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

Tutorial 2,
Plasma Membrane

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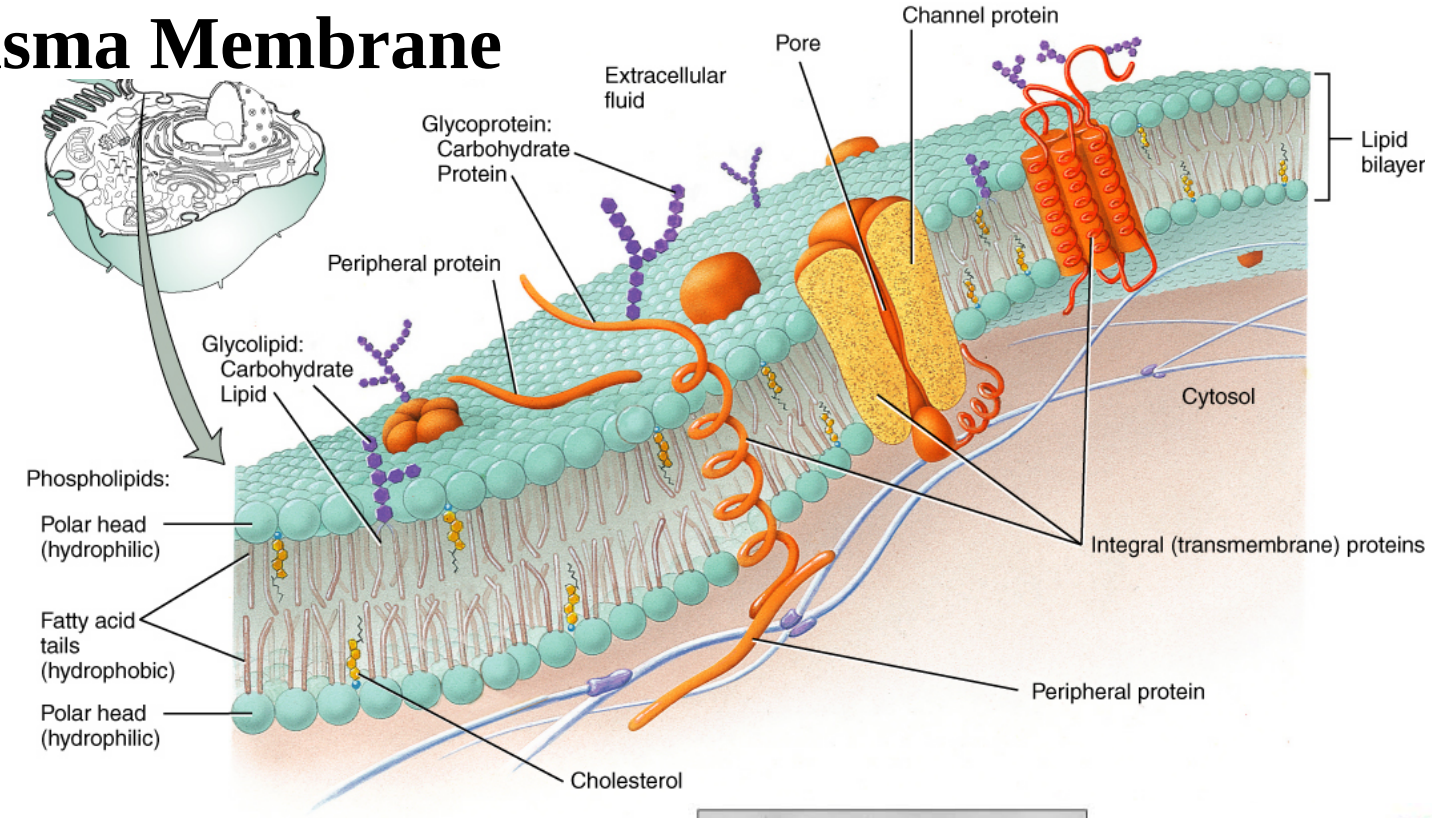
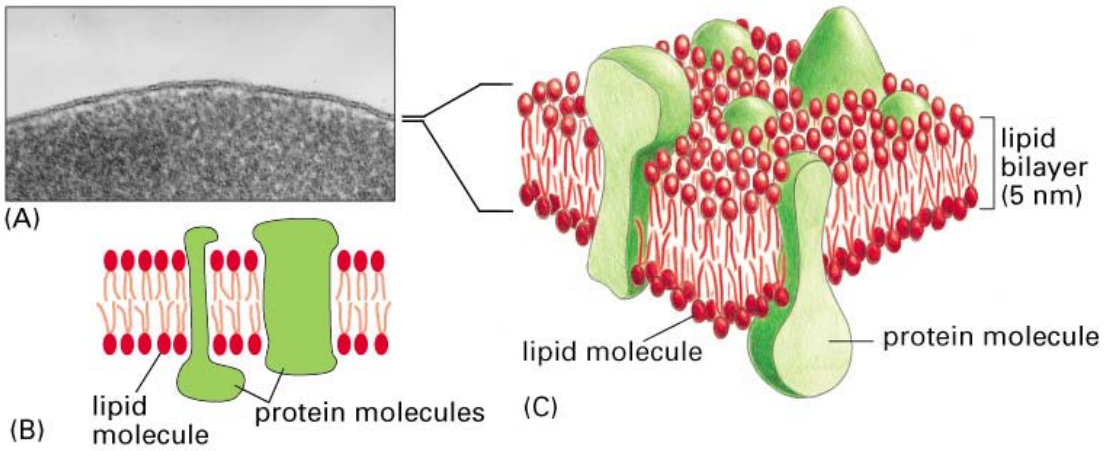
Plasma Membrane



Lipid Bi-layer

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



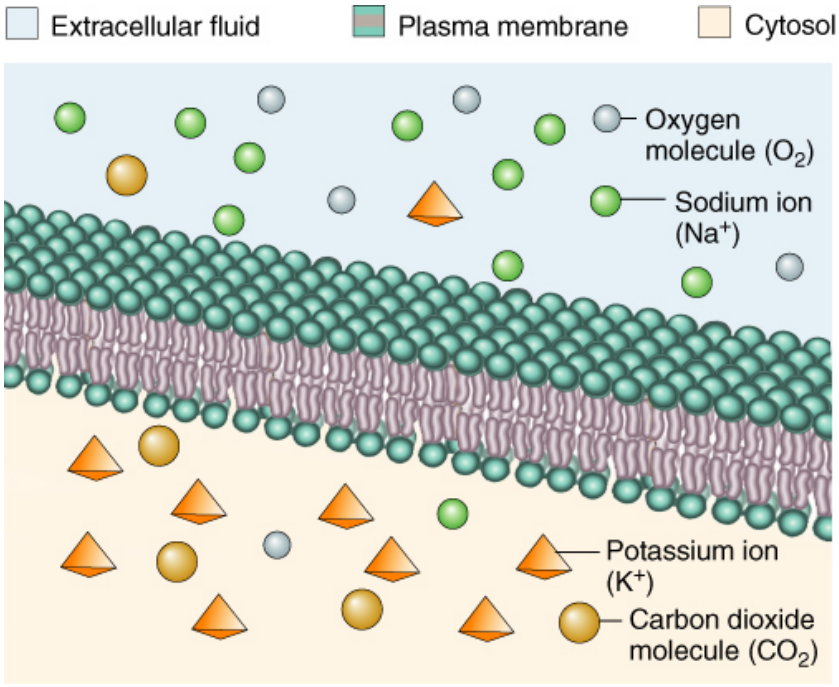
Water : Poorly permeable
O_2, CO_2 : Permeable

Hydrophobic agents (drugs)
Detergent Hydrophobic - Hydrophilic

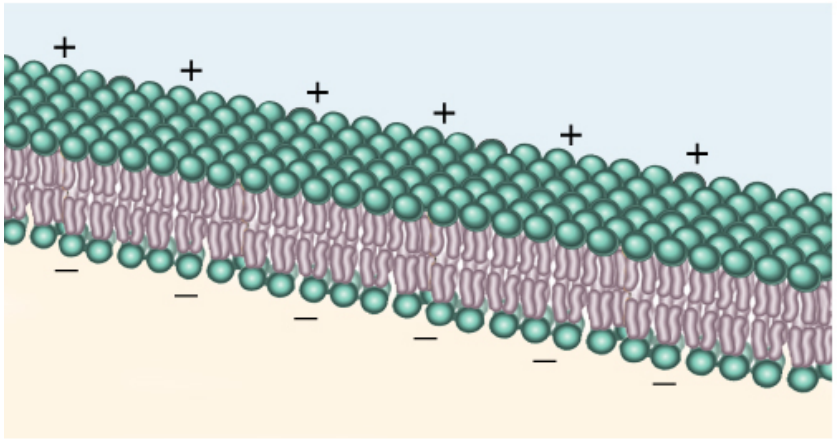
Plasma Membrane: environmental boundary (barrier)

Electrochemical gradient
- **Membrane potential**

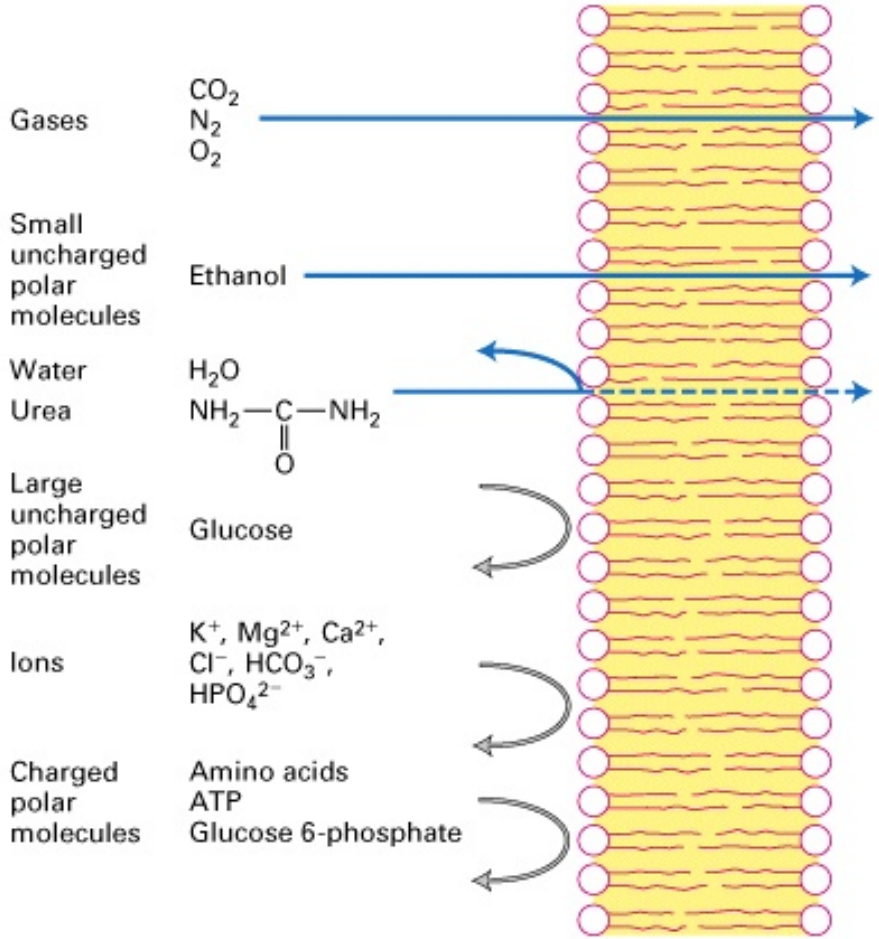
Unique intracellular environment
- **Stabilize pH**
- **Holds molecules inside**



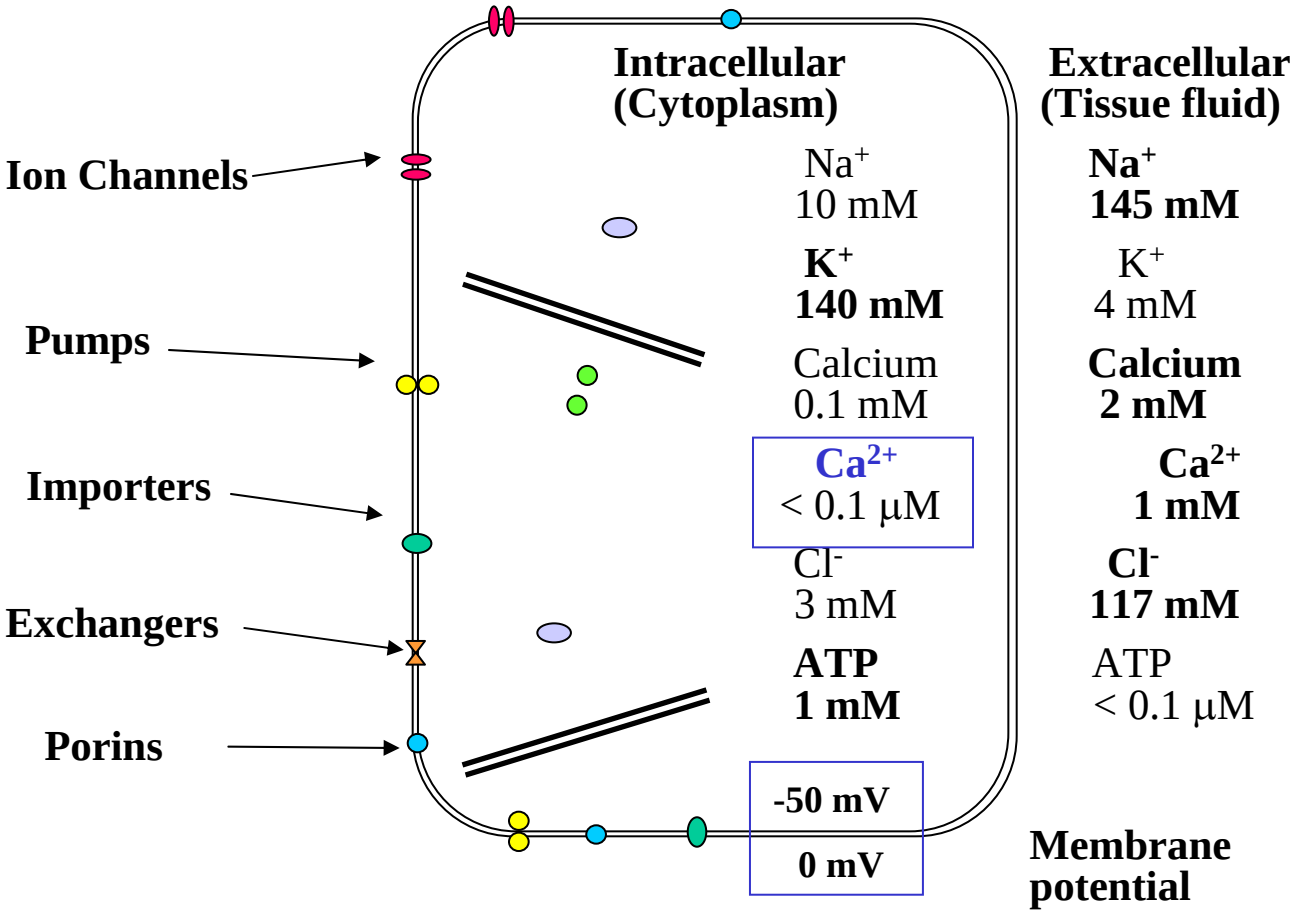
(a) Concentration gradients



(b) Electrical gradient



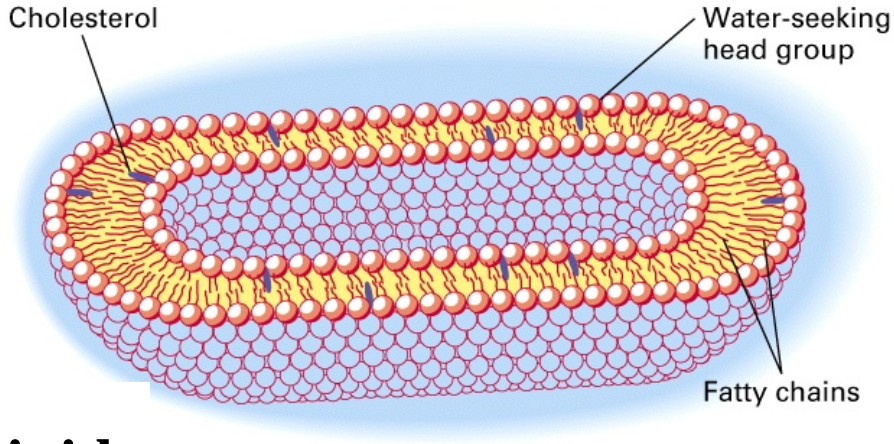
Plasma Membrane: environmental boundary (barrier)

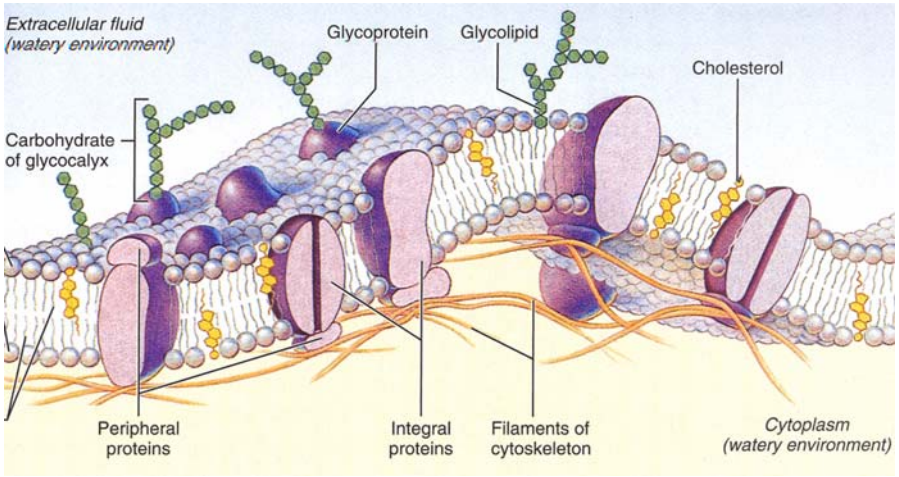


Ionic imbalance (particularly, Na^+ and K^+) between inside and outside a cell, created by membrane ionic pumps, ion exchangers and channels, establishes resting membrane potential. This is used to drive other process (such as molecule import), as well as for information processing (*e.g.* nerve cells).
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

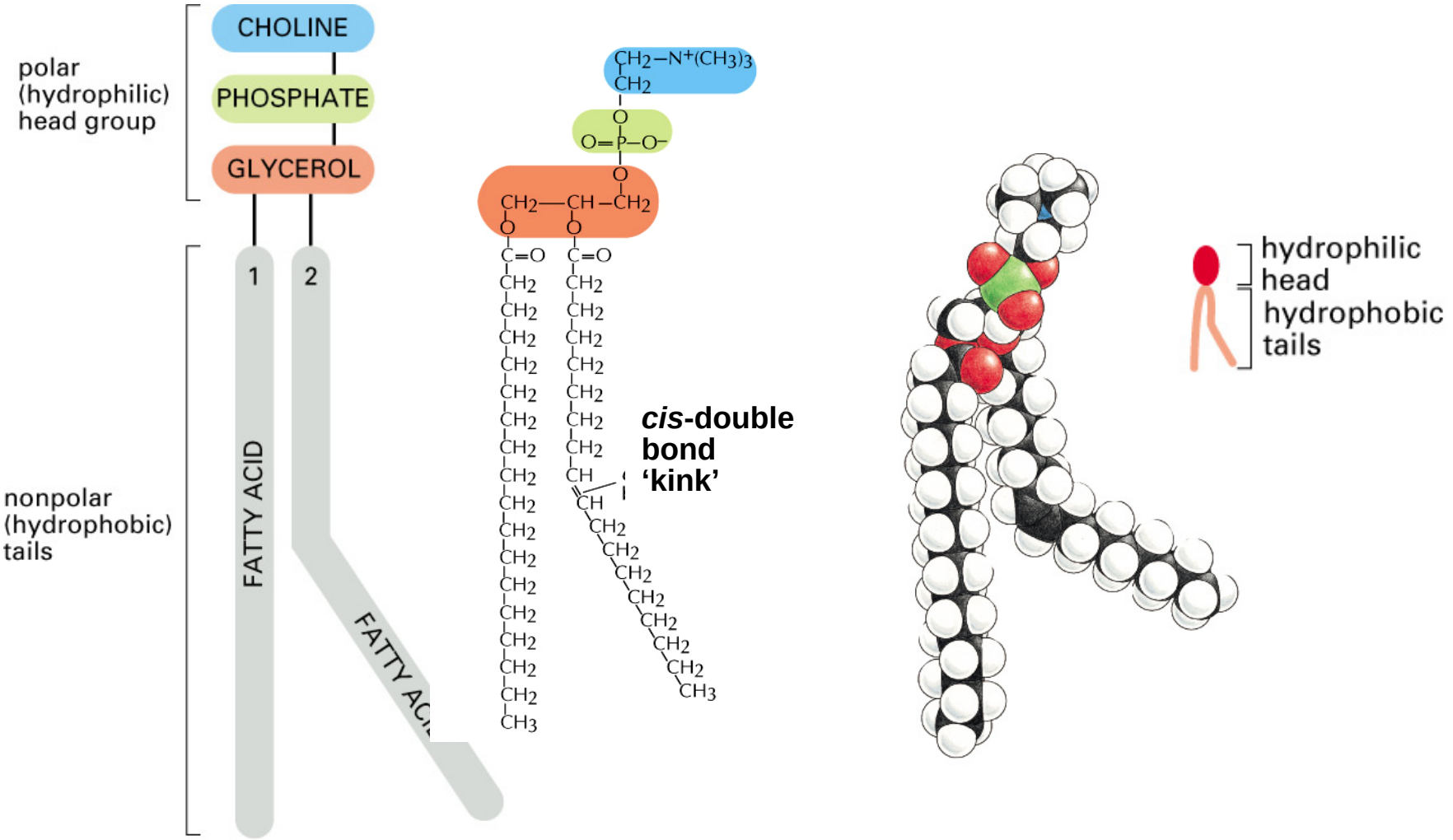
Proteins; transmembrane proteins, peripheral proteins

Many proteins are glycosylated

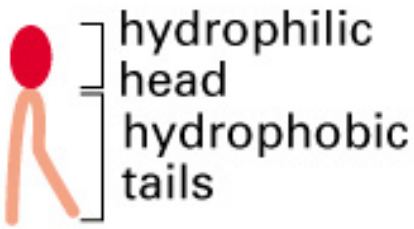
Membrane channels, pumps : Ion concentration gradient (in←→out)
Membrane potential
Transporters : transport molecule across plasma membrane, *e.g.* glucose transporter
Membrane receptors : Information relay
(via particular signaling molecules, *e.g.* hormones, neurotransmitters)
Communication between cells : Gap junctions, integrins
Adhesion molecules (Junctions); cell to extracellular matrix, cell to cell

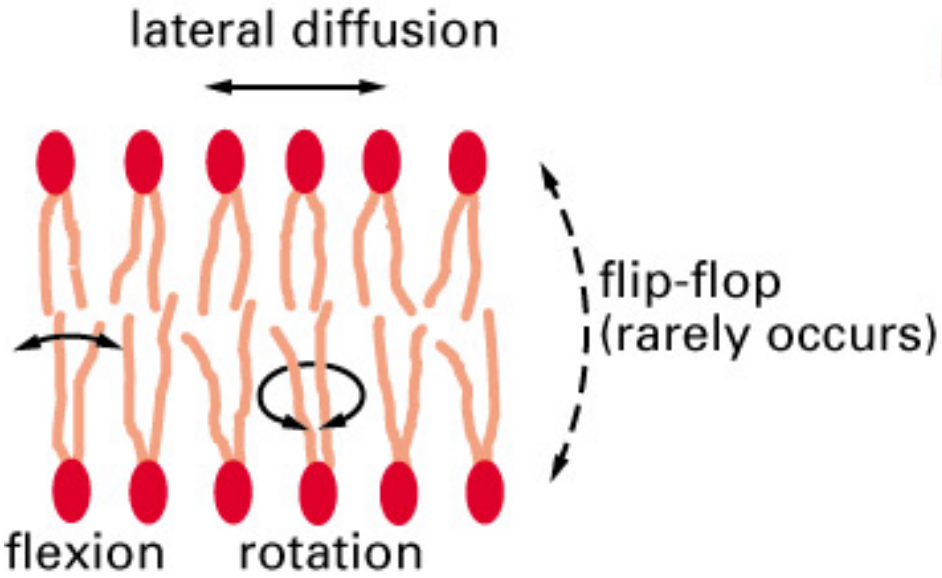
Endocytosis, Exocytosis : Intracellular membrane flow

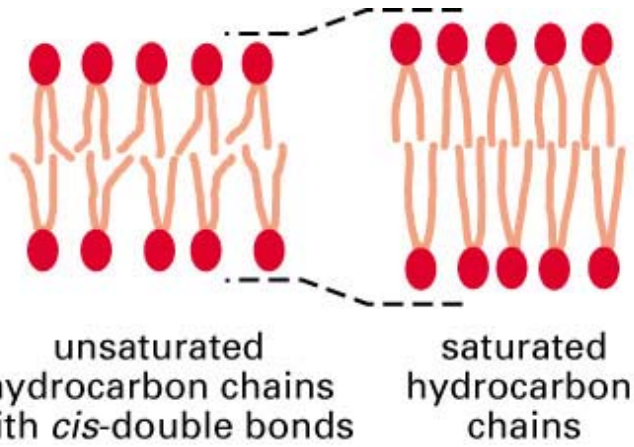
Phospholipid structure: *e.g.* Phosphatidylcholine



Mobility of phospholipid







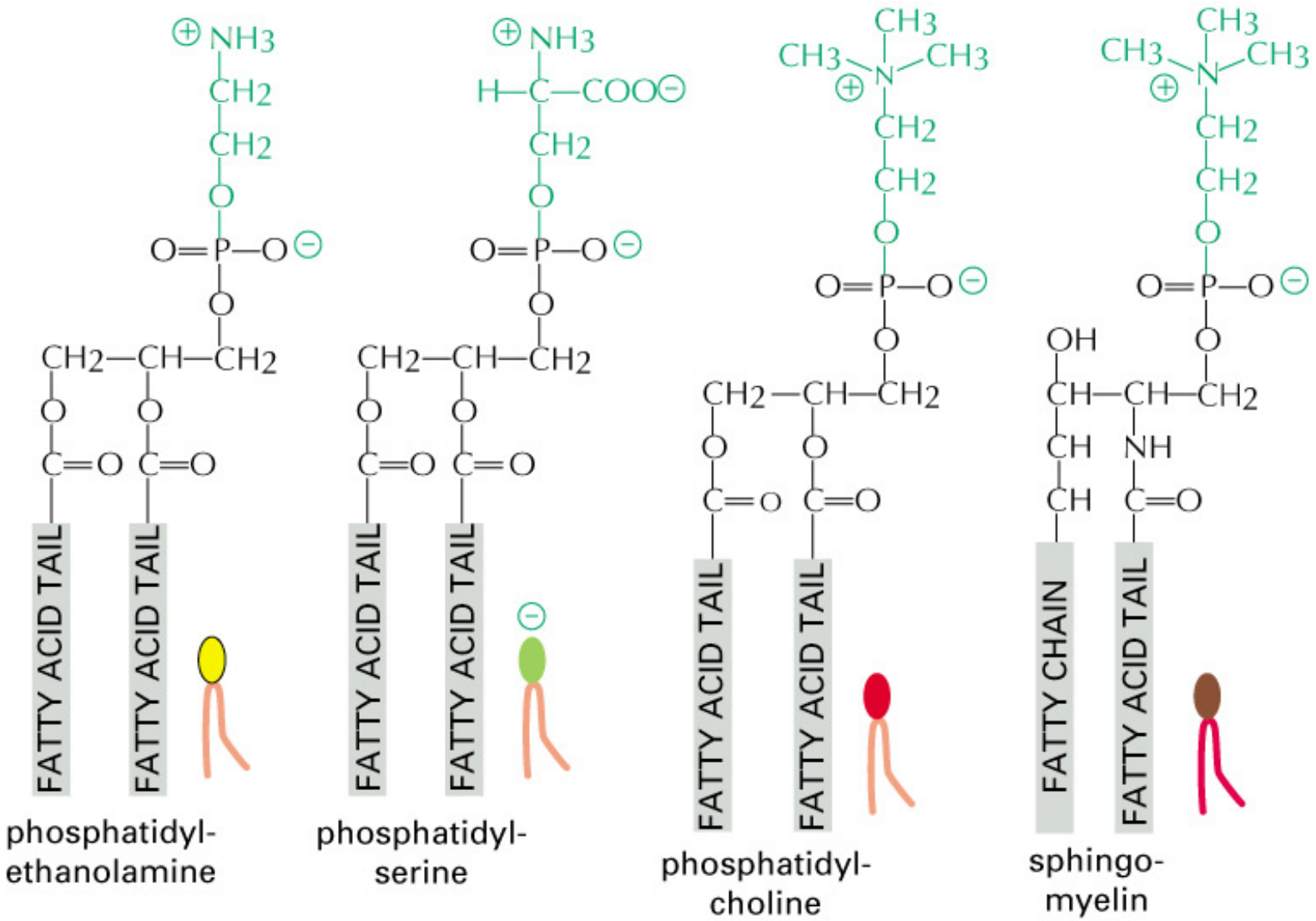
More kinks ➔

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)

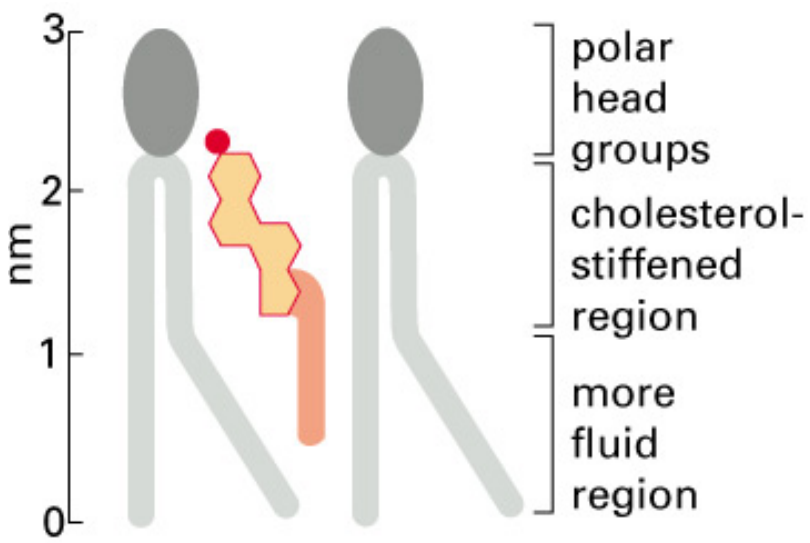
2. The kinks shorten the length of hydrocarbon chains, so that the membrane is thinner.

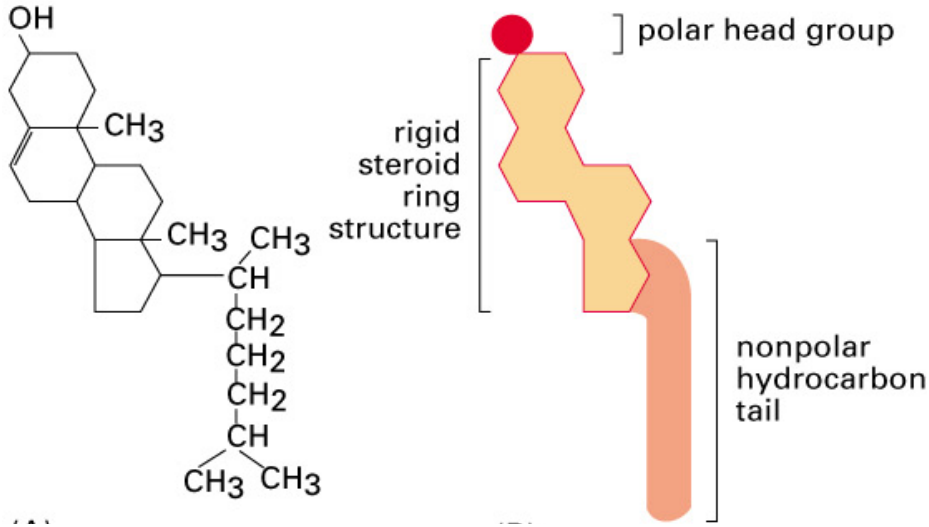
Four <u>major</u> phospholipids found in mammalian plasma membrane

There are many 'minor' phospholipids exists, too.



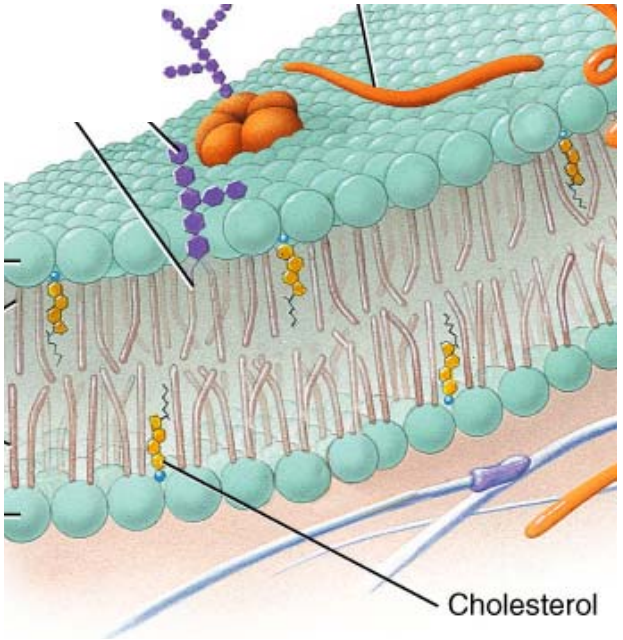
Cholesterol





Unique to plasma membrane

Stabilize membrane

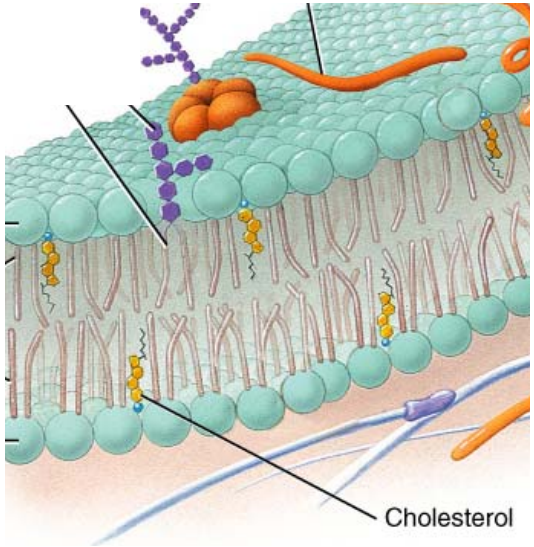


Cholesterol

Unique to plasma membrane

Stabilize membrane

ALSO: Precursor to steroid hormones



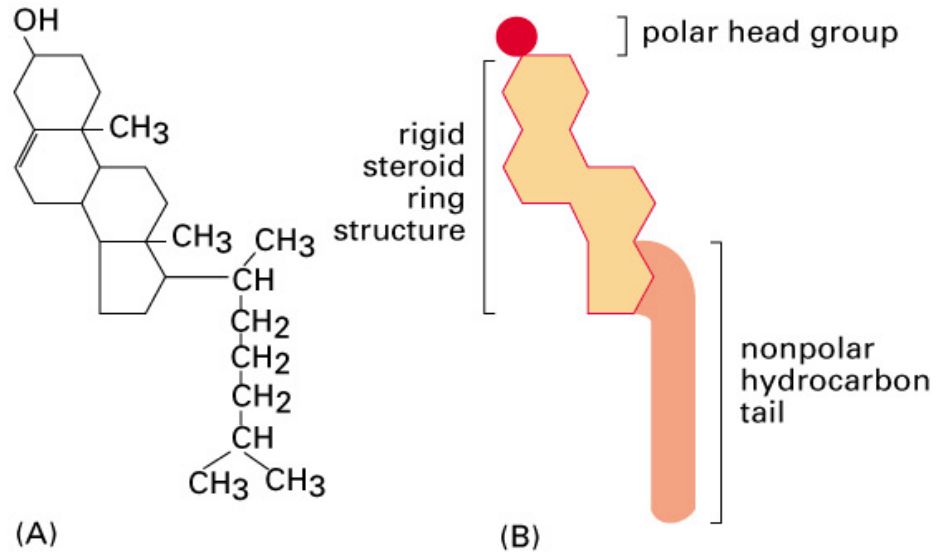
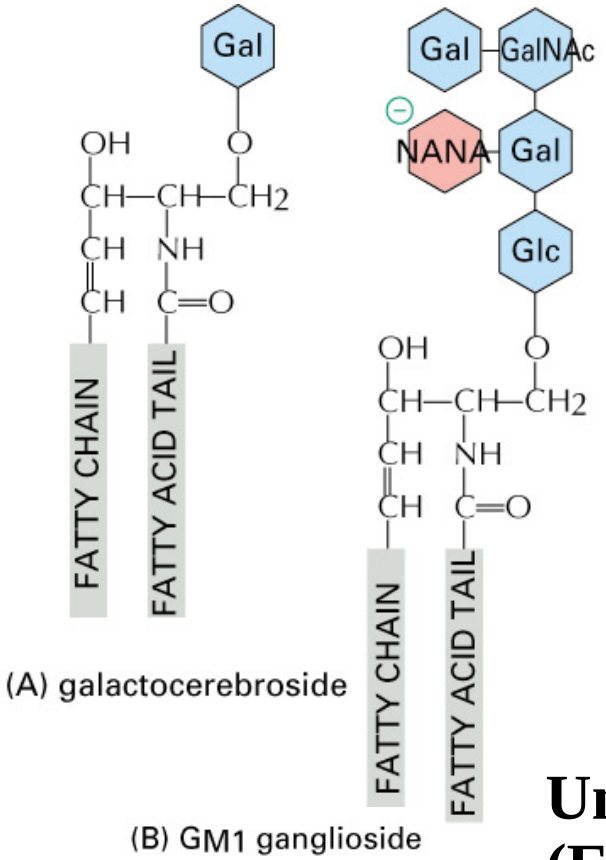


Table 10–1 Approximate Lipid Compositions of Different Cell Membranes

	Percentage of Total Lipid by Weight					
Lipid	Liver Plasma Membrane	Erythrocyte Plasma Membrane	Myelin	Mitochondrion (inner and outer membranes)	Endoplasmic Reticulum	*E. coli*
Cholesterol	17	23	22	3	6	0
Phosphatidyl-ethanolamine	7	18	15	35	17	70
Phosphatidylserine	4	7	9	2	5	trace
Phosphatidyl-choline	24	17	10	39	40	0
Sphingomyelin	19	18	8	0	5	0
Glycolipids	7	3	28	trace	trace	0
Others	22	13	8	21	27	30

Glycolipids



(A) galactocerebroside

(B) GM1 ganglioside

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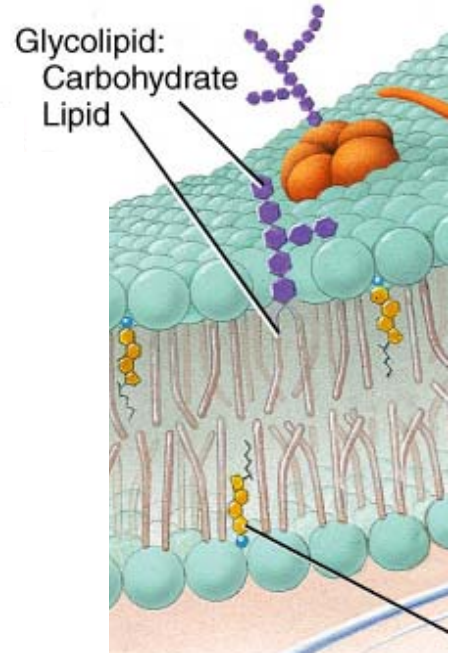
Sphingomyelin	19	18	8	0	5	0
Glycolipids	7	3	28	trace	trace	0
Others	22	13	8	21	27	30

Unique to plasma membrane (Extracellular side)

Neutral glycolipid (A) or, negatively charged (B) (due to sialic acid [NANA])

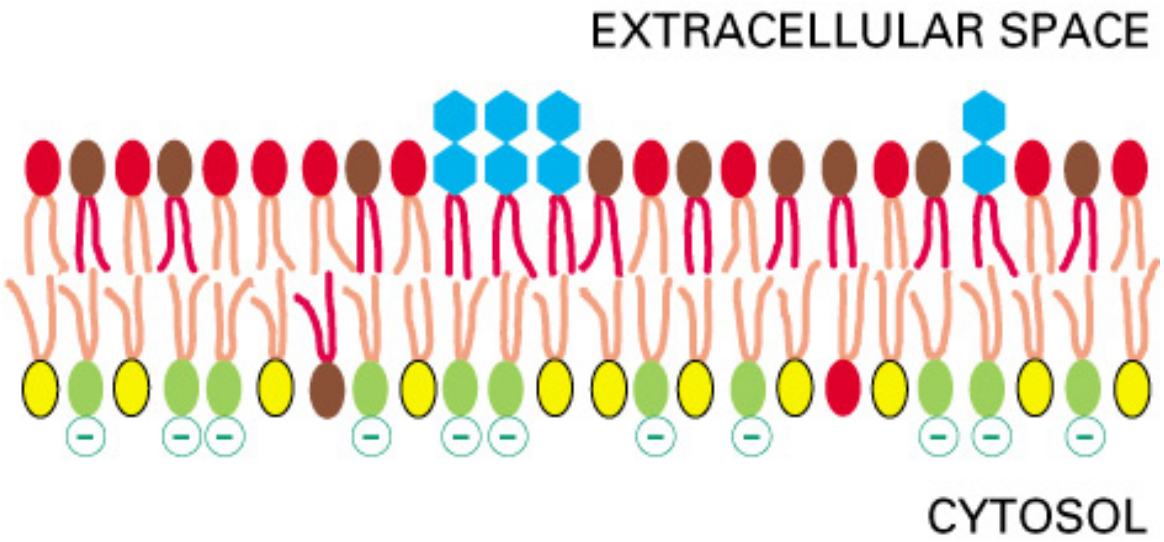


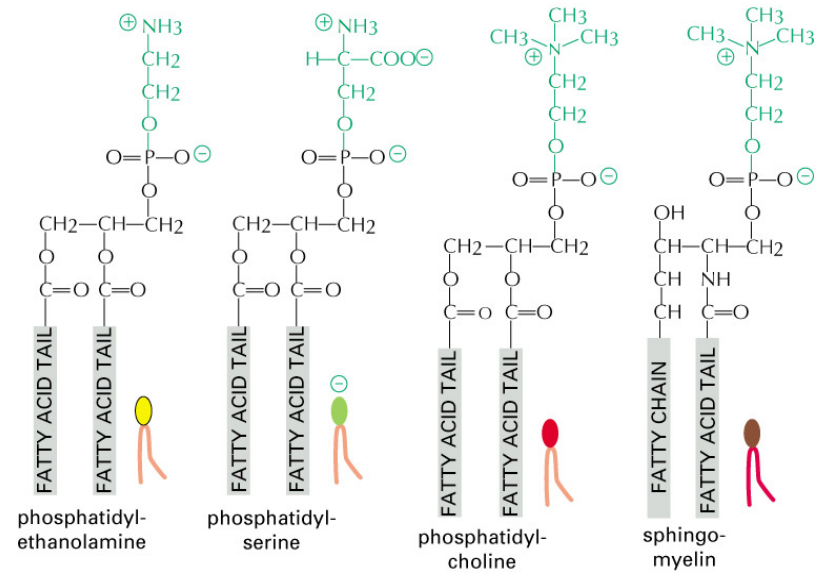
Phospholipid arrangement in Plasma Membrane

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

Cytospsmic Side:
- **PS [negatively charged]**
- **PE**

Cholesterol (not shown) are found in both side.

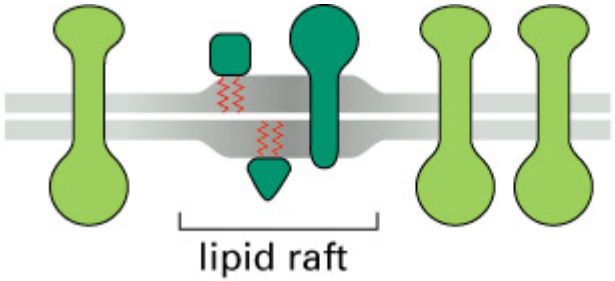


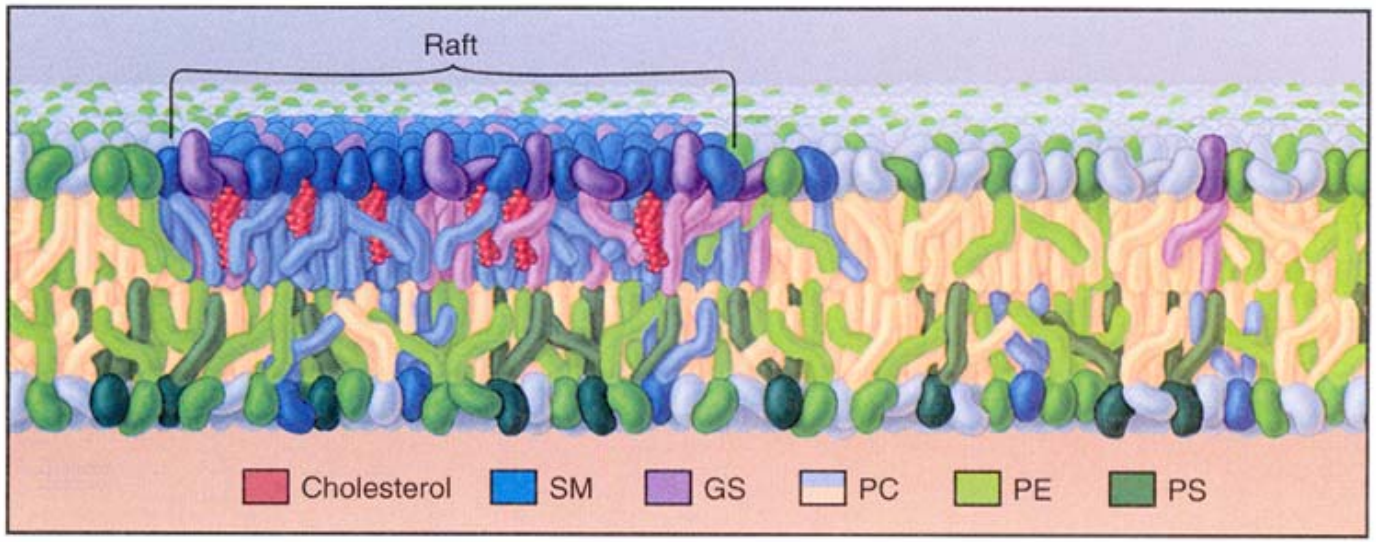


(PE) **(PS)** **(PC)**

Lipid Raft

Local area of a membrane where sphingolipid, cholesterol and membrane proteins are concentrated.

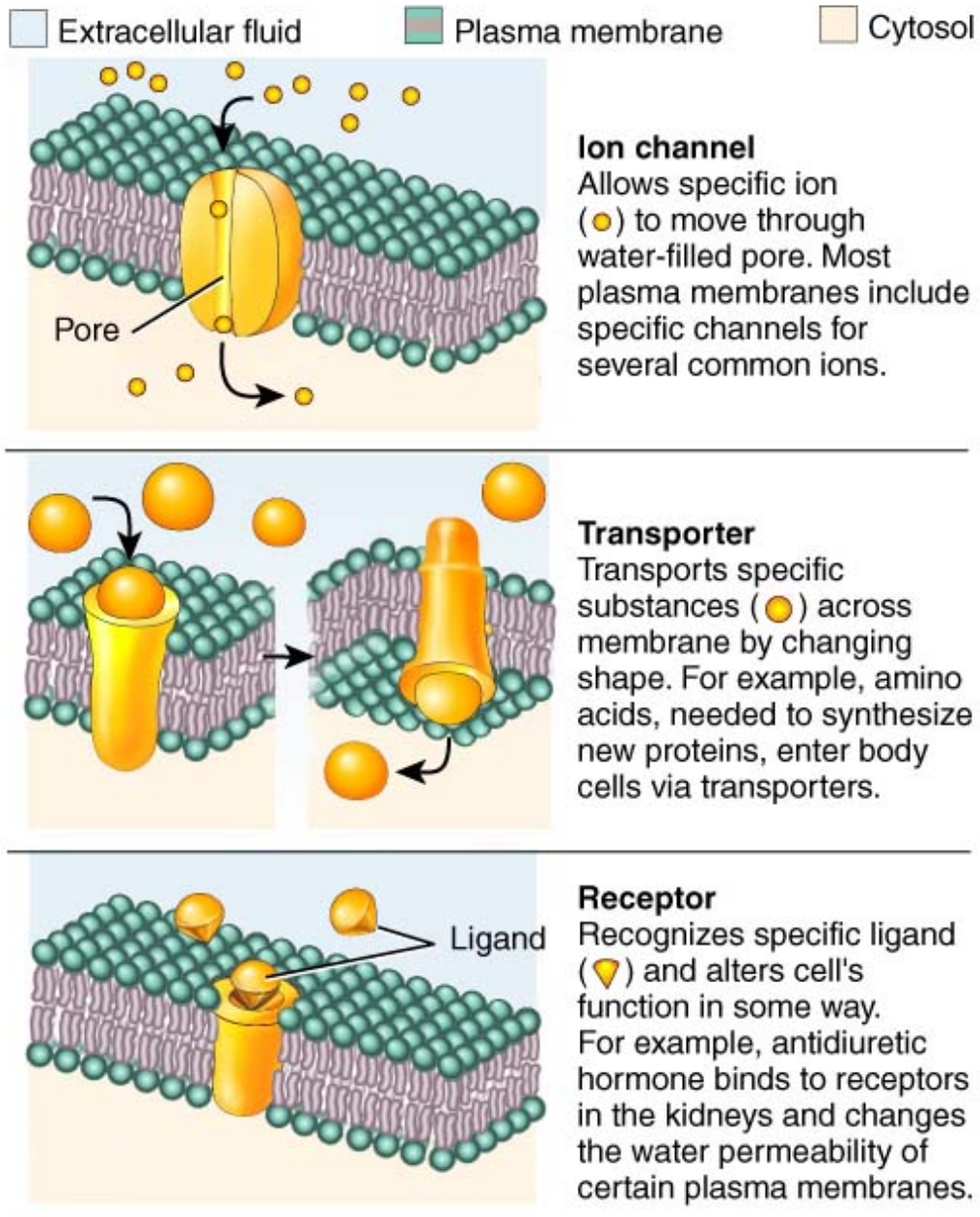




Plasma Membrane : Membrane Proteins

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.

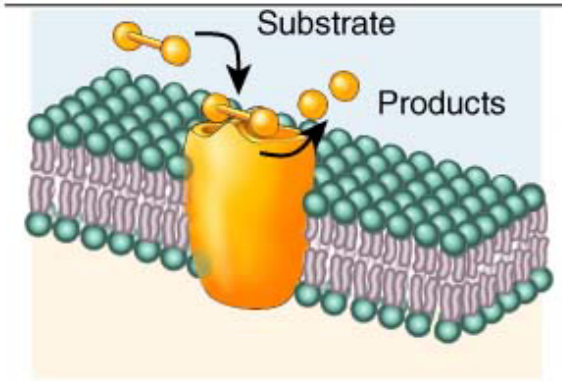
Transporter
Transports specific substances (●) across membrane by changing shape. For example, amino acids, needed to synthesize new proteins, enter body cells via transporters.

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.

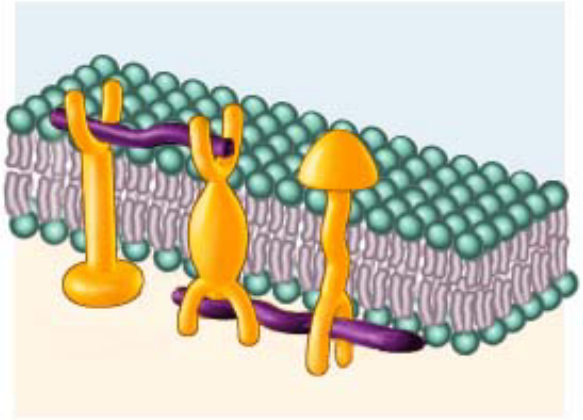
Plasma Membrane : Membrane Proteins

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.

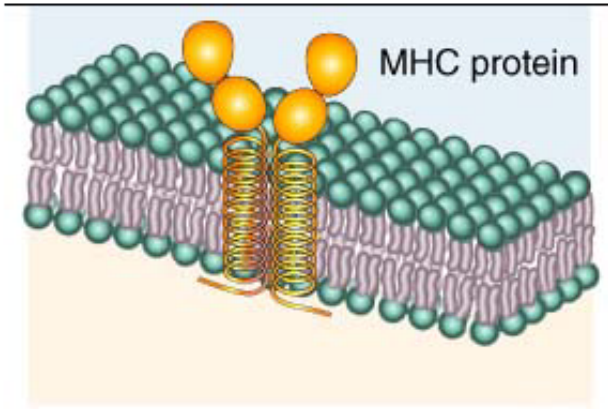


Linker
Anchors filaments inside and outside to the plasma membrane, providing structural stability and shape for the cell. May also participate in movement of the cell or link two cells together.

Plasma Membrane : Membrane Proteins

Functional classification (3)

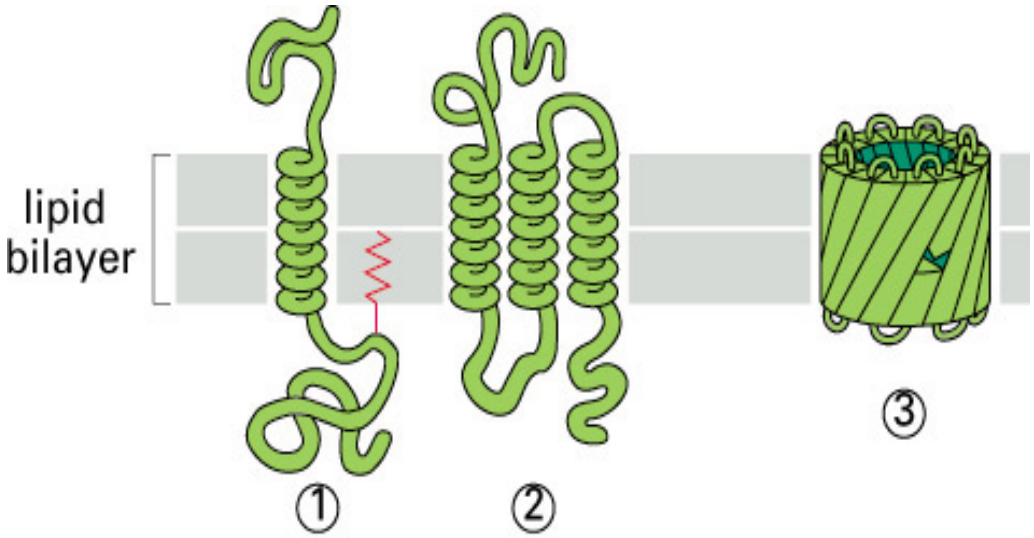
Peripheral Proteins
(only one side of the membrane)



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 histocompatability (MHC) proteins.

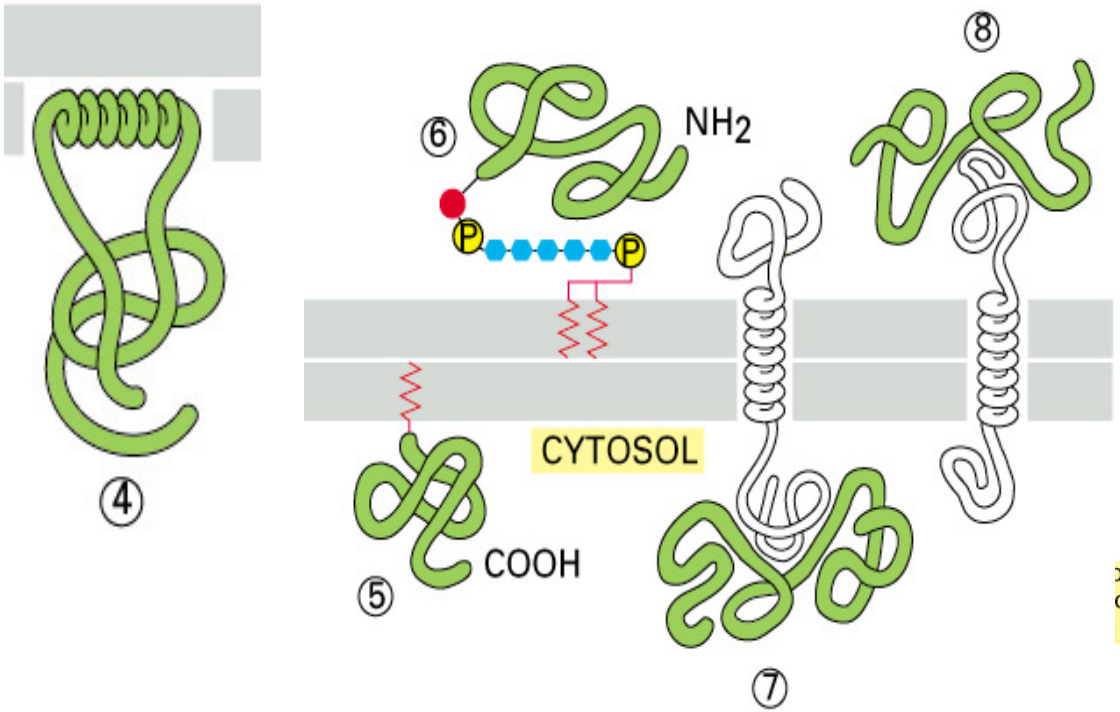
Association of membrane proteins with the lipid bilayer (1)

Transmembrane Proteins

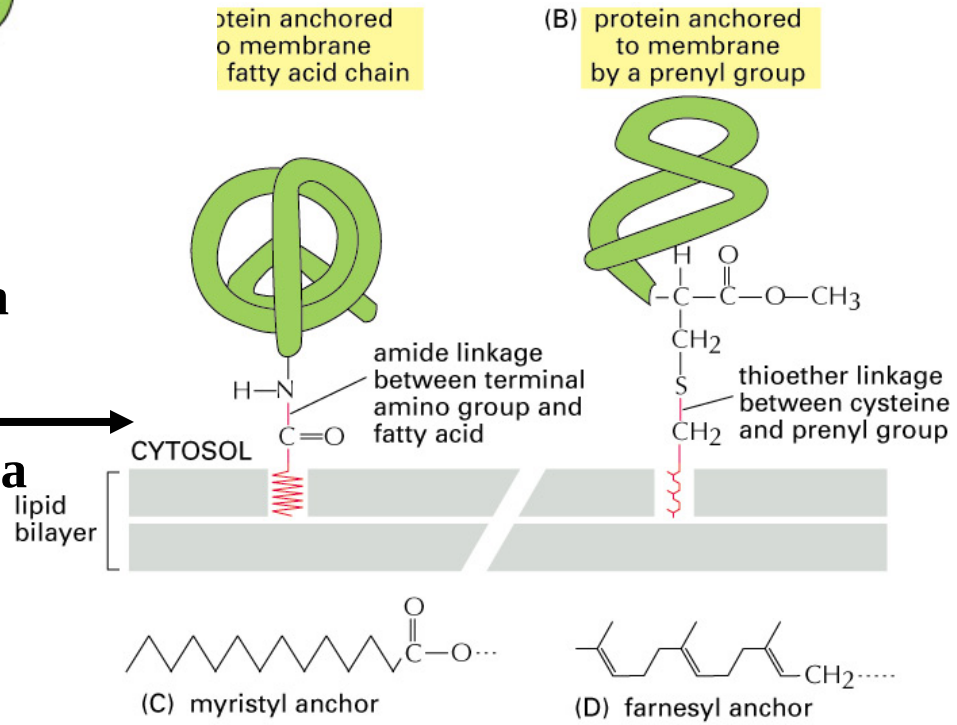


1. A single α-helix
2. Multiple α-helices
3. Rolled up β-sheet

Association of membrane proteins w/ the lipid bilayer (2) Peripheral Membrane Proteins

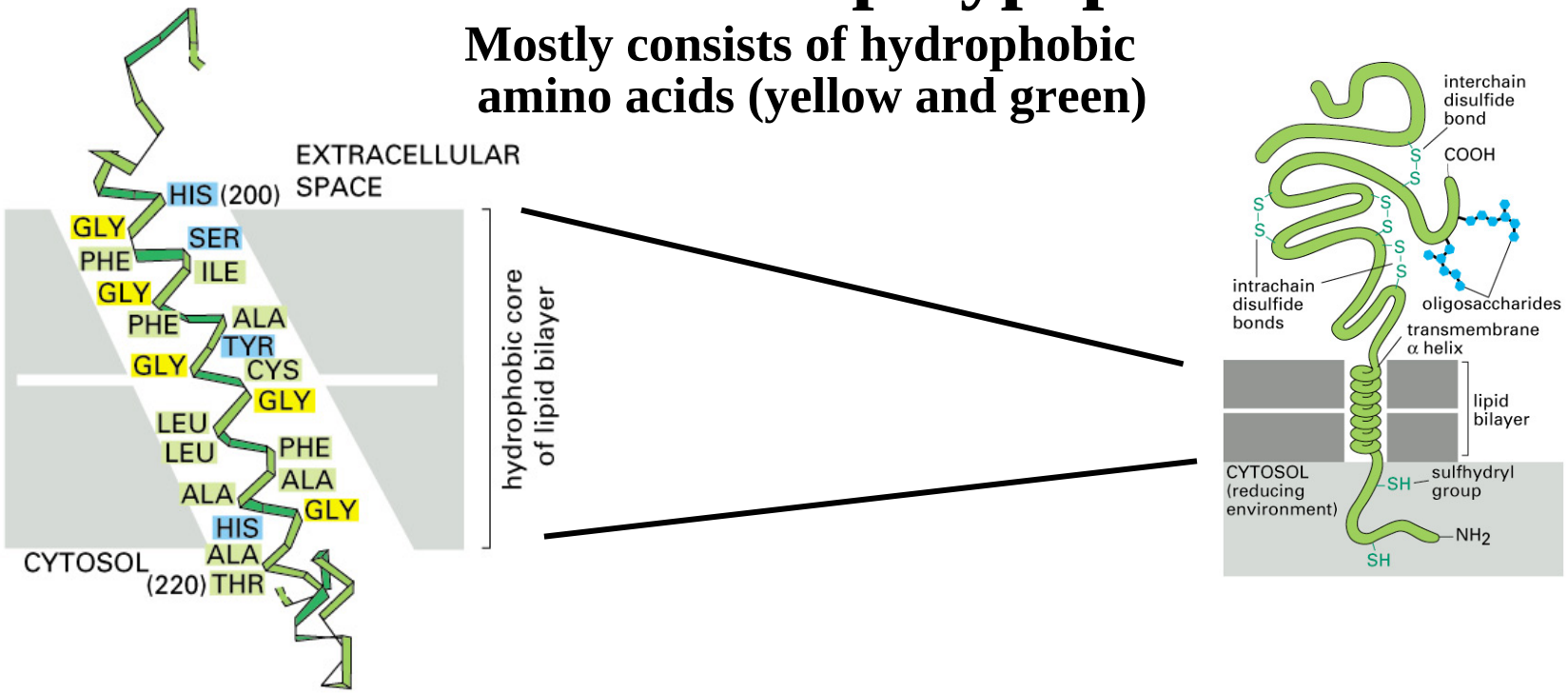


4. α- helix (hydrophobic face) embedded in the lipid bilayer
5. Protein covalently attaches lipid chain – fatty acid chain or prenyl group (cytoplasmic side)
6. Protein attaches phosphatidylinositol via an oligosaccharide linker
7, 8. Noncovalent interaction between proteins



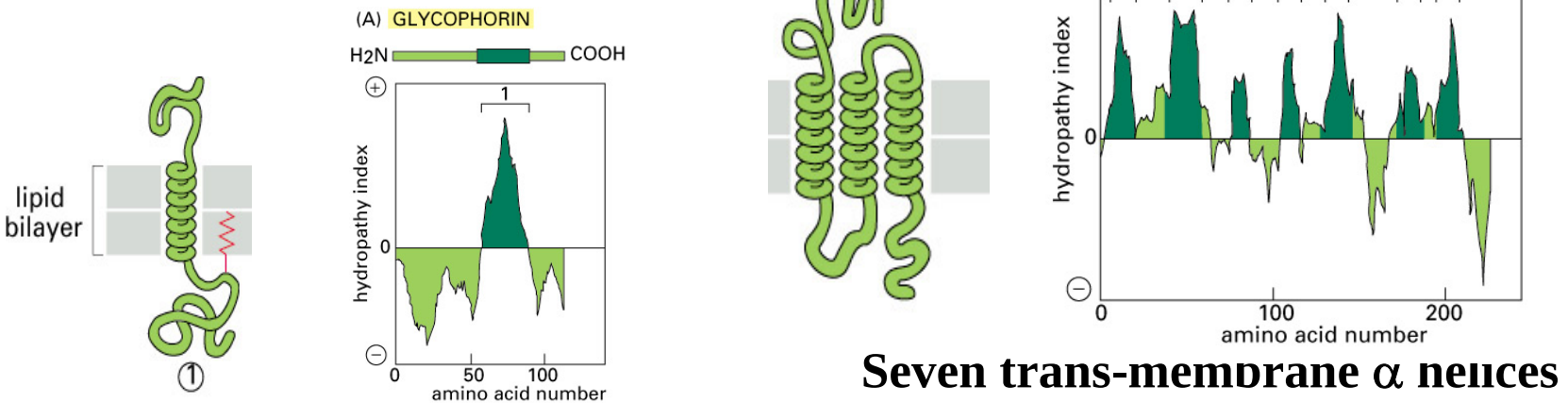
α helical transmembrane polypeptide chain

Mostly consists of hydrophobic amino acids (yellow and green)



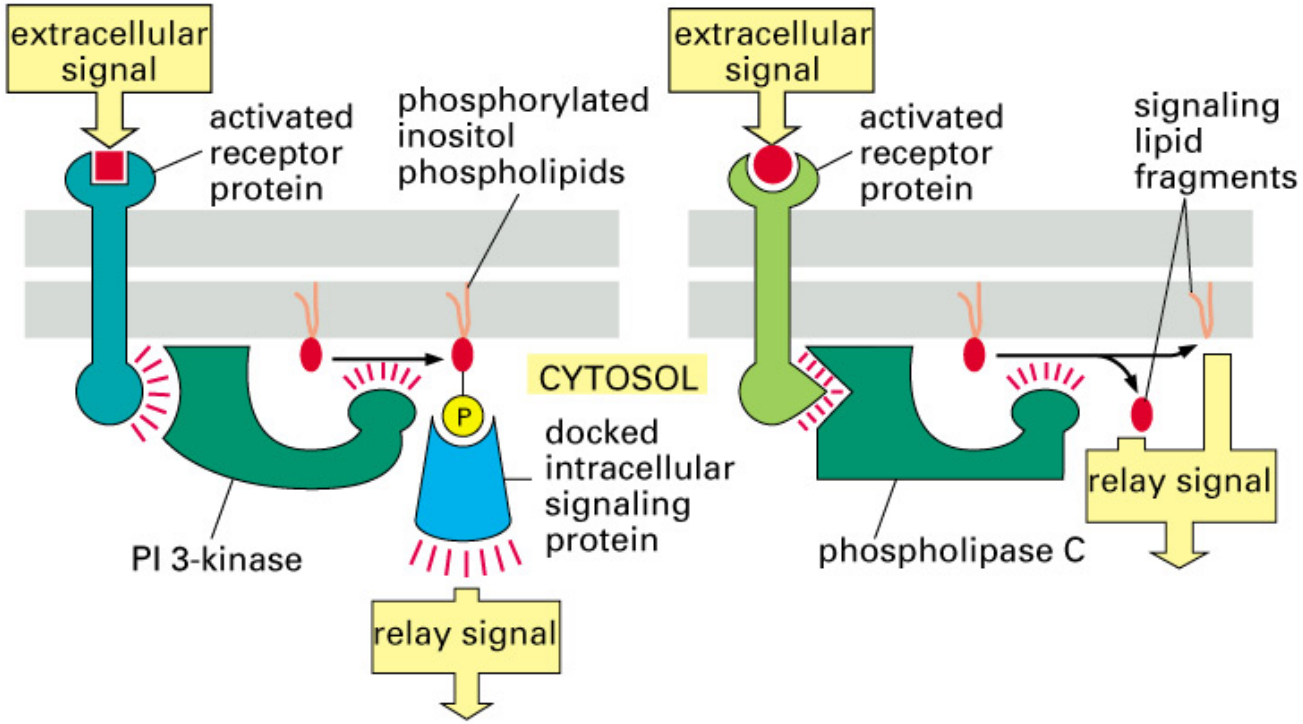
Hydropathy plot

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

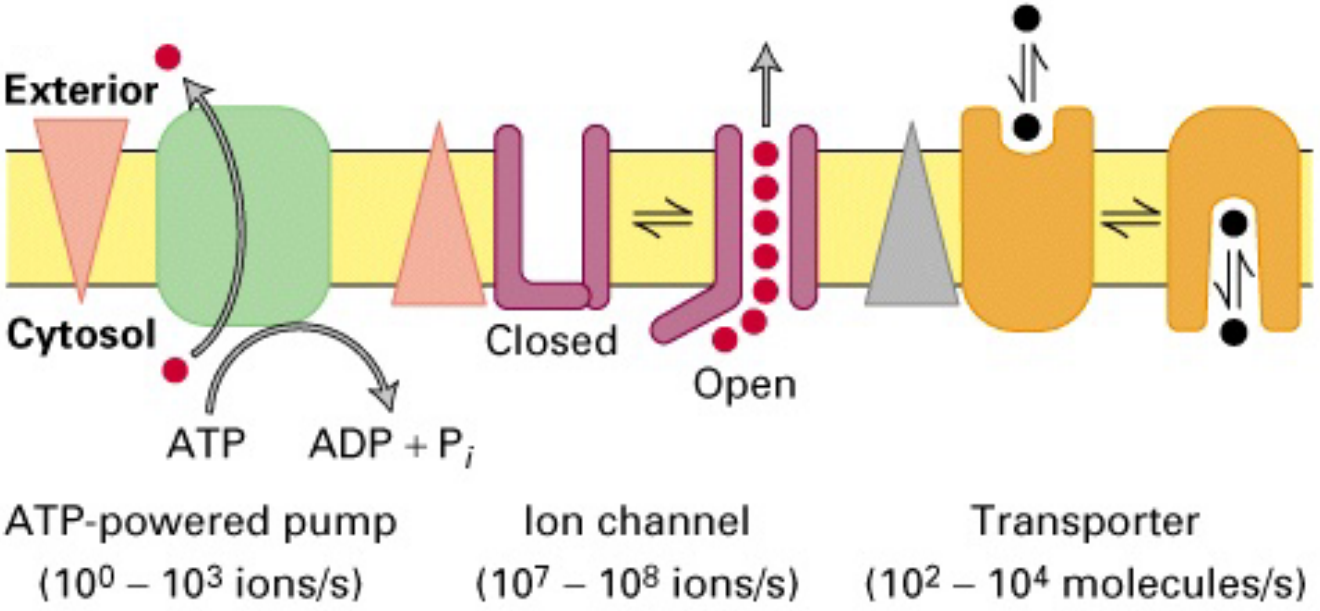
exocytosis / endocytosis

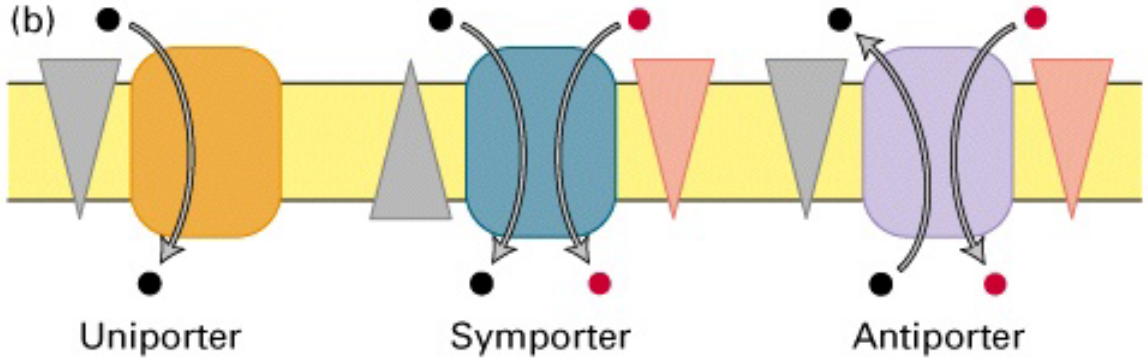
etc

→ Signal Transduction (an another tutorial section)

Overview of membrane transport proteins

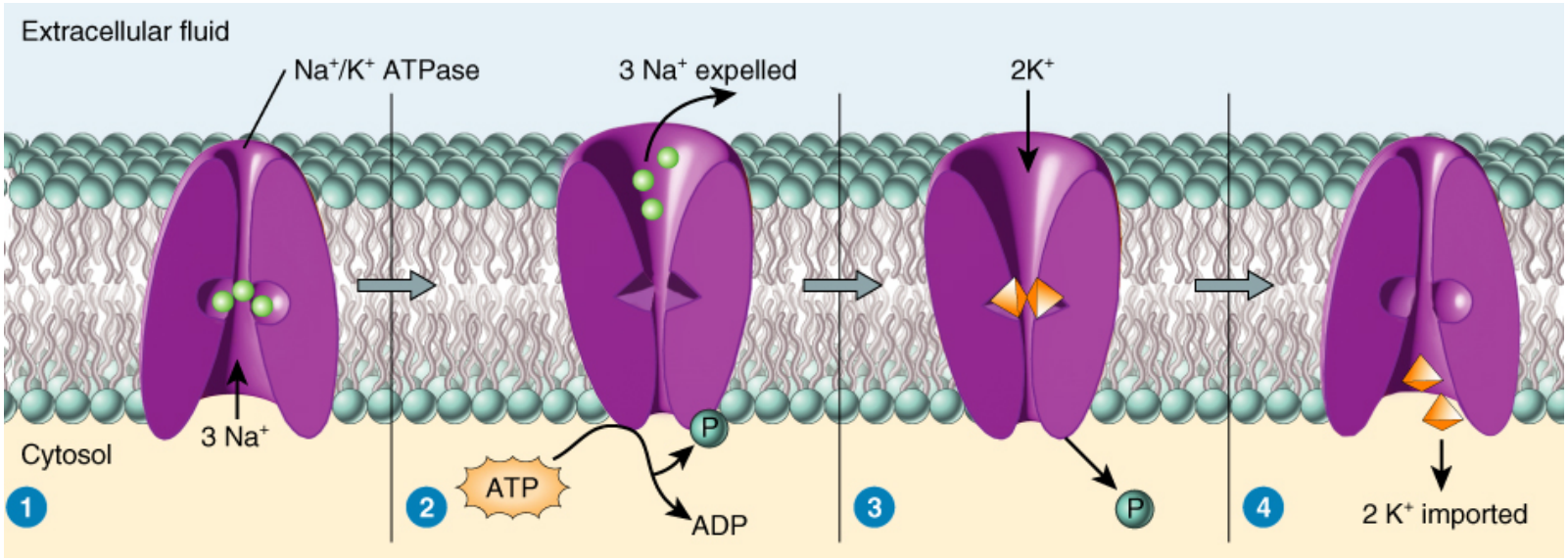
These systems exist not only on plasma membrane, but also many organelle membranes.





Na^+/K^+-ATPase (Na^+/K^+-pump)

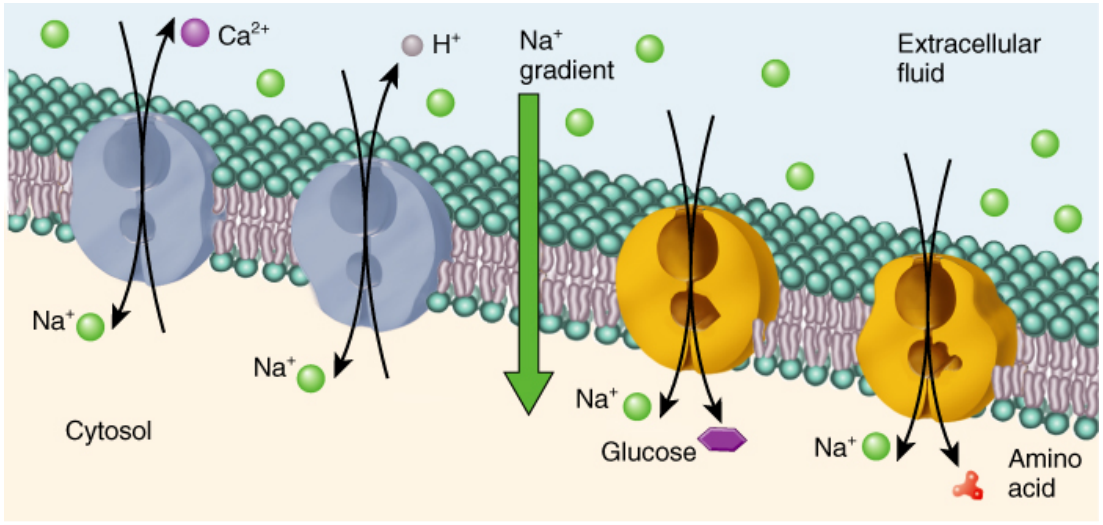
1 ATP used for exporting 3 Na^+ ions and importing 2 K^+ ions.
Crucial for maintaining resting membrane potential.



Other pumps; *e.g.* Ca^{2+} pump

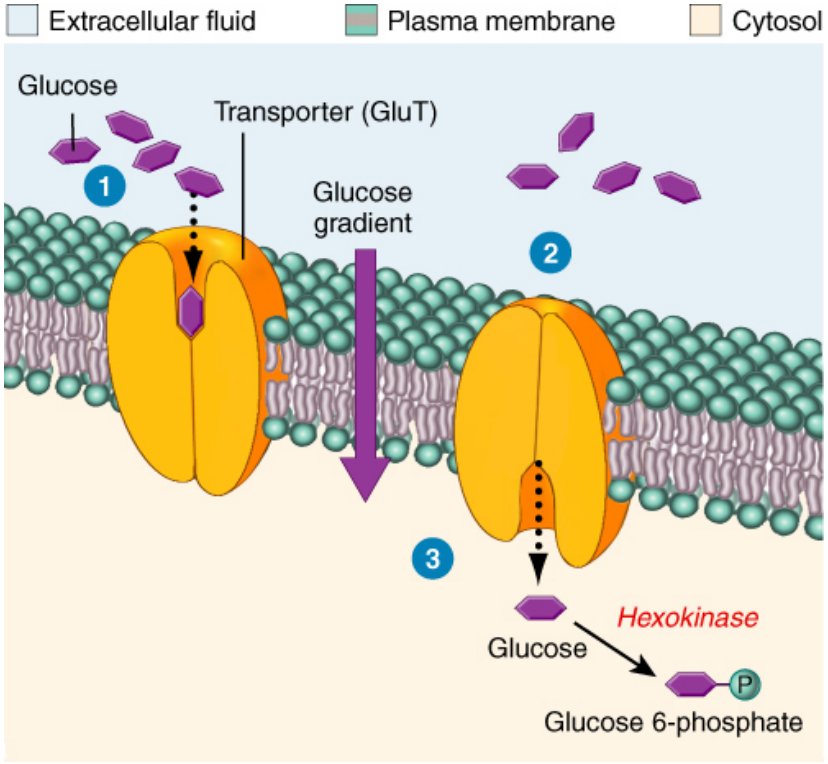
Transporters

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



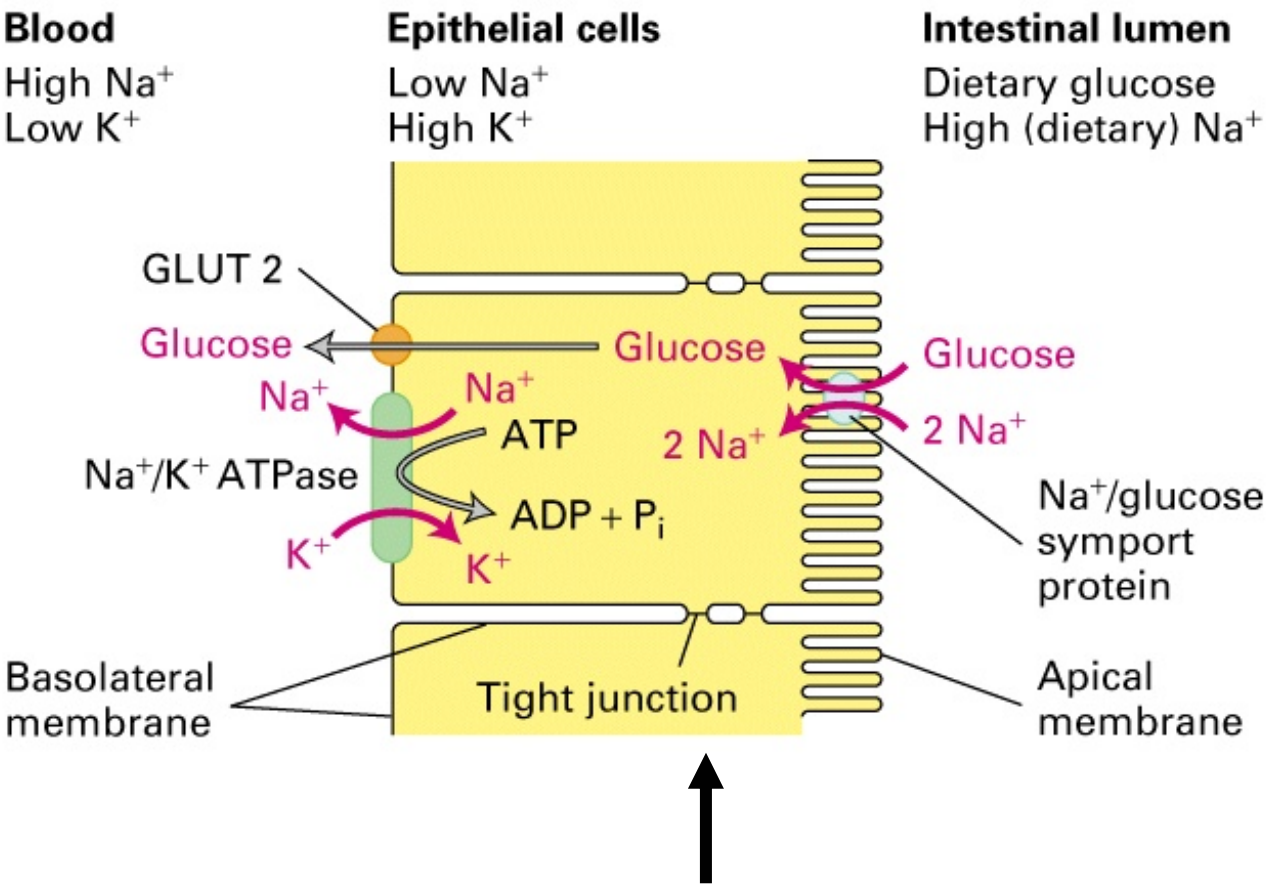
(a) Antiporters (b) Symporters

Glucose transporter



Many of the channels, pumps and transporters are inserted only on particular surface of the cell

Intestinal epithelial cell

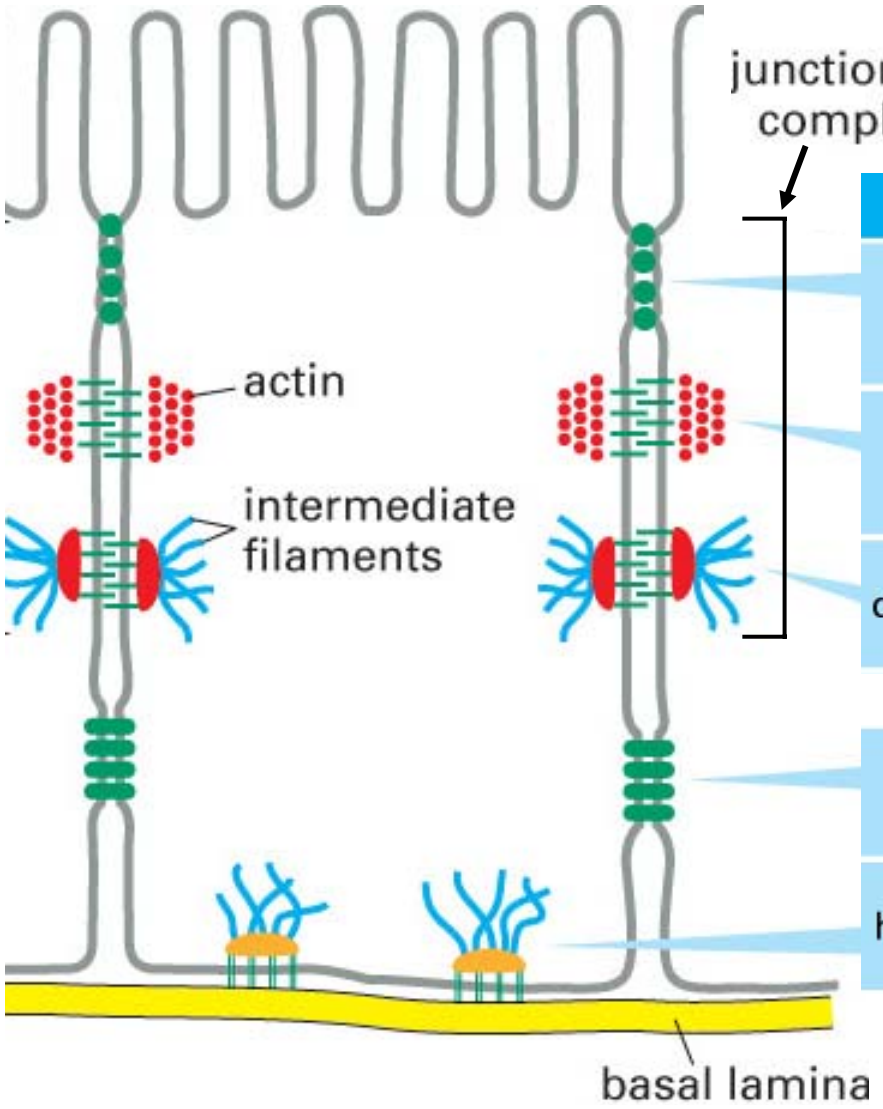


Tight junction serves barriers between apical surface and baso-lateral surface of plasma membrane (many plasma membrane proteins, such as channels, pumps, receptors, are inserted only into one or the other surface of the plasma membrane. These proteins cannot go (move) across the other side due to tight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

Cellular Junctions

Location
Function

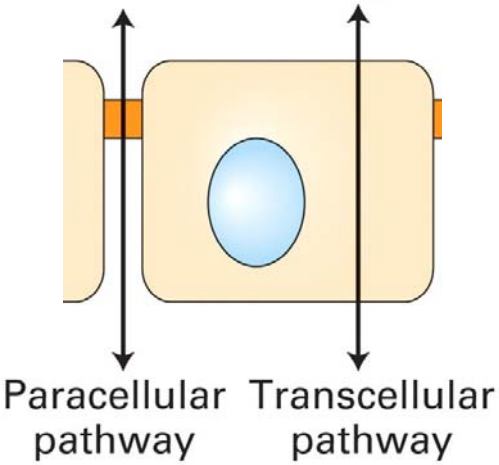
Each junction consists of specific set of adhesion proteins

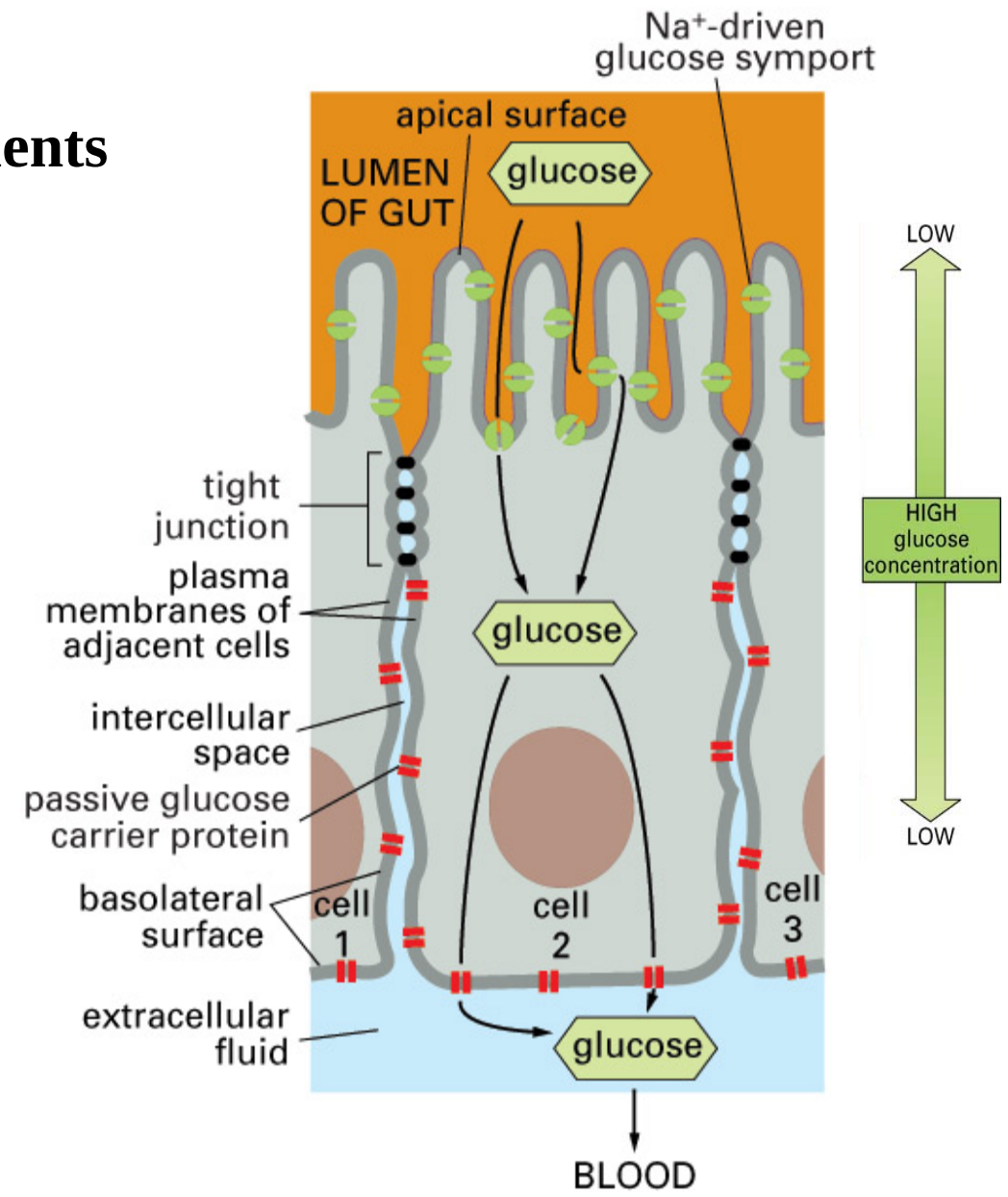


name	function
tight junction	seals neighboring cells together in an epithelial sheet to prevent leakage of molecules between them
adherens junction	joins an actin bundle in one cell to a similar bundle in a neighboring cell
desmosome	joins the intermediate filaments in one cell to those in a neighbor
gap junction	allows the passage of small water-soluble ions and molecules
hemidesmosome	anchors intermediate filaments in a cell to the basal lamina

Occluding Junctions
Tight Junction

Separates two environments



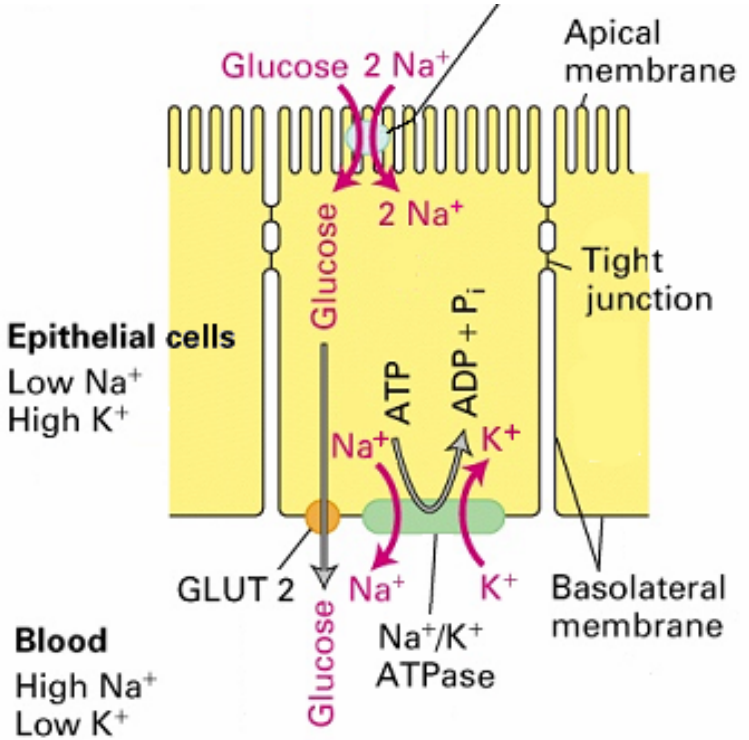


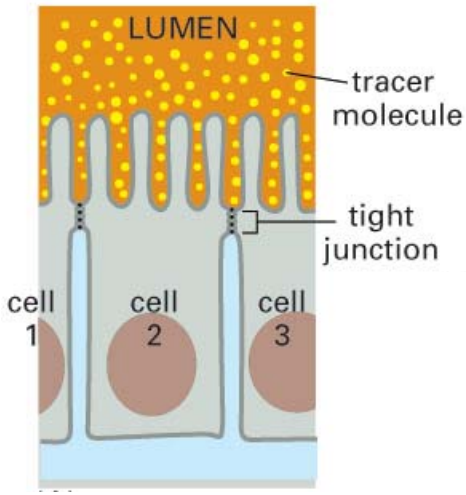
Paracellular pathway:
Passage through tight junction b/w cells
Small(er) molecules
water, ions, etc

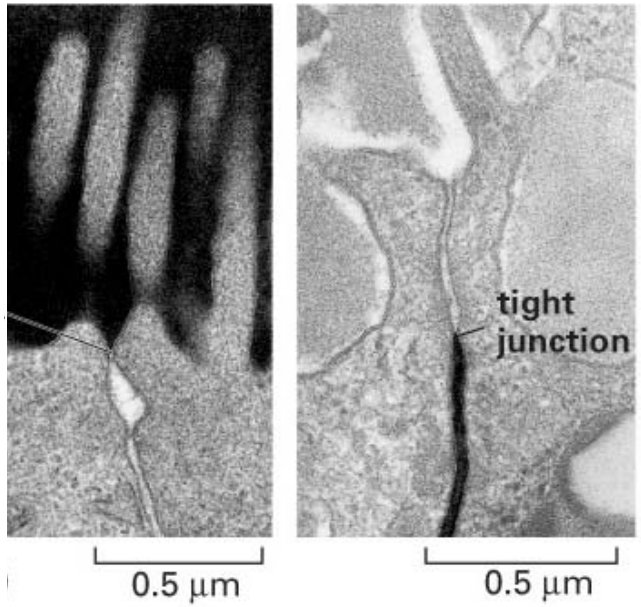
Occluding Junctions
Tight Junction

Separates two environments

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

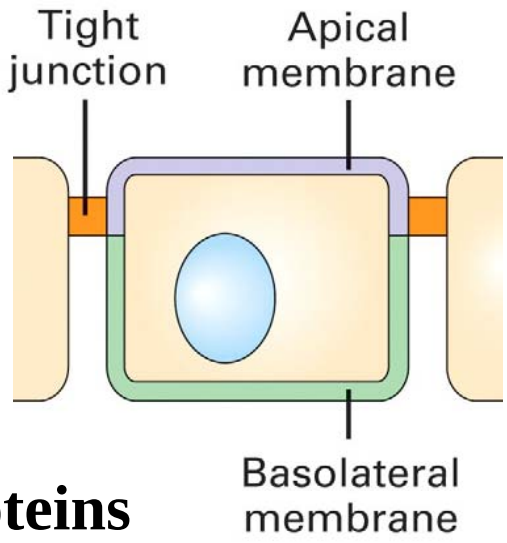






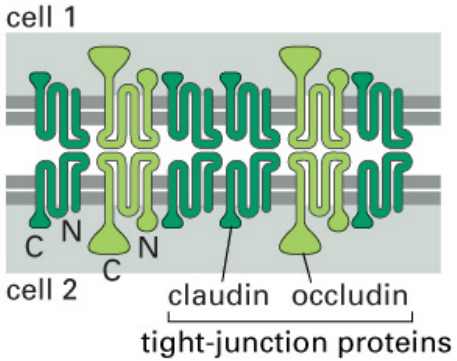
Tight Junction

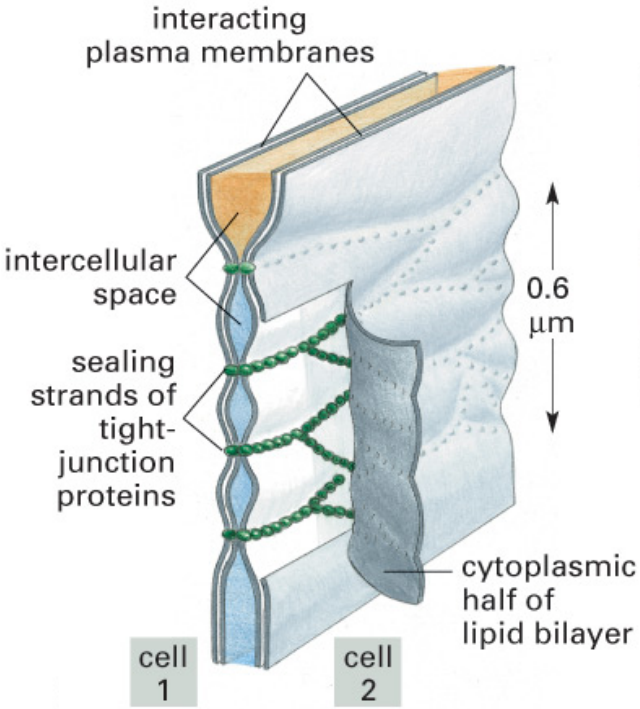
Tight Junction :
Separation of Apical vs basolateral plasma membrane (proteins)

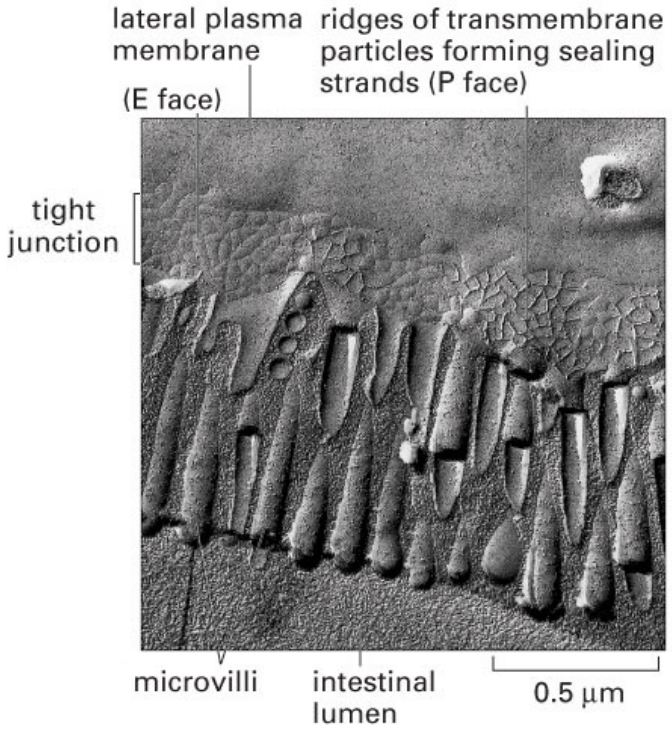


Sealing strands: Plasma-membrane proteins (Occludin, Claudin)
Visualized with freeze-fracture EM

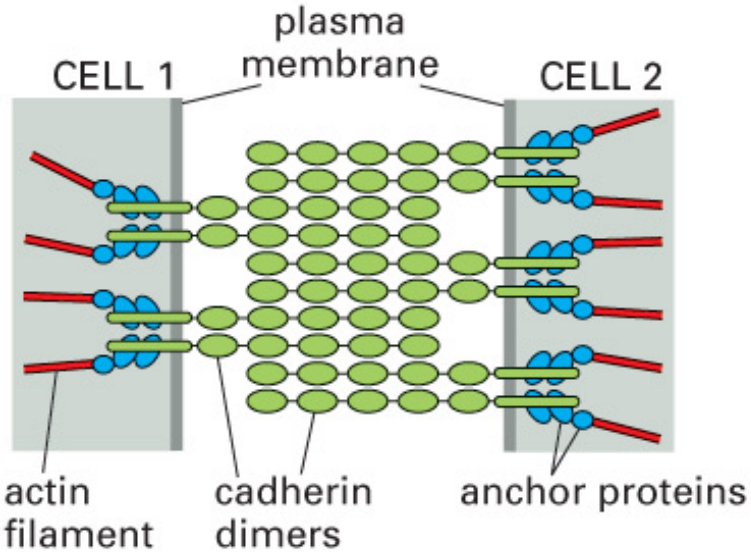
Ca^{2+}-requirement

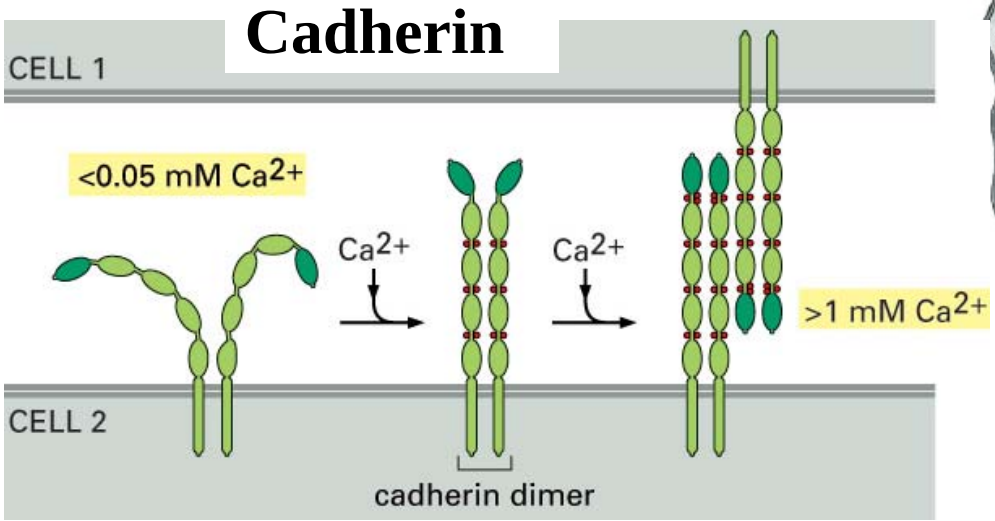


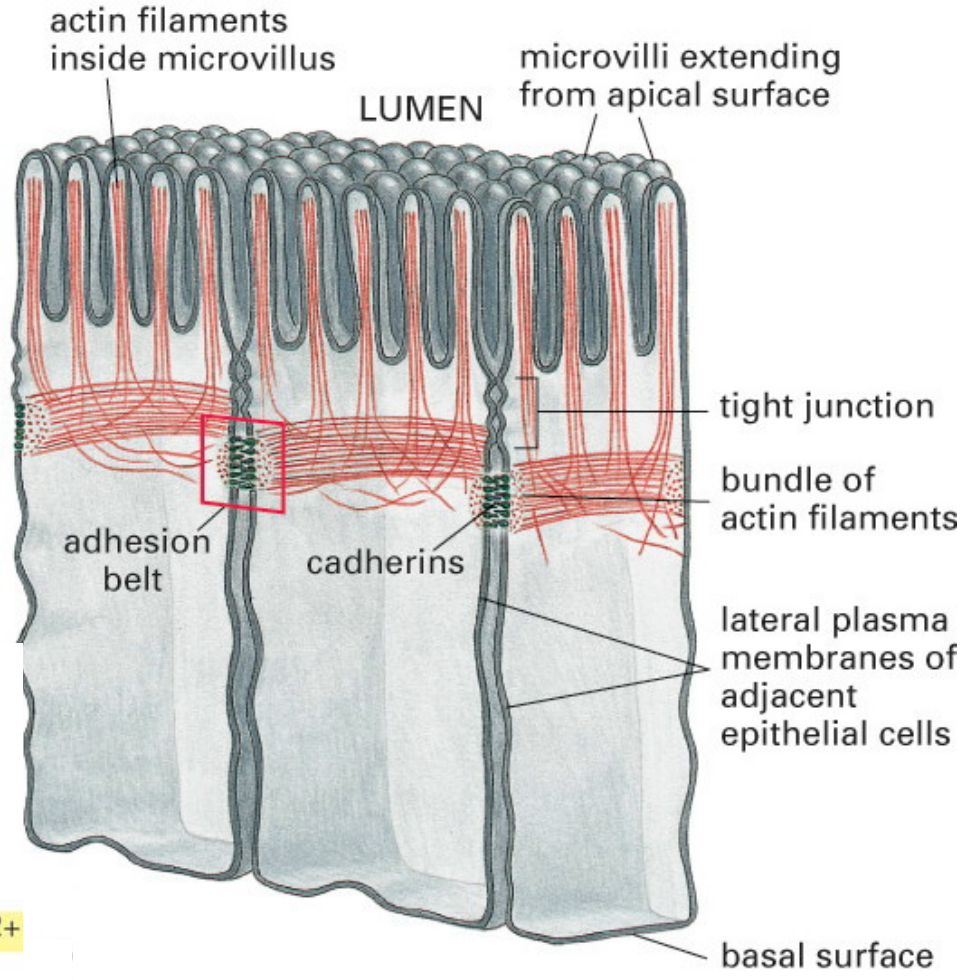




Anchoring Junctions:
Adherens Junctions
(Zonula Adherens; Belt Desmosome)





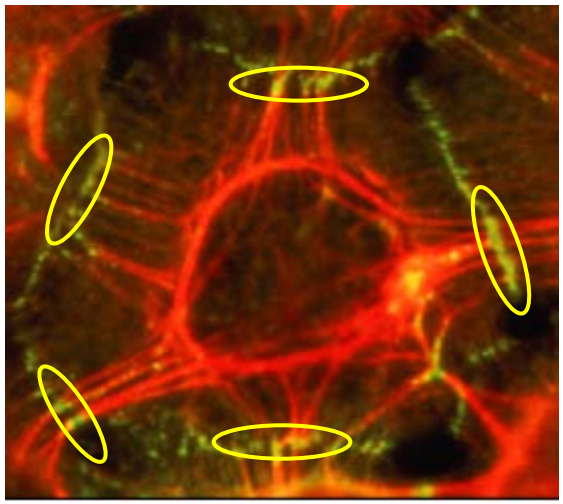


Ca^{2+}-requirement

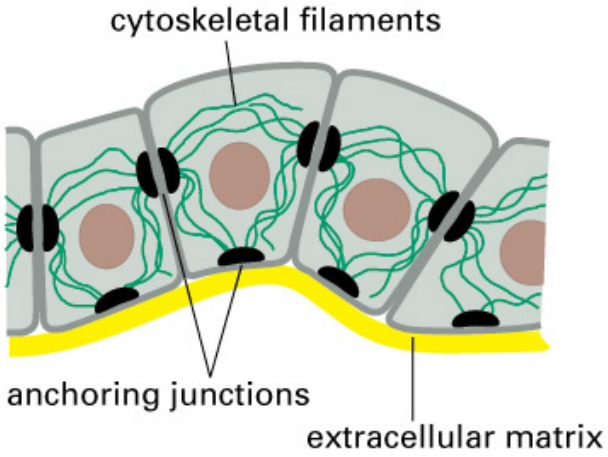
Anchoring Junctions: Desmosomes

Maintain strong cell-cell adhesion

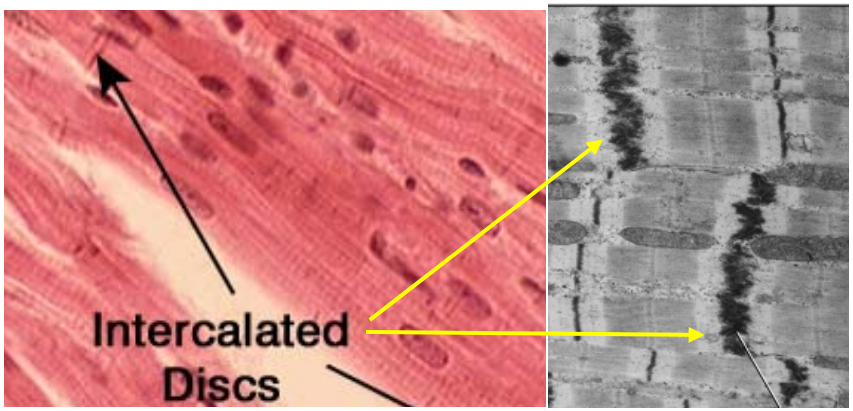
Yellow marks: desmosomes
Keratin filaments attach cytoplasmic side of desmosomes



Epithelial Cells

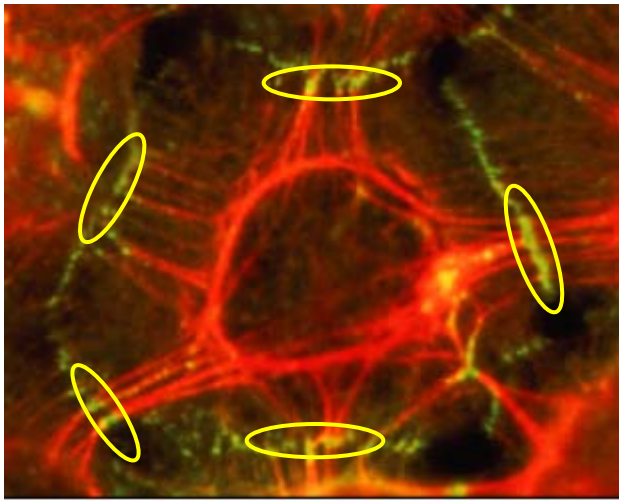


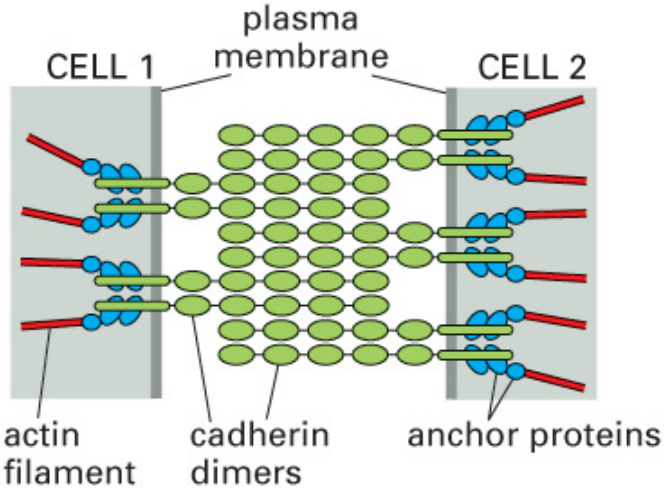
Intercalated Discs in cardiac muscle

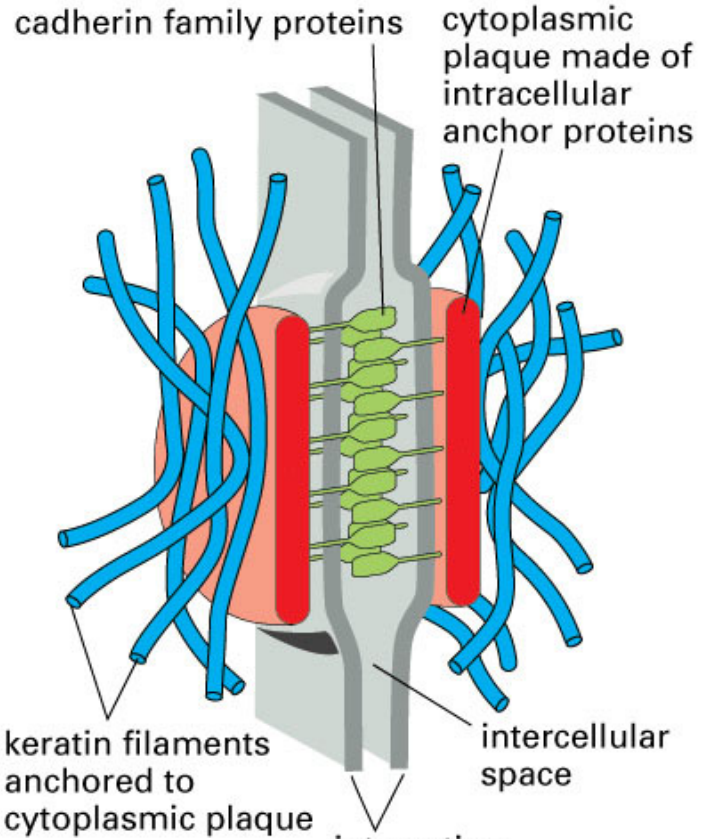


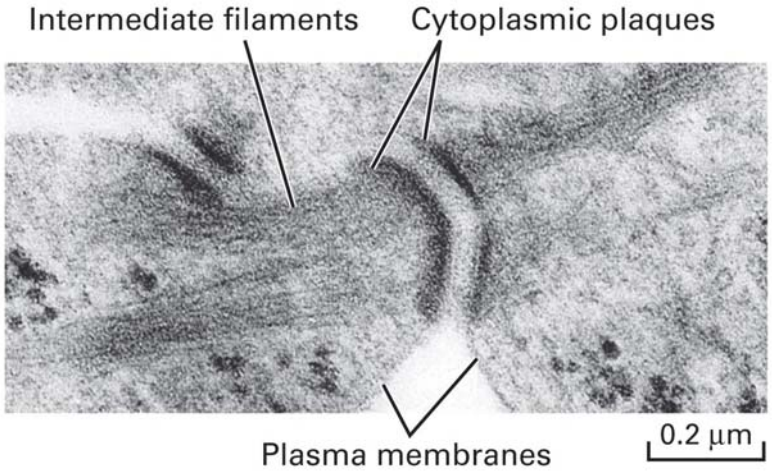
Anchoring Junctions: Desmosomes

Maintain strong cell-cell adhesion

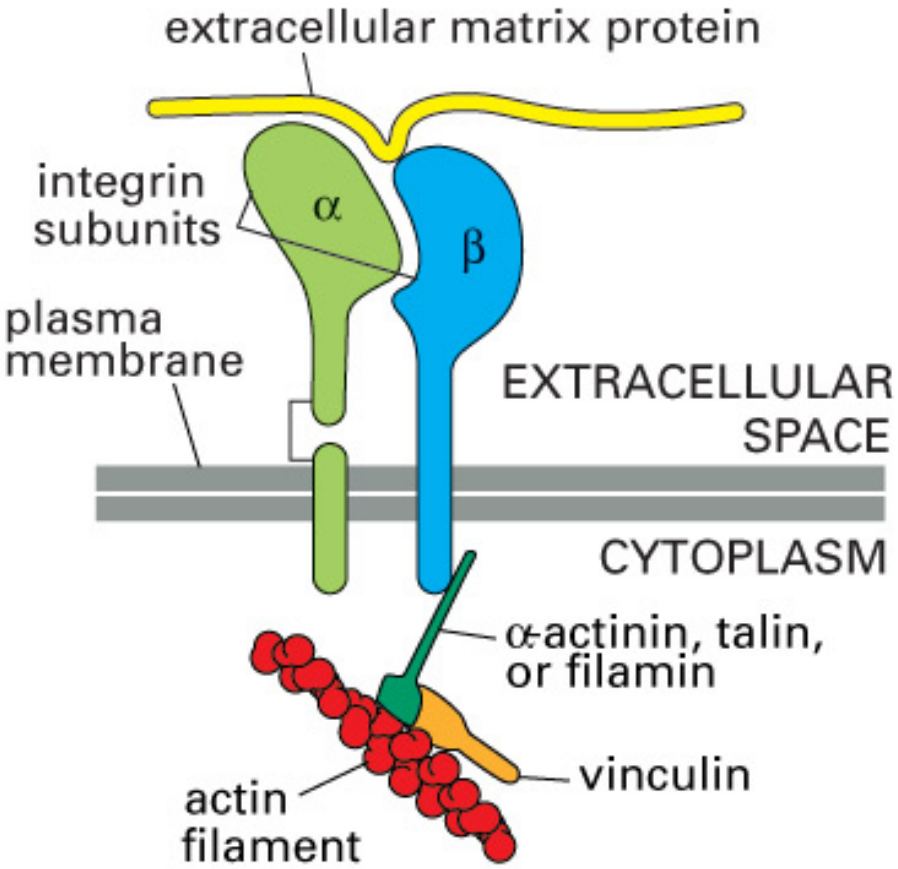








Focal Adhesion
Cell-Matrix adhesion



Integrin

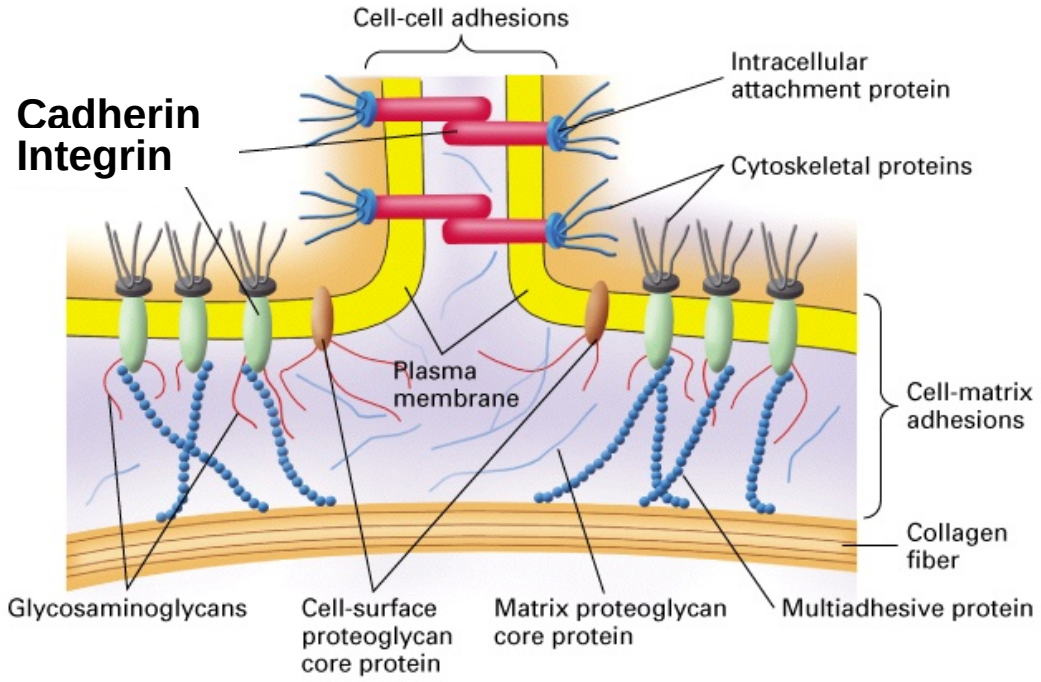
Cytoskeletal fibers associated:

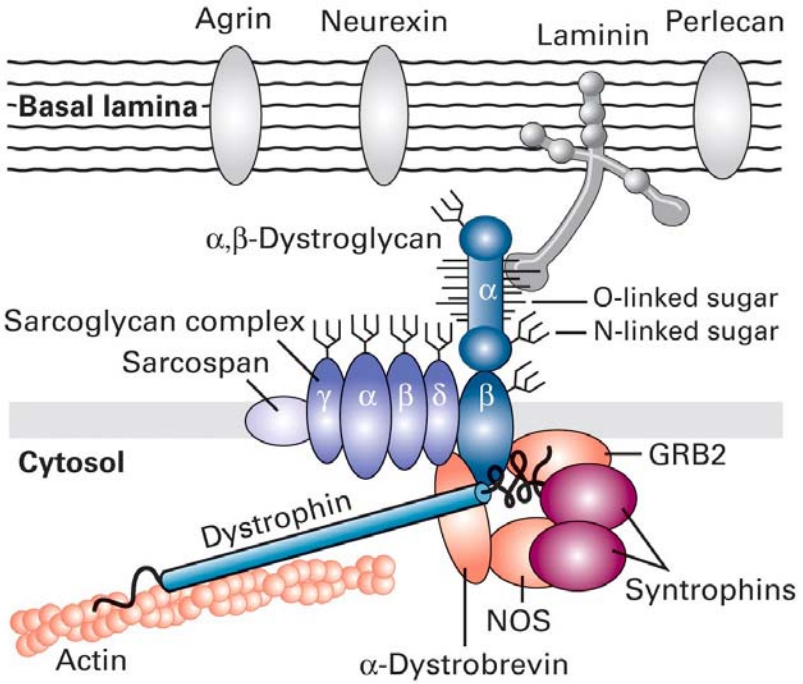
Actin fibers
- **– Focal adhesions**
- **– Muscle (lateral) attachment**

Intermediate filaments
- **– Hemidesmosomes**

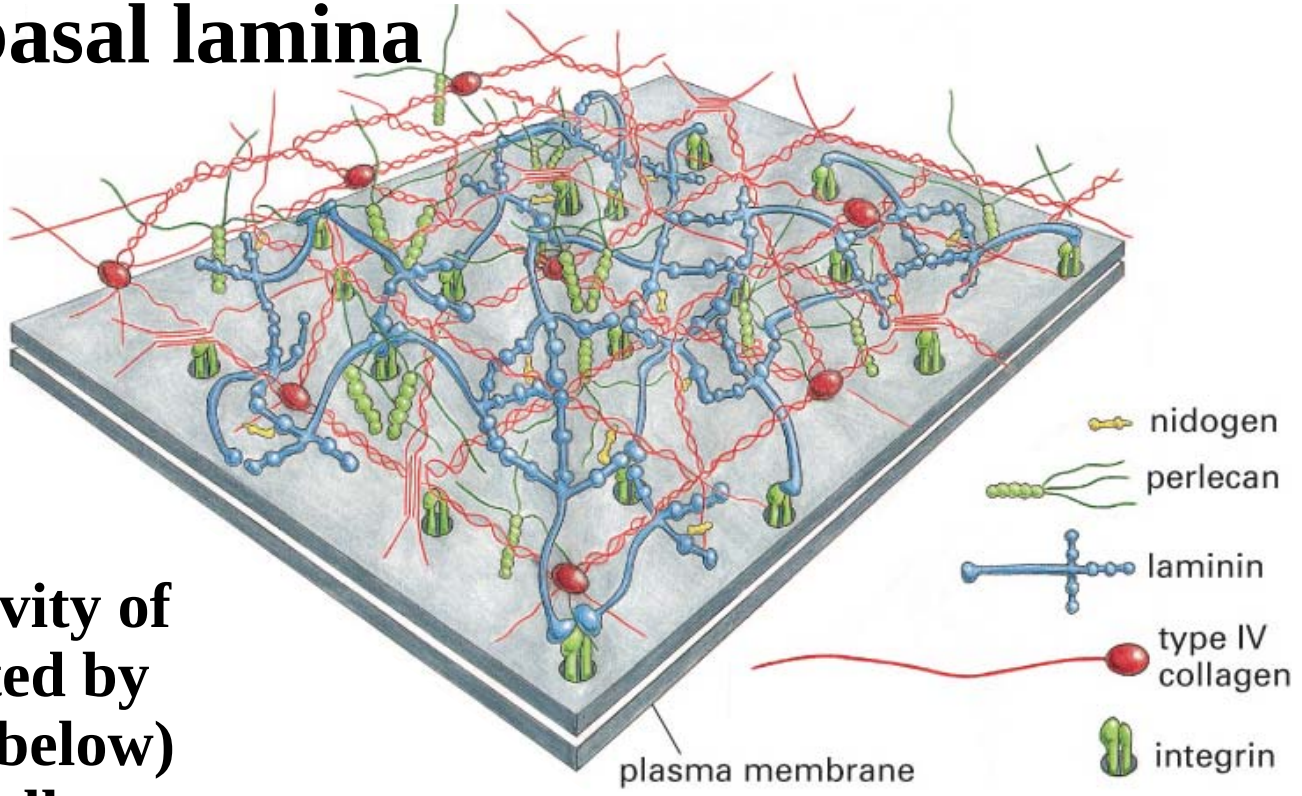
Focal Adhesion
Cell-Matrix adhesion

Hemidesmosome (green)



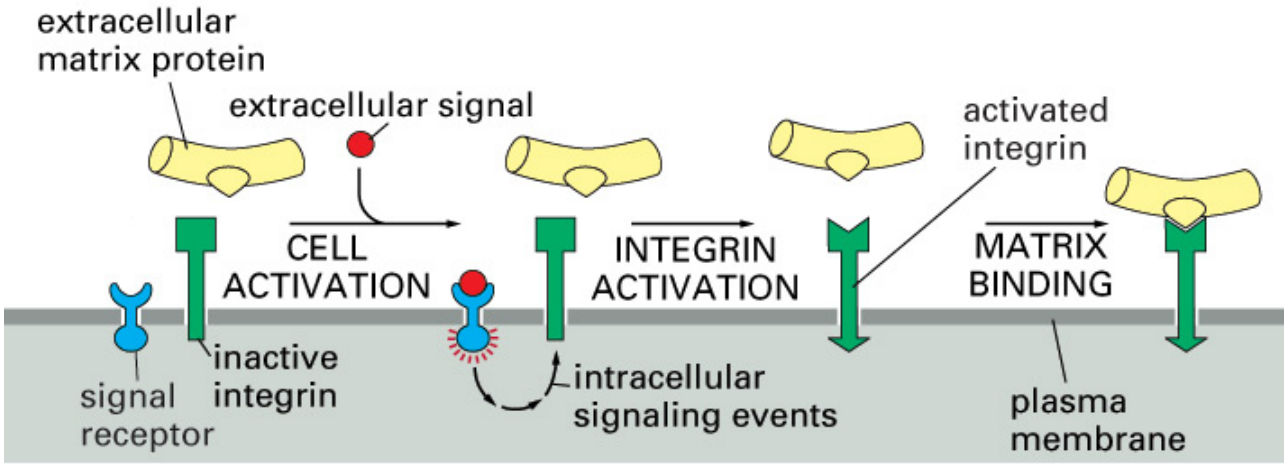


Integrin holds basal lamina



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

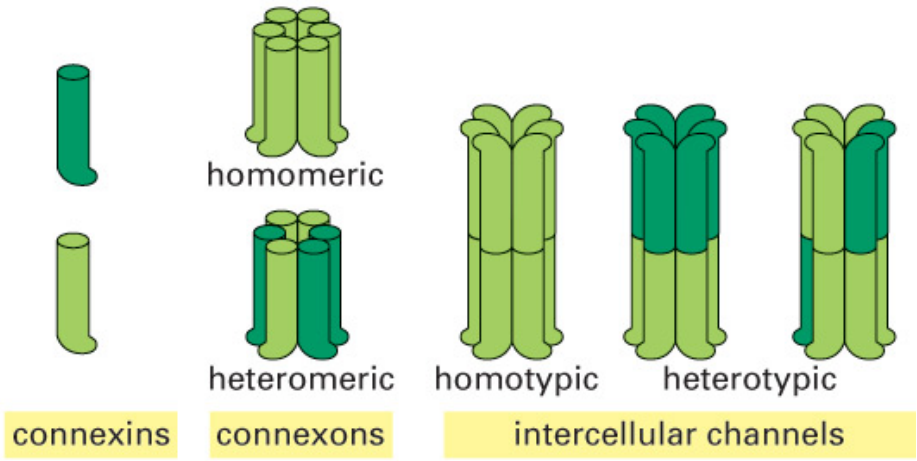
Integrin (cluster) triggers intracellular signalling

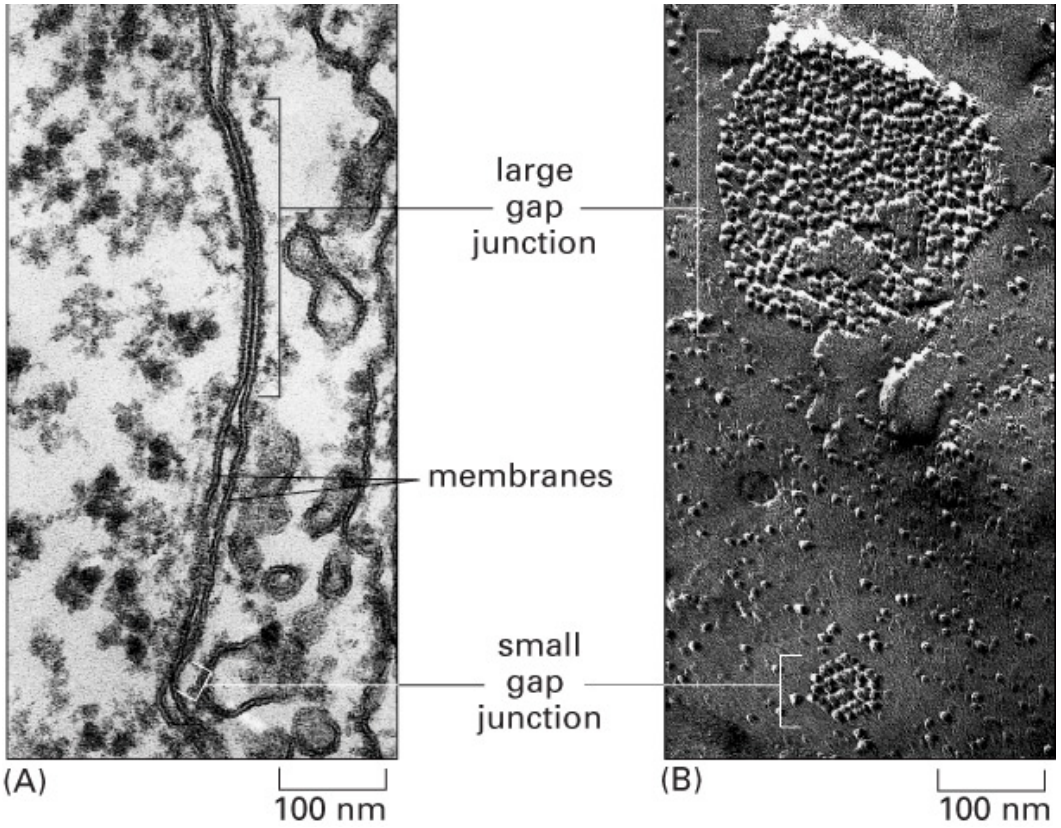


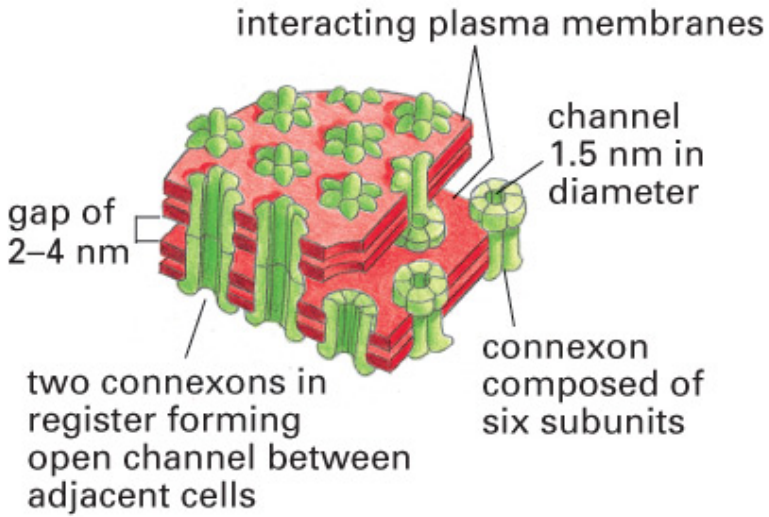
Gap Junction

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

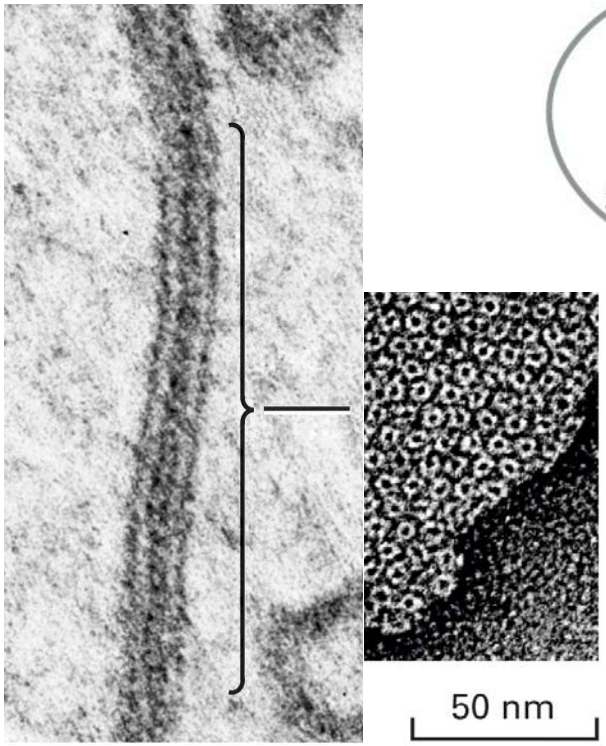
Molecules that pass through gap junctions dependent on type of connexons

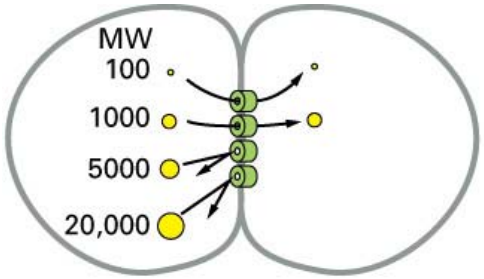
- **Molecular size, charge, else?**

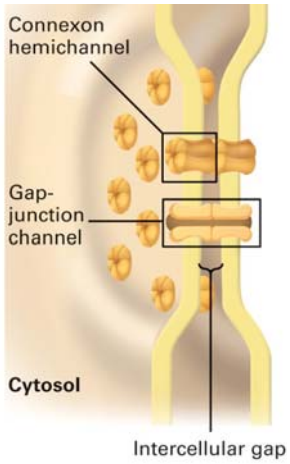
Examples of GAP-junction-connection between cells

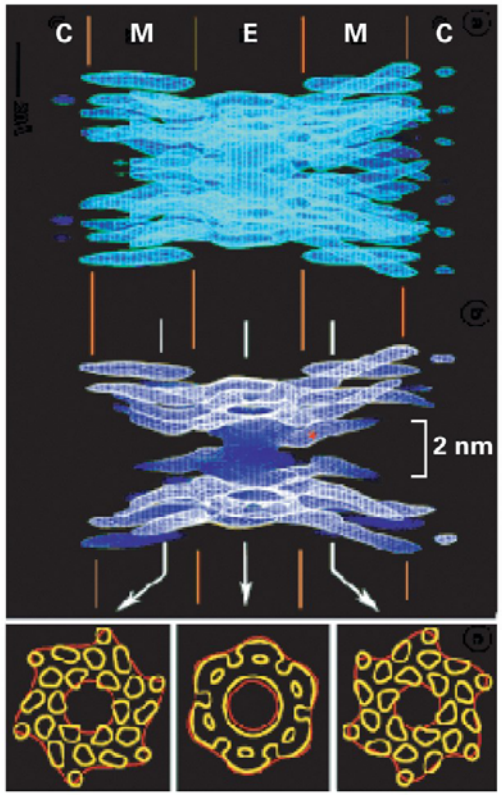
- **Electrical Synapses (Fishes, Insects etc…)**
- **Cardiac muscle cells / smooth muscle cells**
- **Hepatocytes**
- **Tracheal ciliated epithelial cells [IP_3]**

Regulation of the channel (Open ←→ Close)

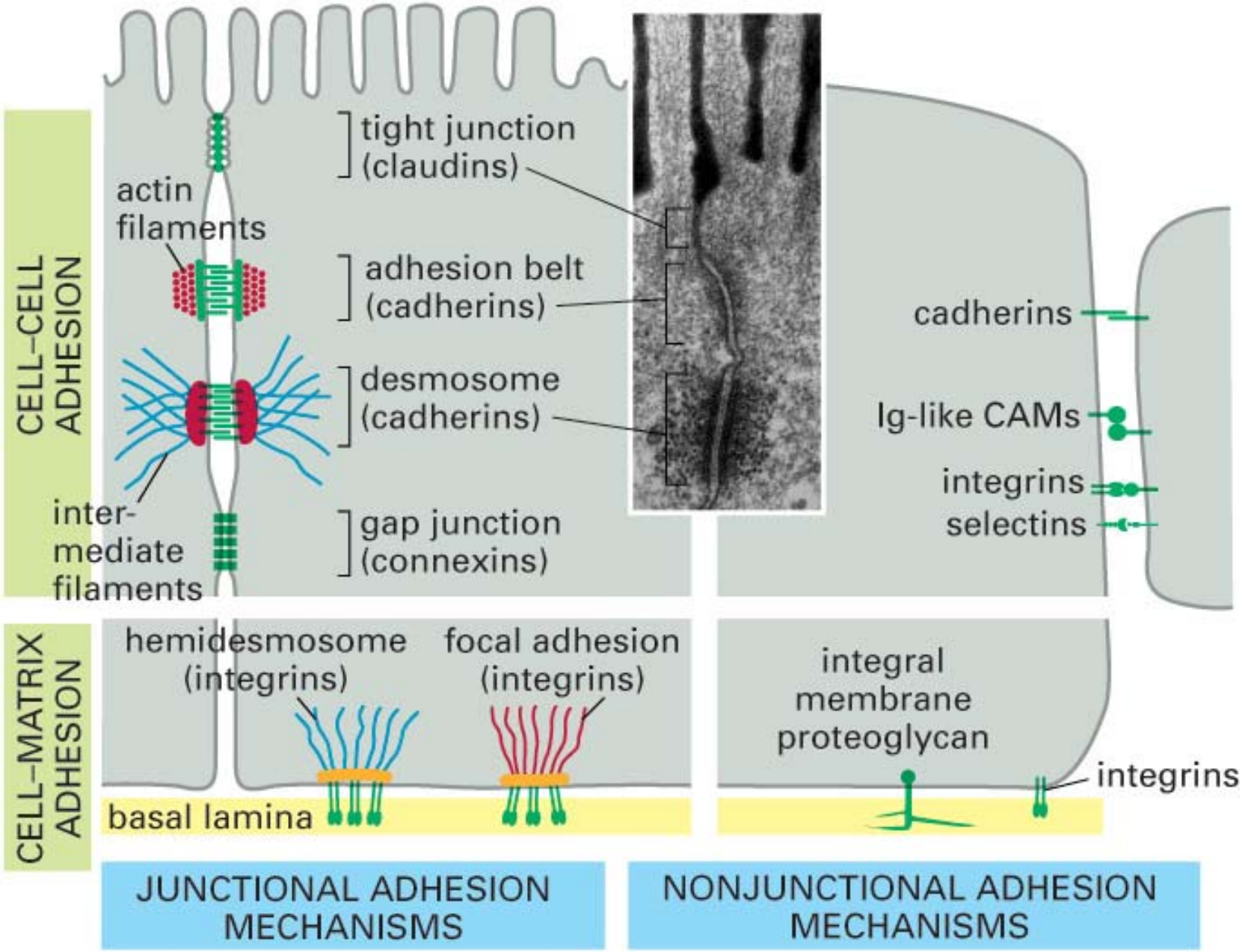




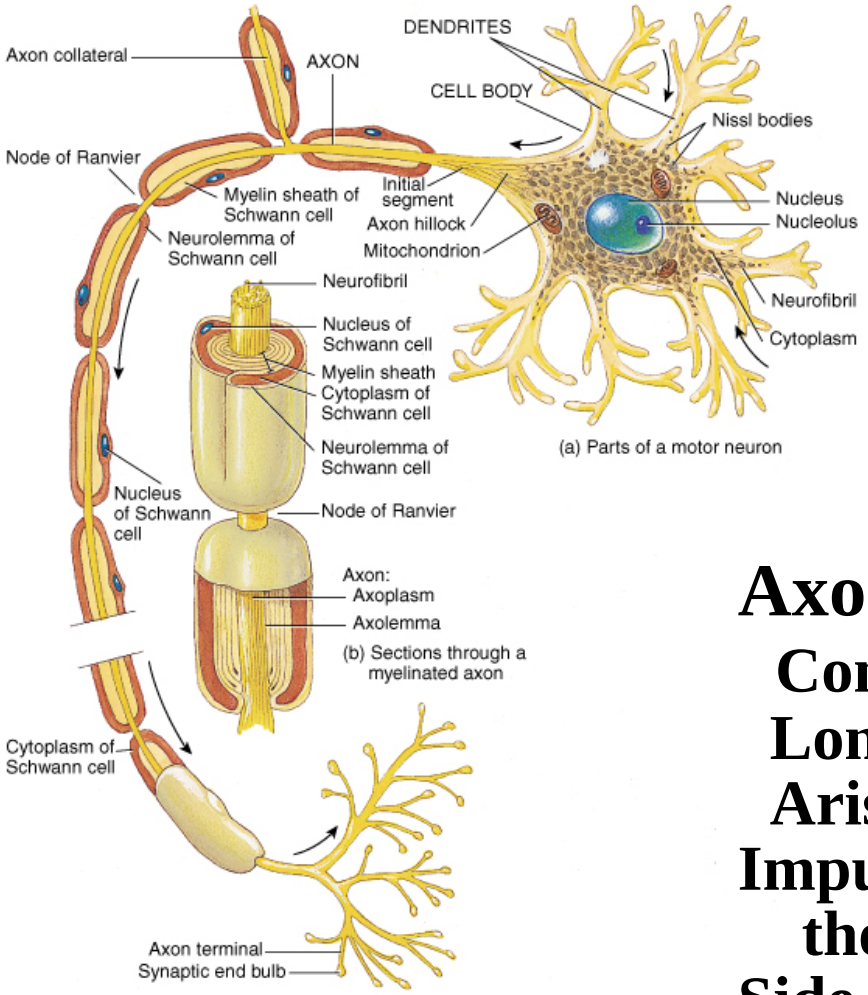




Summary of cell-cell / cell-matrix adhesions



Excitatory Properties of Plasma Membrane: Neuron



Synaptic boutons

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

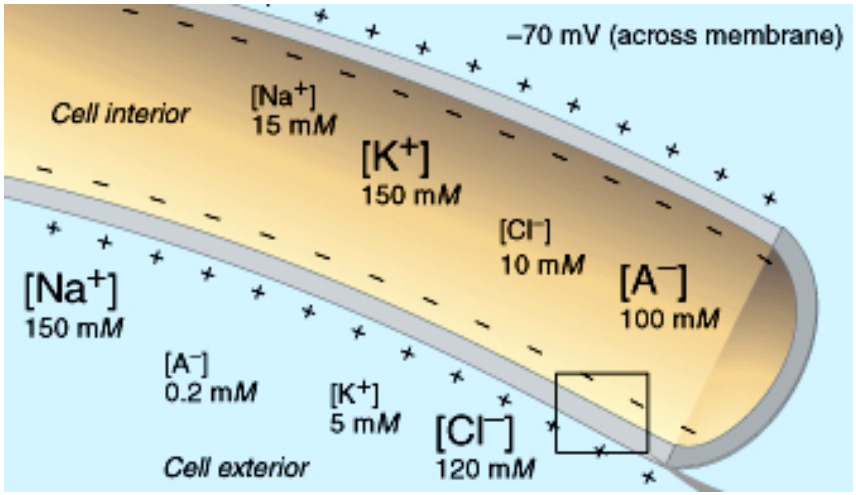
Arises at axon hillock

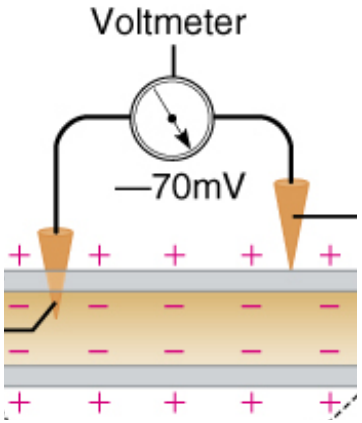
Impulses (Action potentials) arise from the initial segment (trigger zone)

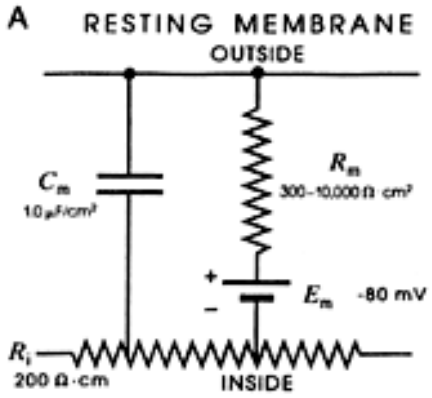
Side branches (collaterals) end in fine processes called axon terminals

Synaptic end bulbs : contain vesicles filled with neurotransmitters

Resting Membrane Potential







Nerve cells, (Neurons, Grial cells)
<u>All the other living cells</u>

Potential energy difference at rest is (about) -70 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^-

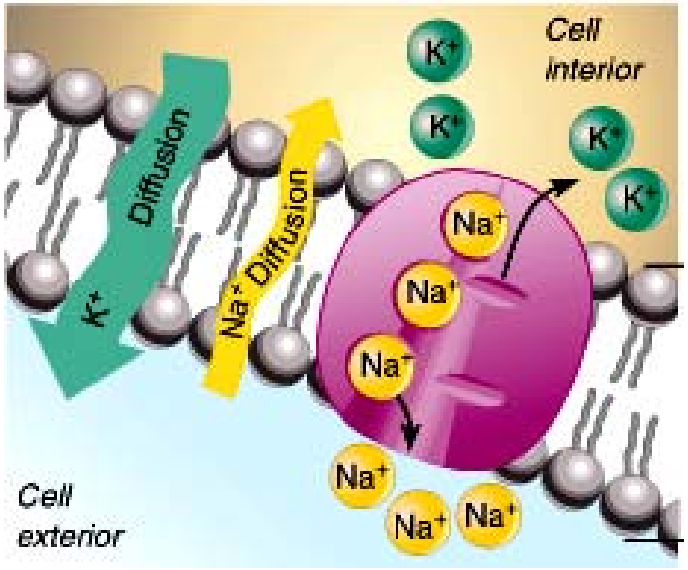
Cytosol: high [K^+], organic phosphate & amino acids

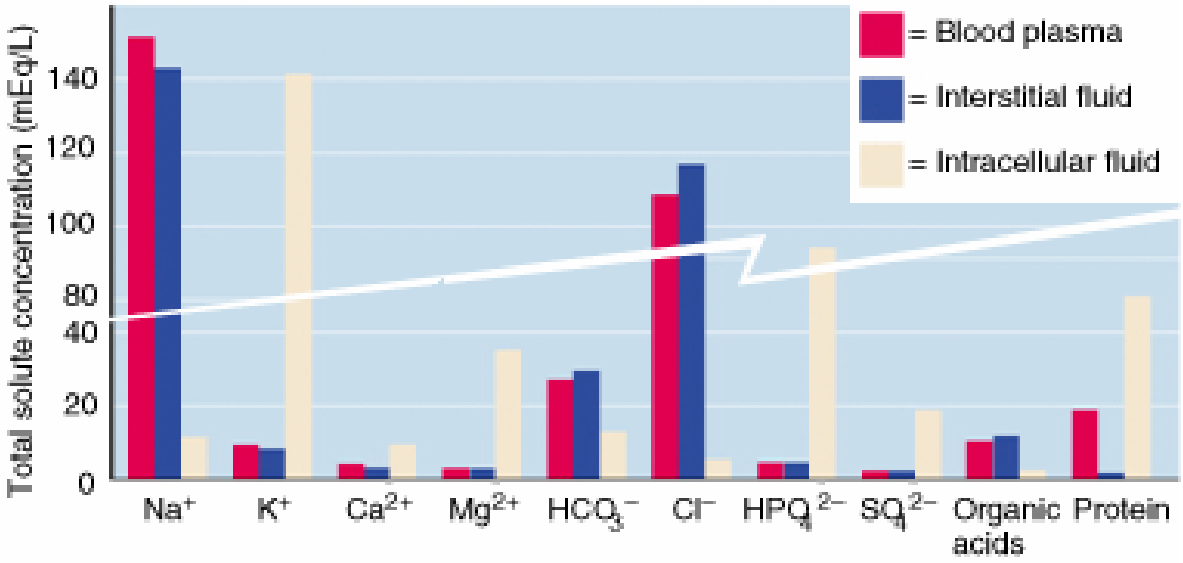
Membrane permeability for Na^+ & K^+:
50-100 greater permeability for K^+

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

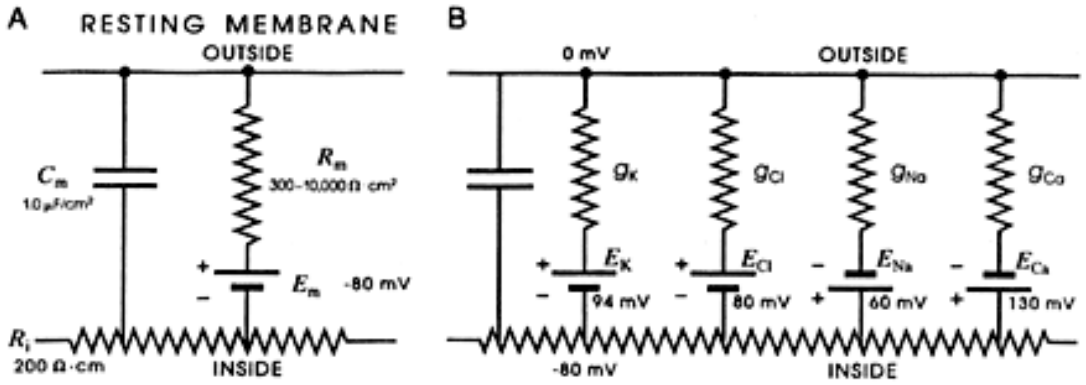


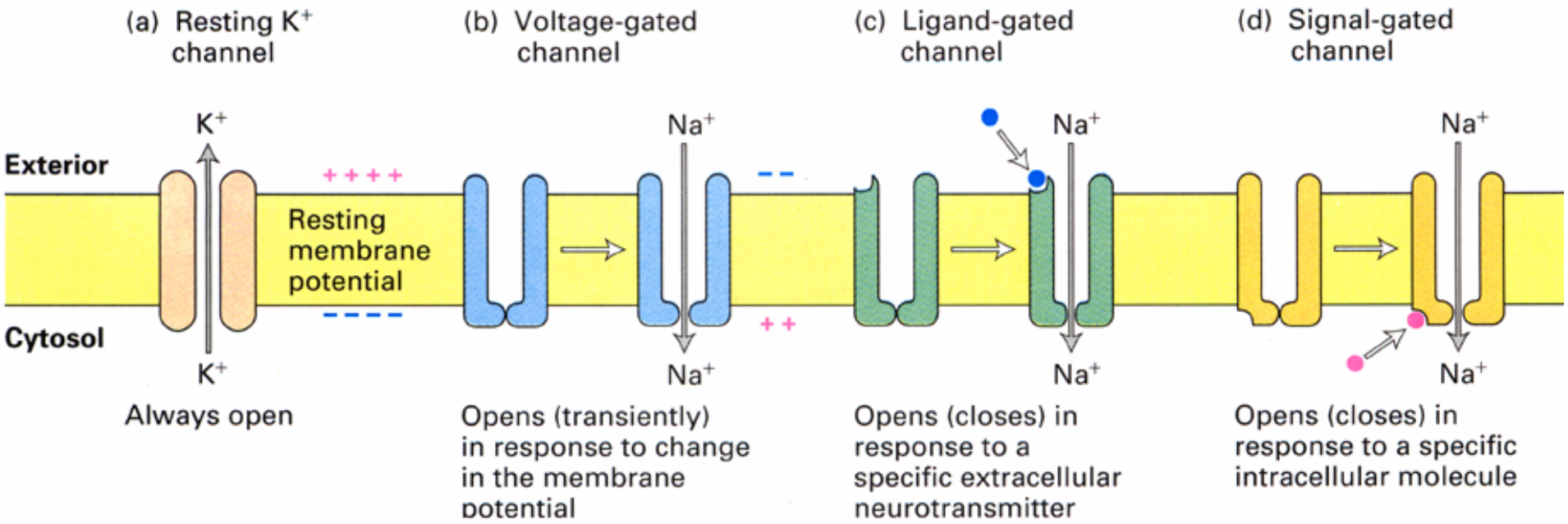


Membrane channels (a partial list): Membrane conductance

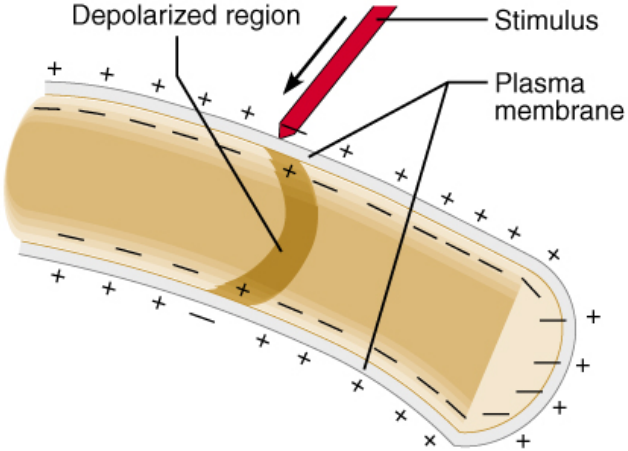
Conductance:
Each carried by specific ion species
Na^+, K^+, Ca^{2+}

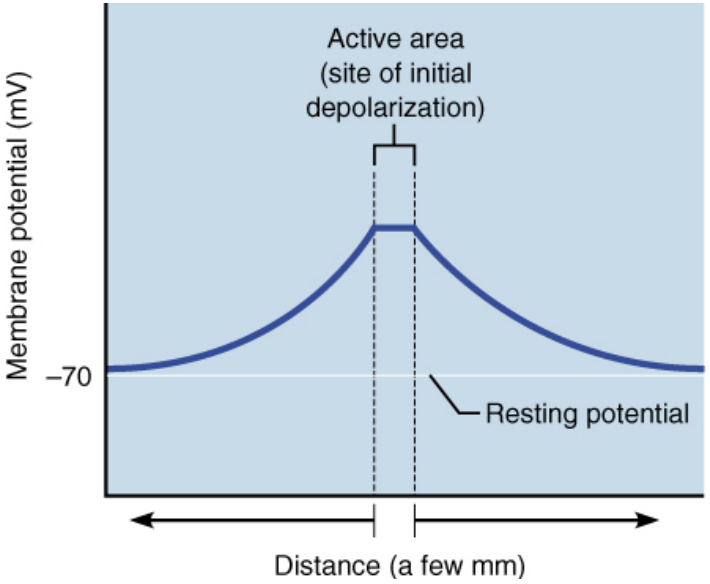
Specific Ion Channels





Depolarization / Hyperpolarization of the Membrane Potential

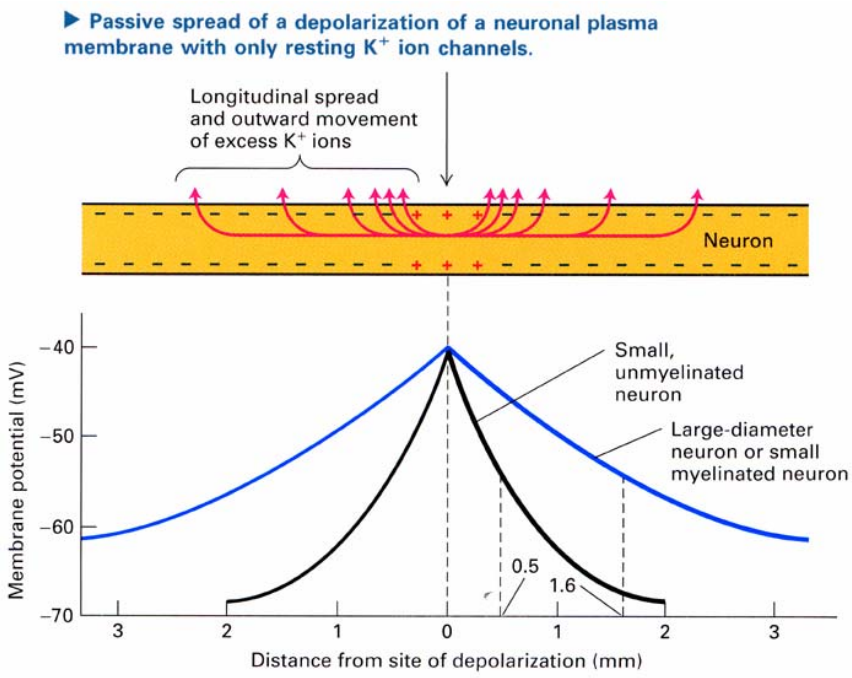




Specific ion channels are opened according to the stimulus

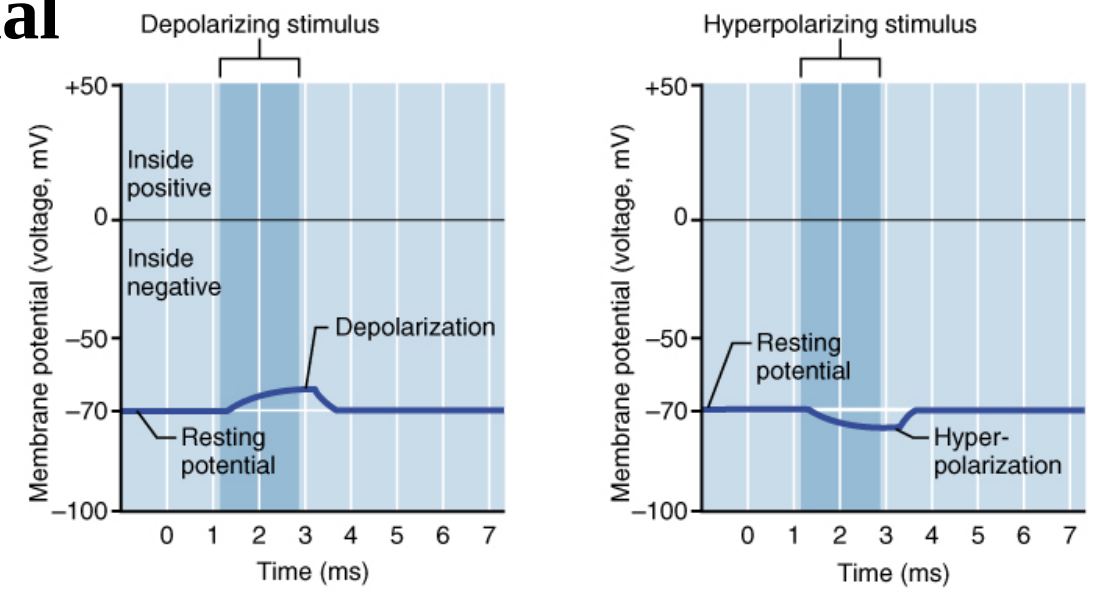
Strength of the stimulus ∝ amount of change in membrane potential
(Not always; also effective range)

Local change in membrane potential spreads through membrane <u>with decay</u>



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

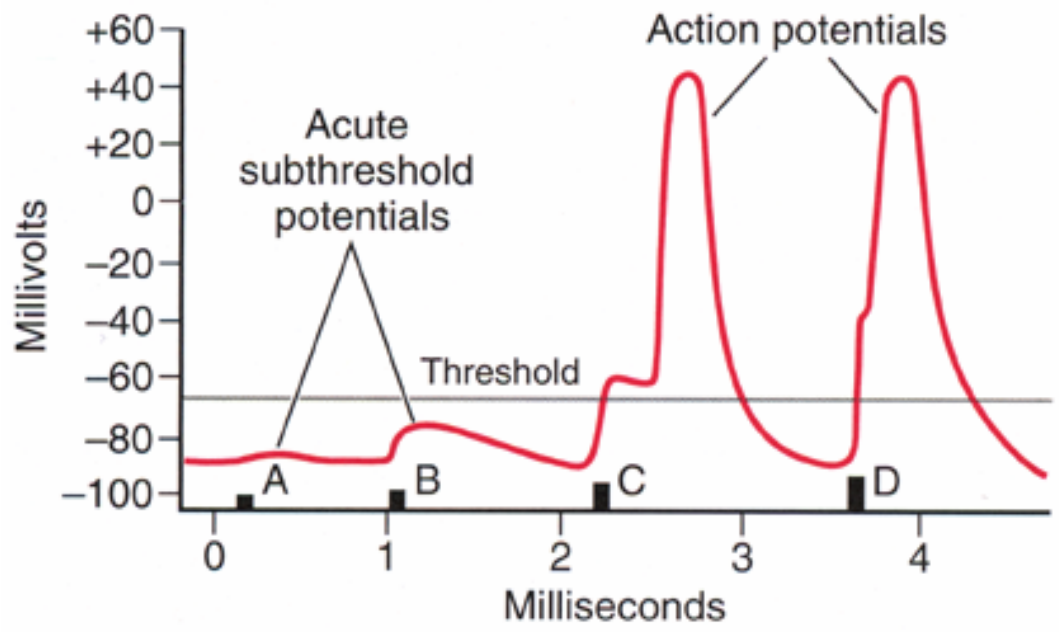
Amount of change varies with strength of stimuli

Flow of current (ions) occurs only locally

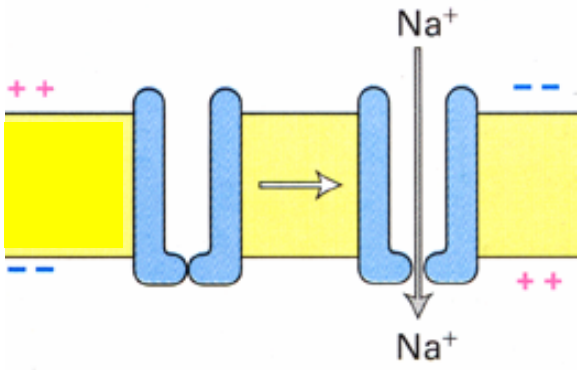
Dendrites and Cell bodies (usually not on axonal membrane)

Action Potential

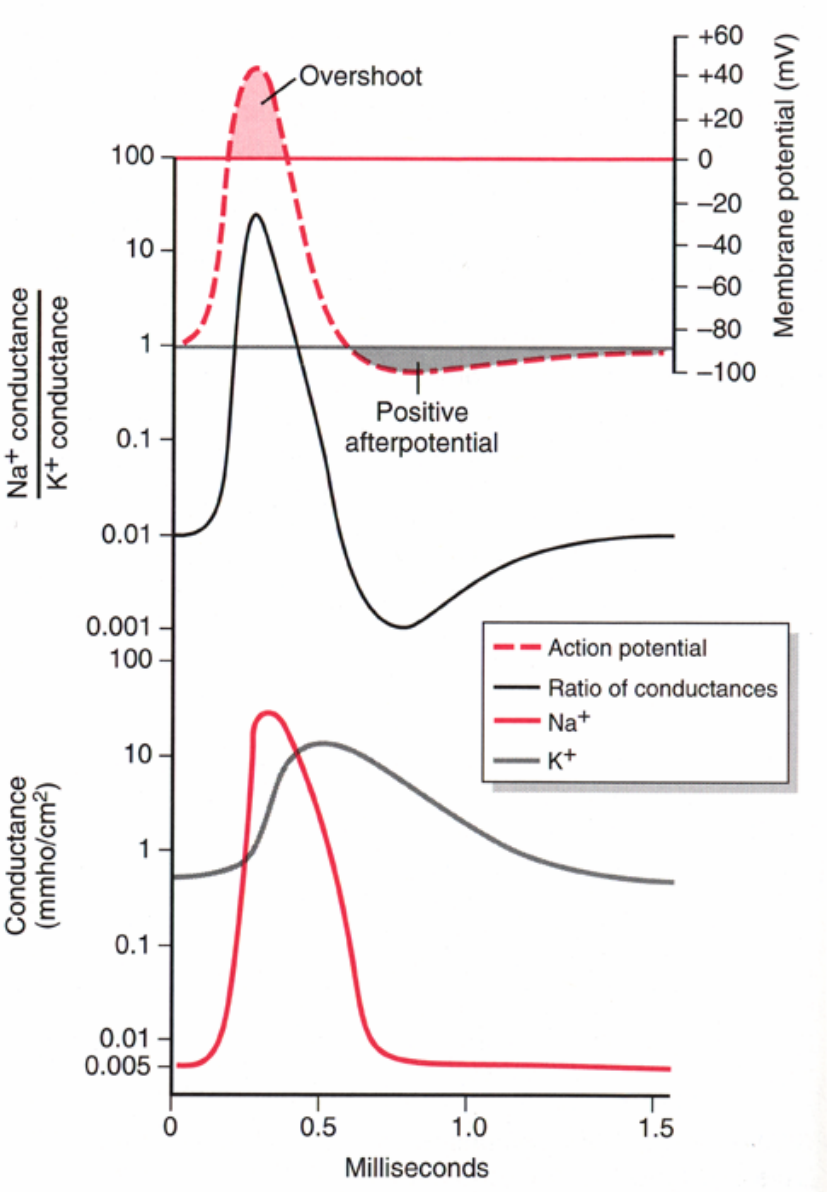
Produced by voltage-gated ion channels
All – or – None
Voltage threshold



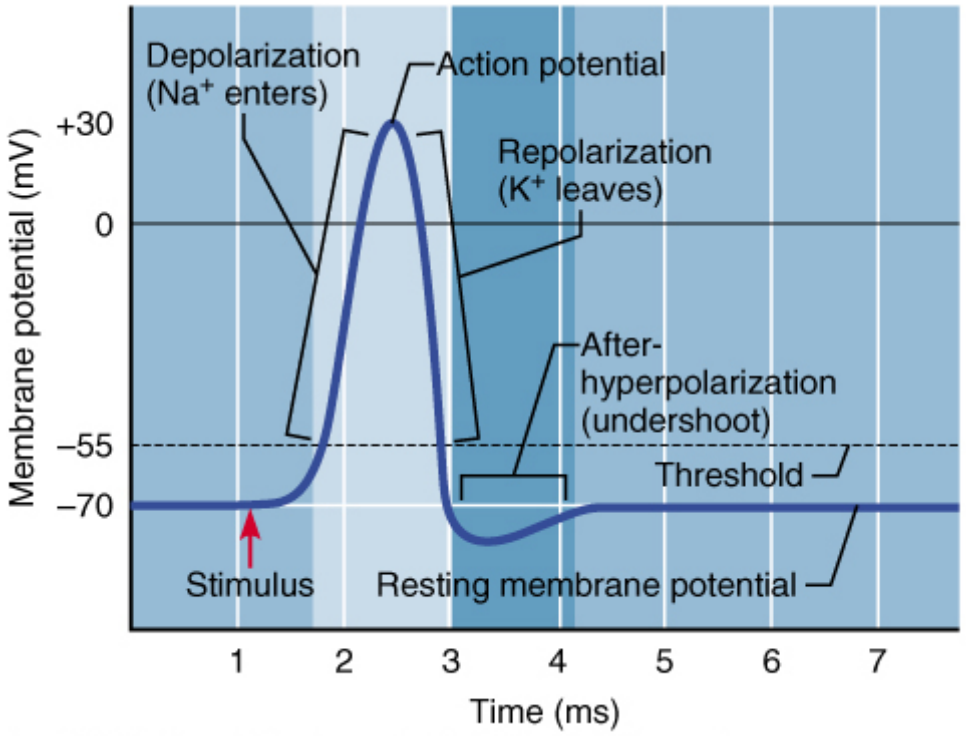
Voltage-gated Na^+ Channel



Components of an Action Potential

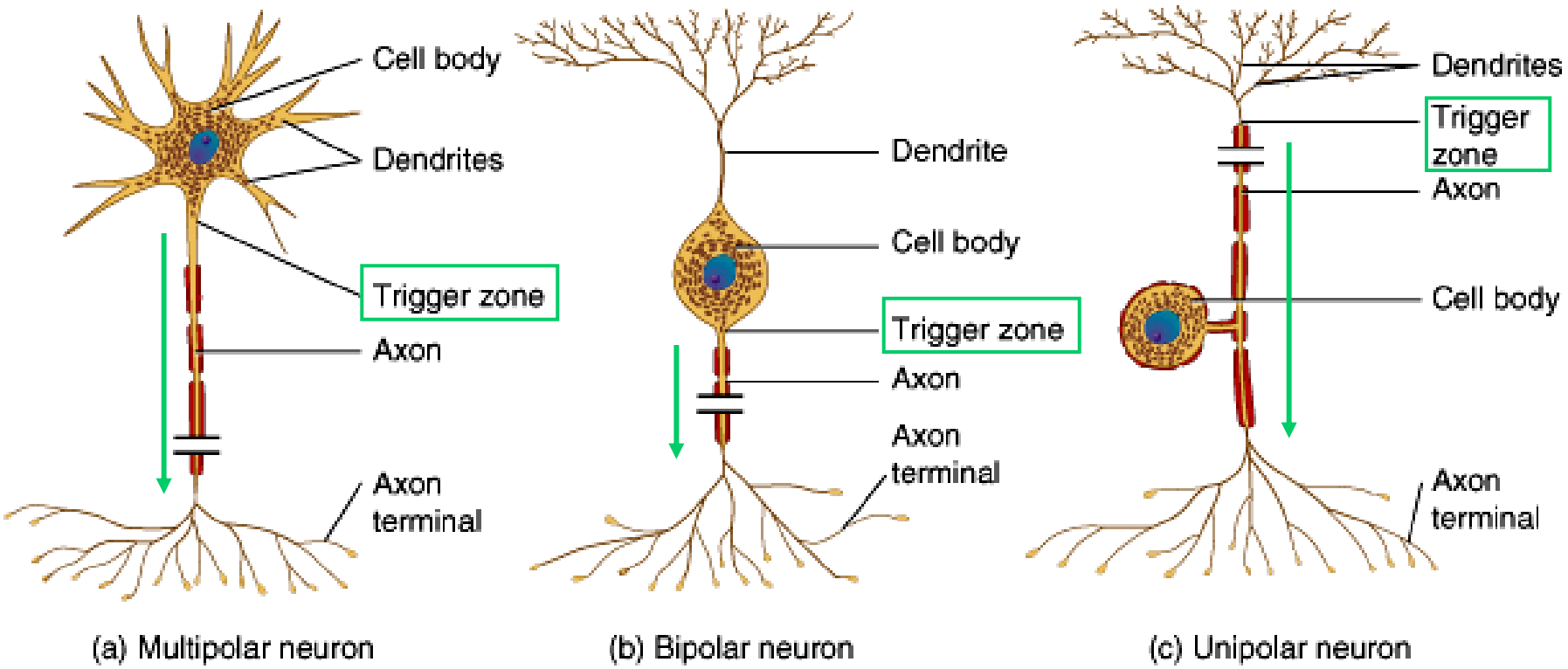


Voltage-gated Na^+ Channel: Deporalization activated Voltage-gated K^+ Channel

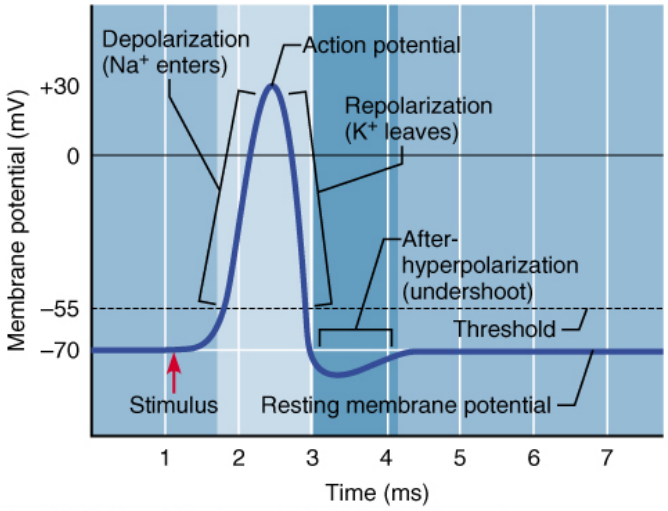


Action Potential

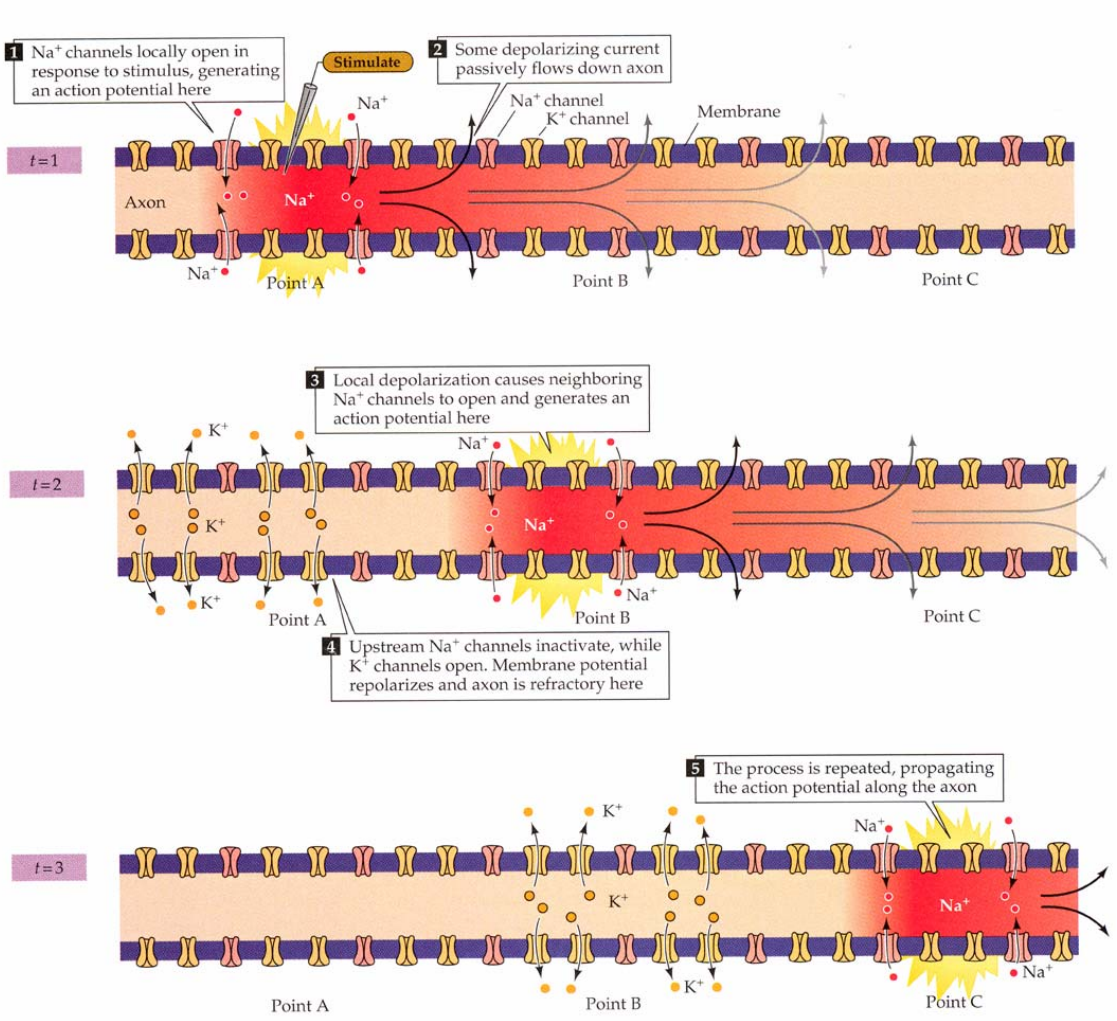
Action potentials start to arise only at **trigger zone** on axon hillock, in response to membrane depolarization due to graded potential(s) generated at dendrites / cell body



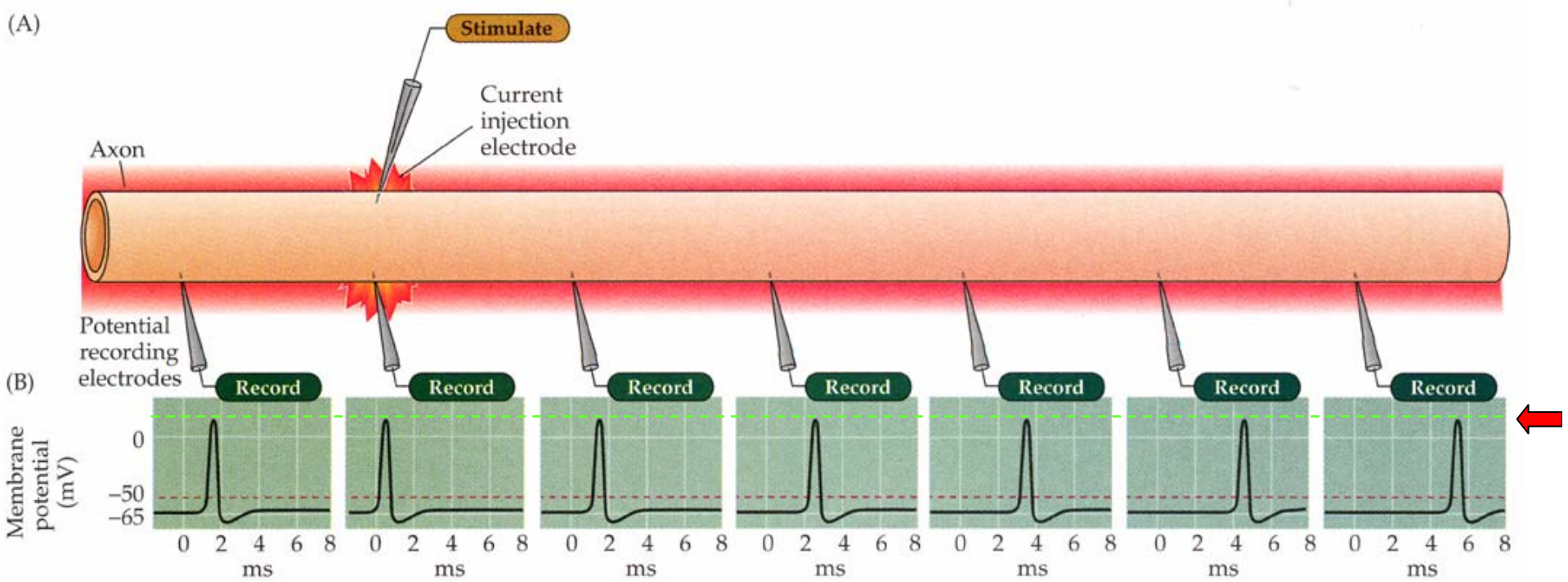
Action potential : enables information processing all-or-none



The refractory period makes action potential to propagate unidirectional



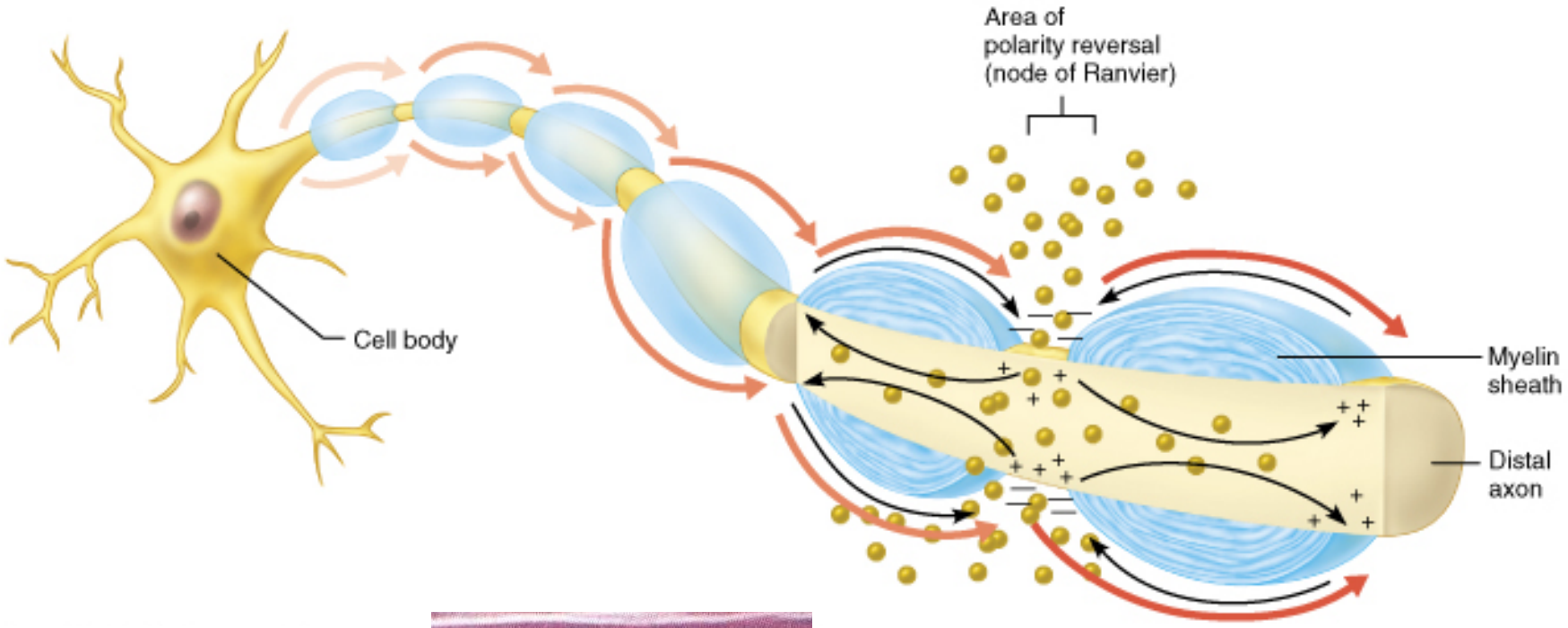
Propagation of an action potential through an axon

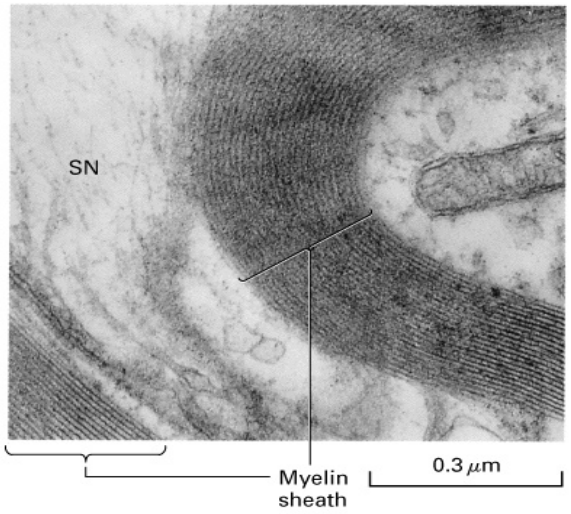


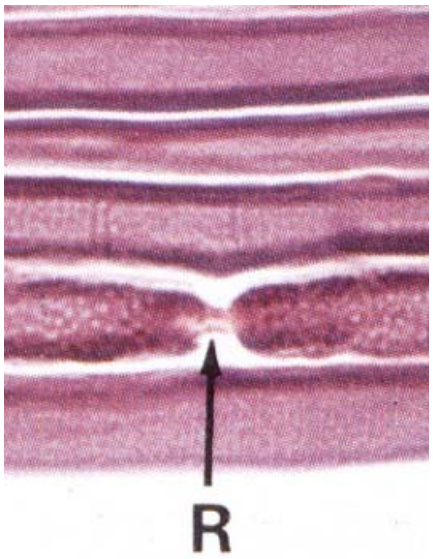
Timing – delays with distance
Slow propagation

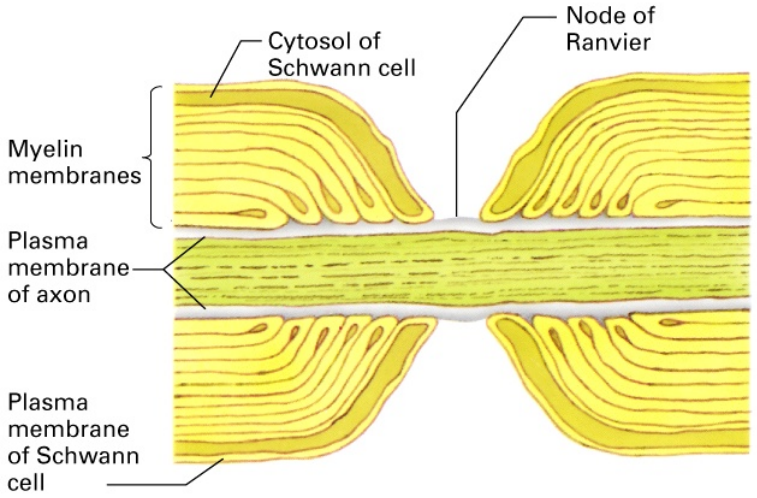
Height – remains same
(red arrow)
<u>All – or - None</u>

Myelination of axon and saltatory action potential conduction at the node of Ranvier





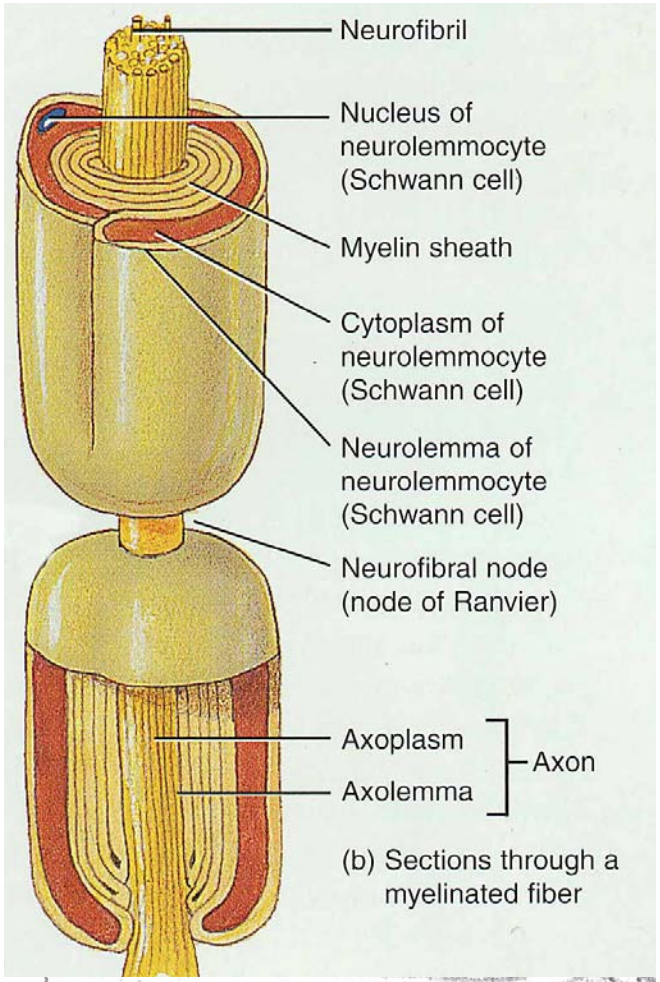


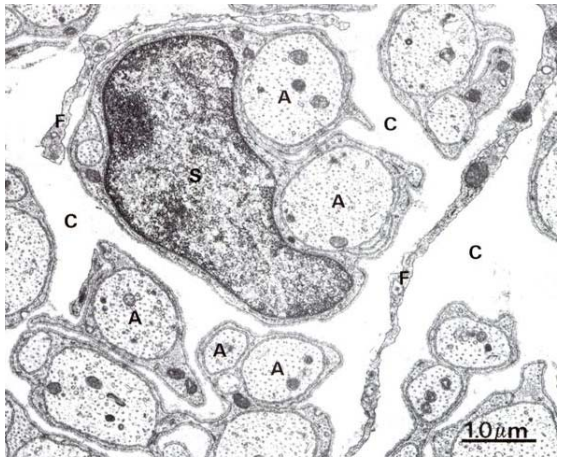


Unmyelinated vs Myelinated axon

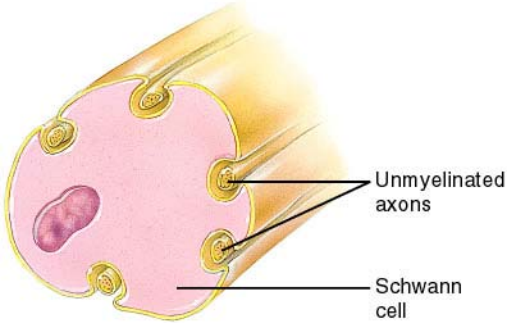
Myelinated fibers: appear white jelly-roll like wrappings
made of lipoprotein = myelin
acts as electrical insulator
speeds conduction of nerve impulses

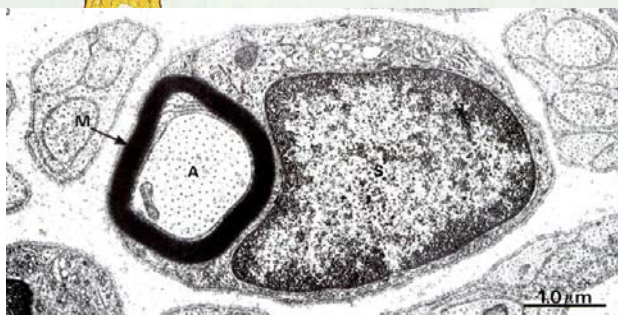
Unmyelinated fibers: slow,
small diameter fibers
only surrounded by neurilemma
but no myelin sheath wrapping





Unmyelinated axones [A] and a schwann cell [S]





A myelinated axon, myelin sheath [M] and a schwann cell [S]

Saltatory action potential conduction :

Speedup the action potential propagation