Alberts • Johnson • Lewis • Raff • Roberts • Walter

Molecular Biology of the Cell

Fifth Edition

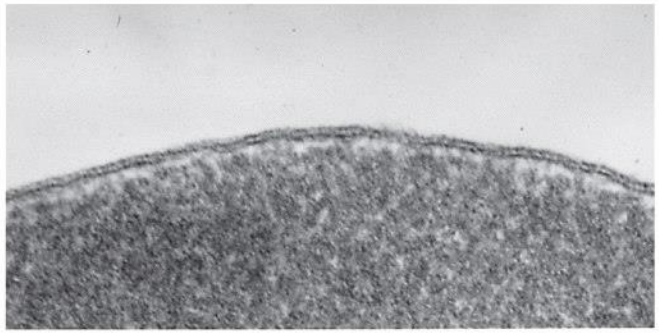
Chapter 10

Membrane Structure

The Lipid Bilayer

The **lipid bilayer** provides the basic structure for all cell membranes.

It is easily seen by **electron microscopy**, and its bilayer structure is attributable exclusively to the special properties of the lipid molecules, which assemble spontaneously into **bilayers** even under simple artificial conditions.



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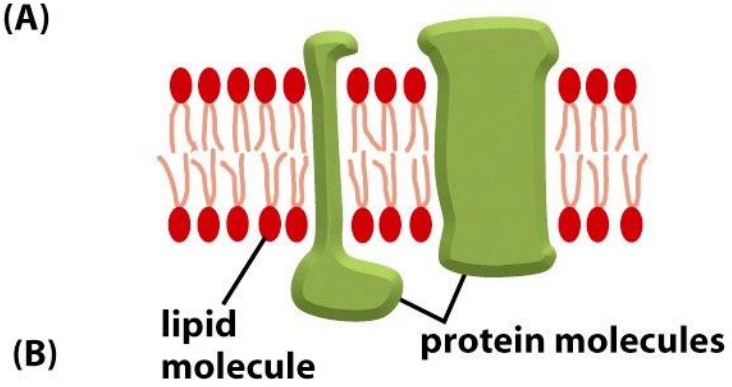

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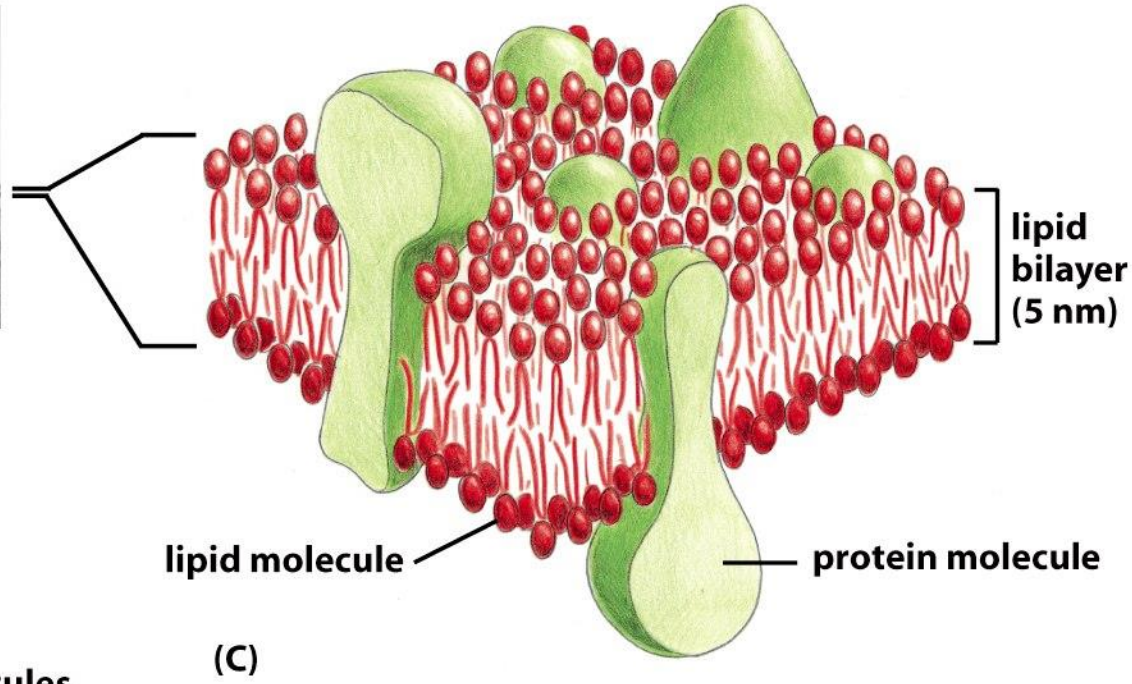


(C)

Phosphoglycerides, Sphingolipids, and Sterols Are the Major Lipids in Cell Membranes

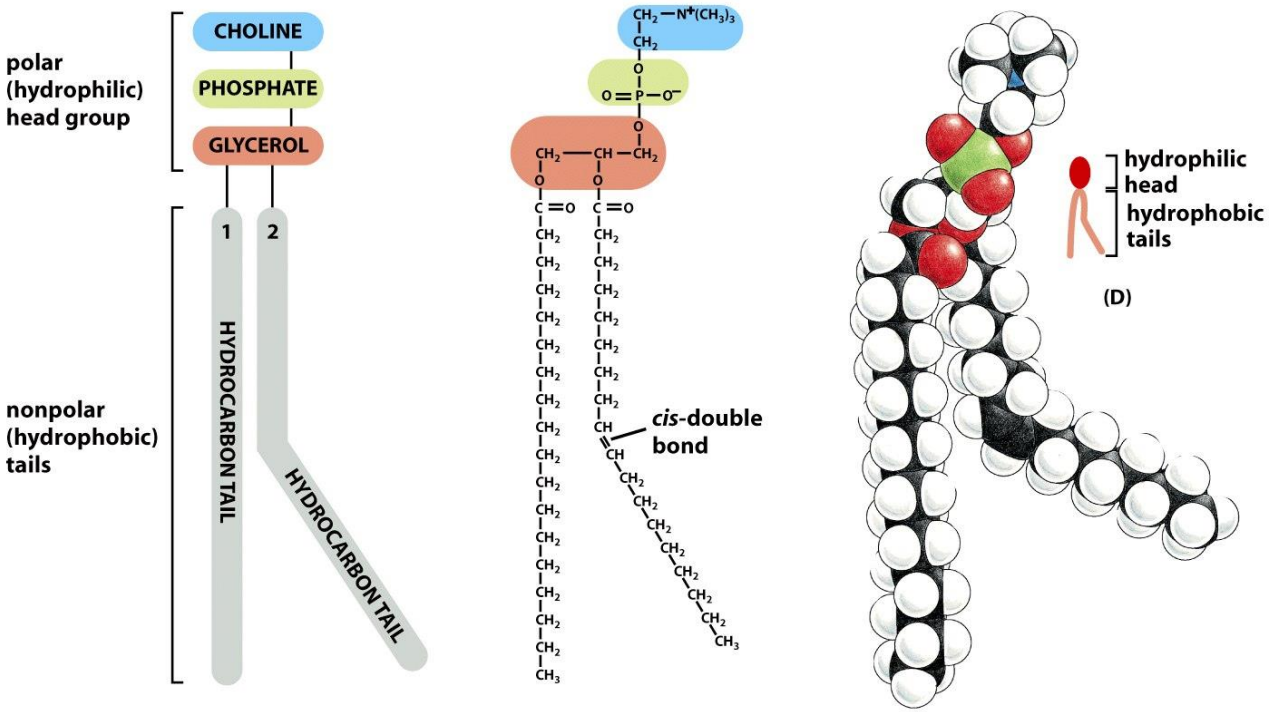
- Lipid molecules constitute about **50%** of the mass of most animal cell membranes, nearly all of the remainder being protein.
- There are approximately 5×10^6 lipid molecules in a 1 μm × 1 μm area of lipid bilayer, or about 10^9 lipid molecules in the plasma membrane of a small animal cell.
- All of the lipid molecules in cell membranes are **amphiphilic**—that is, they have a hydrophilic ("**water-loving**") or polar end and a **hydrophobic** ("**water-fearing**") or nonpolar end.
- The most abundant membrane lipids are the **phospholipids**.
- These have a **polar head group** containing a phosphate group and two **hydrophobic hydrocarbon tails**.
- In animal, plant, and bacterial cells, the tails are usually fatty acids, and they can differ in length (they normally contain between 14 and 24 carbon atoms).
- One tail typically has one or more **cis-double bonds** (that is, it is **unsaturated**), while the other tail does not (that is, it is saturated).

Phosphoglycerides, Sphingolipids, and Sterols Are the Major Lipids in Cell Membranes

- Each cis-double bond creates a **kink** in the tail.

- Differences in the **length** and **saturation** of the fatty acid tails influence how phospholipid molecules pack against one another, thereby affecting the **fluidity of the membrane**.

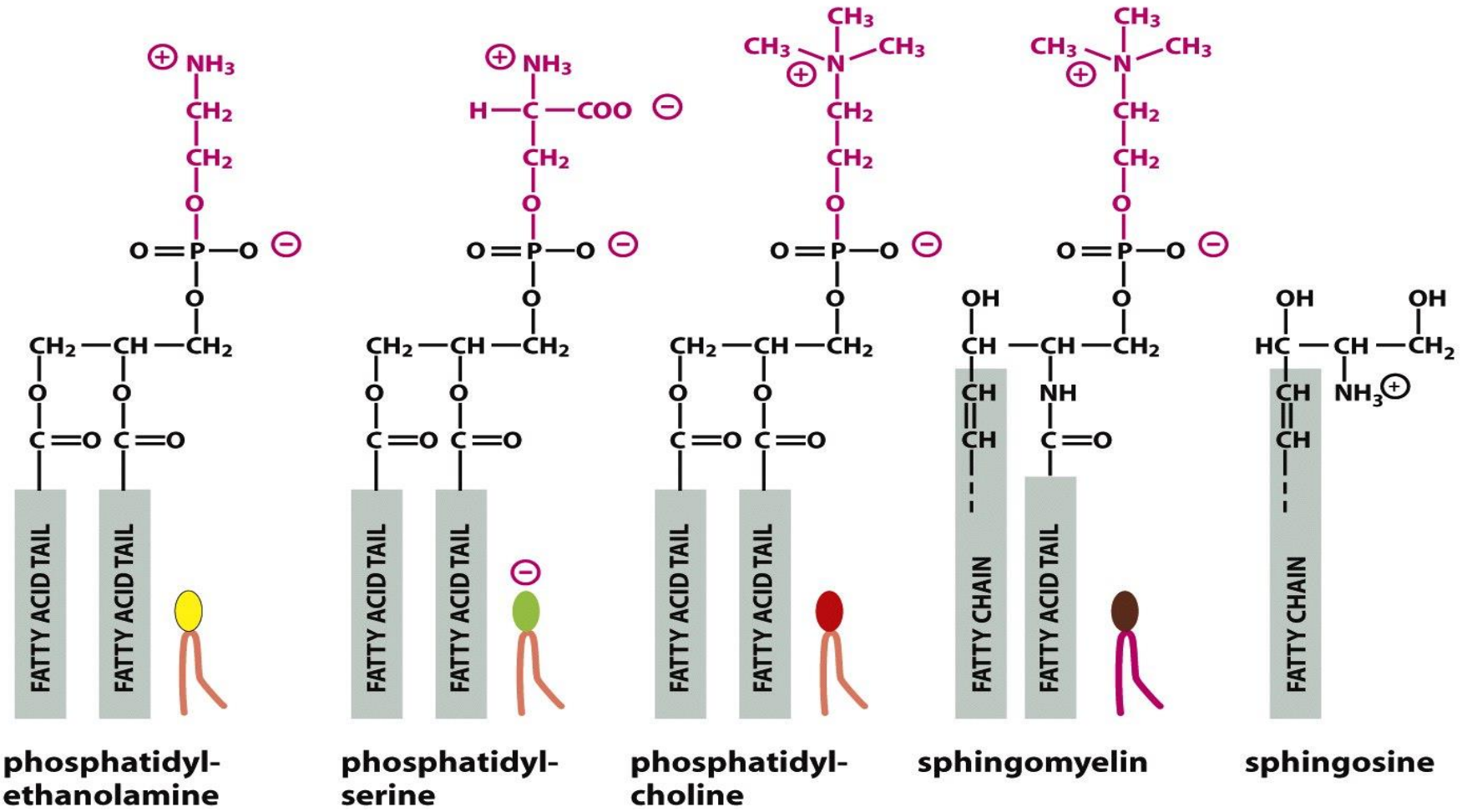
- The main phospholipids in most animal cell membranes are the **phosphoglycerides**, which have a **three-carbon glycerol backbone**.
- Two **long-chain fatty acids** are linked through ester bonds to adjacent carbon atoms of the glycerol, and the third carbon atom of the glycerol is attached to a **phosphate group**, which in turn is linked to one of several types of **head group**.



Phosphoglycerides, Sphingolipids, and Sterols Are the Major Lipids in Cell Membranes

- By combining several different fatty acids and head groups, cells make many different phosphoglycerides.

- **Phosphatidylethanolamine**, **phosphatidylserine**, and **phosphatidylcholine** are the most abundant ones in mammalian cell membranes.



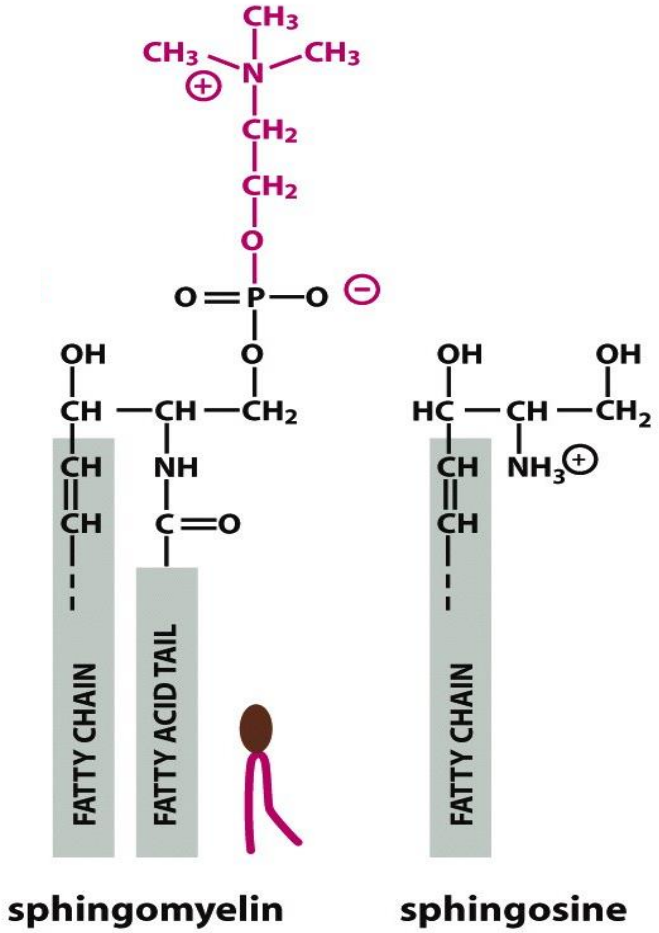
Phosphoglycerides, Sphingolipids, and Sterols Are the Major Lipids in Cell Membranes

- Another important class of phospholipids are the **sphingolipids**, which are built from **sphingosine** rather than glycerol.

- Sphingosine is a **long acyl chain** with an amino group (NH2) and two hydroxyl groups (OH) at one end.

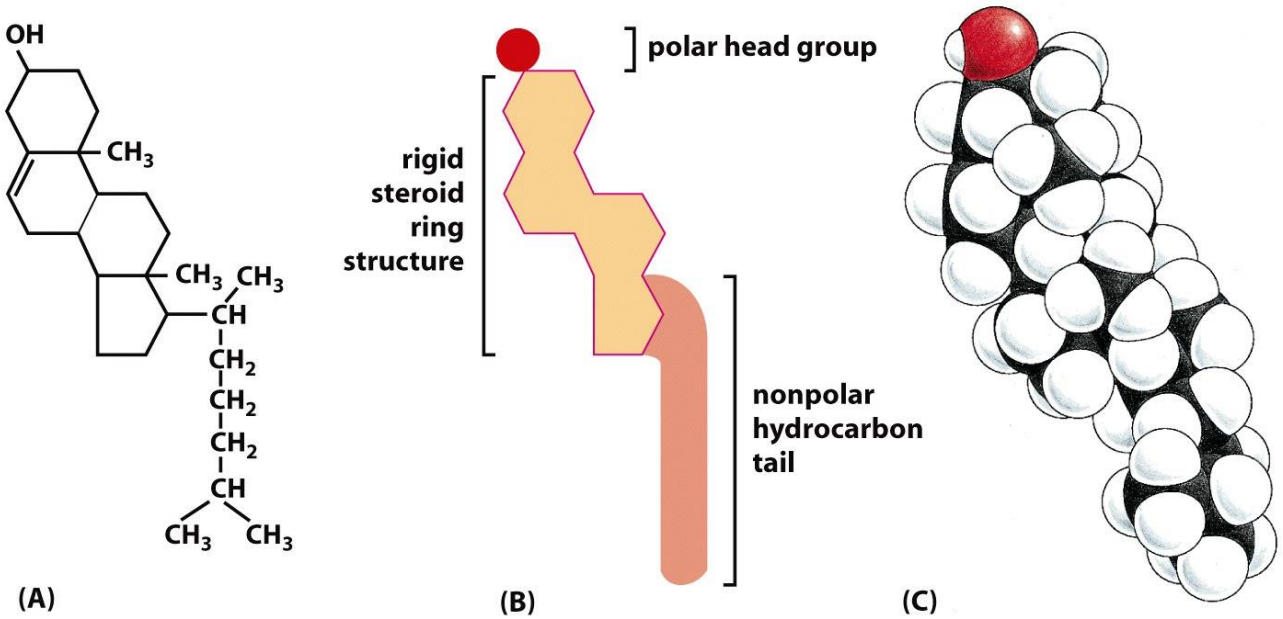
- In **sphingomyelin**, the most common sphingolipid, a fatty acid tail is attached to the amino group, and a phosphocholine group is attached to the terminal hydroxyl group.

- Together, the phospholipids phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and sphingomyelin constitute more than **half** the mass of lipid in most mammalian cell membranes



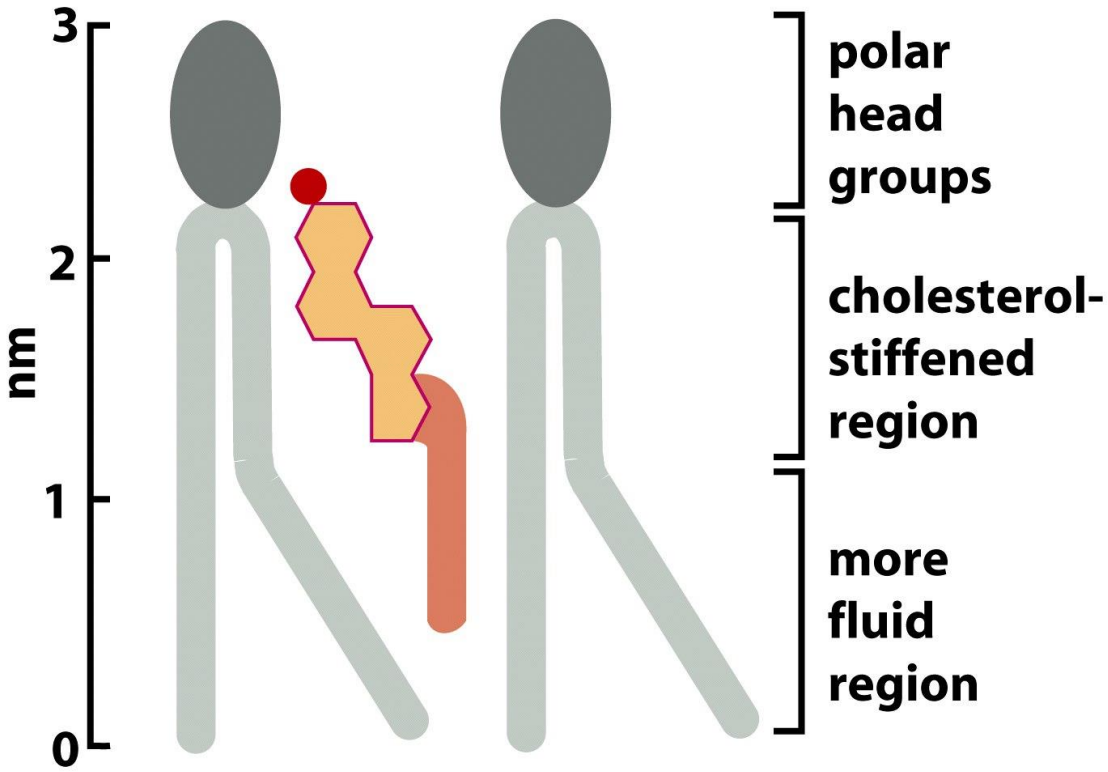
Phosphoglycerides, Sphingolipids, and Sterols Are the Major Lipids in Cell Membranes

- In addition to phospholipids, the lipid bilayers in many cell membranes contain **glycolipids** and **cholesterol**.
- Glycolipids resemble sphingolipids, but, instead of a phosphate-linked head group, they have sugars attached.
- Eukaryotic plasma membranes contain especially large amounts of **cholesterol**—up to one molecule for every phospholipid molecule.
- Cholesterol is a **sterol**. It contains a **rigid ring structure**, to which is attached a single polar hydroxyl group and a short nonpolar hydrocarbon chain.



Phosphoglycerides, Sphingolipids, and Sterols Are the Major Lipids in Cell Membranes

- The cholesterol molecules orient themselves in the bilayer with their hydroxyl group close to the polar head groups of adjacent phospholipid molecules.



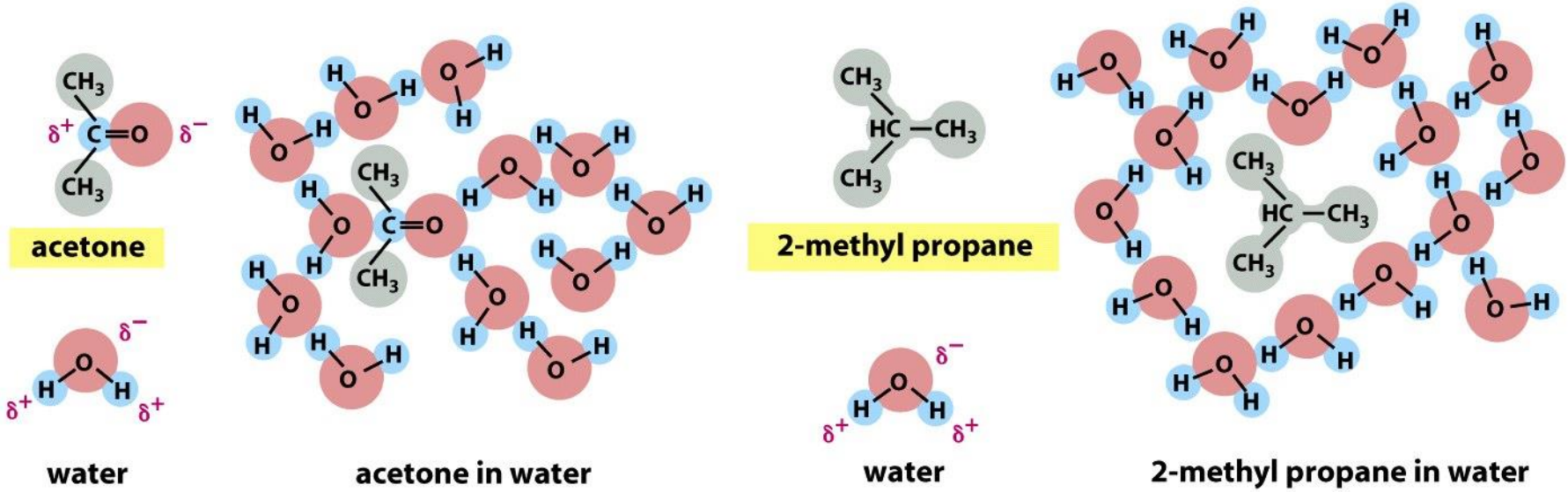
Phospholipids Spontaneously Form Bilayers

- The **shape and amphiphilic nature** of the phospholipid molecules cause them to form bilayers spontaneously in aqueous environments.
- **Hydrophilic** molecules dissolve readily in water because they contain **charged groups or uncharged polar groups** that can form either favorable electrostatic interactions or hydrogen bonds with water molecules.

- **Hydrophobic** molecules, by contrast, are insoluble in water because all, or almost all, of their atoms are **uncharged and nonpolar** and therefore cannot form energetically favorable interactions with water molecules.
- If dispersed in water, they force the adjacent water molecules to reorganize into **icelike cages** that surround the hydrophobic molecule:

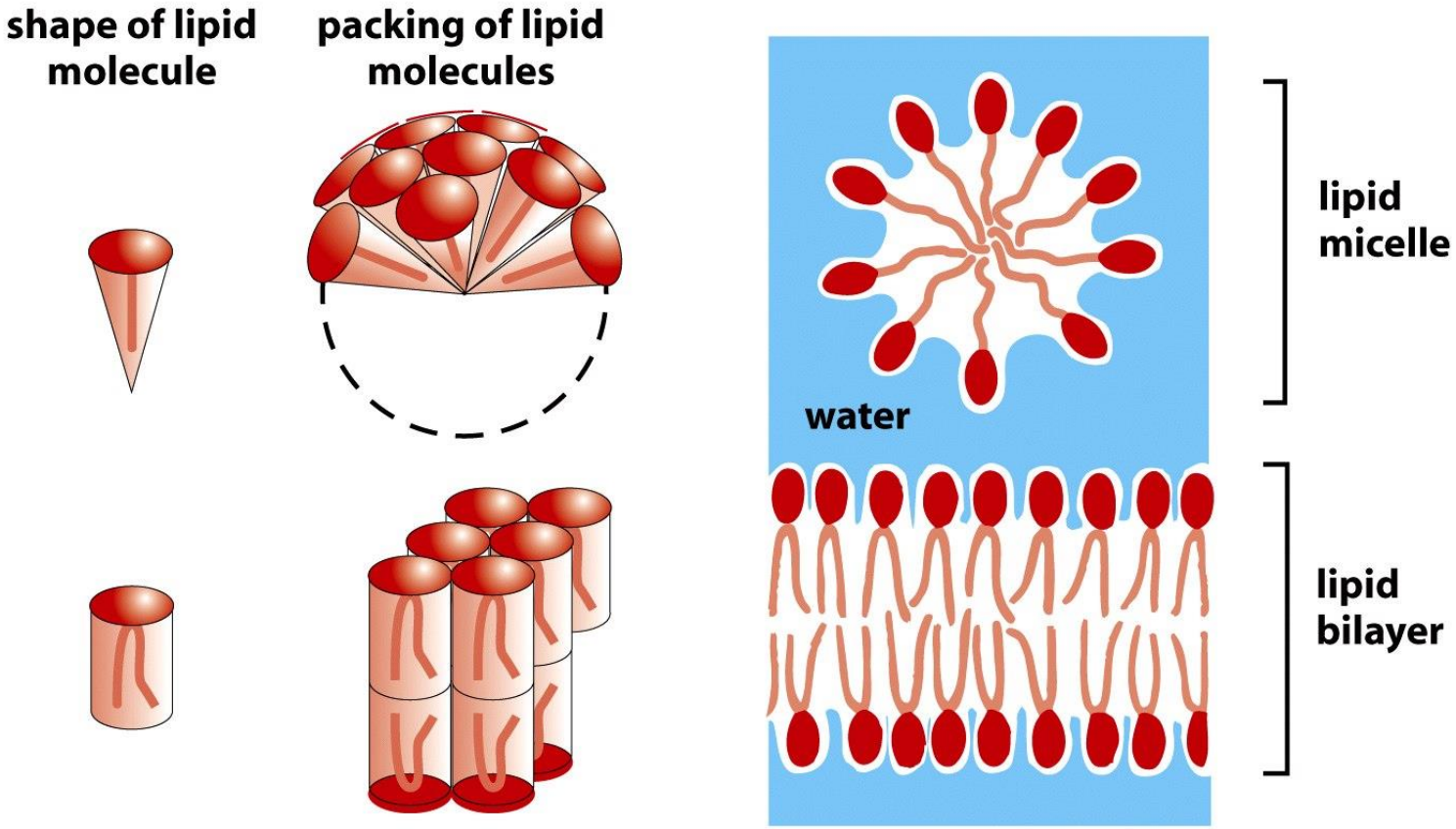
➢ Because these cage structures are more ordered than the surrounding water, their formation increases the free energy.

➢ This free-energy cost is minimized, however, if the hydrophobic molecules (or the hydrophobic portions of amphiphilic molecules) cluster together so that the smallest number of water molecules is affected.



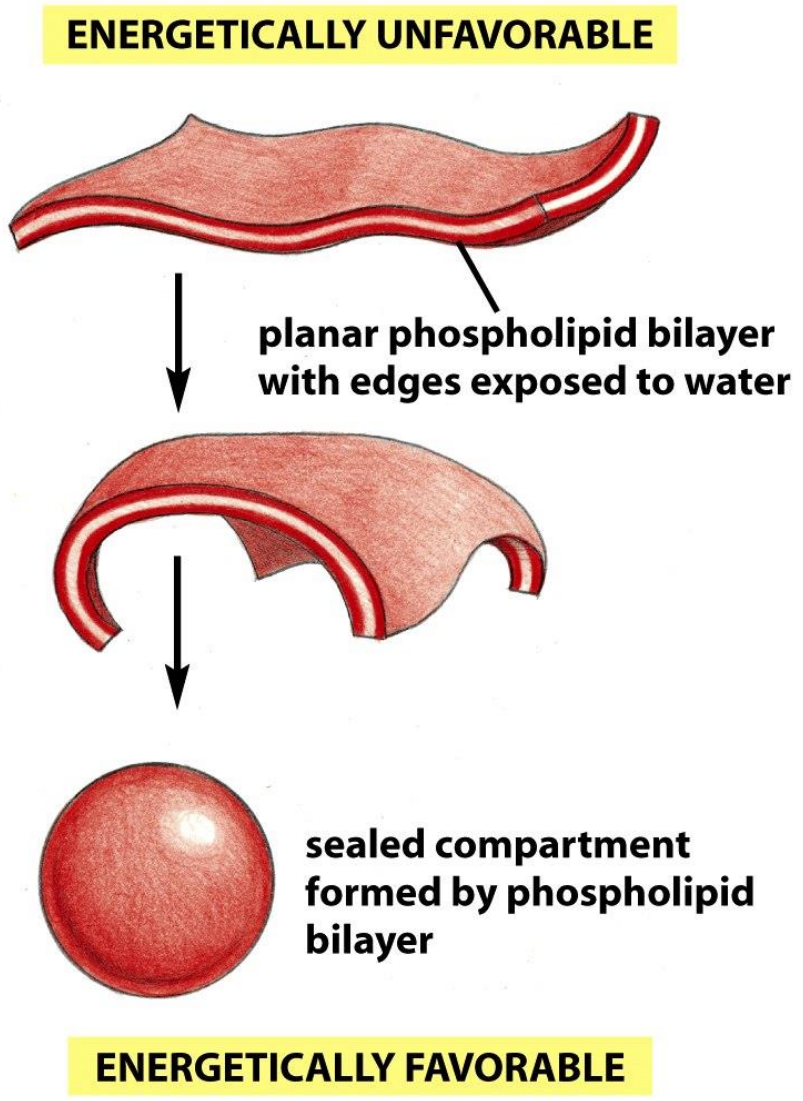
Phospholipids Spontaneously Form Bilayers

- When amphiphilic molecules are exposed to an aqueous environment, they behave as you would expect from the above discussion.
- They spontaneously **aggregate** to bury their hydrophobic tails in the interior, where they are shielded from the water, and they expose their hydrophilic heads to water.
- Depending on their **shape**, they can do this in either of two ways: they can form **spherical micelles**, with the tails inward, or they can form **double-layered sheets**, or **bilayers**, with the hydrophobic tails sandwiched between the hydrophilic head groups.



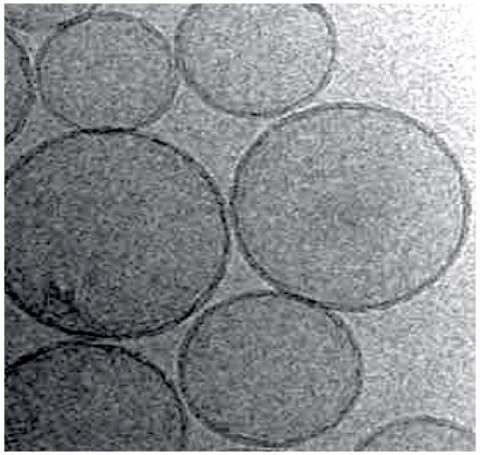
Phospholipids Spontaneously Form Bilayers

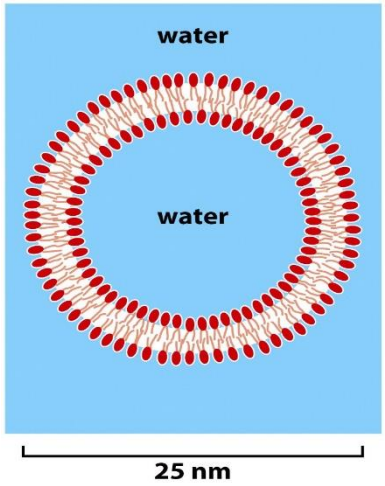
- The same forces that drive phospholipids to form bilayers also provide a **self-sealing property**.
- A small tear in the bilayer creates a free edge with water; because this is energetically unfavorable, the lipids tend to rearrange spontaneously to eliminate the free edge. (In eukaryotic plasma membranes, the fusion of intracellular vesicles repairs larger tears.)
- The prohibition of free edges has a profound consequence: the only way for a bilayer to avoid having edges is by closing in on itself and forming a sealed compartment.
- This remarkable behavior, fundamental to the creation of a living cell, follows directly from the shape and amphiphilic nature of the phospholipid molecule.
- A lipid bilayer also has other characteristics that make it an ideal structure for cell membranes.
- One of the most important of these is its **fluidity**, which is crucial to many membrane functions.

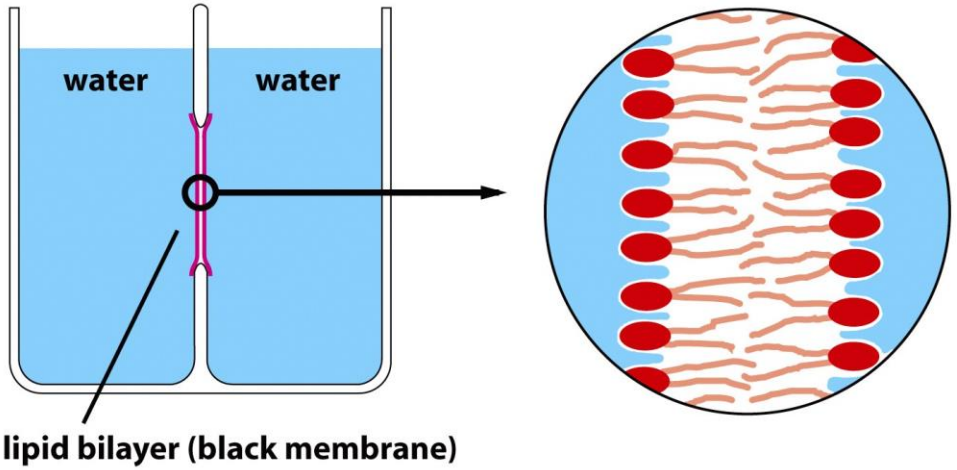


The Lipid Bilayer Is a Two-dimensional Fluid

- Around 1970, researchers first recognized that individual lipid molecules are able to diffuse freely within the plane of a lipid bilayer.
- The initial demonstration came from studies of synthetic (**artificial**) lipid bilayers, which can be made in the form of spherical vesicles, called **liposomes**; or in the form of **planar bilayers** formed across a hole in a partition between two aqueous compartments or on a solid support.

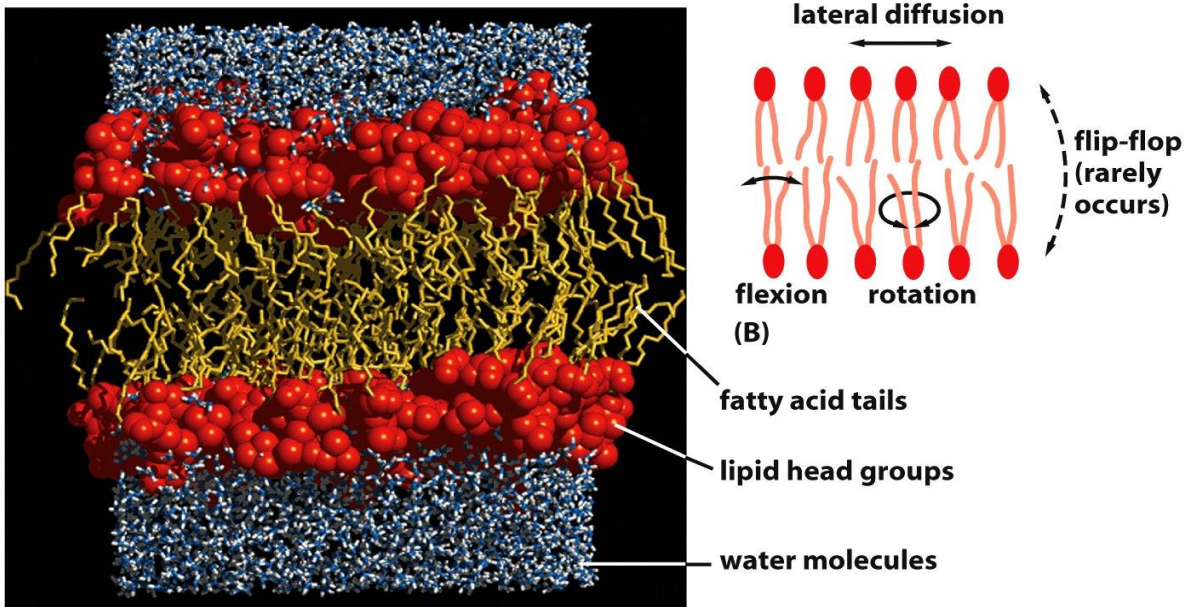






The Lipid Bilayer Is a Two-dimensional Fluid

- Different studies show that phospholipid molecules in synthetic bilayers very rarely migrate from the monolayer (also called a **leaflet**) on one side to that on the other.
- This process, known as "**flip-flop**," occurs on a time scale of hours for any individual molecule, although cholesterol is an exception to this rule and can flip-flop rapidly.
- In contrast, lipid molecules rapidly exchange places with their neighbors within a monolayer (~10^7 times per second).
- This gives rise to a rapid lateral diffusion, with a diffusion coefficient (D) of about 10–8 cm2/sec, which means that an average lipid molecule diffuses the length of a large bacterial cell (~2 μm) in about 1 second.
- These studies have also shown that individual lipid molecules rotate very rapidly about their long axis and have flexible hydrocarbon chains.
- Computer simulations show that lipid molecules in synthetic bilayers are very **disordered**, presenting an irregular surface of variously spaced and oriented head groups to the water phase on either side of the bilayer.



The Lipid Bilayer Is a Two-dimensional Fluid

- Similar mobility studies on labeled lipid molecules in isolated biological membranes and in living cells give results similar to those in synthetic bilayers.
- They demonstrate that the lipid component of a biological membrane is a **two-dimensional liquid** in which the constituent molecules are free to move laterally.
- As in synthetic bilayers, individual phospholipid molecules are normally confined to their own monolayer.
- This confinement creates a problem for their synthesis.
- Phospholipid molecules are manufactured in only one monolayer of a membrane, mainly in the **cytosolic monolayer of the endoplasmic reticulum membrane**.
- If none of these newly made molecules could migrate reasonably promptly to the noncytosolic monolayer, new lipid bilayer could not be made.
- The problem is solved by a special class of membrane proteins called **phospholipid translocators**, or **flippases**, which catalyze the rapid flip-flop of phospholipids from one monolayer to the other.

The Lipid Bilayer Is a Two-dimensional Fluid

Despite the fluidity of the lipid bilayer, liposomes do not fuse spontaneously with one another when suspended in water.

Fusion does not occur because the **polar lipid head groups** bind water molecules that need to be displaced for the bilayers of two different liposomes to fuse.

The hydration shell that keeps liposomes apart also insulates the many internal membranes in a eukaryotic cell and prevents their uncontrolled fusion, thereby maintaining the compartmental integrity of membrane-enclosed organelles.

All cell membrane fusion events are catalyzed by tightly regulated fusion proteins, which force appropriate membranes into tight proximity, squeezing out the water layer that keeps the bilayers apart.

The Fluidity of a Lipid Bilayer Depends on Its Composition

The fluidity of cell membranes has to be precisely regulated.

Certain membrane transport processes and enzyme activities, for example, **cease** when the bilayer viscosity is experimentally increased beyond a threshold level.

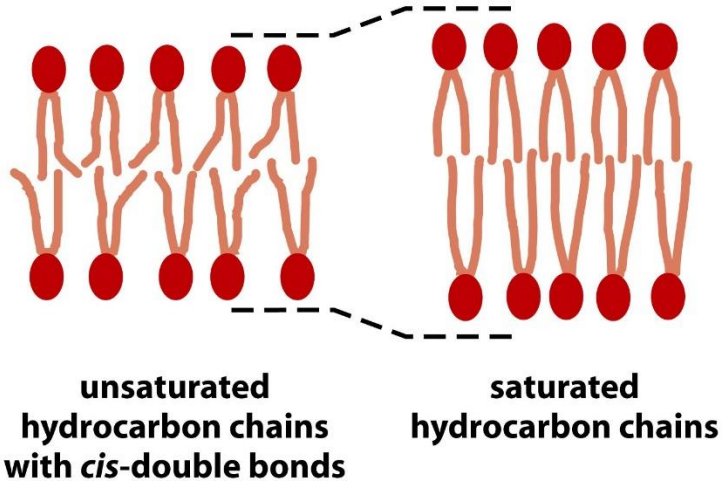
Fluidity of a lipid bilayer depends on:

- ✓ Its composition
- ✓ Its temperature

A synthetic bilayer made from a single type of phospholipid changes from a liquid state to a two-dimensional rigid crystalline (or gel) state at a characteristic temperature. This change of state is called a *phase transition*, and the temperature at which it occurs is lower (that is, the membrane becomes more difficult to freeze) if the hydrocarbon chains are short or have double bonds.

The Fluidity of a Lipid Bilayer Depends on Its Composition

A shorter chain length reduces the tendency of the hydrocarbon tails to interact with one another, in both the same and opposite monolayer, and cis-double bonds produce kinks in the chains that make them **more difficult to pack together**, so that the membrane remains fluid at **lower temperatures**.



-The double bonds make **it more difficult to pack the chains together, thereby making the lipid bilayer more difficult to freeze.**
-In addition, because the hydrocarbon chains of unsaturated lipids are more spread apart, lipid bilayers containing them are **thinner** than bilayers formed exclusively from saturated lipids

Bacteria, yeasts, and other organisms whose **temperature fluctuates** with that of their environment adjust the fatty acid composition of their membrane lipids to maintain a relatively **constant fluidity**.

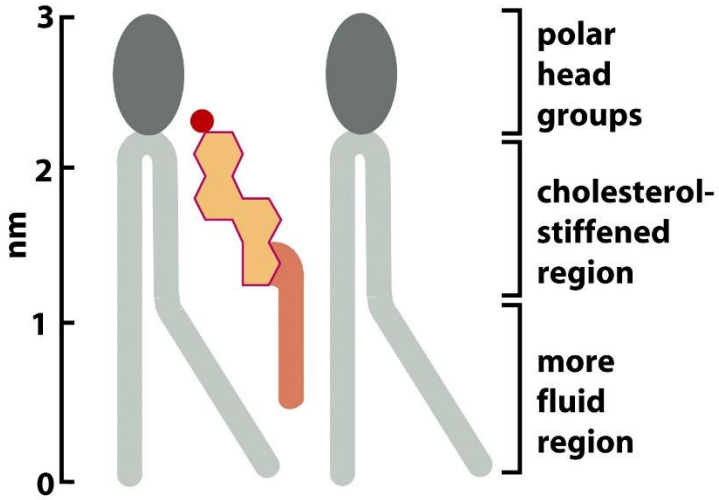
As the **temperature falls**, for instance, the cells of those organisms synthesize fatty acids with more cis-double bonds, thereby avoiding the decrease in bilayer fluidity that would otherwise result from the temperature drop.

Cholestrol and permeability-barrier properties of the lipid bilayer

Cholesterol modulates the properties of lipid bilayers.

When mixed with phospholipids, it **enhances the permeability-barrier properties** of the lipid bilayer.

Cholesterol inserts into the bilayer with its hydroxyl group close to the polar head groups of the phospholipids, so that its rigid, platelike steroid rings interact with— and partly immobilize—those regions of the hydrocarbon chains closest to the polar head groups.



By decreasing the mobility of the first few CH2 groups of the chains of the phospholipid molecules, cholesterol makes the lipid bilayer less deformable in this region and thereby decreases the permeability of the bilayer to small water-soluble molecules. Although cholesterol tightens the packing of the lipids in a bilayer, it does not make membranes any less fluid.

At the high concentrations found in most eukaryotic plasma membranes, cholesterol prevents the hydrocarbon chains from coming together and crystallizing.

Membranes contain a bewildering variety of perhaps 500–2000 different lipid species

Table 10–1 Approximate Lipid Compositions of Different Cell Membranes

LIPID	PERCENTAGE OF TOTAL LIPID BY WEIGHT					
	LIVER CELL PLASMA MEMBRANE	RED BLOOD CELL PLASMA MEMBRANE	MYELIN	MITOCHONDRION (INNER AND OUTER MEMBRANES)	ENDOPLASMIC RETICULUM	*E. COLI* BACTERIUM
Cholesterol	17	23	22	3	6	0
Phosphatidylethanolamine	7	18	15	28	17	70
Phosphatidylserine	4	7	9	2	5	trace
Phosphatidylcholine	24	17	10	44	40	0
Sphingomyelin	19	18	8	0	5	0
Glycolipids	7	3	28	trace	trace	0
Others	22	13	8	23	27	30

- ✓ combinatorial variation in head groups,
- ✓ hydrocarbon chain lengths,
- ✓ Desaturation of the major phospholipid classes,
- ✓ some membranes also contain many structurally distinct minor lipids, The *inositol phospholipids*, for example, in small quantities in animal cell membranes and have crucial functions in guiding membrane traffic and in cell signaling

specific lipids come together in separate domains with certain lipid mixtures in artificial bilayers

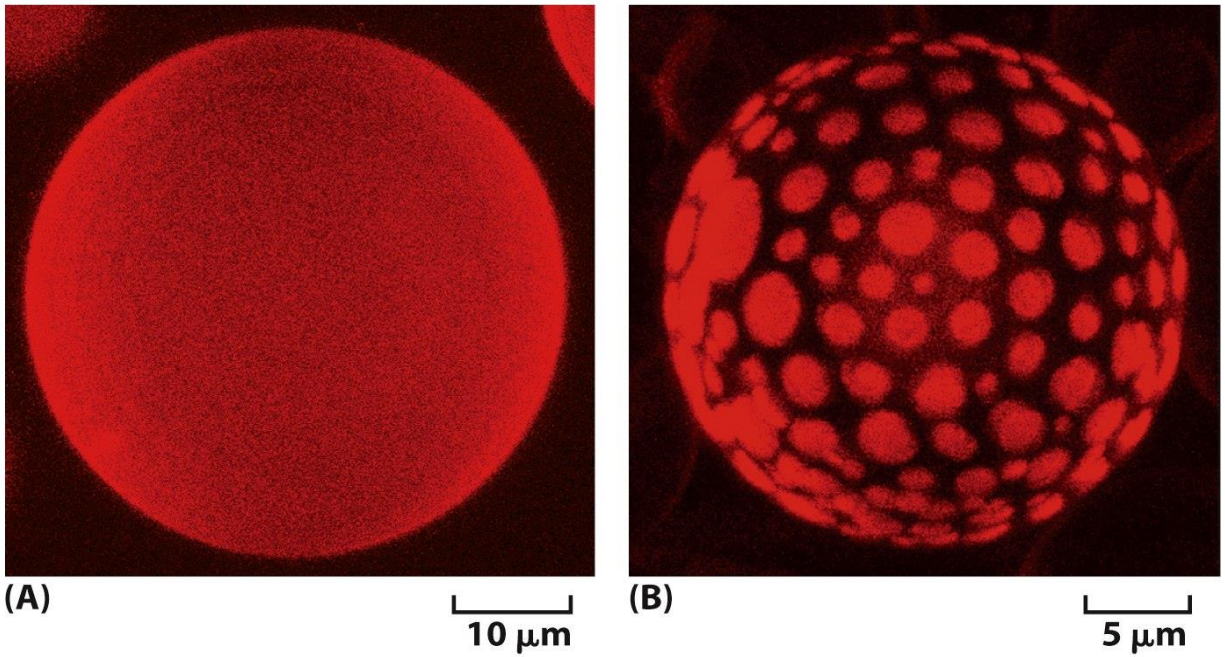
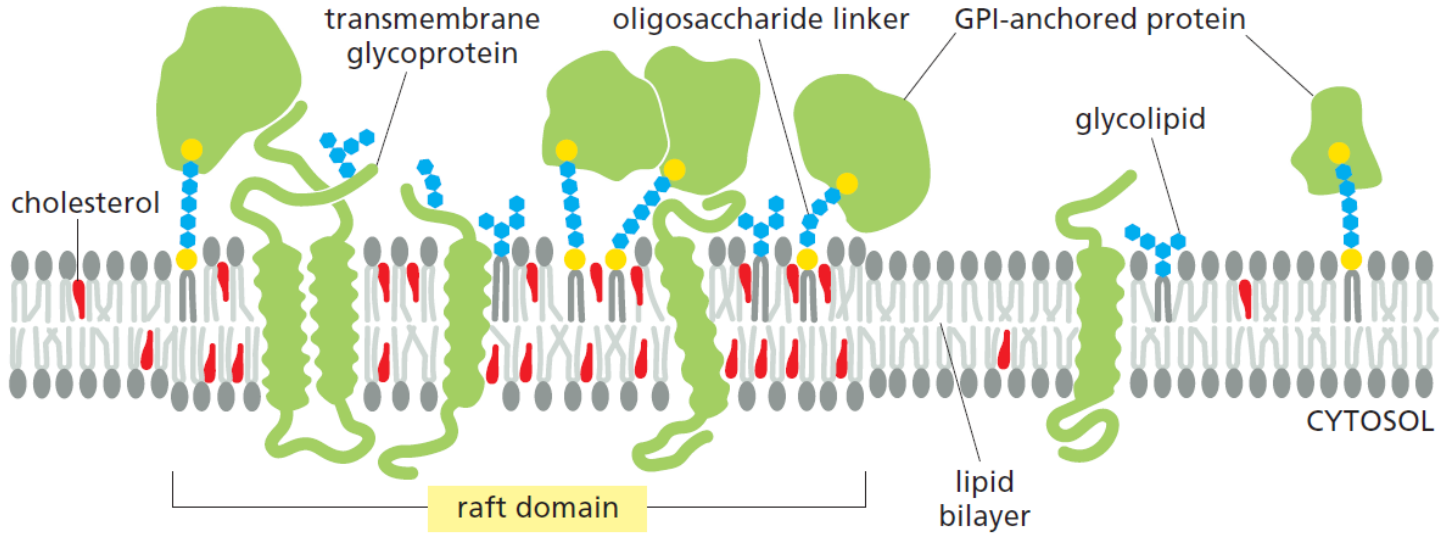
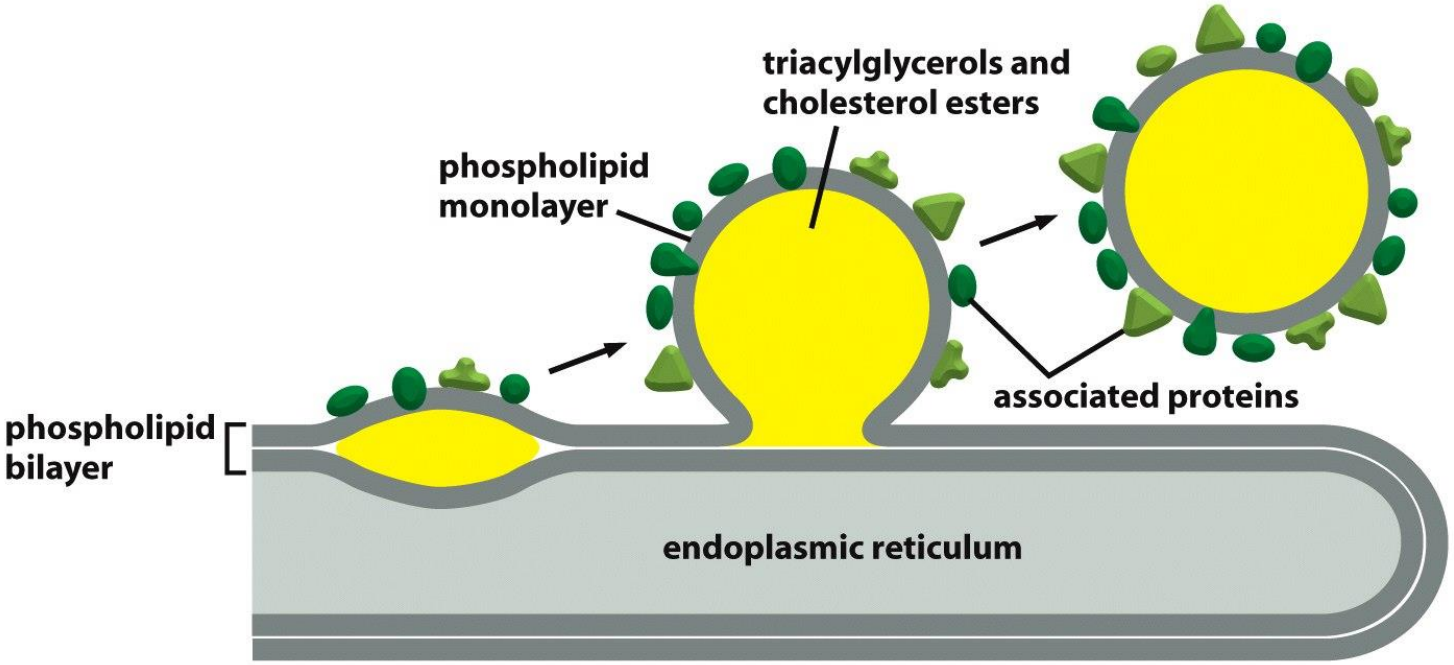


Figure 10–12 Lateral phase separation in artificial lipid bilayers.
(A) Giant liposomes produced from a 1:1 mixture of phosphatidylcholine and sphingomyelin form uniform bilayers.
(B) By contrast, liposomes produced from a 1:1:1 mixture of phosphatidylcholine, sphingomyelin, and cholesterol form bilayers with two separate phases.
The average size of the domains formed in these giant artificial liposomes is much larger than that expected in cell membranes, where "lipid rafts" may be as small as a few nanometers in diameter.



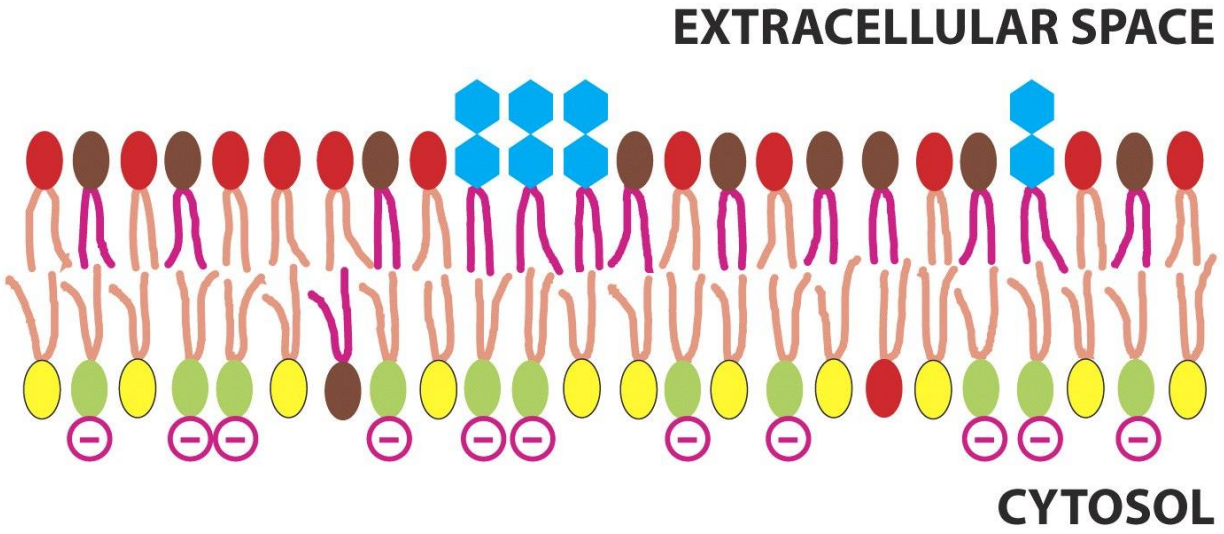
A model of a raft domain. Weak protein–protein, protein–lipid, and lipid–lipid interactions reinforce one another to partition the interacting components into raft domains. Cholesterol, sphingolipids, glycolipids, glycosylphosphatidylinositol (GPI)-anchored proteins, and some transmembrane proteins are enriched in these domains. Note that because of their composition, raft domains have an increased membrane thickness.

The lipid molecules in the plasma membrane of living cells segregate into specialized domains, called **lipid rafts**. Specific membrane proteins and lipids are seen to concentrate in a more temporary, dynamic fashion facilitated by protein– protein interactions that allow the transient formation of **specialized membrane regions**. The tendency of mixtures of lipids to undergo phase partitioning, as seen in artificial bilayers, may help create rafts in living cell membranes—organizing and concentrating membrane proteins either for transport in **membrane vesicles** or for working together in protein assemblies, such as when they convert **extracellular signals into intracellular ones**.



Most cells store an excess of lipids in **lipid droplets**.
Fat cells, or **adipocytes**, are specialized for lipid storage. Fatty acids can be liberated from lipid droplets on demand and exported to other cells through the bloodstream.
Lipid droplets store **neutral lipids**, such as triacylglycerols and cholesterol esters, which are synthesized from **fatty acids** and **cholesterol** by enzymes in the endoplasmic reticulum membrane. Because these lipids do not contain hydrophilic head groups, they are exclusively hydrophobic molecules, and therefore aggregate into **three-dimensional droplets rather than into bilayers**. Lipid droplets are unique organelles in that they are surrounded by a **single monolayer** of phospholipids, which contains a large variety of proteins. Some of the proteins are enzymes involved in lipid metabolism, but the functions of most are unknown.
Lipid droplets form rapidly when cells are exposed to high concentrations of fatty acids. They are thought to form from discrete regions of the endoplasmic reticulum membrane where many enzymes of lipid metabolism are concentrated.

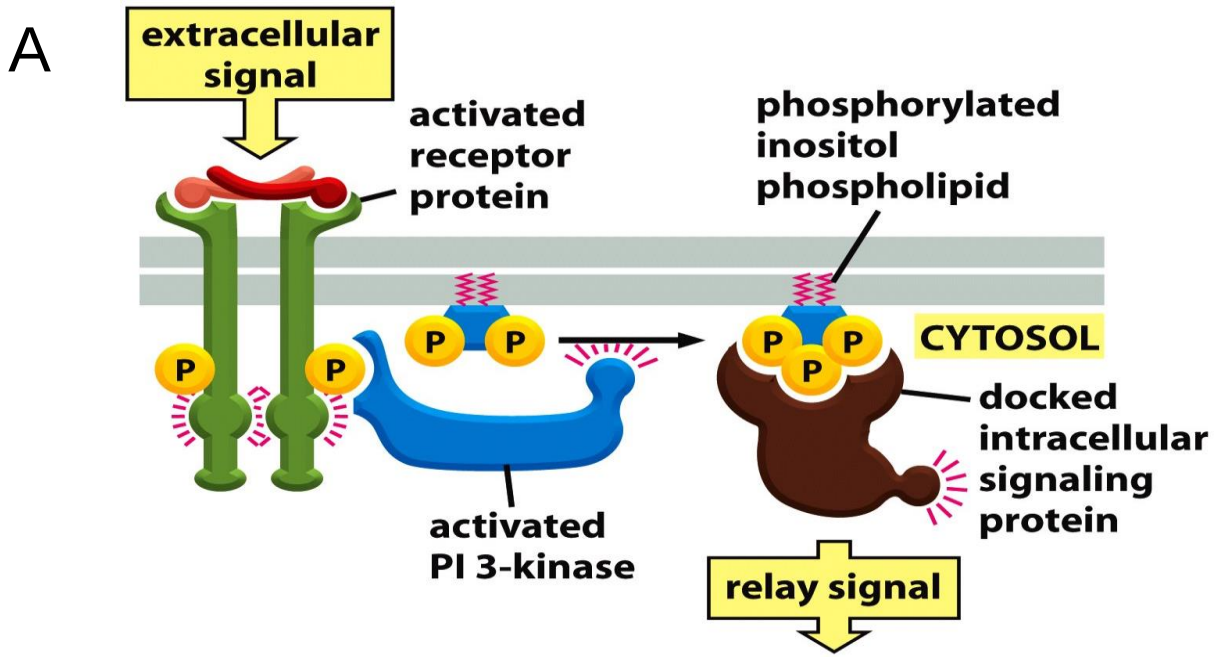
The Asymmetry of the Lipid Bilayer Is Functionally Important



The asymmetrical distribution of phospholipids and glycolipids in the lipid bilayer of human red blood cells

Lipid asymmetry is functionally important, especially in **converting extracellular signals into intracellular ones**:
The enzyme **protein kinase C (PKC),** which is activated in response to various extracellular signals, binds to the cytosolic face of the plasma membrane, where **phosphatidylserine** is concentrated, and requires this negatively charged phospholipid for its activity

The Asymmetry of the Lipid Bilayer Is Functionally Important



specific lipid head groups must first be modified to create **protein-binding sites** at a particular time and place. One example is **phosphatidylinositol (PI),** one of the minor phospholipids that are concentrated in the cytosolic **monolayer** of cell membranes. Various **lipid kinases** can add phosphate groups at distinct positions on the **inositol ring**, creating binding sites that recruit specific proteins from the cytosol to the membrane. An important example of such a lipid kinase is **phosphoinositide 3-kinase (PI 3-kinase),** which is activated in response to extracellular signals and helps to recruit specific intracellular signaling proteins to the cytosolic face of the plasma membrane.

The Asymmetry of the Lipid Bilayer Is Functionally Important

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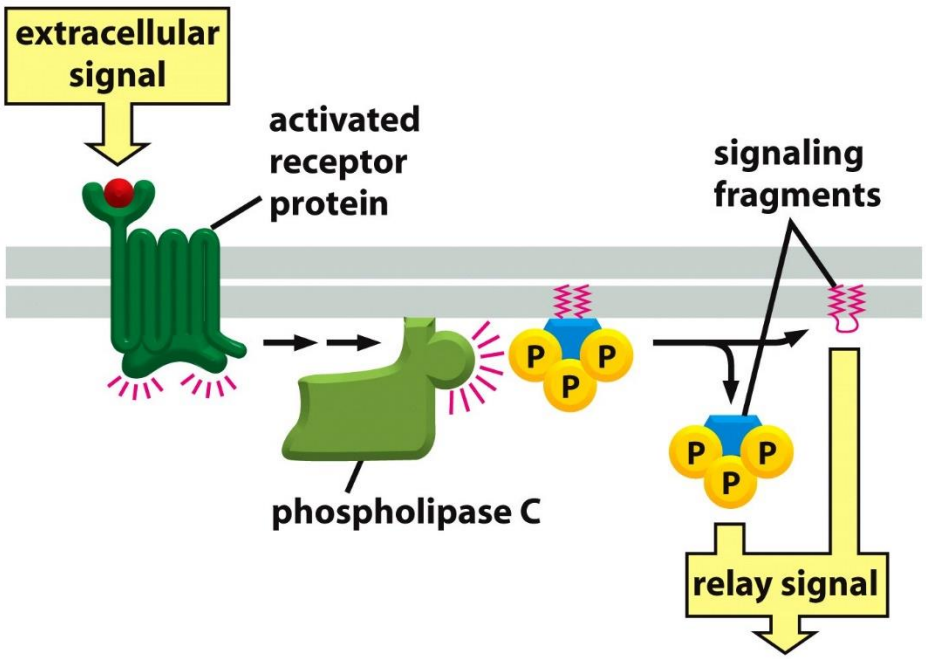

The plasma membrane contains various **phospholipases** that are activated by extracellular signals to cleave specific phospholipid molecules, generating fragments of these molecules that act as **short-lived intracellular mediators**. **Phospholipase C**, for example, cleaves an inositol phospholipid in the cytosolic monolayer of the plasma membrane to generate two fragments, one of which remains in the membrane and helps activate protein kinase C, while the other is released into the cytosol and stimulates the release of Ca2+ from the endoplasmic reticulum