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Conductance and Concentration Relationship in a Reduced Model of the K Channel

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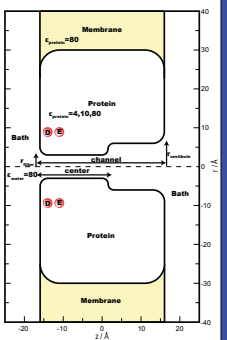
Model & Method

- **Simulation cell**: cylinder of height ~350 Å and radius ~75 Å
- **Channel protein**: doughnut shaped with rotational symmetry and hard walls
- **Protein:** loosely based on MthK crystal structure
  $\varepsilon_{protein}$ = 4,10, 80
  induced charge computation at interface
  $r_{vestibule}$ = 6 Å; r_{filter} = 3 Å, 4 Å
- **Membrane:** hard walls from x = -16 Å to x = 16 Å
  $\varepsilon_{membrane}$ = 80
- **Ions**: charged hard spheres with crystal radii
  diameters: K^+ 2.66 Å; Cl^- 3.62 Å
- **Solvent:** continuum dielectric (ε_{water} = 80)
- **ASP71/GLU80:** 4 pairs of -0.5*e* charge (-4*e* total)
  2 pairs shown
- **Grand Canonical Monte Carlo**
  Allows small bath concentrations
  Ensures equilibrium
  Boltzmann distribution
  1.2 x10^6 Monte Carlo trials per point

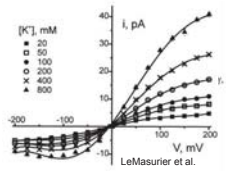


Abstract

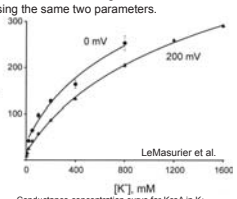
K^+ ions move rapidly through potassium channels more or less ignoring Na^+. The mechanism of selectivity is thought to depend on the solvation of K+ and its electrostatic interactions with carbonyl dipoles of the channel wall, made of the side chains Thr Val Gly Tyr Gly TVGYG in many types of potassium channels. We calculate the conductance of the tetrameric KcsA prokaryotic K^+ channel measured in solutions of different K^+ concentration. The 3D model used here consists of two regions of different dielectric constant, one representing the protein and one representing a bath of implicit water. The geometry of the model is loosely based on the 'open' MthK crystal structure of Jiang's laboratory in which the intracellular half of the channel has a wide (~1.2 nm) pore radius. Ions are represented as hard spheres with Pauling radii. The surface charge on the protein is calculated using the induced charge computation method of Gillespie and collaborators. A Grand Canonical Monte Carlo approach developed by Boda maintains system neutrality while keeping bath concentrations fixed at values comparable to experiments. The Metropolis algorithm maintains a Boltzmann distribution to keep the system in thermodynamic equilibrium. The spatial density distribution of the ions allows an estimate of a characteristic slope conductance, for small driving force. Four pairs of GLU71/ASP80 ionizable residues lie directly behind the K^+ selectivity filter and have a substantial effect on potential energy profile along the selectivity filter. The model will be used to investigate the relationship of the protonation state of the residues, the composition of the bathing solutions, and the slope conductance.

Motivation

- How can spatial distributions of ion density provided by simulation of a reduced model of the K channel explain experimental permeation results like the sublinear KcsA conductance vs. concentration curve?
- Ryanodine receptor model reproduces current-voltage data.
- Reduced models of the L-type calcium channel and the Na channel reproduce experimental results over a wide range of ionic conditions using the same two parameters.



KcsA currents in varying concentrations of K^+. Currents were recorded in symmetrical K^+ solutions at the concentrations indicated,at a holding potential of 200 mV. I-V curves at K^+ concentrations are indicated. Solid lines are polynomial fits for the determination of the zero-voltage conductance. Above 800 mM K^+, open probability becomes so low that full I-V curves could not be measured.



Conductance-concentration curve for KcsA in K^+. Conductance of KcsA in symmetrical K^+ solutions was determined in two ways: by the zero-voltage slope conductance (circles) and from 200 mV chord conductance (triangles). Solid lines have no theoretical meaning.

Computational Methods

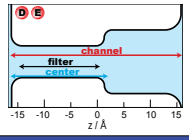
- Compute ion distributions in the channel via particle simulation (equilibrium Monte Carlo)
- Convert distributions into an estimate of slope conductance at small driving force using Drift-Diffusion theory
- Compare computed conductances with experimental conductances

$$-J_i(r) = \frac{D_i(r)}{k_B T}\rho_i \nabla \mu_i(r) \qquad \gamma = e_0 D_i \sum_i \frac{z_i^2 e_0^2}{k_B T}\left(\int_{z_{left}}^{z_{right}} \frac{dz}{n_i(z)}\right)^{-1}$$

(characteristic) Slope Conductance

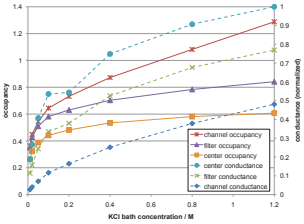
- Reduced models without added chemical effects are sufficient to explain the experimental saturation curve

Regions
- Channel: -16 Å, 16 Å
- Center: -16 Å, 3 Å
- Filter: -14 Å, 0 Å (cylindrical region)



Occupancy and Conductance by Region

$\varepsilon_{protein}$ = 4 and r_{filter} = 4 Å

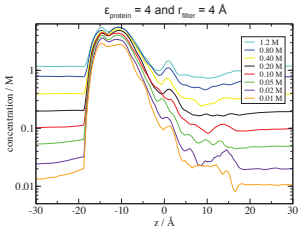


K^+ Occupancy

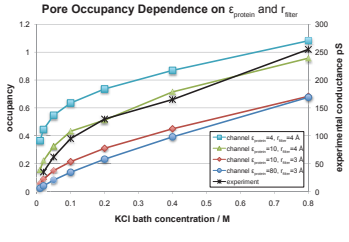
- Occupancy is the sum of ions in the channel between the walls of the membrane.
- Protein dielectric coefficient and filter radius can be adjusted to produce K^+ occupancy which mimics experimental slope conductance (at 0 mV) against KCl bath concentration.
- Model without D71/E80 charges yields linear occupancy with increasing bath concentration.
- Larger negative charge on E80 (with subsequent reduction of D71 charge) gives higher occupancy (not shown).

K^+ Concentration Profiles

$\varepsilon_{protein}$ = 4 and r_{filter} = 4 Å



Pore Occupancy Dependence on $\varepsilon_{protein}$ and r_{filter}



References

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