Components of Excess Chemical Potential

The excess chemical potential of ion, \( \mu^e_i(r) \), can be broken down into following components:

\[
\mu^e_i(r) = \mu^{\text{mean-field}}_i(r) + \mu^{\text{screen}}_i(r) + \mu^{\text{self}}_i(r).
\]

where \( \mu^{\text{mean-field}}_i(r) \) is the hard sphere component indicating that ions cannot overlap (computed by inserting hard spheres from Eq. (2)), \( \mu^{\text{screen}}_i(r) \) is the mean field component (obtained by averaging the ion's mean electrostatic potential), \( \mu^{\text{self}}_i(r) \) is the self component due to the interaction of an ion with changes induced by ion itself (obtained by inserting charged hard spheres from Eq. (2)) and \( \mu^e_i(r) \) is the screening term which describes the efficiency of an ion to screen other ions.

The SC term cannot be computed by Widom's method and so we define the screening from Eq. (3) as:

\[
\Delta \mu_{\text{screen}} = -\frac{1}{2} \log \left( \frac{\mu^e_i(r)}{\mu^e_i(0)} \right) - 1 + \frac{1}{2} \sum \mu^{\text{mean-field}}_i(r) + \frac{1}{2} \sum \mu^{\text{self}}_i(r).
\]

Why is the channel Ca\(^{2+}\) selective?

Ca\(^{2+}\) selectivity arises from a balance of electrostatics and the excluded volume of ions in the crowded selectivity filter.

Reduced Model of L-type Ca Channel

The selectivity filter of the L-type Ca\(^{2+}\) channel is modeled as having radius 3.5 Å, length 10 Å and protein electric 10 Å.

Excess Chemical Potential: The Widom Method

Chemical potential (\( \mu \)) measures the change in energy when a particle is inserted

\[
\mu(x,T) = -kT \ln \left( \frac{\rho(x)}{\rho(x=0)} \right) \quad \text{lognormal profile}
\]

where \( k \) is Boltzmann's constant, \( T \) is temperature, \( \rho \) is the density profile, and \( \mu^e(x) \) is the excess chemical potential profile which describes the deviation of the system from the ideal solution.

Widom’s particle insertion method: A ghost ion is inserted in position \( x \) and the total interaction energy of the inserted ghost ion with the system is computed to obtain \( \mu^e(x) \):

\[
\mu^e(x) = W(U(x)) = -kT \ln \left( \frac{\rho(x)}{\rho(x=0)} \right) \quad \text{lognormal profile}
\]

where \( U \) denotes the Grand Canonical ensemble average.

Components of Excess Chemical Potential

Energetics of Selective Binding in A Reduced Model of L-type Ca Channel

Monte Carlo Simulations of Free Energy Components

Energetics of Equilibrium Binding Selectivity

Binding Selectivity of Ca\(^{2+}\) over Na\(^{+}\): Gives the underlying energetics of Ca\(^{2+}\) favorability in the channel. From Eq. (5) and (6) for Ca\(^{2+}\) and Na\(^{+}\) respectively, we obtain the binding selectivity of Ca\(^{2+}\) over Na\(^{+}\) as follows:

\[
\frac{\log \left( \frac{\mu^e_{Ca}^c(r)}{\mu^e_{Na}^c(r)} \right)}{kT} = \frac{1}{2} \sum \mu^{\text{mean-field}}_{Ca}(r) - \frac{1}{2} \sum \mu^{\text{mean-field}}_{Na}(r) + \frac{1}{2} \sum \mu^{\text{self}}_{Ca} - \frac{1}{2} \sum \mu^{\text{self}}_{Na}.
\]

Advantages for Ca\(^{2+}\) Selectivity in Channel

- Excluded Volume Advantage – win because Ca\(^{2+}\) and Na\(^{+}\) are the same size. NO size selectivity.
- Mean Field Advantage – positive and favors Ca\(^{2+}\) over Na\(^{+}\).
- Screening Advantage – large, positive and favors Ca\(^{2+}\) over Na\(^{+}\).
- Self Advantage – negative, favors Na\(^{+}\) and does not change much.

Referee

References

\[ \mu^e_{Ca}(r) = -kT \ln \left( \frac{\rho_{Ca}(r)}{\rho_{Ca}(0)} \right) \quad \text{lognormal profile} \]

Selectivity: Competition of electrostatics and excluded volume forces.

In L-type Ca channels, electrostatics (mean field + screening) dominates the selective binding of Ca\(^{2+}\) over Na\(^{+}\).

Conclusions

Ca\(^{2+}\) selectivity is determined by electrostatics, in particular screening. Similar results were found in RYFP [3].

Future Work

DEKA Na Channel