Chapter 6: Cell and Organelle Membrane Structure

# Lipid bilayers

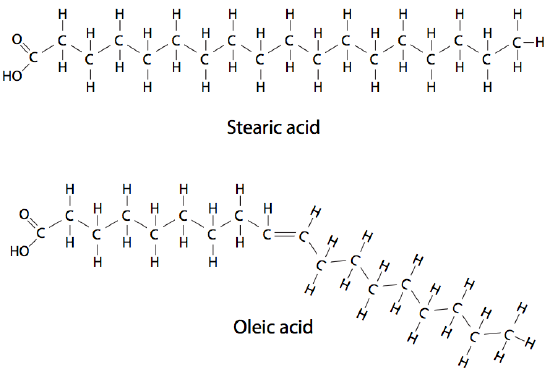
The protective membrane around cells contains many components, including cholesterol, proteins, glycolipids, phospholipids, and sphingolipids. The last two of these will, when mixed vigorously with water, spontaneously form what is called a **lipid bilayer**, which serves as a protective boundary for the cell that is largely impermeable to the movement of most materials across it. With the notable exceptions of water, carbon dioxide, carbon monoxide, and oxygen, most polar/ionic molecules require transport proteins to help them navigate across the bilayer. The orderly movement of these compounds is critical for the cell to be able to 1) obtain food for energy; 2) export materials; 3) maintain osmotic balance; 4) create gradients for transport; 5) provide electromotive force for nerve signaling, and 6) store energy in electrochemical gradients for ATP production (oxidative phosphorylation or photosynthesis).

Though some cells do not have cell walls (animal cells) and others do (bacteria, fungi, and plants), all cells possess plasma membranes. All plasma membranes are made of a lipid bilayer, each containing a significant amount of **amphiphilic** molecules, including phospholipids and sphingolipids.

# Components of lipid bilayers

## Fatty acids

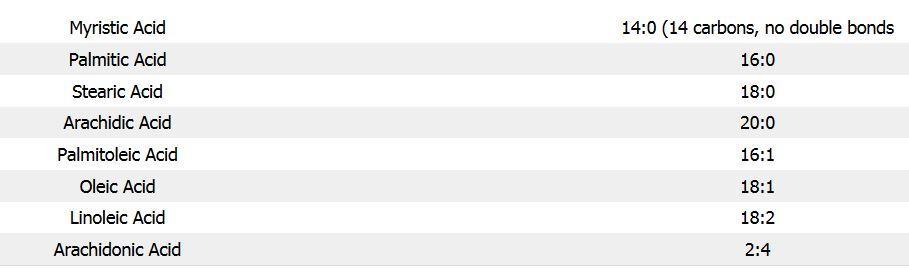
Unlike monosaccharides, nucleotides, and amino acids, fatty acids are not monomers that are linked together to form much larger molecules. Although fatty acids can be linked together, for example, into triacylglycerols or phospholipids, they are not linked directly to one another, and generally no more than three in a given molecule. The fatty acids themselves are long chains of carbon atoms topped off with a carboxyl group. The length of the chain can vary, although most are between 14 and 20 carbons, and in higher-order plants and animals, fatty acids with 16 and 18 carbons are the major species.



**Figure 6-1: Fatty acids.** (Top)Stearic acid is a fully saturated fatty acid with no carbon-carbon double bonds. (Bottom) Oleic acid is an unsaturated fatty acid with one carbon-carbon double bond. The double-bond forms a slight bend in the structure.

Due to the mechanism of synthesis, most fatty acids have an even number of carbons, although odd-numbered carbon chains are possible. Double-bonds between the carbons can generate more variety. Fatty acid chains with no double bonds are **saturated** because each carbon is bonded to as many hydrogen atoms as chemically possible. Fatty acid chains with double or triple bonds are **unsaturated** (Figure 6-1). Those with more than one double or triple bond are called polyunsaturated. The fatty acids in eukaryotic cells contain nearly evenly divided saturated and unsaturated types, and many of the latter may be polyunsaturated (Table 6-1).

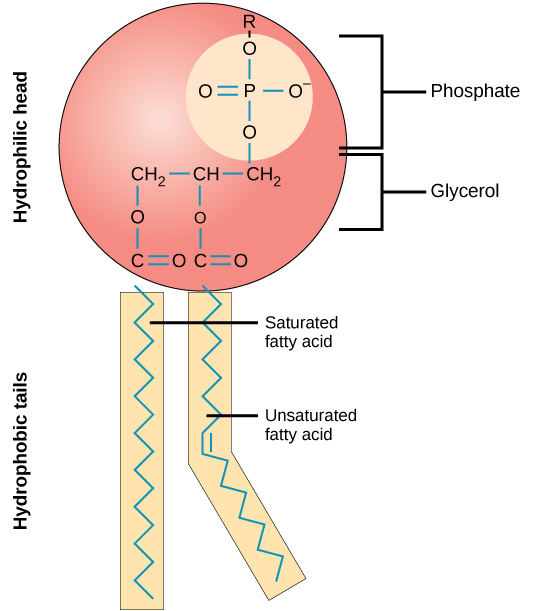
**Table 6-1. Common fatty acids and their carbon length.**



There are significant physical differences between the saturated and unsaturated fatty acids due simply to the geometry of the double-bonded carbons. A saturated fatty acid is very flexible with free rotation around all of its C-C bonds. The usual linear diagrams and formulas depicting saturated fatty acids also serve to explain the ability of saturated fatty acids to pack tightly together, with very little intervening space. Unsaturated fatty acids, on the other hand, are unable to pack as tightly because of the rotational constraint imposed by the double bond. The carbons cannot rotate around the double bond, so there is now a “kink” in the chain.

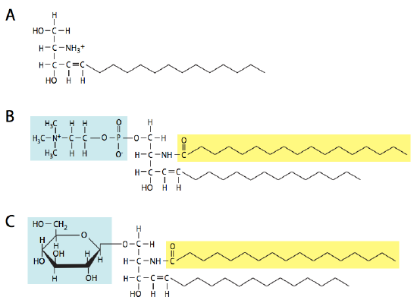
## Phospholipids

**Phospholipids** (also called phosphoglycerides or glycerophospholipids) are also fatty acids attached to glycerol. However, instead of three fatty acid tails, there are only two, and a phosphate group is attached to the third carbon of the glycerol molecule (Figure 6-2). The phosphate group also links to a “head group.” The identity of the head group and the fatty acid tails names the molecule. Phospholipids are **amphipathic.** Amphipathic means that a structure is hydrophobic on one end and hydrophilic on the other. In a phospholipid, the fatty acid tails carry a strong hydrophobic character, and the head group carries a strong hydrophilic character. The amphipathic nature of phospholipids is crucial for their role as the primary component of cellular membranes.



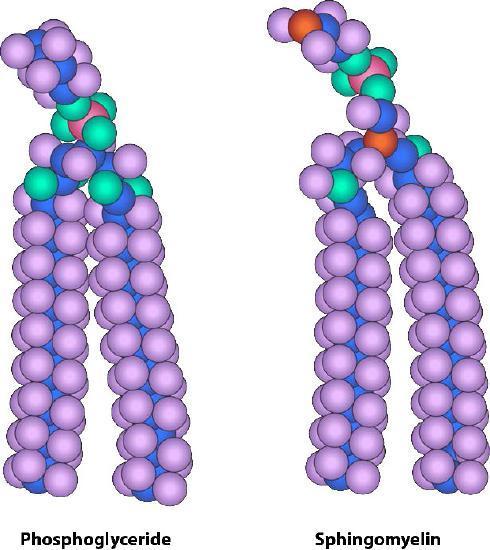
**Figure 6-2: Phospholipid Structure.** A phospholipid: the glycerol backbone connects to two fatty acids and phosphate and polar head group (R). The polar head group orientates toward the hydrophilic locations inside or outside the cell (cytoplasm or extracellular space, respectively). The nonpolar fatty acids orientate to the hydrophobic part of the membrane to interact with the fatty acid tails of the other phospholipids.

Sphingolipids (Figure 6-3 and 6-4) are also important constituents of membranes and are based not upon a glycerol backbone, but on the amino alcohol, sphingosine (or dihydrosphingosine). There are four major types of sphingolipids: ceramides, sphingomyelins, cerebrosides, and gangliosides. Ceramides are



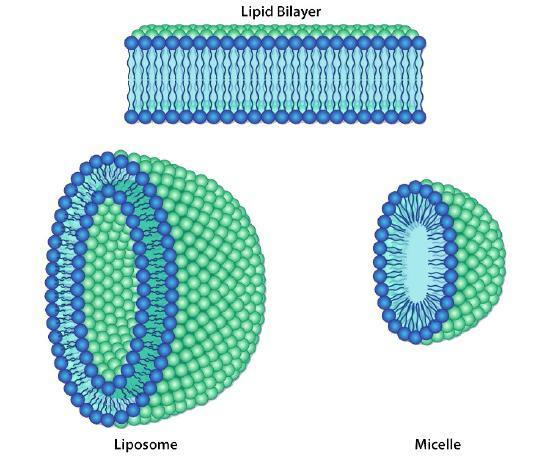
**Figure 6-3: Sphingolipids rely on amino alcohol, sphingosine** (A). Ceramides have a fatty acid tail attached, and ceramide with a phosphocholine head group is sphingomyelin (B). If the head group is a saccharide, then the molecule is a cerebroside.

sphingosine molecules with a fatty acid tail attached to the amino group. Sphingomyelins are ceramides in which a phosphocholine or phosphoethanolamine is attached to the 1-carbon. Cerebrosides and gangliosides are glycolipids, which have a single monosaccharide or multiple saccharides, respectively, attached to the 1-carbon of a ceramide. The oligosaccharides attached to gangliosides all contain at least one sialic acid residue. In addition to being a structural component of the cell membrane, gangliosides are particularly important in cell-to-cell recognition.



**Figure 6-4: Structural Similarity.** Similarity of form between a phosphoglyceride and sphingomyelin.

In each case, the phospholipid or sphingolipid has one polar end and one nonpolar end. As seen in the organization of amino acids with hydrophobic side chains occurring preferentially on the inside of a folded protein to exclude water, so too do the nonpolar portions of these amphiphilic molecules arrange themselves to exclude water, the tendency of molecules, including proteins and phospholipid bilayers, to hide their hydrophobic regions is known as the **hydrophobic effect**. Remember that the cytoplasm of a cell contains a high percentage of water, and the exterior of the cell is also aqueous. It, therefore, makes perfect sense that the polar portions of the membrane molecules arrange themselves as they do - polar parts outside interacting with water and nonpolar parts in the middle of the bilayer avoiding/excluding water (Figure 6-5).



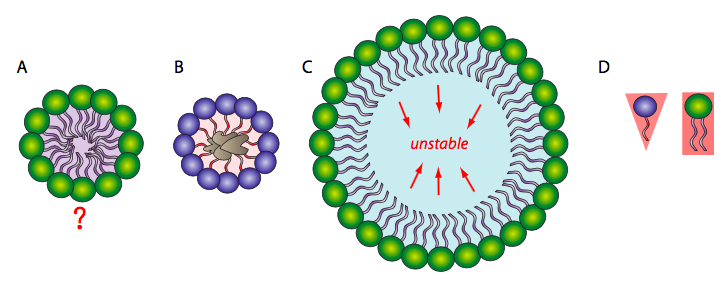
**Figure 6-5: Different lipid bilayer structures.** The structure at the top is demonstrating a small portion of the phospholipid bilayer and the orientation of phospholipids. The structure on the bottom left is a liposome sphere cut in half to show the bilayer. The hollow center of the liposome is hydrophilic. Vesicles form this structure in cells. The structure on the bottom right is a micelle sphere cut in half to show the single layer of phospholipids or fatty acids. The hollow center of the micelle is hydrophobic.

**Folding of the Phospholipid bilayer**

Since most cells live in an aqueous environment and the contents of the cell are mostly aqueous, it makes sense that a membrane that separates one side from the other must be hydrophobicto form an effective barrier against accidental leakage of materials or water. Cellular membranes are composed primarily of phospholipids: molecules consisting of a phosphorylated polar head group attached to a glycerol backbone that has two long hydrocarbon tails. The composition of the hydrocarbons can vary in length and degree of saturation, and there is variation in the head groups.

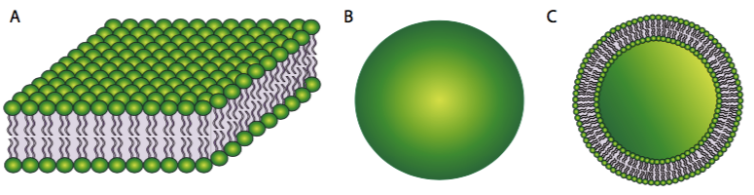
Because the phospholipids are amphipathic, the simplest conformation for a small group of phospholipids in aqueous solution might be expected to be a micelle (Figure 6-6A), but is this the case? Mixtures of hydrophobic molecules and water are thermodynamically unstable, so a micelle would protect the hydrophobic fatty acid tails from the aqueous environment with which the head groups interact. Micelles can form with other amphipathic lipids, the most recognizable being detergents such as SDS (sodium dodecyl sulfate, also called sodium lauryl sulfate), used in common household products such as shampoos. The detergents act by surrounding hydrophobic dirt (Figure 6-6B) and holding it in solution within the micelle to be rinsed away with the water. At smaller sizes, the micelle is fairly stable; however, when there are a large number of phospholipids, the space inside the micelle becomes larger and can trap water in direct contact with the hydrophobic tails (Figure 6-6C), Rendering the micelle unstable. Therefore, a single large layer of phospholipid is unlikely to serve stably as a biological membrane.

Additionally, micelles form easily with SDS and other single-tailed lipids because their overall shape (van der Waals envelope) is conical (Figure 6-6D), which lends itself to fitting tight curvatures. However, phospholipids are more cylindrical, and it is harder to fit them into a tight spherical micelle. If they do form micelles, they tend to be larger, and are likely to collapse.



**Figure 6-6: Determination of folding by the phospholipid bilayer.** A) A micelle structure formed by phospholipids, B) micelle trapping dirt molecules, C) large, unstable hypothetical micelle, and D) general structural shapes of single-tailed lipids and double-tailed lipids.

On the other hand, a **phospholipid bilayer** (Figure 6-7A) could form a fatty acid sandwich in which the polar head groups face outward to interact with an aqueous environment and the sequestered fatty acids in between. However, this does not resolve the problem on the edges of the sandwich. Therefore, the solution to the ideal phospholipid structure in an aqueous environment is a spherical phospholipid bilayer (Figure 6-7B and cutaway in 6-7C): no edges mean no exposed hydrophobicity.

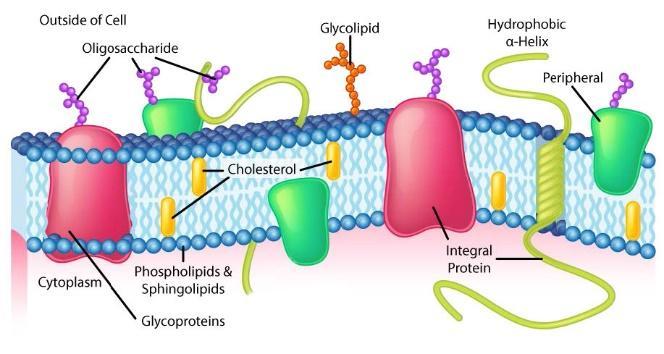


**Figure 6-7: Folding by the phospholipid bilayer.** A) unstable fatty acid “sandwich,” B) spherical phospholipid bilayer, and C) spherical phospholipid bilayer cut in half to demonstrate bi-layer formation.

The stability of the spherical phospholipid bilayer does not imply that it is static in its physical properties. In most physiologically relevant conditions, the membrane is cohesive, but fluid. It can mold its surface to the contours of whatever it is resting on, and the same thermodynamic and hydrophobic properties that make it so stable allow it to seal up minor tears spontaneously.

**Composition Bias**

The composition of plasma membranes is different depending on its location. First, glycosylation (of lipids and proteins) has the sugar groups located almost exclusively on the outside of the cell, away from the cytoplasm (Figure 6-8). Among the membrane lipids, sphingolipids are much more commonly glycosylated than phospholipids. Also, different types of phospholipids can be found preferentially on one side of the membrane or the other. Phosphatidylserine and phosphatidylethanolamine are found preferentially within the inner leaflet (side) of the plasma membrane, whereas phosphatidylcholine tends to locate on the outer leaflet. Notably, in the process of apoptosis, phosphatidylserines flip to the outer leaflet, where they serve as a signal to macrophages to bind and destroy the cell. Sphingolipids are found preferentially in the plasma membrane and are almost completely absent from mitochondrial and endoplasmic reticulum membranes.

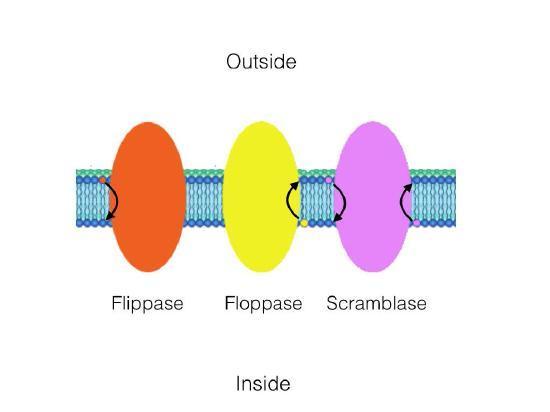


**Figure 6-8: Molecular organization of the lipid bilayer.** The components present in the outer layer of the membrane are different from those in the inner layer, and thus the plasma membrane is asymmetric in the organization. Membrane proteins can span both phospholipid layers (integral) and only one layer (peripheral). Glycosylated lipids and proteins primarily have those carbohydrate extensions orientated to the outside of the cell as they serve a functional purpose.

**Diffusion of lipids within the membrane**

The movement of lipids within each leaflet (side) of the lipid bilayer occurs readily and rapidly due to **membrane fluidity**. This type of movement is called **lateral diffusion**. While the movement in lateral diffusion occurs rapidly, the movement of lipids from one leaflet over to the other leaflet occurs much more slowly or not at all. This type of molecular movement is called **transverse diffusion** and is almost nonexistent in the absence of enzyme action. Remember that there is a bias of distribution of molecules between leaflets of the membrane, which means that something must be organizing them.

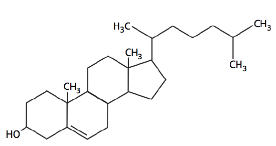
Three enzymes catalyze the movement of compounds in transverse diffusion. Flippases move membrane glycerophospholipids/sphingolipids from the outer leaflet (extracellular space) to the inner leaflet (cytoplasmic side) of the cell. Floppases move membrane lipids in the opposite direction. Scramblases move in either direction.



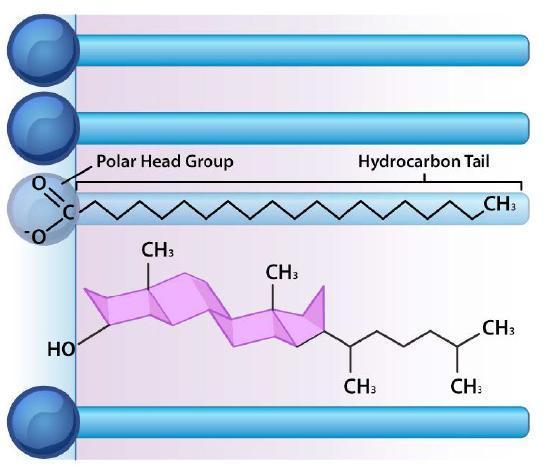
**Figure 6-9: Catalytic action of a flippase, a floppase, and a scramblase.** Flippases move glycosylated phospholipids and sphingolipids from the extracellular space to the cytoplasm. Floppases move them from the cytoplasm to the extracellular space. And scramblases move them in either direction.

## Other components of the lipid bilayer

Besides phospholipids and sphingolipids, there are other materials commonly found in lipid bilayers of cellular membranes. Two important and prominent ones are cholesterol (Figure 6-10) and proteins. Cholesterol is a saturated hydrocarbon consisting of four fused rings, the flatness and hydrophobicity of the sterol rings allow cholesterol to interact with the nonpolar portions of the lipid bilayer. In contrast, the hydroxyl group can interact with the hydrophilic part (Figure 6-11).



**Figure 6-10: Cholesterol.** Cholesterol is an important lipid both as a membrane component and as a steroid precursor. Cholesterol is amphipathic as it has a polar hydroxyl group (bottom left) attached to a nonpolar 4-fused carbon ring structure.



**Figure 6-11: Cholesterol in the lipid bilayer.**  Cholesterol and phospholipids both are amphipathic. This allows each to orientate their polar section toward the hydrophilic water inside or outside the cell. The similar lengths of both allows cholesterol to be positioned within one leaflet, or side, of the phospholipid bilayer.

# Membrane Fluidity

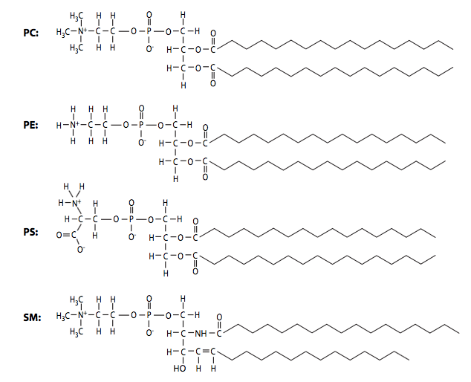
Maintaining a working range of fluidity is important to the cell. If the membrane is too rigid, then it may be unable to move or undergo necessary processes such as endocytosis, in which a cell takes up large extracellular molecules by enveloping them with the cell membrane and pinching it off in a vesicle; while if it becomes too fluid, it may fall apart.

Three major factors govern the fluidity of the membrane:

1. degree of saturation and length of the fatty acid chains,
2. the temperature, and
3. the concentration of cholesterol.

Because there are no ‘kinks’ in fully saturated fatty acid chains they can pack together very tightly, decreasing membrane fluidity. As more unsaturated fatty acid chains are added to the membrane, the kinks in their chains create more space between some of the fatty acid tails, increasing fluidity. Therefore, if a membrane has more saturated fatty acid chains, it will have a more solid-like membrane, while a membrane with more unsaturated fatty acid chains would be more fluid-like. Similarly, at higher temperatures, even saturated fatty acid chains, with their increased energy, move more and create more space between the chains, increasing fluidity. Finally, the structure of cholesterol is fantastic in that its structure allows both an increase and a decrease in membrane fluidity. Its ring structure is rigid (not freely rotatable) causing a reduction in molecular motion and decreasing membrane fluidity. But, the rings are also bulky, which increases the space around the cholesterol, allowing for greater movement of neighboring fatty acid chains, resulting in an increase in membrane fluidity. The ability of cholesterol to both increase and decrease fluidity is sort of like a ‘buffer’ for the fluidity of the membrane. It helps prevent the membrane from becoming too fluid-like or too solid-like.

In addition to the three factors noted above, phospholipid composition can also alter membrane fluidity: shorter acid chains lead to greater fluidity. In comparison, longer chains, with more surface area for interaction, generate membranes with higher viscosity. The phospholipid composition of biological membranes is dynamic and can vary widely. In Figure 6-12, the structures of the major phospholipid species phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), and sphingomyelin (SM) in plasma membranes from two different cell types. As you might expect based on their differing functions, the ratios of plasma membrane lipids of a myelinating Schwann cell are very different from the lipids in the plasma membrane of a red blood cell.



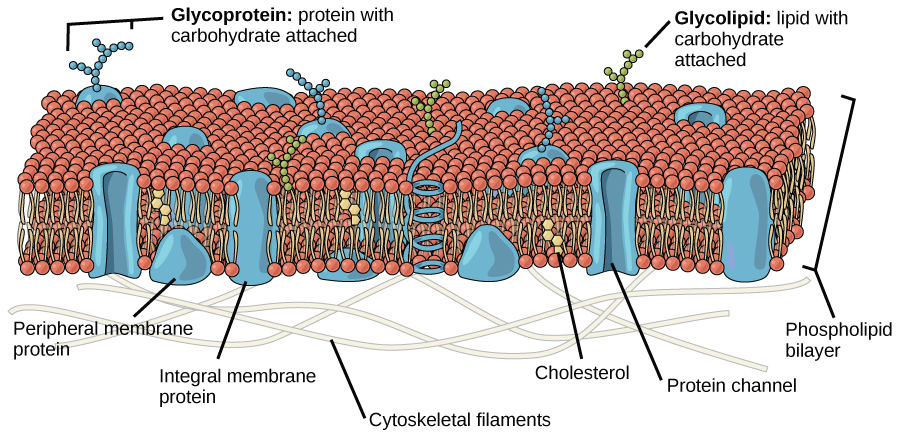
**Figure 6-12: The molecular structures of common phospholipids in the plasma membrane: phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), and sphingomyelin (SM).** The acid chains of all four molecules are of variable length except the 13-C chain of SM. Each of these is present in different cells in different percentages.

However, there are some similarities between most eukaryotic membranes, such as the major component (~50%) is phosphatidylcholine (PC) (Figure 6-13). Phosphatidylcholine structure consists of a choline molecule attached to the phosphate in the phospholipid structure. The fatty acid tails include one straight saturated and one bent unsaturated fatty acid. This bend generates space in the membrane and therefore increases fluidity. As the major components of most eukaryotic membranes, it ensures the overall ability of the membrane to maintain its structure and semi-permeable properties.

## A phospholipid: the glycerol backbone (red) connects to two fatty acids and phosphate and polar head group. The polar head group orientates toward the hydrophilic locations inside or outside the cell (cytoplasm or extracellular space, respectively). The nonpolar fatty acids orientate to the hydrophobic part of the membrane to interact with the fatty acid tails of the other phospholipids

**Figure 6-13: Phosphatidylcholine Structure.** A phospholipid: the glycerol backbone (red) connects to two fatty acids and phosphate and choline polar head group. The polar head group orientates toward the hydrophilic locations inside or outside the cell (cytoplasm or extracellular space, respectively). The nonpolar fatty acids orientate to the hydrophobic part of the membrane to interact with the fatty acid tails of the other phospholipids.

Also, the mosaic characteristic of the membrane helps the plasma membrane remain fluid (Figure 6-14). The integral proteins and lipids exist in the membrane as separate but loosely-attached molecules. The membrane is not like a balloon that can expand and contract; instead, it is fairly rigid and can burst if penetrated or if a cell takes in too much water. However, because of its mosaic nature, a very fine needle can easily penetrate a plasma membrane without causing it to burst; the membrane will flow and self-seal upon removal of the needle.



**Figure 6-14: Membrane Fluidity.** The plasma membrane is a fluid combination of phospholipids, cholesterol, and proteins. Carbohydrates attached to lipids (glycolipids) and proteins (glycoproteins) extend from the outward-facing surface of the membrane. The fluidity of the membrane is a delicate balance to maintain a semi-permeable membrane. The amount of cholesterol, saturated and unsaturated fatty acids, and temperature have an impact on fluidity.

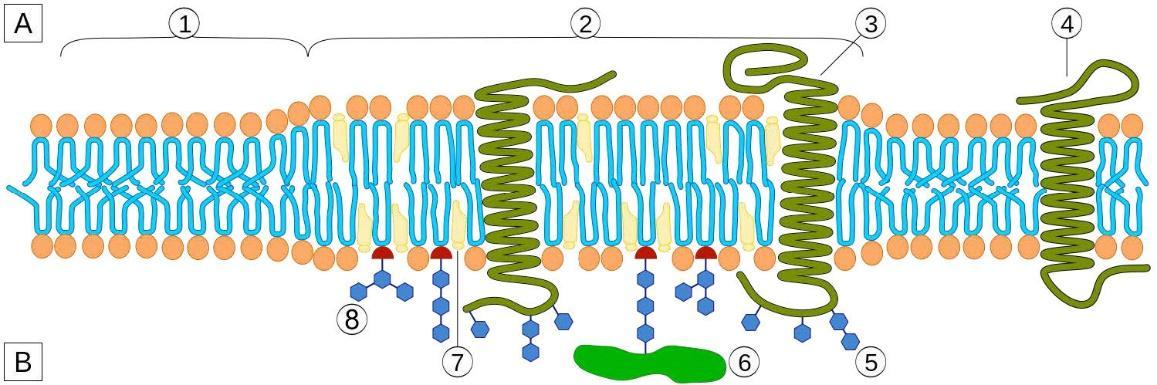
## Lipid Rafts

Even within a single cell, the composition of the plasma membrane differs from that of intracellular organelles. There is even heterogeneity within a membrane itself - the lipids are not distributed randomly in the membrane. Research over the last two decades has identified **lipid “rafts”** that appear to be specific for embedding particular proteins. Since they are unanchored lipids, the rafts can move laterally within the membrane, just like most individual lipid molecules. Finally, there are different ratios of the lipids between the two layers of the bilayer. The cytoplasmic face of every membrane will have different associations and functions than the extracellular face.

In broad terms, the rafts are considered small areas of ordered lipids within a larger undirected membrane. Lipid rafts most often form in association with specific membrane proteins while excluding others. Usually, the included proteins have signaling-related functions, and one model proposes that these proteins may direct the organization of selected lipids around them rather than the other way around.

Although some phospholipids are directly linked to proteins and the cytoskeleton, most are not. Therefore they are free to move within the plane of its layer of the bilayer.

Cholesterol is also abundantly found in membrane structures called lipid rafts. Lipid rafts are organized structures within the membrane, typically containing signaling molecules and other integral membrane proteins (Figure 6-15). Lipid rafts affect membrane fluidity, neurotransmission, and trafficking of receptors and membrane proteins.



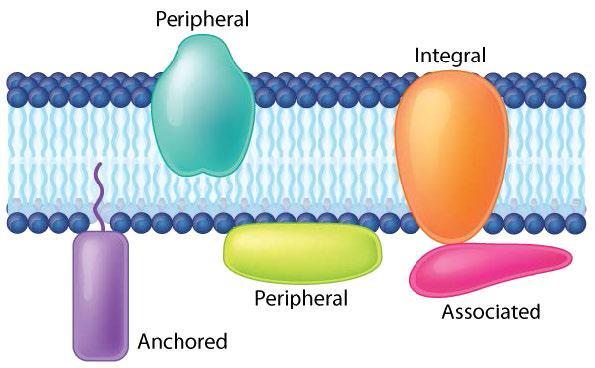
**Figure 6-15: A lipid raft.**  1 = Non-raft membrane, 2 = Lipid raft, 3 = Lipid raft-associated transmembrane protein, 4 = Non-raft membrane protein, 5 = Glycosylation modifications (on glycoproteins and glycolipids), 6 = GPI-anchored protein, 7 = Cholesterol, and 8 = Glycolipid. Note that the lipid raft is a cluster of different molecules (lipid and protein) that move as a unit through the membrane. Note that the side of the raft pointing outside the cell (location B) has components necessary for its function. In this example, the glycosylated phospholipids and proteins will work together for a specific cellular purpose.

## Membrane proteins

Proteins in a lipid bilayer can vary in quantity enormously, depending on the membrane. Protein content by weight of various membranes typically ranges between 30 and 75% by weight. Some mitochondrial membranes can have up to 90% protein. Proteins linked to and associated with membranes come in several types.

**Transmembrane proteins**

**Transmembrane proteins** are integral membrane proteins that completely span from one side of a biological membrane to the other and are firmly embedded in the membrane (Figure 6-16). Transmembrane proteins can function as docking sites for attachment (to the extracellular matrix, for example), as receptors in the cellular signaling system, or facilitate the specific transport of molecules into or out of the cell.



**Figure 6-16: Membrane protein types.** Proteins found in the plasma membrane include peripheral, integral, anchored, and associated proteins.

Examples of integrated/transmembrane proteins include those involved in transport (e.g., Na+/K+ ATPase), ion channels (e.g., potassium channel of nerve cells), and signal transduction across the lipid bilayer (e.g., G-Protein Coupled Receptors).

Peripheral membrane proteins interact with a part of the bilayer (usually does not involve hydrophobic interactions), but do not project through it. Associated membrane proteins typically do not have external hydrophobic regions, so they cannot embed in a portion of the lipid bilayer, but are found near them. Such association may arise as a result of interaction with other proteins or molecules in the lipid bilayer.

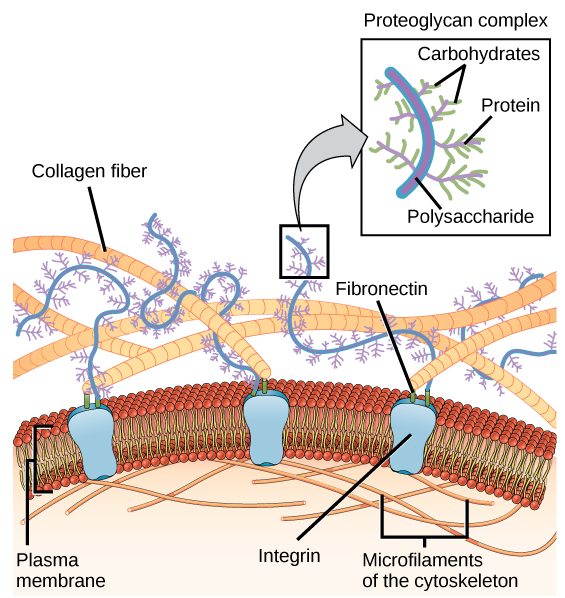
Anchored membrane proteins are not themselves embedded in the lipid bilayer but instead are attached to a molecule (typically a fatty acid) embedded in the membrane.

## Glycocalyx

The “sugar coating” or “carbohydrate coat” of the extracellular surfaces of plasma membranes, identified as the **glycocalyx**, comes from *oligosaccharides* covalently linked to membrane proteins (as *glycoproteins*) or phospholipids (as *glycolipids*). Carbohydrate components of *glycosylated* membrane proteins inform their function. Thus, glycoproteins enable specific interactions of cells with each other to form tissues.

Cells have hundreds to thousands of membrane proteins, and the protein composition of a membrane varies with its function and location. Glycoproteins embedded in membranes play important roles in cellular identification. They also allow interaction with extracellular surfaces to which they must adhere. Also, they figure prominently as part of receptors for many hormones and other chemical communication biomolecules.

Most animal cells release materials into the extracellular space. The primary components of these materials are proteins, and the most abundant protein is collagen. Collagen fibers are interwoven with carbohydrate-containing protein molecules called proteoglycans. Collectively, these materials are called the **extracellular matrix** (Figure 6-17).



**Figure 6-17: The extracellular matrix.** The extracellular matrix consists of a network of proteins and carbohydrates**.**

## Cell-to-Cell Contact Junctions

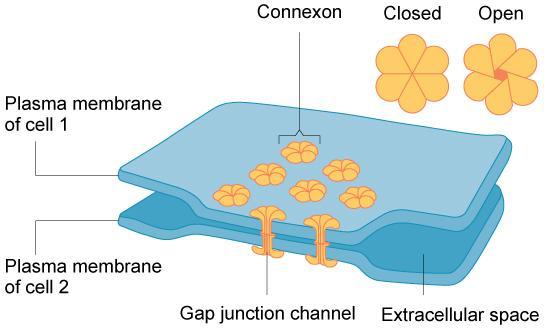
Cells can communicate with each other via direct contact, referred to as intercellular junctions. Examples include the **tight junction** and **gap junction**. A tight junction is a watertight seal between two adjacent animal cells (Figure 6-18). The cells are held tightly against each other by proteins.

Tight junctions form watertight connections between adjacent animal cells. Proteins create tight junction adherence. 


**Figure 6-18: Tight junctions.** Tight junctions form watertight connections between adjacent animal cells. Proteins create tight junction adherence.

This tight adherence prevents materials from leaking between the cells; tight junctions typically found in epithelial tissues, line internal organs and cavities and comprise most of the skin. For example, the tight junctions of the epithelial cells lining your urinary bladder prevent urine from leaking out into the extracellular space.

Gap junctions develop when a set of six proteins (called connexins) in the plasma membrane arrange themselves in an elongated donut-like configuration called a connexon (Figure 6-19). When the pores of connexons in adjacent animal cells align, then a channel forms between the two cells. Gap junctions are regulated to control the flow of molecules, ions, and electrical impulses between cells. Gap junctions are particularly important in cardiac muscle: The electrical signal for the muscle to contract is passed efficiently through gap junctions, allowing the heart muscle cells to contract in tandem.



**Figure 6-19: Gaps junctions.** A gap junction is a protein-lined pore that allows water and small molecules to pass between adjacent animal cells.