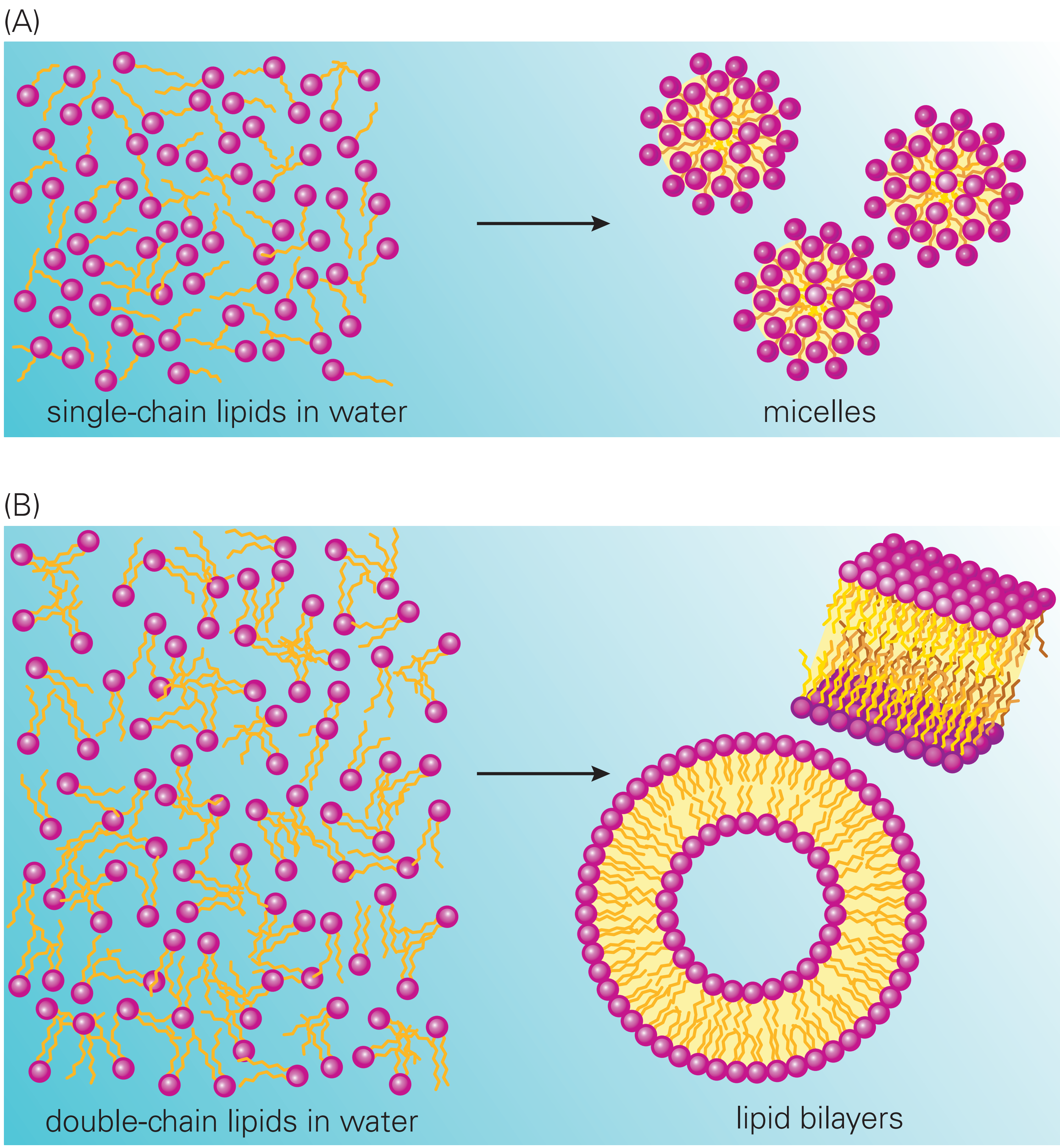
Today's class:

Glycans and lipids…*contd*

This lecture largely follows the chapter 3 in the book
'The Molecules of Life' by Kuriyan, Konforti & Wemmer, 1st Ed, 2013

Lipids and membranes

Lipids spontaneously phase separate in water



Lipids are insoluble in water as individual molecules

Why?

Lipid molecules have two parts

Hydrophilic head-group

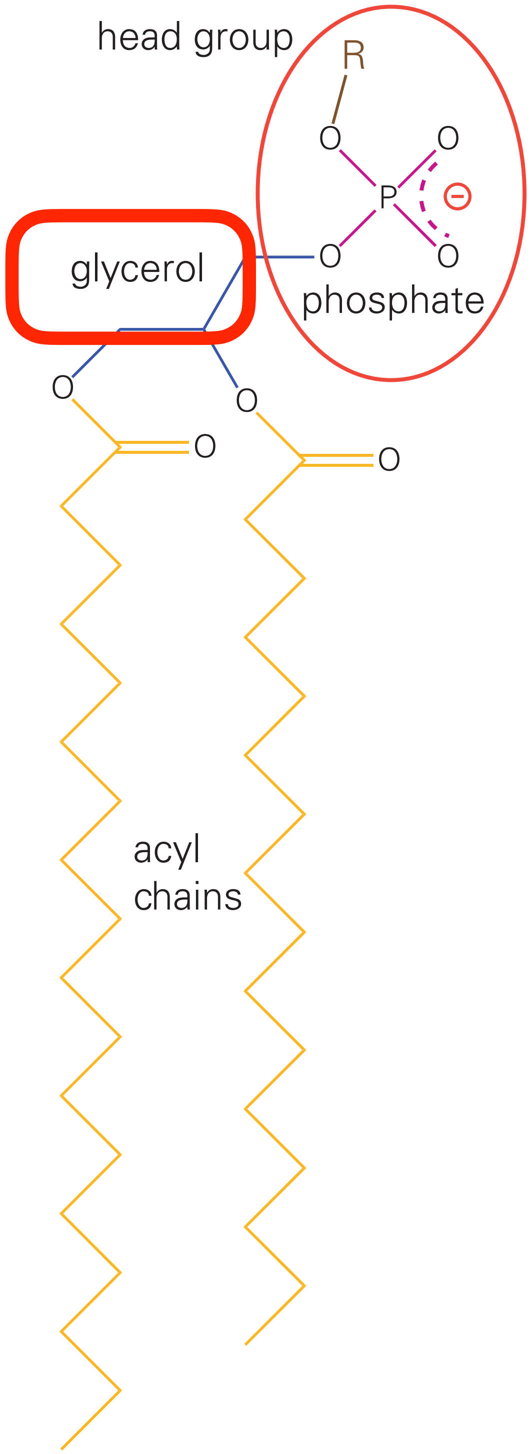
Hydrophobic part

Lipids are amphiphiles

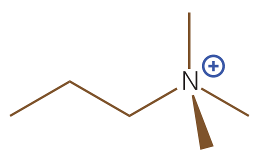
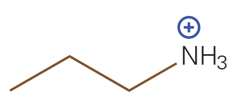
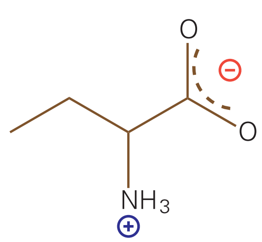
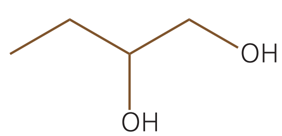
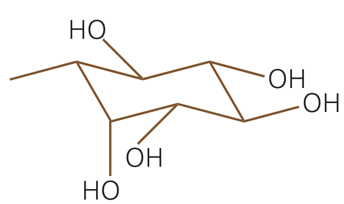
Amphiphiles hide their hydrophobic parts through phase separation

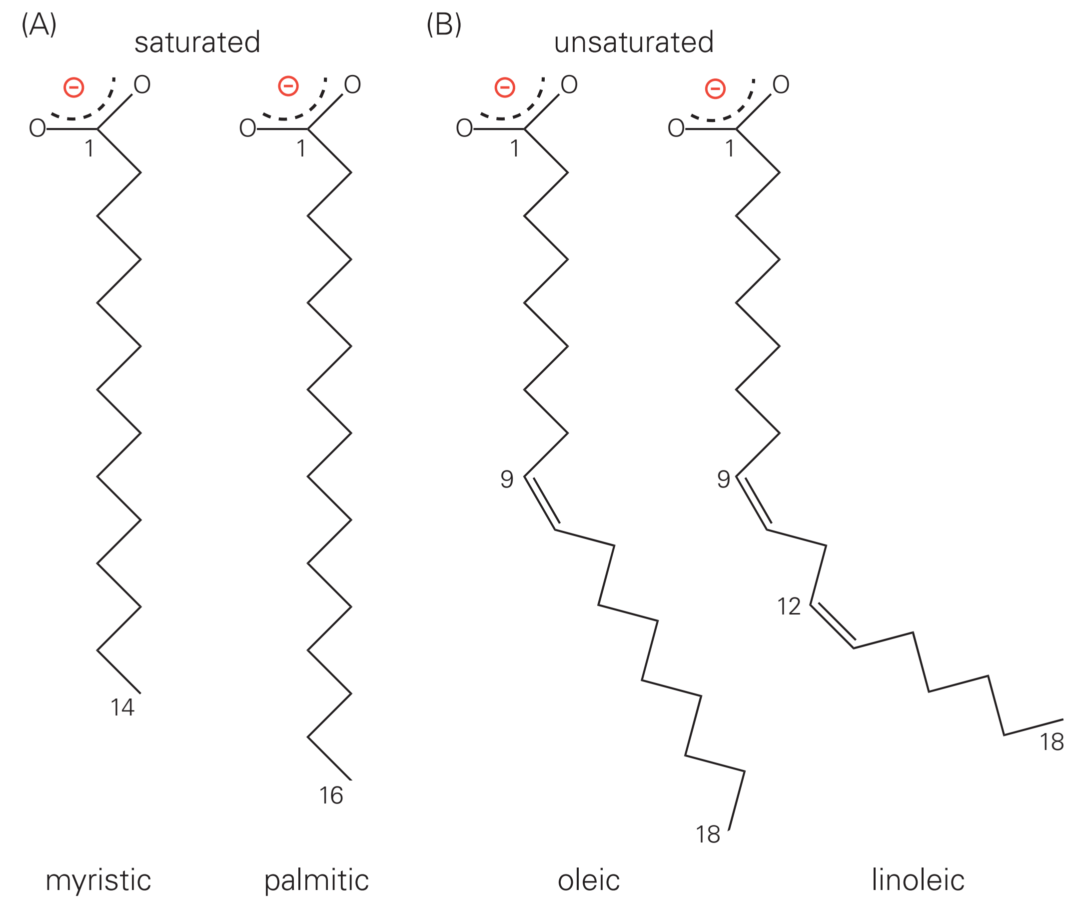
The most abundant lipids are glycerophospholipids

Diacylglycerol Phospholipid



Length ~ C12-C24

head group	substituent name (Name of the lipid)	charge on the lipid
—R =		
	choline (phosphatidylcholine)	neutral
	ethanolamine (phosphatidylethanolamine)	neutral
	serine (phosphatidylserine)	– 1
	glycerol (phosphatidylglycerol)	– 1
	inositol (phosphatidylinositol)	– 1



Naturally occurring fats contain unsaturation mostly in form of *cis*-double bonds

Consumption of artificial fats with *trans*-double bonds is a health risk!

Why?

Lipids with *trans*-double bonds reduce membrane fluidity and also deposit on other membranes of organs in body

Knowing other lipids: sphingolipids

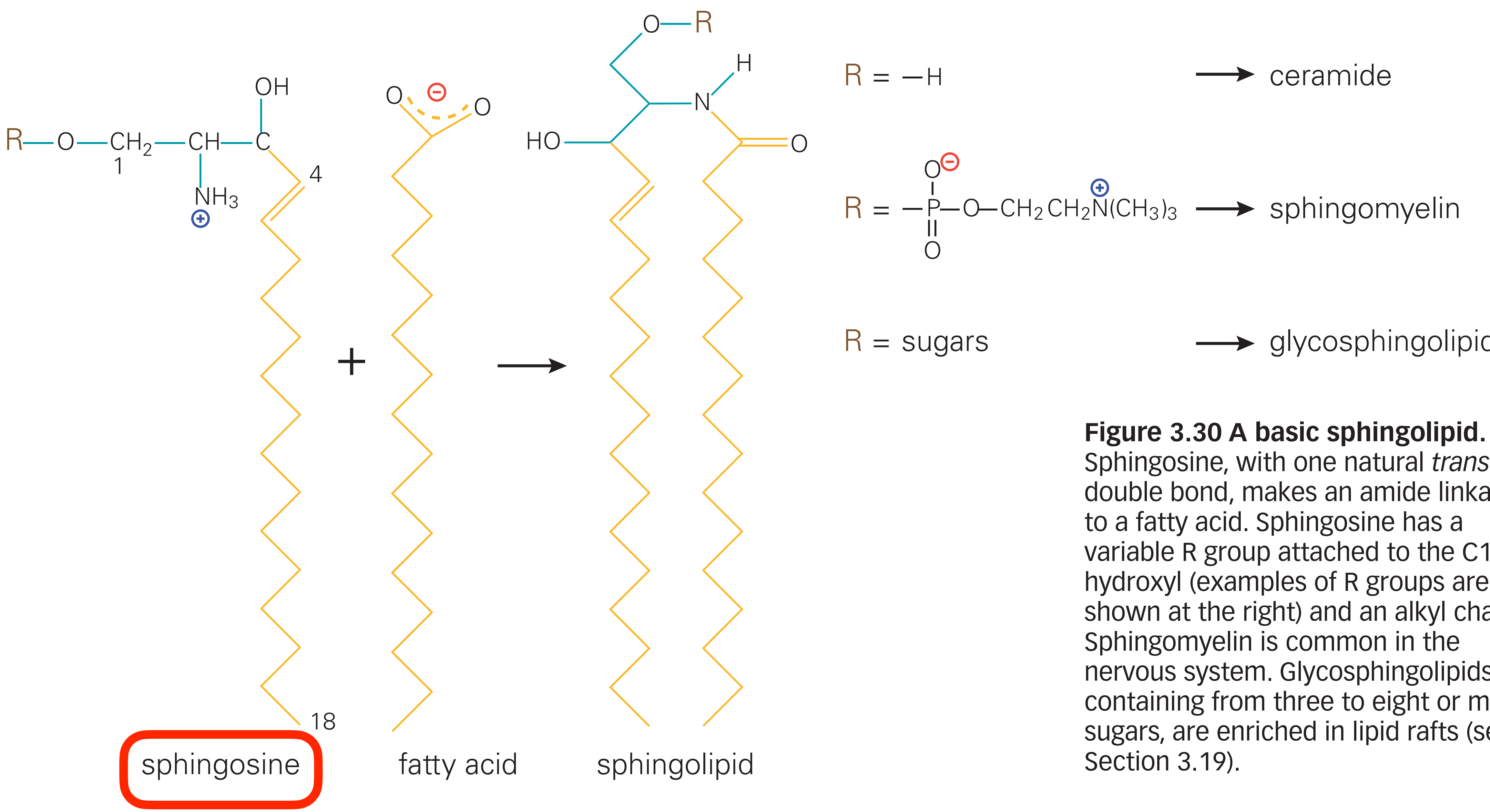


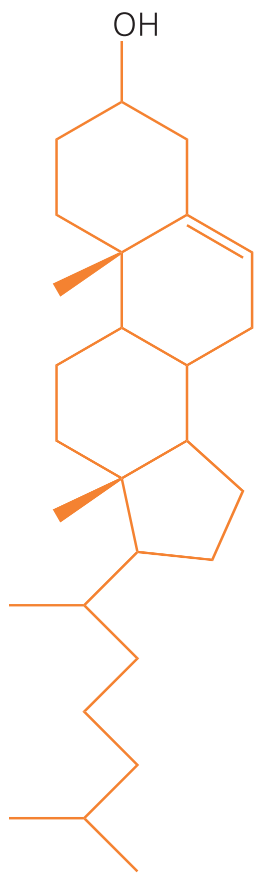
Figure 3.30 A basic sphingolipid. Sphingosine, with one natural *trans* double bond, makes an amide linkage to a fatty acid. Sphingosine has a variable R group attached to the C1 hydroxyl (examples of R groups are shown at the right) and an alkyl chain. Sphingomyelin is common in the nervous system. Glycosphingolipids, containing from three to eight or more sugars, are enriched in lipid rafts (see Section 3.19).

Cerebrosides = sphingolipids with one sugar
Gangliosides = sphingolipids with 3-8 sugars

Cerebrosides first discovered in brain tissue with a concentration of 5% of membrane lipids

Knowing other lipids: cholesterol & co.

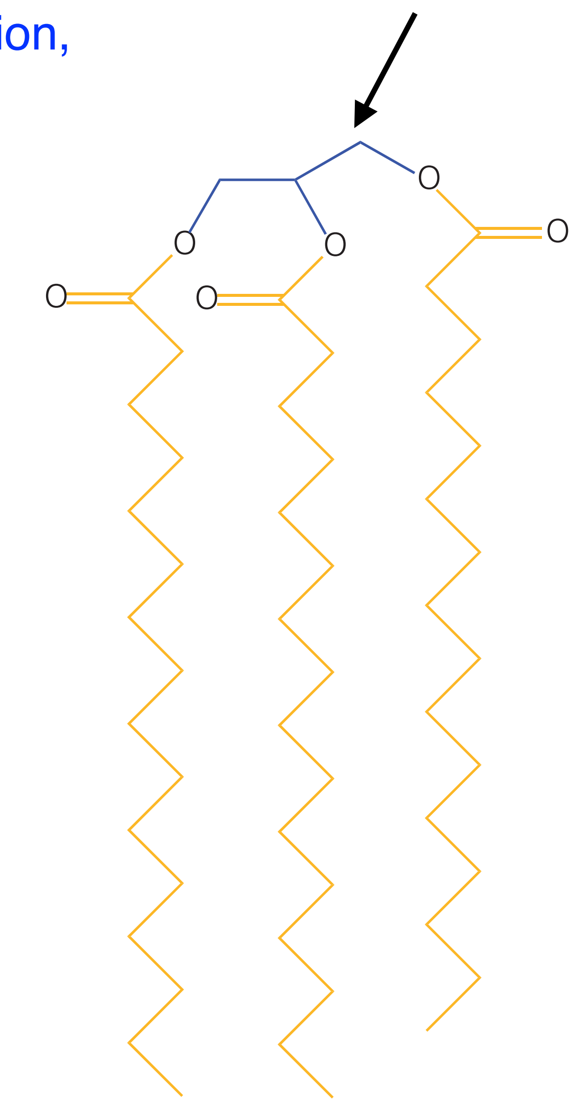
The rigid core of cholesterol packs against alkyl chains of neighboring lipids, reducing their flexibility. This stiffens the membrane against distortion, while retaining fluidity.



cholesterol

Cholesterol can also be modified into esters which are fully hydrophobic and gets into bloodstream as LDL particles

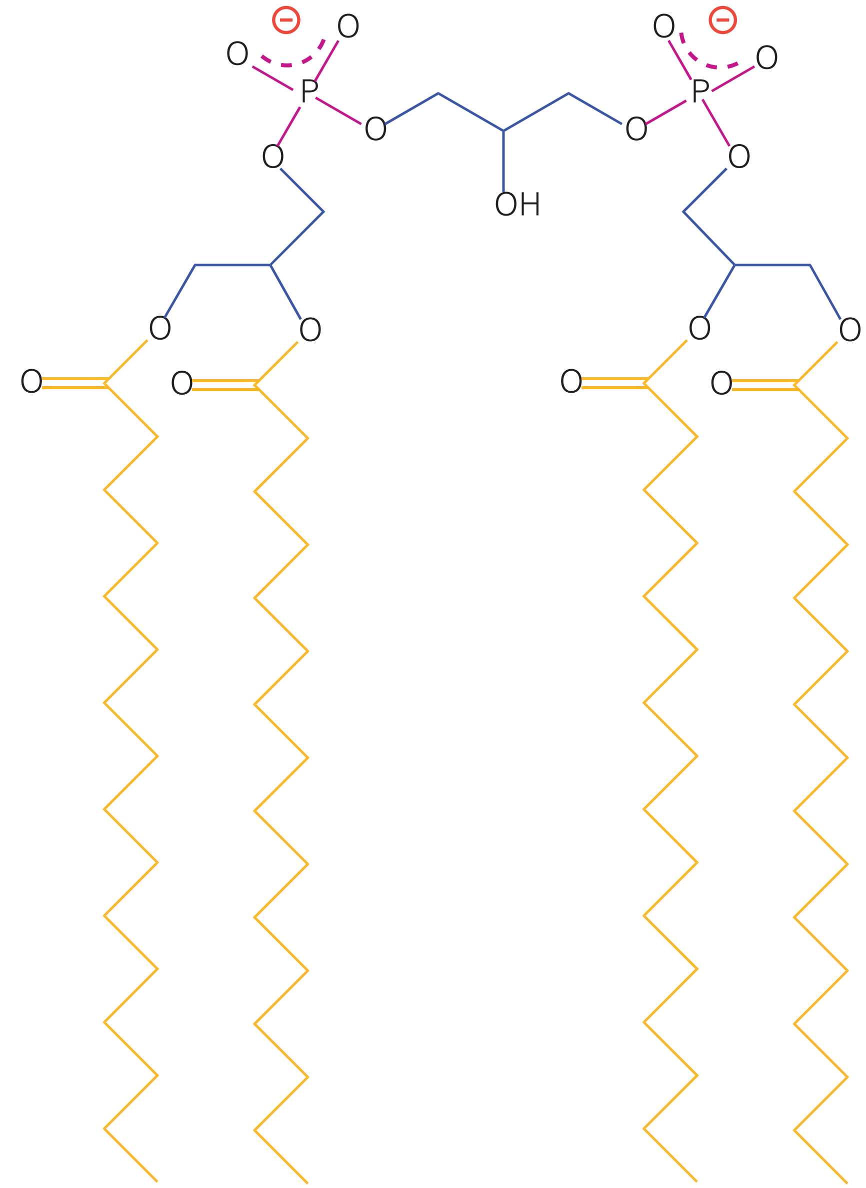
Esterified glycerol backbone



triglyceride

Triglyceride stores and transports fats for metabolism

Dimerized phosphoglycerol lipid

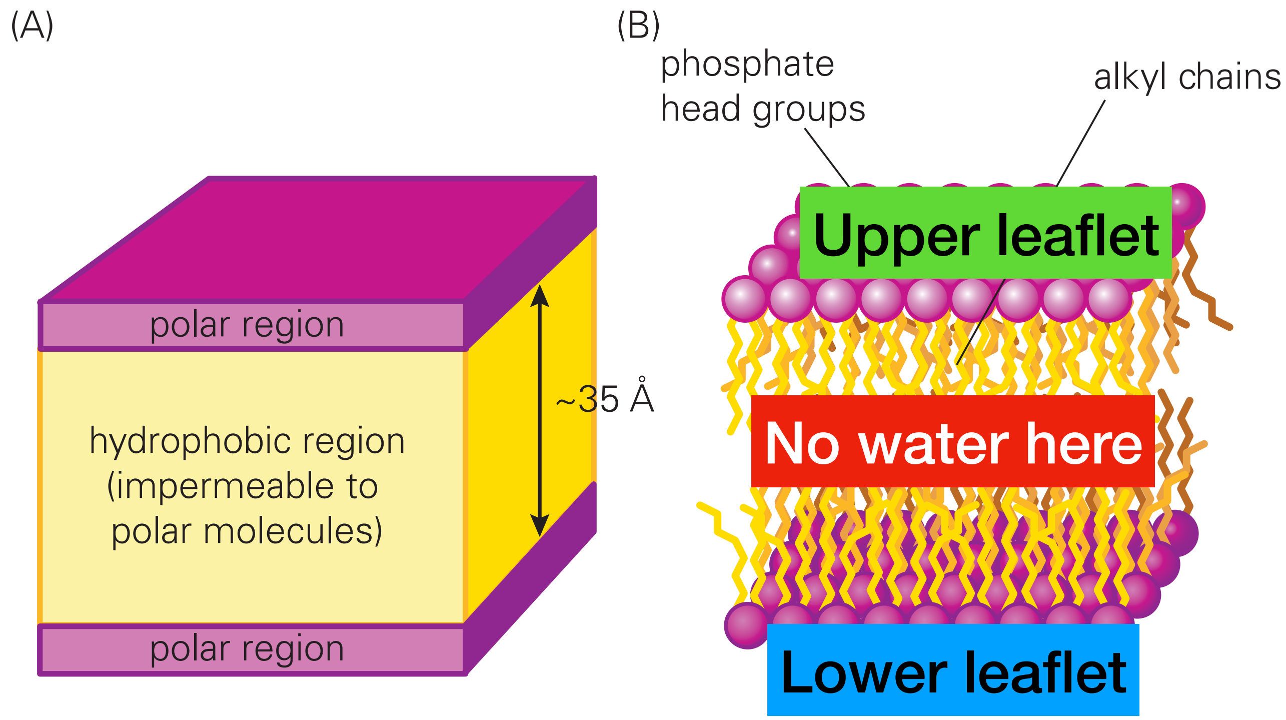


cardiolipin

Cardiopilin comprises 20% of mitochondrial membrane

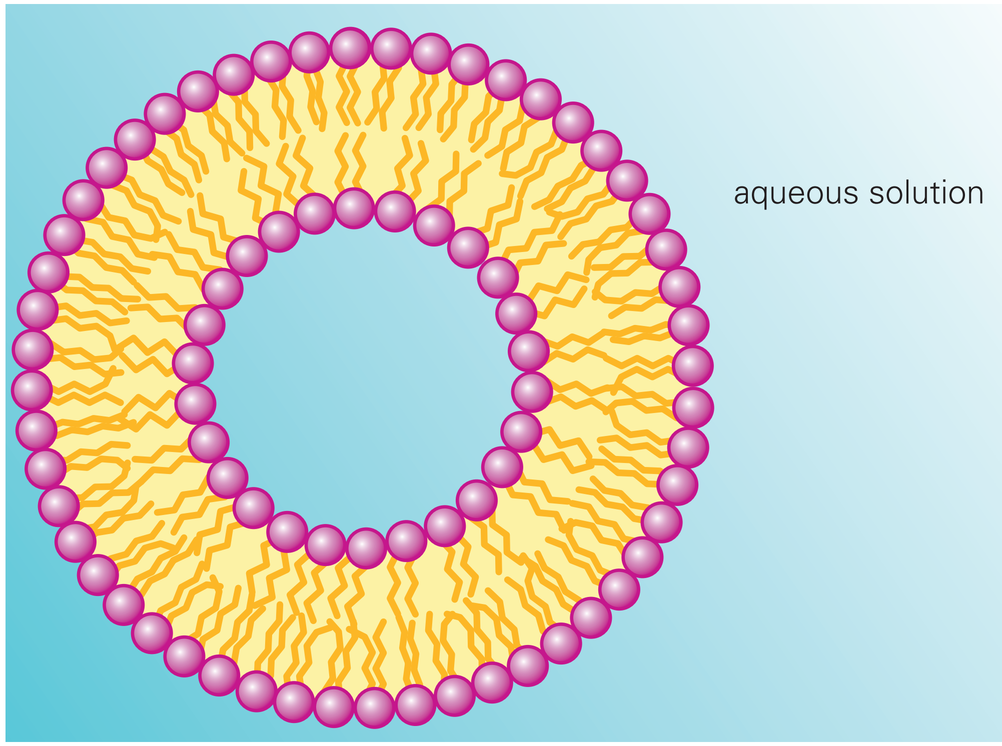
Lipids form different types of organized structures spontaneously

Lipid bilayer

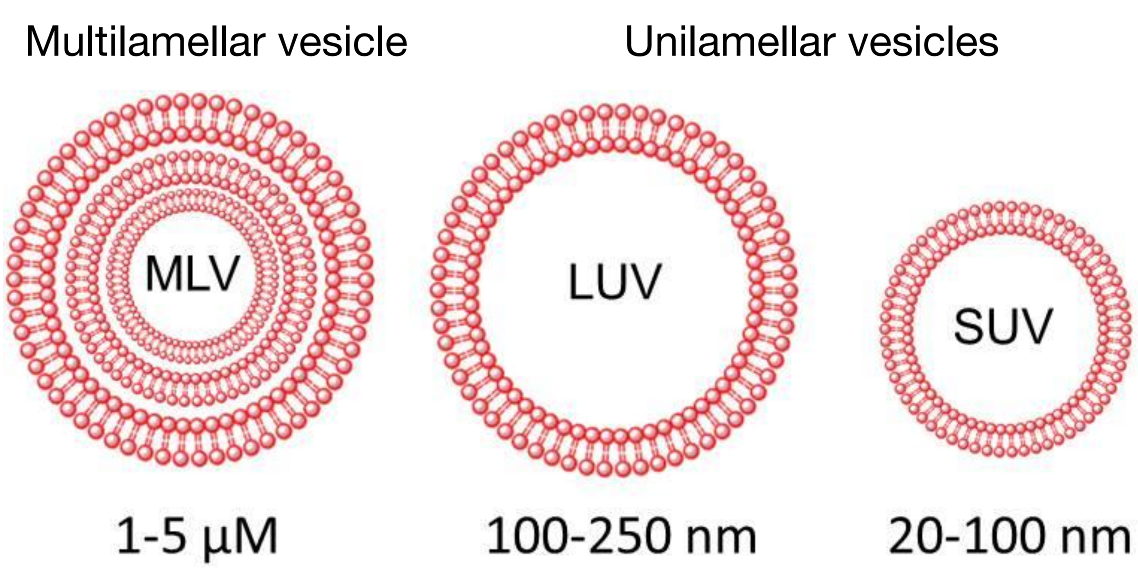


The two leaflets have different composition

Lipid vesicle



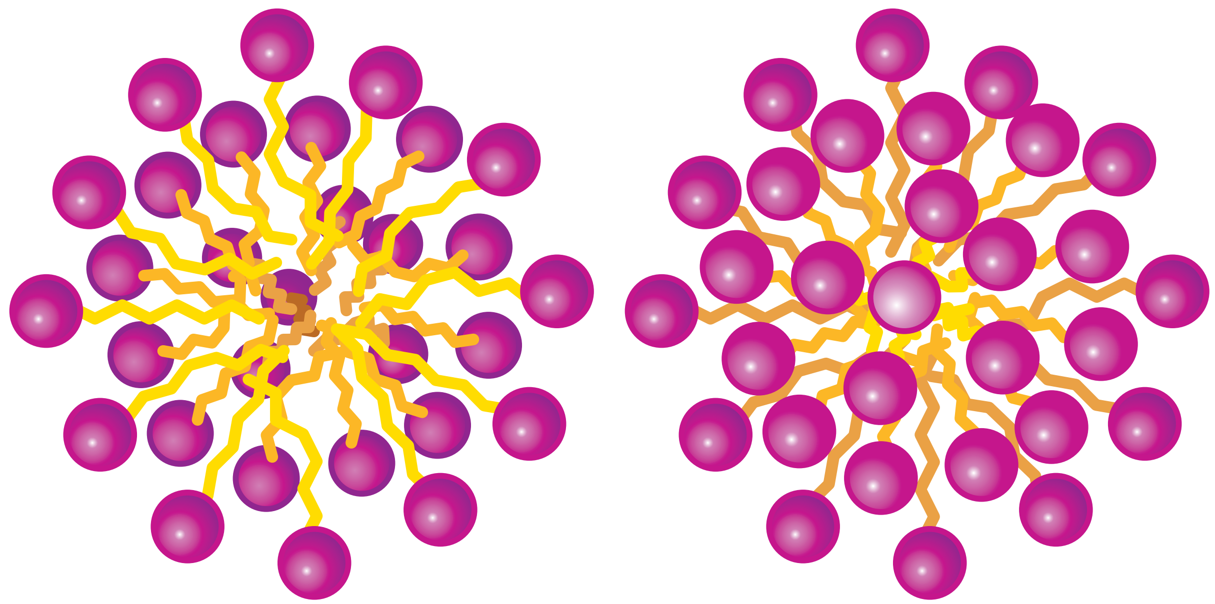
Lipid vesicles are kinetically stable structures formed by sonication of dispersions of lipids in water



What's the driving force here?

Dispersion forces that aggregate hydrophobic parts together

Single-chain lipids form curved structures called micelles



spherical arrays of the lipid molecules with head groups on the outside and chains on the inside

What's the driving force here?

Higher cross-sectional area on the head-group than the hydrophobic part

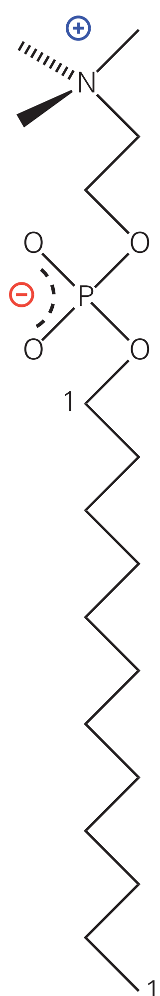
This makes the formation of curved structures preferable than bilayers

Micelles are small in size with small radius of curvature and moves around freely in solution

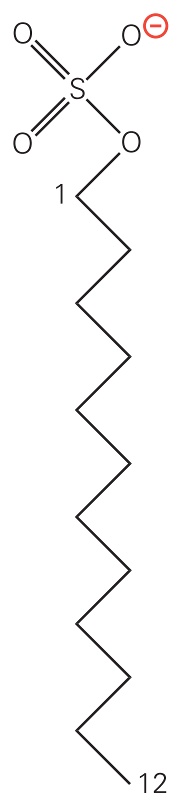
Amphiphilic compounds are soluble up to a certain concentration as individual molecules. Micelles are formed beyond a certain concentration called the Critical Micelle Concentration (CMC)

Micelle size is specific to a substance which can be changed by ionic strength of the medium and impurities

Detergents are lipid-like compounds that form micelle rather than bilayers

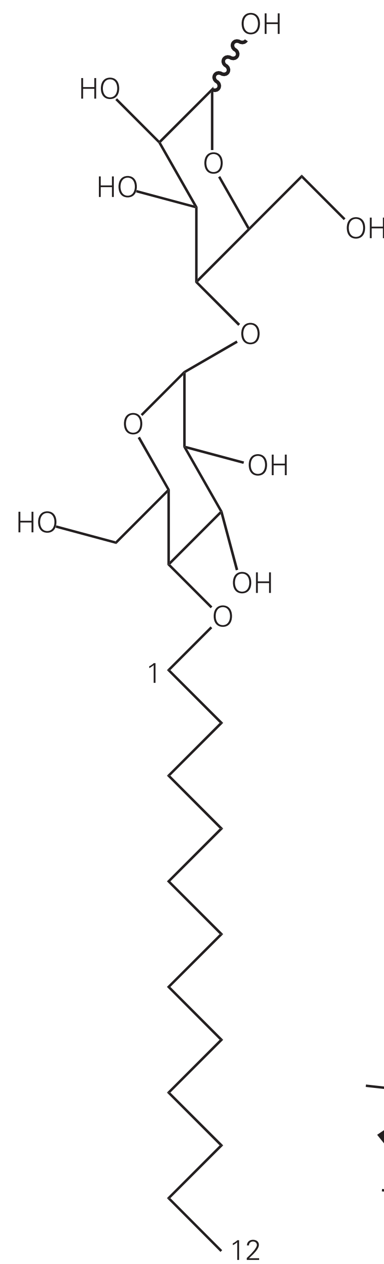


dodecyl-
phosphocholine
(DPC)

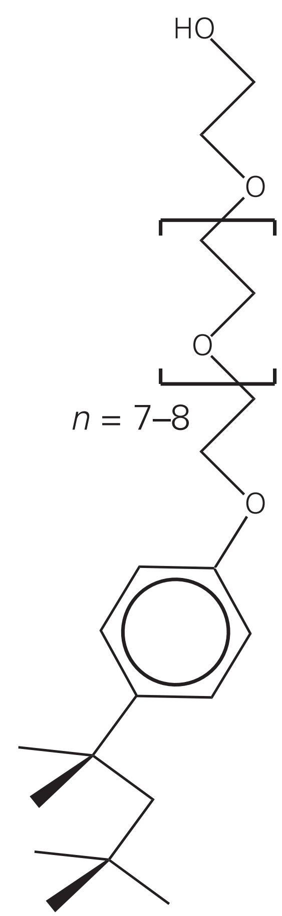


sodium
dodecylsulfate
(SDS)

Common
denaturing agent

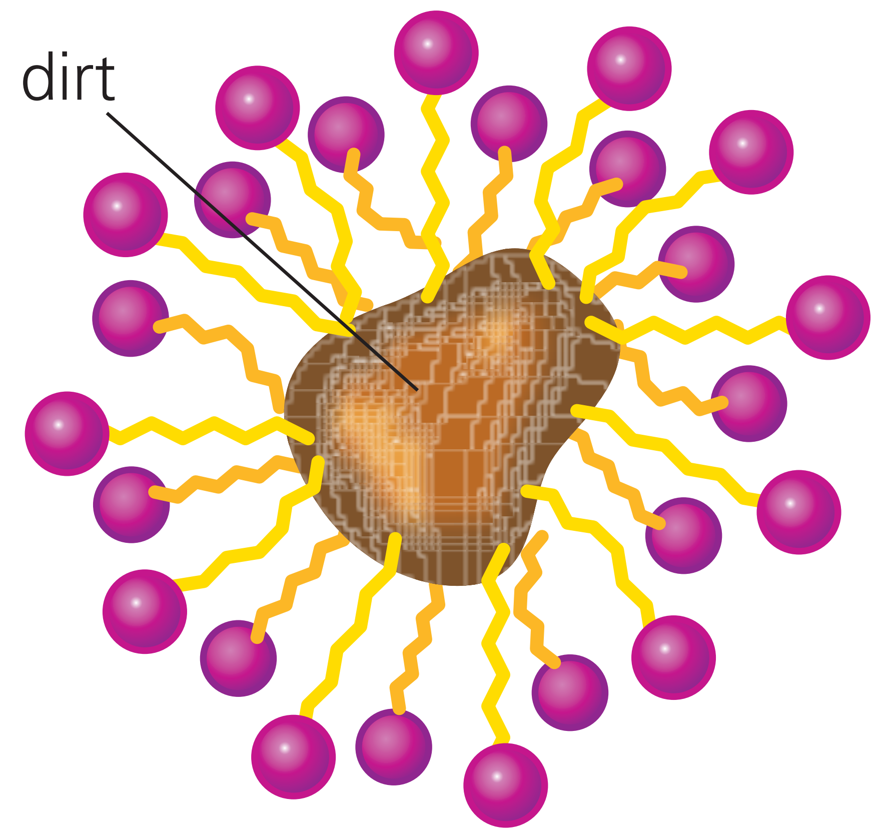


dodecylmaltoside
(DDM)



Triton X-100

Non-denaturing detergents are useful in
protein purification and extraction



Detergents make the dirt particle soluble in
water by forming a micelle around it

Detergents can effectively bind to
hydrophobic residues of proteins and thus
can denature a protein in solution

Lipids in bilayers move freely in two dimensions

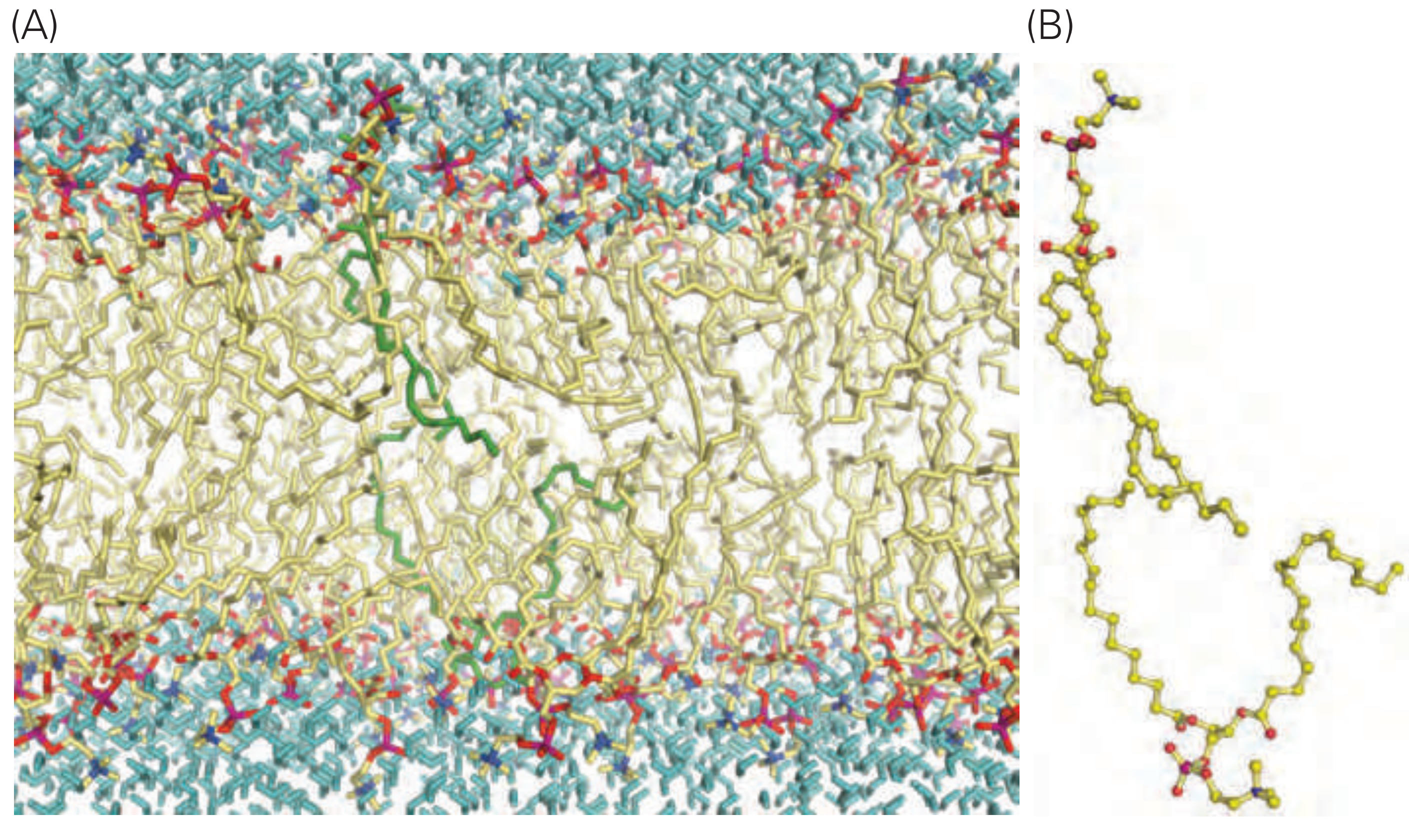
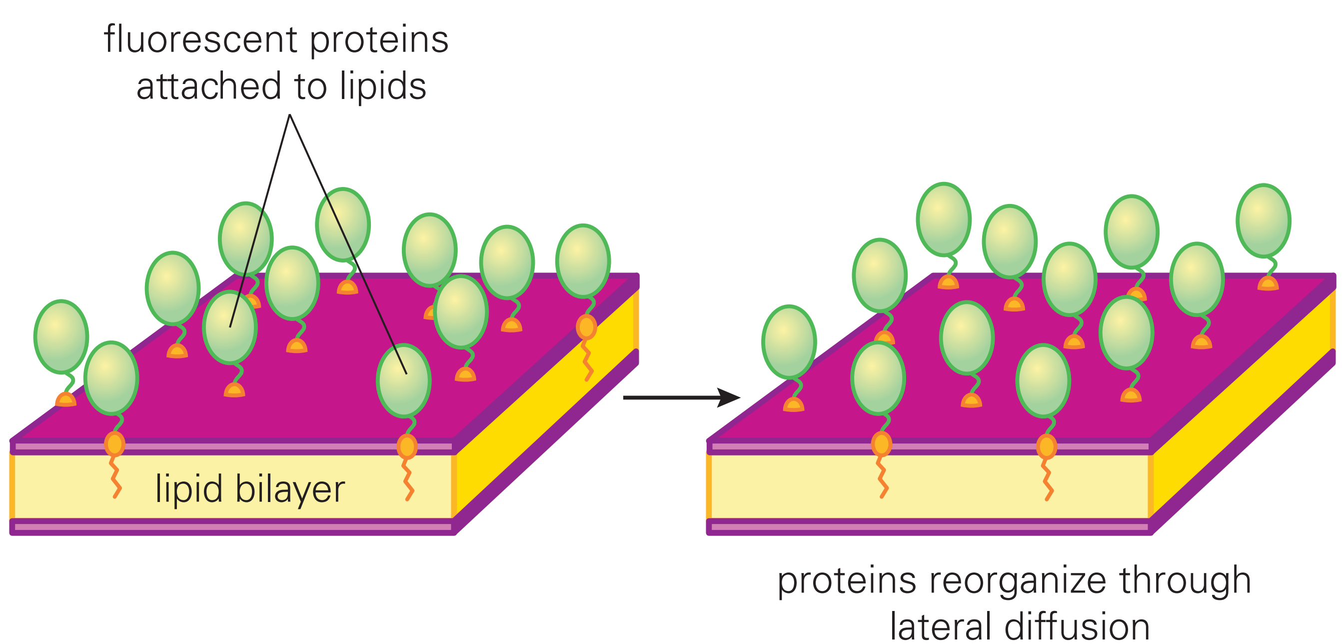


Figure 3.39 A slice through a bilayer membrane. (A) A snapshot from a computer simulation of a lipid bilayer. The glycerophospholipid molecules have choline head groups. Water molecules (*cyan*) can be seen at the top and bottom, with some waters interspersed into the head group region. Two of the lipid molecules are colored in *green* (one from each layer of the membrane). These same molecules are shown separately in (B). Note the variability in conformation of the alkyl chains and the head group. (Atomic coordinates: plpc128.pdb from http://moose.bio.ucalgary.ca)

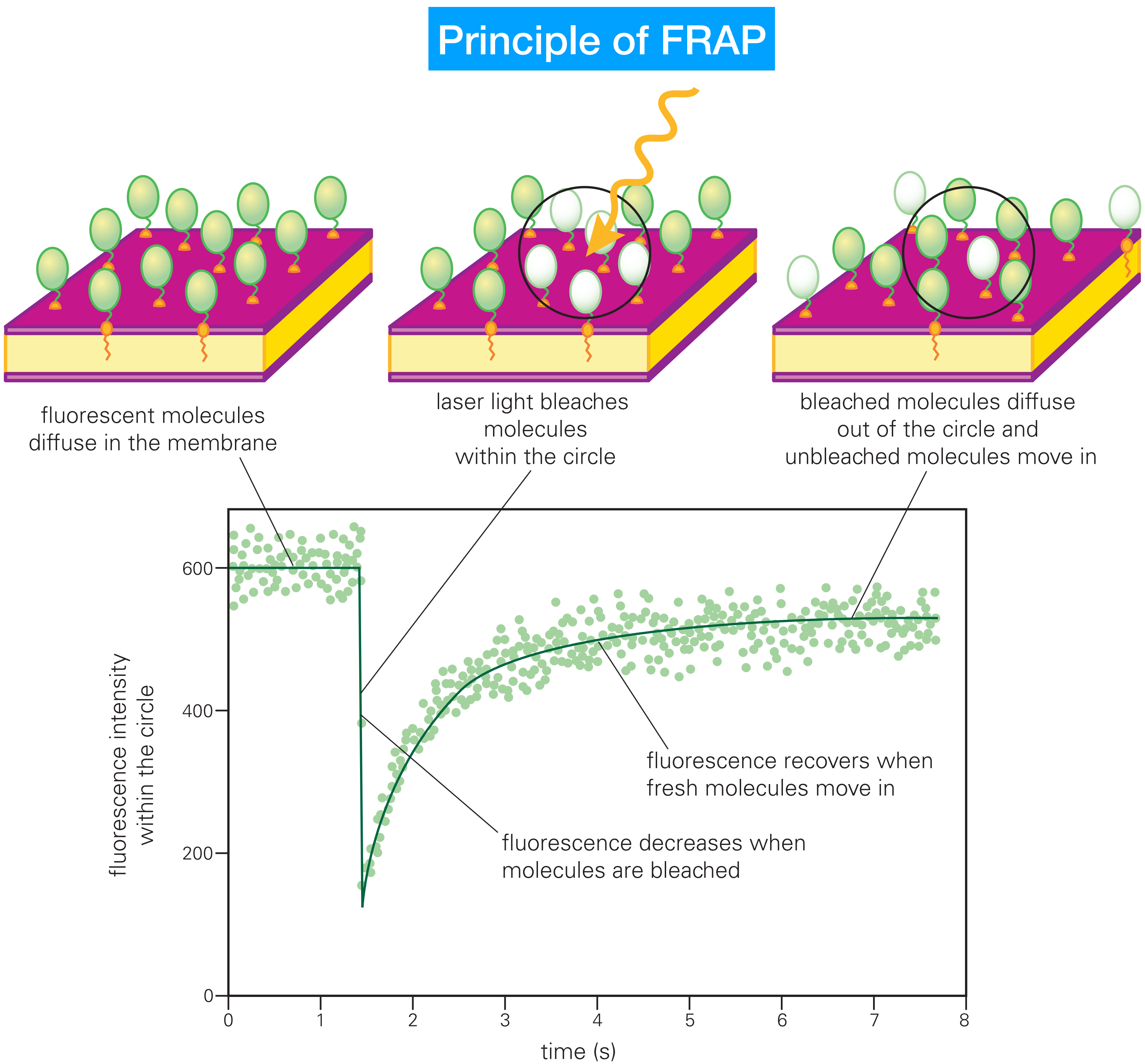


Lipid molecules behave as a two dimensional liquid and diffuse rapidly within the bilayer

Lipids can undergo thermal gel-liquid transition. Biological membranes are always in liquid state

Lipids can be tracked by attaching fluorescent tags. However, tracking can be challenging when tag concentration is high

Lipid movements can be tracked using Fluorescence Recovery After Photobleaching experiment



Lipid rafts are dense patches on the membrane

Lipid raft: phase separated regions of membrane containing rich variety of lipids and proteins

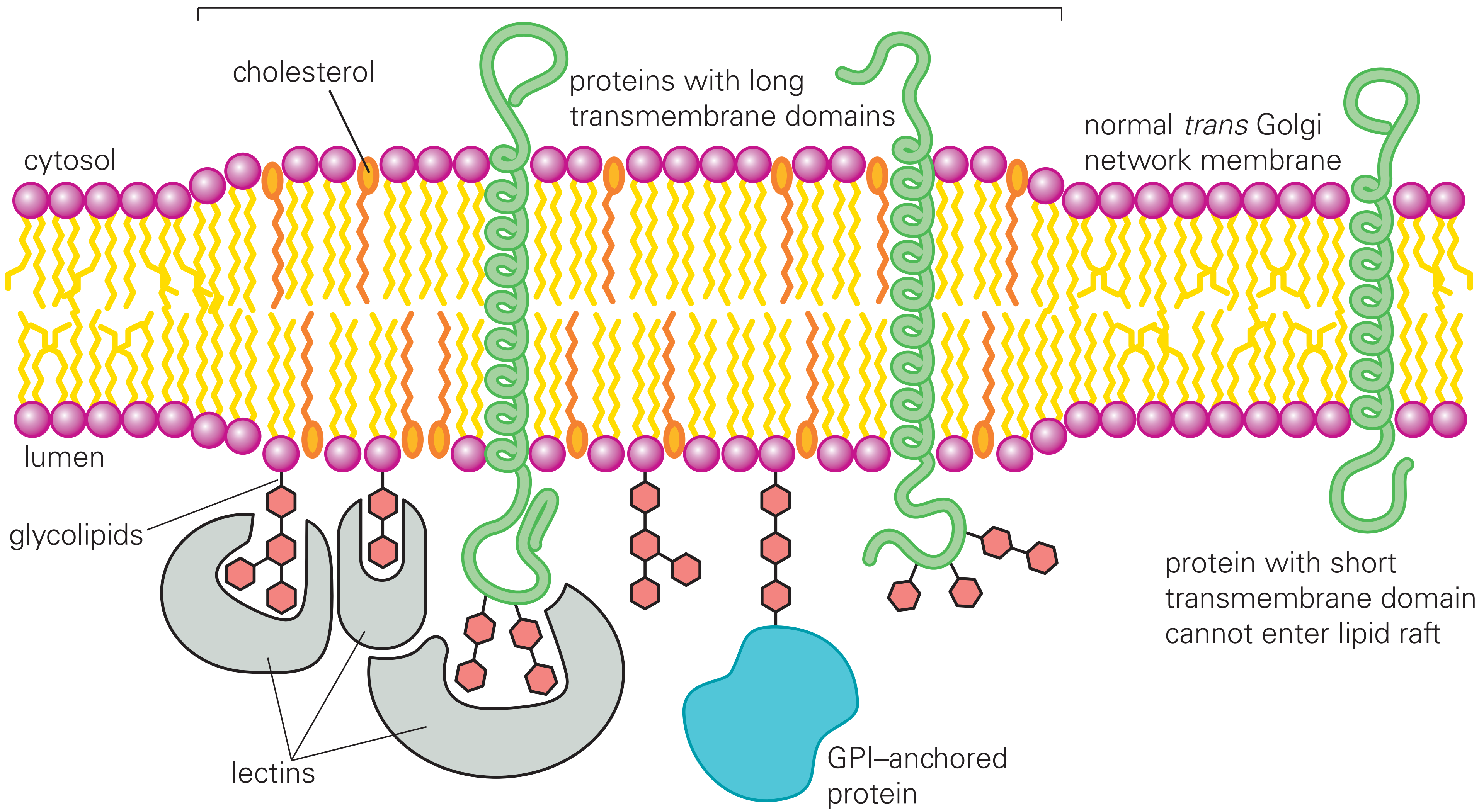
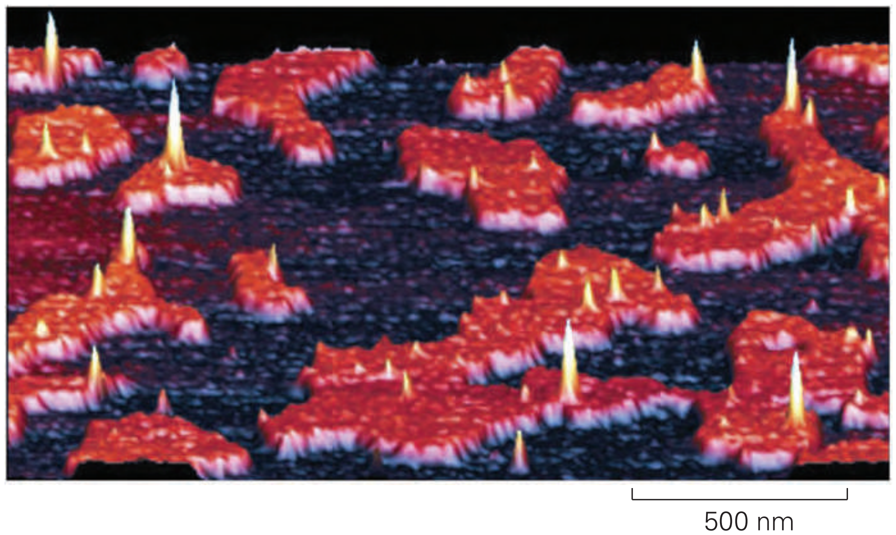


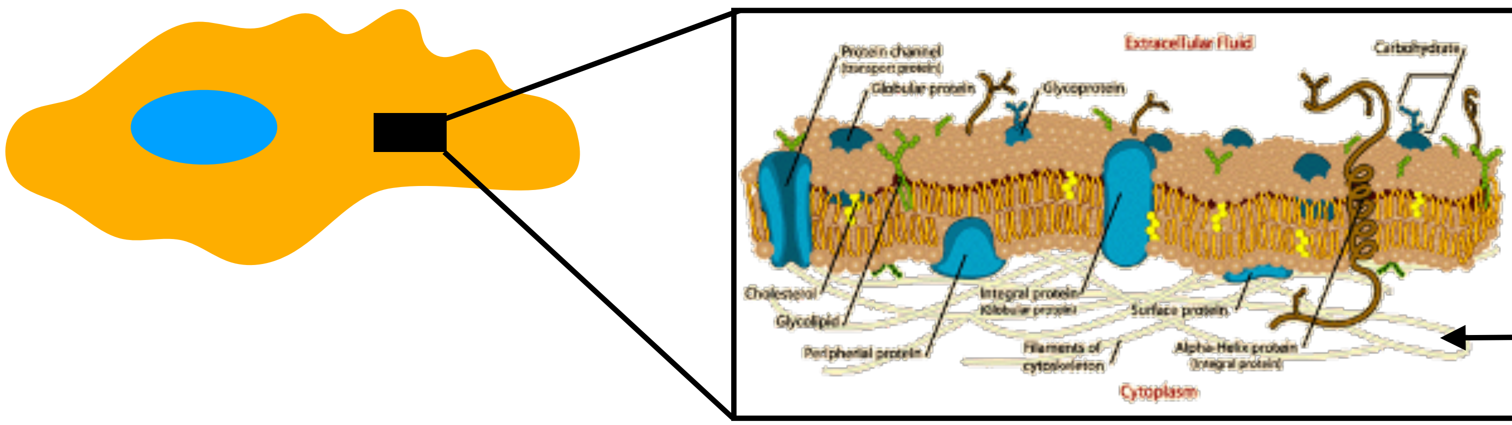
Figure 3.44 An atomic force microscope image shows "rafts" of distinct lipid composition. These regions of thicker membrane protrude above the surface of the surrounding regions. (Courtesy of Robert M. Henderson and J. Michael Edwardson; data from D.E. Saslowsky et al., *J. Biol. Chem.* 277: 26966–26970, 2002.)



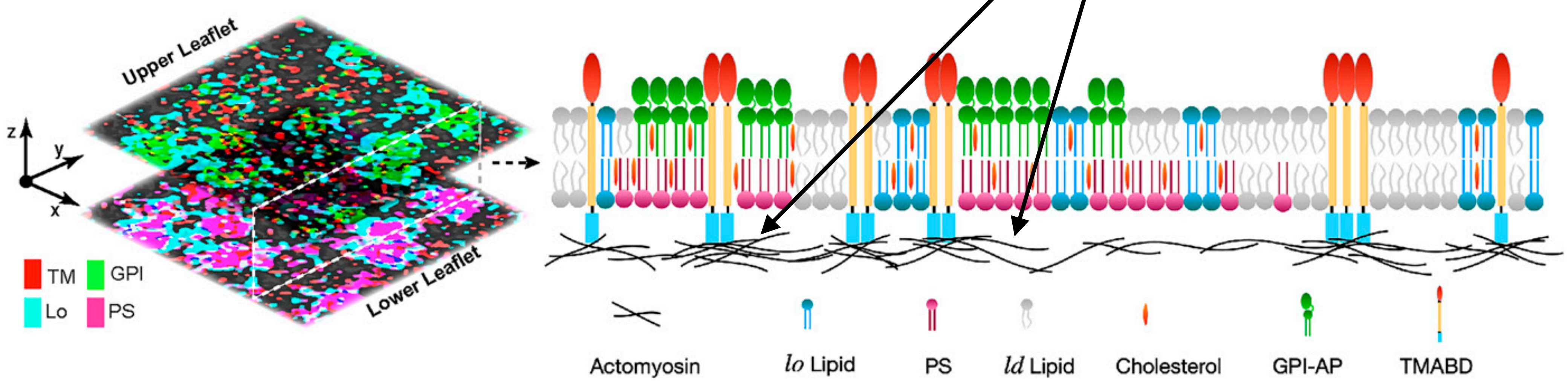
Lipid rafts allow optimization of most favorable interactions among particular combinations of molecules.

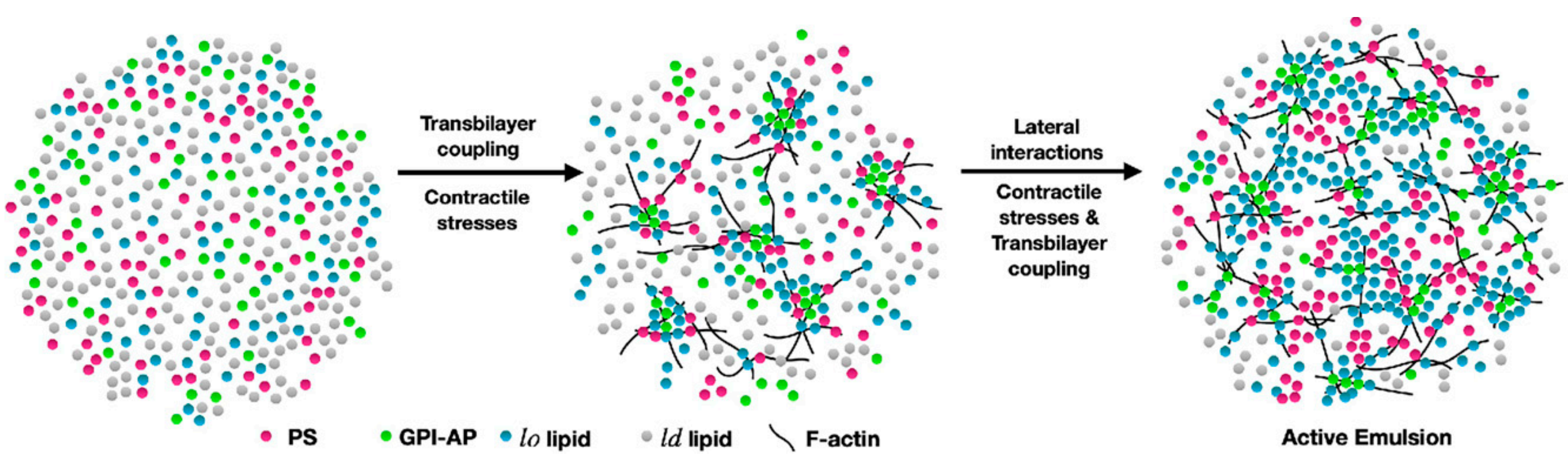
However, rafts have been difficult to be characterized and hence poorly understood

Rafts can be dynamic and understood as emulsions!



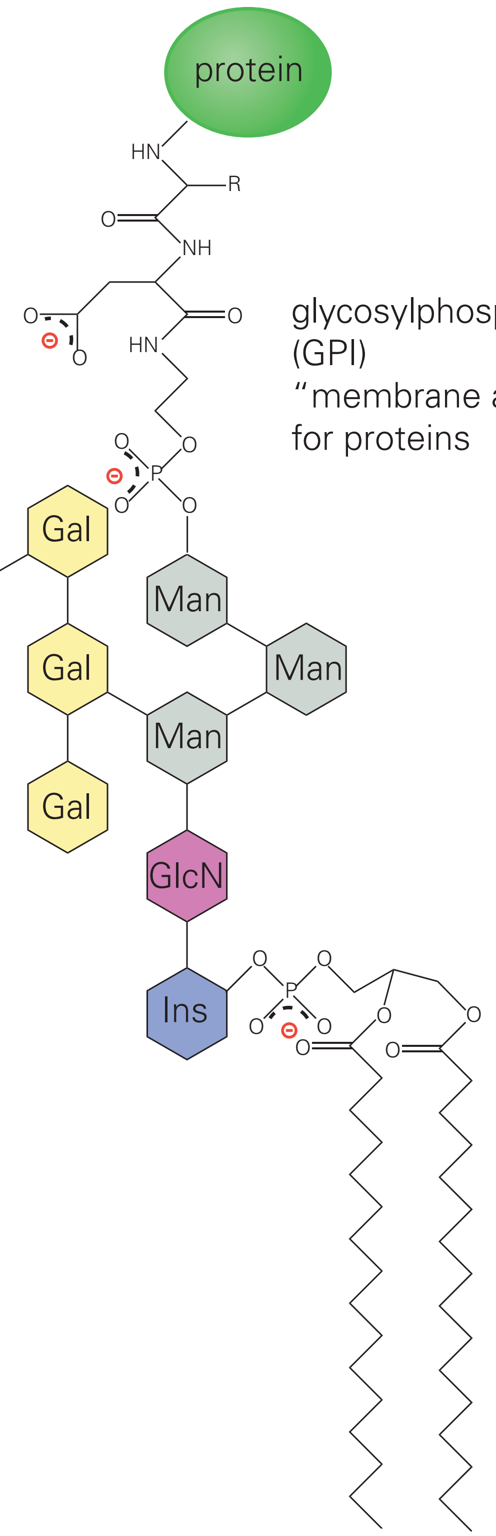
Our proposed mechanism for rafts
flows of cortical actin control dynamic raft-like organization at cell membrane





Saha, Das et al. Proceedings of National Academy of Sciences, USA, 2022

Lipid-anchoring proteins



glycosylphosphatidylinositol (GPI) "membrane anchor" for proteins

galactose (Gal)

mannose (Man)

glucosamine (GlcN)

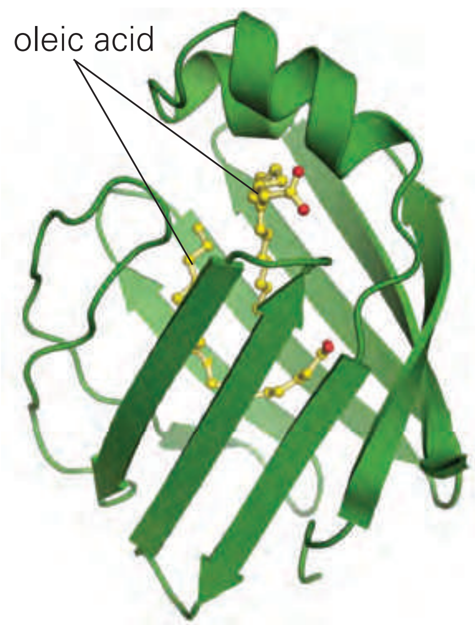
inositol (Ins)

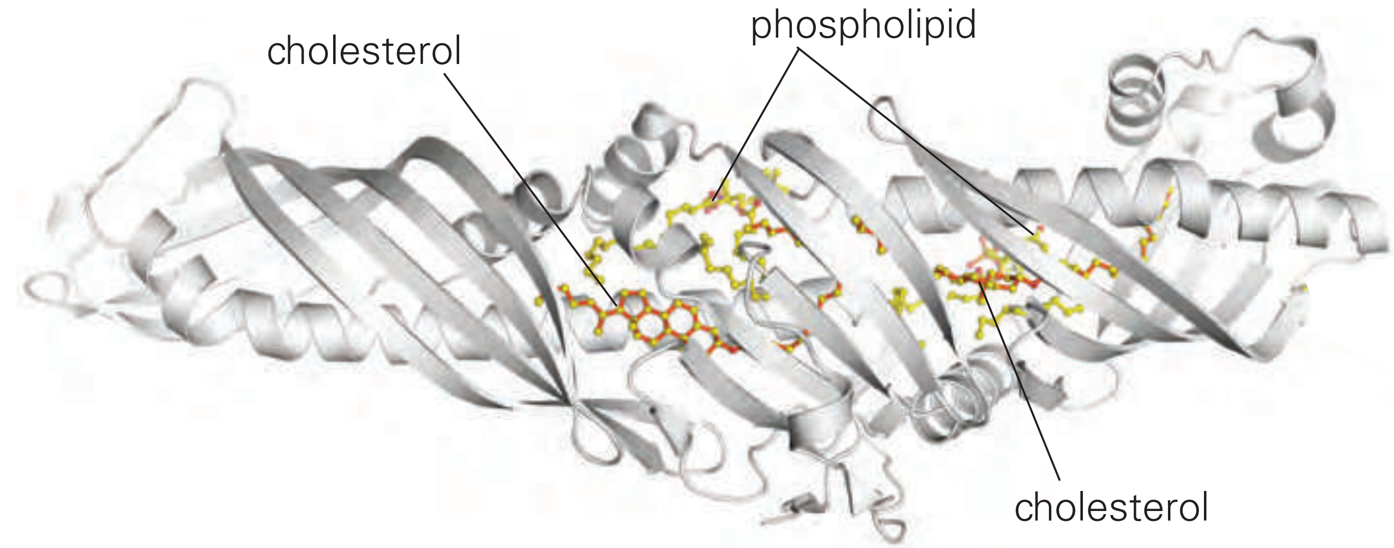
GPI-anchored proteins are often found enriched in lipid rafts

Lipids can be sequestered and transported by proteins

Single-lipid transport

(A)





cholesterol transport protein

Multi-lipid transport

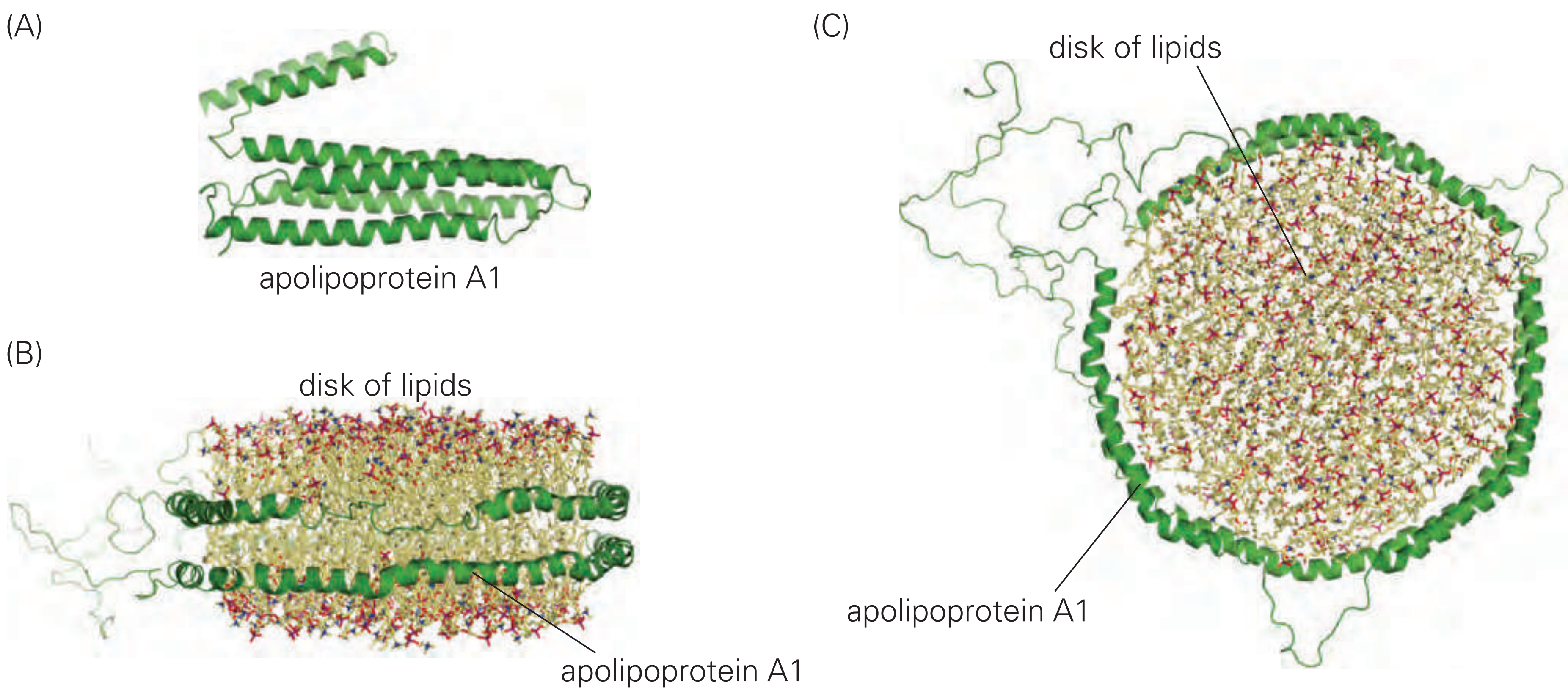
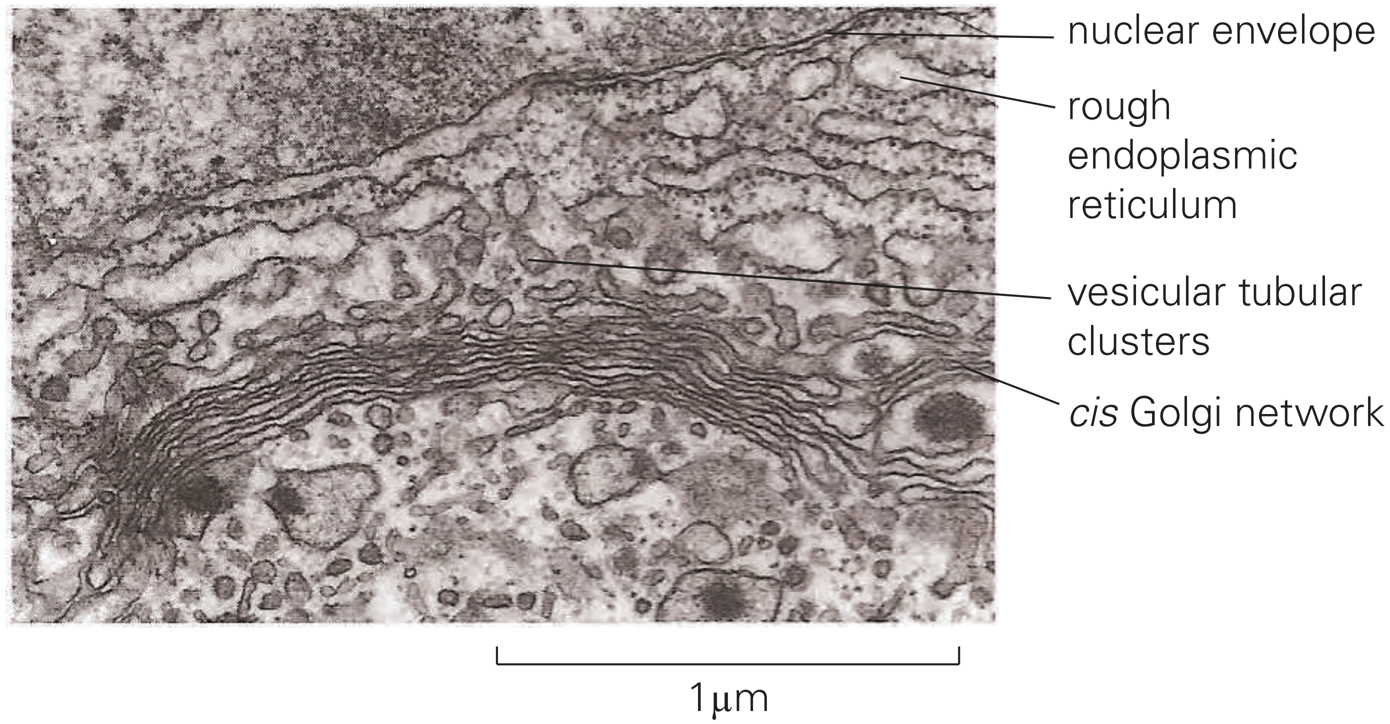


Figure 3.48 Apolipoprotein A1. (A) The structure of the protein in the absence of lipid. (B, C) Two views of a model for the structure in the presence of lipid. The helices move apart and expose a surface that interacts with the edge of a small disk of lipid. There are two protein molecules per lipid disk. (See Protein Model Database mi.caspur.it/ PMDB entry PM0074956; Z. Wu and S.L. Hazen, *Nat. Struct. Mol. Biol.* 14: 861–868, 2007.)

Different kinds of cells and organelles have different membrane compositions

Various membrane protected organelles



Membrane compositions are sometimes regulated by an enzyme called 'Flipase' that recognize and flip specific lipids from one leaflet to another

Table 3.2 The lipid compositions of different membranes.

Lipid	Source					
	E. coli	Red cell	ER	Mitochondrion	Myelin	Liver
Phosphatidylcholine	0	17	40	39	10	24
Phosphatidylserine	0	7	5	2	9	4
Phosphatidylethanolamine	70	18	17	25	15	7
Sphingomyelin	0	18	5	0	8	19
Glycolipids	0	3	~0	~0	28	7
Cholesterol	0	23	6	3	22	17

Many of these membranes have additional minor components, and so the percentages do not add to 100%. (Adapted from B. Alberts et al., Molecular Biology of the Cell, 5th ed. New York: Garland Science, 2008.)

Cell walls are reinforced membranes

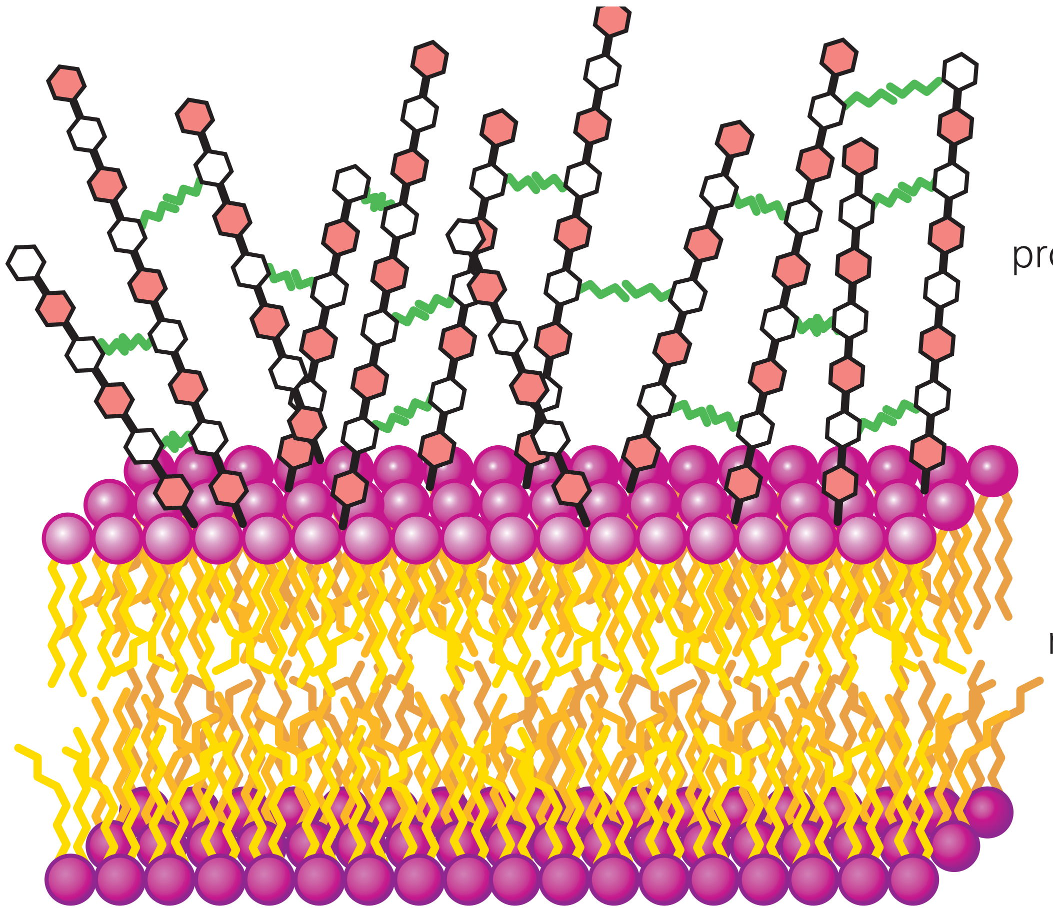


Figure 3.51 The proteoglycan (also called peptidoglycan) cell wall in bacteria. Polysaccharide chains extend from the membrane and are cross-linked by short peptides (*green*).

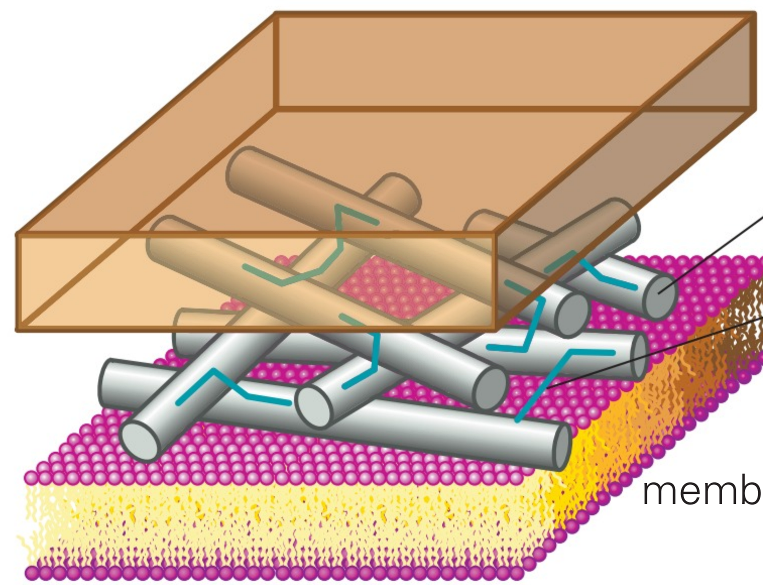


Figure 3.52 A plant cell wall. Outside the cell membrane are cellulose microfibrils with cross-linking polysaccharides. Pectin is interspersed throughout, filling and strengthening the wall. The middle lamella is rich in pectin and helps hold neighboring cells together. (Adapted from B. Alberts et al., Molecular Biology of the Cell, 5th ed. New York: Garland Science, 2008.)