Coulomb Blockade Model of Permeation in Biological Ion Channels

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Introduction: Voltage Gated Calcium Channels

- The ionic permeation of a biological ion channel is a multi-particle, non-equilibrium, stochastic process governed by electrostatic forces.
- Voltage-gated calcium and sodium ion channels play an essential role in controlling muscle contraction, in neurotransmitter secretion and the transmission of action potentials.
- The selectivity of calcium and sodium channels is defined by a narrow selectivity filter with a strong binding site formed by protein residues with a different net negative charge Q_f.
- Sodium and calcium channels have very similar structures but with different selectivity filter loci and Q_f.
- Calcium channel has 4-glutamate EEEE locus (Q_f =4e), while the mammalian sodium channel has a mixed DEKA locus (Q_f =1e)
- Mutant's studies show that the value of Q_f is a crucial factor in determining the Ca^{2+} vs Na^+ valence selectivity.
- Usually, mutations that influence Q_f also destroy channel's selectivity, and hence physiological functionality, leading to "channelopathies".
- An appropriate point mutation of the DEKA sodium channel converts it into a calcium-selective channel with a DEEA locus and *vice versa*.
- The results of mutant's studies aren't properly explained so far.
- **Here we show that the conduction and selectivity of calcium/sodium ion channels can be described in terms of ionic Coulomb blockade, electrostatically and mathematically similar to its electronic counterpart in quantum dots.**

Generic Electrostatic Model of Calcium Channel

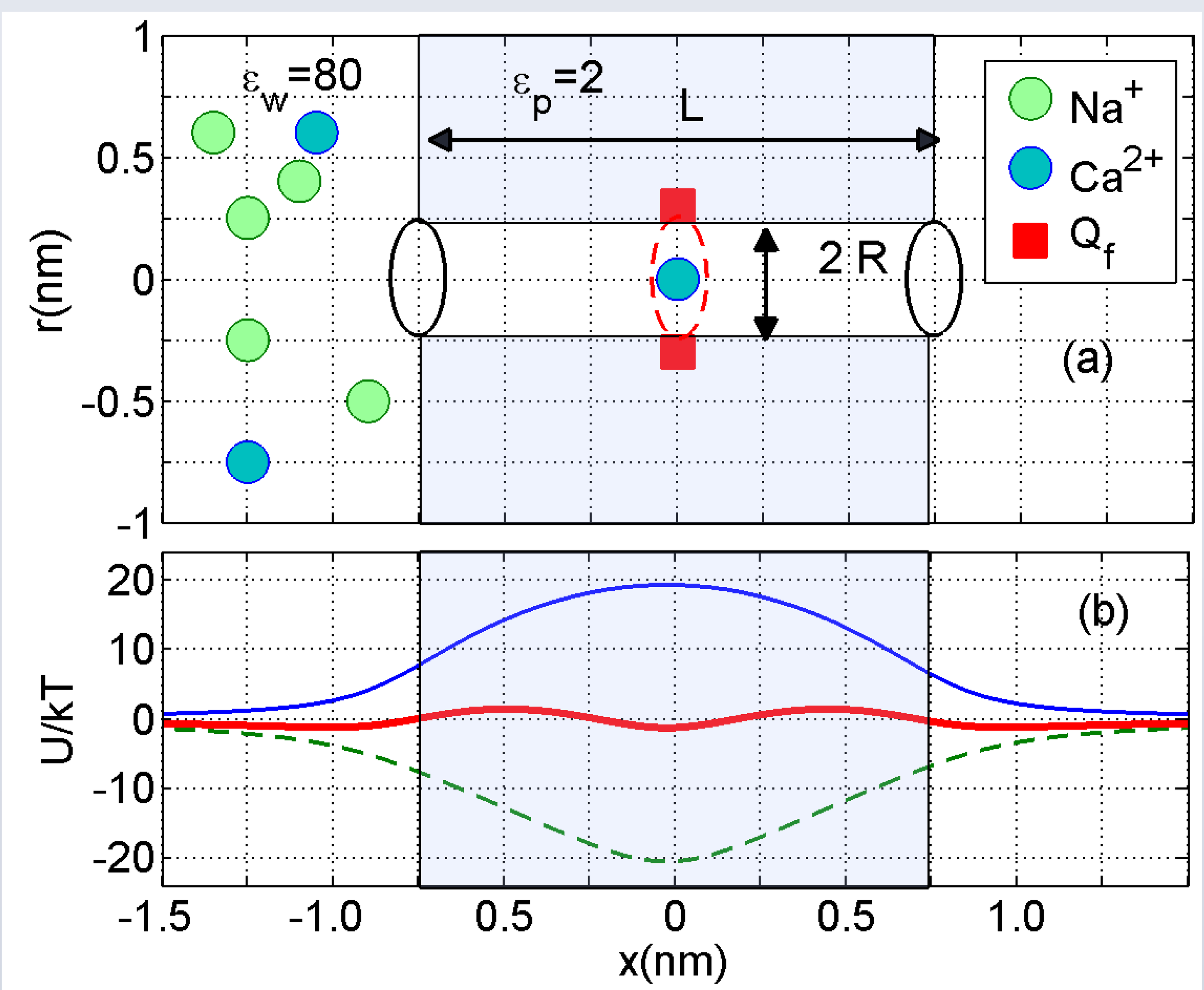


Fig 1. (a) Generic electrostatic model of a Ca^{2+} or Na^+ channel. The channel's selectivity filter is treated as an axisymmetric, water-filled, cylindrical pore of radius R=0.3nm ~and length L=1.6nm ~through the protein hub in the cellular membrane. A centrally-placed, uniform, rigid ring of negative charge Q_f in the range $0 < |Q_f| < 7e$ is embedded in the wall at R_Q=R. Ions inside the channel move in single file along its axis. (b) Energetics of a moving Ca^{2+} ion for fixed charge Q_f =-1e (Point M_0 at Fig.2). The dielectric self-energy barrier U_s (blue solid line) is balanced by site attraction (green dashed line) resulting in an almost barrier-less energy profile (red solid line).

Multi-Ion Calcium Conduction Bands

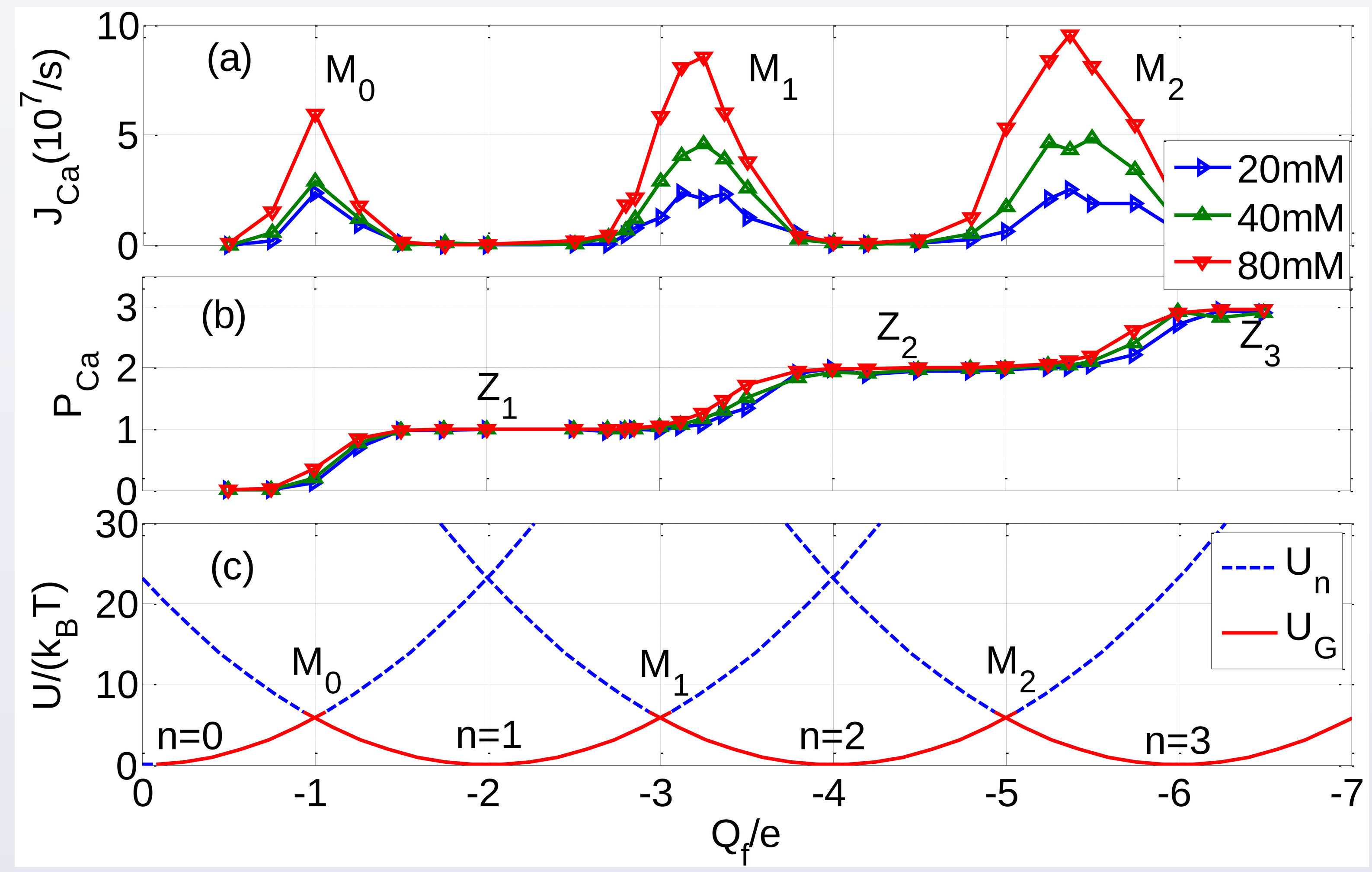


Fig.2. Brownian dynamics simulations of multi-ion Ca^{2+} conduction and occupancy in the Ca^{2+}/Na^+ channel model vs the effective fixed charge Q_f (a) Plots of the J_{Ca} for pure Ca^{2+} baths of concentration 20, 40 and 80mM. (b) The occupancy P_{Ca}.

(c) Plots of electrostatic energy Un(blue, dashed) and resulting oscillations of ground state energy U_G (red, solid) vs Q_f for channels with n=0,1,2 and 3 Ca^{2+} ions inside.

The conduction bands M_0, M_1, M_2 and stop bands Z_1, Z_2, Z_3 (indicated by labels) are discussed in the text.

Coulomb blockade Oscillations of Conductance

To interpret the conduction bands in terms of Coulomb blockade, we investigate dependence of ground state electrostatic energy $U_G(n)=\min(U_n)$ as a function of Q_f for n=0,1,2,3 and its singular points. Coulomb blockade-like quadratic dependence of Un on Q_f is:

$$U_n = (Q_n)^2/2C_s, \qquad \text{(Electrostatic energy)}$$

where C_s stands for the geometry-dependent electric self-capacitance of the channel and $Q_n=(zne + Q_f)$ represents the excess charge at the selectivity filter for the n ions of valence z as a function of Q_f.

The positions of the singular Q_f points Z_n and M_n can be written as:

$$Z_n = -\, z\, e\, n, \qquad \text{(Coulomb blockade)}$$

$$M_n = -\, z\, e\, (n+1/2), \qquad \text{(Resonant conduction)}$$

We interpret the conduction bands at Fig.2(a) as Ionic Coulomb blockade conductance oscillations, and the corresponding occupancy steps at Fig.2(b) as a Coulomb staircase.

Hence we establish a novel Coulomb blockade model of permeation and selectivity of ion channels.

Ionic Coulomb blockade in ion channels is electrostatically and mathematically similar to electronic Coulomb blockade in quantum dots.

The positions of the M_n and Z_n points in the theory and BD simulations [2] at Fig.2 are consistent with an energetics analysis [3], supporting the above interpretation. The deviations in the precise positions of M_n and Z_n can be attributed to field leaks and the model simplifications.

Coulomb Blockade Multi-Ion Conduction Scheme

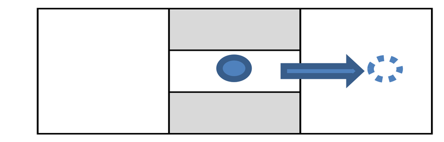
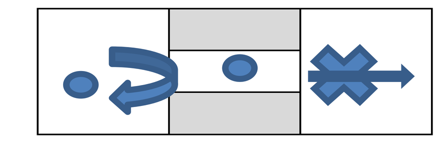
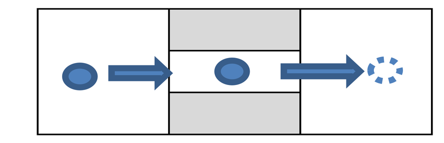
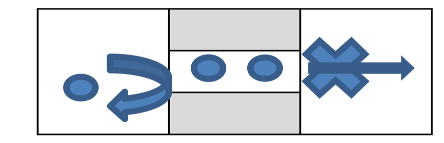
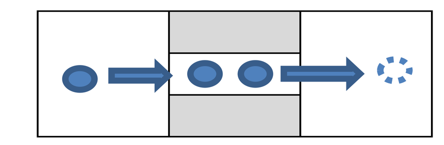
Singular point	Fixed charge	Conduction mode	Conduction event's scheme	Putative identification
M0	1e	Single-ion barrier-less conduction		OmpF porin, NaK channel
Z1	2e	Single-ion Coulomb blockade		
M1	3e	Double-ion knock-on conduction		L-type calcium channel
Z2	4e	Double-ion Coulomb blockade		
M2	5e	Triple-ion knock-on conduction		RyR calcium channel

Fig. 3. Calcium multi-ion conduction mechanisms for sequential Coulomb blockade singular points M_n, Z_n and putative identification with real channels. With growth of Q_f conduction changes from barrier-less single-ion conduction at M_0=1e (OmpF porin) to double-ion knock-on at M_1=3e (L-type channel) and triple-ion knock-on at M_2=3e (RyR channel). Conduction points M_n are interlaced by blockade Z_n.

Conclusions

- **Conduction and selectivity of calcium/sodium ion channels can be described in terms of ionic Coulomb blockade in a simplified electrostatic and Brownian dynamics model of the channel.**
- **The Coulomb blockade model predicts a periodic pattern of Ca^{2+} conduction vs. fixed charge Q_f at the selectivity filter (conduction bands) with a period equal to the ionic charge.**
- **Coulomb blockade model provides a straightforward explanation of numerous conduction and valence selectivity phenomena, including the anomalous mole fraction effect.**
- **Ionic Coulomb blockade are electrostatically and mathematically similar to electronic Coulomb blockade in quantum dots.**
- **The same considerations may also be applicable to other kinds of channel, as well as to charged artificial nanopores.**

Aknowlegements

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References

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