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Abstract
Biological channels are protein molecules that contain a hole and that allow selected ions to pass through a membrane. They provide the mechanism for the control of many physiological functions. For example, a calcium channel selects calcium ions and controls the beating of a heart. We report our Monte Carlo results on model calcium channels. Because of the presence of negatively charged glutamate side chains in the channel, the channel selects calcium ions over sodium ions because of the ability of the divalent calcium ions to deliver twice the charge while occupying the same volume as the monovalent ions in the narrow channel.

1. Introduction

The transport of inorganic ions between the cytosol of a cell and the extracellular space is controlled by ion channels. Ion channels are proteins with a narrow, highly selective pore in their centre protruding from the cell membrane. Voltage-gated channels, while open, selectively allow some ions to pass but not others. The biological importance of voltage-gated ion channels cannot be overestimated. For instance, sodium channels are responsible for the flow of the nervous impulse along the nerve or muscle cell, while calcium channels convert electrical signals into chemical signals at nerve terminals [1].

The selectivity of ion channels depends on the distribution of charged amino acids in their lining. Specifically, the ion-selective properties of a large family of ion channels (that includes Ca and Na channels) seem to arise in small segments (P loops) of the pore that is formed between four homologous motifs within a single polypeptide. Ion selectivity of the Ca and Na channels is thought to be determined by the four residues present in the four P loops. These are glutamate (E) groups in the Ca channel (EEEE-locus), while they are aspartate (D), glutamate (E), lysine (K), and alanine (A) in the Na channel (DEKA-locus).

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The problem lends itself to a statistical mechanical analysis. Nonner *et al* [2] studied a simple model of the EEEE-locus using the mean-spherical approximation (MSA) for the primitive model (PM) of electrolytes to represent the aqueous solution in the pore and the bath. In the PM, the ions are modelled by charged hard spheres, while the solvent is represented by a dielectric background of a given dielectric constant. The model of Nonner *et al* for the Ca channel consisted of a cylindrical pore (the selectivity filter) that contained a cluster of eight half-charged oxygens representing the four unprotonated glutamate residues. The oxygen ions are confined to the small subvolume of the selectivity filter but are otherwise mobile. These charged residues were tethered to the pore wall by flexible carbon chains. The dimensions of the filter were about 0.4–0.5 nm in radius and 1 nm in length.

Since the work of Nonner *et al* [2] was an equilibrium study (no current and electrochemical gradient), the baths on the two sides of the channel are equivalent, meaning that there is only one bath that is in equilibrium with the system inside the filter. The selectivity of this filter is described by the probabilities that the various species of ions enter the filter from the bath. In an equilibrium statistical mechanical description this probability agrees with the local density of the given ionic species in the filter. The input of the study was the density of the oxygen ions in the filter, while, as an output, the densities of the various cations were obtained. The selectivity was determined by adding $CaCl_2$ to the bath while holding the density of the sodium constant in the bath.

Nonner *et al* [2] found that the filter is highly selective for Ca^{2+} ions over Na^+ ions because the divalent ions are more effective in neutralizing the charge of glutamates since they provide twice the charge using the same excluded volume that the monovalent cations do. This mechanism of ionic selectivity has been called the charge/space competition (CSC) mechanism. The crowding of ions produces selectivity.

2. Results of the Monte Carlo simulations

An interesting feature of the study of Nonner *et al* [2] was that they applied a theory of a homogeneous fluid (the MSA approach) to a clearly inhomogeneous problem successfully. One of the goals of our Monte Carlo (MC) simulations was to justify the CSC approach of Nonner *et al* and to show that the application of the bulk MSA theory gives qualitatively correct results for the selectivity of the filter. As a first approach, we developed an infinite cylindrical model for the channel geometry [3, 4]. The simulation cell, which consists of three concentric cylinders, can be seen in figure 1(a). The channel is the region within the innermost cylinder (radius R_1) and the bath is the region between the two outermost cylinders (radii R_2 and R). The cylinder at R confines the whole simulation cell, while a periodic boundary condition is applied in the z-direction. The role of the region between R_2 and R is to separate the channel and the bath. The values of R_2 and R, as long as they are large, are not important.

This geometry is a very simplified model of the real geometry. Nevertheless, it is quite common to represent channels by infinitely long cylinders [5–8]. Moreover, we hope to be able to study this infinite geometry by a density functional theoretical method. The electrolyte was modelled by the PM using 78.5 for the dielectric constant of the solvent. The radius of the channel was 0.5 nm. We started with a pure NaCl solution and added $CaCl_2$ to the system while keeping the Na concentration constant in the bath at 0.1 M. The particulars of the simulation procedure can be found in [3]. A comparison of the selectivity curves obtained by MC simulations and those given by the MSA approach of Nonner *et al* [2] can be seen in figure 2(a). The number of cations in the filter are calculated for a 1 nm long portion of the infinite channel. Here, 0.25 nm was used for the diameter of all ionic species.
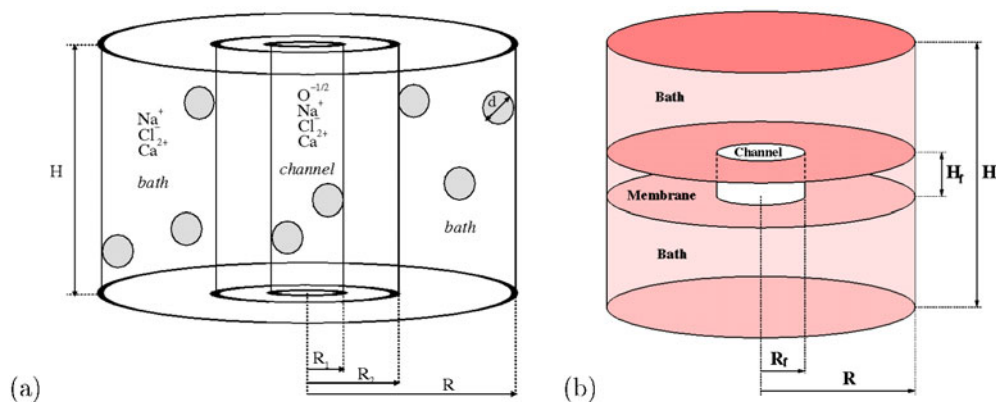
Figure 1. The simulation cells for (*a*) the infinite geometry and (*b*) the finite geometry.
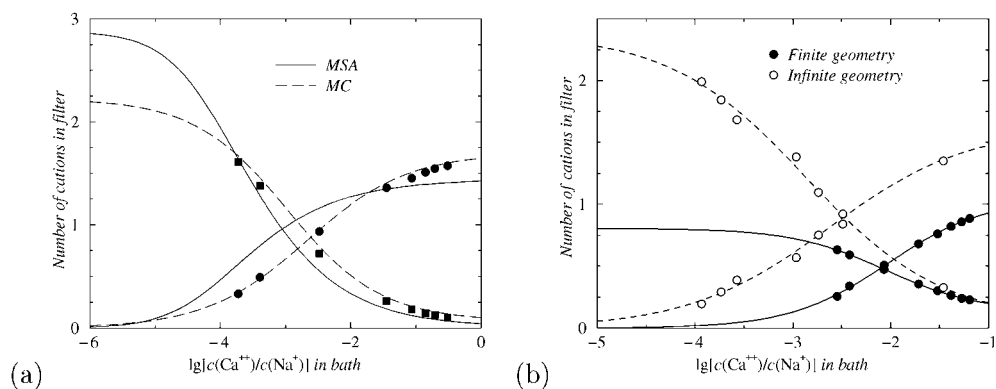(This figure is in colour only in the electronic version)

Figure 2. Selectivity curves. Number of ions in the filter plotted against the bulk Ca^{2+} concentration (relative to the bulk Na^+ concentration, 0.1 M). Decreasing and increasing curves relate to Na^+ and Ca^{2+} ions, respectively. (*a*) Comparison of MSA and MC results for the infinite geometry. (*b*) Comparison of the simulation results obtained for the infinite and finite geometries.

The agreement between the theory and the simulation is very good. This implies that the approach of Nonner *et al* [2] is reasonable.

A step toward a more realistic model of the ion channel can be seen in figure 1(*b*) [9]. The simulation cell is divided by a membrane of thickness H_f with a hole in the middle with a radius R_f. The system is confined by a cylinder of radius R and the periodic boundary condition applied in the z-direction makes the baths on the two sides of the membrane parts of a single bath. The interior of the hole represents the selectivity filter that contains eight half-charged oxygens with diameter 0.25 nm. For the diameters of the Na^+, Ca^{2+}, and Cl^- ions the values 0.19, 0.198, and 0.362 nm were used, respectively. In this simulation a preference sampling was used to accelerate the equilibration between the filter and the bath [9].

Figure 2(*b*) shows a comparison between the selectivity curves obtained for the infinite geometry (using the above ionic diameters and $R_1 = 0.5$ nm) and the finite geometry with $R_f = 0.5$ nm and $H_f = 1$ nm. It can be seen that similar selectivity curves are obtained for the finite geometry and the infinite geometry. In the case of the finite geometry fewer cations

enter the channel and the channel is less selective. There is a space charge around the filter region at the entrances of the filter that extends into the bath. This space charge contributes to the neutralization of the negative charge of the filter.

A possible continuation of this work is to extend the simulations to the solvent PM where the solvent molecules are represented by hard spheres. This problem has already been studied using the MSA approach [10]. Promising simulations for the sodium channel selectivity carried out by transforming the EEEE-locus of the calcium channel to the DEKA-locus of the sodium channel by changing the corresponding residues are in progress.

Acknowledgments

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