Theory of alike selectivity in biological channels

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We introduce a statistical mechanical model of the selectivity filter that accounts for the interaction between ions within the channel and derive Eisenman equation of the filter selectivity directly from the condition of barrier-less conduction.

Selectivity of the canonical K^+ filter, formed by a narrow 15 Å-long tunnel holding four K^+-binding sites, is usually analyzed [1-6] in terms of the difference in the excess chemical potential in the bulk $\bar{\mu}_i$ in and the channel $\bar{\mu}_i^c$ at one binding site

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

The question of how to introduce barrier-less conduction within this formalism elicited a many-voiced debate over decades.

Let n_i^s be a number ions of the i-th type in the solution and n_i their number within the filter. We introduce the free energy of the solution plus the filter in the form

$$G = \sum_i (n_i^s - n_i) kT \ln x_i^s + \sum_i (n_i^s - n_i)\tilde{\mu}_i + \sum_i n_i \tilde{\mu}_i^c + kT \ln\left(\prod_i n_i!\right) + \varepsilon\left(\{n_j\}, n_f\right).$$

In treating the filter filled with ions as excited states of the system, we derive the following grand canonical ensemble for the filter (cf [?])

$$P(\{n_j\}) = \mathcal{Z}^{-1} \prod_{i=1}^{m} \frac{(x_i^s)^{n_i}}{n_i!} e^{\frac{\sum_i n_i \Delta\bar{\mu}_i - \varepsilon\left(\{n_j\}, n_f\right)}{kT}}. \tag{2}$$

The current with a constant voltage drop $\Delta\phi = \phi^L - \phi^R$ through the channel in linear response is proportional to the rate of charge fluctuations passing through the channel [7] $J_{steady} = \frac{\Delta\langle Q^2(t)\rangle}{2kT\Delta t}\Delta\phi$.

For discrete conducting ions, charge fluctuations are proportional to fluctuations in the number of ions in the channel. The variance $\sigma_{n_i}^2 = -kT\left(\frac{\partial^2\Omega}{\partial\Delta\mu_i^2}\right)_{T,V}$ of the number of ions in the filter can be found using the grand potential $\Omega = -kTln\mathcal{Z}$.

To apply obtained results to the KcsA filter, let us consider two types of conducting ions K^+ and Na^+ that can bind to any binding site in the filter, but have to have at

least one water molecule between them. The free energy of the filter filled with n_K and n_{Na} ions (ignoring a prefactor) is $G = -n_K\Delta\tilde{\mu}_K - n_{Na}\Delta\tilde{\mu}_{Na} + \varepsilon(n_K, n_{Na}, n_f)$. The energy of interaction between the ions is $\varepsilon(n_K, n_{Na}, n_f) = \frac{q^2}{2C}(n_K + n_{Na} + n_f)$, where n_f is the number of fixed charges on the channel wall, i.e. the main mutation parameter. The channel capacitance is $C \approx \frac{4\pi\epsilon_0\epsilon_w R^2}{L}$.

The lowest conducting free energy level corresponds to $n_K = 2$. The conditions for fast conduction are: (i) $G(n_K, n_f^*) = G(n_K + 1, n_f^*)$ and (ii) $G(n_K, n_f^*) \approx 0kT$. To tune the selectivity and conductivity of the filter one has to tune: (i) geometry, (ii) $\bar{\mu}_i^c$, and (iii) the n_f. Tuning the filter for fast conduction of K^+ ions gives

$$n_f^* = -(n_K + 1/2) + \frac{C}{q^2}\Delta\mu_K. \tag{3}$$

Substituting this value into the free energy gives the following barrier for Na^+ ion to enter the channel $\Delta G_{Na} = \Delta\mu_K - \Delta\mu_{Na}$, i.e. Eisenman's selectivity relation follows directly from the condition for fast conduction of K^+ ions.

Analysis of the mean and variance for K^+ and Na^+ ions in the filter shows that tuning it for fast conduction of K^+ ions results in effective block of Na^+ conduction if the width of the dispersion peaks is smaller than the separation of the peaks determined by the geometry of the channel and ΔG.

In conclusion, we have introduced a statistical mechanical model for the distribution of alike-charged ions in the K^+ selectivity filter and have shown that the Eisenmann relation for filter selectivity follows directly from the condition for fast barrier-less conduction of K^+ ions in the filter. The results can be extended beyond linear response using a solution of the Nernst-Planck equation. Models of filters with distinguishable binding sites will be considered in future work.

References

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