Molecular Dynamics Simulation of Membrane Channels

Part I. Overview and Examples

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Molecular Dynamics Simulation of Membrane Channels

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

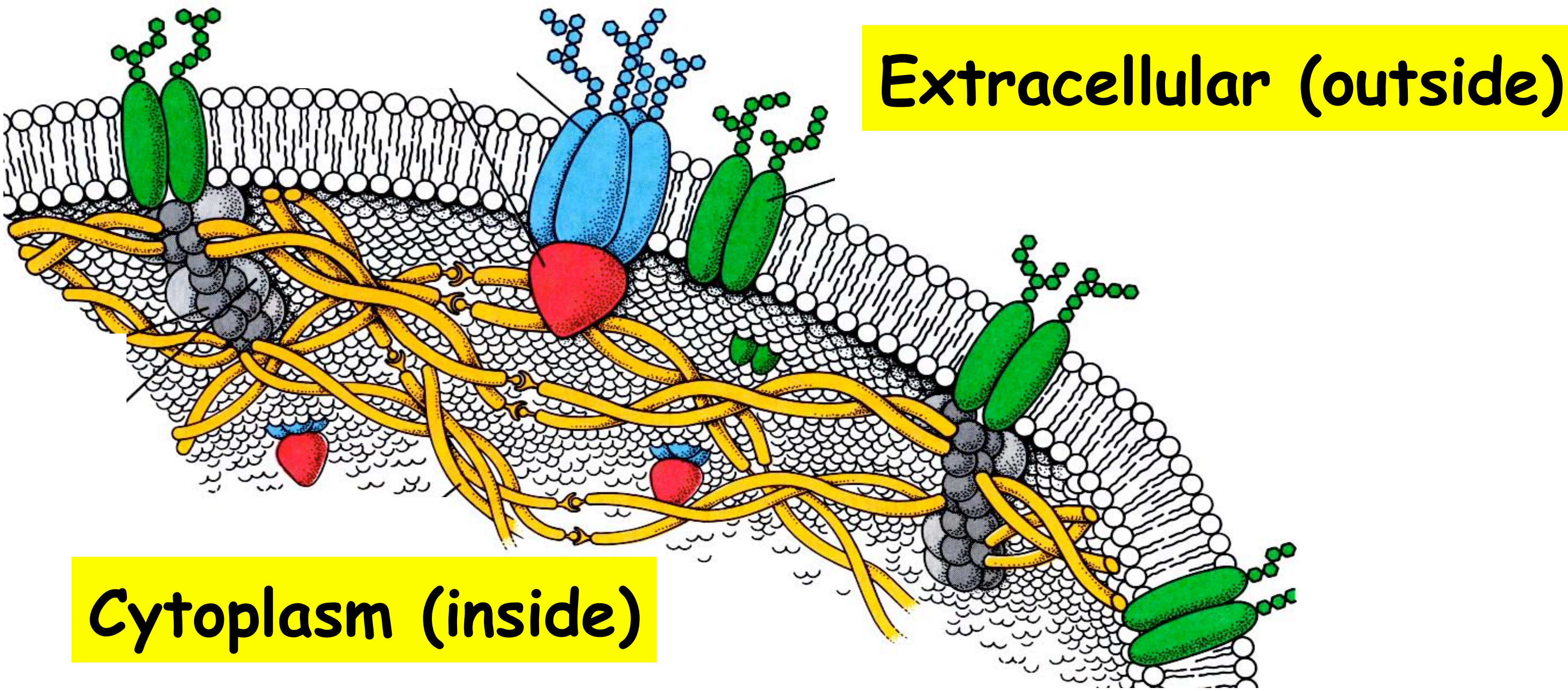
Why Do Living Cells Need Membranes and Membrane Channels?

- **Water is the medium of life: water is the most abundant compound in living cells/organisms, and all biochemical reactions take place in water.**

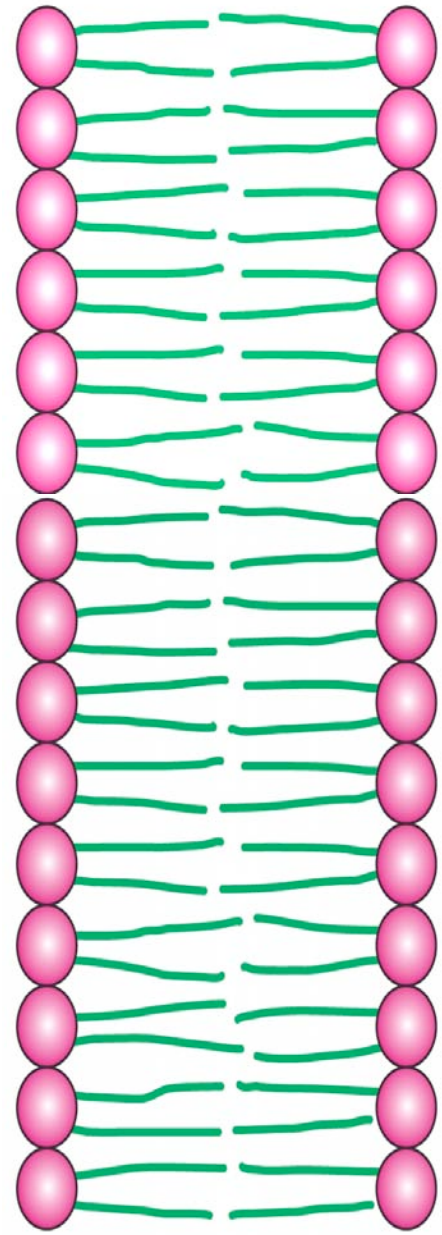
- **Living cells need to isolate their interior compartment from the environment, a task that, in a water-dominated medium, can be best done by fatty molecules.**

The Roles of Cell Membranes

- **Conservation of materials inside the cell**
- **Protection against undesired substances**
- **But Access for desired substances!**



Lipid Bilayers are Excellent for Cell Membranes

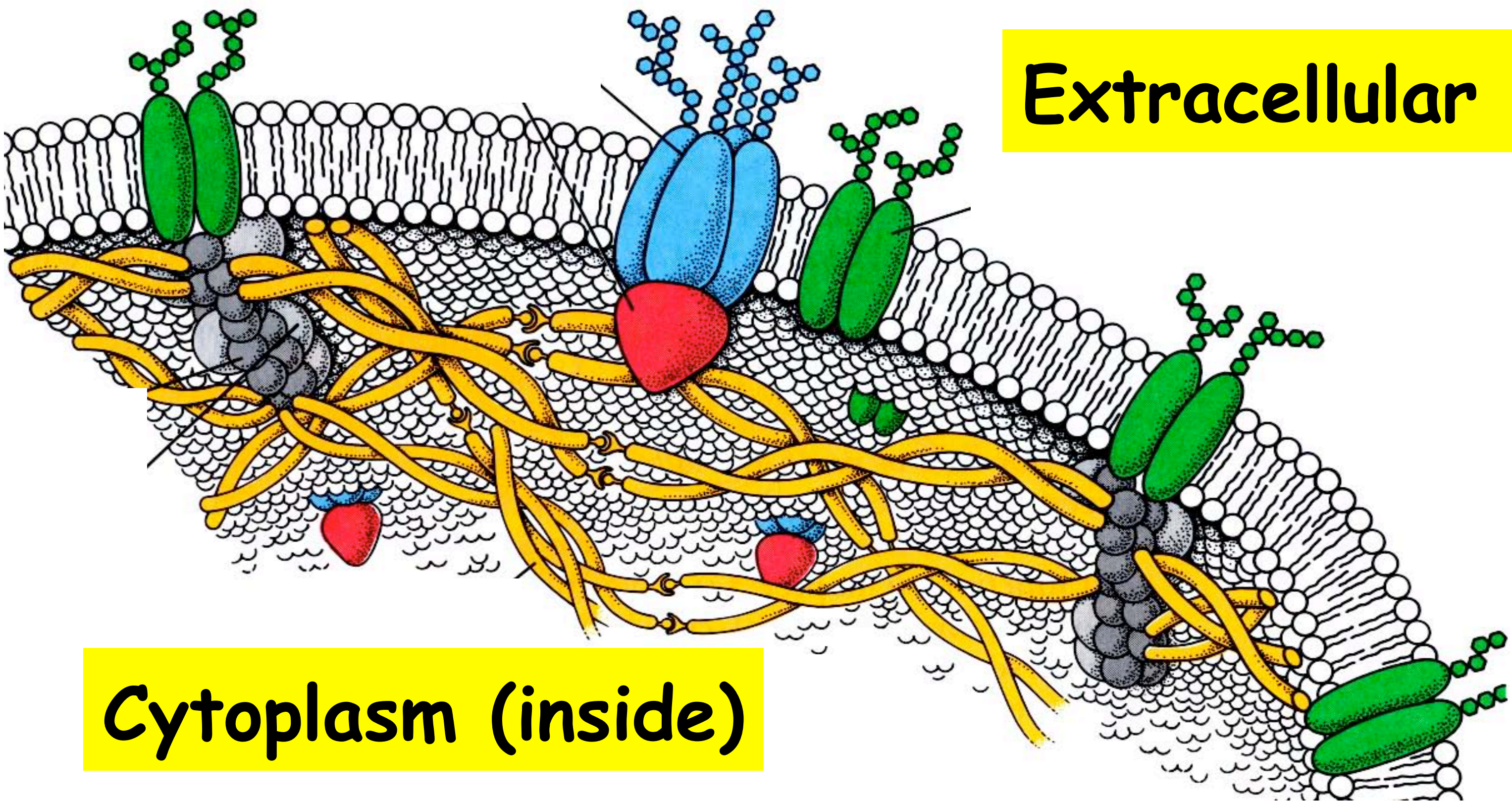


- **Hydrophobic interaction is the driving force for their formation**
- **They self-assembly in water**
- **They tend to close on themselves**
- **They self-seal (holes unfavorable)**
- **They can be extensive: up to mm**

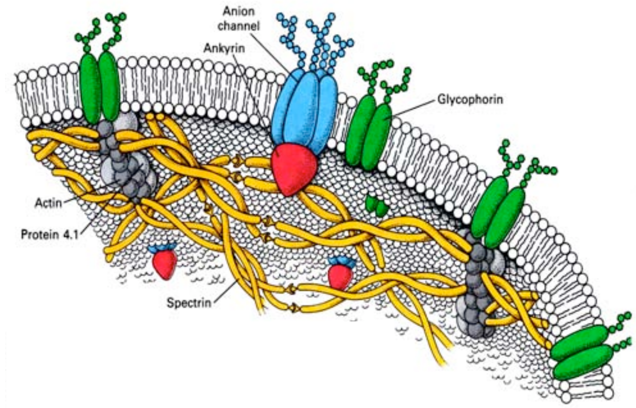
Why Do Living Cells Need Membrane Channels (Proteins)?

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

… however, in a highly <u>selective</u> manner.



Proteins in Membranes

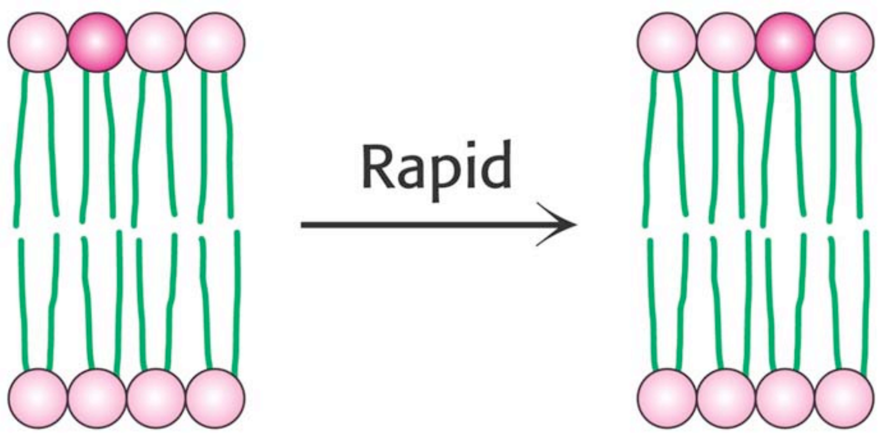


- As receptors, detecting signals from outside:
  - Light
  - Odorant
  - Taste
  - Chemicals
    - Hormones
    - Neurotransmitters
    - Drugs
- As channels, forming gates and pumps
- As generators of electric/chemical potentials
  - Energy storage
  - Neurophysiology
- As energy transducers
  - Photosynthesis
  - Oxidative phosphorylation

A highly selective permeability barrier

Internal membranes for organelles

Lipid Diffusion in Membrane



Lateral diffusion

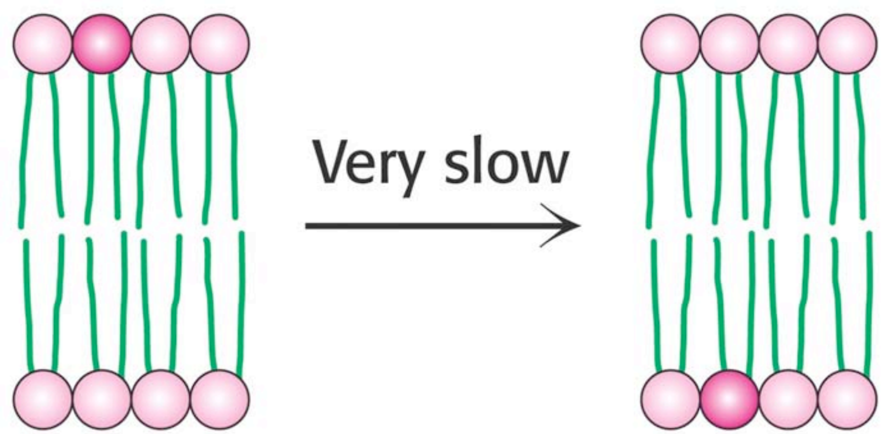
$D = 1\ \mu m^2.s^{-1}$

50 Å in ~ 2.5×10^{-5} s

~9 orders of magnitude difference

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

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

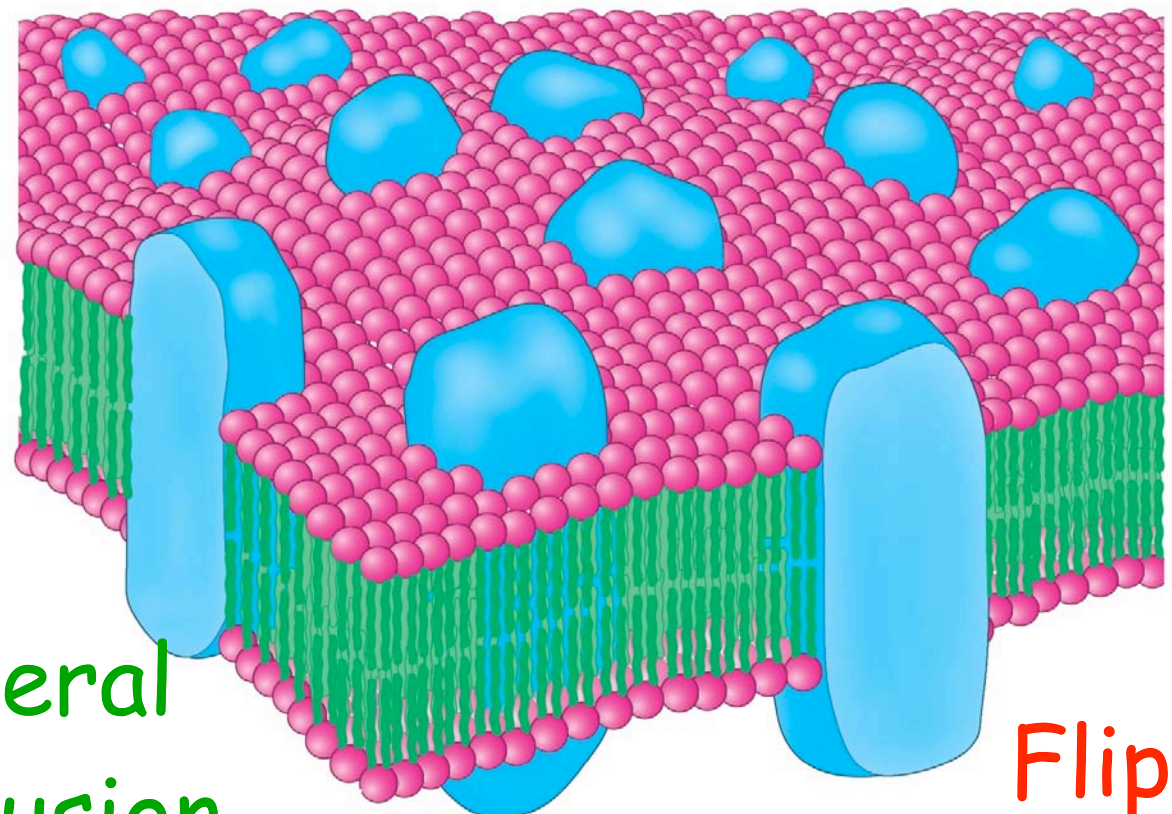


Tranverse diffusion
(flip-flop)

Once in several hours!

(10^4 s)

Fluid Mosaic Model of Membrane



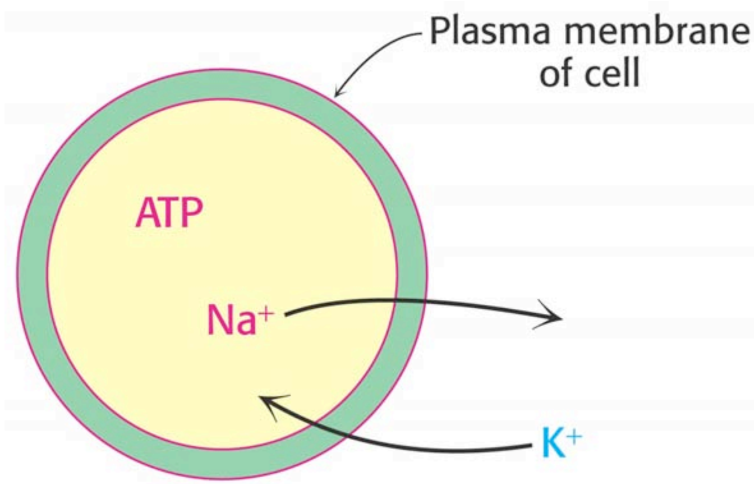
Lateral Diffusion Allowed

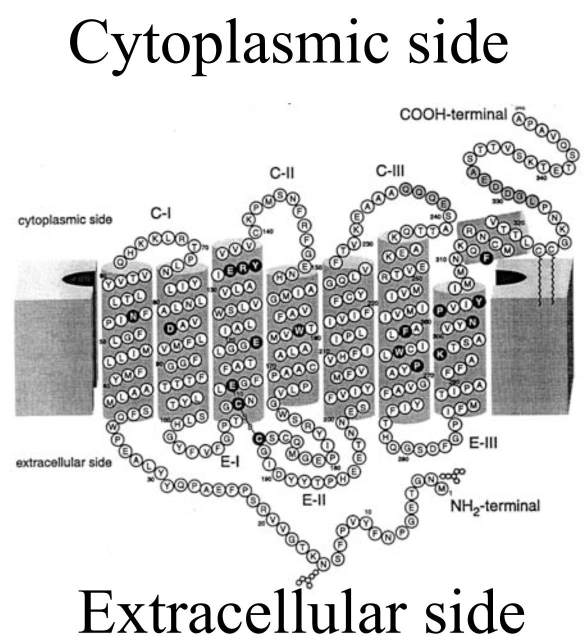
Flip-flap Forbidden

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.



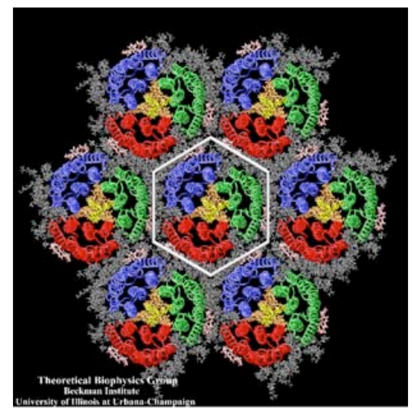


Protein/Lipid ratio

- Pure lipid: insulation (neuronal cells)
- Other membranes: on average 50%
- Energy transduction membranes (75%)

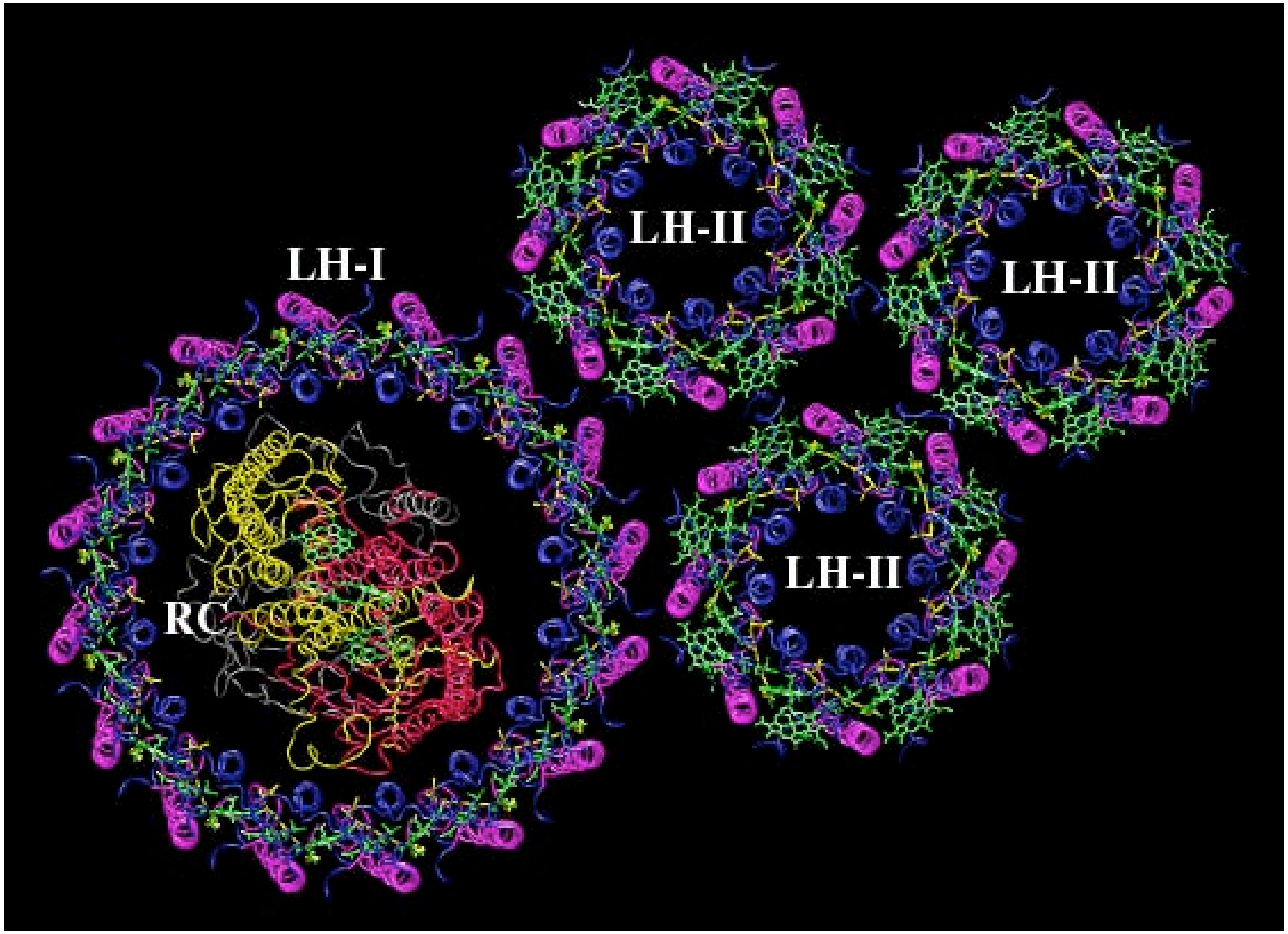
  Membranes of mitocondria and chloroplast

  Purple membrane of halobacteria



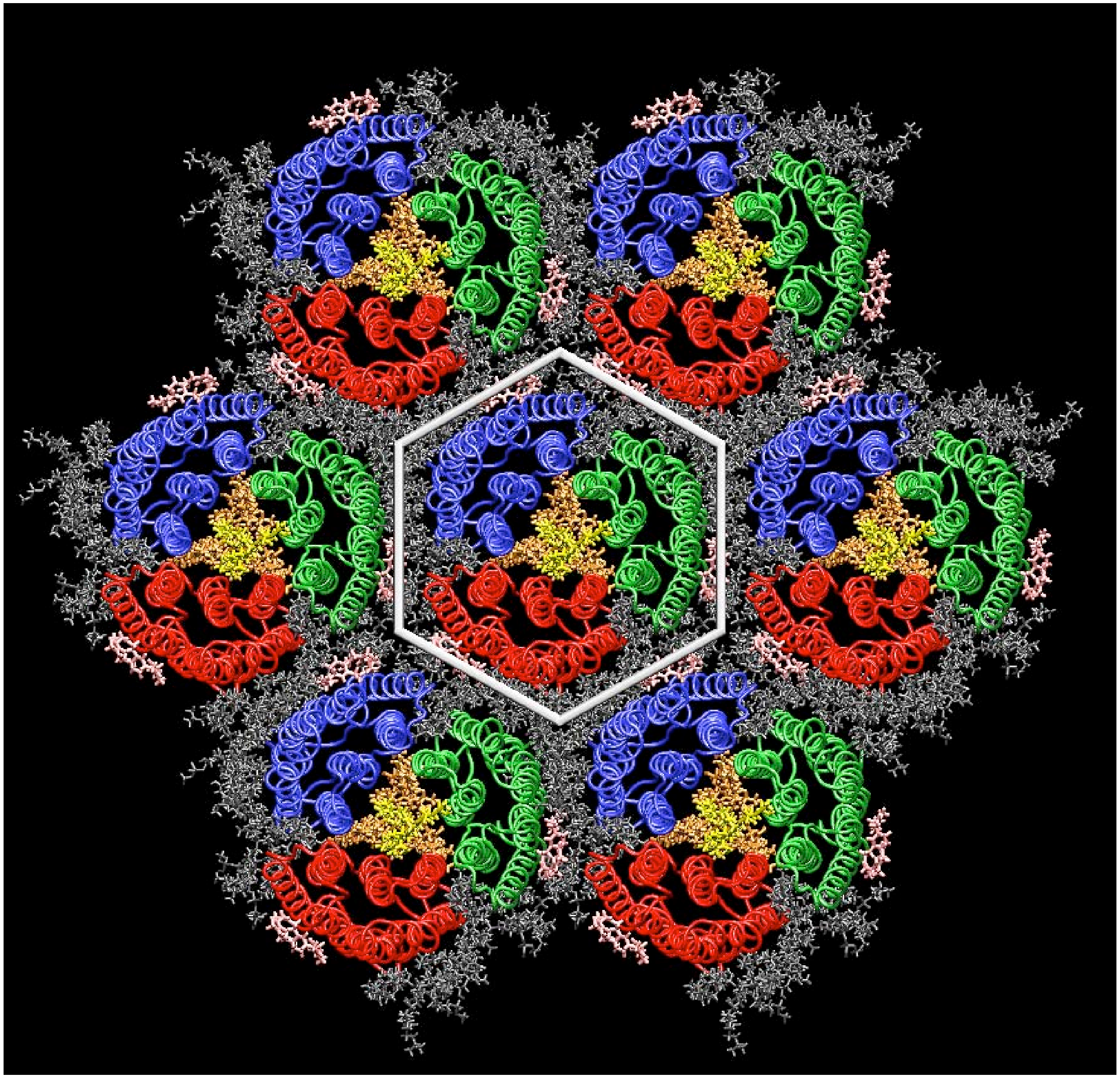
- Different functions = different protein composition

Protein / Lipid Composition



Light harvesting complex of purple bacteria

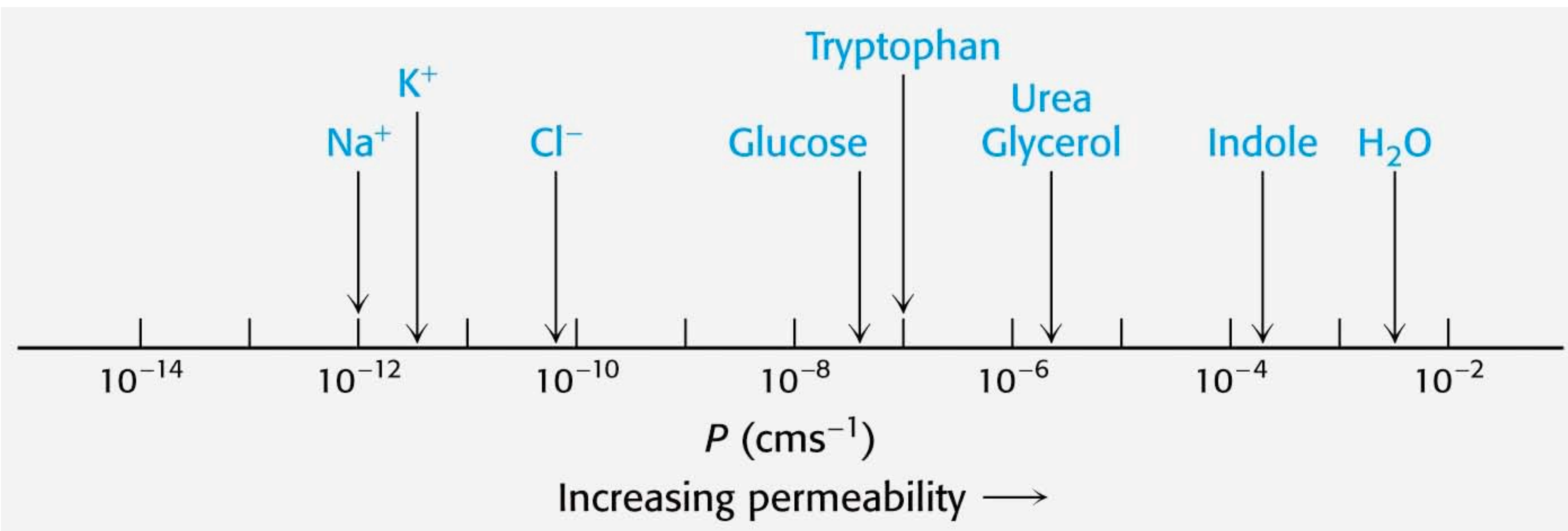
Protein / Lipid Composition



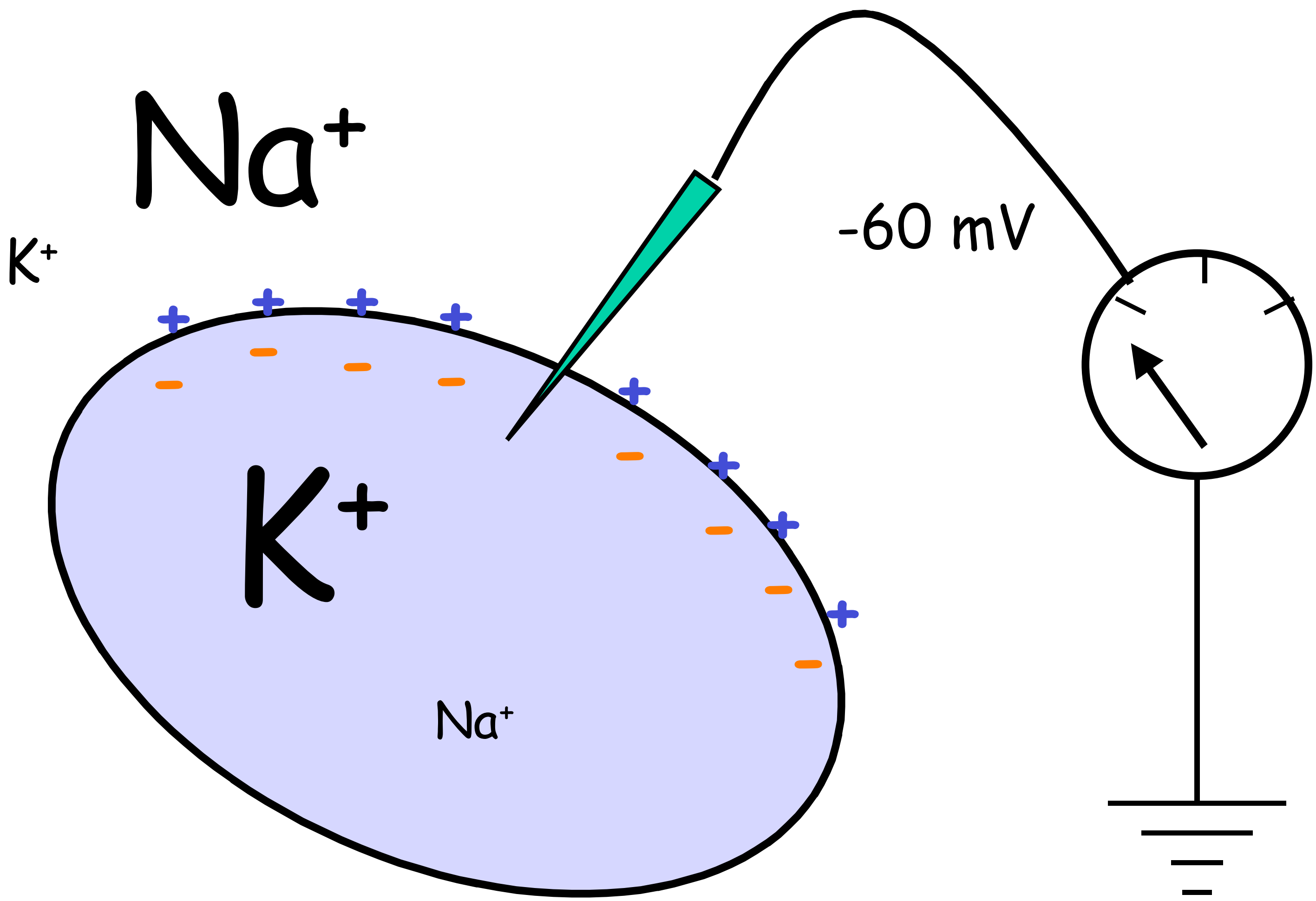
The purple membrane of halobacteria

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

Properties of Ion Channels

Membrane-spanning protein

Hydrophilic ion conductive pathway

- Water-filled
- Traversing ion must lose hydration shell

Selective

- charge screening and size

Gating properties

- Exist in open and closed states

Substrate is charged and the conduction can be measured very precisely, as opposed to water channels.

Control of conduction in ion channels

Gating mechanisms (open-closed transition) due to

Membrane potential change (voltage gated channels)
    K channels

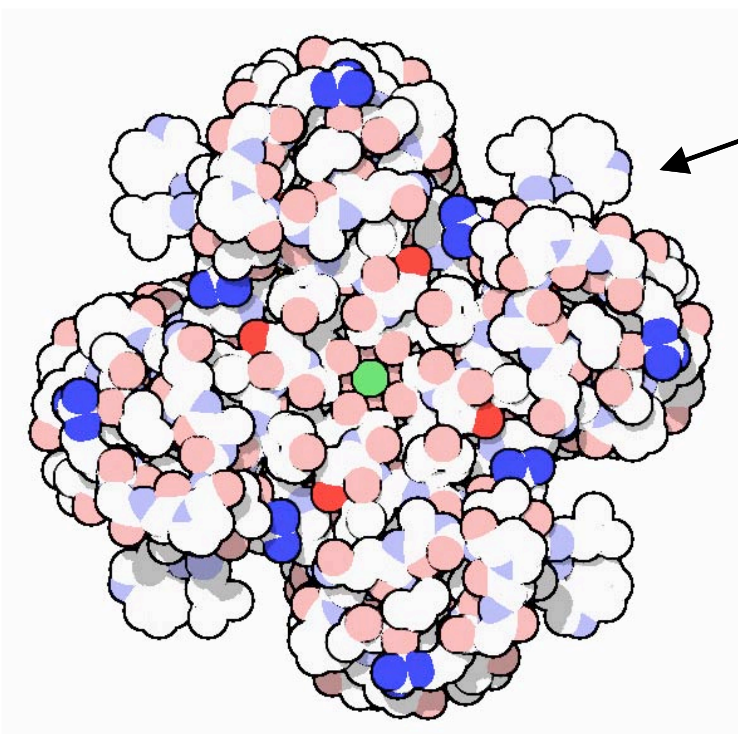
Binding of a molecule (ligand-gated channels)
    Acetylcholine nicotinic receptor (Na channel)
    Glutamate receptor (Ca channel)

Voltage and ligand gating can co-exist

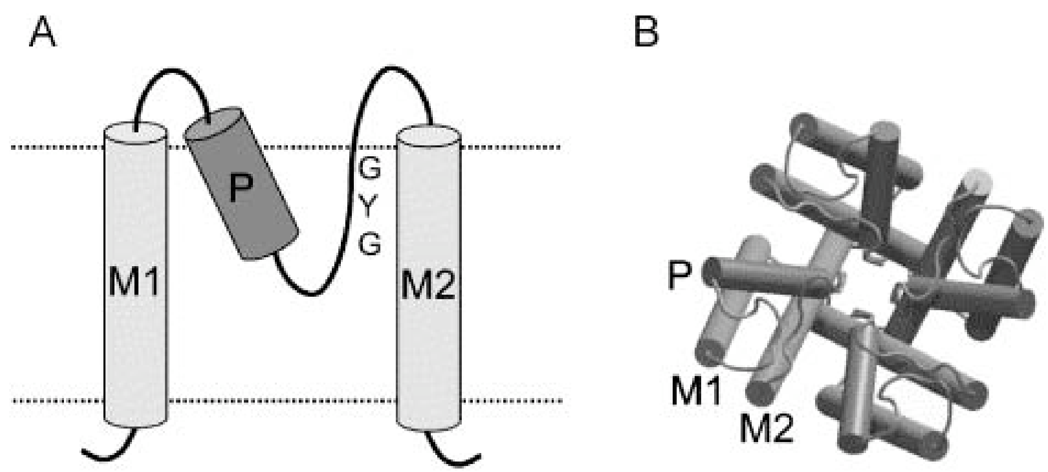
Mechanical gating (MscL)

KcsA Potassium Channel

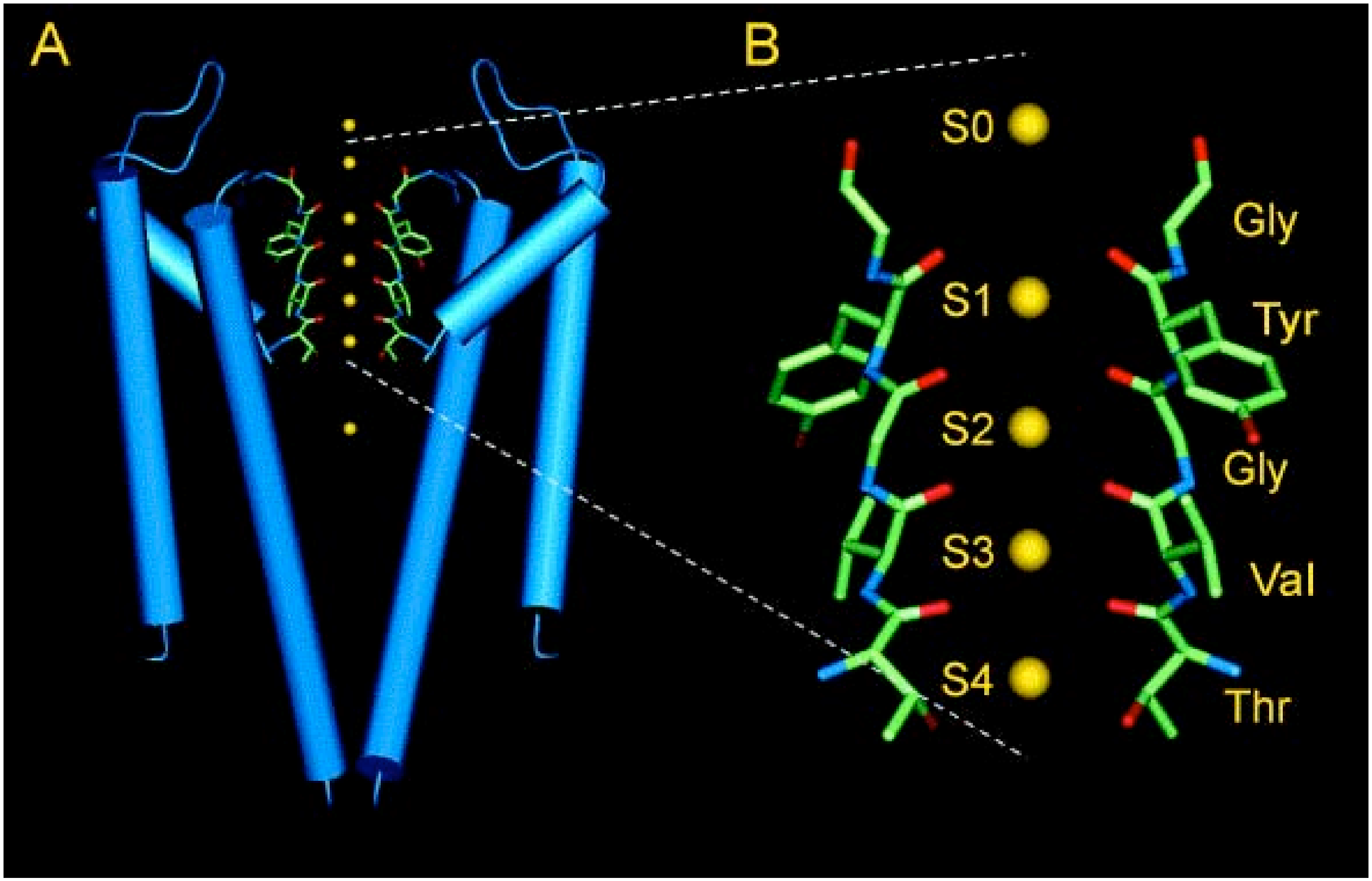
Under physiological conditions, the selectivity filter of the KcsA dehydrates, transfers, and rehydrates one K^+ ion every 10 ns.



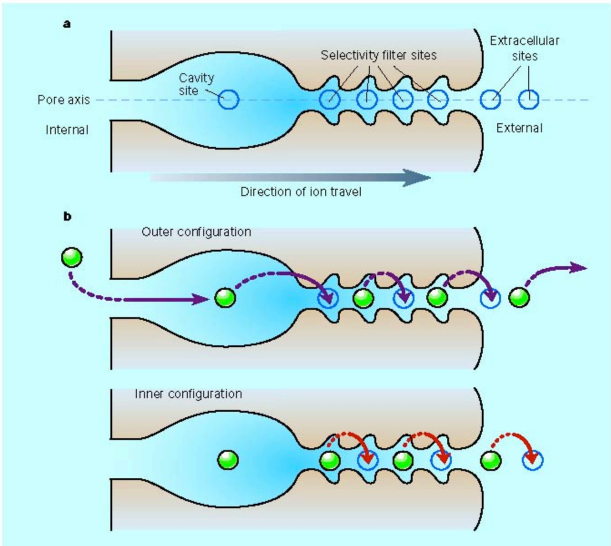
PDB Feb 2003 molecule of the month

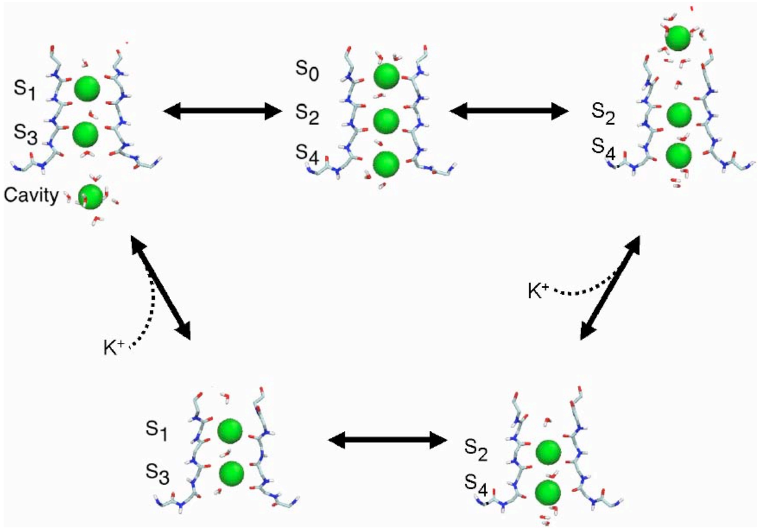


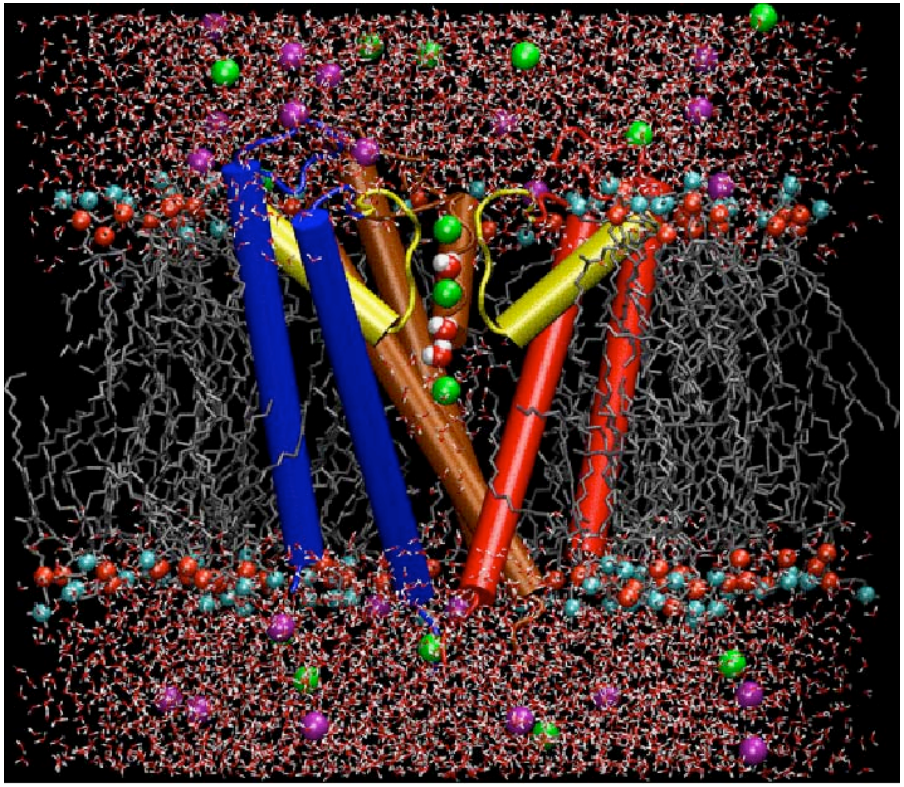
K binding sites in the selectivity filter

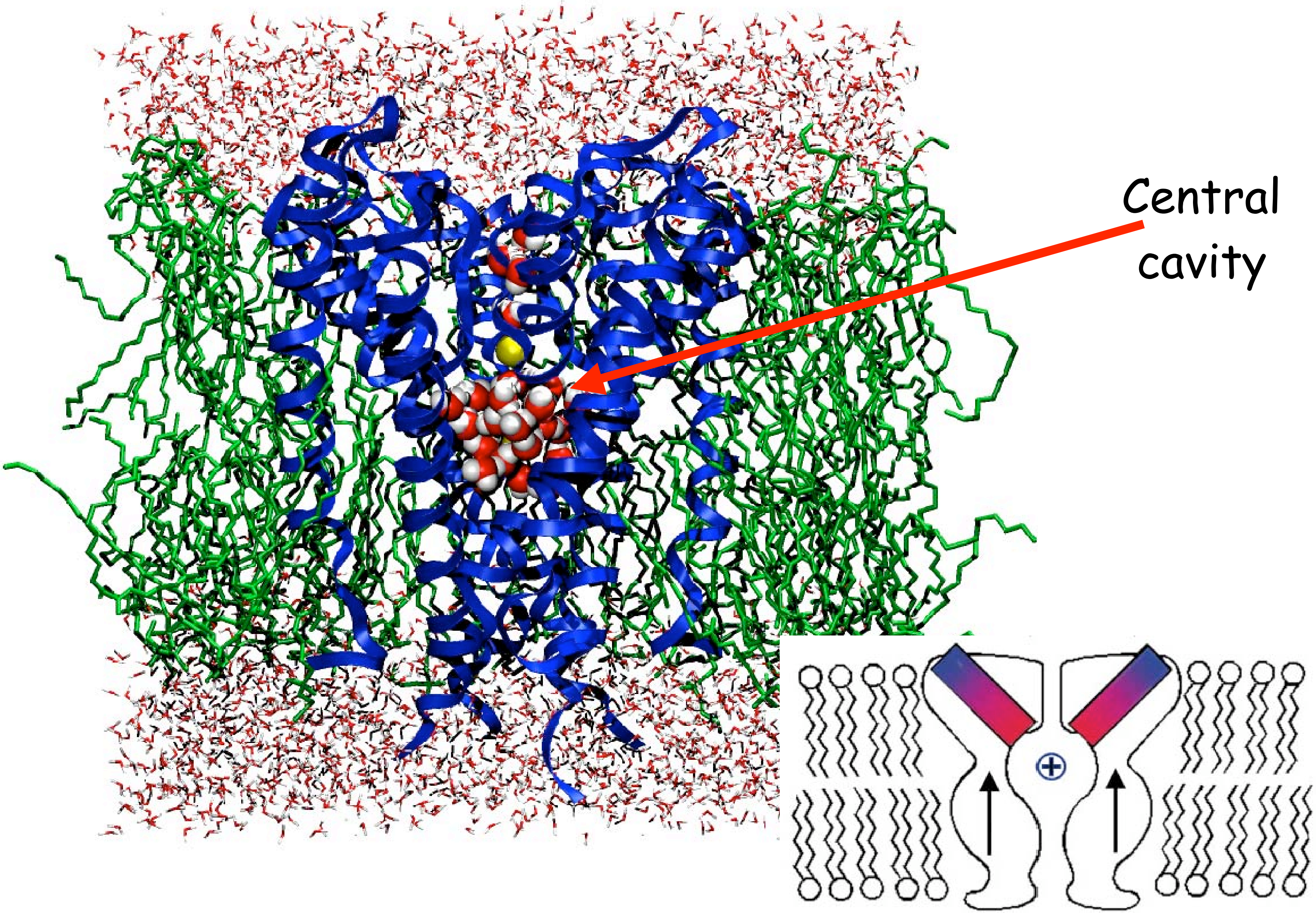


Overall Mechanism of Ion Conduction

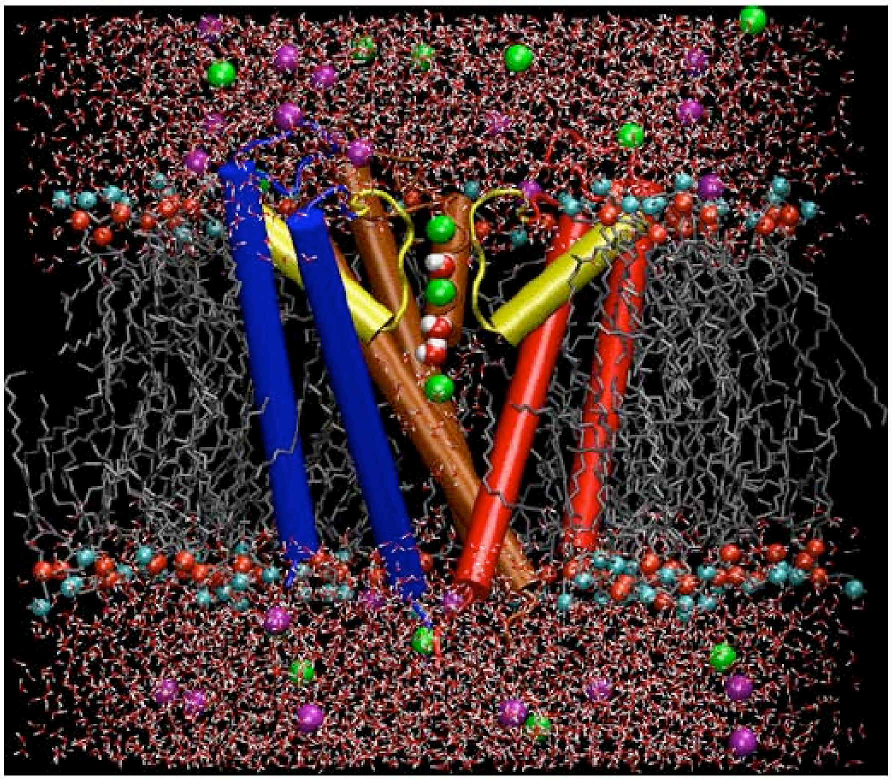


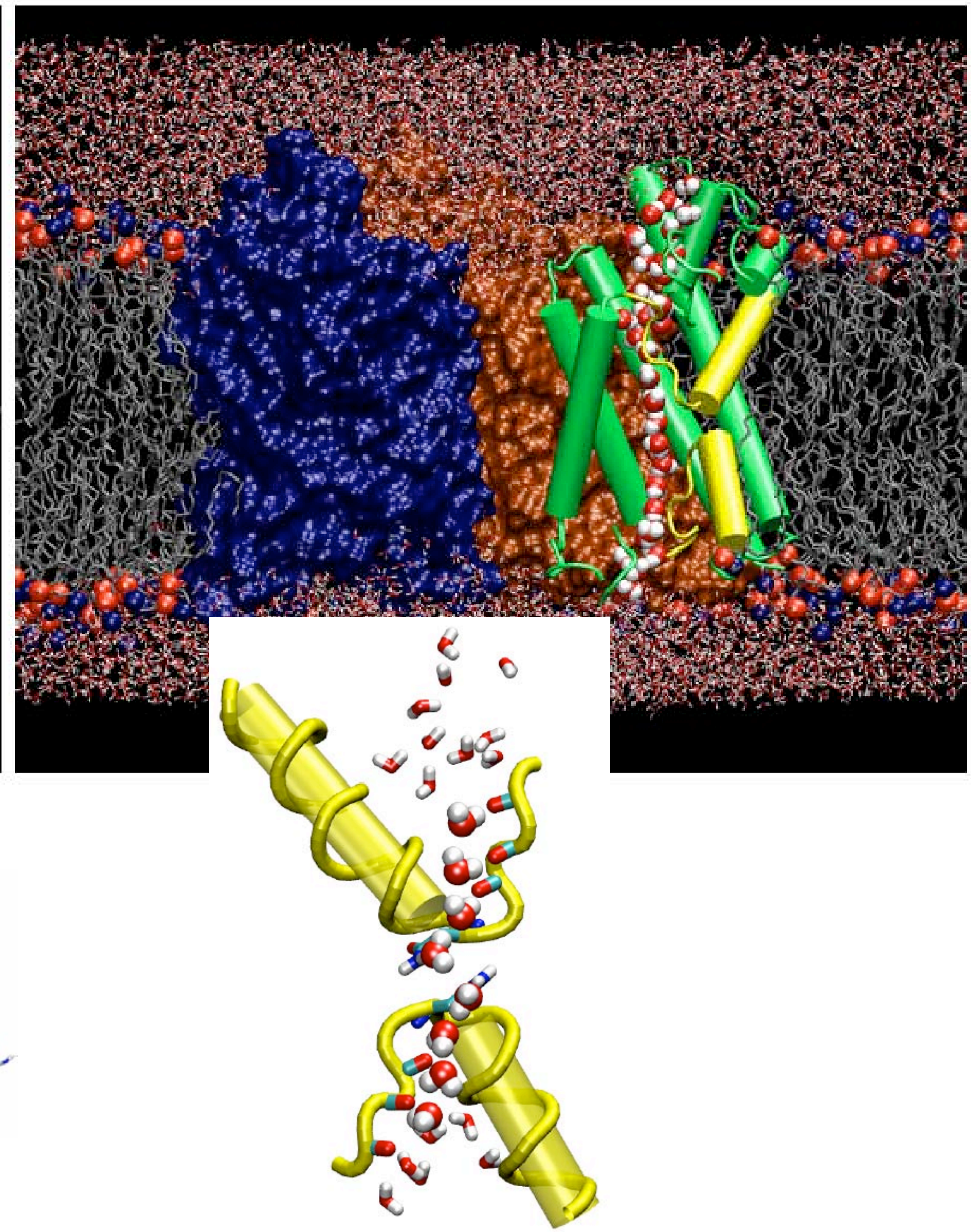


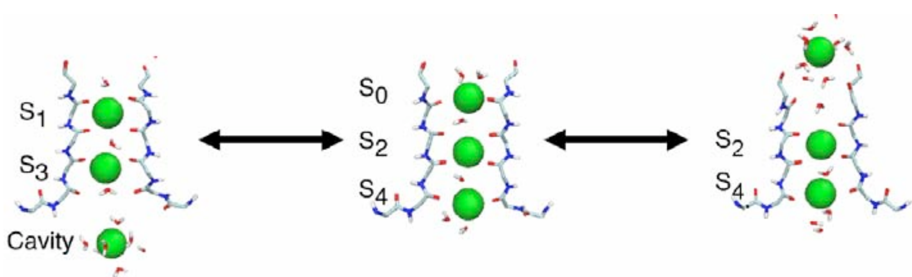



Central
cavity

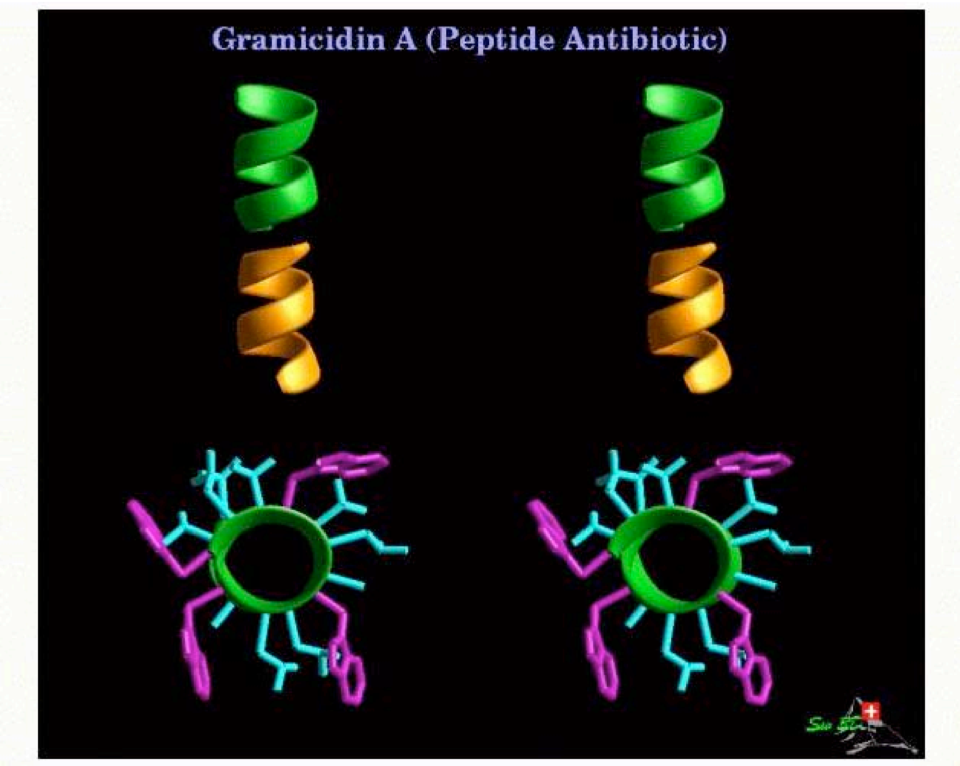
Comparision of Potassium Channel and Water Channel

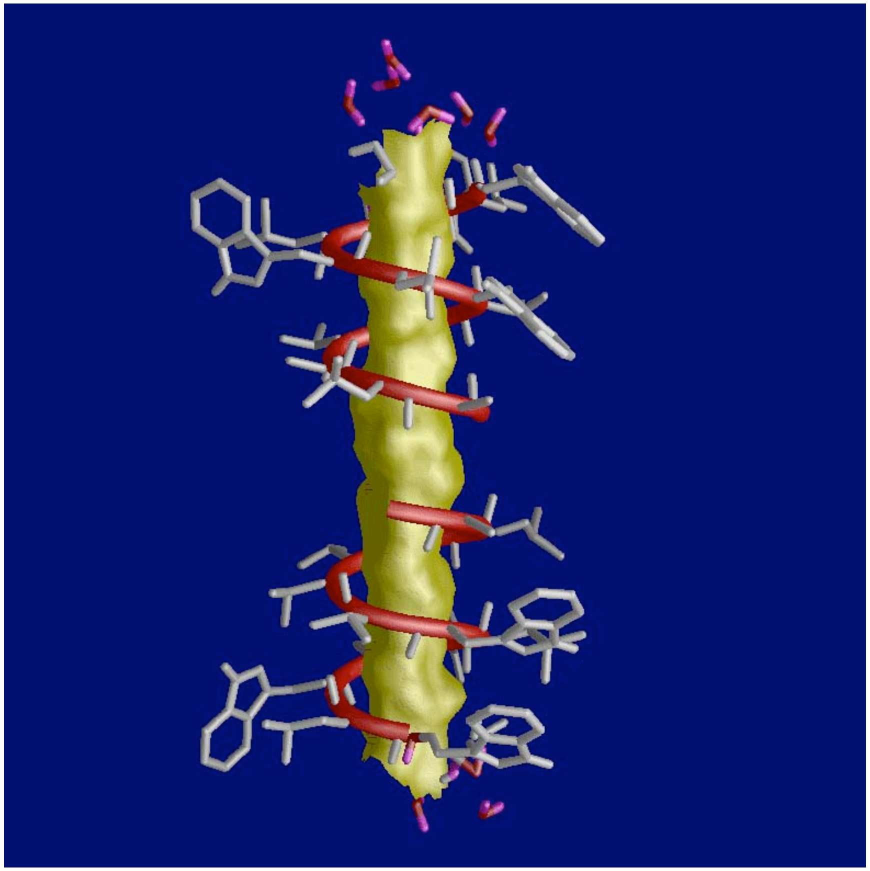






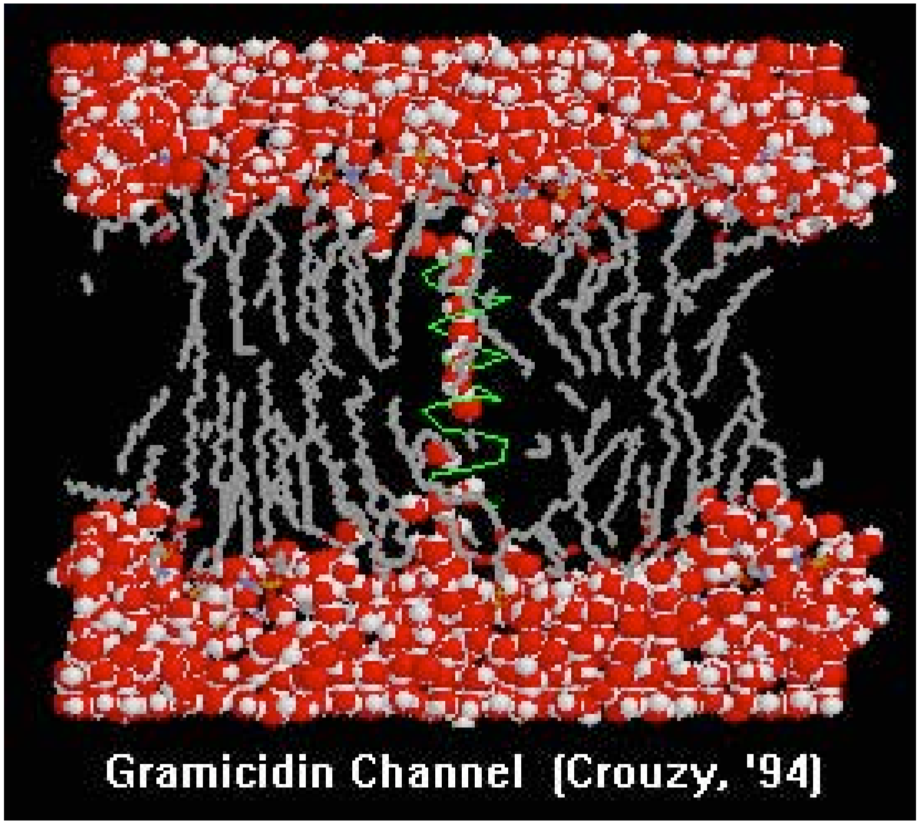
Gramicidin A
an ion leak inside the membrane

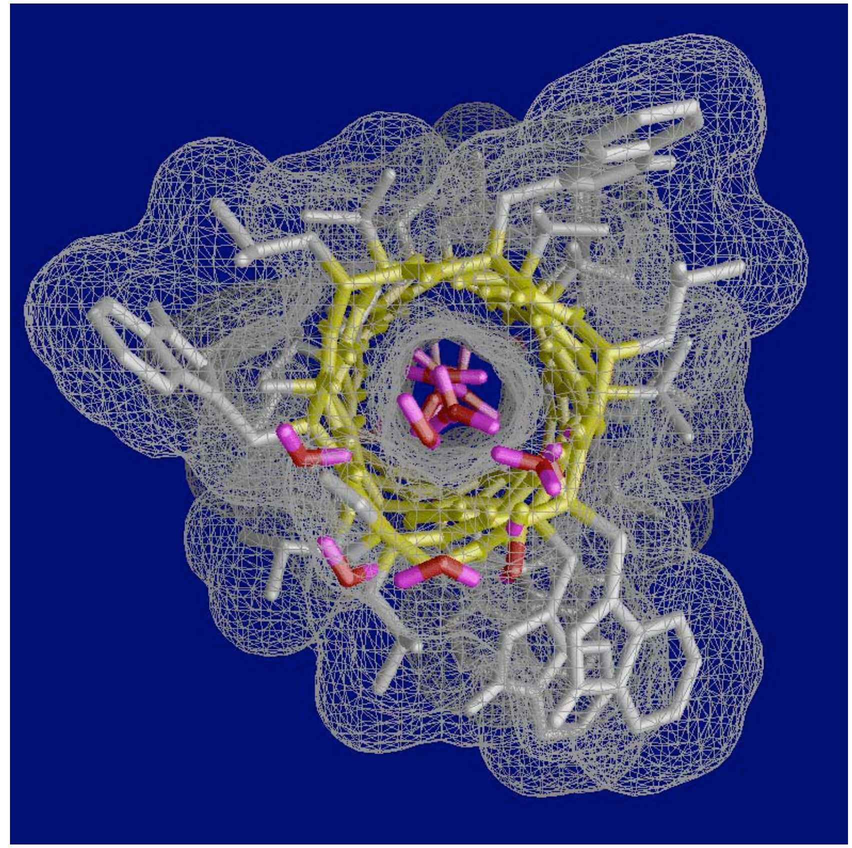




Through dissipating the electrochemical potential of membranes, gramicidin A acts as an antibiotic.

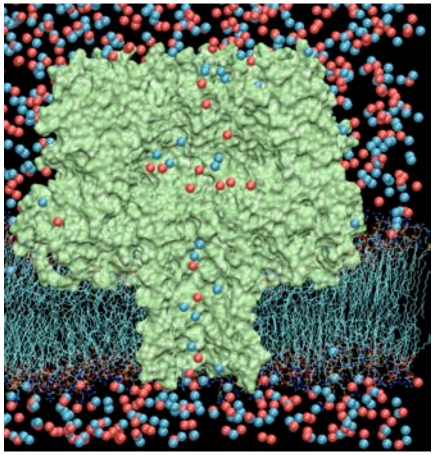
Gramicidin can form a proton wire

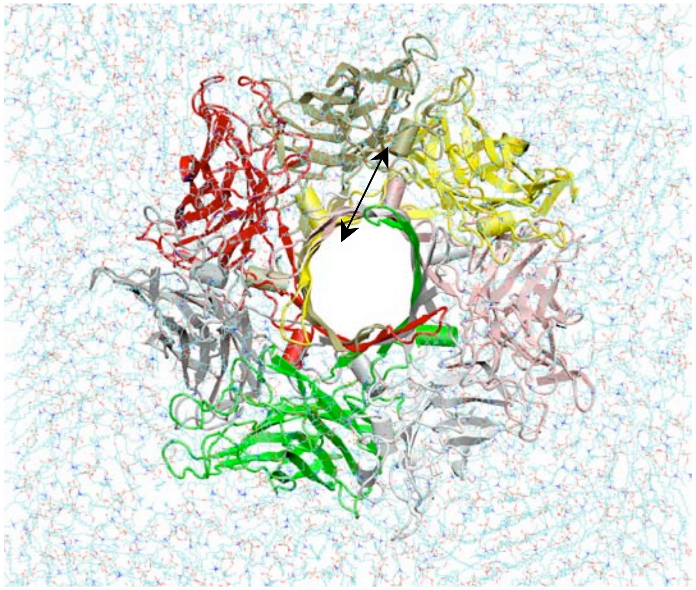


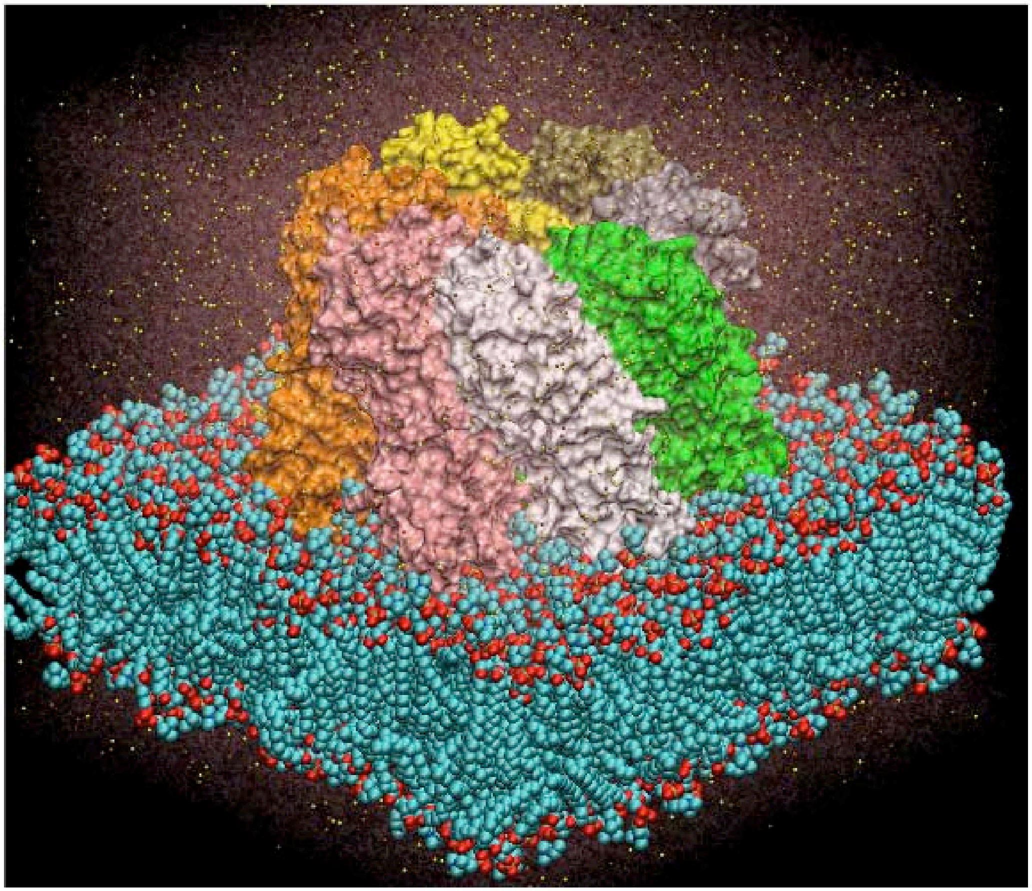


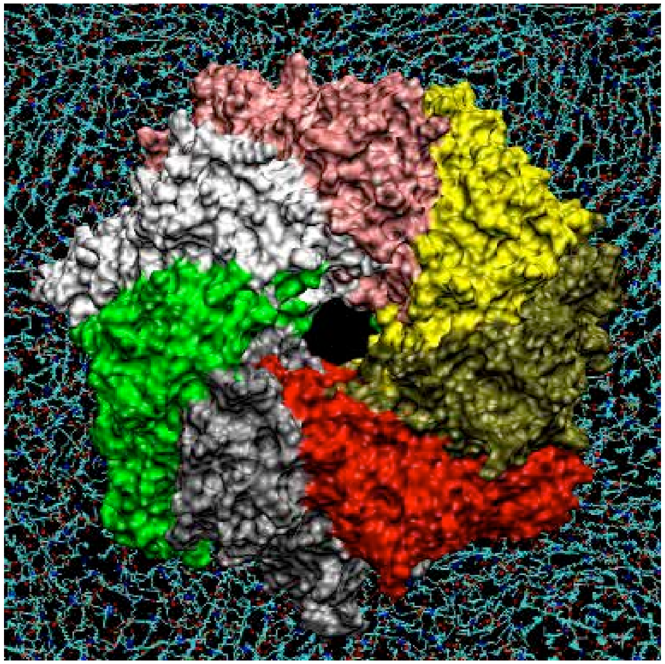
It also provides a membrane channel with a simple structure which can be simulated for a long time.

α-hemolysin channel

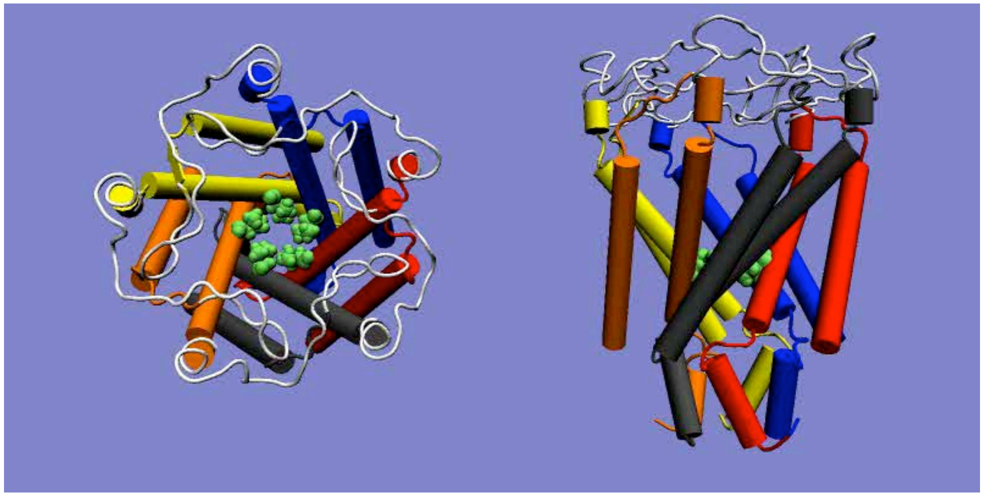








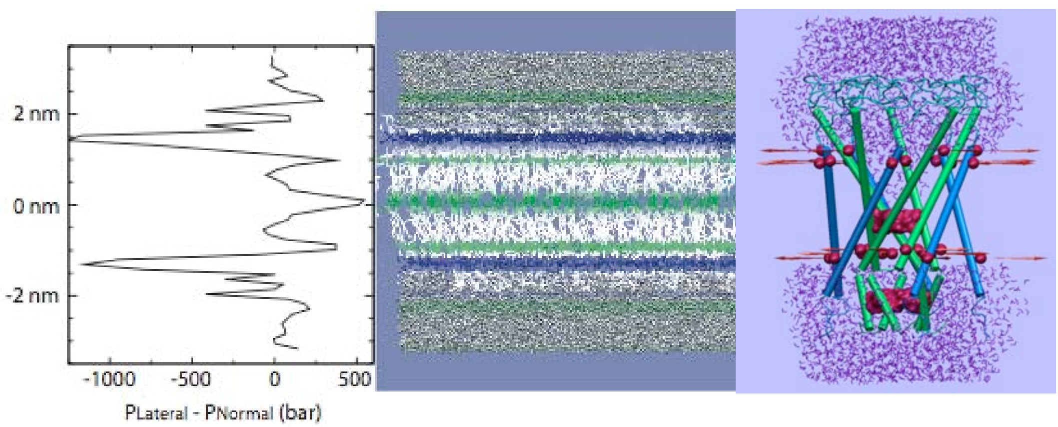
Mechanosensitive Channel of Large Conductance (MscL)

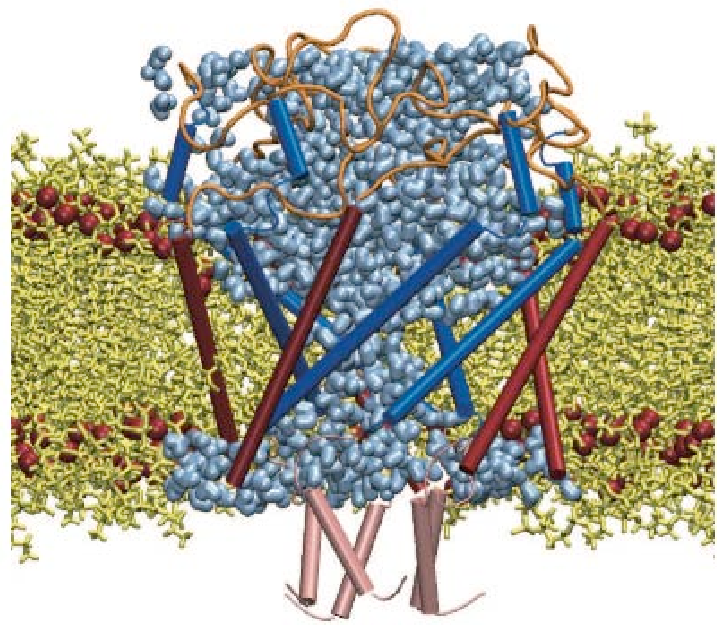


Steered MD simulation

- MscL from *E. coli* based on homology model
- Sufficient water for full hydration of loops and N-terminal helix bundle
- Constant radial force applied to residues at the ends of M1 and M2 (16, 17, 40, 78, 79, 98)
- 10 ns simulation time

Pressure profile in membrane guided simulation

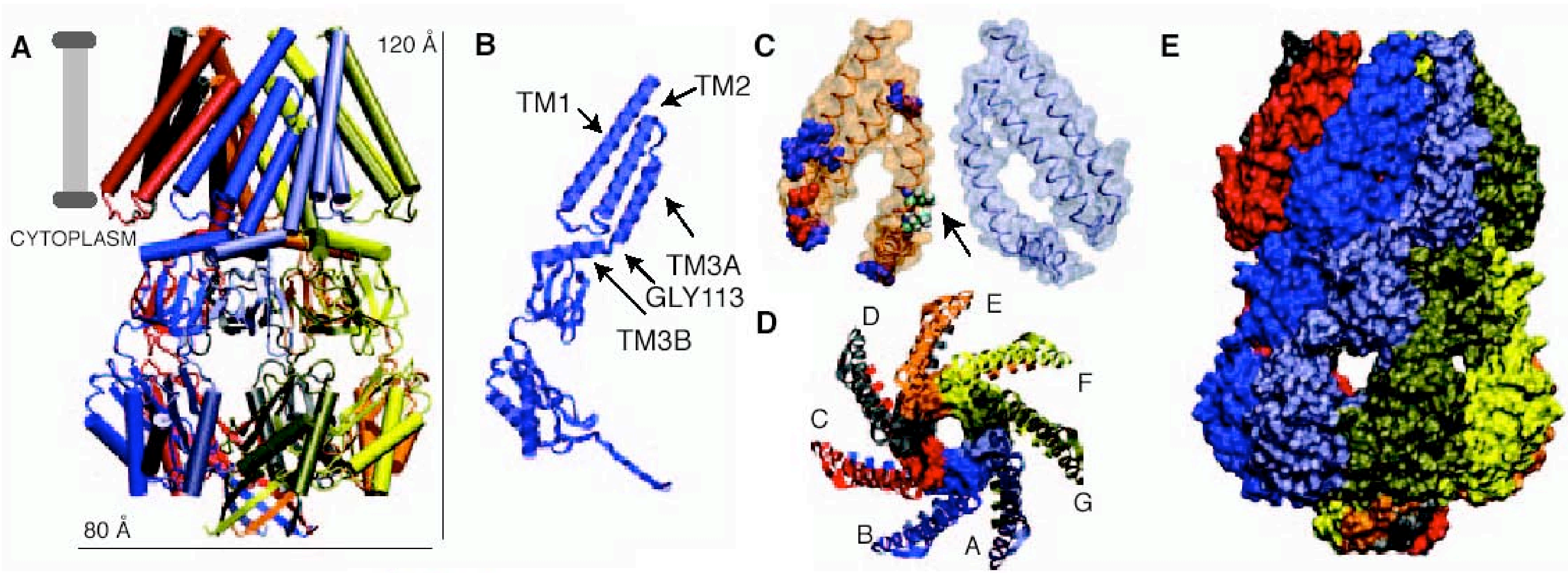


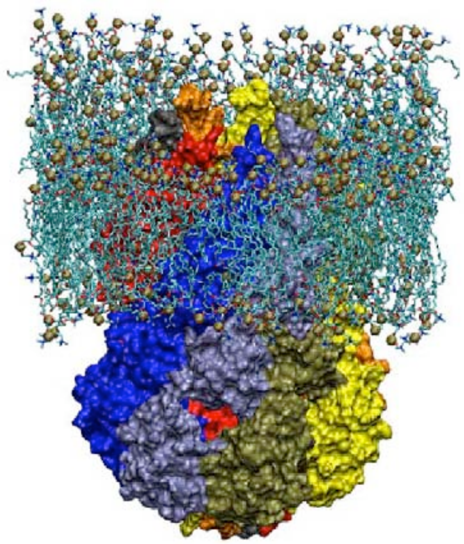


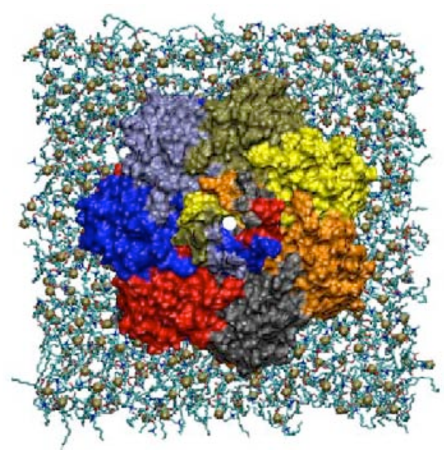
Opening of channel

J. Gullingsrud and K. Schulten, *Biophys. J.* **85:** 2087-2099 (2003)

Mechanosensitive Channel of Small Conductance

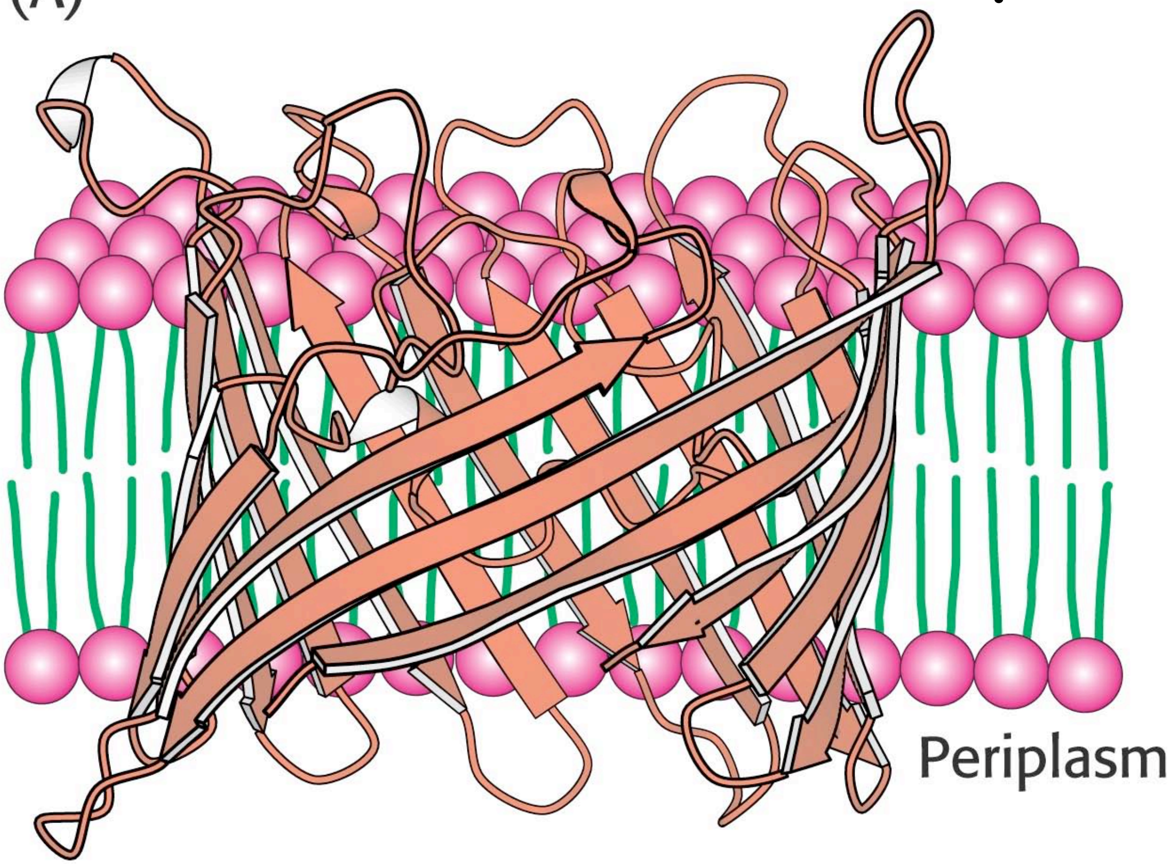


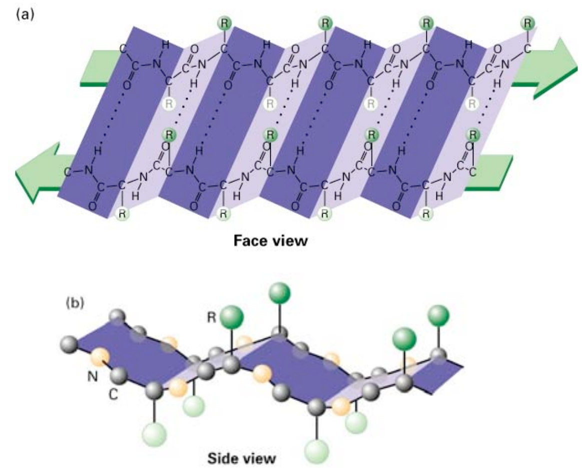




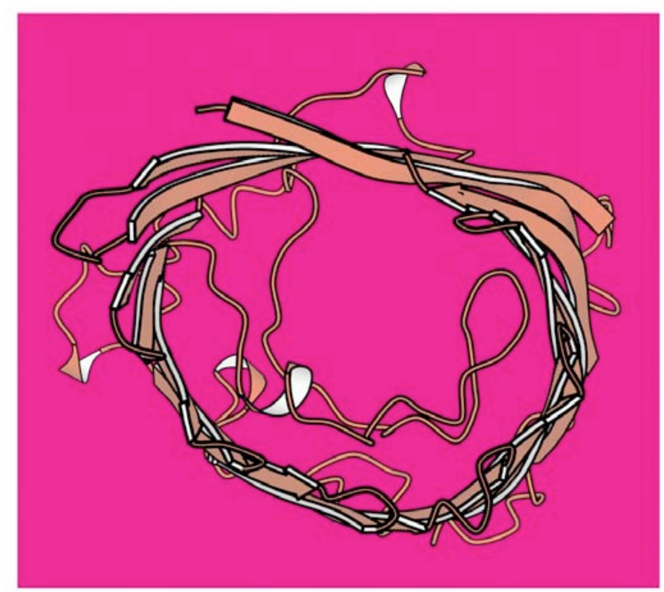
Porins: An example of β-barrel membrane proteins

(A)



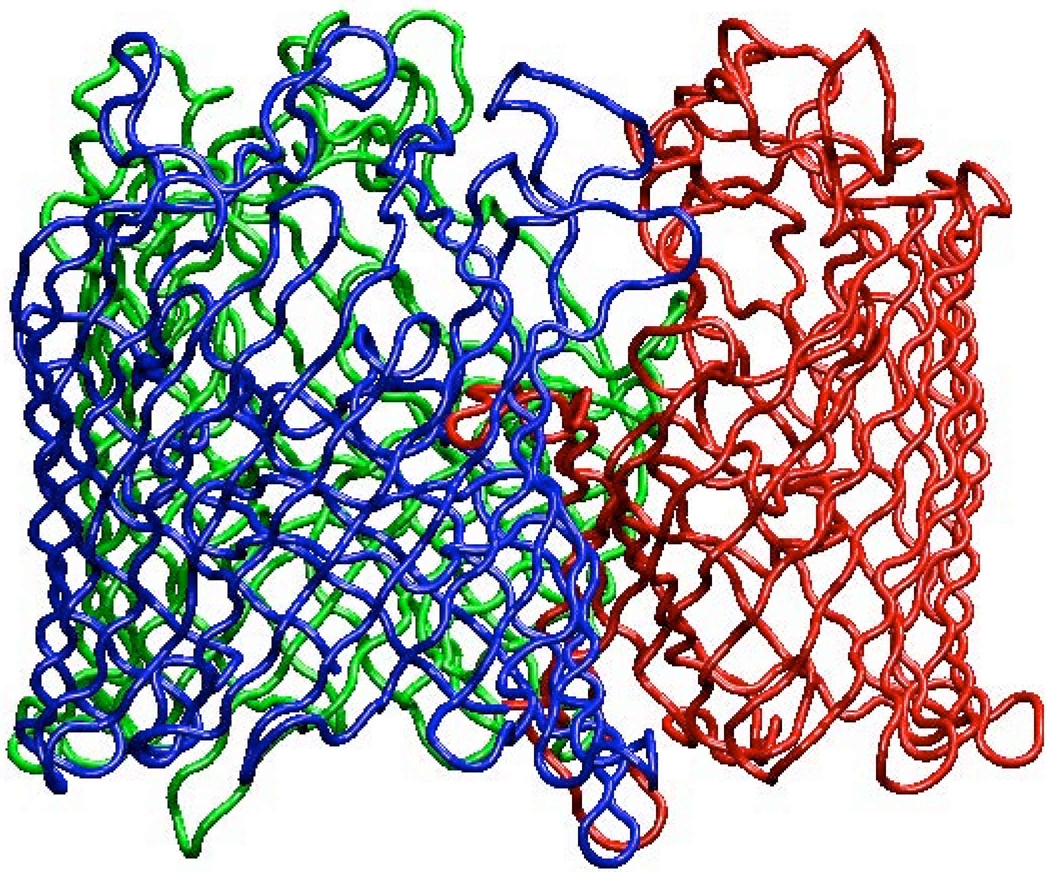


(B)



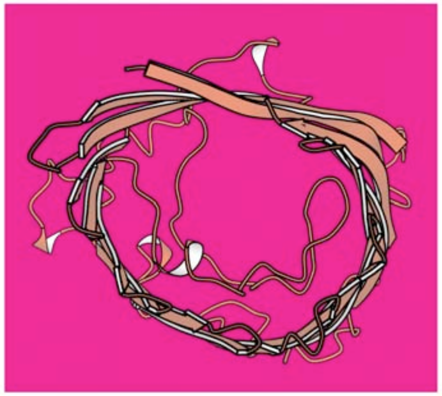
~18 β-strands – found in outer membranes of G⁻ bacteria and mitocondria

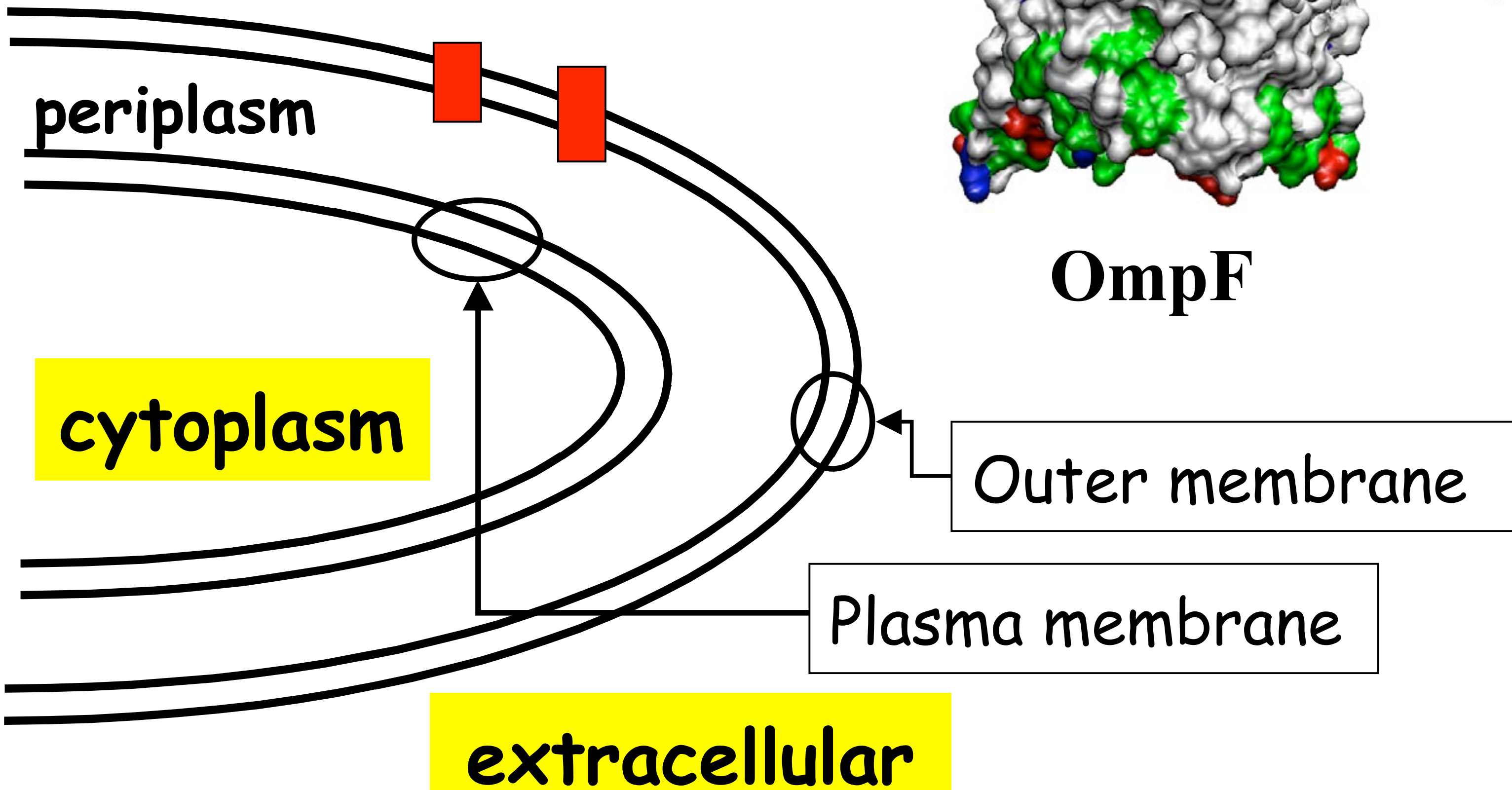
Porins: An example of β-barrel Membrane Proteins

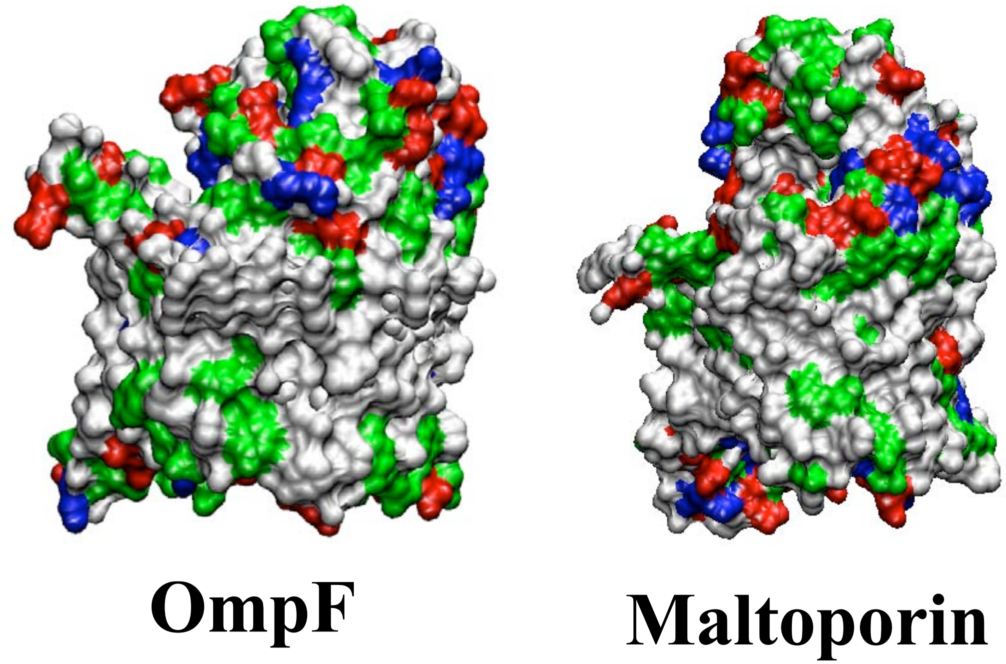


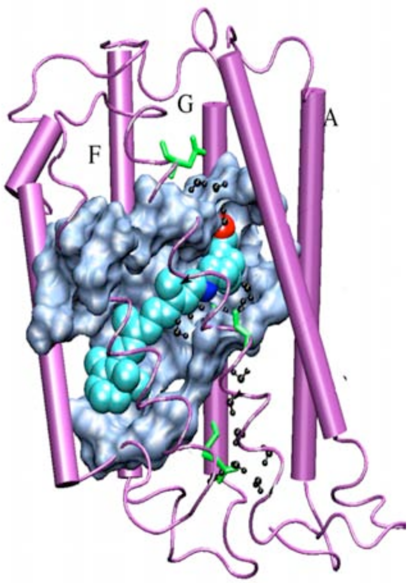
Usually form oligomers in the membrane.

Porins: Non-selective Pores of the Outer Membrane

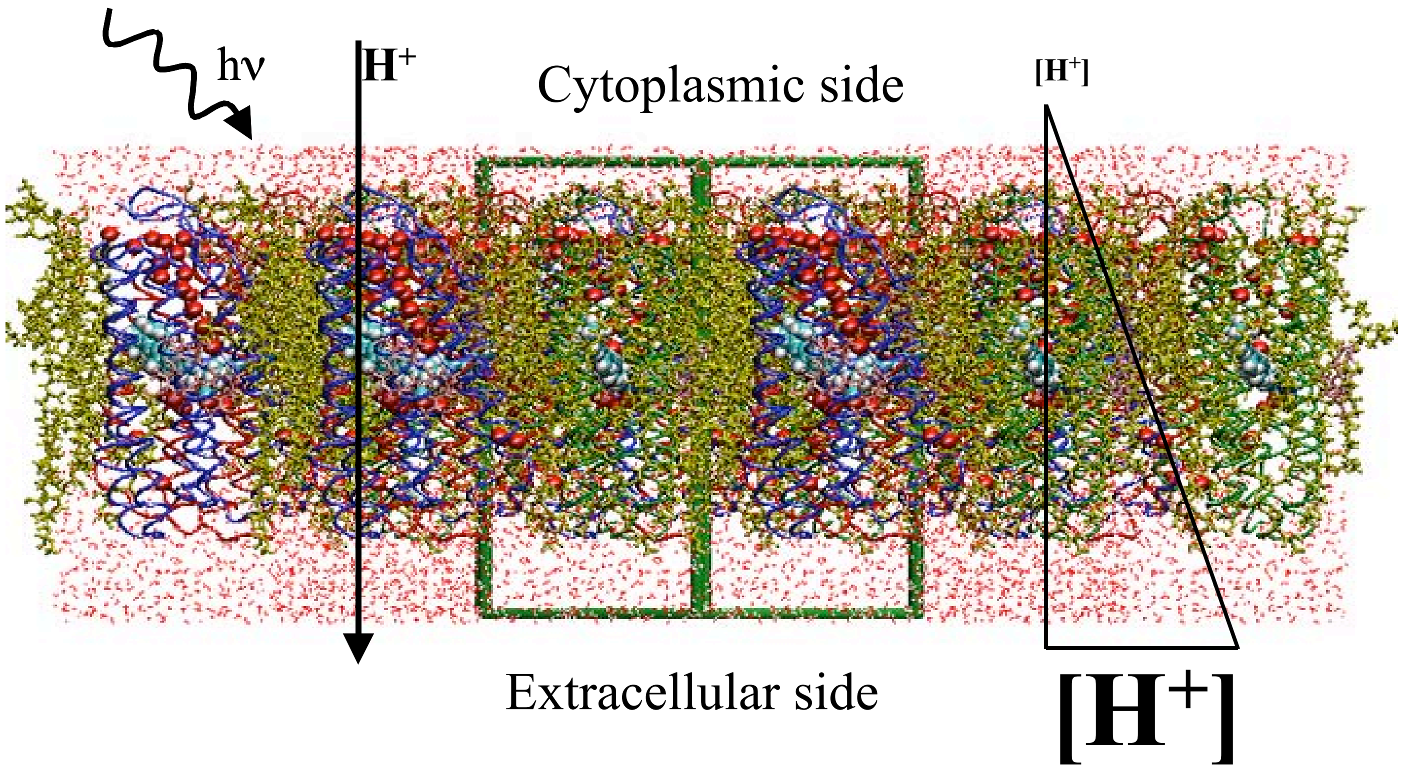








Bacteriorhodpsin uses sunlight and generates a transmembrane proton gradient



ATP synthase uses the proton gradient to produce ATP