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# Ion channels as electrostatic amplifiers of charge fluctuations

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**Abstract.** Electrostatic interactions between ions in an ionic channel and the charge fluctuations in the channel mouth are considered. It is shown that the charge fluctuations can be enhanced in channels of low dielectric constant, resulting in strong modulation of the potential barrier at the selectivity site. It is conjectured that similar effects can alter transition probabilities in other molecular dynamical systems.

## 1. Introduction

Electrostatic interactions and fluctuations play crucial roles in controlling transition probabilities, conduction and selectivity in nanoscale molecular systems. It is well-known that the long-range Coulomb interaction leads to a strong correlation of ion motion and is responsible for the ions' distribution and the energy fluctuations in electrolytes [1, 2]. However, in the traditional approach to the calculation of escape rates in molecular biology, charge fluctuations in the bulk are usually neglected [3]. In particular, volume charge fluctuations are usually not taken into account in relation to the problem of ion passage through an open ion channel [4, 5]. On the one hand it is known that narrow channels of low dielectric constant in the channel walls posses high potential barriers preventing easy passage of ions through the channels [6, 7]. On the other hand, however, ion channels can be very good conductors passing up to $10^8$ ions per second [8]. The difficulties in explaining these and other facts using thermal fluctuations as the only source of noise in molecular systems are also well known [3].

In this paper we consider the effect of charge fluctuations on the probabilities of transition of ions through an open ionic channel in addition to the effect of thermal fluctuations. We argue that open ionic channels can be viewed as electrostatic *amplifiers* of the charge fluctuations. I.e. the change in the potential barrier $\Delta E$ induced by the charge fluctuations can be amplified very significantly in the presence of the channel walls of small dielectric constant. As a result, the transition probabilities for an open channel whose potential barrier is at the selectivity site can be substantially increased.

Specifically, we consider ion transport across a lipid membrane with a small dielectric constant, describing the motion via a self-consistent solution of the coupled Poisson and Langevin equations for ions moving in an open ionic channel [9, 10]. We investigate numerically the distribution of ionic arrival times, and the charge fluctuations at the channel mouth, and compare them with theoretical predictions. Next, the electrostatic energy profile of one ion in an aqueous channel through a lipid membrane, charged at the selectivity site, is calculated in the case when negative charge at the selectivity site produces a potential well for a positive ion in the channel. Finally, we consider the electrostatic coupling between charge fluctuations in the channel mouth and the energy fluctuations for the ion at the selectivity site.

We will show that the volume charge fluctuations in the channel mouth can be modeled as a generalized shot noise. They result in strong modulation of the potential barrier for an ion at the selectivity site on a sub-nanosecond timescale. We provide an analytic approximation of the amplification of the electrostatic interaction between the ions in the channel.

## 2. The conjecture

The key idea of the paper is based on estimation of the force of interaction between two ions of charge $q$ in a medium of dielectric constant $\epsilon$ separated by a distance $r$ (cf. [11])

$$F = \frac{q^2}{4\pi\epsilon\epsilon_0 r^2}. \tag{1}$$

Since $F \propto \frac{1}{\epsilon}$, it is clear that the strength of the interaction between ions in dielectrics of large $\epsilon$ (e.g. water $\epsilon_{\mathrm{H_20}} = 80$) is much weaker than in dielectrics of small $\epsilon$ (e.g. protein $\epsilon_p = 2$). In ionic solutions in water, the interaction between the ions is further weakened by screening.

Therefore, there are at least two main factors contributing to the amplification of the interaction between ions in narrow channels, as compared to interaction between ions in bulk solutions in water. First, narrow channels are likely to be singly occupied. As a consequence an ion situated at the selectivity site in the middle of the channel can feel volume charge at the channel mouth without screening. Secondly, the effective dielectric constant of the channel must have a value intermediate between $\epsilon_{\mathrm{H_20}} = 80$ and $\epsilon_p = 2$. The latter can be seen as follows. Consider a narrow channel of length $d$ and radius $r$ such that $r \ll d$. Introduce an effective value of the dielectric constant of the channel to take account of ion-induced charge on the channel walls. For $r \rightarrow 0$ the effective dielectric constant of the channel must go to that of protein, $\epsilon \rightarrow 2$, while for $r \rightarrow \infty$ $\epsilon$ must go to that of water, $\epsilon \rightarrow 80$. It is therefore clear that, at finite $r$, the effective dielectric constant of the channel has an intermediate value and the smaller the radius $r$ becomes the smaller will be the effective dielectric constant.

In addition, we suggest that, on the timescale of an ion's transition through an open channel, volume charge fluctuations at the channel mouth are of the shot noise type (cf. [4]). They must be amplified by the ion channel leading in turn to a strong modulation of the transition probabilities.

To illustrate this conjecture we model numerically an open ion channel in the standard configuration [12, 13].

## 3. Method

The system considered is comprised of three compartments (see Fig. 1 (left)). The middle block constitutes the protein through which there is a cylindrical hole approximating the open channel. The channel is bathed with a solution of NaCl at its left and right ends. The electrostatic force and potential are produced by the moving ion, and by fixed charge at the surface, particularly the net negative charge carried by a fraction of the protein at the channel's selectivity filter. The fixed charge of value $-1\,\mathrm{e}$ is taken to be at the center of the channel within one finite volume element of the protein as shown in Fig. 1(left). The small dot on the channel axis is the ion moving on the channel axis. Since the dielectric constant of the aqueous pore is not yet known for narrow channels, we use as a first approximation the same dielectric constant as for the aqueous bath $\epsilon_2 = 80$. The dielectric constant of the protein embedded in the membrane is taken to be $\epsilon_1 = 2$.

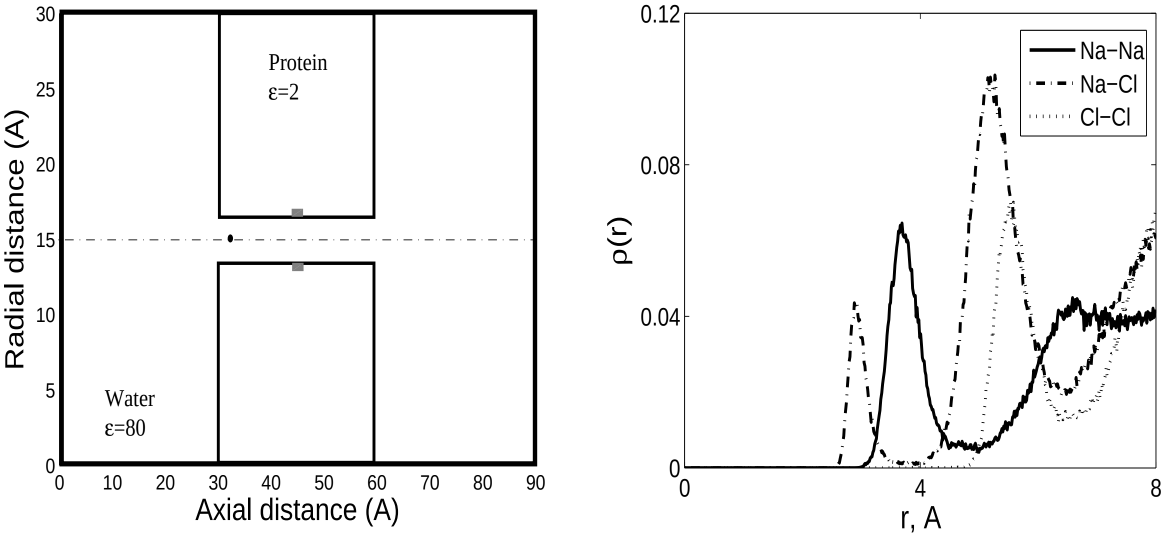

**Figure 1.** (left) A simplified model of ion channels showing the protein (embedded in the membrane) and the hole down its middle forming the channel. One ion (shown by a small dot) is moving on the channel axis. The fixed charge uniformly distributed in one finite volume ring at the centre of the channel (shown by the small rectangular blocks). (right) Radial distribution function in aqueous NaCl solutions at 298 K, for molar concentrations of 400 mM.

The motion of the ions is modeled within a self-consistent framework of Brownian dynamics (BD) (2), (3) coupled to the Poisson equation (4).

$$m_i\ddot{\vec{x}}_i = -m_i\gamma_i\dot{\vec{x}}_i + \sum_{j=1}^{N}\left[\frac{q_iq_j}{4\pi\varepsilon\varepsilon_0 r_{ij}^2} + \frac{9U_0R_c^9}{r_{ij}^{10}} + AU_0\exp\left(\frac{R_{ij}-r_{ij}}{a_e}\right)\sin\left(2\pi\frac{R_{ij}-r_{ij}}{a_w}-\alpha\right)\right]\frac{\vec{r}_{ij}}{r_{ij}} + \vec{F}_{ch} + \sqrt{2m_i\gamma_i k_BT}\vec{\xi}_i(t) \tag{2}$$

$$m_j\ddot{\vec{x}}_j = -m_j\gamma_j\dot{\vec{x}}_j + \sum_{i=1}^{N}\left[\frac{q_iq_j}{4\pi\varepsilon\varepsilon_0 r_{ji}^2} + \frac{9U_0R_c^9}{r_{ji}^{10}} + AU_0\exp\left(\frac{R_{ij}-r_{ij}}{a_e}\right)\sin\left(2\pi\frac{R_{ij}-r_{ij}}{a_w}-\alpha\right)\right]\frac{\vec{r}_{ji}}{r_{ji}} + \vec{F}_{ch} + \sqrt{2m_j\gamma_j k_BT}\vec{\xi}_j(t) \tag{3}$$

Here $\vec{r}_{ij} = \vec{x}_i - \vec{x}_j$, $r_{ij} = |\vec{r}_{ij}|$, $A = \sqrt{1 + (\frac{a_w}{2\pi a_e})^2}$, $\alpha = \arctan(\frac{a_w}{2\pi a_e})$, $m_i$, $\vec{x}_i$ and $q_i$ are the mass, position and charge of the $i$th ion. In the Brownian dynamics simulations, water molecules are not taken into account explicitly and are represented by an average frictional force with a friction coefficient $m_i\gamma_i$ and a stochastic force $\sqrt{2m_i\gamma_i k_BT}\vec{\xi}_i(t)$ arising from random collisions. The long range Coulomb interaction is represented by the $1/r$ potential. The addition of the pairwise repulsive $1/r^9$ [14] soft-core interaction potential insures that ions of opposite charge, attracted by the inter-ion Coulomb force, do not collide and neutralize each other. 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 $R_c$. We note that an experiment [15] and theory [16, 17] demonstrate oscillatory behavior of the potential of the mean force between the like ions in water. The oscillating part of the potential is taken into account explicitly by adding third term in the square brackets to the Eqs. (2) and (3), where $a_w$ is the oscillation length, $a_e$ the exponential drop parameter and $R_{ij}$ is the origin of the hydration force which is slightly shifted from $R_c$ by $+0.2\,\text{Å}$ for like ions and by $-0.2\,\text{Å}$ otherwise [12].

The dielectric force acting on the ion as it moves on the channel axis $F_{ch}$ is calculated numerically by solving the Poisson equation in 3D space with cylindrical symmetry [18]

$$-\nabla\cdot(\epsilon(\vec{r})\nabla\phi(\vec{r})) = \rho(\vec{r}), \qquad \vec{D} = \epsilon\vec{E}, \qquad \vec{E} = -\vec{\nabla}\phi, \tag{4}$$

using the finite volume method (FVM) [19]. In Eq. (4), $\epsilon = \varepsilon_k\varepsilon_0$ is the space dependent dielectric function with k= 1 or 2 and $\varepsilon_0 = 8.85\times10^{-12}$ $\mathrm{CV^{-1}m^{-1}}$ is the dielectric constant of empty space. $\rho$ is the source density, $\phi$ is the potential, $\vec{D}$ and $\vec{E}$ are respectively the displacement vector and the electric field. An effective dielectric constant is introduced at the interface between the water and the protein. The latter procedure is more appropriate when the dielectric function undergoes a severe jump. In order to preserve cylindrical symmetry, the moving ion is required to stay on the channel axis. Dirichlet boundary conditions are used to fix the value of the electrostatic potential on the left and right boundaries of the system, as used in experimental measurement. The Neumann boundary condition is used to set the value of the normal component of the electric field. A standard iterative method is used to solve algebraic linear system derived from the discrete Poisson equation. The results are stored in tables, thus facilitating fast, self-consistent, BD simulations.

We used the following parameters for the simulations:

Dielectric constants: $\varepsilon_2 = 80$, $\varepsilon_1 = 2$;
Masses (in kg): $m_{Na} = 3.8\times10^{-26}$, $m_{Cl} = 5.9\times10^{-26}$;
Diffusion coefficients (in $\mathrm{m^2s^{-1}}$): $D_{Na} = 1.33\times10^{-9}$, $D_{Cl} = 2.03\times10^{-9}$ (Note that D is related to the friction coefficient via $D = \frac{k_BT}{m\gamma}$.);
Ion radii (in Å): $r_{Na} = 0.95$, $r_{Cl} = 1.81$;
Temperature: $T = 298$ K.

To see how the hydration effect can be taken into account at the selectivity filter we consider first the effect of hydration in the bulk following the simplified description adopted in [20, 21]. The parameters of the ion-ion interaction used in the calculations are presented in Table. 1.

| Ions | $U_0$[k$_B$T] | $R_c$[Å] | $R$[Å] | $a_w$[Å] | $a_e$[Å] |
|---|---|---|---|---|---|
| Na-Na | 0.5 | 3.50 | 3.7 | | |
| Na-Cl | 8.5 | 2.76 | 2.53 | 2.76 | 1.4 |
| Cl-Cl | 1.4 | 5.22 | 5.42 | | |

**Table 1.** Parameters used in the calculation of the short range ion-ion interaction with hydration.

A test of accuracy of the simulation is carried by performing the simulation in bulk solutions, with a concentration of 400 mM. Initially, ions are injected randomly with zero velocity in the simulation domain. Reflective boundary conditions are set on the faces of the boxes. When ion passes through the channel (e.g. from the left to the right) an ion is removed from the far right end and injected at the far left end of the system. This way, maintaining the number of ions in the simulation box constant. Ions are then left to relax before the ion-ion radial distribution function is calculated.

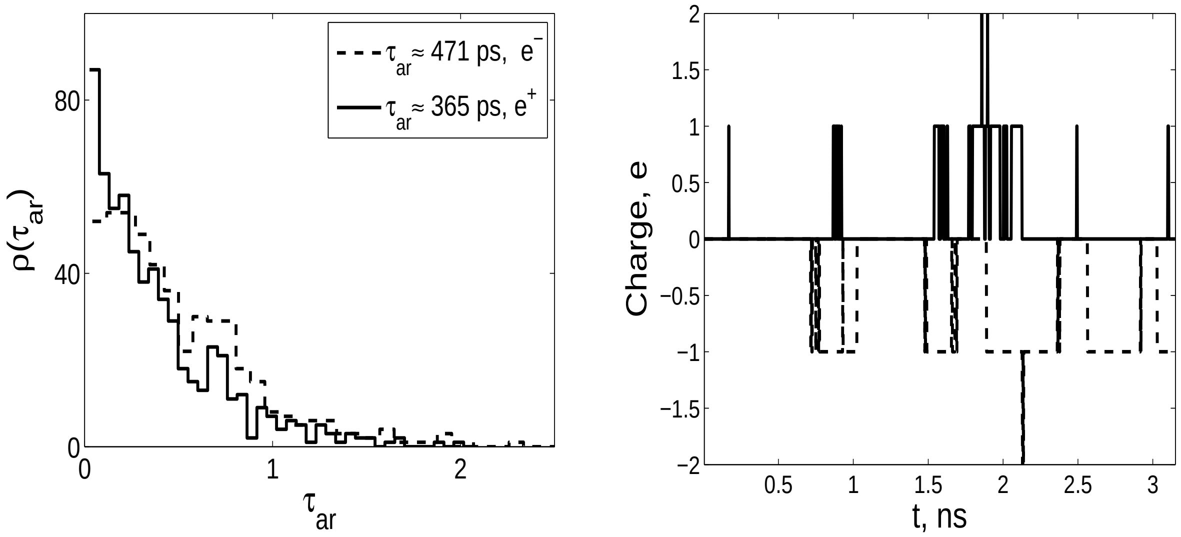

**Figure 2.** (left) The arrival time distributions for positive (solid line) and negative (dashed line) ions for a cylindrical channel of radius $r = 4$ Å. (right) Charge fluctuations at the channel mouth.

The ion-ion pair correlation functions ($\rho(r)$) obtained in our numerical simulations are shown in the Fig. 1 (right). An oscillatory shape (cf. [15, 22–24]) of the distribution (going to zero for distances less than the interionic separation) is clearly seen in the figure. We note that the results shown in the Fig. 1 (right) closely reproduce the earlier results of [23].

## 4. Distribution of arrival times and the charge fluctuations

We focus here on an effect of volume charge fluctuations at the channel mouth on the transition probabilities of the ions through an open ionic channel. To this end we would like to estimate how much time ions spend in the channel mouth and how often they arrive there. On the assumption of charge neutrality and no applied field, the arrival times of ions at the channel mouth from a solution can be estimated [3, 25] 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, $N_A$ Avogadro's number, $z_i$ and $D_i$ the charge valence and the diffusion coefficient of the $i$th ion. For an NaCl solution of concentration $c_0 = 500$mM, the estimated arrival time $\tau_{ar} \sim 2.9 \times 10^{-9}$s for Na$^+$ and $\tau_{ar} \sim 3.8 \times 10^{-9}$s for Cl$^-$.

To estimate the charge fluctuations from the simulations we have recorded continuously (during a few microseconds) the total positive and negative charge in the channel mouth within a volume $v_M = \pi r^2 \times r$, where $r = 6$ Å. The arrival time was estimated by recording the intervals between ion arrivals at the channel mouth. The results of the simulations are summarized in Fig. 2(left). It can be seen from the figure that the arrival time distribution follows an exponential distribution with mean arrival time $\tau_{ar} \sim 3.6 \times 10^{-9}$s for Na$^+$ and $\tau_{ar} \sim 4.7 \times 10^{-9}$s for Cl$^-$. This corresponds to a Poisson process as expected from the theory [4, 26] and have important implications for modeling channel conduction [27, 28]. We show that the presence of a second ion at the channel mouth significantly modulates the energy barrier that a first ion, initially trapped at the channel selectivity filter, has to overcome in order to cross the channel.

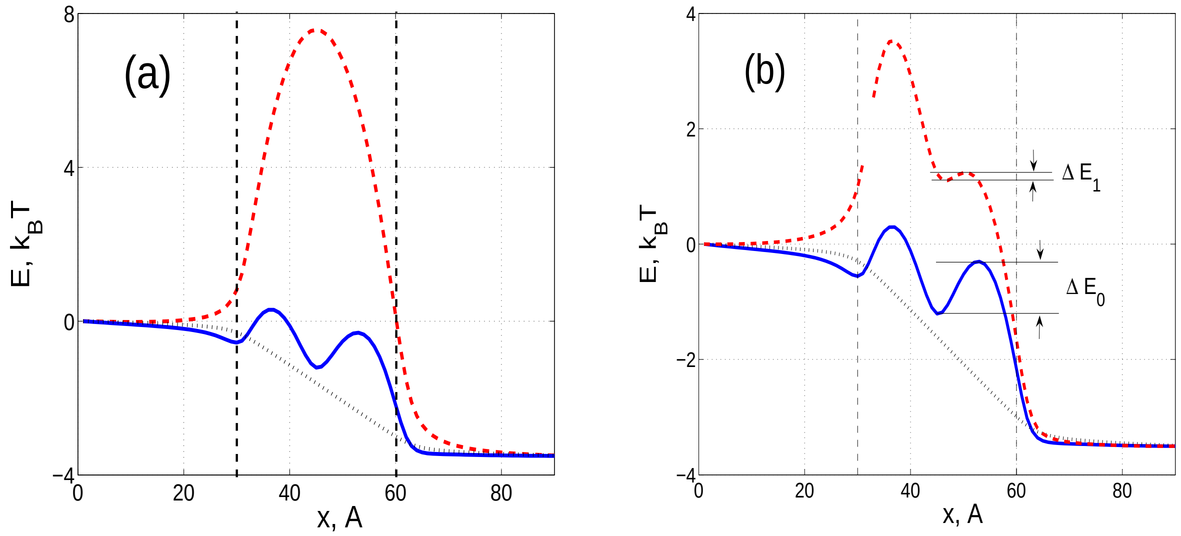

**Figure 3.** **(a)** The potential energy profiles in a cylindrical channel of radius $r = 4$ Å as a function of the ion position when an electric field of $10^7$ V/m is applied in the $x$ direction. The solid (blue) and dashed (red) lines correspond to the channels with and without fixed charges, respectively. The profile of a passive channel ($\epsilon_{\mathrm{protein}} = 80$) is indicated by the dotted (black) line. The channel is situated between 30 and 60 Å, as indicated by the vertical dashed lines. **(b)** The potential energy profiles as a function of the position of the ion when: the first ion is fixed at the channel mouth (dashed line) and the second is moving along the channel axis. The potential energy of the passive channel is shown by dotted line. The vertical dashed lines show the channel entrance and exit. The height of the potential energy barrier seen by a single ion at the selectivity site as it moves from left hand to right hand of the channel is denoted $\Delta E_0$. In the presence of a second ion at the channel's left mouth this barrier is reduced to $\Delta E_1$.

## 5. Amplification of the electrostatic interaction between two ions in the channel

We now consider the effect of the charge fluctuations on the transition probabilities of the ions through an open ionic channel. First, we analyze the energy profile faced by one ion moving through the channel.

The total electrostatic energy required to move one ion from the bulk solution into a bare channel that is 30 Å long and 4 Å in radius as a function of the position of the ion is calculated as shown in Fig. 3(a). The potential drop across the channel is $\Delta\Phi = 90$ mV, the charge at the selectivity site (in the middle of the channel) is $-1\,$e. Note that the value of the potential barrier for the ion at the selectivity site to exit the channel from left to right is $\Delta E_0$ as shown in Fig. 3(b). We now consider the reduction of this potential barrier induced by the second ion situated at the channel's left mouth ($x = 32\,$Å) while the first is moving along the channel axis. The choice of this location follows from our earlier demonstration of the charge fluctuations at the channel's left mouth as we are interested to the effect this will have on the energy of the first ion at the selectivity filter. The potential energy profile as a function of the position of the first ion moving along the channel when the second ion is located at the channel's left mouth is shown by the dashed line in Fig. 3(b). It can be seen that the presence of a second ion at the channel's left entrance decreases the potential energy barrier seen by an ion at the channel's selectivity filter to $\Delta E_1$. We note the reduction of the potential energy barrier from $\Delta E_0$ to $\Delta E_1$ is much stronger in the channel of low dielectric constant. I.e. the effect of charge fluctuation is strongly enhanced by the protein's low dielectric constant compared to water. In the absence of

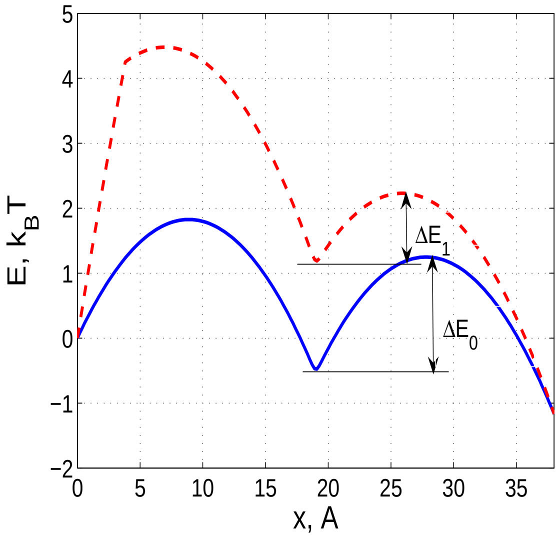

**Figure 4.** Total energy of the channel as a function of the position of the ion when there is an ion located at the channel mouth (dashed line) and when there is only one ion in the channel (solid line).

the protein walls, the interaction between the two ions will be purely due to the Coulomb forces and the corresponding reduction of the potential barrier $\Delta E_C = \frac{e^2}{4\pi\epsilon_2\epsilon_0 r_{12}}$ will be much smaller than the effect induced by the channel $\Delta E_0 - \Delta E_1$.

## 6. Analytic approximation of the effect of the amplification

A simple one-dimensional approximation of the Poisson equation for a channel with $r \ll d$ can be derived [29–31] and written in dimensionless form as:

$$\begin{aligned} \ddot{\Phi} - \beta\Phi &= -\beta\Delta(1-x) - \alpha P(x) - \alpha\delta(x-x_0) - \alpha\delta(x-x_1) \\ \Phi(0) &= 0, \quad \Phi(1) = \Delta \end{aligned} \tag{5}$$

where $\beta = \frac{d^2\tilde{\varepsilon}}{\varepsilon_0\varepsilon_{\mathrm{H_2O}}}$ is a function of the effective dielectric parameter $\tilde{\varepsilon} = \frac{\varepsilon_p}{\varepsilon_{\mathrm{H_2O}}}\frac{2\varepsilon_0}{r^2\ln(d/r)}$. The factor $\alpha = \kappa^2 d^2$ where $\kappa^{-1} = \sqrt{\frac{\varepsilon_0\varepsilon_{\mathrm{H_2O}} v_0 U_T}{e}}$ is the Debye length with $v_0 = \pi r^2 d$; the volume of the cylindrical channel. $U_T = k_B T$ is the thermal energy, where $k_B$ is Boltzmann's constant and $T$ the absolute (room) temperature. $P(x)$ is the permanent charge distribution on the protein atoms, independent of the electric field. The $\delta$ function represents two moving ions at different locations $x_0$ and $x_1$ on the channel axis. Because the Poisson equation is linear, the contributions from the four terms on the right hand side can be considered independently. Here we concentrate on the interaction between two ions in the channel in the presence of an external field corresponding to the applied voltage $\Delta$ in Eq. (5). The analytic solution can easily be obtained by transforming Eq. 5 to a boundary value problem with identical boundaries by linearly changing $\Phi$ [32], and is

$$\Phi(x) = \frac{\Delta}{\sinh\sqrt{\beta}}(\sinh\sqrt{\beta}x + \sinh\sqrt{\beta}(x-1)) - \Delta(x-1)$$
$$-\alpha\int_0^1 G(x,s)P(s)ds$$

$$-\frac{\alpha}{\sqrt{\beta}\sinh\sqrt{\beta}}\begin{cases}\sinh\sqrt{\beta}x\sinh\sqrt{\beta}(x_0-1)+\sinh\sqrt{\beta}x\sinh\sqrt{\beta}(x_1-1), & 0\le x\le x_1\\ \sinh\sqrt{\beta}x_0\sinh\sqrt{\beta}(x-1)+\sinh\sqrt{\beta}x\sinh\sqrt{\beta}(x_1-1), & x_1\le x\le x_0\\ \sinh\sqrt{\beta}x_0\sinh\sqrt{\beta}(x-1)+\sinh\sqrt{\beta}x_1\sinh\sqrt{\beta}(x-1), & x_0\le x\le 1\end{cases} \tag{6}$$

where the Green function is given by:

$$G(x,s) \;=\; \frac{1}{\sqrt{\beta}\sinh\sqrt{\beta}}\begin{cases}\sinh\sqrt{\beta}x\sinh\sqrt{\beta}(s-1), & 0\le x\le s\\ \sinh\sqrt{\beta}s\sinh\sqrt{\beta}(x-1), & s\le x\le 1.\end{cases} \tag{7}$$

The distribution of the permanent charge is modelled using a narrow Gaussian distribution with mean $\mu = 0.5$ (corresponding to the middle of the channel)and variance $\sigma = 0.005$, consistent with the fact that the charge is mainly concentrated in the central part of the channel:

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

Using this approximation, the current–voltage characteristics of the channel can be calculated [32] and compared to experimental result and to full 3D simulation of the Poisson-Nernst-Planck equations [33].

Fig. 4 shows the analytic approximation of the potential energy of the ion as it is moved along the channel axis. The full solid line is obtained when there is only one ion (with coordinate $x_0$) moving along the channel axis. The dashed line is obtained when one ion is fixed (at $x_1$) near the mouth of the channel and the second ion ( $x_0$) is allowed to move along the channel axis. When there is an additional ion located at the channel mouth, there is a reduction in the depth of the potential well as obtained in previous numerical simulation. Note that this approximation refers only to an ion inside the channel; it does not take into account the variation of the potential as the ion approaches the channel mouth from the bulk solution.

## 7. Conclusion

We have shown that energy fluctuations due to the correlated motion of ions in strong electrolytes can be substantially enhanced in open ionic channels of low dielectric constant. Ion channels can therefore be perceived as electrostatic amplifiers of the charge fluctuations. This may in turn lead to an exponentially strong modulation of the potential barrier for the ion at the selectivity site. The resulting enhancement of the transition probabilities of ions through the open channels may be the leading order contribution to transition probabilities calculated using standard theories that neglect the effect of charge fluctuations. Electrostatic amplification of charge fluctuations seems likely to play a substantial role in nanoscale protein dynamics including, in particular, protein folding.

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