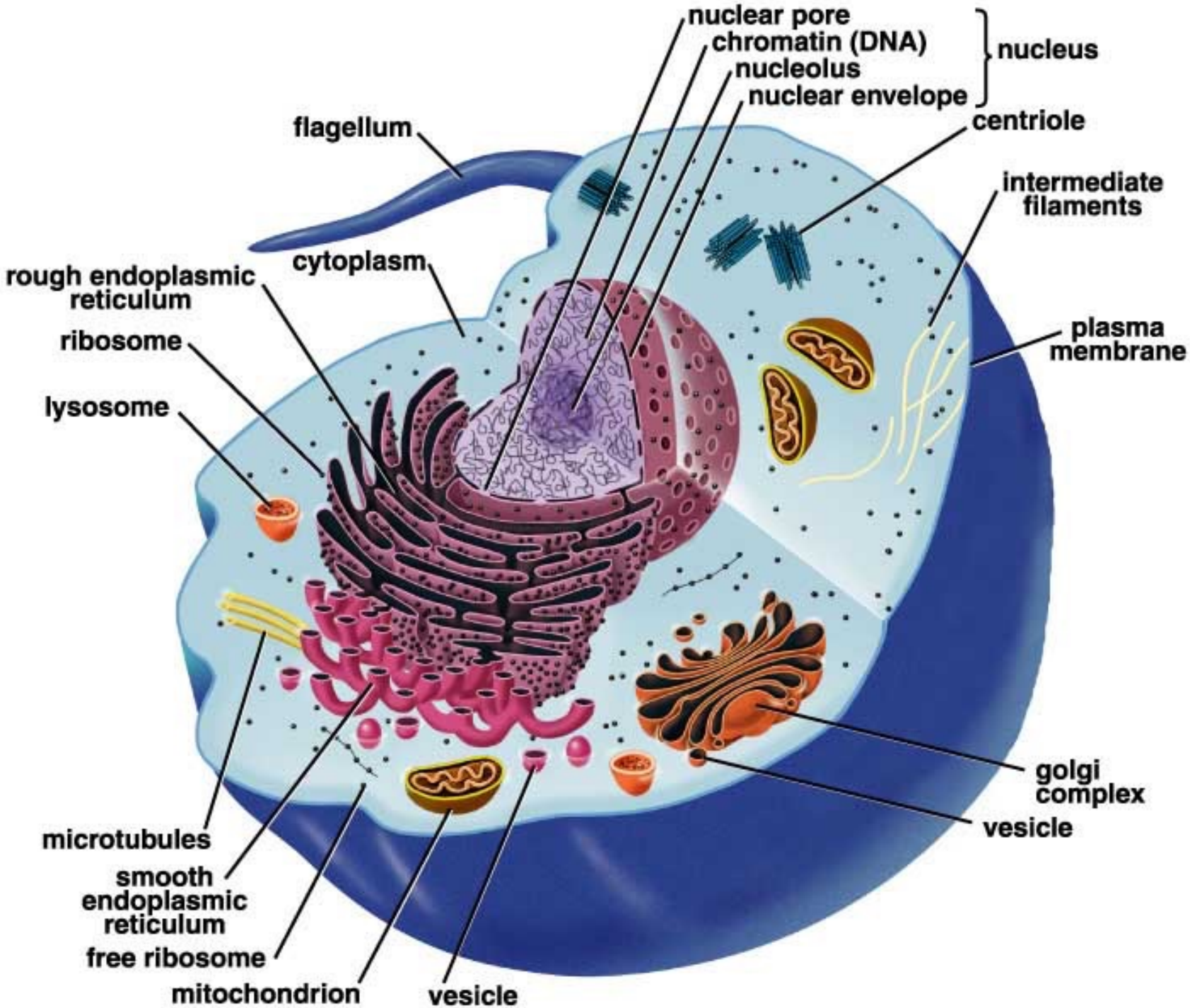
Lecture 2a

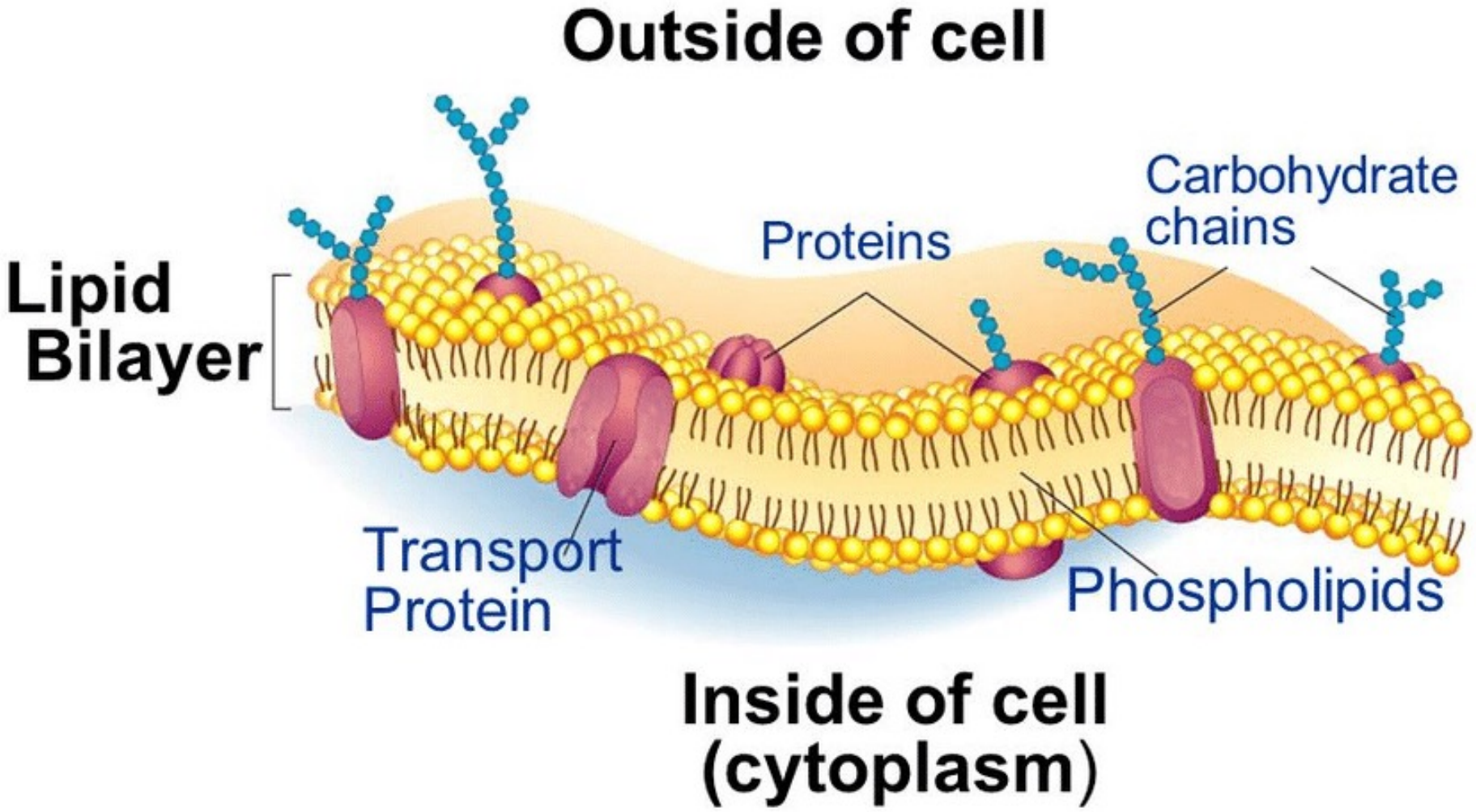
Membrane transports


nuclear pore
chromatin (DNA)
nucleolus
nuclear envelope
nucleus
flagellum
centriole
intermediate filaments
cytoplasm
rough endoplasmic reticulum
ribosome
plasma membrane
lysosome
golgi complex
vesicle
microtubules
smooth endoplasmic reticulum
free ribosome
mitochondrion
vesicle

Physiological Function of the Cells

- Transport across the cell membrane
- Bioelectrical phenomena of the cell
- Contraction of muscle

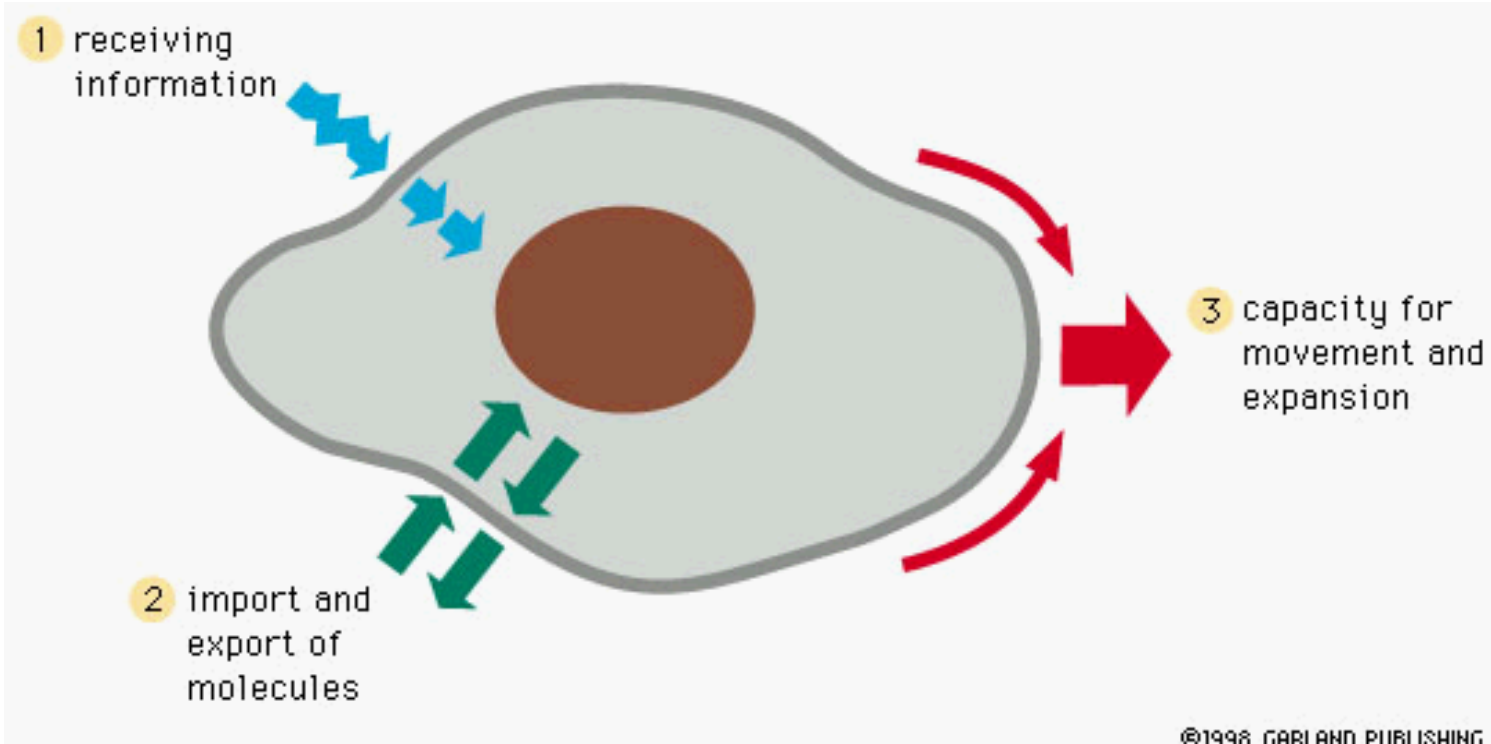
Transport of Ions and Molecules through the Cell Membrane



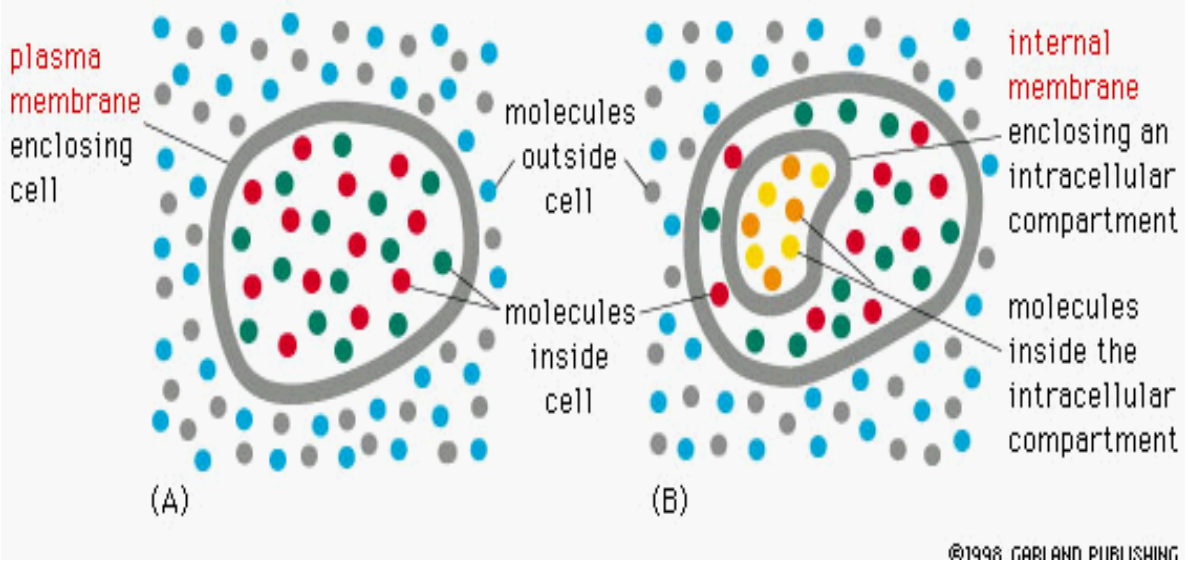
What do membranes do?

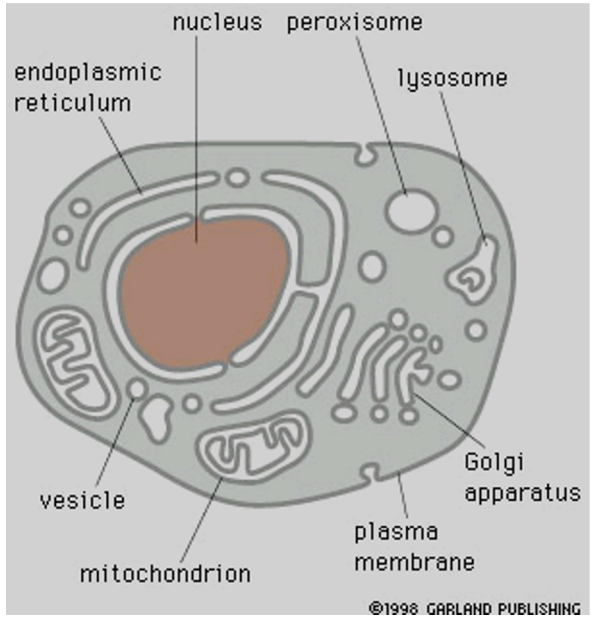
- Act as a barrier AND…
- Receive information
- Import/export molecules
- Move/expand

Membranes are Active Dynamic !



The Cell Membrane System



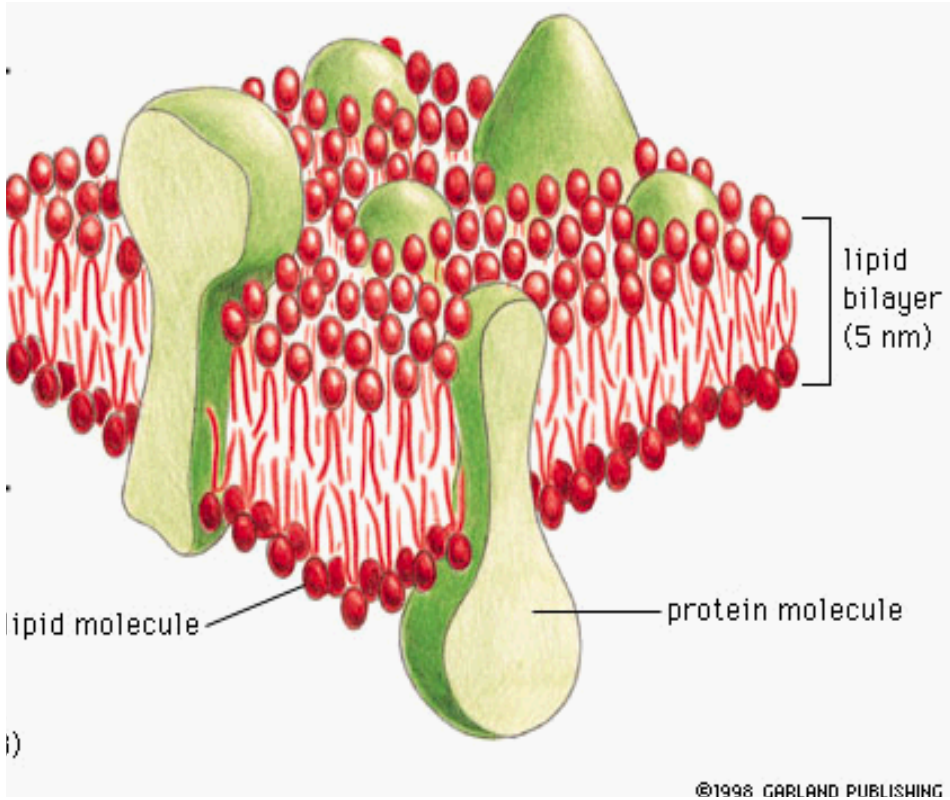


- **Membranes surrounding the cell**
- **Membrane systems inside the cell**
  - **The nucleus, endoplasmic reticulum, golgi apparatus,**

  Endosomes and lysosomes form the endomembrane system

Composition of the cell membrane

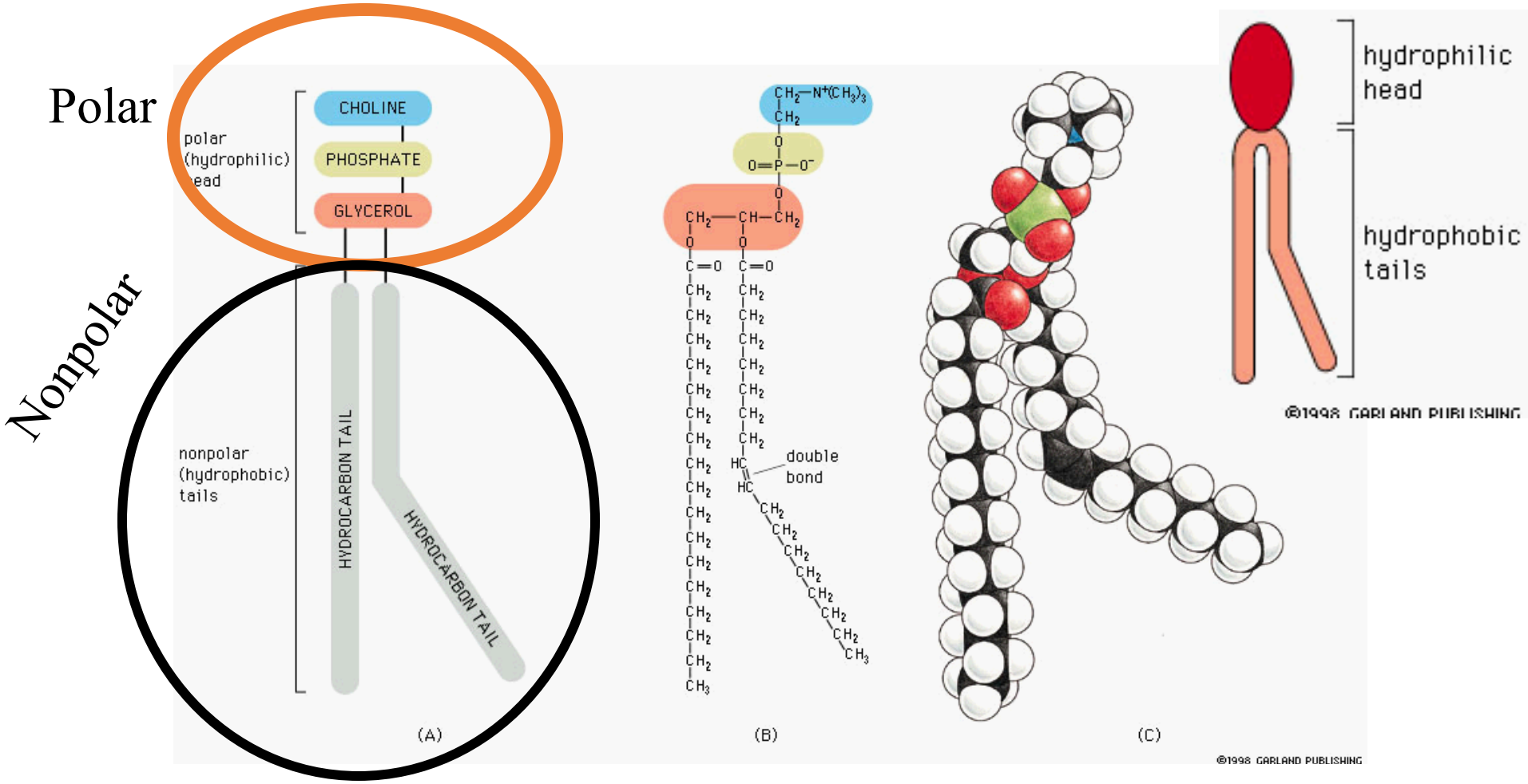
- **Protein 55%**
- **Phospholipids 25%**
- **Cholesterol 13%**
- **Other lipids 4%**
- **Carbohydrates 3%**



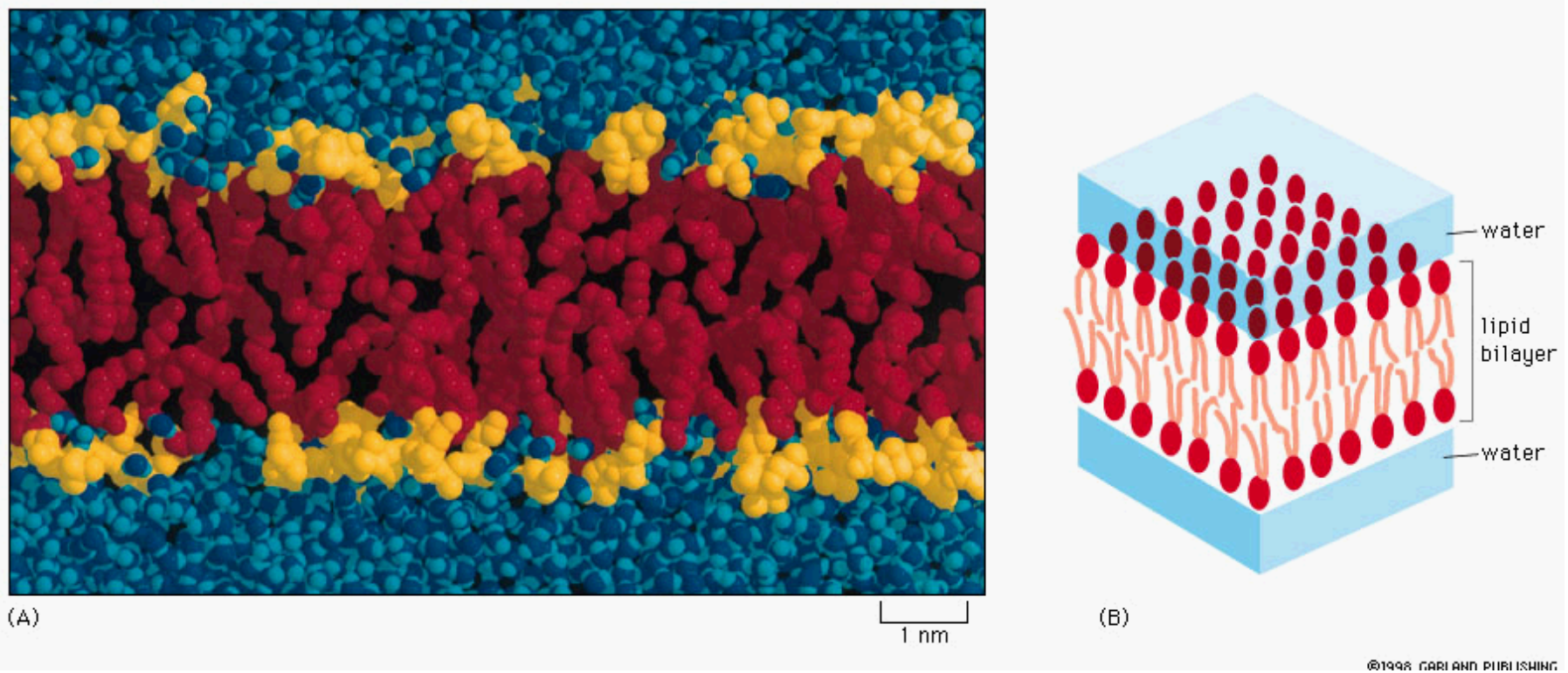
Lipids

- Amphipathic
- Spontaneously form lipid bilayers

Lipids are amphipathic



Lipids spontaneously form structures



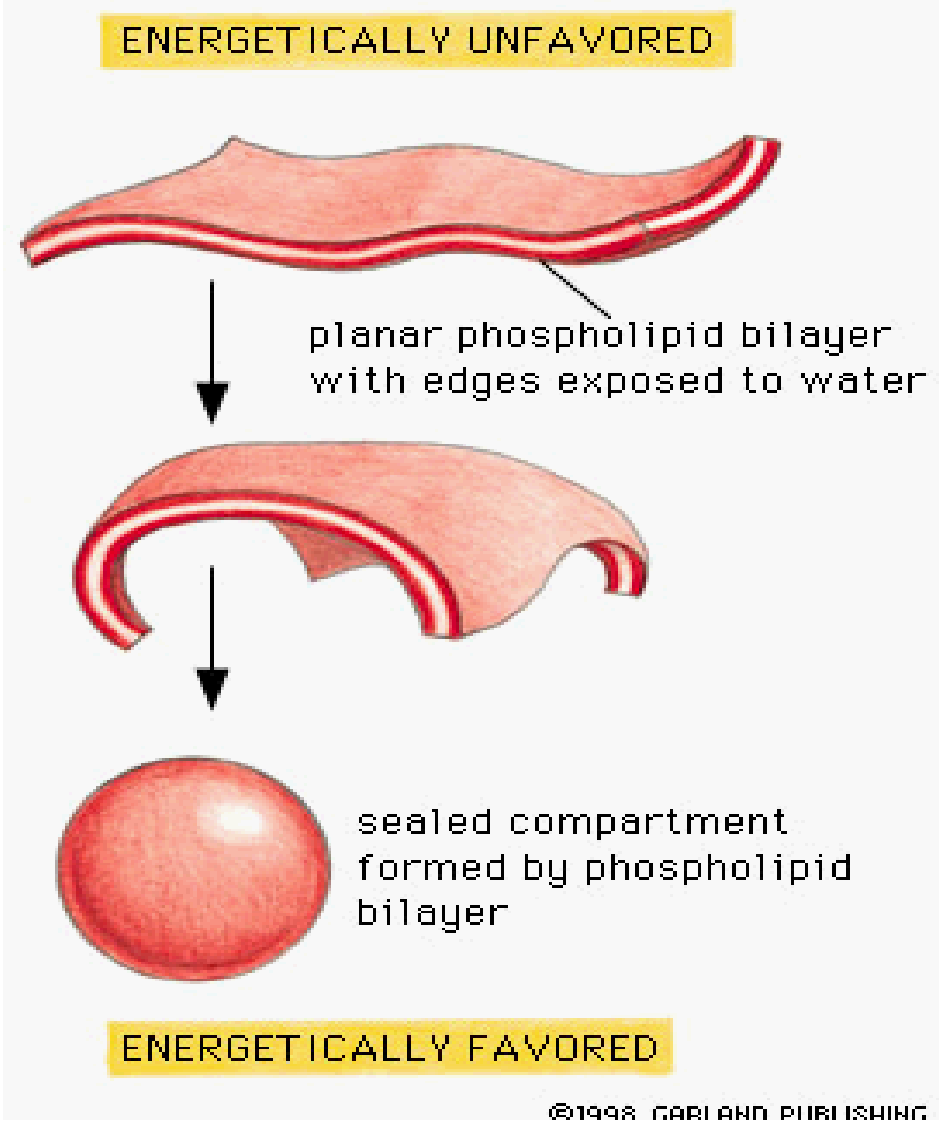
A lipid bilayer is a stable, low energy structure
Self sealing structure/eliminate free edge

What drives this structured association?

Exclusion of Lipids from Water… not lipid association

Lipid bilayers will form closed structures

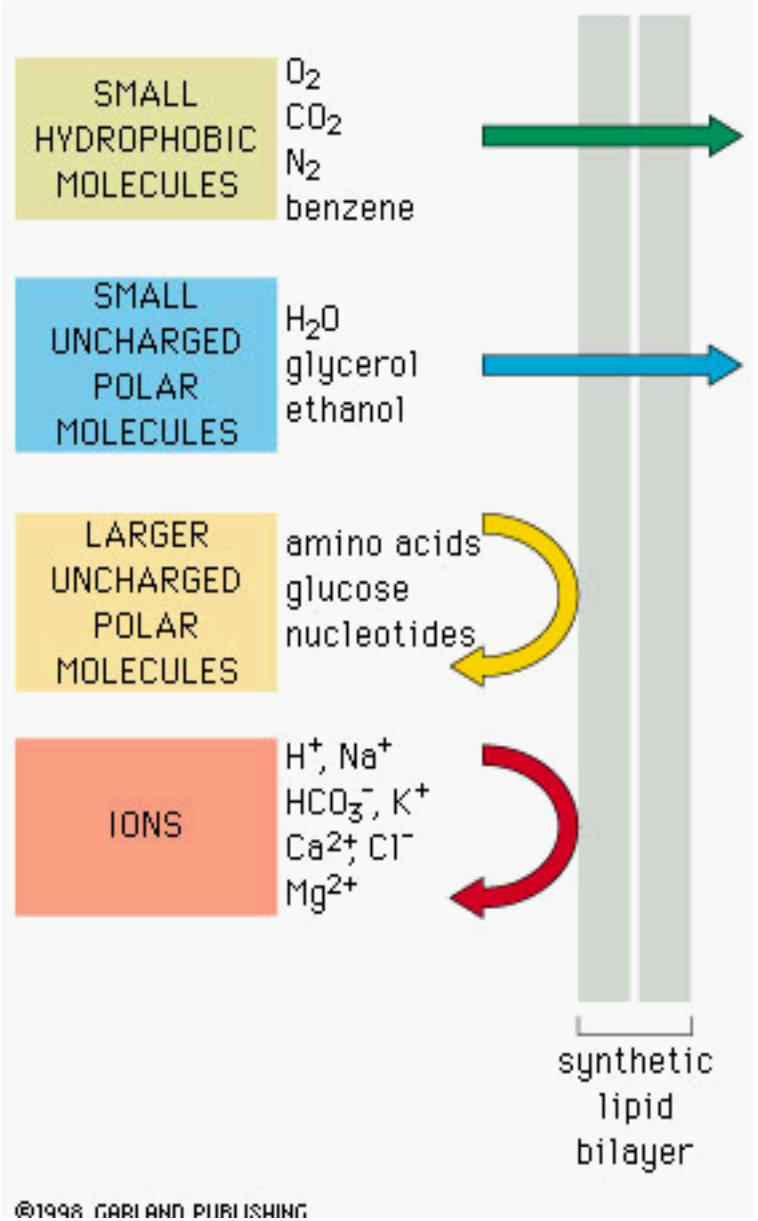
- Compartments
- Self seal if disrupted



Lipids are effective barriers to some compounds

- Hydrophobic compounds can reach equilibrium quickly
- "Unfavored" compounds can be brought across by transport proteins

Need for .....Transport Mechanisms

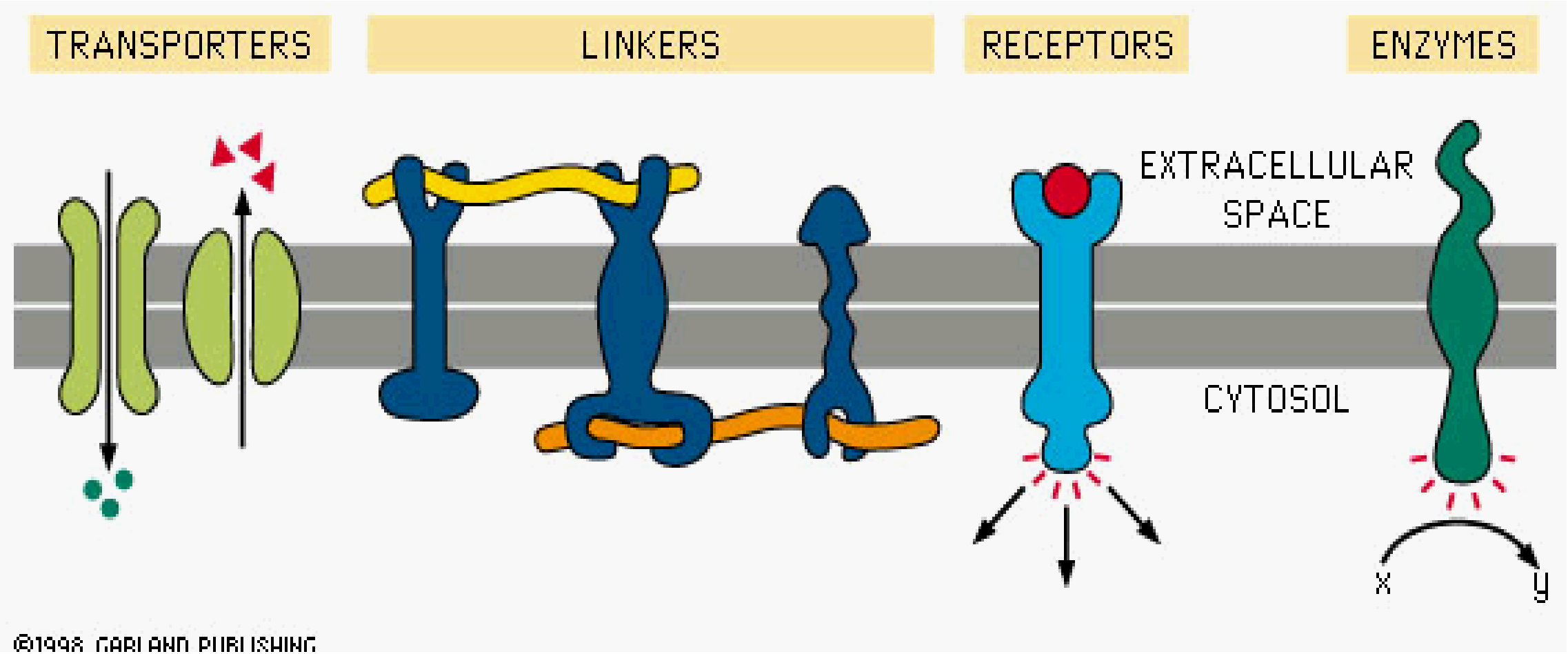


Proteins in Membrane Bilayer

Types:

- Integral - Transmembrane:
  - ionic channel
  - ionic pump
  - carrier
  - controller (G protein)

Integral proteins



Functions of the integral proteins :

1.making transporters and channels for small molelcules and ions;

2.acting as enzymes for the active transport of materials into the cell against a gradient;

3.acting as receptor sites for hormones to enter into the cell;

4.acting as structural supports inside the cell attaching to cytoskeleton structures, which hold organelles in place in the cytoplasm;

Proteins in Membrane Bilayer

Types:

- Peripheral – located mainly at the inside of membrane surface:
  - enzymes, controllers

Peripheral proteins

Peripheral membrane proteins are those membrane proteins that lie on the surface of the cell membrane.

These proteins are attached on either side of the lipid bilayer or may be attached with integral protein, but do not penetrate through the membrane.

The interaction of peripheral membrane proteins is facilitated by both covalent and non-covalent interactions.

However, their interaction with lipid is weaker than that of integral proteins.

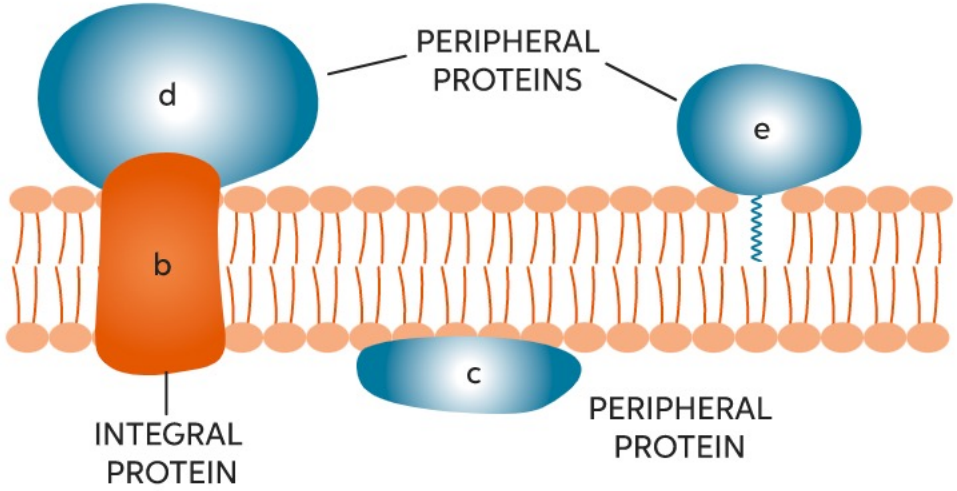
Peripheral proteins get dissociated when the cell membrane is treated with polar solvents.

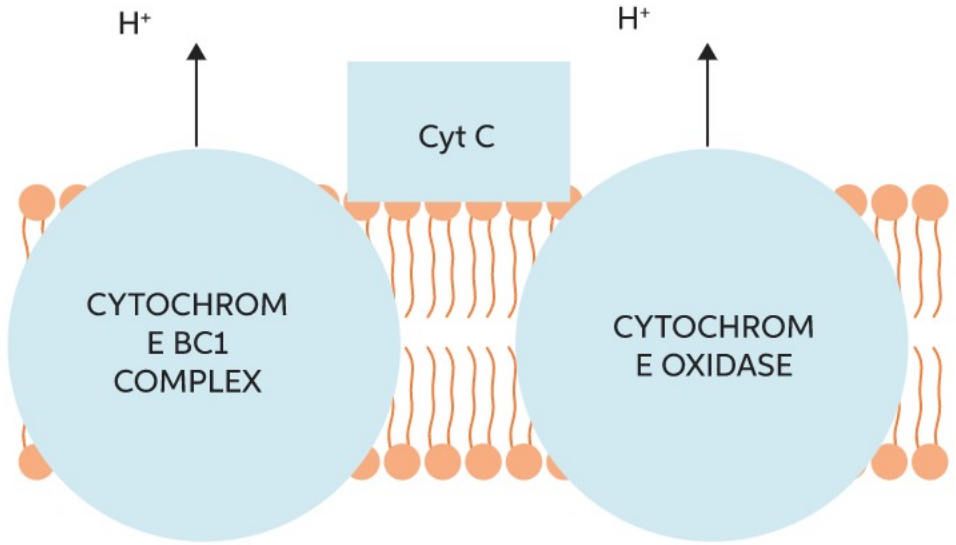
Peripheral proteins

Example: Proteins of electron transport chain-like cytochrome-c.

FUNCTIONS:

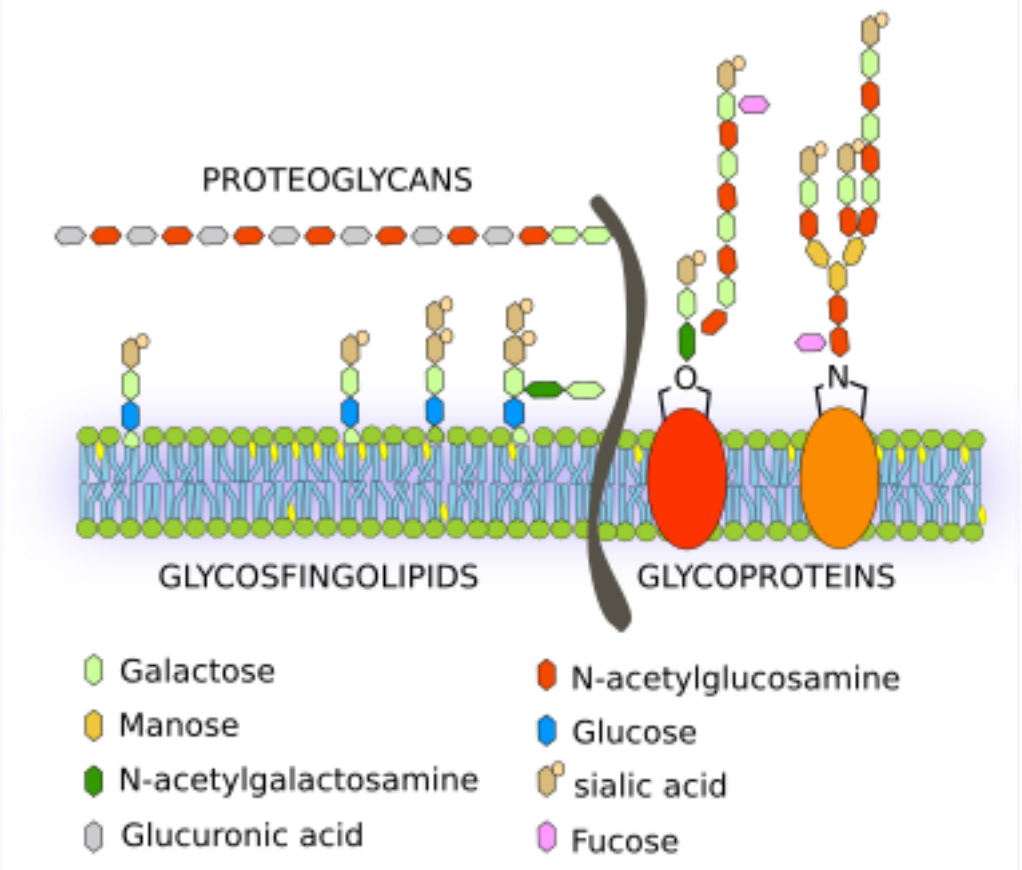
- Peripheral proteins exclusively act as enzymes.
- They also help in regulating the transport of substances through the cell membrane.

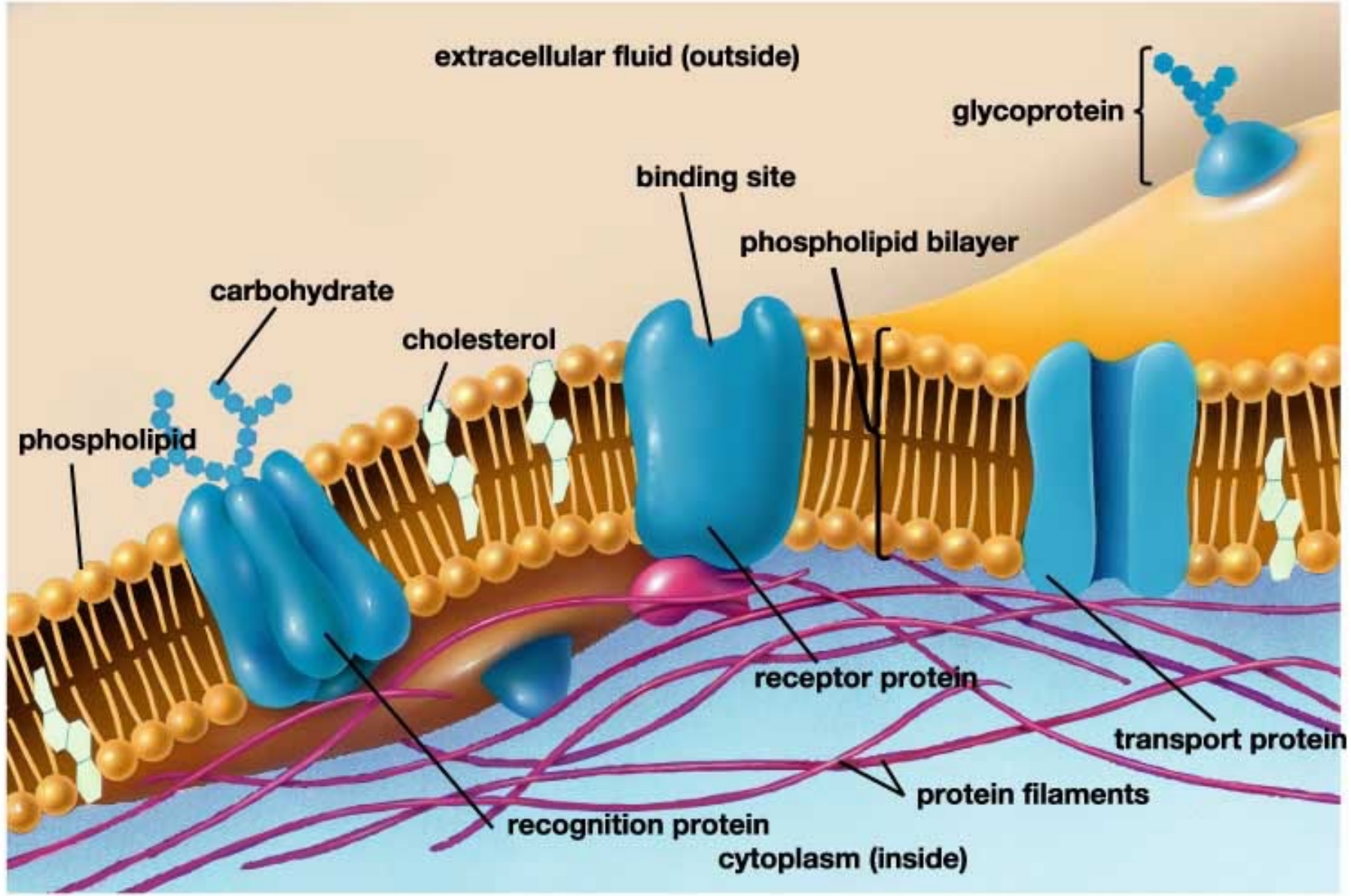




Membrane Carbohydrates:

- Small amounts
- located at the extracellular surface.
- in combination with membrane proteins or lipids
  - glycoproteins or glycolipids.
- Functions:
  - Negatively charged, let the cell to repel negative objects
  - Attach cells one to another
  - Acts as receptor substance for binding hormone such as insulin
  - Participate in immune reaction as antigen

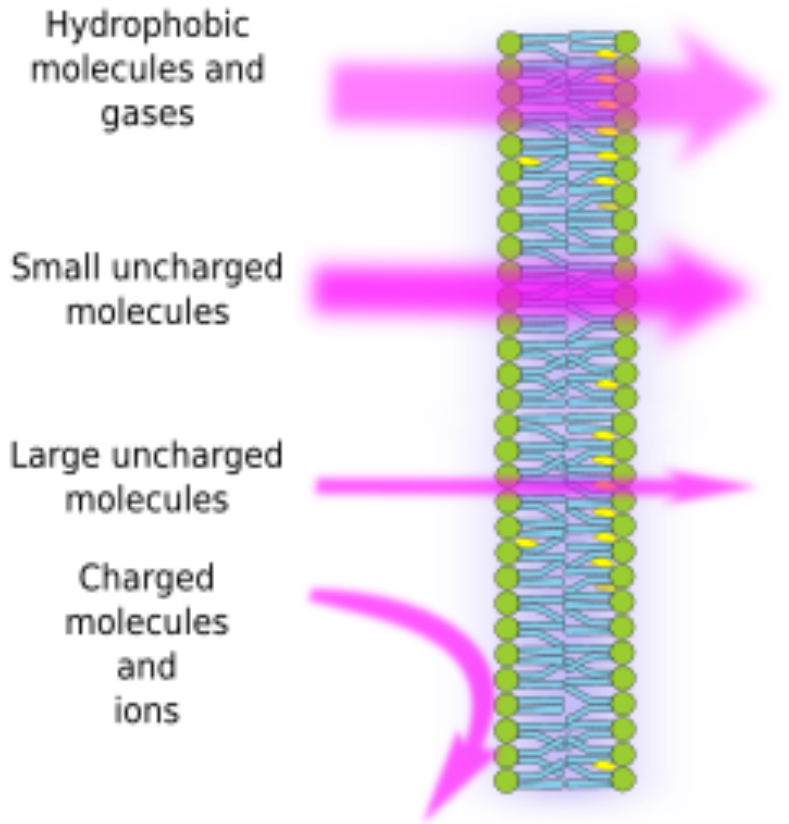



extracellular fluid (outside)
glycoprotein
binding site
phospholipid bilayer
carbohydrate
cholesterol
phospholipid
receptor protein
transport protein
protein filaments
recognition protein
cytoplasm (inside)

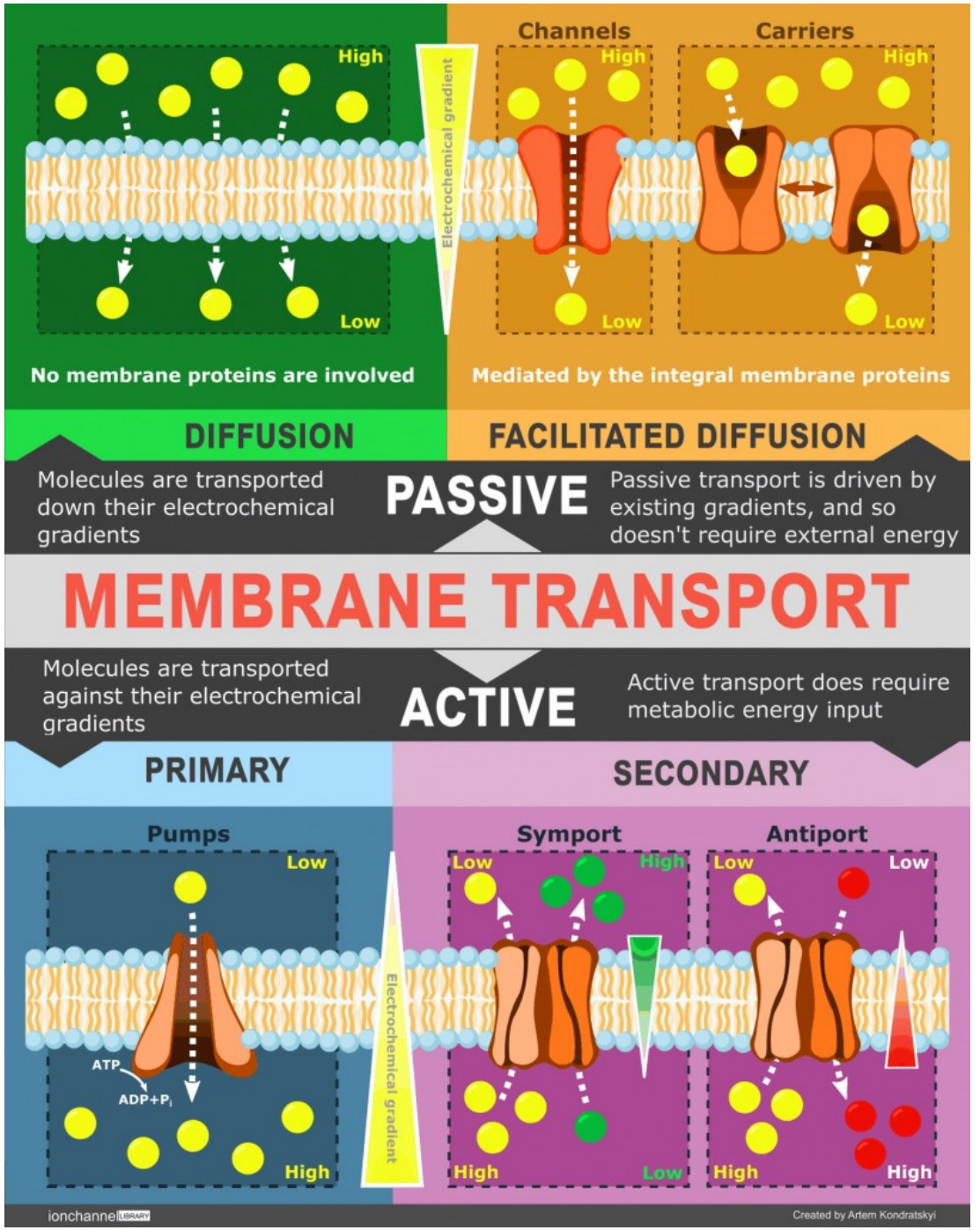
Transport Through the Cell Membrane

Categories of Transport Across the Plasma Membrane

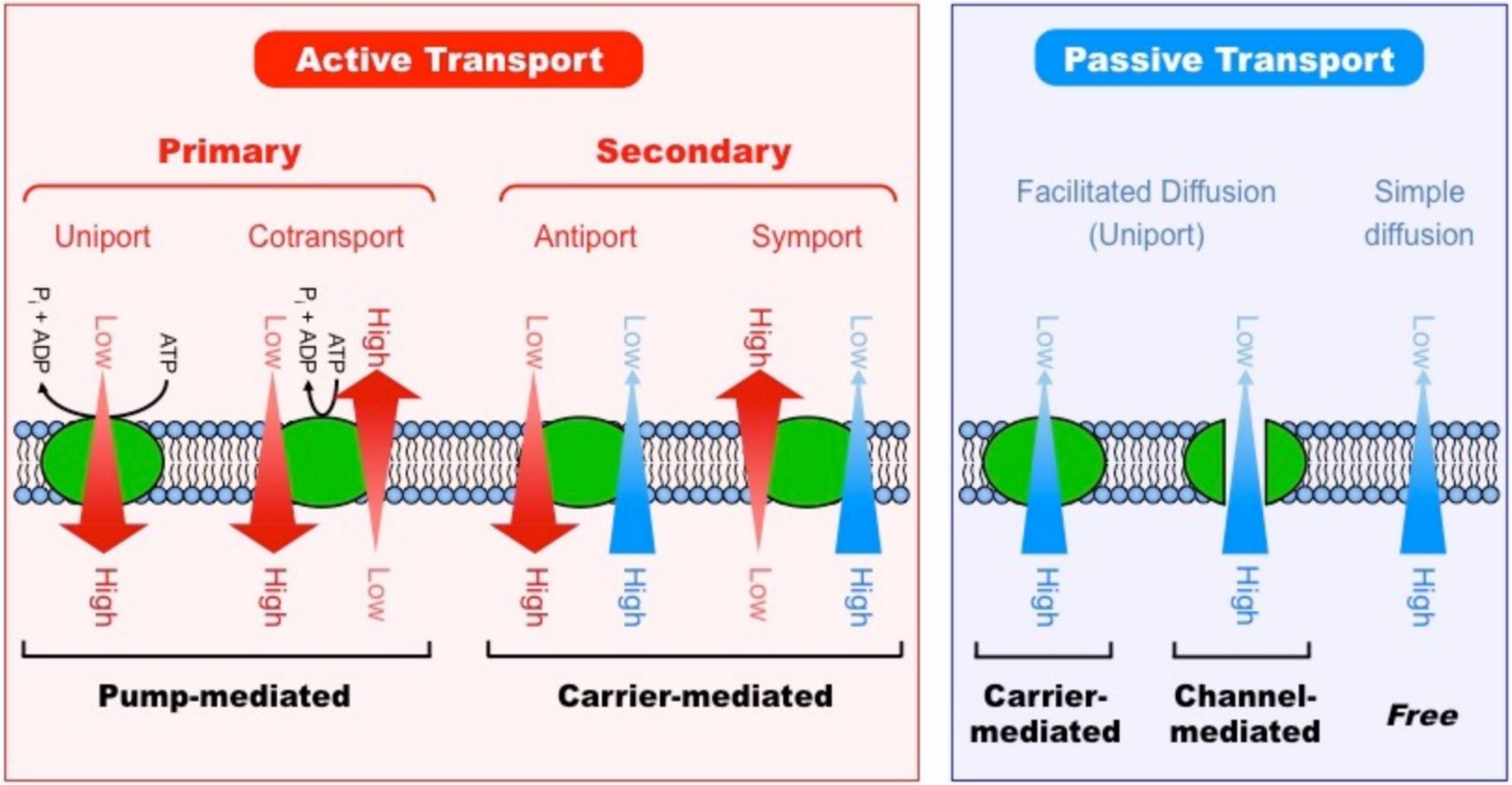
- Cell membrane is selectively permeable to some molecules and ions.
- Mechanisms to transport molecules and ions through the cell membrane:
  - Non-carrier mediated transport.
    - Simple Diffusion.
  - Facilitated Diffusion:
    - Via Carrier
    - Channel
      - Voltage, Chemical and Mechanical gating channel
  - Active Transport



Categories of Transport Across the Plasma Membrane



Categories of Transport Across the Plasma Membrane

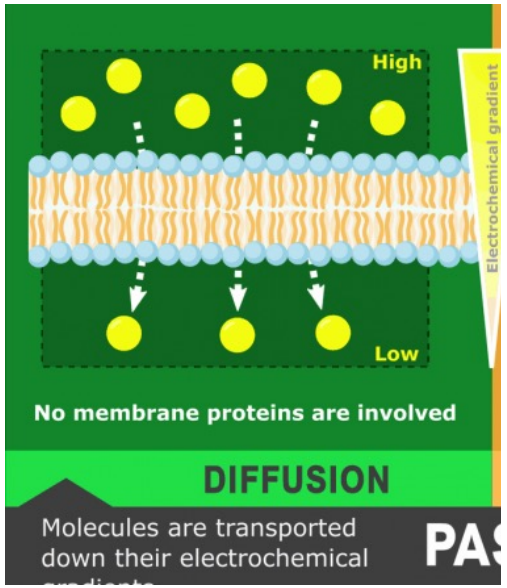


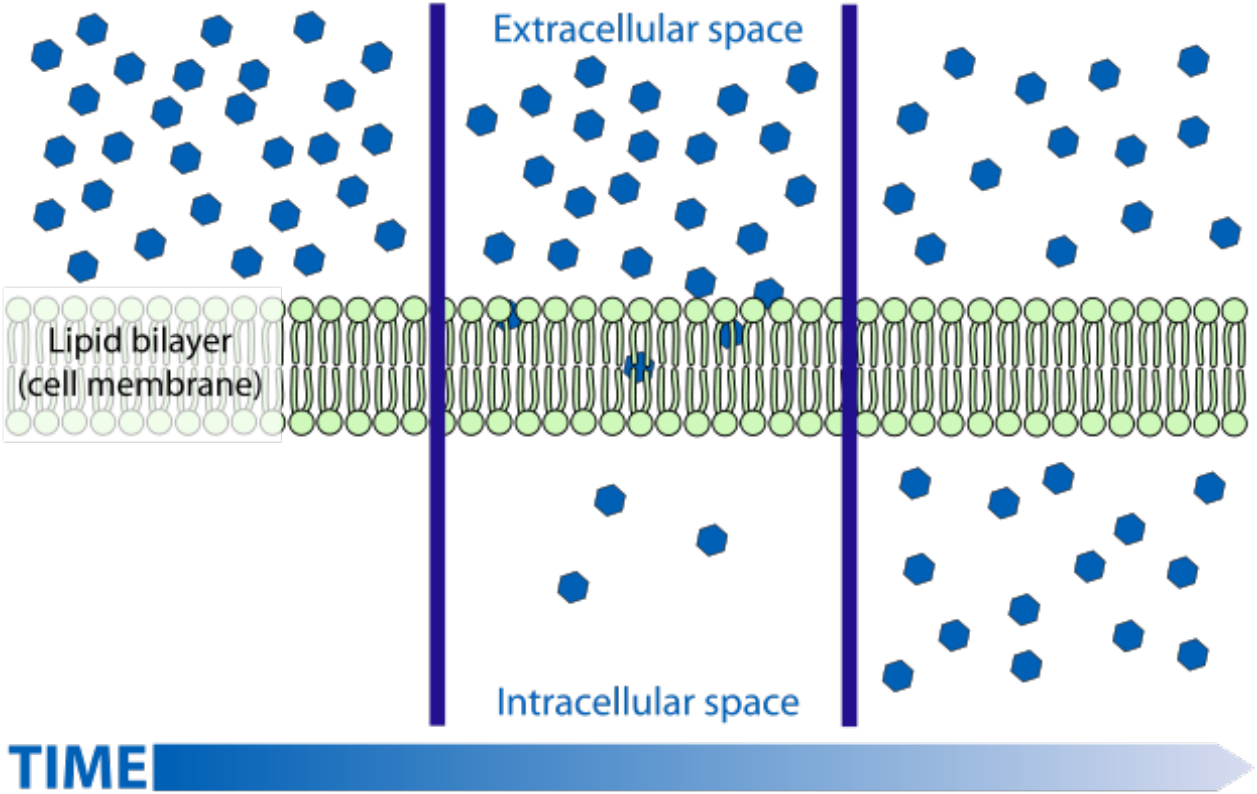
Categories of Transport Across the Plasma Membrane

- May also be categorized by their energy requirements:
  - Passive transport:
    - Net movement down a concentration gradient
    - does not need ATP
  - Active transport:
    - Net movement against a concentration gradient
    - needs ATP

1. Simple Diffusion

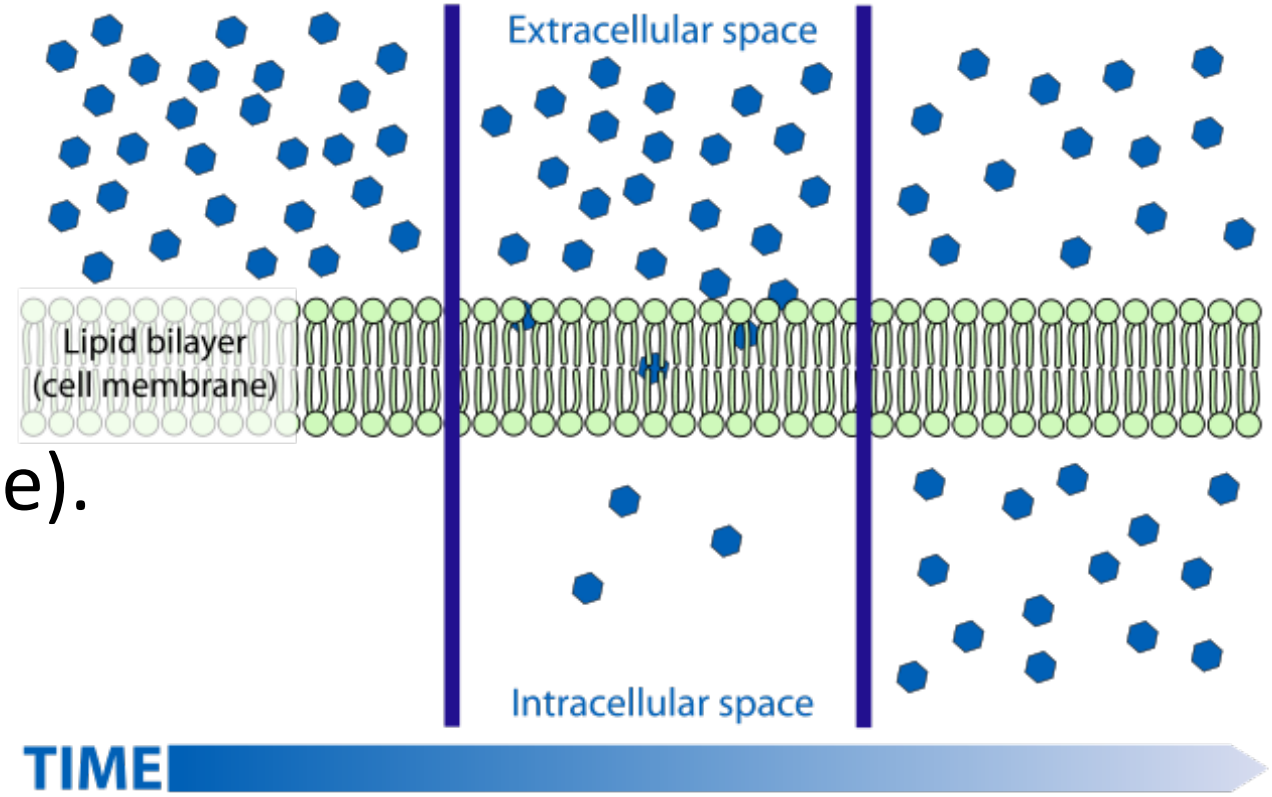
- Molecules/ions are in constant state of random motion due to their thermal energy.
- Simple diffusion occurs
  - whenever there is a concentration difference across the membrane
  - the membrane is permeable to the diffusing substance.





Simple Diffusion Through Plasma Membrane

- Cell membrane is permeable to:
  - Non-polar molecules (0_2).
  - Lipid soluble molecules (steroids).
  - Small polar covalent bonds ($C0_2$).
  - H_20 (small size, lack charge).
- Cell membrane **impermeable** to:
  - Large polar molecules (glucose).
  - Charged inorganic ions (Na^+).

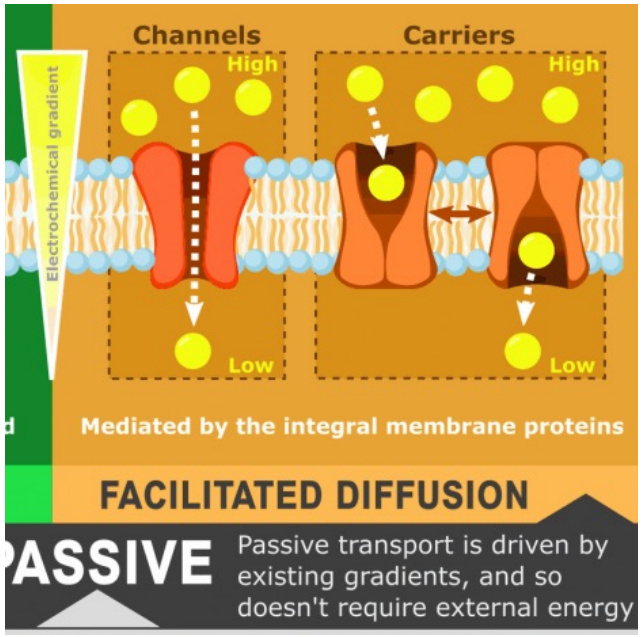


Rate of Diffusion

Temperature	• Higher temperature → Diffuse Faster
Surface Area	• Larger surface → Diffuse Faster
Concentration Gradient	• Higher Gradient → Diffuse faster
Size of Particles	• Smaller particles → Diffuse faster
Diffusion Medium	• Solid → Slowest • Liquid → Faster • Gas → Fastest

Video: Membrane Transports

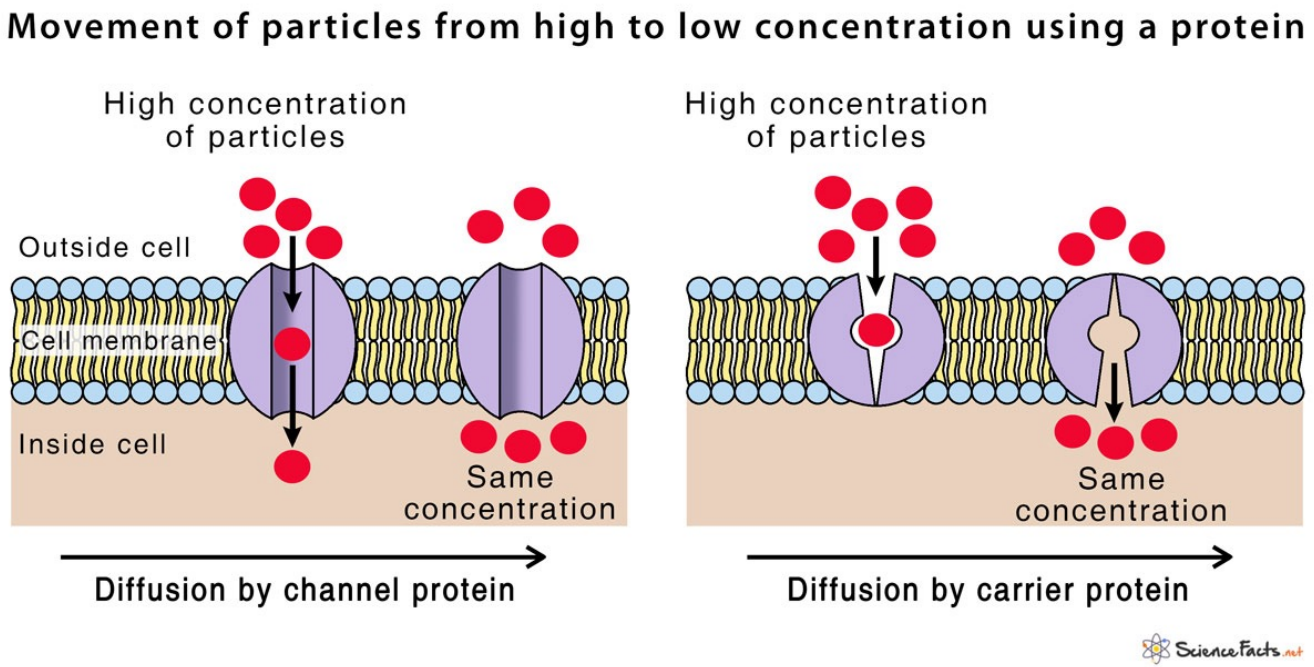
2 Facilitated Diffusion



- Definition:
  - the diffusion of lipid insoluble or water soluble substance
  - across the membrane
  - down their concentration gradients by aid of membrane proteins
    - (carrier or channel)
  - Substances: K^+, Na^+, Ca^{2+}, glucose, amino acid, urea etc.

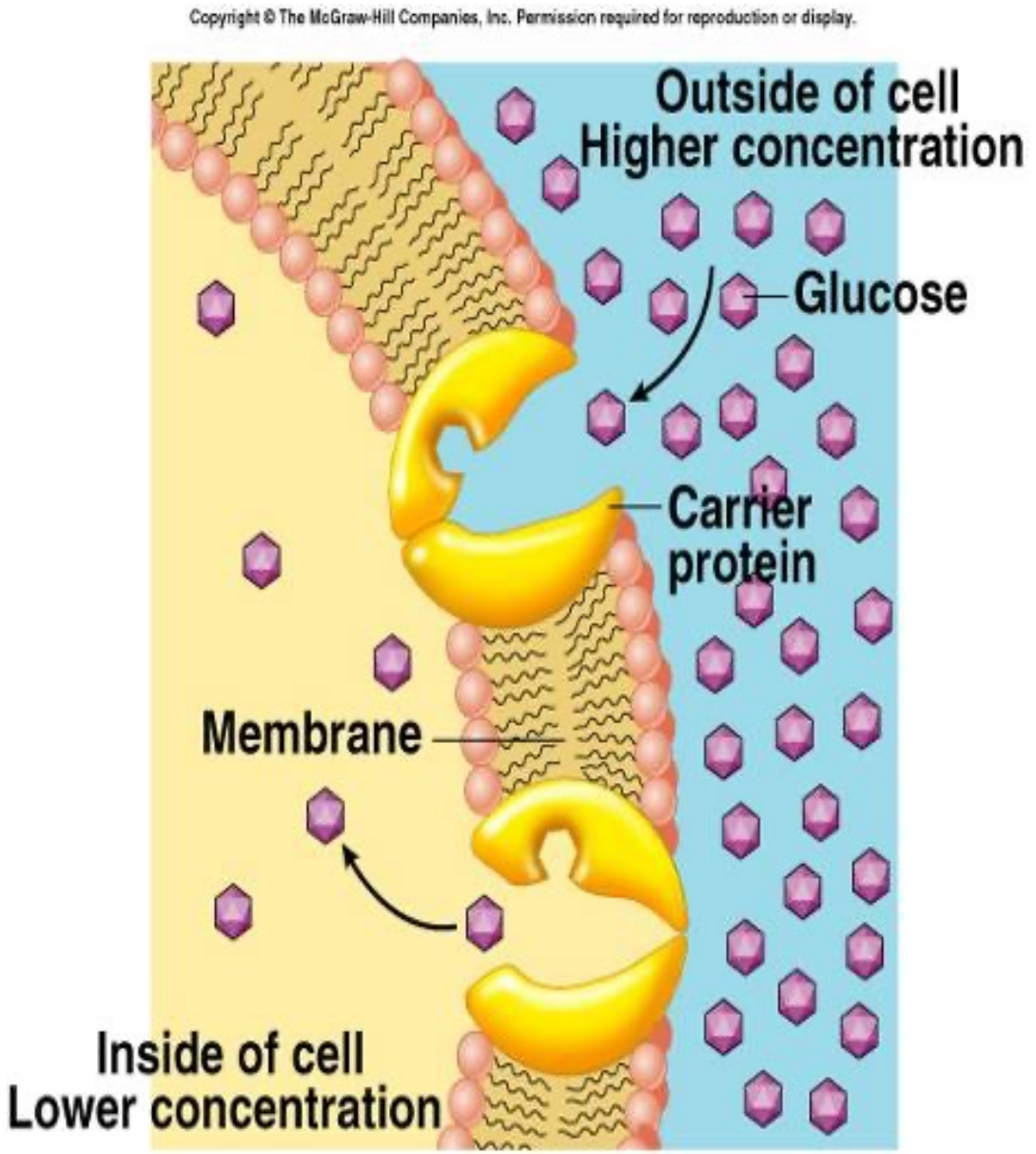
2 Facilitated Diffusion

- 2.1 Facilitated diffusion via carrier
- 2.2 Facilitated diffusion through channel
  - 2.2.1 Voltage-gated ion channel
  - 2.2.2 Chemically-gated ion channel
  - 2.2.3 Mechanically-gated ion channel
  - 2.2.4 Water channel



2.1 Facilitated Diffusion via carrier

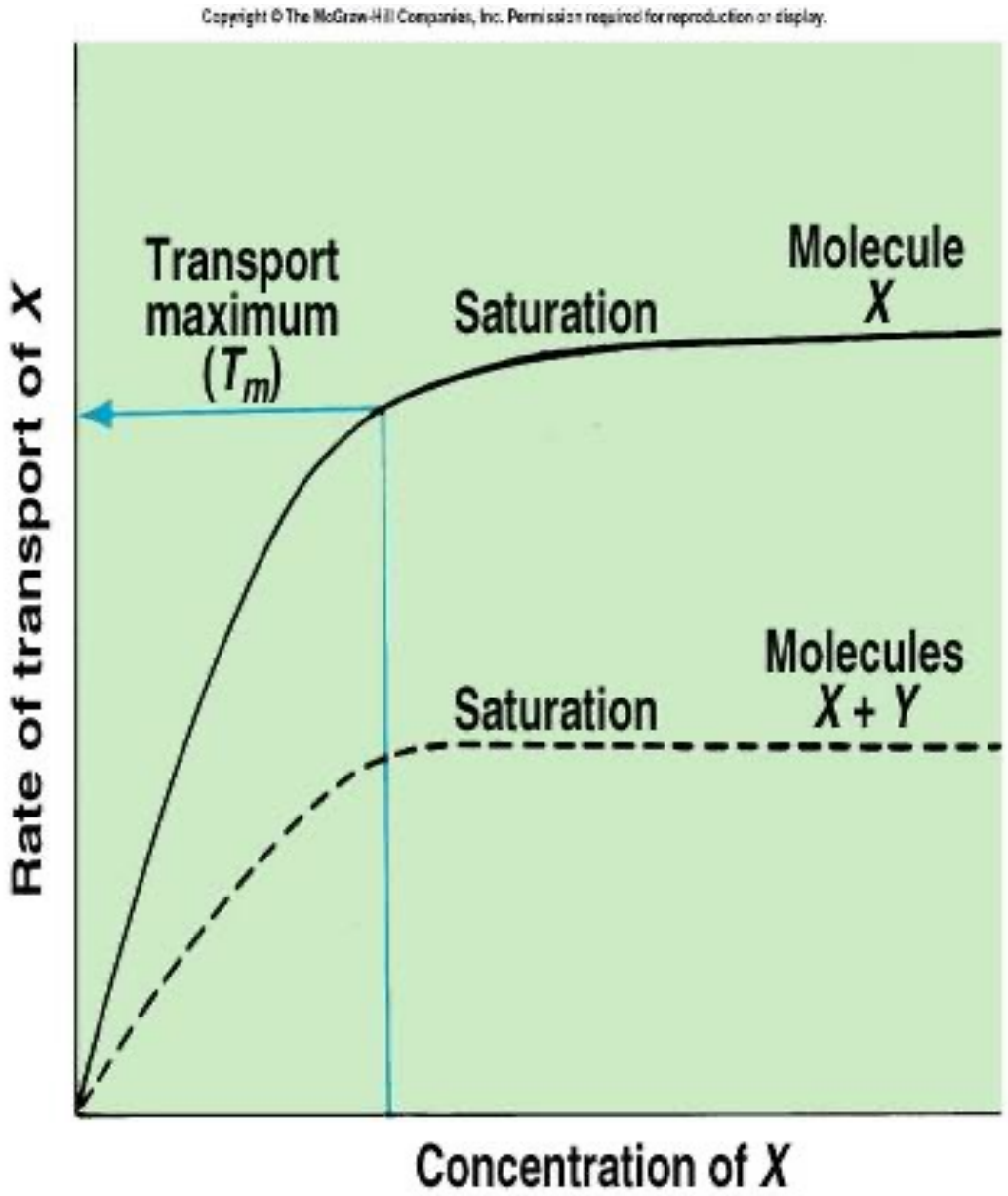
- Concept: Diffusion carried out by carrier protein
- Substance: glucose, amino acid
- Mechanism: a “ferry” or “shuttle” process



2.1 Facilitated Diffusion via carrier

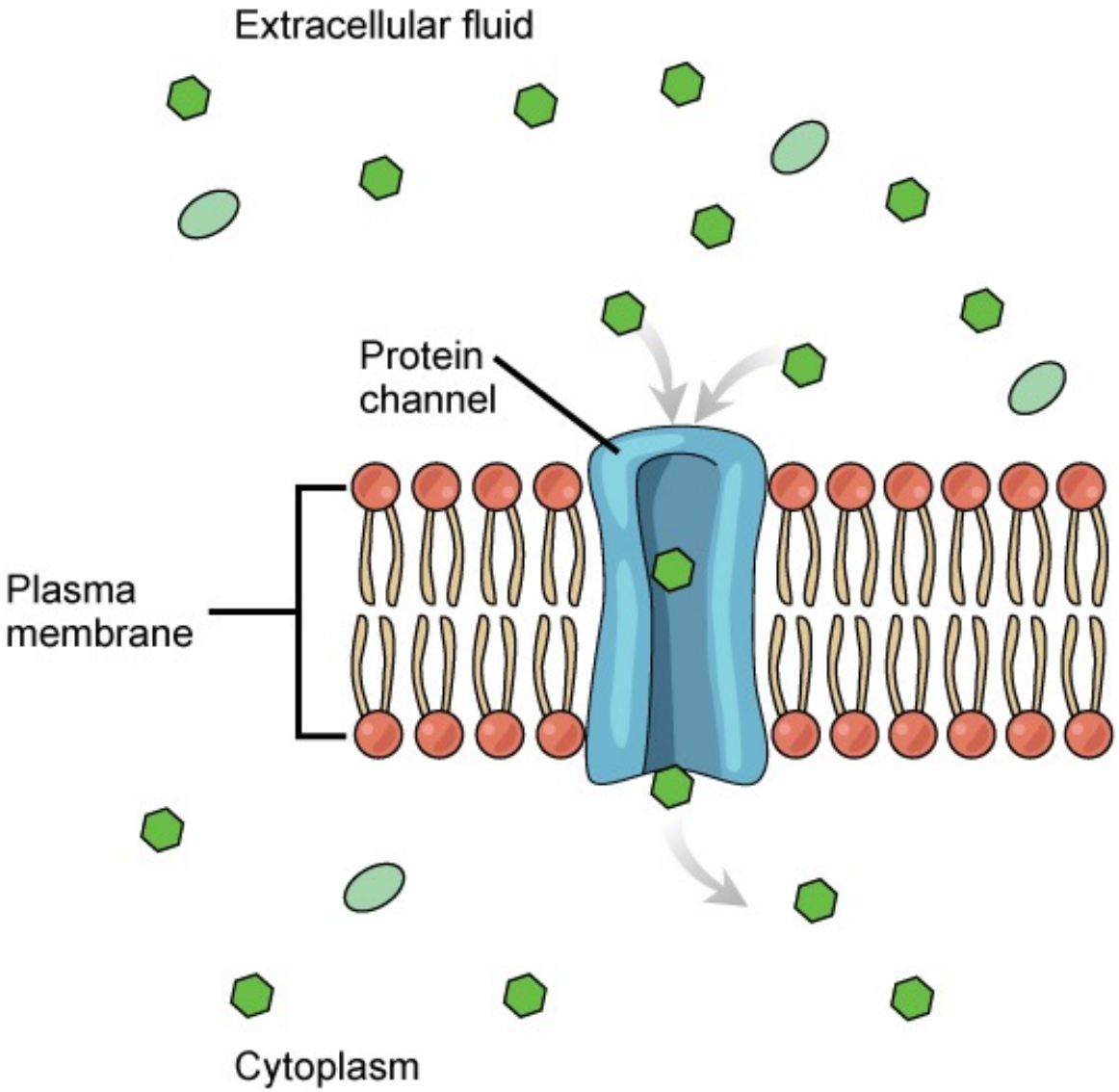
Characteristics of carrier mediated diffusi

- Down concentration Gradient
- Chemical Specificity:
  - Carrier interact with specific molecule only.
- Competitive inhibition:
  - Molecules with similar chemical structures compete for carrier site.
- Saturation:
  - V_{max} (transport maximum):
    - Carrier sites have become saturatec



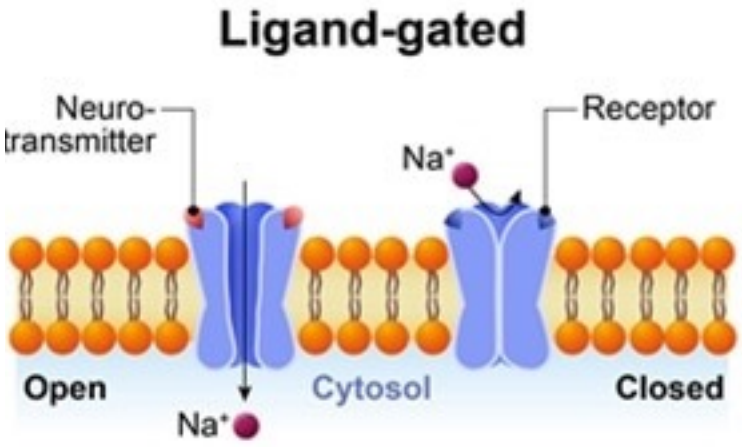
2.2 Facilitated diffusion through channels

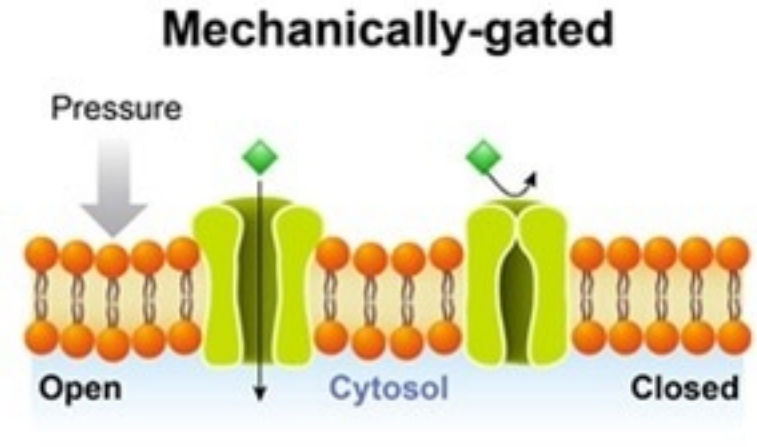
- Definition
  - Some transport proteins
  - have watery spaces all the way through the molecule
  - allow free movement of certain ions or molecules. They are called **channel proteins.**
- Diffusion carried out by protein channel is termed channel mediated diffusion.

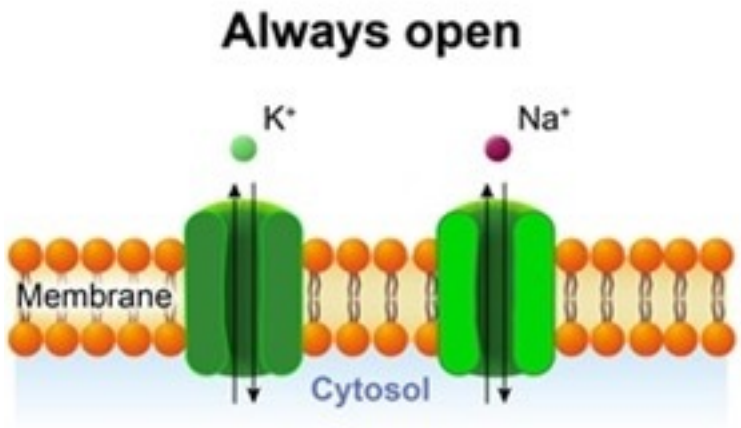


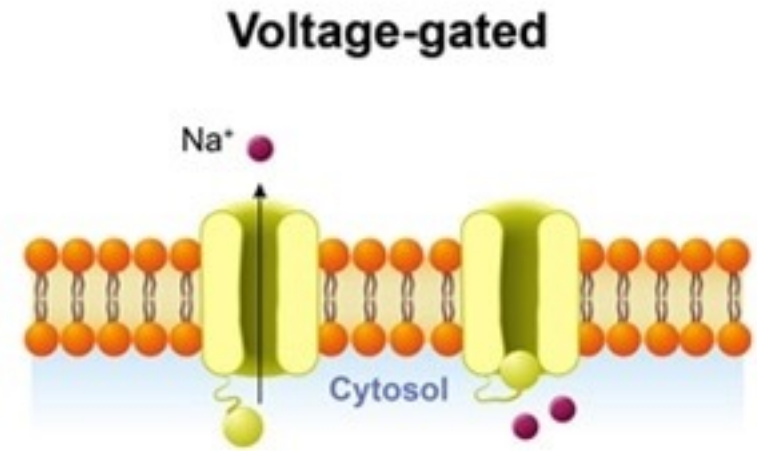
2.2 Facilitated diffusion through channels

- Two important characteristics of the channels:
  - selectively permeable to specific substances
  - opened or closed by gates



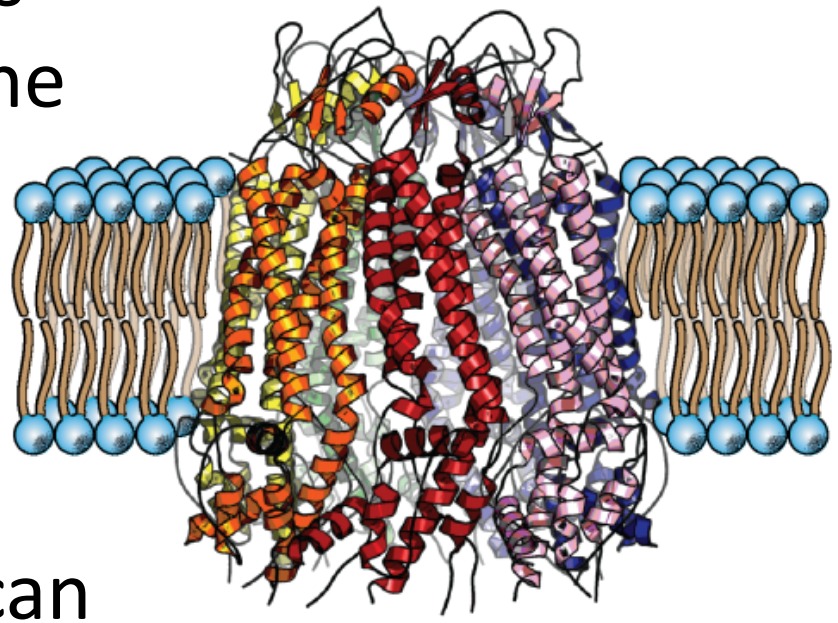


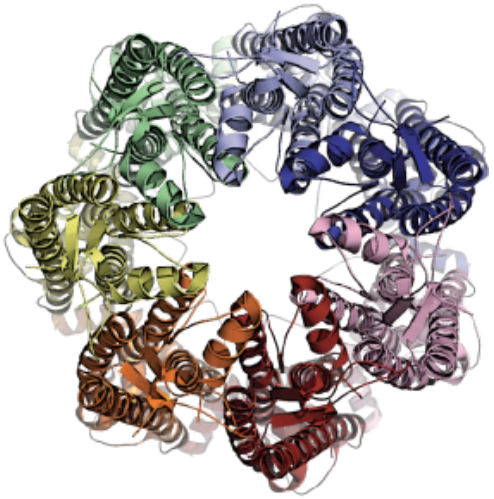




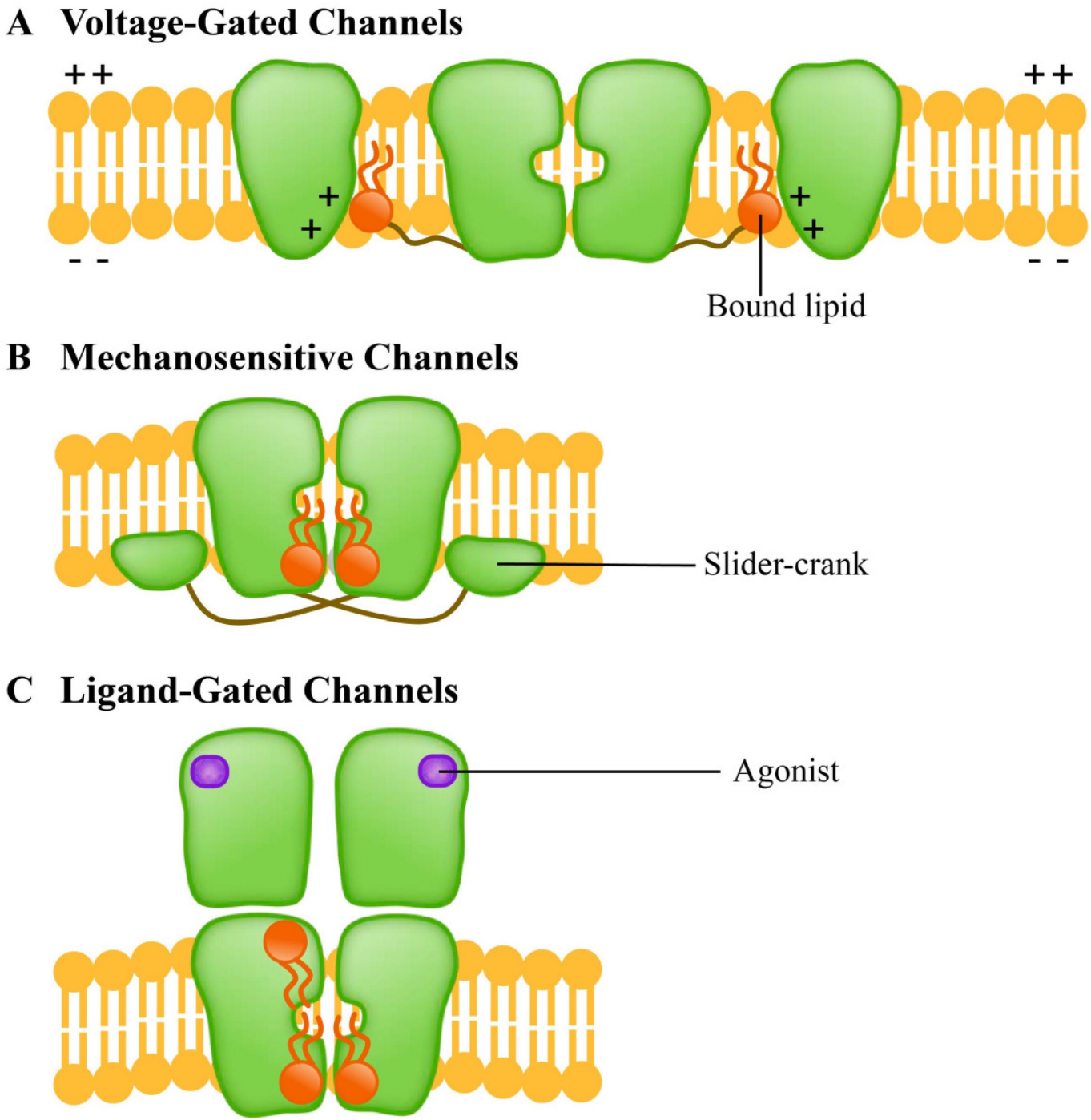
2.2 Facilitated diffusion through channels

- Channel: aqueous pathways through the interstices of the protein molecules.
- Each channel molecule is a protein complex.
  - through which the ions can diffuse across the membrane.





- According to the factors that alter the conformational change of the protein channel, the channels are divided into 3 types:
  - Voltage gated channel
  - Mechanically gated channel
  - Chemically gated channel

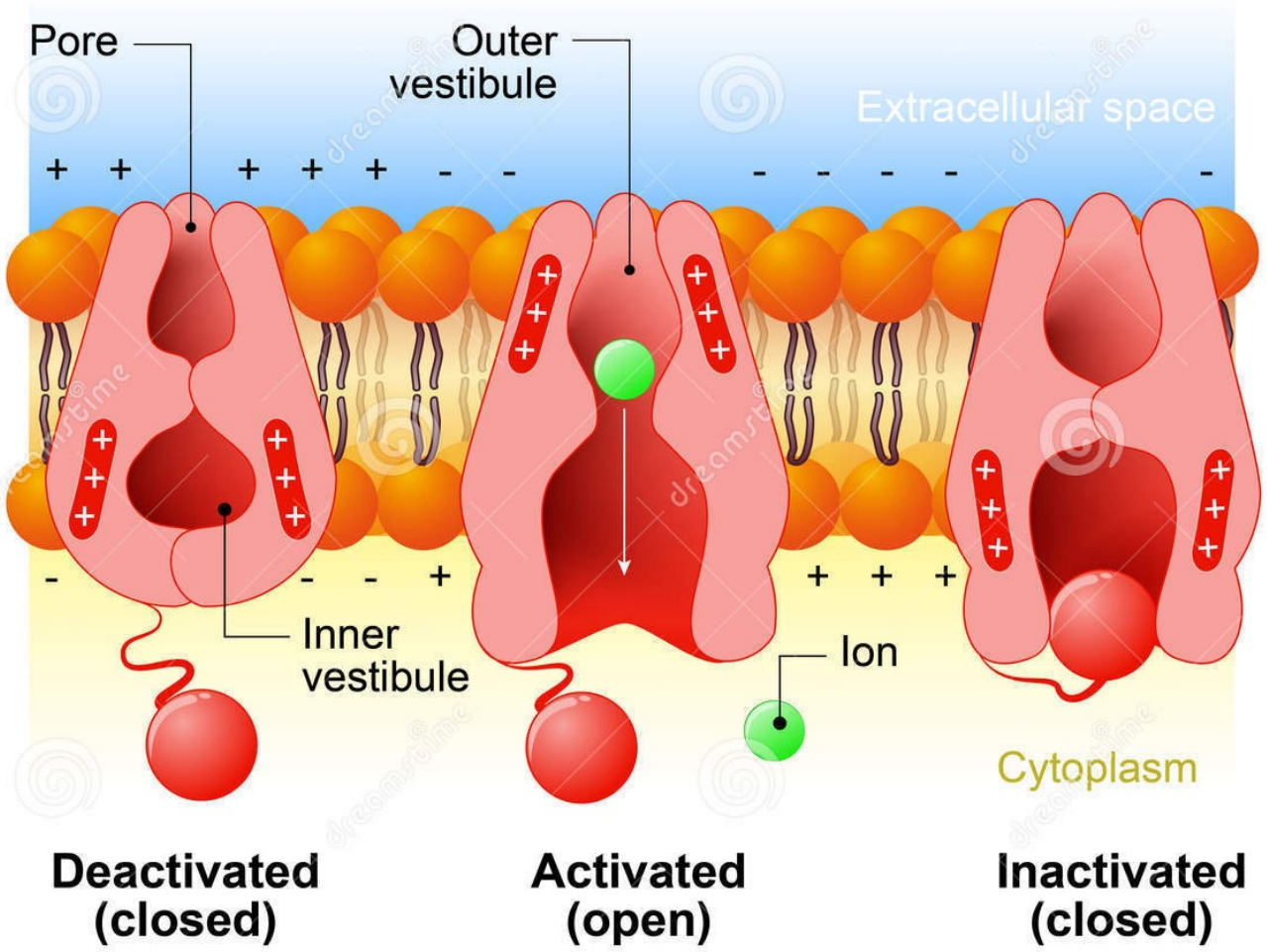


2. Facilitated Diffusion

- 2.1 Facilitated diffusion via carrier
- 2.2 Facilitated diffusion through channel
  - 2.2.1 Voltage-gated ion channel
  - 2.2.2 Chemically-gated ion channel
  - 2.2.3 Mechanically-gated ion channel
  - 2.2.4 Water channel

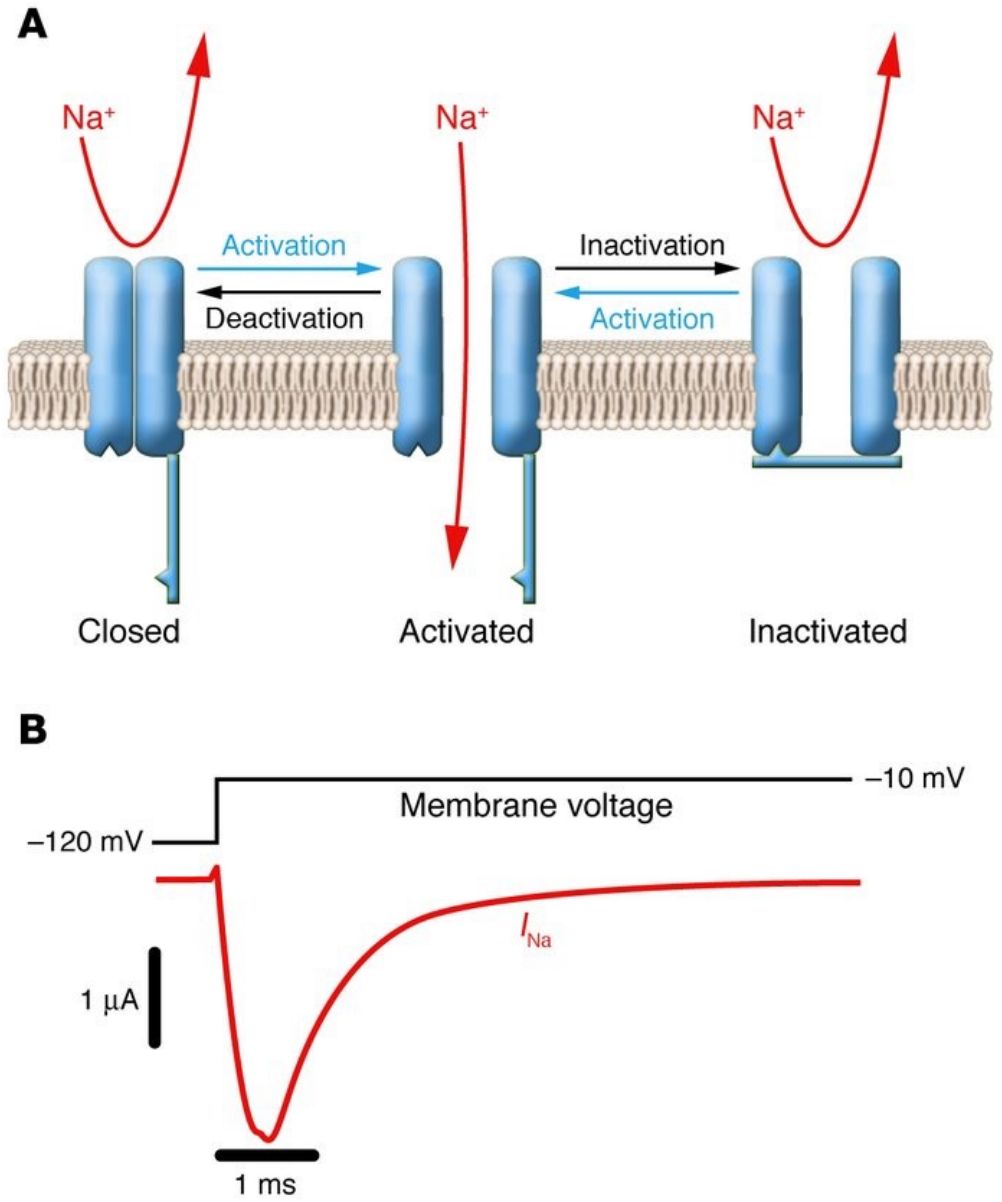
2.2.1 Voltage-gated Channels

- The molecular conformation of the gate responds to the electrical potential across the cell membrane

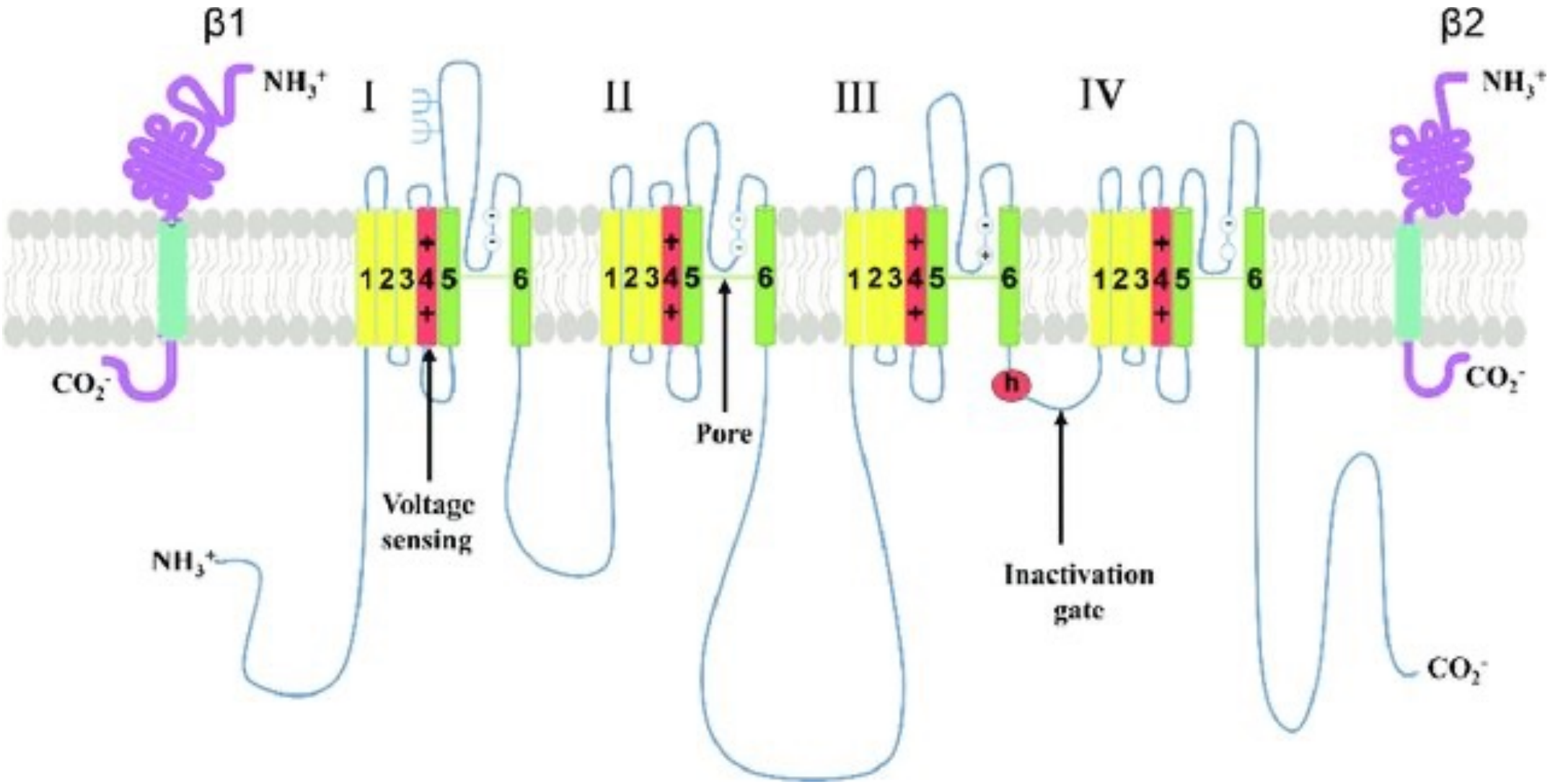


2.2.1 Example: Voltage-gated Na^+ Channels

- Many types
  - neurons, glia, heart, skeletal muscle
- Primary role is action potential initiation
- Multi-subunit channels (~300 kDa)
  - Skeletal Na^+ Channel: a_1 (260 kDa) and b_1 (36kDa)
  - Neuronal Na^+ Channel: a_1, b_1, b_2 (33 kDa)
  - gating/permeation machinery in a_1 subunits
- Three types of conformational states (close, open or active, inactive) - each controlled by membrane voltage



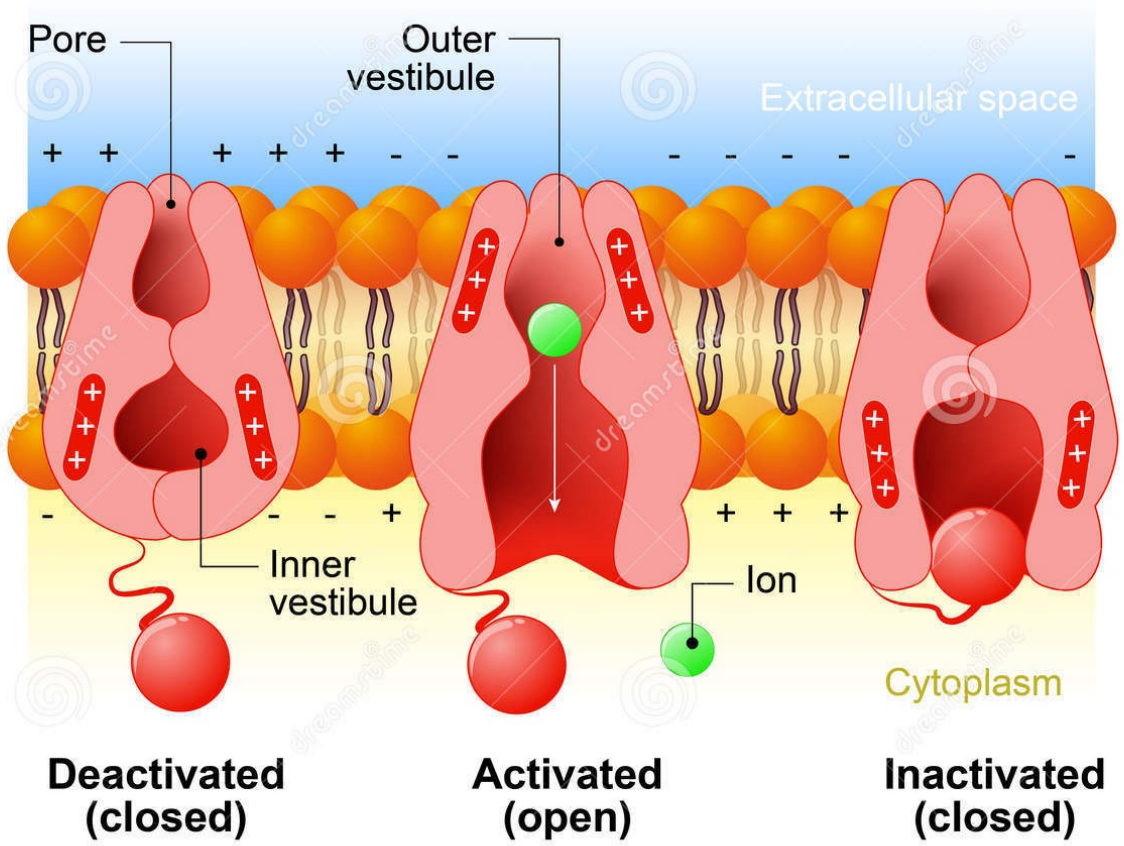
2.2.1 Example: Voltage-gated Na^+ Channels



2.2.1 Example: Voltage-gated Na^+ Channels

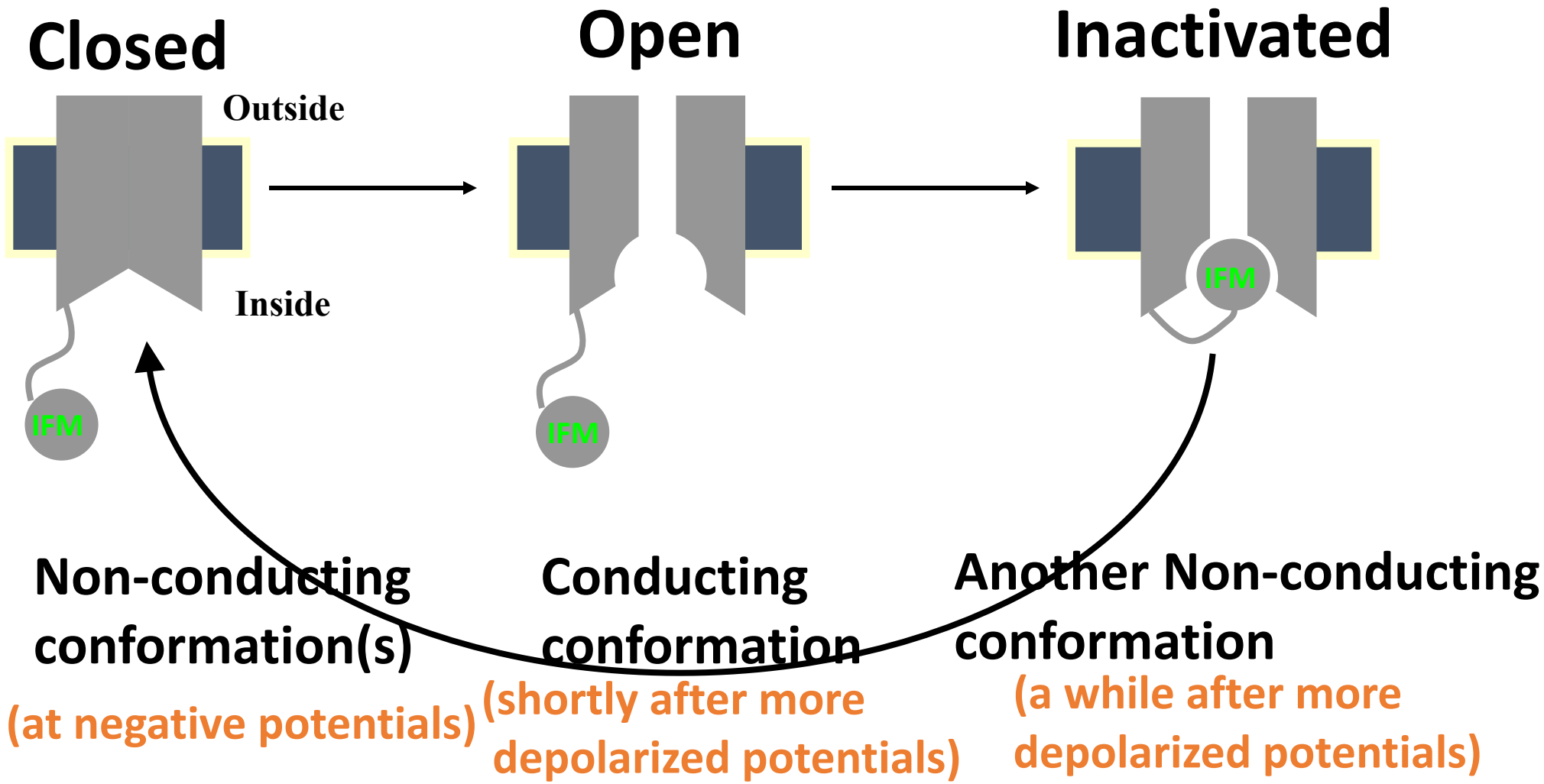
How these voltage-gated ion channels work

- movement of the voltage sensor generates a gating current
- S4 transmembrane segment may be voltage sensor
- pore formed by a nonhelical region between helix 5 and 6 (postulated to form b sheets)
- inactivation gate is in the cytoplasm



2.2.1 Example: Voltage-gated Na^+ Channels

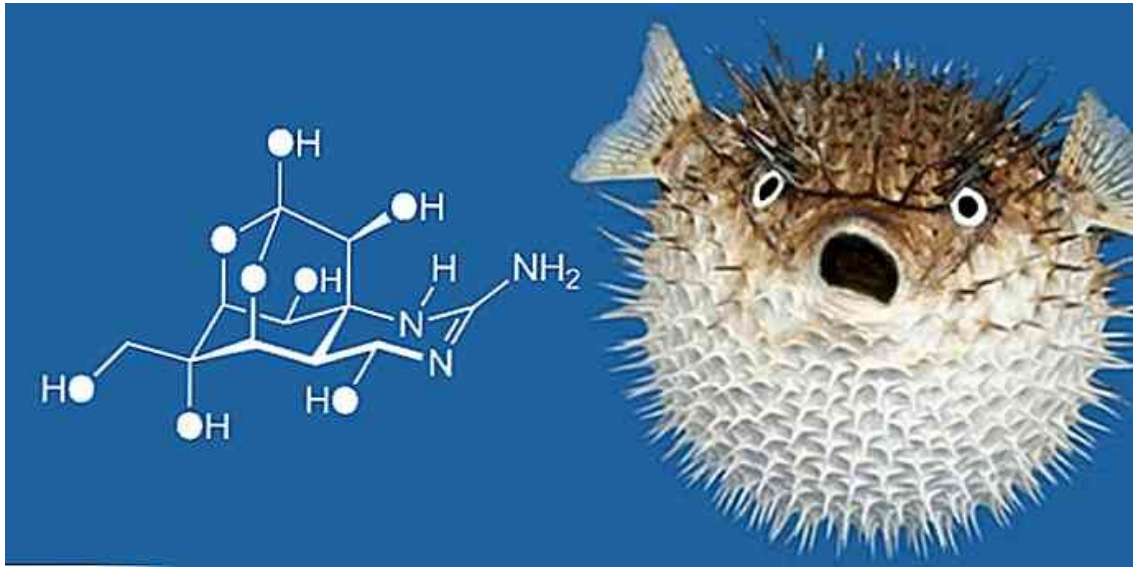
Na^+ Channel Conformations

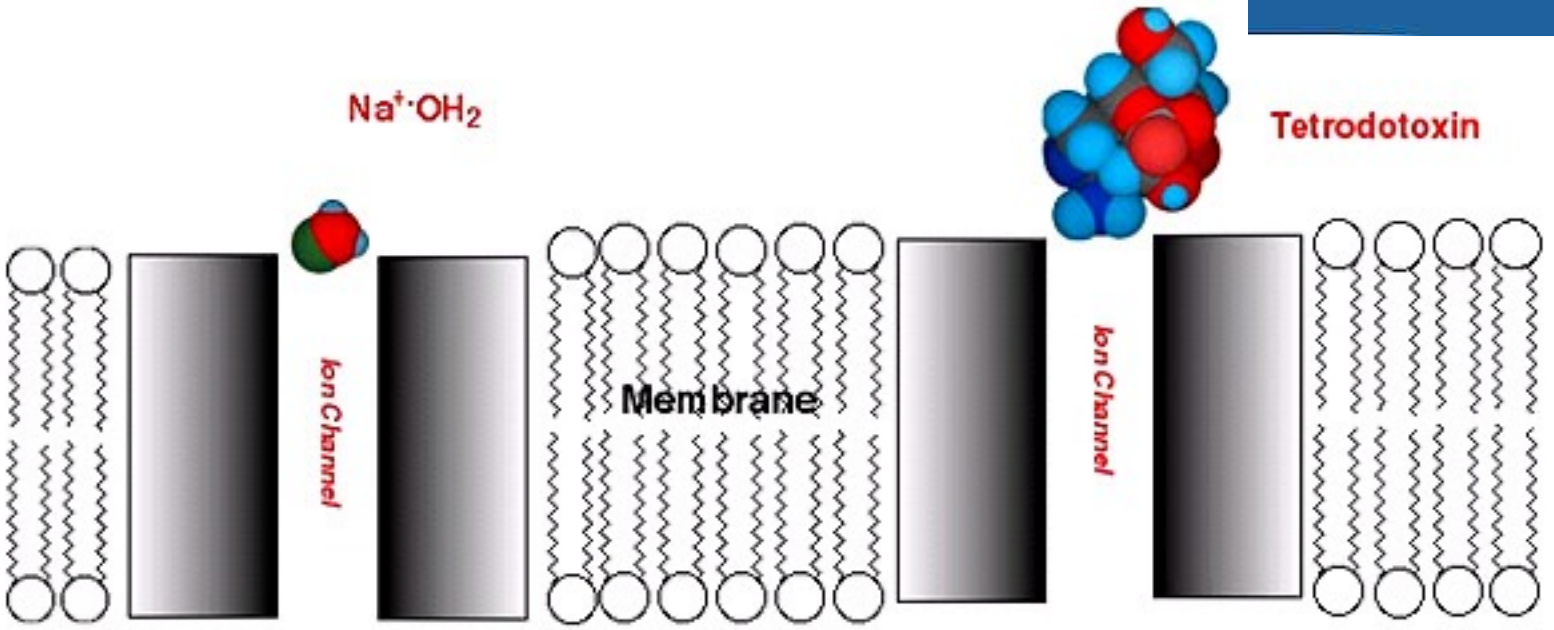


2.2.1 Example: Voltage-gated Na^+ Channels

Tetrodotoxin (TTX)

selectively blocks voltage-gated Na^+ channels

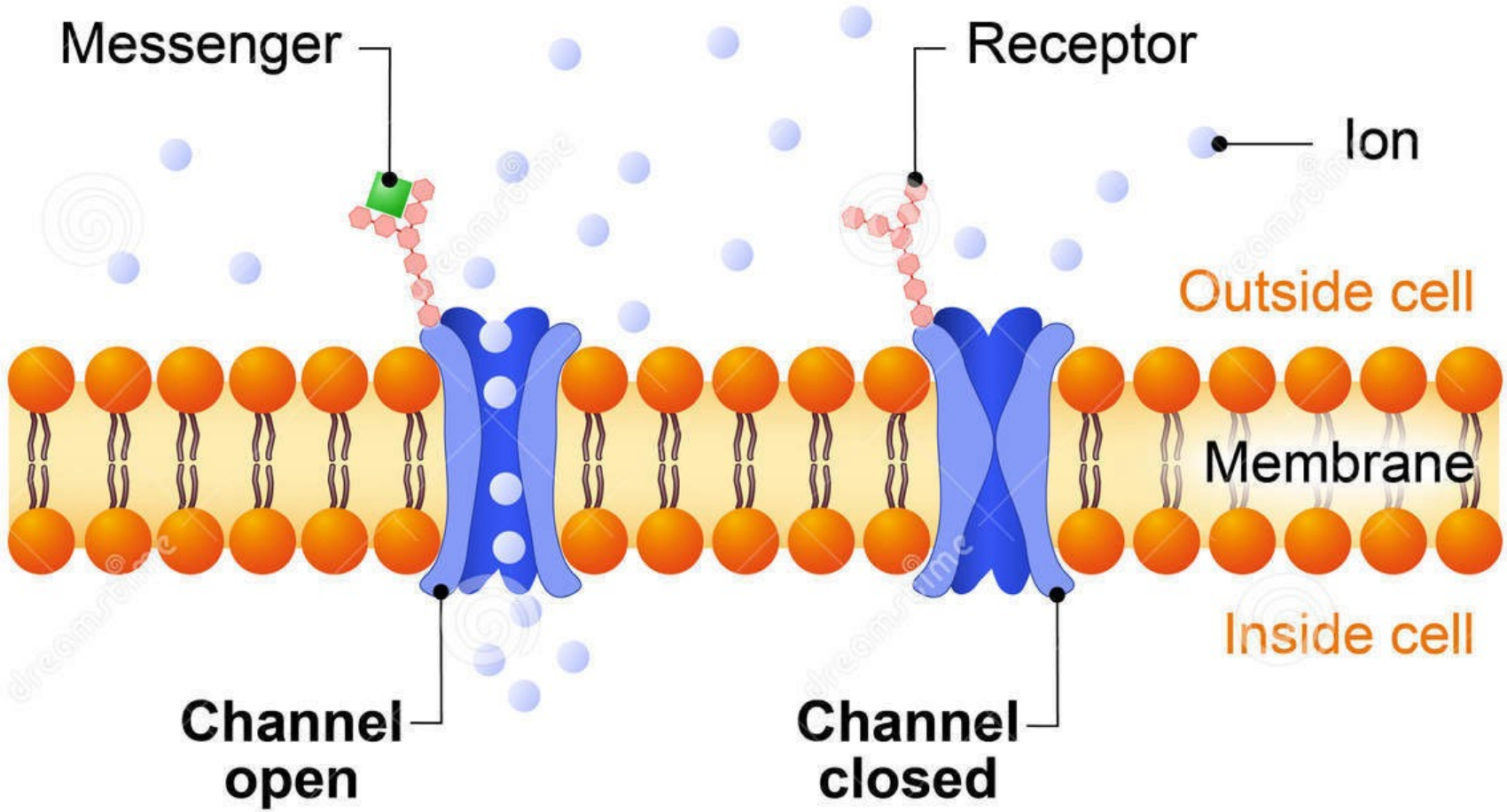




2.2.2 Chemically/Ligand -Gated Ion Channels

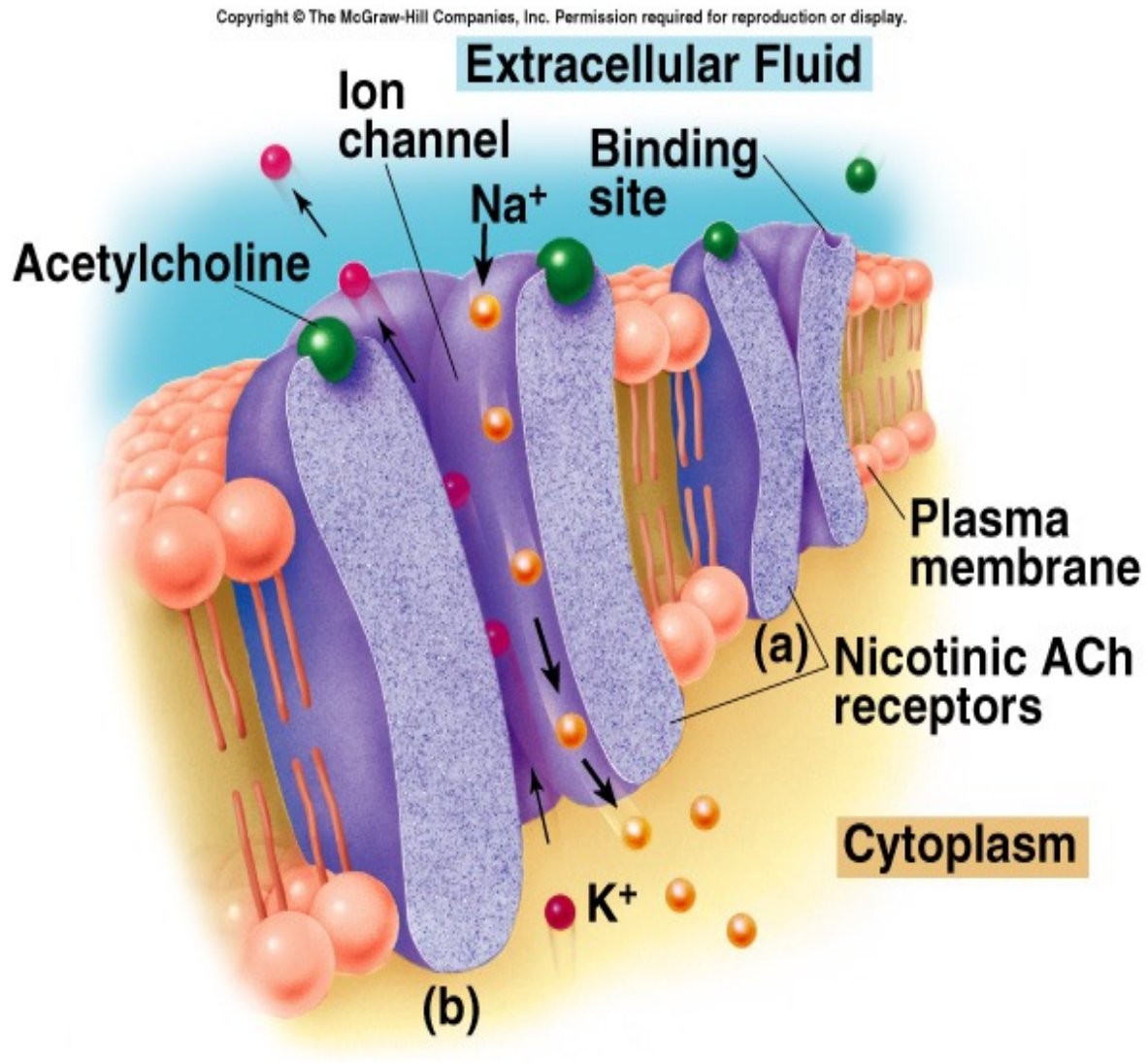
- channel gates are opened by the binding of another molecule with the protein;
  - causing conformational change in the protein molecule that opens or closes the gate.

Ligand-gated ion channel



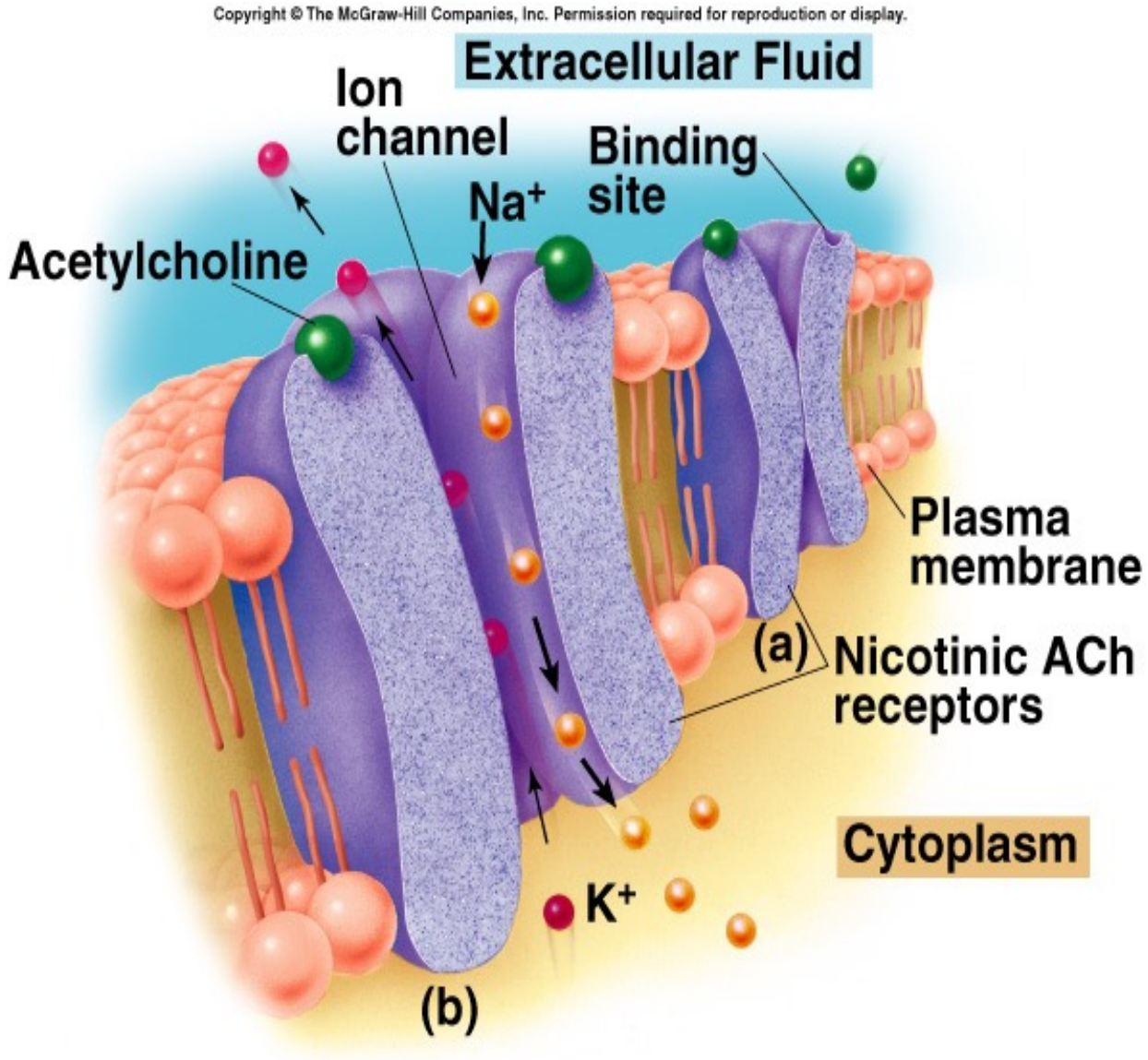
2.2.2 Example: ACh-Gated Ion Channels

- Ion channel runs through receptor.
  - Receptor has 5 polypeptide subunits that enclose ion channel.
  - 2 subunits contain ACh binding sites.



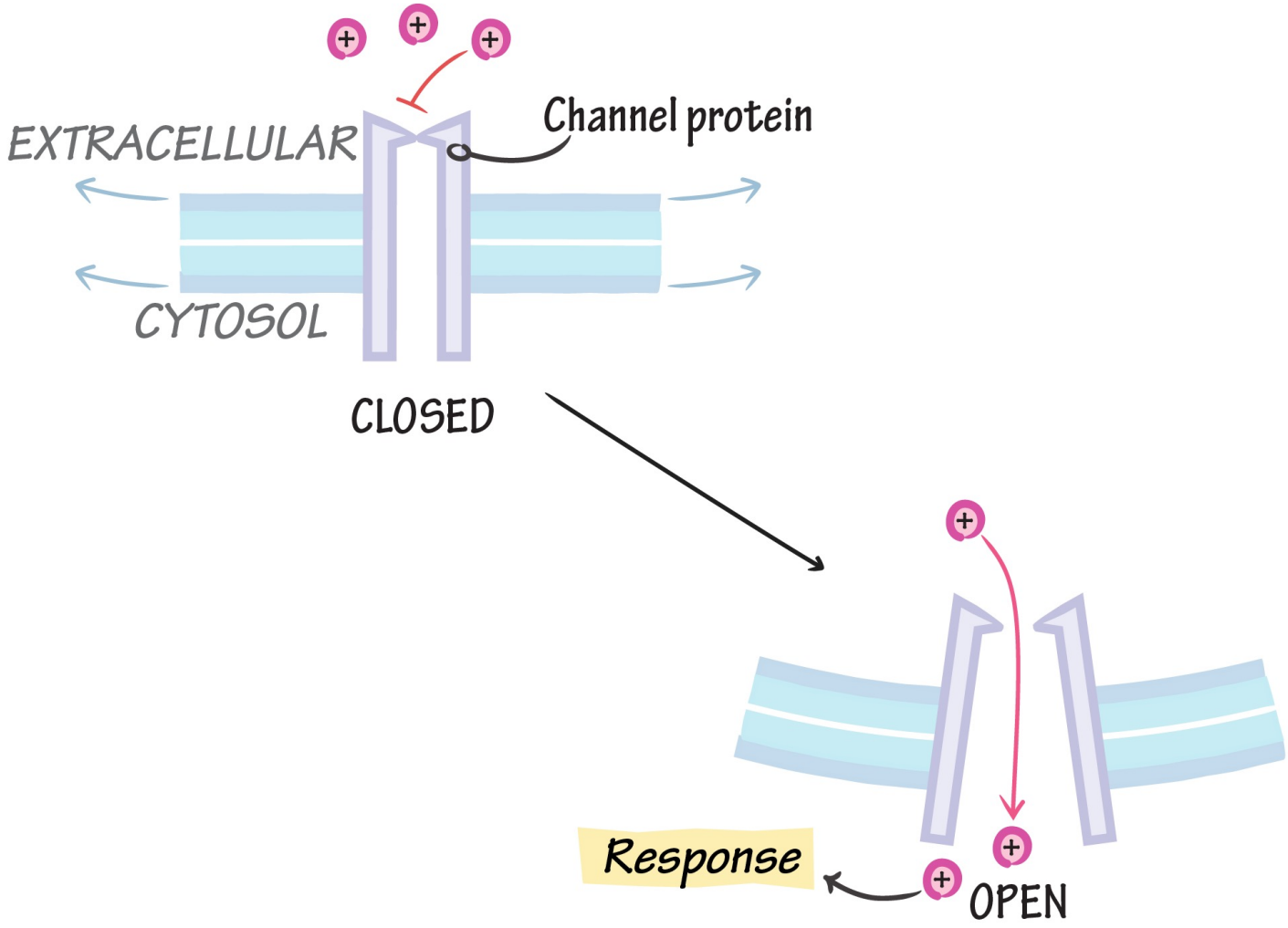
2.2.2 Example: ACh-Gated Ion Channels

- Channel opens when both sites bind to ACh.
  - Permits diffusion of Na^+ into and K^+ out of postsynaptic cell.
- Inward flow of Na^+ dominates at RMP.
  - Produces EPSPs.



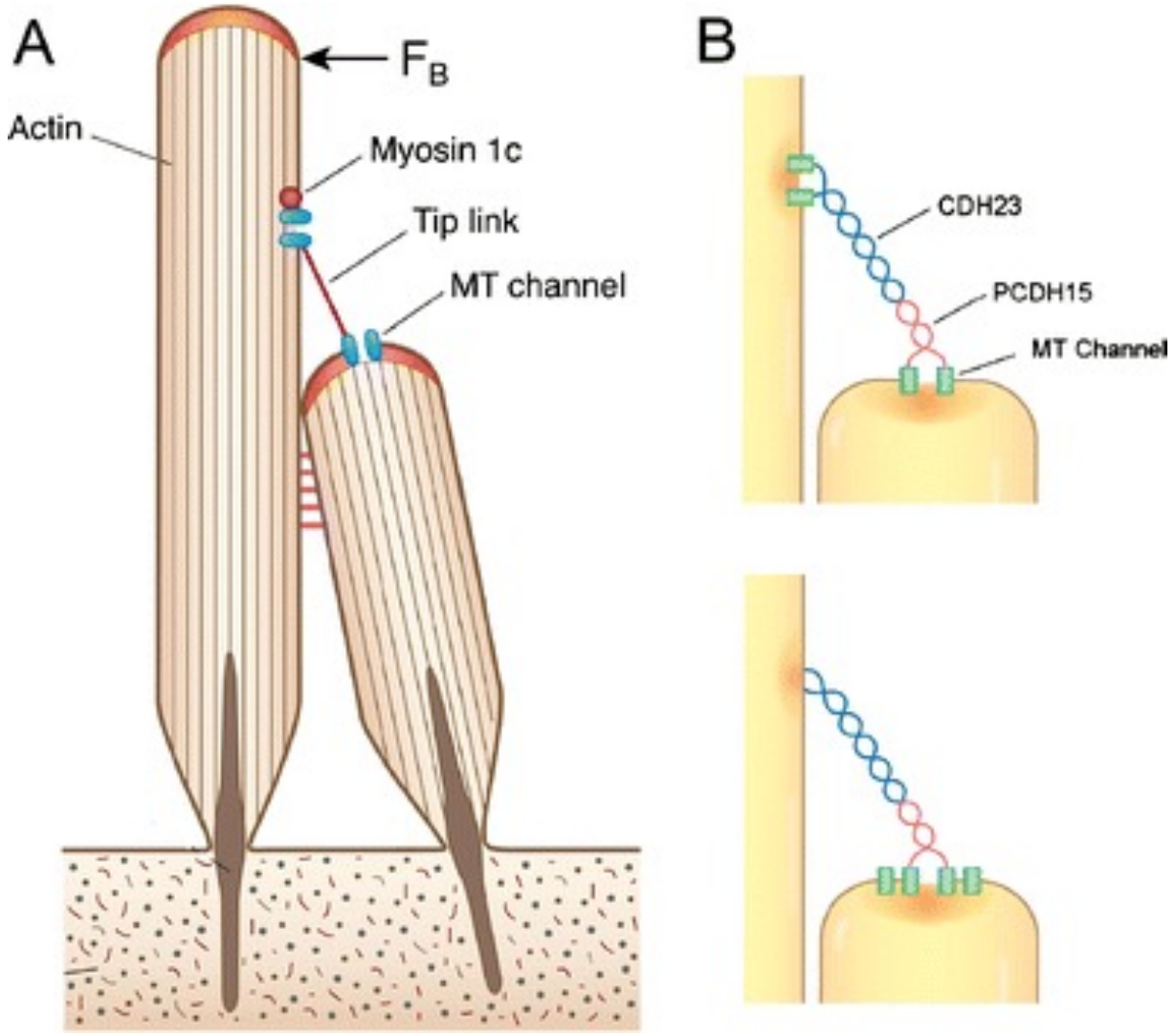
2.2.3 Mechanically-gated channels

- channels opened by the mechanical deformation of the cell membrane.
  - mechanically-gated channels.
- play a very important role in the genesis of excitation of the hair cells

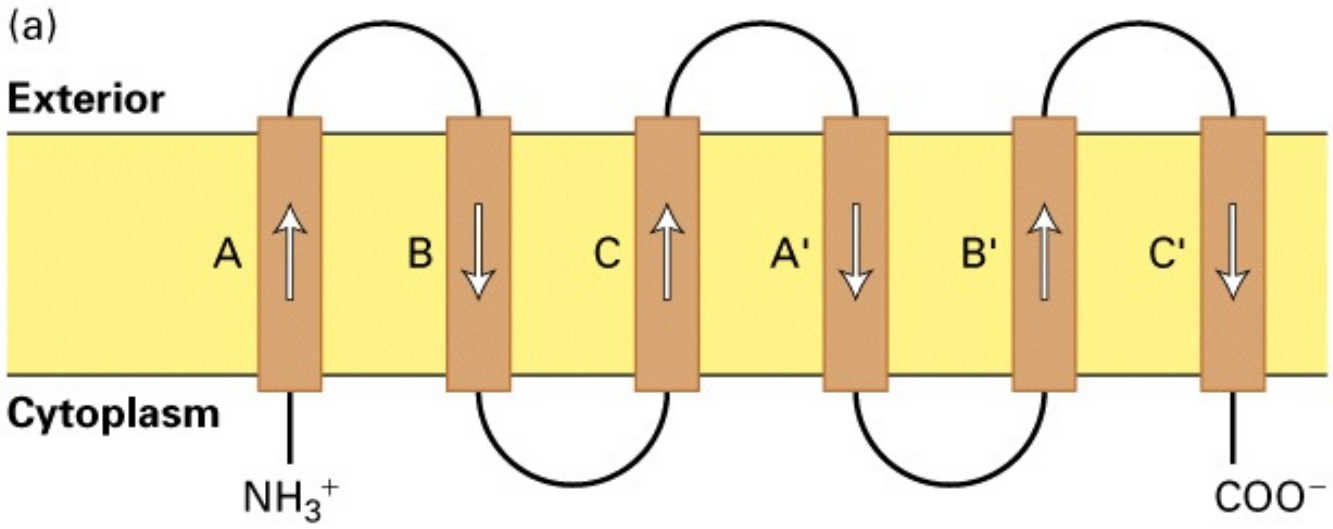


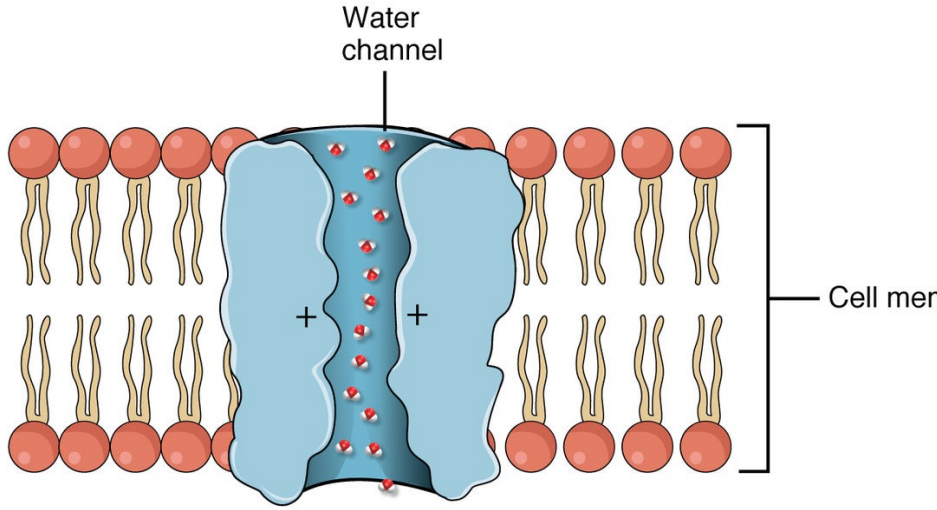
2.2.3 Example: Organ of Corti MET Channels

- When sound waves move the basilar membrane it moves the hair cells that are connected to it,
- The tips of the hair cells are connected to the tectorial membrane
  - the hair cell get bent .
- There are mechanical gates on each hair cell that open when they are bent.
- **K^+ goes into the cell and Depolarizes the hair cell.** (concentration of K^+ in the endolymph is very high)



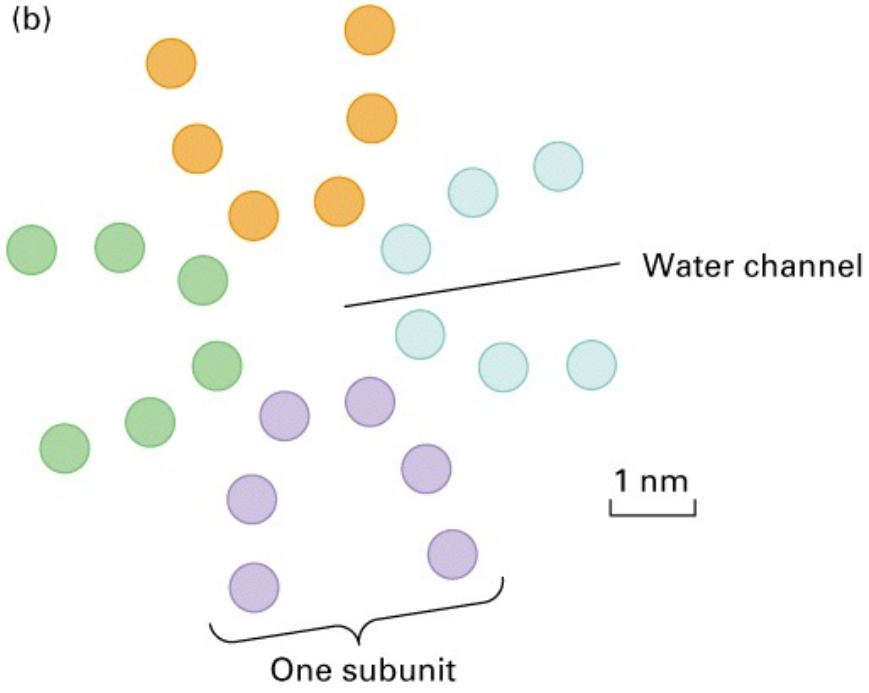
2.2.4 Water Channel



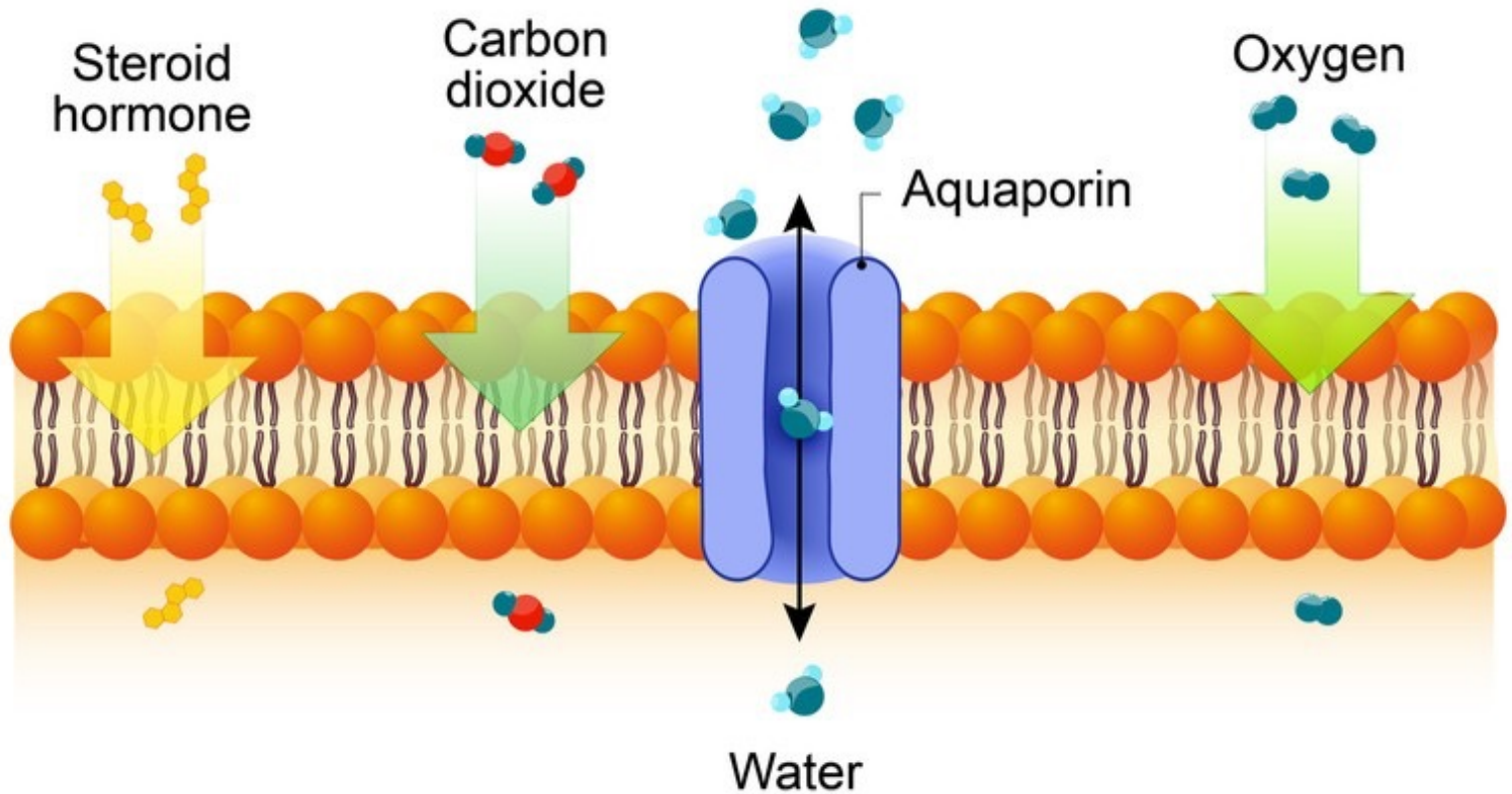


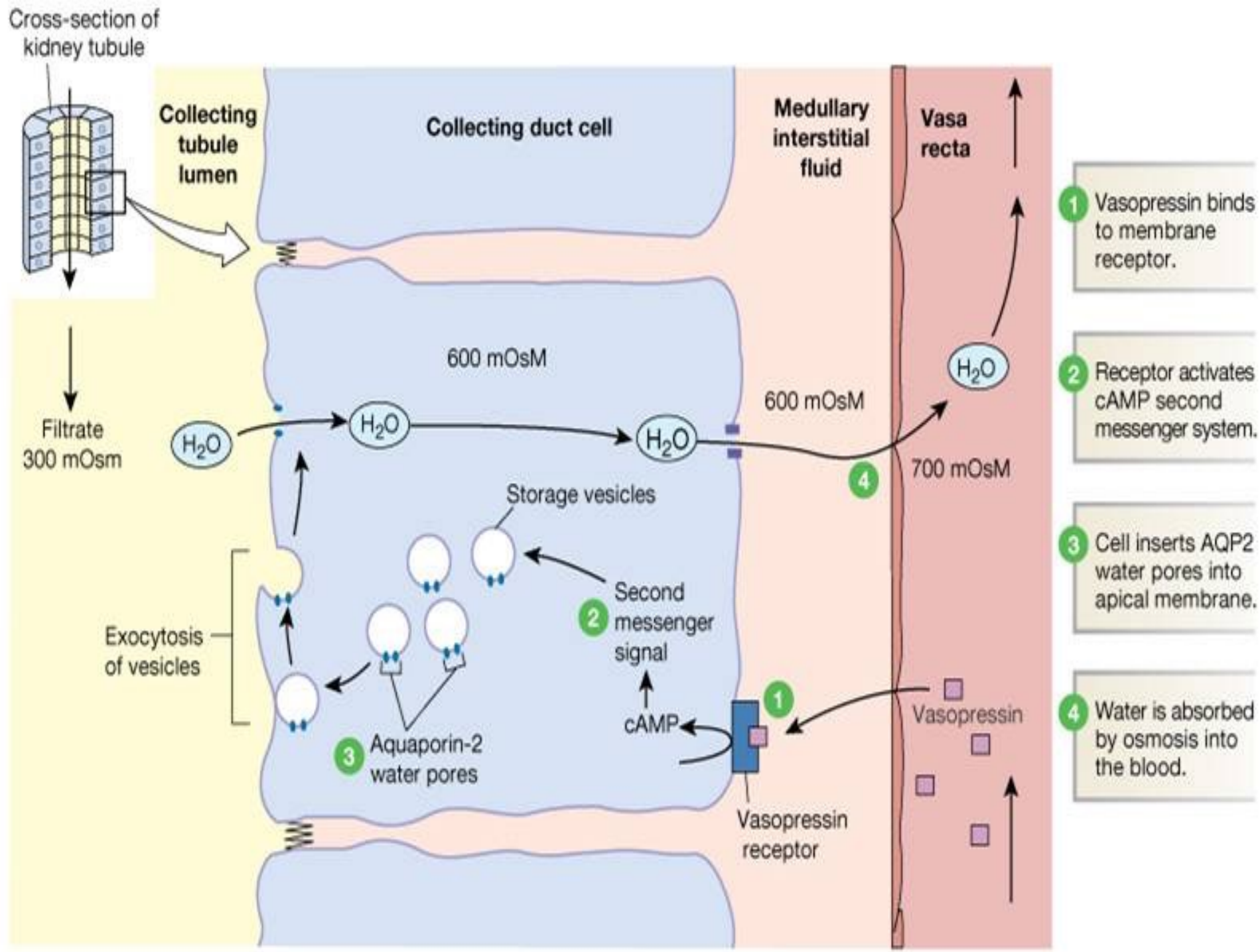
The structure of aquaporin

(AQP)



AQUAPORIN

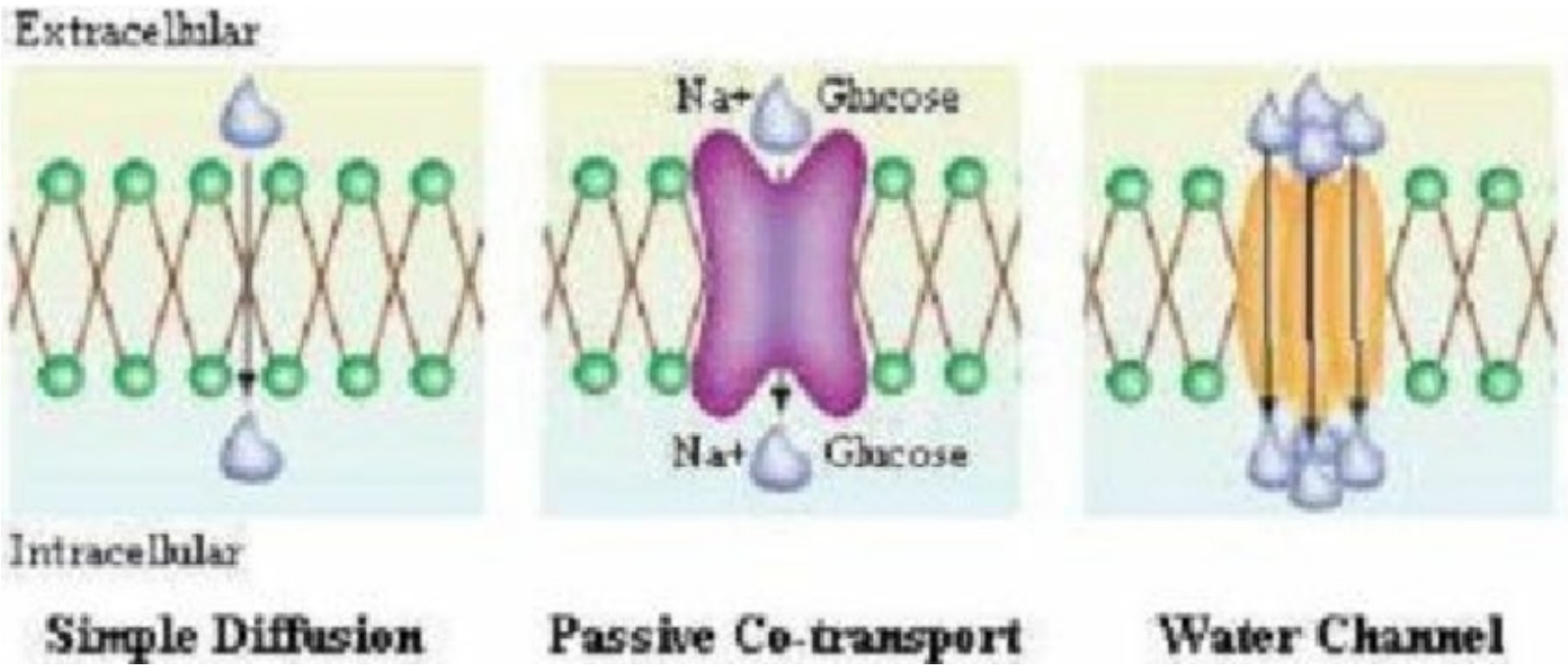



Cross-section of kidney tubule
Collecting tubule lumen
Collecting duct cell
Medullary interstitial fluid
Vasa recta
Filtrate 300 mOsm
600 mOsM
H2O
H2O
H2O
600 mOsM
H2O
700 mOsM
Storage vesicles
Second messenger signal
Exocytosis of vesicles
cAMP
Aquaporin-2 water pores
Vasopressin receptor
Vasopressin
1 Vasopressin binds to membrane receptor.
2 Receptor activates cAMP second messenger system.
3 Cell inserts AQP2 water pores into apical membrane.
4 Water is absorbed by osmosis into the blood.

Osmosis Video

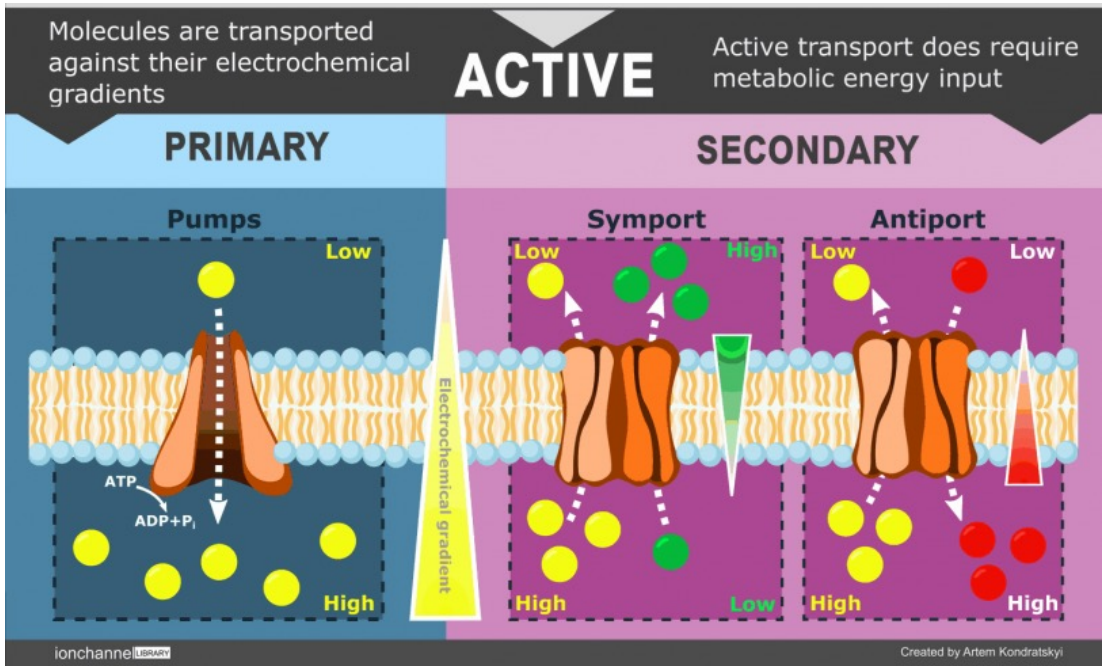
2.2.4 Water Transport across cell membrane

- Simple diffusion
- Ion channel
- Water channel



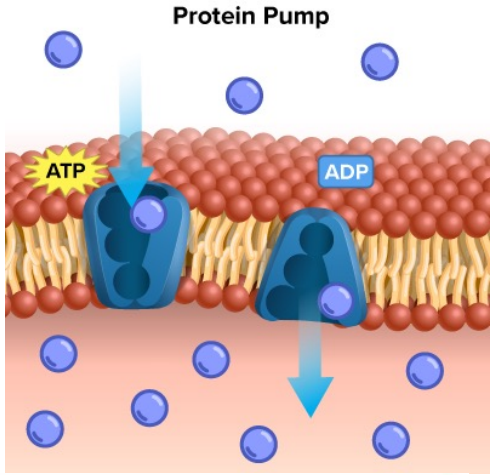
3 Active transport

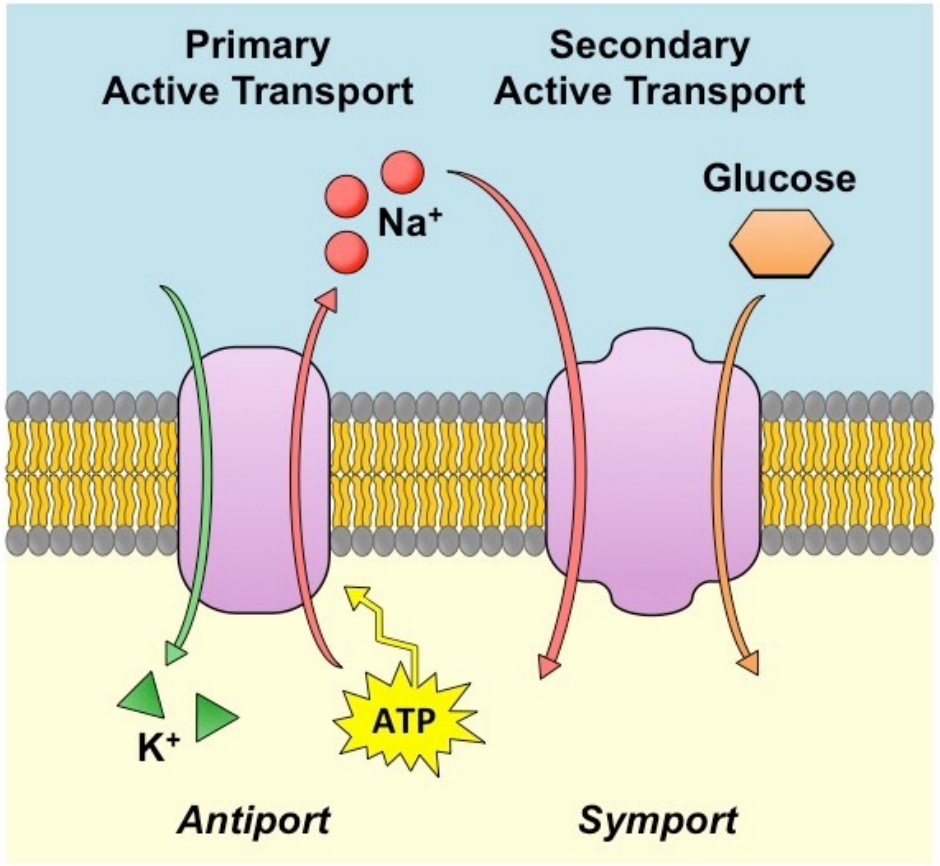
- When the cell membrane moves molecules or ions **uphill** against a concentration gradient
- (or uphill against an electrical or pressure gradient),
- the process is called active transport
  - 3.1 **Primary active transport**
  - 3.2 Secondary active transport:



3 Active transport

- 3.1 **Primary active transport**:
  - the energy used to cause the transport is derived **directly** from the breakdown of ATP or some other high-energy phosphate compound
- 3.2 Secondary active transport:
  - The energy is derived **secondarily** from energy
    - stored in the form of ionic concentration differences between the two sides of the membrane
    - created by primarily active transport



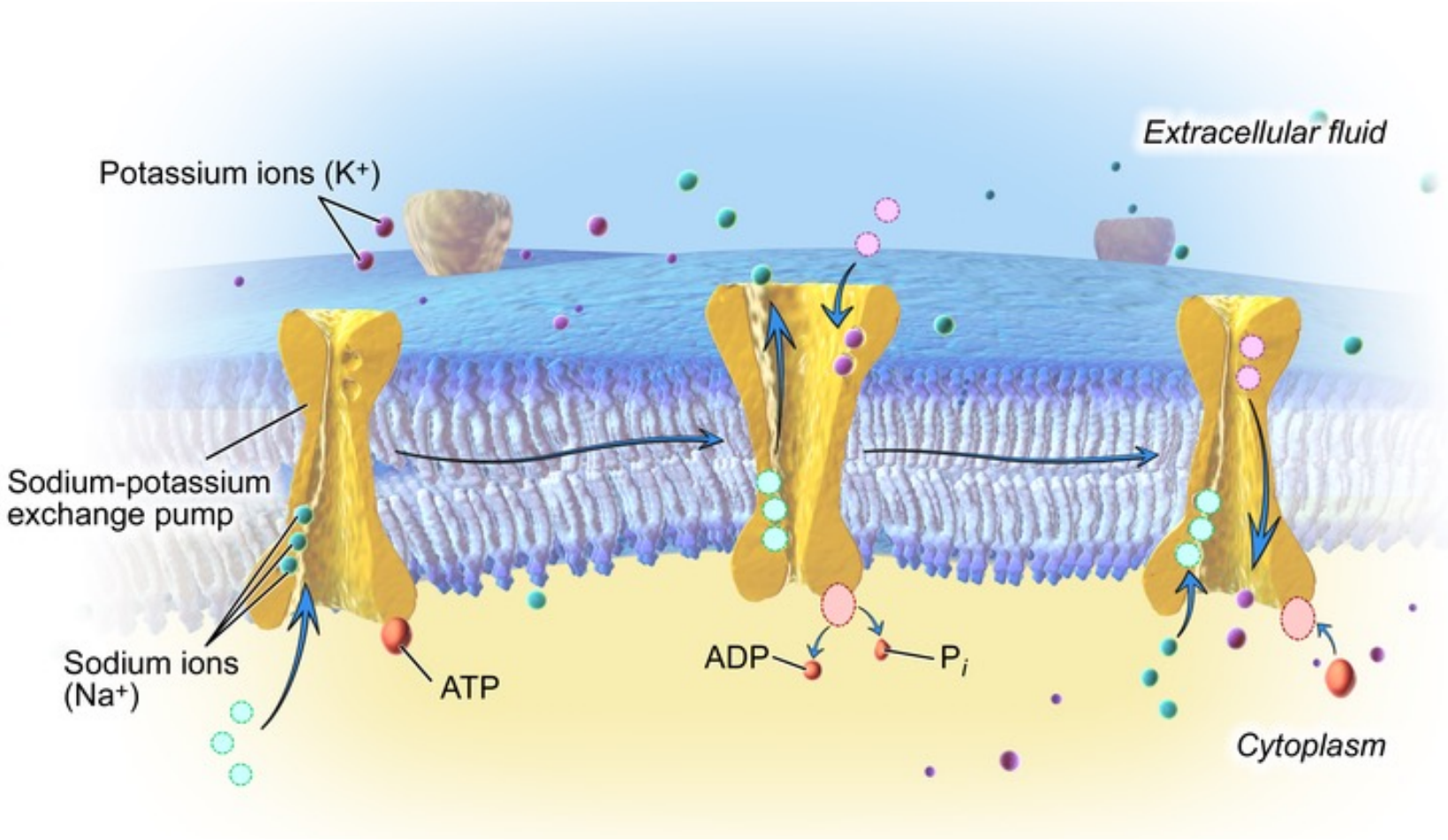


Intracellular vs extracellular ion concentrations

Substance	Extracellular Fluid	Intracellular Fluid
Na^+	140 mmol/L	10 mmol/L
K^+	4 mmol/L	140 mmol/L
Ca^{2+} (free)	2.5 mmol/L	0.1 µmol/L
Mg^{2+}	1.5 mmol/L	30 mmol/L
Cl^-	100 mmol/L	4 mmol/L
HCO_3^-	27 mmol/L	10 mmol/L
PO_4^{3-}	2 mmol/L	60 mmol/L
Glucose	5.5 mmol/L	0–1 mmol/L
Protein	2 g/dL	16 g/dL

3.1 Primary Active Transport

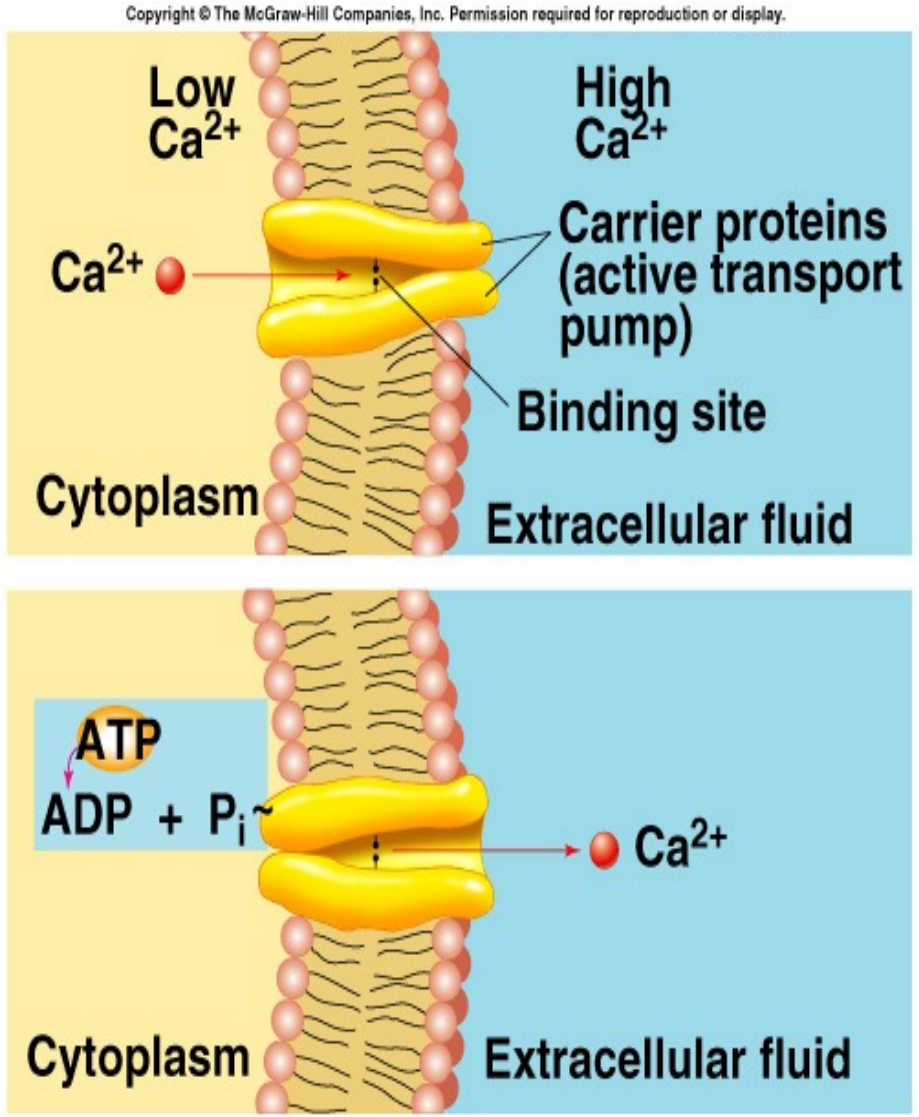
- Hydrolysis of ATP directly required for the function of the carriers.
- Molecule or ion binds to "recognition site" on one side of carrier protein.



3.1 Primary Active Transport

- Binding stimulates phosphorylation (breakdown of ATP) of carrier protein.

- Carrier protein undergoes conformational change.
  - Hinge-like motion releases transported molecules to opposite side of membrane.



3.1 Example: Na^+/K^+ Pump

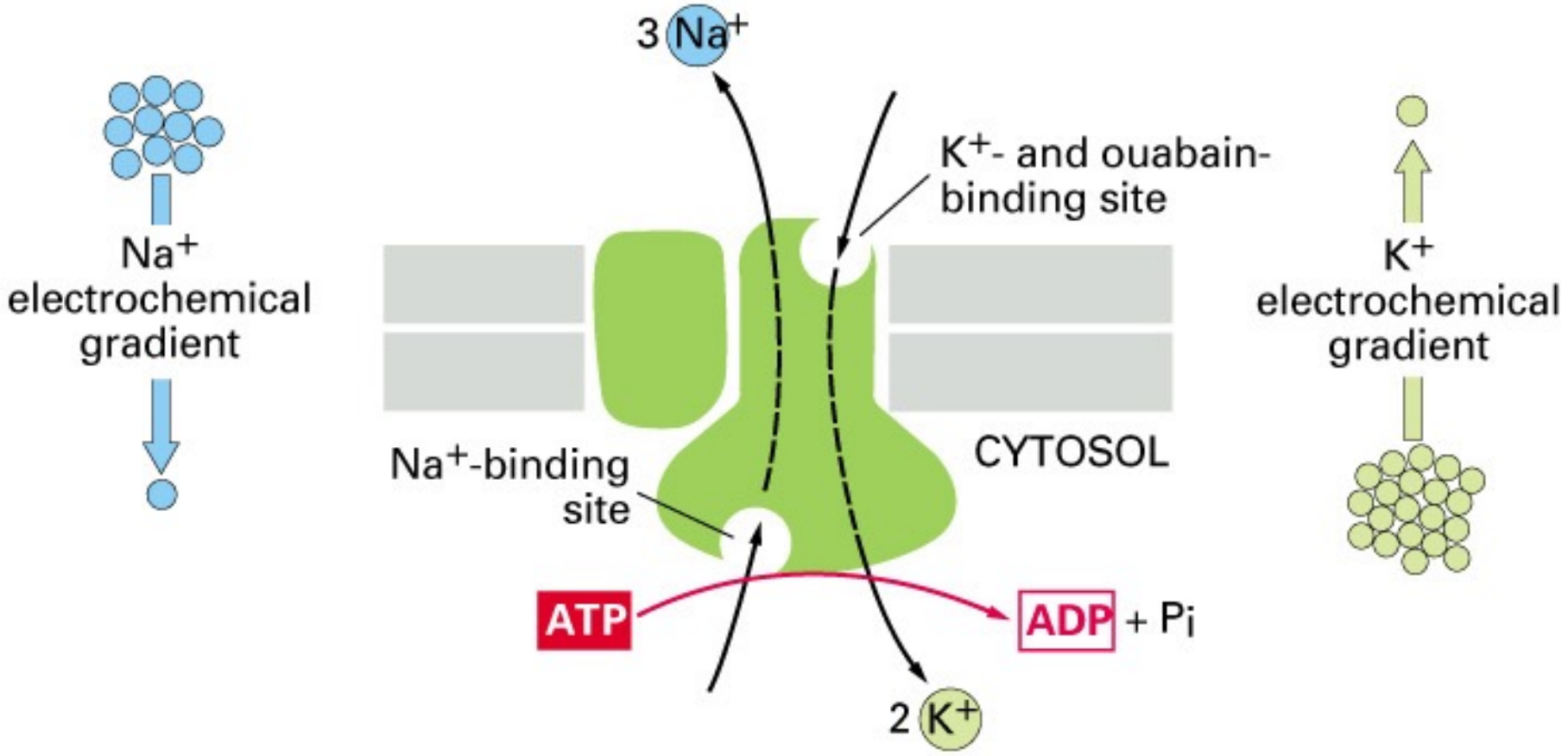


Figure 11–13. Molecular Biology of the Cell, 4th Edition.

3.1 Example: Na^+/K^+ Pump

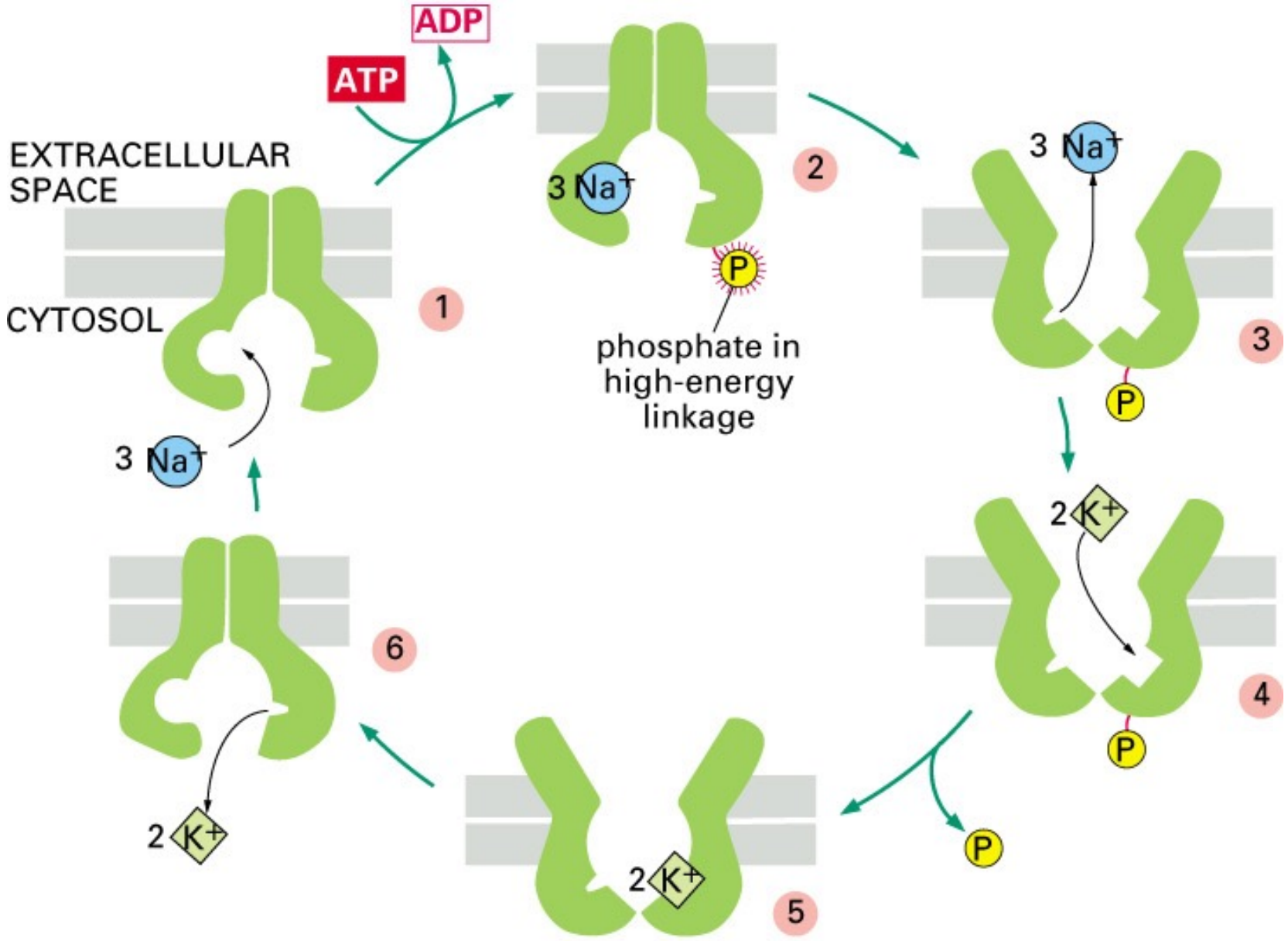


Figure 11–14. Molecular Biology of the Cell, 4th Edition.

3.1 Example: Na^+/K^+ Pump

Characteristics of the Transport by Na+ pump

- Directional transport
- Coupling process
- ATP is directly required
- Electrogenic process

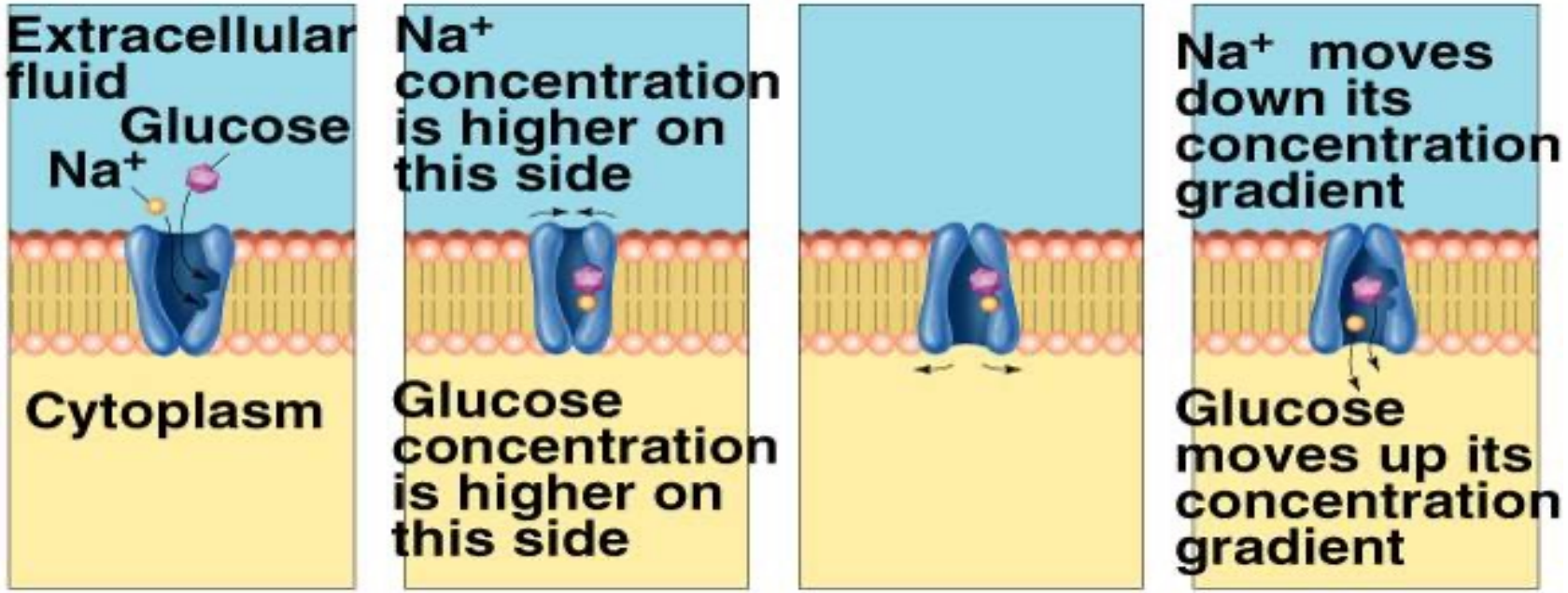
3.1 Example: Na^+/K^+ Pump

Importance of the Na^+-K^+ Pump

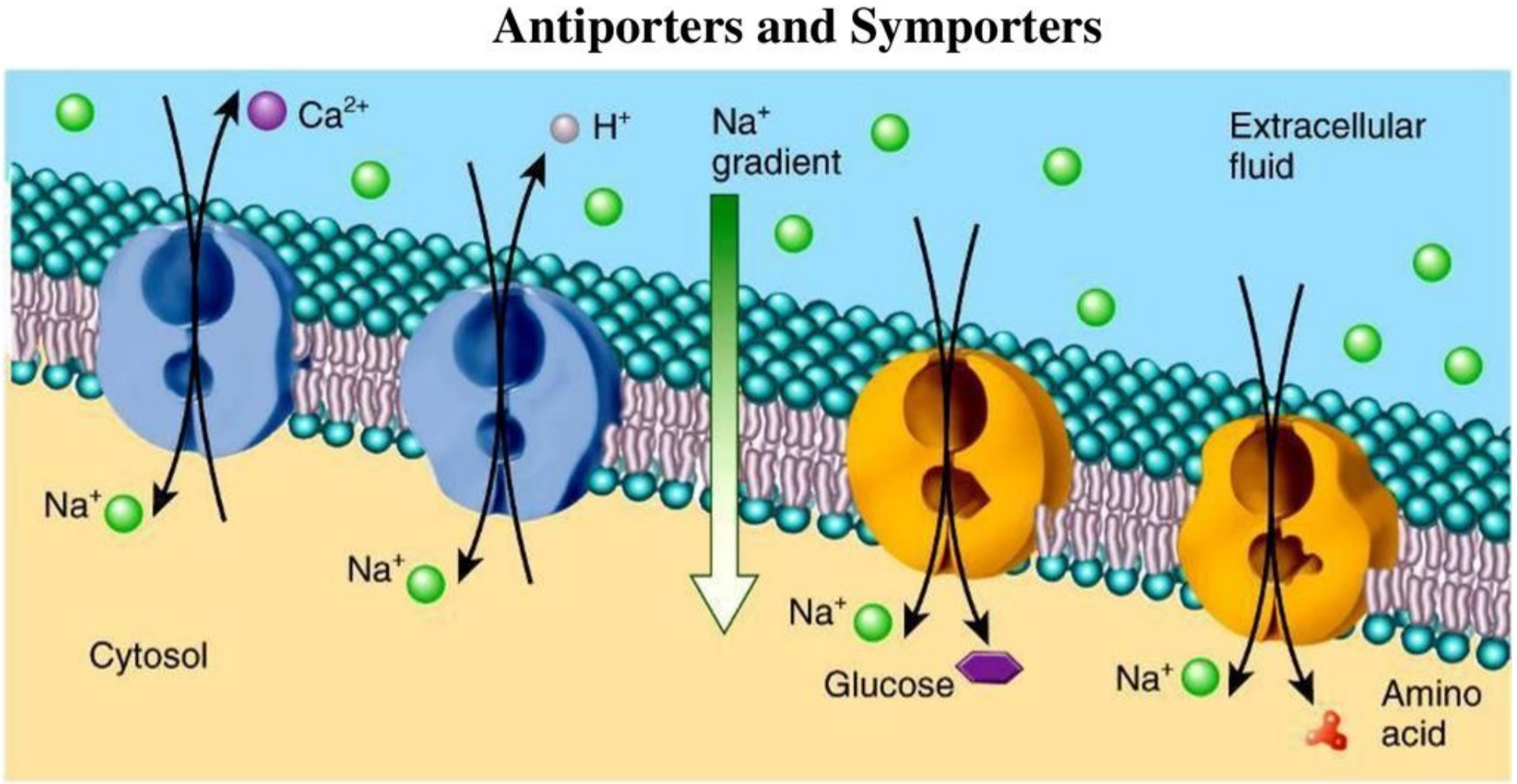
- Maintains high intracellular K^+ concentration gradients across the membrane.
- Controls cell volume and phase
- Maintains normal pH inside cell
- Develops and Maintain Na^+ and K^+ concentration gradients across the membrane
- Electrogenic action influences membrane potential
- Provides energy for secondary active transport

3.2 Secondary Active Transport

- Coupled transport.
- Energy needed for “uphill” movement obtained from “downhill” transport of Na^+.
- Hydrolysis of ATP by Na^+/K^+ pump required indirectly to maintain [Na^+] gradient.



3.2 Secondary Active Transport



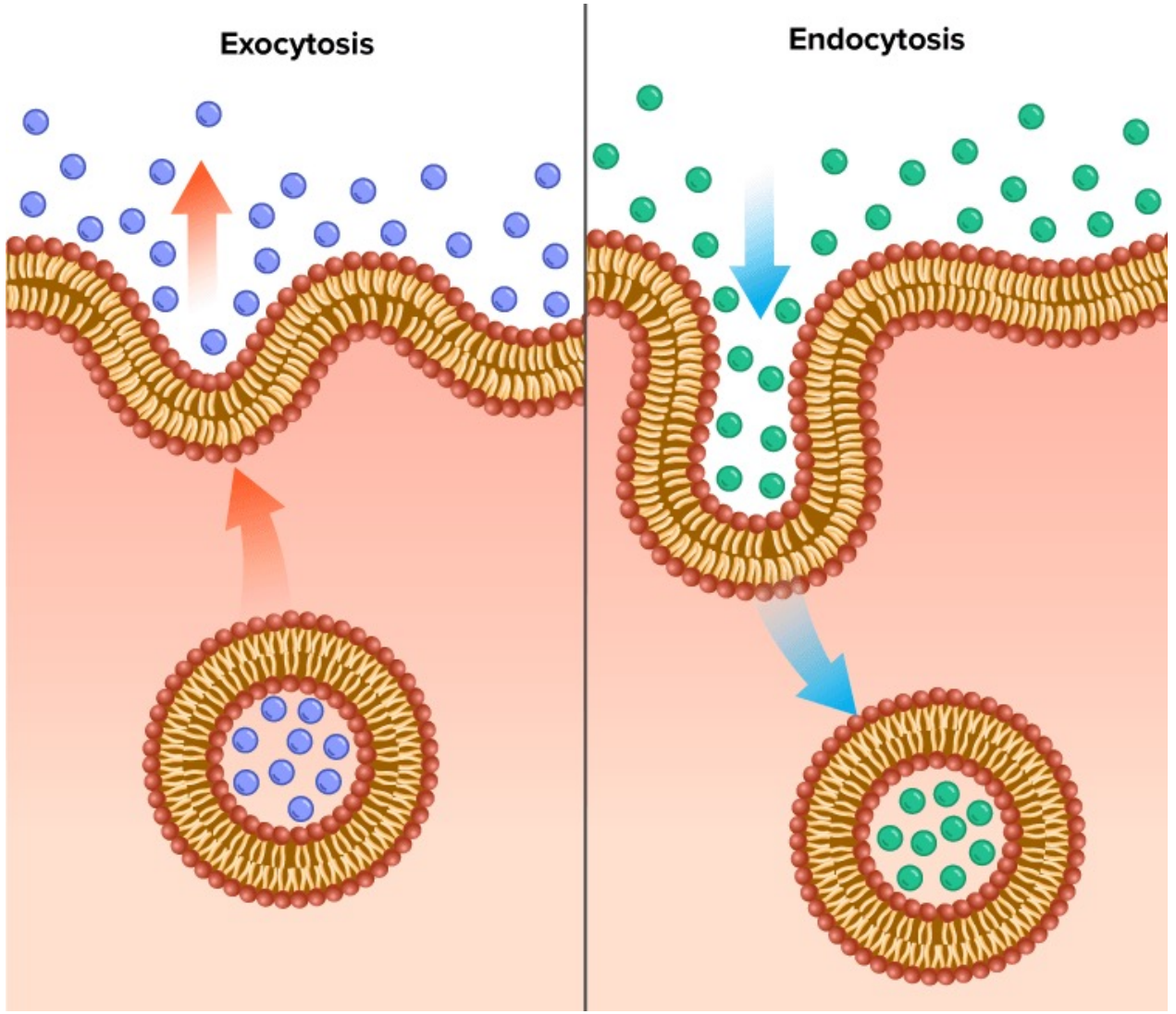
Antiporters will move one moiety, e.g. H^+, in the opposite direction to the Na^+.

Symporters will move one moiety, e.g. glucose, in the same direction as the Na^+.

Video: Active Transport

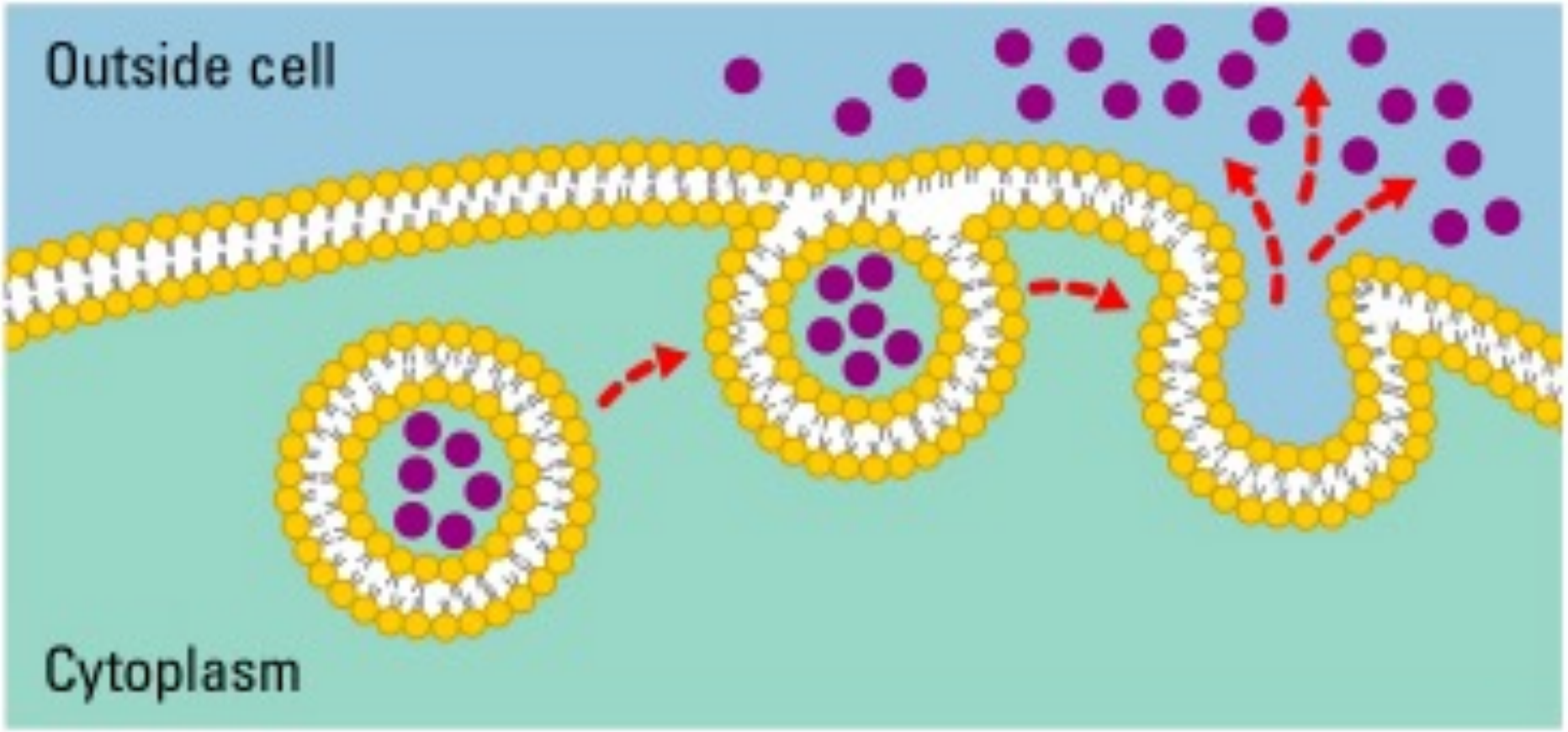
4 Bulk Transport (Endocytosis and Exocytosis)

- Movement of many large molecules, that cannot be transported by carriers.
- Exocytosis:
  - A process in which some large particles move from inside to outside of the cell by a specialized function of the cell membrane
- Endocytosis:
  - Exocytosis in reverse.
  - Specific molecules can be taken into the cell because of the interaction of the molecule and protein receptor.



4 Exocytosis

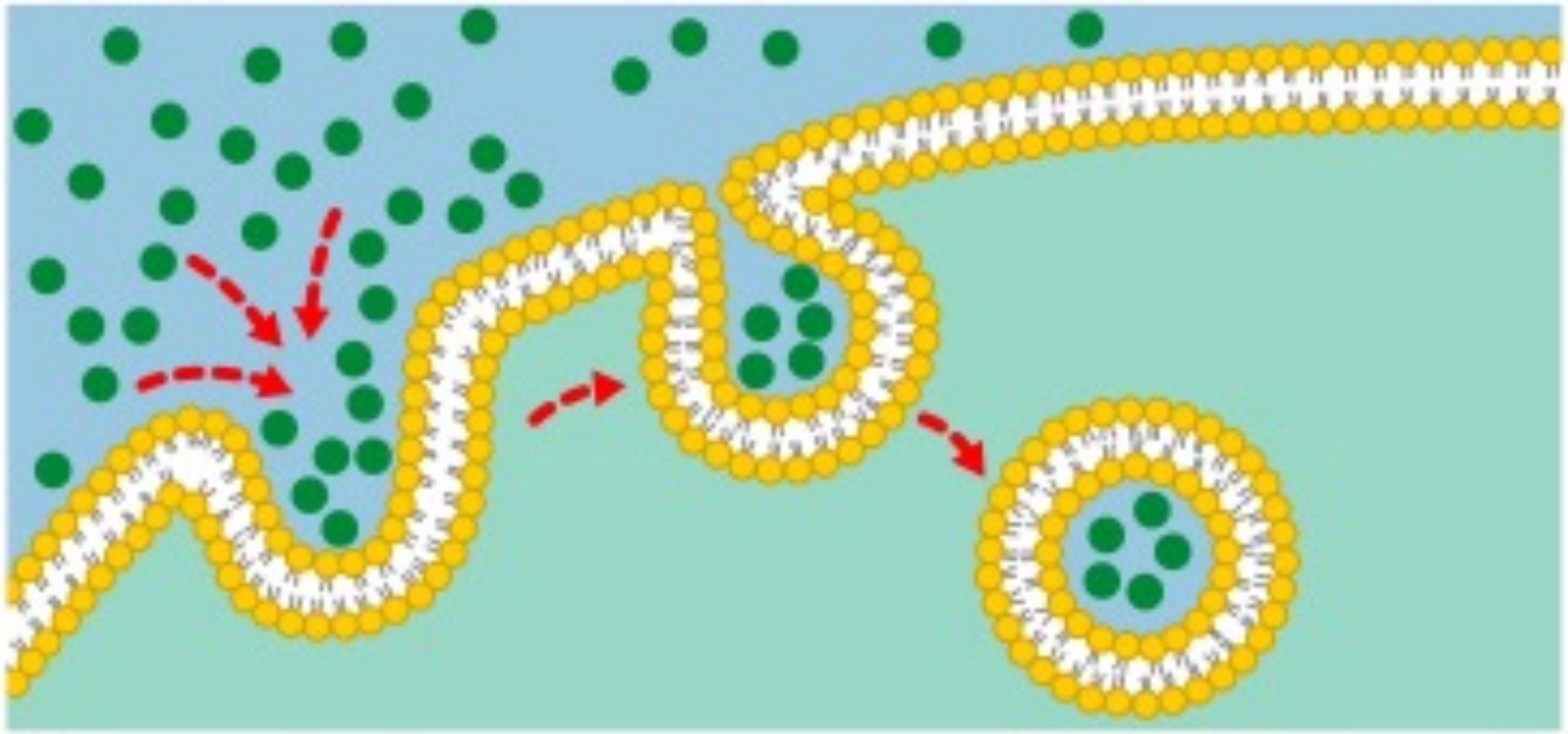
Vesicle containing the secretory protein fuses with plasma membrane, to remove contents from cell.



(a) Exocytosis

4 Endocytosis

Material enters the cell through the plasma membrane within vesicles.



(b) Endocytosis

4 Types of Endocytosis

- **Phagocytosis** - ("cellular eating") cell engulfs a particle and packages it with a food vacuole.
- **Pinocytosis** – ("cellular drinking") cell gulps droplets of fluid by forming tiny vesicles. (unspecific)
- **Receptor-Mediated** – binding of external molecules to specific receptor proteins in the plasma membrane. (specific)