Two-state Toy Model of a Passive Ion Channel

Y. D. Chong[*]
Department of Physics, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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Protein ion channels are pores in cell membranes that transport ions between the cell and the extracellular medium. I study a toy model originally developed by Shklovskii *et. al.* In this model, the ion channel possesses two internal states, in which there is either an equal number of cations and negative wall charges or one extra cation. The difference in free energy between the two states is found to be around $1.8k_BT$ for typical biological parameters. This toy model is shown to imply a two-state hopping model for ion diffusion.

Ion channels are proteins that functions as pores in cell membranes through which ions such as K+, Na+, CaK2+, and Cl− can travel [1]. In the absence of such channels, ions would not be able to cross cell membranes due to their electrostatic self-energy. As Parsegian pointed out long ago [2], if an ion with charge q and ionic radius a is embedded in a uniform dielectric medium with dielectric constant ϵ, its self-energy is $\sim q^2/\epsilon a$. Since the dielectric constant of hydrocarbon ($\epsilon_{hc} \approx 2$) is much smaller than that of water ($\epsilon_w \approx 80$), there is a substantial energy cost, on the order of $16k_BT$, to move the ion out of solution and into the cell membrane. The finite thickness of the cell membrane (about 5 nm) reduces this energy cost by a negligible amount [2]. The existence of an ion channel, however, dramatically reduces this transport barrier. For instance, a passive K^+ channel can conduct 10^7 to 10^8 ions per second for typical cellular electrochemical gradients, a rate limited by the diffusion of K^+ ions from the bulk to the entrance of the channel. This ion transport is important for many biological processes, such as electrical signaling in the nervous system. In this report, I will focus on passive channels (and specifically on passive K^+ channels), which are more easily modelled in terms of basic thermodynamic processes; I will ignore "active ion channels", which pump ions up against an electrochemical potential.

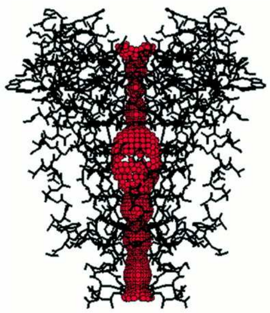

FIG. 1: Structure of the K^+ channel. The red regions denote the minimum radial distance from the center of the channel pore to the nearest van der Waals protein contact. From Doyle *et. al.* (1998) [3].

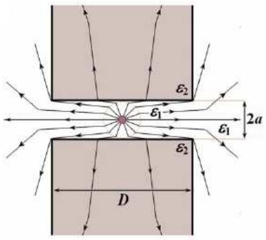

FIG. 2: Toy model of ion channel. Within the channel, the electric field lines are almost parallel to the axis of the channel. From Finkelstein *et. al.* (2006) [6].

According to X-ray studies [3], a K^+ channel consists of several components: a set of "inner helices" that extrude into the body of the cell, a large water-filled central cavity, and finally a narrow "selectivity filter" opening into the extracellular medium (Fig. 1). The central cavity has radius 5 nm and is located near the middle of the channel. In the equilibrium state of the channel, the cavity is filled with water molecules plus a single K^+ ion, which is stabilized by the presence of negatively-charged protein structures in the cavity walls. Attached to this cavity is the selectivity filter, a narrow channel with radius 0.4 nm and length 1.2 nm which is responsible for obstructing the passage of other ion species such as Na^+. The selectivity filter accomplishes this by means of electronegative carbonyl oxygen atoms arranged periodically along the walls of the channel. These form "cages" around K^+ ions in the channel, similar to the oxygen atoms surrounding hydrated ions, and therefore compensate for the energy of dehydration. This allows the channel to filter out Na^+ ions, even though they are smaller than K^+ ions: Na^+ ions do not experience this compensation because they are too small for the cages.

Many detailed numerical studies of the K^+ channel have been carried out [4]. It is useful, however, to see if any of the features of actual channels can be deduced from its basic physical properties, without recourse to numerical methods. One toy model, which was recently developed by Shklovskii *et. al.* [5], is based on reducing the problem to 1D. Although this study was based on the application of field theoretical methods to the 1D Coulomb plasma, the basic results can be obtained from elementary thermodynamic considerations.

Due to the presence of water molecules, the dielectric constant within the channel is $\epsilon_w \gg \epsilon_{hc}$. The mismatch in ϵ causes the electric field lines within the channel to point almost parallel to the channel, and those outside the channel to point almost perpendicular to it [6]. This situation is shown in Fig. 2. For sufficiently short channels, the electric field outside the channel turns out to be negligible. If we model the channel as a cylinder of radius a and length L, and take the field within the channel to be independent of the radial distance (as long as it lies in the channel), Gauss' law states that a charge q in the channel produces an electric field

$$E_0 = \frac{2q}{\epsilon_w a^2}\,, \tag{1}$$

independent of the distance along the channel. (Here, we have used cgs units). For a unit charge and $a = 0.7$ nm, $E_0 = 7.3 \times 10^7$ Jm^{-1}C^{-1}. If there is only one charge present in the channel, the electric field energy is

$$U_0 = \frac{\pi a^2 L}{8\pi}\,\epsilon_w E_0^2 = \frac{eE_0 L}{4}\,. \tag{2}$$

For $L = 5$ nm, $U_0 = 3.55\,k_BT$.

Let us model the negative "wall charges" present in a ion channel as a set of N charges, each with charge $-e$, located within the channel with uniform spacing L/N. Consider the situation with exactly N cations present in the channel, which we will refer to as the N-state. It can easily be seen that the lowest-energy configurations in the N-state occur when each cation is bound to a negative wall charge, as shown in Fig. 3a. In such a configuration, the electric field strength is $|E_0|$ between each cation/wall-charge pair, and zero between pairs. Thermal fluctuations will not cause bound pairs to overlap, because the thermal length of each bound pair is $k_BT/e|E_0| \sim 0.35$ nm, which is significantly smaller than the typical spacing between wall charges (which is on the order of 1 nm). Neglecting kinetic energies and all higher-energy configurations, the partition function in the N-state is:

$$\begin{aligned} Z_N &= \zeta^N, & (3)\\ \zeta &= \frac{1}{\ell}\int_{-\infty}^{\infty} dx e^{-e|E_0|x/k_BT} = \frac{2k_BT}{e|E_0|\ell} & (4) \end{aligned}$$

where ℓ is a quantization length. The corresponding Helmholtz free energy is

$$F_N = -k_BT \ln Z = Nk_BT \ln\left(\frac{2\ell}{L}\,\frac{U_0}{k_BT}\right). \tag{5}$$

Now consider the situation with $N+1$ cations in the channel, which we will call the $(N+1)$-state. The presence of the extra cation polarizes the N bound pairs in such way that the charges in the channel alternate between cations and negative wall charges. Again, we ignore higher-energy configurations where charges with the same sign are adjacent to one another. In the alternating-charges configuration, the magnitude of the electric field is constant throughout the channel, although its sign changes between each pair of positive and negative charges, as shown in Fig. 3b. The total energy is U_0, independent of the position of the cations as long as the charges remain in alternating sequence. The number of microstates is

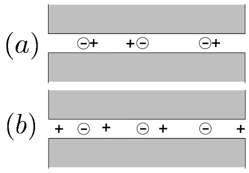

FIG. 3: The ion channel with $N = 3$ wall charges. (a) In the N-cation state, the cations are tightly bound to the wall charges. (b) In the $(N+1)$-cation state, the cations become unbound, but the charges remain in alternating order.

$$\Omega = \left(\frac{L}{2N\ell}\right)\left(\frac{L}{N\ell}\right)^{N-1}\left(\frac{L}{2N\ell}\right) \tag{6}$$

Therefore, the free energy $F_{N+1} = U_0 - TS$, where $S = k_B \ln \Omega$, is

$$F_{N+1} = U_0 - (N+1)k_BT \ln\left(\frac{L}{N\ell}\right) + k_BT\ln 4. \tag{7}$$

The difference in free energies for the two states, $\Delta F \equiv F_{N+1} - F_N$, is

$$\Delta F = U_0\left[1 + \frac{Nk_BT}{U_0}\ln\left(\frac{Nk_BT}{2U_0}\right)\right] + \cdots \tag{8}$$

where $\cdots$ denotes non-extensive terms that we will omit. They probably arise from approximations that we have made; the more sophisticated methods of Shklovskii *et. al.* yield (8) with no additional terms. For $N \sim 5$ (corresponding to a spacing of 1 nm between wall charges), $Nk_BT/2U_0 = 0.704 < 1$, so the term in the logarithm is negative. We thus obtain $\Delta F \sim 1.8 k_BT$.

The mechanism of ion transport in this model thus consists of a two-step process. At the start of the cycle, the channel is in the N-state. An ion enters the channel from either end, causing the bound pairs to delocalize and moving the channel to the $(N+1)$-state. Finally, a delocalized ion leaves the channel at either side of the solution, and the channel returns to the N-state. We can thus model the transport of ions using a two-state hopping model. Let n denote the state with n ions in the extracellular medium and $n_{\max} - n$ ions in the cell, with the channel in its N-state; let n' denote the state with $n-1$ ions in the extracellular medium and $n_{\max} - n$ in the cell, with the channel in its $(N+1)$-state. It seems reasonable that when the channel goes from the

$(N+1)$-state to the N-state, the exiting ion has equal probability to leave by each end of channel. Therefore, the $n' \to n$ and $n' \to (n+1)$ transition rates should have the same value, which we denote by r_{out}. Let r_L denote the $n \to n'$ transition rate (ion entering from the extracellular medium) and r_R the $(n+1) \to n'$ transition rate (ion entering from the cell). Then the transport rate is

$$\Gamma = \frac{r_{\text{out}}(r_L - r_R)}{2r_{\text{out}} + r_L - r_R}. \tag{9}$$

The fact that ΔF is on the order of $k_B T$, as calculated above, indicates that the rate at which ions leave the channel should be quite rapid. Extracting the actual rates, however, would require a kinetic theory calculation beyond the scope of this report. Note, however, that if $r_{\text{out}} \gg r_{L/R}$, then

$$\Gamma \approx \frac{r_L - r_R}{2}. \tag{10}$$

This corresponds to the diffusion-limited rate observed in actual ion channels. It is one-half the rate predicted by a one-state hopping model, in which ions enter and exit the channel without spending significant time in the channel. This theory can therefore be verified experimentally, at least in principle.

In this toy model, we have neglected many pertinent aspects of real ion channels. One glaring omission is the absence of ion selectivity. Because this model treats cations as featureless charges, it is unable to incorporate the hydration-cage mechanism by which Na^+ ions are blocked in an actual K^+ channel. As for other structural characteristics of real K^+ channels that have been omitted, such as the mid-channel cavity, their importance to the qualitative picture constructed here remains unclear. We have also neglected the possibility of screening “image charges” forming near the entrance and exit of the channel, which might have an important effect on the energetics of the problem [5].

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[*] Electronic address: `cyd@mit.edu`

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