

Effect of charge fluctuations on the permeation of ions through biological ion channels

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Abstract. The effect of charge fluctuations at the mouth of an open ion channel on its conduction mechanism is analyzed within the framework of self-consistent Brownian dynamics simulations. It is shown that volume charge fluctuations at the channel mouth can be modelled as a generalized shot noise and result in strong modulation of the potential barrier for an ion at the selectivity site, on a sub-nanosecond time scale.

Keywords: ion channels, Poisson equation, Langevin equation, self-consistent approach, charge fluctuation

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INTRODUCTION

Ion channels are holes through the membrane of a biological cell that allow transport of ions in and out of the cell, once open. Without ion channels, life would not be possible since they lie at the heart of many physiological process, such as the generation of action potentials, or muscle contraction. They provide the target for many drugs. Although huge progress has been made in recent decades in the simulation of conduction in ion channels, much remains to be understood before we attain a complete explanation of the structure-function relationship for ion channels. As a step towards this goal, we investigate specifically the effect of charge fluctuations on the properties of the channel. We emphasize that, in the traditional approach to calculation of the escape rate in molecular biology, charge fluctuations in the bulk are usually neglected [1].

Our investigation is based on the self-consistent solution of coupled Poisson and Langevin equations for ions moving in an open channel [2, 3]. It is shown that, once an ion is sitting at the channel's selectivity filter, the presence of another ion of the same valence at the channel mouth will have the effect of reducing the barrier that the first ion must overcome in order to exit at the far end of the channel. The paper starts by presenting details of the method used. This is followed by results and their discussion. We close with concluding remarks, emphasizing the relevance of charge fluctuations and their amplification to the permeation of ions through their channels.

THE BROWNIAN DYNAMICS SIMULATIONS

The motion of ions is modelled within a self-consistent framework of Brownian dynamics (BD) for the simulations of ionic trajectories, coupled to the Poisson equation for the determination of the force acting on each ion:

$$m_i \ddot{\vec{x}}_i = -m_i \gamma_i \dot{\vec{x}}_i + \left[\frac{q_i q_j}{4\pi\epsilon\epsilon_0 r_{ij}^2} + \frac{9U_0 R_c^9}{r_{ij}^{10}} \right] \frac{\vec{r}_{ij}}{r_{ij}} + \vec{F}_{ch} + \sqrt{2m_i \gamma_i k_B T} \vec{\xi}_i(t), \quad (1)$$

$$m_j \ddot{\vec{x}}_j = -m_j \gamma_j \dot{\vec{x}}_j + \left[\frac{q_i q_j}{4\pi\epsilon\epsilon_0 r_{ji}^2} + \frac{9U_0 R_c^9}{r_{ji}^{10}} \right] \frac{\vec{r}_{ji}}{r_{ji}} + \vec{F}_{ch} + \sqrt{2m_j \gamma_j k_B T} \vec{\xi}_j(t), \quad (2)$$

$$-\nabla \cdot (\epsilon(\vec{r}) \nabla \phi(\vec{r})) = \frac{\rho(\vec{r})}{\epsilon_0}, \quad \vec{D} = \epsilon \vec{E}, \quad \vec{E} = -\vec{\nabla} \phi, \quad (3)$$

where m_i , x_i and q_i are the mass, position and charge of the i th ion. The distance between ions i and j is r_{ij} . The overall strength of the potential and the contact distance between ions pairs are represented respectively by U_0 and R_c [4]. Water molecules are represented through the viscous friction coefficient γ_i and a white Gaussian noise $\xi_i(t)$ with zero mean and intensity unity. The dielectric force F_{ch} is calculated numerically by solving Poisson's equation using a finite volume method [5]. In Eq. (3), $\epsilon = \epsilon_k \epsilon_0$ is the space dependent dielectric function with $k = 1$ or 2 and $\epsilon_0 = 8.85 \cdot 10^{-12} \text{ CV}^{-1} \text{ m}^{-1}$ is the dielectric constant of empty space. ρ is the source density, ϕ is the potential, \vec{D} and \vec{E} are respectively the displacement vector and the electric field. By introducing an effective dielectric coefficient at the boundary between water and the protein, our Poisson solver is able to handle the severe jump between the water ϵ_2 and protein ϵ_1 dielectric constants. Dirichlet Boundary conditions are used to fix the potential across the membrane and Neumann conditions are used in the direction perpendicular to the channel axis. For simplicity, and in order to preserve the cylindrical symmetry, ions are bound to move only on the channel axis, and the electrostatic field acting on them as they move is then calculated. The following parameters are used for the simulations:

Dielectric constants	$\epsilon_2 = 80, \epsilon_1 = 2$
Masses (kg)	$m_{Na} = 3.8 \times 10^{-26}, m_{Cl} = 5.9 \times 10^{-26}$
Diffusion coefficients ($\text{m}^2 \text{s}^{-1}$)	$D_{Na} = 1.33 \times 10^{-9}, D_{Cl} = 2.03 \times 10^{-9}$
Ionic radii (\AA)	$r_{Na} = 0.95, r_{Cl} = 1.81$
Temperature	$T = 298 \text{ K}$

Note that D is related to the friction coefficient via $D = \frac{k_B T}{m\gamma}$.

RESULTS AND DISCUSSION

Charge fluctuations at the channel mouth are estimated by solving Eqs. (1) and (2) numerically. The total positive and negative charge in the channel mouth, of volume $v_M = \pi r^2 \times r$, where $r = 6 \text{ \AA}$, were recorded continuously (during a few microseconds).

The arrival time was estimated by recording the time intervals between the sequential arrivals in this volume. Figure 1(left) shows the distributions of arrival times. They follow exponential laws with mean arrival times $\tau_{ar} \sim 3.6 \times 10^{-10}$ sec for Na^+ and $\tau_{ar} \sim 4.7 \times 10^{-10}$ sec for Cl^- .

The total electrostatic energy required to move one ion from the bulk solution into a channel of length 30 Å, radius 4 Å, with a unit $-e$ charge at its middle, as a function of the position of the ion is calculated for a potential drop across the channel of $\Delta\Phi = 90$ mV. Figure 1(right) illustrates the fact that the presence of a second ion at the channel entrance reduces significantly the energy barrier ΔE_0 seen by the first ion located at the channel selectivity filter to $\Delta E_1 < \Delta E_0$. For this particular example the distribution of fixed charge at the ion channel wall has the form

$$P(x) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(-\frac{(x-\mu)^2}{2\sigma^2}\right)$$

with $\sigma \approx 0.2\text{Å}$ and μ corresponding to the location in the middle of the channel. The corresponding potential barrier for the ion trapped at the selectivity filter is of the order of $\Delta E_0 = 1k_B T$. It can be seen from the figure that this potential barrier is completely compensated by a second ion of the same charge arriving at the channel mouth with average arrival time $\approx 0.5 \cdot 10^{-9}$ sec.

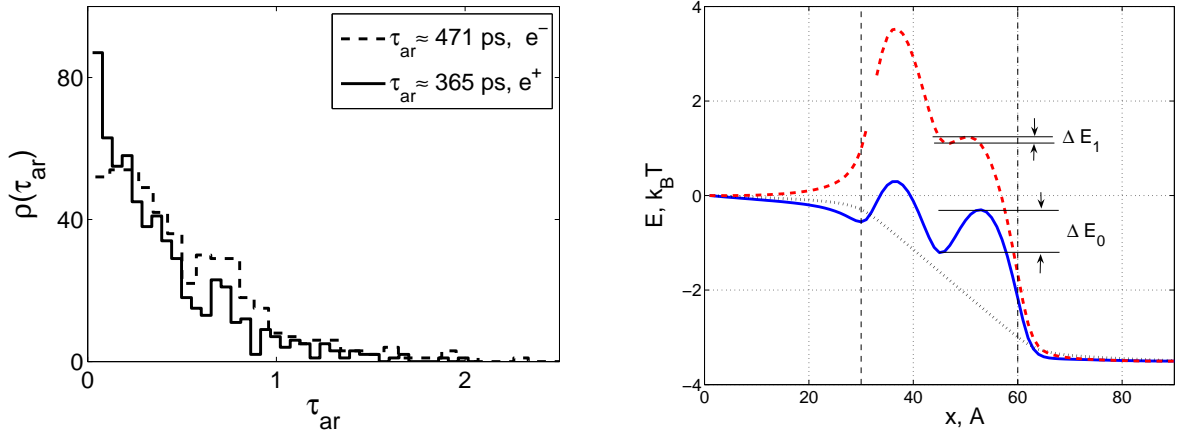


FIGURE 1. (left): The arrival time distributions for positives (solid line) and negative (dashed line) ions for cylindrical channel of radius $r=6\text{Å}$. (right) Total energy of the channel as a function of the position of the ion when: the first ion is located at the channel mouth and the second is moving on the channel axis(dashed line); the channel is empty(solid line); no channel(dotted line). The vertical dashed-dotted lines show channel entrance.

The calculated arrival time is comparable to that obtained by considering pure diffusion of ions through the hemisphere at the mouth of the channel and is given by $\tau_{ar} = 1/(2\pi z_i N_A D_i r c_0)$, where r is the channel radius, c_0 the bulk concentration, N_A the Avogadro number, and z_i and D_i are respectively the charge valence and the diffusion coefficient of the i th ion [1, 6]. The estimations give $\tau_{ar}^{es} \sim 2.9 \times 10^{-10}$ sec for Na^+ and $\tau_{ar}^{es} \sim 3.8 \times 10^{-10}$ sec for Cl^- .

CONCLUSION AND PERSPECTIVES

It was shown that charge fluctuations at the channel mouth can modulate the height of the potential barrier by $1 k_B T$ under physiological conditions, on a sub-nanosecond time scale. Such strong modulation is due to the effect of the amplification of the ion-ion interaction in the channel as compared to the interaction between the ions in the water. A simple intuitive explanation of this effect is related to the fact that Coulomb interaction is inversely proportional to the dielectric constant. Accordingly, the ion-ion interaction will be amplified by $40\times$ in the infinitely narrow channel, as compared to the infinitely wide channel. In an actual channel the amplification factor depends on its geometry, as will be discussed in detail elsewhere.

As a result of this amplification, the charge fluctuation at the channel mouth can reduce the escape time across the potential barrier at the selectivity site. In particular, for the parameters chosen in our numerical example, the escape time is reduced to ≈ 0.5 ns as compared to the estimates of 1 ns or more based on Kramers theory of the escape rate from this barrier due to thermal fluctuations only.

This could help to explain the fast conduction of ion channels combined with their strong selectivity between alike ions. Indeed, strong selectivity between alike ions implies that the probability of finding a favorable ion at the selectivity filter is much larger than the probability of finding another ion at this site. This in turn implies that the conducting ion should have a deep potential minimum at the selectivity filter. Yet the transition rate of the conducting ions through the channel corresponds to almost free diffusion. Taking into account the effect of the amplification of the charge fluctuations at the channel mouth can contribute to the solution of this apparent paradox.

Other effects that may impact significantly on channel conductivity and selectivity include wall vibrations, coupled to the effect of hydration at the selectivity filter, as will be discussed in more detail elsewhere.

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