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Simulations of biological ion channels by molecular dynamics

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The transport of sodium ions through a model membrane channel in the presence of static magnetic fields has been investigated by non-equilibrium molecular dynamics. The effect of static magnetic fields appears to be exerted not mainly on the transiting ions, but rather on the water molecules, favouring statistically their polarization during the ion passages and leading indirectly to a slight increase of the ion current.

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1. Introduction

The great importance of investigating biological membrane channels is reflected eloquently by the award of the Nobel Prize in Chemistry for 2003 to Peter Agre and Roderick MacKinnon "for discoveries concerning channels in cell membranes".

Ion channels are proteins that control the passage of ions across cell membranes, and thus regulate important biological functions, such as the generation of action potentials in nerves and muscles, or the hormone release from endocrine cells. They are highly selective for particular ion types (Na^+, K^+ etc.) and show high transport rates (of the order of 10^8 ions/s), corresponding to currents of several tens of pA.

Ion channels are assumed to play an important role in pain control [1], and their functionality is believed to be influenced by magnetic fields. The present work is a contribution to the elucidation by means of non-equilibrium molecular dynamics (NEMD) simulations at atomic level of several aspects regarding the transport through ion channels in the presence of magnetic fields.

The Monte Carlo and molecular dynamic methods have been largely used for simulation of the biomolecular systems [2,3].

Some of the most realistic and detailed simulations concerning the ion dynamics in membrane channels in the absence of magnetic fields are those recently published by Crozier et al. [4,5], and many of the models and simulation details therein have been adopted in the present work, too. The main modelling differences regard the consideration of homogeneous magnetic fields (1 and 10 T) and the usage of a more elaborate four-site water molecule model, meant to more accurately account for the polarization and structural properties of water. Technically, rigid-body dynamics for water in the quaternion representation was employed to make the computations more efficient and to allow for a better statistics.

2. Model

The channel model considered here is the one proposed by Crozier et al. [2,3], consisting of a cylindrical rigid atomic pore with polar walls, 25 Å long and 10.625 Å in diameter, embedded in a rigid uncharged membrane. 388 interaction sites are distributed on a 10 atoms × 10 atoms square lattice on both membrane surfaces, with an atom-atom spacing of 2.5 Å, and on the channel, forming eleven 20-site rings, with a spacing of 2.5 Å along the channel axis. All sites feature Lennard-Jones interactions with $\sigma = 2.5$ Å and $\varepsilon/k = 60$ K. Additionally, the channel sites carry charges equal to -0.5e, -0.35e, +0.35e, +0.5e, disposed cyclically on the rings, with a relative rotation of 9° between adjacent rings to produce a helical charge distribution.

The 1M NaCl solution considered in the present calculations was modelled by 600 water molecules, 8 Na^+ and 8 Cl^- ions. The water molecules have been represented by the rigid four-site model TIP4P of Jorgensen et al. [4], intensively used in the last two decades in simulations of aqueous solutions and clusters and known to describe more accurately than other three-site model potentials the thermodynamic and structural properties of water. The Lennard-Jones parameters for ion-ion and ion-water interactions are summarized in Table 1 of Ref. [3].

The simulation cell was considered a parallelepiped 25 Å × 25 Å × 55 Å in the x, y, and z directions respectively, with the membrane channel centred along the z-axis and two reservoirs (designated as “entry” and “exit”) formed symmetrically on both sides of the membrane.

The dynamics of the water molecules was decomposed in centre-of-mass translation and rotation, described in the quaternion formalism 0, thus substantially reducing the total number of degrees of freedom (roughly by 1/3) and making unnecessary a supplementary “shake”-type algorithm, which is usually employed to preserve the equilibrium structure of the water molecules. A Gaussian thermostat [5] for the translational degrees of freedom of the water molecules was used to fix the system temperature at 300 K. The rotational degrees of freedom of the water molecules and the translational degrees of freedom of the ions were allowed to relax freely to the equilibrium temperature.

To simulate the continuous flow of ions and water molecules without repositioning or recycling, periodic boundary conditions were applied in all three directions. However, to account correctly for the long-range electrostatic interactions of the charges and their periodic images, additionally Ewald sum techniques were employed [6]. By using the P^{3}M particle-particle/particle-mesh FFT-accelerated Ewald method as described by Deserno and Holmes [7], simulations over 200 ns have been possible, in order to measure current flow. Reciprocal space contributions were treated according to the particle-mesh methodology of Deserno and Holmes, with a seventh-order charge assignment function on a $16 \times 16 \times 64$ mesh point grid. The potential due to the particles and channel sites was obtained by solving the Poisson equation for the ensemble-averaged mesh-based charge distribution in the reciprocal space by using FFT.

A homogeneous electric field (0.02 V/Å) was applied parallel to the channel axis (z-axis) to mimic the potential gradient that drives ions through biological channels. Additionally, homogeneous magnetic fields of 1 and 10 have been considered along and, respectively, transverse to the channel.

For each magnetic field configuration, 20 simulations spanning 10 ns have been performed, up to a total of 200 ns of data collection. In order to allow for a more conclusive analysis of the trends, the individual runs for all magnetic field configurations were started from the same 20 initial configurations, which were prepared themselves from unique structured lattices of randomly placed water molecules and ions, which were equilibrated for 0.25 ns.

The MD integrator employed, both for the translational and rotational degrees of freedom, was a fifth order Gear-type algorithm [5], used throughout with a time step of 0.25 ps.

3. Results and discussion

The lower panel of Fig. 1 shows the instantaneous z-positions of the Na$^+$ ions for a typical simulation interval of 10 ns. The average cosine of the polarization angle θ of the water molecules, defined between their electric dipole and the direction of the channel axis, is shown in the upper panel for the channel and the reservoirs. The ion passages can be seen to be accompanied by a pronounced polarization of the water, followed by relaxation.

The water polarization in the channel features large fluctuations as compared to the reservoirs and a more rapid relaxation, as well. After ion passages, the average polarization typically reverses the sign, the dipole of the water molecules showing a tendency to follow the ion as it moves along the channel. The average polarization in the channel is found to be lower than in the reservoirs, where in addition it persists for a longer time due to the larger number of molecules.

The channel appears to be structured, the water molecules forming boundary layers both inside the channel and at the membrane surfaces (see the radial density profiles in Fig. 2 and the axial profiles in Fig. 3). It is obvious, that while passing through the channel, the ions prefer certain paths along the axis. The most probable radial position of the water molecules in the channel is around 3.5 Å (in the vicinity of the walls), while for the Na$^+$ ions (having a transition rate more than one order of magnitude higher than for the Cl^- ions), the radial density peaks around 1.5 Å. Both the radial and the axial density profiles turn out to depend little on the applied magnetic field, implying essentially that the water structure is little sensitive to the magnetic field.

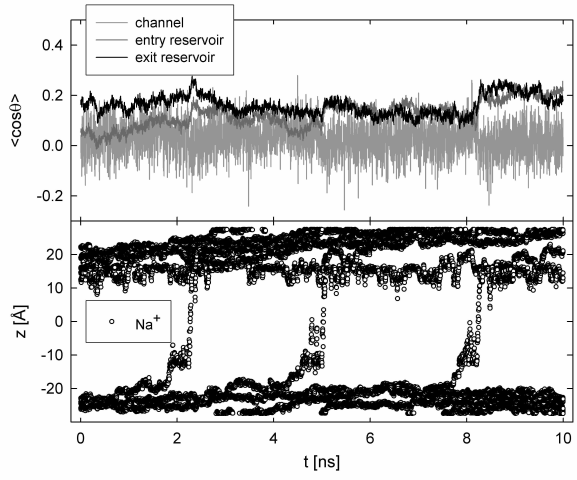

Fig. 1. Positions of the Na$^+$ ions along the channel axis and average polarization angle of the water molecules over a typical time interval of 10 ns.

The potential drop is found mainly across the channel, rather than across the reservoirs, reflecting the formation of a spatial charge at the membrane walls. The double layer partially neutralizes the applied electric field in the reservoirs.

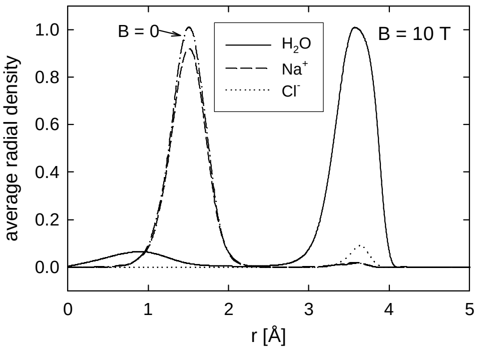

Fig. 2. Ensemble averaged radial density profiles. The water profile is normalized to its maximum value. The ion profiles are normalized to the maximum radial ion density for B = 0.

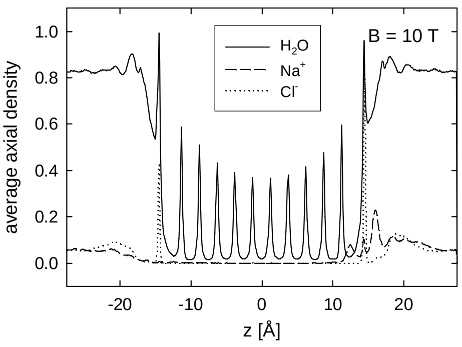

Fig. 3. Ensemble averaged density profiles along the channel axis. The water profile is normalized to its maximum value. The ion profiles are normalized to the maximum axial ion density for B = 0.

Table 1 summarizes the relevant quantities which characterize the ion transport over the ensemble of 20 simulations making up the entire data collection interval of 200 ns. For each magnetic field value considered (1 and 10 T), simulations were performed for the perpendicular (⊥) and parallel (||) orientations relative to the channel axis and the corresponding results enter the derived quantities with the weights 2/3 and 1/3, respectively. The ion passages have been identified by the entrance of the ion into the channel from one of the reservoirs and the subsequent exit to the opposite reservoir (without intermediate re-entrance to the initial reservoir). The ion passage times have been defined as ensemble averages of the individual passage times and together with the channel length have been used to express the average passage velocities. The net current was derived from the net charge transfer across the channel.

The total number of passages is around 60 for the Na^+ ions (~0.3 passages/ns) and slightly increases with the intensity of the applied magnetic field. Quite opposite, at most one Cl^- ion passage in the negative z-direction was observed irrespective of the applied magnetic field. As an exception, in the case B = 0, the Cl^- ion was rather dragged by a Na^+ ion in the positive electric field direction. The simulations of Crozier et al. [2] for B = 0 evidenced typically 12 complete Na^+ ion passages and no Cl^- ion passages over the considered interval of 100 ns. Possible causes of this smaller transport rate could be the different initial configurations of the simulations, the shorter data collection interval, and the different water model, as well. It should be noted that the selectivity of the channel with respect to the ion species does not appear to be influenced by the magnetic fields.

Table 1. Statistics of ion passages over a time interval of 200 ns. Negative numbers of passages imply net motions in the negative z-direction (opposed to the applied electric field). The average passage times and velocities refer to the channel only.

B [T]		No. of ion passages		Average passage time [ps]		Average passage velocity [m/s]		Average water polarization <cosθ>			Net current [pA]
		Na^+	Cl^-	Na^+	Cl^-	Na^+	Cl^-	entry reservoir	Channel	exit reservoir	
0		61	1	32.4	1610	77.1	1.55	0.078	0.030	0.104	48.1
1	⊥ ||	62 62	-1 -1	27.3	2978	91.6	0.84	0.084	0.028	0.110	50.5
10	⊥ ||	66 60	0 -1	26.0	563	96.0	4.44	0.091	0.027	0.114	51.5

From Table 1 it can be seen that the average passage times of the Na^+ ions across the channel are around 30 ps, not showing any apparent correlation with the magnetic field. The corresponding passage time reported by Crozier et al. amounts to 0.8 ns, and the appreciable difference to the present result is obviously due to the different definitions: total time in which there is an ion in the channel divided by the net number of passages, in contrast with the average interval of the successful passages only, used in the present work.

The net currents through the channel amount to approximately 50 pA, in qualitative agreement with experiments and the result reported by Crozier et al. (24.7 pA) for conditions compatible with those in our simulations. They show a tendency of increasing (up to 10%) with the applied magnetic field, contrasting with the intuitive expectation for the ion transport rate to decrease due to the magnetic deflections.

As pointed out by St. Pierre et al. [8], the Lorenz forces corresponding to technologically available magnetic fields are not capable of producing notable deflections on the cellular scale and thus to lead to a decrease of the ion flow. For the average velocities listed in Table 1, and even for the maximum instantaneous velocities, the associated Larmor radii turn out to be orders of magnitude over the channel size. Instead, by corroborating the magnetic field dependence of the net current with the behaviour of the ensemble averaged water polarization, showing itself an increasing trend in the reservoirs with increasing magnetic field, a different picture emerges.

Ion passages induce the water polarization, whereas the tilting of the water molecules is stochastically enhanced by the presence of the magnetic field, which acts like a small perturbation (especially in the case of the transverse orientation with respect to the channel axis). In turn, the more persistent polarization in the reservoirs causes the ions to experience a locally increased driving electric field. Already a modest magnetic field of 1 T produces the effect, higher field intensities enhancing the effect less, with a certain saturation tendency. The effect cannot be identified in the channel itself, where, due to the little number of water molecules, the relaxation subsequent to polarization is much faster than in the reservoirs.

4. Conclusions

The ion channel is structured – water forms boundary layers in the channel and at the membrane walls. It shows high transport rates ($\sim 3\times10^8$ ions/s) and high selectivity (Na^+ passages are roughly 60 times more probable than Cl^- passages).

Ion passages cause a pronounced water polarization and the quantitative description of the process relies on the appropriateness of the water model. Water polarization in magnetic fields as compared to the field-free case is enhanced in reservoirs, but remains practically unchanged in the channel. The magnetic fields technologically available cause a slight increase of the ion current (up to 10%), not a decrease as intuitively expected, acting as perturbations enhancing ion transport. The channel selectivity, however, is not affected by magnetic fields.

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