Conductance of ion channels and nanopores with charged walls: a toy model

J. Zhang, A. Kamenev, B. I. Shklovskii
Department of Physics, University of Minnesota, Minneapolis, MN 55455, USA
(Dated: February 2, 2008)

We consider ion transport through protein ion channels in lipid membranes and water–filled nanopores in silicon films. It is known that, due to the large ratio of dielectric constants of water and the surrounding material, an ion placed inside the channel faces a large electrostatic self–energy barrier. The barrier leads to an exponentially large resistance of the channel. We study reduction of the electrostatic barrier by immobile charges located on the internal walls of the channel. We show that the barrier practically vanishes already at relatively small concentration of wall charges.

Protein ion channels functioning in biological lipid membranes is a major frontier of biophysics\(^1\). An ion channel can be inserted in an artificial membrane in vitro and studied by physical methods. Similar artificial devices – water–filled nanopores, are studied in silicon, silicon oxide films and polymer membranes\(^2\). In both cases, one can study a single water filled channel connecting two reservoirs with salty water (Fig. 1). A static voltage applied between these reservoirs drops almost entirely in the channel due to the high conductivity of the bulk solution. The voltage drives salt cations and anions through the channel. One can measure the ohmic resistance of the channel.

This resistance may be exponentially large due to the fact that the dielectric constant of water \(\kappa_1 \approx 80\) greatly exceeds that of the surrounding media \(\kappa_2\) (\(\kappa_2 \approx 2\) for lipids and \(\kappa_2 \approx 4\) for silicon oxide). Indeed, in this case the electric field of an ion traversing the channel is forced to stay inside the channel (Fig. 1). This creates a barrier \(U(x)\), where \(x \in [-L/2, L/2]\) is the ion coordinate inside the channel. The barrier is the difference between the self–energy of the ion at the point \(x\) inside the channel and the self–energy in the bulk. It is the maximum of the barrier, \(U(0) = U_L\), that determines the resistance of the channel. If a channel is very long the electric lines leak through the protein walls and lipids so that the barrier saturates as a function of \(L\). Roughly speaking this happens\(^3\) at \(L \sim a(\kappa_1/\kappa_2)^{1/2}\), where \(a\) is the channel radius. In this paper we assume that the channel is shorter, so that we can neglect the field leakage. In this case, calculation of the barrier height is very simple\(^4,5\). The electric field at a distance \(x > a\) from a cation located in the middle of the short channel is uniform and according to the Gauss theorem is \(E_0 = 2e/\kappa_1 a^2\).

The energy of such field in the volume of the channel is

\[
U_L(0) = \frac{\kappa_1 E_0^2 \pi a^2 L}{8\pi} = \frac{e^2 L}{2\kappa_1 a^2} = \frac{e E_0 L}{4},
\]

where the zero argument is added to indicate that there are no other charges in the channel. \(U_L(0)\) is proportional to \(L\) and (for a narrow channel) can be much larger than \(k_B T\), making the channel resistance exponentially large.

At large concentration of salt in surrounding water the electrostatic barrier is reduced by screening\(^6\). In biological channels the nature uses more effective approach. Channels designed for the transport of cations (K, Na, Ca) have negative charges on internal walls. For example, the potassium channel has 8 amino-acids with negatively charged radicals build into the wall of the protein\(^7\). Walls of artificial nanopores, generally speaking, are charged as well and one can control these charges by a chemical treatment and/or tuning pH of the solution.

The goal of this paper is to study the effect of immobile wall charges on the electrostatic barrier and the channel resistance. For certainty we assume that wall charges are negative and equally spaced along the channel with the linear density \(n_w\).

We show below that in a large range of salt concentrations, \(c\), the wall charges attract equal number of cations from the solution in order to make the channel neutral. Our theory is based on the observation that the Coulomb interaction of all charges in the short channel obeys the one dimensional Coulomb law: \(\Phi(x) \sim |x|\), same as for parallel uniformly charged planes. Indeed, let us consider a negative charge fixed at the wall and a cation, which arrived to the channel in order to screen it (Fig. 2). The uniform electric field between them creates the confining “string” potential \(\Phi(x) = eE_0|x|\). This situation reminds two quarks confined in a meson. Condition \(\Phi(x) = k_B T\) defines the characteristic thermal length of such classical ”atom”, \(x_T = k_B T/eE_0 = a^2/l_B\), where \(l_B \equiv e^2/(\kappa_1 k_B T)\) is the Bjerrum length (for water at the room temperature \(l_B = 0.7\ nm\)). This ”atom” is similar to an acceptor in a semiconductor (the classical length

---

FIG. 1: Electric field of a cation in a short cylindrical channel with the large dielectric constant \(\kappa_1 \gg \kappa_2\). \(L\) is the channel length, \(a\) is its radius. The self–energy barrier is shown as a function of the coordinate \(x\).
It is clear that at a small dimensionless concentration of wall charges $\gamma \equiv n_w x_T \ll 1$, each of them binds only one cation (Fig. 3). Resulting neutral atoms do not interact or overlap with each other. This system reminds a lightly doped $p$-type semiconductor at very low temperatures when all holes are located at their acceptors. Let us show that already for relatively small $\gamma < 1$ the electrostatic barrier $U_L$ may be substantially reduced.

The equilibrium partition function of the channel is $Z = (2\pi a^2 x_T/\nu)^{n_w L}$, where $\nu$ is the normalization cell volume. This gives for free energy in the ground state $F_g = -4 U_L(0) \gamma \ln (2\pi a^2 x_T/\nu)$. To evaluate the transport barrier one needs to know the free energy conditioned to the situation where an extra cation is placed in the middle of the channel, $F_s$. It creates the electric field $E_0$ which orients the dipole moments of all "atoms" along its direction. In other words, it orders all charges in an alternating sequence of positive and negative ones. Due to the 1d nature of the problem, this field unbinds each cation from its wall host and makes it free to move between nearest neighbor wall charges (Fig. 3). Indeed, according to the Gauss theorem the wall charge closest to the extra cation changes electric field from $E_0$ to $-E_0$, then its cation changes it back to $E_0$ and so on. Thus, at any position of cations between their nearest neighbor wall charges, the electric field is $E = \pm E_0$ i. e. $|E|$ is constant throughout the channel. Therefore, the total electrostatic energy is again given by Eq. 1. One could think that the transport barrier is still given by $U_L(0)$. This is incorrect, because the barrier is actually determined by the difference of the free energies $F_s - F_g$ of the collective transport saddle point and the ground state. This difference is reduced by a large entropy $S$ of the saddle point configurations.

To simplify the calculations let us imagine that the wall charges form a periodic one-dimensional lattice along the $x$-axis. Then $F_s = U_L(0) - TS$, where the entropy of the channel, enhanced by the charge unbinding, is $S = n_w L \ln (\pi a^2/2n_w \nu)$. This gives for $\gamma \ll 1$:

$$U_L(\gamma) = F_s - F_g = U_L(0) \left[1 - 4\gamma \ln (1/2\gamma)\right]. \tag{2}$$

In the opposite limit, $\gamma > 1$, one may expect that atoms overlap and destroy each other making cations free. In other words, one could expect an insulator–to–metal (or deconfinement) transition at some critical $\gamma \sim 1$. This does not happen, however. We show below that, due to the peculiar nature of the 1d Coulomb potential, the barrier proportional to the system’s length persists to any concentration of the wall charges, no matter how large it is. Its magnitude, though, decreases exponentially at $\gamma \gg 1$,

$$U_L(\gamma)/U_L(0) \propto \exp(-11.03 \sqrt{\gamma}). \tag{3}$$

Using numerical procedure outlined in the end of the paper we calculated the ratio $f(\gamma) \equiv U_L(\gamma)/U_L(0)$ at any $\gamma$ and plotted it along with the asymptotic Eq. (2) in Fig. 4. Let us discuss the range of the salt concentration in the bulk solution $c$, where the above results are valid.

A convenient dimensionless variable for $c$ is $\alpha \equiv \pi a^2 x_T$. Eq. (2) is valid only when $\gamma \gg \alpha$, when due to neutrality the total number of cations in the channel is close to $n_w L$. In the opposite case, $\alpha > \gamma$, additional cations together with equal number of anions enter the channel. In order to minimize the energy all positive and negative charges should alternate along the length of the channel or in other words they have to be ordered. This means that each segment of the channel between two nearest neighbor wall charges gets an integer number $k$ of additional cation-anion pairs.

Let us now calculate the linear in $L$ transport barrier $U_L(\alpha, \gamma)$ at arbitrary $\alpha, \gamma \ll 1$. At the transport saddle point, when an extra cation resides in the center of channel and creates the field $E_0$ in both directions, all mobile
charges become free to move while keeping alternating in charge order. The energy of all such states is again equal to $U_L(0)$, because $|E| = E_0$ everywhere. This barrier is reduced by a significant entropy term. To evaluate it let us first consider entropy of a segment between two wall charges. If $k$ cation-anion pairs reside in the segment, the total number of free ions there is $2k + 1$. The total entropy of these $2k + 1$ ions is

$$k_B \ln[(\pi a^2/n_w v)^{2k+1}/(2k+1)!].$$

The factor $1/(2k+1)!$ reflects the fact that when cations and anions are ordered it is impossible to obtain a new configuration by exchanging them. Moving $2k$ ions from the bulk leads to the entropy loss $2k k_B \ln(1/e^w)$ there. Subtracting this entropy from Eq. 4 and taking sum over all $k$ from 0 to $\infty$ we obtain the total entropy of the saddle point configuration and the renormalized barrier

$$U_L(\alpha, \gamma) = U_L(0) \left[ 1 - 4\gamma \ln \left( \frac{1}{2\alpha} \sin \frac{\alpha}{\gamma} \right) \right].$$

In the case $\alpha \ll \gamma$ Eq. 5 matches Eq. 2. In the opposite case $\alpha \gg \gamma$ Eq. 5 crosses over to the result $U_L(\alpha) = U_L(0)(1 - 4\alpha)$ obtained previously for an uncharged channel.

So far we presented results for a periodic lattice of wall charges. To understand the role of random distribution of wall charges along the $x$-axis let us return to the case $\alpha \ll \gamma \ll 1$. It is easy to show that averaging over random nearest neighbor distances substitutes Eq. 3 by $U_L(\gamma) = U_L(0)[1 - 4\gamma \ln(e^{-C}/2\gamma)]$, where $C = 0.577$ is the Euler constant. Thus, the result for randomly distributed wall charges is similar to those for the periodic one.

Until now we concentrated on the barrier proportional to the channel length $L$. If $\alpha \ll \gamma$ there is an additional, independent on $L$, contribution to the transport barrier. It is related to a large difference of concentrations of cation inside and outside the channel. Corresponding contact (Donnan) potential $U_D$ is created by double layers at each end consisting of one or more negative wall charges and screening (positive) charge in water.

For $\gamma \ll 1$ one finds $|U_D| \ll U_L(\gamma)$ and the channel resistance remains exponentially large. When $\gamma$ grows the barrier $U_L(\gamma)$ decreases and becomes smaller than $U_D = -k_B T \ln(\gamma/\alpha)$, which increases with $\gamma$ and makes the channel strongly cation selective. In this case the measured resistance may be even smaller than the naive geometrical diffusion resistance of the channel.

Let us, for example, consider a channel with $L = 5$ nm, $a = 0.7$ nm, $T = 0.35$ nm at $c = 0.1$ M and $n_w = 1$ nm$^{-1}$ (5 wall charges in the channel), which corresponds to $\alpha = 0.035$ and $\gamma = 0.35$. The bare barrier $U_L(0) = 3.5 k_B T$ is reduced down to $U_L(\gamma) = 0.2 k_B T$. At the same time $U_D = -2.5 k_B T$. Thus due to 5 wall charges, instead of the bare parabolic barrier of Fig. 1 we arrived at the wide well with the almost flat bottom (Fig. 3).

The contact potential $U_D$ may be augmented by the negative surface charge of the lipid membrane or by affinity of internal walls to a selected ion, due to ion-specific short range interactions. It seems that biological channels have evolved to compensate large electrostatic barrier by combined effect of $U_D$ and short range potentials. Our theory is helpful if one wants to study different components of the barrier or modify a channel. In narrow artificial nanopores there is no reason for compensation of electrostatic barrier. In this case, our theory may be verified by titration of wall charges. Nanopores can also be longer than $\alpha(\kappa_1/\kappa_2)^{1/2}$ so that electric field lines leakage through the walls becomes substantial. This leads to flatterting of the parabolic barrier, but its dependencies on $\alpha$ and $\gamma$ remain qualitatively the same.

Let us elaborate now on the technical aspects of the derivations. As was first realized in Ref. 2, the partition function of the 1d mobile Coulomb plasma may be written as a trace of an (imaginary time) “evolution” operator, $Z(q) = \text{Tr} \exp\{-\bar{H}(q)L/2T\}$ with the Mathieu Hamiltonian $H(q) = (i \partial_\theta - q)^2 - 2\alpha \cos \theta$. The variable $q$ has a meaning of a not-necessarily-integer screening charge induced at the channel opening. The ground state of the channel corresponds to $q = 0$, while the collective saddle point, having an uncompensated cation in the middle of the channel, to $q = 1/2$. The transport barrier is given by the difference between the two free energies: $F_q(1/2) - F_q(0)$. As a result, the transport barrier of an uncharged channel is proportional to the width of the lowest Mathieu–Bloch band. It is a rapidly decreasing function of the mobile salt concentration $\alpha$.

The immobile charges are represented by the charge “creation” operators $\hat{e}^{\pm \theta}$, where the sign is given by the sign of the static unit charge. For example, the partition function of the channel with the negative charges fixed at the positions $x_1, x_2, \ldots$ is given by $Z(q) = \text{Tr} \left\{ e^{-\bar{H}(x_1 + L/2)/2T} e^{-i\theta} e^{-\bar{H}(x_2 - x_1)/2T} e^{-i\theta} \ldots \right\}$. In the simplest case of periodically placed charges with the dimensionless concentration $\gamma$ one faces the spectral problem for the non–hermitian operator $\hat{U}(q) = e^{-\bar{H}(q)/T} e^{-i\theta}$. The barrier may be expressed in terms of its largest eigenvalue $e^{-\lambda_0^{(0)}}$ as $U_L(\gamma) = k_B T(\lambda_1^{(0)} - \lambda_0^{(0)}) \gamma L/2T$, where $U_L(q) \Psi_n = e^{-\lambda_n^{(0)}} \Psi_n$. One may demonstrate that, despite of being non–hermitian, the operator $\hat{U}(q)$ possesses only real eigenvalues.

In the limit of small concentration, $\gamma \ll 1$, one may write the operator $\hat{U}$ in the eigenbasis of the Hamiltonian

![FIG. 5: The electrostatic potential for cations for the channel with 5 wall charges considered in the text.](image-url)
The corresponding equation for Eq. (2). Therefore, one arrives at Eq. (5), which in the limit \( \alpha \approx 0 \) at two almost degenerate eigenvalues at \( \tilde{\epsilon} \). As a result, one may employ a variant of the WKB approximation to find a spectrum of \( \tilde{\mathcal{U}} \). To this end one writes the eigenfunction as \( \Psi(\theta) = e^{i\sqrt{\gamma}(\theta)} \) and retains only the leading order in \( \gamma \). The corresponding equation for \( S(\theta) \) reads as:

\[
[S'(\theta)]^2 + i\theta - \lambda = \frac{\alpha}{\gamma} (e^{i\theta} + e^{-i\theta}).
\]  (6)

The two terms on its right hand side represent positive and negative mobile ions correspondingly. For large concentration of fixed negative charges, \( \gamma > 1 \), and moderate concentration of mobile salt, \( \alpha \ll \gamma \), one may consider only positive ions entering the channel and disregard the negative ones. This amounts omitting the \( e^{-i\theta} \) term on the r.h.s. of Eq. (6) (the fixed negative charge is encoded in the \( i\theta \) term on the l.h.s.). Then shifting the \( \theta \) variable in the complex plane: \( \theta \rightarrow \theta + i \ln(\gamma/\alpha) \) and defining \( \tilde{\lambda} \equiv \lambda - i \ln(\gamma/\alpha) \), one brings Eq. (6) into the parameter-less form: \( S'(\theta) = \sqrt{\tilde{\lambda} - i\theta} + e^{i\theta} \). The right hand side of this expression is an analog of the canonical momenta in the hermitian WKB scheme. In particular its zeros play the role of the classical turning points and determine the structure of the branch cuts on the complex \( \theta \)-plane. The integrals of the canonical momenta along such branch cuts determine both the spectrum and the band-width upon changing the boundary parameter \( q \).

In the strip of the complex \( \theta \)-plane bounded by \(|\Re \theta| < \pi \) there are two turning points at \( \theta = \pm \delta - i\delta^2/2 \), where \( \delta \ll 1 \) is defined as \( \tilde{\lambda} = -1 + \delta^2/2 \). The structure is then periodically replicated outside this strip. Choosing the branch cut to run between the two turning points and applying the Bohr–Sommerfeld quantization rule, one finds the spectrum: \( \tilde{\lambda}(n) = -1 + (n+1/2)\sqrt{2/\gamma} \). Since \( \tilde{\lambda} \to -1 \) in the limit \( \gamma > 1 \), the two turning points are essentially close to the origin. To find the band-width one needs the “tunnelling” probability between the adjacent strips of the \( \theta \)-plane. To this end one chooses the branch cuts, which emanates from the turning points outwards, approaching \( \theta = \pm \pi - i\infty \). The (exponentiated) integral of the canonical momenta along such a cut gives the WKB tunnelling probability and hence the band-width \( \lambda_{1/2} - \lambda_0 \). Such an integration leads to Eq. (3).

For numerical calculation it is convenient to choose the basis of the angular momentum, \( e^{i\theta} \), to evaluate \( Z(q) \). In this basis the charge creation operator \( e^{-i\theta} \) takes the matrix form \( [\delta_{m,m'}] \), while the Hamiltonian \( \tilde{H}_{m,m'} = [(m + q)^2\delta_{m,m'} - \alpha(m + q + 1) - \alpha(m + q - 1)] \). Truncating these infinite matrices with some large cut-off, one may directly exponentiate, multiply and trace them to find the free energy for any arrangement of fixed charges.

As emphasized by the title of this paper we study here only a very simple model of a channel with charged walls. This is the price for asymptotically exact Eqs. (3), (4), (5), which show that already relatively small concentration of wall charges dramatically reduces the self-energy transport barrier. This conclusion is in qualitative agreement with general statement on the role of transitional binding inside the channel on transit probability. Our results, of course, can not replace powerful numerical methods used for description of specific biological channels.

We are grateful to S. Bezrukov, A. I. Larkin and A. Parsegian for interesting discussions. A. K. is supported by the A.P. Sloan foundation and the NSF grant DMR–0405212. B. I. S is supported by NSF grant DMI–0210844.

---

1. B. Hille, Ion Channels of Excitable Membranes, Sinauer Associates, Sunderland, MA (2001).
2. D. A. Doyle et al., Science, 280, 69 (1998); R. MacKinnon, Nobel Lecture. Angew Chem Int Ed Eng 43 4265 (2004).
3. J. Li, D. Stein, C. McMullan, D. Branton, M. J. Aziz, J. A. Golovchenko, Nature 412, 166 (2001); D. Stein, M. Kruithof, C. Dekker, Phys. Rev. Lett. 93, 035901 (2004); A. Aksimentiev, J. B. Heng, G. Timp, and K. Schulten, Biophys. J. 87, 2086 (2004); Z. Siwy, I. D. Kosinska, A. Fulinski, and C. R. Martin, Phys. Rev. Lett. 94, 048102 (2005).
4. A. Parsegian, Nature 221, 844 (1969); P. C. Jordan, Biophys J. 39, 157 (1982).
5. A. V. Finkelstein, D. N. Ivanov, and A. M. Dykhne, in preparation; S. Teber, cond-mat/0501962.
6. A. Kamenev, J. Zhang, A. I. Larkin, B. I. Shklovskii, accepted to Physica A (2005); cond-mat/0503027.
7. P. C. Jordan, R. J. Bacquet, J. A. McCammon and P. Tran, Biophys. J. 55, 1041 (1989).
8. H. J. Appel, E. Bamberg, H. Alpes, and P. Lauger, J. Membrane Biol. 31, 171 (1977).
9. S. F. Edwards and A. Lenard, J. Math. Phys. 3, 778 (1962).
10. A. M. Berezkhovskii, M. A. Pustovoit, S. M. Bezrukov, J. Chem. Phys. 116, 6216, 9952 (2002); 119, 39-43 (2003).
11. S. Kuyucak, O. S. Andersen, and S-H. Chung, Rep. Prog. Phys. 64, 1427 (2001); B. Nadler, U. Hofferbach, R. S. Eisenberg, Phys. Rev. E 68, 021905 (2003); B. Nadler, Z. Schuss, U. Hofferbach, R. S. Eisenberg, Phys. Rev. E 70, 051912 (2004); B. Roux, T. Allen, S. Berneche, W. Im, Quart. Rev. Biophys. 37, 15 (2004).