IPAM Cells and Materials:
At the Interface between Mathematics, Biology and Engineering

Tutorial 2,
Plasma Membrane

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Plasma Membrane

Lipid Bi-layer
- Creates Hydrophobic Barrier
- Higher Cholesterol contents (~20%) than Organelle membrane
- Glycolipid (external surface of Plasma Membrane)

Water: Poorly permeable
O₂, CO₂: Permeable
Hydrophobic agents (drugs)
Detergent Hydrophobic - Hydrophilic
Plasma Membrane: environmental boundary (barrier)

- Electrochemical gradient
- Membrane potential
- Unique intracellular environment
- Stabilize pH
- Holds molecules inside
Ionic imbalance (particularly, Na\(^+\) and K\(^+\)) between inside and outside a cell, created by membrane ionic pumps, ion exchangers and channels, establishes resting membrane potential. This is used to drive other process (such as molecule import), as well as for information processing (e.g. nerve cells). Activities of plasma membrane ionic pumps are energized by hydrolysis of ATP. All the ‘live’ cells establish and maintain the membrane potential.
Plasma Membrane
Components of plasma membrane

Lipids
- Phospholipids
- Glycolipid
- Cholesterol

Proteins; transmembrane proteins, peripheral proteins
Many proteins are glycosylated
- Membrane channels, pumps: Ion concentration gradient (in↔out)
- Membrane potential
- Transporters: transport molecule across plasma membrane, e.g. glucose transporter
- Membrane receptors: Information relay (via particular signaling molecules, e.g. hormones, neurotransmitters)
- Communication between cells: Gap junctions, integrins
- Adhesion molecules (Junctions); cell to extracellular matrix, cell to cell
- Endocytosis, Exocytosis: Intracellular membrane flow
Phospholipid structure: *e.g.* Phosphatidylcholine
Mobility of phospholipid

1. More difficult to pack phospholipid together – membrane stays fluid at lower temp (Bacteria, yeast adjust the fatty acid composition according to temp, to maintain membrane fluidity)

2. The kinks shorten the length of hydrocarbon chains, so that the membrane is thinner.
Four **major** phospholipids found in mammalian plasma membrane:

There are many ‘minor’ phospholipids exists, too.
Cholesterol

Unique to plasma membrane
Stabilize membrane
**Cholesterol**
Unique to plasma membrane
Stabilize membrane

**ALSO:** Precursor to steroid hormones

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Liver Plasma Membrane</th>
<th>Erythrocyte Plasma Membrane</th>
<th>Myelin</th>
<th>Mitochondrion (inner and outer membranes)</th>
<th>Endoplasmic Reticulum</th>
<th>E. coli</th>
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<tr>
<td>Cholesterol</td>
<td>17</td>
<td>23</td>
<td>22</td>
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<tr>
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<td>15</td>
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<td>9</td>
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<tr>
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<td>18</td>
<td>8</td>
<td>0</td>
<td>5</td>
<td>0</td>
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<tr>
<td>Glycolipids</td>
<td>7</td>
<td>3</td>
<td>28</td>
<td>trace</td>
<td>trace</td>
<td>0</td>
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<tr>
<td>Others</td>
<td>22</td>
<td>13</td>
<td>8</td>
<td>21</td>
<td>27</td>
<td>30</td>
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</table>
Glycolipids

(A) galactocerebrosides

(B) GM1 ganglioside

Unique to plasma membrane (Extracellular side)

Neutral glycolipid (A)
or,negatively charged (B)(due to sialic acid [NANA])
Phospholipid arrangement in Plasma Membrane

Ext. Cellular Side:
two unique lipids
Glycolipids (blue)
Sphingomyelin (brown)

Cytospsmic Side:
PS [negatively charged] PE

Cholesterol (not shown) are found in both side.
Lipid Raft

Local area of a membrane where sphingolipid, cholesterol and membrane proteins are concentrated.
Plasma Membrane: Membrane Proteins

Functional classification (1)

Transmembrane Proteins

**Ion channel**
Allows specific ion (●) to move through water-filled pore. Most plasma membranes include specific channels for several common ions.

**Transporter**
Transports specific substances (●) across membrane by changing shape. For example, amino acids, needed to synthesize new proteins, enter body cells via transporters.

**Receptor**
Recognizes specific ligand (●) and alters cell's function in some way. For example, antidiuretic hormone binds to receptors in the kidneys and changes the water permeability of certain plasma membranes.
Plasma Membrane: Membrane Proteins

Functional classification (2)

Transmembrane Proteins

**Enzyme**
Catalyzes reaction inside or outside cell (depending on which direction the active site faces). For example, lactase protruding from epithelial cells lining your small intestine splits the disaccharide lactose in the milk you drink.

**Linker**
Anchors filaments inside and outside to the plasma membrane, providing structural stability and shape for the cell. May also participate in movement of the cell or link two cells together.
Plasma Membrane: Membrane Proteins
Functional classification (3)

Peripheral Proteins
(only one side of the membrane)

Cell Identity Marker
Distinguishes your cells from anyone else's (unless you are an identical twin). An important class of such markers are the major histocompatibility (MHC) proteins.
Association of membrane proteins with the lipid bilayer (1)

Transmembrane Proteins

1. A single \( \alpha \)-helix
2. Multiple \( \alpha \)-helices
3. Rolled up \( \beta \)-sheet
Association of membrane proteins w/ the lipid bilayer (2)

Peripheral Membrane Proteins

4. α-helix (hydrophobic face) embedded in the lipid bilayer
5. Protein covalently attaches lipid chain – fatty acid chain or prenyl group (cytoplasmic side)
6. Protein attaches phosphatidylinositol via an oligosaccharide linker
7, 8. Noncovalent interaction between proteins

(C) myristyl anchor
(D) farnesyl anchor
α helical transmembrane polypeptide chain

Mostly consists of hydrophobic amino acids (yellow and green)

Hydropathy plot
Prediction of transmembrane α helix by sequence of amino acids

Seven trans-membrane α helices
Membrane receptor proteins
Signal transduction across the membrane

The signals are used to activate:
- gene transcription(s) → cell differentiation
- cell locomotion
- exocytosis / endocytosis
- etc

→ Signal Transduction (an another tutorial section)
Overview of membrane transport proteins

These systems exist not only on plasma membrane, but also many organelle membranes.
**Na\(^+\)/K\(^+\)-ATPase (Na\(^+\)/K\(^+\)-pump)**

1 ATP used for exporting 3 Na\(^+\) ions and importing 2 K\(^+\) ions. Crucial for maintaining resting membrane potential.

Other pumps; *e.g.* Ca\(^{2+}\) pump
Transporters

ATP-independent systems
(However, Na$^+$ gradient drives these transporters; ATP-driven Na$^+$/K$^+$-pump generates the gradient.)

Glucose transporter

(a) Antiporters
(b) Symporters
Many of the channels, pumps and transporters are inserted only on particular surface of the cell.

Intestinal epithelial cell

Blood
High Na⁺
Low K⁺

Epithelial cells
Low Na⁺
High K⁺

Intestinal lumen
Dietary glucose
High (dietary) Na⁺

Tight junction serves barriers between apical surface and basolateral surface of plasma membrane (many plasma membrane proteins, such as channels, pumps, receptors, are inserted only into one or the other surface of the plasma membrane. These proteins cannot go (move) across the other side due to tight junction.
Cellular Junctions

**Location**

- junctional complex
- actin
- intermediate filaments
- basal lamina

**Function**

Each junction consists of a specific set of adhesion proteins.

<table>
<thead>
<tr>
<th>Name</th>
<th>Function</th>
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</thead>
<tbody>
<tr>
<td>tight junction</td>
<td>seals neighboring cells together in an epithelial sheet to prevent leakage of molecules between them</td>
</tr>
<tr>
<td>adherens junction</td>
<td>joins an actin bundle in one cell to a similar bundle in a neighboring cell</td>
</tr>
<tr>
<td>desmosome</td>
<td>joins the intermediate filaments in one cell to those in a neighbor</td>
</tr>
<tr>
<td>gap junction</td>
<td>allows the passage of small water-soluble ions and molecules</td>
</tr>
<tr>
<td>hemidesmosome</td>
<td>anchors intermediate filaments in a cell to the basal lamina</td>
</tr>
</tbody>
</table>
Occluding Junctions
Tight Junction

Separates two environments

Paracellular pathway: Passage through tight junction b/w cells
Small(er) molecules water, ions, etc

Paracellular pathway
Transcellular pathway

Na^+-driven glucose symport
LUMEN OF GUT
apical surface

intercellular space
plasma membranes of adjacent cells

passive glucose carrier protein
tight junction

basolateral surface
extracellular fluid

BLOOD

LOW
HIGH glucose concentration

glucose
Occluding Junctions
Tight Junction

Separates two environments

External body <incl. Intestine lumen, urinary-tract lumen> vs Extracellular fluid (body fluid) <incl. Blood, lymph>
Tight Junction

Tight Junction:
Separation of Apical vs basolateral plasma membrane (proteins)

Sealing strands: Plasma-membrane proteins (Occludin, Claudin)
Visualized with freeze-fracture EM
Ca\(^{2+}\)-requirement
Anchoring Junctions: Adherens Junctions
(Zonula Adherens; Belt Desmosome)

**Cadherin**

CELL 1

- <0.05 mM Ca\(^{2+}\)

CELL 2

- Cadherin dimer

**Ca\(^{2+}\)-requirement**

CELL 1

- Cadherin dimer

CELL 2

- Cadherin dimer

Plasma membrane

Actin filaments

Cadherin dimers

Anchor proteins

Microvilli extending from apical surface

Tight junction

Bundle of actin filaments

Lateral plasma membranes of adjacent epithelial cells

Basal surface
Anchoring Junctions: Desmosomes

Maintain strong cell-cell adhesion

Yellow marks: desmosomes
Keratin filaments attach cytoplasmic side of desmosomes

Epithelial Cells

Intercalated Discs in cardiac muscle
Anchoring Junctions: Desmosomes
Maintain strong cell-cell adhesion
Focal Adhesion
Cell-Matrix adhesion

Integrin

Cytoskeletal fibers associated:
- Actin fibers
  - Focal adhesions
  - Muscle (lateral) attachment
- Intermediate filaments
  - Hemidesmosomes
Focal Adhesion
Cell-Matrix adhesion

Hemidesmosome (green)
Integrin holds basal lamina

Matrix-binding activity of Integrin is regulated by signaling events (below) e.g. white blood cells

Integrin (cluster) triggers intracellular signalling
Gap Junction
Connexin hexamer (per cell)
‘Connexon’ (hemichannel)
Two connexons from adjacent cells to form intracellular channels
Often found as ‘patch’ (cluster) on a plasma membrane
Gap Junction
Molecules that pass through gap junctions dependent on type of connexons
Molecular size, charge, else?

Examples of GAP-junction-connection between cells
Electrical Synapses (Fishes, Insects etc…)
Cardiac muscle cells / smooth muscle cells
Hepatocytes
Tracheal ciliated epithelial cells [IP₃]

Regulation of the channel (Open ↔ Close)
Summary of cell-cell / cell-matrix adhesions
Excitatory Properties of Plasma Membrane: Neuron

**Dendrites**
- Conducts impulses towards the cell body
- Typically short, highly branched & unmyelinated
- Surfaces specialized for contact with other neurons (Post-synaptic terminals)

**Axons**
- Conduct impulses away from cell body
- Long, thin cylindrical process of cell
- Arises at axon hillock
- Impulses (Action potentials) arise from the initial segment (trigger zone)
- Side branches (collaterals) end in fine processes called axon terminals
- Synaptic end bulbs: contain vesicles filled with neurotransmitters

(a) Parts of a motor neuron

(b) Sections through a myelinated axon
Nerve cells, (Neurons, Grial cells)
All the other living cells

Potential energy difference at rest is (about) $-70 \text{ mV}$
(depending on the cell types)
Establishment of the Resting Membrane Potential

Concentration of ions different; inside & outside the cell
Extracellular fluid: rich in Na⁺ and Cl⁻
Cytosol: high [K⁺], organic phosphate & amino acids

Membrane permeability for Na⁺ & K⁺:
50-100 greater permeability for K⁺

Inward flow of Na⁺ can’t keep up with outward flow of K⁺
Na⁺/K⁺ pump removes Na⁺ as fast as it leaks in.
Potential energy difference at rest is (about) -70 mV
Membrane channels (a partial list): Membrane conductance

Conductance:
Each carried by specific ion species
Na⁺, K⁺, Ca²⁺

Specific Ion Channels
Specific ion channels are opened according to the stimulus

Strength of the stimulus $\propto$ amount of change in membrane potential (Not always; also effective range)

Local change in membrane potential spreads through membrane with decay
Depolarization / Hyperpolarization of the Membrane Potential

Graded Potentials

Source of stimuli
- Mechanical stimulation of membranes with mechanical gated ion channels (pressure)
- Chemical stimulation of membranes with ligand gated ion channels (neurotransmitter, hormone)

Graded/postsynaptic/receptor or generator potential
- Ions flow through ion channels and change membrane potential locally
- Amount of change varies with strength of stimuli
- Flow of current (ions) occurs only locally
- Dendrites and Cell bodies (usually not on axonal membrane)
Action Potential
Produced by voltage-gated ion channels
All – or – None
Voltage threshold

Voltage-gated Na⁺ Channel
Components of an Action Potential

Voltage-gated $\text{Na}^+$ Channel:
Depolarization activated

Voltage-gated $\text{K}^+$ Channel
Action Potential

Action potentials start to arise only at **trigger zone** on axon hillock, in response to membrane depolarization due to graded potential(s) generated at dendrites / cell body.
Action potential: enables information processing all-or-none

The refractory period makes action potential to propagate unidirectional
Propagation of an action potential through an axon

Timing – delays with distance
Slow propagation

Height – remains same
(red arrow)
All – or - None
Myelination of axon and saltatory action potential conduction at the node of Ranvier
Unmyelinated vs Myelinated axon

Myelinated fibers: appear white jelly-roll like wrappings
made of lipoprotein = myelin
acts as electrical insulator
speeds conduction of nerve impulses

Unmyelinated fibers: slow,
small diameter fibers
only surrounded by neurilemma
but no myelin sheath wrapping
Saltatory action potential conduction:
Speed up the action potential propagation