BME 2901-BIOCHEMISTRY

Biological Membranes and Transport

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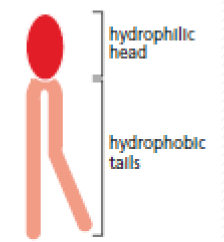
Biological Membranes

- Membranes:
  - define the external boundaries of cells and regulate the molecular traffic across that boundary;
  - in eukaryotic cells, they divide the internal space into discrete compartments to segregate processes and components;
  - organize complex reaction sequences;
  - are central to both biological energy conservation and cell-to-cell communication.
- They are essential components of all living cells.
- A typical membrane consists of two layers of lipid molecules called **lipid bilayer** and many embedded proteins.

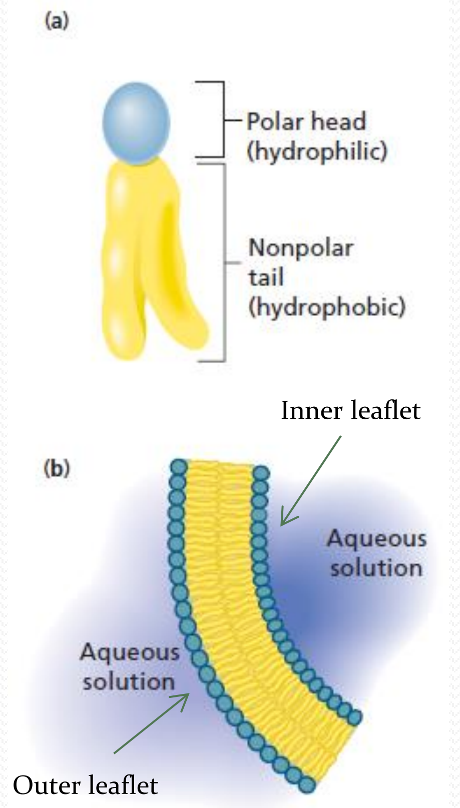
All Biological Membranes Share Some Fundamental Properties

- They consist of lipid bilayers in which proteins are embeded.
- They are impermeable to most polar or charged solutes, but permeable to nonpolar compounds.
- They are 5 to 8 nm (50 to 80 Å) thick.
- The lipids in cell membranes combine two very different properties in a single molecule: each lipid has a hydrophilic ("water-loving") head and a hydrophobic ("water-fearing") tail.
- The most abundant lipids in cell membranes are the phospholipids, which have a phosphate-containing, hydrophilic head linked to a pair of hydrophobic tails.



Formation of a lipid bilayer

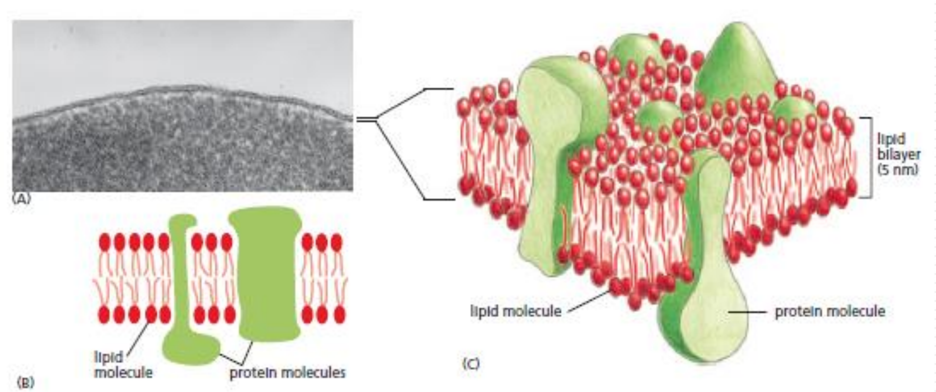
- Having both hydrophilic and hydrophobic parts plays a crucial part in driving these lipid molecules to assemble into bilayers in an aqueous environment.
- In bilayer, the polar head groups of amphipathic lipids are in contact with the aqueous medium and the nonpolar hydrocarbon tails point toward the interior of the bilayer.
- The spontaneous formation of lipid bilayers is driven by the hydrophobic interactions.
- When lipid molecules associate, the entropy of the solvent molecules increases and this favors formation of the lipid bilayer.



Properties of Biological Membranes

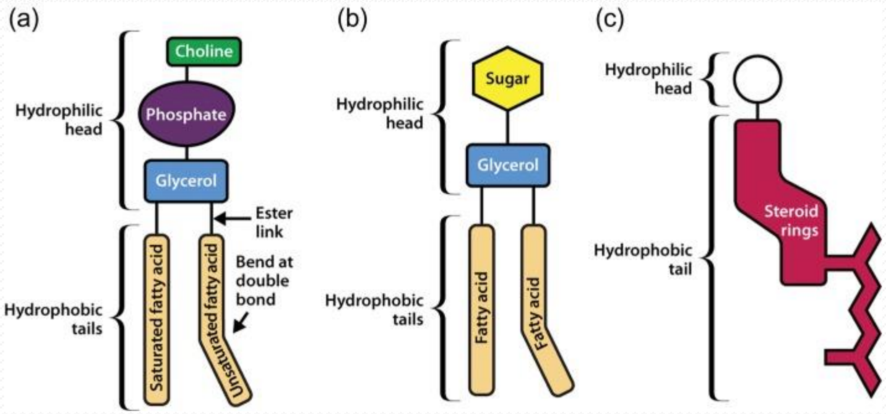
- Membranes are flexible, self-sealing, and selectively permeable to polar solutes.
- Their flexibility permits the shape changes that accompany cell growth and movement.
- With their ability to break and reseal, two membranes can fuse, as in exocytosis, or a single membrane-enclosed compartment can undergo fission to yield two sealed compartments, as in endocytosis or cell division, without creating gross leaks through cellular surfaces.

- Membranes are not merely passive barriers. They are **selectively permeable**, thus, they retain certain compounds and ions within cells and within specific cellular compartments, while excluding others.
- To do this, they include an array of proteins specialized for promoting or catalyzing various cellular processes.
- At the cell surface, transporters move specific organic solutes and inorganic ions across the membrane; receptors sense extracellular signals and trigger molecular changes in the cell; adhesion molecules hold neighboring cells together.
- Within the cell, membranes organize cellular processes such as the synthesis of lipids and certain proteins, and the energy transductions in mitochondria and chloroplasts.



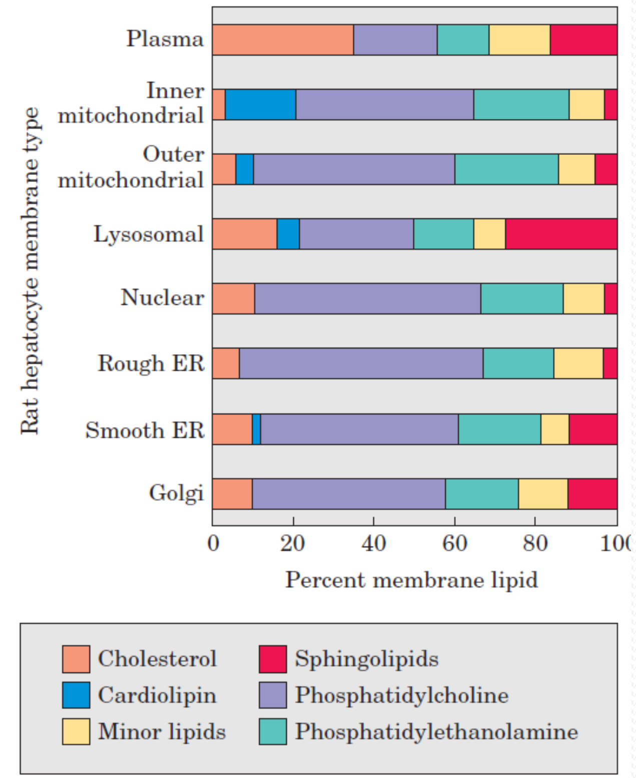
Lipid profile of the membranes

- Three types of lipid are commonly found in biological membranes, namely **glycerophospholipids, glycolipids and sterols**.
- Phosphatidylcholine (PC), which has a choline molecule attached to the phosphate group, is a glycerophospholipid that is commonly found in biological membranes. Serine and ethanolamine can replace the choline in this position, and these lipids are called phosphatidylserine (PS) and phosphatidylethanolamine (PE), respectively.



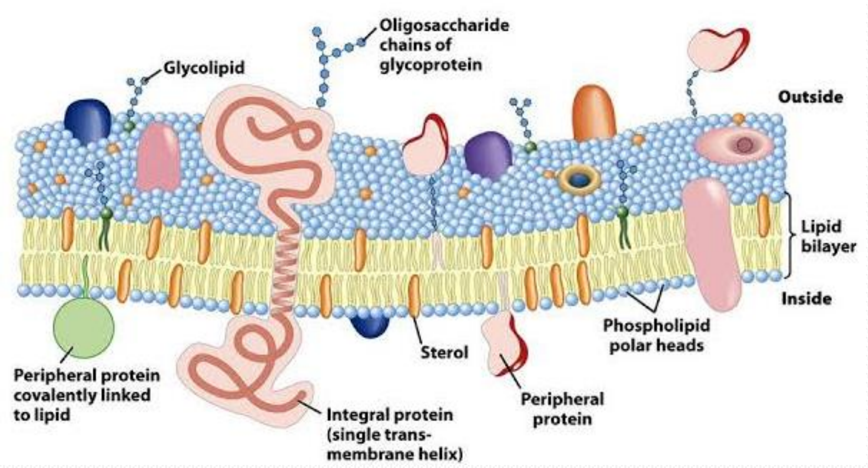
Each Type of Membrane Has Characteristic Lipids and Proteins

- The relative proportions of protein and lipid vary with the type of membrane, reflecting the diversity of biological roles.
- Each kingdom, each species, each tissue or cell type, and the organelles of each cell type have a characteristic set of membrane lipids.
- Plasma membranes, for example, are enriched in cholesterol and contain no detectable cardiolipin; in the inner mitochondrial membrane of the hepatocyte, this distribution is reversed: very low cholesterol and high cardiolipin. Cardiolipin is essential to the function of certain proteins of the inner mitochondrial membrane.
- The protein composition of membranes from different sources varies even more widely than their lipid composition, reflecting functional specialization.
- In a rod cell of the vertebrate retina, one portion of the cell is highly specialized for the reception of light; more than 90% of the plasma membrane protein in this region is the light-absorbing glycoprotein rhodopsin.
- The less specialized plasma membrane of the erythrocyte has about 20 prominent types of proteins as well as scores of minor ones; many of these are transporters, each moving a specific solute across the membrane.



- The structure of biological membranes is best described via the **fluid mosaic model**. The lipids in a bilayer are in constant motion giving lipid bilayers many of the properties of fluids.The individual lipid and protein units in a membrane form a fluid mosaic with a pattern that is free to change constantly.
- The membrane mosaic is fluid because most of the interactions among its components are noncovalent, leaving individual lipid and protein molecules free to move laterally in the plane of the membrane.
- Phospholipids form a bilayer in which the nonpolar regions of the lipid molecules in each layer face the core of the bilayer and their polar head groups face outward, interacting with the aqueous phase on either side.
- Proteins are embedded in this bilayer sheet, held by hydrophobic interactions between the membrane lipids and hydrophobic domains in the proteins. Some proteins protrude from only one side of the membrane; others have domains exposed on both sides. The orientation of proteins in the bilayer is asymmetric, giving the membrane "***sidedness***": the protein domains exposed on one side of the bilayer are different from those exposed on the other side, reflecting **functional asymmetry**.

Fluid Mosaic Model

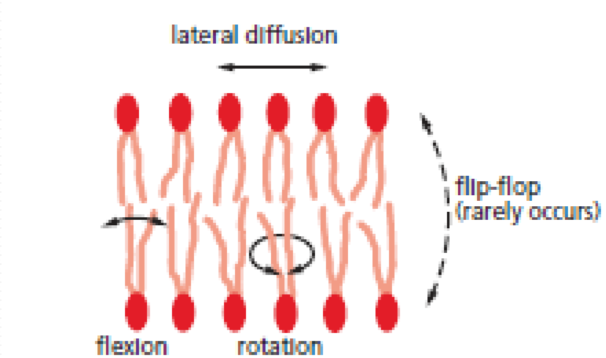


Fluidity of membranes

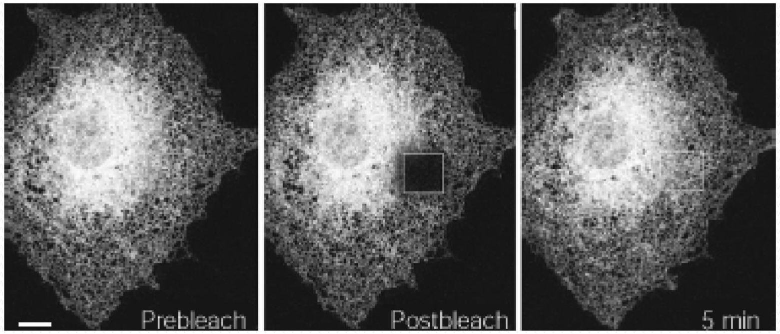
- The fluidity of a cell membrane—the ease with which its lipid molecules move within the plane of the bilayer—is important for membrane function and has to be maintained within certain limits.
- Just how fluid a lipid bilayer is at a given temperature depends on its phospholipid composition and, in particular, on the nature of the hydrocarbon tails: the closer and more regular the packing of the tails, the more viscous and less fluid the bilayer will be.
- Two major properties of hydrocarbon tails affect how tightly they pack in the bilayer: their length and the number of double bonds they contain:
  - A shorter chain length reduces the tendency of the hydrocarbon tails to interact with one another and therefore increases the fluidity of the bilayer.
  - Each double bond in an unsaturated tail creates a small kink in the tail, which makes it more difficult for the tails to pack against one another. For this reason, lipid bilayers that contain a large proportion of unsaturated hydrocarbon tails are more fluid than those with lower proportions.

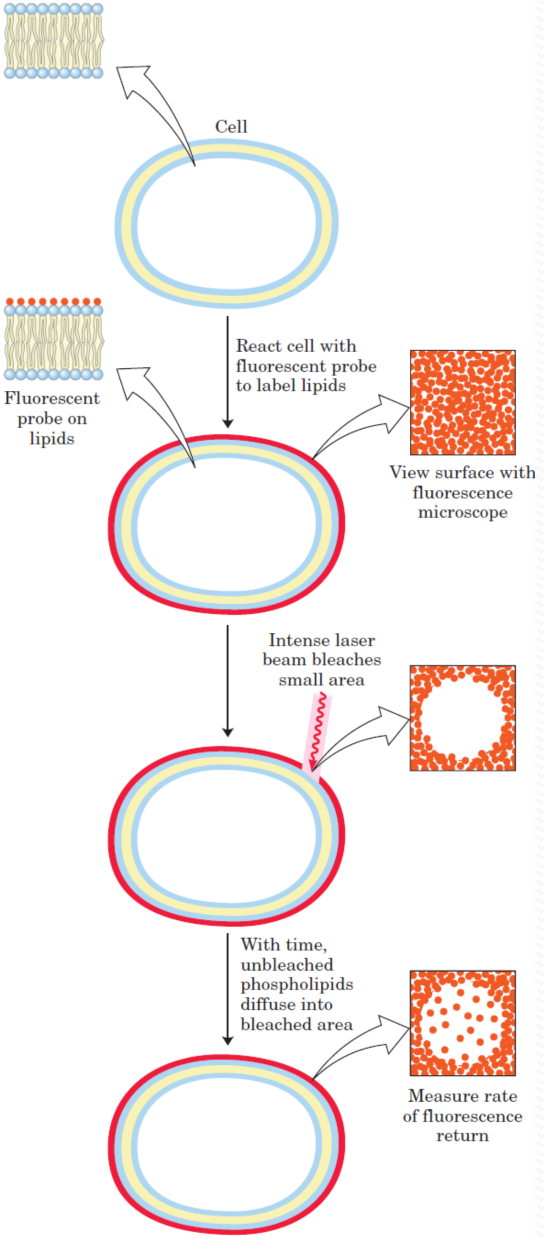
Motion of phospholipids in bilayer

- Lipids undergo several types of molecular motion within bilayers.
- The rapid movement of lipids within the plane of one monolayer is an example of two-dimensional lateral diffusion.
- In contrast, transverse diffusion (or flip-flop) is the passage of lipids from one monolayer of the bilayer to the other.
- Transverse diffusion is much slower than lateral diffusion.



- **F**luorescence **R**ecovery **A**fter **P**hotobleaching, or **FRAP,** is a measure of the rate of lateral diffusion of the lipids and proteins in the membrane.
- Once a a lipid or a protein has been labeled, a small patch of membrane is irradiated with an intense pulse of light from a sharply focused laser beam.
- This treatment irreversibly "bleaches" the fluorescence from the labeled proteins in that small patch of membrane.
- The fluorescence of this irradiated membrane is monitored in a fluorescence microscope, and the amount of time it takes for the neighboring, unbleached fluorescent proteins to migrate into the bleached region of the membrane is measured.
- The rate of this "fluorescence recovery" is a direct measure of the rate at which the proteins or lipids can diffuse within the membrane .





Cholesterol decreases fluidity

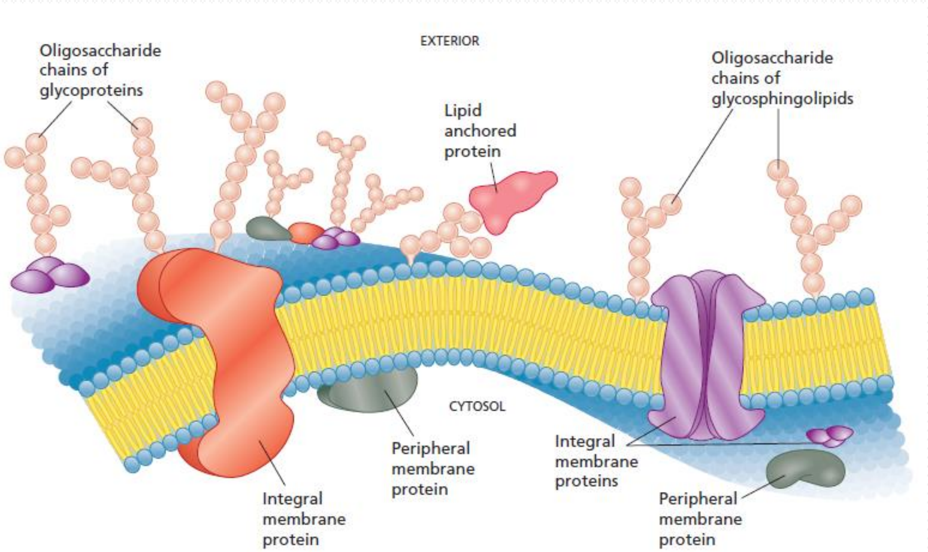
- In animal cells, membrane fluidity is modulated by the inclusion of the sterol cholesterol.
- This molecule is present in especially large amounts in the plasma membrane, where it constitutes approximately 20% of the lipids in the membrane by weight.
- Because cholesterol molecules are short and rigid, they fill the spaces between neighboring phospholipid molecules left by the kinks in their unsaturated hydrocarbon tails.
- In this way, cholesterol tends to stiffen the bilayer, making it less flexible, as well as less permeable.

Importance of fluidity

- For all cells, membrane fluidity is important for many reasons. It enables many membrane proteins to diffuse rapidly in the plane of the bilayer and to interact with one another.
- It permits membrane lipids and proteins to diffuse from sites where they are inserted into the bilayer after their synthesis to other regions of the cell.
- It ensures that membrane molecules are distributed evenly between daughter cells when a cell divides.
- And, under appropriate conditions, it allows membranes to fuse with one another and mix their.
- If biological membranes were not fluid, it is hard to imagine how cells could live, grow, and reproduce.
- It also allows cells cells to move and migrate.

Membrane Proteins

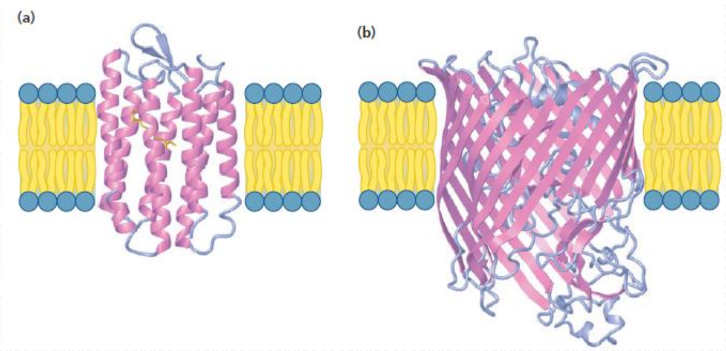
- Cellular and intracellular membranes contain specialized membrane-bound proteins.
- These proteins are divided into three classes based on their mode of association with the lipid bilayer: **integral membrane proteins**, **peripheral membrane proteins**, and **lipid anchored membrane proteins**.



Integral membrane proteins

- *Integral membrane proteins*, also referred to as transmembrane proteins, contain hydrophobic regions embedded in the hydrophobic core of the lipid bilayer.
- Integral membrane proteins usually span the bilayer completely, with one part of the protein exposed on the outer surface and one part exposed on the inner surface.
- Some integral membrane proteins are anchored by only a single membrane-spanning portion of the polypeptide chain, whereas other membrane proteins have several transmembrane segments connected by loops at the membrane surface.
- The membrane-spanning segment is often an α helix or β barrel.

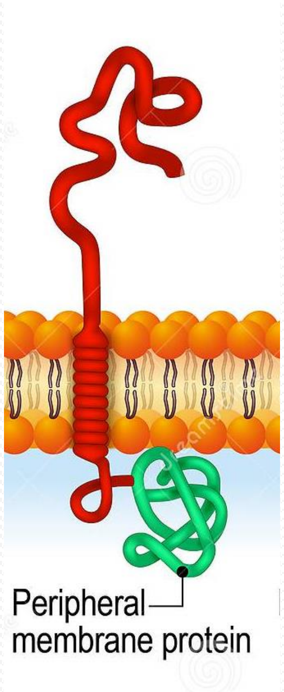
amino acids in α helical transmembrane regions are hydrophobic and a tendency to be present in α-helices



The exterior surface of the β strands contacts the membrane lipids and the center of the barrel often serves as a pore or channel for passing molecules from one side of the membrane to the other.

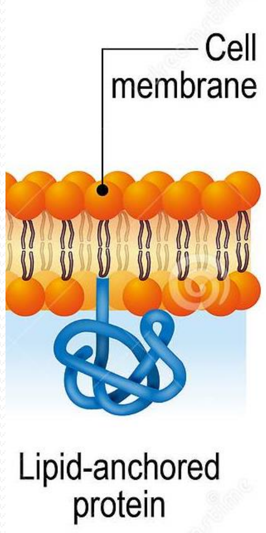
Peripheral membrane proteins

- *Peripheral membrane proteins* are associated with one face of the membrane through charge–charge interactions and hydrogen bonding with integral membrane proteins or with the polar head groups of membrane lipids.
- Peripheral membrane proteins are more readily dissociated from membranes by changes in pH or ionic strength.



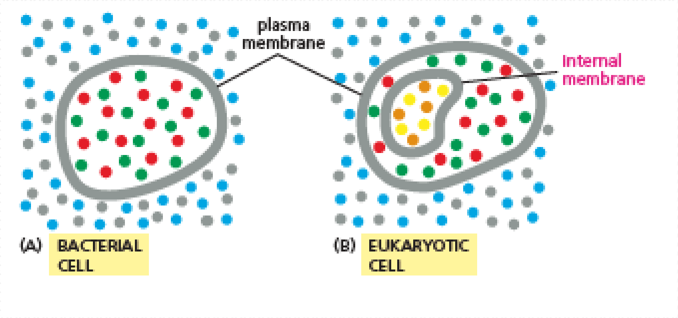
Lipid anchored membrane proteins

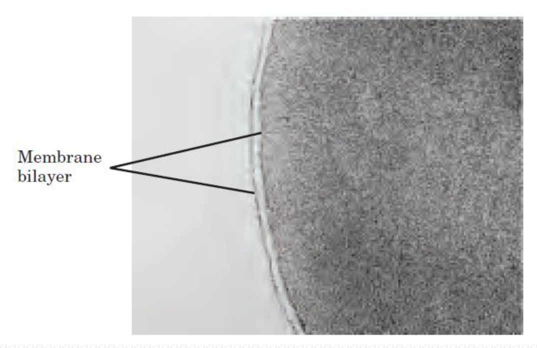
- *Lipid anchored membrane proteins* are tethered to a membrane through a covalent bond to a lipid anchor.
- The fatty acid is inserted into the cytoplasmic side of the bilayer, anchoring the protein to the membrane.
- Lipid anchors are covalently linked to amino acid residues posttranslationally, that is, after the protein has been synthesized.
- Like integral membrane proteins, most lipid anchored proteins are permanently associated with the membrane, although the proteins themselves do not interact with the membrane.
- Once released by treatment with phospholipases, the proteins behave like soluble proteins.



Plasma Membrane

- Although it serves as a barrier to prevent the contents of the cell from escaping and mixing with the surrounding medium, the plasma membrane does much more than that.
- If a cell is to survive and grow, nutrients must pass inward across the plasma membrane, and waste products must pass out.

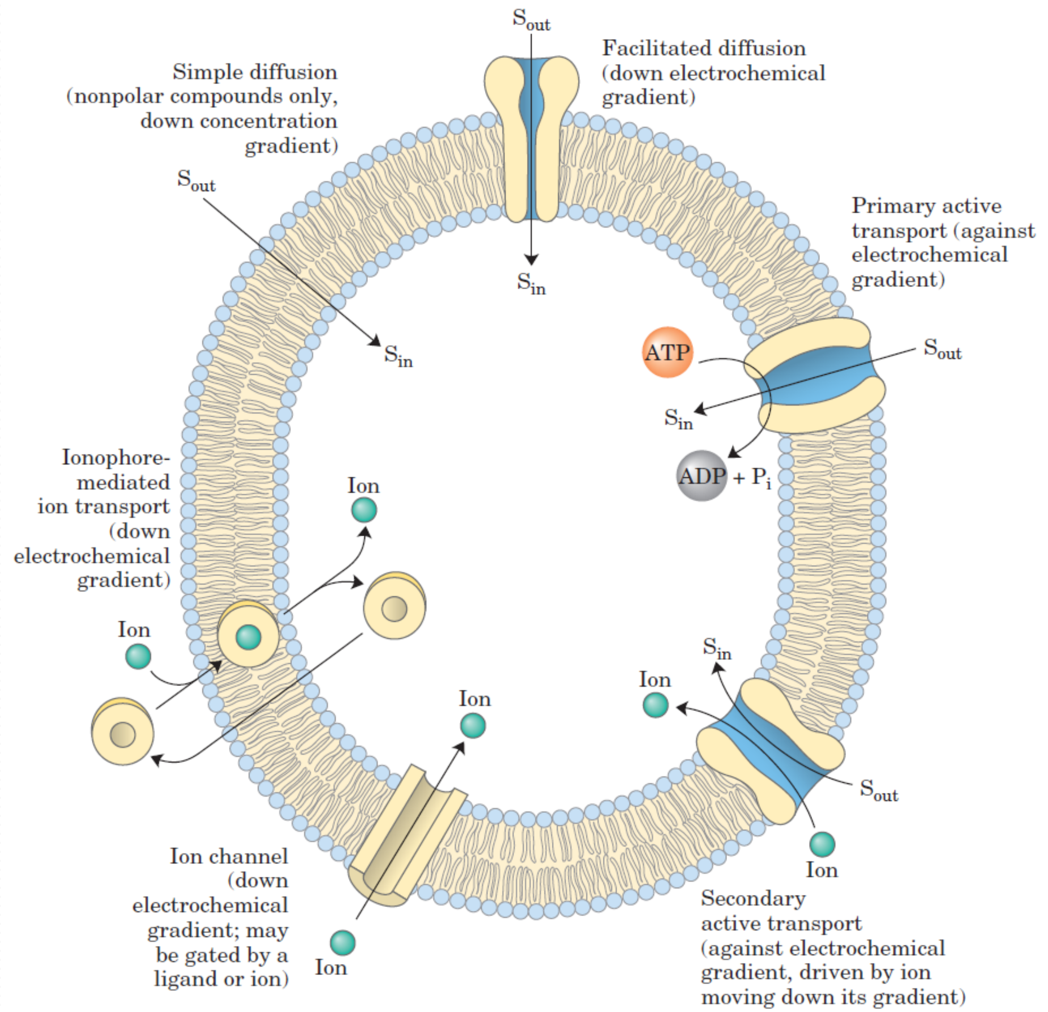




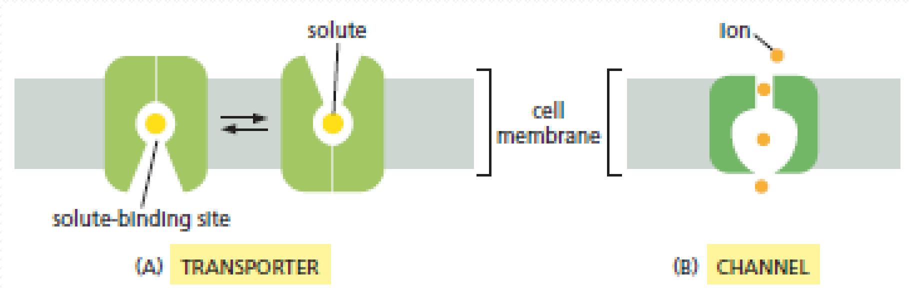
Membrane Transport

- Every living cell must acquire from its surroundings the raw materials for biosynthesis and for energy production, and must release to its environment the by products of metabolism. In general,
  - The smaller the molecule and the more hydrophobic, or nonpolar, it is, the more rapidly it will diffuse across the membrane.
  - Polar or charged compounds or ions, a membrane protein is essential for transmembrane movement.
- Some small uncharged molecules or lipid soluble molecules pass between the phospholipids to enter or leave the cell, moving from areas of high concentration to areas of low concentration (they move **down their concentration gradient**) by **diffusion**. Oxygen and carbon dioxide and most lipids enter and leave cells by this way. Water can also pass across the cell membrane via diffusion **(osmosis)**.
- In some cases a membrane protein simply facilitates the diffusion of a solute down its concentration gradient **(facilitated diffusion)**, but transport often occurs against a gradient of concentration, electrical charge, or both, in which case solutes must be "pumped" in a process that requires energy.
- The energy may come directly from ATP hydrolysis or may be supplied in the form of movement of another solute down its electrochemical gradient with enough energy to carry another solute up its gradient.

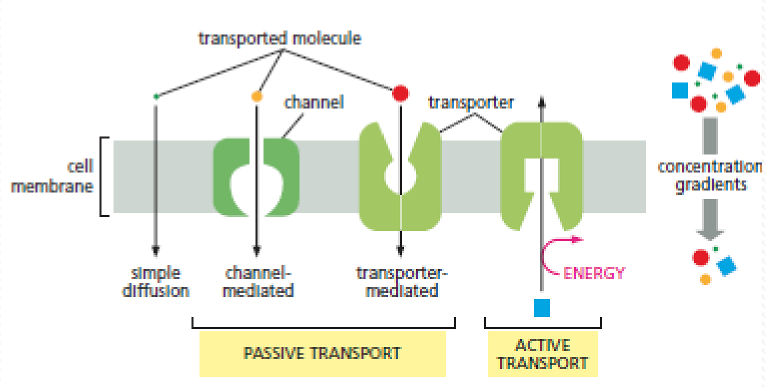
- Within the eukaryotic cell, different compartments have different concentrations of metabolic intermediates, products and ions which must move across intracellular membranes in tightly regulated, protein-mediated processes.
- Membrane transport proteins are responsible from the passage of substances.



- Membrane transport proteins are multipass transmembrane proteins.
- By crisscrossing across the bilayer, the polypeptide chain of transmembrane protein forms a continuous protein-lined pathway that allows selected small, hydrophilic molecules to cross the membrane without coming into direct contact with the hydrophobic interior of the lipid bilayer.
- There are two main classes of membrane transport proteins: **transporters** and **channels**.
- *Channels* discriminate mainly on the basis of size and electric charge: when the channel is open, any ion or molecule that is small enough and carries the appropriate charge can pass through.
- A *transporter*, on the other hand, transfers only those molecules or ions that fit into specific binding sites on the protein.
- Transporters bind their solutes with great specificity, in the same way an enzyme binds its substrate, and it is this requirement for specific binding that gives transporters their selectivity.

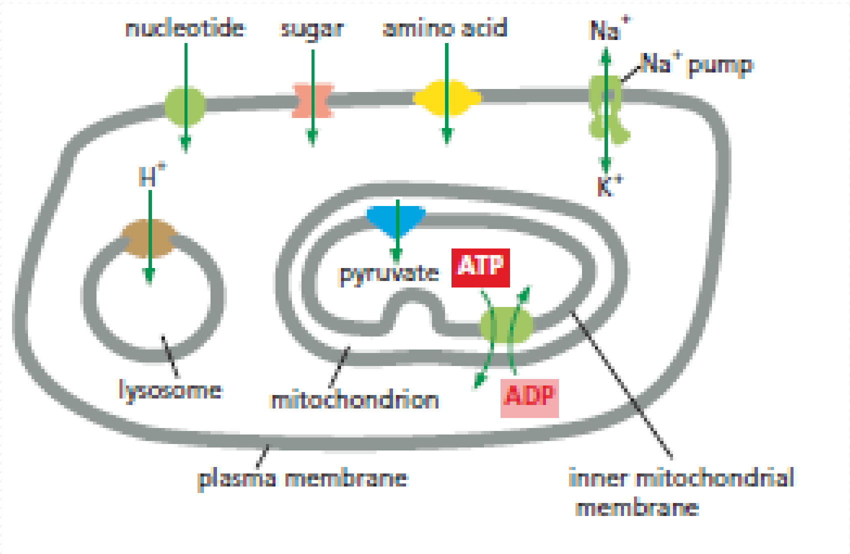


- If a molecule is present at a higher concentration outside the cell than inside, and an appropriate channel or transporter is present in the plasma membrane, the molecule will move into the cell by **passive transport**, without expenditure of energy by the transport protein or channel.
- Passive transport includes simple **diffusion** across a membrane.When pores, channels, and transporters are involved, we call the process **facilitated diffusion**.
- The movement of a molecule against its concentration gradient in this way is termed **active transport**, and it is carried out by special types of transporters called *pumps*, which utilize an energy source to power the transport process.



Transporters

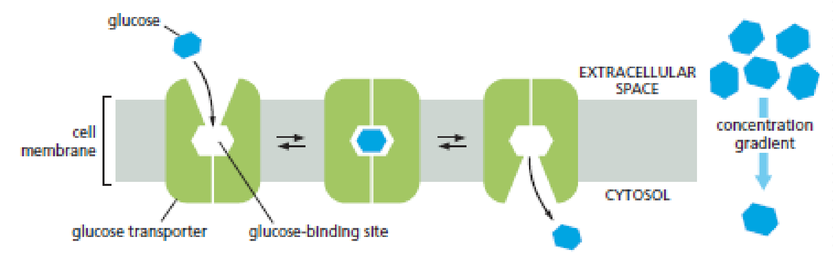
- Transporters are responsible for the movement of most small, water-soluble, organic molecules and some inorganic ions across cell membranes.
- Each transporter is highly selective, often transferring just one type of molecule.
- To guide and propel the complex traffic of solutes into and out of the cell, and between the cytosol and the different membrane-enclosed organelles, each cell membrane contains a characteristic set of different transporters appropriate to that particular membrane.



- For example,
  - The plasma membrane contains transporters that import nutrients such as sugars, amino acids, and nucleotides;
  - The lysosome membrane contains an H+ transporter that imports H+ to acidify the lysosome interior and other transporters that move digestion products out of the lysosome into the cytosol;
  - The inner membrane of mitochondria contains transporters for importing the pyruvate that mitochondria use as fuel for generating ATP, as well as transporters for exporting ATP once it is synthesized.

Passive Transporters Move a Solute Along Its Electrochemical Gradient

- An important example of a transporter that mediates passive transport is the *glucose transporter* in the plasma membrane of many mammalian cell types.
- Because glucose is uncharged, the chemical component of its electrochemical gradient is zero. Thus the direction in which it is transported is determined by its concentration gradient alone.
- When glucose is plentiful outside cells, as it is after a meal, the sugar binds to the transporter's externally displayed binding sites; when the protein switches conformation—spontaneously and at random—it carries the bound sugar inward and releases it into the cytosol, where the glucose concentration is low.
- Conversely, when blood glucose levels are low as they are when you are hungry—the hormone glucagon stimulates liver cells to produce large amounts of glucose by the breakdown of glycogen. As a result, the glucose concentration is higher inside liver cells than outside. This glucose binds to the internally displayed binding sites on the transporter. When the protein switches conformation in the opposite direction, the glucose is transported out of the cells, where it is made available for others to import.

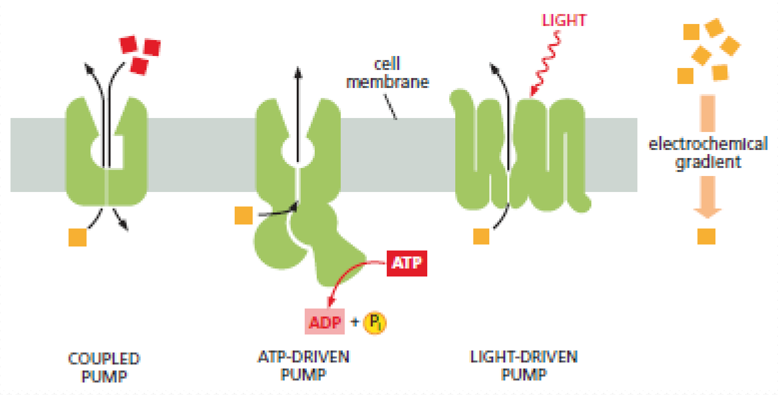


- The net flow of glucose can thus go either way, according to the direction of the glucose concentration gradient across the plasma membrane: inward if glucose is more concentrated outside the cell than inside, and outward if the opposite is true.
- Although passive transporters of this type play no part in determining the direction of transport, they are highly selective.
- For example, the binding sites in the glucose transporter bind only D-glucose and not its mirror image, L-glucose, which the cell cannot use for glycolysis.

- Because cell membranes are impermeable to inorganic ions, living cells are able to maintain internal ion concentrations that are very different from the concentrations of ions in the media that surrounds them.
- These differences in ion concentration are crucial for a cell's survival and function.
- Among the most important inorganic ions for cells are Na^+, K^+, Ca^{2+}, Cl^-, and H^+ (protons).
- For a cell to avoid being torn apart by electrical forces, the quantity of positive charge inside the cell must be balanced by an almost exactly equal quantity of negative charge, and the same is true for the charge in the surrounding fluid.
- The high concentration of Na^+ outside the cell is electrically balanced chiefly by extracellular Cl^-, whereas the high concentration of K^+ inside is balanced by a variety of negatively charged organic and inorganic ions including nucleic acids, proteins, and many cell metabolites.

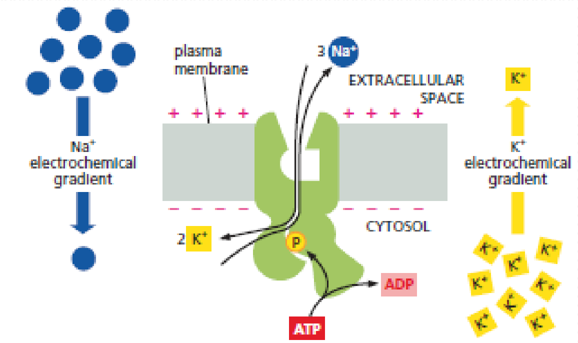
Pumps Actively Transport a Solute Against Its Electrochemical Gradient

- An active transport of solutes against their electrochemical gradient is essential to maintain the appropriate intracellular ionic composition of cells and to import solutes that are at a lower concentration outside the cell than inside.
- For these purposes, cells depend on transmembrane pumps, which can carry out active transport in three main ways: (i) *ATP-driven pumps* hydrolyze ATP to drive uphill transport. (ii) *Coupled pumps* link the uphill transport of one solute across a membrane to the downhill transport of another. (iii) *Light-driven pumps*, which are found mainly in bacterial cells, use energy derived from sunlight to drive uphill transport.



Na^+-K^+ Pump

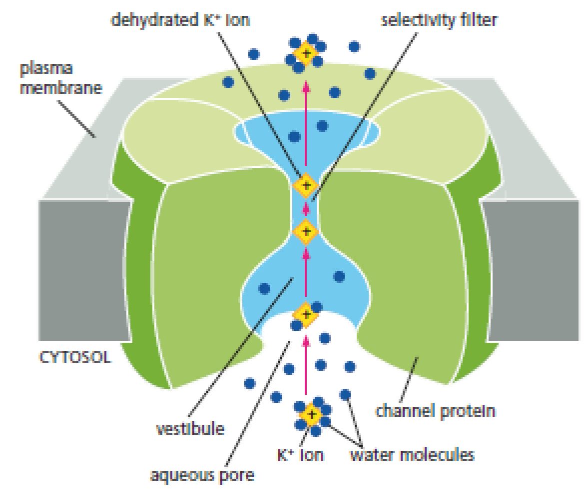
- This pump uses the energy derived from ATP hydrolysis to transport Na^+ out of the cell as it carries K^+ in.
- The energy from ATP hydrolysis induces a series of protein conformational changes that drive the Na+/K+ ion exchange. As part of the process, the phosphate group removed from ATP gets transferred to the pump itself.
- The Na^+ pump functions to expel the Na^+ that is constantly entering the cell through other transporters and ion channels in the plasma membrane.
- In this way, the pump keeps the Na^+ concentration in the cytosol about 10–30 times lower than in the extracellular fluid and the K^+ concentration about 10–30 times higher.

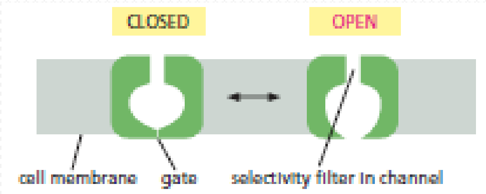


Channels

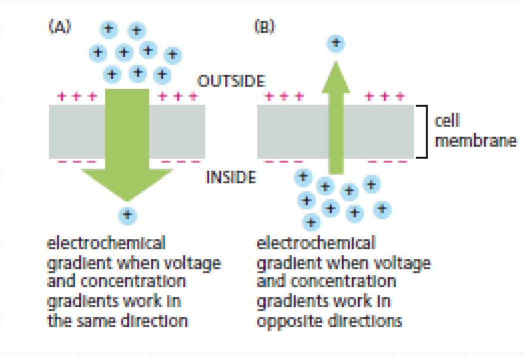
- In principle, the simplest way to allow a small water-soluble molecule to cross from one side of a membrane to the other is to create a hydrophilic channel through which the molecule can pass.
- Channel proteins, or channels, perform this function in cell membranes, forming transmembrane pores that allow the passive movement of small water-soluble molecules into or out of the cell or organelle.
- The bulk of a cell’s channels facilitate the passage of inorganic ions.

- Two important properties distinguish ion channels from simple holes in the membrane.
  - First, they show *ion selectivity*, permitting some inorganic ions to pass but not others. Ion selectivity depends on the diameter and shape of the ion channel and on the distribution of the charged amino acids that line it.
  - Second, ion channels are not continuously open. Ion transport would be of no value to the cell if the many thousands of ion channels in a cell membrane were open all the time and there were no means of controlling the flow of ions through them. Instead, ion channels open only briefly and then close again.



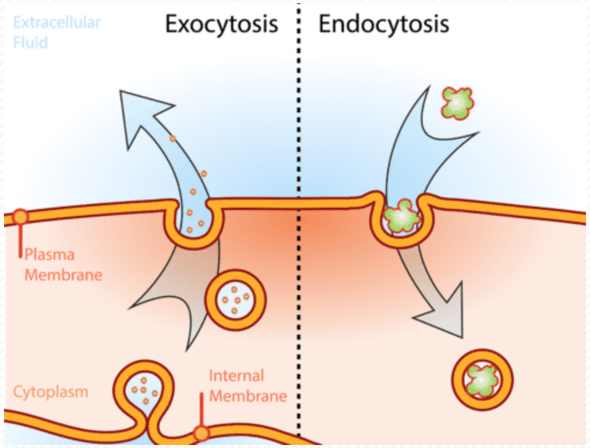


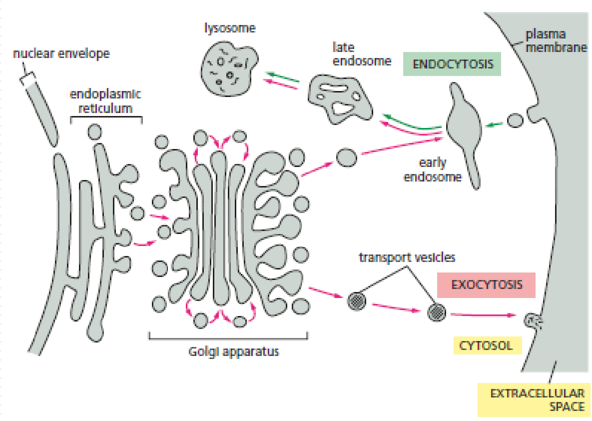
- Unlike a transporter, an open ion channel does not need to undergo conformational changes with each ion it passes.
- Channels cannot couple the ion flow to an energy source to carry out active transport: most simply make the membrane transiently permeable to selected inorganic ions, mainly Na^+, K^+, $Ca2^+$, or Cl^-.
- Thanks to active transport by pumps, the concentrations of most ions are far from equilibrium across a cell membrane. When an ion channel opens, therefore, ions usually flow through it, moving rapidly down their electrochemical gradients. This situation creates **the membrane potential**.
- The membrane potential exerts a force on any molecule that carries an electric charge. The cytosolic side of the plasma membrane is usually at a negative potential relative to the extracellular side, so the membrane potential tends to pull positively charged solutes into the cell and drive negatively charged ones out.



- The transport we have discussed so far occurs by the flow of molecules or ions across an intact membrane.
- Cells also need to import and export molecules too large to be transported via pores, channels, or transport proteins.
- Prokaryotes possess specialized multicomponent export systems in their plasma and outer membranes that allow them to secrete certain proteins (often toxins or enzymes) into the extracellular medium.
- In eukaryotic cells, many—but not all—proteins (and certain other large substances) are moved into and out of the cell by **endocytosis** and **exocytosis**, respectively.
- In both cases, transport involves formation of a specialized type of lipid vesicle.

- **Endocytosis** is the process by which macromolecules are engulfed by the plasma membrane and brought into the cell inside a lipid vesicle.
- Receptor-mediated endocytosis begins with the binding of macromolecules to specific receptor proteins in the plasma membrane of the cell. The membrane then invaginates, forming a vesicle that contains the bound molecules.
- Once inside the cell, the vesicle can fuse with an endosome (another type of vesicle) and then with a lysosome.
- **Exocytosis** is similar to endocytosis except that the direction of transport is reversed. During exocytosis, materials destined for secretion from the cell are enclosed in vesicles by the Golgi apparatus. The vesicles then fuse with the plasma membrane releasing the vesicle contents into the extracellular space.





Summary

Small water soluble molecules → Channels → Only Passive Transport; No conformational change

Small water soluble molecules → Transporters → Passive or Active Transport; Undergoes conf. change; Driven by ATP or ligth or coupled to another transport

Large molecules → Endocytosis, Exocytosis