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-assemble 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 selective 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
Lipid Diffusion in Membrane

Lateral diffusion

\[ D = 1 \, \mu m^2.s^{-1} \]

50 Å in \( \sim 2.5 \times 10^{-5} \) s

~9 orders of magnitude difference

\[ D_{\text{lip}} = 10^{-8} \, cm^2.s^{-1} \]
\[ D_{\text{wat}} = 2.5 \times 10^{-5} \, cm^2.s^{-1} \]

Once in several hours!
(10^4 s)

Tranverse diffusion (flip-flop)
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
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
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
Mechanosensitive Channel of Small Conductance
Porins: An example of β-barrel membrane proteins

~18 β-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

cytoplasm

extracellular

OmpF

Maltoporin

Outer membrane

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