Modeling Ion Transport through Biological Channels:

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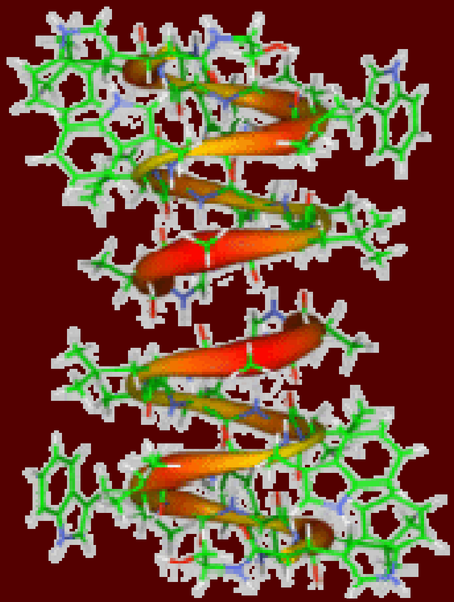
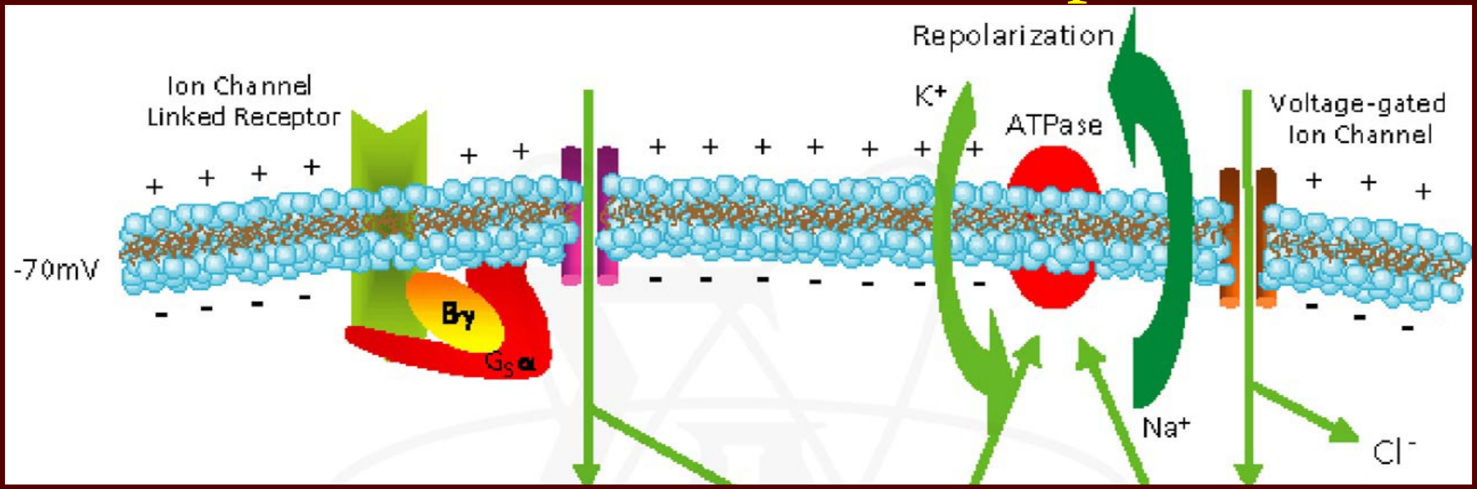


Transmembrane Transport



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

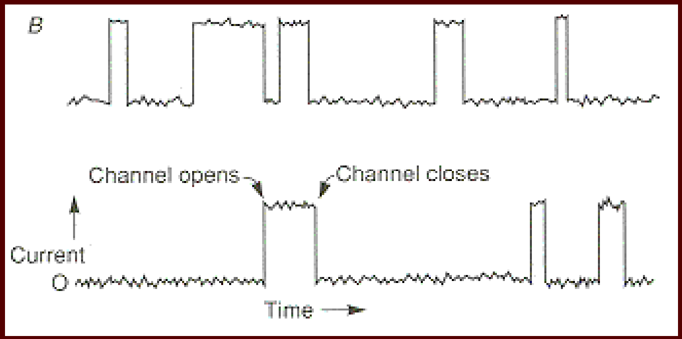
Channel malfunction

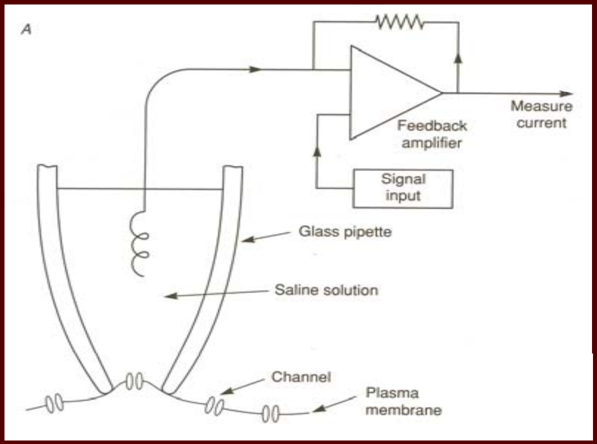
Cystic fibrosis
Epilepsy
Diabetes
Migraines
Neuro-toxins

50% of drugs on the market target ion channels!

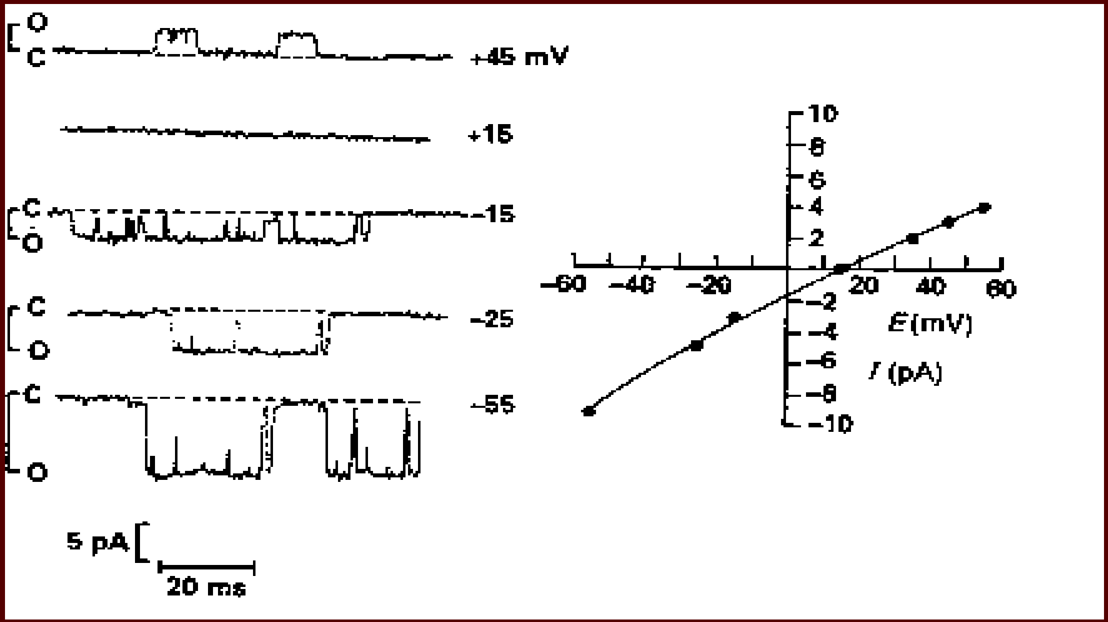
Recording Single Channel Ion Currents

Patch-Clamp Experiment

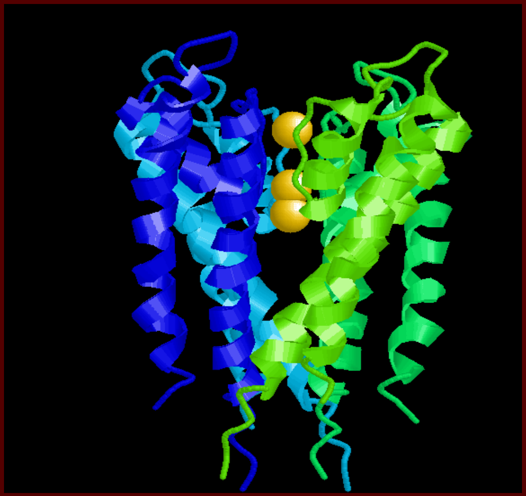




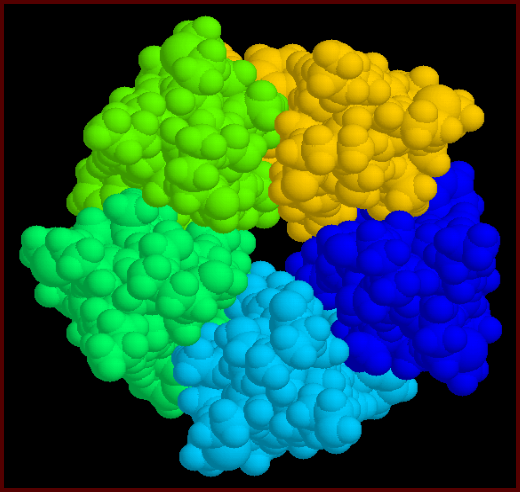
Plotting Current-Voltage Curve



Typical Ion Channels with Known Structure:



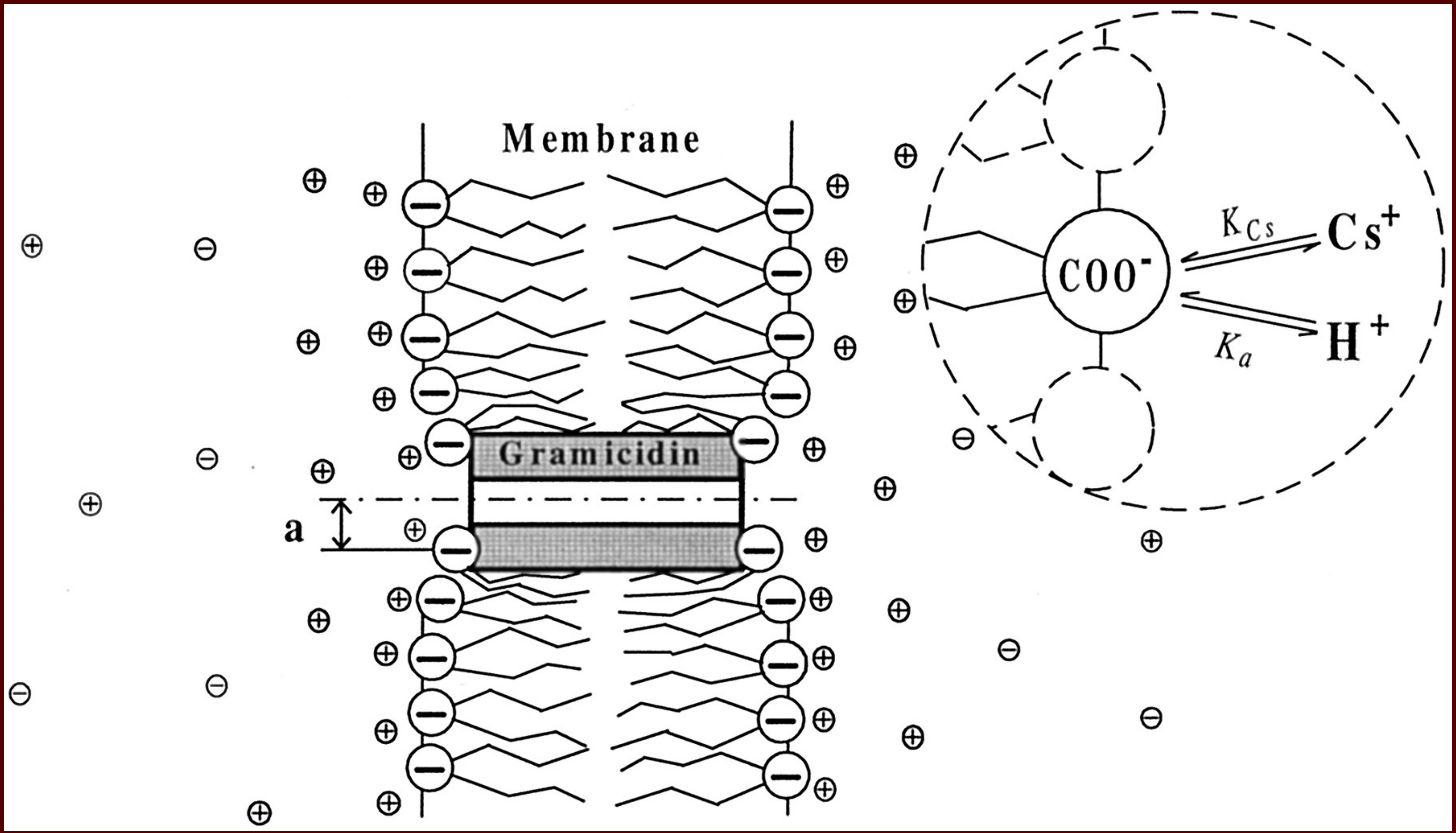
K^+ channel (KCSA)



Acetylcholine receptor
transmembrane domain

Types of ion channels:

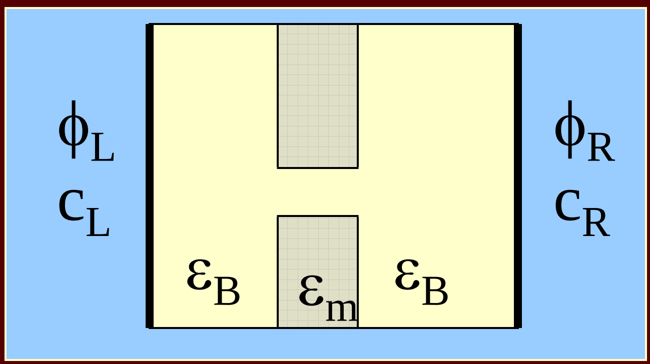
- ✓ Simple pores (GA, GAP junctions)
- ✓ Substrate gated channels (Nicotinic receptor)
- ✓ Voltage-gated channels (K-channels)
- ✓ Pumps (ATP-synthase, K^+,Na^+-ATPase)



Membrane Surface-Charge Titration Probed by Gramicidin A Channel Conductance -- Rostovtseva et al., Biophys. J. **75**, 1783 (1998).

Poisson - Nernst -Planck Theory (PNP)

- Dielectric slab with a pore in electrolyte solution



Membrane $\varepsilon_m = 2$
Water $\varepsilon_B = 80$

✓ $j_\perp = 0$ no flux through the channel wall

Flux: *Nernst-Planck (NP)*

$$div(\vec{j}_i) = 0$$ <--*Steady state current*

$$\vec{j}_i = -D_i \vec{\nabla} c_i - D_i q_i c_i \beta \vec{\nabla} \varphi$$

Electrostatics: *Poisson (P)*

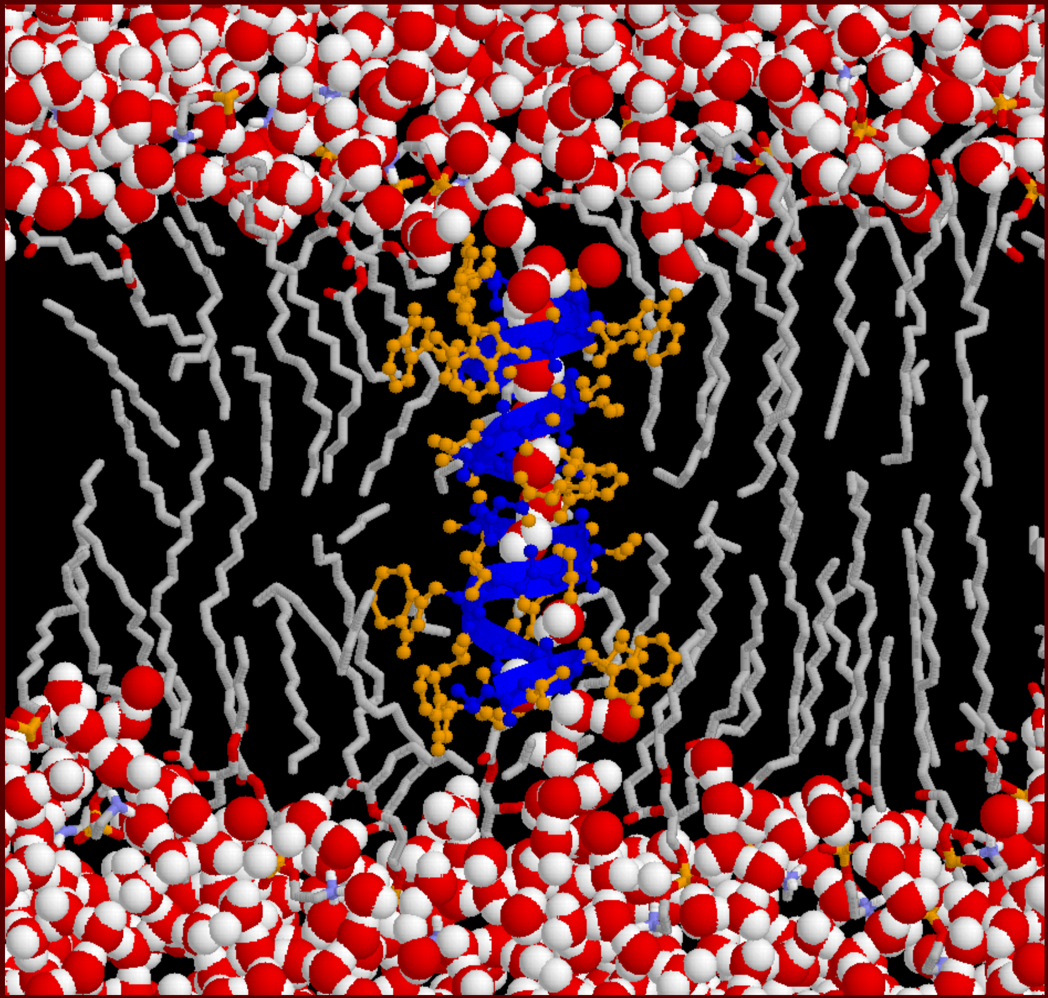
$$\vec{\nabla} \cdot (\varepsilon \vec{\nabla} \varphi) = -4\pi \left(\sum_{j=1}^{\text{protein atoms}} \rho_j + \sum_{i=1}^{\text{ions}} z_i e c_i \right)$$

Boundary Conditions: at the box boundaries

✓ Applied Potential
ϕ_L, ϕ_R =const – dirichlet bc for potential

✓ Known salt concentrations
c_L, c_R =const – dirichlet bc for concentrations

Gramicidin A in DMPC lipid bilayer and water



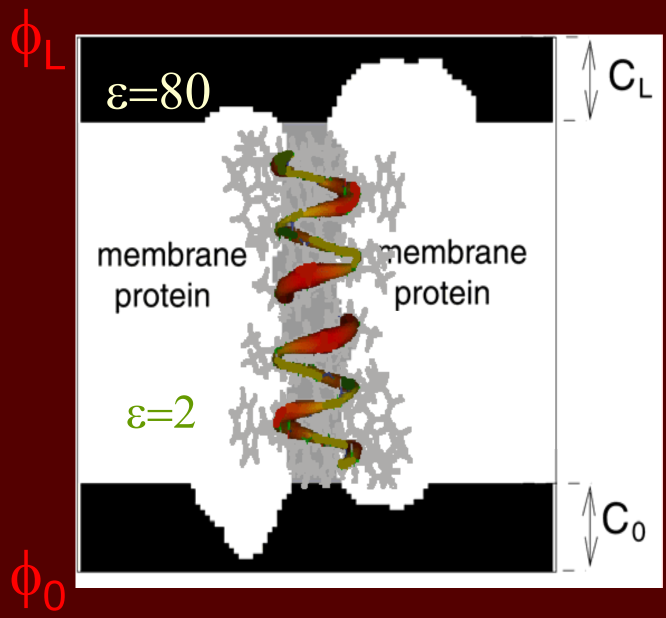
✓Antibiotic peptide

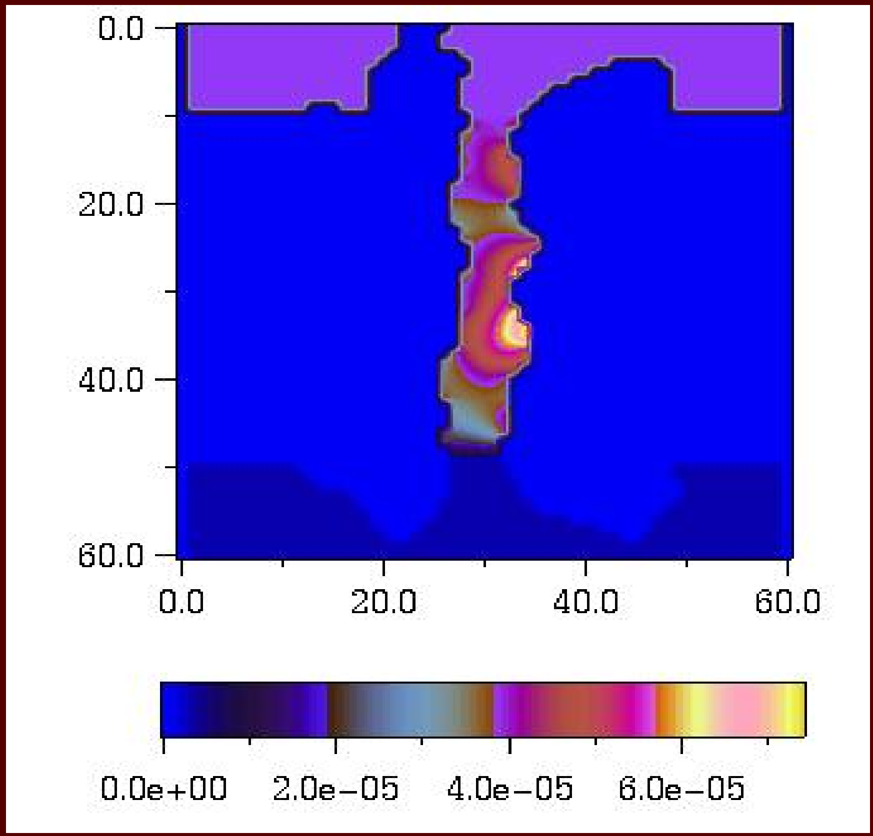
Forms a pore in the cell wall of a bacteria and lets out monovalent cations (K+, Na+)
Membrane potential disappears and bacteria dies.

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

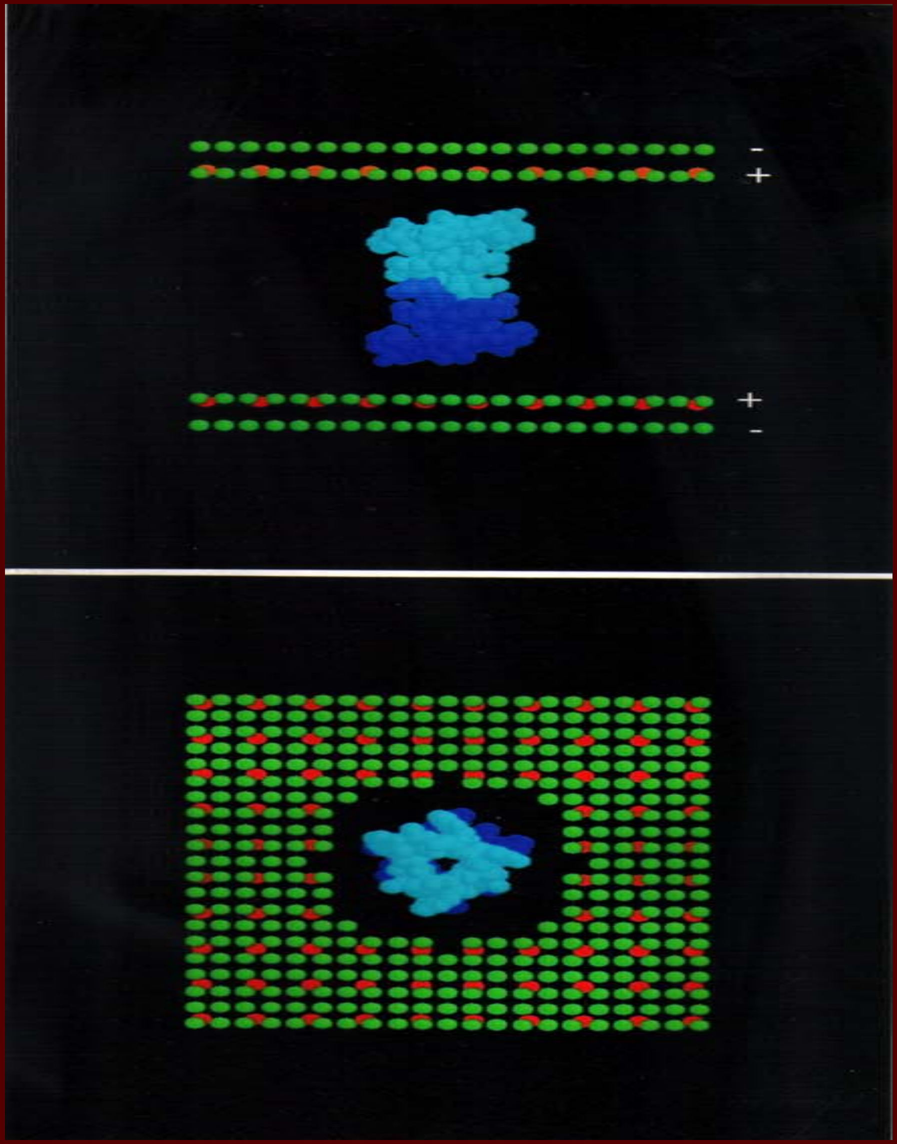
✓ NMR structure of protein with partial charges
✓water, membrane and mobile ions - continuum

Cation Density in Gramicidin A Channel From PNP Calculation





Cation density maxima indicate possible binding sites inside the channel protein



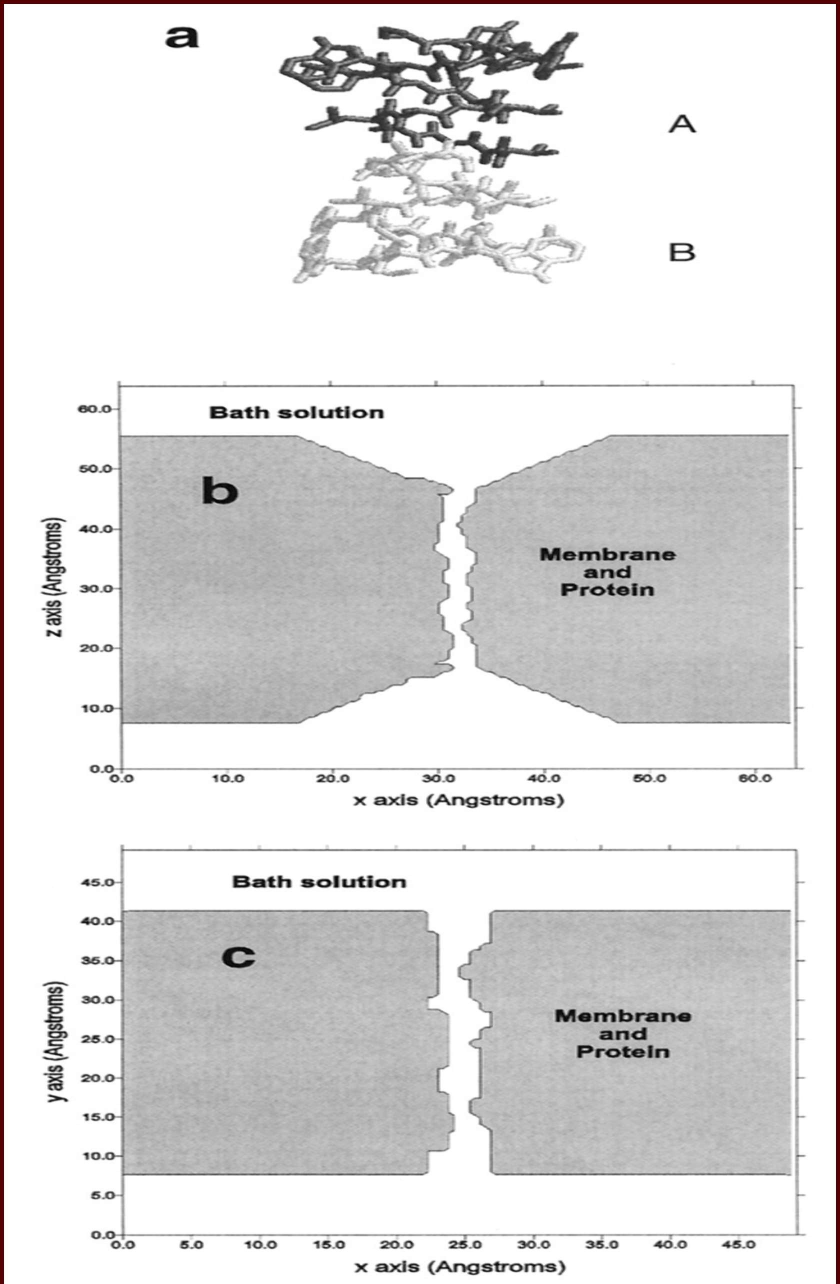
Theory/Modeling results from:
A.E. Cárdenas, R. D. Coalson and M. G. Kurnikova,
"3D Poisson-Nernst-Planck Theory Studies: Influence of Membrane Electrostatics on Gramicidin A Channel Conductance", Biophys. J. ***79***, 80-93 (2000).

- GA with charges and dipoles embedded on the membrane surface

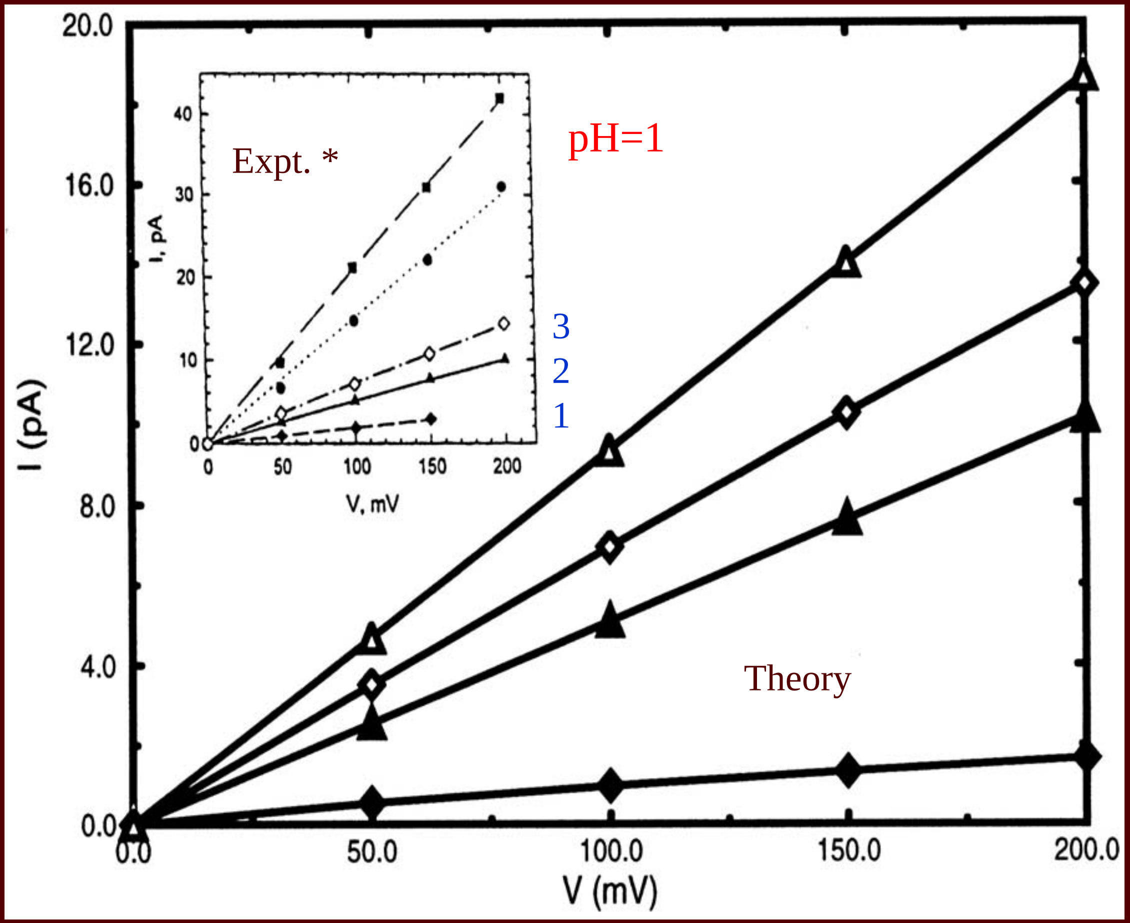
GA

PC (uncharged)/
PS (charged)
Lipid Bilayer

GMO (non-dipolar)
Lipid Bilayer



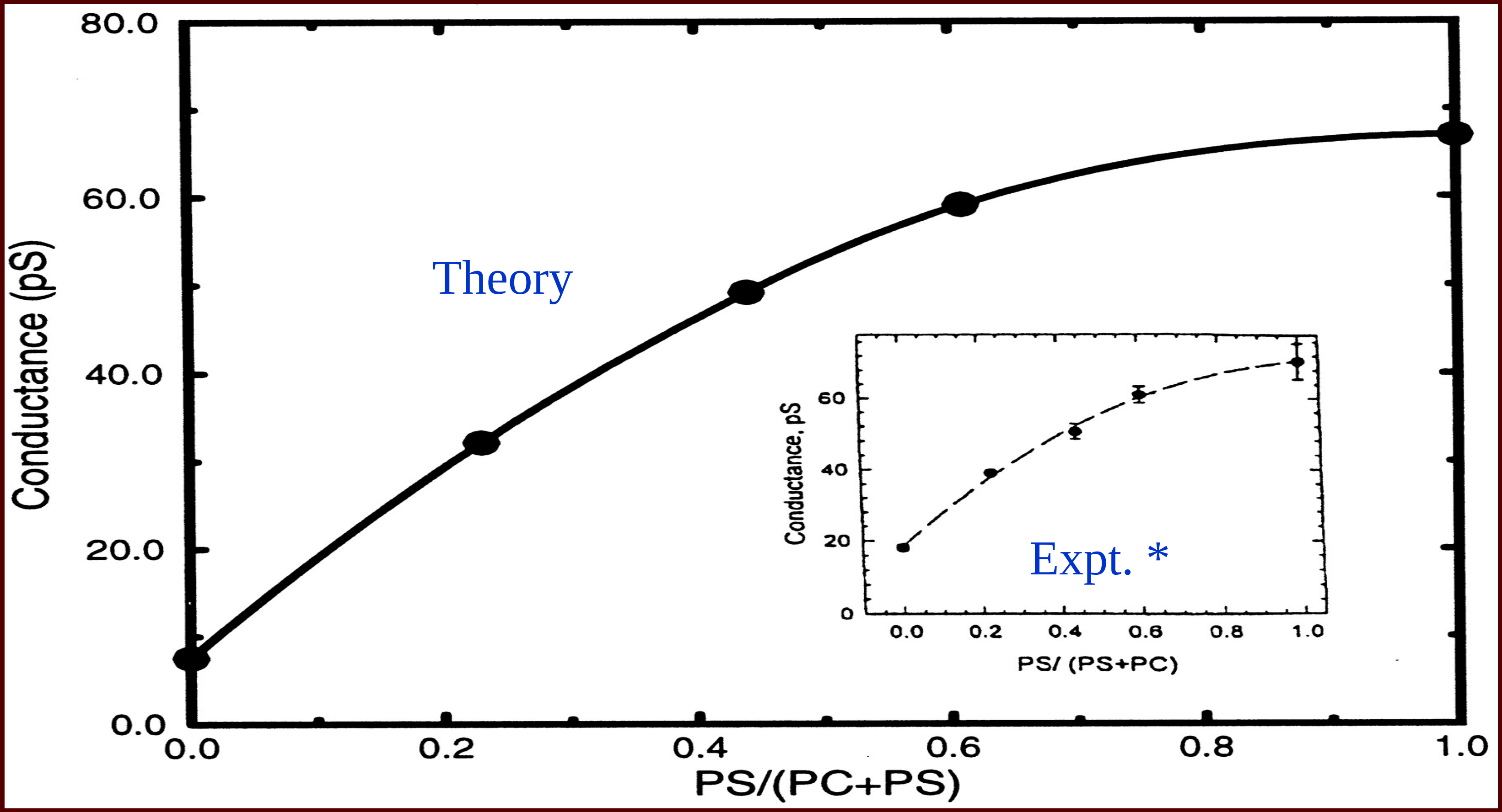
I-V curves for GA embedded in PC (uncharged) and PS (charged) Membranes at neutral pH



* Rostovtseva et al

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

Conductance for GA in mixed bilayers at neutral pH
[CsCl] = 0.1M



* Rostovtseva et al.