Modeling Ion Transport through Biological Channels:

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Transmembrane Transport

- **neural systems:**
  - a) communication among neurons
    * action potential
    * synaptic signaling
  - b) receptor – brain communication
- **heart muscle**
- **signaling and regulatory processes**

Channel malfunction
- Cystic fibrosis
- Epilepsy
- Diabetes
- Migraines
- Neuro-toxins

50% of drugs on the market target ion channels!
Recording Single Channel Ion Currents

Patch-Clamp Experiment

Plotting Current-Voltage Curve
Typical Ion Channels with Known Structure:

K⁺ channel (KCSA)  Acetylcholine receptor transmembrane domain

Types of ion channels:

- Simple pores (GA, GAP junctions)
- Substrate gated channels (Nicotinic receptor)
- Voltage-gated channels (K-channels)
- Pumps (ATP-synthase, K⁺,Na⁺-ATPase)
Poisson - Nernst -Planck Theory  (PNP)

- Dielectric slab with a pore in electrolyte solution

Flux:  **Nernst-Planck (NP)**

\[ \text{div}(\vec{j}_i) = 0 \]

\[ \vec{j}_i = -D_i \nabla c_i - D_i q_i c_i \beta \nabla \phi \]

Electrostatics: **Poisson (P)**

\[ \nabla \cdot (\varepsilon \nabla \phi) = -4\pi \left( \sum_{j=1}^{\text{protein atoms}} \rho_j + \sum_{i=1}^{\text{ions}} z_i e c_i \right) \]

Boundary Conditions: at the box boundaries

- Applied Potential \( \phi_L, \phi_R = \text{const} \) – dirichlet bc for potential
- Known salt concentrations \( c_L, c_R = \text{const} \) – dirichlet bc for concentrations

\( \varepsilon_m = 2 \)

Membrane \( \varepsilon_B \)

Water \( \varepsilon_B = 80 \)

\( j_\perp = 0 \) no flux through the channel wall
Gramicidin A in DMPC lipid bilayer and water

- Antibiotic peptide
  
  Forms a pore in the cell wall of a bacteria and lets out monovalent cations (K⁺, Na⁺)
  
  Membrane potential disappears and bacteria dies.

- 15 amino acids, helical
- Channel is formed by a head-to-head dimer

- NMR structure of protein with partial charges
- Water, membrane and mobile ions - continuum
Cation Density in Gramicidin A Channel From PNP Calculation

Cation density maxima indicate possible binding sites inside the channel protein
• GA with charges and dipoles embedded on the membrane surface

Theory/Modeling results from:
A.E. Cárdenas, R. D. Coalson and M. G. Kurnikova,
GA

PC (uncharged)/
PS (charged)
Lipid Bilayer

GMO (non-dipolar)
Lipid Bilayer
I-V curves for GA embedded in PC (uncharged) and PS (charged) Membranes at neutral pH

Legend: open triangle = 1.0M (charges); open diamond = 0.1M (charges); closed triangle = 1.0M (neutral); closed diamond = 0.1M (neutral)

* Rostovtseva et al
Conductance for GA in mixed bilayers at neutral pH
$[\text{CsCl}] = 0.1\text{M}$

* Rostovtseva et al.