Biological Membranes

- Structure
- Function
- Composition
- Physicochemical properties
- Self-assembly
- Molecular models

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

Internal membranes for organelles

Bilayer Permeability

- Low permeability to charged and polar substances
- Water is an exception: small size, lack of charge, and its high concentration
- Shedding solvation shells for ions is very unlikely

<table>
<thead>
<tr>
<th>Substance</th>
<th>Permeability (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K⁺</td>
<td>10⁻¹⁵</td>
</tr>
<tr>
<td>Na⁺</td>
<td>10⁻¹⁵</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>10⁻¹⁵</td>
</tr>
<tr>
<td>Glucose</td>
<td>10⁻⁶</td>
</tr>
<tr>
<td>Urea</td>
<td>10⁻⁴</td>
</tr>
<tr>
<td>Glycerol</td>
<td>10⁻²</td>
</tr>
<tr>
<td>Indole</td>
<td>10⁻¹</td>
</tr>
<tr>
<td>H₂O</td>
<td>10⁻¹</td>
</tr>
</tbody>
</table>

Increasing permeability →

Common Features of Biological Membranes

- Sheet-like structure
- Two-molecule thick (60-100Å)
- Lipids, Proteins, and carbohydrates
- Lipids form the barrier. Proteins mediate distinct functions.
- Non-covalent assemblies (self-assembly, protein-lipid interaction)
- Asymmetric (always)
- Fluid structures: 2-dimensional solution of oriented lipids and proteins
- Electrically polarized (inside negative ~60mV)
- Spontaneously forming in water
- Protein/lipid ratio = 1/4 - 4/1
- Carbohydrate moieties are always outside the cell

Protein/Lipid ratio

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

**General features of Lipids**

- Small molecules
- Amphipathic (amphiphilic)
- Hydrophobic/hydrophilic moieties
- Spontaneously form vesicles, micelles, and bilayers in aqueous solution

**Micelle / Bilayer**

- Fatty acids (one tail)
- Phospholipids (two tails)
- Micelle max 20 nm
- Bilayer up to millimeters
- Self-assembly process
- Hydrophobic interaction is the driving force (also in protein folding and in DNA stacking)
- Extensive; tendency to close on themselves; self-sealing (a hole is unfavorable)

**Vesicles**

- Phospholipids
- Sonicating (~50nm)
- Evaporation (1 micron)
- Experimental tool for studying membrane proteins
- Clinical use (drug delivery)

**Phospholipids**

- Hydrophobic
- Hydrophilic

**Structure of fatty acids**

cis

cis

H₂C=CH(C₃H₇)[CH₂][CH₂]CH₃

H₂C=CH(C₃H₇)[CH₂][CH₂][CH₂]CH₃

H₂C=CH(C₃H₇)[CH₂][CH₂][CH₂][CH₂]CH₃

H₂C=CH(C₃H₇)[CH₂][CH₂][CH₂][CH₂][CH₂]CH₃

H₂C=CH(C₃H₇)[CH₂][CH₂][CH₂][CH₂][CH₂][CH₂]CH₃

**Table**

<table>
<thead>
<tr>
<th>No. of carbons</th>
<th>No. of double bonds</th>
<th>Number of unsaturated bonds</th>
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</thead>
<tbody>
<tr>
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<td>18</td>
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<tr>
<td>14</td>
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<td>18</td>
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<td>16</td>
<td>0</td>
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<td>18</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>18</td>
</tr>
</tbody>
</table>

No. of carbon
No. of unsaturated bonds
18:2
Einstein relation for diffusion:

\[ 6D_t = \langle \Delta r(t) - \Delta r(0) \rangle^2 \]

\[ |\Delta r(t) - \Delta r(0)| = S \]

- in a 3 dimensional space
- in 2 dimensions (in-plane diffusion in a membrane)
- in 1 dimension

**Lipid Diffusion in Membrane**

- Rapid diffusion
  - \( D_{lip} = 10^{-8} \text{ cm}^2 \text{s}^{-1} \)
  - \( D_{ext} = 2.5 \times 10^{-5} \text{ cm}^2 \text{s}^{-1} \)
- Lateral diffusion
  - \( D = 1 \mu \text{m}^2 \text{s}^{-1} \)
  - \( 50 \AA \text{ in } 2.5 \times 10^{-5} \text{ s} \)
- Transverse diffusion (flip-flap)
  - 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 some passive transport mechanisms, all membrane proteins function in a directed way, and their correct insertion in the cell membrane is essential for their biological function.

Highly asymmetric and inhomogeneous lipid composition of membrane

Polyunsaturated lipids 22:6ω3: 47% in membrane
PC : PE : PS
45 : 42 : 14

Outside leaflet
Phosphatidylethanolamine
Phosphatidylserine
Phosphatidylcholine

Inside leaflet

Fluorescence recovery after photobleaching (FRAP)

Lipid Diffusion in Membrane

FRAP - fluorescent recovery after photobleaching (Albert’s movie)

Fluid disordered state
Lipid crystalline

E. coli:
@ 42°C  sat/unsat = 1.6
@ 27°C  sat/unsat = 1.0

“FRAP experiment movie”
The Molecular Biology of the Cell
A Brief Introduction to Molecular Dynamics Simulations

Macroscopic properties are often determined by atomic-level behavior.

Quantitative and/or qualitative information about macroscopic behavior of macromolecules can be obtained from simulation of a system at atomistic level.

Molecular dynamics simulations calculate the motion of the atoms in a molecular assembly using Newtonian dynamics to determine the net force and acceleration experienced by each atom. Each atom $i$ at position $r_i$ is treated as a point with a mass $m_i$ and a fixed charge $q_i$.

What is the Force Field?

In molecular dynamics a molecule is described as a series of charged points (atoms) linked by springs (bonds).

To describe the time evolution of bond lengths, bond angles and torsions, also the non-bonding van der Waals and electrostatic interactions between atoms, one uses a force field.

The force field is a collection of equations and associated constants designed to reproduce molecular geometry and selected properties of tested structures.

Energy Terms Described in the CHARMm Force Field

Energy Functions

$$U(\vec{r}) = \sum_{\text{bonds}} k_{\text{bond}} (r_i - r_j)^2 + \sum_{\text{angles}} k_{\text{angle}} (\theta_i - \theta_j)^2 + \sum_{\text{dihedrals}} k_{\text{dihedral}} [1 + \cos (n_i \phi_i + \delta_i)] + \sum_{\text{impropers}} k_{\text{improper}} \left[ \frac{\beta_i}{\tau_i} \right]^{12} - \left[ \frac{\beta_i}{\tau_i} \right]^6 + \sum_{\text{nonbonds}} U_{\text{nonbond}}$$

- $U_{\text{bond}}$ = oscillations about the equilibrium bond length
- $U_{\text{angle}}$ = oscillations of 3 atoms about an equilibrium bond angle
- $U_{\text{dihedral}}$ = torsional rotation of 4 atoms about a central bond
- $U_{\text{improper}}$ = non-bonded energy terms (electrostatics and Lenard-Jones)

Time Scale of Biological Events

<table>
<thead>
<tr>
<th>Motion</th>
<th>Time Scale (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bond stretching</td>
<td>$10^{-14}$ to $10^{-13}$</td>
</tr>
<tr>
<td>Elastic vibrations</td>
<td>$10^{-10}$ to $10^{-11}$</td>
</tr>
<tr>
<td>Rotations of surface sidechains</td>
<td>$10^{-10}$ to $10^{-11}$</td>
</tr>
<tr>
<td>Hinge bending</td>
<td>$10^{-10}$ to $10^{-7}$</td>
</tr>
<tr>
<td>Rotation of buried side chains</td>
<td>$10^{-6}$ to $1$ sec</td>
</tr>
<tr>
<td>Allosteric transitions</td>
<td>$10^{-5}$ to $1$ sec</td>
</tr>
<tr>
<td>Local denaturations</td>
<td>$10^{-5}$ to $10$ sec</td>
</tr>
</tbody>
</table>

The 1 fs Time Step Limit

- Dynamics simulations are limited by the highest frequency vibration.
- Ideally the timestep should be $1/10$ of the period of the highest frequency vibration.
- X-H bond stretching ($10^{-14}$ s) is the fastest mode.
Technical difficulties in Simulations of Biological Membranes

- Time scale
- Inhomogeneity of biological membranes

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

Coarse grain modeling of lipids
by: J. Siewert-Jan Marrink and Prof. Dr. Alan E. Mark, University of Groningen, The Netherlands

150 particles
9 particles!