Molecular Dynamics Simulation of Membrane Channels

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Summer School on Theoretical and Computational Biophysics
June 2003, University of Illinois at Urbana-Champaign
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
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Part I. Introduction
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 selective 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

Lateral diffusion
\[ D = 1 \ \mu m^2.s^{-1} \]
50 Å in \( \approx 2.5 \times 10^{-5} \) s

\(~9\) orders of magnitude difference

Transverse diffusion (flip-flop)

Once in several hours! (\(10^4\) s)

\[ D_{lip} = 10^{-8} \ \text{cm}^2.\text{s}^{-1} \]
\[ D_{wat} = 2.5 \times 10^{-5} \ \text{cm}^2.\text{s}^{-1} \]
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 mitochondria and chloroplast
  Purple membrane of halobacteria

- Different functions = different protein composition
Protein / Lipid Composition

Light harvesting complex of purple bacteria
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.
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
Central cavity
Gramicidin A
an ion leak inside the membrane

Through dissipating the electrochemical 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 $\beta$-barrel Membrane Proteins

~18 $\beta$-strands - found in outer membranes of G- bacteria and mitochondria
Porins: An example of $\beta$-barrel Membrane Proteins

Usually form oligomers in the membrane.
Porins: Non-selective Pores of the Outer Membrane

periplasm

OmpF

Maltoporin

cytoplasm

Outer membrane

Plasma membrane

extracellular
Bacteriorhodopsin uses sunlight and generates a transmembrane proton gradient.
ATP synthase uses the proton gradient to produce ATP