Effect of Local Binding on Stochastic Transport in Ion Channels

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Abstract—Ionic Coulomb blockade (ICB) is an electrostatic phenomenon recently discovered in low-capacitance ion channels/nanopores. Depending on the fixed charge that is present, ICB strongly and selectively influences the ease with which a given type of ion can permeate the pore. The phenomenon arises from the discreteness of the charge-carriers, the dielectric self-energy, an electrostatic exclusion principle, and sequential pore neutralization, and it manifests itself strongly for divalent ions (e.g. Ca2+). Ionic Coulomb blockade is closely analogous to electronic Coulomb blockade in quantum dots. In addition to the non-local 1D Coulomb interaction considered in the standard Coulomb blockade approach, we now propose a correction to account for the singular part of the attraction to the binding site (i.e. local site binding). We show that this correction leads to a geometry-dependent shift of one of the barrierless resonant conduction points MCB. We will also find that the geometry-dependent shift of the ICB calcium interaction considered in the standard ICB approach [2]. We show that this correction leads to a splitting of Ca2+ profiles observed earlier in Brownian dynamics simulations.

I. INTRODUCTION

Ion channels provide for the selective transport of physiologically important ions (e.g. Na+, K+ and Ca2+) through the bilipid membranes of biological cells. The channels consist of nanopores through proteins embedded in the membrane. Their selectivity for particular ions is determined by the electrostatically-driven stochastic motion of ions within a short, narrow selectivity filter (SF) carrying a binding site with fixed negative charge Qf.

The permeation of ions through the pore is governed by ionic Coulomb blockade (ICB), a phenomenon that manifests itself in low-capacitance systems. It arises as a consequence of the discreteness of the charge-carriers, the dielectric self-energy Uε, an electrostatic exclusion principle, and sequential pore neutralisation as additional ions enter the pore [1]–[3]. ICB manifests itself strongly for divalent ions (e.g. Ca2+) [2]. ICB is closely similar to its electronic counterpart in quantum dots [4].

The basic ICB description of the permeation and selectivity of ion channels has already been presented [3]. Here we extend this basic model by the introduction of corrections to allow for the singular part of the attraction of ions to the binding site (i.e. local site binding), in addition to the non-local 1D Coulomb interaction considered in the standard ICB approach [2]. We will find that the geometry-dependent shift of the ICB calcium resonant point MCB resulting from this correction leads to a changed threshold IC50 for divalent blockade. We will also show that the presence of local (singular) ion-ion repulsion is what leads to the splitting of the Ca2+ probability density seen earlier in Brownian dynamics simulations [5], [6].

In what follows we use dimensionless Gaussian units assuming the proton charge e = 1, 4πε0e = 1 and kBT = 1, where ε0 is the permittivity of free space, kB is Boltzmann’s constant and T is the temperature.

II. EXTENDED ELECTROSTATIC MODEL OF ION CHANNEL

Fig. [1](a) shows the extended electrostatic model of the SF of a calcium/sodium ion channel. We represent it as a negatively-charged, axisymmetric, water-filled, cylindrical pore of radius Rc = 0.3 – 0.5nm and length Lε = 1.2 – 1.6nm through the protein hub in the cellular membrane. The x-axis is coincident with the channel axis and x = 0 in the center of channel. There is a uniformly-charged, rigid ring of negative charge |Qf| = 0 – 8 of radius RQ. Ions move in single file along the channel axis. (b) Energetics of moving Ca2+ ion for fixed charge Qf = −1e (by Brownian dynamics simulations). The dielectric self-energy barrier UεSF (full blue line) is balanced by the site attraction UεQB (dashed green line) resulting in an almost barrier-less energy profile U0 (red solid line). See text for details.
with the channel axis and $x = 0$ in the center of channel. There is a symmetrically-placed, uniformly-charged, rigid ring of negative charge $Q_f$ so that $|Q_f| = 0 - 8$. Extending the earlier model, the radius of this charged ring $R_Q$ could be different from the channel radius $R_c$, corresponding to the charged residues moving partially into the channel. We take both the water and the protein to be homogeneous continua with dielectric constants $\varepsilon_w = 80$ and $\varepsilon_p = 2$, respectively.

Fig. 2(b) illustrates the phenomenon of resonant barrierless conduction, which is typical of electrostatic models and which occurs when the energy of ion-site attraction $U_{SE}$ balances the dielectric self-energy barrier $U_{qQ}^SE$.

This generic electrostatic channel model is similar to that used previously. Details of the model, and its validity and limitations, have already been discussed.

### III. IONIC COULOMB BLOCKADE

We consider the stochastic transport of a fully-hydrated ion of charge $q = e$ through the above model channel, focusing on the divalent case ($z = 2$).

Fig. 2(a) illustrates the multi-ion Ca$^{2+}$ conduction bands and (b) shows the corresponding Coulomb staircase in occupancy, as revealed by Brownian dynamics simulations. The ground state energy diagram for such conductance is plotted in (c). The ICB model states that resonant (barrier-less) ground state energy diagram for such conductance is plotted in (c). The ICB model [3] states that resonant (barrier-less) ground state energy diagram for such conductance is plotted in (c). The ICB model [3] states that resonant (barrier-less) ground state energy diagram for such conductance is plotted in (c). The ICB model [3] states that resonant (barrier-less) ground state energy diagram for such conductance is plotted in (c). The ICB model [3] states that resonant (barrier-less) ground state energy diagram for such conductance is plotted in (c). The ICB model [3] states that resonant (barrier-less) ground state energy diagram for such conductance is plotted in (c). The ICB model [3] states that resonant (barrier-less) ground state energy diagram for such conductance is plotted in (c).

The standard ICB model assumes that $U_n$ with $\{n\}$ similar ions near the centre is equal to the dielectric self-energy $U_{nSE}$ of the excess or total charge of the SF $Q_n$:

$$ Q_n = nq + Q_f; \quad U_n = U_{nSE} = \frac{Q_n^2}{2C_s} \quad (2) $$

$$ C_s = \frac{R_c^2}{\lambda q L_c}; \quad \lambda_R = \frac{q^2}{\varepsilon_w k_B T} \quad (3) $$

where $C_s$ is the SF self-capacity and $\lambda_R$ is the Bjerrum length (for water $\lambda_R = 0.7 \text{nm}$).

For simplicity, we consider the first resonant point $M_0$ corresponding to the movement of a single ion through an otherwise empty SF (the $s_0 \rightarrow s_1 \rightarrow s_0$ transition) so we temporarily ignore the ion-ion interaction term $U_{qq}$. Expanding the quadratic form in (3) gives us the following decomposition (for $n = 1$)

$$ U_1 = U_{qSE}^0 + U_{qQ} + U_{qQ}^CB \quad (4) $$

$$ U_{qQ}^SE = \frac{q^2}{2C_s}; \quad U_{qQ}^SE = \frac{Q_f^2}{2C_s}; \quad U_{qQ}^CB = \frac{qQ_f}{C_s}; \quad (5) $$

where $U_{qQ}^SE$ and $U_{qQ}^CB$ are respectively the ion and fixed charge self-energies, and $U_{qQ}^CB$ is the 1D Coulomb ion-site attraction energy.

The base position (without the entropy term) for resonant conduction is defined by the condition for barrierless motion $\Delta U_n = U_{n+1} - U_n = 0$

$$ U_{CB}^q = 0; \quad \Rightarrow M_0^CB = -q/2; \quad Z_1 = -q \quad (5) $$

where $Z_n$ corresponds to the $Q_n = 0$ SF neutralisation condition. Inclusion of the entropy term $T \Delta S$ leads to a concentration-related shift of the resonance point:

$$ M_0^{TS} = M_0^{CB} + \delta M_0^{TS}; \quad \delta M_0^{TS} = \log(n_b) \quad (6) $$

where $n_b$ is the number density of selected ions in the bulk, $n_0 = 1/V_{SF}$ is the reference density, and $V_{SF} = \pi R_c^2 L_c$ is the volume of the SF; note that $\delta M_0 = 0$ for $n_b = n_0$. The reference concentration $c_0$ for a typical SF geometry corresponds to $c_0 \approx 200 \text{mM}$. The dependence of the resonance point’s position on $V_{SF}$ coincides with both simulations and with earlier analytic results.

### IV. LOCAL BINDING

Next we introduce a local binding correction by adding the direct but $e$-screened Coulomb $q \leftrightarrow q_f$ interaction [15] with energy $U_{qq}^LB$ to the total energy balance. It leads to a geometry-dependent shift in the resonance point $M_0^{LB}$:

$$ U_1 = U_1^{CB} + \delta U_{qq}^LB; \quad U_{qq}^LB = U_{qq}^SE - \frac{Q_f^2}{\delta R_Q}; \quad (7) $$

$$ M_0^{LB} = \frac{M_0^{CB} \beta_Q}{\beta_Q + \beta_R} \quad (8) $$

where $R_Q$ is the radius of the charged ring at the binding site and we introduce two dimensionless geometrical factors: the “charge offset ratio” $\beta_Q = R_Q/R_c$ and the “SF shape ratio” $\beta_R = R_Q/R_c$.
Additional local binding correction can be calculated from Coulomb's law \([15]\):

\[
\delta U_{qf}^{LB} = \frac{q^2 q_f \lambda_B}{R_f^2}; \quad \delta U_{qf}^{LB} = \frac{q^2 \lambda_B}{2x_q}.
\]

V. LOCAL ION-ION REPULSION

In the above analyses we ignored ion-ion repulsion, but here we take it explicitly into account and work out its consequences. For simplicity we consider 2 similar ions located symmetrically \((-x_q, +x_q)\) around \(Q_f\) at \(x = 0\). In such a case, the 1D Coulomb ion-ion interaction \(U_{qf}^{LB}\) and the additional local Coulomb repulsion \(\delta U_{qf}^{LB}\) are respectively:

\[
U_{qf}^{LB} = \frac{q^2 4 \pi \lambda_B}{R_c^2}; \quad \delta U_{qf}^{LB} = \frac{q^2 \lambda_B}{2x_q}.
\]

The total energy of an ion inside the SF, allowing for both local binding and local repulsion, can be expressed as:

\[
U_{qf}^{SF} = U_{qf}^{LB} + \frac{1}{2} \left( \epsilon_{LB} + \delta U_{qf}^{LB} \right)
\]

Hence for the neutralization point \(Z_1\) \((Q_n = 2q + Q = 0)\), the profile is defined by local components only.

Fig. 3(a) shows that the energy function \(U_{qf}^{LB}(x)\) has two off-center minima \(x_{min}\) defining a splitting of the \(Ca^{2+}\) occupancy profile. Thus, by taking account of local binding and of the local ion-ion interaction in the SF, we arrive at an explicit, self-consistent, analytic explanation of the splitting of the multi-ion occupancy profiles observed earlier in Brownian dynamics simulations \([5, 6, 16]\), in self-consistent numerical solutions of the Poisson equation \([16]\), and in analytic calculations \([19]\), modelling non-self-consistent potentials. The splitting leads to significant increases in ionic energy and eventually to knock-on escape. Note that the “binding points” \((\pm x_{min})\) are unconnected with any physical binding sites different from the main \(Q_f\)-related site. This situation can be described as dynamic site binding and/or self-organisation of ions inside the SF (see also \([11, 21]\)).

Fig. 3(b) compares the \(Ca^{2+}\) occupancy profile \(\rho(x)\) returned by BD simulations (green histogram) with that estimated from the potential energy profile \(U(x)\) as \(\rho(x) = \exp(-U(x))\) (red solid line). The satisfactory agreement obtained can be regarded as confirming the consistency of our model.

Fig. 4 shows the evolution of the \(Ca^{2+}\) profile with varying \(Q_f\) as found from BD simulations \([16, 22]\). Fig. 4(a) shows the simulated calcium occupancy \(P\) of the SF vs \(Q_f\) for one bath concentration, demonstrating the standard Coulomb staircase shape. The single-ion \(Z_1 \approx 2e\) and double-ion \(Z_2 \approx 4e\) neutralisation points are indicated. In (b) there is an (unsplit) single-ion occupancy profile for the \(Z_1\) point, which appears due to ICB and local binding of the ion to \(Q_f\). In (c) the local repulsion provides for self-organisation of the ions and splitting of the occupancy profile for the double-ion \(Z_2\) point. Note that, for intermediate points (between \(Z_1\) and \(Z_2\)), the profiles will be mixed, having one to three peaks.
Fig. 4. Evolution of calcium profile vs. fixed charge $Q_f$ from Brownian dynamics simulations. (a) Simulated calcium occupancy $P$ of the selectivity filter vs $Q_f$ (red solid line) for bath concentration $[\mathrm{Ca}]=80\,\text{mM}$. Single-ion $Z_1$ and double-ion $Z_2$ neutralization points are labelled. (b) Single-ion (unsplit) occupancy profile for $Z_1$ point. (c) Double-ion (split) occupancy profile for $Z_2$ point.

VI. CONCLUSIONS

The analytic result (10) is found to agree with Brownian dynamics simulations, thus putatively accounting for how the position of the resonant point $M_{\text{CB}}$ is influenced by the radius of the Glutamate/Aspartate ring in NaChBac channels and their mutants [18], [23], [24]. The splitting of the $\text{Ca}^{2+}$ profile is found in reasonable quantitative agreement with the results of BD simulations [6]. The local binding/repulsion leads to corrections of about $20\,k_BT$ and to an observable splitting of the $\text{Ca}^{2+}$ occupancy profiles. These results are also applicable to artificial sub-nm pores [25].

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