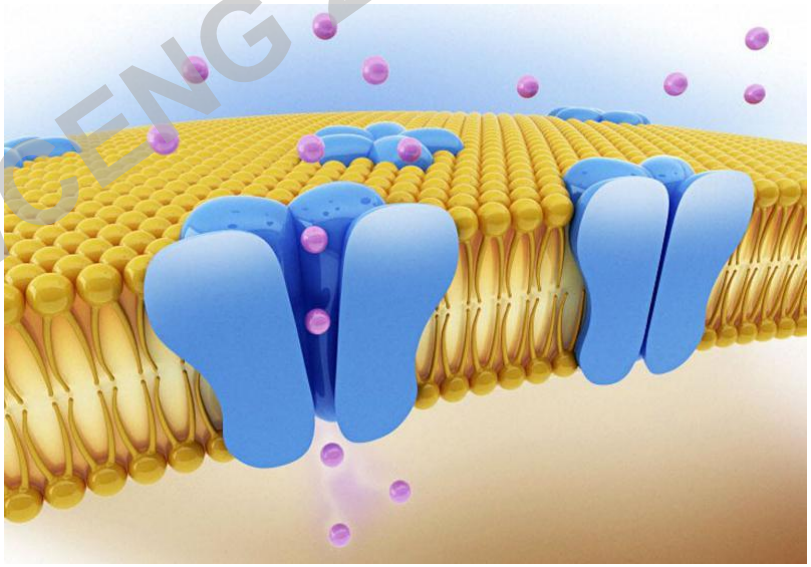
L9. Drug Permeation Through Biological Barriers

May 3, 2018



1. Lipid and Lipid Membrane

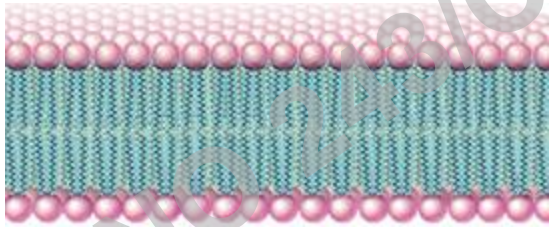
Lipids

Phospholipid: an amphiphilic molecule with a hydrophilic head and 1~2 hydrophobic tails.

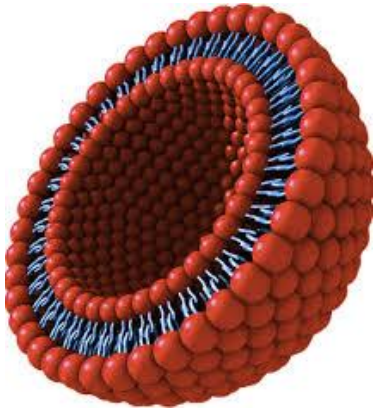
Head: 0.5 nm^2
Length: ~ 2.5 nm

Phosphatidylcholine (PC, +/-); phosphatidylserine (PS, -); phosphatidylethanolamine (PE, +/-); cholesterol; sphingomyelin (SM), glycolipids, etc.

Lipid Self-Assemblies



Lipid bilayer: 4~5 nm



Lipid vesicle (liposome): 50 nm ~ 10 μm

1. Lipid and Lipid Membrane

- Lipids & lipid assemblies are now “star” research topic in various fields (biology, chemistry, physics, materials sciences, engineering etc).

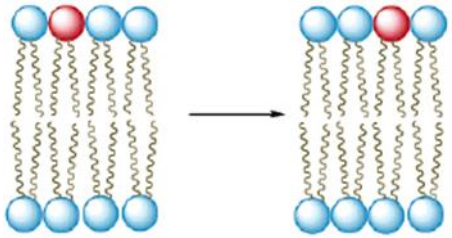
  It’s hyped as a third biological building block after protein and nucleic acid.

- 40 years ago, lipids were just a component of cell membrane, “A sausage casing with the interesting stuff inside”.

  Ordinary structure, trivial structure, cannot offer any fancy functions such as folding-unfolding, self-duplication, and transportation of O_2, etc.

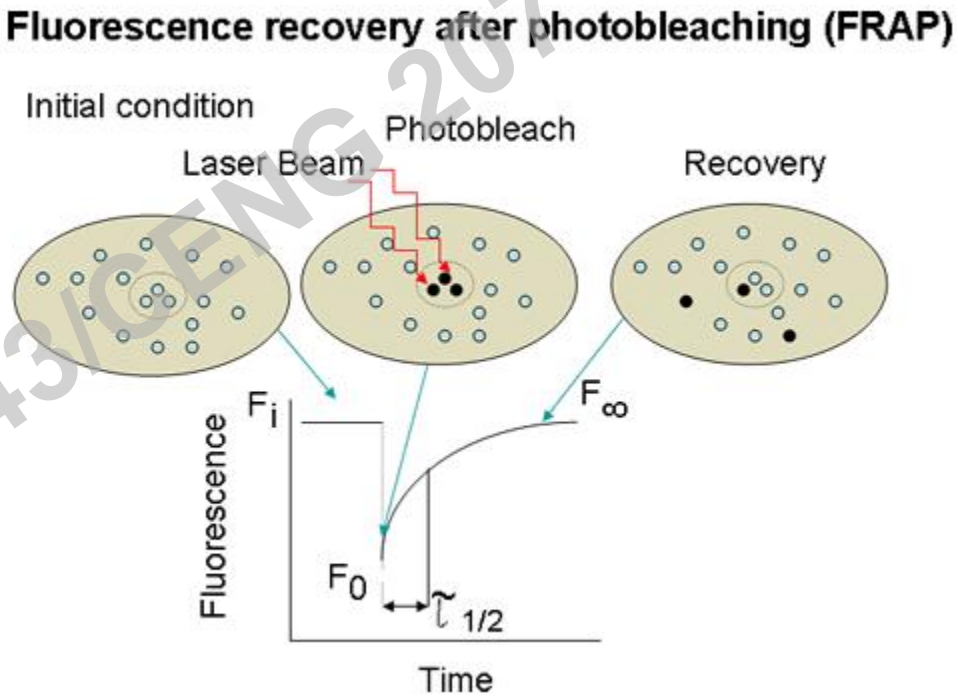
2. Dynamic Properties of Lipids in the Membrane

(1) Translational diffusion



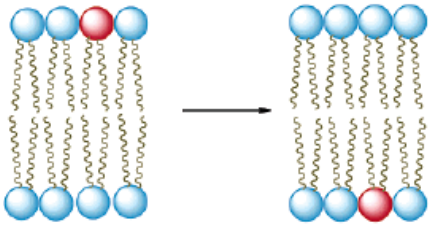
Diffuse laterally from one spot to another spot

$D \approx 1\ \mu m^2/s$



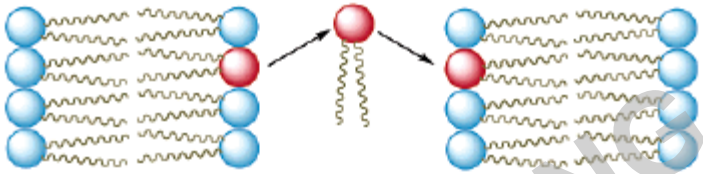
2. Dynamic Properties of Lipids in the Membrane

(2) Transmembrane diffusion (flip-flop)



Diffuse from one leaflet to another leaflet

(3) Cross-membrane diffusion



Diffuse from one membrane
to another membrane

(4) Rotation

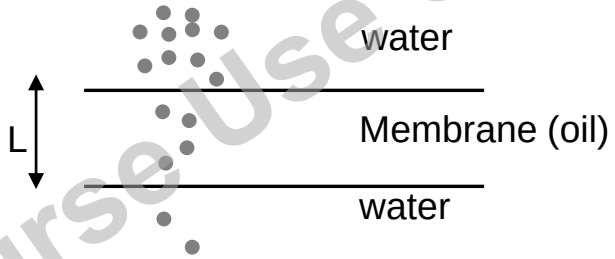
(5) Rocking

All these dynamic properties together determine membrane permeability.

3. Permeation Through Lipid Membranes

(1) Non-charged molecules (non-electrolyte)

Permeability: P or k_s



$$P = k_s = \frac{KD_m}{L}$$

K: equilibrium oil/water partition coefficient
(the relative solubility of a solute within a membrane)

$$K = \frac{solubility\ (oil)}{solubility\ (water)}$$

D_m: solute diffusion coefficient in the membrane

L: thickness of the membrane

3. Permeation Through Lipid Membranes

Diffusion through a membrane is often empirically correlated by power law expressions:

$$D_m = D_m^0 (M_w)^{-S_m}$$

M_w: molecular weight of the diffusing species

D_m^0, S_m: coefficients determined by the characteristics of the membrane

$$P = \frac{K D_m^0 (M_w)^{-S_m}}{L} = P_0 K (M_w)^{-S_m} \qquad P_0 = \frac{D_m^0}{L}$$

e.g., permeability of lipid vesicles:

P(water, 18) = 5×10^{-3} cm/s
P(glycerol, 92) = 1.5×10^{-6} cm/s
P(glucose, 180) = 6×10^{-8} cm/s
P(sucrose, 342) = 0 cm/s

M_w < 300 Da, M_w increases => P decreases
M_w > 300 Da, excluded from the membrane

Solute permeability is also a function of membrane composition (PC, PS, PE, SM, etc).

3. Permeation Through Lipid Membranes

(2) Charged molecules (electrolyte)

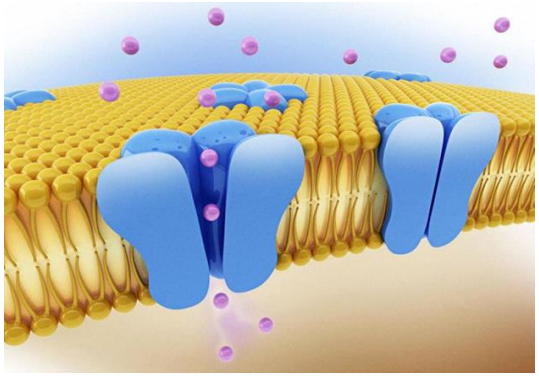
Do not partition into lipid bilayer: K = 0

$P \Rightarrow 0$

Ions have very low permeability in lipid membranes.

The low intrinsic permeability of ions underlies the ability of membrane to support an electrical potential difference.

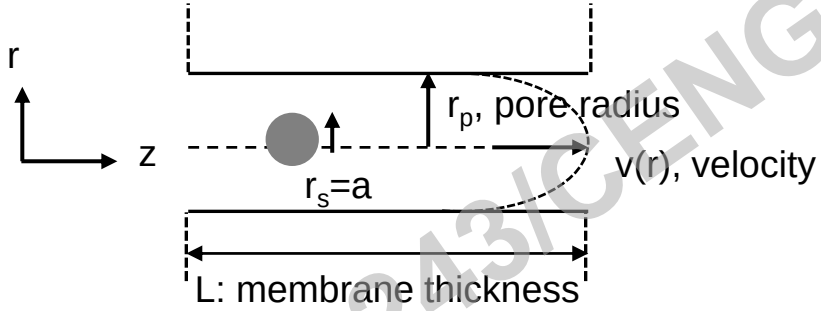
4. Permeation Through Porous Membranes



Porous membrane:

Cell membranes and cellular barriers are not perfectly uniform. For example, there are multiple protein ion channels within the membranes.

Hindered transport through a cylindrical pore



$$\lambda = \frac{r_s}{r_p} = \frac{a}{r_p}$$

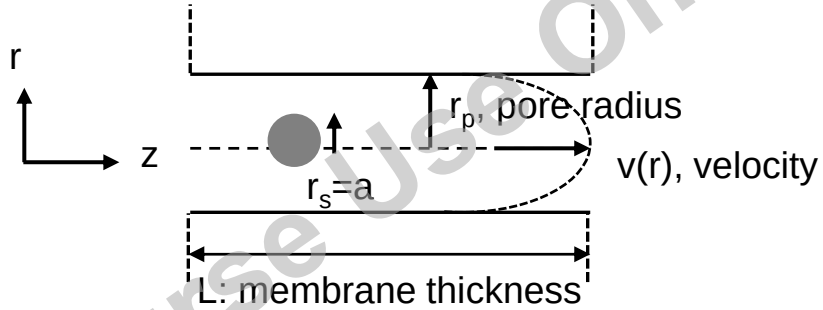
$\lambda \rightarrow 1$: pore walls become an increasingly important obstacle for particle transport

$\lambda \rightarrow 0$: unbound transport

$0 < \lambda < 1$: of great biological interest

4. Permeation Through Porous Membranes

$0 < \lambda < 1$



The driving force for particle movement through the pore, the gradient of chemical potential, is balanced by drag force acting on the particle:

$$-\nabla\mu = F$$

Chemical potential ~ local solute concentration, c

$$\mu = k_B T \ln c$$

Considering only axial gradient:

$$-\frac{\partial\mu}{\partial z} = F$$

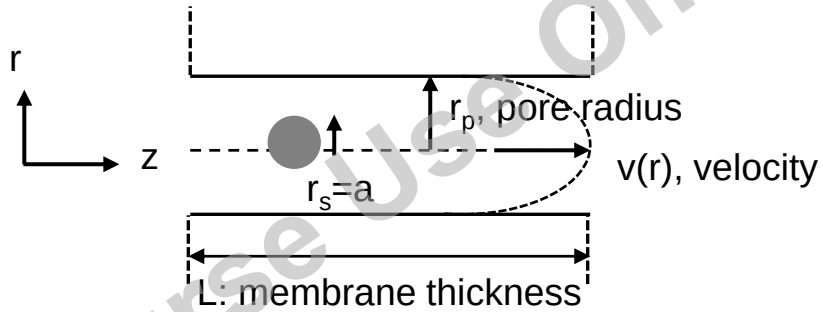
$$F = -\frac{k_B T}{c}\cdot\frac{\partial c}{\partial z}$$

4. Permeation Through Porous Membranes

On the other hand: F ~ v(x)

Drag force F = f·v(x)

f: frictional drag coefficient
v(r): velocity of solute



Particle moving in a confined cylindrical pore

$$\boldsymbol{F = f_{\infty} K[U - Gv]}$$

f_{∞}: frictional drag coefficient
K: enhanced friction due to the presence of the pore walls
U: local net velocity of the particle with respect to the pore walls
v: velocity of the fluid
G: lag coefficient accounting for the decreased approach velocity of the fluid due to the presence of the pore walls

v(x) = U-Gv

4. Permeation Through Porous Membranes

In unbound fluid:

K = 1, G = 1

$$\boldsymbol{F} = \boldsymbol{f}_\infty[\boldsymbol{U} - \boldsymbol{v}] = \boldsymbol{f}_\infty \boldsymbol{v}(\boldsymbol{x})$$

In bound fluid:

K > 1, G < 1

$$f_\infty K[U - Gv] = -\frac{k_B T}{c} \cdot \frac{\partial c}{\partial z}$$

$$Uc = -\frac{k_B T}{f_\infty} \cdot \frac{1}{K} \cdot \frac{\partial c}{\partial z} + Gvc$$

Define: N_z = *Uc (local particle flux in the axial direction)*

$$N_z = -\frac{k_B T}{f_\infty} \cdot \frac{1}{K} \cdot \frac{\partial c}{\partial z} + Gvc$$

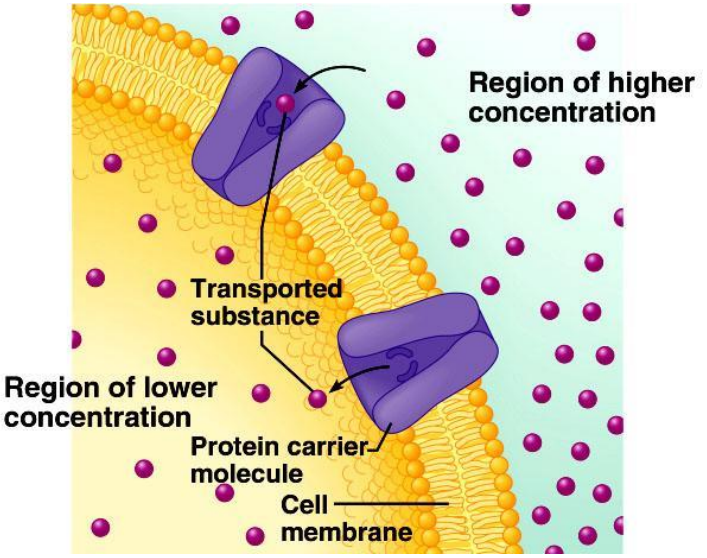
First term: particle diffusion
Second term: bulk fluid movement

When the particle is diffusing in an unbound pore (K=G=1) and stagnant fluid (v=0):

$$N_z = -\frac{k_B T}{f_\infty} \cdot \frac{\partial c}{\partial z} = -D\frac{\partial c}{\partial x} = J_x$$

Fick's first law

5. Facilitated Diffusional Transport



Take glucose as an example:

$c_{glucose}$(extracellular) >> $c_{glucose}$(intracellular)

$P_{water} = 10^5 P_{glucose}$

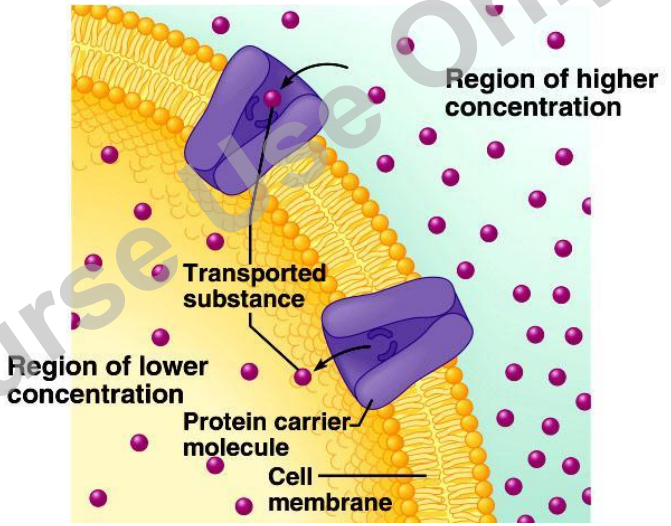
- Not enough glucose (passive transport) for cell metabolism
- Glucose transport protein (shuttle glucose through the hydrophobic layer)

- The glucose transporter facilitates glucose permeation by periodic changes in conformation.
- Conformational changes occur due to natural thermal fluctuations in the membrane (permits the passage of glucose without the addition of any additional energy.
- Glucose can move in either direction across the bilayer and the net flux will occur from the region of high concentration to low concentration.
- # of glucose transporters is limited. They will be saturated when extracellular glucose concentration is high, which leads to a maximal net rate.

5. Facilitated Diffusional Transport

Define the system:

To-be-transported solute: S
Transmembrane carrier protein: C_p
Carrier-solute complex: S-C_p
Transported solute: S*



$$S + C_p \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{S–Cp} \xrightarrow{k_2} \text{S}*\text{–Cp} \xrightarrow{k_3} S^* + C_p$$

If the rate of release of transported solute (k_3) is rapid compare to the rate of conformational change (k_2), $k_3 >> k_2$

The concentration of solute on the opposite side is negligible, $[S^*] \approx 0$

At equilibrium state:

The flux of solute across the membrane can be calculated as:

$$N_{S^*} = \frac{1}{A} \cdot \frac{d[S^*]}{dt} = k_2[\text{S–Cp}]$$

5. Facilitated Diffusional Transport

The concentration of S-C_p is assumed constant at equilibrium state:

Rate of formation of S-C_p = Rate of dissociation of S-C_p

$$S + C_p \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{S}-\text{Cp} \xrightarrow{k_2} \text{S}*-\text{Cp} \xrightarrow{k_3} S^* + C_p$$

$$k_1[S][C_p] = k_{-1}[\text{S}-\text{Cp}] + k_2[\text{S}-\text{Cp}]$$

The total number of transporter proteins is assumed constant:

$$C_{TOT} = [\text{C}_\text{p}] + [\text{S}-\text{Cp}]$$

5. Facilitated Diffusional Transport

Combining these equations together:

$$N_{S^*} = k_2[\text{S–Cp}] = \frac{k_2 C_{TOT}}{1 + \frac{k_{-1} + k_2}{k_1} \cdot \frac{1}{[S]}}$$

Define: $V_{max} = k_2 C_{TOT}$

$$K_m = \frac{k_{-1} + k_2}{k_1}$$

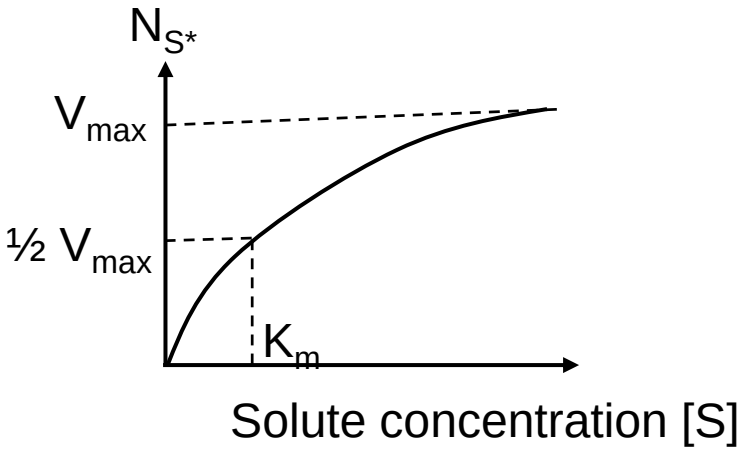
$$N_{S^*} = \frac{V_{max} \cdot [S]}{K_m + [S]}$$ (kinetics of product formation in enzyme-catalyzed reactions)

Assuming transporter protein confirmation change is the rate-limiting step, $k_2 << k_1$

$$K_m \approx \frac{k_{-1}}{k_1} = K_d$$ (dissociation constant for the binding of solute to transporter)

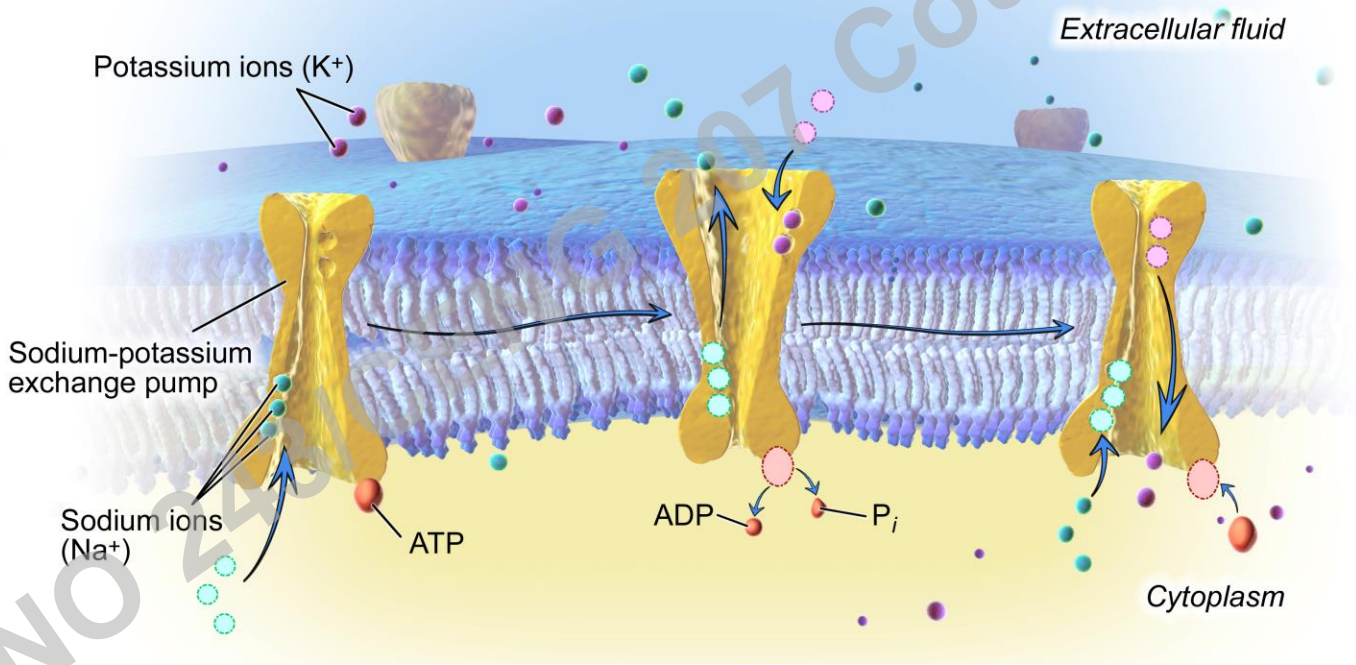
K_m: "Affinity" of the solute to transporter protein

Max(N_{S^*}) = V_{max}
when [S] is very high (binding is saturated)



6. Active Transport

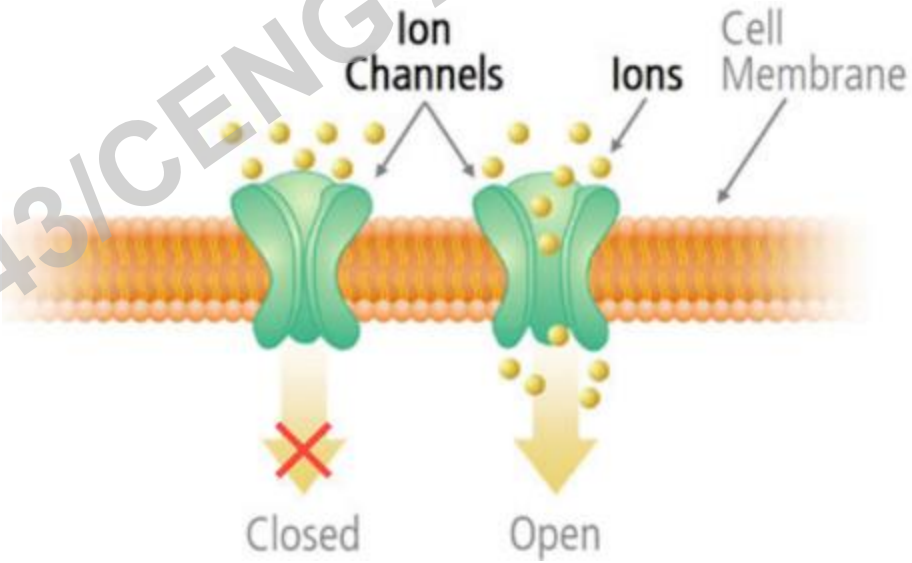
- Active transport also involves the participation of transmembrane proteins that bind a specific solute.
- Energy is required to drive the conformational change that leads to solute transport.



e.g., Na^+/K^+ pump: each cycle 3 Na^+ to extracellular; 2 K^+ to intracellular

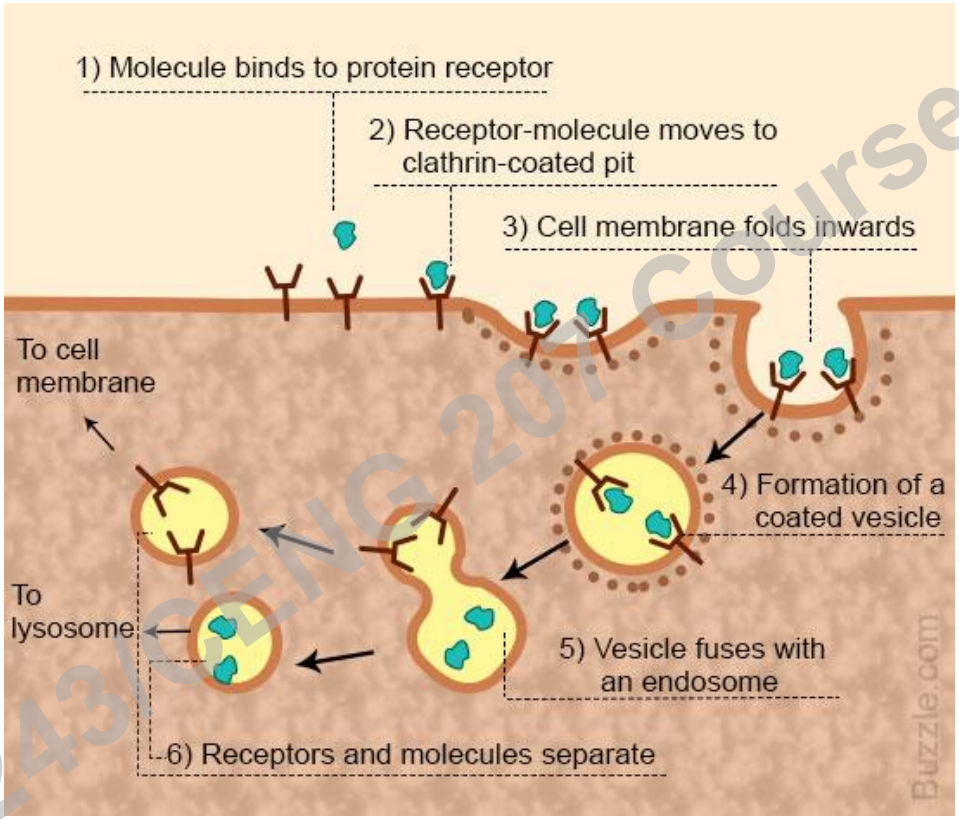
7. Ion Channel

- Ion channels are pore-forming proteins that help establish and control the small voltage gradient across the plasma membrane to enable ion movement across the membrane.
- The close/open state of the channel is regulated by extracellular or intracellular conditions
  - Voltage-gated channel (membrane potential)
  - Ligand-gated channel (ligand molecule binds to extracellular receptor)
  - Mechanosensitive ion channel (mechanical stretching)



8. Ligand-Receptor Mediated Endocytosis

- Binding of some ligands to membrane receptor proteins can lead to rapid internalization of both receptor and ligand by a process called endocytosis.



- Early endosome → late endosome → lysosome
- Receptor: recycled or digested (degraded)
- Ligand: escape from endosome or degraded in lysosome