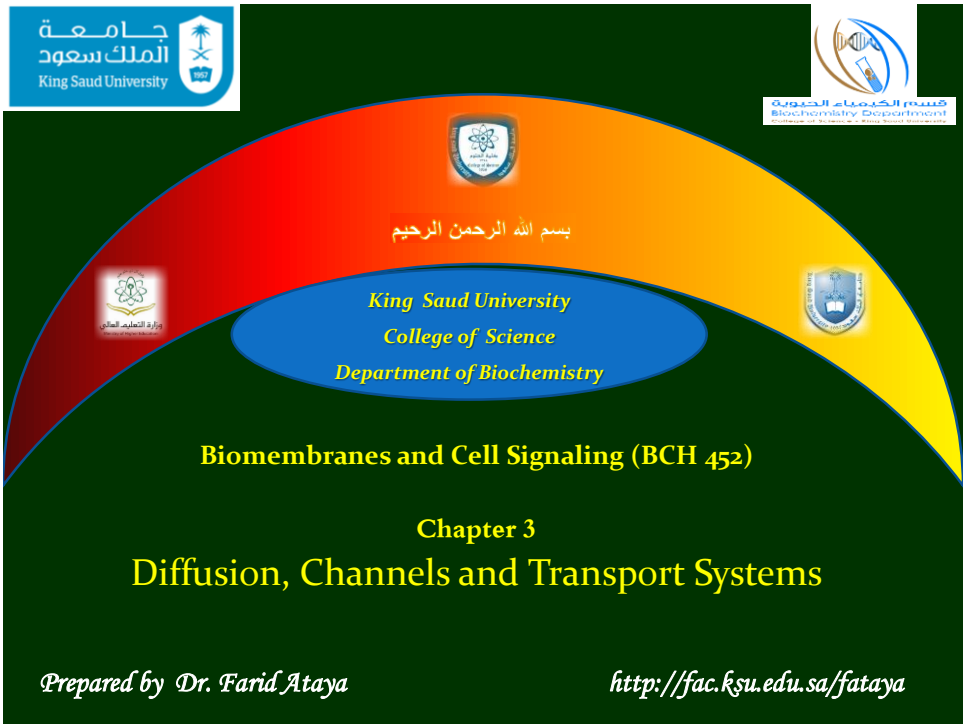


Topics to be covered	Lect No.
Role of cell surface carbohydrates in recognise ion, as receptor of antigens, hormones, toxins, viruses and bacteria. Their role in histocompatibility and cell-cell adhesion.	7
Diffusion. Diffusion across biomembranes. Ficks law. Structural types of channels (pores): α-type, β-barrel, pore forming toxins, ionophores. Functional types of channels (pores): • voltage-gated channels e.g. sodium channels, • ligand-gated channels e.g. acetylcholine receptor (nicotinic-acetylcholine channel), • c-AMP regulated.	8
Gap junctions and nuclear pores. Transport systems: • Energetics of transport systems, G calculation in each type. • Passive Transport (facilitated diffusion).	9

Topics to be covered	No. Lect
Kinetic properties. Passive transport: • Glucose transporters (GLUT 1 to5), • $C1^-$, HCO_3 exchanger (anion exchanger protein) in erythrocyte membrane	9
Kinetic properties. Active transport: Types of active transport: Primary ATPases (Primary active transporters): P transporters (e.g. Na^+, K^+, ATPase)	10
First assessment Exam	
ATP binding cassettes (ABC transports) • (e.g. cystic fibrosis transmembrane conductance regulator-chloride transport). Multidrug resistance protein transporter. V transporters, F transporters. • Secondary active transporters (e.g. Na^+ -dependent transport of glucose and amino acids). To be covered under intestinal brush border	11
Transport of large molecules (Macromolecules) Types: Exocytosis, Endocytosis-pinocytosis and phagocytosis Types of pinocytosis: • Absorptive pinocytosis, characteristics and examples. • Fluid phase pinocytosis, characteristics and examples	12

The role of cell surface carbohydrates: Glycoproteins

- Membrane glycoproteins are proteins that contain 1-30% carbohydrate in their structure.
- They are found attached to biomembranes inside and outside the cells:
  - Inside cells: they are found in specific organelles such as Golgi complexes, secretory granules, and lysosomes.
  - Outside the cell on the outer face of the plasma membrane.
    - Notice, there are many soluble glycoproteins in the cytoplasm, blood and in the extracellular matrix.
  - The oligosaccharide portions of glycoproteins are rich in information, forming highly specific sites for recognition and high-affinity binding by other proteins.

Functions of membrane glycoproteins

- Gylcoproteins have many biological functions:
- 1- Immunological protection and antigenic determinants
- 2- Mediators for cell-cell recognition and interaction
- 3- Blood clotting
- 4- Host-pathogen interaction

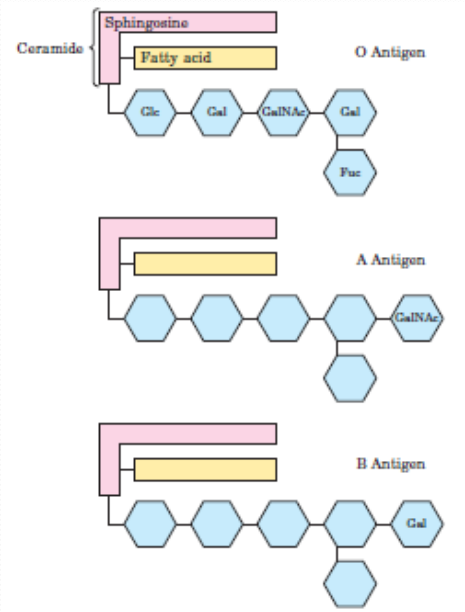
Linkage between sugar and protein part in glycoproteins

- Carbohydrates link through the *anomeric* carbon to:
  - The amide nitrogen in the side chain of *asparagine* (N-glycosidic bond) or
  - The hydroxyl oxygen of *serine or threonine* (O-glycosidic bond).

Do you remember the meaning of anomeric carbon?

The addition of sugar moiety determines the blood group

- Sugars attached to glycoproteins and glycolipids on the surfaces of red blood cells determine the blood group termed A, B, and O.
- The A and B antigens differ from the O antigen by the addition of one extra monosaccharide *N*-acetylgalactosamine (for A) or galactose (for B) through an α -1,3 linkage to a galactose moiety of the O antigen.,
- The addition of *N*-acetylgalactosamine or galactose is mediated by specific enzyme called glycosyltransferases which add the extra monosaccharide to the O antigen.
- Each person inherits the gene for one glycosyltransferase of this type from each parent.
  - The type A transferase specifically adds *N*-acetylgalactosamine,
  - The type B transferase adds galactose.
  - The O phenotype lack that enzyme due to mutation that leads to premature termination of translation and, hence, it produces inactive glycosyltransferase.



Sugars determining blood groups.
Abbreviations:
Fuc, fucose;
Gal, galactose;
GalNAc, *N*-acetylgalactosamine;
GlcNAc, *N*-acetylglucosamine.

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- **Type A**
  - has lots of sugar bound but there is a different sugar at non-reducing end
  - people have antibodies against B sugars
  - donors (receive blood from): A or O

- **Type B**
  - has lots of sugar bound but there is a different sugar at non-reducing end
  - people have antibodies against A sugars
  - donor (receive blood from): B or O

- **Type AB**
  - mix of both types of sugars as A and B
  - people have no antibodies towards A or B
  -donors (receive blood from): A, B or AB or O

- **Type O**
  - Lack of sugars specific for A and B (lack of terminal *N*-acetylgalactosamine; or terminal galactose)
  i.e. missing sugar at non-reducing end
  - people have antibodies towards both A or B
  - donors (receive blood from): O only
  - Universal donor : give blood to all groups (A, B, AB and O)

Transport across the membrane

Why transport is important?

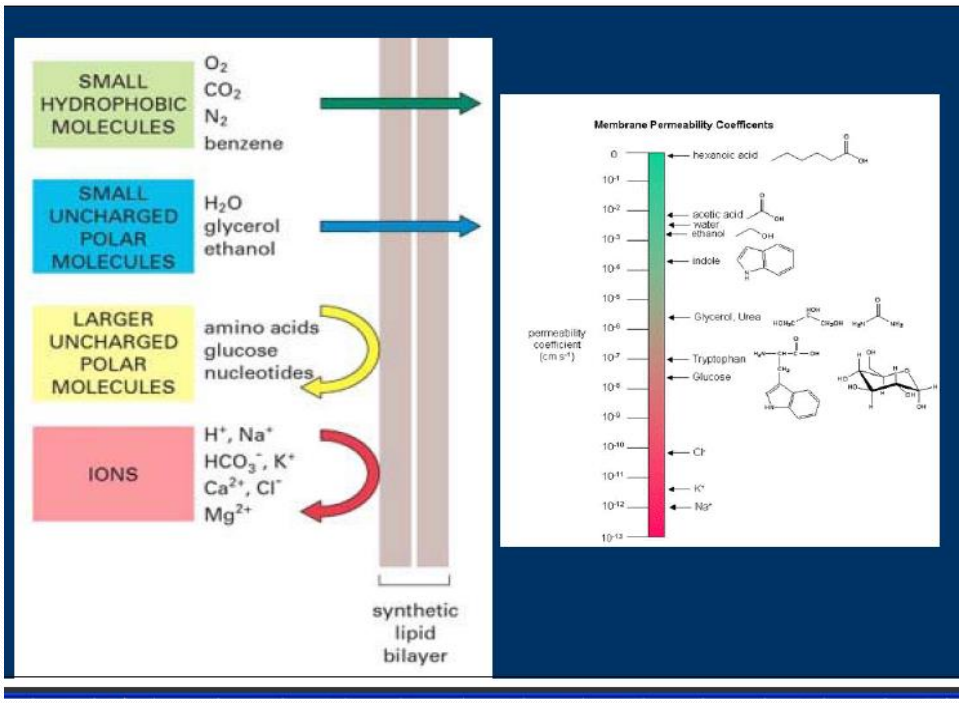
- Every living cell must acquire from its surroundings the raw materials for biosynthesis and for energy production, and must release to its environment the byproducts of metabolism. So, the transport across biological membranes are important.

Biological membrane is a supramolecular characterized by their selective permeability.

The selective nature of membrane comes from both the discriminating nature of phospholipids and the specific transporter proteins.

Lipid bilayer is:

- *Permeable* to small nonpolar molecules such as CO_2 and O_2.
- *Impermeable* to ions and polar molecules such as glucose, sucrose. Na^+. Cl^-.
  - Polar molecules and water enters to the cell through special transport proteins that make the cell permeable to them.



Three ways of Transport

1. Passive Transport: Diffusion across the membrane down the concentration gradient.

a- Osmosis: Passive transport of water

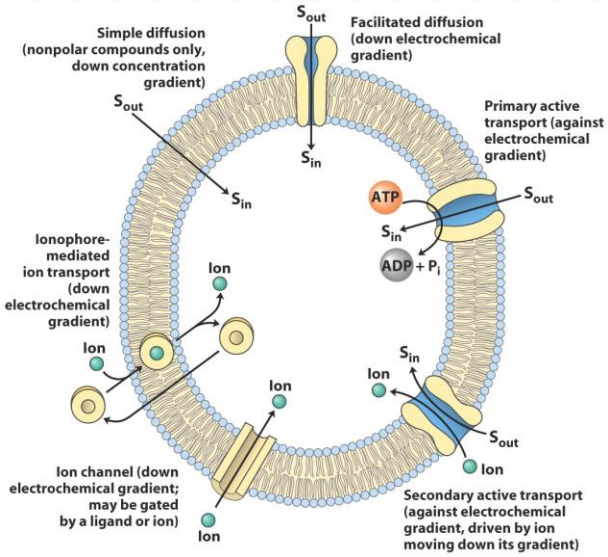
b- Facilitated Diffusion: Specific protein helps in transport of water and other nutrients

2. Active Transport: Pumping of solutes against the concentration gradient.

Co transport: membrane protein helps in transport of one solute to another

3. Exocytosis and Endocytosis: Transport of large molecules.

Types of Membrane Transport



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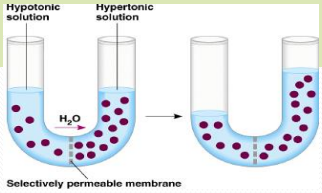
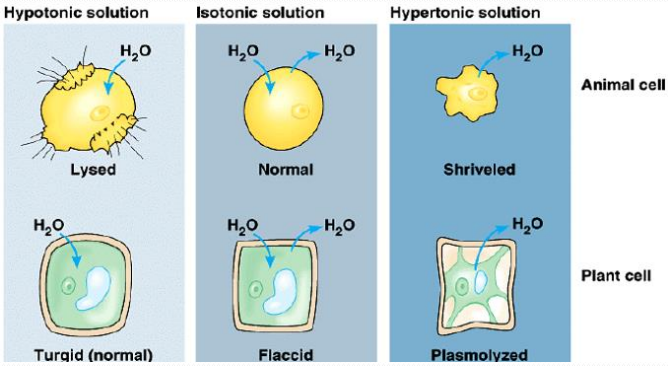
Passive Transport of water: a- Osmosis



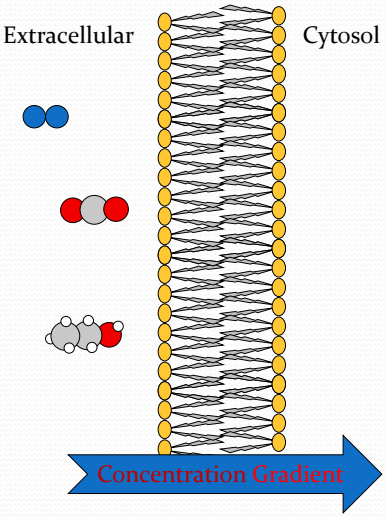
If a cell is put in water, the transport of water is determined according to its concentration in both sides of the cell membrane. Water moves from less concentration (hypotonic solution) to higher concentration (hypertonic solution).

Osmosis is the movement of a solvent (e.g. water) across a semipermeable membrane toward a higher concentration of solute (e.g. salts and ions).

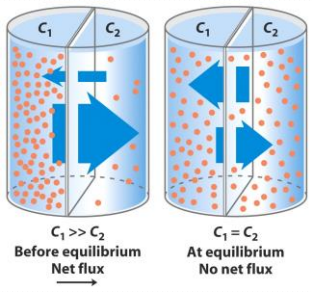


Passive Transport: Simple diffusion

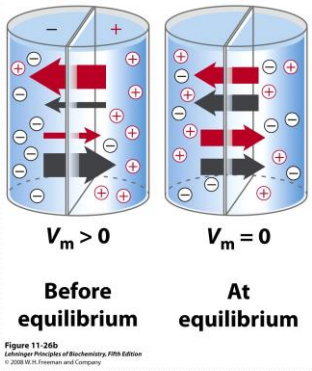
- The movement of solute from higher concentration to lower concentration without needing energy.
- <150 Da, uncharged species, going down their concentration gradient
  - O_2
  - CO_2
  - Alcohol
  - Anaesthetics
  - Pesticides



When two aqueous compartments containing unequal concentrations of a soluble compound (C1 & C2) are separated by a permeable divider (membrane), the solute moves by **simple diffusion** from the region of higher concentration, through the membrane, to the region of lower concentration, until the two compartments have equal solute concentrations (C1=C2).



When ions of opposite charge are separated by a permeable membrane, there is a transmembrane electrical gradient, a **membrane potential, *V*m** (expressed in volts or millivolts). The net movement of electrically charged solutes is dictated by a combination of both the electrical potential (*V*m) and the chemical concentration difference across the membrane; net ion movement continues until this electrochemical potential reaches zero.



Diffusion is passive and occurs only down a concentration gradient.
It can be calculated by Fick's Law:

Fick's First Law measures the amount of substance that will flow through a unit area during a unit time interval.

$$J = \frac{dN}{dt} = -DA\frac{dC}{dx}$$

- D, diffusion coefficient
- A, area
- dC, concentration difference (C1-C2)
- dx, thickness of hydrophobic phase

Negative sign indicates direction
Diffusion also depends on the solubility.

Passive Transport: b- Facilitated diffusion

- Specific ions and polar molecules can cross the lipid bilayer by passing through **transport proteins** *(also known as permeases)* that span the membrane.
  - Example: channel proteins and carrier proteins

a- Channel proteins

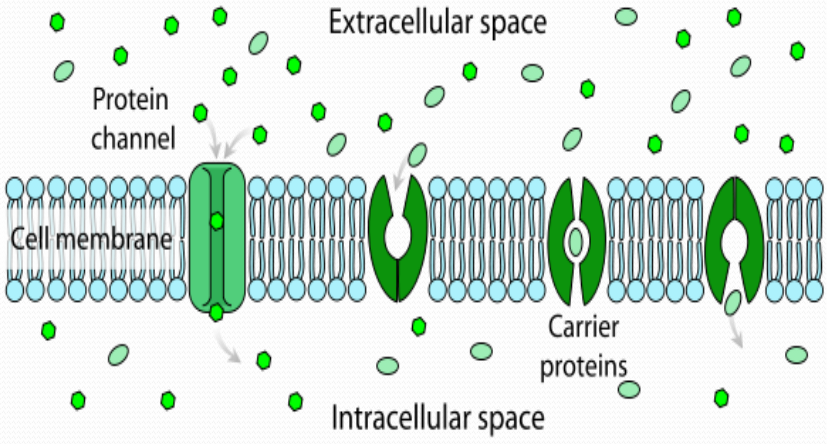
- *Channel proteins,* are membrane transport proteins having a hydrophilic channel that facilitate the passage of certain molecules by acting as a tunnel in the membrane.
  - For example, **aquaporins are** channel proteins that greatly facilitate the passage of water to the cell through the membrane**.**

Passive Transport: b- Facilitated diffusion (cont.)

b- Carrier proteins

- They are proteins that bind to molecules and change their shape to shuttle such molecules across the membrane. Each transport protein is specific to the substances that it will translocate.
  - Example, the glucose transport protein in the liver will carry glucose into the cell but will not transport fructose.
- Some transport proteins do not provide channels but appear to actually translocating the solute-binding site and solute across the membrane as the transport protein changes shape.
- These shape changes may be triggered by the binding and release of the transported molecule.

Passive Transport:
b- Facilitated diffusion (cont.)



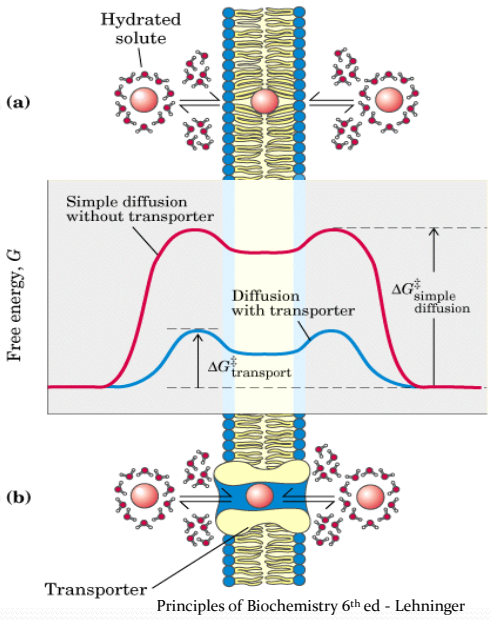
To pass through a lipid bilayer, the polar or charged solute must give up its interactions with the water molecules in its hydration shell, then diffuse about 3 nm (30 Å) through the lipid bilayer.

After passing, the polar compound will gain water again just when it leaves the membrane and inters the cytoplasm.

The intermediate stage of transmembrane passage is a high-energy state comparable to the transition state in an enzyme-catalyzed chemical reaction.

The energy of activation ($\Delta G^{\ddagger}$) for translocation of a polar solute across the bilayer is so large that pure lipid bilayers are virtually impermeable to polar and charged species over periods of time relevant to cell growth and division.

Membrane proteins lower the activation energy for transport of polar compounds and ions by providing an alternative path using **facilitated diffusion,** or **passive transport pathway that depend on specific membrane proteins.**



These proteins are called ***transporters*** *or* ***permeases*****.**
They are NOT enzymes, they lower the energy needed for activation like enzymes but their "substrates" are not converted into products.
The only change is the transport of the substrate from one compartment to another, without changing their chemical structure.

Like enzymes, transporters bind their substrate with stereochemical specificity through multiple weak, noncovalent interactions.
The negative free-energy change associated with these weak interactions, $\Delta G_{binding}$, counterbalances the positive free-energy change that accompanies loss of the water of hydration from the substrate, $\Delta G_{dehydration}$, thereby lowering $\Delta G‡$ for transmembrane passage.
Transporters span the lipid bilayer several times, forming a transmembrane channel lined with hydrophilic amino acid side chains.
The channel provides an alternative path for a specific substrate to move across the lipid bilayer without its having to dissolve in the bilayer, further lowering $\Delta G‡$ for transmembrane diffusion.
The result is an increase of several orders of magnitude in the rate of transmembrane passage of the substrate.

- Free energy of transporting materials across the membrane depends on concentration gradient across the membrane. Where C1 and C2 are the two concentration gradient.

$$\Delta G_t = RT \ln \frac{C_2}{C_1}$$

  - Solutes move spontaneously ($\Delta Gt < 0$) ***from*** compartment of ***higher*** concentration ***to*** compartment of ***lower*** concentration
  - **$\Delta G = 0$** when **C1 = C2 (equilibrium)**
  - Diffusion "down" the concentration gradient (from region of greater concentration to region of lower concentration, toward equilibrium of equal concentrations) is a manifestation of the **2nd law of thermodynamics** -- molecules tend spontaneously to assume the distribution of greatest ***randomness*** until system is maximally randomized.

- A transport process must be active when G is positive, whereas it can be passive when G is negative.
  - For example, consider the transport of an uncharged molecule from C 1 = 10^{-3} M to C 2 = 10^{-1} M. At 25°C (298 K),

$$\begin{aligned}\Delta G &= 2.303RT\log_{10}(10^{-1}/10^{-3}) \\ &= 2.303 \times 1.99 \times 298 \times 2 \\ &= +2.7\ \text{kcal mol}^{-1}\ (+11.3\ \text{kJ mol}^{-1})\end{aligned}$$

- G is + 2.7 kcal mol^{-1} (+11.3 kJ mol-1), indicating that this transport process requires an input of free energy.
- It could be driven, for example, by the hydrolysis of ATP, which yields -12 kcal mol^{-1} (-50.2 kJ mol^{-1}) under typical cellular conditions.
- If ΔG is negative, the transport process can occur spontaneously without free-energy input

$$\Delta G_t = RT \ln \frac{C_2}{C_1} + ZF\Delta\Psi$$

where

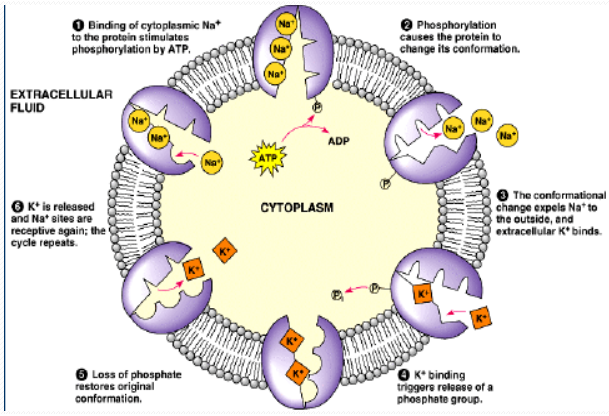
- Z = charge on the ion,
- F = the Faraday constant (96.5 kJ/(V•mol) and
- $\Delta\Psi$ = the membrane potential (the charge gradient across the membrane, in *volts*, or *millivolts*, etc.)

- If ΔY is negative, going from outside to inside, then the transport of cations into the cell is favored over anions. The opposite would be true if ΔY were positive

- In certain inherited diseases, specific transport systems may be defective or absent.
- Cystinuria is a human disease characterized by the absence of a protein that transports cysteine and other amino acids across the membranes of kidney cells.
- An individual with cystinuria develops painful kidney stones as amino acids accumulate and crystallize in the kidneys.

Active transport

- Pumping of solutes against the concentration gradient, which requires energy. Plants usually takes up nutrients in this way.



Active Transport

- Special transport proteins, **electrogenic pumps,** generate the voltage gradient across a membrane.
- The sodium-potassium pump in animals restores the electrochemical gradient not only by the active transport of Na+ and K+, setting up a concentration gradient, but because it pumps two K+ inside for every three Na+ that it moves out, setting up a voltage across the membrane.
- The sodium-potassium pump is the major electrogenic pump of animal cells.

Comparison of different transport mechanism