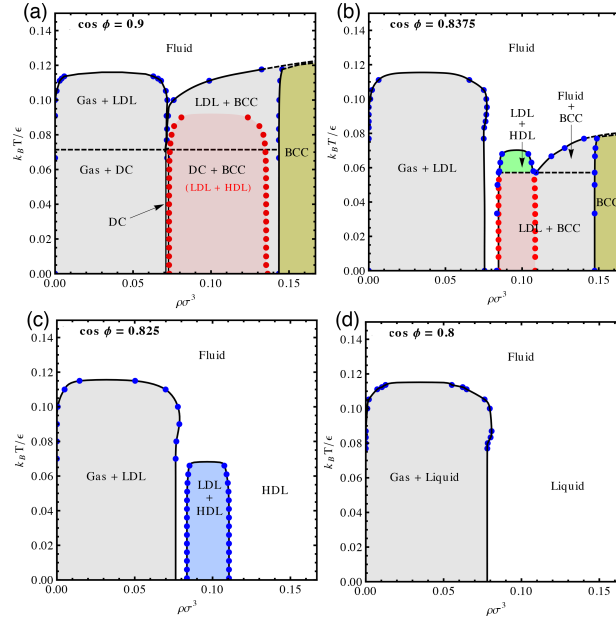
Fig. 6. Schematic graph showing the evolution of the phase diagram in the temperature-density plane, on varying bond flexibility, for a system composed of tetrahedral particles. (a) Highly directional bonds. The liquid-liquid phase separation is in no-man's land, e.g. metastable with respect to the open crystal diamond phase. (b) Intermediate flexibility. The liquid-liquid phase separation emerges outside from the crystal stability field, which remains the more stable phase at low temperature. (c) Flexible bonds. The crystal phase is never stable and the liquid-liquid transition emerges in full glory. (d) Very flexible bonds. Even the liquid-liquid transition is suppressed by the enhanced flexibility and one single liquid phase persists down to vanishing temperatures. Reprinted by permission from Springer Nature: Ref. [125]. Copyright 2014.

Fig. 7. Schematic of the evolution of the liquid-liquid critical temperature T_c and of the liquid-crystal melting temperature T_m evaluated at the LLCP density, as a function of the bond

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flexibility. The shaded area indicates metastable liquid conditions, which vanish beyond a critical value of the bond flexibility. This behavior is a characteristic of the ST2 model.
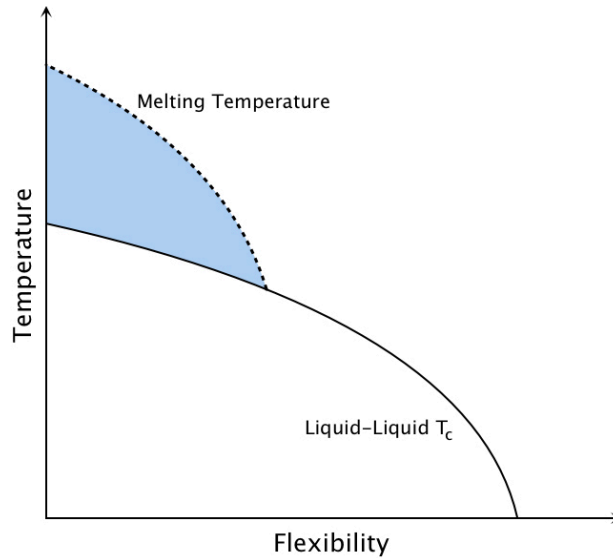
More recently, the idea of modulating the liquid-crystal melting temperature and the LLCP by modifying the bond flexibility has also been applied to the ST2 model with reaction field treatment of long-ranged electrostatics (ST2-RF), to provide a proof of the existence of an LLCP in ST2 that does not require kinetic information[8]. To modulate the flexibility of the hydrogen bonds, the vectors pointing toward the H and massless lone pair (LP) point-charge sites of the model were allowed to fluctuate (with no additional energy cost) with respect to the original direction, with a maximum angle θ_{max} (see Fig. 8(a)). When $\theta_{max} = 0°$ the modified model coincides with the original ST2 model.
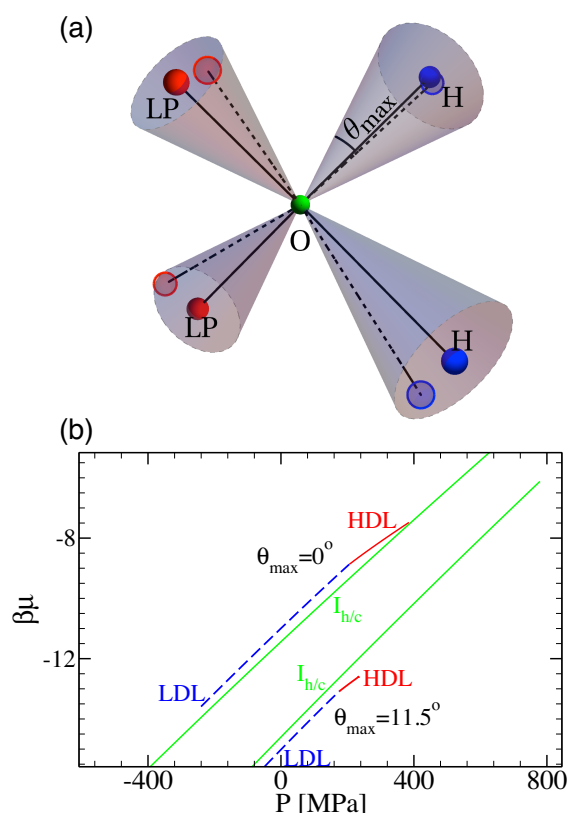
Fig. 8. (a) Schematic representation of the ST2 water model and of its extension to modulate hydrogen bond flexibility. Solid lines indicate the position of the H and LP sites in the rigid original ST2 model. The cones of angular amplitude θ_{max} define the volume limiting the position of the same sites in the flexible model (dashed lines). (b) Chemical potential (at the LL critical temperature) for $I_{h/c}$, LDL, and HDL for two different values of the angular flexibility (θ_{max}). For the rigid model (i.e., $\theta_{max} = 0°$), the chemical potential of the LDL and HDL phases is higher than the chemical potential for $I_{h/c}$. In contrast, for the flexible model with $\theta_{max} = 11.5°$, the chemical potential of the coexisting liquids is lower than the one of $I_{h/c}$. Hence, the liquid-liquid phase transition becomes thermodynamically stable with respect to nucleation of $I_{h/c}$ when flexibility is introduced. Reprinted figure with permission from Ref. [8]. Copyright 2015 by the American Physical Society.

By tuning just this single parameter in the ST2 model it is possible to modulate *continuously* the relative stability of the liquid and of the hexagonal (or cubic) ice $I_{h/c}$ such that the melting temperature of $I_{h/c}$ drops below the LL critical temperature, offering the possibility to observe the LLT in the absence of crystallization. Fig. 8(b) shows the main results of Ref. [8], e.g. the P dependence of the liquid and ice $I_{h/c}$ chemical potential at the LL critical temperature T_c . In the case of the original ST2 model ($\theta_{max} = 0°$), the chemical potential of $I_{h/c}$ is always lower than the liquid one, consistent with the location of T_c in no-man's land. For $\theta_{max} = 11.5°$, at T_c the liquid phase has gained a significant stability compared to the open crystal lattice. Under this condition, there is no possibility that the low-density liquid phase in flexible ST2 will ever convert into the $I_{h/c}$ structure. Thus, the investigation of the flexibility in ST2 – a molecular (as opposed to colloidal) model – provides results fully consistent with the ones based on colloidal models[122, 125]. Specifically, the continuous path of the LLCP as a function of the flexibility (connecting the original ST2-RF model with the flexible ST2-RF) proves that the liquid-liquid transition in ST2-RF is NOT the reflection of a transition between liquid and crystal but a genuine first-order transition. The low-density liquid phase is, without any ambiguity, a phase by itself, definitively disproving the arguments in Ref. [4, 5].

3.3 Analysis of the Limmer-Chandler HMC Code

The studies by Palmer et al.[7] and Smallenburg et al.[8] demonstrated that the ST2 water model exhibits a reversible LLT, thereby resolving the long-standing controversy over its low-temperature phase behavior. Nevertheless, they did not identify the origin of the discrepancy with the Limmer-Chandler studies[4, 5], which report no evidence of an LLT in ST2. Years later, however, the simulation code used in the Limmer-Chandler studies was made available to Palmer et al. for scrutiny. Subsequent analysis of the code[6] uncovered a fundamental flaw in the HMC sampling algorithm that Limmer-Chandler used to perform their free energy calculations for ST2.

In the standard HMC algorithm[138, 200-202], short MD trajectories are used as trial MC moves. The trajectories are initiated by randomly drawing initial velocities from the Maxwell-Boltzmann (MB) distribution at the target sampling temperature and subsequently propagated using a time-reversible and volume-preserving integrator (e.g., the velocity-Verlet algorithm)[138, 200-202]. The final configuration at the end of each trajectory is either accepted or rejected according to the Metropolis-Hastings criterion: $\min[1, \exp(-\beta[\Delta K + \Delta U])]$, where $\beta = (k_B T)^{-1}$ is the inverse temperature, k_B is Boltzmann's constant, and $\Delta K = K_{\mathrm{new}} - K_{\mathrm{old}}$ and $\Delta U = U_{\mathrm{new}} - U_{\mathrm{old}}$ are the changes in kinetic and potential energy during the trajectory, respectively. The Metropolis-Hastings criterion enforces detailed balance and thus ensures that, in the absence of equilibration issues, the standard HMC algorithm will correctly sample configurations from the canonical (N, V, T) ensemble[138, 200-202]. As was done in the Limmer-Chandler code[4, 5], HMC moves can also be used in conjunction with standard volume change MC moves to sample configurations from the isothermal-isobaric (N, P, T) ensemble[40].

The inclusion of the kinetic energy term ΔK in the HMC acceptance criterion accounts for the fact that trial moves are proposed by drawing initial velocities from the MB

distribution[200, 202]. The standard HMC acceptance criterion is thus formulated based on the explicit assumption that the velocities used to initialize each trial MD trajectory obey MB statistics[200, 202]. Of course, initial velocities may be drawn from other distributions, but the HMC acceptance criterion should be redefined accordingly to avoid detailed balance violations [201-203]. Limmer and Chandler's HMC algorithm, by contrast, used the standard HMC acceptance criterion, but did not correctly draw initial velocities from the MB distribution[6]. The velocity initialization procedure employed in their code failed to properly account for the fact that ST2 is a rigid water molecule with no internal degrees of freedom[6]. Consequently, the initial velocities generated by the Limmer-Chandler HMC algorithm were inconsistent with the MB distribution for rigid bodies and violated equipartition, such that the molecules were translationally hot and rotationally cold compared to the target sampling temperature[6].

Palmer et al. showed that velocity initialization errors in the Limmer-Chandler HMC algorithm resulted in severe sampling problems[6]. The sampling errors distorted ST2's equation of state (Fig. 9) and caused the Limmer-Chandler HMC algorithm to fail several rigorous, statistical mechanics-based consistency checks[6]. Palmer et al. also demonstrated that these sampling issues could be resolved by modifying the Limmer-Chandler HMC code to correctly generate initial velocities from the MB distribution. When this was done, the corrected code accurately predicted ST2's equation of state (Fig. 9) and passed each consistency test[6]. Importantly, free energy calculations performed with Limmer and Chandler's original, uncorrected HMC code reproduced their published results[4, 5], which showed only a single liquid basin at conditions where other studies have reported two liquid phases[7, 8, 49, 131, 143] (Fig. 9). In striking contrast, however, clear evidence of two liquid phases was observed when free energy calculations were performed under the same conditions using the corrected code[6] (Fig. 9). Hence, this recent analysis demonstrates that a fundamental design flaw in the Limmer-Chandler HMC algorithm underlies the irreconcilable discrepancy between their free energy calculations and those reported by other researchers. In particular, the fundamental error not only prevented Limmer and Chandler from properly sampling the underlying free energy surfaces for molecular models of water, but it also gives rise to a serious violation of equipartition whereby molecules are translationally "hot" and rotationally "cold". This latter serious error fully explains the origin of the incorrect claim by Limmer and Chandler that density relaxation is significantly faster than bond orientational relaxation, a central assumption of their "theory of artificial polyamorphism."[5, 141 6].

We conclude this section by sharing our hope that the debate on the mistaken claim of absence of an LLCP in ST2 will elicit a broad discussion in the scientific community about the paramount importance of openness and transparency in scientific controversies. We believe that allowing public access to code and data should be a requirement, especially in cases where the debate hinges on code-related matters. Such debates are healthy for science, but can be prolonged artificially by the absence of open and transparent data sharing practices.
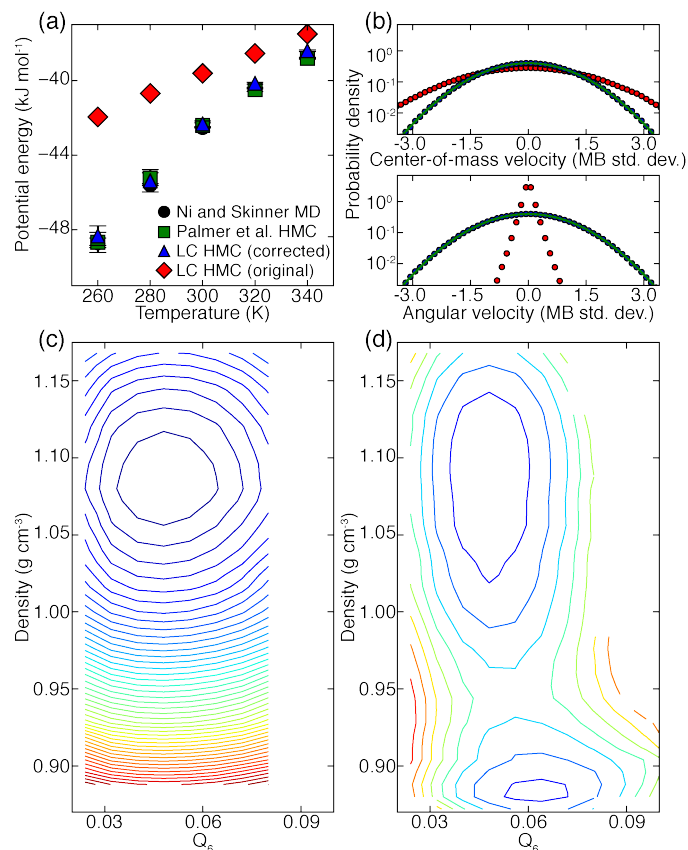
Fig. 9. (a) Potential energies for ST2 with Ewald treatment of long-range electrostatics and vacuum boundary conditions (ST2b) at 1 bar. Average energies from the hybrid Monte Carlo (HMC) that Limmer and Chandler (LC) used to perform their free energy calculations for ST2[4, 5] (red diamonds) are incorrect and deviate significantly from those calculated using Palmer et al.'s HMC code[7] (green squares) and Ni and Skinner's molecular dynamics code[160] (black circles). The correct equation of state is recovered, however, when sampling is performed using a version of the LC HMC code that Palmer et al.[6] corrected to draw initial velocities from the Maxwell-Boltzmann distribution (blue triangles). (b) Distributions of the *x*-components of the initial center-of-mass translational velocity (top) and initial body-frame angular velocity (bottom) at 300 K from LC's code (red circles) deviate significantly from the Maxwell-Boltzmann (MB) distribution (green line) and violate equipartition (the translational and rotational temperatures are ca. 597 K and 3 K, respectively). Velocities from the code corrected by Palmer et al. (blue circles, indistinguishable from the green line) obey MB statistics. Velocities are in units of MB standard deviation at 300 K. Free energy surfaces for ST2a at 230 K and 2.8 kbar for 216 molecules computed using LC's original code (c) and the version that Palmer et al. corrected (d). Reprinted from Ref.[6], with the permission of AIP Publishing.

4. Discussion and Conclusions

More than 25 years ago, Poole et al.[3] discovered that in the region of the supercooled liquid, the equation of state of the ST2 model develops a van der Waals-like loop, which was

interpreted as evidence of a liquid-liquid phase transition terminating at a critical point. In the following years, the idea of a one-component system with more than one critical point has permeated the liquid matter community and has stimulated a large body of theoretical, numerical and experimental studies. Despite this considerable effort, and despite the importance of water as a liquid, no consensus has yet been reached on the existence or absence of such a critical point in real supercooled water.

The difficulty of proving or disproving the existence of an LLCP resides in the out-of-equilibrium nature of supercooled water and the ease with which it transforms to ice. Experiments must be performed within a carefully controlled window of time scales, greater than the liquid equilibration time (the time required to properly sample the phase space associated with disordered configurations), and less than the crystal nucleation time. The equilibration time progressively increases on supercooling, exceeding any experimentally attainable time scale at the glass transition. The nucleation time instead usually decreases on cooling (due to the increasing difference in chemical potential between crystal and liquid), sometimes passing through a minimum when the approach to the glass transition significantly slows down molecular mobility. As a result, in water, metastable equilibrium measurements on bulk liquid samples are limited to moderate supercooling, i.e. for T greater than the so-called homogeneous nucleation temperature (the upper limit of the "no-man's land"[38]). Attempts to approach the LLCP from below, by progressively heating the LDA and HDA ice phases are also hampered by crystallization.

As often happens, these challenges have stimulated tremendous creativity. Over the years, increasingly innovative methodologies and experimental approaches have been developed and applied to investigate supercooled water under previously unattainable conditions. Noteworthy are the experimental developments in the study of water under tension[28-30]; the study of the distinct forms of amorphous ice and the appreciation of the important role of preparation and annealing protocols[37, 85]; the study of the interrelationship of different amorphous structures and of the nature of their calorimetric glass transition[36, 86]; and last but not least, the development of ultrafast scattering methods in the perpetual fight to defeat crystallization[19, 20], and to enter into what was previously considered water's no-man's land.

Alongside experiments, computer simulation studies have played an important role. In simulations, heterogeneous ice nucleation, i.e. nucleation stimulated by the presence of contaminants or confining surfaces, is suppressed. At the same time, homogeneous ice nucleation can be carefully monitored and controlled, by running numerical trajectories shorter than the homogeneous nucleation time, and by testing for the presence or absence of crystalline seeds. Understanding supercooled water, and its crystallization to ice, has provided strong motivation for the development of modern computational techniques, which when coupled to ever more powerful computational resources, now allow the accurate evaluation of the model system's free energy, its nucleation barriers, and the associated nucleation rates.

This review has focused on the most recent computational studies of the liquid-liquid transition in water-like models. In the last five years, an impressive number of developments has taken place, many of them triggered by the claim, now definitively proven to be incorrect[6-8, 125], that the liquid-liquid transition observed in computer simulations was a misinterpreted liquid-solid transition[4, 5]. Debates in science are decided by facts, as established by reproducible

experiments, and in this case, reproducible simulations. The conclusive identification of the source of the recent discrepancies and contention has now settled the debate: liquid-liquid phase transitions exist in some models of water, and are not misinterpreted crystallization transitions. Fortunately, controversies in science are often a driving force for progress and new discoveries. The work of Limmer and Chandler[4, 5], despite its errors[6], forced the water simulation community to deeply interrogate the evidence in favor of and against the LLCP and poured renewed energy into this important question. Significant progress has come out of this collective effort:

- A much more detailed and deeper understanding of the free energy surface of supercooled water, now projected onto a combination of order parameters, including density and crystalline order[7].
- Investigation of different possible crystallization routes and evaluation of the barriers to ice nucleation; and estimates of the influence of density fluctuations on the nucleation barriers[95].
- A deeper understanding of the time scales for translational and orientational ordering in water[141].
- The identification of bond directionality as the key parameter controlling the relative stability of the crystal-liquid and liquid-liquid transitions, and the resulting ability to generate models in which the LLCP occurs in a thermodynamically stable liquid above the melting line for the crystal[8, 125].
- Novel methodologies for checking the thermodynamic consistency of new simulation techniques[7].
- The widespread adoption of increasingly sophisticated sampling techniques by a community that had hitherto relied largely on more traditional methods (e.g., MD) to investigate a deep and subtle question[7].

Despite the fact that we now have conclusive evidence that the LLCP exists in some classical water and water-like models, much work remains to be done from a computational point of view. In particular, it is natural to ask how our ability to directly study a LLT in simulations can assist in resolving the question of whether the LLT exists in real water, especially given the experimental difficulties associated with penetrating no man's land. There are a number of interesting opportunities for future simulation work, and also some significant challenges:

- In the long term, full *ab initio* quantum mechanical calculations should be applied to the evaluation of the low T equation of state of water. Although rapid advances are being made in this area [204], the most accurate quantum mechanical calculations available today provide reasonable structural information, but fail in correctly reproducing the P and T dependence of most thermodynamic quantities. We also note that recent studies suggest that nuclear quantum effects in water and other light molecules might affect structure and dynamics with signatures which extend up to ambient temperature[205, 206].
- In the short term, one can expect progress in the development of artificial neural network-based models parameterized using data from *ab-initio* calculations. These models can accurately reproduce *ab initio* data and are significantly less computationally demanding than full quantum calculations [207, 208]. They are limited by

the accuracy of existing quantum mechanical methods, however, which still cannot predict water's thermodynamic properties as well as optimized classical models.

- Classical models can be exploited to investigate the details of the interference between ice crystallization and liquid-liquid phase separation. There are hints that crystallization can be facilitated at the interface between low- and high-density water,[92] thus combining the concepts of homogeneous nucleation and self-generated heterogeneous nucleation.

- As computational power and techniques improve, it should soon be possible to fully characterize the nucleation and growth of LDL from HDL. The interplay between time scales for liquid relaxation and for the nucleation kinetics when crossing the LLT may produce unusual effects, such as a kinetic stabilization of the HDL phase, especially if the LDL phase is glassy.

- Estimates of the separation of time scales between phase separation and nucleation is also conceptually relevant when discussing the nature of metastable critical points, a phenomenon of considerable relevance in protein crystallization.

- More generally, a fundamental understanding of the influence of force-field details on the relative magnitudes of characteristic times for relaxation, nucleation, and phase separation across a broad range of models is lacking[209].

- Classical models for which a clear LLCP exists can also be exploited to investigate the structural and dynamic properties of the two liquids and to highlight the connection of these two liquids with their amorphous counterparts. Recent increases in computational power suggest that it will be soon possible to characterize the fragility of these two liquids and their associated activation energies.

- The nature of the glass transition in water continues to be of interest. For example, Shephard and Salzman[210] have recently argued that the glass transition at 136 K actually corresponds to the unfreezing of the orientational degrees of freedom on heating the glass, and that molecular translations only become possible at higher temperature. Direct modelling of the experimental glass transition in water using realistic potentials requires access to simulation time scales that are presently inaccessible. However, it may be possible to use modified water-like models, in which the dynamics of a nearly fully bonded network are more accessible, to test for a separation of the temperatures at which rotations and translations become arrested.

- Related to the previous point, it is also possible that the LDL phase formed via a LLT in real water has such low mobility that it is already a glass at the LLT; i.e. that the liquid-liquid transition is in practice a discontinuous liquid-glass transition. This would be consistent with the behavior observed recently in water-rich solutions[89] and earlier work by Tanaka and coworkers on tri-phenylphosphite[211]. While this behavior is not observed in ST2 water, where liquid-like relaxation of the LDL phase is observed near the LLCP, it should be possible to realize this case and explore its implications in other water and water-like models.

- It will also be useful to enlarge the search for model systems, both in the atomic and in the colloidal world, for which a clear LLCP exists.

After this argumentative but productive period in the study of supercooled water, simulations have provided a solid foundation for the physical basis of a possible LLT in water. Of course, the existence or lack thereof of such a phenomenon in real water will ultimately have to be demonstrated experimentally, not computationally. The impressive recent experiments reporting the presence of compressibility maxima as a function of temperature at negative and ambient pressure strengthens the case for an LLT in water, by eliminating some alternative thermodynamic scenarios. The time-resolved dynamics of LDA and HDA ices, and the promising possibility to approach the supercooled liquid state from the glass regime add further hope. In sum, although our knowledge of the phase behavior of supercooled water remains fluid, there is every reason to expect that new approaches, both in simulations and experiments, will in due course provide a final, solid understanding of this fascinating liquid.

Acknowledgements

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