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Anisotropic and sub-diffusive water motion at the surface of DNA and of an anionic micelle CsPFO

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Abstract

We use long atomistic molecular dynamics simulations to address certain fundamental issues regarding water dynamics in the hydration layer of a 38 base long (GCCGCGAGGTGTCAGGGATTGCAGCCAGCATCTCGTCG) negatively charged hydrated DNA duplex. The rotational time correlation function of surface water dipoles is found to be *markedly non-exponential*, with a slow component at long time, whose magnitude depends on the initial ($t = 0$) residence of the water in the major or minor groove of the DNA. The surface water molecules are also found to exhibit anisotropic diffusion in both the major and minor grooves: diffusion in the direction parallel to the DNA surface exhibits a crossover from higher to lower than that in the direction normal to the surface at short-to-intermediate times. In the same time window, translational motion of water molecules in the minor groove is sub-diffusive, with mean square displacement (MSD) growing as t^{α} with $\alpha \simeq 0.43$. In general, water molecules in the major group exhibit faster dynamics than those in the minor groove, in agreement with earlier results (Bonvin *et al* 1998 *J. Mol. Biol.* **282** 859–73). We compare these results with dynamics of water molecules at the surface of an anionic micelle, cesium perfluorooctanoate (CsPFO). Water molecules on the surface of CsPFO also exhibit slow translation and non-exponential orientational dynamics.

1. Introduction

Water molecules in the hydration layer around a biomolecule (protein, DNA) or a self-assembly (micelle, microemulsion, dendrimer in water) exhibit unique dynamical properties which are markedly different from those in the bulk [1–12]. It is of great interest to elucidate the factors responsible for the peculiar features of the hydration water in the proximity of the macromolecular surface and to find out what role they play in regulating the structure,

dynamics and functionality of a biomolecule. While a lot of attention has been devoted of late to the dynamics of the hydration layer around proteins and polypeptides in recent years [1–3], relatively less attention seems to have been devoted to the hydration layer around a DNA molecule. DNA is a highly complex heteropolymer where the constituent four types of monomer (the nucleotides) are aromatic molecules with varying polar character and hydrogen bond forming ability. While DNA is a remarkable flexible molecule for a long length scale, it is rigid and rod-like on a molecular scale because the DNA persistence length is around 500 Å (∼150 base pairs) [3]. To perform its different biological activities, such as replication and protein binding, the DNA must undergo certain critical motions or fluctuations. The timescales of these motions may determine the reaction pathway and also the rate. Since biological activity is connected to the hydration level of a DNA molecule, it is natural to enquire how these water molecules participate in the dynamical events that lead to biological activity. Thus a microscopic level understanding of the dynamical coupling between a DNA molecule and the interfacial water molecules (hydration layer) is crucial to understand microscopic aspects of biological processes. Ultrafast laser spectroscopic techniques [4] and computer simulation studies [5, 6] have played a crucial role in answering some of the questions regarding the timescale and the nature of the dynamics near a DNA surface.

The water molecules in the hydration layer around DNA experience a surface that is spatially heterogeneous, even on a molecular length scale, and the interaction with the surface is often quite strong, leading to a disruption of the regular hydrogen bond network of bulk water and giving rise to multiple timescales, ranging from the bulk-like timescale to at least an order of magnitude slower than that of the bulk. In the case of DNA surface, an additional complexity arises due to two distinct micro-environments: the major and minor grooves of DNA. It is already known that water molecules in these two grooves exhibit different dynamics [5, 7]. This article deals with our attempt to quantify the differential dynamics of water molecules at the major and minor grooves of DNA in aqueous solution.

In an important study, van Gunsteren *et al* [5] used computer simulations to study the structure and dynamics of water molecules around a hexadecamer duplex by a 1.4 ns MD simulation in water. The DNA hydration was characterized in terms of hydrogen bond percentages and the corresponding residence times. These authors have calculated the residence times of the water molecules which are within a distance of 0.35 nm and compared their results with the NMR studies [7, 8]. The average residence time of hydrogen bonded water molecules was only 11 (±11) ps with a maximum of 223 ps. However, when all the water molecules within 0.35 nm were considered, the average residence time increased to 100 ps with a maximum of 608 ps. The existence of residence times less than 1 ns was concluded to be in agreement with the earlier experiments of Sunnerhagen *et al* [8]. This important simulation work [5] also found interesting differences in the dynamical behaviour among water molecules in the major and minor grooves of the DNA. In another important paper, Makarov *et al* [9] used computer simulation to investigate water diffusion around a DNA decamer duplex. These authors found that the overall diffusion rate at the interface is lower than in the bulk. The rate is higher than the average in the direction parallel to the solute surface, and lower in the direction normal to the surface, up to 15 Å away from the solute. The rate is also lower in the solvation shells of the macromolecules, producing characteristic depressions in the radial profiles of the diffusion coefficient that can be correlated with peaks in the corresponding radial distribution functions. However, the magnitude of these depressions is small compared to the overall change in solvent mobility at the interface. Makarov *et al* [9] also pointed out that the effect of DNA on water mobility is similar to that of a protein surface on surrounding water. Note that a large number of simulations already exist of water dynamics in the hydration layer of protein [10–12], which demonstrate that translational and rotational

diffusion of water molecules at protein surface exhibits somewhat slower dynamics than the bulk.

We would like to ask the following specific questions regarding water dynamics in the hydration layer of DNA. (i) How non-exponential is the water orientational dynamics in the hydration layer? That is, how many time constants are needed to describe the dynamics? (ii) How different is the water translational motion in the hydration layer? Is there any anisotropic diffusion of water molecules in the layer? (iii) How different is the hydrogen bond lifetime dynamics near the surface?

In order to answer the above questions, we have studied the water dynamics in the hydration layer of a 38 base long hydrated duplex using atomistic MD simulations. The paper is organized as follows. In the next section, we present the details of the MD simulations. Section 3 presents the analytical study of a model, namely the dynamic exchange model (DEM), describing the bound $\rightleftarrows$ free transition of water molecules in the macromolecule–water system. Section 4 presents the reorientational dynamics of water molecules present both at major and minor grooves, while section 5 contains results on translational diffusion of major and minor groove water. In section 6 we present the phosphate oxygen and water hydrogen bond lifetime correlation functions. Section 7 contains reorientational and translational dynamics of water molecules at the surface of an anionic micelle of cesium perfluorooctanoate (CsPFO). We close the paper with a few conclusions in section 8.

2. Simulation details for the DNA structure

The DNA MD simulations reported in this article used the AMBER7 software package [13] with the all-atom AMBER95 force field (FF) [14]. The AMBER95 FF has been validated for molecular dynamics (MD) simulations of B-DNA in explicit water with salt, starting from the crystal structure [15–19]. These validation studies found that the CRMS deviation from the crystal structure for a dodecamer structure is typically less than 4 Å. The electrostatic interactions were calculated with the particle mesh Ewald (PME) method [20, 21] using a cubic B-spline interpolation of order four and a 10^{-4} tolerance set for the direct space sum cut-off. A real space cut-off of 9 Å was used both for the electrostatics and van der Waals interactions with a non-bond list update frequency of 10. First we create a regular B-DNA molecule using the nucleic acid builder program Namot2 [22] (version 2.2). Using the LEAP module in AMBER, the DNA structure was immersed in a water box using the TIP3P model for water. The box dimensions were chosen in order to ensure a 10 Å solvation shell around the DNA structure. In addition, some water molecules were replaced by Na^+ counter-ions to neutralize the negative charge on the phosphate groups of the backbone of the DNA structure. This procedure resulted in solvated structures, containing approximately 25 000 atoms. The solvated structures were then subjected to 1000 steps of steepest descent minimization of the potential energy, followed by 2000 steps of conjugate gradient minimization. During this minimization the DNA molecule was kept fixed in its starting conformations using harmonic constraints with a force constant of 500 kcal mol^{-1} $Å^{-2}$. This allowed the water molecules to reorganize to eliminate bad contacts with the DNA molecule.

The minimized structure was then subjected to 40 ps of MD, using a 2 fs time step for integration. During the MD, the system was gradually heated from 0 to 300 K using weak 20 kcal mol^{-1} $Å^{-2}$ harmonic constraints on the solute to its starting structure. This allows for slow relaxation of the built PX structures. In addition SHAKE constraints [23] using a geometrical tolerance of 5×10^{-4} Å were imposed on all covalent bonds involving hydrogen atoms. This is needed to prevent dynamically changes in the NH and OH bonds from disrupting associated hydrogen bonds. Subsequently, MD was performed under constant

pressure–constant temperature conditions (NPT), with temperature regulation achieved using the Berendsen weak coupling method [24] (0.5 ps time constant for heat bath coupling and 0.2 ps pressure relaxation time). This was followed by another 5000 steps of conjugate gradient minimization while decreasing the force constant of the harmonic restraints from 20 kcal mol^{-1} Å^{-2} to zero in steps of 5 kcal mol^{-1} Å^{-2}. We then carried out 100 ps of unconstrained NPT MD to equilibrate the system at 300 K. We have found for other systems that the above equilibration protocol produces very stable MD trajectories for simulating large DNA nanostructures [25, 26]. Finally, for analysis of structures and properties, we carried out 3 ns of NVT MD using a heat bath coupling time constant of 1 ps.

Dynamics of all water molecules which are within 3.5 Å of any atom in the base pair have been included in this study.

3. Theoretical description of constrained water dynamics

Water molecules at an attractive interface (charged micelle, DNA, proteins) can form strong hydrogen bonds with charged/polar groups of the biological molecule/self-assembly. Such hydrogen bonding can give rise to slow orientational and translational motions.

The dynamic exchange model [27, 28] envisages the emergence of multiple (especially slow) timescales due to the existence of a dynamic equilibrium between the bound and free water molecules in the surface of biomolecules or self-assembly. At the centre of this model lies the assumption that some of the water molecules at the surface of protein/DNA can be considered as distinct species because of their strong hydrogen bonding to the biomolecular surface, and they are called bound water. The bound water molecules are also not permanently bound but remain bound longer than the average residence time of a quasi-free water molecule. The water not directly bonded to the macromolecular surface but still in the hydration layer is called free water. Simulations have shown that there is constant exchange between these bound and free water molecules [10]. This equilibrium can be symbolically written as

$$\text{Bound water} \;\Leftrightarrow\; \text{Free water}.$$

Bound water is not a unique species because there is a distribution of the water–macromolecule, say protein, binding energies ($\varepsilon_{\mathrm{wp}}$), which according to simulation studies is an exponential with a very sharp fall at low values of $\varepsilon_{\mathrm{wp}}$. Low values of $\varepsilon_{\mathrm{wp}}$ correspond to quasi-free water molecules near the hydrophobic surface, whereas the bound water molecules are expected to have a broad distribution centred around a relatively large binding energy.

An expression for the slow relaxation in the hydration layer has been derived, where we model the protein surface as an infinite wall in the x–y plane. The starting point is coupled reaction–diffusion equations which describe the time evolution of bound and free water densities [27],

$$\frac{\partial}{\partial t}\rho_{\mathrm{f}}(r,\Omega,t) = D\nabla^2\rho_{\mathrm{f}}(r,\Omega,t) + D_{\mathrm{R}}\nabla^2_{\Omega}\rho_{\mathrm{f}}(r,\Omega,t) - \Bigg[\rho_{\mathrm{f}}(r,\Omega,t)\int \mathrm{d}\Omega_1\, k_{\mathrm{fb}}(\Omega,\Omega_1) - \int \mathrm{d}\Omega_1\, \rho_{\mathrm{b}}(r,\Omega_1,t)k_{\mathrm{bf}}(\Omega_1,\Omega)\Bigg]h(z_L - z) \tag{1}$$

$$\frac{\partial}{\partial t}\rho_{\mathrm{b}}(r,\Omega,t) = -\rho_{\mathrm{b}}(r,\Omega,t)\int \mathrm{d}\Omega_1\, k_{\mathrm{bf}}(\Omega,\Omega_1) + \int \mathrm{d}\Omega_1\, \rho_{\mathrm{f}}(r,\Omega_1,t)k_{\mathrm{fb}}(\Omega_1,\Omega) \qquad \text{at } 0 < z < z_L, \tag{2}$$

where $\rho_{\mathrm{f}}(r,\Omega,t)$ and $\rho_{\mathrm{b}}(r,\Omega,t)$ are the densities of free and bound water, respectively. The first two terms on the right-hand side of equation (1) describe the change in free water density

due to rotational and translational motion (D and D_R are the translational and rotational diffusion coefficients respectively), which is valid in the entire semi-infinite space $0 < z < \infty$. The third term represents the loss of free water due to free to bound conversion, where $k_{fb}(\Omega, \Omega_1)$ is the transition rate from free water with orientation Ω to bound water with orientation Ω_1. The last term accounts for the creation of free water from bound water where $k_{bf}(\Omega, \Omega_1)$ is the transition rate from bound water with orientation Ω_1 to free water with orientation Ω. Since the bound water exists only in the surface layer, the last two terms are defined only in this layer which is taken into account by the presence of the Heaviside step function, $h(z_L - z)$, where z_L is the width of the surface layer. In the case of bound water, since it cannot translate or rotate by itself, its density can change only because of transition between bound and free water. All terms in equation (2) are defined only in the surface layer. After some simplifications, the timescales of collective reorientational dynamics in the asymptotic limit are given by [27, 28]

$$\tau_{fast}(q_\parallel) = (2D_R + Dq_\parallel^2)^{-1} \tag{3}$$

where $q_\parallel$ is the wavenumber parallel to the surface. The fast timescale is found to be similar to the timescale of the bulk dynamics. However, due to the breakdown of the translational symmetry of the system by the presence of the protein surface, the wavenumber is conjugate only to the x–y plane.

The slow timescale is given by [28]

$$\tau_{slow}(q_\parallel) = \frac{1}{k_{bf}} + \frac{k_1 z_L}{Dk_{bf}\left(\frac{2D_R + Dq_\parallel^2}{D}\right)^{1/2}} \propto \frac{1}{k_{bf}}. \tag{4}$$

Thus, while one time constant remains fast, of the order of 4–5 ps, the other is predicted to slow down appreciably, even to the extent of hundreds of picoseconds (ps). The model predicts that the slow timescale is proportional to the inverse of k_{bf}, which is of course determined by the binding energy, and for the majority of sites the time constant may range between 20 and 500 ps or so. Note that the slow timescale is slower than the inverse of the bound to free conversion rate because the free to bound conversion further slows down the relaxation of a free water molecule. Only a few water molecules may be so slow as to have a residence time of 500 ps or above.

If the water molecules are strongly bonded (by a double hydrogen bond, for example) to the protein/DNA surface, then k_{bf} can be quite small. Then both the orientational relaxation time and the residence time of these molecules are determined by $(k_{bf})^{-1}$.

In the restricted environment, short time diffusion is often different from long time diffusion. Recently, a theoretical study of diffusion based on a dynamic exchange model at an attractive interface indicated that existence of such an exchange can lead to a crossover from sub-diffusive to super-diffusive dynamics before becoming diffusive at long time as the particle escapes from the hydration layer to the bulk [29]. The reason for the sub-diffusive dynamics is the return of the quasi-free water molecules to the bound state, while the existence of the super-diffusive behaviour is more subtle. The latter occurs because after a certain time diffusion gets enhanced because molecules start escaping from the layer to the bulk. This rate of escape adds on to the particle displacement to give rise to super-diffusive time dependence. As we show below, such a cross-over is observed in this work.

It should be noted that the dynamic exchange model assumes the existence of two kinds of ‘bound’ water molecules at the surface—those bound by single hydrogen bond to the polar surface, distinct from those which are bound by double hydrogen bonds to the surface. It is the latter species which exhibit slowest dynamics.

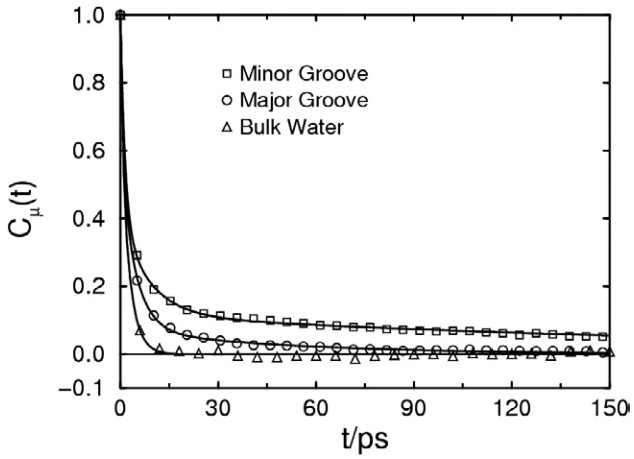

Figure 1. Time dependence of water dipole–dipole time correlation function (DDTCF), $C_\mu(t)$, for the water molecules initially ($t = 0$) present at the minor and major grooves of DNA. The same function for bulk water is shown for comparison. Symbols are the simulation data and continuous lines are the multi-exponential fit. Data points are shown infrequently for clarity. Note the non-exponential relaxation of DDTCF.

4. Single-water-molecule orientational dynamics

An important determinant of the dynamics of the water molecule is the reorientation of its dipole vector. This orientational motion of the surface water molecule is severely affected near a macromolecular interface. Here, we focus our attention on the contribution from the water molecules in the major and minor grooves of DNA. Recently, Arai *et al* [30] studied the complicated water orientations in the minor groove of a decamer duplex using neutron diffraction measurements. Their study demonstrates that the spine of hydration is built up around the minor groove not only by a simple hexagonal hydration pattern, but also by many other water bridges hydrogen-bonded to the DNA strands.

The rotational motion of water can be investigated by measuring the reorientational dynamics of its electrical dipole vector $\vec{\mu}$, defined as the vector connecting the oxygen atom of the water molecule to the centre of the line connecting the two hydrogen atoms. The time evolution of $\vec{\mu}$ can be estimated by measuring the dipole–dipole time correlation function (TCF), defined as

$$C_\mu(t) = \frac{\langle \vec{\mu}_i(t) \cdot \vec{\mu}_i(0) \rangle}{\langle \vec{\mu}_i(0) \cdot \vec{\mu}_i(0) \rangle} \tag{5}$$

where $\vec{\mu}_i(t)$ is the dipole moment vector of the ith water molecule at time t, and the angular brackets denote time averaging over the trajectory of the water molecules, as well as over the initial configurations, $\vec{\mu}_i(0)$.

We have studied the reorientational motion of water molecules that are in proximity to the major and minor grooves of DNA. To be specific, we have performed the calculations for those water molecules that reside within 3.5 Å of any atoms of the major and minor grooves. The correlation functions were calculated by averaging over these water molecules only. In figure 1 we show the variation of $C_\mu(t)$ against time for the water molecules near major and minor grooves of the DNA. For comparison, we have also shown the relaxation for bulk water. Water molecules both at the major and minor grooves show slow dynamics compared to the bulk. It is evident that the water molecules around major grooves reorient noticeably faster

Table 1. Parameters of multi-exponential fit to the dipole–dipole time correlation function of the water molecules present initially ($t = 0$) in the minor and major grooves of DNA.

	Time constant (ps)	Amplitude (%)	Average time constant (ps)
Minor groove	1.4	61	25.8
	8.9	28	
	200.4	11	
Major groove	1.0	49	6.0
	5.0	45	
	54.6	6	

than those around minor grooves. The faster water dynamics in the major groove than those in the minor groove has been well known for a long time from earlier NMR [7] and the pioneering simulations by Pettitt and co-workers [6, 9].

We have fitted the computed dipole–dipole TCFs to a multi-exponential form. Amplitudes and time constants of the fitting are provided in table 1. The average rotational time constants for the major and minor groove water are 6 and 25.8 ps, respectively. For bulk water, the average rotational time constant is 2 ps. The water reorientation in the minor groove is slower by an order of magnitude. The interesting feature to note from table 1 is the presence of the 200 ps component for minor groove water with an amplitude of 11%. This component mainly comes from those minor groove water molecules which are doubly hydrogen bonded between the bases.

The dynamic exchange model [27] can be applied to understand the slow timescale in the orientational dynamics. According to the DEM, this slow timescale is due to doubly hydrogen bonded (to the surface) water molecules. One indeed finds that 10% of water molecules in the minor groove and about 5% of the water molecules in the major groove are doubly hydrogen bonded, in agreement with the amplitudes given in table 1.

5. Translational diffusion at DNA surface

Water mobility in the proximity of the DNA surface exhibits a wide range of dynamical behaviours: from very tightly bound water to extremely mobile water diffusing on the DNA surface. A good reporter of this mobility is represented by the diffusion coefficient (D) which is widely used in both spectroscopic investigations and MD simulation approaches of liquids. The mean squared displacement (MSD) of the surface water molecules is used to obtain an idea of their mobility. The MSD is defined as

$$\mathrm{MSD}(t) = \langle |\vec{r}_i(t) - \vec{r}_i(0)|^2 \rangle \tag{6}$$

where $\vec{r}_i(t)$ and $\vec{r}_i(0)$ are the coordinates of the ith water molecule at times t and zero, respectively; the brackets '$\langle\,\rangle$' indicate the average over both the time origin $t = 0$ and the water molecules. The diffusion coefficient is related to the slope of the MSD by the Einstein relation [31]

$$D = \lim_{\Delta t \to 0} \frac{\langle |\vec{r}_i(t) - \vec{r}_i(0)|^2 \rangle}{2d\Delta t} \tag{7}$$

where d is the dimensionality of the system.

We have calculated the MSD of water molecules present in both the major and minor grooves of DNA. For this calculation we have considered all the water molecules which are

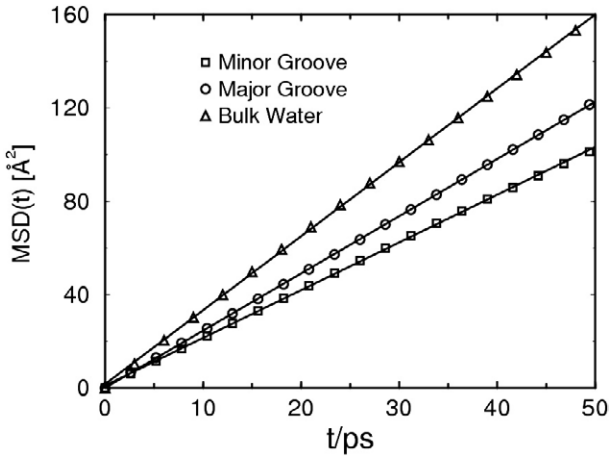

Figure 2. Time dependence of mean square displacement (MSD) of water molecules present initially ($t = 0$) in the minor and major grooves of DNA. Bulk water MSD is also shown for comparison. Symbols are the simulation data and continuous lines are the linear fit. Data points are show infrequently for clarity.

within a distance of 3.5 Å from any major/minor groove atoms. The diffusion coefficients obtained from these MSD data are 3.4, 4.1 and 5.3 (units of 10^{-5} cm^2 s^{-1}) for minor, major and bulk water, respectively. Water molecules in both the major and minor grooves show slow dynamics compared to the bulk. A significant feature to note from the curves of figure 2 is that the mobility of water molecules near the minor groove is lower than those in the major groove. This is in agreement with the NMR study of the residence time of the surface water in the major and minor grooves [7] of DNA.

After the ballistic regime, the MSD follows the power law, i.e. MSD$(t) \simeq At^{\alpha}$. Generally, deviation of the exponent (α) value from unity is a signature of anomalous diffusion. Water molecules present in the major and minor grooves of DNA show highly anisotropic diffusion. In order to quantify the anisotropy of the water motion on the DNA surface, we have decomposed the MSD along and perpendicular to the DNA axis. For these calculations we have adopted the following procedure. First, we calculated the end to end unit vector of the DNA and then projected the water displacement vector along and perpendicular to the surface of DNA. In figures 3(a) and (b), we show the short time MSD of minor and major groove water along and perpendicular to the DNA surface. In short-to-intermediate time, the diffusion of the water molecule both in major and minor grooves is higher in the direction parallel to the DNA surface and lower in the direction perpendicular to the DNA surface. The MSD of the minor groove water shows an interesting sub-diffusive dynamics with exponent value of 0.43. The sub-diffusive behaviour of the water molecules at the macromolecular surface is a well known phenomenon. The occurrence of anomalous diffusion in the proximity of the protein surface has already been demonstrated by neutron scatting experiment [32] and MD simulations [10a].

The origin of the sub-diffusive translational motion may be the traps in the minor groove for the migrating water molecules. Again this trap may be the configurations leading to double hydrogen bonds with the nucleotide base groups, as envisaged in the dynamic exchange model [27]. As discussed by Klafter *et al*, sub-diffusion can result from the presence of long-tailed trapping events [33]. It has been demonstrated that such trapping events can lead to the macroscopic observation of fractional diffusion [33]. Such deep traps are absent in the major

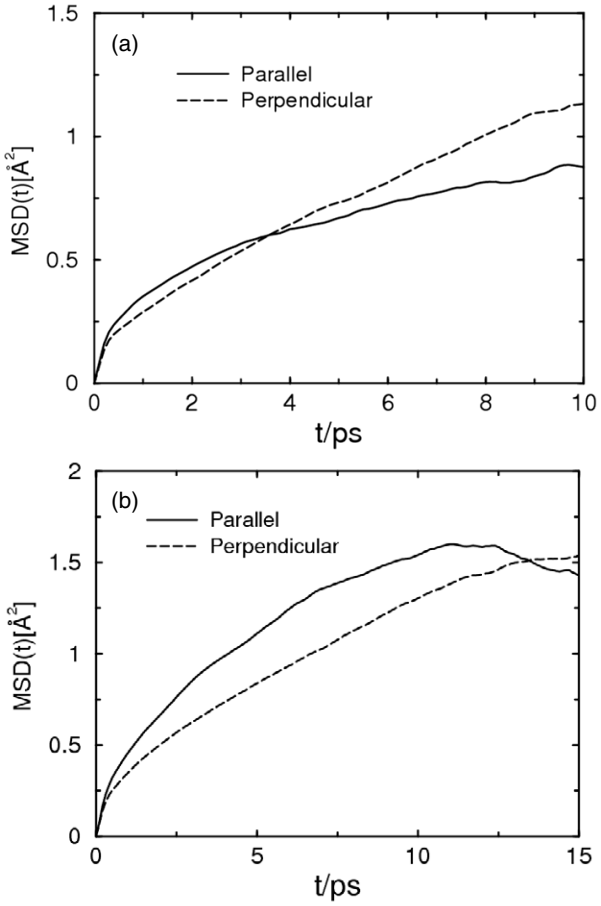

Figure 3. Short time dependence of the mean square displacement (MSD) of water molecules along and perpendicular to the DNA axis. (a) MSD for water molecules present in the minor grooves of DNA; (b) MSD of water molecules present in the major grooves of DNA. For these calculations we have considered only those water molecules which are continuously present at the minor/major groove.

groove, which, therefore, cannot give rise to sub-diffusive water motion. As already discussed, super-diffusion can arise from the contribution of the water molecules freed from hydrogen bonding to the bases [29].

6. Hydrogen bond lifetime dynamics

Dynamics of surface water and its structural organization are strongly correlated with the hydrogen bonds that they form with the DNA molecule. Breaking and formation of hydrogen bonds between water and DNA plays an important role to determine the biological activity of DNA in aqueous solution. Luzar and Chandler [34] have explored the various aspects of hydrogen bond lifetime dynamics in bulk water using molecular dynamics simulations. We have demonstrated that the Luzar–Chandler treatment can be extended to study the protein–water [11] and micelle–water hydrogen bond lifetime dynamics [35].

Hydrogen bond lifetime dynamics can be defined in terms of hydrogen bond lifetime correlation functions (HBLTCFs) defined as [34]

$$S_{\mathrm{HB}}(t) = \frac{\langle h(0)H(t)\rangle}{\langle h\rangle} \tag{8}$$

$$C_{\mathrm{HB}}(t) = \frac{\langle h(0)h(t)\rangle}{\langle h\rangle} \tag{9}$$

where $h(t)$ and $H(t)$ are the population variables monitoring the presence or absence of a particular hydrogen bond. $h(t) = 1$ if a particular pair is hydrogen bonded at time t, and 0 otherwise. $H(t)$, on the other hand, is equal to unity if a particular pair is *continuously* hydrogen bonded up to time t and zero otherwise. Thus, $S_{\mathrm{HB}}(t)$ decays as soon as the bond breaks for the first time while $C_{\mathrm{HB}}(t)$ allows bond breaking at intermediate times. The true lifetime of a hydrogen bond lies between the two time constants obtained from these correlation functions.

In order to define a hydrogen bond one can use a geometric or an energetic criterion. Here we have used a purely geometric criterion to define a hydrogen bond between phosphate oxygen (PO) and water hydrogen (WH). A water–DNA hydrogen bond is said to exist if the water oxygen (WO) is within the first coordination shell of the phosphorus atom of the phosphate group (i.e. with a distance of 4.45 Å), and if the WO is within the first coordination shell of the phosphate oxygen (i.e. with a distance of 3.25Å), and if the WO–water hydrogen (WH) (which is forming the hydrogen bond with the phosphate oxygen)–phosphate angle is greater than 140°.

We have studied the water–DNA hydrogen dynamics at both the major and minor grooves. Figures 4(a) and (b) display the water–DNA HBLTCFs $S_{\mathrm{HB}}(t)$ and $C_{\mathrm{HB}}(t)$, respectively, and compare with the bulk. Note the pronounced slow relaxation of the DNA–water hydrogen bond. $S_{\mathrm{HB}}(t)$ functions show marginally slower relaxation for the minor groove water–DNA than the major groove water–DNA hydrogen bond. In the case of $C_{\mathrm{HB}}(t)$, the minor groove water–DNA hydrogen bond shows considerably slower relaxation than the major groove water–DNA hydrogen bond. The fact that hydrogen bond lifetime dynamics is slower in the minor groove than in the major groove is in agreement with the observations made above regarding rotational and translational motions in the minor groove.

7. Water dynamics in aqueous micellar solution

Micelles have certain characteristics which are similar to the DNA or protein surface in several respects, while different in a number of ways. Micelles have a dense hydrophobic core while polar head groups (PHGs) are exposed to the surface. It is expected that water molecules on the surface are constrained by hydrogen bonds with the PHGs of the micelle [35–37]. An anionic micelle can mimic some aspects of negatively charged DNA. This is particularly so in the case of the micelle CsPFO, where water molecules at the micellar surface are hydrogen bonded to negatively charged oxygen atoms, similar to the case of hydrogen bonding to the phosphate groups of DNA.

We have carried out detailed atomistic MD simulation studies of water dynamics at the surface of CsPFO micelles [35, 37]. In particular, we have studied the orientational and translational dynamics of surface water. As the details of the simulation for this system have been discussed elsewhere [37, 38], we directly proceed to the discussion of the results.

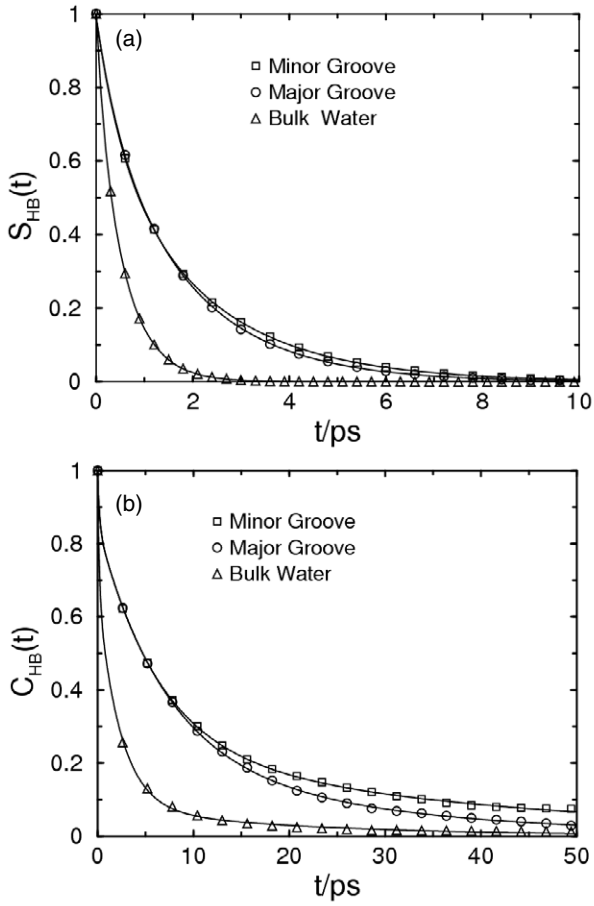

Figure 4. (a) Decay of the hydrogen bond lifetime correlation function $S_{\mathrm{HB}}(t)$ (defined by equation (8)) for the hydrogen bond between phosphate oxygen and water molecules present in the minor and major grooves of DNA. For comparison, we show the same function for a pair of water molecules in the bulk. (b) Decay of the $C_{\mathrm{HB}}(t)$ (defined by equation (9)) for the hydrogen bond between phosphate oxygen and water molecules present in the minor and major grooves of DNA. For comparison, we show the same function for a pair of water molecules in the bulk.

7.1. Reorientational dynamics at micellar surface

We have studied the single-particle dipolar orientational relaxation ($C_\mu(t)$) of interfacial water molecules in the CsPFO micellar solution. Interfacial water molecules are those that are within the first coordination shell of the carbonyl carbon atom i.e. within a distance of 4.35 Å. In figure 5, we show the decay of the dipole–dipole TCF of surface water molecules, and compare it to its relaxation in bulk [38]. Note the pronounced slower decay of surface water molecules. Similar results have been observed by Bruce *et al* [36] in their atomistic MD simulations of water dynamics in aqueous SDS micelles, where they found a slow component for a long time, with time constants in the range of 100 ps or above. We have fitted the dipole–dipole TCF to a multi-exponential form. Fitted parameters (time constants and amplitudes) are provided in table 2. Here, one finds an intermediate slow decay with a time constant of about 19 ps, which is again much slower than that for neat SPC/E water, which is about 4 ps, and

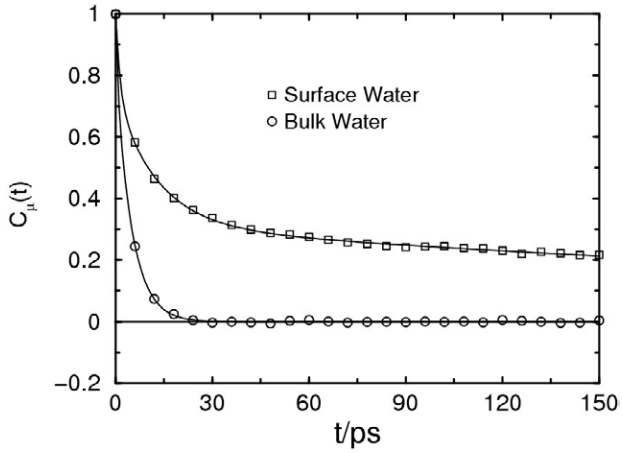

Figure 5. Time dependence of water dipole–dipole time correlation function (TCF), $C_\mu(t)$, for water molecules present at the CsPFO micellar surface. The same function for bulk water is also shown for comparison. Symbols are the simulation data and continuous lines are the multi-exponential fit. Data points are shown infrequently for clarity.

Table 2. Multi-exponential fitting parameters for the dipole–dipole time correlation function of water molecules present at the CsPFO micellar surface.

Time constant (ps)	Amplitude (%)	Average time constant (ps)
0.4	14	154
5.0	29	
19.5	28	
507	29	

the decay in neat water is single exponential. The orientational time correlation function for hydration water exhibits an additional slow decay of time constant of 507 ps with an amplitude of 30%. We have discussed elsewhere that this ultraslow component is due to the doubly hydrogen bonded water molecules with the PHG of the micelle.

7.2. Translational dynamics

Like orientational motion, the translational motion of the water molecules is also affected near the micellar surface. We have calculated the MSD of the surface water molecules and bulk water. These results are shown in figure 6. Note the restricted motion of the surface water. Diffusion constants (D) are obtained using the Einstein relation for both surface and bulk water. The values of D are 0.8×10^{-5} and 2.5×10^{-5} cm^2 s^{-1} for surface and bulk water, respectively.

8. Concluding remarks

Here we briefly summarize the main results of this work. We have used atomistic MD simulations to explore the differing water dynamics in the major and minor grooves of DNA. We find that generally water molecules move and rotate faster in the major groove than in the minor groove, in agreement with known simulation results. However, water motion slows

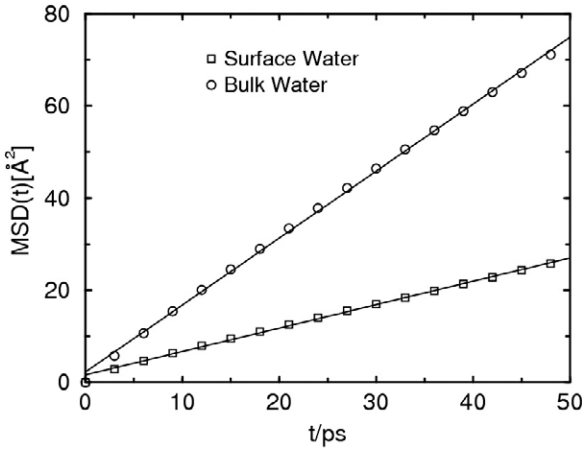

Figure 6. Time dependence of mean square displacement (MSD) of water molecules present at the CsPFO micellar surface. Bulk water MSD is also shown for comparison. Symbols are the simulation data and continuous lines are the multi-exponential fit. Data points are shown infrequently for clarity.

down noticeably in both the grooves. What we believe is new is the markedly non-exponential nature of water reorientational dynamics, with a slow component which is close to 200 ps for water molecules in the minor groove. Thus, the dielectric relaxation of the water molecules in a DNA solution is expected to be markedly non-Debye, which has been known for a long time [3b, 39, 40] but eluded theoretical explanation. Other interesting results are the sub-diffusive water motion in the minor groove and a cross-over in diffusion between the parallel and perpendicular components. We have also discussed hydrogen bond lifetime dynamics of the bonding between negatively charged phosphate oxygen atoms and the water molecules. Here also the minor groove exhibits slower dynamics.

The study of the ion effect on water dynamics is itself a worthwhile exercise [41–43]. In the present case, the simulation time is rather short, given that Feig *et al* [41] suggested several nanoseconds of equilibration almost a decade ago, while more recent work [42] suggested tens of nanoseconds long trajectories for equilibration. It may, however, be noted that most of the water dynamics reported in this article relaxes within a few hundred picoseconds (ps), while the ion atmosphere effect becomes important in the nanosecond (ns) timescale.

The results on DNA hydration dynamics have been compared with water dynamics at the surface of an anionic micelle, CsPFO. This is similar to the DNA surface because in this case the negatively charged oxygen atoms of the polar head group form rather strong hydrogen bonds with the water molecules. It is found that this micelle also sustains slow water dynamics. It may be noted that the water molecules can slow down near a hydrophobic surface [44]. We thus have both confinement and hydrogen bonding effects contributing to slow water dynamics. Further efforts are needed to separate these two effects.

Several authors have reported that the solvation dynamics (SD) in the hydration layer of protein/DNA slow down considerably (see [1, 4, 5]). A recent fluorescence Stoke shift (FSS) study by Nilsson and Halle [45] also found that the SD in the hydration layer of protein (monellin) slows down by one to three orders of magnitude. These authors have argued that the slow component in the SD arises due to protein motion, but such a slow component has not been observed in NMR experiments. Our observations are in partial agreement with the Nilsson and Halle experiments [45]. However, water dynamics, particularly orientational relaxation,

slow down noticeably near the surface. So, there are certainly two different views on the subject at present and more work is required to find the answer. Note that time dependent FSS experiments often measure a non-equilibrium time correlation function (TCF) while here we calculate an equilibrium TCF, and so do NMR experiments. In future, we will explore the relation between the simulation results and known experimental results, in particular, with dielectric relaxation and solvation dynamics [40].

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