

BEHAVIOUR OF WATER AT MEMBRANE SURFACES — A MOLECULAR DYNAMICS STUDY

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ABSTRACT

The molecular dynamics method was used to study the structure and dynamics of water above a layer of phosphatidylethanolamine headgroups, modelling the surface of a membrane. The simulation box contains one headgroup with sixteen ST2-water molecules. Planar periodic boundary conditions model a headgroup–water interface. The density distribution and the orientation profile along the layer normal were calculated. The water builds highly structured regions up to a ratio of ten water molecules per headgroup which compensate the dipole moments of the lipids. The velocity, angular velocity and direction autocorrelation functions show that the bound water molecules oscillate around minimum potential positions at preferred hydration sites.

INTRODUCTION

Membranes are the most common structures in both plants and animals. On the one side they realize stability and on the other side they control the interaction of cells with their environment. The organization of water near the membrane surface is important for transport processes across the membrane, the mobility of membrane components and for the membrane–membrane interaction. There is much information about water at membranes (see, e.g., [1]). Generally speaking we know that the dynamics data of water molecules within the force field of membranes are drastically changed in comparison with free water and favoured hydration sites at the membrane surface act as water “traps”. Structural data are available, e.g., from X-ray or neutron scattering experiments. These types of experiment must be done under extreme conditions for biological systems and the results are not relevant in all cases for situations *in vivo*. The most prominent method for determining dynamic data is to make NMR measurements of relaxation times, but the typical time scale in NMR is in the order of 10^{-7} s. In this time water molecules have made more than one hundred reorientations around their principle axes and undergo a mean displacement of about 0.4 nm, even near membranes [1, 2]. Experimental results alone cannot answer the questions about special structural and dynamic properties in a direct way.

In most cases model assumptions must be made. A new type of experiment opens the way to look into time and distance regions with very high resolution — the computer experiment. Using the new computational technique we can model the behaviour of many-particle systems and determine local properties or the development of properties in short time steps.

THE MODEL AND METHOD

The most widely accepted model of biological membranes is the so-called fluid-mosaic model developed by Singer and Nicholson [3]. The supporting unit of the membrane is built up by phospholipids. They are necessary to realize the self-organization of the membrane in a double layer. Enclosed proteins are responsible for the special function of the membrane. Because of their amphiphilic nature phospholipids build supermolecular structures in water with lyotropic and thermotropic mesomorphism [4]. As a typical model membrane we study a part of the lamellar phase of a phospholipid—water system. For the layer modelling the zwitterionic headgroups in their crystalline structure were used [5]. The periodic boundary conditions were constructed corresponding to the hexagonal arrangement of phospholipids known from X-ray experiments [5] (see Fig. 1). The basic simulation cell contains one headgroup of phosphatidylethanolamine interacting with water molecules. The first eight water molecules were added to the simulation box in an ice Ih arrangement. The water—water interaction was described by the well-known ST2-potential [6]. While the water—phosphate group interaction was described in the same manner but with slightly changed parameters, the water—ammonium group interaction could be handled by a special 1—10—12

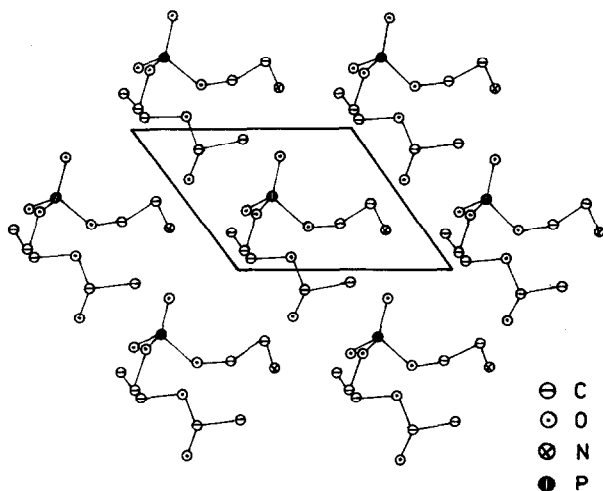


Fig. 1. Top view of the hexagonal arrangement of phosphatidylethanolamine headgroups with indicated simulation cell.

potential [7, 8]. The form and the parameters of the used potential functions are dictated by the computational efficiency and by the wish to reproduce the results of quantum-chemically calculated interaction energies. With a sufficient accuracy we could recalculate the interaction energies of water with the dimethylphosphate anion of Frischleder et al. [9] and of Pullman [10] and obtain interaction energies for water with the ammonium cation in the region given in [11]. After a step-by-step minimization of the potential energy dependent on the configuration of water molecules we started the simulation run. As a simulation technique we used the molecular dynamics method [12]. In this procedure the coupled differential equations of motion of all water molecules, with assumed fixed headgroup structure, must be solved for all spatial and angular degrees of freedom. The equations of motion are integrated numerically with a time step of 2.5×10^{-16} s. Using a predictor-corrector procedure, as described in [6], we could follow the eight water molecules within 10 000 time steps [13]. Afterwards the next eight water molecules were added and their configuration was optimized. The modified system was studied during 12 350 time steps, the averaging was carried out through the last 2 580 steps. The simulation temperature of 372.3 K is somewhat above room temperature. Because of the strong force field of the headgroups [14] the motion of water molecules could be drastically hindered and the statistics of dynamic data would be very poor or the simulation run must be extended for a scaled-down temperature. The time evolution of the simulation temperature is shown in Fig. 2.

The calculated constant-volume heat capacity $C_v = 15.5 \text{ J mol}^{-1} \text{ K}^{-1}$ is significantly smaller than for bulk water [6]. Qualitatively this result agrees with measured decreasing values of C_v of water near interfaces [15]. The lowering of C_v of water near the membrane surface compared to free water is probably due to the strong orientation-dependent external force field of the headgroups which mainly influences the motions of the water molecules.

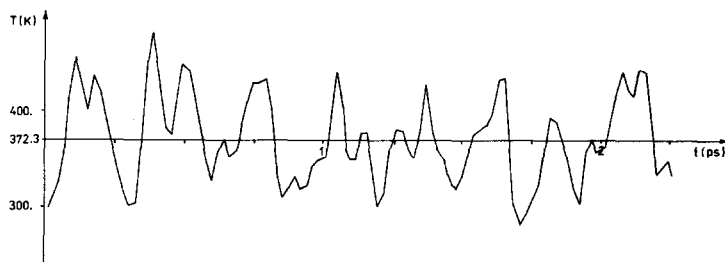


Fig. 2. Time evolution of the simulation temperature during some time steps.

RESULTS AND DISCUSSION

Static properties

The water molecules near a membrane interact on the one hand with the force field of the structured interface and on the other hand with the surrounding water. This competition of interactions, each of them with strong orientation dependence, causes the structure of the water near the interface. The density distribution $\rho(z) = \langle N(z) \rangle / (A \cdot \Delta z)$, where $\langle N(z) \rangle$ is the mean number of water molecules within the volume $A \cdot \Delta z$ (A is the area of the simulation cell, Δz is the grid width for the calculated histogram) ranging from z to $z + \Delta z$, shows some narrow peaks representing distinct layers of up to ten water molecules per headgroup perpendicular to the layer plane (see fig. 3). Some broad gaps in the picture of $\rho(z)$ at 0.3 nm, about 0.45 nm and 0.7 nm indicate the sharp distinction of different layers. The number of five and six water molecules per headgroup within the distinct hydration layers is in good agreement with experimental findings [16, 17]. While the first five water molecules are directly attached to the lipid, the further molecules are mainly determined in their behaviour by the first layer. This situation can be underlined by an analysis of the energetic picture (see Table 1). For six water molecules we find energies of interaction with the headgroup layer smaller than -10 kJ mol^{-1} , but only for five molecules the headgroup–water interaction is stronger than the water–water interaction. For all other molecules the headgroup–water interaction is weaker than the respective thermal energy of the simulation temperature. The water–water interaction energy is in most cases in the range of about -20 kJ mol^{-1} , higher than the potential energy of bulk water at room temperature [18] but in the same range as Stillinger and Rahman found for ST2 water at 392 K [6]. Not only the position of water molecules above the model membrane shows a typical picture. Because of the mainly electrostatic interaction of the water molecules with the strongly polar headgroups [19] also the orientation is

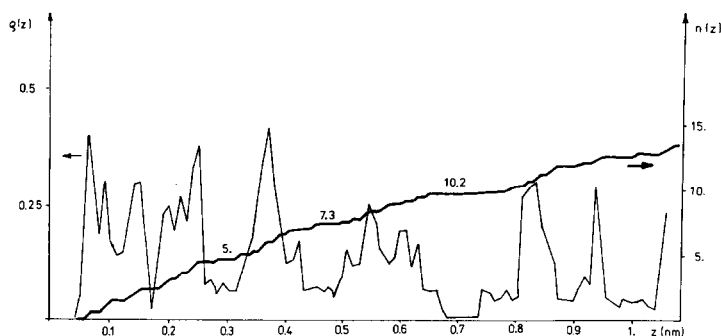


Fig. 3. Density distribution $\rho(z)$ and running count $n(z) = \int_0^z \rho(z') A \cdot dz'$, of the centre of mass of the water molecules along the membrane normal.

TABLE 1

The water-headgroup and water-water contributions of the potential energy of the first fourteen water molecules above the phosphatidylethanolamine layer (all values in kJ mol^{-1})

The average distance of the water molecules from the layer increases with increasing number of the molecules

No. of water molecules	Interaction energy	
	Water-headgroup	Water-water
1	-30.53	-7.04
2	-30.12	-14.03
3	-27.71	-17.74
4	-22.30	-6.68
5	-14.79	-11.37
6	-5.96	-16.38
7	-12.57	-17.47
8	-4.30	-17.85
9	-2.59	-22.80
10	-3.77	-20.84
11	-0.54	-22.75
12	+1.36	-20.81
13	-0.24	-14.42
14	+1.59	-18.53

influenced. In fig. 4 is drawn the orientation profile of the water molecules along the layer normal (z -direction). To characterize the orientational behaviour we calculated the mean value $\langle \cos \theta \rangle$, where θ is the angle between the headgroup and the water dipole moments. Up to distances of about 0.7 nm we find negative values of $\langle \cos \theta \rangle$, that means a preferred antiparallel orientation of water molecules with respect to the headgroup dipole moment. Thus the strong in-plane component of the headgroup dipole moment is screened by the water molecules. In fact the water reduces the dipole moment of the system to about one half of the headgroup dipole moment. Due to this screening effect the intermolecular interaction between neighbouring lipids is reduced to some extent and can be used to explain the decrease of the activation energy for the lateral diffusion for hydrated lipids [20] and a higher mobility of the lipid chains [21].

Dynamic properties

The static properties of the water molecules near to membranes reflect the underlying dynamic properties. For our limited simulation system, exposed to the nonhomogeneous force field of lipids, we studied mainly dynamic properties of individual molecules. In Fig. 5 are shown the normalised velocity autocorrelation functions (acf) of some water molecules representing the distance dependence. Evidently, for the bound water molecules

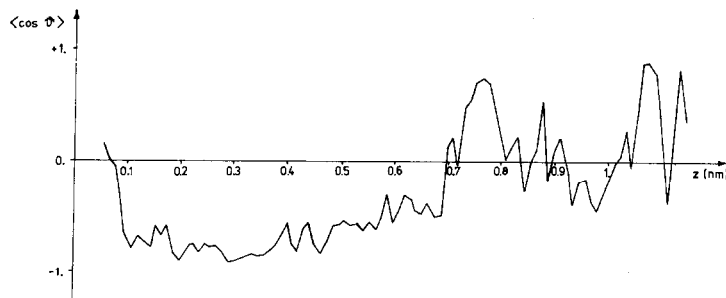


Fig. 4. Orientation profile $\langle \cos \theta \rangle$ of water molecules with respect to the headgroup dipole moment along the membrane normal.

(numbers 2 and 6) the velocity acf decreases faster than the acf of more distant water. The oscillations for longer times indicate the hindered motion around the minimum of potential energy at distinct hydration sites.

In addition the mean square displacement of the centre of mass motion of the four water molecules nearest to the membrane reaches a constant value of about 0.01 nm^2 after $3 \times 10^{-13} \text{ s}$. This means that during the simulation time there is no exchange of water between neighbouring hydration sites. The mean square displacement of all water molecules more distant from the layer increases over the whole time range.

The diffusion coefficients of these molecules are calculated from the Fourier transform of the velocity acf's

$$D = \frac{1}{3} \lim_{\omega \rightarrow \infty} \int_0^{\infty} \langle V(t) \cdot V(0) \rangle \exp(i\omega t) dt$$

and the mean square displacements of individual molecules

$$D = \lim_{t \rightarrow \infty} \frac{\langle (r(t) - r(0))^2 \rangle}{6t}$$

The diffusion coefficients increase from $0.7 \times 10^{-8} \text{ m}^2 \text{ s}^{-1}$ up to $3.3 \times 10^{-8} \text{ m}^2 \text{ s}^{-1}$ with increasing water layer distance. The calculated diffusion coeffi-

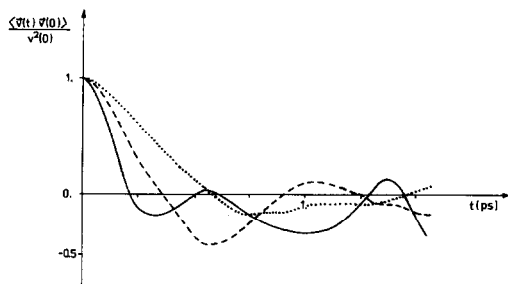


Fig. 5. Velocity acf's of single water molecules: (—) molecule 2; (---) molecule 6; (···) molecule 13.

cients can be compared with simulation results for water at 270 K [6]. They are in agreement with measured diffusion coefficients of water around amphiphilic molecules [17, 22].

The coupling between oscillations of the centre of mass motions at distinct hydration sites and regular angular vibrations is evident from the acf of the angular velocity (see Fig. 6). This vibration of bound water is only weakly damped even for a longer time.

Only water molecules more distant from the layer behave like bulk water. To study the angular motion more exactly we calculate the acf for the water dipole directions

$$\Gamma_{\parallel}(t) = \langle \cos \theta_{\parallel}(t) \rangle$$

where $\theta_{\parallel}(t)$ denotes the angle between the dipole moment direction at times zero and t . We get $\Gamma_{\perp}(t)$ from the same relation, but take into account the vector connecting the water hydrogens instead of the dipole moment. Because of the large moment of inertia for rotations of the water molecules around their dipole direction $\Gamma_{\parallel}(t)$ decays faster than $\Gamma_{\perp}(t)$ in the short-time range (see Fig. 7). The positive values of both direction acf's of molecule 2 over the whole observation time indicate a strong orientation correlation of the motion.

From the significant difference between the $\Gamma_{\parallel}(t)$ and $\Gamma_{\perp}(t)$ values we conclude first that the strong electrostatic interactions between the water and the headgroups cause a permanent orientation of the water dipole moments antiparallel to the headgroup dipole moment with small fluctuations only. Secondly, there are much larger vibrations around the water dipole axis.

The direction acf's of the water molecules more distant from the membranes are less different. For longer times the reorientational behaviour with respect to different rotation axes seems to be similar.

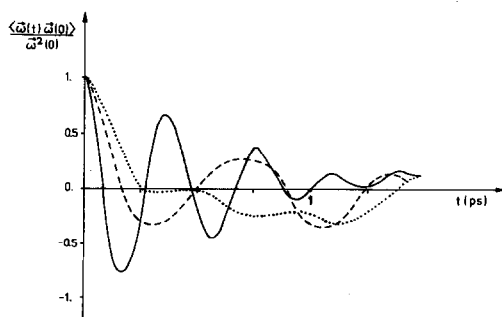


Fig. 6. Angular velocity acf's of single water molecules. Notation as in Fig. 5.

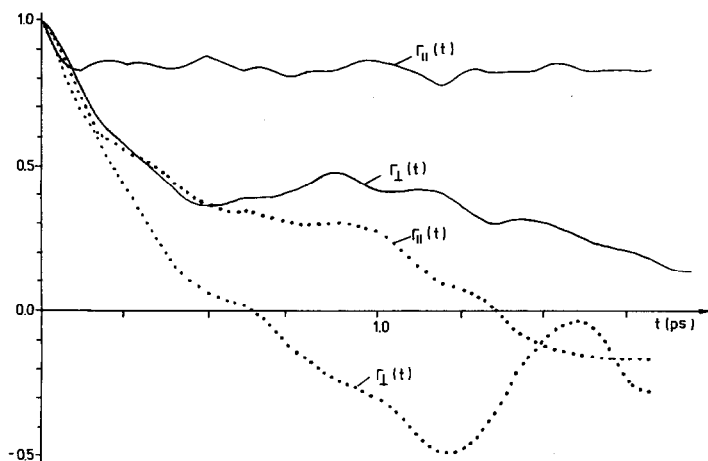


Fig. 7. Direction acf's $\Gamma_{\parallel}(t)$ and $\Gamma_{\perp}(t)$ of single water molecules. Notation as in Fig. 5.

CONCLUSIONS

In addition to recently published results of computer experiments on water near membranes [14, 23] we have presented a molecular dynamics study of the behaviour of water exposed to the strong force field of zwitterionic headgroups. There is no doubt that the simulation model used is too small to describe the complex situation in a biological system: we ignored the motion of the phospholipids themselves and the number of water molecules is insufficient to give good statistics.

Some of the properties of the hydration water, such as the reduction of the freezing temperature near membranes [1] or the reduced heat capacity of water near solid surfaces [15] can be explained in terms of a limited simulation model.

Unlike the results of computer experiments on water films with free surfaces [24] or on water between soft repulsive walls [25] we find a characteristic structure of the water network above the membrane-modelling headgroup layer, which is not determined only by the steric properties of the interface. The results are comparable with those of Anastasiou et al. for water in contact with an ion-crystal surface [26].

In agreement with experimental findings on membranes [16, 17] we can identify two hydration layers with a tendency to compensate the large in-plane dipole moment components. This result can be explained by the restricted motion of water molecules in the strong orientation-dependent force field. Looking at the velocity angular velocity and direction acf's for individual molecules we see that the bound water molecules mainly oscillate around minimum potential positions. The respective diffusion coefficients increase from the first hydration layer to the next one. To overcome the shortcomings of the simulations presented here — especially long-range elec-

trostatic contributions to energies are underestimated by the small simulation cell and the possibility cannot be excluded that periodic boundary conditions cause correlations between the water molecules in the basic cell and their images which influence the results — extended calculations are in progress.

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