Molecular Dynamics Simulation of Membrane Channels

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http://www.ks.uiuc.edu/training/SumSchool03/

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 exercises
    - Nanotubes as simple models for membrane water channels
    - Theory of water transport and its modeling using MD simulations

Molecular Dynamics Simulation of Membrane Channels

Part I. Introduction

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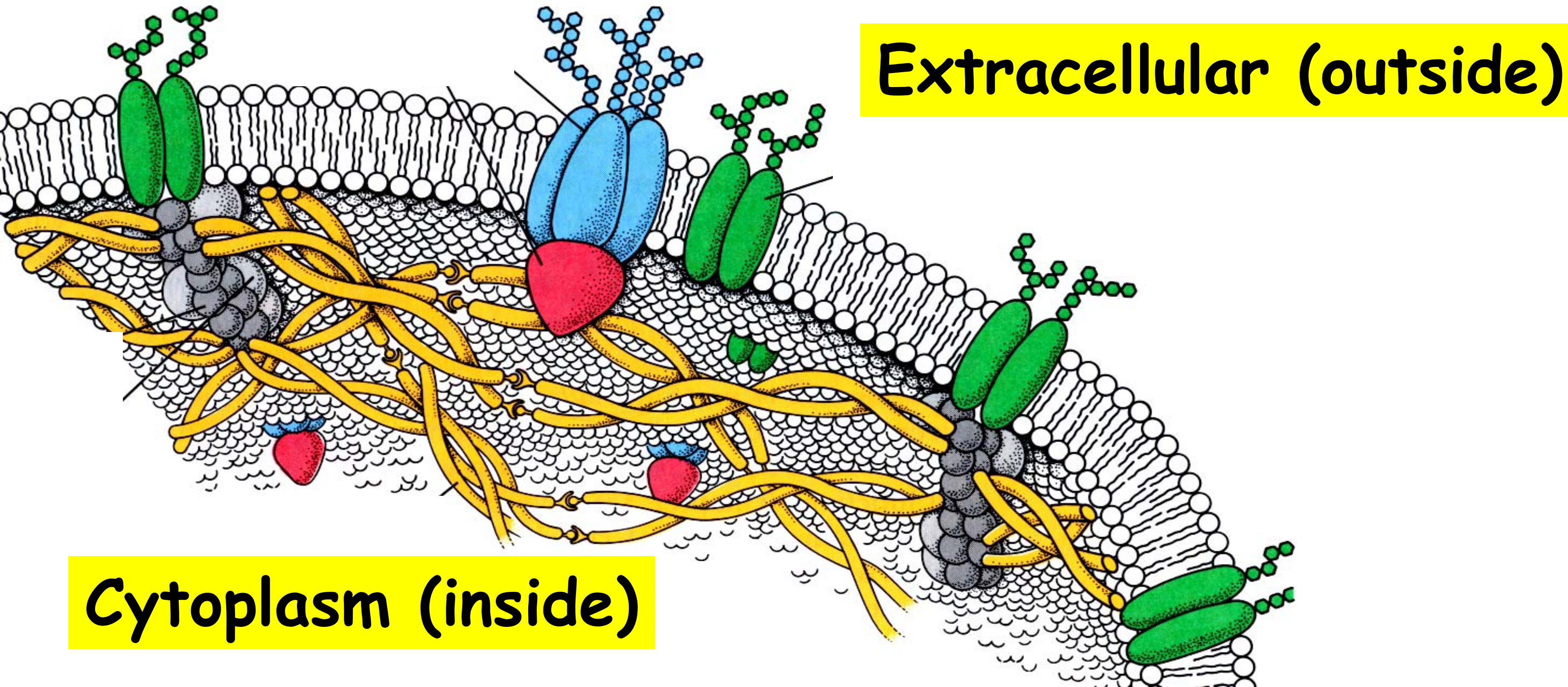
Why Do Living Cells Need Membranes and Membrane Channels?

- **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 fat molecules.

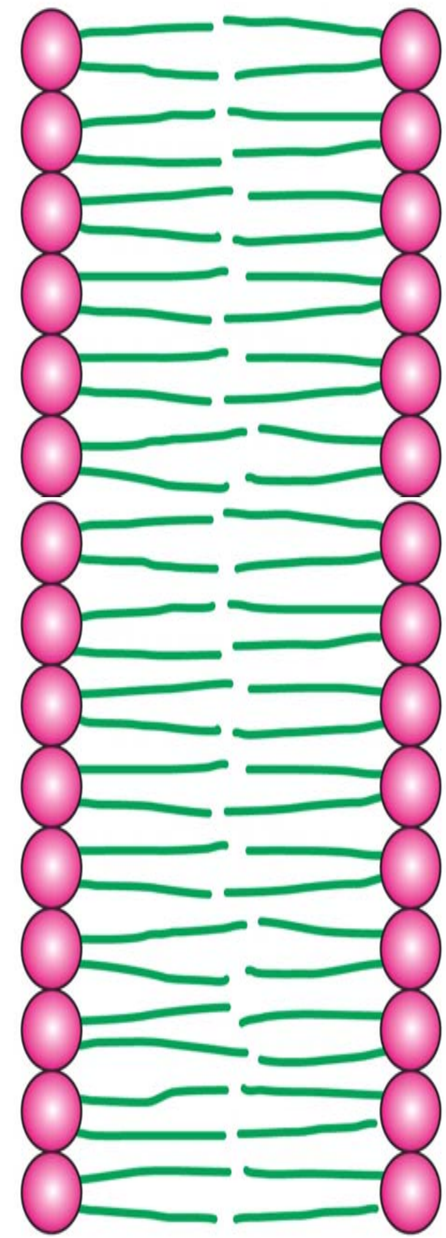
Why Do Living Cells Need Membranes?

- **Conservation of materials inside the cell**
- **Protection against undesired substances**



Lipid Bilayers Are Excellent For Cell Membranes

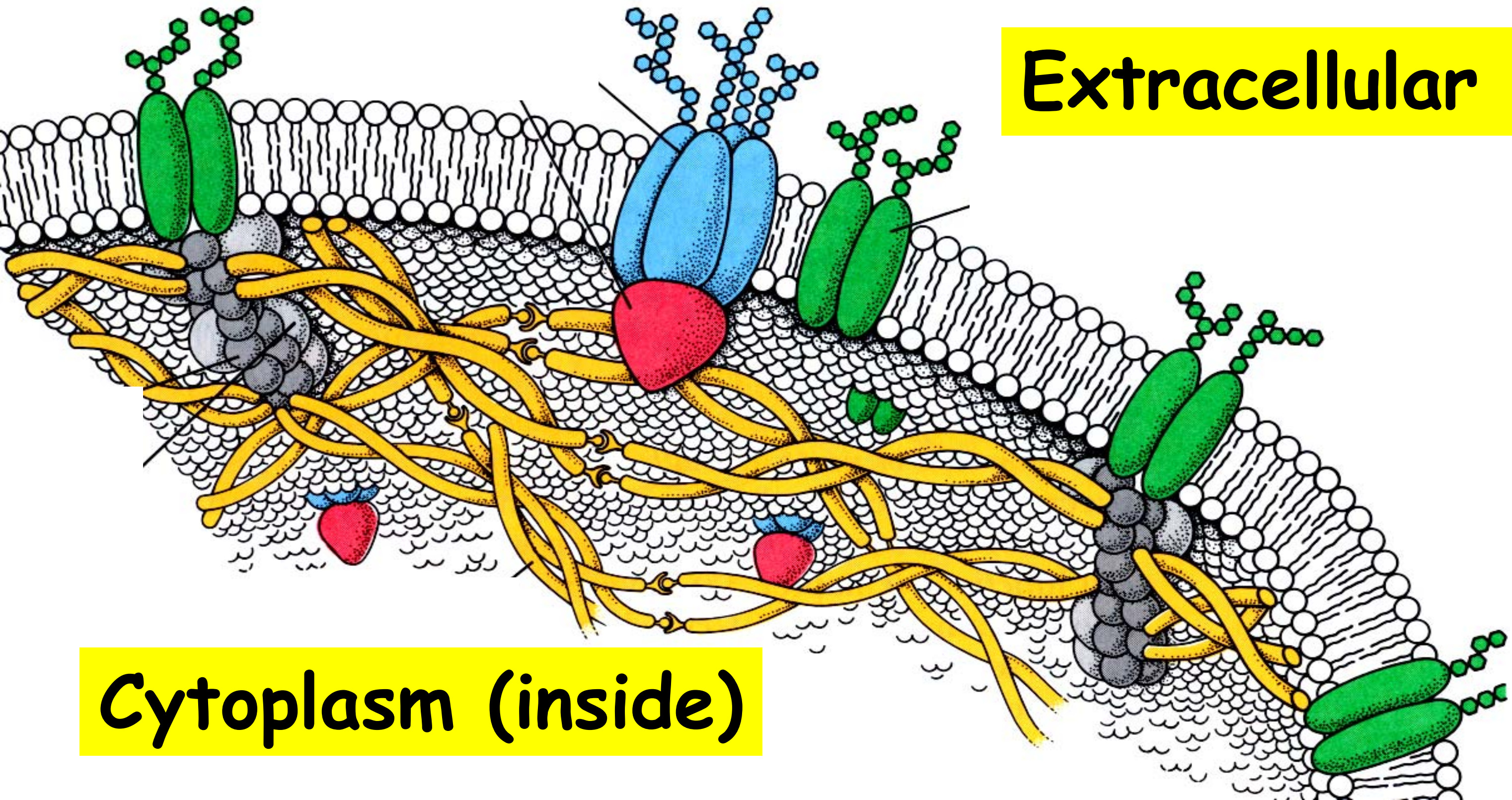
- **Hydrophobic interaction is the driving force**
- **Self-assembly in water**
- **Tendency to close on themselves**
- **Self-sealing (a hole is unfavorable)**
- **Extensive: up to millimeters**



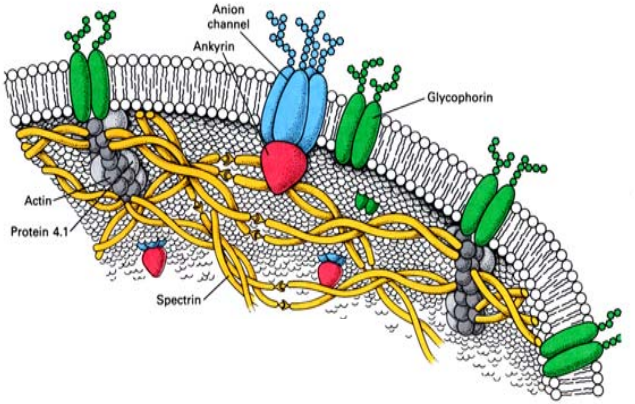
Why Do Living Cells Need Membrane Channels (Proteins)?

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

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



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

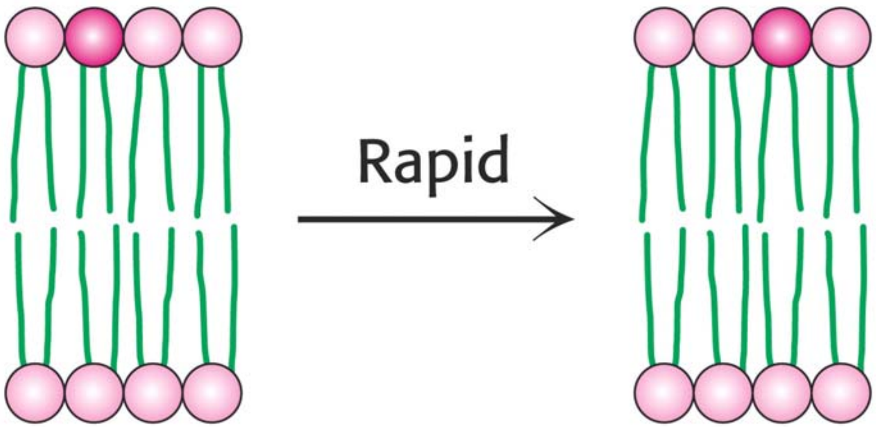
A highly selective permeability barrier

Internal membranes for organelles

Lipid Diffusion in Membrane

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

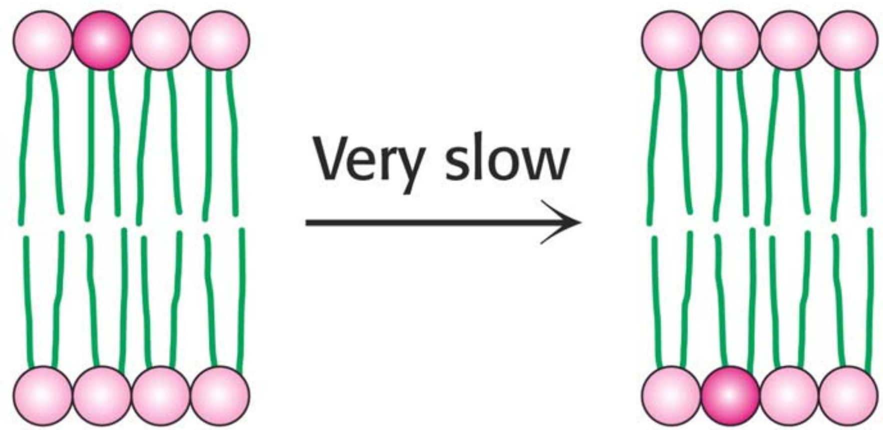
$D_{wat} = 2.5 \times 10^{-5}\ cm^2.s^{-1}$



Lateral diffusion

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

50 Å in ~ 2.5×10^{-5} s



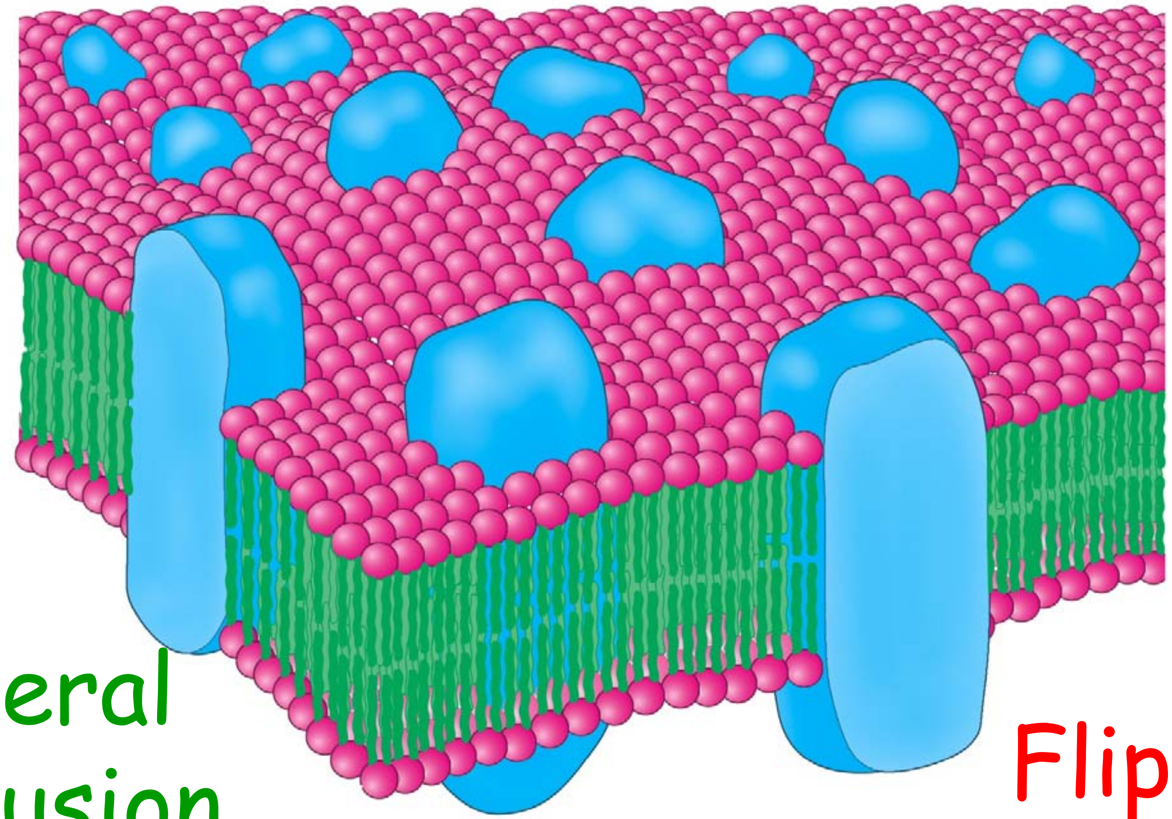
Tranverse diffusion
(flip-flop)

Once in several hours!

(10^4 s)

~9 orders of magnitude difference

Fluid Mosaic Model of Membrane



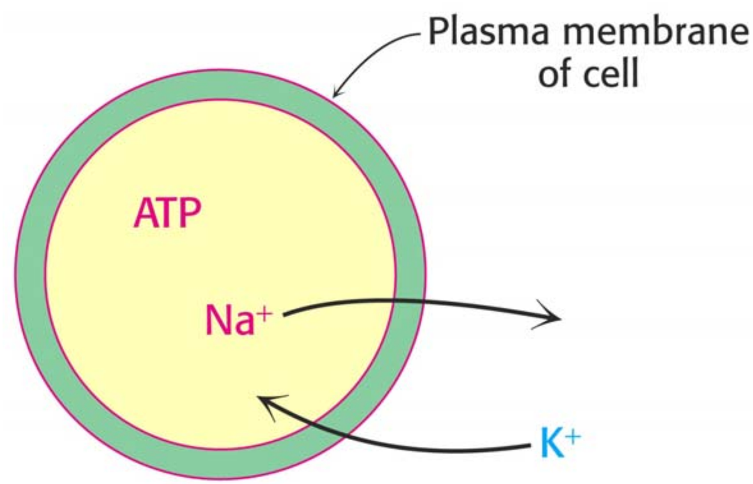
Lateral Diffusion Allowed

Flip-flap Forbidden

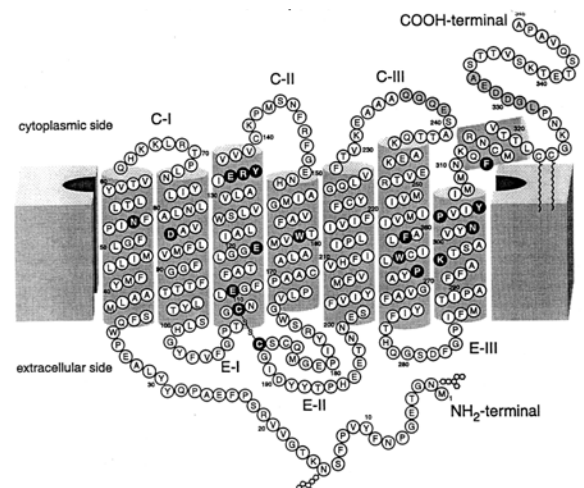
Ensuring the conservation of membrane asymmetric structure

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



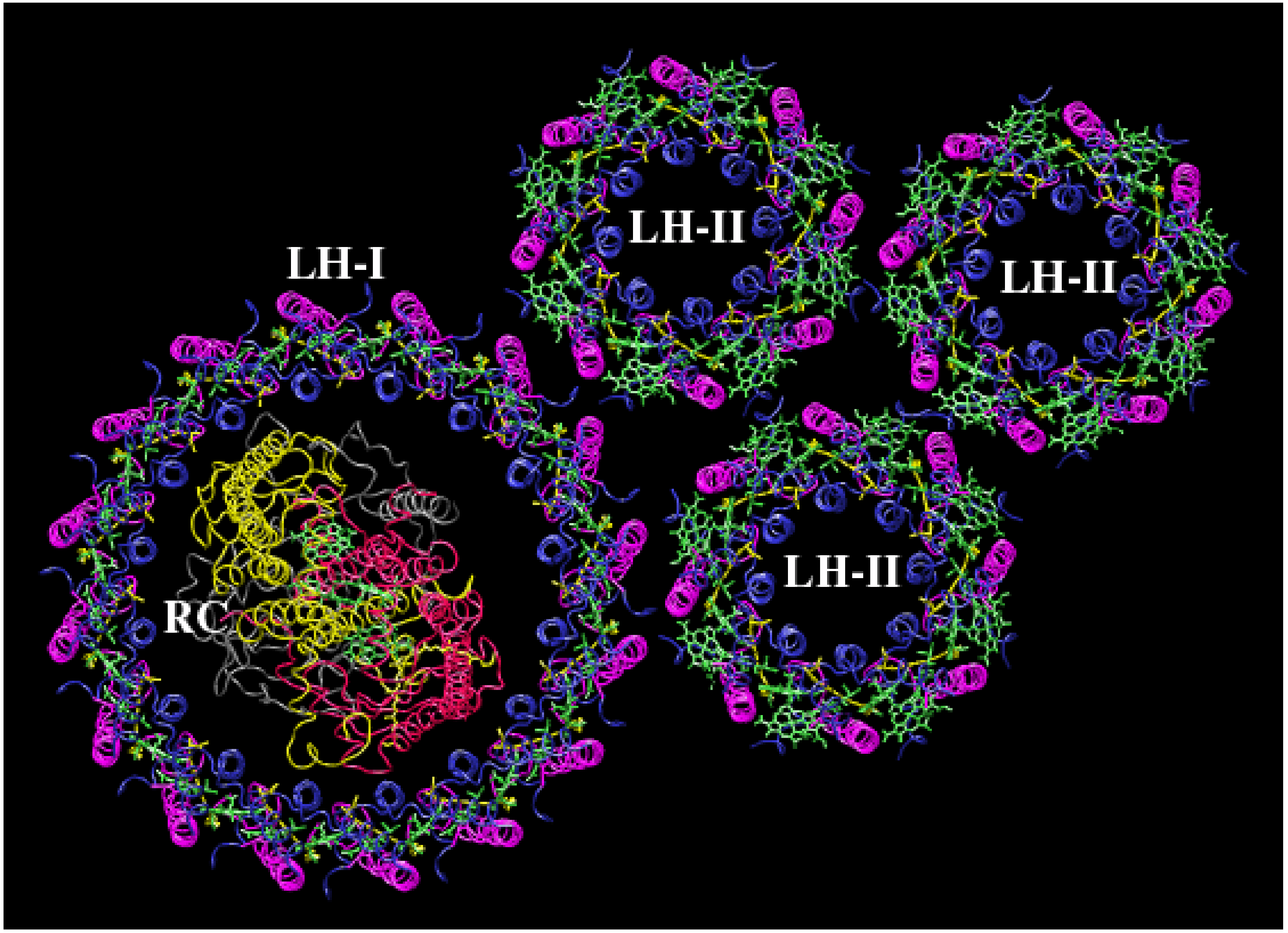
Extracellular side

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

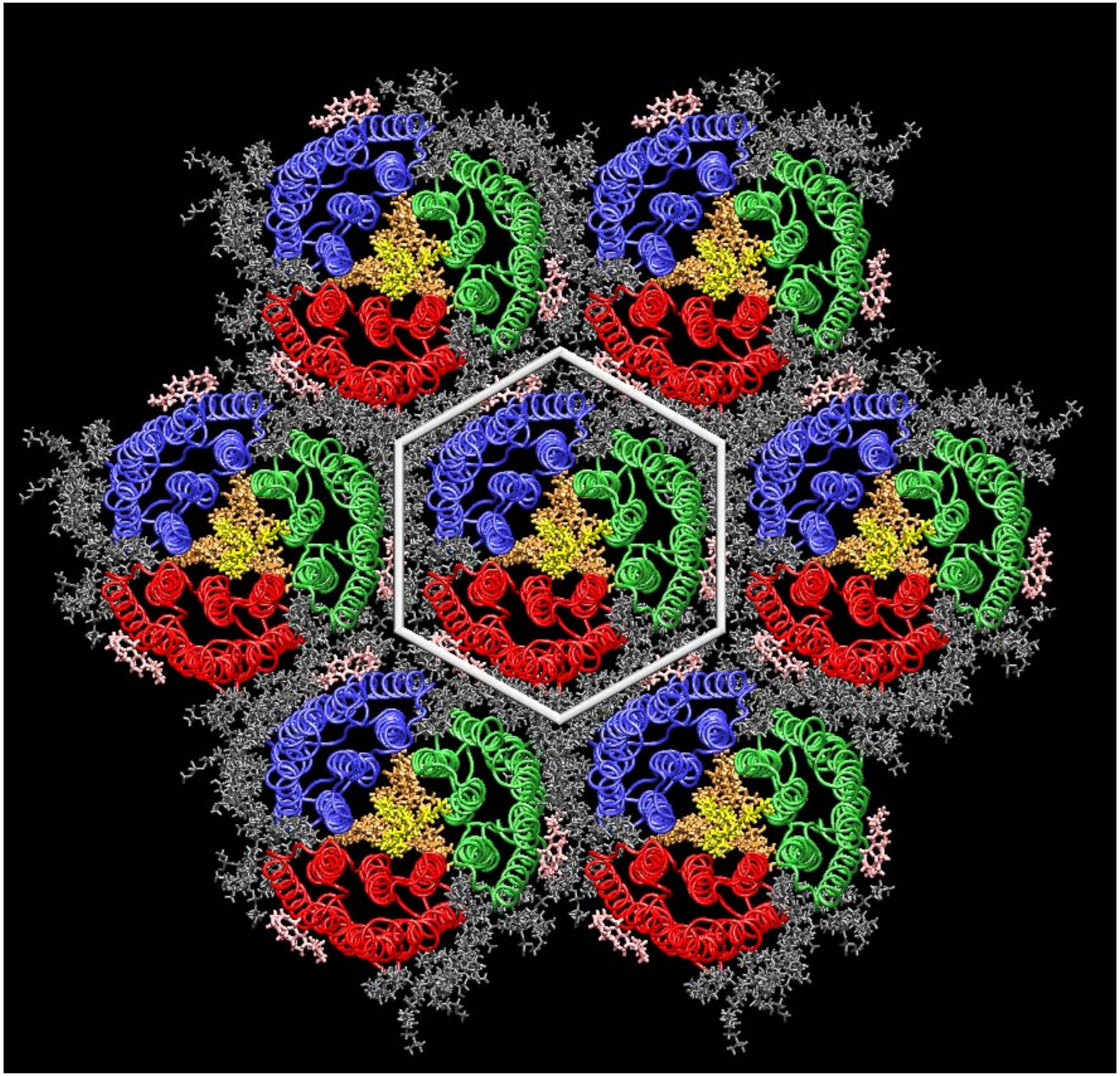
- Different functions = different protein composition

Protein / Lipid Composition



Light harvesting complex of purple bacteria

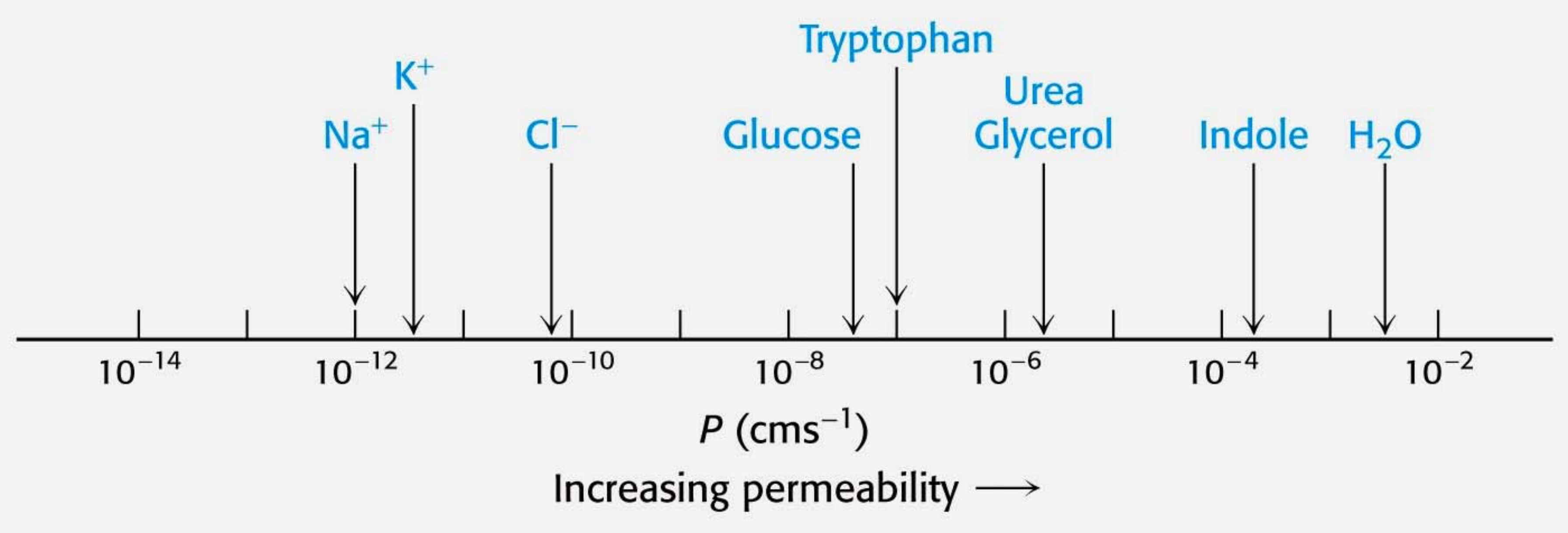
Protein / Lipid Composition



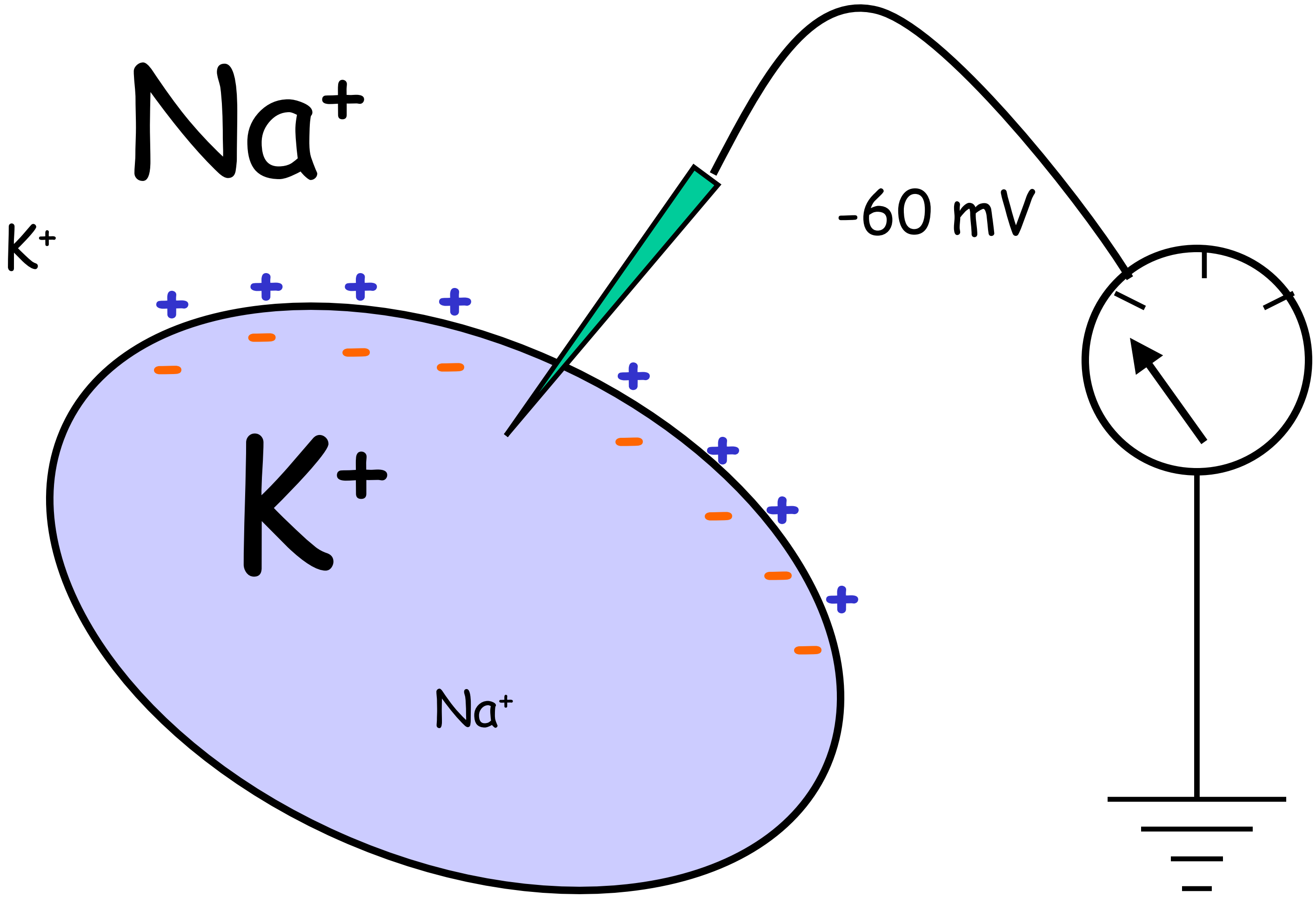
The purple membrane of halobacteria

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)

Membrane potential change (Voltage gated channels)
- K channels

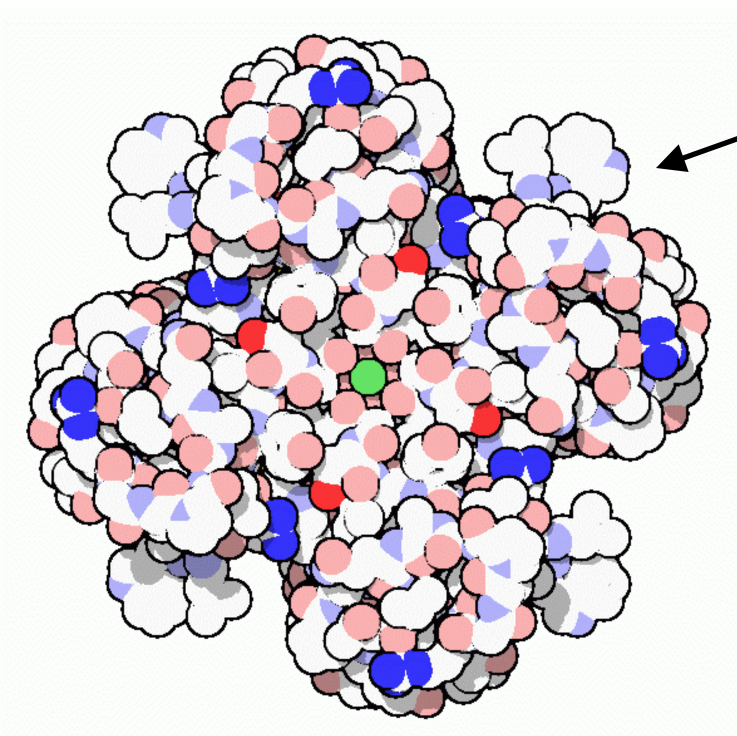
Binding of a molecule (Ligand-gated channels)
- Acetylcholine nicotinic receptor (Na channel)
- Glutamate receptor (Ca channel)

Both voltage and ligand gating

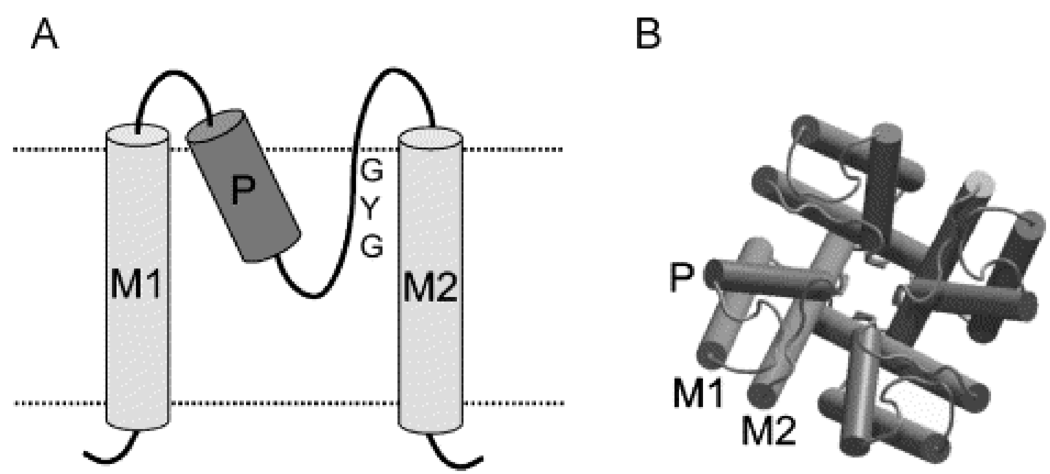
Mechanical gating (MscL)

KcsA Potassium Channel

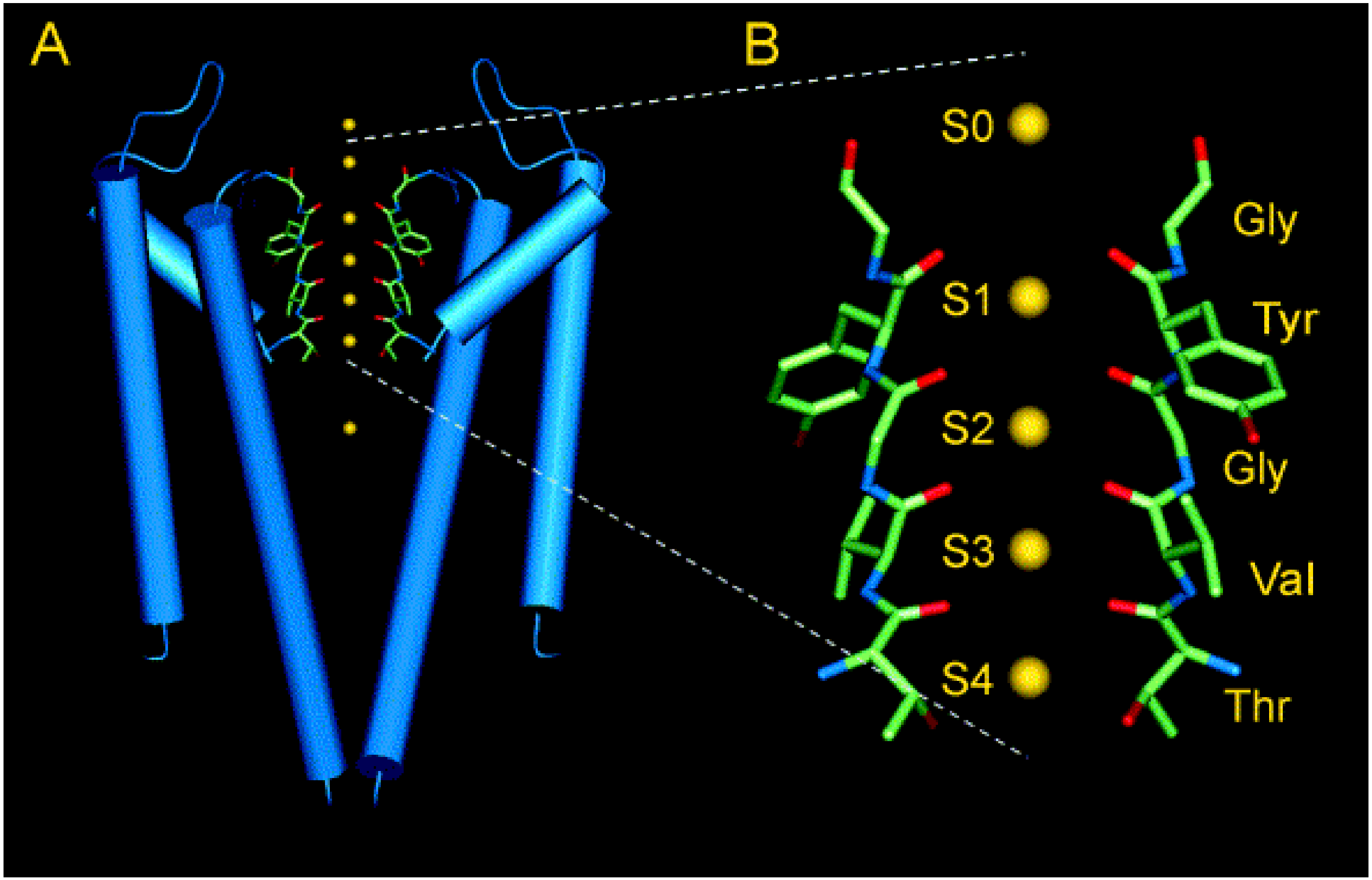
Under physiological conditions, the selectivity filter of the KcsA dehydrates, transfers, and rehydrates one K^+ ion every 10 ns.

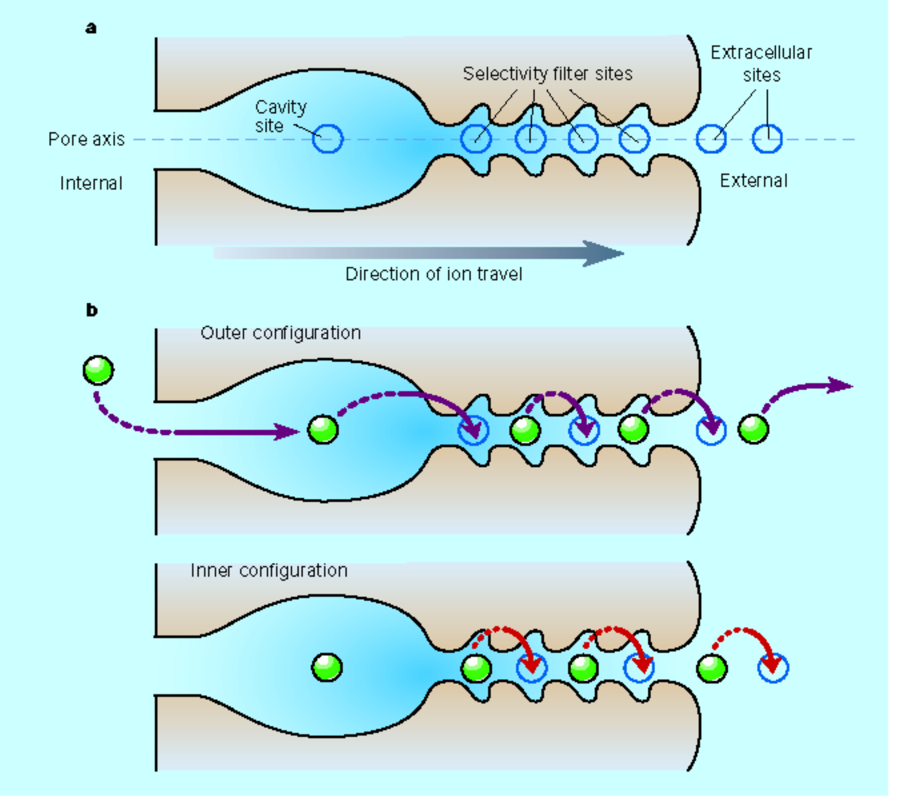


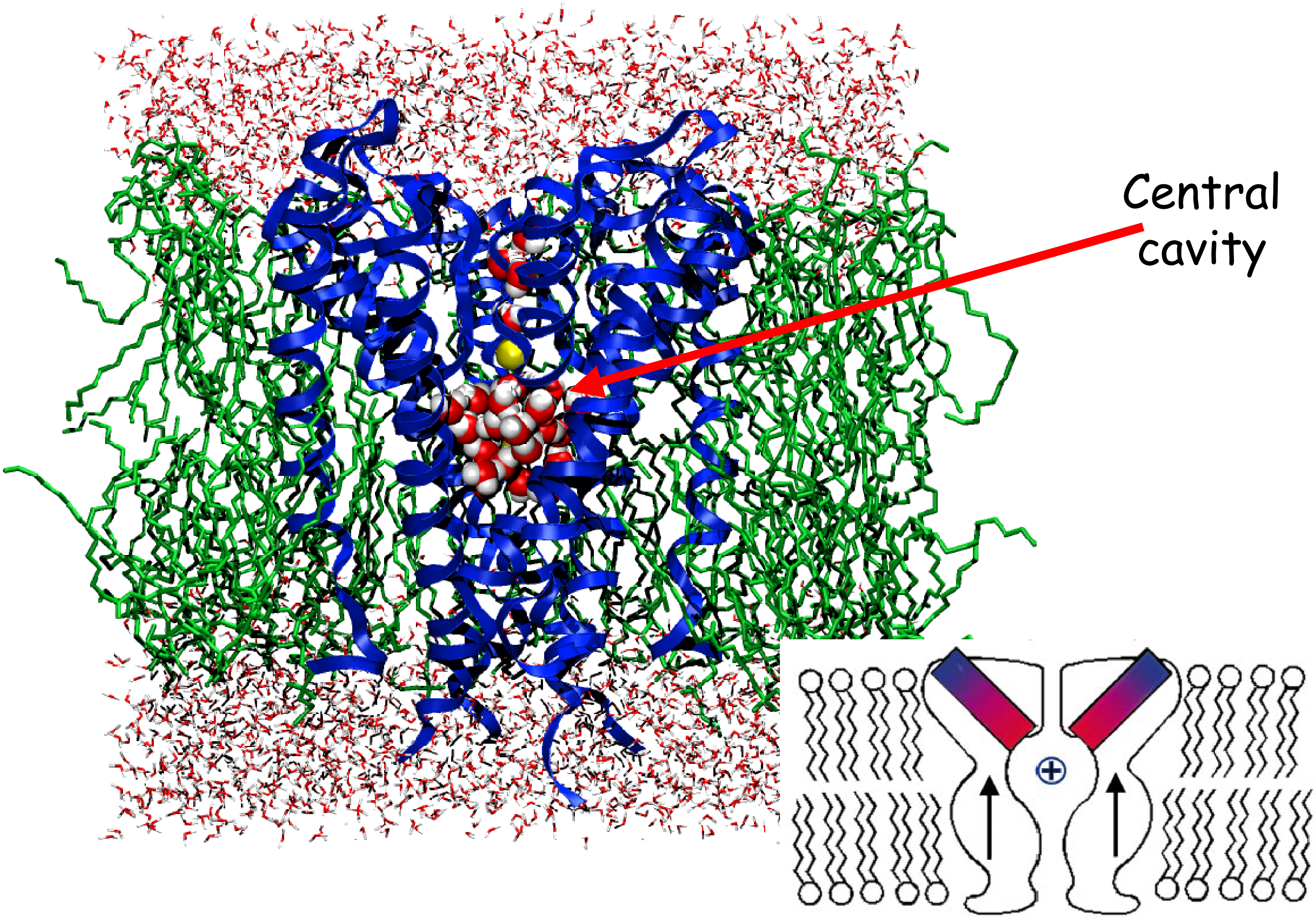
PDB Feb 2003
molecule of the month



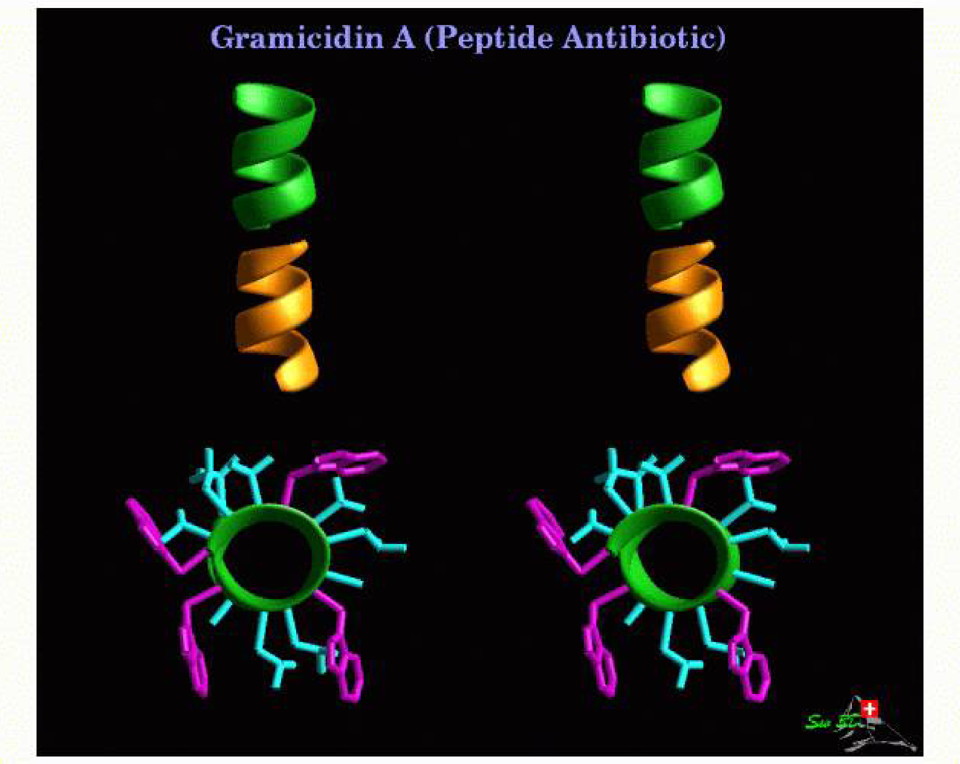
K binding sites in the selectivity filter

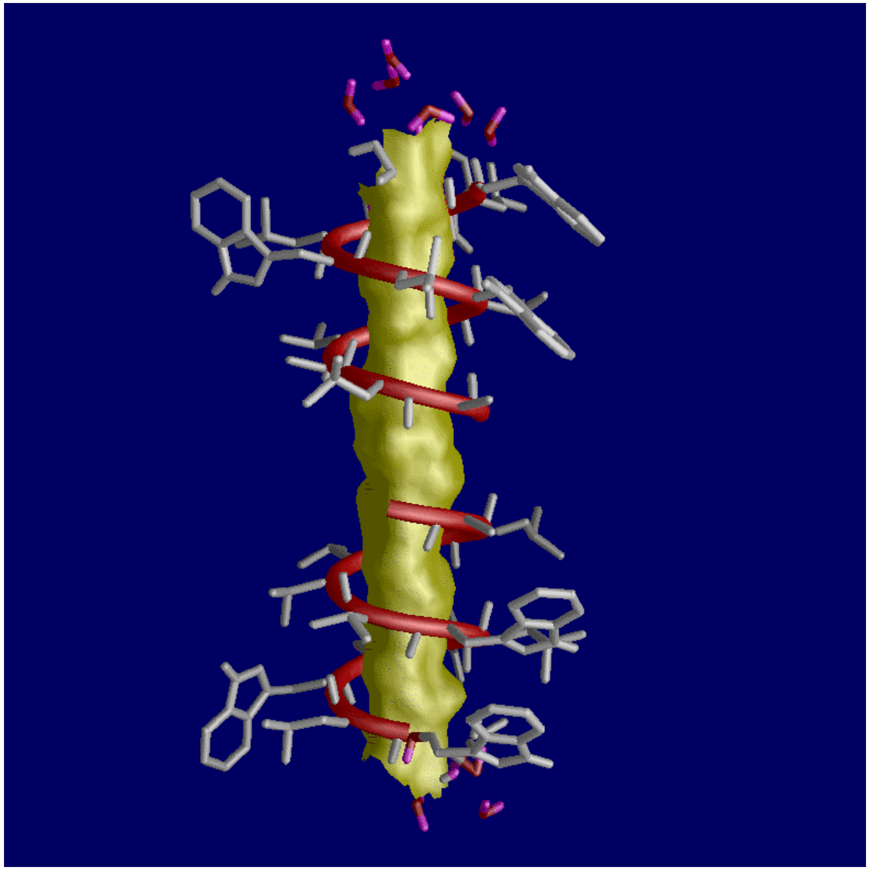



a
Selectivity filter sites
Extracellular sites
Cavity site
Pore axis
Internal
External
Direction of ion travel
b
Outer configuration
Inner configuration


Central
cavity

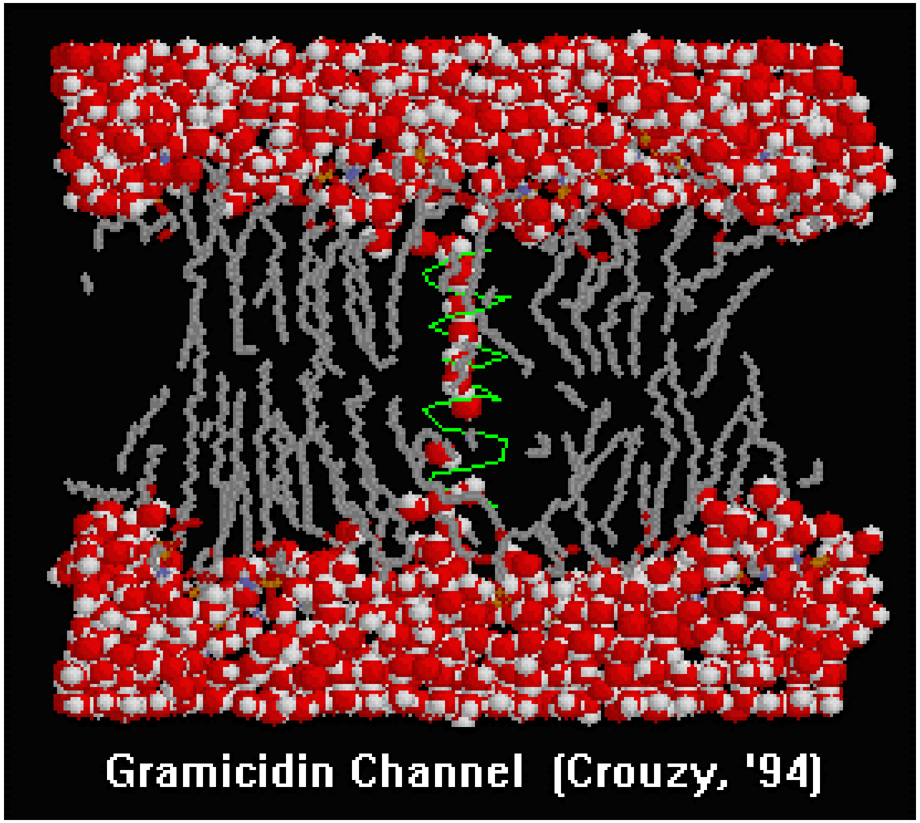
Gramicidin A
an ion leak inside the membrane

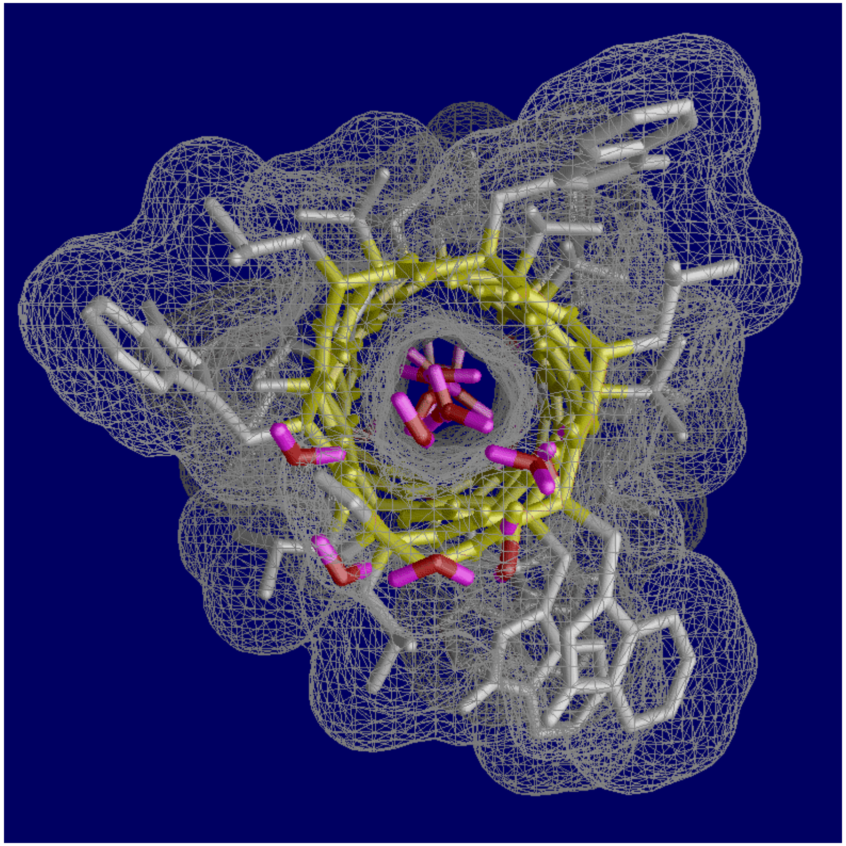




Through dissipating the electrochecmical potential of membrane, gramicidin A acts as an antibiotic.

Gramicidin can form a proton wire

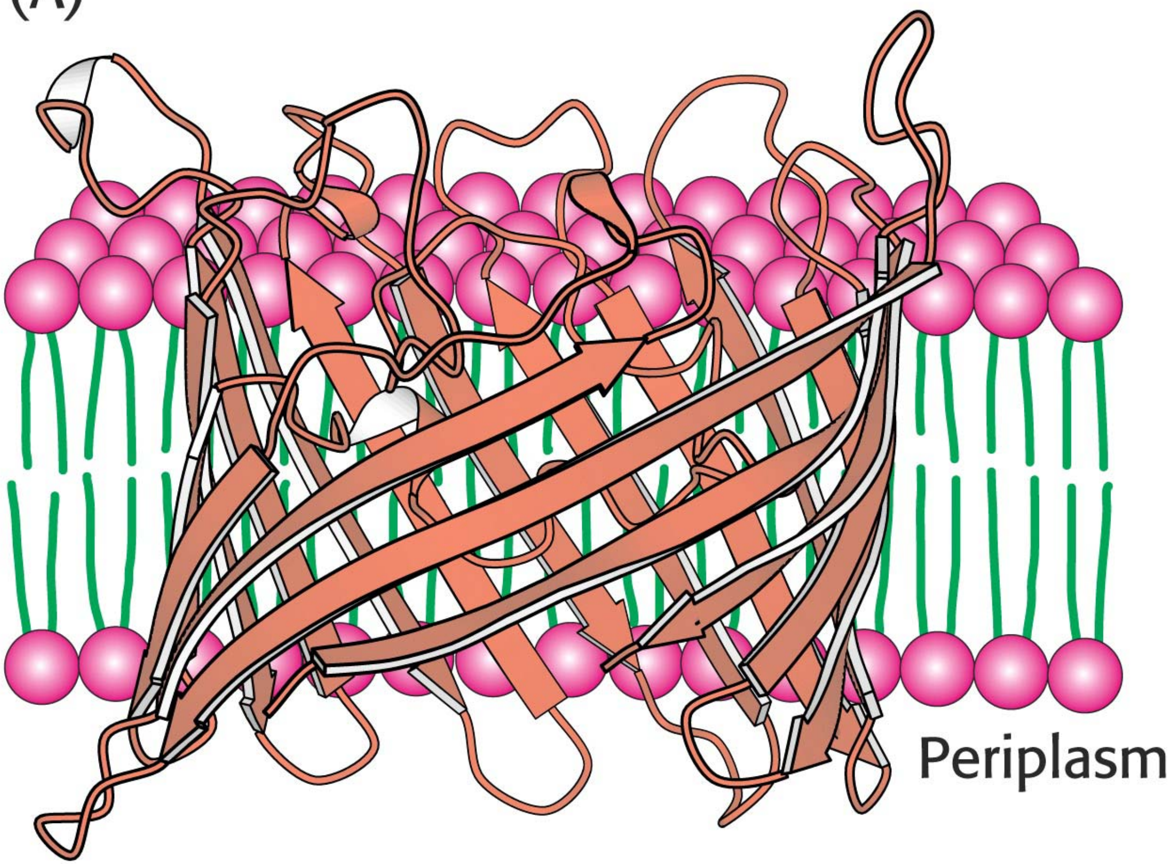


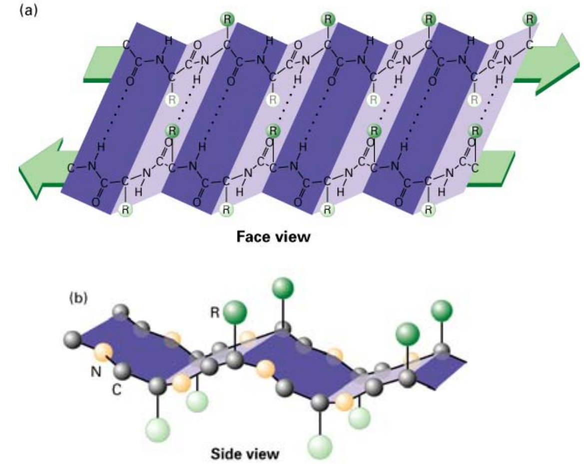


It also provides a membrane channel with a simple structure which can be simulated for a long time.

Porins: An example of β-barrel Membrane Proteins

(A)

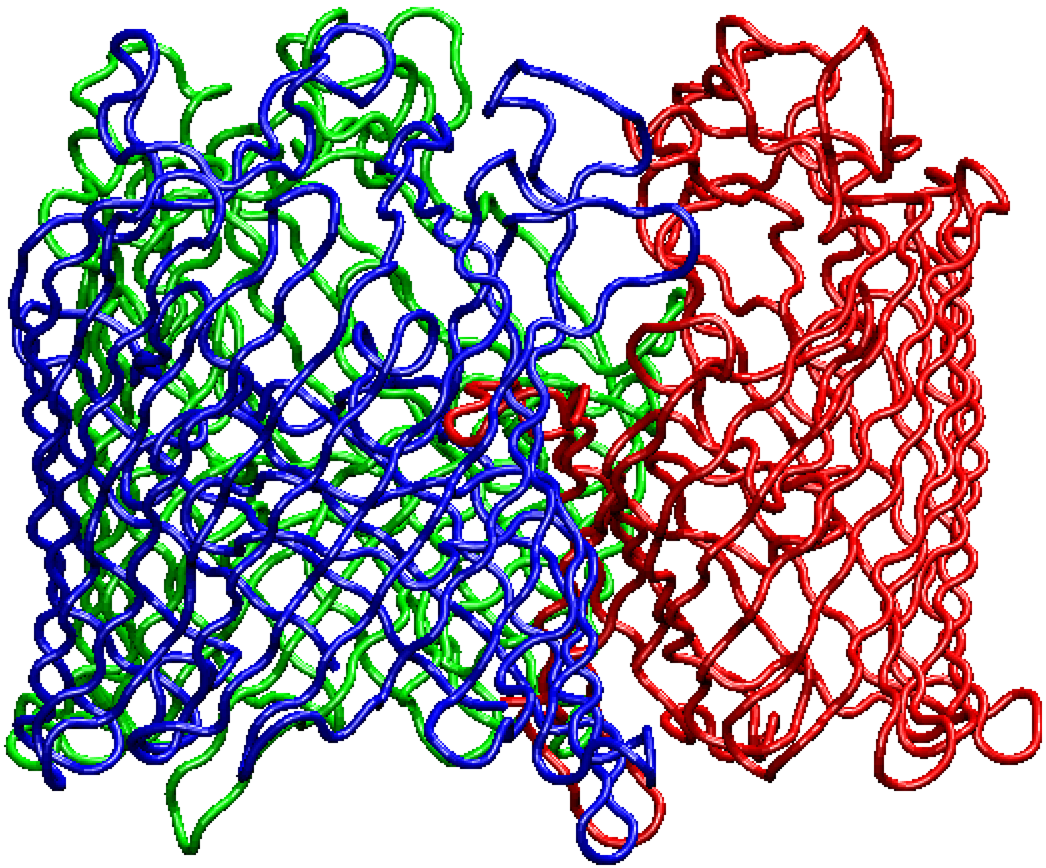




(B)

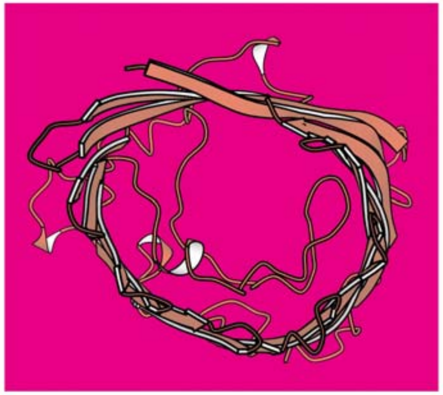
~18 β-strands – found in outer membranes of G^- bacteria and mitocondria

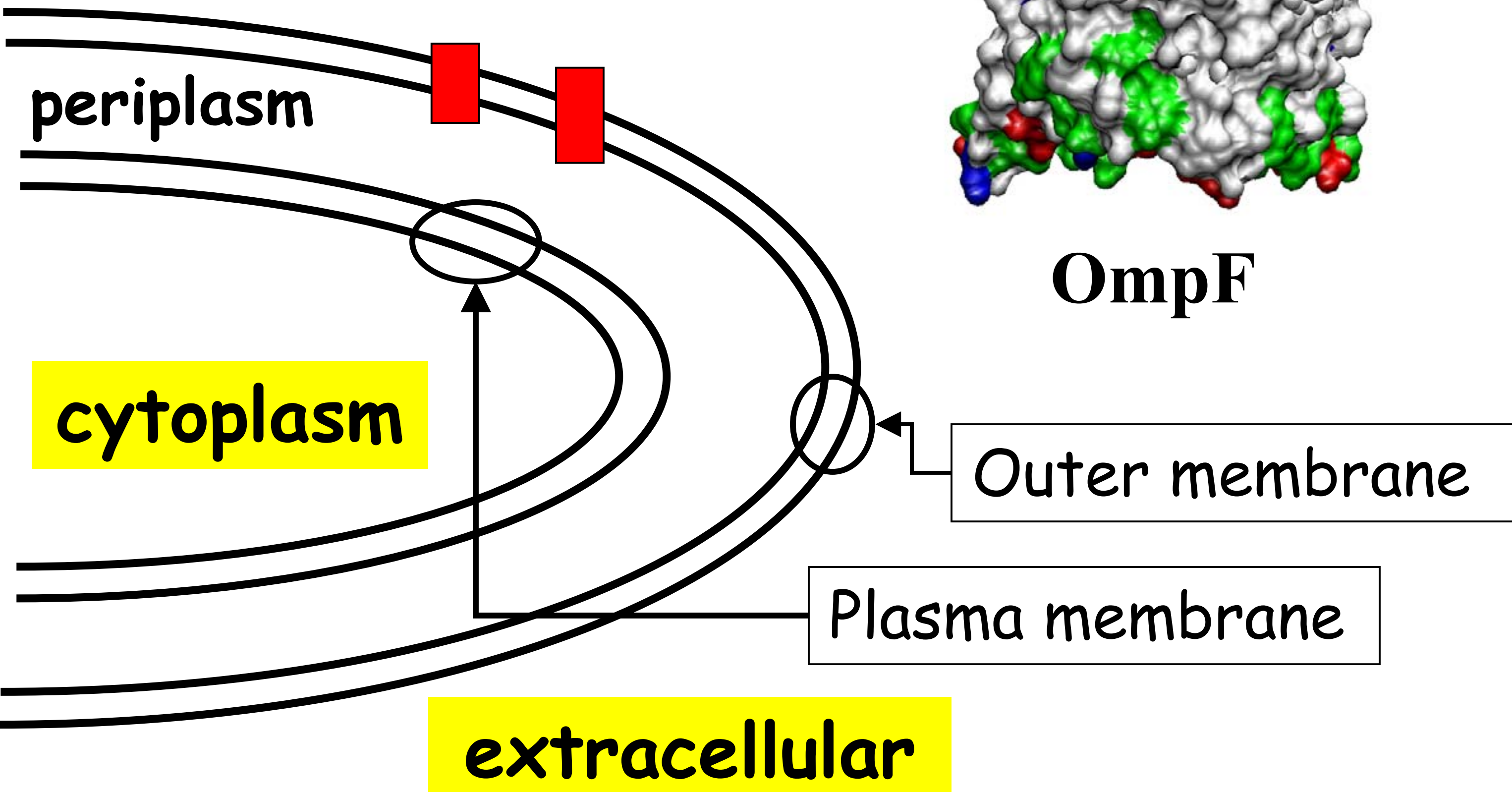
Porins: An example of β-barrel Membrane Proteins

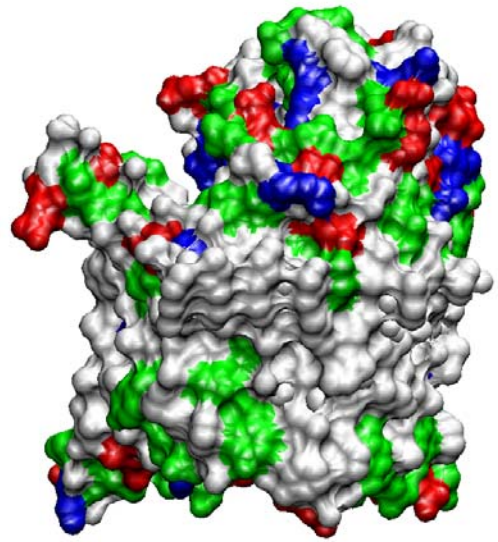


Usually form oligomers in the membrane.

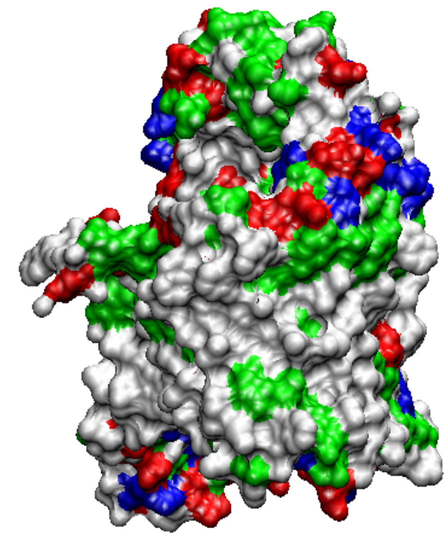
Porins: Non-selective Pores of the Outer Membrane





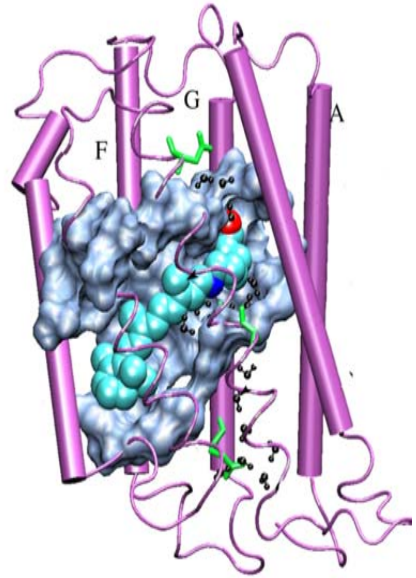


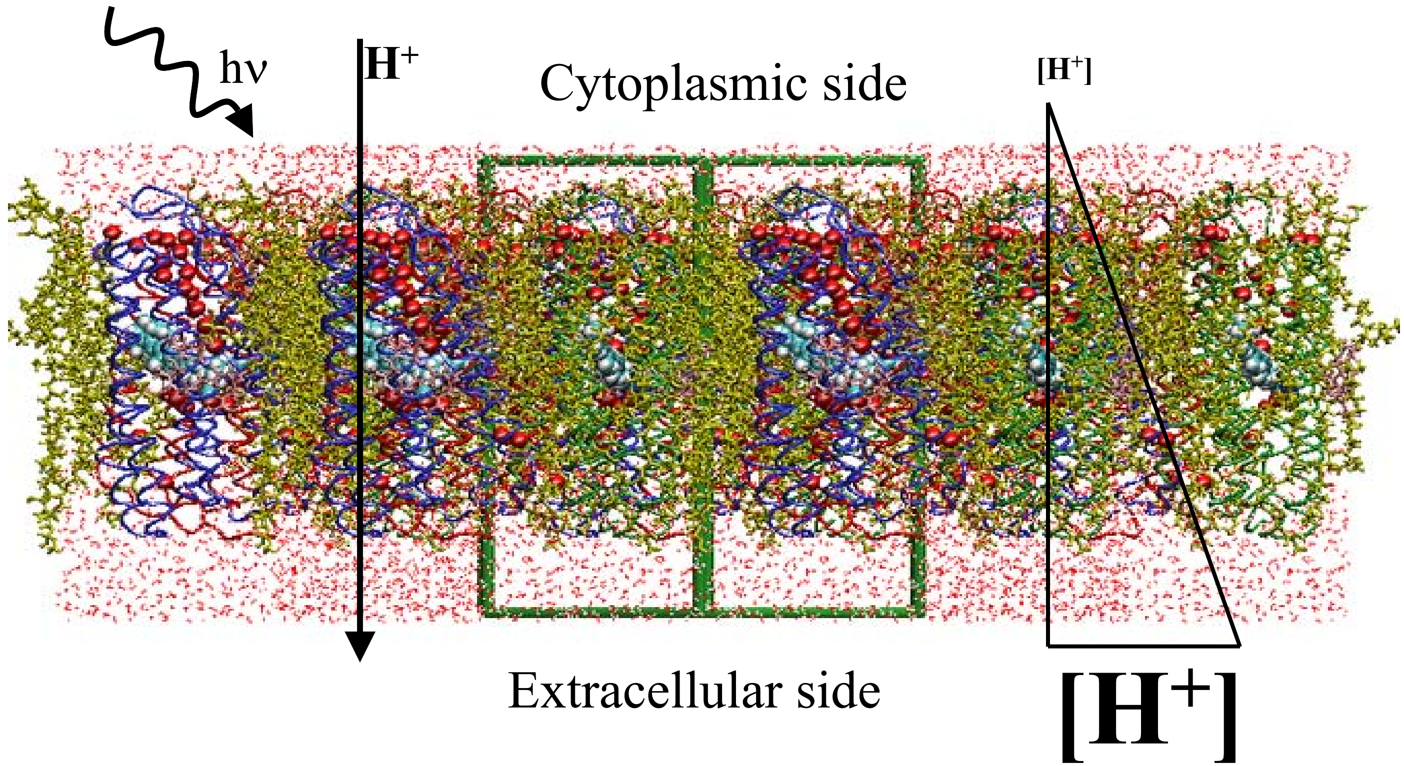
OmpF



Maltoporin

Bacteriorhodpsin uses sunlight and generates a transmembrane proton gradient





ATP synthase uses the proton gradient to produce ATP