Simulation of the role of water in ion channel gating

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INTRODUCTION

Fluids behave differently in confined spaces than in bulk; for example, viscosity changes drastically for hydrophobic liquids at least, as does the activation volume for flow (Granick, 1991). Also, there is evidence for the formation of structure at mica surfaces, even for hydrophobic liquids (Israelachvili and Kott, 1988). Water is somewhat more difficult to study, but is expected to behave similarly in many respects, even if the intermolecular interactions are quite different. An ion channel is certainly a confined space, with a small number of water molecules held within a pore of nanometer dimensions. The water must move through the pore when the channel is open. The channel produces significant forces on the water; the most important appears to be the electric field produced by the ionic groups on the proteins. In an earlier work (Green, 1989), I proposed that the water would be ordered by the external field across the membrane; this appears to be incorrect. However, it is entirely possible that the water, held by the force of the electric field provided by ionic groups, closes the channel. Monte Carlo simulations using the TIP4P potential indicated a strong effect on the water which did imply that the channel would close under these conditions (Green and Lewis, 1991). However, the calculation did not include mobile ions. Whereas including more details in the calculation will be necessary for quantitative comparison with experiment, the only qualitative difference in the system which seems likely to be significant is the inclusion of mobile charges. Further work has now been done with a "pseudoion," keeping the TIP4P potential, but adding an extra negative charge to one of the water molecules. This molecule thus functions as a mobile anion in the simulation. It does not have the specific local potential of a chloride ion, nor is it a hydroxide ion; in fact, it could as easily have been positive. Nevertheless, the longer range forces, including in particular the Coulombic forces, will be reasonably faithfully modeled in this way, while keeping the calculation as simple as possible.

METHODS

A standard Monte Carlo simulation using the Metropolis technique (Metropolis et al., 1953) was used. In the simulations shown in the figures, a channel model with a conical lower section and cylindrical upper section is used, the boundary coming at (nearly) 11 Å above the vertex of the cone. The system is cut off so that any molecule moving below ≈ 4.5 Å above the vertex is counted as passing through the cone. These molecules reenter from the top (which is set at (nearly) 21.1 Å above the vertex), maintaining the density at that of bulk water. The simulations shown were run on a Fountain 486/25 computer with Weitek coprocessor, programmed in FORTRAN (model FTN77; University of Salford, England).

Quantities calculated included the average mobility of the molecules, the energy, and for the case of fixed charges, the orientation of the molecules with respect to the center of fixed charge. The figures

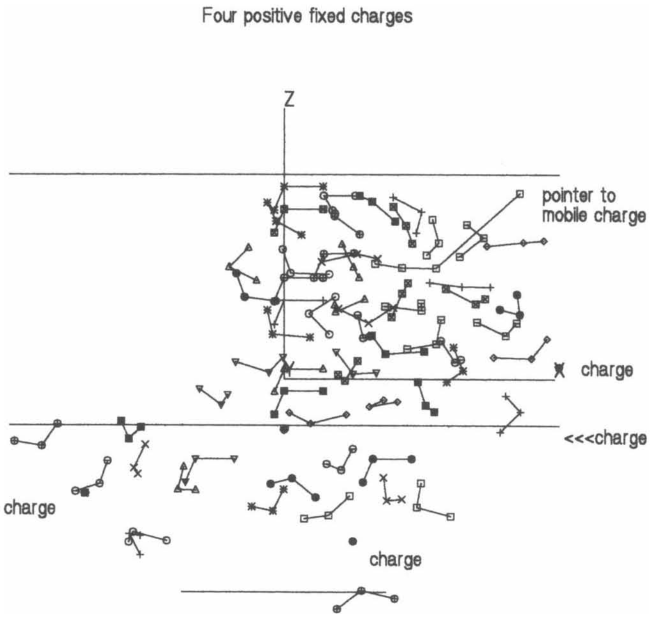

FIGURE 1 Four fixed positive charges, each marked by a solid circle; one appears to be directly under the *z* axis, as plotted. Observe the electrostriction and orientation of the water around each charge.

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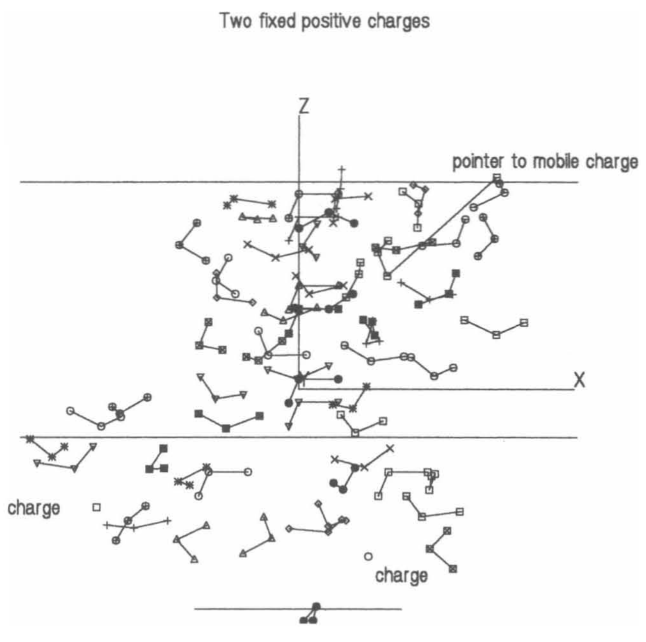

FIGURE 2 Two fixed positive charges, locations marked.

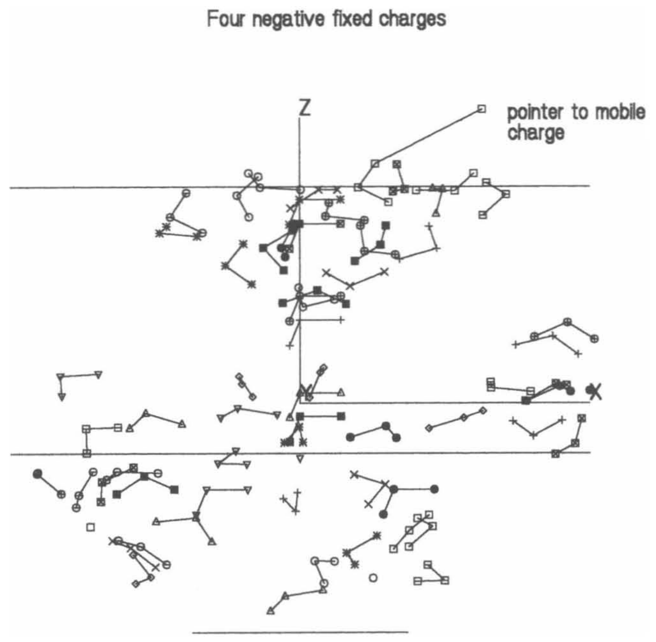

FIGURE 4 Charges have same positions as in Fig. 1, and same sign as mobile charge, which stays far away.

show the final position of the molecules in several cases, and offer the clearest presentation of the results.

The chief limitations of the present calculation are the failure to include the dielectric constant of the protein and the failure of the TIP4P model to include the polarization of the molecule. Work now in progress uses the polarization model of Stillinger and David (1978) to represent water and calculates the field using a relaxation method suggested by Professor Joel Gersten (Dept of Physics, City College, NY), including a dielectric constant of five for the protein. The field is being calculated on a 2 Å lattice, with five dimensions (only two for the source, three for the field, because cylindrical symmetry allows one dimension to be dropped). Each molecule is polarized by all its neighbors. Various polarization potentials have been proposed, but

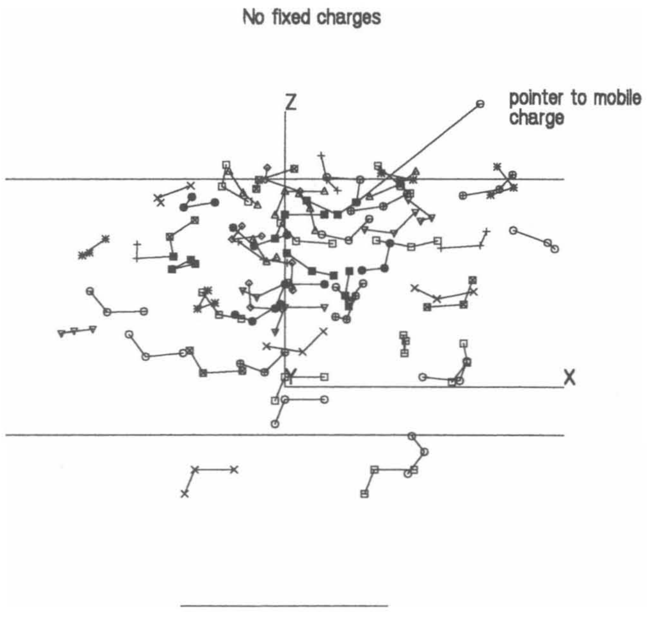

FIGURE 3 Mobile charge only; water clusters around this charge.

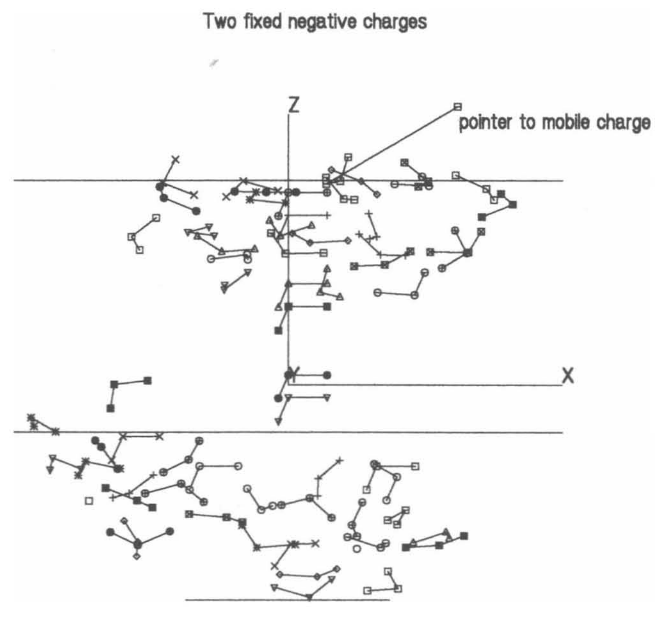

FIGURE 5 Same as Fig. 2, except fixed negative charges.

Stillinger and David's (1978) model which only polarizes the oxygen in water is still adequate. The field is on a 2 Å lattice because, with five dimensions, no finer lattice can fit in the computer memory. Linear interpolation is used to obtain the field at each oxygen atom. With this complete, it will be possible to go on to hydronium and hydroxide ions, testing the possibilities of altering the pK of ionizable groups more quantitatively than can be done with the present "pseudoions."

DISCUSSION

The figures show the molecules strongly oriented toward the charges. There are 54 mobile molecules, one of which acts as an anion, plus eight molecules immobilized on the boundary. The bottom line marks the opening of the simulation volume, the center line 11 Å above the cone vertex, and the top 21.1 Å (all these values slightly modified to adjust density to the 300 K temperature of the simulation). The most obvious point in the figures is the strong condensation of the charges around the charges (electrostriction). Even the mobile ion causes the water molecules to cluster. In Figs. 1 and 2, charges of opposite sign pull the mobile ion partially into the channel; Fig. 3 shows the "pseudoion" with no fixed charge, while Figs. 4 and 5 have fixed negative charges which repel the H_2O.

In spite of the problems which exist in this simulation, it is clear that charges create sufficiently large forces to greatly alter the behavior of water and the motion of ions in the channel, to the point that the charges could account for channel gating. It is likely that a more detailed calculation would make the effect smaller, so that a more realistic number of ions would be required.

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