Simulating Membrane Channels

Emad Tajkhorshid
Beckman Institute, UIUC

Theoretical and Computational Biophysics
Dec 2004, Boston, MA
http://www.ks.uiuc.edu/Training/

Simulating Membrane Channels

- Brief Introduction to Membrane and a few examples of Membrane Channels
- Aquaporin Water Channels
  - How to model membrane proteins in membrane
  - How much can we learn from simulations?
  - How to analyze the data? Where to look?
- Nanotubes and today's exercises
  - Nanotubes as simple models for membrane water channels

Simulating Membrane Channels

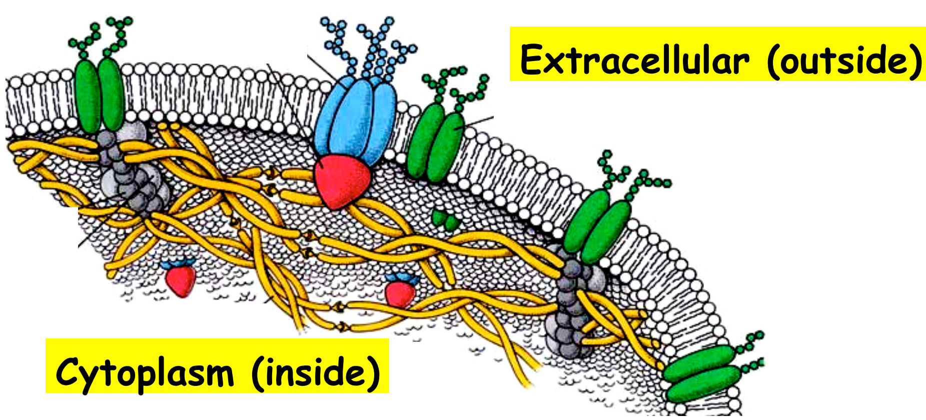
Part I. Introduction

Theoretical and Computational Biophysics
Dec 2004, Boston, MA
http://www.ks.uiuc.edu/Training/

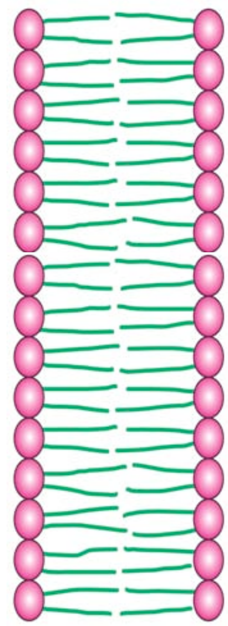
Why Do Living Cells Need Membrane Channels (Proteins)?

- **Living cells also need to exchange materials and information with the outside world**

… however, in a highly selective manner.

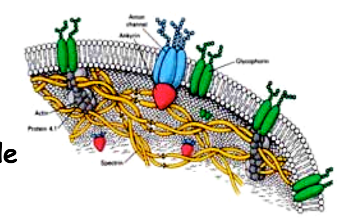


Lipid Bilayers Are Excellent For Cell Membranes



- **Hydrophobic interaction is the driving force**
- **Self-assembly in water**
- **Tendency to close on themselves**
- **Self-sealing (a hole is unfavorable)**
- **Extensive: up to millimeters**

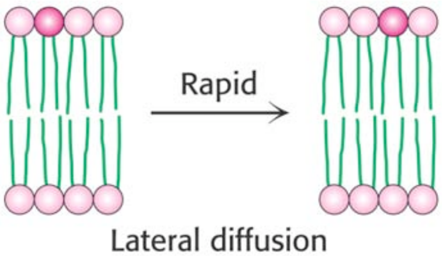
Lipid Membranes



- **Receptors, detecting the signals from outside**
  - **Light**
  - **Odorant**
  - **Taste**
  - **Chemicals**
    - **Hormones**
    - **Neurotransmitters**
    - **Drugs**
- **Channels, gates and pumps**
- **Electric/chemical potential**
  - **Neurophysiology**
  - **Energy**
- **Energy transduction:**
  - **Photosynthesis**
  - **Oxidative phosphorylation**

A highly selective permeability barrier

Lipid Diffusion in Membrane



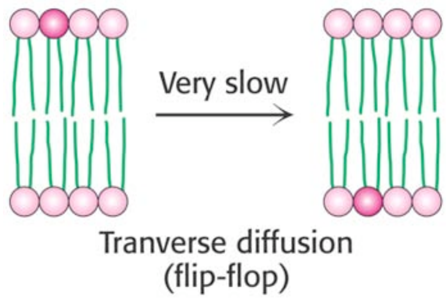
$D = 1 \text{ mm}^2.s^{-1}$

50 Å in ~ 2.5×10^{-5} s

~9 orders of magnitude difference

$D_{lip} = 10^{-8} \text{ cm}^2.s^{-1}$

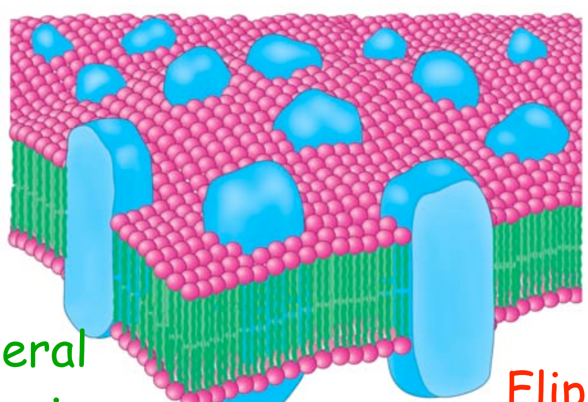
$D_{wat} = 2.5 \times 10^{-5} \text{ cm}^2.s^{-1}$



Once in several hours!

(10^4 s)

Fluid Mosaic Model of Membrane



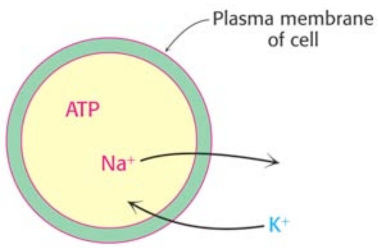
Lateral Diffusion Allowed

Flip-flap Forbidden

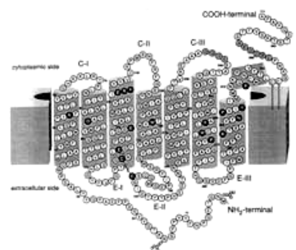
Ensuring the conservation of membrane asymmetric structure

Importance of Asymmetry

Apart from passive transport mechanisms, all membrane proteins function in a directed fashion, and their correct insertion into the cell membrane is essential for their biological function.



Cytoplasmic side

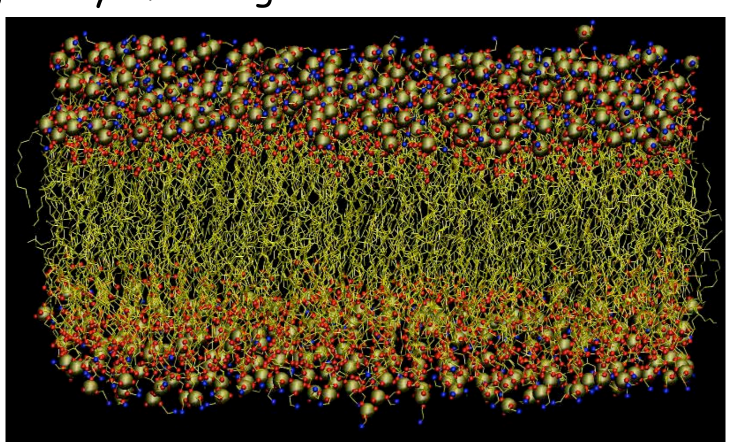


Extracellular side

Technical difficulties in Simulations of Biological Membranes

- Time scale
- Heterogeneity of biological membranes ☹

60 x 60 Å
Pure POPE
5 ns
~100,000
atoms

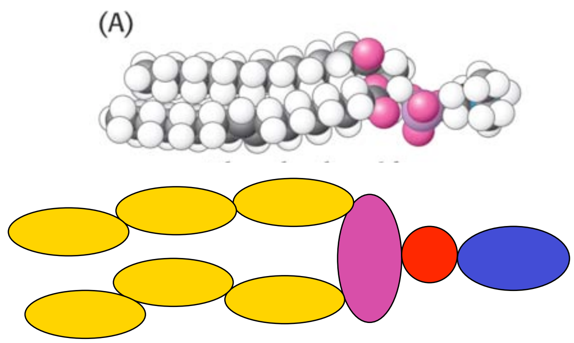


Coarse grain modeling of lipids

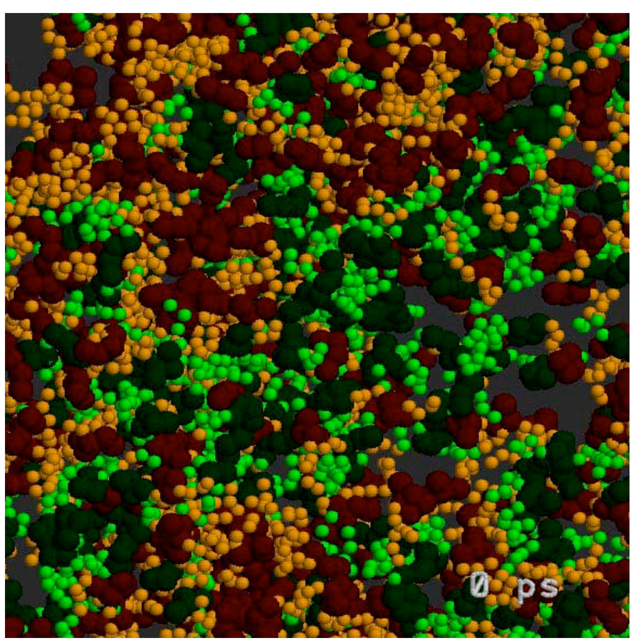
150 particles

↓

9 particles!



Also, increasing the time step by orders of magnitude.



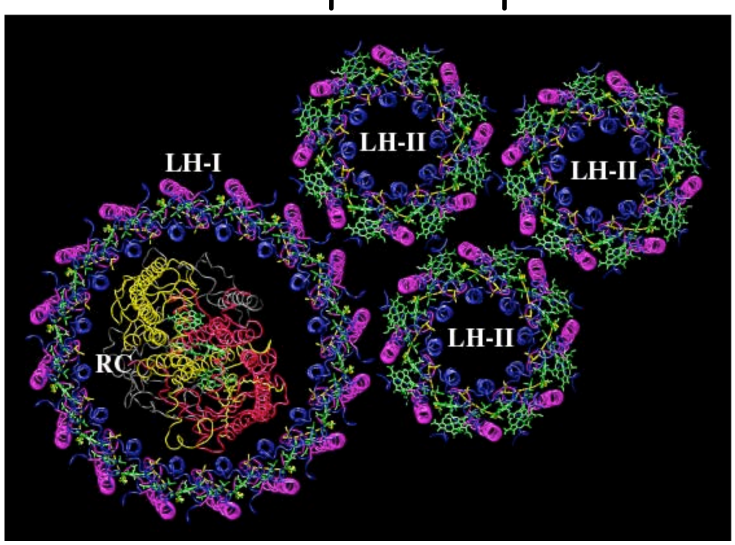
by: J. Siewert-Jan Marrink and Alan E. Mark, University of Groningen, The Netherlands

Protein/Lipid ratio

- Pure lipid: insulation (neuronal cells)
- Other membranes: on average 50%
- Energy transduction membranes (75%)
  Membranes of mitocondria and chloroplast
  Purple membrane of halobacteria

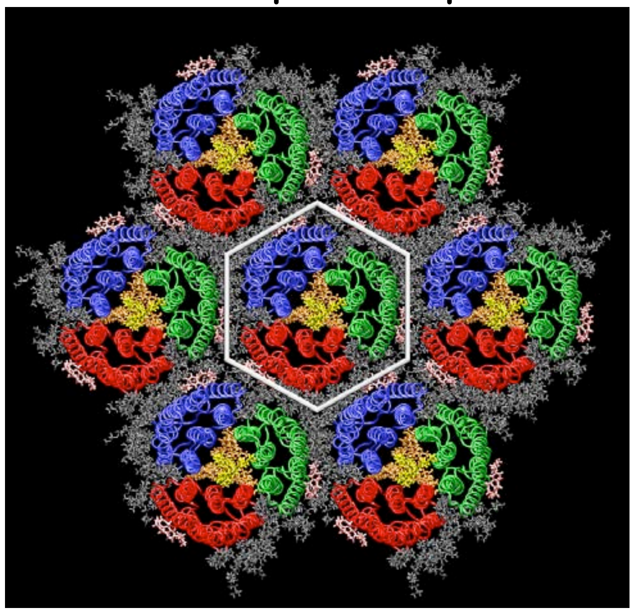
- Different functions = different protein composition

Protein / Lipid Composition



Light harvesting complex of purple bacteria

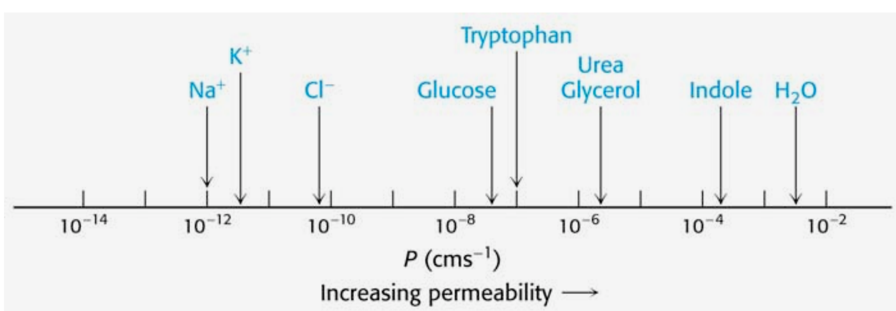
Protein / Lipid Composition



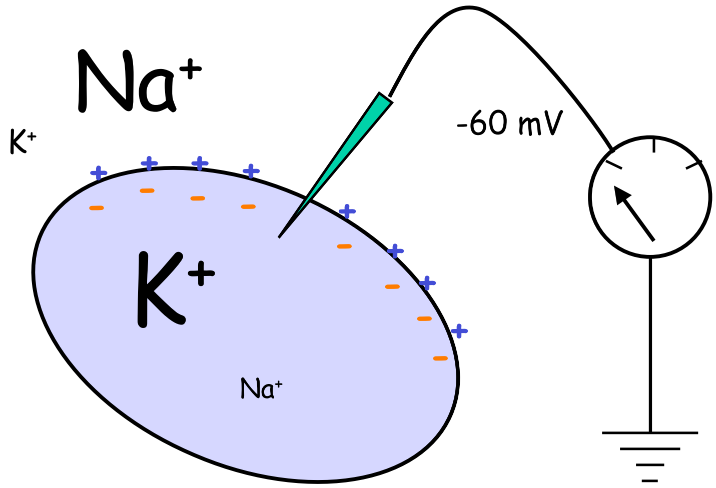
The purple membrane of halobacteria

Bilayer Permeability

- Low permeability to charged and polar substances
- Water is an exception: small size, lack of charge, and its high concentration
- Desolvation of ions is very costly.



Membrane Electrical Potential

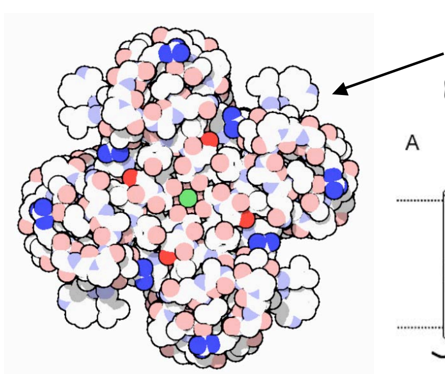


The ratio of ions is about 1 to 10

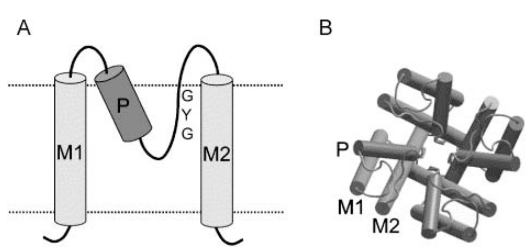
Action potential in excitable cells

KcsA Potassium Channel

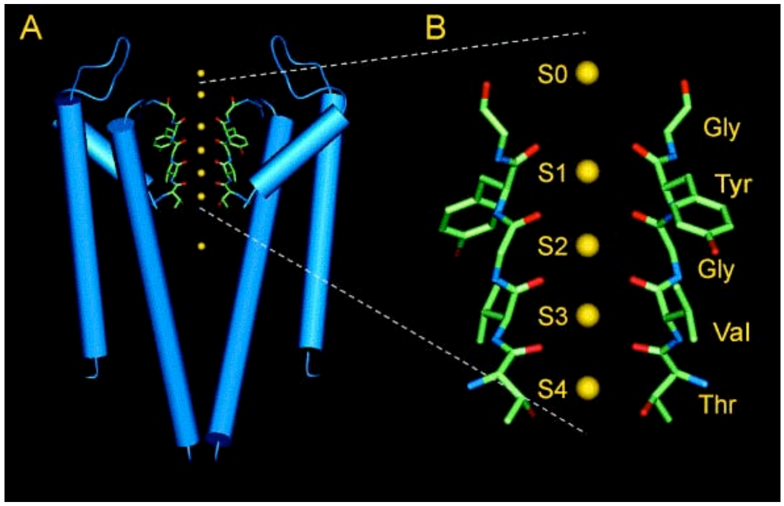
Under physiological conditions, the selectivity filter of the KcsA dehydrates, transfers, and rehydrates one K^+ ion every 10 ns.

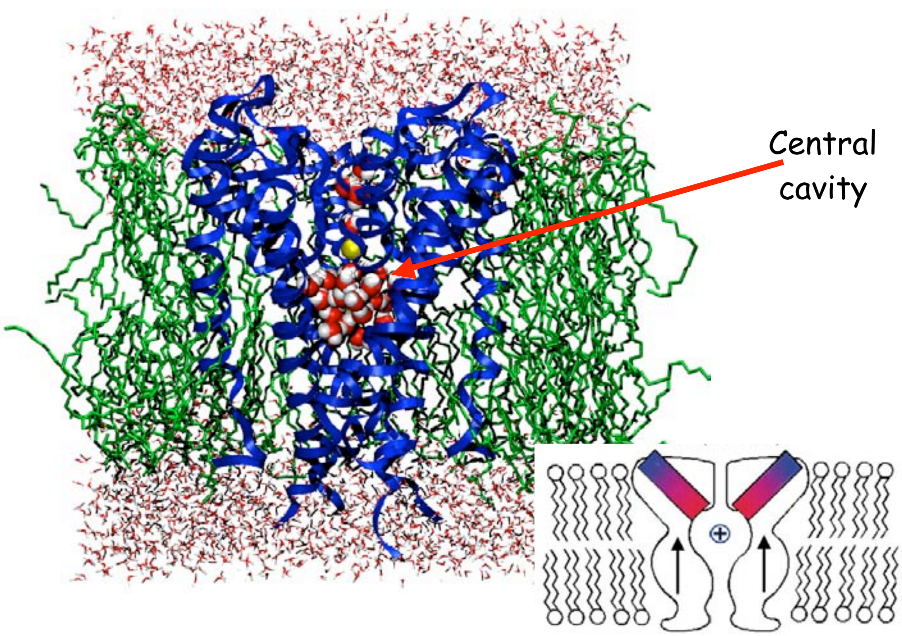


PDB Feb 2003 molecule of the month

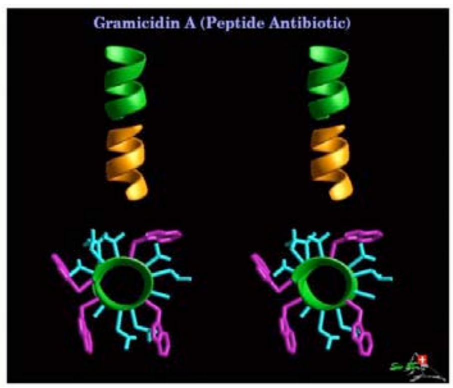


K binding sites in the selectivity filter





Gramicidin A
an ion leak inside the membrane



Through dissipating the electrochecmical potential of membrane, gramicidin A acts as an antibiotic.