Lecture 15

The Lipid Bilayer: A Dynamic Self-Assembled Structure of Multiple Lipid Classes

LIPIDS-Biological molecules with low solubility in water and high solubility in non-polar solvents

-Lipids form biological membranes

-Lipids are the most efficient way to store energy

EXAMPLES:

Fats and oils, Vitamins and hormones, membrane components.

Lipids are indispensable to metabolism & cell structure.

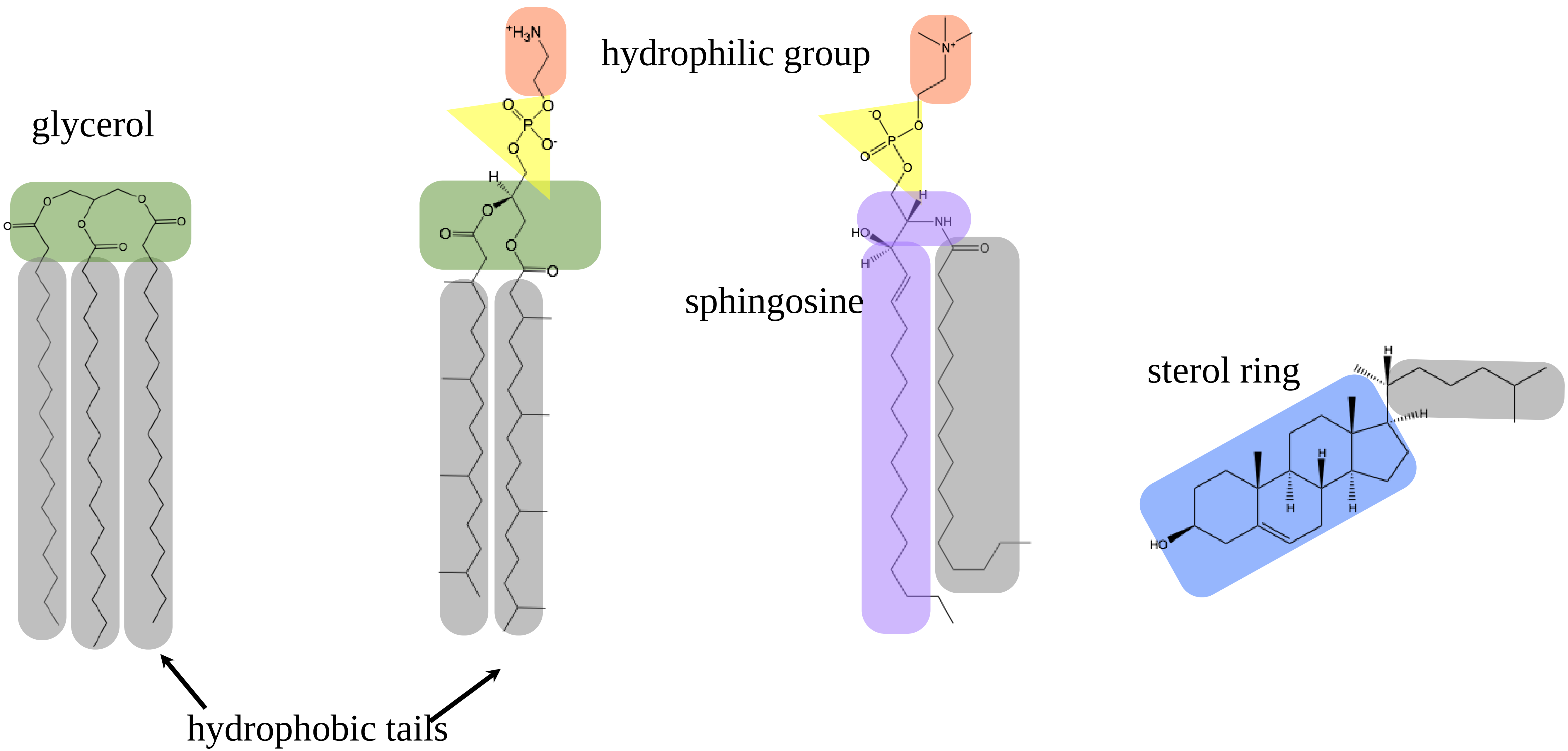
Outline:

1) Classification and Properties of Lipids

2) Biological Functions of Lipids

3) Lipids in Bioscience

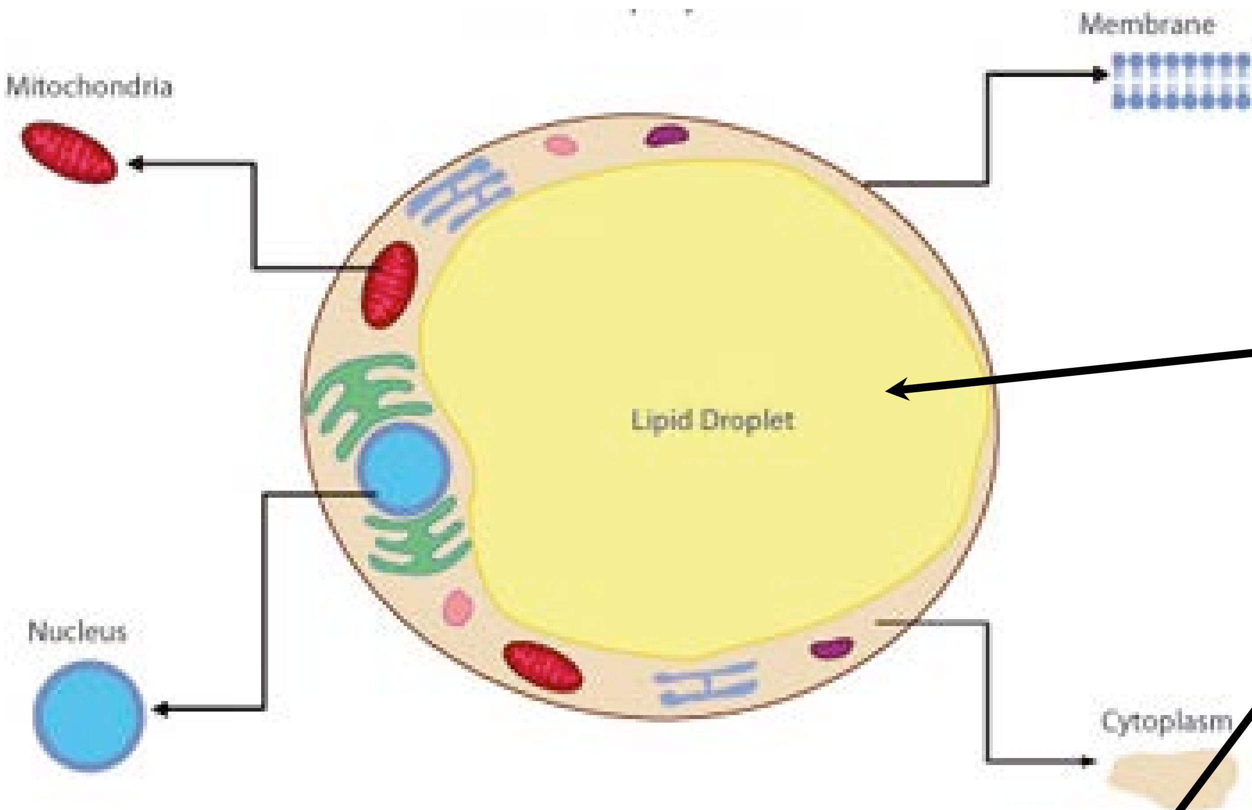
Classification of Biological Lipids



Triacylglycerol | Phospholipid | Sphingolipid | Cholesterol

Storage lipids | Membrane Lipids

Lipid Type is Specialized for Biological Function



http://proteome.biochem.mpg.de/adipo/

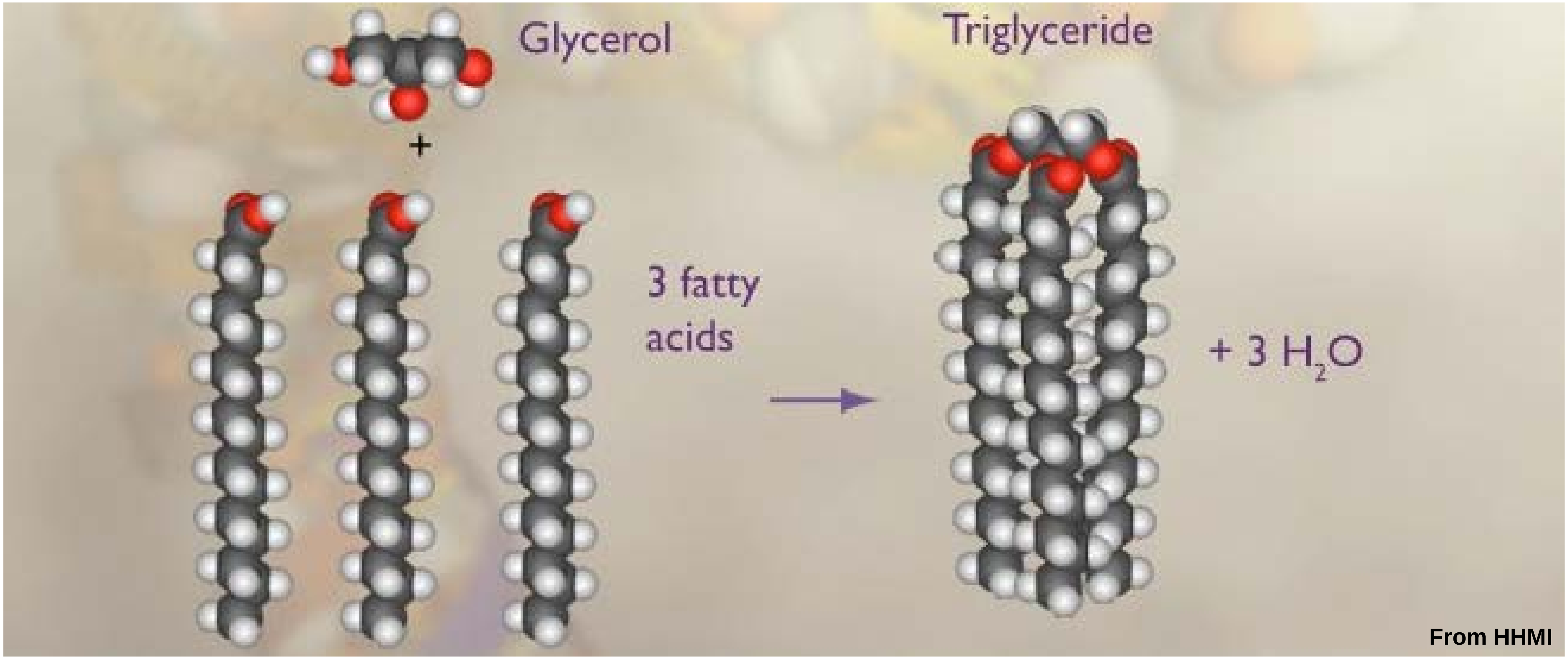
Heid et al., PLOS ONE, 2014

Storage lipids: Triglycerides, they are the main component of lipid droplets in adipocyte cells.

Membrane Lipids: Phospholipids, Sphingolipids, etc. They are the polar lipids that make up biological membranes.

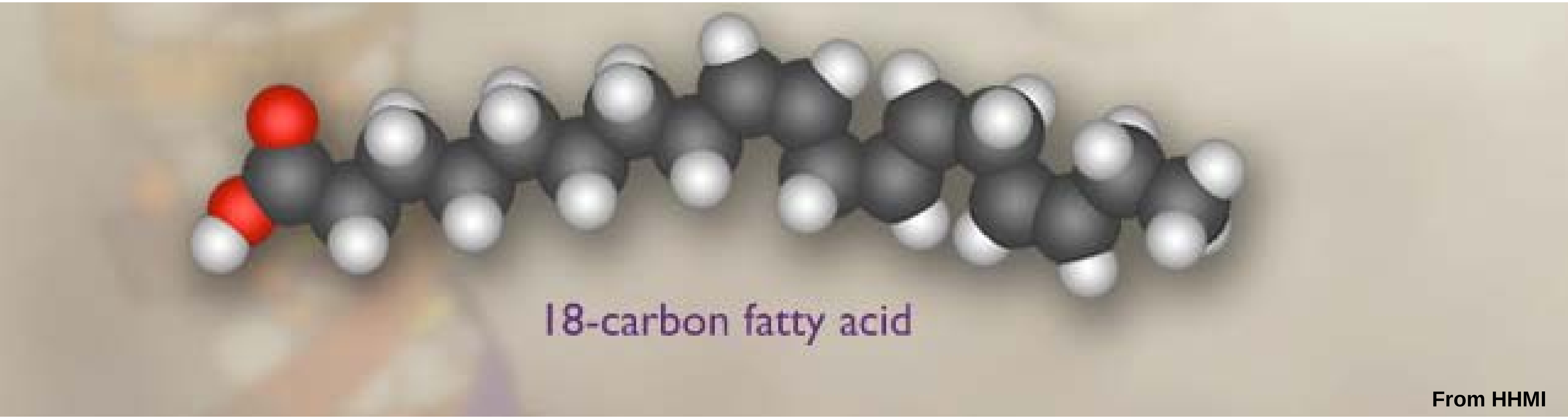
Composition of Triglycerides

Triglycerides are neutral lipids. They are composed of one glycerol molecule and three long carbon chain acids known as fatty acids



Fatty Acids

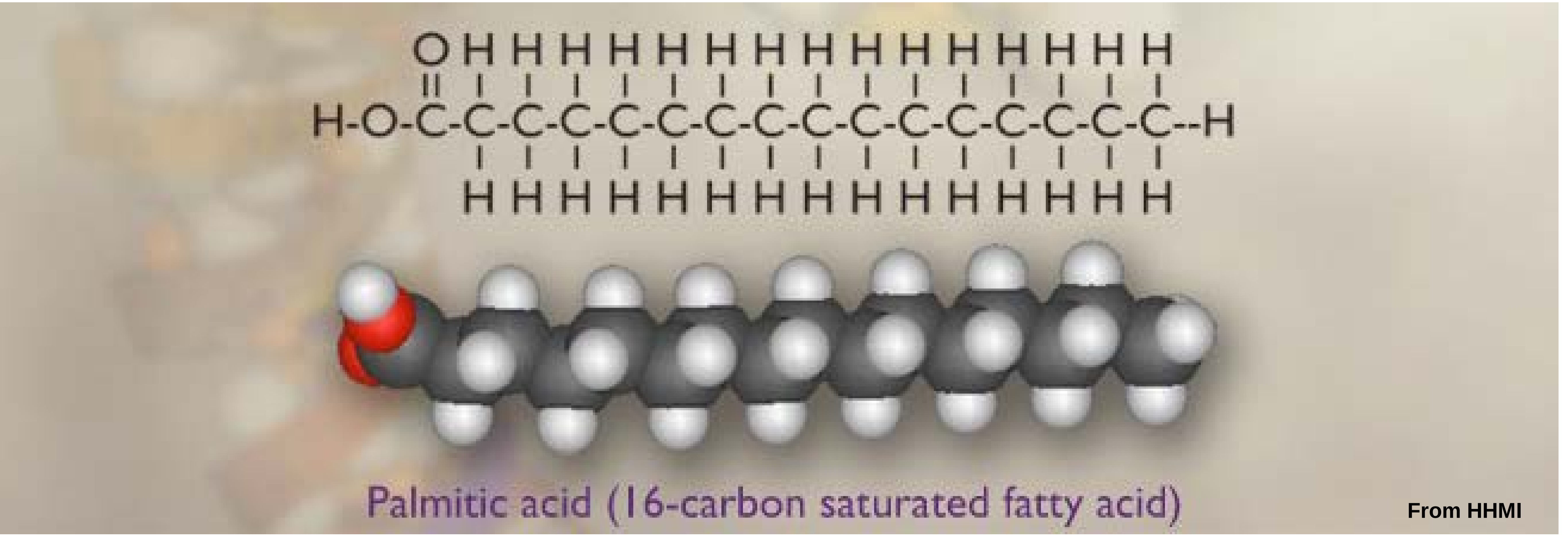
Fatty acids are straight hydrocarbon chain organic acids. The most common number of carbon atoms in the chain is 16-18.



Saturated Fatty Acids

-When fatty acids are saturated, no more hydrogen atoms can be added. All bonds between carbon atoms are single bonds. -The hydrocarbon chain is straight in saturated fatty acids. As a result, the molecular packing is dense and the melting point is high.

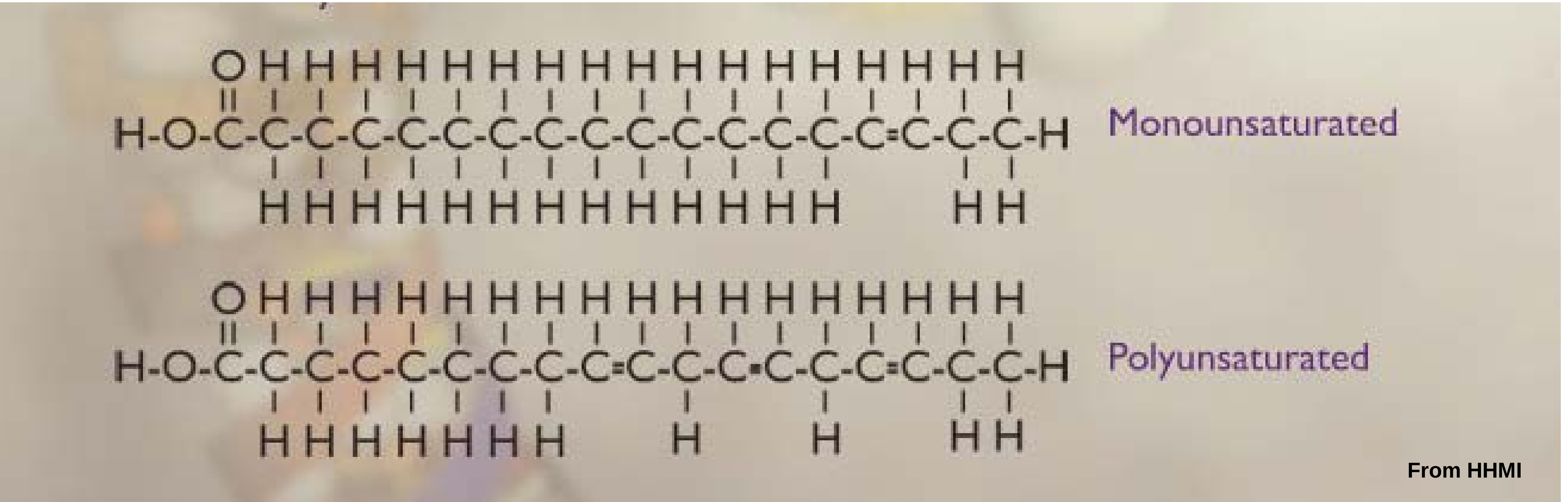
-Example: Butter.



From HHMI

Unsaturated Fatty Acids

-Unsaturated fatty acids have one or more double bonds between carbon atoms are single bonds. Monounsaturated: one double bond. Polyunsaturated: more than one double bond.

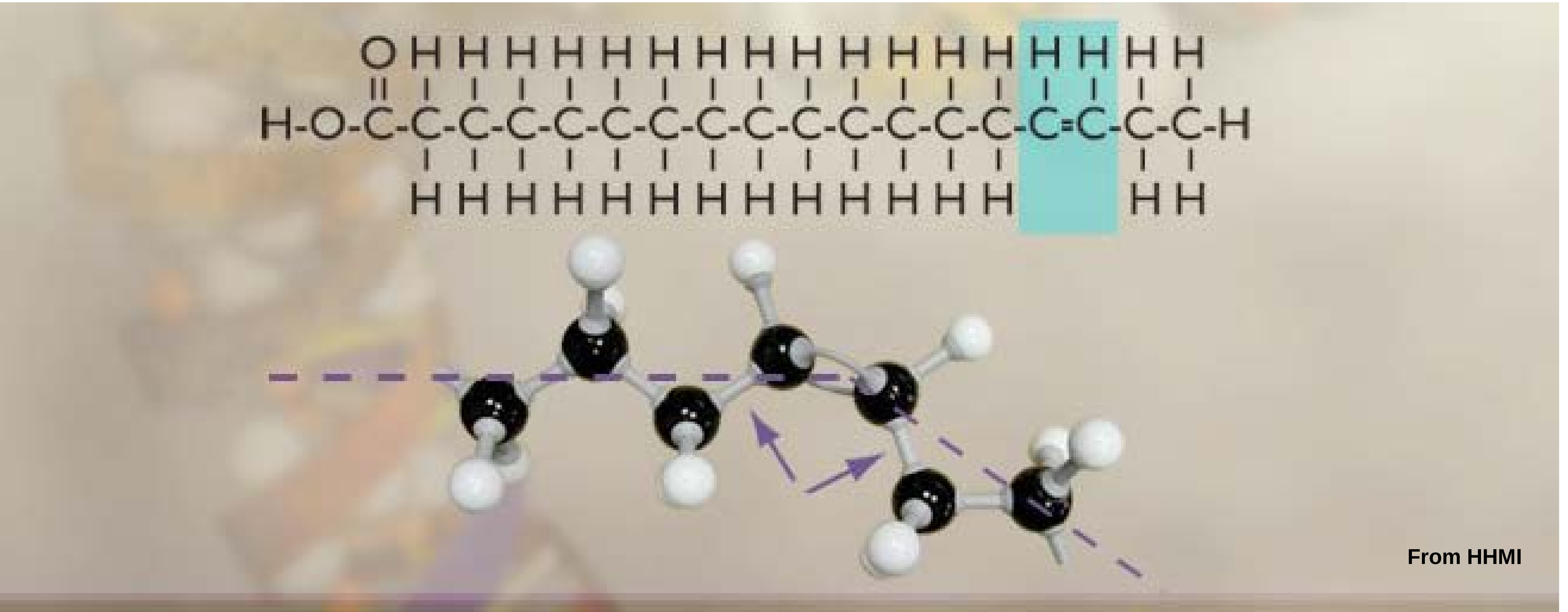


Cis-Unsaturated Fatty Acids

-Most naturally occurring unsaturated fatty acids are in *cis*. Carbon-carbon bonds adjacent to double bonds are on the same side.

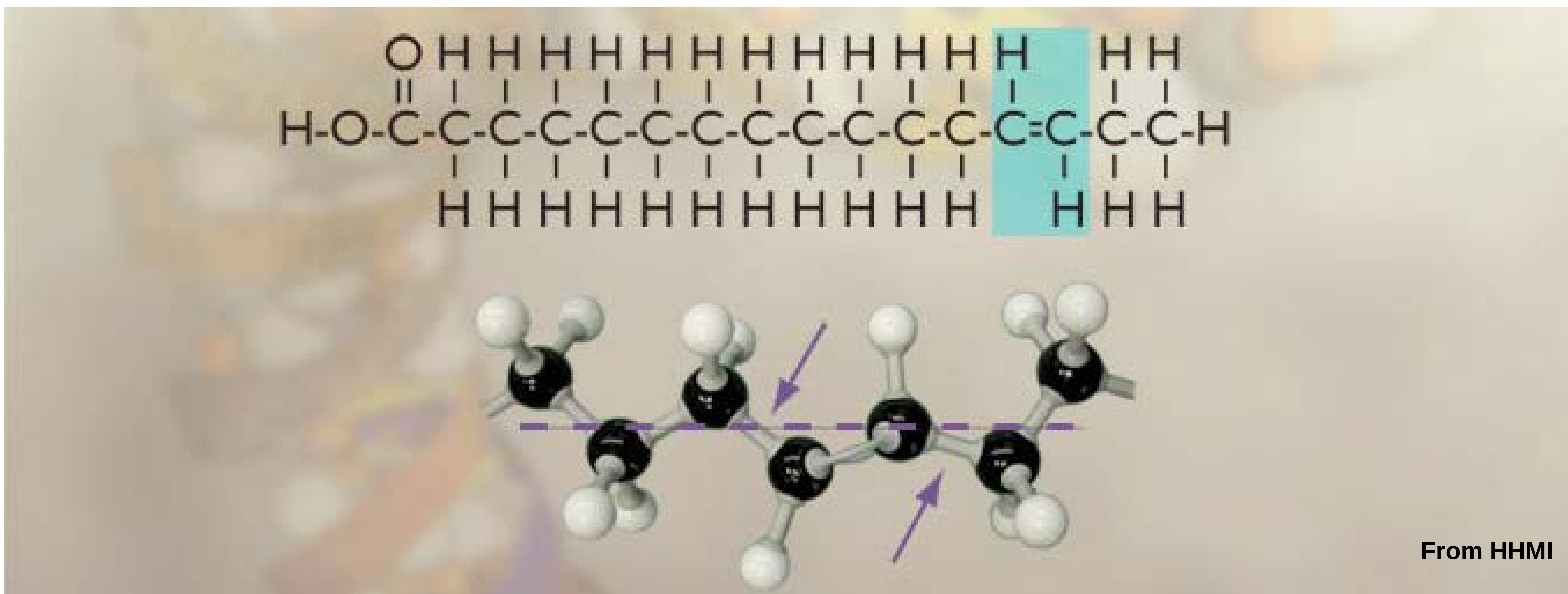
-The hydrocarbon chain is bent in cis-un saturated fatty acids, so the molecular packing is less dense and the melting point is lower than saturated fatty acids.

-Example: Olive oil.



Trans Fatty Acids

-Most trans fatty acids are created in an industrial process that adds hydrogen to liquid vegetable oils to make them more solid. The carbon bonds adjacent to double bonds are on the opposite side.
-The hydrocarbon chain is straight in *trans* fatty acids, so the molecular packing is more dense and the melting point is higher than saturated fatty acids.
-Example: Crisco



The trans fat cookie challenge: GONE!!

The FDA has proposed that trans fats no longer be "generally recognized as safe."

Trans fats raise your bad (LDL) cholesterol levels and lower your good (HDL) cholesterol levels. Eating trans fats increases your risk of developing heart disease and stroke. It's also associated with a higher risk of developing type 2 diabetes.

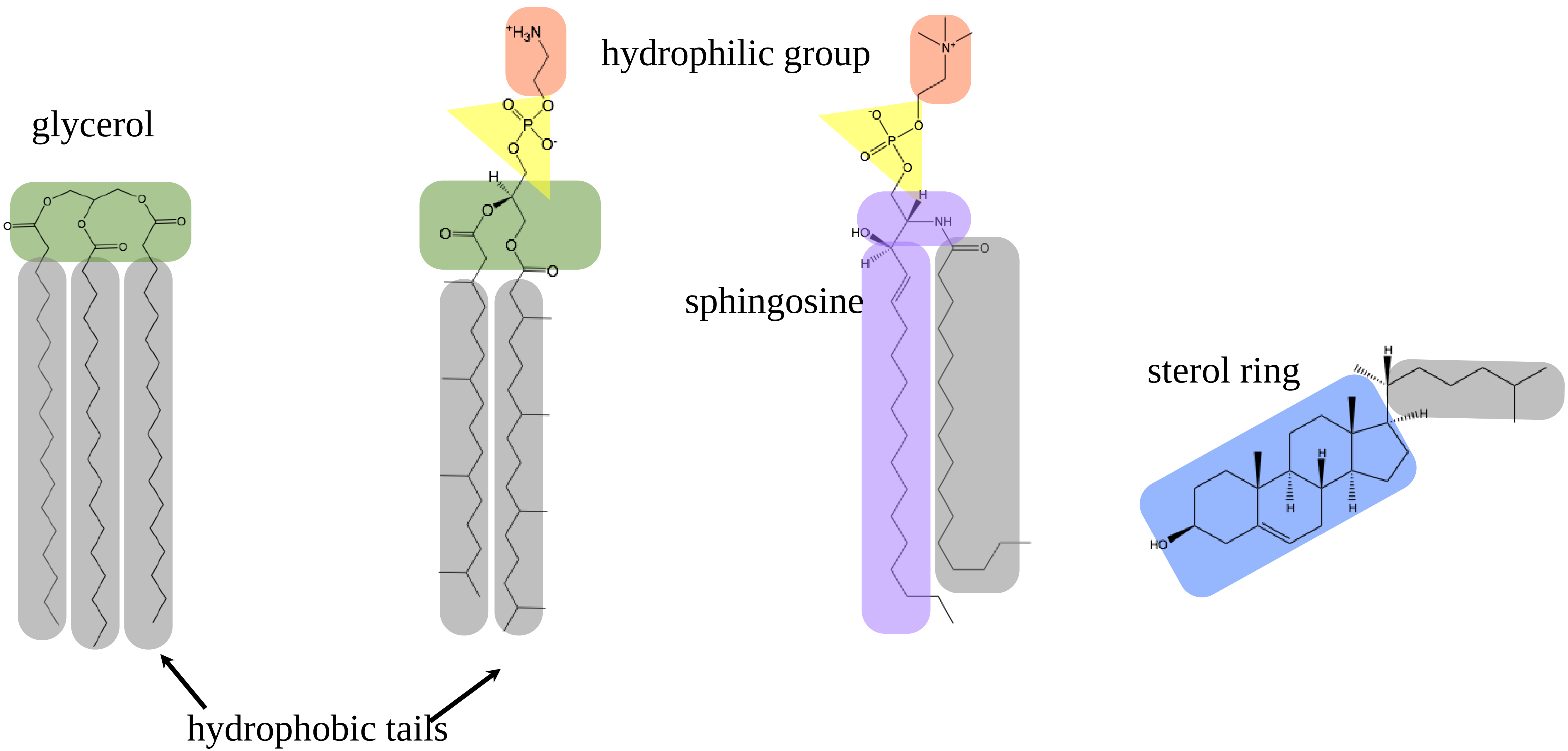
It is estimated that 7,000-20,000 deaths a year could be prevented by eliminating trans fats.

Chemical Properties of Triglycerides

FAT SUMMARY

Type of fat	Saturated	Unsaturated (*cis*)	Unsaturated (*trans*)
			
Shape of carbon chain	Straight	Bent	Straight
Molecular packing	Dense	Less Dense	Dense
Melting point	High	Low	High

Classification of biological lipids



Triacylglycerol | Phospholipid | Sphingolipid | Cholesterol

Storage lipids | Membrane Lipids

Phospholipid Structure

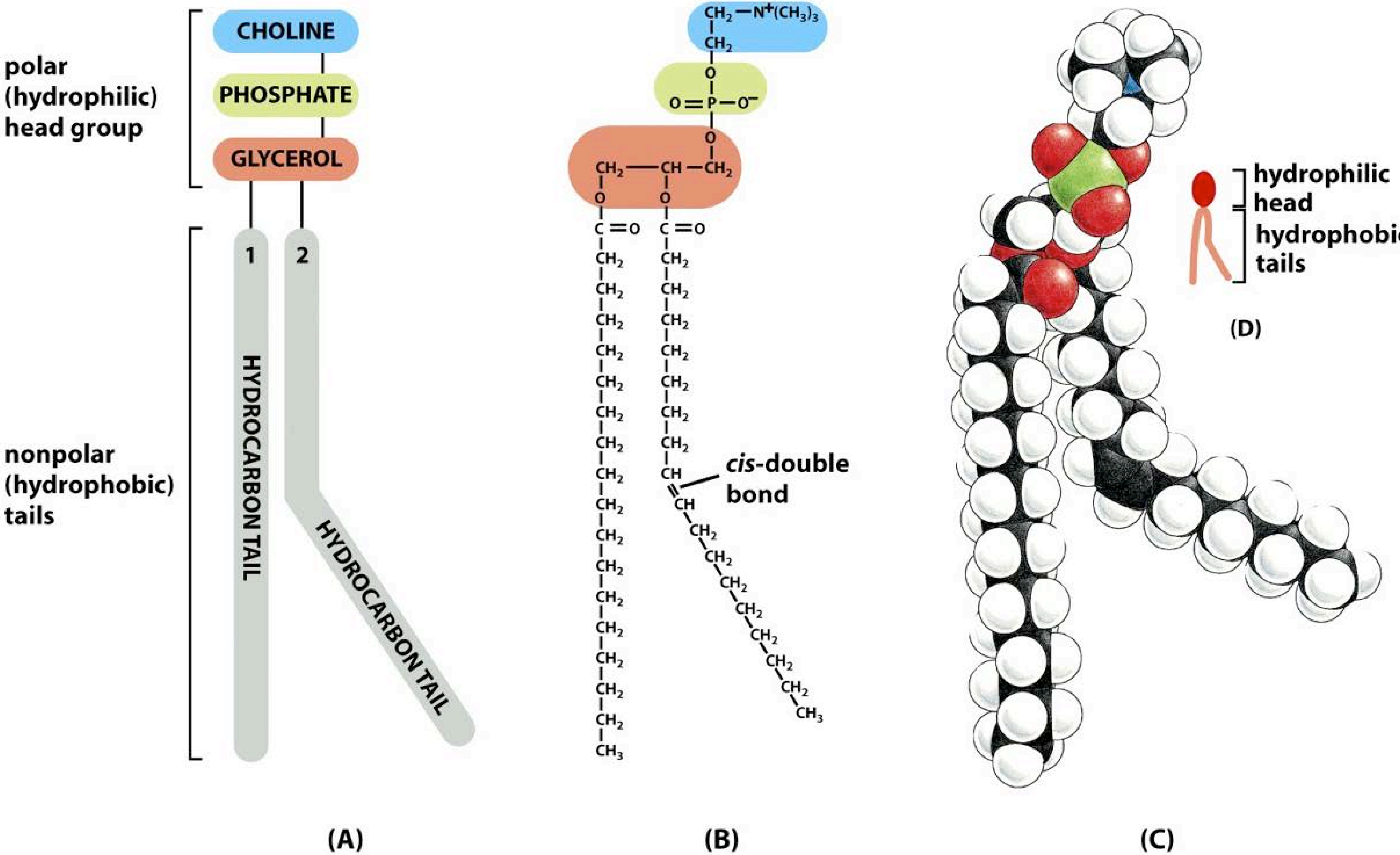


Figure 10-2 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Types of Phospholipids

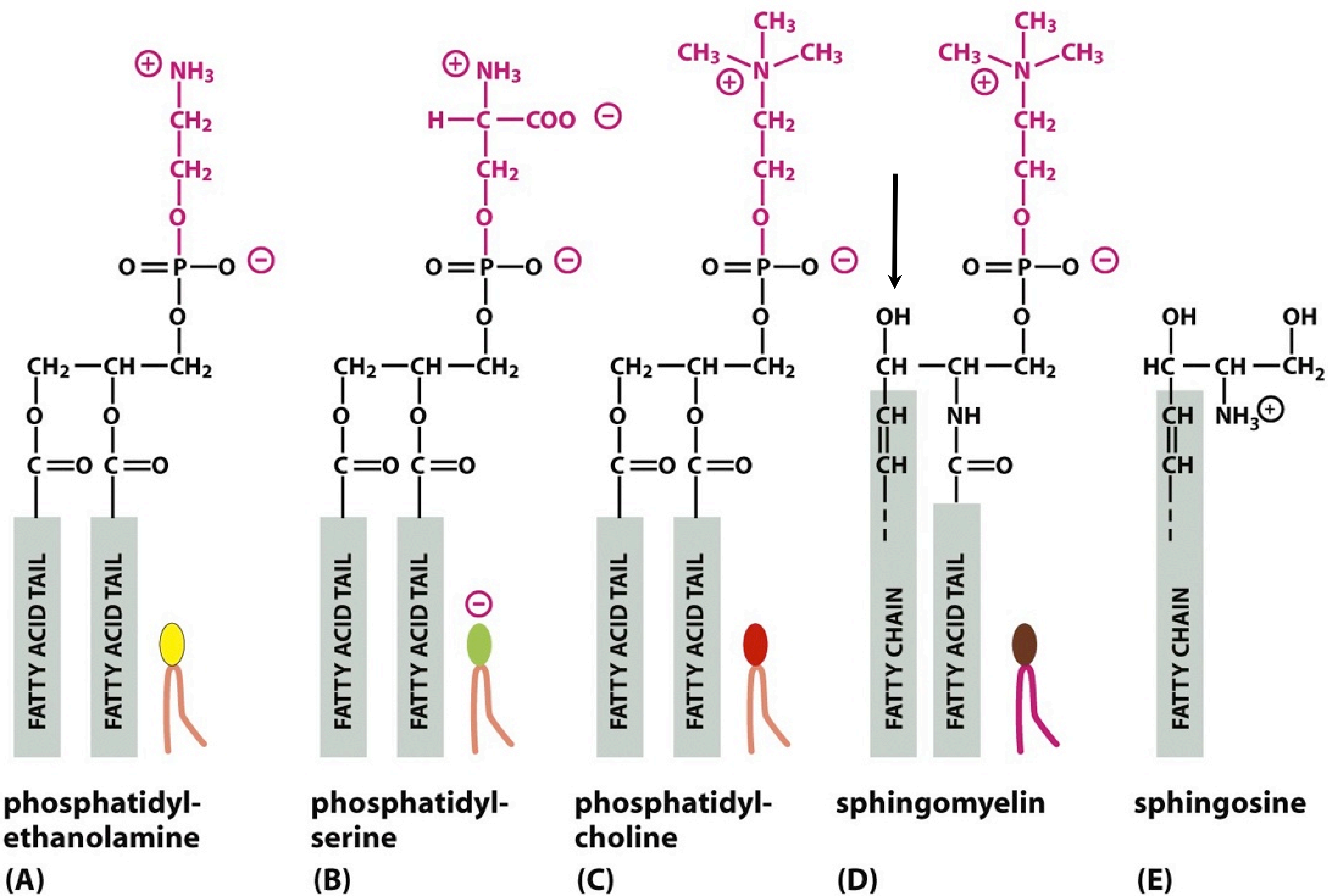


Figure 10-3 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Shape of the Lipid Dictates its Packing Arrangement

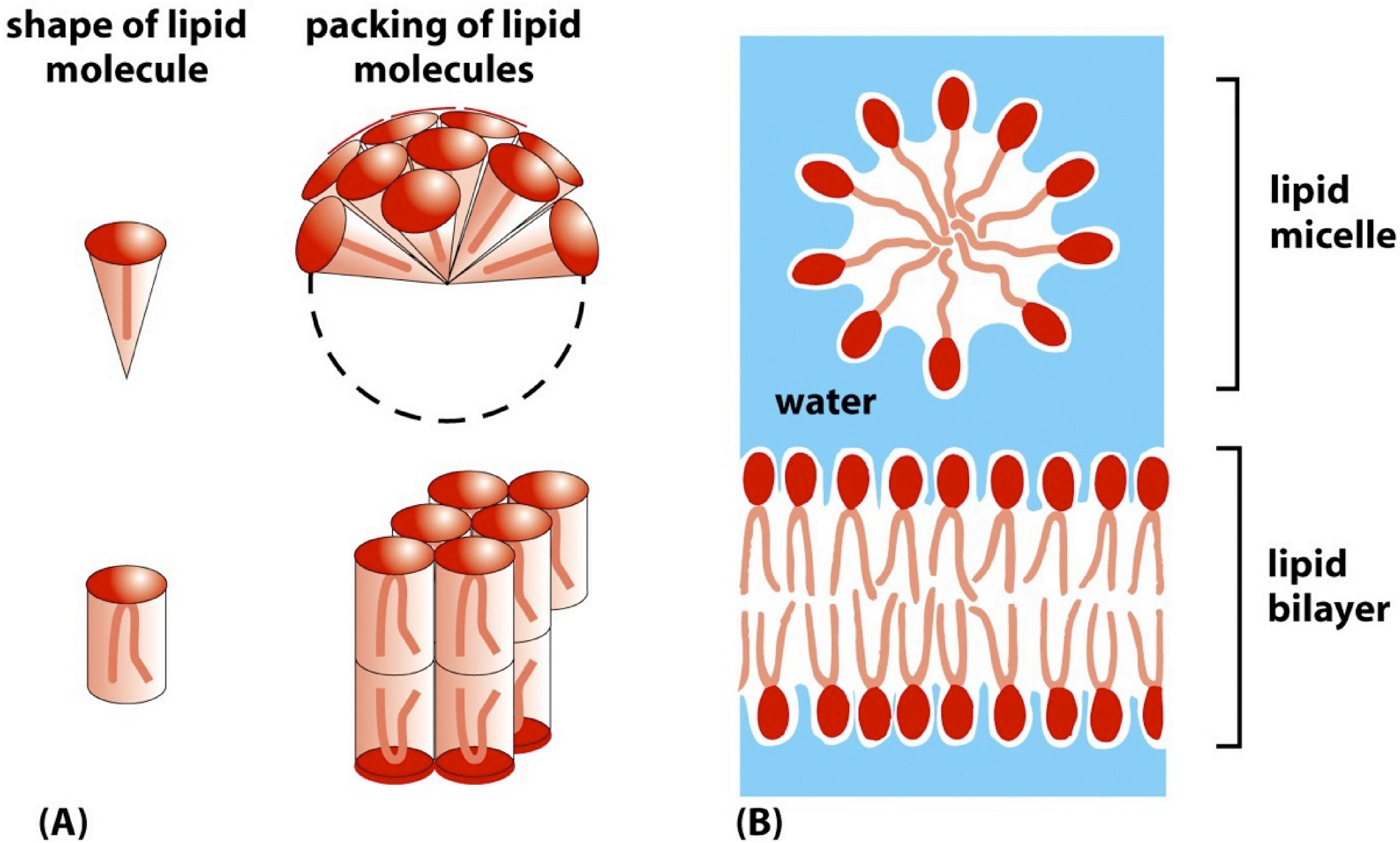


Figure 10-7 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Critical micelle concentration (cmc) is the concentration above which amphiphiles aggregate into micelles.

Phospholipids Form Liposomes

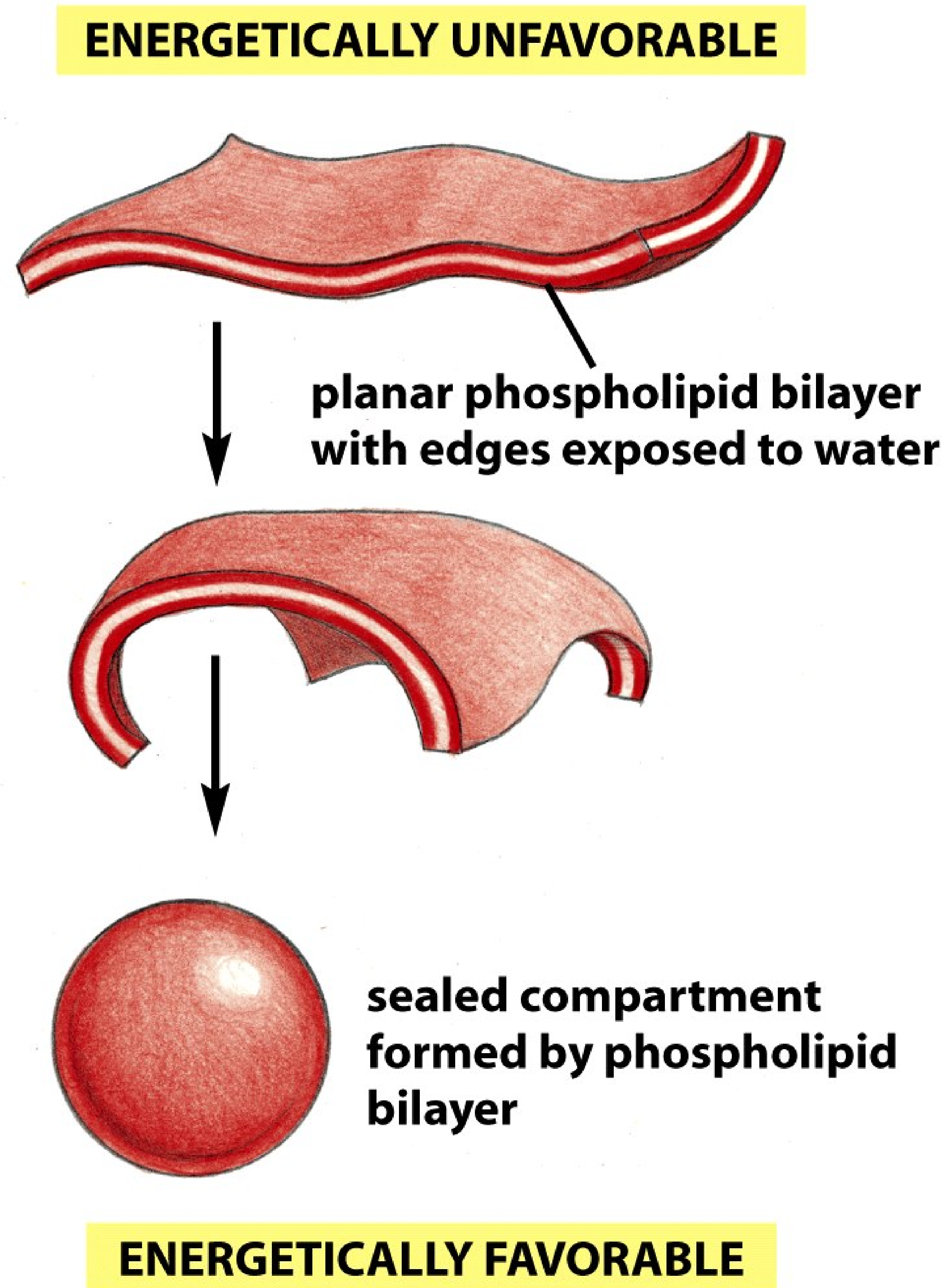


Figure 10-8 Molecular Biology of the Cell 5/e (© Garland Science 2008)

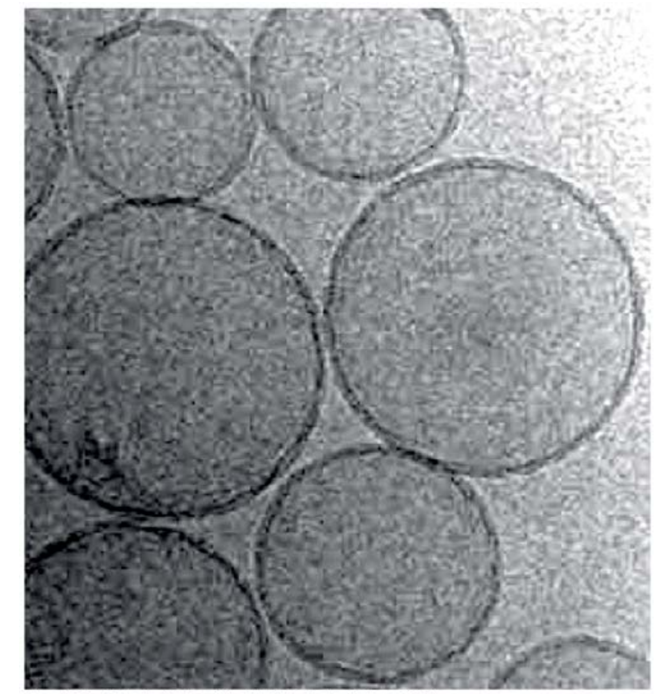


Figure 10-9a Molecular Biology of the Cell 5/e (© Garland Science 2008)

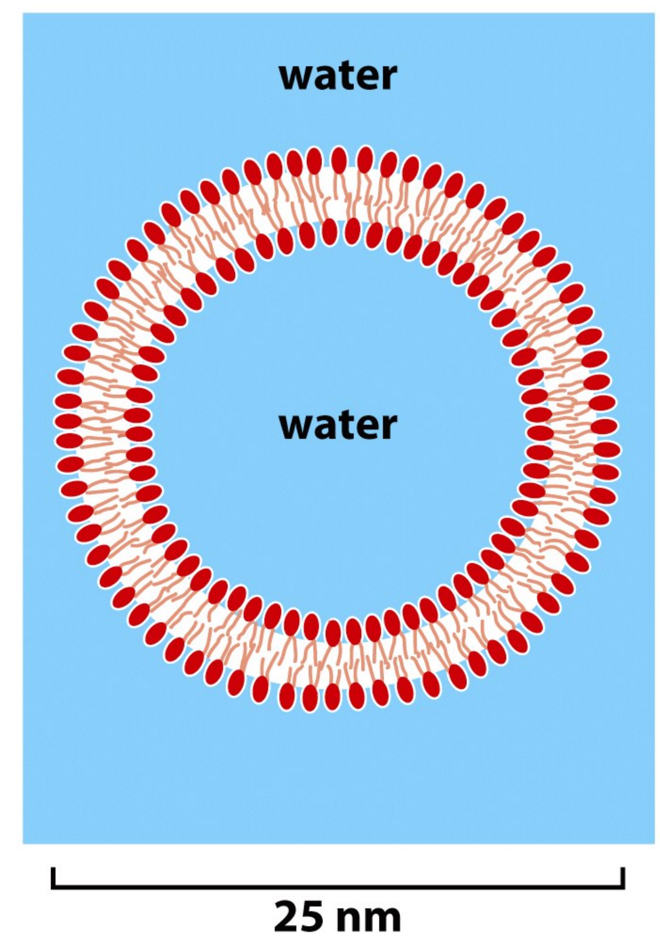


Figure 10-9b Molecular Biology of the Cell 5/e (© Garland Science 2008)

Properties of Lipids in Bilayers

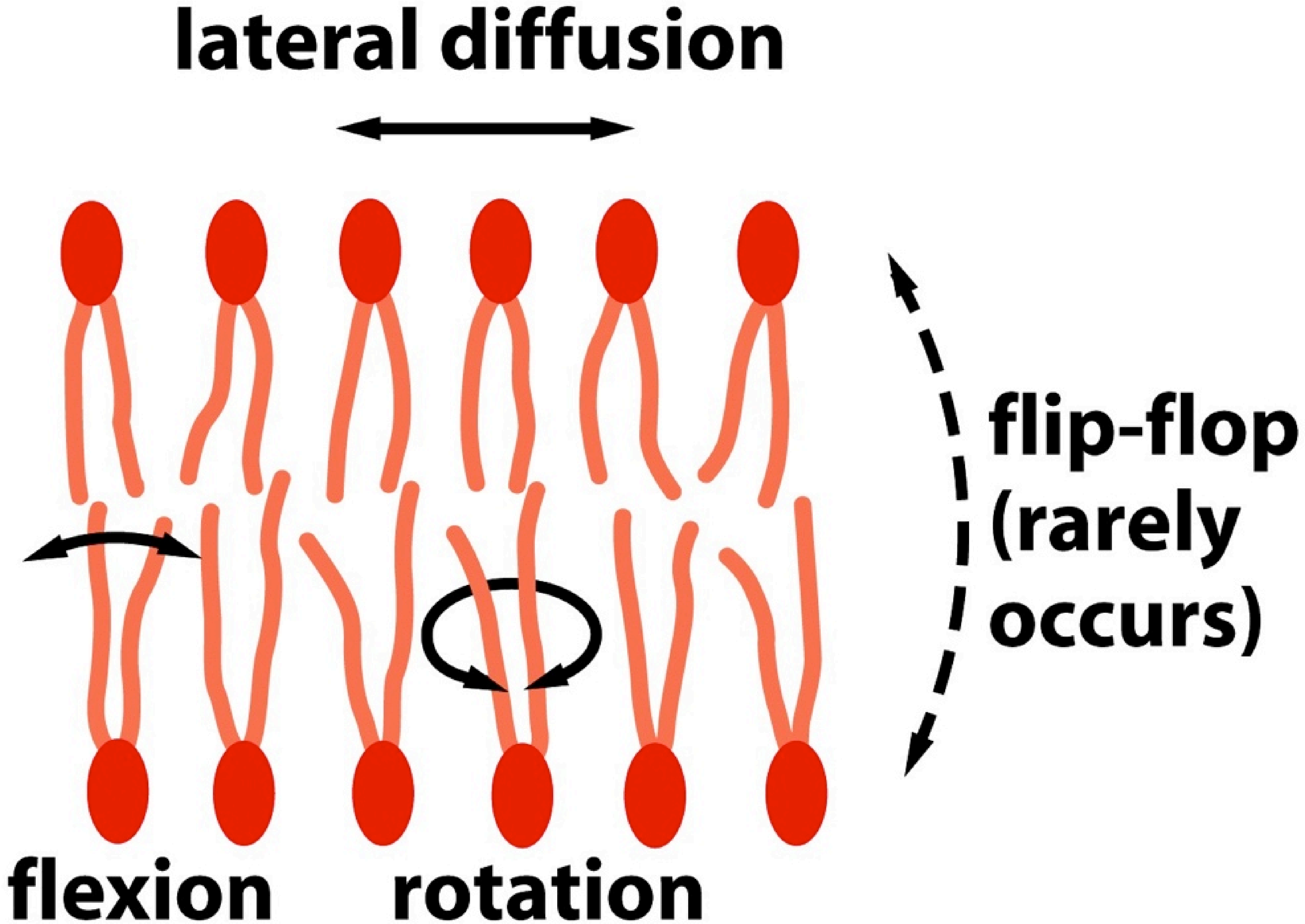
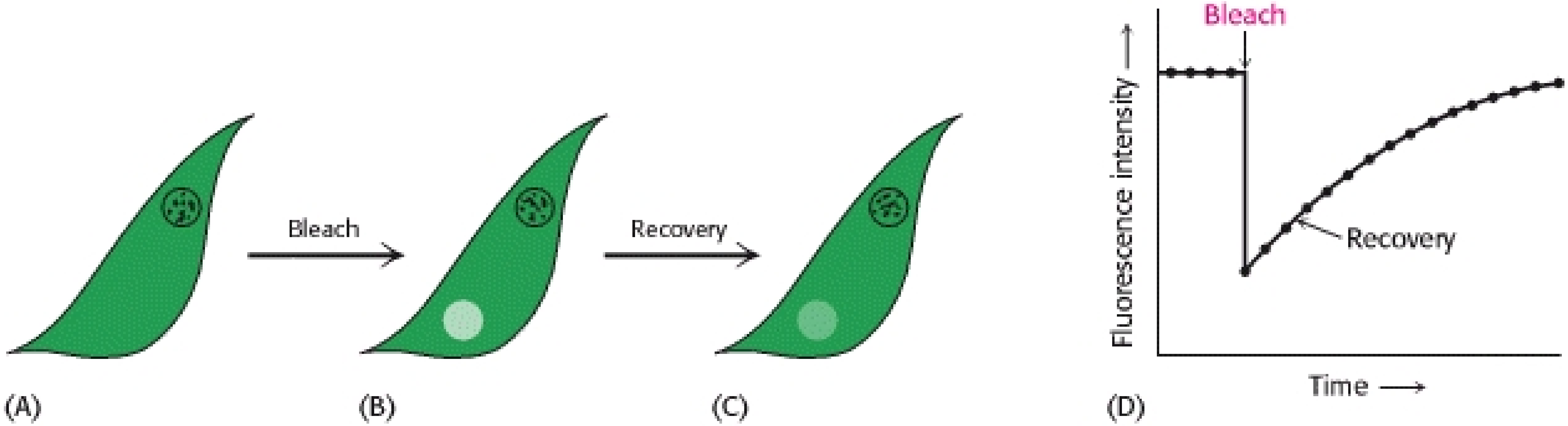


Figure 10-11b Molecular Biology of the Cell 5/e (© Garland Science 2008)

Lateral diffusion is fast: a lipid in a bilayer could diffuse the length of a bacterial cell (1-2 υm) in less than a second. Transverse diffusion (flip-flopping) is slow, when measured half-times are several days.

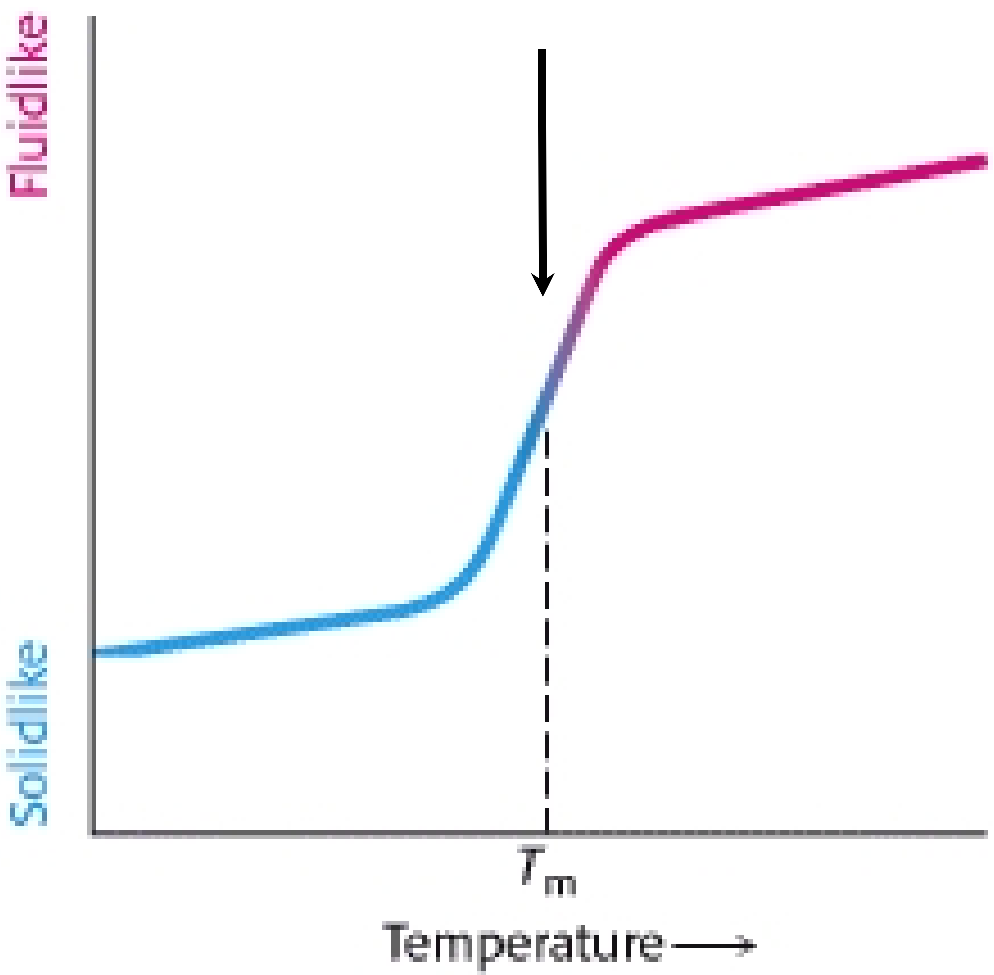
FRAP Demonstrates Rapid Lateral Diffusion in Membranes



Biochemistry. 5th edition.
Stryer L. 2002.

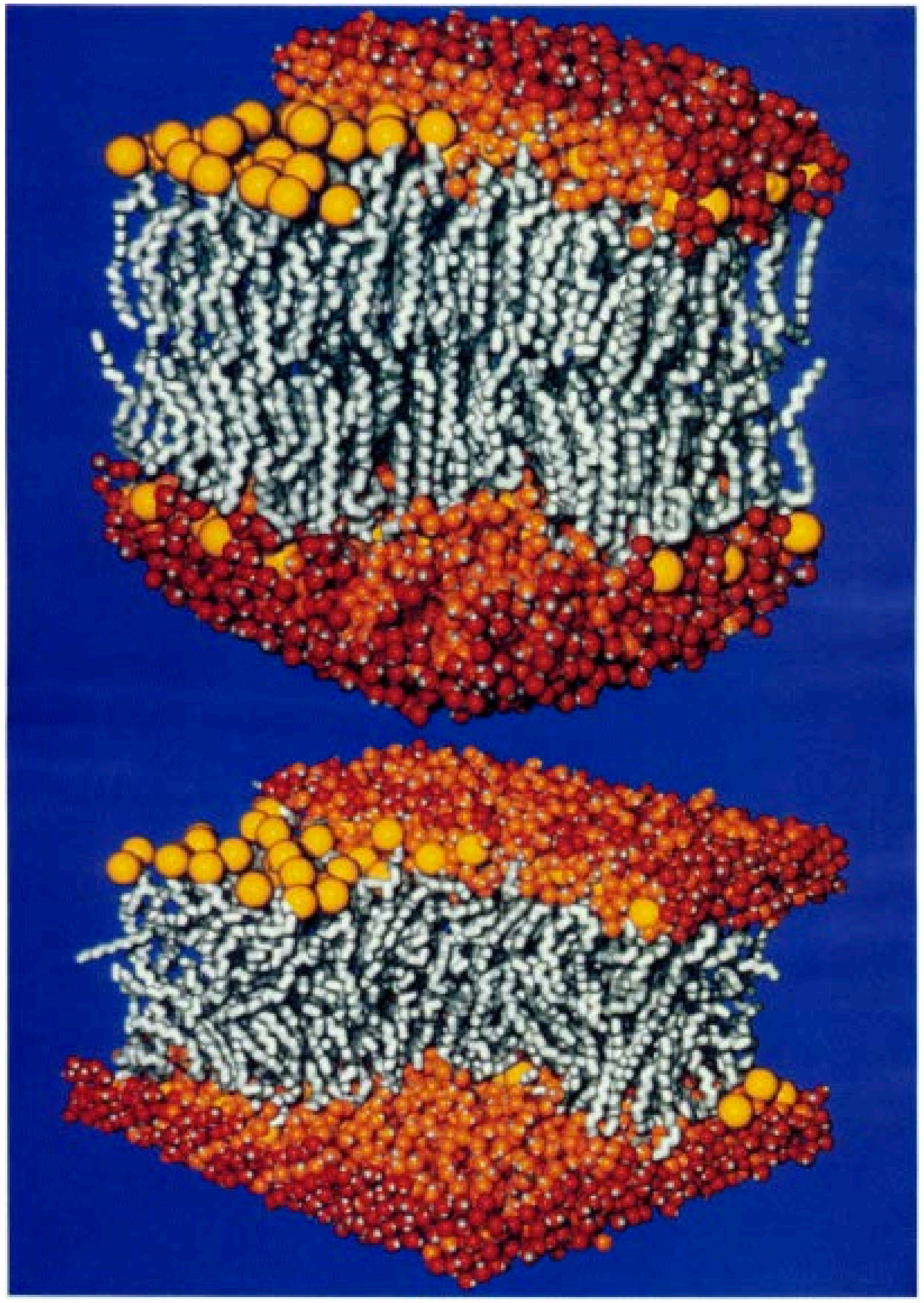
Bilayer Fluidity Varies with Temperature

Phase transition temperature



Below the phase transition temperature: gel phase

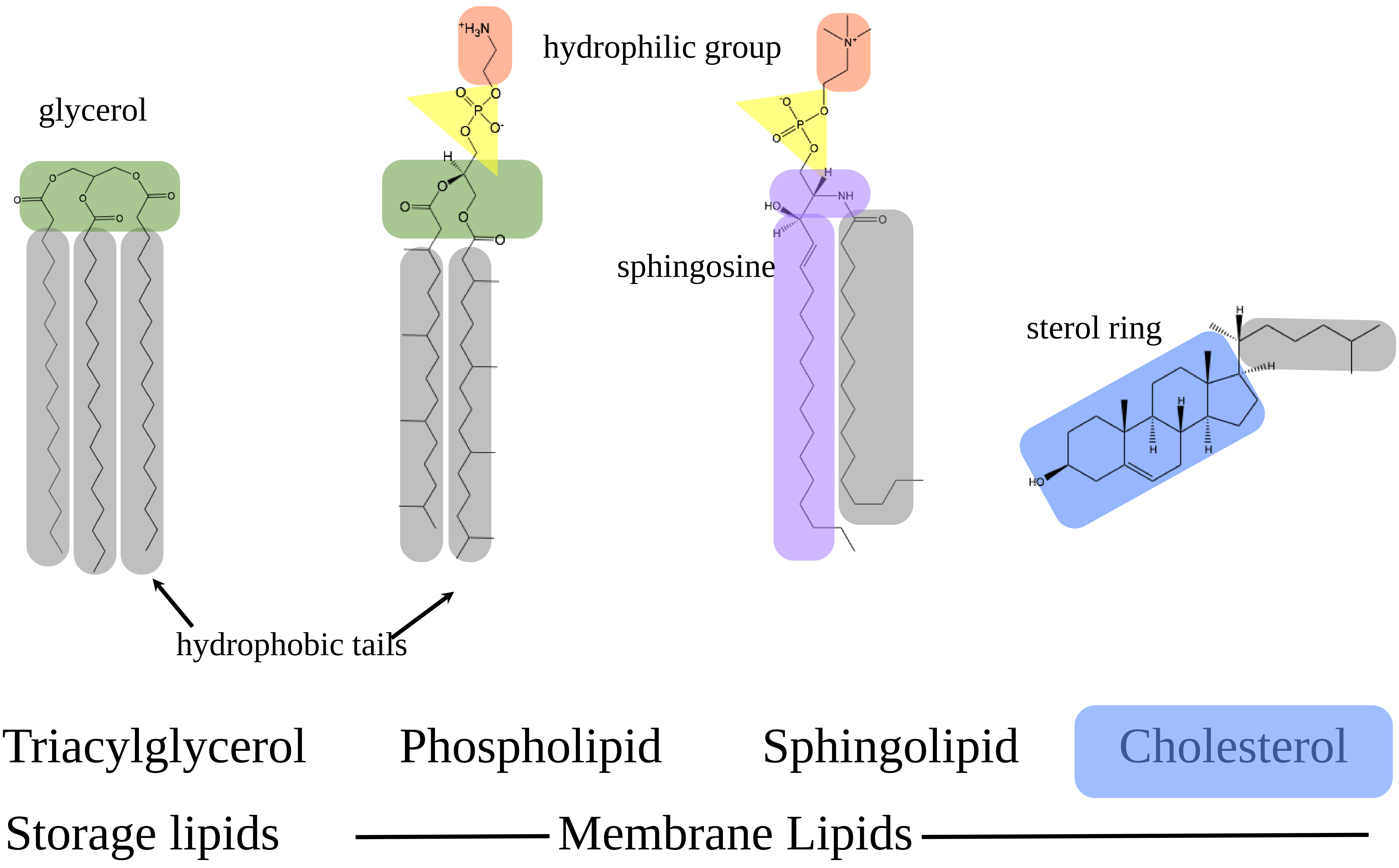
Above the phase transition temperature: liquid crystal phase



Biochemistry. 5th edition, Stryer

Heller et al., J. Phys. Chem 1993

Classification of biological lipids



Eukaryotic Plasma Membranes Contain Cholesterol

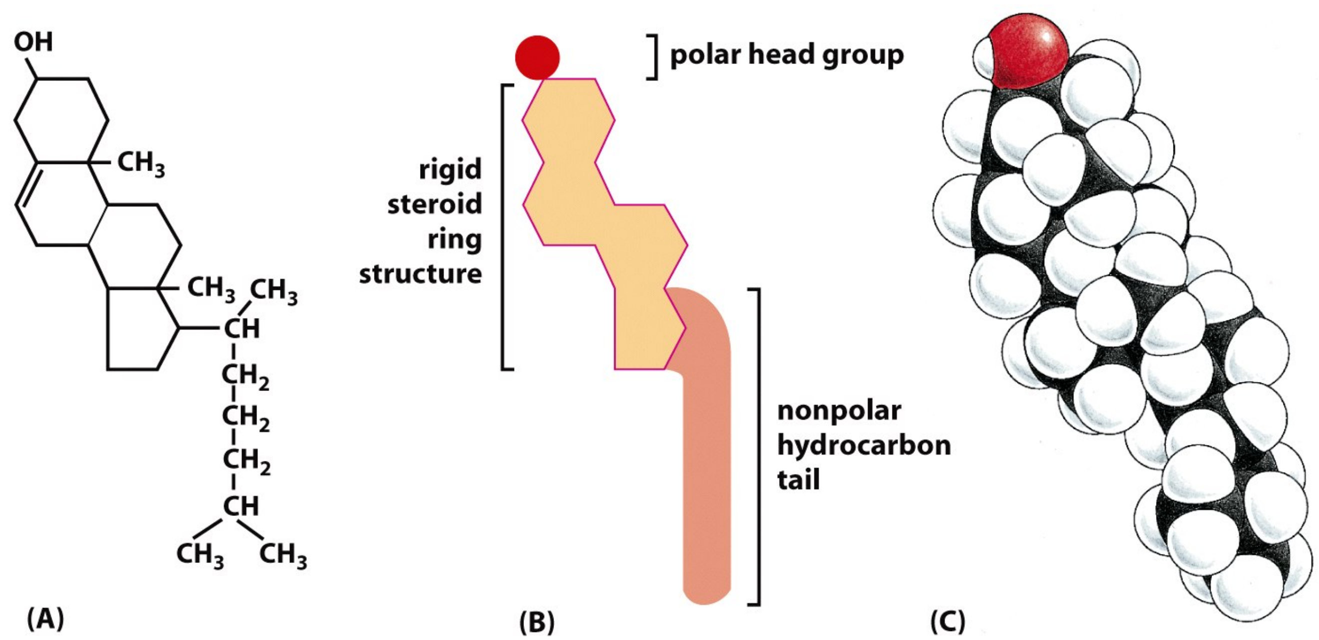


Figure 10-4 Molecular Biology of the Cell 5/e (© Garland Science 2008)

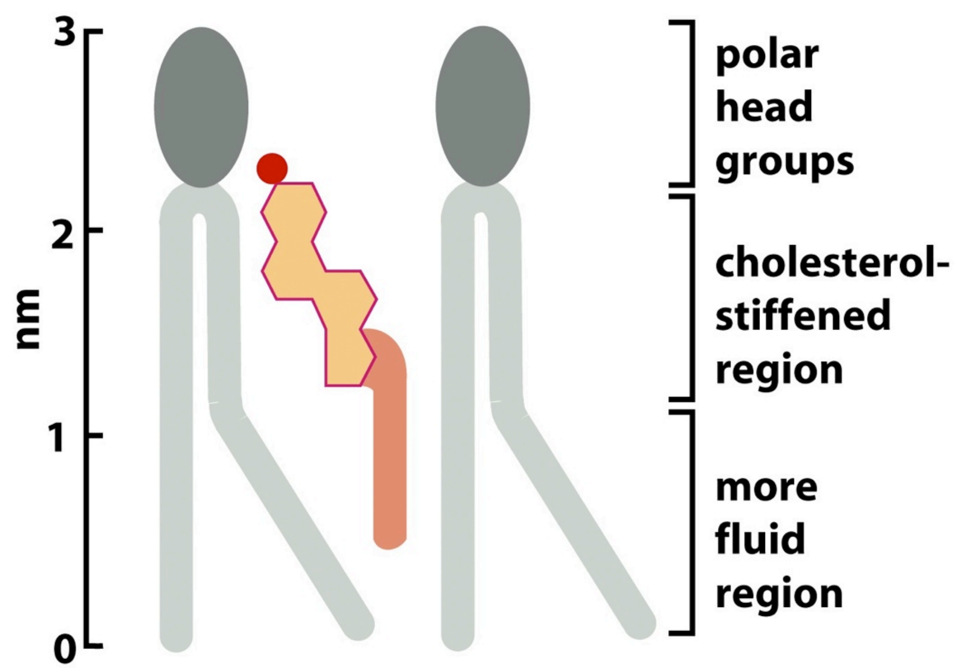


Figure 10-5 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Cholesterol makes the plasma membrane less permeable. It's rigid sterol ring interacts with the hydrocarbon chain closest to the polar head group and thus partially immobilizes it. Cholesterol also broadens the temperature range for the order-disorder phase transition.

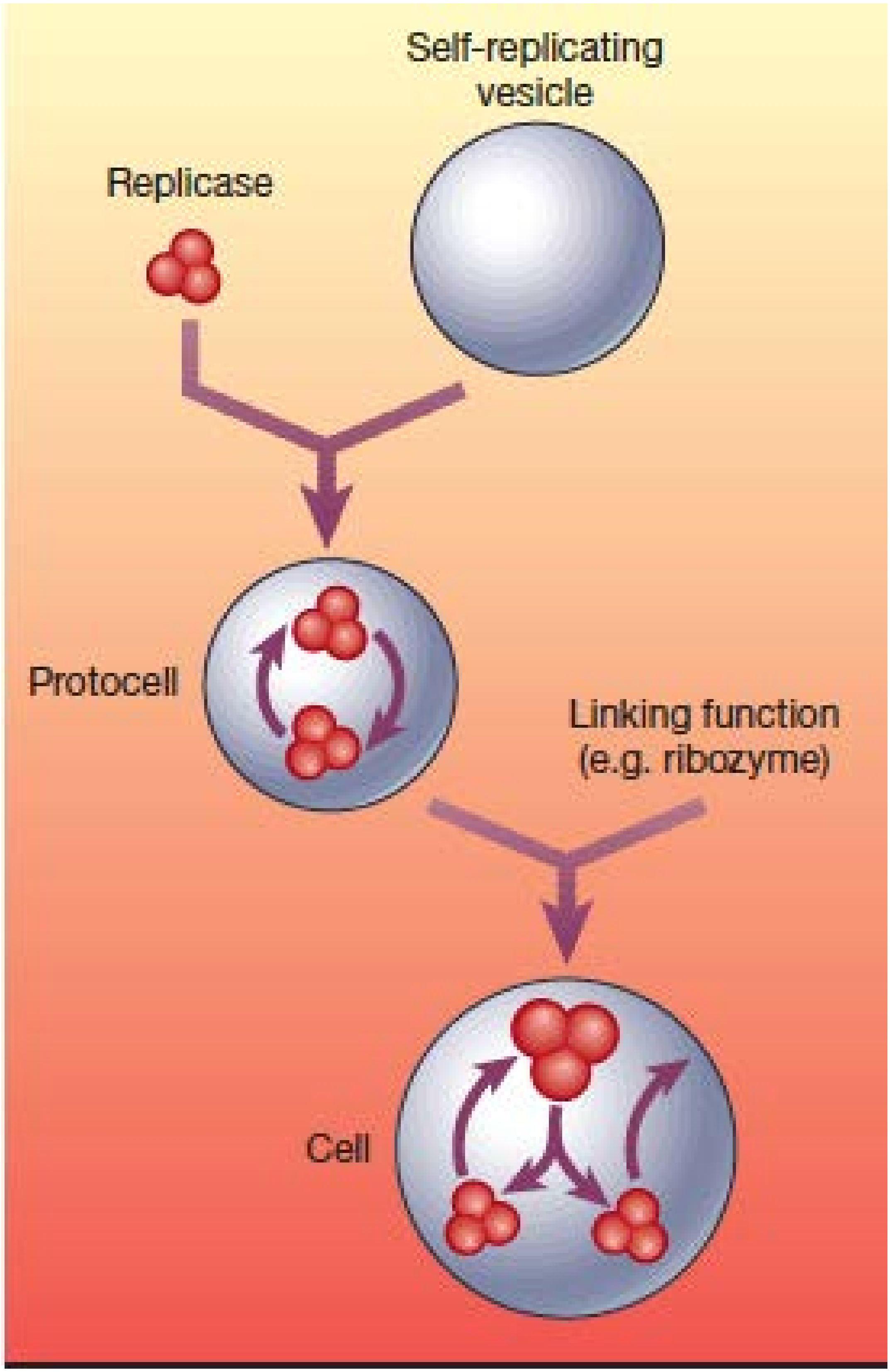
Outline:

1) Classification and Properties of Lipids

2) Biological Functions of Lipids

3) Lipids in Bioscience

Why are Membranes Needed?



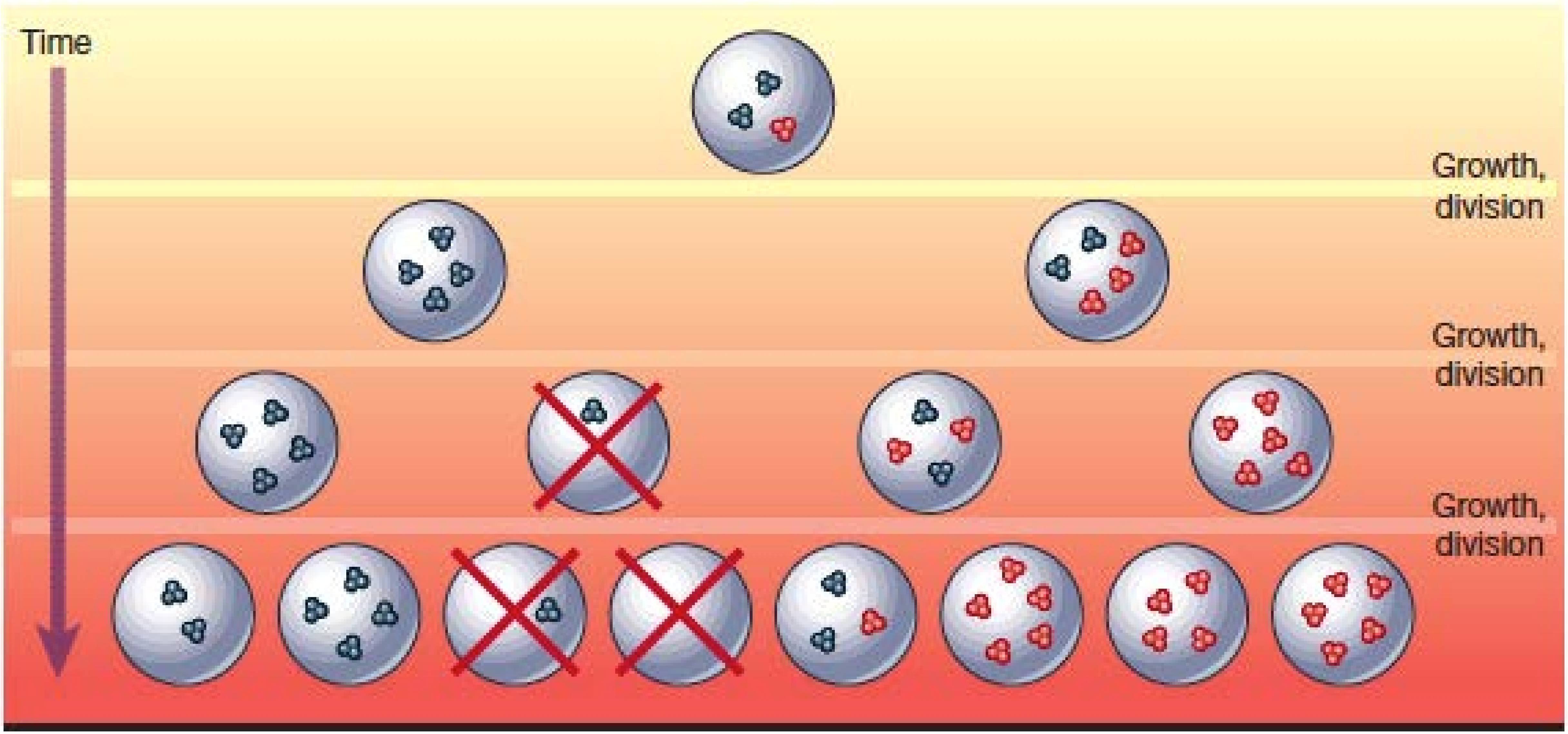
What would you need to synthesize a cell *de novo*, or how did the first protocell come to be?

Let's operationally define a living cell as one that can autonomously replicate, and that is subject to Darwinian evolution.

It needs a membrane, to keep everything together, and a biopolymer that can replicate itself (such as RNA) and hopefully also make more membrane.

Szostack et al., Nature 2001

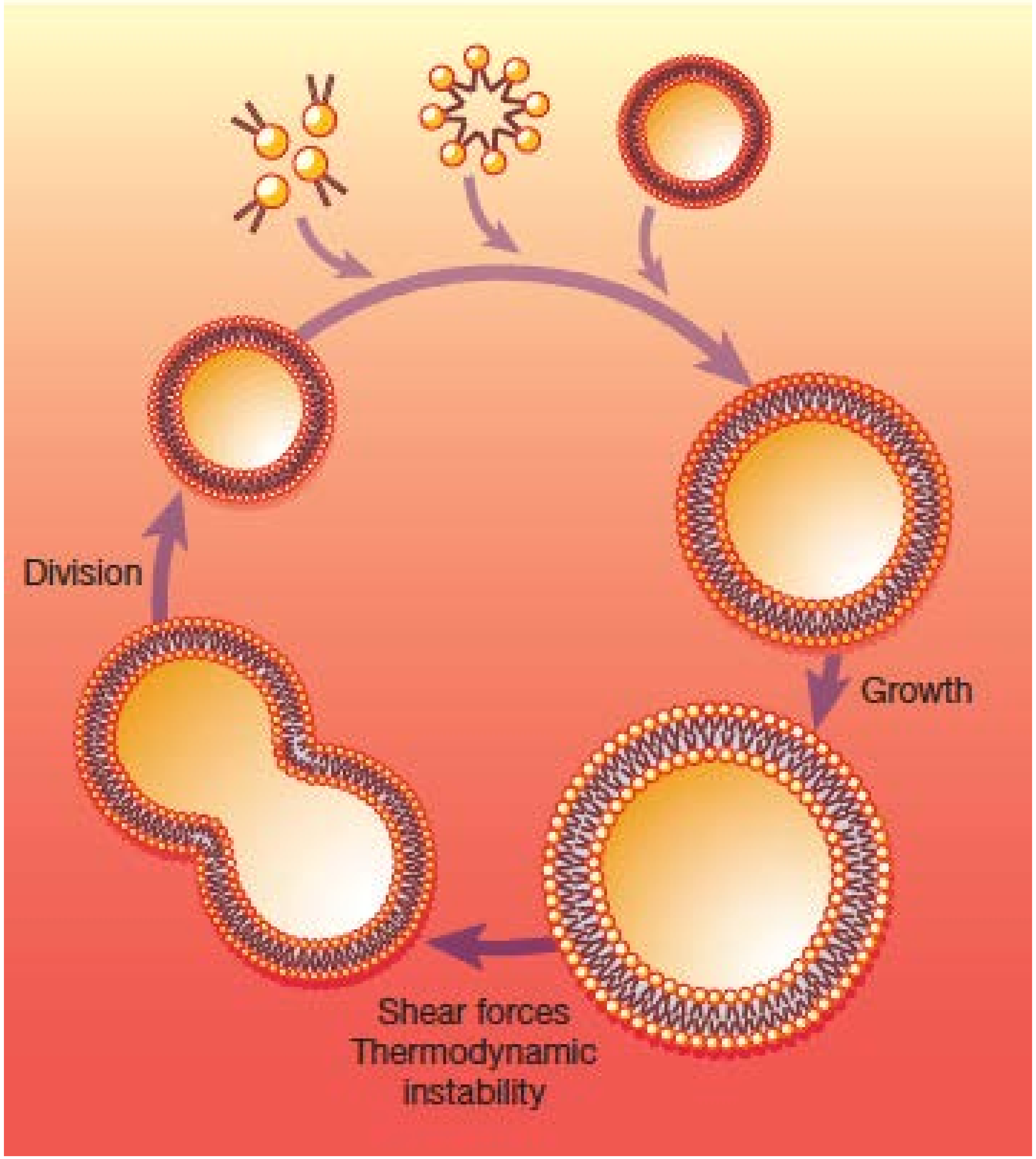
The protocell evolves



A membrane can separate the protocell from the environment. If each cell needs a molecule to serve as a template and a molecule to serve as an enzyme, then any protocell with a more efficient replicase will outcompete a cell with an inefficient replicase. The membrane vesicle enables this evolution.

Szostack et al., Nature 2001

Vesicle growth and division



The vesicle could fuse with smaller vesicles and obtain fresh nucleotides from the environment. Alternately it could be permeable to small molecules, and lipids could be catalytically generted and incorporated from the inside. Vesicles that grew too big would divide.

Szostack et al., Nature 2001

Cells contain many types of membranes

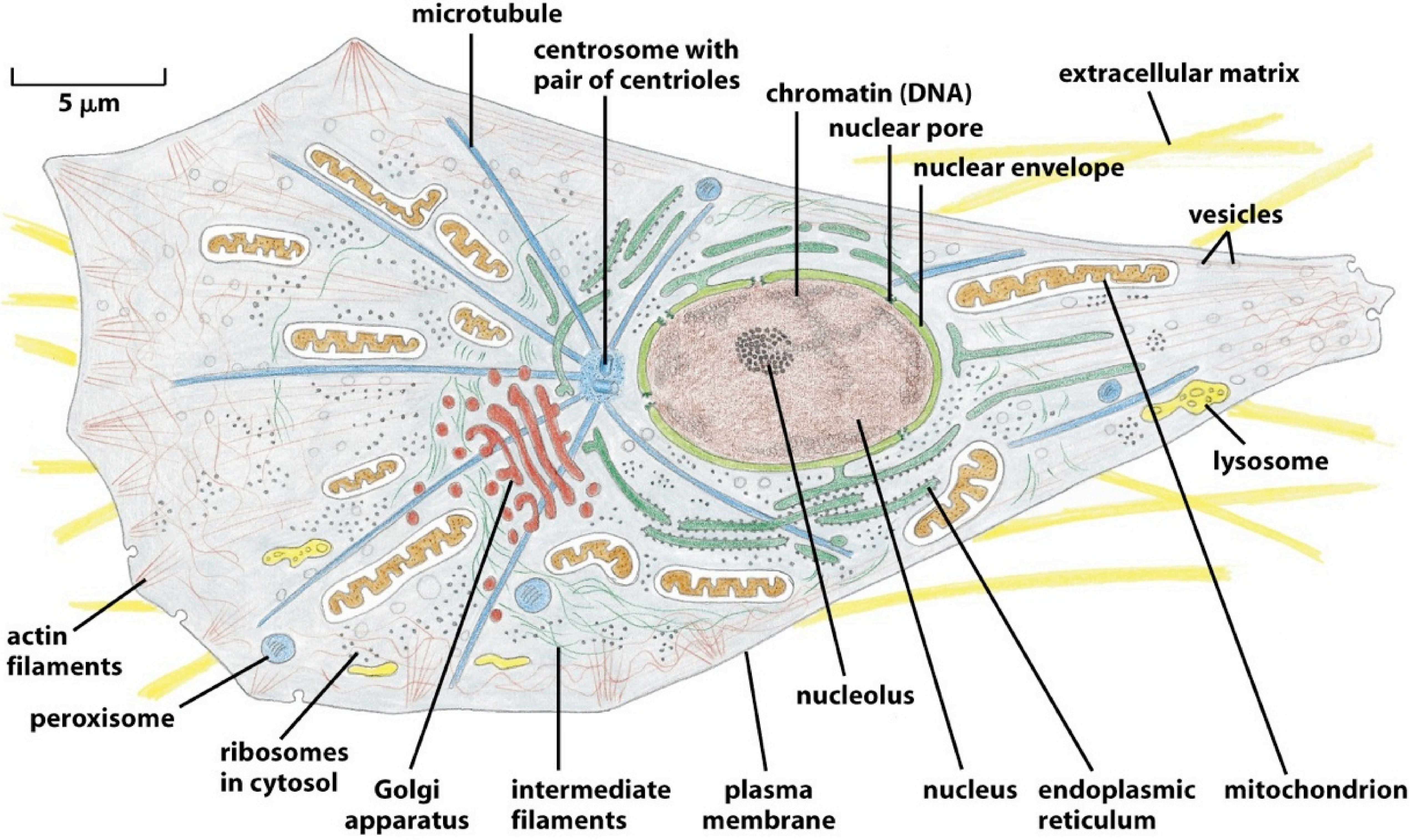


Figure 1-30 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Phospholipids, Sphingolipids and Sterols are the Major Lipid Components of Cell Membranes

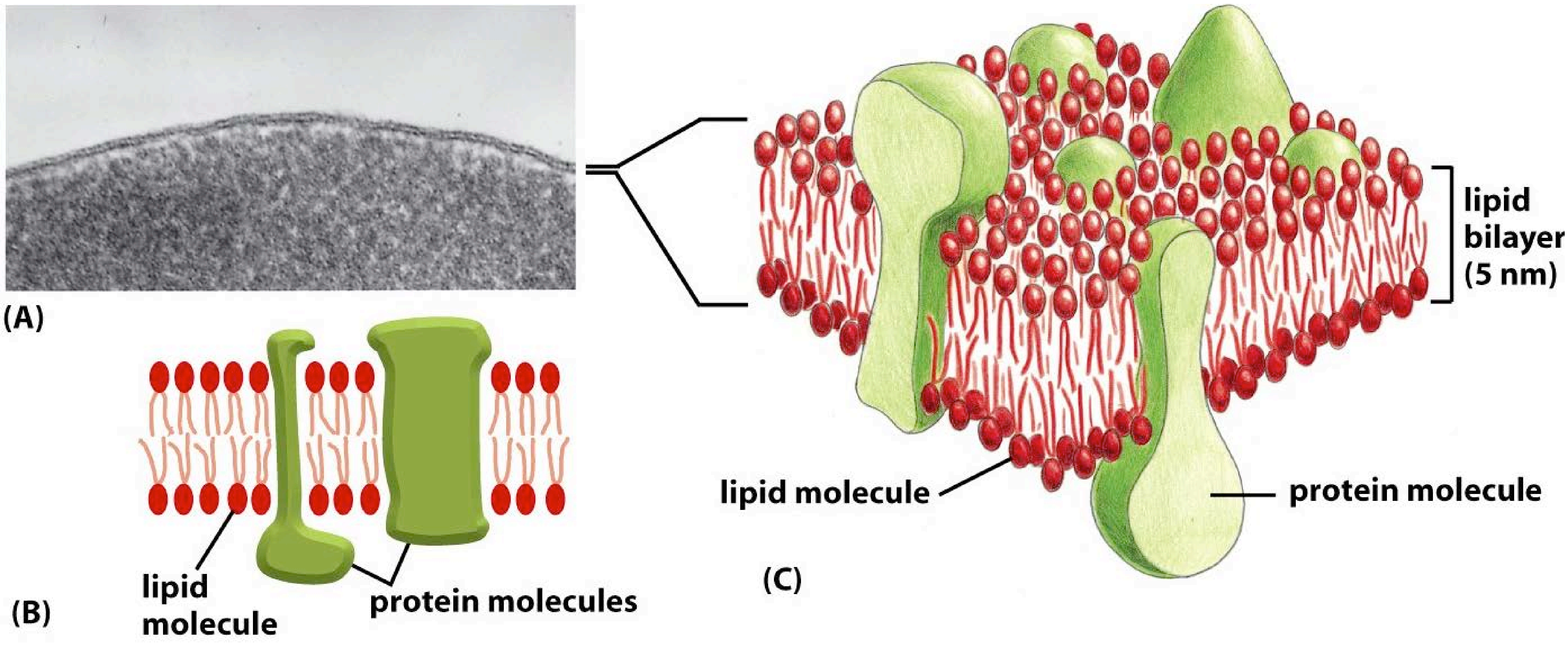


Figure 10-1 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Lipid Composition of Different Membranes

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

Table 10-1 Molecular Biology of the Cell 5/e

Biological Membranes are Asymmetrical

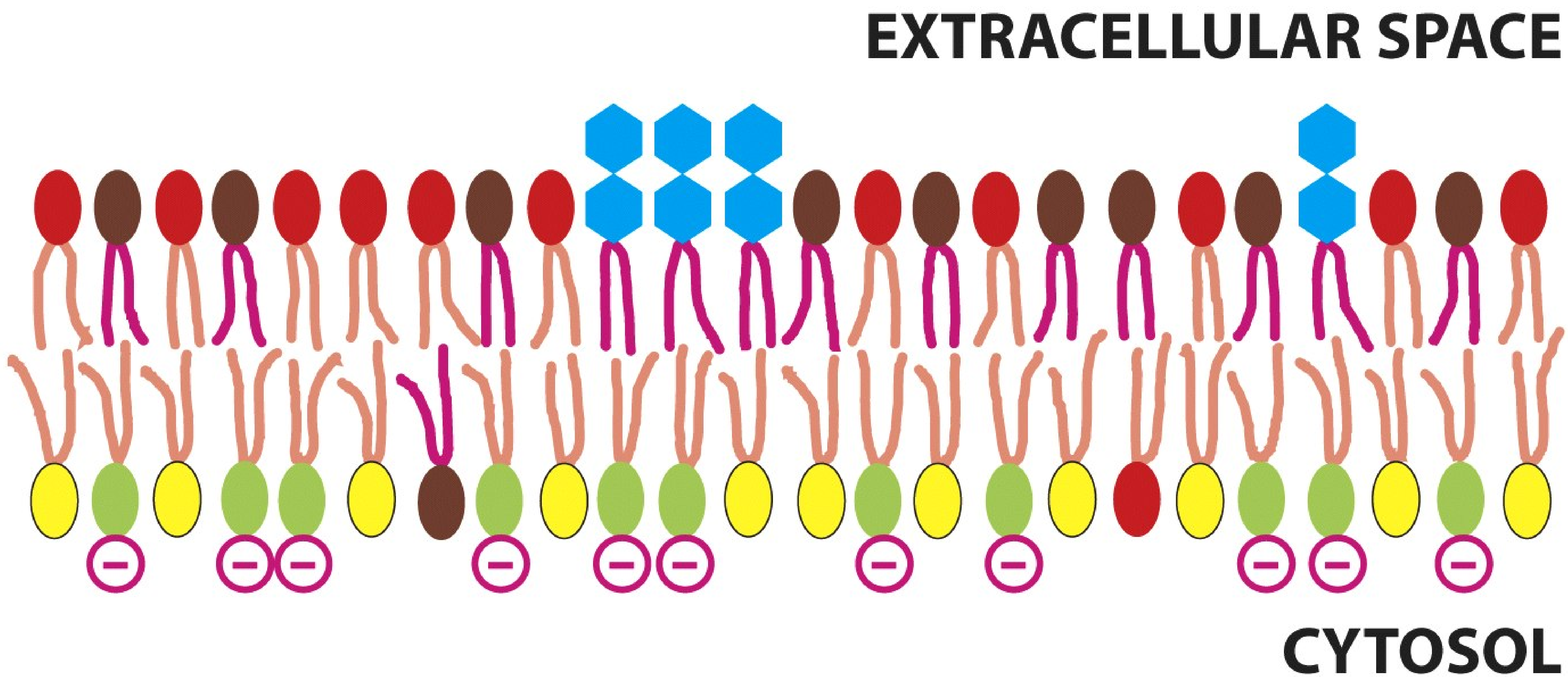
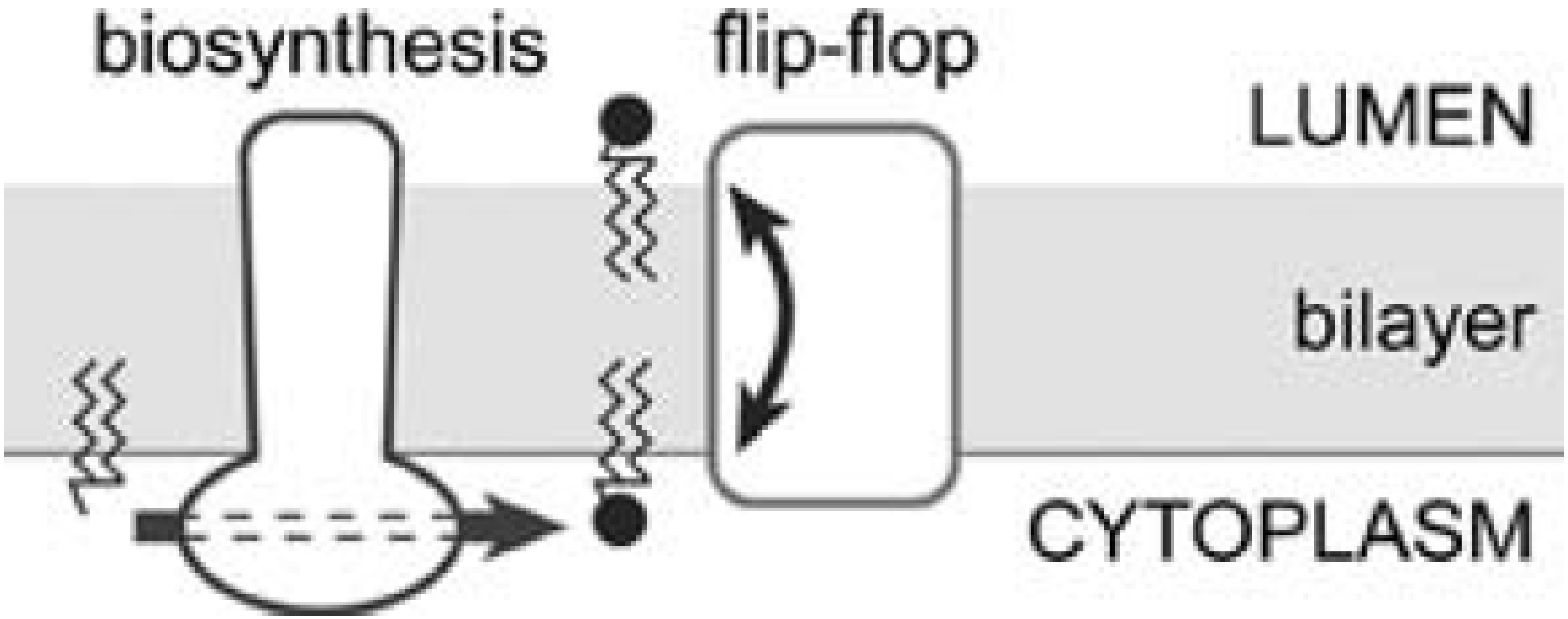


Figure 10-16 Molecular Biology of the Cell 5/e (© Garland Science 2008)

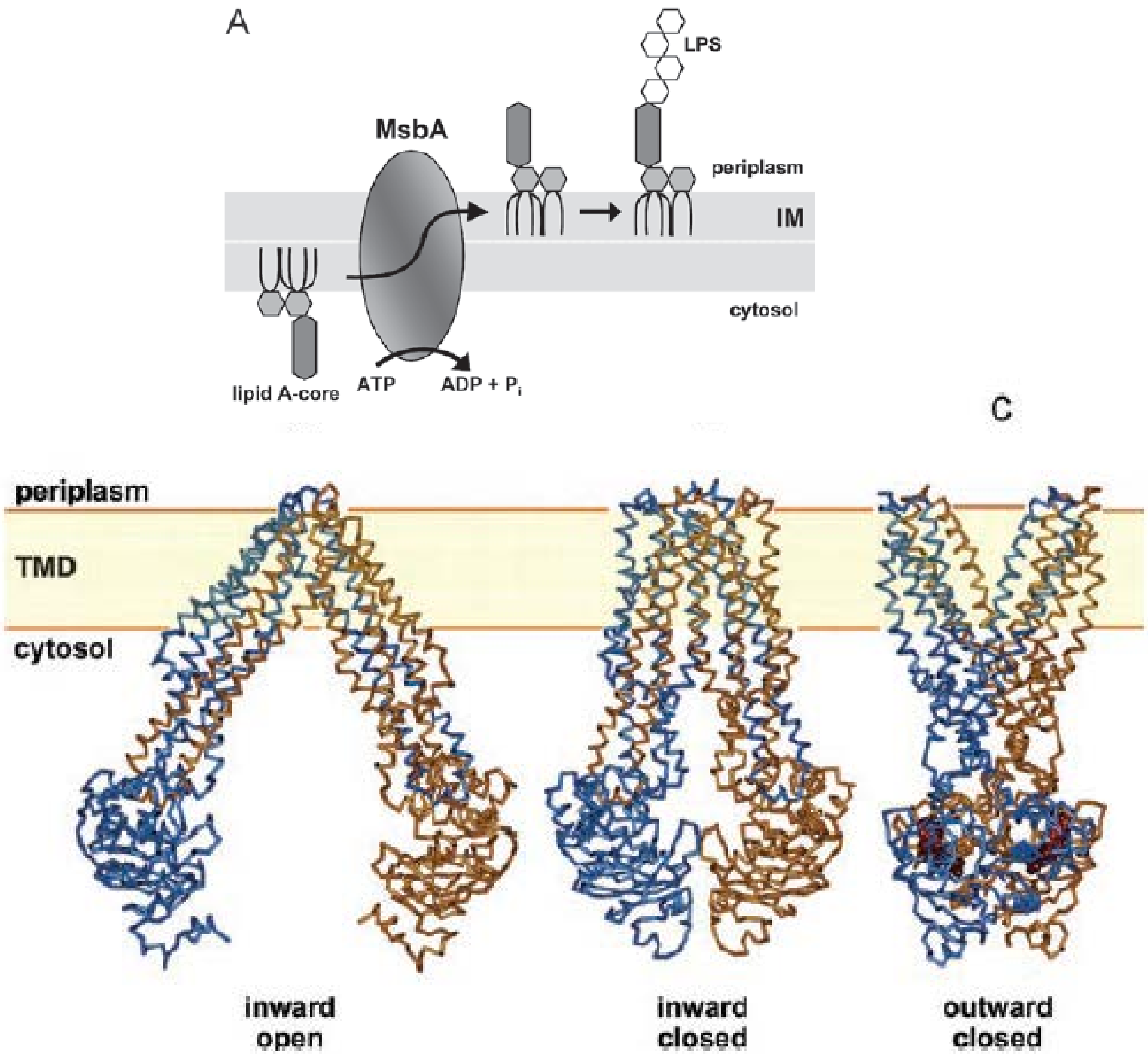
Membrane asymmetry is important for signaling, providing binding sites for specific proteins, and exocytosis.

Phospholipid Flipases Speed Transverse Diffusion in the Membrane



Pomorski and Menon Cell. Mol. Life Sci. 2006.

Example Flippase from Gram-negative Bacteria: MsbA



Thought to help move lipopolysaccharide across bacterial inner membrane, controversial.

King and Sharom, Critical Rev. Biochem. 2012

Biological Membranes are Not Homogeneous: Lipid Rafts

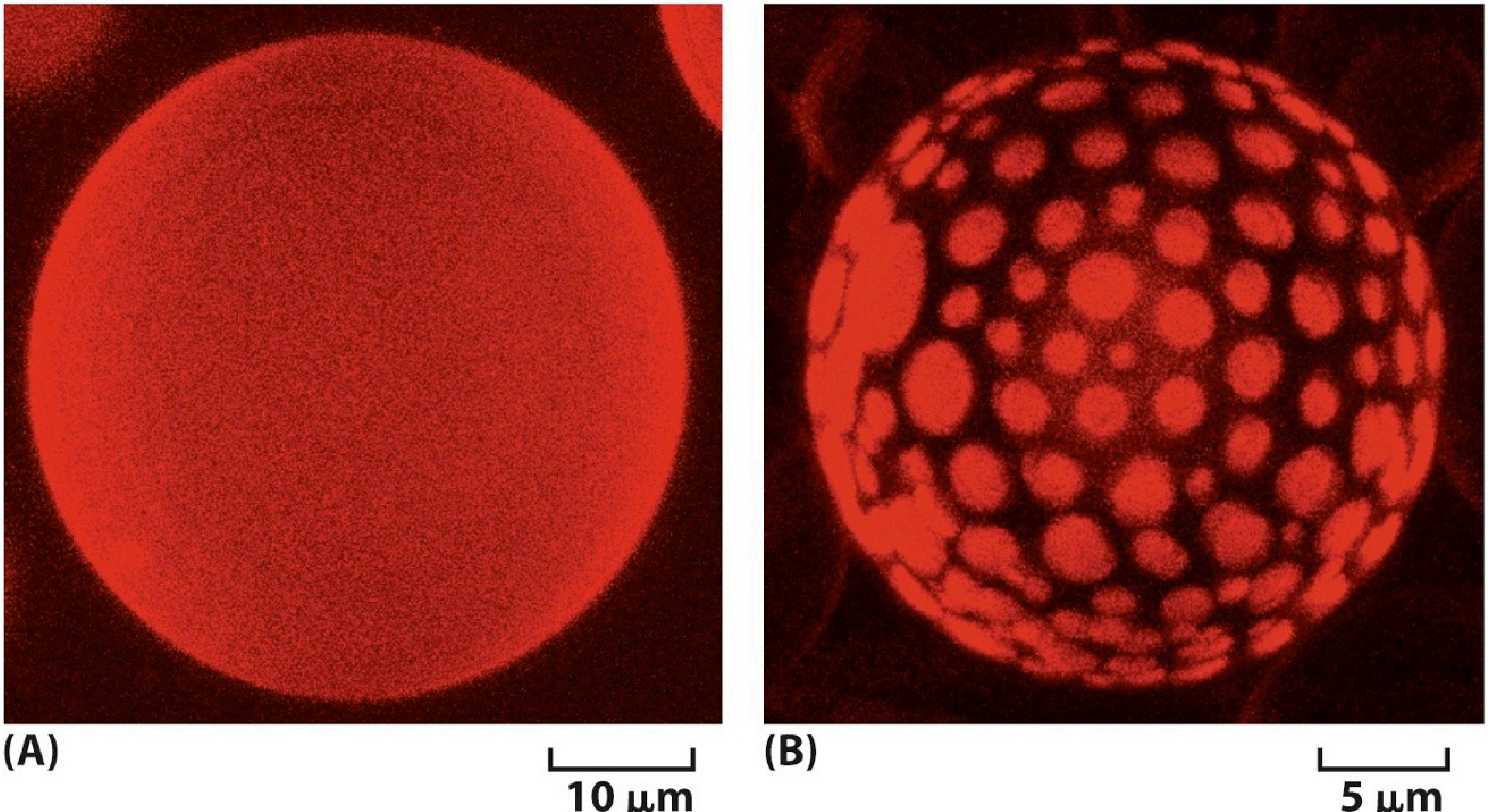
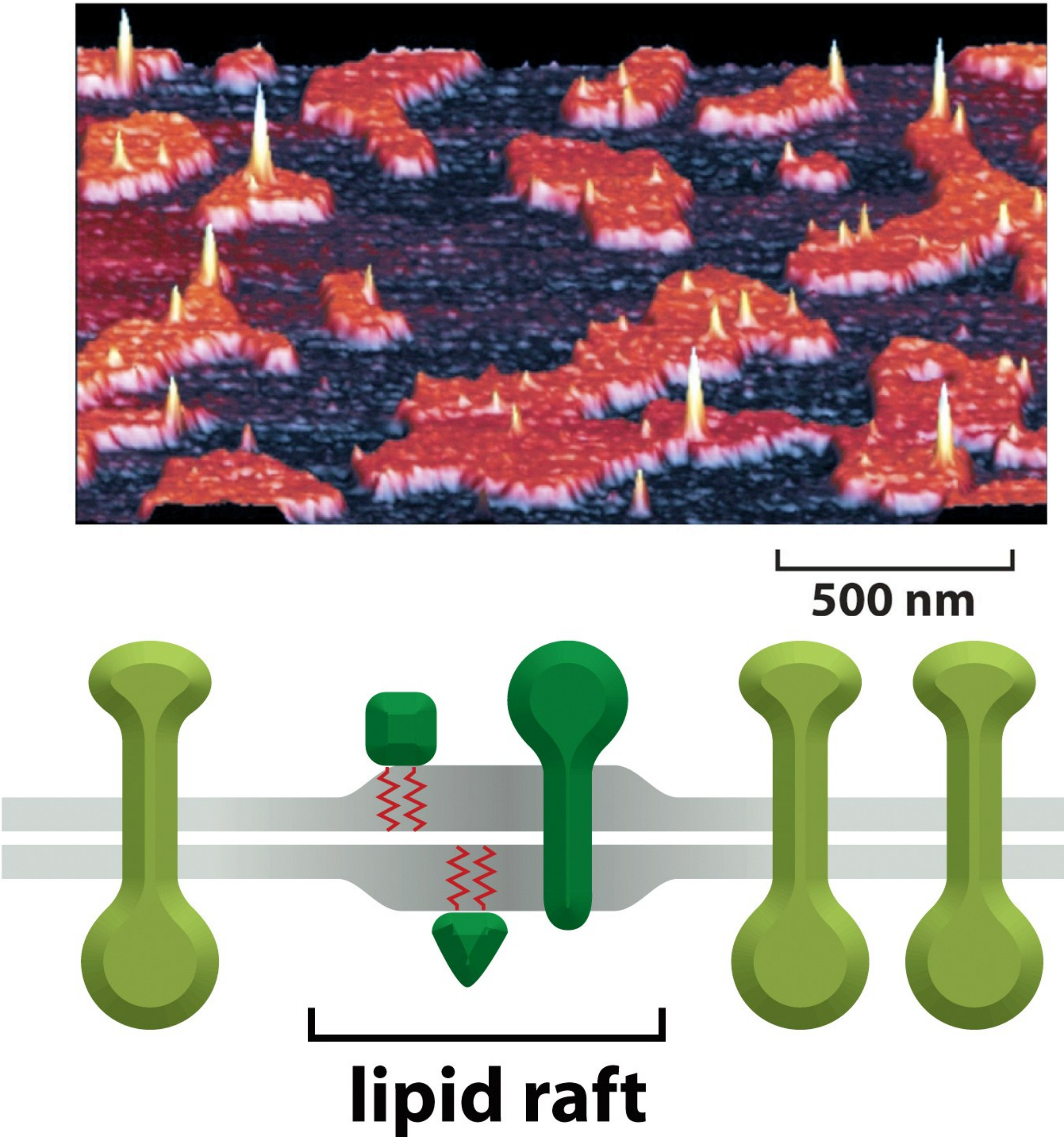


Figure 10-13 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Left: liposomes made from 1:1 phosphatidylcholine and spingomyelin are homogeneous. Right: liposomes made from 1:1:1 phosphatidylcholine, spingomyelin and cholesterol form immiscible phases. The dye preferentially partitions into one of the phases.

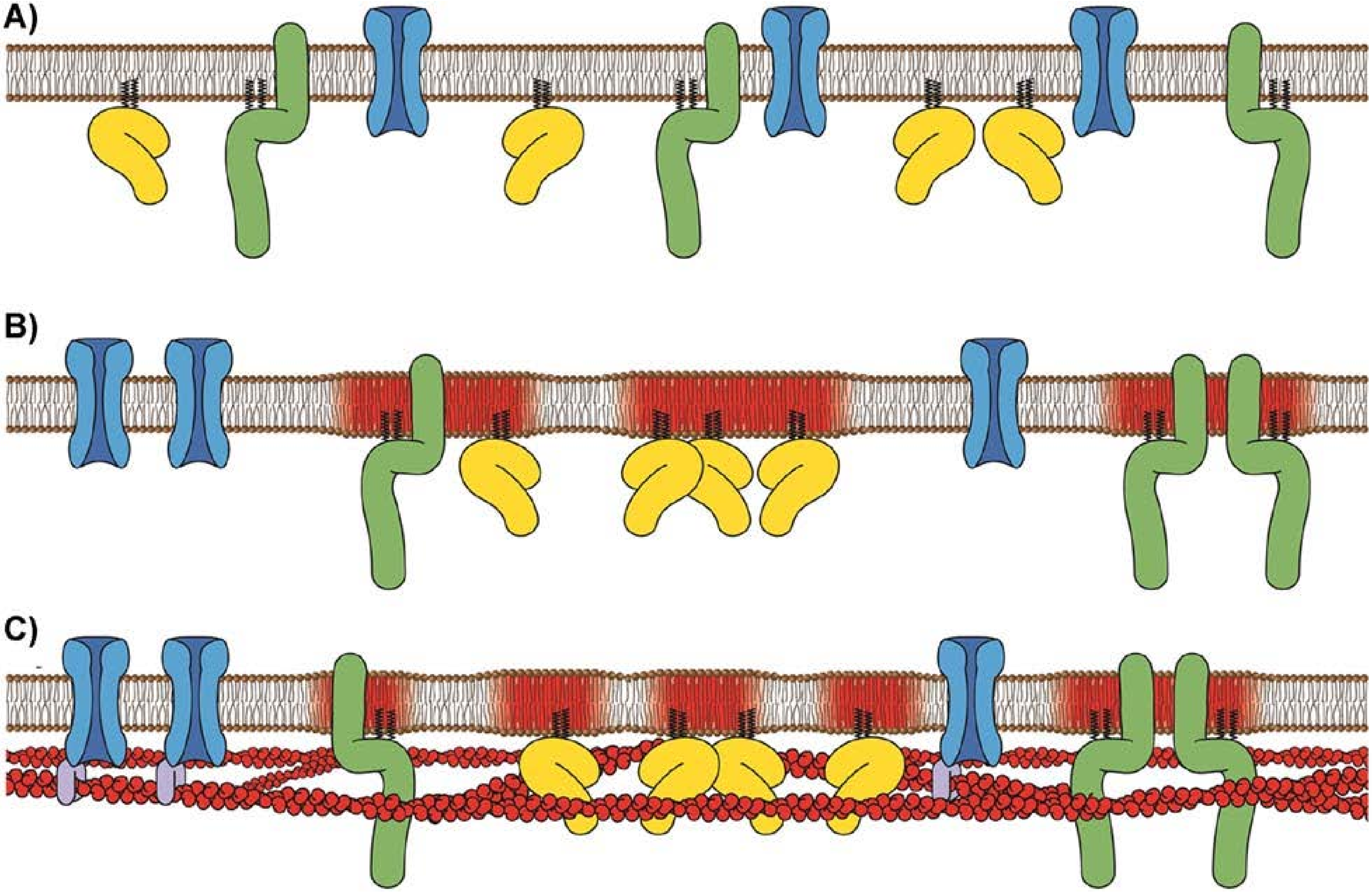
Biological Membranes are Not Homogeneous: Lipid Rafts



Lipid raft areas are thicker than the rest of the bilayer, as they are made of cholesterol and spingomyelin. An AFM image shows the surface of the rafts. Yellow is protein molecules, which rafts are thought to concentrate.

Figure 10-14b Molecular Biology of the Cell 5/e ()

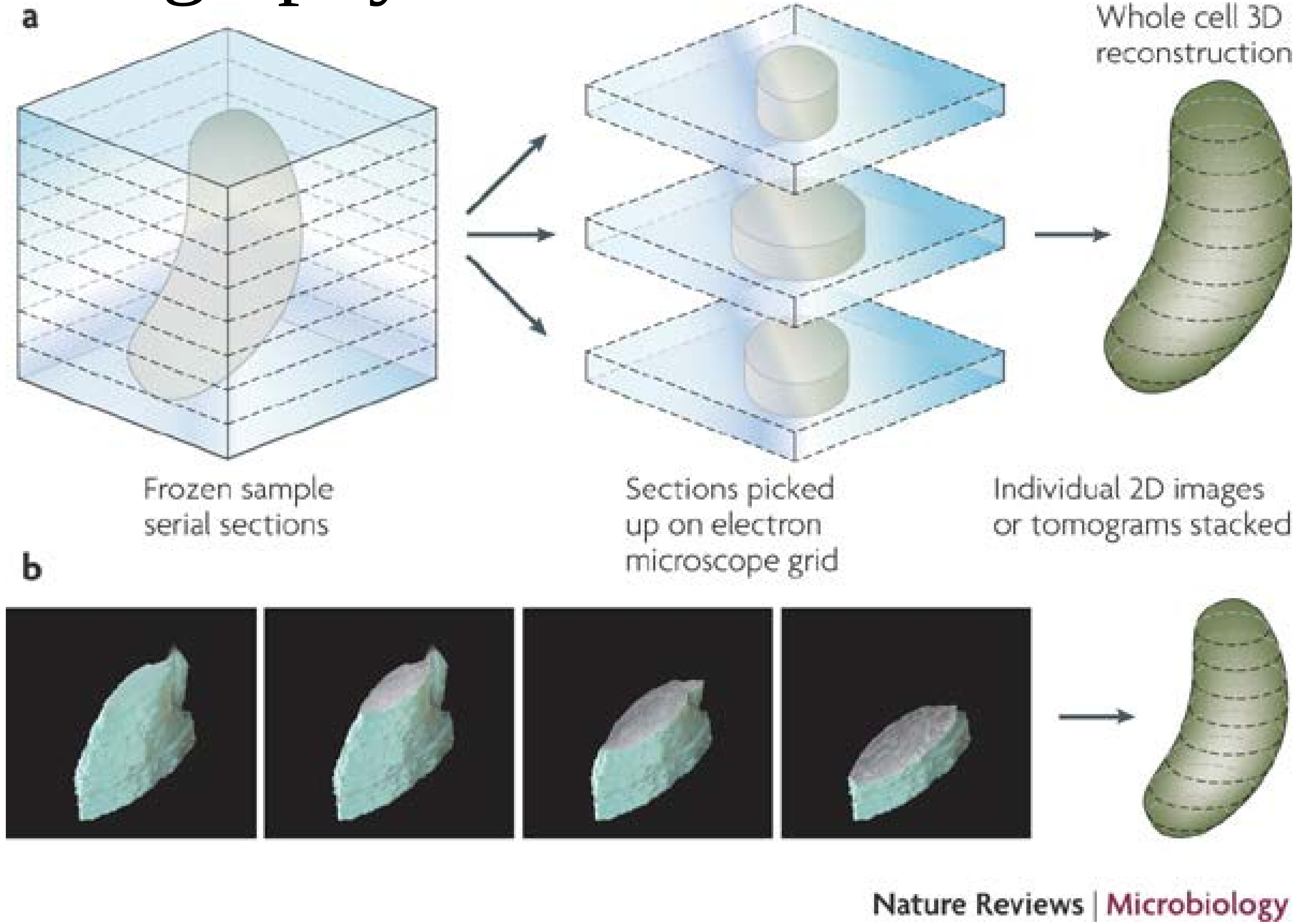
Biological Membranes are Inhomogeneous: Lipid Rafts



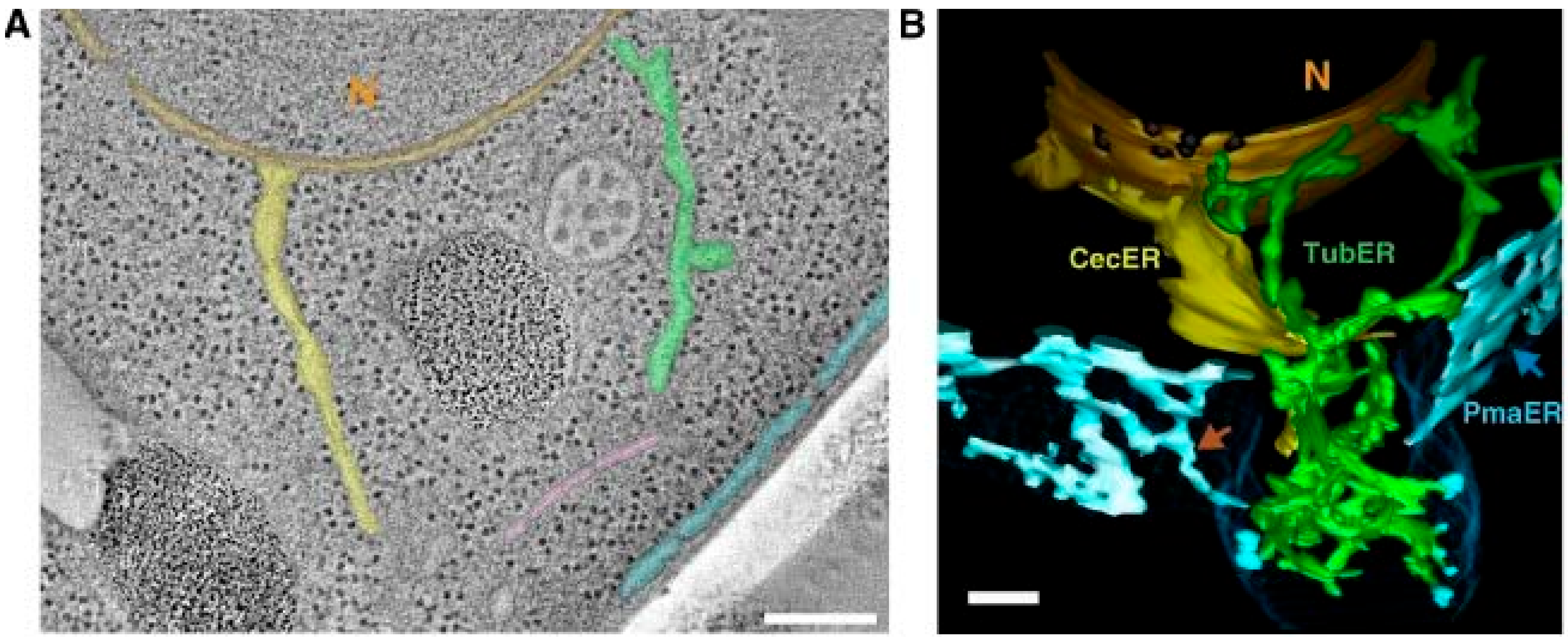
Owen et al., Bioessays 2012

Phospholipids in the Cells: Visualizing Cellular Membranes

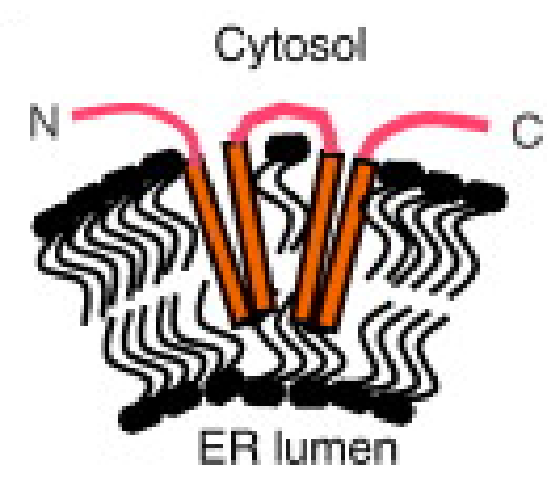
Tomography of cellular membranes



Using Tomography to Determine How Reticulons Shape the ER



From: West et al., 2011 JCB: A 3D analysis of yeast ER structure reveals how ER domains are organized by membrane curvature



Tomography of WT ER

QuickTime™ and a
decompressor
are needed to see this picture.

From: West et al., 2011 JCB

Tomography of Cells Lacking ER-shaping Proteins

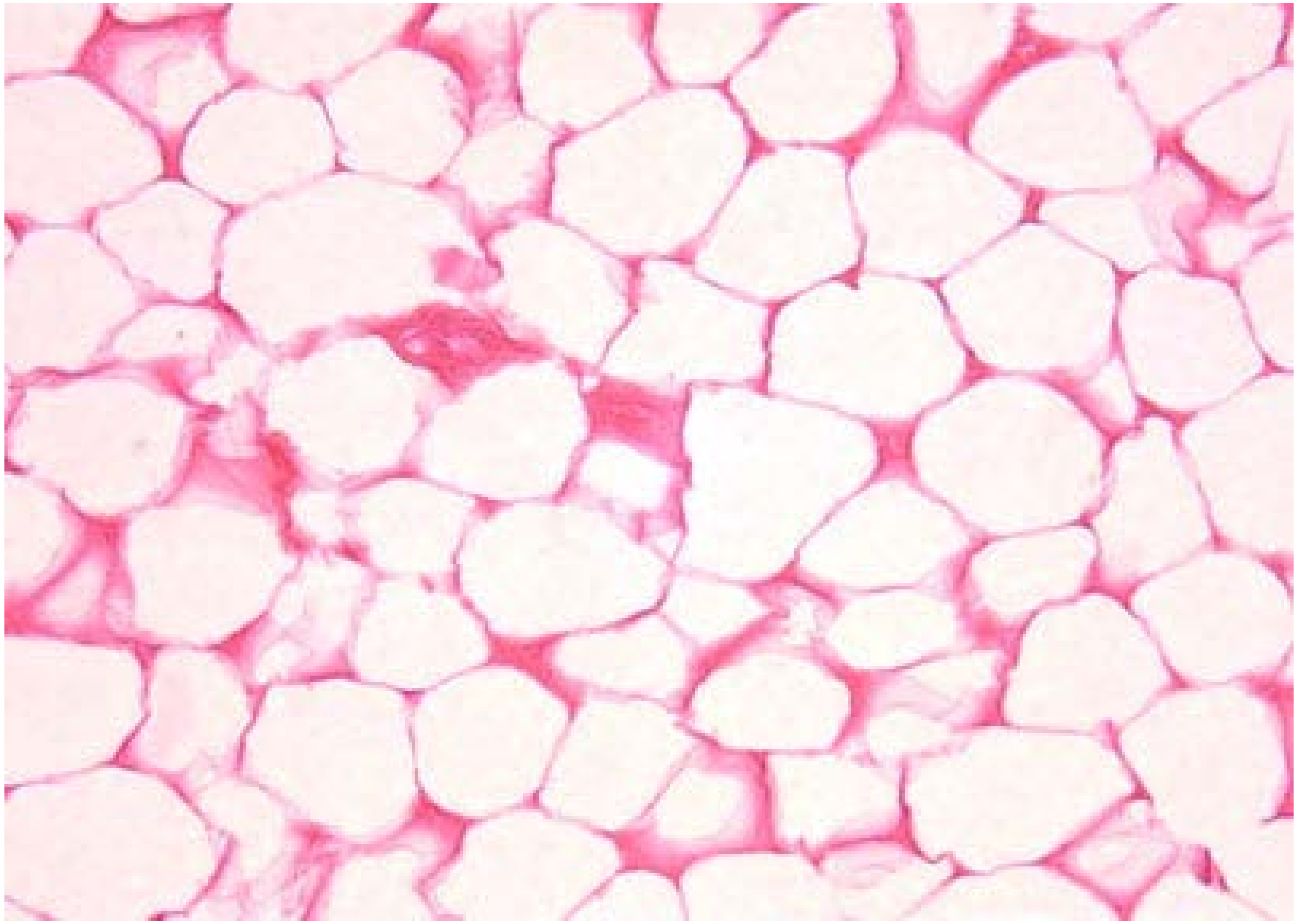
QuickTime™ and a
H.264 decompressor
are needed to see this picture.

- TubER
- CecER
- PmaER
- Golgi
- ~30 nm Vesicles
- ~60 nm Vesicles
- Nuclear Envelope

From: West et al., 2011 JCB

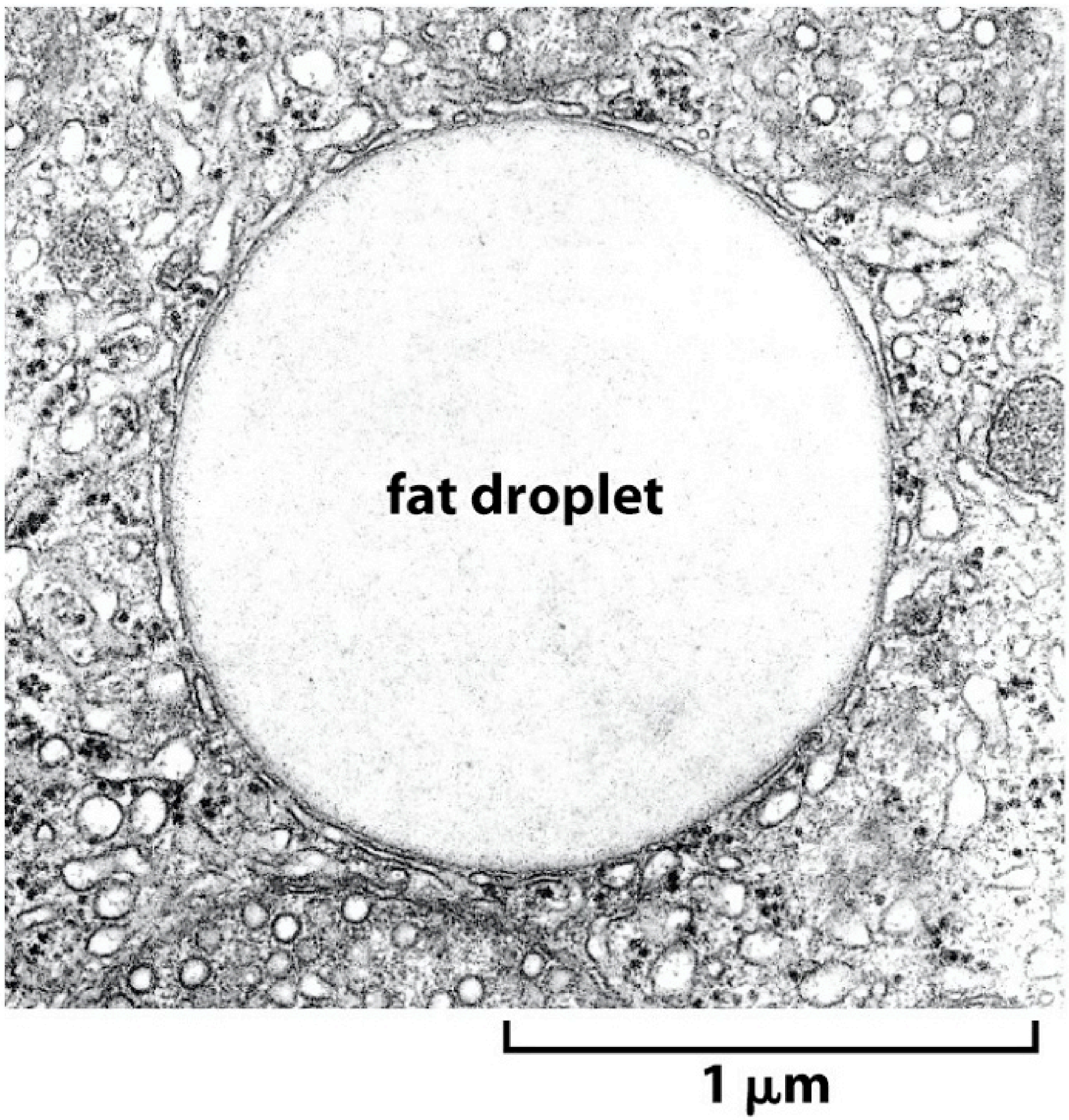
Triacylglycerides in the Cell: Lipid Storage

Using Fats Stores



Adipocytes are professional fat storage cells, and lipid droplets can occupy the majority of the cytoplasm.

Triacylglycerols are Stored in Lipid Droplets



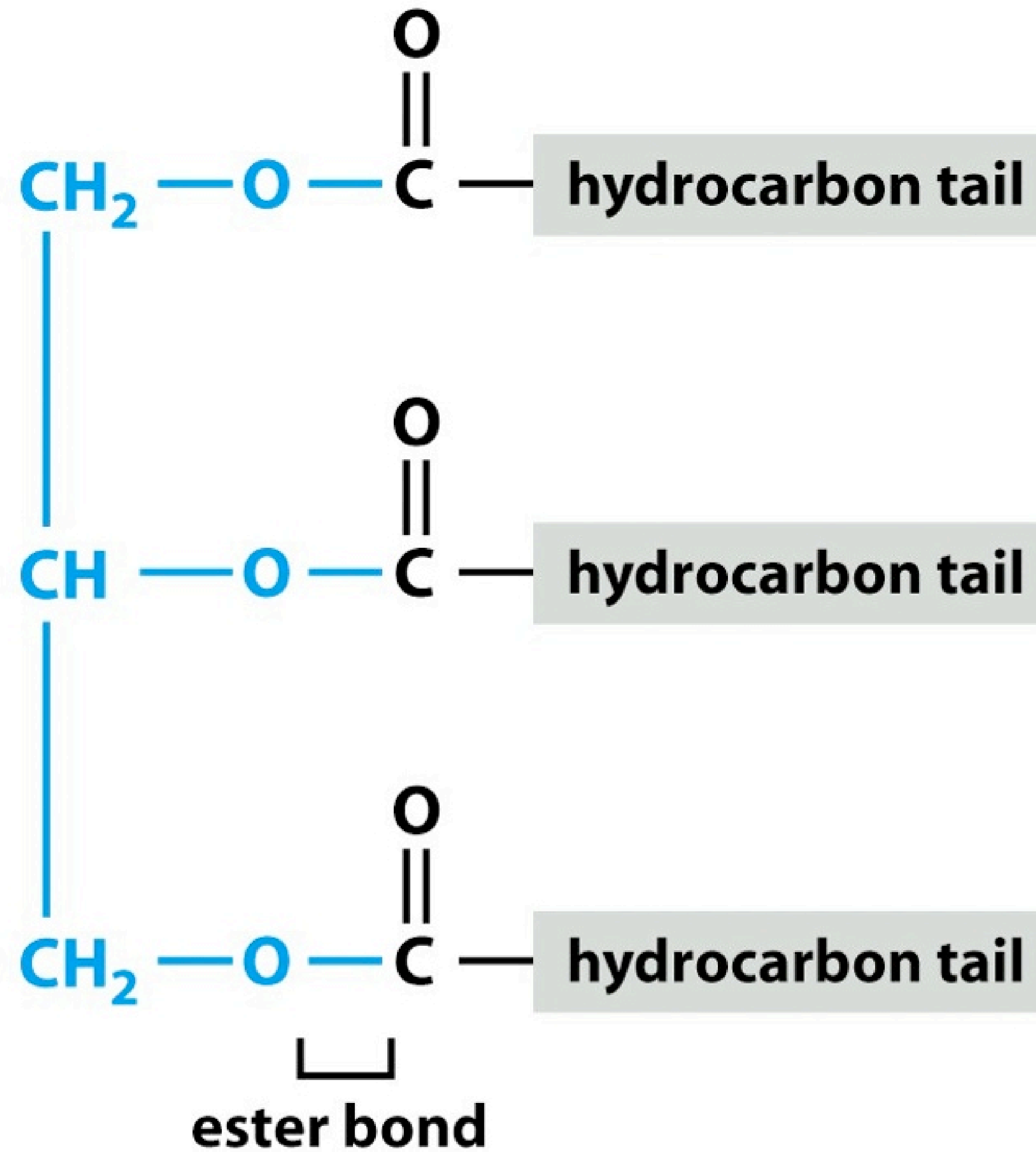
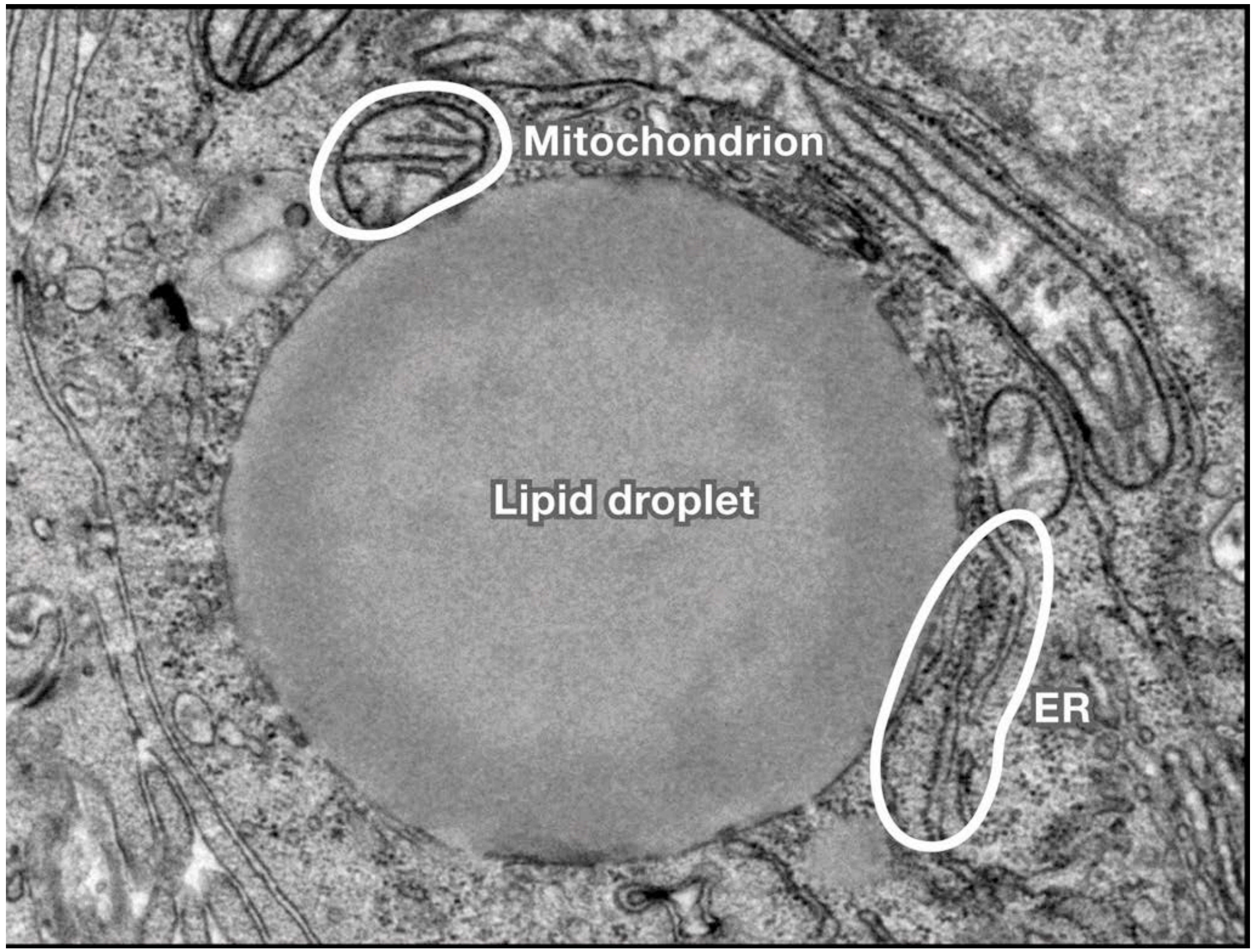


Figure 2-81a Molecular Biology of the Cell 5/e (© Garland Science 2008)

Lipid Droplets are Dynamic Organelles



Lipid droplets:

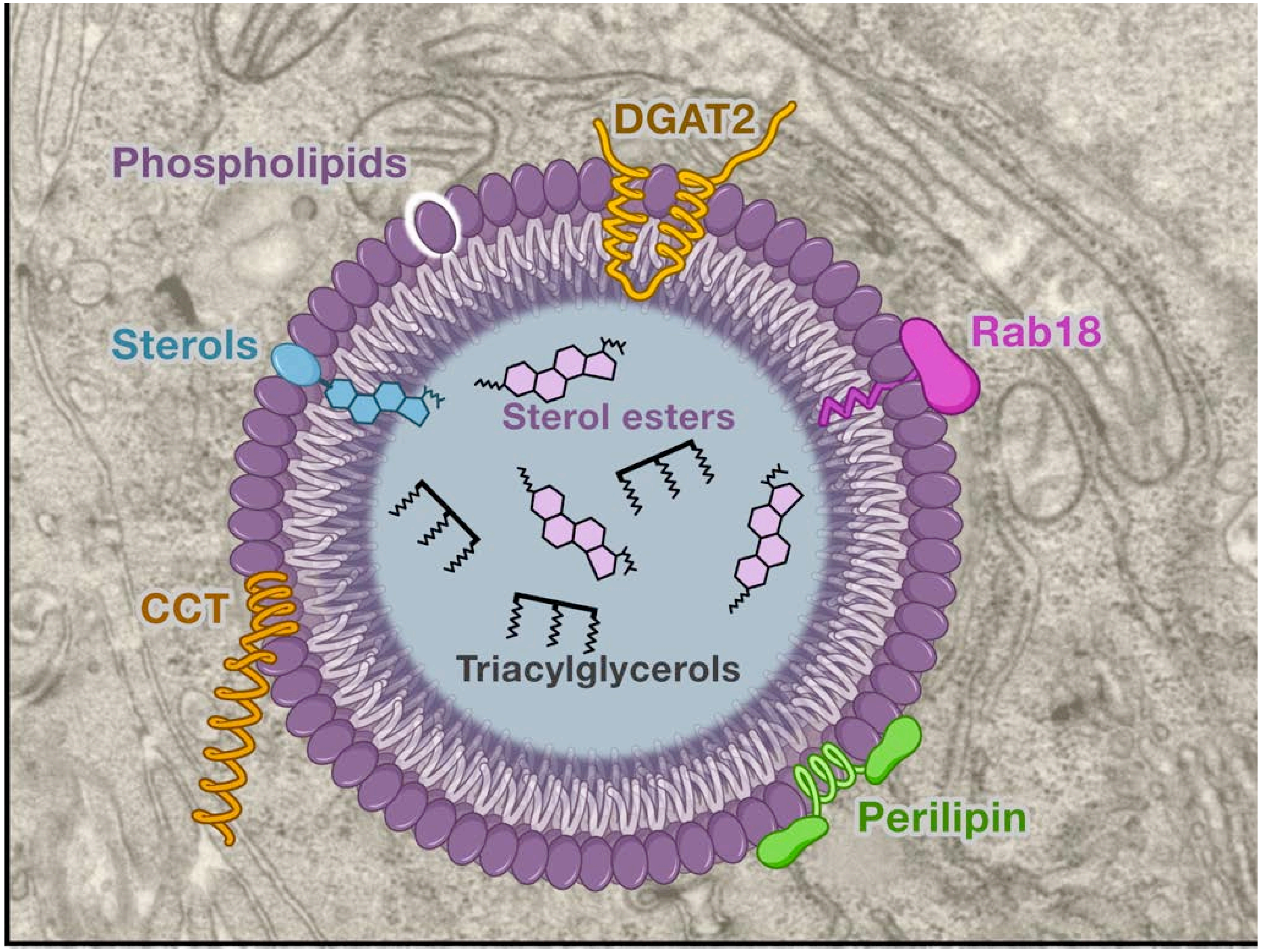
-Store energy in the form of triacylglycerides.

-Are a repository for the building blocks of biological membranes

-Compartmentalize lipids to buffer cells from the toxic effects of excessive lipids.

From Farese and Walther, Cell, 2009

What's in a lipid droplet?



-Polar lipids at the surface (phospholipids and sterols)
-Neutral lipids at the core
-Proteins on the surface including perilipin, lipid synthesizing enzymes, membrane-trafficking proteins and lipases

From Farese and Walther, Cell, 2009

Outline:

1) Classification and Properties of Lipids

2) Biological Functions of Lipids

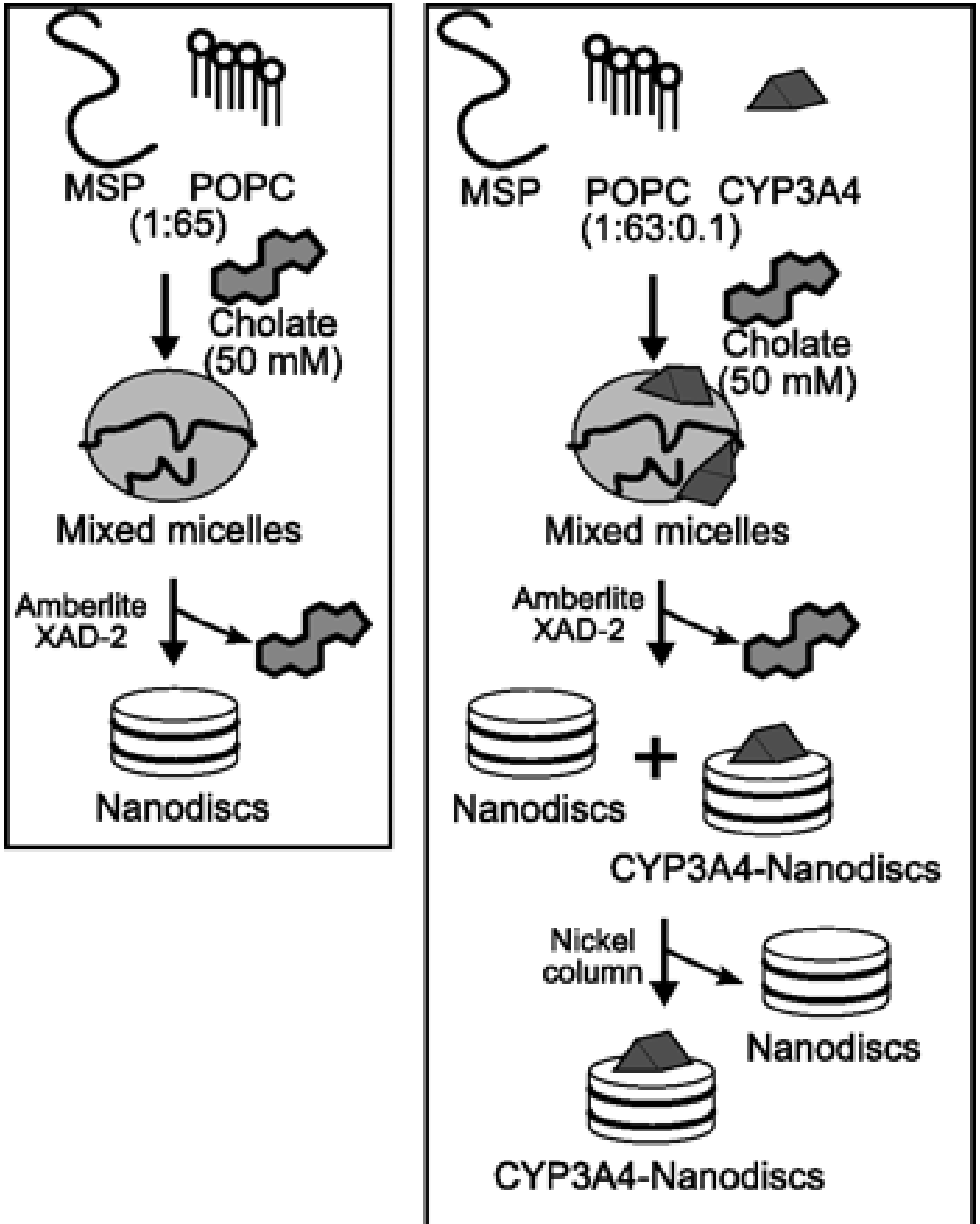
3) Lipids in Bioscience

Artificial membrane systems

For biochemical studies of membranes/membrane proteins, membrane mimetics include:

- -nanodiscs
- -bicelles
- -micelles
- -unilaminar vesicles

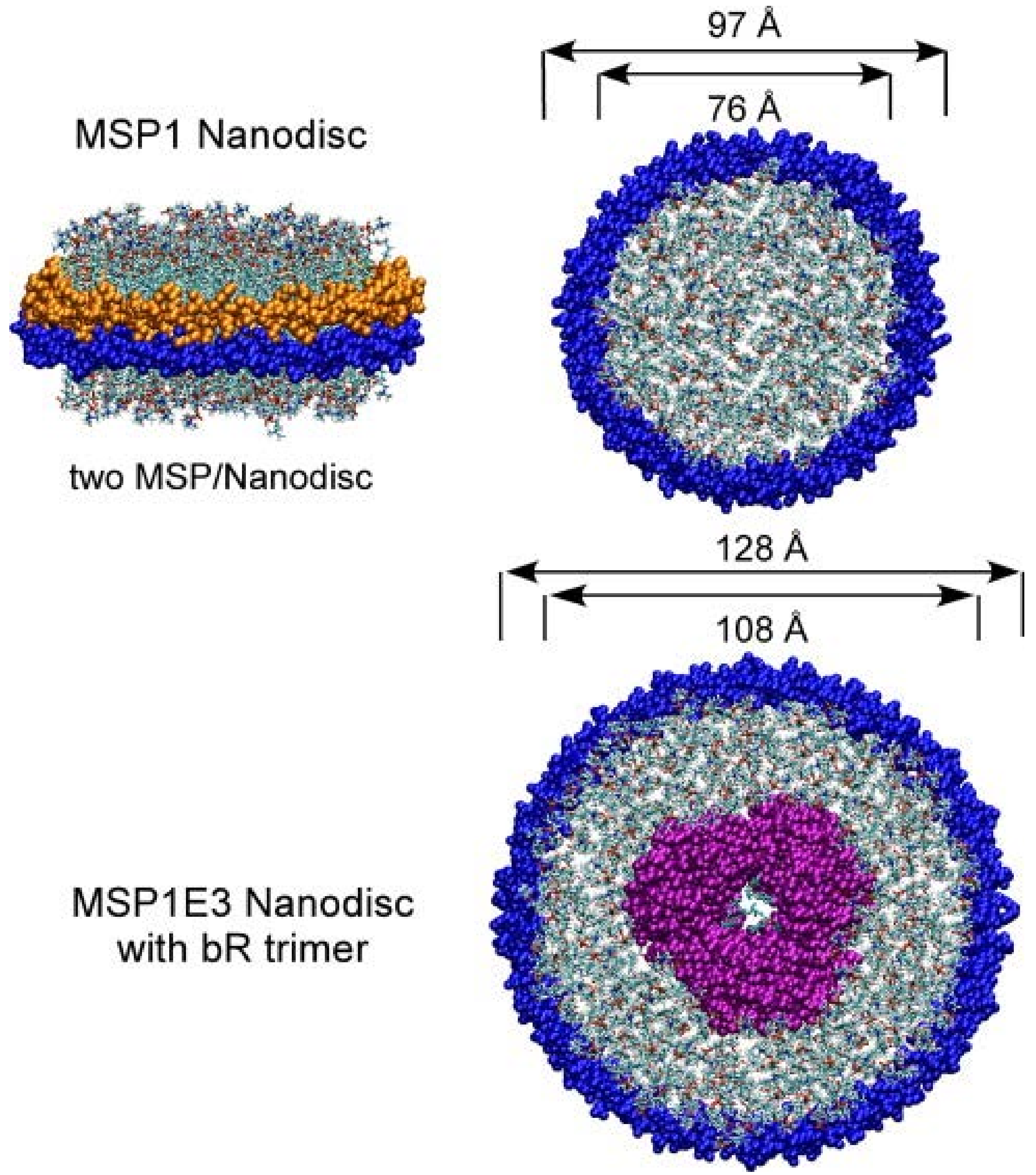
Artificial membrane systems: Nanodiscs



Nanodiscs allow incorporation of a membrane protein into an artificial lipid bilayer of defined size.

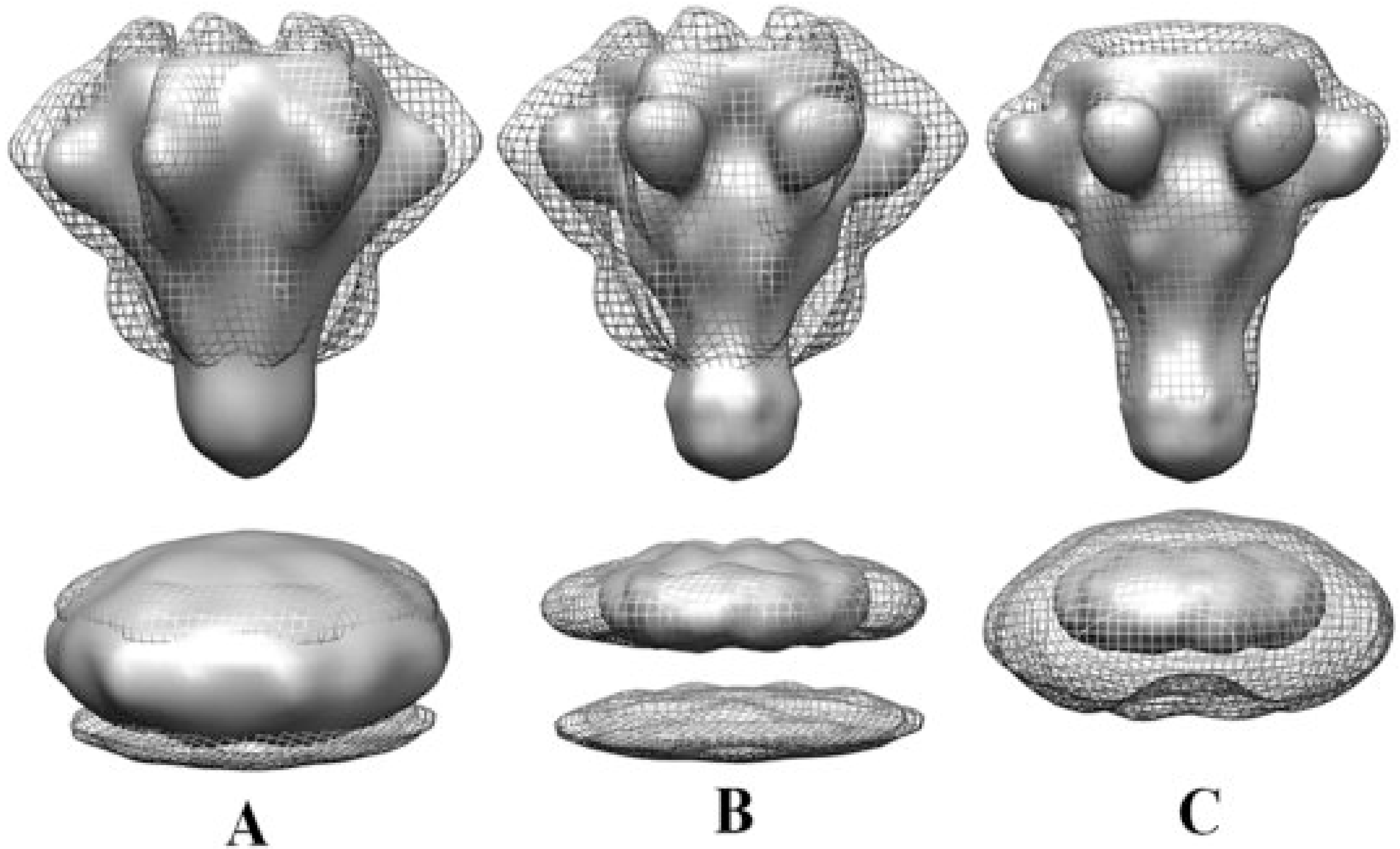
Jath et al., JBC 2007

Artificial Membrane Systems: Nanodiscs



Bayburt TH and Sligar SG, FEBS Letters, 2010.

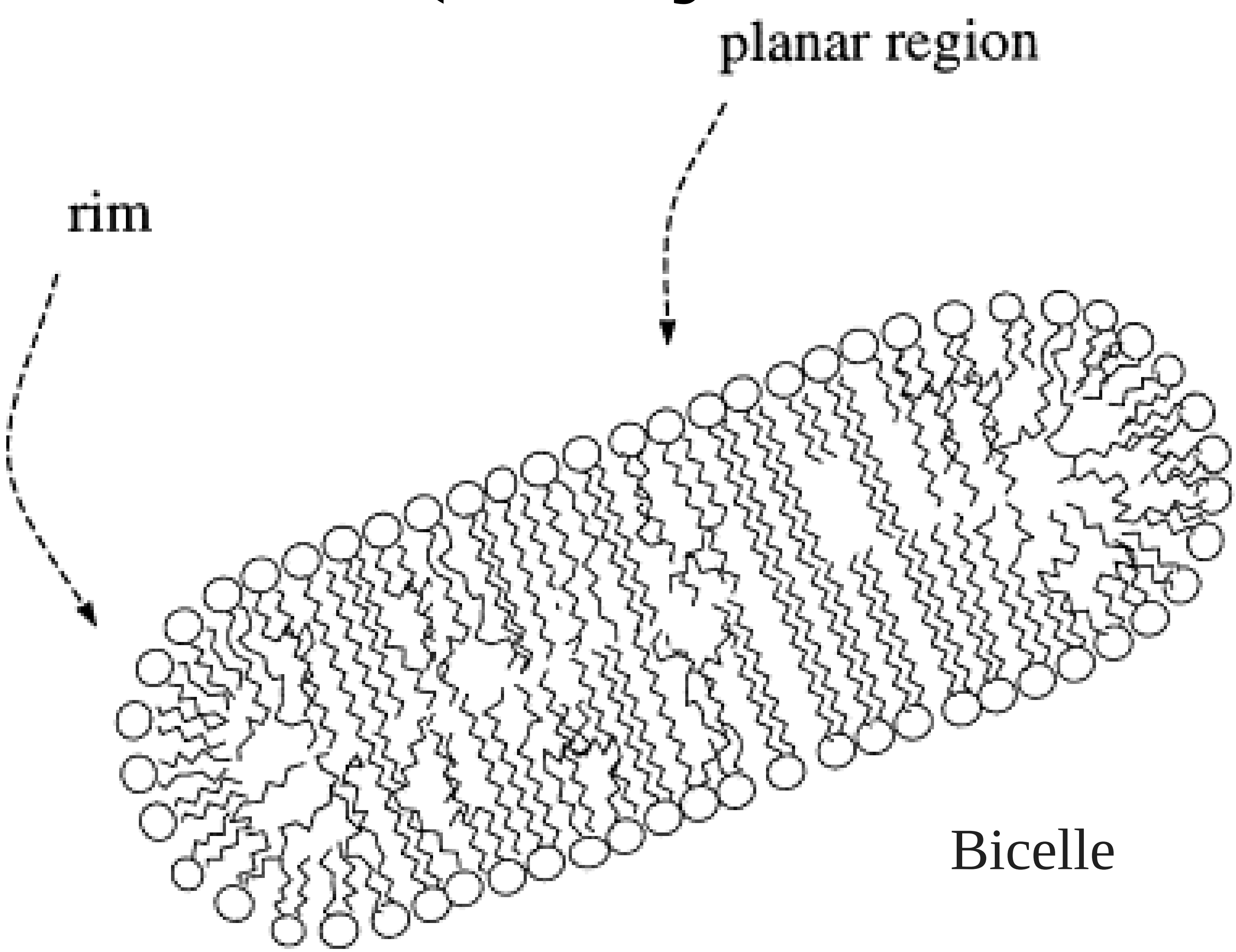
Applications of Nanodics: Anthrax Toxin Translocon



The protective antigen (PA) component of anthrax toxin forms a pore that delivers the two enzymatic components of the toxin to the cytosol of cells. Here, they solve a 16 A structure of the whole pore containing one of the enzymatic factors (Lethal factor N) using cryo-Em of nanodisc embedded PA.

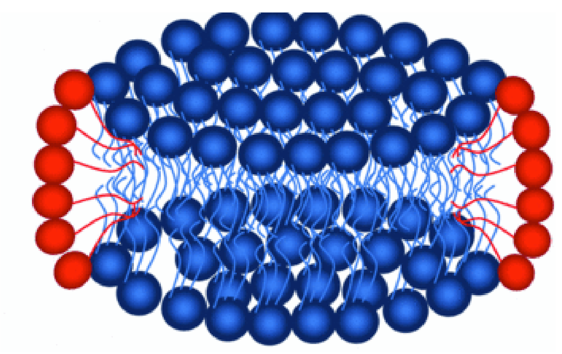
Gogol et. al., Protein Science 2013

Artificial Membrane Systems: Bicelles (Bilayered Micelles)

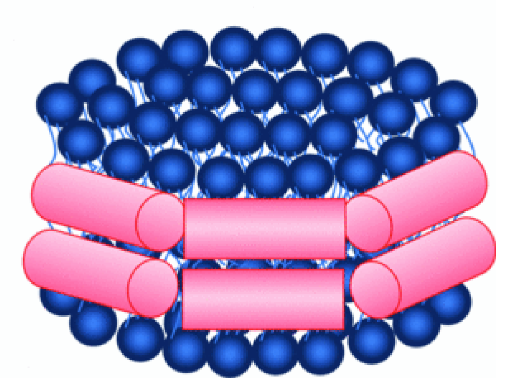


Bicelles: they are discoidal lipid aggregates composed of long-chain phospholipid and either detergent or short-chain phospholipid. They are useful for NMR studies and as substrates for lipolytic enzymes.

Bicelle



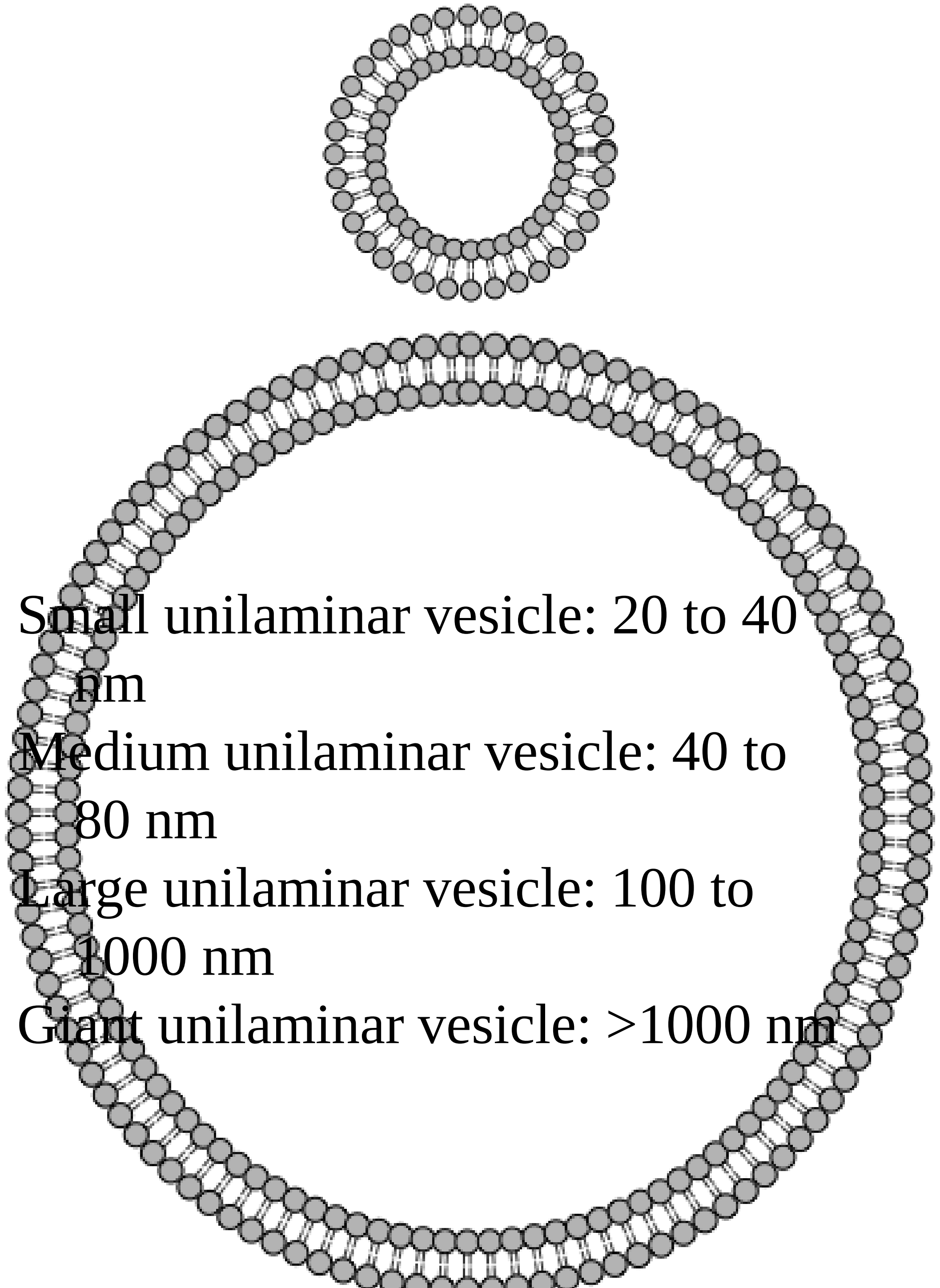
Nanodisc



Whiles et. al., Bioinorganic Chemistry 2002
Biochem society transactions

Artificial membrane systems: unilaminar vesicles

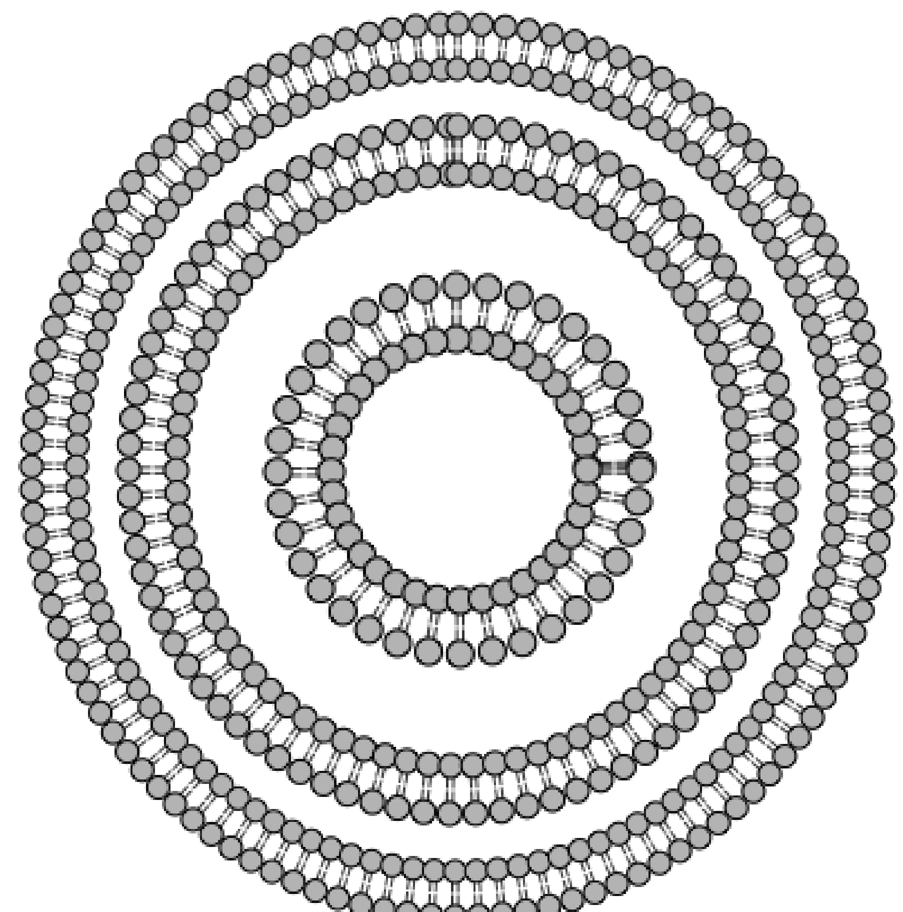
Unilaminar Vesicles



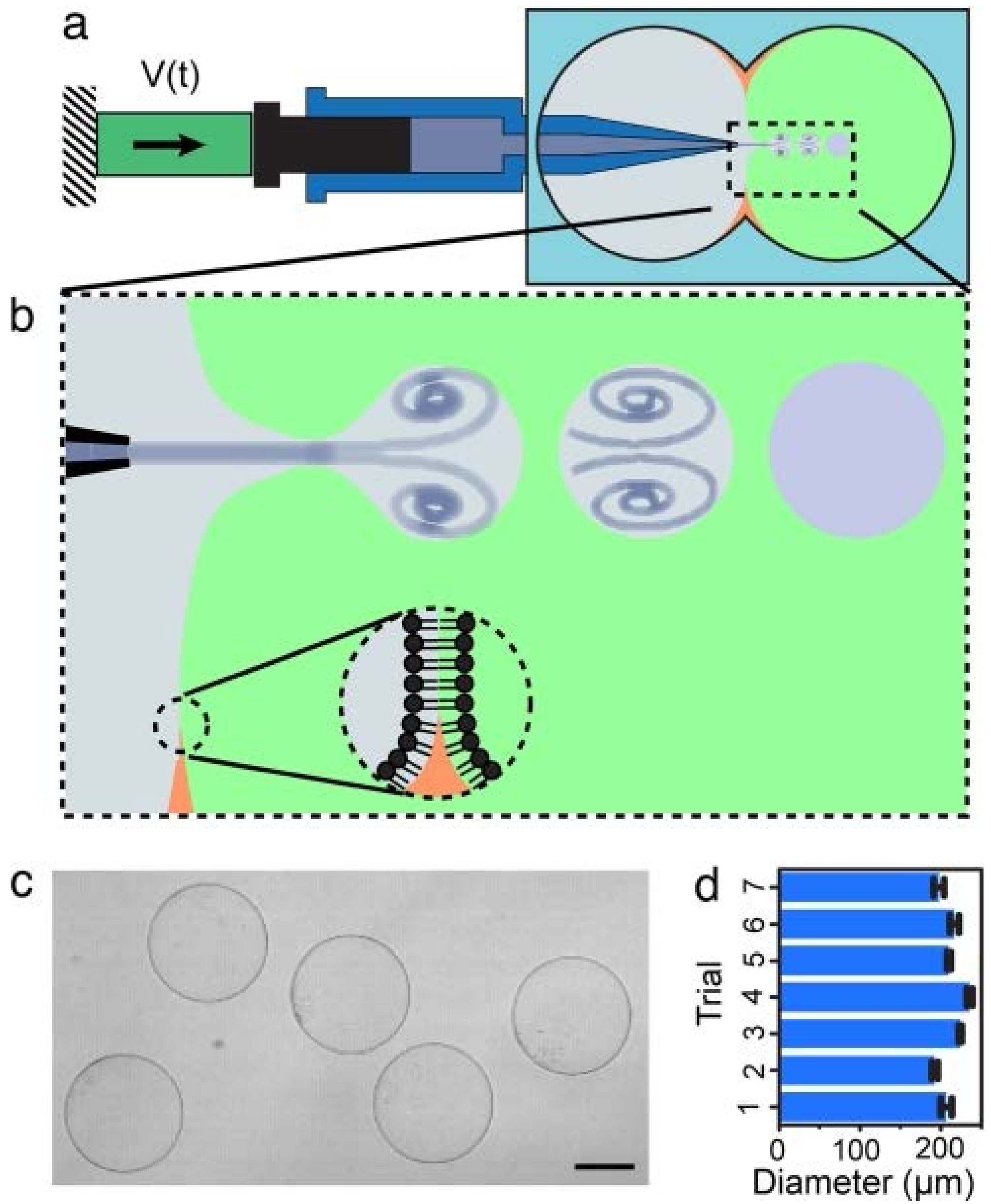
Small unilaminar vesicle: 20 to 40 nm
Medium unilaminar vesicle: 40 to 80 nm
Large unilaminar vesicle: 100 to 1000 nm
Giant unilaminar vesicle: >1000 nm

Useful for: chemical microreactors, delivery vehicles for pharmaceuticals, and platforms for synthetic biological systems

Multilaminar Vesicle



Microfluidics for Unilaminar Vesicles



Stachowiak et al., Proc Natl Acad Sci U S A. 2008

Microfluidics for Unilaminar Vesicles

QuickTime™ and a
Animation decompressor
are needed to see this picture.

Stachowiak et al., Proc Natl Acad Sci
U S A. 2008

For Wednesday:

Download UCSF Chimera

http://www.cgl.ucsf.edu/chimera/download.html

or Pymol if you haven't already

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Read Van den Berg et al., Nature 2003