Lipids: Membranes

Models for Membrane Structure

NEW MODEL (1972)
Fluid Mosaic Model proposed by Singer & Nicholson

- Lipids form a viscous, two-dimensional solvent into which proteins are inserted and integrated more or less deeply.
- Proteins can either be embedded in or associated with the membrane:
  - Integral membrane proteins are firmly associated with the membrane, often spanning the bilayer.
  - Peripheral membrane proteins are weakly associated and can be removed easily.
    - Some are non-covalently attached.
    - Some are linked to membrane lipids (amphitrophic)(more later). This model was also testable!

Lipids: Membranes

Testing Fluid Mosaic Model of Membrane Structure: Cellular Fusion

[Diagram showing cellular fusion process]
Lipids: Membranes

Testing Fluid Mosaic Model of Membrane Structure: FRAP

- **Fluorescence Recovery After Photobleaching (FRAP)** allows us to monitor lateral diffusion by monitoring the rate of fluorescence return.
- From the rate of return of fluorescently labeled lipids, the rate of diffusion of a lipid in the leaflet can be determined.

\[
\text{Distance} = \sqrt{4Dt}
\]

Set distance by radius of laser target area, measure \( t \), calculate \( D \)

- \( D \) is rate of diffusion in \( \text{m}^2/\text{sec} \)
- Rates of lateral diffusion are high (up to 1 \( \mu \text{m}^2/\text{sec} \)).
  - A lipid can circumnavigate an *E. coli* cell in one second.
  - A protein has a variable rate: 0.4 to 0.0001 \( \mu \text{m}^2/\text{sec} \).

------- but not so fast!

Lipids: Membranes

Testing Fluid Mosaic Model of Membrane Structure: FRAP

**Lateral Movement is fast**

A Single Lipid in 56 ms

**Transverse Movement is SLOW**

Uncatalyzed lateral diffusion

![Uncatalyzed lateral diffusion](Image)

very fast (1 \( \mu \text{m}/s \) )

Uncatalyzed transbilayer ("flip-flop") diffusion

![Uncatalyzed transbilayer diffusion](Image)

very slow (1/12 in days)

Spontaneous flips from one leaflet to another are rare because the charged head group must transverse the hydrophobic tail region of the membrane.
Lipids: Membranes

The Fluid Mosaic Model: Details

Outside

Lipid bilayer

Inside

Lipids: Membranes

The Fluid Mosaic Model: Details

Outside

Glycolipid

Oligosaccharide chains of glycoprotein

GPI-anchored protein

Lipid bilayer

Inside

Sterol

Phospholipid polar heads

Peripheral protein covalently linked to lipid

Integral protein (single transmembrane helix)

Sphingolipids

Peripheral protein
Lipids: Membranes

The Structure of the Red-blood Cell Membrane

Let's look closer at one of these integral membrane proteins, glycophorin.

Nonpolar Amino Acids of Integral Membrane Proteins are within the Membrane
Lipids: Membranes

**Introduction**

**The 4 S’s**
- Size
- Solubility
- Shape
- Stability

**Models for Membrane structure**
- Old Model
- Data
- Fluid Mosaic Model
- Testing the model

**The Red-Blood Cell Membrane**

**Membrane Asymmetry**

- **Lipids**
  - transverse
  - lateral
- **Protein**
  - anchoring
  - glycoproteins

**Membrane Fluidity**

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**Lipids: Membranes**

**Asymmetry**

- Membranes are very asymmetric.
- All kinds of asymmetry: lipids, proteins, transverse, and lateral asymmetry
  - Lipids (transverse):
    - Two leaflets have different lipid compositions.
    - The outer leaflet is often more positively charged (recall PS is –).

![Rat liver plasma membrane](image)

- If Phosphatidylserine is found outside, it has a special meaning:
  - platelets: activates blood clotting
  - other cells: marks the cell for destruction

How is this asymmetry maintained?
Lipids: Membranes

Asymmetry

– Lipids (transverse): Flippases

• Special enzymes catalyze transverse diffusion.
  – Though often referred to by category name “flippase,” there are unique unidirectional and bidirectional enzymes to catalyze lipid movement.
• Some flippases use energy of ATP to move lipids against the concentration gradient.

Lipids: Membranes

Asymmetry

Lipids (lateral):

1) On the inner leaflet, can induce phosphoserine to coalesce with calcium.

2) On the outer leaflet, can induce “raft” formation; the coalescence of particular membrane lipids (cholesterol, sphingoglycolipids, sphingomyelin, etc.)
Lipid distribution in a single leaflet is not random or uniform.

Lipid rafts:
- contain clusters of sphingoglycolipids with longer-than-usual tails and cholesterol
- are more ordered (not as fluid)
- contain specific doubly or triply acylated proteins
- allow segregation of proteins in the membrane
Lipids: Membranes

Proteins: Asymmetry

1) anchored
2) glycoproteins

- Some membrane proteins are lipoproteins containing a covalently linked lipid molecule.
- The lipid part inserts into the membrane.
- The protein is then anchored to the membrane.
- These are the aforementioned “Amphitropic” membrane proteins
  - This allows targeting of proteins to the membrane, either internally (FA or isoprenes), or externally (GPI-linked).
  - Some, such as GPI anchors are found only on the outer face of plasma membrane.
  - This is a reversible process.
Lipids: Membranes

Proteins: Asymmetry

1) anchored
2) glycoproteins

Found ONLY ever on the OUTSIDE of Cells

Introduction

The 4 S’s
Size
Solubility
Shape
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The Red-Blood Cell Membrane

Membrane Asymmetry
Lipids
transverse
lateral
Protein
anchoring
glycoproteins

Membrane Fluidity
Cells must maintain fluidity for membranes to function properly.

Depending on their composition and the temperature, the lipid bilayer must maintain a fluid phase; if cooled, it undergoes a phase transition and goes to a gel state.

- liquid-ordered state (i.e., “gel phase”): individual molecules do not move around – NOT ACTIVE
- liquid-disordered (or liquid crystal) state (i.e., “fluid phase”): individual molecules can move around – ACTIVE

Lipids: Membranes

Fluidity

Membrane Phase Transition

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Plot membrane thickness vs. temperature
**Lipids: Membranes**

**Membrane Phase Transition**

- Cooperativity is modified by cholesterol.
- Cooperative phase transition, or melting temperature.
- Lipids: Membranes

**Fluidity**

- Cholesterol increases membrane rigidity and permeability.
- Cholesterol: A “Fluidity Buffer”

- Below $T_m$, cholesterol disrupts close packing of acyl chains, increasing fluidity.
- Above $T_m$, cholesterol constrains motion of acyl chains, decreasing fluidity.
- Broadens/abolishes phase transitions.

- Due to its small polar head, it lies deeper in the bilayer than the phospholipids.
- Cell membranes of many eukaryotes contain sterols:
  - Cholesterol in animals
  - Phytosterols in plants
  - Ergosterol in fungi
- Cell membranes of aerobic prokaryotes contain hopanols.
Lipids: Membranes

Fluidity

Organisms Can Adjust the Temperature of the Phase Transition by Changing the Membrane Composition

- Membrane fluidity is determined mainly by the fatty acid composition and melting point.
- The temperature of the phase transition ($T_m$):
  - Melting temperature higher with more saturated fatty acids.
  - Melting temperature higher with longer fatty acids.
  - Melting temperature lower with more unsaturated fatty acids.
  - Melting temperature lower with shorter fatty acids.
- Therefore, at higher temperatures, cells need more long, saturated fatty acids.
- And at lower temperatures, cells need more shorter, unsaturated fatty acids.

<table>
<thead>
<tr>
<th>Percentage of total fatty acids$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 °C</td>
</tr>
<tr>
<td>Myristic acid</td>
</tr>
<tr>
<td>Palmitic acid</td>
</tr>
<tr>
<td>Palmitoleic acid</td>
</tr>
<tr>
<td>Oleic acid</td>
</tr>
<tr>
<td>Hydroxymyristic acid</td>
</tr>
<tr>
<td>Ratio of unsaturated to saturated$^b$</td>
</tr>
</tbody>
</table>


$^a$The exact fatty acid composition depends not only on growth temperature but on growth stage and growth medium composition.

$^b$Ratios calculated as the total percentage of 16:1 plus 18:1 divided by the total percentage of 14:0 plus 16:0. Hydroxymyristic acid was omitted from this calculation.