The effect of the protein dielectric coefficient and pore radius on the Na^+ affinity of a model sodium channel

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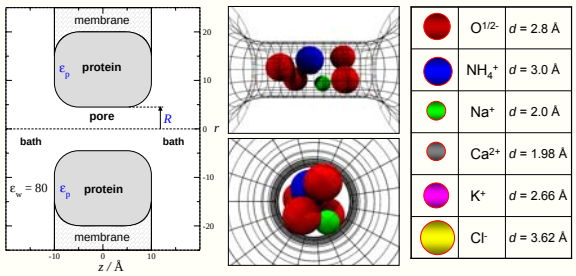
Abstract

Na channels that produce the action potentials of nerves and muscles include a selectivity filter formed by both positively and negatively charged amino acid residues. We study equilibrium ion accumulation of various ions in the filter for different compositions of the bath electrolyte using Monte Carlo simulations. We use a reduced model of the channel by allowing the protein to have a different dielectric coefficient from the solution. Ions and tethered carboxylate and amino groups (that are restricted to the filter) are treated as charged hard spheres. We find that (1) decreasing the dielectric coefficient of the protein improves the Na^+ vs. Ca^{2+} affinity of the filter; and that (2) decreasing the radius of the filter improves Na^+ vs. K^+ affinity of the filter. Electrostatic effects play the dominant role in (1), the effect of dielectric constant; while excluded volume effects play the dominant role in (2), the effect of radius.

Model of channel and electrolyte



$O^{1/2-}$	d = 2.8 Å
NH_4^+	d = 3.0 Å
Na^+	d = 2.0 Å
Ca^{2+}	d = 1.98 Å
K^+	d = 2.66 Å
Cl^-	d = 3.62 Å

- **Channel**: is a doughnut shaped object with a pore in the middle.
- Its relevant parameters: **dielectric coefficient** (ε_p) and **pore radius** (R).
- It is embedded in a membrane that separates two baths.
- **Ions**: charged hard spheres, **solvent**: continuum dielectric (ε_w = 80)
- **Selectivity filter**: central pore containing characteristic amino acid side chains
- **Side chains**: hard sphere ions model the end groups of the side chains:
  - **D** or **E**: two half charged oxygens ($O^{1/2-}$)
  - **K**: a positive ammonium ion (NH_4^+)
- **Method**: Equilibrium **Monte Carlo Simulations** (Grand Canonical Ensemble)
- ***R* = 3 Å and ε_p = 10** (if not stated otherwise)

Structural charges ($O^{1/2-}$ and NH_4^+) are mobile. The filter contains a high density liquid-like structure that distribute according to minimal free energy: this structure is an output of the simulation and depends on conditions.

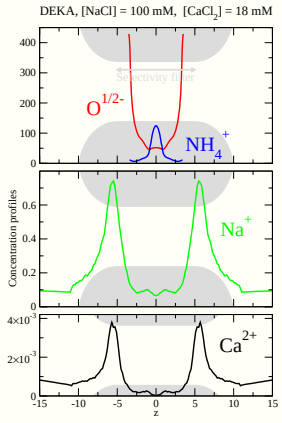
References

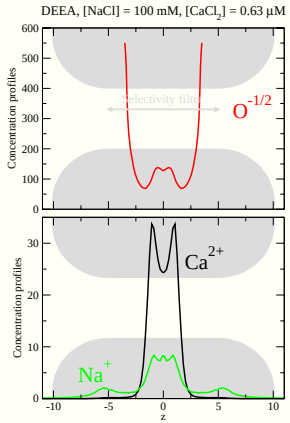
- Nonner et al, Binding and selectivity in L-type calcium channels: A mean spherical approximation *Biophys. J*, **79**, 1976 (2000).
- Boda et al, Monte Carlo simulations of the mechanism for channel selectivity: The competition between volume exclusion and charge neutrality *J. Phys. Chem. B* **104**, 8903 (2000).
- Boda et al, The effect of protein dielectric coefficient on the ionic selectivity of a calcium channel J. Chem. Phys. **125**, 034901 (2006).

Na^+ vs. Ca^{2+} selectivity

Mutating a Na channel (DEKA) into a Ca channel (DEEA)

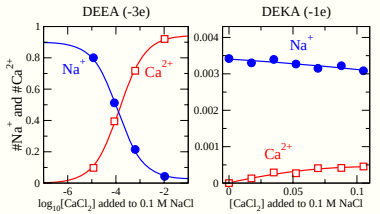
DEKA: 4 $O^{1/2-}$ and 1 NH_4^+ (-1e charge) → Mutation K→E → **DEEA**: 6 $O^{1/2-}$ (-3e charge)

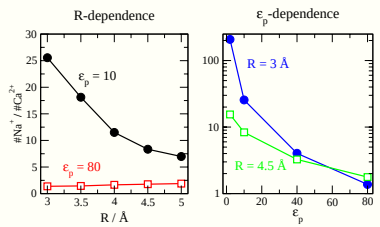




Ca^{2+} is **excluded** from the middle of the filter more: **Na channel**

Ca^{2+} is **attracted** to the middle of the filter more: **Ca channel**





Occupancy: average number of various ions (#Na^+, #Ca^{2+}, or #K^+) in the central 5 Å portion of the selectivity filter.

- **Decreasing protein dielectric coefficient**: increases the **electrostatic penalty** for Ca^{2+}
- **Decreasing pore radius**: makes the filter more crowded → increases the **excluded volume penalty**
- **Both amplify the effect of electrostatics** → a **better Na channel** is obtained

- **Balance of electrostatic and entropic forces produces a rich selectivity behavior.**

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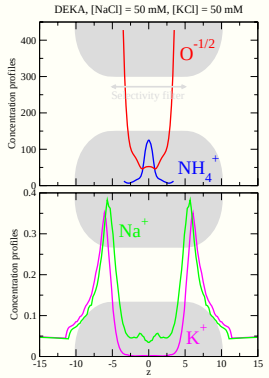
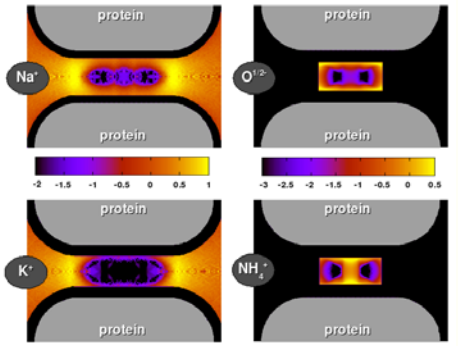
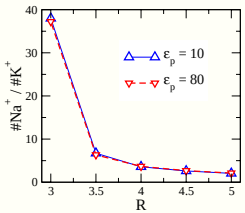
Na^+ vs. K^+ selectivity

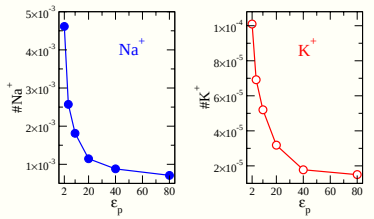
K^+ ions excluded from the center of the crowded filter





The most selective region of the filter is its center. Na^+ vs. K^+ selectivity works on the basis of exclusion, not binding. The binding sites (defined as high concentration spots) are not selective.





Decreasing pore radius: **improves Na^+ vs. K^+ selectivity**

Decreasing protein dielectric coefficient: **increases occupancy**, but not #Na^+ / #K^+ ratio

Conclusions

- On the basis of a **reduced model** using known structural information (amino acid sequences of the selectivity filter) we can explain the **selectivity properties of Na and Ca channel** in a wide range of conditions.
- The mechanism works on the basis of a competition between electrostatic and excluded volume effects: **ions compete for space in the crowded selectivity filter**.
- The degree of selectivity can be tuned by the **engineering variables** of the reduced model (R, ε_p, and amino acid side chains) – these variables can be controlled by protein structure, e. g., the genetic code.
- **Only basic physical forces (electrostatic and excluded volume) were used to develop this mechanism: no specific chemical binding forces were assumed.**