Structural inhomogeneity of water by complex network analysis

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There is still an open debate regarding the structure forming capabilities of water at ambient conditions. In order to probe the presence of such inhomogeneities, we apply complex networks analysis methods to a molecular dynamics simulation at room temperature. This study provides both a structural and quantitative characterization of kinetically homogeneous substates present in bulk water. We find that the conformation-space-network is highly modular, and that structural properties of water molecules are spatially correlated over at least two solvation shells. From a kinetic point of view, the free energy surface is characterized by multiple heterogeneous metastable regions with different populations and marginal barriers separating them. The typical timescale of hopping between them is 200-400 fs. A scanning in temperature reveals that those substates can be stabilized either entropically or enthalpically. The latter resembles an ice-like domain that extends for at least two solvation shells.

I. INTRODUCTION

The many abnormalities of water, such as the density maximum at 4 °C, are related to the complex and highly dynamic network of hydrogen bonds it can form. Starting with a paper by Röntgen more than a century ago [1], there has been a long-standing debate about the relative importance of local ice-like structures, both in bulk water [2–5] as well as in the context of the hydrophobic effect [6, 7]. The density maximum at 4 °C is a manifestation of the competition between two driving forces, i.e. the directionality of hydrogen bonding that favors a low-density, tetrahedral (ice-like) form of water in order to minimize enthalpy, and maximizing entropy by nondirectional hydrogen bonds and disorder, resulting in a closer packing. Furthermore, recent small angle x-ray scattering evidenced that water is structurally inhomogeneous with spatial correlations over ≈10 Å [8]. Even though these measurements were performed between room temperature and close to the boiling point, the experiments were discussed in the context of the liquid-to-liquid phase transition of water in the deeply supercooled regime, i.e. in the so-called “No Man’s Land” of the $(p,T)$-phase-diagram that is, as of yet, not accessible experimentally [9].

From a theoretical point of view, the tetrahedral order parameter [10], pairwise and higher order orientational correlation functions [11], as well as local hydrogen bonding [12] have been used to characterize correlations between neighboring water molecules. However, as with any complex molecular system, it is very difficult to physically capture the structural properties of water with the help of an _a priori_ choice of one or a few geometric order parameters.

In the case of protein folding, the archetypal complex system, a new arsenal of graph-based theoretical tools have been recently developed to circumvent this limitation [13–15]. Network approaches have pointed out the presence of multiple stable structures in the unfolded state of a protein, which is a somewhat surprising result, giving the fact that folding often appears to be a two-state process [13, 16]. Complex network analysis methods, which initially have been inspired by social and computer sciences (e.g. analysis of friendship networks or the World Wide Web [17, 18]), have proven to be very useful to understand protein conformational changes in general [19–22].

The essential idea of these methods is to map a molecular dynamics (MD) trajectory into a discrete set of _structurally_ homogeneous microstates without assuming any _a priori_ knowledge of the relevant degrees of freedom. In turn, the dynamics of the simulation is represented as a kinetic network – the conformation-space-network – where the microstates and the transitions between them observed during the simulation represent the nodes (vertices) and the links (edges), respectively. Conformation-space-networks represent a high resolution mapping of the underlying free-energy surface where highly interconnected groups of nodes indicate _kinetically_ homogeneous free-energy valleys [16, 20].

The generalization of this approach to describe the thermodynamics as well as the kinetics of bulk water is difficult. In contrast to a protein, a missing definition of microstates and the intrinsically entropic nature of a liquid have prevented the application of the above graph-based methods. In this work, we present such a generalization by introducing the conformation-space-network of water at room temperature. We found that bulk water is characterized by a number of substates which are normally hidden in conventional approaches. Our study provides a quantitative description of those substates in terms of their thermodynamics, kinetics, and structural properties.
II. MATERIALS AND METHODS

The work is based on 10 ps to 1 ns long MD trajectories of SPC water (except where noted otherwise), using the Gromacs program package [23], in the NVT ensemble at 300 K, 1019 water molecules at experimental density, 1 fs time-step with a saving-frequency of 4 fs, periodic boundary conditions, with the long range electrostatic forces approximated by the Particle-Mesh-Ewald approximation. The hydrogen bond definition that we employ is based on the work of Skinner et al. [24, 25] who found an empirical correlation between the occupancy \( N \) of the O–H σ* orbital (electron density which is donated by the hydrogen-bond acceptor) from electronic structure calculations and the geometries observed in MD simulations. They parametrized the orbital occupancy in terms of the H–O–O intermolecular distance \( r \) and the angle \( \psi \) that the O–H ray makes with the out-of-plane unit vector of the acceptor molecule:

\[
N(r, \psi) = \exp(-r/0.343 \text{ Å})(7.1 - 0.050 \psi + 0.00021 \psi^2),
\]

(1)

and consider a hydrogen bond to be formed if this occupancy exceeds a certain threshold (\( N > 0.0085 \)).

Alternatively, we also tested a simple geometry criterion in which a hydrogen bond is said to be formed if the O–O–O distance is smaller than 3.3 Å and the angle between the O–H and the O–O–O rays is smaller than 30°. The essential layout of the conformation space network does not depend on the hydrogen bond criterion (Supplemental Fig. S4).

III. THE CONFORMATION SPACE NETWORK OF WATER

Water is the classic associating liquid; the directionality of hydrogen bonding significantly changes the structure of the fluid, e.g. the the number of nearest neighbors, relative to simple liquids like xenon. Hence, we adopted the view that it is the topology of hydrogen-bond-network around a given water molecule that determines the structural and dynamical properties of the bulk. However, the binding partners to any central water molecule are not predefined, but keep exchanging on a fast picosecond timescale. Therefore, any approach to define a microstate must be invariant to interchanging water molecules, as well as oxygen binding sites (we distinguish the hydrogen-binding sites, which could be achieved experimentally by isotope labelling). Fig. 1 shows two examples of hydrogen-bond-networks, as they appear during a molecular dynamics (MD) simulation. In some cases, all four binding sites of each water molecule connect to new water molecules (Fig. 1a), but in others there are loops and/or broken hydrogen bonds (Fig. 1b). We describe each structure by a unique string that encodes the connectivity through hydrogen-bonds. For each water molecule, we search for neighboring water molecules that hydrogen-bond to it, using a criterion for hydrogen-bonding which is based on an orbital-mixing point of view, and which has been introduced recently by Skinner et al. [24, 25] (if not stated otherwise). From these waters of the first solvation shell, the search expands in a tree-like manner (Fig. 1 right). We assumed that each water molecule has a maximum of four binding sites, one to each of the two hydrogens (blue lines in Fig. 1 right) and two to the oxygen (red). For a fully hydrogen-bonded network of a central water and two solvation shells, there are then a maximum of 17 possible waters. In the relatively rare occasions when two water molecules hydrogen-bond to one of the hydrogens, or three water molecules hydrogen-bond to the oxygen, we selected those with the larger occupancy numbers. We did, however, explicitly consider structures with fewer than four hydrogen-bond partners, (e.g. molecule 5) in the example Fig. 1b). Each subsequent solvation shell is a new generation and follows, in order, in the microstate string, numbered by their position in the fully hydrogen-bonded tree (Fig. 1a, right). The order of appearance of water molecules at the two oxygen binding sites is arbitrary. We resolved this symmetry by determining all possible permutations of interchanging the labelling of oxygen binding sites, and uniquely chose one string to represent them all. For example, (1)|0 0 4 5|0 0 0 0 0 0 12 13 14|0 0 0) and (1)|0 0 4 5|0 0 0 0 0 0 15 16 17) encode identical conformational, and we choose the first. In contrast, we distinguished the two hydrogen sites, which could be achieved in a real experiment by isotope labelling.
We had to truncate the tree after the second generation (second solvation shell), as we found that further generations make the number of microstates unmanageably large ($>10^2$ instead of $5 \times 10^4$ for a 100 ps trajectory).

Each hydrogen-bond-network string represents a microstate of a single water molecule. The analysis of the time evolution of those microstates allows a network description of the system, in analogy to Ref. [13, 20]. Two microstates (nodes) are linked if they appear subsequently in the trajectory; nodes and links are weighted by how many times a microstate appears and a transition occurs, respectively. This conformation-space-network is a representation of a kinetic matrix. It was shown that nodes connected with each other by many edges interconvert rapidly and are kinetically homogeneous, while poorly connected nodes are kinetically separated [20]. Network visualization represents a successful approach to infer such kinetic properties, at least at a first qualitative level [13]. Here, in order to obtain a three-dimensional layout of the conformation-space-network of water, we apply multidimensional scaling (MDS) [26–28], which is essentially the same as a principal coordinate analysis [29, 30] (both would be identical if the metric is Euclidean [28]). In general, the MDS algorithm starts from a matrix of node pairwise distances (restraints). Consider four points in 3D space, then a matrix of mutual distances defines these points uniquely modulo an overall translation and rotation. The same holds for $N$ points in $(N - 1)D$ space (in case the distance matrix would be Euclidean), i.e., represents an object embedded into a highly dimensional space (in our case several thousands).

The aim of the MDS algorithm is then to reduce the effective dimensionality of the full set of restraints by spectral analysis, i.e. combining those dimensions that are redundant in the restraints space. In the most simple implementation of the MDS algorithm, distance would be the minimum number of links between two nodes [26, 27]. In contrast, here we give distances the meaning of a travelling time, so the MDS algorithm will lump together those distances that correspond to fast interconversions (i.e. grouping kinetically homogeneous nodes) while separating slowly relaxing nodes.

Having this physical picture in mind, we choose for the mutual distances between two directly linked nodes, $\tau_{ij}$, the time it takes for two isolated nodes to equilibrate (assuming first-order kinetics):

$$\tau_{ij} = \frac{2\Delta t}{u_{ij}} \left( \frac{1}{p_i} + \frac{1}{p_j} \right)^{-1}$$

(2)

where, $p_i$ and $p_j$ are the statistical weights of nodes $i$ and $j$, respectively, $u_{ij}$ that of their link, and $\Delta t$ the saving time of trajectory snapshots (4 fs). If two nodes are not directly linked, the pathway with the shortest total distance $\tau_{ij}$ is chosen, taking the sum $\tau_{ij} = \tau_{ik} + \tau_{kj}$. A pathway over more than one link might be faster than a direct link. If that is the case, we replace the length of the direct link by that of the faster indirect pathway, thereby enforcing a triangle inequality with $\tau_{ij} \leq \tau_{ik} + \tau_{kj}$.

From an analysis of the largest MDS eigenvalues (see Supplemental Fig. S1a), we conclude that the first 3 dimensions carry most of the essential information, whereas subsequent eigenvalues decay exponentially and represent only Gaussian noise. This means that, in the present case, a three-dimensional layout of the network is sufficient to capture the most important properties of the dynamics. Note that the distance metric $\tau_{ij}$ is not Euclidean, as evidenced by negative MDS eigenvalues (the largest negative eigenvalue is about 20% of the largest positive one).

IV. RESULTS AND DISCUSSION

The three-dimensional MDS layout of the conformation-space-network of SPC-water at 300 K is highly modular with clusters of kinetically homogeneous microstates (Fig. 2 a–b). The number of hydrogen bonds at the hydrogen sites (encoded by the colors in Fig. 2a–b; blue two; red, green one; yellow none) as well as at the oxygen site (encoded by the color saturation) determine to a certain extent which cluster a node belongs to, but that assignment is not complete.

In particular, there is a sub-structuring within fully hydrogen-bonded states (blue nodes), i.e., the four fingers pointing down in Fig. 2a. In other words, while the hydrogen bonding to the first solvation shell (represented by the color coding) plays an important role in determining the dynamic properties of a given water molecule, this information alone is not sufficient, and the topology of the hydrogen-bond-network including more distant water molecules contributes as well. These results are obtained using the SPC model but we show in Supplemental Figs. S2–S4 that the essential structure of the conformation-space-network does not depend on the water model (i.e., SPC, SPC/E, TIP4P, TIP5P), the length of the MD trajectory (from 10 ps to 1 ns), nor the hydrogen-bond criterion (i.e., the one introduced by Skinner et al. [24, 25] versus a simple geometry cut-off criterion, see Material and Methods).

Towards a more quantitative analysis of the free-energy surface in terms of kinetically homogeneous regions, or substates, we use a recently introduced procedure to partition the landscape into free-energy basins [31] (which is a simpler version of the Stochastic Steepest Descent algorithm introduced in [32]). To that end, we build a transition-gradient-network from the original one by keeping only one link per node, the one with the highest weight (excluding self links). The physical justification for doing so is that nodes in the neighborhood of a barrier between two valleys will maintain only the link to the valley to which they relax the fastest. Following the most probable transition results in a “steepest descent” on the free-energy surface where microstates in the neighborhood of a barrier will connect to either one basin or another. We call the resulting basins of attraction gradient-clusters for convenience. Most of the conformation net-
FIG. 2: Conformation-space-network of SPC water at 300 K from a 100 ps MD trajectory. To avoid overcrowding, we only considered nodes and links with a statistical weight above a certain threshold, >200 and >30 respectively. These two threshold values reduce the number of nodes from ~50,000 to ~4,000, covering 95% of the total population, and reducing the number of links to typically 15'000-20'000. a) Stereo view and b) three orthogonal views of the conformation-space-network embedded in three dimensions by the MDS algorithm. Each microstate is represented by a node; distances represent the transition times between microstates; the volume of each node represents the logarithm of its statistical weight (i.e. its free energy); the color represents the number of hydrogen bonds donated: yellow, none, green and red, one (by either one or the other hydrogen), blue two (one per hydrogen); and the color saturation encodes the number of hydrogen bonds accepted: full colors two, light colors one, and very light colors none. c) Mapping of the 12 most important gradient cluster (Fig. 3) onto the MDS representation, all in different colors. Nodes that do not belong to any of the 12 most populated gradient cluster are omitted.
The definition of a reaction barrier is the same used in a cut-based free-energy profile (cFEP) \[33\] and relates the work can be represented by the \( M = 12 \) most populated gradient-clusters, which account for the 88% of the total population (at 300 K, see Fig. 3d). Subsequent gradient-clusters have significantly smaller population (see Supplemental Fig. S1b). Although this approach is completely independent from the MDS analysis, we find a remarkable mapping between the two as shown in Fig. 2c, where network nodes (i.e. water microstates) belonging to one of the 12 most populated gradient-clusters are shown in different colors. The properties of these gradient-clusters are summarized in Table I.

![Diagram of coarse-grained gradient-clusters](image)

The barrier between two gradient-clusters \( a \) and \( b \), composed of nodes \( a_i \) and \( b_i \), is computed as

\[
\Delta G_{a\rightarrow b}^\ddagger = -k_B T \log \left( \frac{W_{a\rightarrow b}}{\sum_{a_i \neq a_0} w_{a_0 \rightarrow a_i}} \right) \tag{3}
\]

where \( W_{a\rightarrow b} \) represents the number of transitions between cluster \( a \) and \( b \) (i.e. \( \sum a_i \sum b_i w_{a_i \rightarrow b_i} \)), \( a_0 \) is the most populated node in cluster \( a \), and \( \sum_{a_i \neq a_0} w_{a_0 \rightarrow a_i} \) is the sum of the outgoing transitions from node \( a_0 \), excluding the self link, to all the other nodes of cluster \( a \). This definition of a reaction barrier is the same used in a cut-based free-energy profile (cFEP) \[33\] and relates the reactive flux between basins to the flux around the minimum of a basin. With that definition, we find that the complete conformation-space-network can be traversed over only marginal barriers which are in the order of \( \approx k_B T \) (Fig. 3d). Nevertheless, certain gradient-cluster nodes are not directly connected. For example, gradient-cluster 4, which is four-coordinated, has to react through an intermediate state (gradient-cluster 2 or 3) to reach an hydrogen-bond broken cluster (gradient-cluster 8 or 9, respectively; see Fig. 3d).

The correlation function \( \langle c_n(t) c_n(0) \rangle \) is calculated to investigate the lifetimes of those substates. In this formula, \( c_n(t) = 1 \) when the trajectory populates a gradient-cluster \( n \) at time \( t \), and \( c_n(t) = 0 \) otherwise (see Supplemental Fig. S5). The correlation functions decay bi-exponentially with a fast component in the range of \( \approx 30-40 \) fs, which we attribute to recrossing-noise at the edges of our gradient clusters, and a slower component between \( \approx 200 \) fs and \( \approx 400 \) fs, which reflects the actual life-time of the cluster. Within classical transition state theory, the cluster lifetime is expected to be \( k = k_0 e^{-\Delta F^1/k_B T} \). With a pre-exponential factor of \( k_0 = k_B T/h = (160 \text{ fs})^{-1} \), the observed timescales are consistent with barriers \( \Delta F^1 \) on the order of \( \approx k_B T \).

In Fig. 4a,b tetrahedral order parameter distributions \[34\] and radial distribution functions of the 12 most populated gradient-clusters are shown. They group into three types, which can be classified as four, three and two-coordinated water. For example, waters in gradient-clusters 1–4 are all four-coordinated and hence more ordered than on average, causing a higher tetrahedral order parameter (Fig. 4a), as well as a higher peak at 2.8 Å and a more pronounced minimum between first and second solvation shells in the radial distribution function (Fig. 4b). Nevertheless, the 3D hydrogen and oxygen distributions of clusters with the same coordination number can be distinctively different, see e.g. cluster 1–4 in Fig. 5a. This emphasizes that the radial distribution functions are not decisive enough to characterize the 3D structure of hydrogen-bonded water. Note that clusters 6 and 7, 8 and 9, as well as 10 and 11 are mirror images of each other with the left and right hydrogen bond donation site interchanged (see Tab. I). In some cases, the important information is hidden for the view angle chosen in the representation of Fig. 5a. For example, clusters 5 and 10 look very similar in this representation, but when inspecting cluster 11 instead of cluster 10, the difference is very obvious.

In Fig. 4c we investigate the conditional radial distribution functions \( g_{O,O}(r) \). That is, we plot the probability of finding a water from the cluster \( n \) next to a water from the same cluster \( n \) (whereas Fig. 4b plots the probability \( g_{O,O}(r) \) of finding any water next to a water molecule from cluster \( n \)). With regard to this property, gradient-clusters 1 and 4 deviate the strongest from the average. The probability to find two neighboring molecules in gradient-cluster 1 is significantly enhanced, while the opposite is true for gradient-cluster 4.

**TABLE I: Characterization and relative population (in %) of the 12 most populated gradient-clusters at three temperatures (at constant volume).** The first digit in the hydrogen-bond characterization (second line) refers to the number and site of donating hydrogen bonds (2, from the (l)eft or (r)ight hydrogen, 0), the second to the number of accepting hydrogen bonds.

<table>
<thead>
<tr>
<th>#</th>
<th>h-bond</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
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<tr>
<td>22</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>270 K</td>
<td>19.7</td>
<td>6.4</td>
<td>6.4</td>
<td>1.8</td>
<td>37</td>
<td>5.4</td>
<td>5.4</td>
<td>1.7</td>
<td>1.7</td>
<td>-</td>
<td>-</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>300 K</td>
<td>13.2</td>
<td>5.9</td>
<td>5.9</td>
<td>2.0</td>
<td>23.4</td>
<td>5.3</td>
<td>5.3</td>
<td>2.2</td>
<td>2.2</td>
<td>10.1</td>
<td>10.1</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>330 K</td>
<td>9.5</td>
<td>5.3</td>
<td>5.3</td>
<td>2.0</td>
<td>23.7</td>
<td>5.1</td>
<td>5.1</td>
<td>2.6</td>
<td>2.6</td>
<td>10.4</td>
<td>10.4</td>
<td>2.4</td>
<td></td>
</tr>
</tbody>
</table>

* At 270 K, clusters 10 and 11 merge with cluster 5.
The local oxygen distribution shown in Fig. 5 explains the mechanism. In cluster 1, neighboring waters are also four-coordinated (3.61 bonds on average, see arrows in Fig. 5a for cluster 1), forming an extended tetrahedral hydrogen-bond network. This correlation manifests the onset of forming translational symmetry, or, in simple words, the onset of ice-forming. In accord with this view, the gradient-cluster 1 has the longest of all lifetimes (400 fs, see Fig. S5). In cluster 4, in contrast, neighboring waters are three-coordinated, (2.55 bonds on average). This under-coordination creates a void or groove around the central water which is then filled by waters more distant in the hydrogen bond network (see arrow in Fig. 5a for cluster 4).

The population of cluster 1, which is the most ordered ice-like structure, decreases by more than a factor two from 270 K to 330 K (see Tab. I). Thus, this structure is stabilized enthalpically, as expected. From the eleven other structures, some slightly increase in population with temperature and some decrease, but the overall effect is that all increase to compensate for the population loss of cluster 1. The temperature dependence of the radial distribution function of cluster 1 and 4 (i.e. the most enthalpic and the most entropic cluster) is shown in Fig. 6. The profiles are essentially conserved, becoming slightly more structured as the temperature is lowered. Consequently, the structural organization of the substates is conserved for different temperatures. This result suggests that the overall properties of water are mostly determined by the change of the relative populations of the various substates (Table. I).

Water is often discussed on the level of two states [5], i.e. a low-enthalpy, low-density form, and a high-entropy, high-density form of water, which ultimately leads to the suspected liquid-to-liquid phase transition at low enough temperatures. Nevertheless, there has been
V. CONCLUSION

In this study, we have investigated the conformation-space-network of water at ambient conditions. Both the visual inspection of the network and a more quantitative analysis, based on transition gradients, have pointed out to the presence of multiple coexisting metastable states in bulk water. A kinetic and thermodynamic description of the substates as well as their structural characterization have been provided. The latter has elucidated a critical difference in the second solvation shell between two four-coordinated water clusters which may be reminiscent of a postulated liquid-to-liquid phase transition at low temperatures. The typical timescales of inter-conversion of the found metastable states is 200-400 fs.

We conclude that liquid water is structurally inhomogeneous, with spatial correlations that extend over at least two solvation shells. These observations are compatible with the known structure forming properties of water, which are responsible for the many forms of ice at lower temperatures (15 are now known [35]). In contrast to previous MD studies on the hydrogen-bond dynamics of water, which focused on the hydrogen bonds of a water molecule to its immediate partners solely [25, 36–38], we include here the influence of at least the second solvation shell – without having to invoke a pre-determined order parameter. This achievement is made possible by introducing a network description of the dynamics.

The conformation-space-network structure is intrinsic to all water models we tested (SPC, SPC/E, TIP4P, TIP5P) (Supplemental Fig. S2), suggesting evidence that it exists also in real water. 3D-IR spectroscopy, which is able to disentangle inhomogeneities of conformational degrees of freedom of water [39], will allow us to test these ideas experimentally. Finally, we propose here a framework to characterize the inhomogeneities of water in terms of structure and dynamics in more complex environments, such as confined water, water around ions, and water at protein surfaces, as well as hydrogen-bond chains that are important in the context of the Grotthus mechanism of proton transport and the autoionization of water [40].

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Supporting Information Available: Figs. S1 to S5 as well as a movie rotating the 3D conformation-space-network of Fig. 2a,b is available free of charge via the Internet at http://pubs.acs.org.

TOC: The conformation-space-network (middle) groups into various kinetically homogeneous clusters that are related to particular hydrogen-bond network pattern (left and right).