

Transport across cell membrane

1. Non-carrier mediated

- Diffusion
- Osmosis

2. Carrier-mediated

- Facilitated diffusion
- Active transport

3. Vesicle mediated

- Exocytosis
- Endocytosis
 - Pinocytosis
 - phagocytosis

Non carrier mediated

Diffusion

- Diffusion is the tendency for molecules to spread out evenly into the available space
- Substances diffuse down their concentration gradient, the difference in concentration of a substance from one area to another
- The diffusion of a substance across a biological membrane is passive transport because it requires no energy from the cell to make it happen

Rate of Diffusion dependent upon

- The magnitude of concentration gradient.
- Permeability of the membrane.
- Temperature.
 - Higher temperature, faster diffusion rate.
- Surface area of the membrane.
 - Microvilli increase surface area.

The rate of diffusion of a gas into a liquid is:

- Directly proportional to:
 - the partial pressures of the gas above the liquid
 - surface area of available for gas exchange
 - solubility co-efficient of the gas
- Inversely proportional to:
 - Gram molecular weight of the molecules
 - Thickness of the membrane



Fick's Law

✓ Diffusion Equation

$$\dot{V}_{gas} = \frac{D * (P_1 - P_2) * A}{T}$$

- Diffusion Coefficient (D)
- Partial pressure gradient ($P_1 - P_2$)
- Surface area (A)
- Thickness of barrier (T)

$$V_{gas} \propto \left(\frac{A}{T} \right) \times D \times (P_1 - P_2)$$

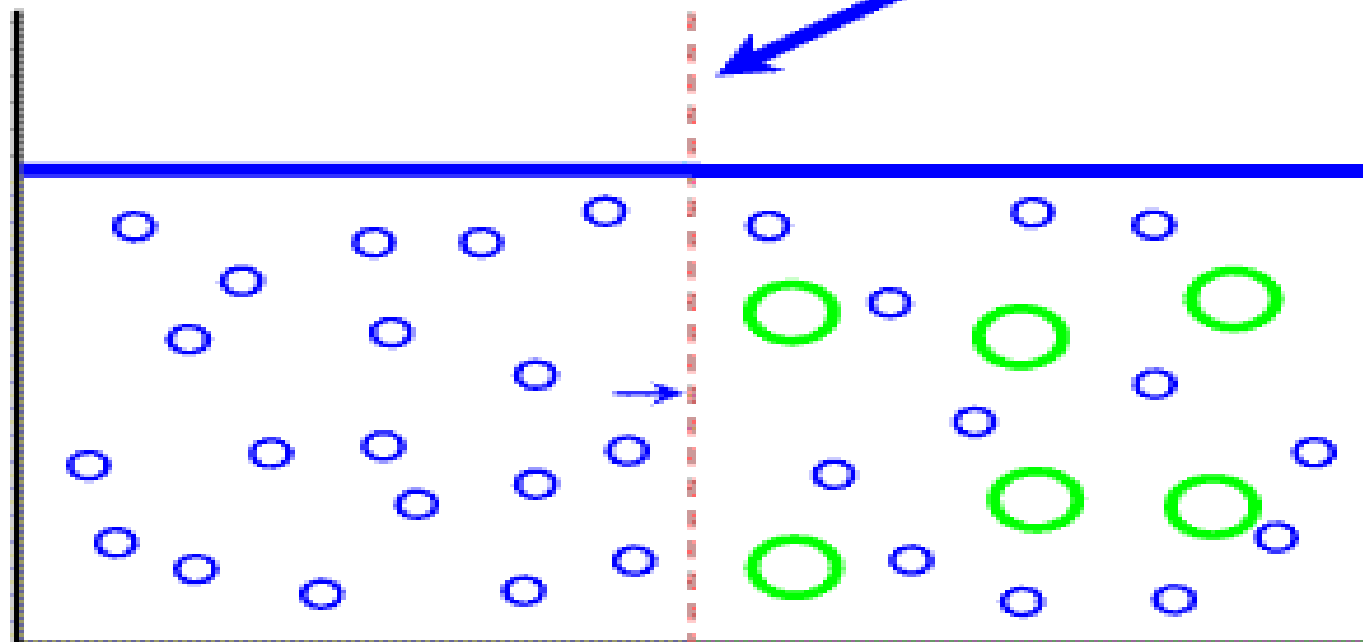
Osmosis

- **Osmosis** is the diffusion of water across a selectively permeable membrane
- Water diffuses across a membrane from the region of lower solute concentration to the region of higher solute concentration

Osmosis

○ - Water
○ - Sugar

Selectively Permeable Membrane



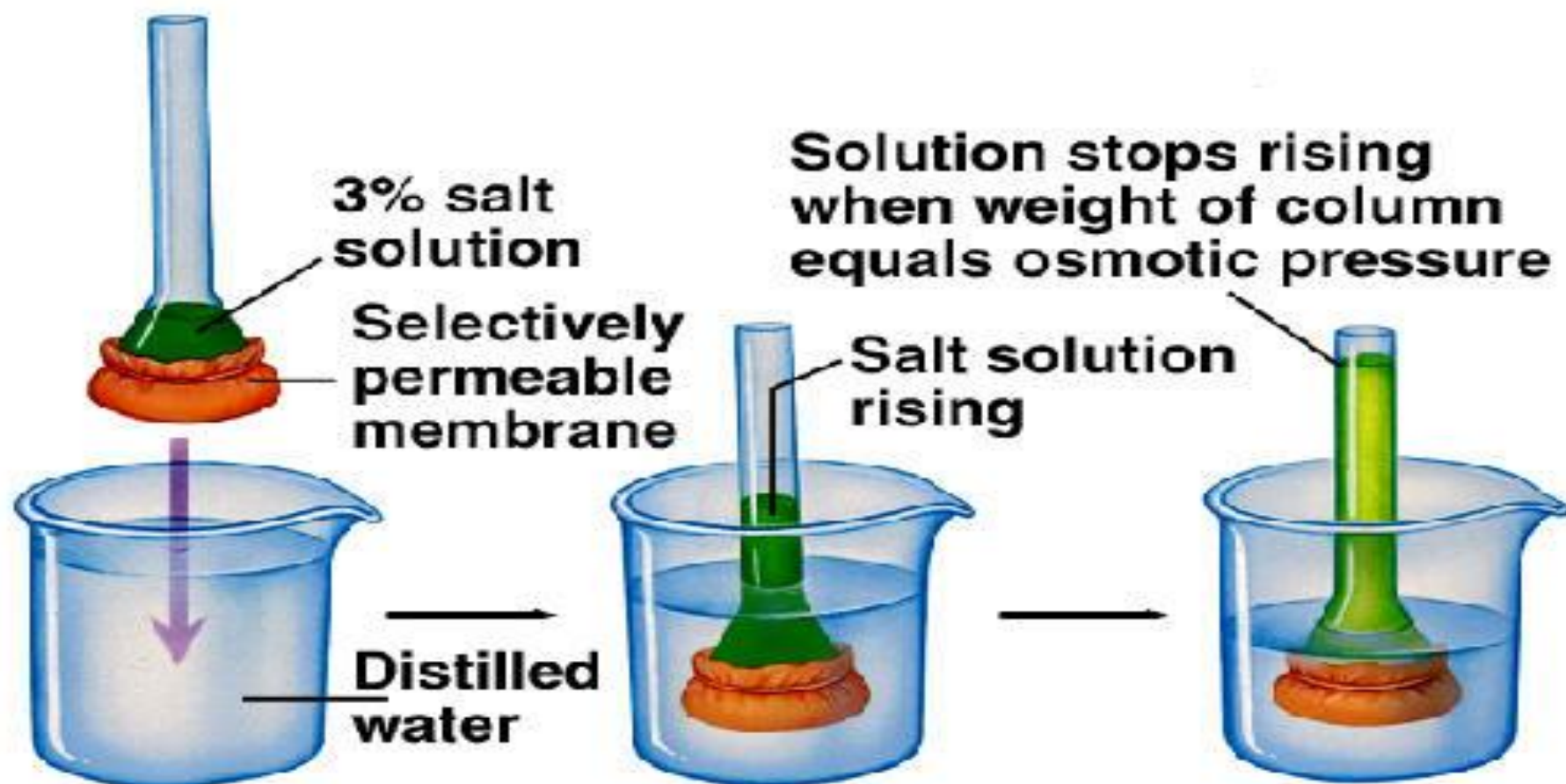
Low Sugar Concentration
High Water Concentration

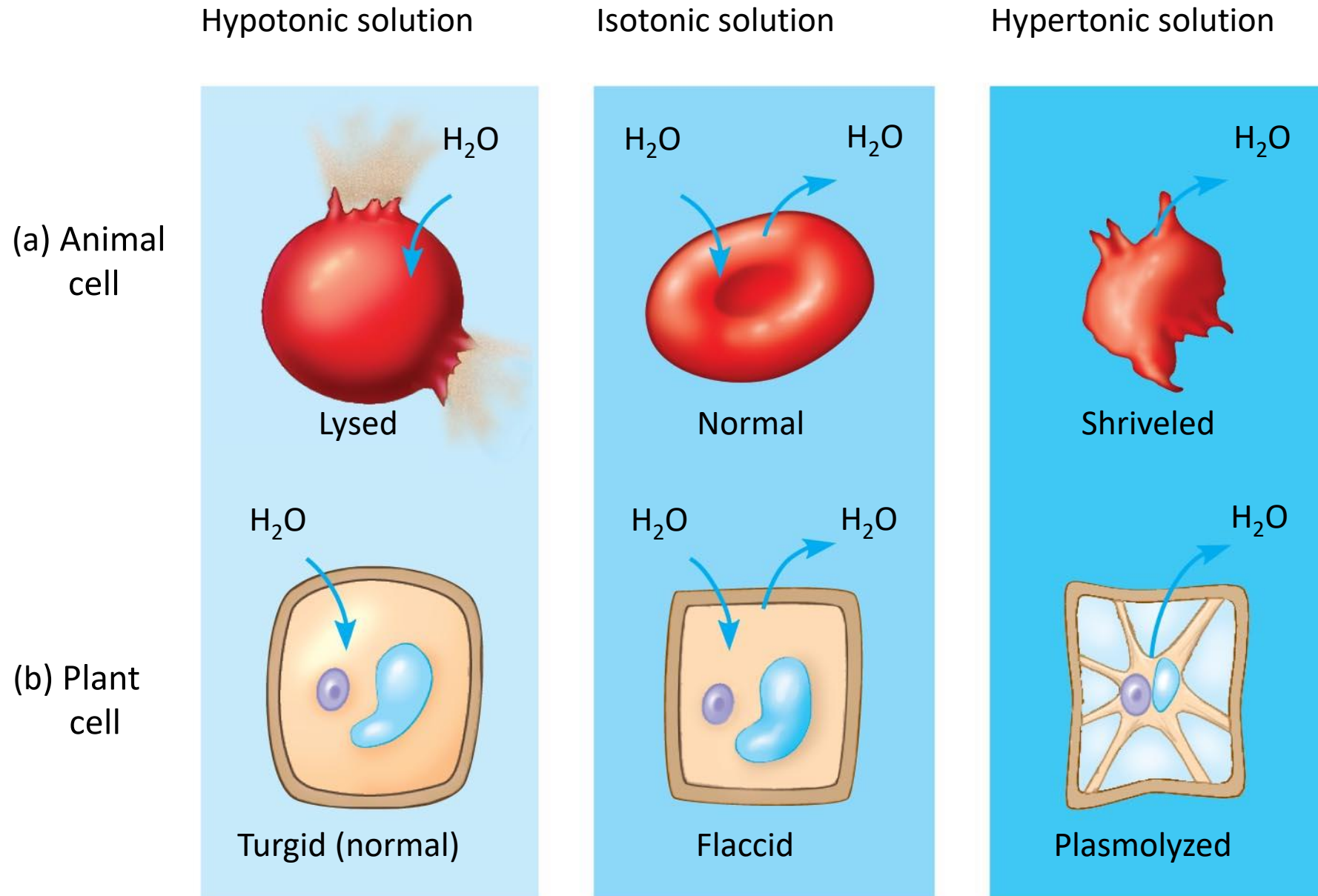
High Sugar Concentration
Low Water Concentration

Water Balance of Cells Without Walls

- **Tonicity** is the ability of a solution to cause a cell to gain or lose water
- **Isotonic** solution: Solute concentration is the same as that inside the cell; no net water movement across the plasma membrane
- **Hypertonic** solution: Solute concentration is greater than that inside the cell; cell loses water
- **Hypotonic** solution: Solute concentration is less than that inside the cell; cell gains water

Osmosis Demonstration





OSMOSIS	DIFFUSION
It involves movement of solvent molecules	It involves movement of solute molecules
Molecules move from lower concentration of solute to higher concentration of solute	Molecules move from higher concentration of solute to lower concentration of solute
It occurs only across a semi-permeable membrane	It does not require semi-permeable membrane
Example: Shrinking of Potato slice when kept in concentrated sucrose solution	Example: Spreading of ink when a drop of it is put in a glass of water.

Reverse osmosis

A way to get clean water out of dirty water or salt water by forcing water under pressure through a membrane. An example of reverse osmosis is the **process** of filtering polluted water under pressure.

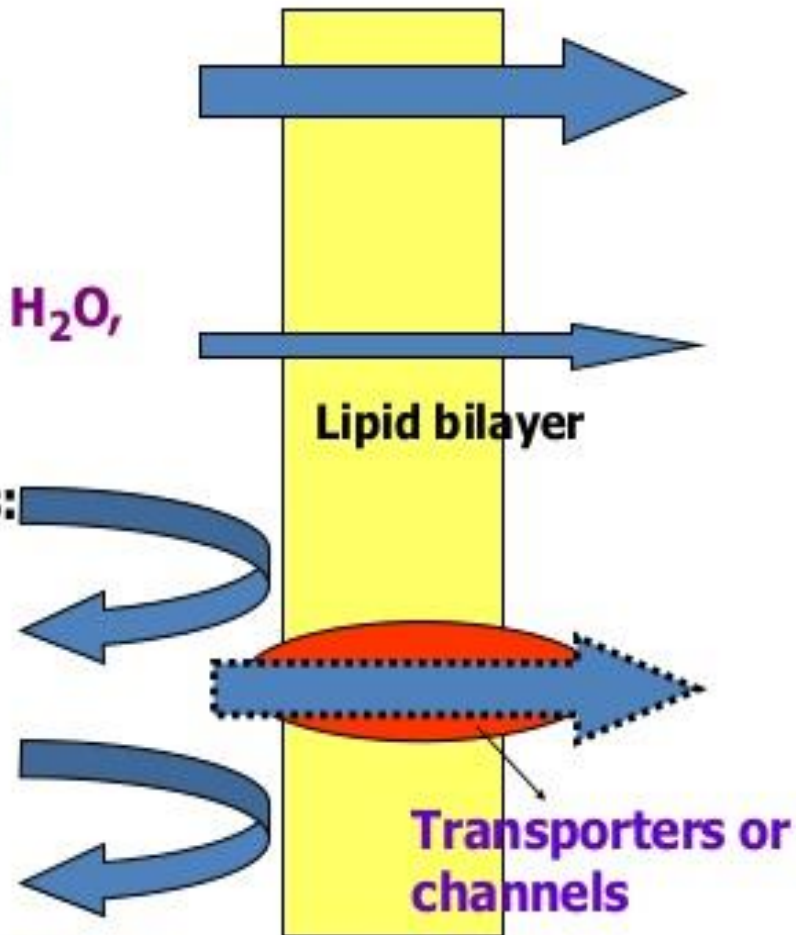
Plasma membrane is a semi-permeable (selective) membrane

Small hydrophobic molecules: O_2 , CO_2 , N_2 , benzene

Small uncharged polar molecules: H_2O , ethanol, glycerol

Larger uncharged polar molecules: glucose, amino acid, nucleotides

Ions: H^+ , Na^+ , HCO_3^- , K^+ , Ca^{2+} , Mg^{2+} , Cl^- , etc.

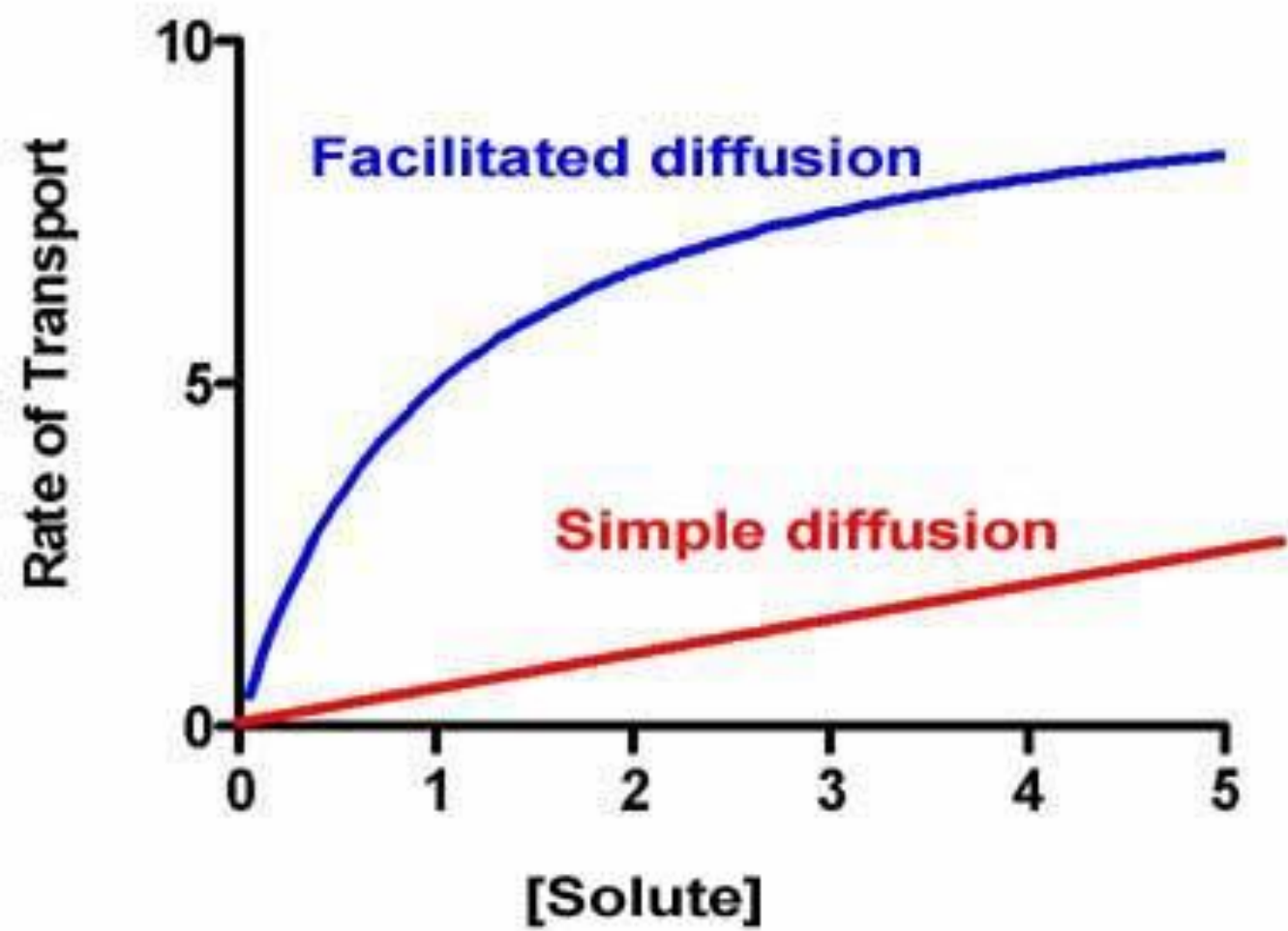


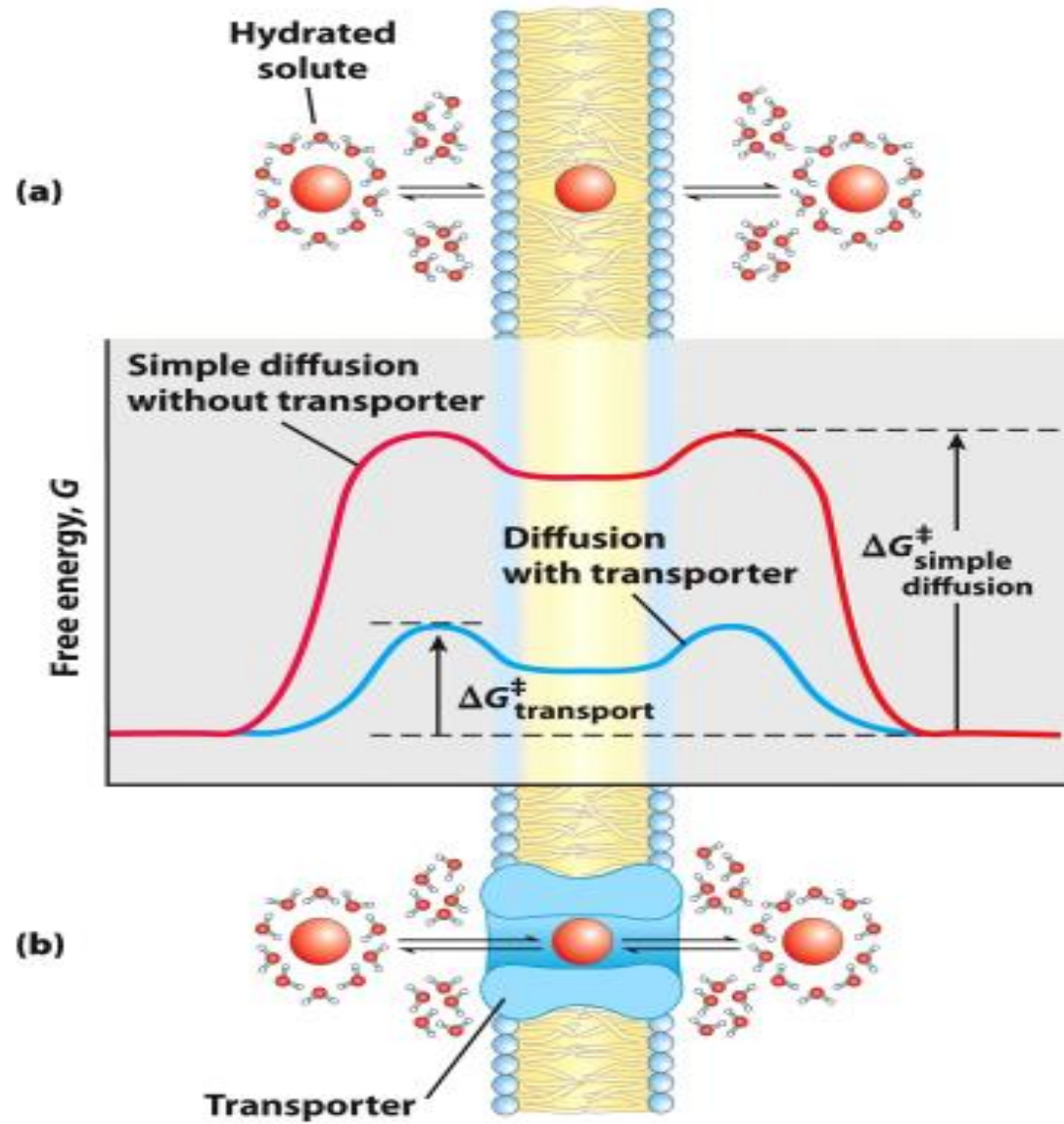
Facilitated Diffusion: Passive Transport Aided by Proteins

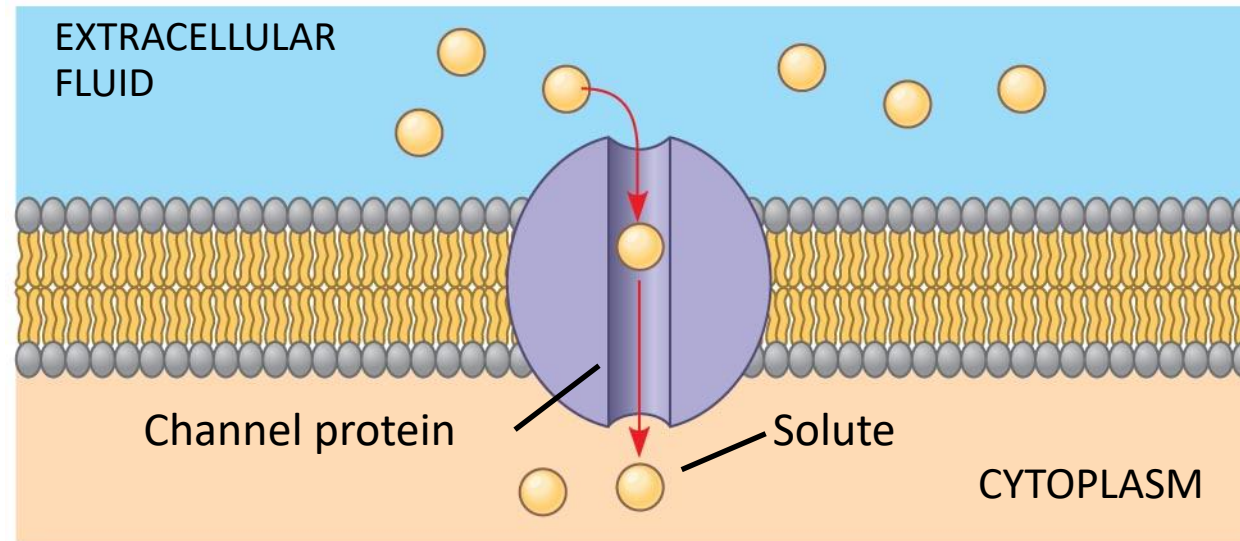
- Ion channels that open or close in response to a stimulus (gated and nongated channels)
- Aquaporins, for facilitated diffusion of water
- Glucose Transporter
- Bicarbonate-chloride Co- transporter

Channels and Transporters differs in

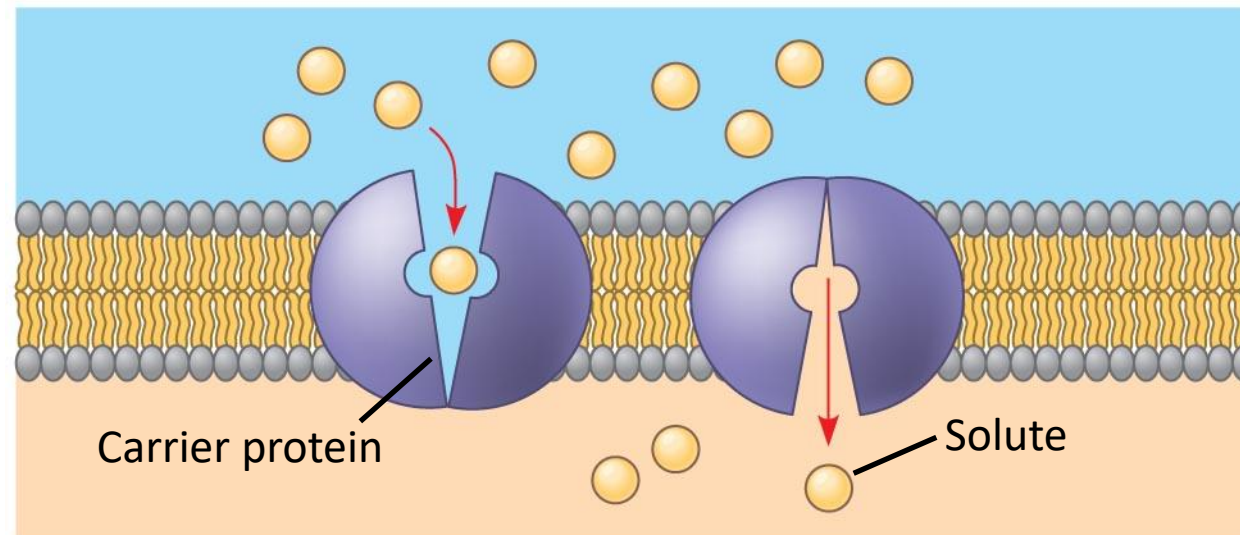
1. Stereo specificity
2. Rate Of Diffusion
3. Saturation







(a) A channel protein



(b) A carrier protein

Summary of transport pathways for solutes across the cell membrane

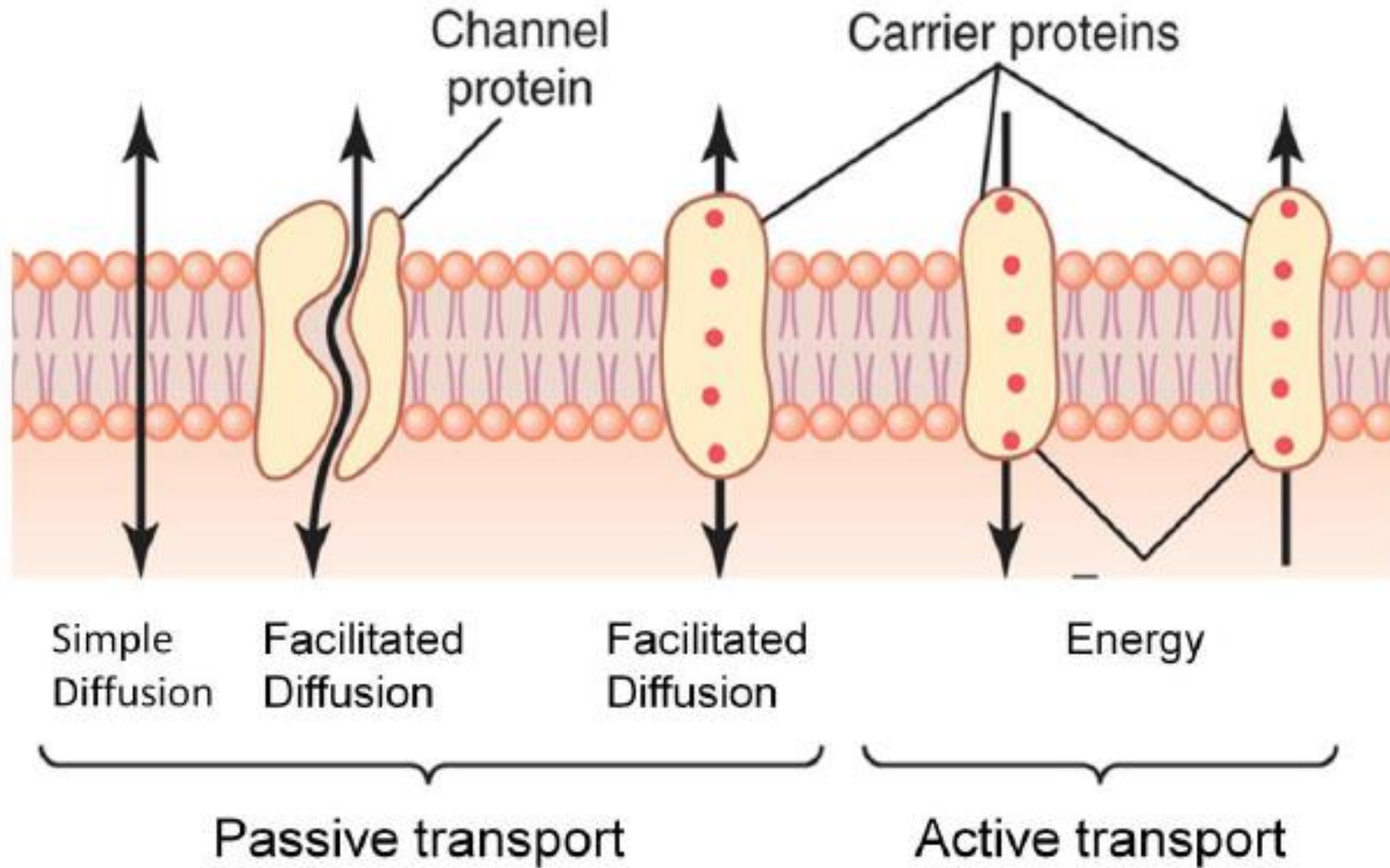
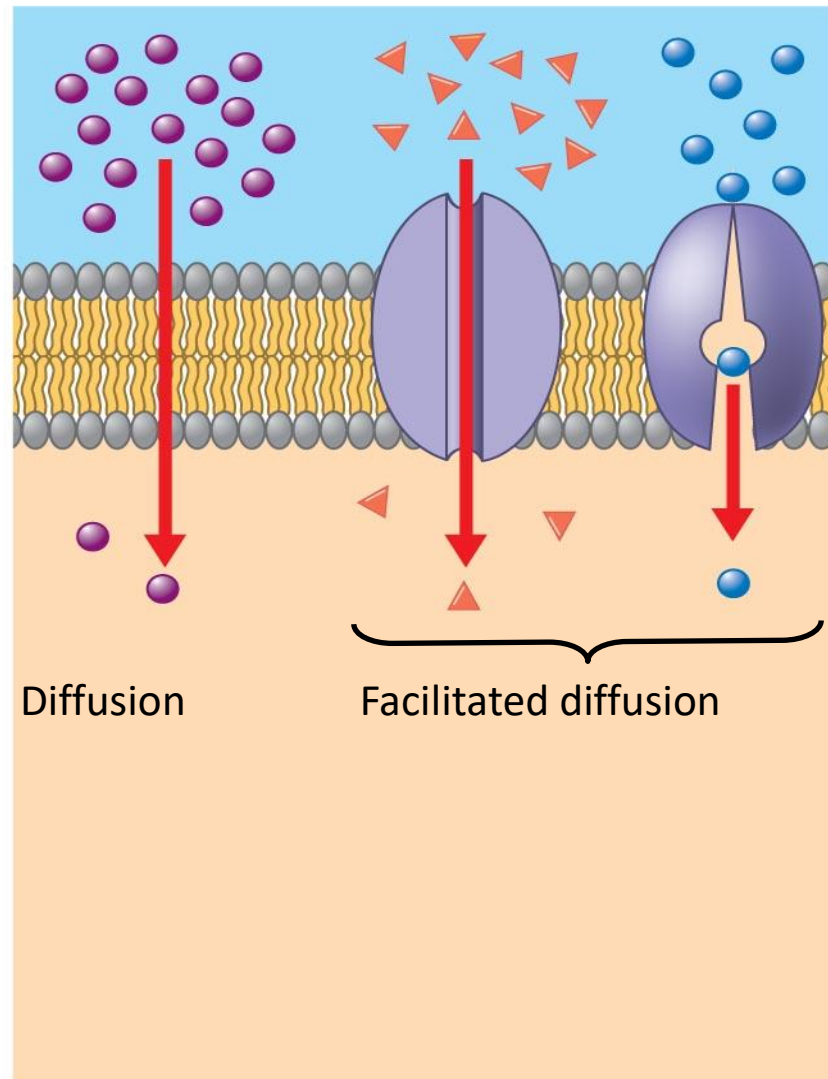


Fig. 7-17

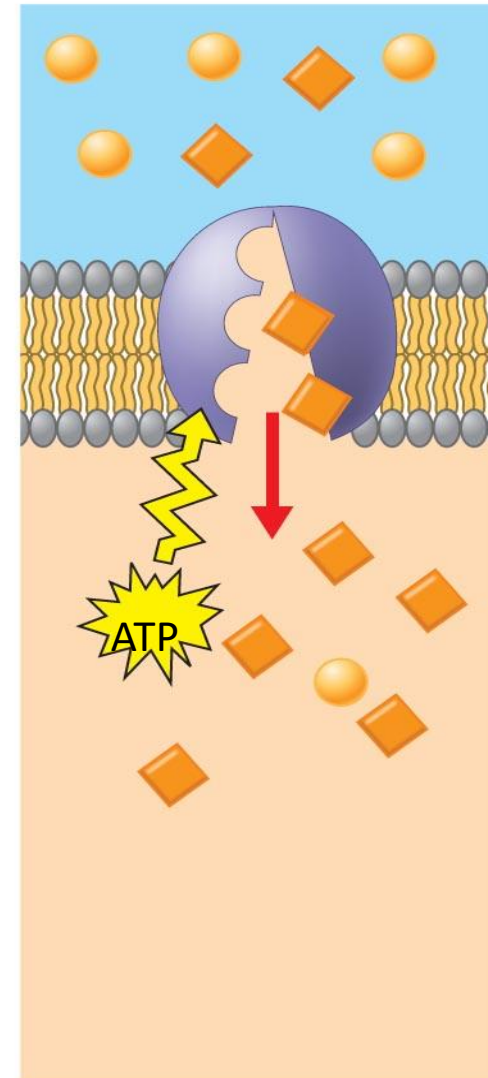
Passive transport



Diffusion

Facilitated diffusion

Active transport



Ion Channels: Structure and Function

Ion channels are membrane protein complexes

Ion channels provide a high conducting, **hydrophilic pathway** across the hydrophobic interior of the membrane.

The channel, or pore structure, is said to catalyze the 'reaction' of transporting charged molecules across The 'catalytic site', the central channel, is either *open or closed*.

The open channel conformation can be compared to the transition state of the enzyme-substrate complex, where ions are tightly associated to the catalytic site.

The conformational change between closed and open state is called *gating*.

Ion channels can be *classified according to which chemical or physical modulator controls their gating activity*.

➤ Leakage (ion) channel = Nongated (ion) channel

➤ Gated (ion) channel

- **Leakage (ion) channel = Nongated (ion) channel** - an integral membrane protein which is an ion channel within a cell's outer cell membrane which is always open and permits the diffusion of one or more ions in the direction which is in accord with their concentration and charge gradients.
- **Gated (ion) channel** - an integral membrane protein which is an ion channel within an excitable cell's outer cell membrane which opens and closes in response to some stimulus, ie..Membrane potential (voltage) changes, the arrival and binding of a specific ligand or signal molecule (hormone, neurotransmitter, local hormone) or to mechanical pressure or to light energy.

Voltage gated (ion) channel –

Opens and closes in response to a stimulus which is a change in membrane potential (voltage)

Propagation in excitable cells such as neurons, muscle cells, and gland cells

Chemically gated (ion) channel –

Opens and closes in response to a stimulus which is the arrival and binding of a specific ligand or signal molecule (hormone, neurotransmitter, local hormone)

Mechanically gated (ion) channel

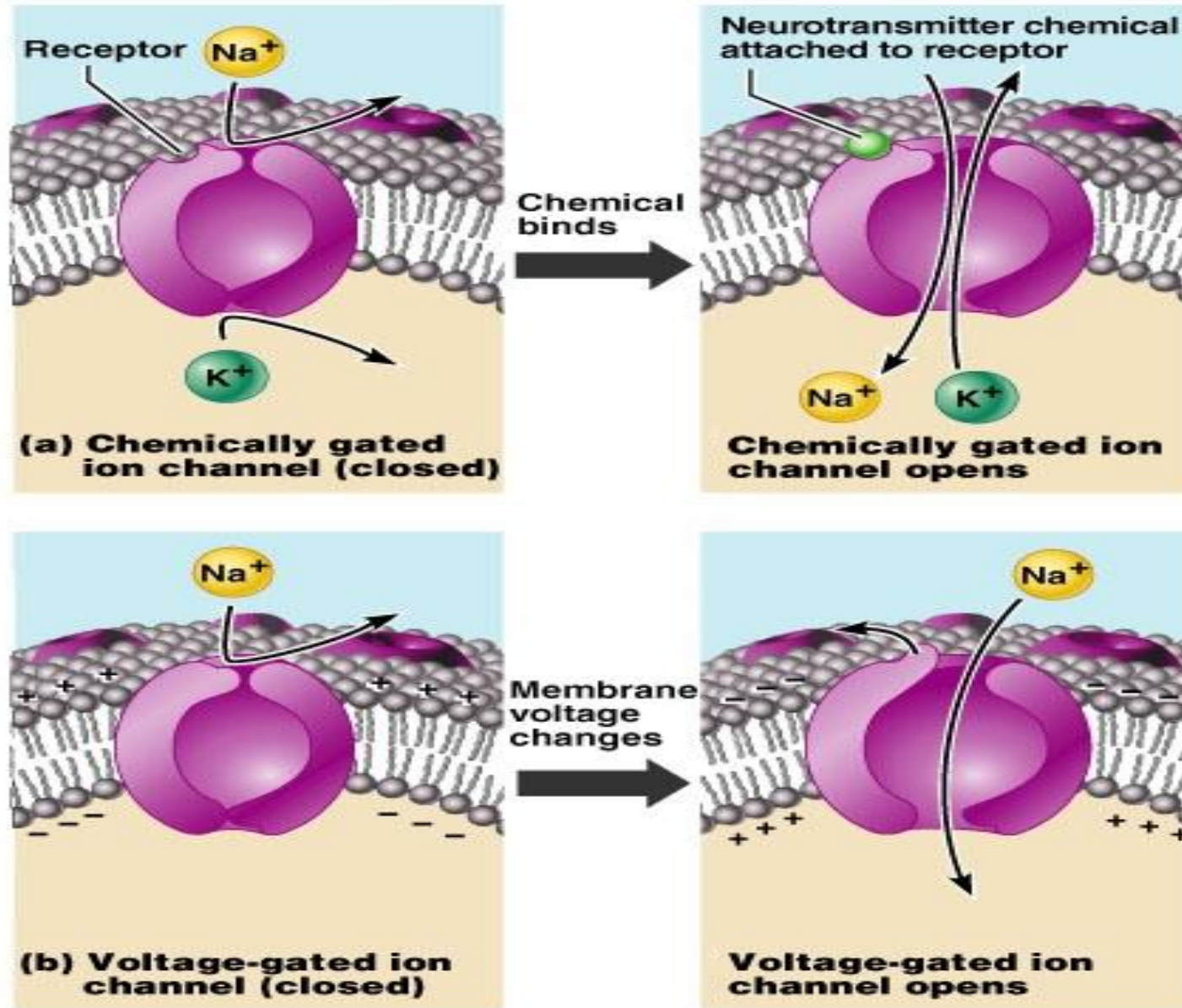
opens and closes in response to a stimulus which is a mechanical pressure or vibration;

(sensory cell responding to touch, vibration, compression or stretch).

Light-gated (ion) channel –

a photosensitive excitable cell's outer cell membrane which opens in response to a stimulus which is the arrival of a photon of light energy;

(sensory cells, rods and cones responding to light in the retina of the eye).



Ionophores-Valinomycin(K^+), Monensin(Na^+)

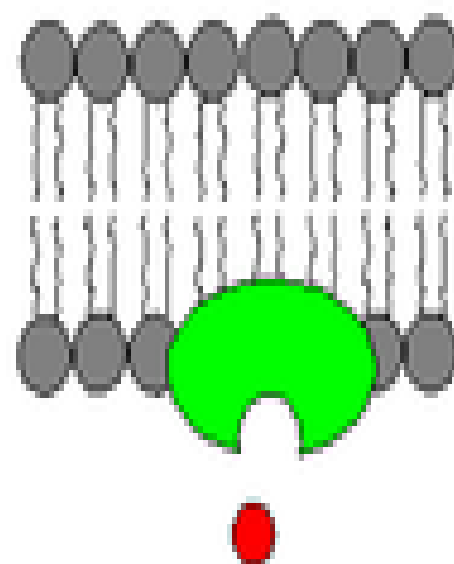
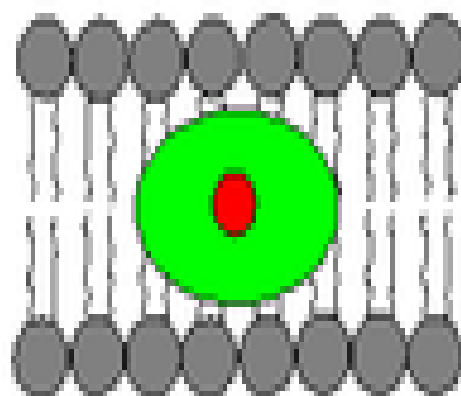
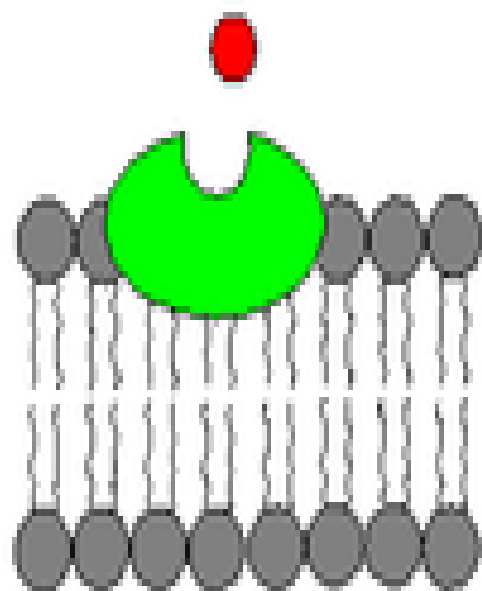
An ionophore is a chemical species that reversibly binds ion
Neutralises the charge of ions and carry them down its
concentration gradient.

Disrupts secondary transport processes.

Thus kills microbial cells

Carrier ionophores that bind to a particular ion and shield its charge from the surrounding environment. This makes it easier for the ion to pass through the hydrophobic interior of the lipid membrane. valinomycin, potassium cation. Carrier ionophores may be proteins or other molecules.

Channel formers that introduce a hydrophilic pore into the membrane, allowing ions to pass through without coming into contact with the membrane's hydrophobic interior. An example of a channel former is gramicidin A. Channel forming ionophores are usually large proteins.

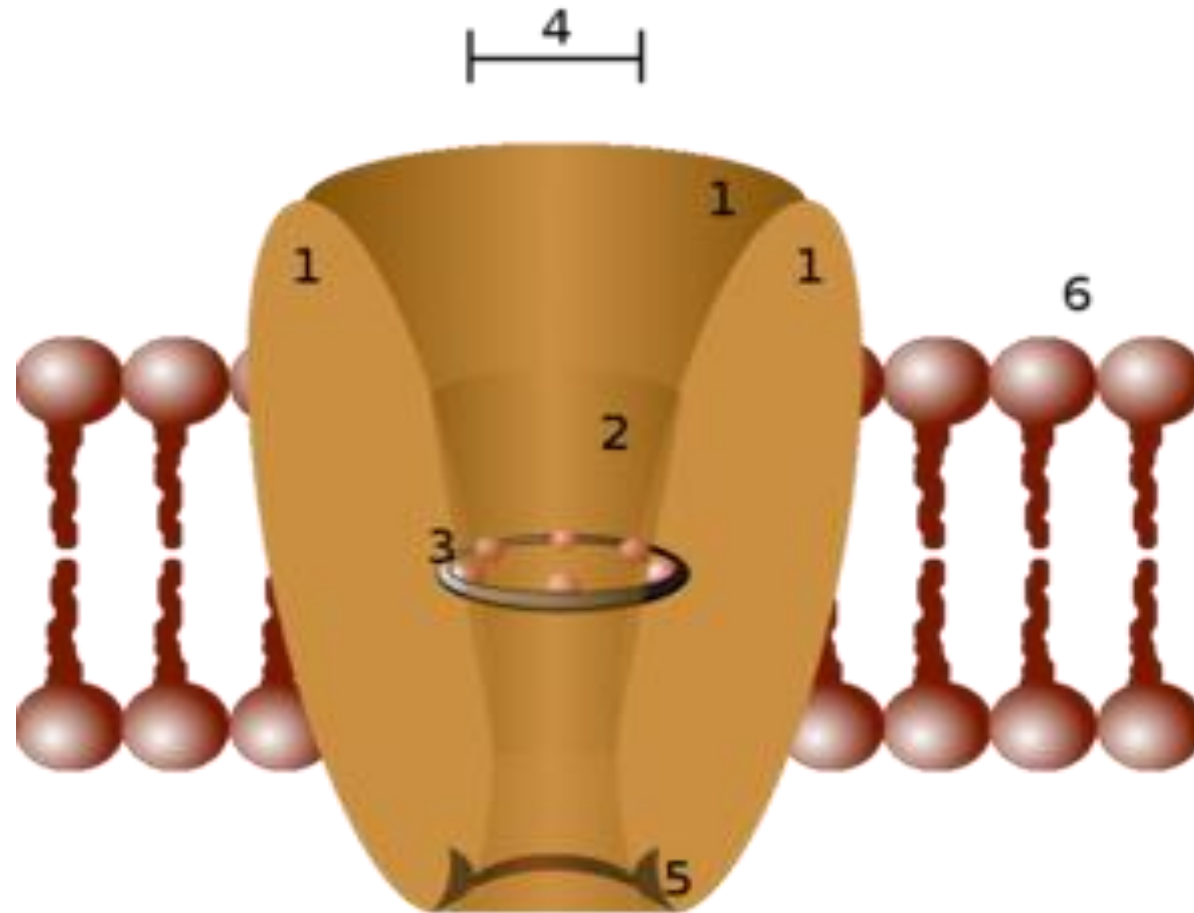


- **Tetrodotoxin (TTX)**, used by puffer fish and some types of newts for defence. It blocks sodium channels.
- **Saxitoxin** is produced by a dinoflagellate also known as "Red tide". It blocks voltage-dependent sodium channels.
- **Conotoxin** is used by Cone snails to hunt prey.
- **Lidocane** and **Novocane** belong to a class of local anaesthetics which block sodium ion channels.
- **Dendrotoxin** is produced by Mamba snakes, and blocks potassium channels.
- **Iberiotoxin** is produced by the *Bunthus tamulus* (Eastern Indian scorpion) and blocks potassium channels.
- **Heteropodatoxin** is produced by *Heteropoda venatoria* (brown huntsman spider or laya) and blocks potassium channels.

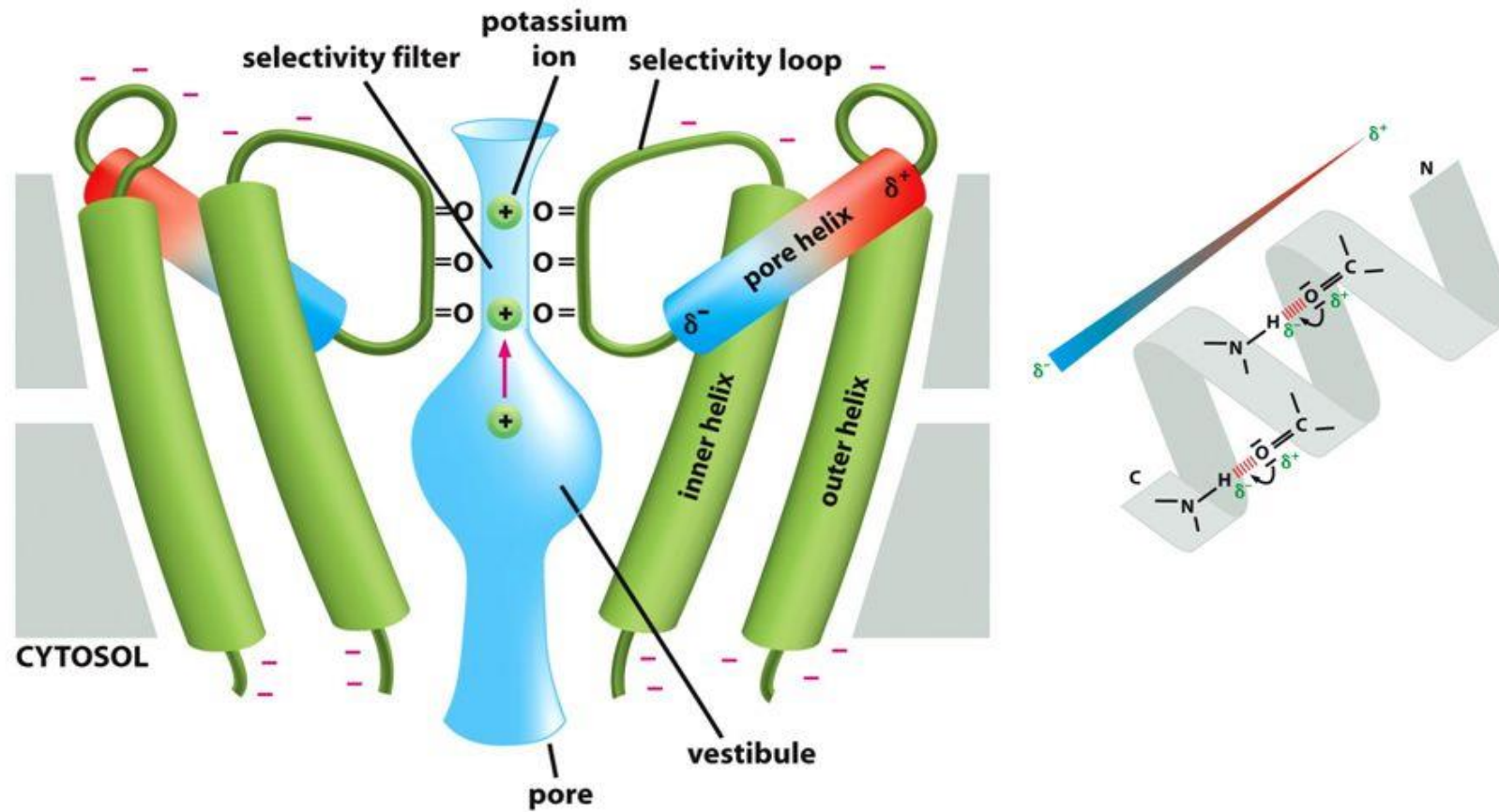
Block acetylcholine receptors or prevent the opening of its ion channel

- Turbocurarine or curare- Arrow poison in Amazon region-
- Cobratoxin- Cobra
- Bungaro toxin- Krait

Ion channels



The three-dimensional structure of a bacterial K^+ channel shows how an ion channel can work



The structure of a *bacterial* K⁺ *channel* was determined by x-ray crystallography

- The channel is made from four identical transmembrane subunits, which together form a central pore through the membrane.
- Negatively charged amino acids are concentrated at the cytosolic entrance to the pore and are thought to attract cations and repel anions, making the channel cation-selective.
- Each subunit contributes two transmembrane helices, which are tilted outward in the membrane and together form a cone, with its wide end facing the outside of the cell where K⁺ ions exit the channel.

- The polypeptide chain that connects the two transmembrane helices forms a short α helix (the *pore helix*) and a crucial loop that protrudes into the wide section of the cone to form the selectivity filter.
- The selectivity loops from the four subunits form a short, rigid, narrow pore, which is lined by the carbonyl oxygen atoms of their polypeptide backbones. Because the selectivity loops of all known K^+ channels have similar amino acid sequences, it is likely that they form a closely similar structure. (GYGVT)
- The crystal structure shows two K^+ ions separated by about 8 Å. Mutual repulsion between the two ions is thought to help move them through the pore into the extracellular fluid.

- 5 oxygen rings (4 carbonyl, 1 threonyl) Each ring with 4 O atoms
- 8 O atoms can coordinate with a single K^+ ion replacing its normal water of hydration.
- 4 K^+ binding sites, but only 2 are occupied at a time.
- Na^+ smaller ,can't perfectly co-ordinate with carbonyl oxygens.

Carrier/Transporter proteins undergo a subtle change in shape that translocates the solute-binding site across the membrane

1.Uniporter

2.Co transporter

- Symporter

- Antiporter

Aquaporins -water channels

- AQP1- water reabsorption PCT, Aqueous humour secretion
- AQP2- Renal collecting duct(ADH/Vassopressin)
- AQP3-Water retention in collecting duct
- AQP4-CNS
- AQP5-Salivary gland
- AQP7-Glycerol and urea, adipocytes
- γ tip- Plant vacuole, turgor pressure

Transport proteins/carrier proteins speed the passive movement of molecules across the plasma membrane

-Glucose transporters

Glut-1 Ubiquitous

Glut-2 Liver, pancreas islets, intestine-insulin release regulation

Glut-3 Brain

Glut-4 Muscle, adipocytes,

Glut-5 Intestine, testis, kidney, sperm-Fructose

Glut-6 Spleen, leucocytes, brain- No transporter function

Chloride-bicarbonate exchanger

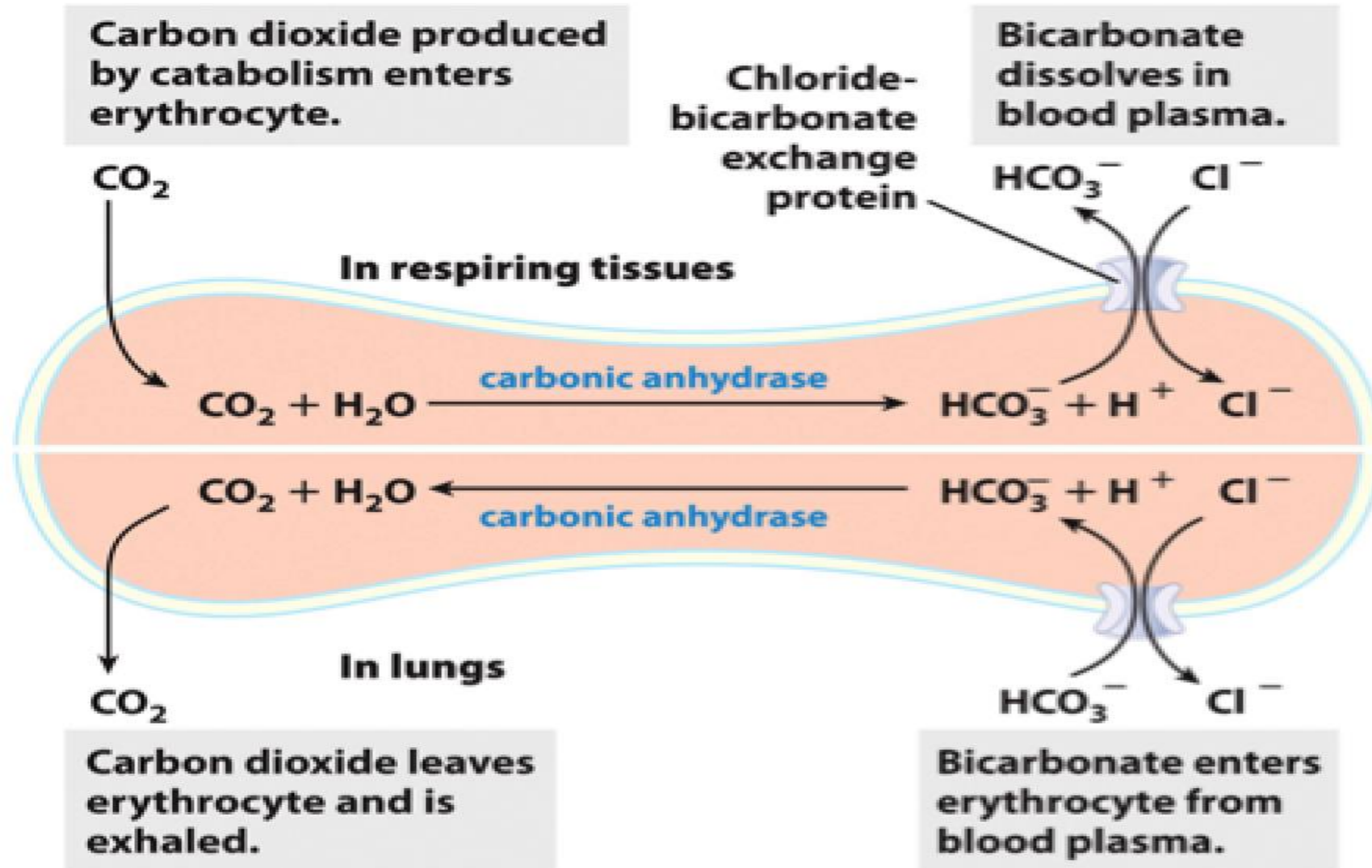
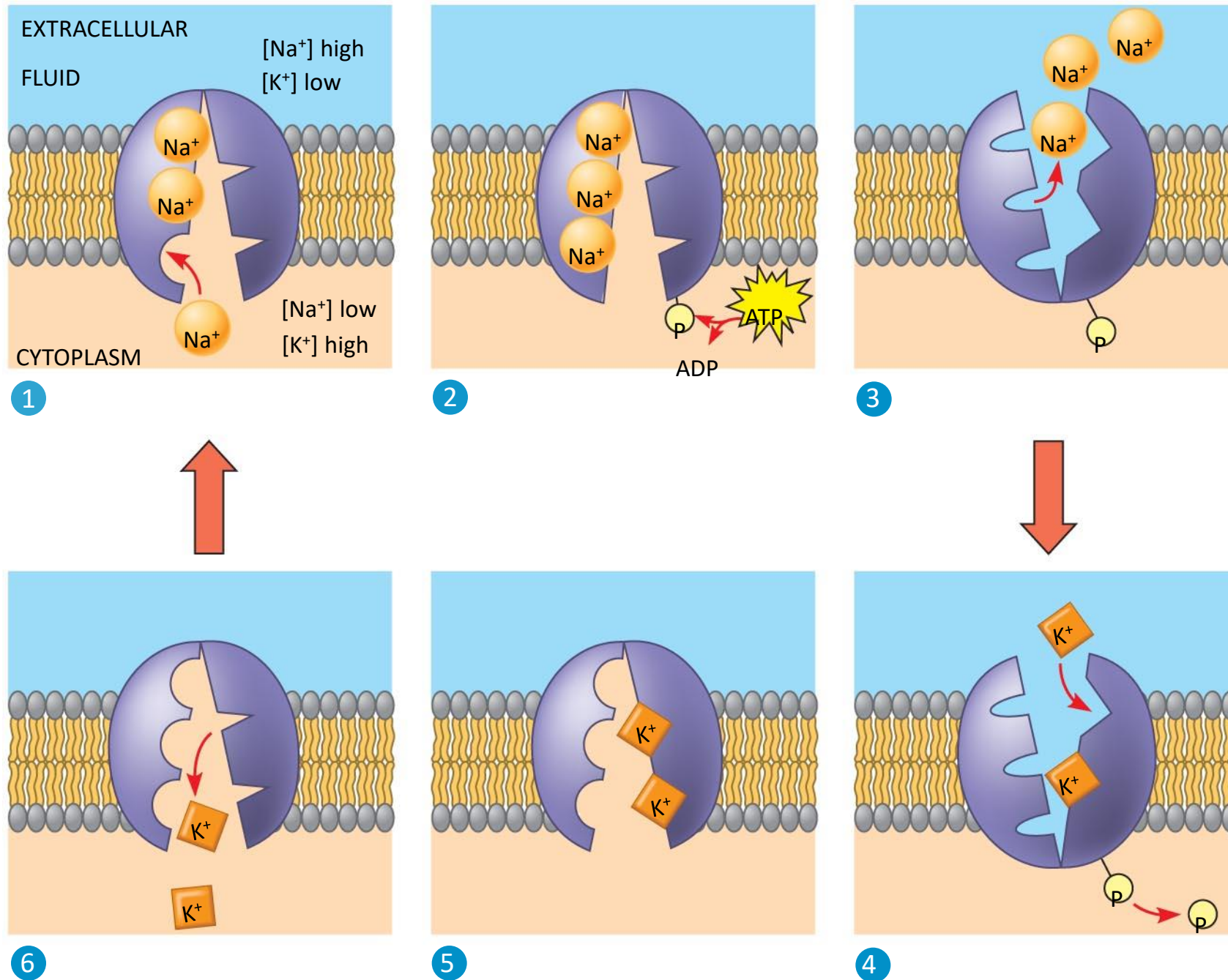
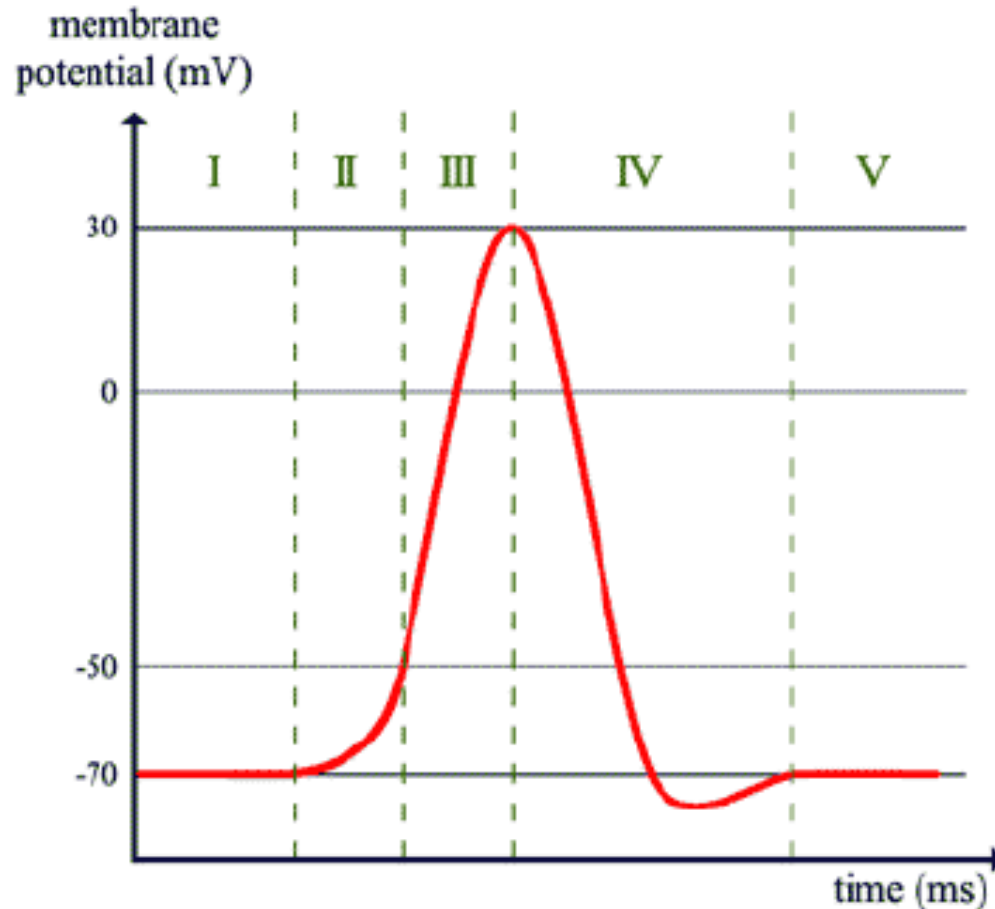


Fig. 7-16-7



- A resting (non-signaling) neuron has a voltage across its membrane called the **resting membrane potential**, or simply the **resting potential**.
- The resting potential is determined by concentration gradients of ions across the membrane and by membrane permeability to each type of ion.



ACTION POTENTIAL :

I : Resting state

I-II : Stimulation

II&III : Depolarization

IV : Repolarization & hyperpolarization

V : Resting state

IONIC SCALE :

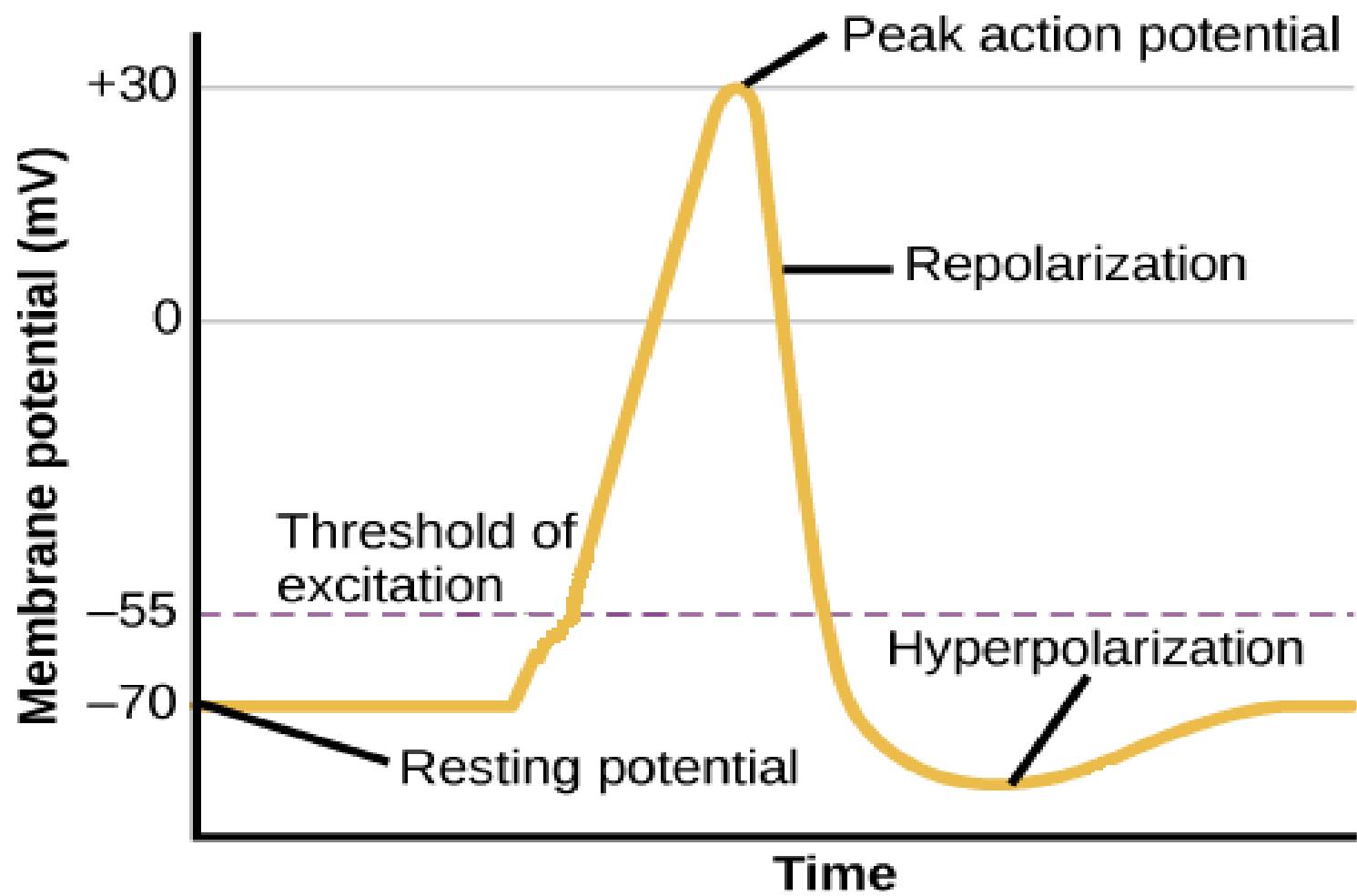
II : Sodium channels open

III : More sodium channels open

III-IV : Sodium channels close

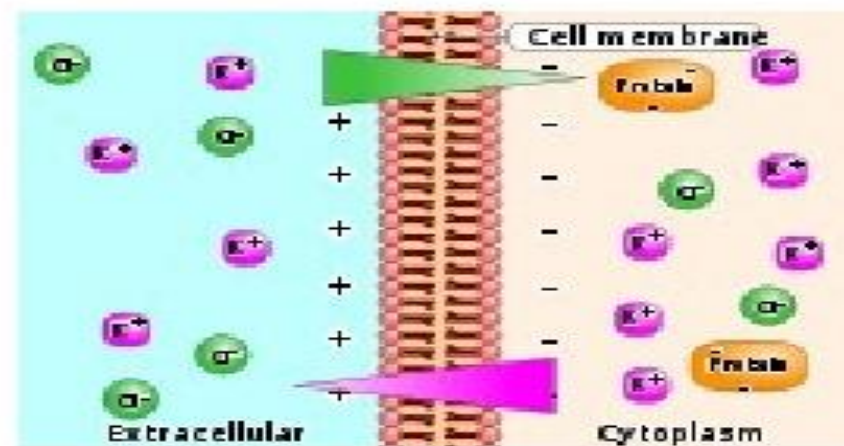
III-IV : Potassium channels open

IV-V : Potassium channels close



Gibbs Donnan Equilibrium

- When two solutions containing ions are separated by membrane that is permeable to some of the ions and not to others an electrochemical equilibrium is established
- Electrical and chemical energies on either side of the membrane are equal and opposite to each other



- $10K^+, 10P^- = 10K^+, 10Cl^-$
- Cl^- gradient (5 Cl^- -move in So 5=5) ionic gradient
- Electric gradient-Inside more Negative will attract K^+ ions ,So $15K^+ = 5K^+$ (Ele.Gra)..balanced EG
- $15K^+, 5Cl^-, 10P^- == 5K^+, 5Cl^-$
- Then K^+ gradient develop
- So 3 K^+ move out ...12 $K^+ = 8K^+$
- Electrical gradient

- When both gradients equal G.D Equilibrium
- Presence of an impermeable molecule will initiate unequal distribution of charges

Calculating equilibrium potential The Nernst Equation

- at which an ion will be in electrochemical equilibrium.

At this potential: total energy inside = total energy outside

$$\text{Equilibrium potential (mV), } E_{\text{ion}} = E_K = \frac{RT}{ZF} \log \frac{[K^+]_o}{[K^+]_i}$$

Electrical Energy Term: zFV

Chemical Energy Term: $RT \cdot \ln[\text{Ion}]$

$$\begin{aligned} E_K &= -90\text{mV} \\ E_{Na} &= +60\text{mv} \end{aligned}$$

Z is the charge, 1 for Na^+ and K^+ , 2 for Ca^{2+} and Mg^{2+} , -1 for Cl^-

F is Faraday's Constant = 9.648×10^4 Coulombs / mole

R is the **Universal** gas constant = 8.315 Joules / °Kelvin * mole

T is the absolute temperature in °Kelvin

Examples of diffusion in living systems

Location	Substances	From	To	Adaption
lung	oxygen	air space	red blood cells	alveoli (moist lining, good blood supply)
lung	carbon dioxide	blood plasma	air space	alveoli (moist lining, good blood supply)
digestive system	food molecules eg glucose	stomach, intestine	blood	villi, microvilli, good blood supply
uterus	food molecules and oxygen	mother's blood supply	foetus's blood supply	placenta with villi, thin walls and good blood supply
leaf	oxygen	leaf cell	air space	thin leaves, with air spaces and spongy layer

Everyday examples of Diffusion

Some everyday examples of diffusion are:

1. Smelling your mother's cooking from the kitchen while you are studying in the living room.
2. Smelling garbage on the street before you can see the garbage truck.
3. Smelling someone's perfume.
4. A drop of ink spreading to colour the water in a beaker, without stirring.

- In the digestive system, osmosis plays a key role in nutrient absorption. Osmosis allows your body to absorb these nutrients into the intestines and individual cells.
- Cells get rid of their waste by osmosis.
- Osmosis is largely important to plants because the root cells absorb water by this process.

Osmosis Examples in Daily Life

▶ When your hands are immersed in dishwater for a long time, your skin looks bloated. This is an effect of osmosis.

When you pour salt onto a slug, water diffuses and slug shrinks as a result of osmosis.

When you cook food and put sauce in the liquid part of your dish, some part of the solute moves inside the solid part of the food you are cooking. The solid part could be an egg, piece of meat but the sauce is made of solute and not water, so it will move into the food.

...

Osmosis also plays an important part in the body .

“It helps in the transfer of water and various nutrients between blood and fluid of cells”.

“Plants also use osmosis to take in water and minerals essential for its growth “ .

“Reverse osmosis is a type of osmosis which is used to convert sewage water into clean drinking water”

Van Hoff's theory of Osmotic pressure

- Solute particles in solutions possess kinetic energy and move in random directions
- Similar behaviour as Gas molecules
- They exert OP against semipermeable membrane

VanHoff's Equation

- VanHoff's Boyles law of solution

$$\pi \propto 1/v \text{ (because } C=n/V \text{)}$$

- VanHoff's Charles law of solution

$$\pi \propto T$$

- General equation

$$\pi = T/V$$

$$\pi V = KT$$

$$\pi V = RT \text{ for 1 mole}$$

$$\pi V = nRT \text{ for } n \text{ moles}$$

$$\pi = n/V \cdot RT$$

$$\pi = CRT$$

STEADY STATE DIFFUSION

- *At Steady state* - conditions do not vary with time
- In case of diffusion mass transfer remains constant with time OR mass transfer takes place at constant rate through the study and diffusion process is not allowed to attain equilibrium
- If condition vary with time then the system is under *unsteady* state

Flux

- Rate of mass transfer (dM/dt) expressed as of flux(J)
- Flux (J) is rate of mass transfer across unit surface area of a barrier and mathematically expressed as:

$$J \equiv \text{atoms} / \text{area} / \text{time}$$

$$J = \frac{1}{S} \frac{dM}{dt}$$

dM = change in mass of material, g
 S = surface area.cm²
 $d t$ = change in time.sec

Units for flux are $\text{g.cm}^{-2}\text{sec}^{-1}$ OR $\text{kg .meter}^{-2}\text{sec}^{-1}$

Flux is always positive quantity because it increases continuously during process

Fick's I law

- Fick's first law states that the flux is directly proportional to the concentration gradient

$$J \equiv \text{atoms} / \text{area} / \text{time} \propto \text{concentration gradient}$$

$$J \propto \frac{dc}{dx} \quad \text{OR} \quad J = -D \frac{dc}{dx} \dots (2)$$

flux in steady state flow

Negative sign indicates a decrease in concentration
But flux is positive quantity

dc=change in conc. of material g/cm³.

D=diffusion coefficient of a penetrant, cm/sec².

Dx=change in the distance, cm.

Combining equation $J = \frac{1}{S} \frac{dM}{dt}$ and $J = -D \frac{dc}{dx}$ i.e. $J = \frac{1}{S} \frac{dM}{dt} = -D \frac{dc}{dx}$

We get $\frac{dM}{dt} = -DS \frac{dc}{dx} \dots (3)$

Eqn 3 explains Rate of mass transfer as per Fick's first law

D is effected by temperature, pressure etc hence it is not constant it is coefficient

Fick's I law

No. of atoms
crossing area A
per unit time

$$\frac{dM}{dt}$$

=

$$-DS$$

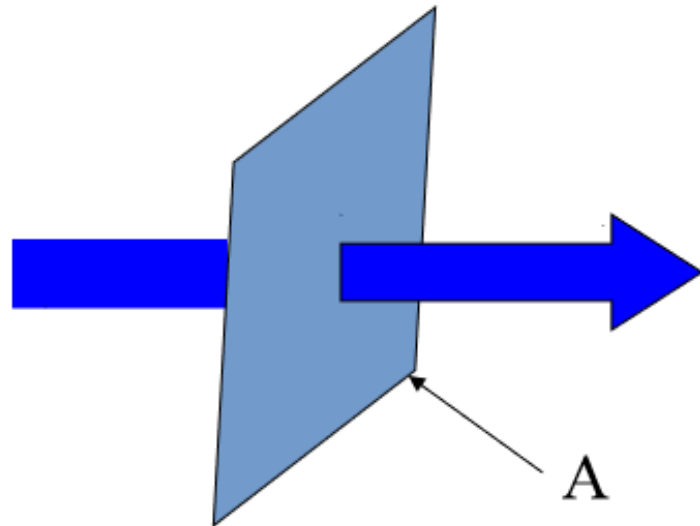
$$\frac{dc}{dx}$$

Diffusion coefficient/ diffusivity

Cross-sectional area

Concentration gradient

Mass transport is down the concentration gradient

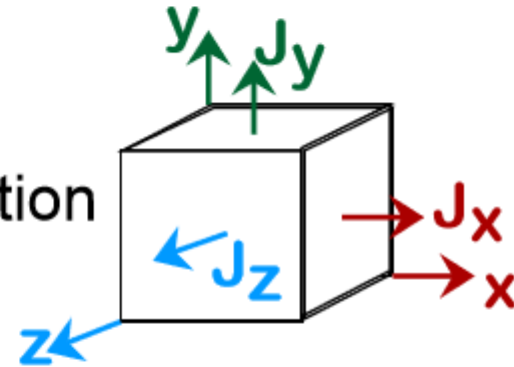


Flow direction

Fick's Second Law ; Non-steady state Diffusion

It explains the change in conc. at definite location with respect to x , y and z axes(or direction)

Fick's second law states that the change in concentration With time in a particular region is proportional to the change In the concentration gradient at that point of time



The concentration ∂c i.e. $\left(\frac{\Delta c}{\Delta t}\right)$ changes with time due to change in amount or flux ∂J i.e. $\left(\frac{\Delta J}{\Delta x}\right)$ of diffusing molecules with in the x direction

- The relationship can be expressed w.r.t -x ,y and z

$$\frac{\partial C}{\partial t} = -\frac{\partial J}{\partial x} \quad \frac{\partial C}{\partial t} = -\frac{\partial J}{\partial y} \quad \frac{\partial C}{\partial t} = -\frac{\partial J}{\partial z}$$

Partial derivatives notation used due to
concentration is a function of both x or y or z and t

$$J = -D \frac{dc}{dx} \quad J = -D \frac{dc}{dy} \quad J = -D \frac{dc}{dz}$$

Differentiating above equation w.r.t x ,y and z respectively

$$\frac{\partial J}{\partial x} = -D \frac{\partial^2 C}{\partial x^2} \quad \frac{\partial J}{\partial y} = -D \frac{\partial^2 C}{\partial y^2} \quad \frac{\partial J}{\partial z} = -D \frac{\partial^2 C}{\partial z^2}$$

substituting for $\frac{\partial C}{\partial t}$, $\frac{\partial C}{\partial t}$ and $\frac{\partial C}{\partial t}$ in above equation for $\frac{\partial J}{\partial x}$, $\frac{\partial J}{\partial y}$ and $\frac{\partial J}{\partial z}$

$$\frac{\partial C}{\partial t} = -D \frac{\partial^2 C}{\partial x^2} \quad \frac{\partial C}{\partial t} = -D \frac{\partial^2 C}{\partial y^2} \quad \frac{\partial C}{\partial t} = -D \frac{\partial^2 C}{\partial z^2}$$

$$\frac{\partial C}{\partial t} = -D \left[\frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 C}{\partial y^2} + \frac{\partial^2 C}{\partial z^2} \right]$$

Fick's second law refers to change in concentration of diffusant with time at any distance x i.e. non steady state flow

- Diffusivity m^2/s
- Measure of capability of a substance to diffuse
- $\alpha/k/D$

Diffusion refers to the random, microscopic movement of water and other small molecules due to thermal collisions. Diffusion is also known as ***Brownian motion***, named in honour of Scottish botanist Robert Brown who first observed spontaneous vibration of pollen particles under the microscope in 1827.

In the mid-19th Century German physicist Adolf Fick modelled diffusion as the movement of particles from a region of higher concentration to a region of lower concentration. Fick showed that flux of particles was directly proportional to the concentration gradient, related by the factor ***D***, the ***diffusion coefficient***. Because ***D*** reflects the flux of particles through a surface during a certain period of time, it therefore has units of area/time (e.g. mm²/sec).

- It was not until 1905 that Albert Einstein developed a comprehensive mathematical theory to explain Brownian motion and incorporate Fick's laws of diffusion.
- Einstein also incorporated into his random walk theory a principle of fluidic friction developed in the 19th Century by George Stokes. This became known as the ***Stokes-Einstein equation***,
- Showing that the diffusion coefficient (D) is directly proportional to the absolute temperature (T) and Boltzmann constant (k), but inversely proportional to the radii of the particles (r) and the viscosity of the medium (η):

Stokes-Einstein Relation

- For free diffusion

$$D = \frac{kT}{6\pi r \eta}$$

- Assumes a spherical molecule
 - i.e., not valid for a long-chain protein

- k = Boltzman Constant

- $1.38 \times 10^{-23} \text{ J/K}$

- η = solvent viscosity
(kg/ms)

- T is temperature (K)

- r is solute molecule
radius

- related to molecular
weight

- The **mobility of a molecule in the cellular environment** is affected by the following parameters:
- The **size of the molecule**: an eightfold increase of the size of a soluble spherical protein decreases D by factor 2.
- the **viscosity of the cellular environment**: e.g. membranes have a much higher viscosity than cytoplasm
- **protein-protein-interactions** and **binding to macromolecules** can also slow down the diffusion
- if **flow or active transport** is involved in the movement of the probed molecule, the measured movement rate can become **significantly higher than the theoretical diffusion rate**

An electrochemical gradient is a gradient of electrochemical potential, usually for an ion that can move across a membrane. The gradient consists of two parts, the chemical gradient, or difference in solute concentration across a membrane, and the electrical gradient, or difference in charge across a membrane.

When there are unequal concentrations of an ion across a permeable membrane, the ion will move across the membrane from the area of higher concentration to the area of lower concentration through [simple diffusion](#). Ions also carry an electric charge that forms an [electric potential](#) across a membrane. If there is an unequal distribution of charges across the membrane, then the difference in electric potential generates a force that drives ion diffusion until the charges are balanced on both sides of the membrane.

An electrochemical gradient has two components. First, the electrical component is caused by a charge difference across the lipid membrane. Second, a chemical component is caused by a differential concentration of [ions](#) across the membrane. The combination of these two factors determines the thermodynamically favourable direction for an ion's movement across a membrane.

- The generation of a transmembrane electrical potential through ion movement across a cell membrane drives [biological processes](#) like [nerve](#) conduction, [muscle contraction](#), [hormone secretion](#), and [sensory](#) processes. By convention, a typical animal cell has a transmembrane electrical potential of -50 mV to -70 mV inside the cell relative to the outside

- Electrochemical gradients also play a role in establishing proton gradients in oxidative phosphorylation in mitochondria. The final step of cellular respiration is the [electron transport chain](#). Four complexes embedded in the inner membrane of the mitochondrion make up the electron transport chain. However, only complexes I, III, and IV pump protons from the [matrix](#) to the [intermembrane space](#) (IMS).
- the [light-dependent reactions](#) of photosynthesis pump protons into the [thylakoid lumen](#) of chloroplasts to drive the synthesis of ATP by ATP synthase. The proton gradient can be generated through either noncyclic or cyclic photophosphorylation