

Coulomb Blockade of Stochastic Permeation in Biological Ion Channels

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I. INTRODUCTION

Although the passage of ions through ion channels¹ in the bilipid membranes of biological cells clearly involves thermally-driven Brownian diffusion in an electrostatic field, there remain many unsolved problems of long standing. The central conundrum is that a channel's powerful selectivity – whereby it may allow a particular ion species to pass while barring others by a factor of up to 1000:1 – is combined with a speed of passage comparable to the rate of free diffusion, i.e. as though the channel were just an open hole.

Other unsolved problems include: (i) the role played by the fixed charge Q_f known to exist inside the channel at its selectivity filter; (ii) why mutations that change Q_f can alter the selectivity (e.g. convert a Na^+ to a Ca^{2+} channel) or eliminate conduction altogether; (iii) the anomalous mole fraction effect (AMFE), whereby Na^+ ions can pass easily through a Ca^{2+} channel in a pure NaCl electrolyte, but are blocked by tiny traces of Ca^{2+} in the bath. Brownian dynamics simulations of a very simple model of the permeation process reveal² that the current and selectivity exhibit the unexpected pattern of conduction bands and stop bands as a function of Q_f shown in Fig. 1(a).

We now propose that the conduction bands and, quite generally, the permeation and selectivity of biological ion channels may be governed by ionic Coulomb blockade³, an electrostatic phenomenon closely analogous to its electronic counterpart in quantum dots^{4,5}, but with stochastic dynamics rather than quantum tunnelling as the underlying mechanism, and we show that several hitherto unsolved problems of ion channel conduction can apparently be explained on this basis. We will refer to Ca^{2+} ion channels, but the underlying ideas can have wider applicability.

II. MODEL TO BE ANALYSED

We analyse the properties of a self-consistent electrostatic model² of the selectivity filter of a generic calcium channel considered as a negatively-charged, axisymmetric, water-filled, cylindrical pore through a protein hub in the cellular membrane. The pore is taken to be of radius $R = 0.3$ nm, length $L = 1.6$ nm, and the x -axis coincides with the channel axis, with $x = 0$ at the center of the channel. A centrally-placed ring of fixed negative charge $0 \leq |Q_f| \leq 7e$ is embedded in the wall at $R_Q = R$. A potential difference of $0 - 75$ mV is applied between the

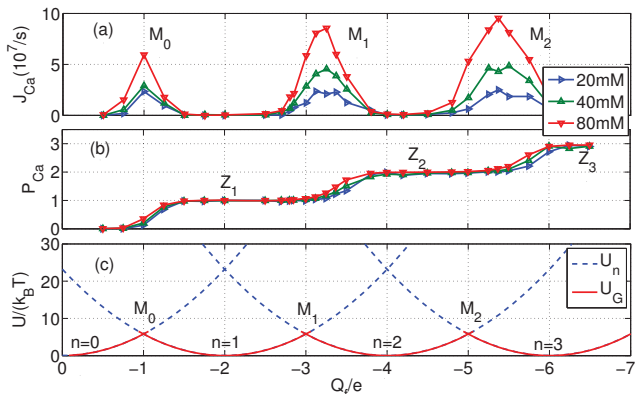


FIG. 1. Brownian dynamics simulations of multi-ion Ca^{2+} conduction and occupancy in the $\text{Ca}^{2+}/\text{Na}^+$ channel model *vs.* the effective fixed charge Q_f ; (a),(b) are reworked from². (a) Plots of the Ca^{2+} current J_{Ca} for pure Ca^{2+} baths of concentration 20, 40 and 80mM. (b) The occupancy P_{Ca} . (c) Plots of electrostatic energy U_n (blue, dashed) and resulting oscillations of ground state energy (red, solid) *vs.* Q_f for channels with $n = 0, 1, 2, \dots$ Ca^{2+} ions inside. The conduction bands M_0, M_1, M_2 stop bands Z_1, Z_2, Z_3 (indicated by labels) are discussed in the text.

left and right channel boundaries to represent the membrane potential. The mobile Ca^{2+} ions are described as charged spheres of radius $R_i \approx 0.1$ nm, with a diffusion coefficient⁶ of $D_{\text{Ca}} = 0.79 \times 10^{-9}$ m²/s. We assume an asymmetrical ionic concentration: $C_L > 0$ on the left, and $C_R = 0$ on the right and take both the water and the protein to be homogeneous continua describable by relative permittivities $\varepsilon_w = 80$ and $\varepsilon_p = 2$, respectively, together with an implicit model of ion hydration the validity of which is discussed elsewhere. The Brownian dynamics simulations (Fig. 1) involved the self-consistent numerical solution of Poisson's equation for this model, coupled with a Langevin equation for the moving ions.

III. IONIC COULOMB BLOCKADE

The alternating conduction and stop bands as Q_f is increased (Fig. 1(a)) can be considered as oscillations. We propose that both they and the occupancy steps (Fig. 1(b)) are attributable to ionic Coulomb blockade³, an electrostatic phenomenon closely similar to electronic Coulomb blockade in quantum dots⁵.

The discreteness of the charge allows us to introduce

exclusive “eigenstates” $\{n\}$ of the channel for fixed integer numbers of ions inside its selectivity filter, with total electrostatic energy U_n . The transition $\{n\} \rightarrow \{n+1\}$ corresponds to entry of a new ion, whereas $\{n\} \rightarrow \{n-1\}$ corresponds to escape of a trapped ion. The n eigenstates form a discrete exclusive set of $\{n\}$ -states:

$$n = \{0, 1, 2, \dots\} \quad \sum_n \theta_n = 1; \quad P_c = \sum_n n\theta_n, \quad (1)$$

where θ_n is the occupancy of the state $\{n\}$ and P_c is the average selectivity filter occupancy. In equilibrium an *electrostatic exclusion principle* (1) leads to Fermi-Dirac statistics for θ_n (and P_c):

$$\theta_n = \left(1 + \exp\left(\frac{U_n - \mu}{k_B T}\right) \right)^{-1}, \quad (2)$$

where μ is the chemical potential. The total energy U_n for a channel in state $\{n\}$ is $U_n = U_{n,s} + U_{n,a} + U_{n,int}$, where $U_{n,s}$ is the self-energy, $U_{n,a}$ is the energy of attraction, and $U_{n,int}$ is the ions’ mutual interaction energy. We approximate U_n as the dielectric self-energy $U_{n,s}$ of the excess charge Q_n , assuming that both the ions and Q_f are within the central part of the selectivity filter, leading to a quadratic dependence of U_n on Q_f ,

$$U_n = \frac{Q_n^2}{2C_s} \quad (\text{Electrostatic energy}) \quad (3)$$

Here, C_s is the geometry-dependent channel self-capacitance and $Q_n = zen + Q_f$ is the excess charge.

With (3) we arrive at the electronic Coulomb blockade equation and our further consideration follows standard Coulomb blockade theory⁴. Remarkably, however, the ionic version of phenomenon exhibits valence selectivity.

Strong Coulomb blockade oscillations appear in low-capacitance systems on account of quantization of the quadratic energy in (3) on a grid of discrete states (1), provided that the ground state $\{n_G\}$ is separated from its neighbouring $\{n_G \pm 1\}$ states by large Coulomb energy

gaps $\Delta U = z^2 e^2 / (2C_s) \gg k_B T$. This is the applicability condition for the strong electrostatic exclusion principle.

Fig. 1(c) shows the ground state energy $U_G(Q_f) = \min_n(U_n(Q_f, n))$, as functions of Q_f . It follows from (3) that U_n vs. Q_f for given z is described by an equidistant set of identical parabolæ of period equal to the ionic charge ze , providing oscillations in U_G . We note that $U_G(Q_f)$ exhibits two different kinds of ground state singular points, marked as M_n and Z_n . The positions of these singular Q_f points can be written as:

$$Z_n = -zen \quad (\text{Coulomb blockade}) \quad (4)$$

$$M_n = -ze(n + 1/2) \quad (\text{Resonant conduction}) \quad (5)$$

We propose that the stop bands in Fig. 1(a) correspond to neutralisation points Z_n where the total charge at the selectivity filter $Q_n = 0$, while the conduction bands correspond to crossover points M_n allowing barrier-less conduction between different n -states. The occupancy plots in Fig. 1(b) can therefore be interpreted as a Coulomb staircase.

IV. CONCLUSIONS

Our identifications of the Brownian dynamics-simulated conduction bands (Fig. 1(a)) that appear with increasing $|Q_f|$ as Coulomb blockade conductance oscillations⁴, and of the corresponding occupancy steps (Fig. 1(b)) as a Coulomb staircase⁵, represent a fresh vision of conduction in biological ion channels. It offers immediate explanations of the fast conduction and mutation shifts and, because the pattern is valence-dependent, it can also account for valence selectivity and AMFE.

We point out that the Coulomb blockade model should also be applicable to other ion channels as well as to artificial nanopores.

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