

Relation between selectivity and conductivity in narrow ion channels

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Abstract—To establish the general statistical mechanical properties of highly conductive but selective nano-filters we develop an equilibrium statistical-mechanical theory of the KcsA filter, find the probabilities for the filter to bind ions from the mixed intra- and extra-cellular solutions, and evaluate the conductivity of the filter in its linear response regime. The results provide first principles analytical resolution of the long-standing paradox – how can narrow filter conduct potassium ions at nearly the rate of free diffusion while strongly selecting them over sodium ions – and are applicable to a wide range of biological and artificial channels.

I. INTRODUCTION

Ion channels are located within the membrane of most cells and can conduct ions at very high rate with input of metabolic energy. Their malfunction may have disastrous consequences for the organism. Recent studies of ion channels have unravelled many secrets of their structure-function relationship, but their ability to conduct larger ions at almost the free diffusion rate, while discriminating strongly against smaller ions of the same valence remains at the centre of a “many-voiced debate” [1], [2], [3] over decades [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13].

Let us consider e.g. the potassium channel’s ability [6], [8], [9] to conduct up to $\sim 10^8$ K^+ ions per second, while discriminating strongly against the smaller Na^+ ion. A widely-accepted explanation of this extraordinary phenomenon is based on the idea of a “snug fit” [4], [6] and an iso-energetic pathway [6], [8], [2] for K^+ , whereas a Na^+ ion is confronted by a large free energy barrier. The latter is defined through the Eisenman [5] relation

$$\Delta\Delta\bar{\mu}_{K,Na} = (\bar{\mu}_{Na}^c - \bar{\mu}_{Na}^b) - (\bar{\mu}_K^c - \bar{\mu}_K^b), \quad (1)$$

where we use $\Delta\bar{\mu}_i^b = \bar{\mu}_i^b - \bar{\mu}_i^c$ to define the change in excess chemical potential during the transition of an ion of the i -th type from the bulk (b) to the channel (c).

However, this picture reflects neither the observed high-affinity of K^+ binding sites, nor multi-ion nature of the transition mechanism [9], [14], nor the reality of flexible channel walls [15], [3]. It was also argued [3] that this picture can be self-contradictory because, if an ion binds to the channel too tightly, it cannot move rapidly through it. The

assumption was that the solution of the problem might require the development of a multi-particle non-equilibrium theory [3], [16] to encompass possible conformational changes and the “knock-on” mechanism of conduction [9], [14], [10], [17].

Theoretical analysis of this problem has benefited from a number of important contributions including e.g. statistical theory of selective ion channels [18], [19], [20], theory of transport in one-dimensional Coulomb gases [21], [22], theory of single-file multi-particle diffusion in narrow pores [23], [24], theory of ion selectivity and permeation [25], [26], [27], [28], theory of ion conductivity in trans-membrane channels [29], non-equilibrium thermodynamics of ion channels [30], and Coulomb blockade [31], [32], [33], [34] and dehydration theory [35] of channels to mention a few.

Despite all this progress the relationship between selectivity and conductivity in these channels remains elusive [2], [3].

Here we present an *equilibrium* statistical theory that describes key properties of the KcsA selectivity filter including its conductivity, the “snug fit” and “knock-on” conditions, and the Eisenman selectivity relations. A first-principles resolution of the above mentioned long-standing paradox is obtained by deriving an effective grand canonical ensemble of the filter that leads to an analytical expression for its conductivity and by showing that the Eisenman-type selectivity relation for ions of equal valence follows from the condition of diffusion-limited conductivity.

We consider the KcsA filter to be a narrow tunnel of length 12 Å lined with 20 oxygen atoms providing four binding sites, numbered S_1 - S_4 from the extracellular to intracellular side [7], [8], [9], [2], [10], [11], [12], [13], [3], [14], [15], [16], [20], (inset of Fig. 1). Under physiological conditions, this filter contains two resident K^+ ions separated by a water molecule. We consider conduction through the K^+ selectivity filter immersed in bath solutions containing a mixture of different ions. Conduction occurs when a third ion enters, knocking-on [14], [10], [17], [23] the ion on the opposite side.

II. THEORY

To derive conditions for the latter conduction mechanism we write the current density of the filter j_i as [36], [37], [38]

$$j_i = -\frac{\sigma_i}{q} \nabla (kT \ln(c_i/c_0) + \bar{\mu}_i + q\phi), \quad (2)$$

Here q is the unit charge, c_i are the number densities, c_0 is the normalization constant, T is the temperature, ϕ is the electrostatic potential, and $kT \ln(c_i/c_0) + \bar{\mu}_i + q\phi$ is the electrochemical potential μ_i of the ions in the filter.

We show [39] that conductivity σ_i of narrow filters for coordinated single-file motion of ions is given by generalized Einstein relation [40]

$$\sigma_i = q^2 D_i \partial c_i / \partial \eta_i \propto -T (\partial^2 \Omega / \partial \eta_i^2)_{T,V}, \quad (3)$$

here D_i is the chemical diffusion coefficient and η_i is the chemical potential of the ions. To find the grand potential Ω we derive [39] the free energy of the system's state in the form

$$G(\{n_j\}, n_f) = -kT \sum_i n_i \ln x_i^b - \sum_i n_i \Delta \tilde{\mu}_i^b + \quad (4)$$

$$kT \sum_i \ln n_i! + \varepsilon(\{n_j\}, n_f).$$

Here, x_i^b and n_i are the mole fraction numbers of ions of the i -th type in the bulk and in the filter, $\Delta \tilde{\mu}_i^b = \Delta \bar{\mu}_i^b + q\Delta\phi^b$ is the difference in excess chemical and electrostatic potentials between ions in the bulk and in the channel, $\varepsilon(\{n_j\}, n_f)$ is the correlation corrections [21], [22], [33], [41] to the energy of the state due to ion-ion and ion-wall-charge interactions, and n_f is determined by the total fixed charge on the filter's wall, $Q_f = qz_f n_f$. Here we defined [39] the state of the system by the set of numbers of ions of each type present in the filter $\{n_j\} = \{n_1, n_2, \dots, n_M\}$.

The grand canonical ensemble of the filter can now be written as [39]

$$P(\{n_j\}, n_f) = \mathcal{Z}^{-1} \left(\prod_{i=1}^m \frac{(x_i^b)^{n_i}}{n_i!} \right) \times \quad (5)$$

$$\exp \left(\frac{1}{kT} \left(\sum_i n_i (\Delta \tilde{\mu}_i^b) - \varepsilon(\{n_j\}, n_f) \right) \right),$$

The effective grand partition function Z is defined by the normalization condition for $P(\{n_i\}, n_f)$ and the grand potential is: $\Omega = -kT \ln Z$. The analytic forms of the probabilities $P(\{n_i\}, n_f)$ and the effective grand partition function can be related [39] to those obtained [18], [19], [20] in the form of configuration integrals.

The theory that we introduce relates σ_i to key parameters of the system such as the mole fraction of conducting ions in the bulk solutions, the difference in excess chemical potential between the bulk and the filter, the fixed charge on the filter's wall, the filter's geometry, and the energy of the multi-particle interactions in the filter. This in turn allows us to establish explicit analytical relationships between filter's conductivity and selectivity.

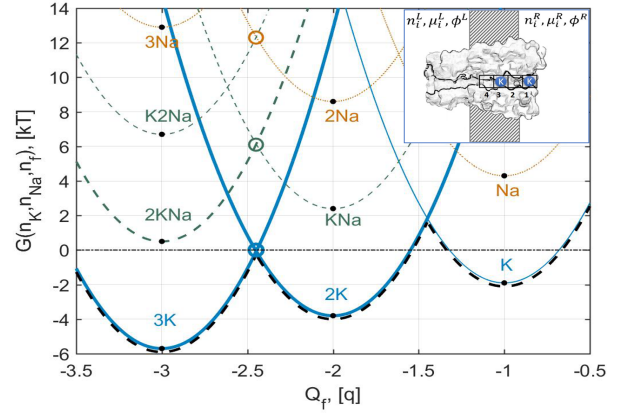


Fig. 1. Levels of free energy as a function of Q_f for K^+ (blue lines), Na^+ (orange dotted lines) and mixed (green dashed lines) conduction as given by Eq. (4) for the following parameters: $\Delta \bar{\mu}_K = 2kT$; and $\Delta \bar{\mu}_{Na} = -4.3kT$; $U_c \approx 18.7kT$. Black dots show positions of the energy level minima; the ground state is indicated by the bold black-dashed line; and open circles show locations of the resonant conduction. The labels at the origin of each parabola indicate the number of ions of each type in the filter. The inset shows schematic representation of the selectivity filter coupled to both solutions. The binding sites $S_1 - S_4$ for cations are indicated by black squares.

To calculate the conductivity (3) we use $\langle \Delta n_i^2 \rangle = -kT \partial \Omega / \partial \eta_i$, the mean number of particles and their variance in the form [42]

$$\langle n_i \rangle = \sum_{\{n_i\}} n_i P(n_i, n_f), \quad \langle n_i^2 \rangle = \sum_{\{n_i\}} n_i^2 P(n_i, n_f), \quad (6)$$

$$\langle \Delta n_i^2 \rangle = \langle n_i^2 \rangle - \langle n_i \rangle^2,$$

III. APPLICATION TO KCSA CHANNEL

To find the free energy in each state of the KcsA filter we consider only K^+ and Na^+ ions as conducting species and limit the maximum total number of ions in the filter to three. The free energy (4) of the resultant nine system states containing non-zero numbers of ions is shown in Fig. 1. Here the correlation corrections $\varepsilon(n_K, n_{Na}, n_f)$ were approximated by the filter's dielectric barrier energy [22], [39], [43]

$$\varepsilon(n_K, n_{Na}, n_f) = U_c (n_K + n_{Na} + z_f n_f)^2. \quad (7)$$

The energy minimum of each parabola corresponds to the most probable combination of ions in the filter, given by the condition

$$n_K + n_{Na} = -z_f n_f = 1, 2, \text{ or } 3.$$

The lowest levels, shown by solid blue lines, correspond to the filter being filled with one, two, or three K^+ ions, respectively. The highest energy levels (orange dotted lines) correspond to system states with Na^+ , $2Na^+$, and $3Na^+$. The mixed states of the filter filled with K^+ and Na^+ ions are of intermediate energy as shown by green dashed lines. The shift of the energy levels for each type of ions is controlled by $\Delta \mu_i$.

The condition for barrier-less diffusion-limited conduction is given by [39] (cf [41], [32], [44], [23])

$$G(n_K + 1, n_f) = G(n_K, n_f) \approx 0 \quad (8)$$

For the total charge on the filter's wall $Q_f \approx -2.5q$ and $\Delta\bar{\mu}_K = 2kT$ the barrier-less "knock-on" mechanism of pure K^+ conduction ($2K^+ \leftrightarrow 3K^+$) corresponds to the minimum energy in the system.

Fig. 2 presents the filter's conductivity/selectivity relations for potassium and sodium ions as a function of the key filter parameters $\Delta\mu_K$ and Q_f . It can be seen in the figure that for small absolute values of $\Delta\mu_K < 0.5$ (left-hand side of figure) the filter is non-selective and both conductivities σ_K and σ_{Na} are relatively large for any value of the wall charge Q_f . With $\Delta\mu_K$ increasing above 1 the free energy for sodium to enter the channel becomes $\Delta G_{Na} > 5kT$ ($\Delta\bar{\mu}_{Na} = -4.3kT$), the filter's conductivity becomes strongly selective for K^+ ions. The increasing affinity of K^+ ions results in a strong attenuation of the σ_K as was conjectured earlier [3]. However, narrow bands of high conductivity remain, similar to those observed for divalent ions in Brownian dynamics modeling of calcium channel [41], [32]. The width of these conductivity bands is $\sim 1/U_c$. Therefore, simultaneous strong selectivity and high conductivity of the channel can be achieved only at the locations of the peaks of σ_K .

To derive an exact conductivity/selectivity relationship we write the potential barrier for a K^+ ion to enter the channel when occupied by two potassium ions in the form $\Delta G_K = G(3K, 0, n_f) - G(2K, 0, n_f)$; and compare it with the barrier for a sodium ion to enter the channel $\Delta G_{Na} = G(2K, Na, n_f) - G(2K, 0, n_f)$.

Solving [39] the Eqs. (8) with respect to optimal values of $n_f^* = (z_f n_f)^*$ and $\Delta\mu_K^*$ we have

$$\begin{aligned} n_f^* &= -\left(n_K + \frac{1}{2}\right) + \frac{C}{q^2} (kT \ln(n_K + 1) - \Delta\mu_K^*), \\ \Delta\mu_K^* &= \frac{1}{n_K} \varepsilon(n_K, 0, n_f^*) - \frac{kT}{n_K} \ln n_K!. \end{aligned} \quad (9)$$

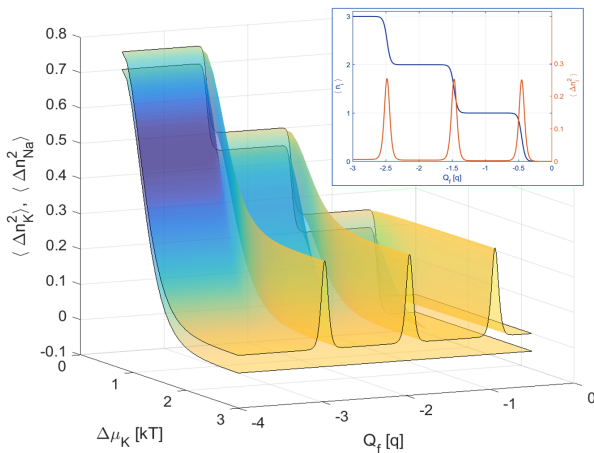


Fig. 2. Conductivity of K^+ (top sheet) and Na^+ (bottom sheet, shifted down by 0.05) as a function of the system parameters $\Delta\mu_K$ and Q_f . When $\Delta\mu_K \approx 0 kT$ the conductivities are nearly same. With increasing $\Delta\mu_K$, however, conductivity becomes increasingly selective: sharp ridges corresponding to conductivity bands for σ_K as a function of Q_f are clearly evident, and $\sigma_{Na} \approx 0$ for all Q_f . $\Delta\mu_{Na} \approx -4.3kT$ for this figure.

With the resultant optimal values of $n_f^* = (z_f n_f)^*$ and $\Delta\mu_K^*$ given by Eqs. (9), the filter allows for the unimpeded (diffusion-limited) barrier-less $\Delta\Delta G_K \approx 0$ passage of potassium ions, while selectively blocking the entry of Na^+ ions. The barrier $\Delta\Delta G_{Na}$ for sodium ions can now be immediately derived leading to the well-known Eisenman result

$$\begin{aligned} \Delta\Delta G_{Na} &= (\bar{\mu}_{Na}^c - \bar{\mu}_{Na}^b) - (\bar{\mu}_K^c - \bar{\mu}_K^b) + \\ kT \ln \frac{c_K}{3c_{Na}} &= \Delta\Delta\bar{\mu}_{K,Na} + kT \ln \frac{c_K}{3c_{Na}}. \end{aligned} \quad (10)$$

To derive conductivity of potassium ions we use eqs. (3)-(6) and obtain [39]

$$\sigma_K = q^2 D_K e^{-\Delta G_K/kT} / V_c kT \left(1 + e^{-\Delta G_K/kT}\right)^2, \quad (11)$$

where V_c is the volume of the filter.

IV. CONCLUSIONS

We conclude, that Eqs. (10) and (11) resolve the selectivity vs. conductivity paradox. It can be seen from this expression [39] that the conductivity of the filter has a very sharp peak at the resonant transition point $2K^+ \leftrightarrow 3K^+$, where $\Delta G_K \approx 0$, approaching the diffusion limit as illustrated in Fig. 2. The proposed approach allows one to obtain analytically the key properties of the KcsA filter including its conductivity, the Eisenman selectivity relations, and the snug fit and knock-on conditions. It also provides independent first-principles estimates of the values of the filter parameters $\Delta\mu_{Na}$, $\Delta\mu_K$, and of Q_f , as functions of channel structure required for potassium filter to function in accordance with experimental observations.

Estimates based on Eqs. (9)-(11) and realistic filter parameters [39], [45] show that the value of the fixed charge on the filter wall is $Q_f \approx -2.5q$, the partial valence of the oxygen atoms is $z_f \approx 0.125$, the excess chemical potentials are $\bar{\mu}_K = 2kT$; and $\Delta\bar{\mu}_{Na} = -4.3kT$, and a flow rate through the filter is of the order $\sim 10^8$ ions per second for a potential difference of 50 mV, while filter is discriminating 1:1000 against the (smaller) Na^+ ion. These values are consistent with the experimental observations reported by MacKinnon and other authors.

Finally, we comment that the results obtained are applicable far beyond the KcsA channel, and may be expected to describe conduction in a wide class of narrow, ion-selective, biological and artificial nano-filters [34], [46].

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