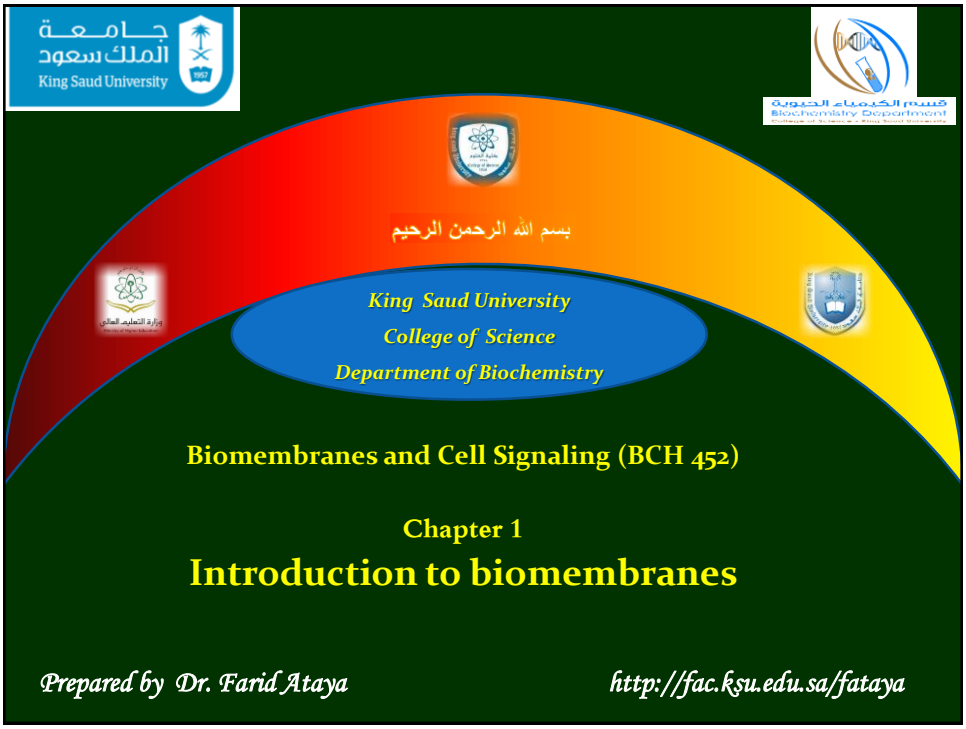


Topics to be covered	Lect No.
Definition of Membranology. General functions of biomembranes Composition of biomembranes: Lipids, proteins and carbohydrates.	1-2
Micelles, liposomes and vesicles, their preparation and applications in drug delivery. Structural and functional asymmetry of membranes with respect to carbohydrates, lipids and proteins.	3
Fluid mosaic model.	4

https://www.youtube.com/watch?v=B_zD3NxSsD8
https://www.youtube.com/watch?v=FzcTgrxMzZk

Definition of Membranology

- Membranology is the science which deals with membranes.
- Membrane is one of the most important constituent of livening cells.
- The origin of the first cell probably came into being when a membrane formed, enclosing a small volume of aqueous solution and separating it from the rest of the universe.
- This membrane must be insoluble to the surrounding to ensure its persistence.

General Characteristics of Biomembranes

- **The biological activities of membranes is determined by their remarkable physical properties.**
- Membranes are sheet like structure, only a few molecules thick that form closed boundaries between compartments of different composition.
  - The thickness of most membranes is between 60 and 100A
- Membranes are flexible and self-sealing.
  - Their flexibility permits the shape changes that accompany cell growth and movement.
    - In exocytosis, two membranes can fuse or seal.
    - In endocytosis and cell division, single membrane undergo fission to yield two sealed compartments
- Membrane lipids are relatively small molecules that have both hydrophilic and hydrophobic moiety.
- These lipids spontaneously form closed bimolecular sheets in aqueous media.
- These lipid bilayers are barrier to the flow of polar molecules.

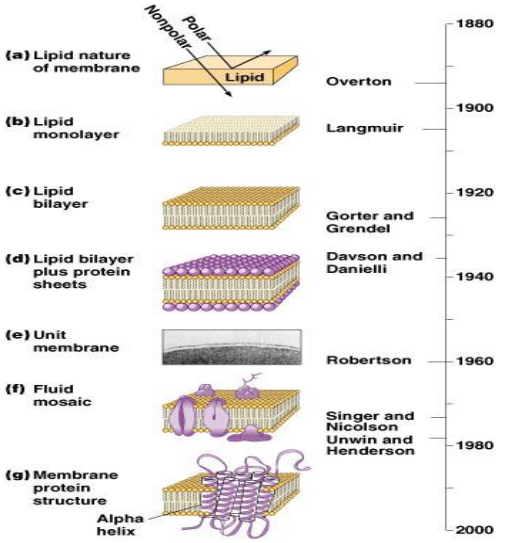
General Characteristics of Biomembranes (Cont.)

- They are selectively permeable to polar solutes in the surrounding.
  - i.e. they retain certain compounds and exclude others.
- They consist mainly of lipids and proteins and some carbohydrates.
  - The weight ratio of protein to lipid ranges from 1:4 to 4:1.
- Membranes are not merely passive barriers.
  - i.e. some molecules pass thoroughly and others need some sort of help, carrier or energy.
- Many compound are located at the cell surface like:
  - transporters that move specific solutes and ions across the membrane;
  - receptors that 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,
  - the energy transductions in *mitochondria* and *chloroplasts*.

General functions of biomembranes

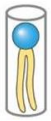
- Membranes define the external boundaries of cells.
- They regulate the molecular traffic across that boundary through *selective permeability.*
  - i.e. It acts as a barrier to unwanted or toxic molecules and help accumulate nutrients
- In eukaryotic cells, they divide the internal space into discrete compartments (organelles) to segregate processes and components.
- They organize complex reaction sequences and are central to both biological energy conservation *(like respiratory chains enzyme complex)*
- They mediate cell-to-cell interaction.
- They modulate signal transduction
- They facilitate cell motion like in paramecium and amoeba
- They assist in reproduction

History of biomembrane discovery



The behavior of lipids with aqueous medium

Depending on the precise conditions and the nature of the lipids, three types of lipid aggregates can form when amphipathic lipids are mixed with water. These are micelles, bilayer and liposomes



Individual units are cylindrical (cross section of head equals that of side chain)

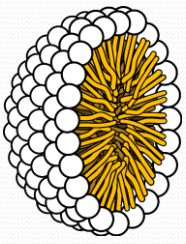
Micelles:

They are spherical structures.

The hydrophobic chains of the fatty acids are sequestered at the core of the sphere.

There is virtually NO water in the hydrophobic interior.

Ex: free fatty acids, lysophospholipids and lipids in detergents (SDS).



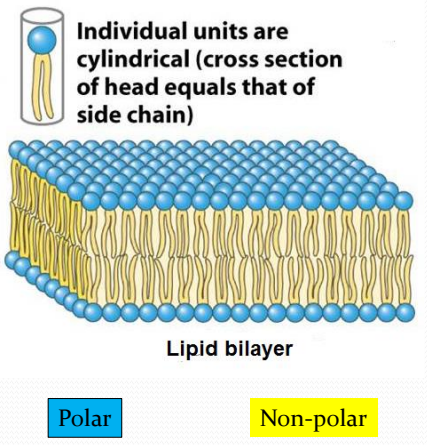
Micelle

The behavior of lipids with aqueous medium (cont.)

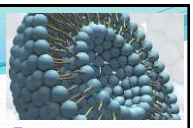
2. Lipid Bilayer:

The hydrophilic head groups interact with water at each surface of the bilayer. The hydrophobic portions in each monolayer, excluded from water, interact with each other.

Ex: in glycerophospholipids and sphingolipids.



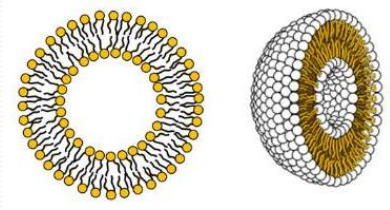
Polar Non-polar



The behavior of lipids with aqueous medium (cont.)

3. Liposomes

- When the bilayers lose their hydrophobic edge regions, it forms bilayer vesicles enclose water in the core.



Liposome
10's nm to submicrometer

Uses of liposome

- Liposome can be used for drug delivery.
- Used for gene therapy
- As vaccine carrier
- Liposome have been useful in the field of cell physiology to understand the functions of proteins in a natural membranes.
- Used as diagnostic agents.

Composition of Biomembranes: Lipids, proteins and carbohydrates

- The molecular components of membranes are:
  - proteins and polar lipids, which account for almost all the mass of biological membranes,
  - carbohydrates, present as part of glycoproteins and glycolipids.
- Each type of membrane in different organisms has characteristic lipids and proteins The relative proportions of protein and types of lipid vary with the type of membrane, reflecting the diversity of biological roles.

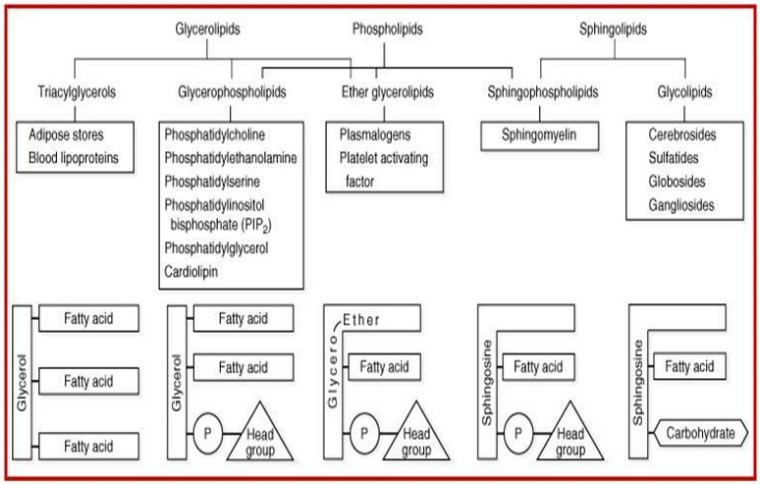
TABLE 11–1 Major Components of Plasma Membranes in Various Organisms

	Components (% by weight)				
	Protein	Phospholipid	Sterol	Sterol type	Other lipids
Human myelin sheath	30	30	19	Cholesterol	Galactolipids, plasmalogens
Mouse liver	45	27	25	Cholesterol	—
Maize leaf	47	26	7	Sitosterol	Galactolipids
Yeast	52	7	4	Ergosterol	Triacylglycerols, steryl esters
Paramecium (ciliated protist)	56	40	4	Stigmasterol	—
E. coli	75	25	0	—	—

Different forms of membrane lipids

The three major classes of membrane lipids:

1. Phosholipids, 2. Glycolipids, 3. Cholesterol



Different forms of membrane lipids: Phospholipids

Phospholipids in animal membranes are derived from either glycerol or sphingosine.

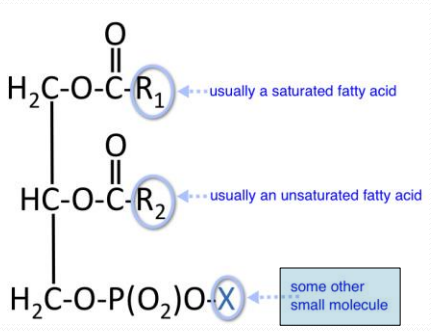
- **GlyceroPhosphoLipids** and called phosphoglyceroids.
  - it consists of a glycerol backbone (3-OH, 3-C alcohol), two fatty acid chains and a phosphorylated alcohol.
- **SphingoPhosphoLipids.**
  - It consists of sphingosine (complex alcohol) and fatty acids.

- The fatty acid chain usually contain even number of C atom, between 14-24. the 16 and 18 are most common.
- Fatty acids may be saturated or unsaturated.
- The configuration of double bonds in unsaturated fatty acids is nearly always cis.
- The length and the degree of unsaturation of fatty acids chains affect the membrane fluidity.

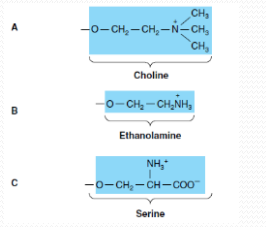
Different forms of membrane lipids: GlyceroPhospholipid structure

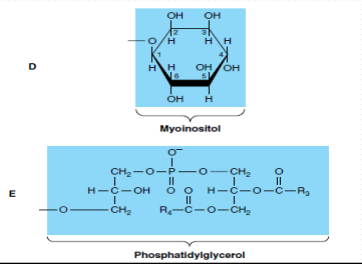
Glycerol + R1 saturated fatty acid + R2 unsaturated fatty acid + phosphate

The phosphate is bound to: Choline, ethanolamine, serine, myoinositol or phosphatidylglycerol.



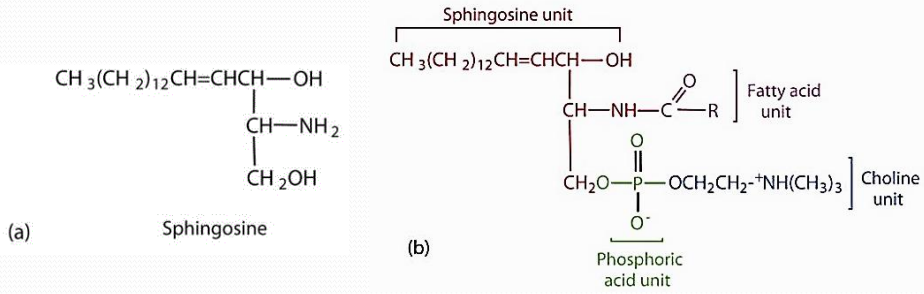
Phosphatidic acid





Different forms of membrane lipids: Sphingosine and Sphingomyelin Structures

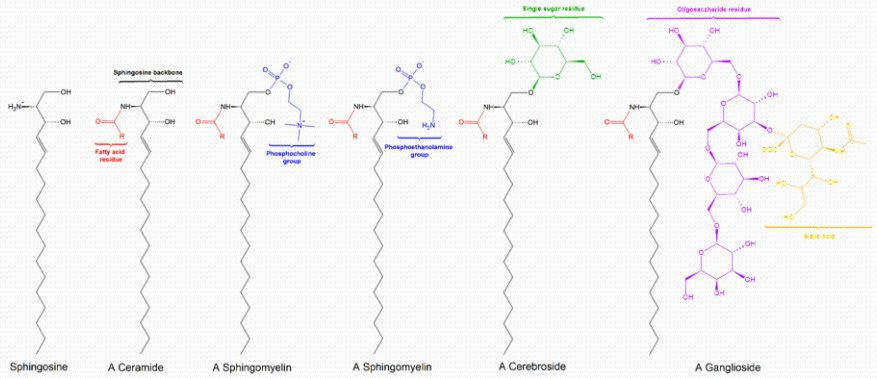
- Sphingosine is unsaturated amino alcohol that contains a long, unsaturated hydrocarbon chain ($C_{18}H_{37}NO_2$).
- Sphingolipids are sphingosine bound to ONE fatty acid through AMIDE bond. Some other compounds may bind to the lateral CH2OH group to give many derivatives.



Different forms of membrane lipids: Derivatives of sphingosine

Sphingosine + 1 FF → Ceramide

Ceramide + Phosphocholine → A Sphingomyelin	(Phospholipid)
Ceramide + Phosphoethanolamine → A Sphingomyelin	(Phospholipid)
Ceramide + Sugar → A Cerebroside	(Glycolipid)
Ceramide + many Sugars → A Ganglioside	(Glycolipid)



Essential Cell Biology, 4th ed.

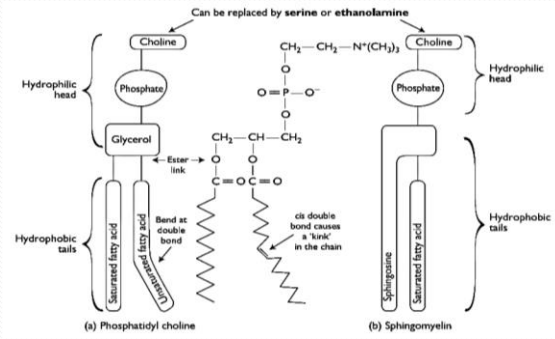
Different forms of membrane lipids glycerophospholipid vs sphingomyelin

Both contain:

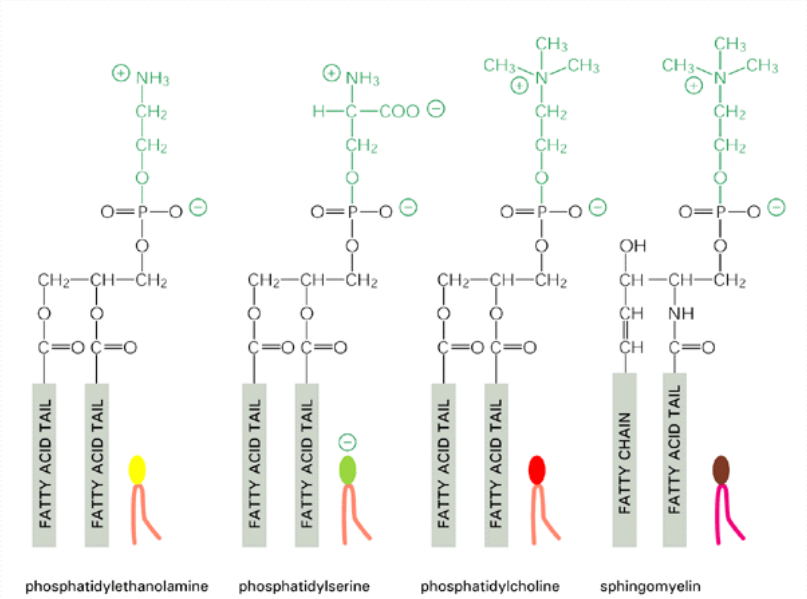
- hydrophilic head composed of alcohol –phosphate and ligand that may be choline, serine or ethanolamine
- Hydrophobic tails of fatty acids

They differ in:

- Glycerophospholipids have glycerol + 2 fatty acids + Phosphate + ligand
- The bonds between glycerol and each of the two FFs are ester bond
- Sphingomyelin have sphingosine + 1 fatty acid +phosphate + ligand
- The bond between sphingosine and the FF is amide bond



Summary of membrane phospholipids:



Glycolipids

Glycolipids* are *sugar-containing lipids.

The animal glycolipids are derived from sphingosine.

Plant glycolipids (mainly galactolipid) are derived from glycerol.

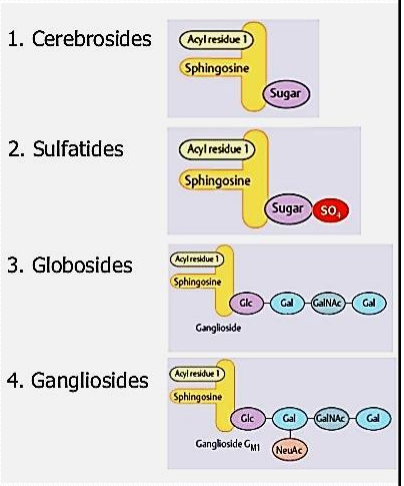
The amino group of the sphingosine backbone is acylated by a fatty acid, as in sphingomyelin.

- Glycolipids differ from sphingomyelin in the identity of the unit that is linked to the primary hydroxyl group of the sphingosine backbone.
- In glycolipids, one or more sugars (rather than phosphoryl choline) are attached to this group.
- The simplest glycolipid, called a *cerebroside*, contains a single sugar residue, either glucose or galactose.
- Gangliosides contain a branched chain as many as 7 sugar residues.

Glycolipids: Types and functions

Ex. Cerebrosides, sulfatides, globosides and gangliosides

- The role of membrane glycolipids is to maintain stability of the membrane and to facilitate cellular recognition.
- The carbohydrates are found on the outer surface of all eukaryotic cell membranes.
- They are used for:
  - cell-cell interaction
  - Identify the blood type
  - Immune response



Glycolipids: Role in membrane Asymmetry

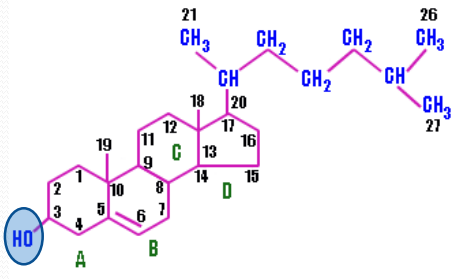
- Glycolipids present in all animal plasma membranes, constitute about 5% of the lipid molecules in the *outer monolayer*.
- The asymmetric lipid molecules in cell membrane are the glycolipids due to the addition of sugar groups to the lipid molecules in the lumen of the Golgi apparatus, through self association and partly by hydrogen bonding and van del Waals attraction.
- The sugar groups are exposed at *the outer cell surface* and this enables the cell to interact with its surroundings.
- They are also found in some intracellular membranes.
- **Gangliosides,** contain oligosaccharides with one or more sialic acid residues, which give gangliosides a net *negative charge.*
- More than 40 different gangliosides have been identified, mostly in the plasma membrane of nerve cells, where they constitute 5–10% of the total lipid mass.

Essential Cell Biology, 4th ed. Albert et al., 2014

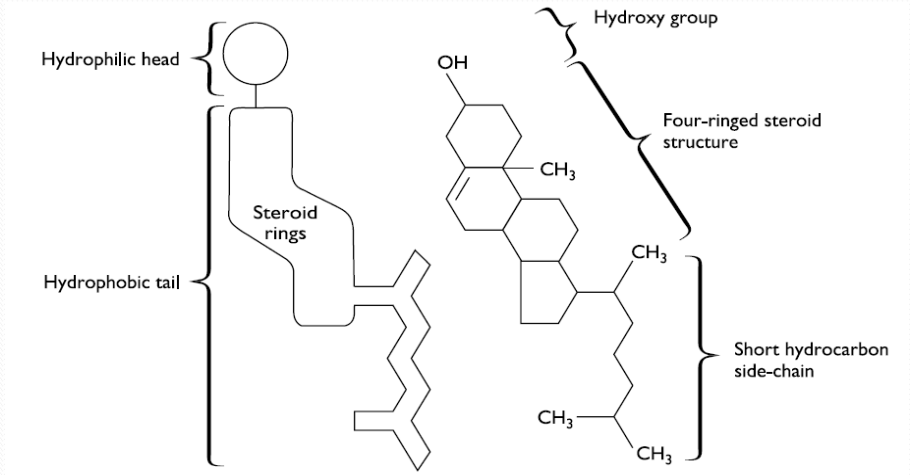
Cholesterol

- It is amphipathic steroid compound contains 27 C ($C_{27}H_{46}O$). It is a major constituent of *biomembrane* and *plasma lipoproteins*
- It presents in eukaryotes and not in most prokaryotes.

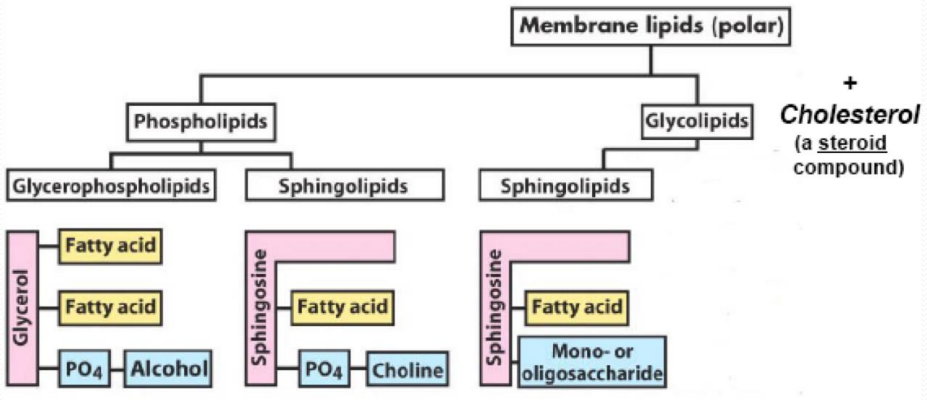
- It constitutes almost 25% of the membrane lipids in certain nerve cells but is essentially absent from some intracellular membranes.
- It is often found as cholesteryl ester, where the hydroxyl group on position 3 is esterified with a long-chain fatty acid.



Cholesterol: Its structure in membrane

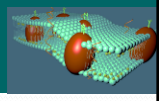


Summary of membrane lipids



All Biological Membranes Share Some Fundamental Properties

Fluid Mosaic Model



- Membranes are impermeable to most polar or charged solutes, but permeable to nonpolar compounds.
- They are 5 to 8 nm (50 to 80 Å) thick.
- They are formed from phospholipids bilayer arranged in the following order:
  - the polar head groups face outward, interacting with the aqueous phase on either side.
  - the nonpolar regions (hydrophobic) of the lipid molecules in each layer face the core of the bilayer

All Biological Membranes Share Some Fundamental Properties

Fluid Mosaic Model (cont.)

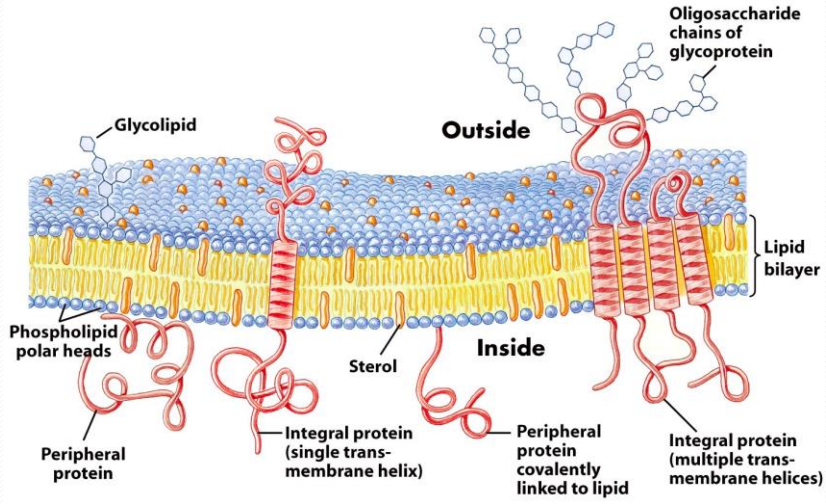
- Some proteins are embedded in this bilayer sheet, held by hydrophobic interactions between the membrane lipids and hydrophobic domains in the proteins.

Give example for the hydrophobic domains of proteins

- The orientation of proteins in the bilayer is *asymmetric*, giving the membrane "sidedness"
  - i.e. the protein domains exposed on one side of the bilayer are different from those exposed on the other side. This variation reflects functional asymmetry.
- Specific proteins mediate distinctive function of membranes.
  - Proteins serve as pumps, gates, receptors, energy transducers and enzymes.
  - Membrane protein are intercalated into lipid bilayers, which create a suitable environment for the action of these proteins.

All Biological Membranes Share Some Fundamental Properties

Fluid Mosaic Model (cont.)



All Biological Membranes Share Some Fundamental Properties

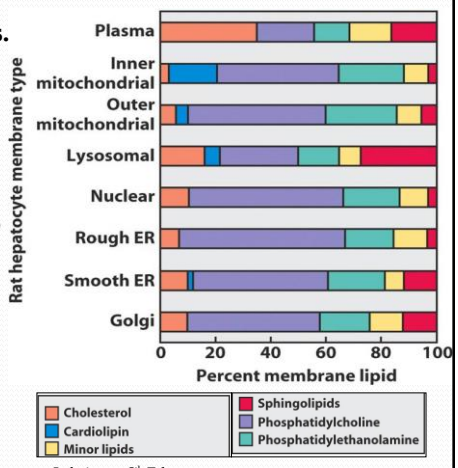
Fluid Mosaic Model (cont.)

- The individual lipid and protein units in a membrane form *a fluid mosaic* with a pattern that is free to change constantly.
- Why it is fluid in nature?
  - 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.
  - Protein molecules diffuse rapidly in the plane of the membrane, unless anchored by specific interactions.
- Most cell membranes are electrically polarized (-60 mV).

The Type of Lipid differ from the plasma membrane to organelle membranes

The functional specialization of each membrane type is reflected in its unique lipid composition. Example rat hepatocytes.

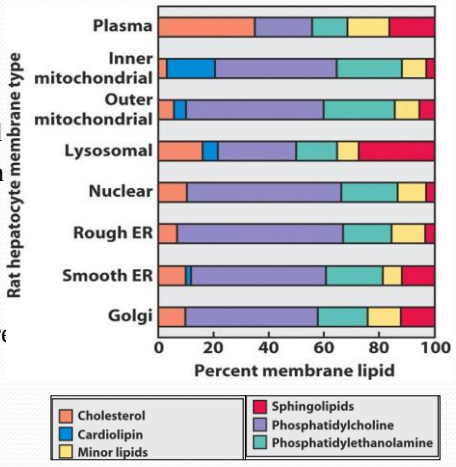
- **Cholesterol** is prominent in plasma membranes but barely detectable in mitochondrial membranes.
- **Phosphatidylserine, phosphatidylinositol, and phosphatidylglycerol** are relatively minor components (yellow) of most membranes but serve critical functions; phosphatidylinositol and its derivatives, for example, are important in signal transductions triggered by hormones.



Lehninger, 6th Ed.

The Type of Lipid differ from the plasma membrane to organelle membranes (cont.)

- **Cardiolipin** is a major component of the inner mitochondrial membrane but not of the plasma membrane.
- **Sphingolipids**, **phosphatidylcholine**, and **phosphatidylethanolamine** are present in most membranes, but in varying proportions.
- Glycolipids, which are major components of the chloroplast membranes of plants, are virtually absent from animal cells.

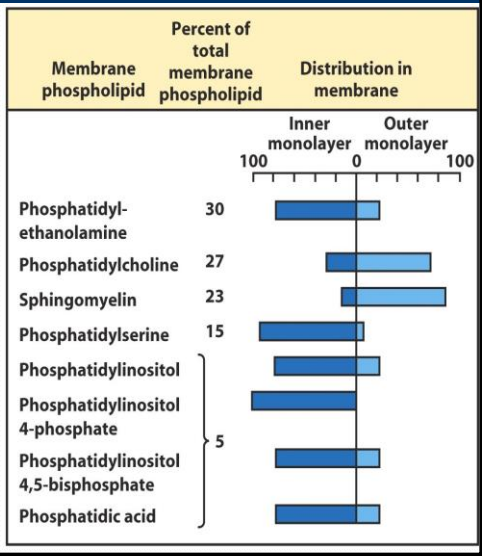


Lehninger, 6th Ed.

The membrane phospholipids are *asymmetrically distributed* between the inner and outer monolayers

The plasma membrane contains many types of lipids in specific distribution:

- phosphatidylcholine and sphingomyelin (choline containing) are found in the outer face of the plasma membrane
- phosphatidylserine, phosphatidyl-ethanolamine, and the phosphatidyl-inositols are found in the inner face.



31

The membrane phospholipids are *asymmetrically distributed* between the inner and outer monolayers (Cont.)

Changes in the distribution of lipids between plasma membrane have biological consequences.

- If the phosphatidylserine in the plasma membrane moves into the outer layer this means that the cell is able to play its role in formation of a blood clot.
- If phosphatidylserine moves to the outer surface this indicates that the cell take the way programmed cell death.

Proteins & carbohydrates of the biomembranes

- 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* called *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 plasma membrane of *Escherichia coli* contains hundreds of different proteins, including transporters and many enzymes involved in energy-conserving metabolism, lipid synthesis, protein export, and cell division.

Proteins & carbohydrates of the biomembranes (Cont.)

- Some membrane proteins are covalently linked to carbohydrate.
- For example:
  - in the glycoprotein called *glycophorin* of the erythrocyte plasma membrane, 60% of the mass consists of complex oligosaccharide units covalently attached to Ser, Thr, and Asn.
  - rhodopsin of the rod cell plasma membrane contains just one hexasaccharide.
- The sugar moieties of surface glycoproteins have different roles:
  - They influence the folding, stability and intracellular destinations of the proteins
  - they play a significant role in the specific binding of ligands to glycoprotein surface receptors.

Functions of membrane glycolipids

- In the epithelial plasma cells membrane, glycolipids are confined to the exposed apical surface, where they may help protect the membrane against the harsh conditions frequently found there (such as low pH and degradative enzymes).
- Charged glycolipids, such as gangliosides, may be important for their electrical effects: their presence alters the electrical field across the membrane and the concentrations of ions—especially Ca2+ at the membrane surface.
- Glycolipids function in cell-recognition processes, in which membrane-bound carbohydrate-binding proteins (lectins) bind to the sugar groups on both glycolipids and glycoproteins in the process of cell-cell adhesion.
- Some glycolipids provide entry points for certain bacterial toxins. The ganglioside GM1, for example, acts as a cell-surface receptor for the bacterial toxin

Glycoprotein in cell membrane

- The exterior of the eukaryotic cells are decorated, clothed, or hidden by carbohydrates.
- Carbohydrates occur is plasma membrane as:
  - Glycoproteins, an oligosaccharide chains covalently bound to membrane proteins
  - Glycolipids
  - lipids polysaccharide chains of *integral membrane proteoglycan* molecules.
- The term *cell coat*, or *glycocalyx*, is often used to describe the carbohydrate-rich zone on the cell surface.
- About 15 sugar residue, often branched, can be attached.
- The arrangement of these sugars in the glycoproteins and glycolipids determine their function in the cell.
- It may function in specific cell-recognition processes.
- It may protect cell against mechanical and chemical damage and to keep foreign objects and other cells at a distance, preventing undesirable protein-protein interactions.
- It may have role in cell-cell adhesion processes, including those occurring in sperm-egg interactions, blood clotting, lymphocyte recirculation, and inflammatory responses.

•Membrane proteins may be divided into two groups:

•**Integral proteins** are very firmly associated and embedded within the membrane.

•It can be removed only by detergents, organic solvents, or denaturants that interfere with hydrophobic interactions.

•**Peripheral proteins** associate with the membrane surface through:

- electrostatic interactions
- hydrogen bonding with the hydrophilic domains of integral proteins
- hydrogen bonding with the polar head groups of membrane lipids.

•They can be released by reagents that interfere with electrostatic interactions or break hydrogen bonds; a commonly used agent is carbonate at high pH.

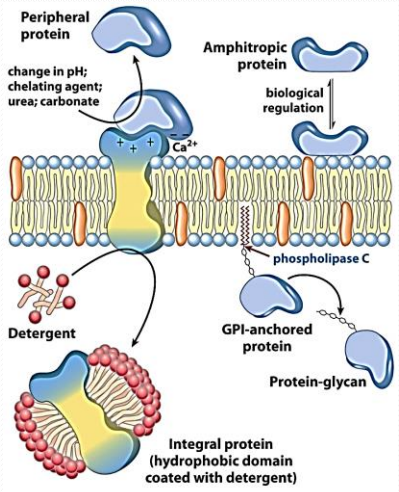


Figure 11-7
Lehninger Principles of Biochemistry, Sixth Edition
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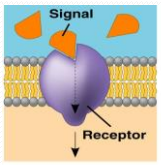
Functions of membrane proteins

1-Receptors: detecting signals from outside

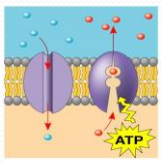
- Light (opsin)
- Hormones (insulin receptor)
- Neurotransmitters (acetylcholine receptor)
- Pheromones (taste and smell receptors)



(c) Signal transduction

2-Channels, gates, pumps

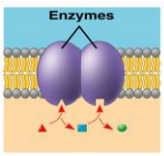
- Nutrients (maltoporin)
- Ions (K-channel)
- Neurotransmitters (serotonin reuptake protein)



(a) Transport

3-Enzymes

- Lipid biosynthesis (some acyltransferases)
- ATP synthesis (F_0F_1 ATPase/ATP synthase)



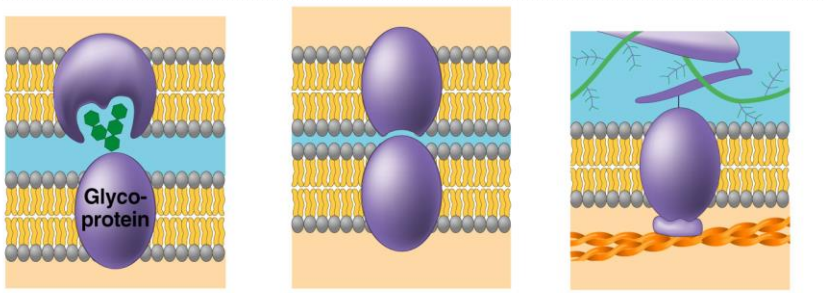
(b) Enzymatic activity

Functions of membrane proteins (Cont.)

4- Cell-cell recognition

5- Intercellular joining

6- Attachment of cytoskeleton



(d) Cell-cell recognition (e) Intercellular joining (f) Attachment to the cytoskeleton and extra-cellular matrix (ECM)

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