A Stochastic Model of Conductance Transitions in Voltage-Gated Ion Channels

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Abstract. We present a statistical physics model to describe the stochastic behavior of ion transport and channel transitions under an applied membrane voltage. To get pertinent ideas we apply our general theoretical scheme to an analytically tractable model of the channel with a deep binding site which interacts with the permeant ions electrostatically. It is found that the interaction is modulated by the average ionic occupancy in the binding site, which is enhanced by the membrane voltage increases. Above a critical voltage, the interaction gives rise to a emergence of a new conducting state along with shift of S4 charge residues in the channel. This exploratory study calls for further investigations to correlate the complex transition behaviors with a variety of ion channels, with parameters in the model, potential energy parameters, voltage, and ionic concentration.

Key words: channel conformational transition, ion transport, on-channel interaction, S4 charge group

Biomembranes play an essential role in maintaining life by forming boundaries between the inside and outside of organells. Mother nature endowed the membrane with a dielectric constant much smaller than that of water. For an ion, it costs the electrostatic energy much higher than of thermal energy to cross the barrier, and thus the lipid bilayer is highly impermeable. It is matter of life that the cell should allow the communication across the membrane. The mother nature thus orders certain membrane proteins to form the channels through which specific ions can transverse. The ion channels are flexible, a self-organizing nanoscale machines to regulate the conductive pathway.

One of two basic function of ion channel is the ion selectivity, the mechanism by which specific ions are allowed to pass. There has to be in the channel a hydrophillic region, called selectivity filter, which is a binding site where permeant ions reside for a while before crossing the membrane. The other function is gating, by which the channel can open and close depending upon external stimuli. For voltage-gated channels conductance levels can change depending upon transmembrane voltage, as depicted by Figure 1.

The molecular structures of the voltage-gated ion channels are not completely determined. It is deduced from many experiments [1, 2] that many of the voltage-gated channel consist of four identical subunits, each having six membrane spanning regions, labelled S1 to S6. Among them, the positive charge residues of the

Figure 1. A schematic picture of a voltage-gated ion channel.

S4 helix, depicted in Figure 1, is widely believed to be the major component of the voltage sensor [2–5]. An increase in membrane voltage may cause the S4 helix to twist toward the extracellular direction (Fig. 1). Presumably the movement of the S4 helix is coupled to the movement of permeant ions and other charges, which allows the opening of the channel.

In this paper, we present a theoretical, stochastic model to describe the salient features of ion transport and channel transition (gating mechanism) in a mesoscopic level. Rather than detailed information on channel microstructure, which is not available now, the basic and relevant features experimentally deduced is the guiding criteria for developing the model. We consider the channel with a binding site so that it can occupy an ion at most (singly occupied channel) [6].

In order to model complex biological phenomena in a requisite coarse-grained level, it is first necessary to determine the relevant variables. In studying the coupling dynamics of ion transport and channel conformation, it is natural to consider two variables, namely q_1 and q_2 [12]. The q_1 , representative of ionic degree of freedom, is simply considered to be the position of an average ion in the channel. On the other hand, the q_2 , the channel degree of freedom descriptive of the conformational transition, is to be identified depending upon the problem. It needs not to be specified in the general framework we will describe below.

The minimal stochastic model is the overdamped Markovian Langevin equations.

$$\gamma_1 \dot{q}_1 = -\frac{\partial \mathcal{F}}{\partial q_1} + \xi_1(t), \quad (1)$$

$$\gamma_2 \dot{q}_2 = -\frac{\partial \mathcal{F}}{\partial q_2} + \xi_2(t). \quad (2)$$

The free energy or the potential $\mathcal{F}(q_1, q_2)$ is composed of three parts, $\mathcal{F}_1(q_1)$ from the ionic contribution, $\mathcal{F}_2(q_2)$ from the channel contribution, and $\mathcal{F}_{12}(q_1, q_2)$ the interaction between average permeant ion and channel. γ_1 and γ_2 are the friction

coefficients that incur by temporal change of q_1 and q_2 . ξ_1 and ξ_2 are the Gaussian and white noises that satisfy the fluctuation-dissipation theorem,

$$\langle \xi_i(t) \xi_j(t') \rangle = 2D\gamma_i \delta_{ij} \delta(t - t'). \quad (3)$$

The D is the noise strength, which is temperature ($k_B T$) for our case. Because of the theorem, the system tends to be stationary states in the long term.

Equivalent to the coupled Langevin equation is the Fokker-Plank equation (FPE) for the joint distribution $p(q_1, q_2, t)$, the probability density for finding q_1 and q_2 simultaneously at a time t ,

$$\begin{aligned} \frac{\partial}{\partial t} p(q_1, q_2, t) = & \left\{ \frac{1}{\gamma_1} \frac{\partial}{\partial q_1} \left(\frac{\partial \mathcal{F}}{\partial q_1} + k_B T \frac{\partial}{\partial q_1} \right) \right. \\ & \left. + \frac{1}{\gamma_2} \frac{\partial}{\partial q_2} \left(\frac{\partial \mathcal{F}}{\partial q_2} + k_B T \frac{\partial}{\partial q_2} \right) \right\} p(q_1, q_2, t). \end{aligned} \quad (4)$$

We are interested in the stationary state ($\frac{\partial p}{\partial t} = 0$) solution in the presence of a constant applied membrane voltage. For that we factorize the distribution function in the form,

$$p(q_1, q_2) = p(q_1|q_2)p(q_2), \quad (5)$$

and seek the stationary solutions of $p(q_1|q_2)$, the distribution of the ion in a channel given its conformation q_2 , and $p(q_2)$, the distribution of channel conformation itself. We substitute it into the stationary FPE, which is rewritten as

$$0 = \frac{1}{\gamma_1} p(q_2) \frac{\partial j(q_1|q_2)}{\partial q_1} + \frac{1}{\gamma_2} \frac{\partial}{\partial q_2} \left(\frac{\partial \mathcal{F}}{\partial q_2} + k_B T \frac{\partial}{\partial q_2} \right) p(q_1, q_2), \quad (6)$$

where $j(q_1|q_2)$ is the ionic current through the channel given channel conformation q_2 :

$$j(q_1|q_2) = \frac{1}{\gamma_1} \left(\frac{\partial \Phi(q_1, q_2)}{\partial q_1} + k_B T \frac{\partial}{\partial q_1} \right) p(q_1|q_2). \quad (7)$$

Φ is net potential experienced by the ion:

$$\Phi(q_1, q_2) = \mathcal{F}_1(q_1) + \mathcal{F}_{12}(q_1, q_2). \quad (8)$$

For the channel of uniform crosssectional area A , the stationary current is independent of position, $j(q_1|q_2) = J(q_2)$. Along with this, the boundary conditions at the ends of the channel will determine the solution. Assuming the channel can accommodate an ion at most, namely, the singly occupied channel, the following boundary conditions hold at intracellular side of the channel (at $q_1 = 0$) and extracellular side of the channel (at $q_1 = L$) [6]

$$p(0|q_2) = P_e(q_2) A C_{in}, \quad (9)$$

$$p(L|q_2) = P_e(q_2) A C_{out}, \quad (10)$$

where C_{in} and C_{out} are the intracellular and extracellular side in bulk concentrations, and

$$P_e(q_2) = 1 - \int_0^L dq_1 p(q_1|q_2) = 1 - P_o(q_2). \quad (11)$$

Here $P_e(q_2)$, $P_o(q_2)$ are the probabilities that the channel is empty and occupied respectively when the channel is at a state q_2 .

The stationary solution of $P(q_1|q_2)$, $J(q_2)$ then are given as

$$p(q_1|q_2) = P_e(q_2) p^0(q_1|q_2), \quad (12)$$

$$J(q_2) = P_e(q_2) J^0(q_2), \quad (13)$$

where

$$p^0(q_1|q_2) = e^{-\beta\Phi(q_1, q_2)} (AC_{in}e^{\beta\Phi(0, q_2)} - \beta\gamma_1 J^0(q_2) \int_0^{q_1} ds' e^{\beta\Phi(s', q_2)}), \quad (14)$$

$$J^0(q_2) = \frac{AC_{in}e^{\beta\Phi(0, q_2)} - AC_{out}e^{\beta\Phi(L, q_2)}}{\beta\gamma_1 \int_0^L ds e^{\beta\Phi(s, q_2)}}, \quad (15)$$

$$P_e(q_2) = \frac{1}{\int_0^L dq_1 p^0(q_1|q_2) + 1}. \quad (16)$$

The $p^0(q_1|q_2)$ and $J^0(q_2)$ are the ionic distribution and current for a hypothetical channel that can accommodate an arbitrary number of ions. The $P_e(q_2)$ given as Equation 16, represents the steric effect of the singly occupied channel. This, the $p(q_1|q_2)$ and $J(q_2)$ are strongly dependent upon the bulk concentrations and membrane voltage. Before the information on q_2 is obtained, however, these formally exact solutions remain incomplete.

The equation for the channel degree of freedom is obtained as

$$\frac{1}{\gamma_2} \frac{\partial}{\partial q_2} \left(\frac{\partial \mathcal{F}_R(q_2)}{\partial q_2} + k_B T \frac{\partial}{\partial q_2} \right) p(q_2) = 0. \quad (17)$$

Here $\mathcal{F}_R$ is the channel renormalized free energy which is different from $\mathcal{F}_2(q_2)$ by the factor in the second term of the equation,

$$\mathcal{F}_R(q_2) = \mathcal{F}_2(q_2) - \int^{q_2} dq'_2 f_m(q'_2) \quad (18)$$

Figure 2. The ionic free energy, $\mathcal{F}_1(q_1)$, (a) from dielectric background; (b) with a binding site at a position x_b and membrane voltage U_0 .

where

$$f_m(q_2) = - \int dq_1 \frac{\partial \mathcal{F}_{12}(q_1, q_2)}{\partial q_2} p(q_1|q_2) \quad (19)$$

Figure 3. The channel free energy, $\mathcal{F}_2(q_2)$.

is the mean force with which the permeant ions acts on the channel degree of freedom. Unlike $\mathcal{F}_2$, which is entirely determined by the channel structure, $\mathcal{F}_R$ is a highly nonlinear function of the external condition such as the membrane voltage and bulk concentrations as incorporated by the boundary conditions. This implies that, depending upon such external conditions, the channel behavior undergoes renormalization, that is, self-organization leading to possibility of channel conformational transitions. Since there is no stationary current of channel charges, the distribution of channel degree of freedom is given by

$$p(q_2) = \frac{e^{-\beta \mathcal{F}_R(q_2)}}{\int dq_2 e^{-\beta \mathcal{F}_R(q_2)}}. \quad (20)$$

In order to get some numbers and concrete concepts that result from the general formulation, we now consider specific models of the potentials. First, ionic potential $\mathcal{F}_1(q_1)$, for an ion within a simple pore in the membrane, the dielectric backgrounds gives the potential looking like Figure 2(a) [7]. With a binding site introduced, and a membrane potential applied, we can consider the ionic potential that looks like Figure 2(b). By considering the case with the energy barriers much higher than thermal energy, we can find the closed analytic form of $p(q_1|q_2)$ and $J(q_2)$.

We are now in the position to specify the q_2 , the channel degree of freedom. As mentioned before, there are evidences that the S4 charge residues are the major components of the voltage sensor that leads to gating [2, 4, 5]. In this preliminary study, therefore, let us consider that q_2 be the center of S4 charges. Since the S4 helix undergoes screw/sliding confined within the membrane, we assume that the $\mathcal{F}_2(q_2)$, the potential of S4 charge center in the absence of permeant ions is a localized monostable function of q_2 (Figure 3). Monostability means that there is a single minimum in $\mathcal{F}_2(q_2)$, i.e. a single root of equation $\frac{\partial \mathcal{F}_2}{\partial q_2} = 0$.

With the permeant ions residing in a channel, the S4 charges will interact via electrostatic repulsion. For simplicity, we model the interaction in a quadratic form.

$$\mathcal{F}_{12}(q_1, q_2) = \Delta V - \frac{1}{2}K(q_1 - q_2)^2. \quad (21)$$

Here K is the ion-channel interaction strength. Due to the interaction, the channel potential is renormalized to $\mathcal{F}_R(q_2)$. Then, the renormalized potential can have double minima, or the equation $\frac{\partial \mathcal{F}_2}{\partial q_2} - f_m = 0$ has triple roots, depending upon the strength of the mean force. Using our exemplar models, the mean force is given by $f_m(q_2) = K P_o(q_2)(q_2 - q_1)$. Therefore as $P_o(q_2)$, or K increases, the channel potential undergoes bifurcation.

Figure 4 shows the change of the renormalized channel free energy as membrane voltage increases. We fix the concentration of cations on the extracellular side and intracellular side to be $C_{out} = 8.5$ mM and $C_{in} = C_{out}e^{-\beta U_R} = 140$ mM respectively so that at the rest potential $U_0 = U_R = -70$ mV there is no current, which corresponds to the curve A of Figure 4. As membrane potential voltage increases, the ionic occupancy at the binding site $q_2 = q_b$ tends to increase as shown

Figure 4. Bifurcation of renormalized free energy by change of membrane voltage. For illustrative purpose, we consider the following parameters: $C_{out} = 8.5$ mM and $C_{in} = C_{out}e^{-\beta U_R} = 140$ mM $U_R = -70$ mV, $U_1 + \Delta V = U_2 + \Delta V = 5k_B T$, $U_b + \Delta V = -5.6k_B T$, $k_1 = k_2 = 100k_B T/\text{nm}^2$, $k_b = 100k_B T/\text{nm}^2$, are the curvatures of the ionic potential $\mathcal{F}_1$ at x_1 , x_2 , and x_b , $x_1 = 0.8$ nm, $x_b = 1$ nm, $x_2 = 1.2$ nm, $L = 2$ nm, $K = 35k_B T/\text{nm}^2$, $A = \pi (0.46 \text{ nm})^2$, $D = k_B T/\gamma = 7.5 \times 10^{-5} \text{ cm}^2/\text{s}$. The channel potential is taken to be $\mathcal{F}_2(q_2) = b_3(q_2 - q_c)^4/4 + b_2(q_2 - q_c)^3/3 + b_1(q_2 - q_c)^2/2 + b_0(q_2 - q_c) - 6eU_0/L$, where $b_3 = 250k_B T/\text{nm}^4$, $b_2 = -60k_B T/\text{nm}^3$, $b_1 = k_B T/\text{nm}^2$, $b_0 = -0.5k_B T/\text{nm}$, $q_c = 0.7$ nm.

Figure 5. The dependence of ionic occupancy $P_o(q_2)$ in the binding site on membrane voltage when the S4 group is situated at binding site ($q_2 = q_b$).

Figure 6. The dependence of current level on membrane voltage. A high conducting level $J(q_2^+)$ (solid line) appears discontinuously when membrane voltage exceeds a critical value. Below the critical membrane potential, there exists only low conducting level $J(q_2^-)$ (dashed line).

Figure 7. The dependence of average current J_{av} on membrane voltage.

in Figure 5. This promotes the bifurcation in channel potential: As the membrane voltage increases (upon depolarization) above a threshold value $U_0 = -30$ mV (B), the free energy tends to have two minima at $q_2 = q_2^-$ and q_2^+ . The calculated values of the currents at these channel states, $J(q_2^-)$ and $J(q_2^+)$ indeed show that a new conductance level emerges above threshold voltage (Figure 6), above which the ionic current fluctuates between two conductance levels (Figure 4). Associated with the bifurcation is the hopping of S4 charge between $q_2 = q_2^-$ and q_2^+ , resulting in net shift toward the intracellular side. It is qualitatively in agreement with the

experiment [8, 9]. In contrast to conductance levels that emerge discontinuously, the average current given by

$$J_{av} = \int dq_2 p(q_2) J(q_2) \quad (22)$$

shows gradual increase of sigmoid type with saturation as the potential increases (Figure 7). We can call this phenomena of the channel conformational transition a self-organization, in the sense of Haken [10] that the channel can modulate the transport via conformational transition in response to nonspecific external conditions [11, 12]. As has been demonstrated, this transitional behavior originated from the interaction between the ion in the binding site and channel degree of freedom.

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