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## The importance of water molecules in ion channel simulations

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### Abstract

Crozier *et al* (2001 *Biophys. J.* **81** 3077) have simulated an electrically neutral but polar model channel under an applied field and found that there was a current of positive Na<sup>+</sup> ions but there was no current of negative Cl<sup>-</sup> ions unless the concentration was high or a very large field was applied. They suggested that this asymmetry in an electrically symmetric model was not due to differences in ion size but was due to the asymmetry of the water molecules, that results in frustrated orientations of the solvation water molecules near the Cl<sup>-</sup> ions in the confined geometry of the channel. This suggestion is tested by two simulations that are reported here. In the first simulation, we repeat the Crozier *et al* simulations but with the ion sizes reversed, with the cation having the Cl ion diameter and the anion having the Na ion diameter. As before, it is the cations that pass through the channel. The second simulation is a Langevin dynamics simulation for the Crozier *et al* channel but without explicit water molecules. In this second simulation, both Na<sup>+</sup> and Cl<sup>-</sup> ions pass through the channel with roughly equal currents. Both simulations confirm the important role of water in channel simulations.

Recently, we have developed [1] an applied field molecular dynamics (AFMD) method for ion channels and simulated the passage of Na<sup>+</sup> and Cl<sup>-</sup> ions, under an applied field, through an electrically neutral but polar model channel that is similar to gramicidin or the KcsA channel but somewhat larger in diameter. This study yielded a number of useful insights. One that we consider here is that, despite the fact that there is no charge asymmetries in the structure of the channel, only Na<sup>+</sup> ions crossed the channel. The Cl<sup>-</sup> ions could enter the channel, but, except when the applied field and ion concentration were very large, did not cross the channel. In agreement with experiment on these channels, these channels are cation selective and their current is due to the Na<sup>+</sup> ions.

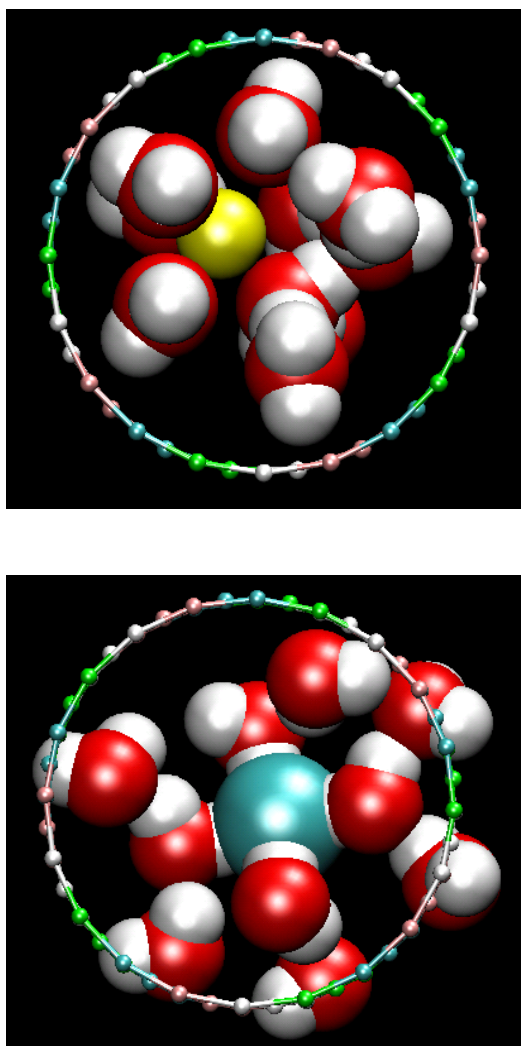
The question ‘what is the source of this asymmetry in a channel with a symmetric structure?’ is interesting. One possibility is that it is an artifact of the periodic boundary conditions that were used to simulate a macroscopic system with a relatively small simulation cell. However, further study [2] with two different larger simulation cells led to nearly identical results and seems to have laid that possibility to rest. Another possibility is the larger size of the  $\text{Cl}^-$  ions. However, Crozier *et al* [1] suggested that it was the unnatural orientations of the water molecules near negative  $\text{Cl}^-$  ions in the confined geometry of the channel that made the channel unfavourable for negative ions.

The suggestion of Crozier *et al* can be tested by considering a model electrolyte with positive ions whose diameter is that of the  $\text{Cl}^-$  ions and negative ions whose diameter is that of the  $\text{Na}^+$  ions. Such an electrolyte does not exist in nature but can be simulated and sheds light on the competing roles of water and ion diameter in channel permeation. Here we report an AFMD simulation using these *hypothetical* ions, with water molecules and a channel that are identical with those used in the Crozier *et al* study. As before, we use a  $25 \text{ \AA} \times 25 \text{ \AA} \times 55 \text{ \AA}$  ( $x, y, z$ ) simulation cell with a 1.1 V externally applied potential in the  $z$  direction and use periodic boundary conditions. The model membrane consists of neutral Lennard-Jones spheres placed on a square lattice at  $z = 15$  and  $40 \text{ \AA}$ . A  $4 \text{ sphere} \times 4 \text{ sphere}$  section, centred at  $x = y = 12.5 \text{ \AA}$ , is removed and replaced with a channel consisting of 11 20-atom rings, each consisting of a repeated sequence of four atoms with charges of  $\pm 0.5e$  and  $\pm 0.35e$ ,  $e$  being the electron charge. Each successive ring is offset by  $9^\circ$ . Eight positive ions, eight negative ions, and 600 SPC/E (extended simple point charge) model water molecules, corresponding to a 1 M solution, are placed in the cell. Each 10 ns simulation is run in parallel across ten processors for a total of 100 ns. The first simulation is a check and is a repeat of the Crozier *et al* simulation, using the Lennard-Jones (LJ) parameters listed in table 1 of their paper, and the second simulation is identical except that the cations and anions are given  $\text{Cl}^-$  and  $\text{Na}^+$  LJ parameters, respectively, from the Crozier *et al* paper. The Lorentz–Bertholet rules are used for cross interactions.

We obtain a current of 17 pA for the NaCl simulation and 40 pA for the large cation/small anion simulation. In both cases, the current is due to the passage of cations. Size is not a factor in preventing the passage of anions. In fact, increasing the size of the cations has resulted in a larger current, presumably due to decreased solvation. The structure of a typical  $\text{Na}^+$  and  $\text{Cl}^-$  ion in the first simulation and a typical cation and anion in the second simulation are shown in the snapshots given in figures 1 and 2. In both simulations the coordination of the solvation water molecules around an anion is frustrated.

Also, to examine the role of the water molecules, we have performed some simulations with no water molecules. In all other respects, the simulation cell, the structure of the membrane and channel, the LJ potential parameters and number of  $\text{Na}^+$  and  $\text{Cl}^-$  ions, and the 1.1 V applied potential are identical to those of the Crozier *et al* study and the first of the AFMD studies mentioned here. To compensate, in part at least, for the absence of the water molecules, we used Langevin dynamics. In principle, Langevin dynamics can be incorporated into our AFMD code. However, it was more convenient to use CHARMM, in which Langevin dynamics has been added already. We would have preferred to use a different relaxation time in the channel and bath but a position and species dependent relaxation time is not available in CHARMM. We established that a relaxation time of about 60 ps gives a conductance that is similar to experiment for a bulk NaCl aqueous electrolyte. However, since the results of our Langevin dynamics study are mainly of qualitative interest, the precise value of the relaxation time is unimportant.

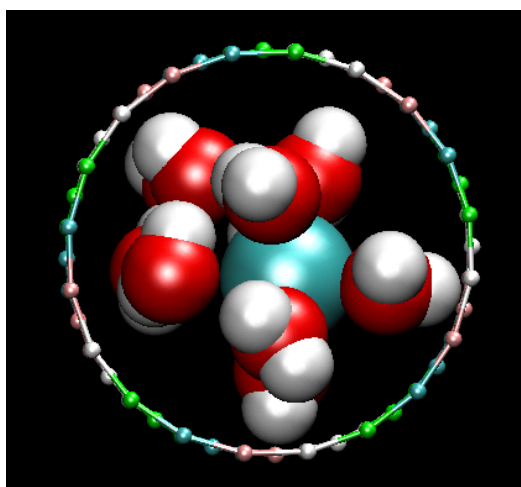
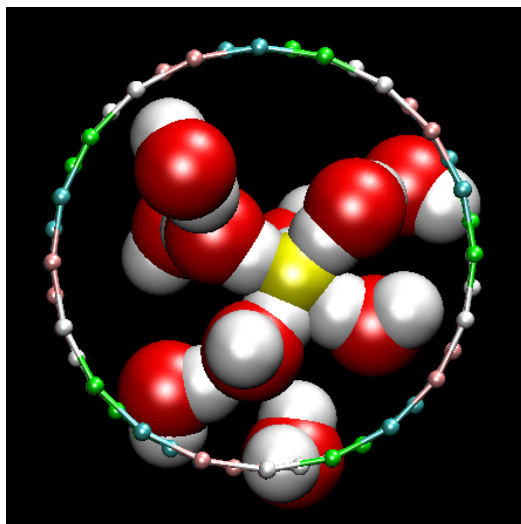
To be sure that the precise value of the relaxation time is unimportant, the Langevin dynamics program was used for a range of relaxation times and the effect of differences on  $\text{Na}^+$



**Figure 1.** Snapshot of a  $\text{Na}^+$  ion in the channel and a  $\text{Cl}^-$  ion at the mouth of the channel with all water molecules and channel atoms (shrunk in size for easier viewing) that are within  $3 \text{ \AA}$  of the ion, as obtained from the first AFMD simulation. The  $\text{Na}^+$  ion is yellow and the  $\text{Cl}^-$  ion is blue-green.

and  $\text{Cl}^-$  ion conductances was examined. In all cases, we found that with the water molecules represented by frictional relaxation both the  $\text{Na}^+$  and  $\text{Cl}^-$  ions pass through the channel with approximately equal currents. This illustrates the crucial role of the water molecules in channel dynamics. To account for the lack of  $\text{Cl}^-$  conductance in, say, gramicidin or the KcsA channel, and to represent better the effect of the water molecules with Langevin dynamics, might require, for example, different relaxation times for  $\text{Na}^+$  and  $\text{Cl}^-$  ions in the channel.

Dorman *et al* [3] have studied the origin of the cation selectivity of gramicidin-like channels by means of what they call a semi-microscopic Monte Carlo simulation. Their model channel has smooth walls and is not atomistic, in contrast to ours. Similarly to our model channel, the orientation of the carbonyls of the channel backbone is simplified. Their cations and anions are equal in size and a symmetric model (point dipoles) is used for water. They conclude that gramicidin-like channels are cation selective because, for ions of equal size, anions bind their waters of hydration more strongly than cations. This is true, but this tendency is offset by the fact that anions are generally larger than cations. In particular, the free energy of hydration of



**Figure 2.** Snapshot of a large cation in the channel and a small anion at the mouth of the channel with all water molecules and channel atoms (shrunk in size for easier viewing) that are within 3 Å of the ion, as obtained from the second AFMD simulation with a large cation and a small anion. The small anion is yellow and the large cation is blue-green.

$\text{Na}^+$  is about 30% more negative than that of  $\text{Cl}^-$ , due to the greater size of the  $\text{Cl}^-$  ion. In any case, we have shown that our gramicidin-like channel is cation selective even when the cation is larger than the anion. It is the asymmetry of the water molecule that produces the frustrated orientations of the water molecules that is the source of cation selectivity.

#### Acknowledgments

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