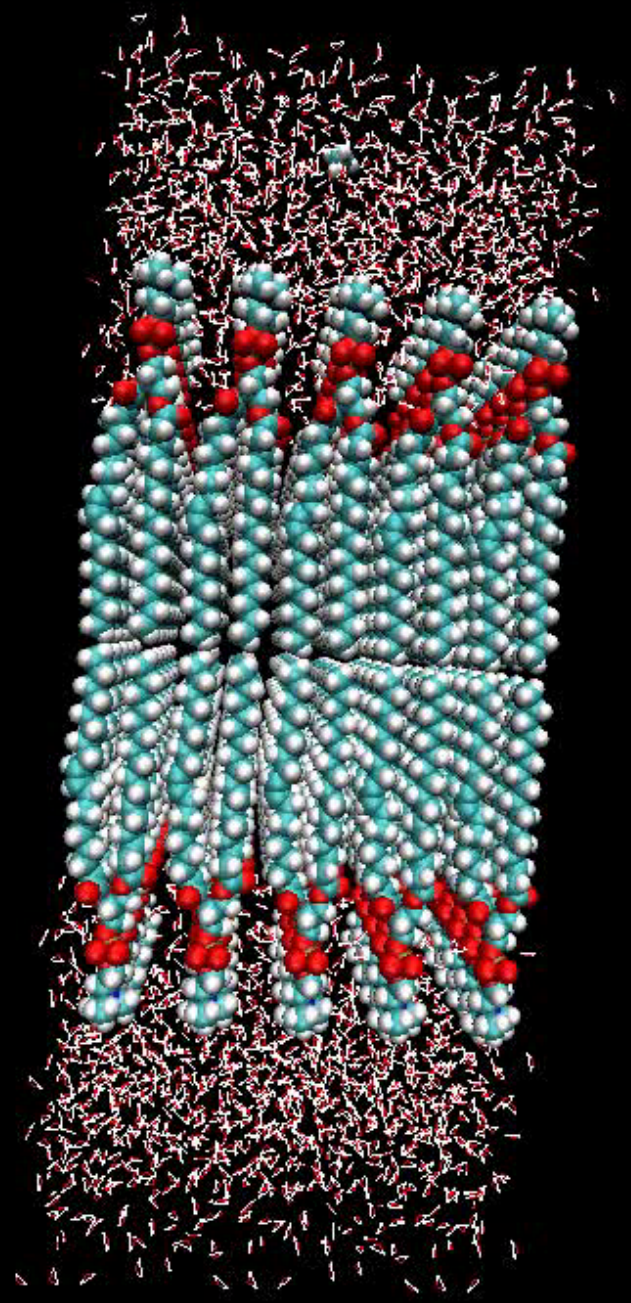


Lipid bilayer

the fundation of biological membrane

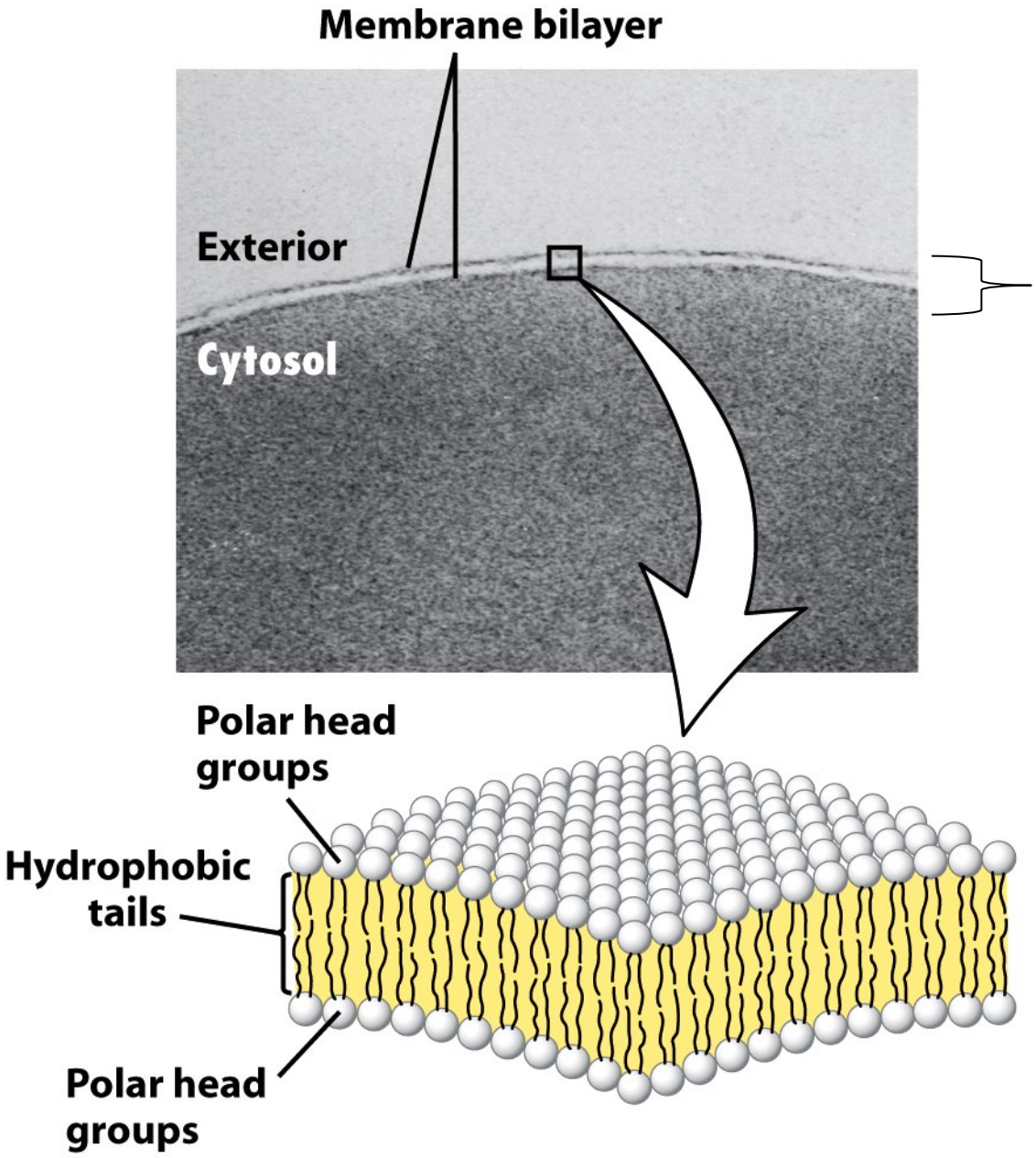


Figure 10-6ab
Molecular Cell Biology, Sixth Edition

Staining artifact

due to binding of a contrasting agent (Uranyl or Osmium) to the polar headgroups

Lipid bilayer stability

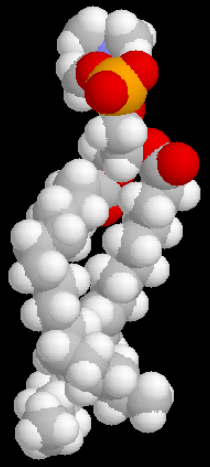
It takes ≈ ***55 kcal/mole*** to remove a single acyl chain from a bilayer and put it into water.

The energy of stabilization of the membrane is equivalent to about 16 high energy phosphate bonds (ATP → ADP) per lipid molecule!
Even a 20 nm edge of a ruptured membrane would expose about a hundred lipids or cost 11 000 kcal/mole.

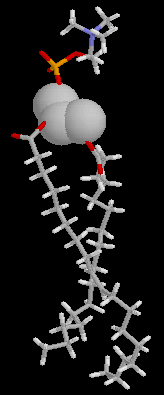
No other physical force comes close to generating this amount of energy.

More than 95% of the hydrophobic lateral area of a typical biological membrane is occupied by lipids.

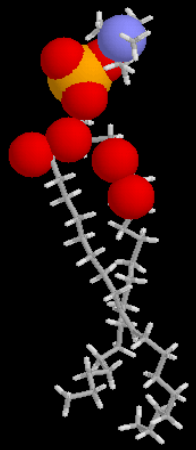
A phospholipid is an amphiphilic molecule

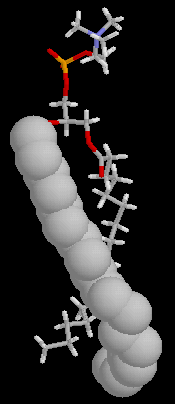


The hydrophobic regions

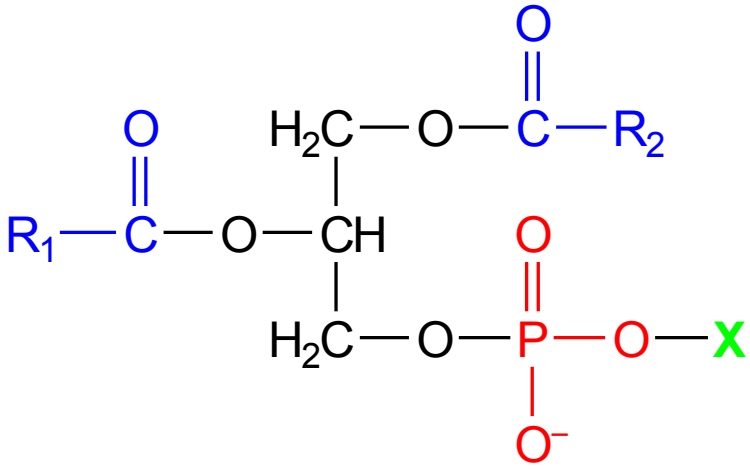


The polar regions

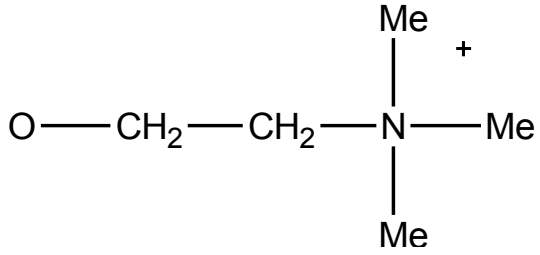




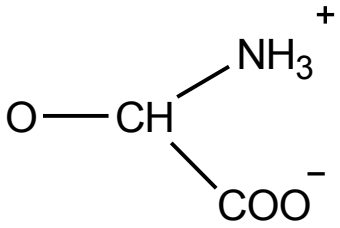
According to the head group X, there are several kinds of lipids.



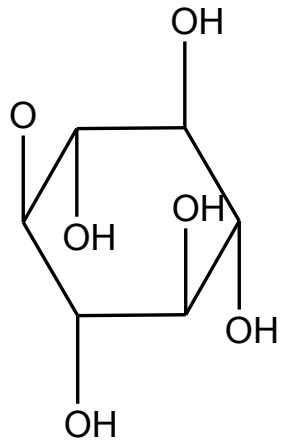
X=



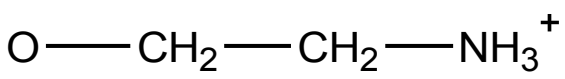
Choline (PC)



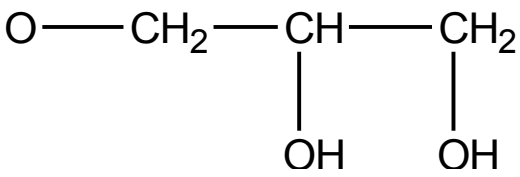
Serine (PS)



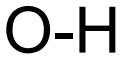
Inositol (PI)



Ethanolamine (PE)



Glycerol (PG)

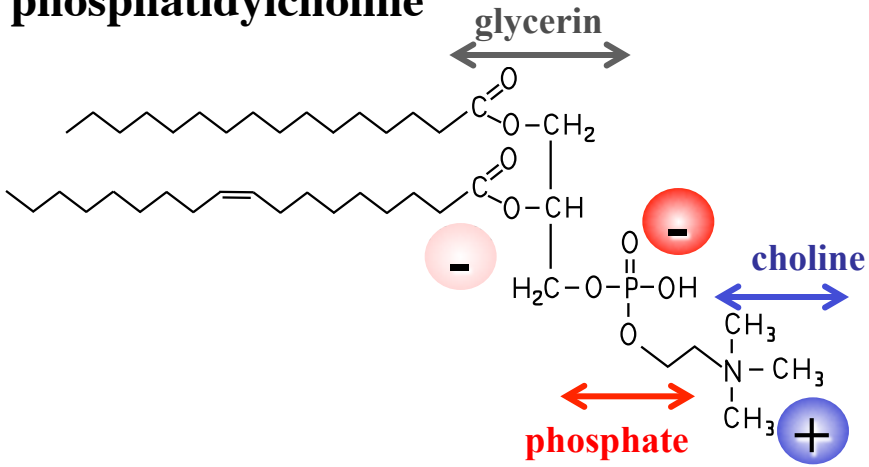


Acid(PA)

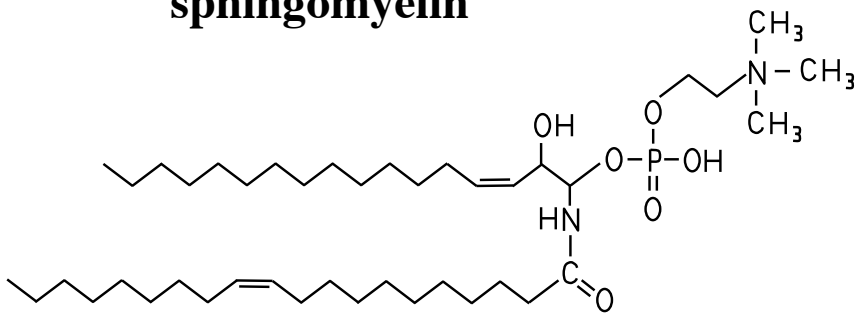
There are 1500 types of lipids.

PHOSPHOLIPIDS

phosphatidylcholine



sphingomyelin

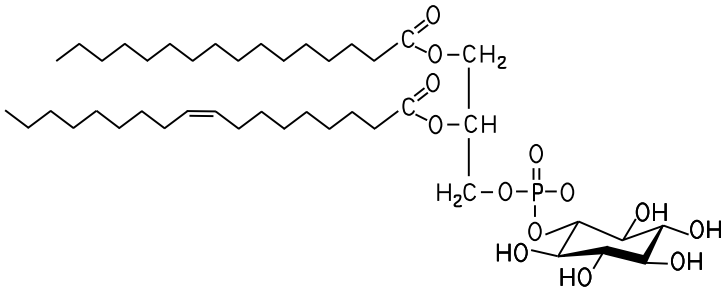


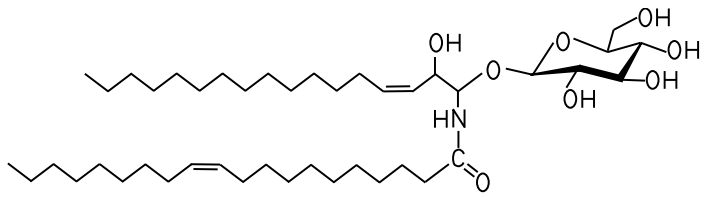
GLYCEROLIPIDS

SPHINGOLIPIDS

GLYCOLIPIDS

phosphatidylinositol

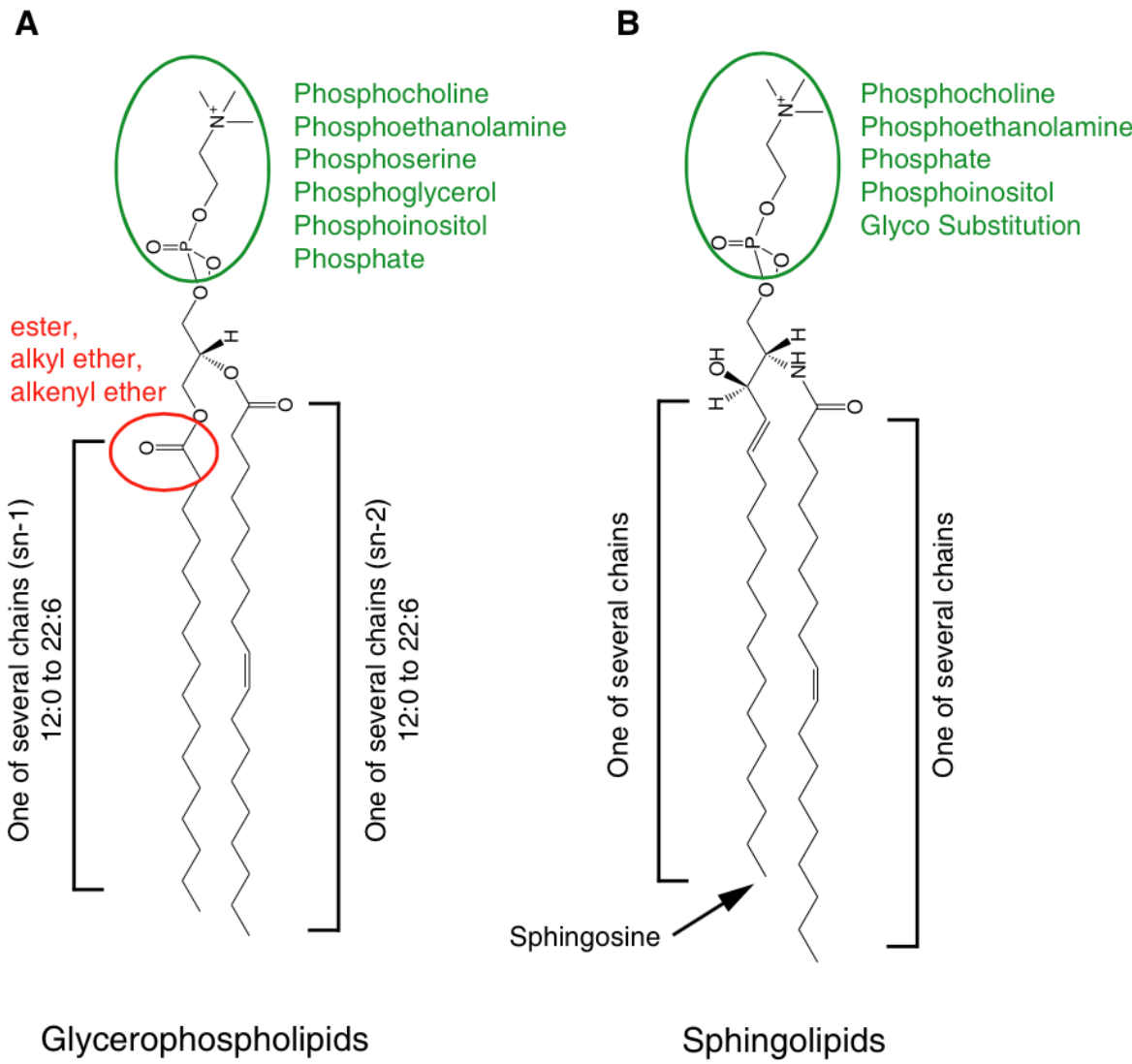




Chemical Diversity of Glycerophospholipids and Sphingolipids

Chemical modification of head groups (green circle), fatty acid chain length, and numbers of double bonds (degree of saturation) contribute to the diversity and complexity of (A) glycerophospholipid and (B) sphingolipids.

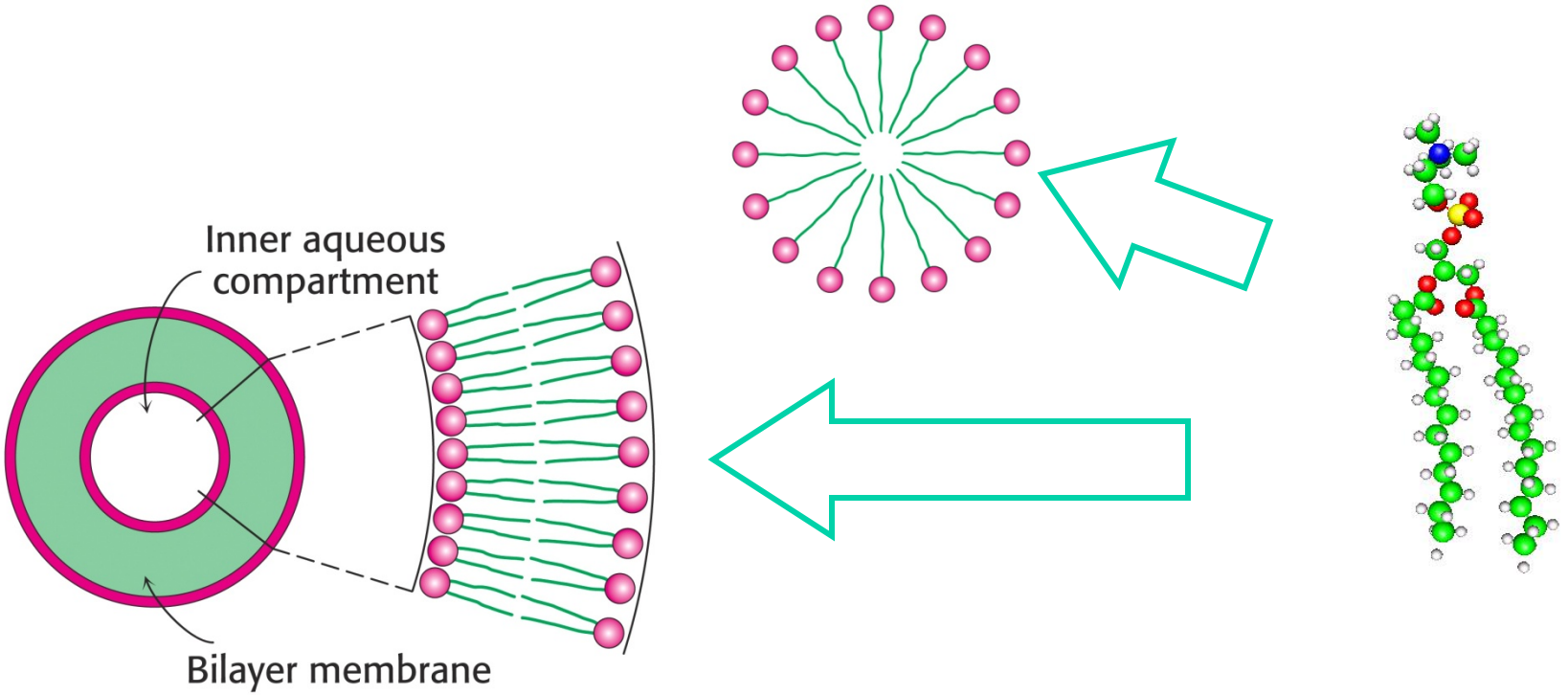
The linkage in glycerol in the sn-1 in glycerophospolipids (red circle) increases the variety further. Instead of a glycerol, sphingolipids contain a backbone of sphingoid base, including sphingosine, which is amide bound to a fatty acid to form ceramide.



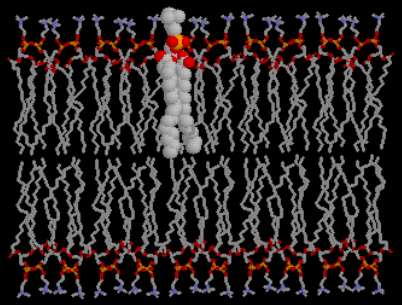
Lipid self assembly is a water (entropy)-driven process. The hydrophobic Effect

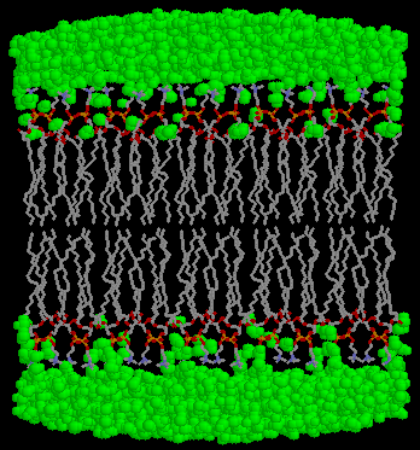
- Molecules with a fatty acid chain of 4 carbons or less have reasonable solubility in water.

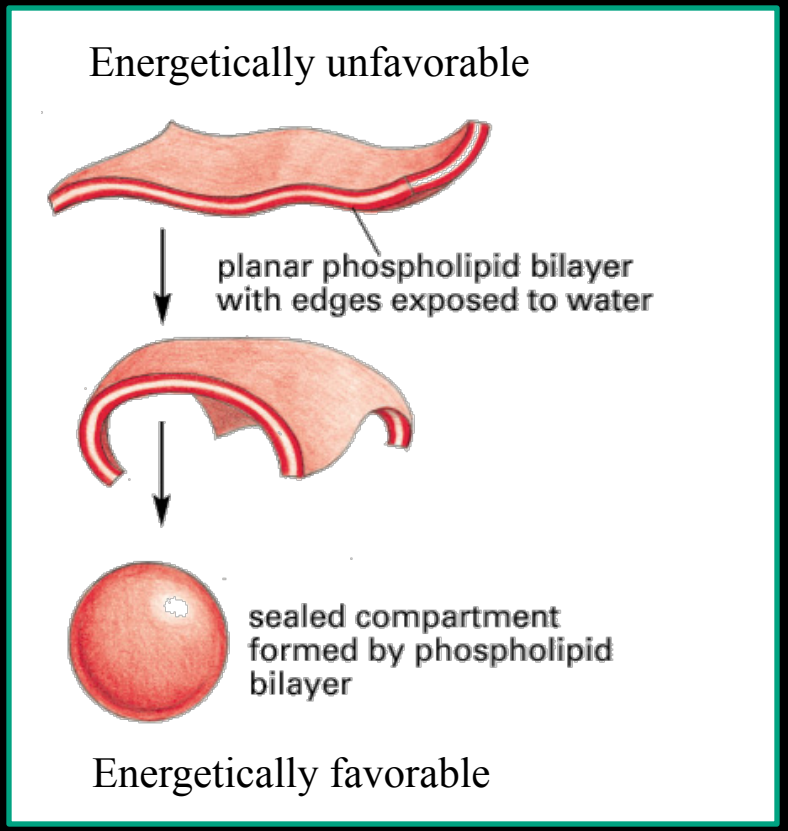
- Above 8 carbons, molecules bind strongly to a membrane or proteins with hydrophobic pockets.

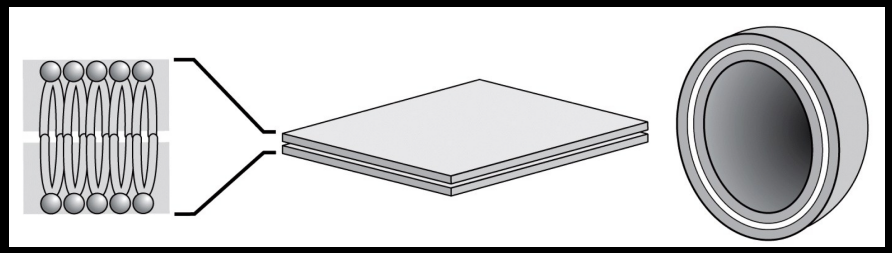


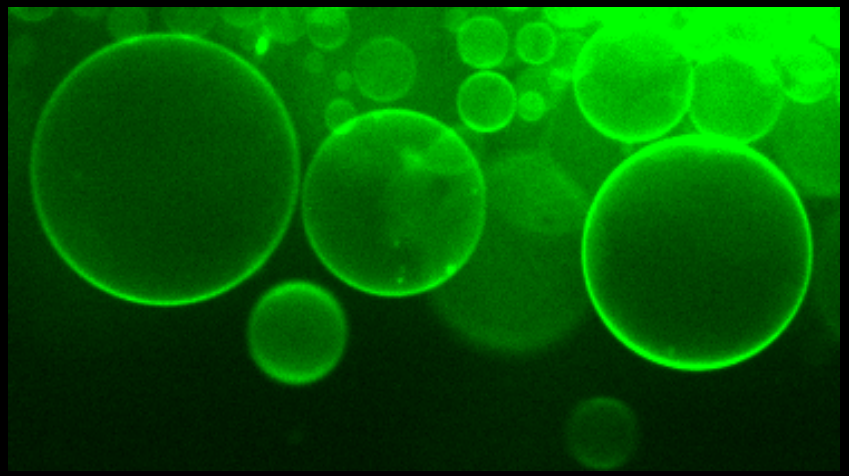
The lipid bilayer





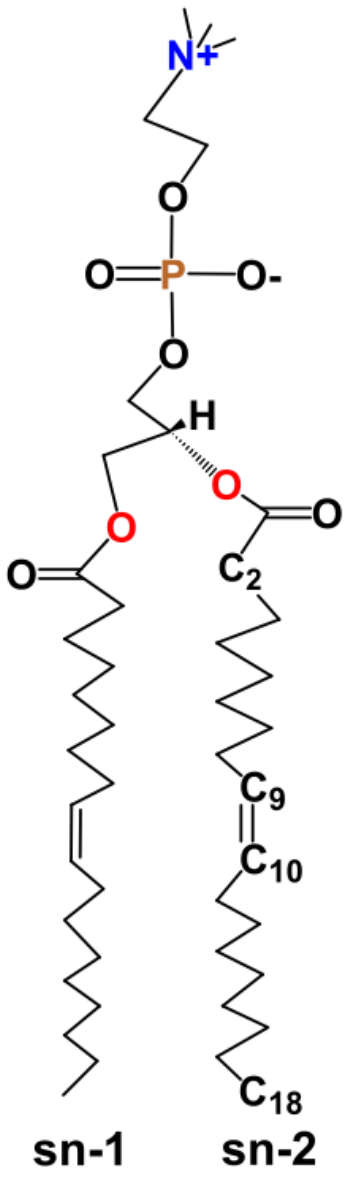


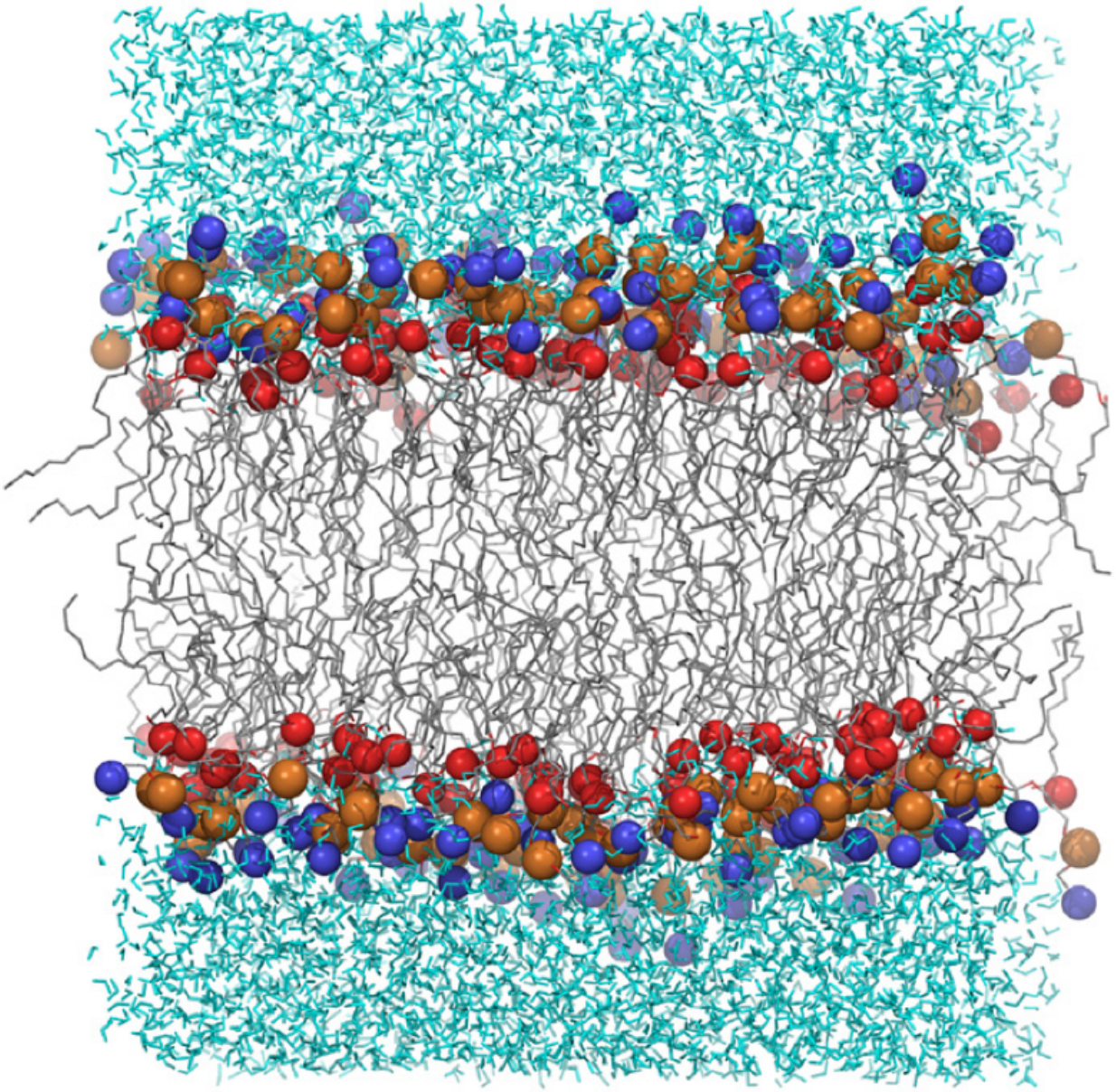




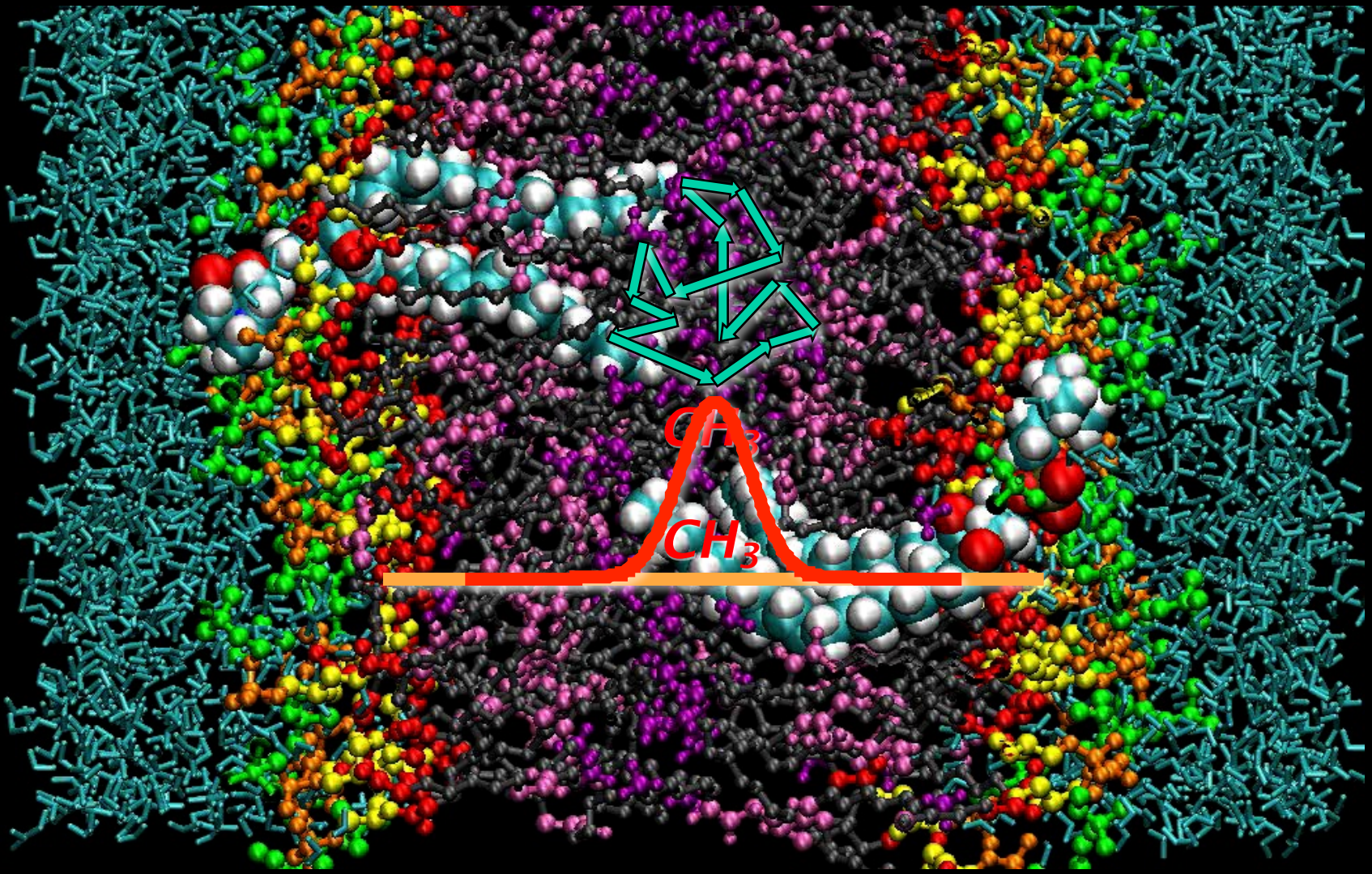
Giant vesicle with a diameter d=50 μm

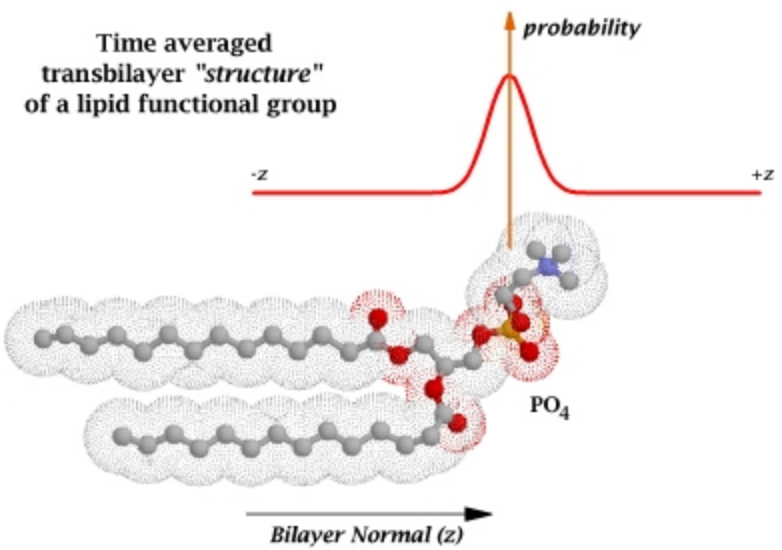
The structure of DOPC lipid molecule and a snapshot of the bilayer model used comprising of 128 DOPC molecules.



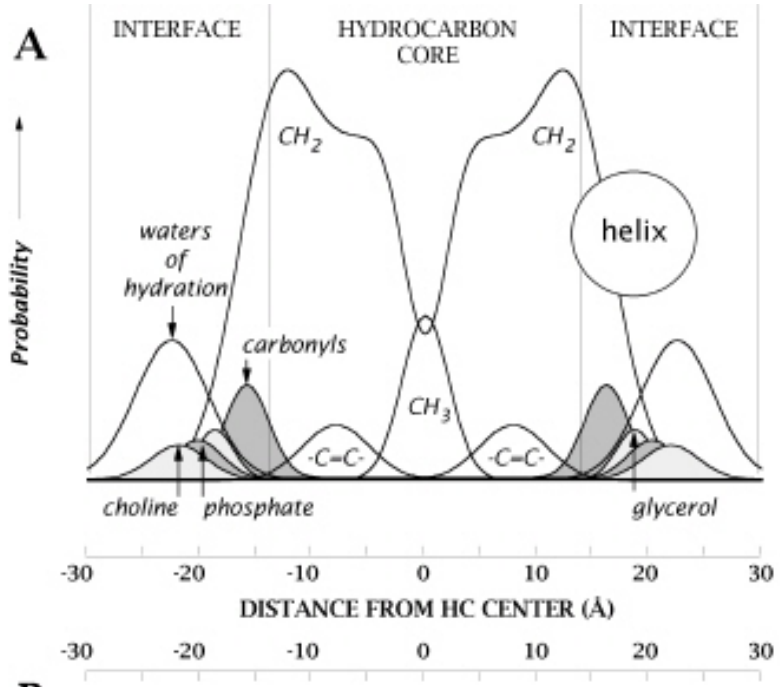


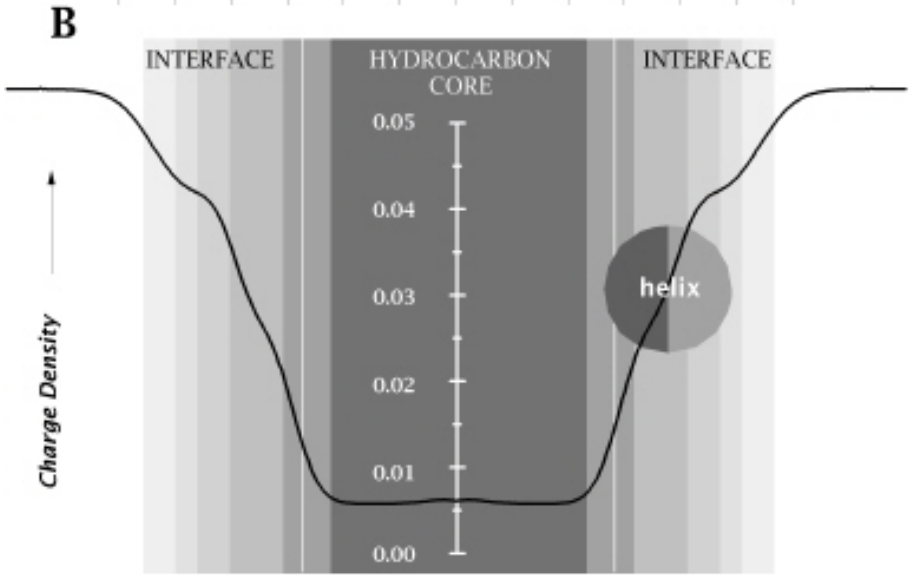
Defining "The Structure" of Fluid Bilayers



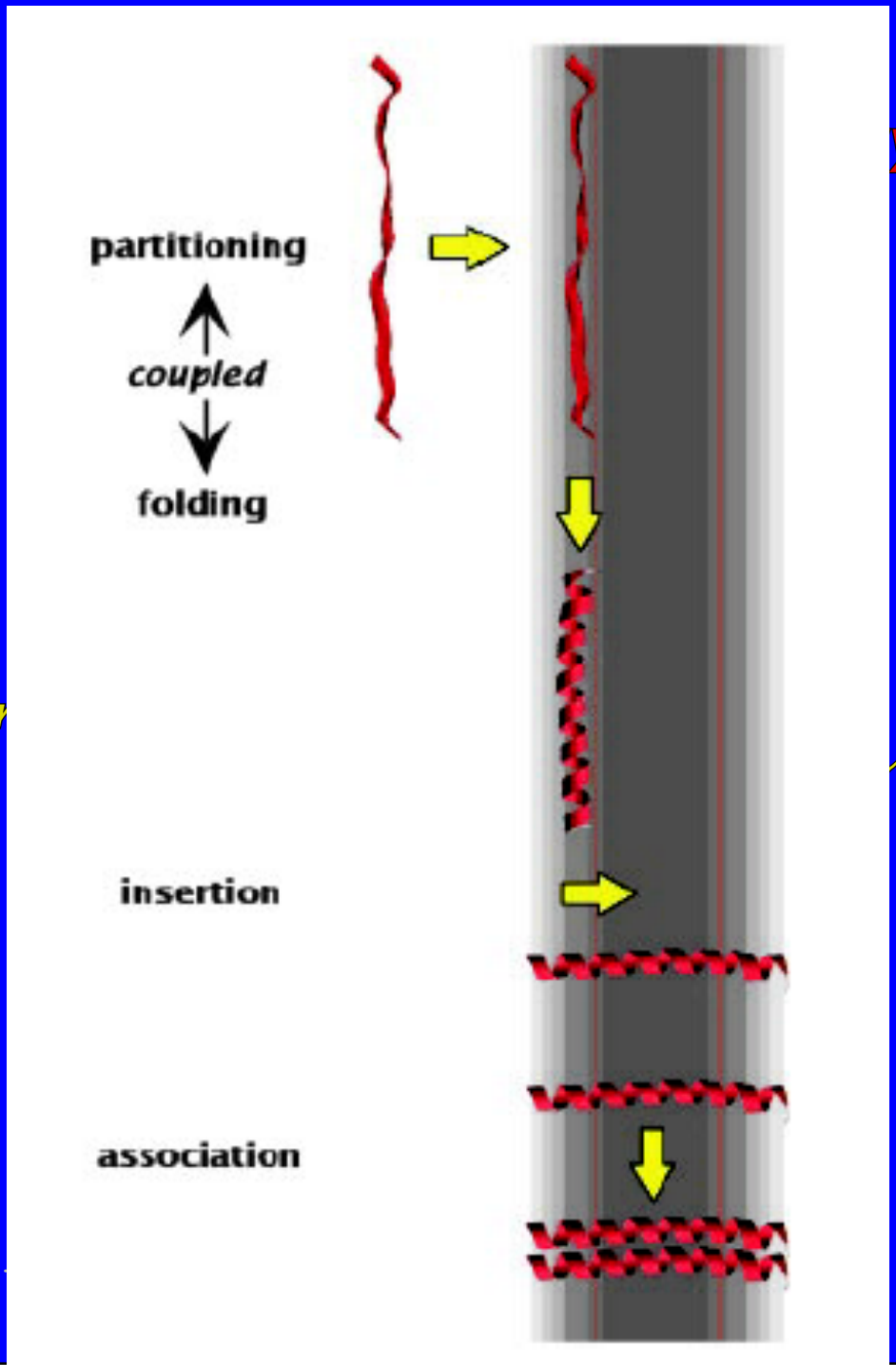


Distribution of groups along the z-axis





from S. White



y

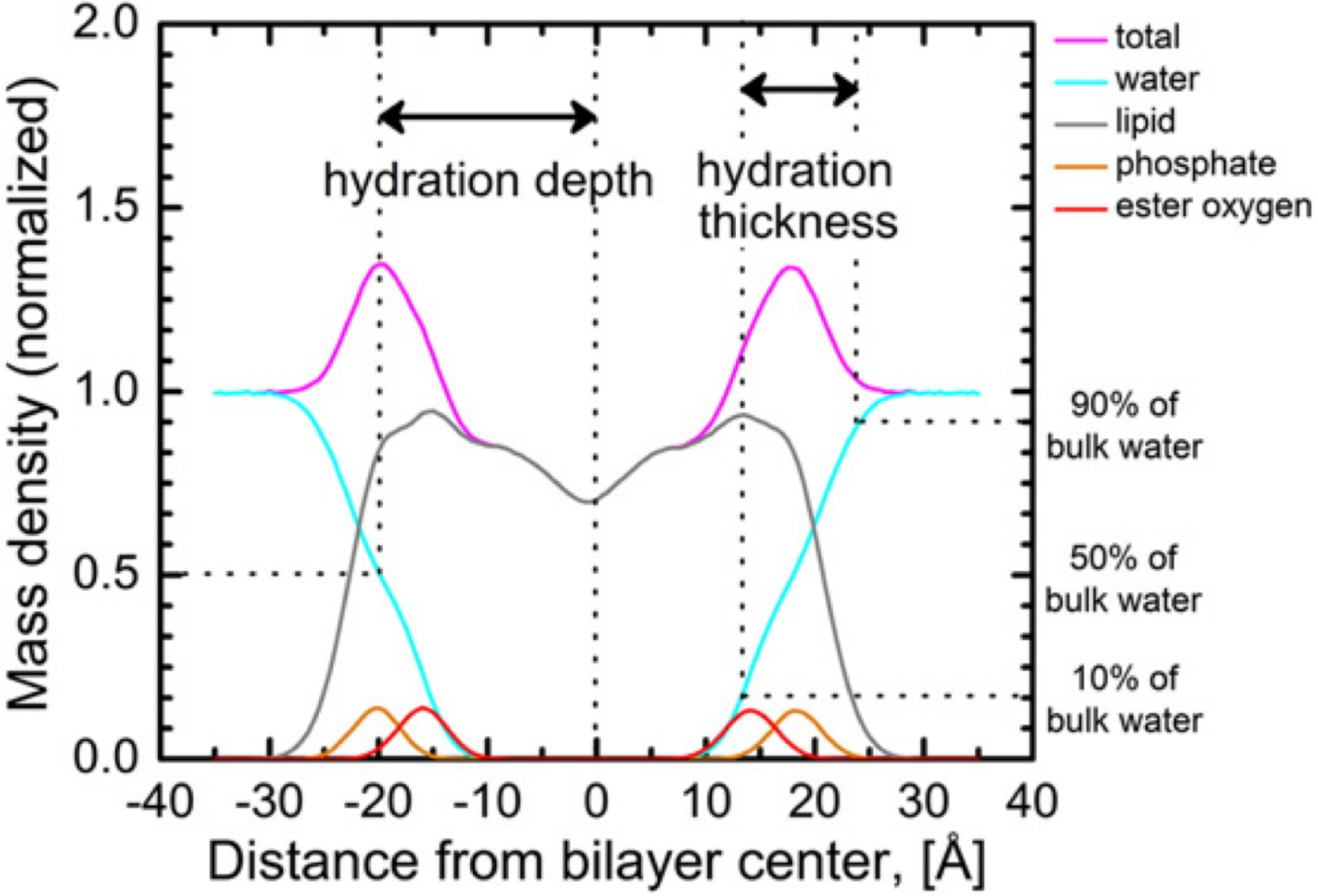
M. C. Wiener & S. H. White (1992)
Biophys. J. 61:434-447

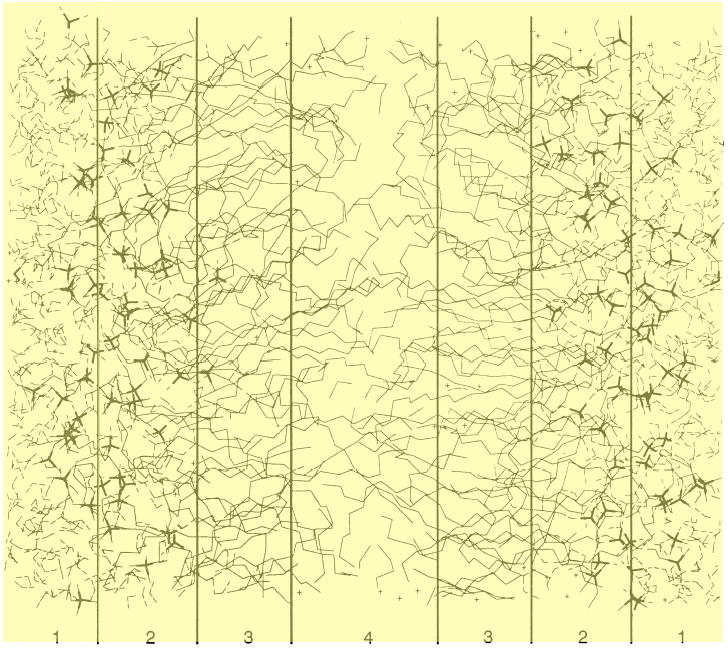
Bilayer Polar Profile

S. H. White & W. C. Wimley (1998)
Biochim. Biophys. Acta 1376:339-352

[profiles_perturbed_10.

Time averaged mass density profiles of the DOPC groups relative to bulk water at 0 dyn/cm membrane tension.





The lipid bilayer

Region 1: perturbed water

Low headgroup density –
20-27 Å from the bilayer center

Region 2: interphase

High headgroup density –
13-20 Å from the bilayer center

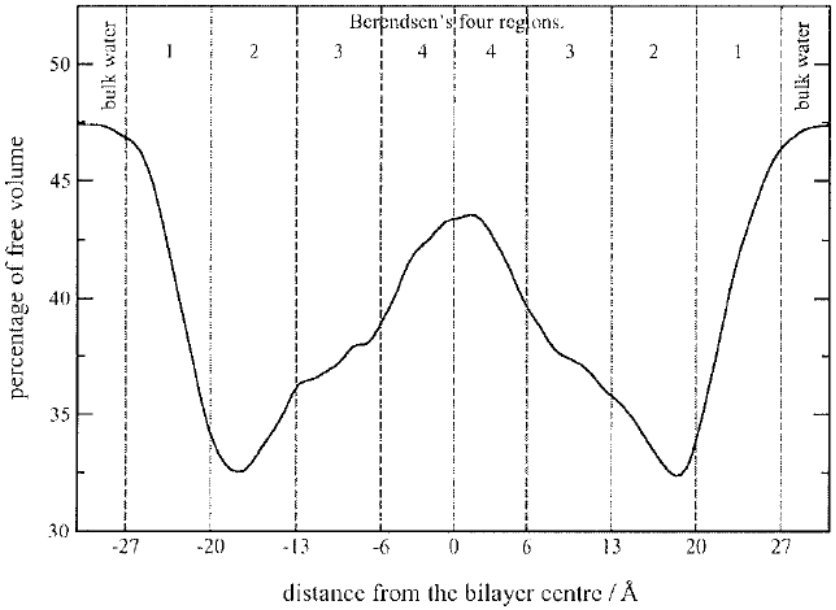
Region 3: soft polymer

High tail density –
6-13 Å from the bilayer center

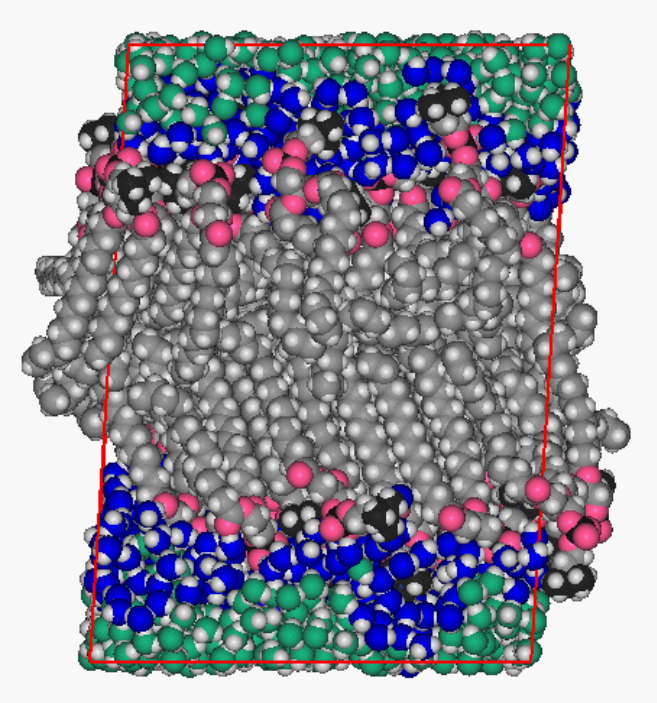
Region 4: decane

Low tail density –
0-6 Å from the bilayer center

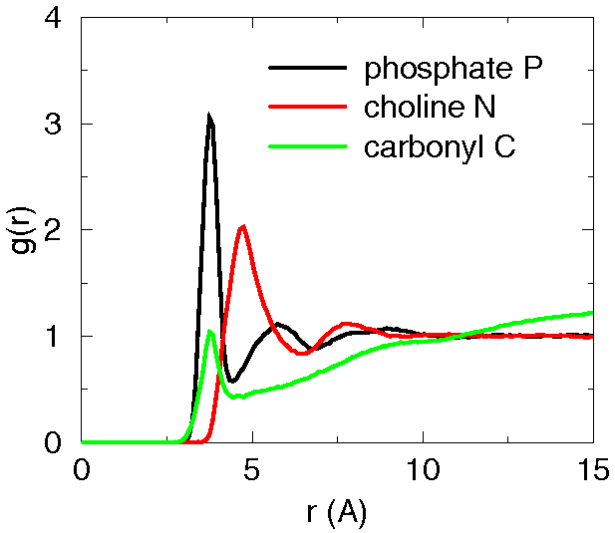
Free vilume distribution



"Bound" water

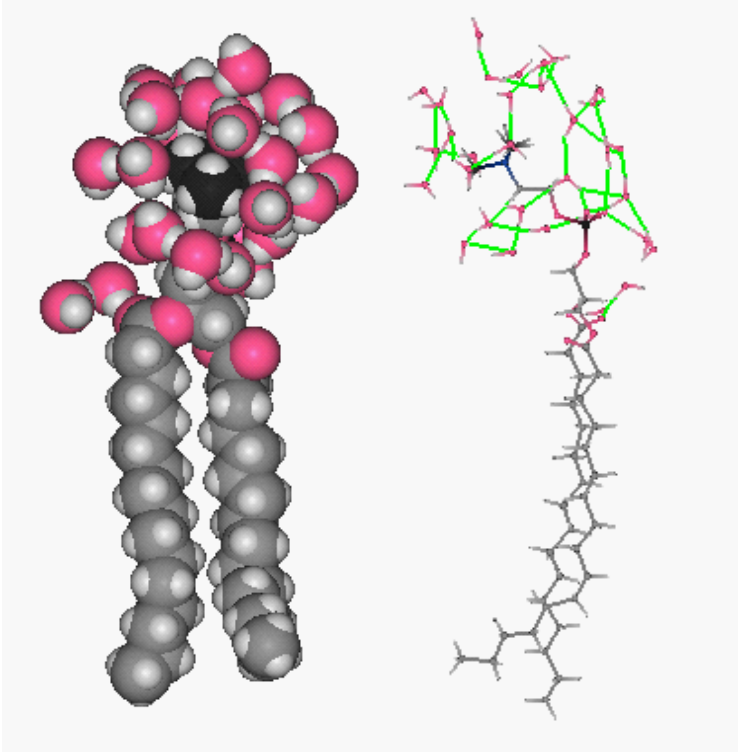


Radial distribution of water O



phosphate P – 4
choline N - 15
carbonyl C - 1.5
total bound - 21

First solvation shell

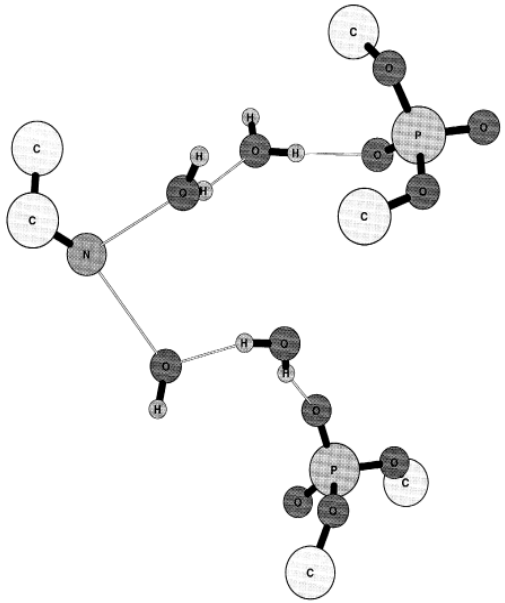


Diffusion constants of water

DPPC bilayer (nw = 28, 50˚C)

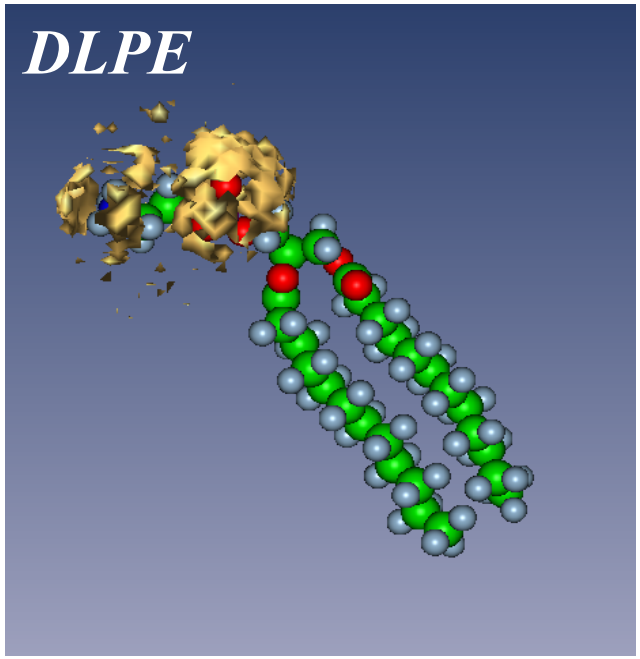
	D (10^{-5} cm^2/s)
bulk	6.2
N bound	4.1
P bound	3.0
CO bound	2.2

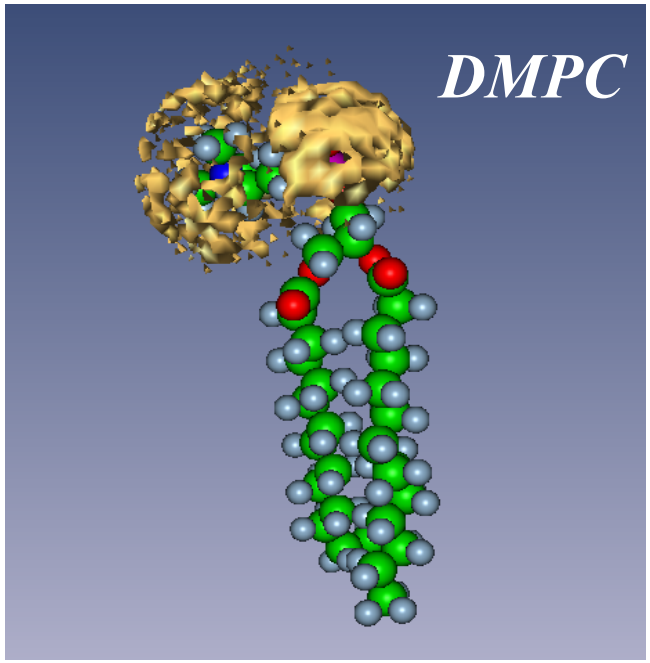
[Tobias, in "Hydration Processes in Biology," NATO ASI, ISO Press (1999)]

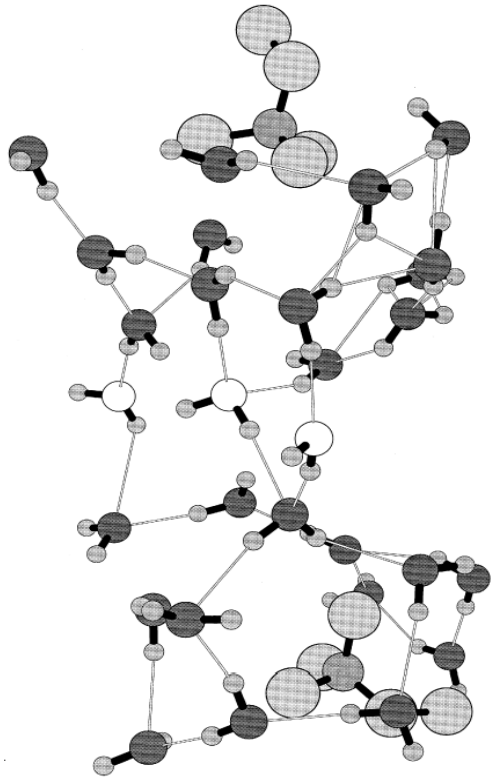


Water bridges between PE headgroups.

The clathrate cages around $N(CH_3)_3$ groups from two PC headgroups from opposing bilayers.

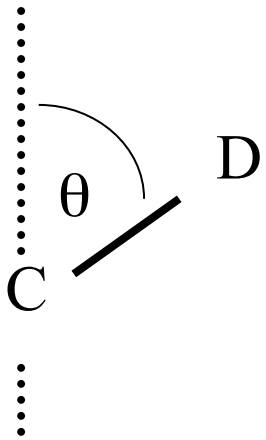


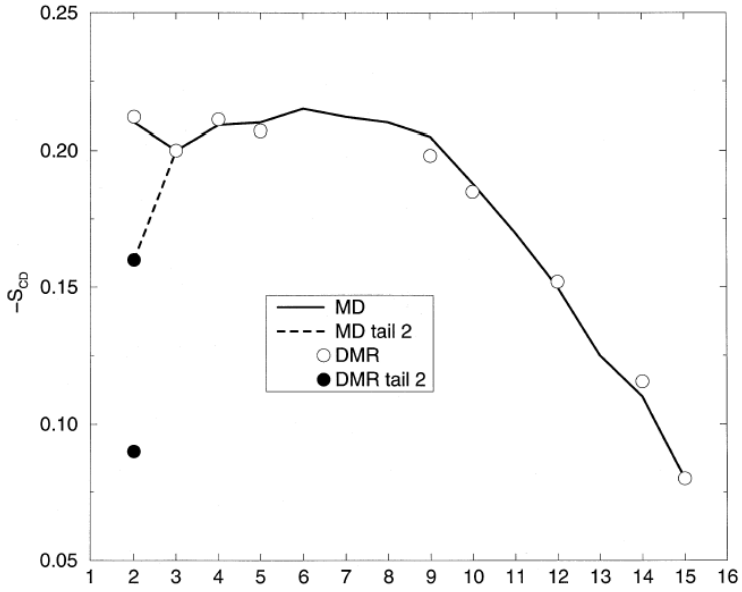




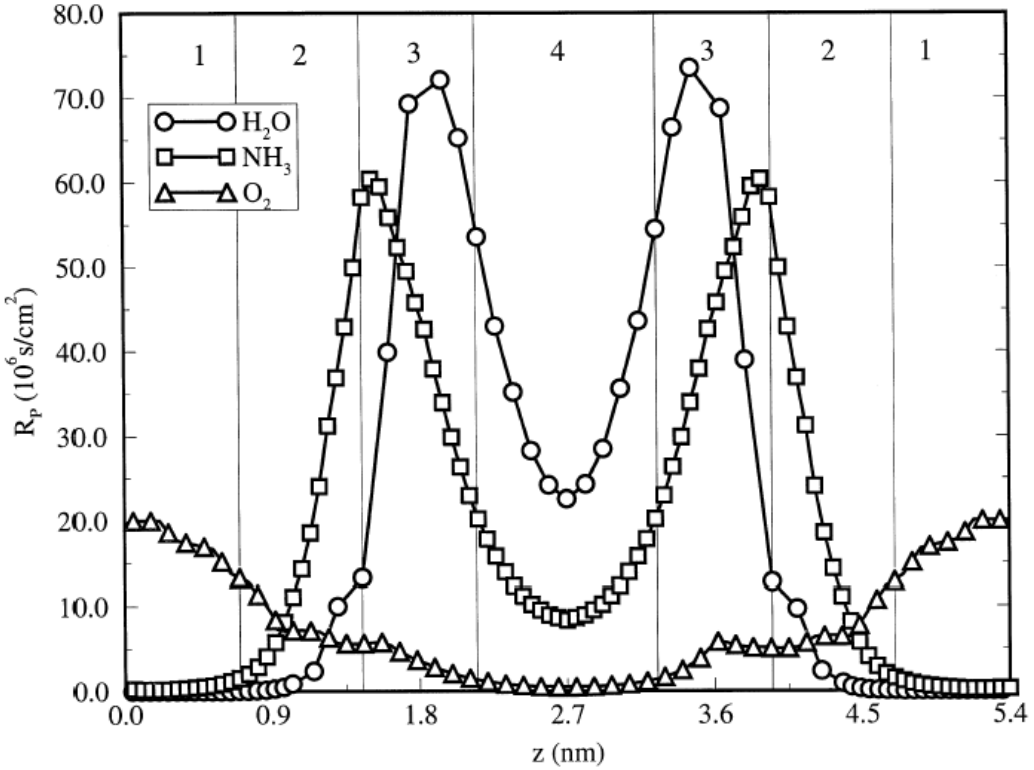
- The chain order parameters are at their plateau values.

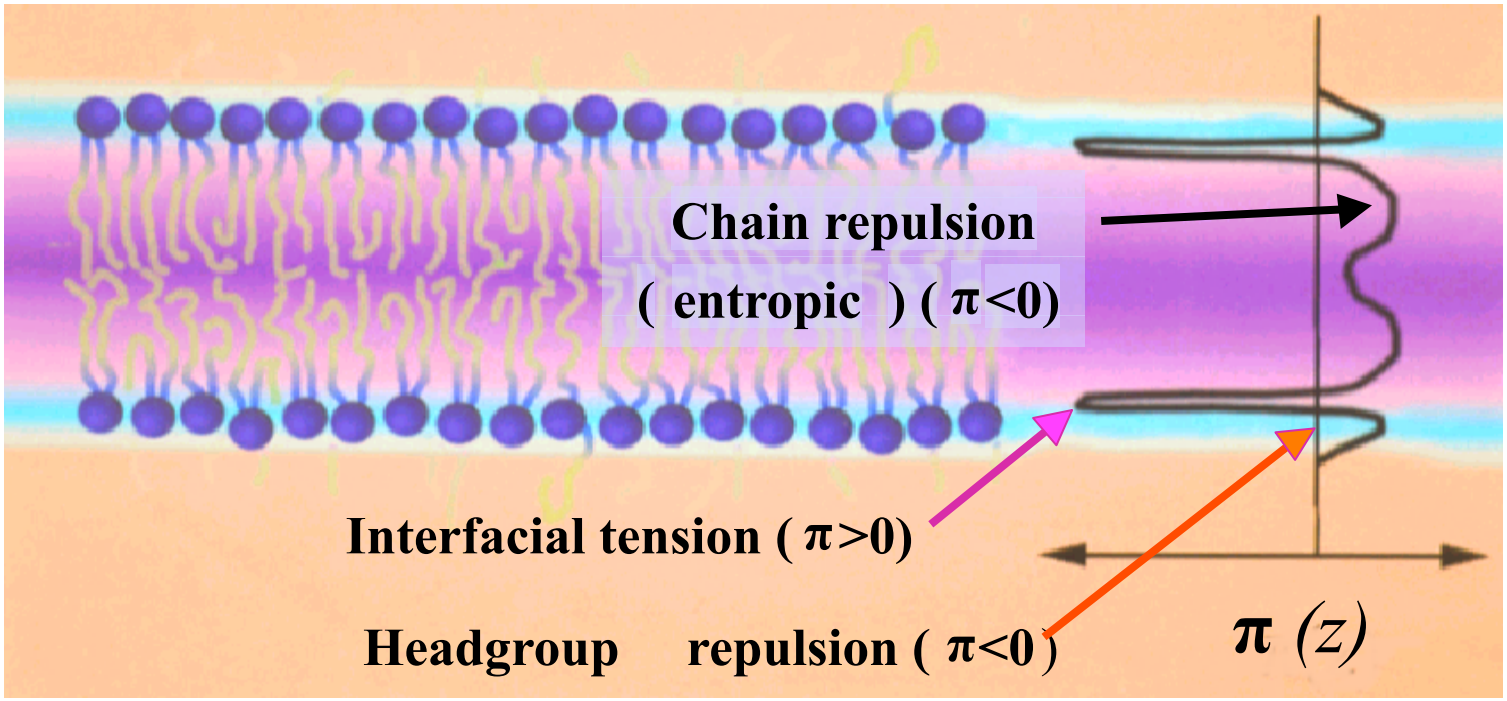
$$S_{CD} = \frac{1}{2}\left[3\left\langle \cos^2\theta(t)\right\rangle - 1\right]$$

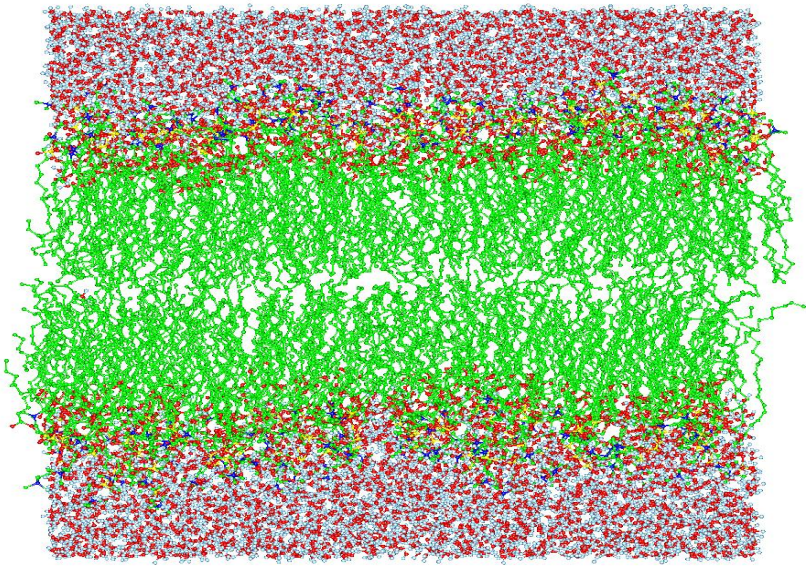




- The main barrier to permeation of small molecules.







Electrostatic repulsion

Hydrogen bonding

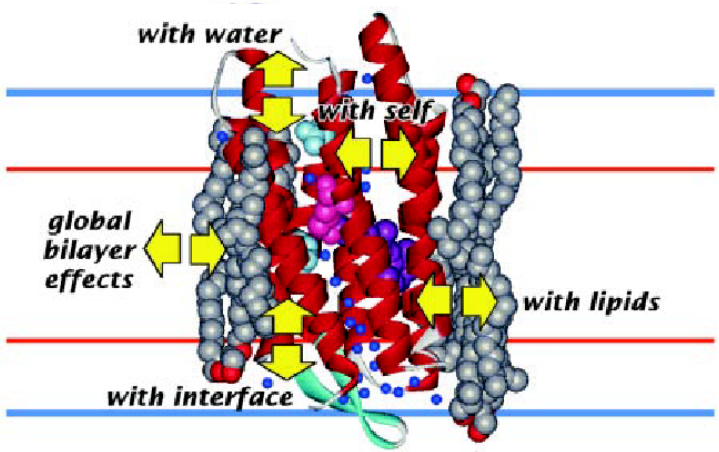
Steric repulsion

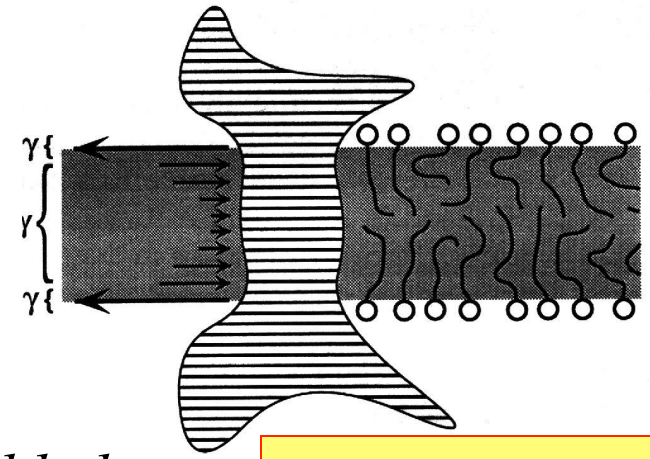
van der Waals attraction

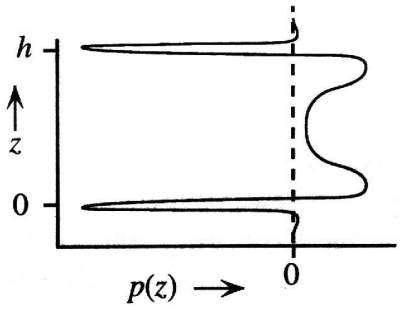
Hydrophobic effect

Hydration forces

Lateral pressure in membranes
(a mechanism for modulation of protein function)



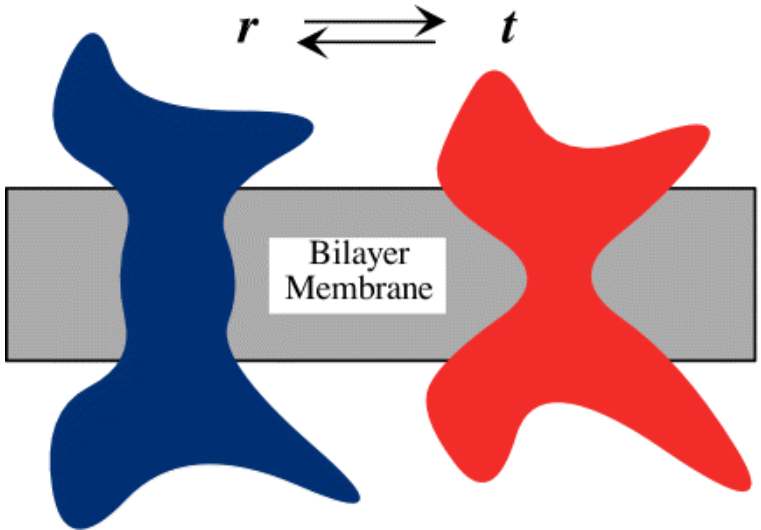


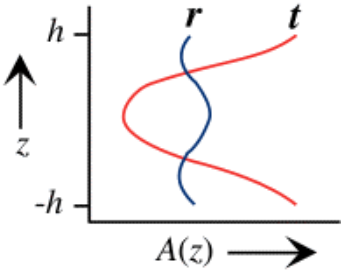


The membrane is self-assembled structure – there is no overall stress.

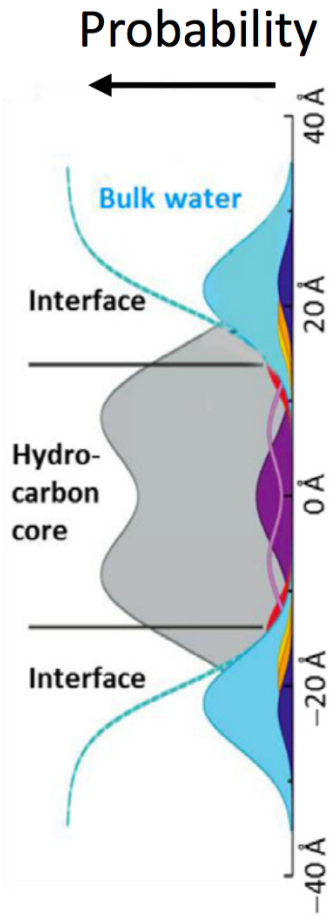
$$\pi = \int \partial\pi = \int p(z)\partial z \approx 0$$

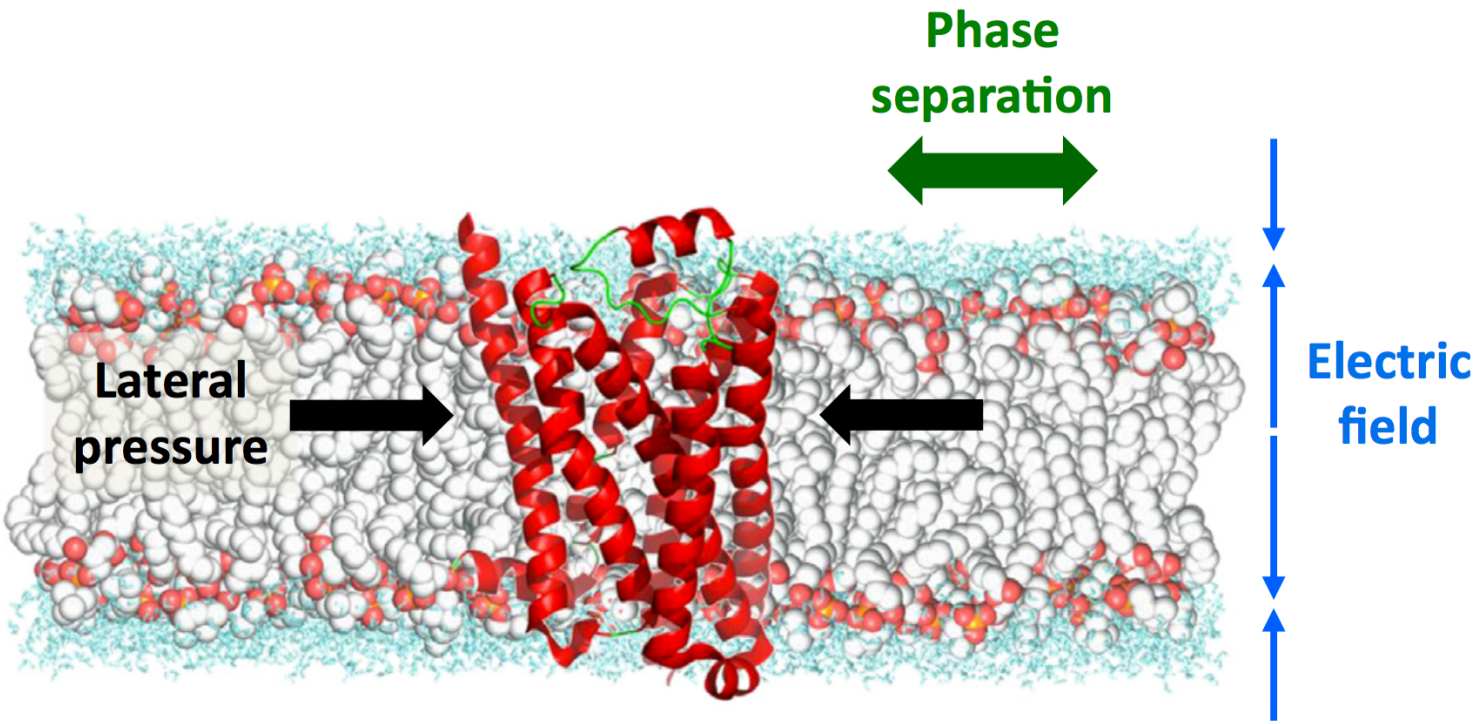
Many protein functions depend on a transition between conformational states.





Membrane proteins are stabilized in lipid bilayers which constitute cell membranes.



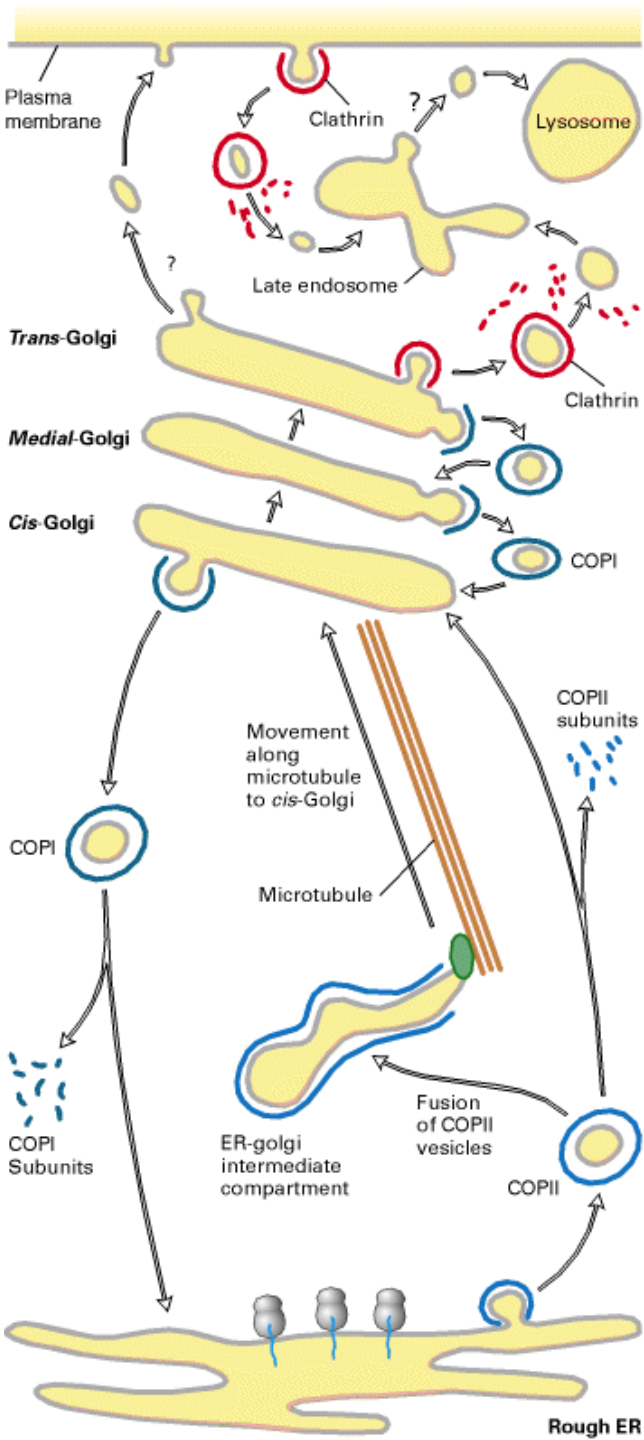


Unique physical properties of a lipid bilayer, which may affect the folding, stability and function of membrane proteins.

Biological membrane dynamics

An aggregate is an excellent material for cell membranes

- *Hydrophobic effect is the driving force – self-assembly in water*
- *Tendency to close on themselves*
- *Extensive: up to millimeters*



Biological membranes

Structure, composition and assembly;

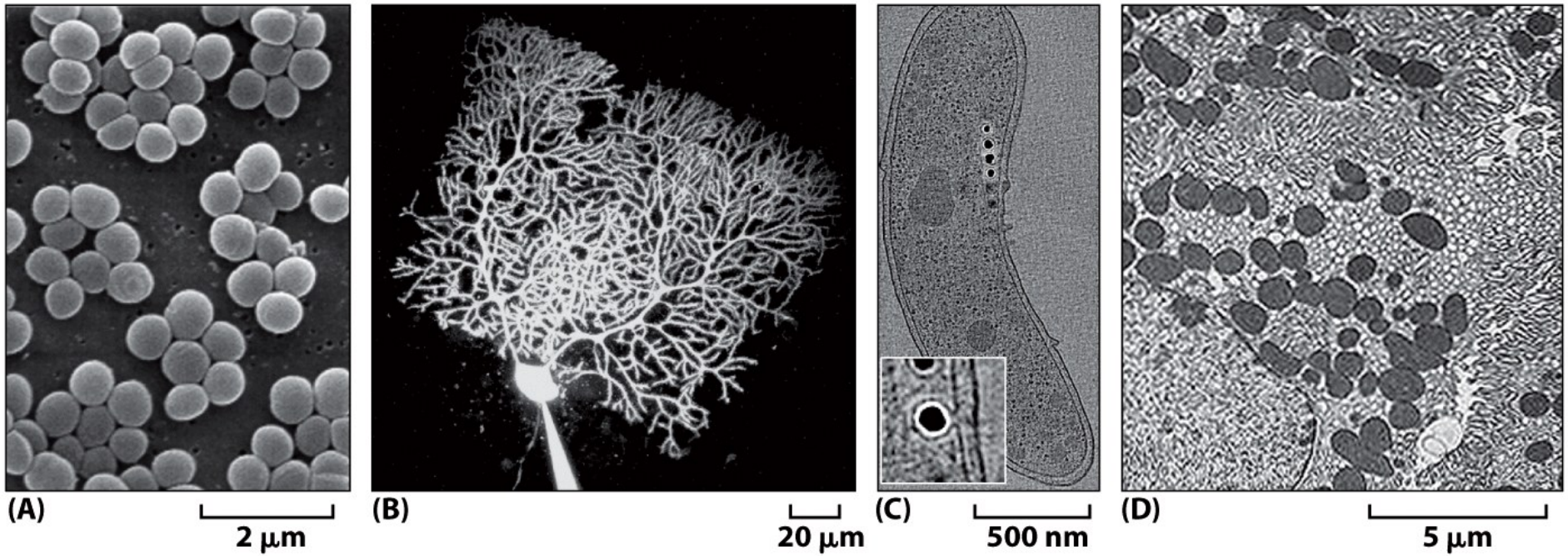
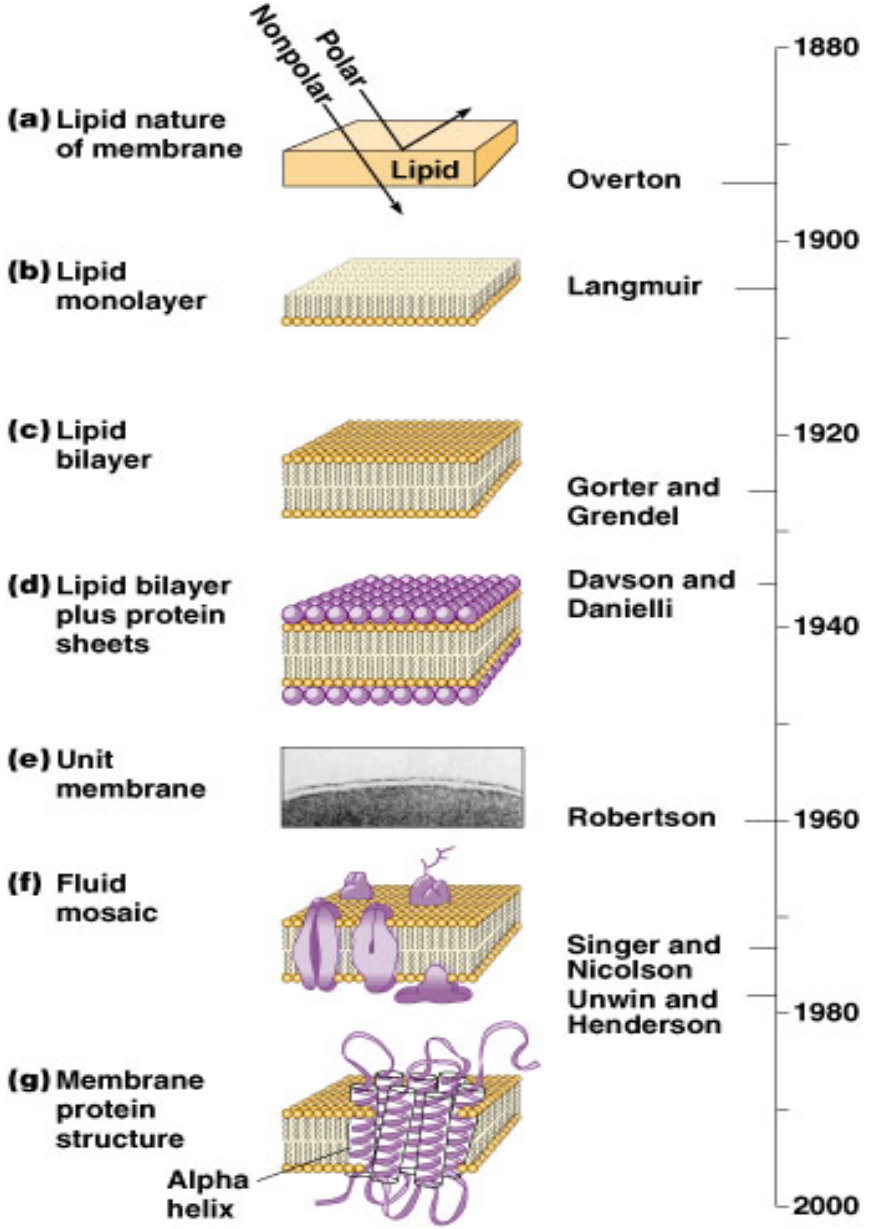


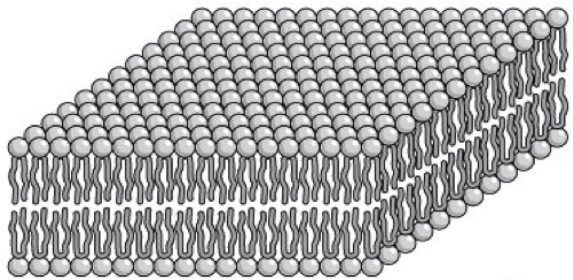
Figure 11.33 Physical Biology of the Cell (© Garland Science 2009)

Biological membrane model development

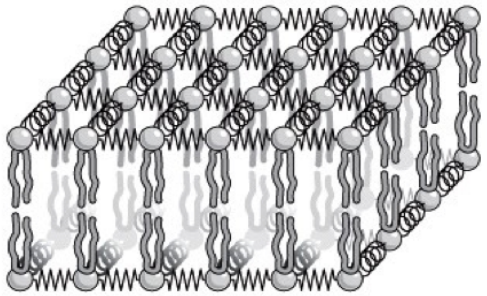
- A third of the dry weight of a cell is membrane.
- Almost half of all proteins encoded by a eukaryotic genome are membrane proteins.
- Roughly half of biological processes occur on membranes.
- The phospholipid bilayer membrane is the solvent for membrane proteins and forms the basis of the biological membrane.



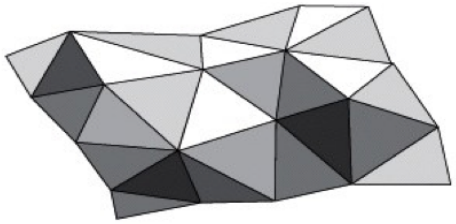
Membrane models:



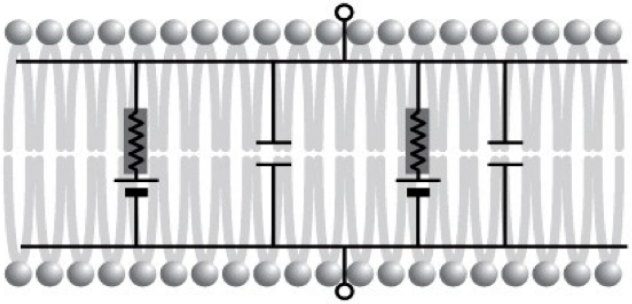
ARRAY OF SPRINGS



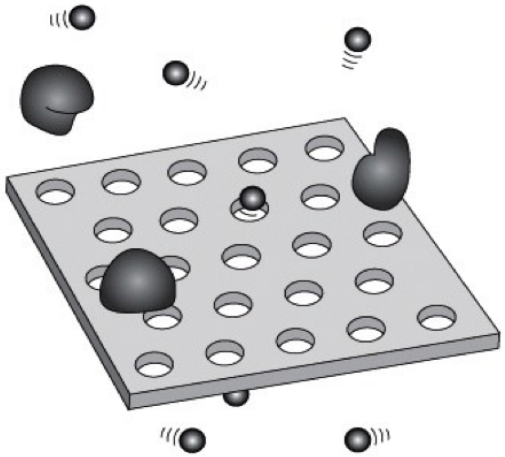
RANDOM SURFACE



RC CIRCUIT

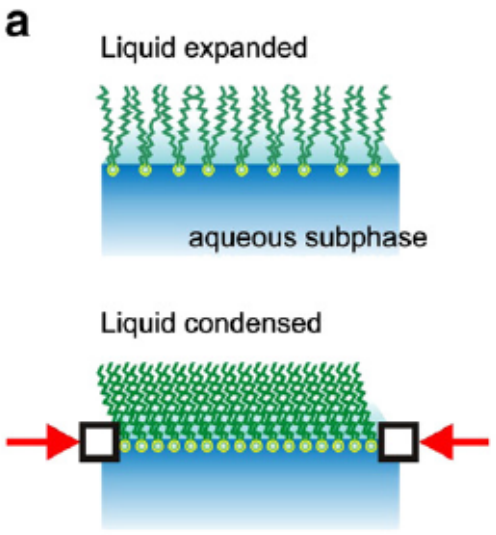


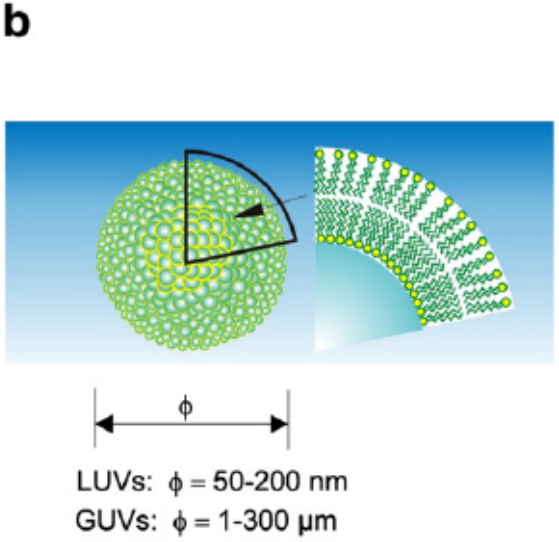
SEMI-PERMEABLE BARRIER

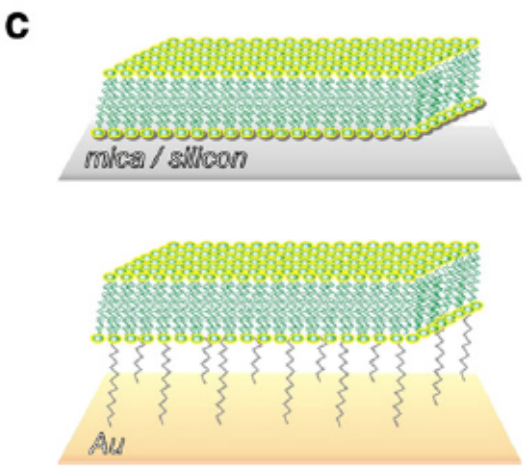


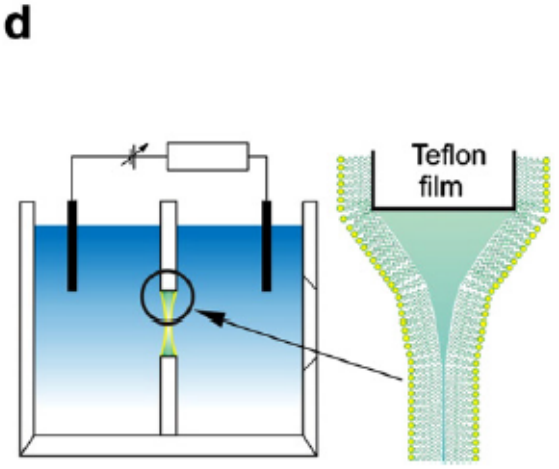
Typical model lipid membranes:

a) Langmuir monolayer in expanded or condensed state.
b) Lipid liposomes and GUVs.
c) Supported lipid bilayers on mica or silicon and tethered bilayer lipid membranes on a gold solid support.
d) Chamber for studying electrical properties and ion transport of bilayers (black) lipid membranes.

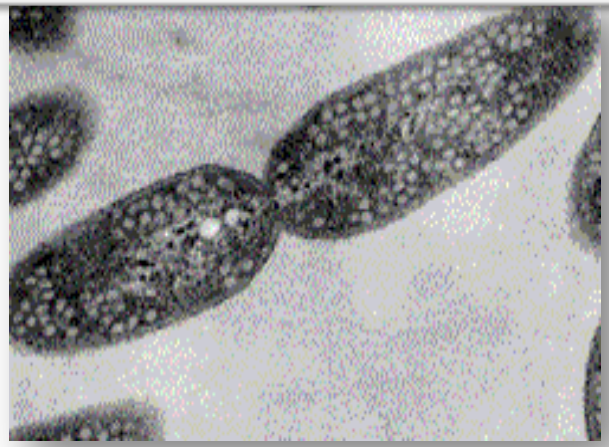






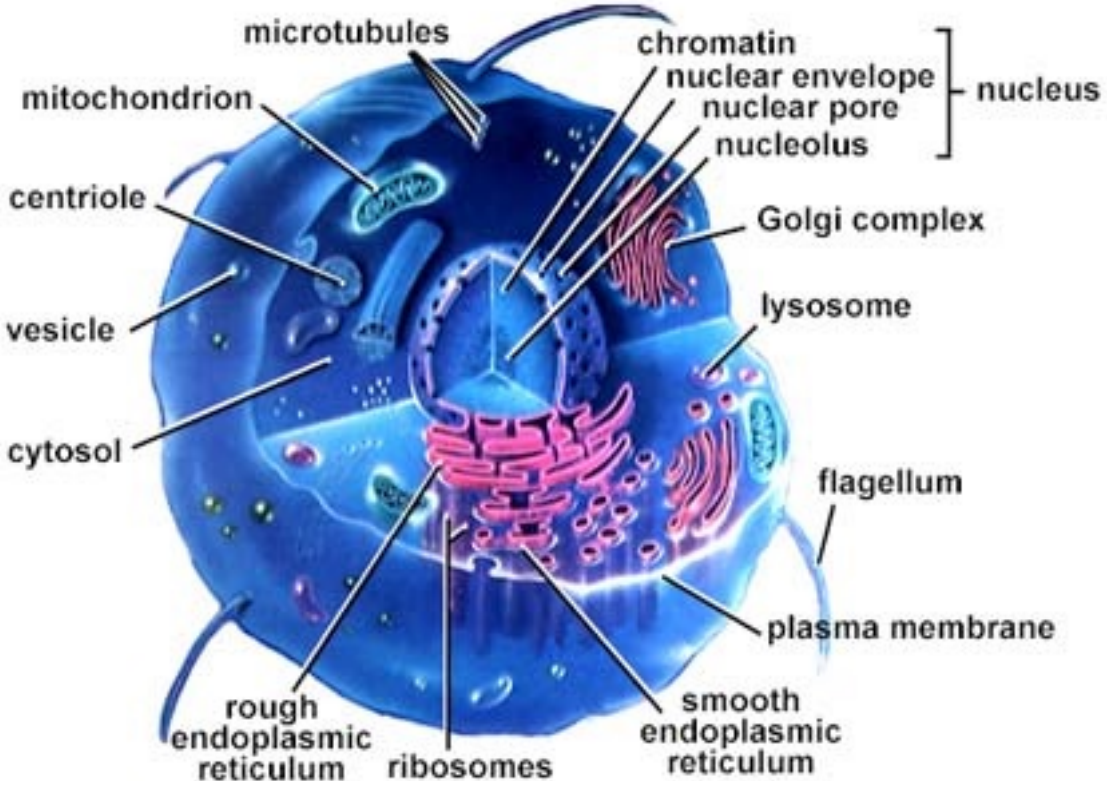


Biological membranes are flexible, non-extendible, self-sealing, differentially permeable barriers that separate "IN" from "OUT"



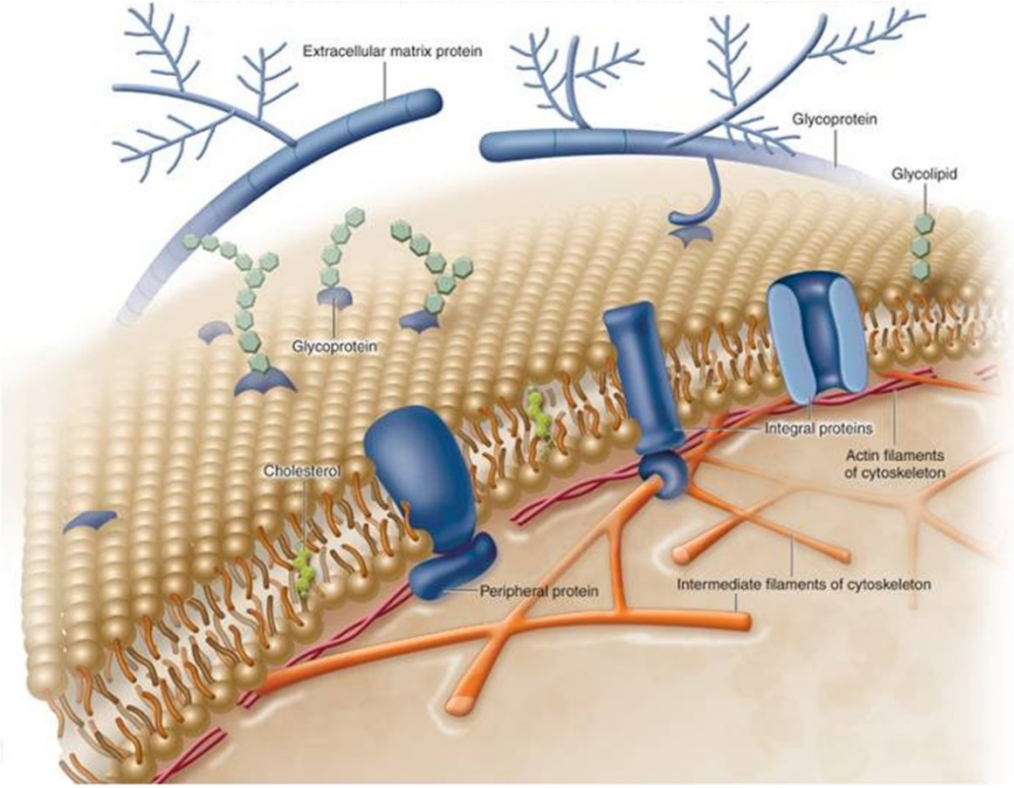
Prokaryote

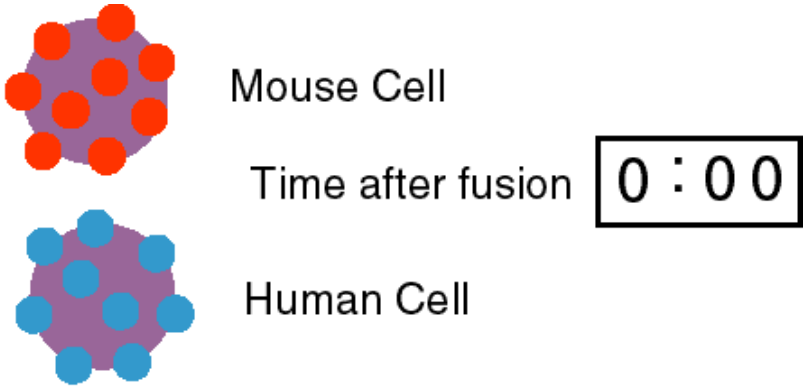
Eukaryote



Biological membrane - Life's Border

Its thermodinamical stability results from molecular non-covalent interactions within the phospholipid bilayer and water phase.

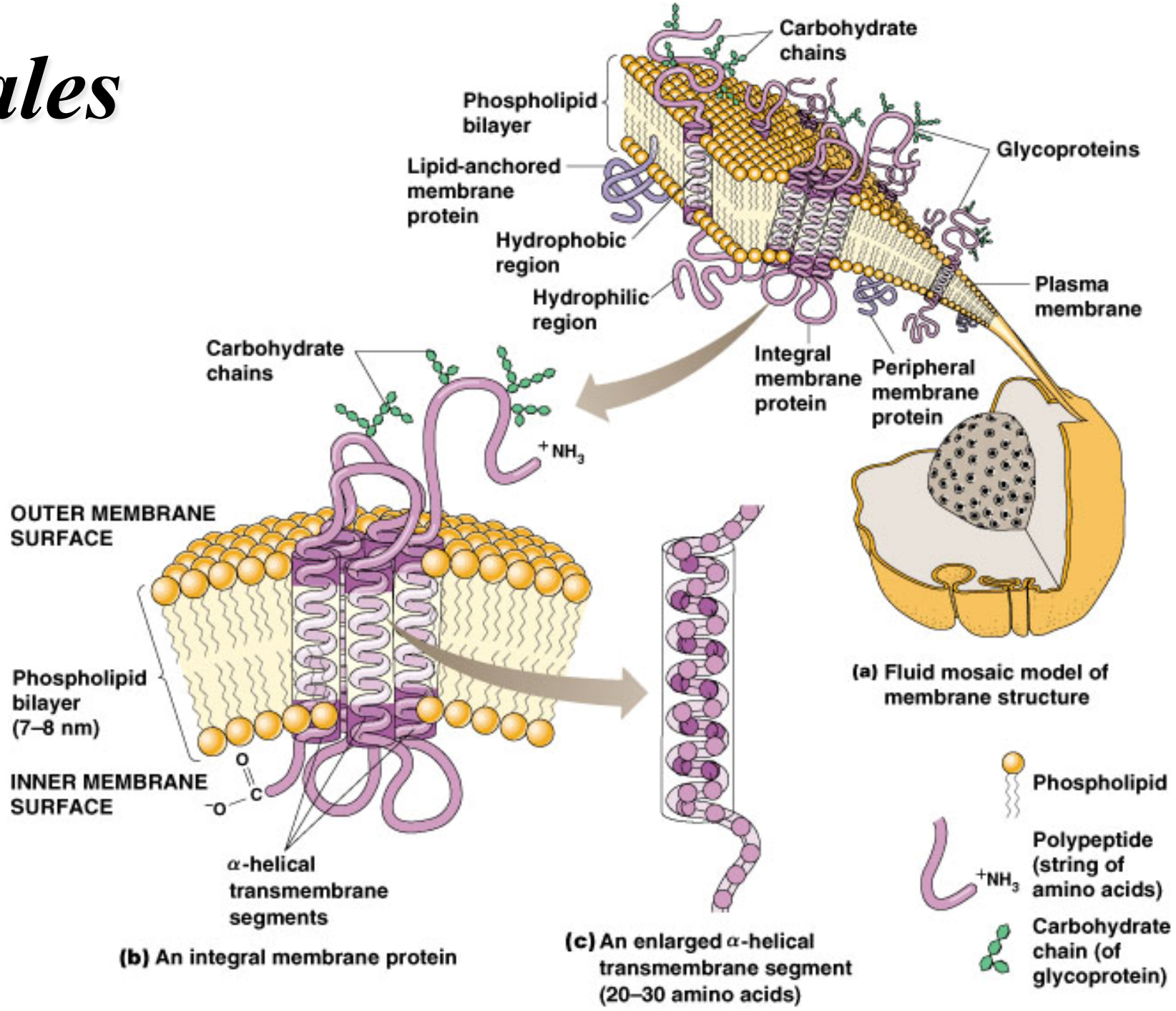




"Membranes are two-dimensional solutions of oriented lipids and globular proteins."

J. Singer & G. Nicolson, 1972

Scales


Carbohydrate chains
Phospholipid bilayer
Lipid-anchored membrane protein
Glycoproteins
Hydrophobic region
Hydrophilic region
Plasma membrane
Integral membrane protein
Peripheral membrane protein
(a) Fluid mosaic model of membrane structure
Carbohydrate chains
+NH3
OUTER MEMBRANE SURFACE
Phospholipid bilayer (7–8 nm)
INNER MEMBRANE SURFACE
O
C
−O
α-helical transmembrane segments
(b) An integral membrane protein
(c) An enlarged α-helical transmembrane segment (20–30 amino acids)
Phospholipid
Polypeptide (string of amino acids)
+NH3
Carbohydrate chain (of glycoprotein)

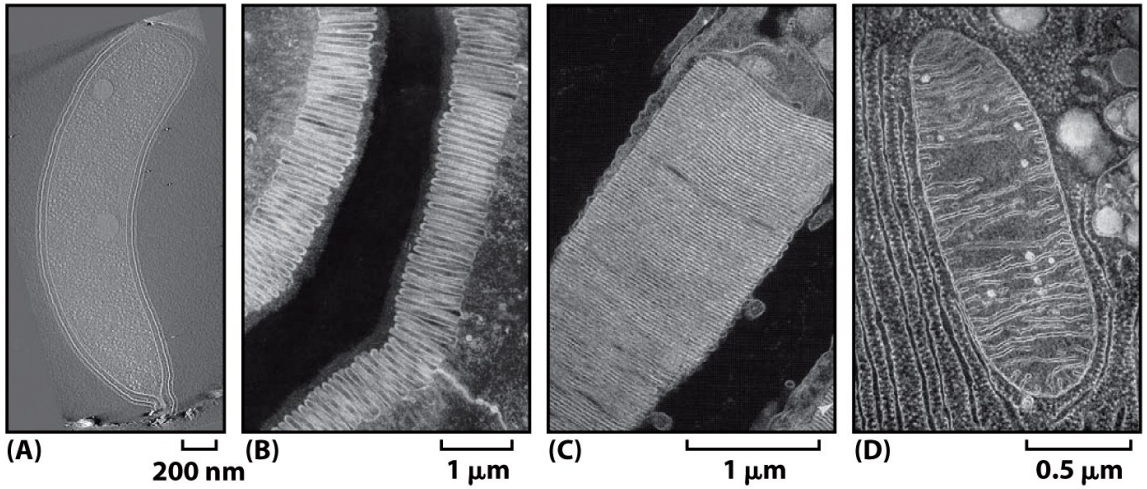
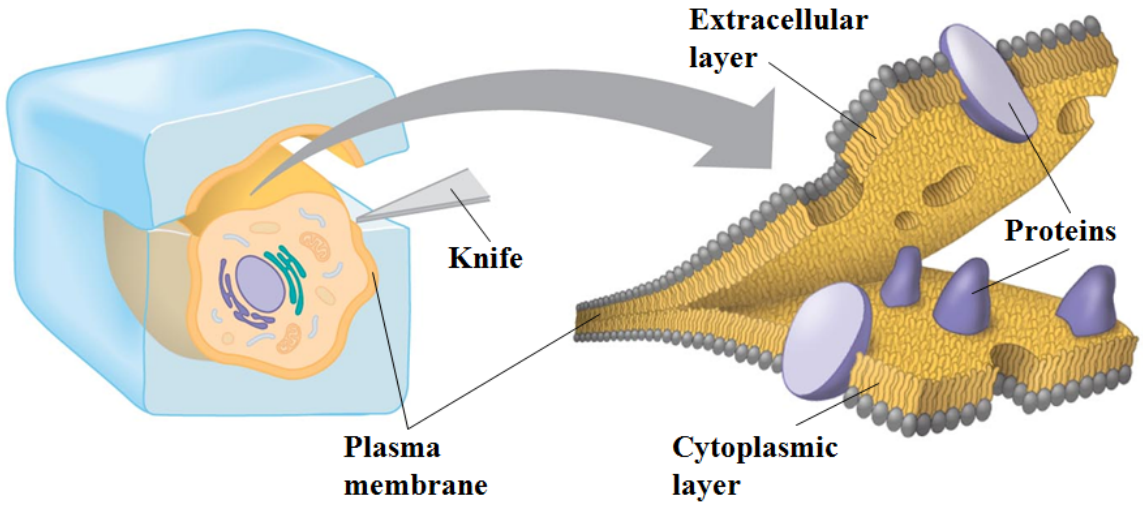


Figure 11.3 Physical Biology of the Cell (© Garland Science 2009)

Electron microscopy of biological membranes

Freeze-facture is a specialized preparation technique that splits a membrane along the middle of the phospholipid bilayer



Extracellular layer

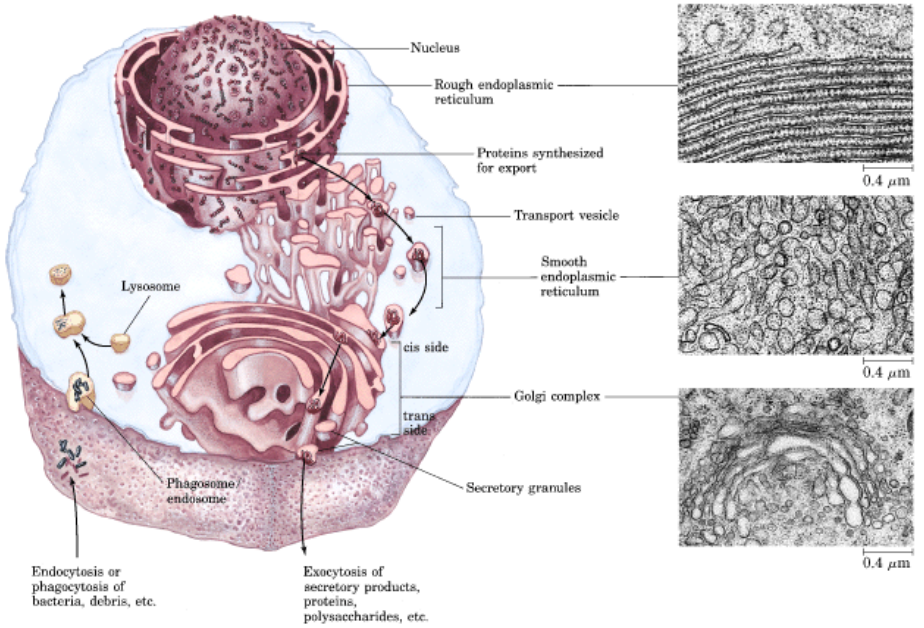
Cytoplasmic layer

Functions of the cell membrane

Isolation, compartmentalization, protection

Regulate mass transport

Diffusion
Active transport
Vesicular transport



Electric activity

Membrane potencial

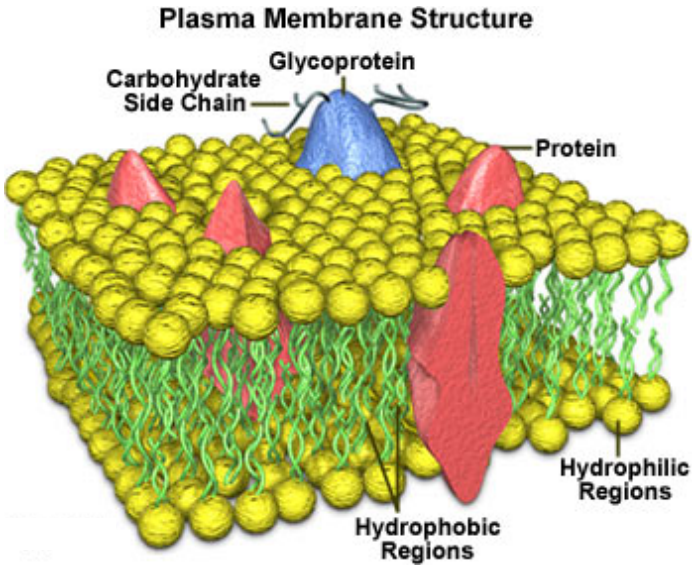
Signaling, signal processing

Receptor –ligand interaction
(hormons, growth factors, neurotransmitters, etc.)

Selective signal recognition and transduction by transmembrane receptors

Functions of the cell membrane

Cell to cell interaction, cell recognition



Immune recognition,
synchronization of cellular activities

Biochemical activity

Provide stable site for the binding and catalysis of enzymes

Compartment separation for chemiosmosis

ATP sysnthesis in mitochondria and chloroplasts

Cell shape and motility

cytoskeleton,
cilia and flagella

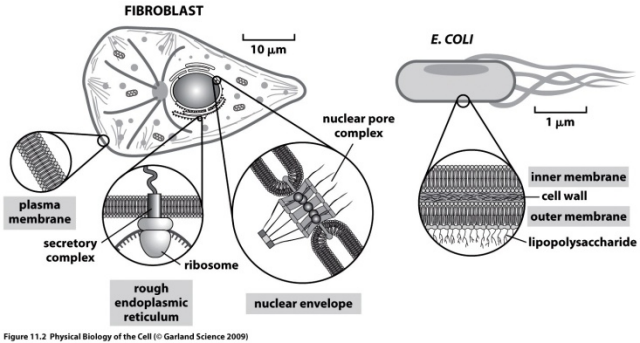
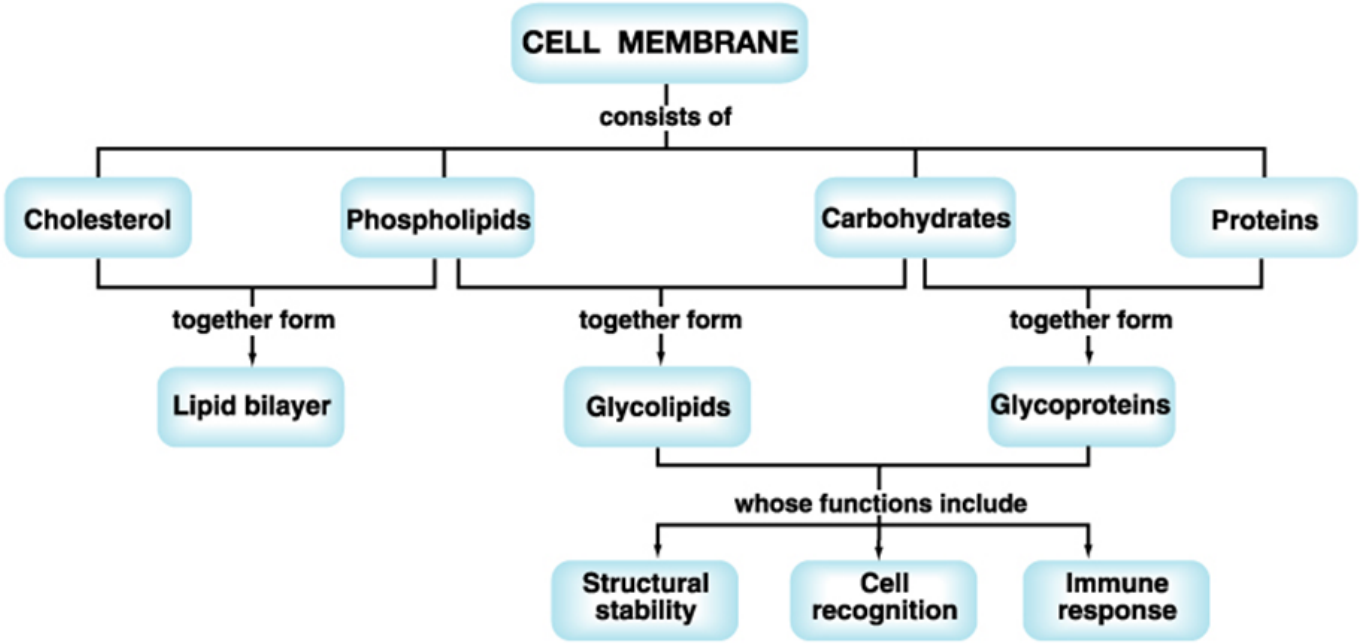


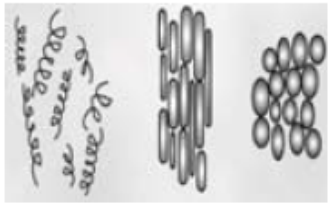
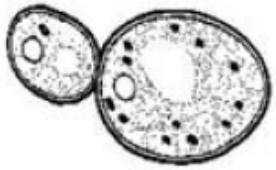
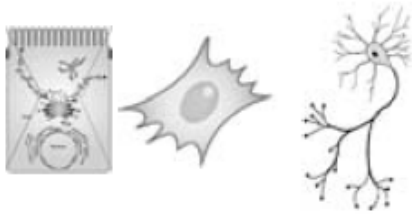
Figure 11.2 Physical Biology of the Cell (© Garland Science 2009)



Plasma membrane lipid composition (in mol%) of various cell types

Lipid type	Net charge at neutral pH	Human erythrocytes, outer leaflet	Human erythrocytes, inner leaflet	Human fibroblasts	Human HeLa	G^- bacteria (*E. coli*, outer membrane)	G^+ bacteria (*B. subtilis*)	Yeast (*S. cerevisiae*)	Plant (oat root)
Cholesterol	0	11.1	33.3	13	25.3				
Other sterols	0							48.5	39.1
Phosphaditylcholine (PC)	0	10.3	4.1	43.2	39.5			8.8	14.3
Phosphatidylethanolamine (PE)	0	3.7	11.6	16.1	16.8	83.5	8.4	7.2	15.3
Spingolipids (SM)	0	11.8	2	12.2	3.1			15.8	10.1
Diacylglycerol (DG)	0						28.2		
Phosphatidylserine (PS)	1-	0.7	8.2	6.4	9.9	0.6		2	4.2
Phosphatidylglycerol (PG)	1-					12.3	49		1.3
Phosphatidic acid (PA)	1-	0.3	0.9	1.5		0.5		1.3	11.8
Cardiolipin (CL)	2-				4.3	0.6	2.8	2.2	
Phosphatidylinositol (PI)	1-, 2-, 3-	0.5	1.5	7.6	1			14.3	1.5
Others						1.5	11.6		1.7

Correlation between lipid compositional complexity and cellular architecture and function

	Bacteria	Yeast	Higher Organisms
			
Lipid composition	Mainly PE and PG	4 SPs, GPs, and sterols	GPs, sterols, and tissue-specific SPs
Membrane properties	Robust Different shapes	Robust Different shapes Complex organelle morphology	Robust Different shapes Complex organelle morphology Complex and specific cellular architecture
Functionalities	Membrane protein incorporation	Membrane protein incorporation Membrane budding Vesicular trafficking	Membrane protein incorporation Membrane budding Vesicular trafficking Specific functions depending on the cell type

Sphingolipids (SPs) and sterols enable eukaryotic cellular membranes with the property of vesicular trafficking important for the establishment and maintenance of distinct organelles. Tissue-specific SPs in higher organisms enable the generation of specific architecture and function

Protein, lipid, and carbohydrate content of different cell membranes

Membrane	Approximate Percent by Weight			Protein/Lipid Ratio
	Protein	Lipid	Carbohydrate	
Plasma membrane				
Human erythrocyte	49	43	8	1.14
Mammalian liver cell	54	36	10	1.50
Amoeba	54	42	4	1.29
Myelin sheath of nerve axon	18	79	3	0.23
Nuclear envelope	66	32	2	2.06
Endoplasmic reticulum	63	27	10	2.33
Golgi complex	64	26	10	2.46
Chloroplast thylakoids	70	30	0	2.33
Mitochondrial outer membrane	55	45	0	1.22
Mitochondrial inner membrane	78	22	0	3.54
Gram-positive bacterium	75	25	0	3.00

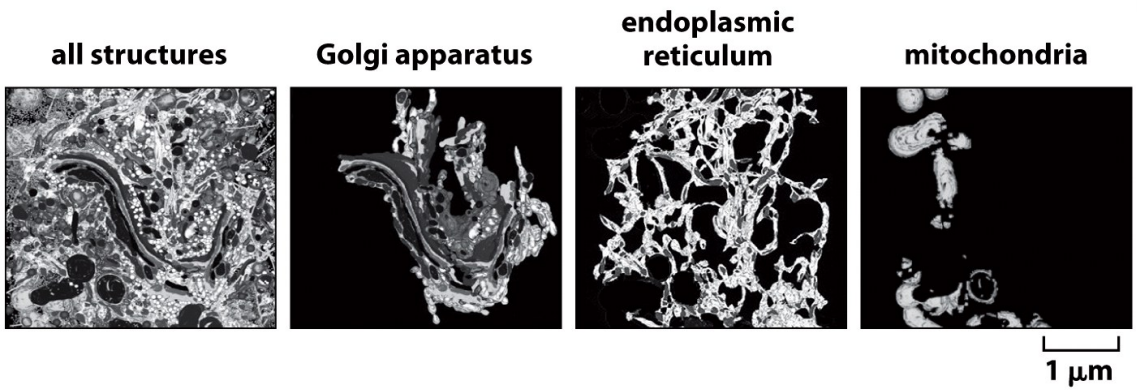
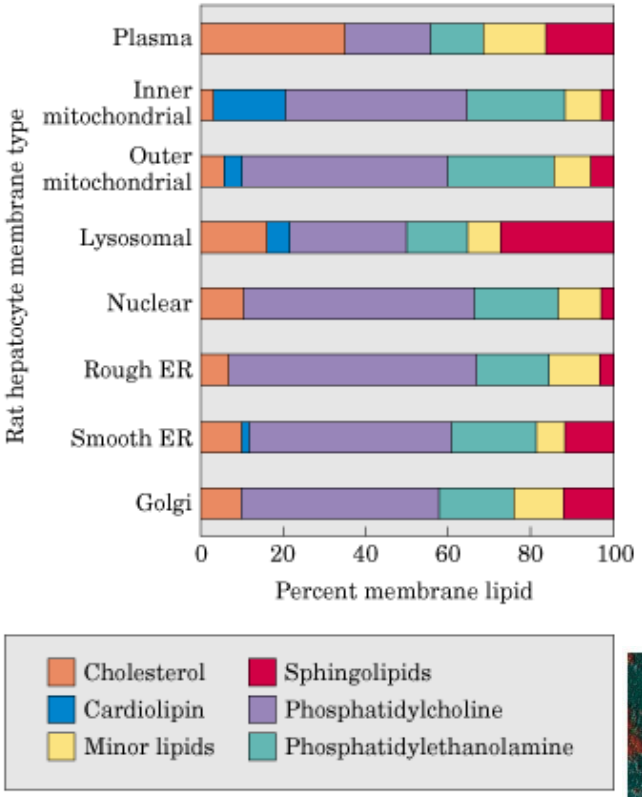
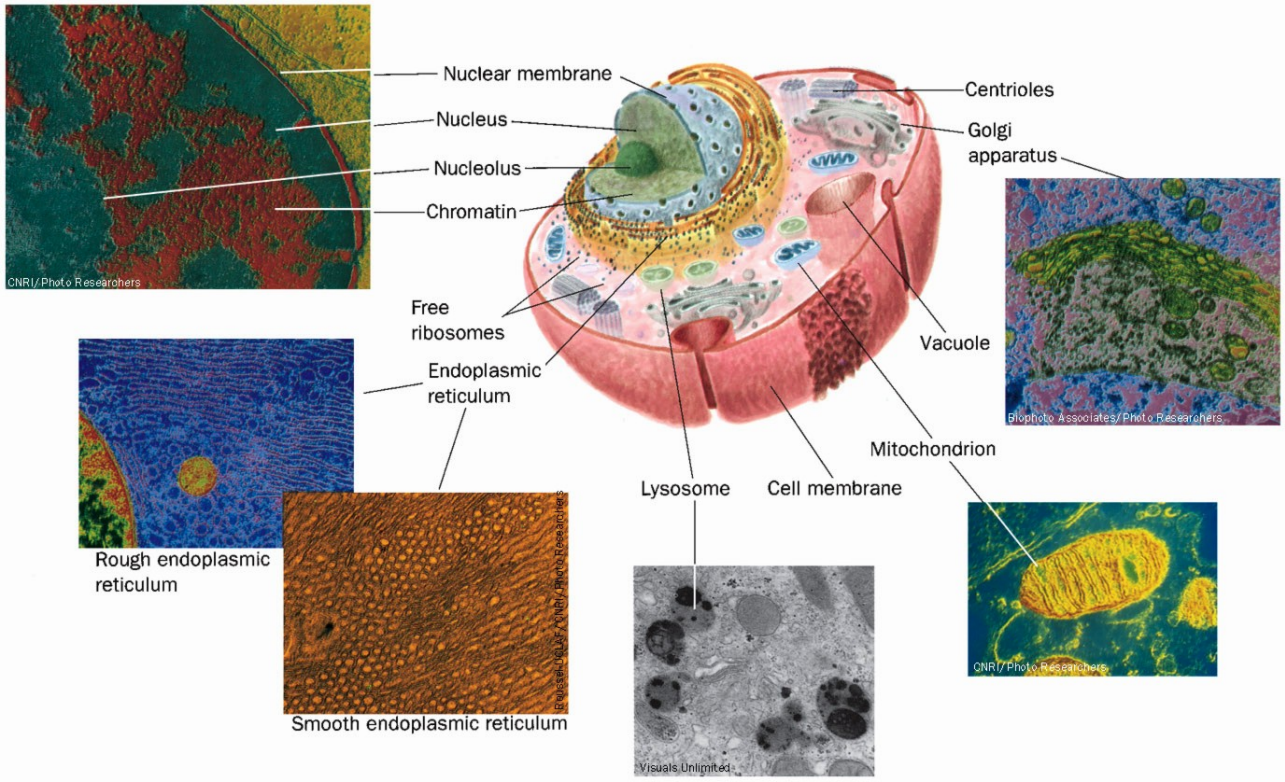


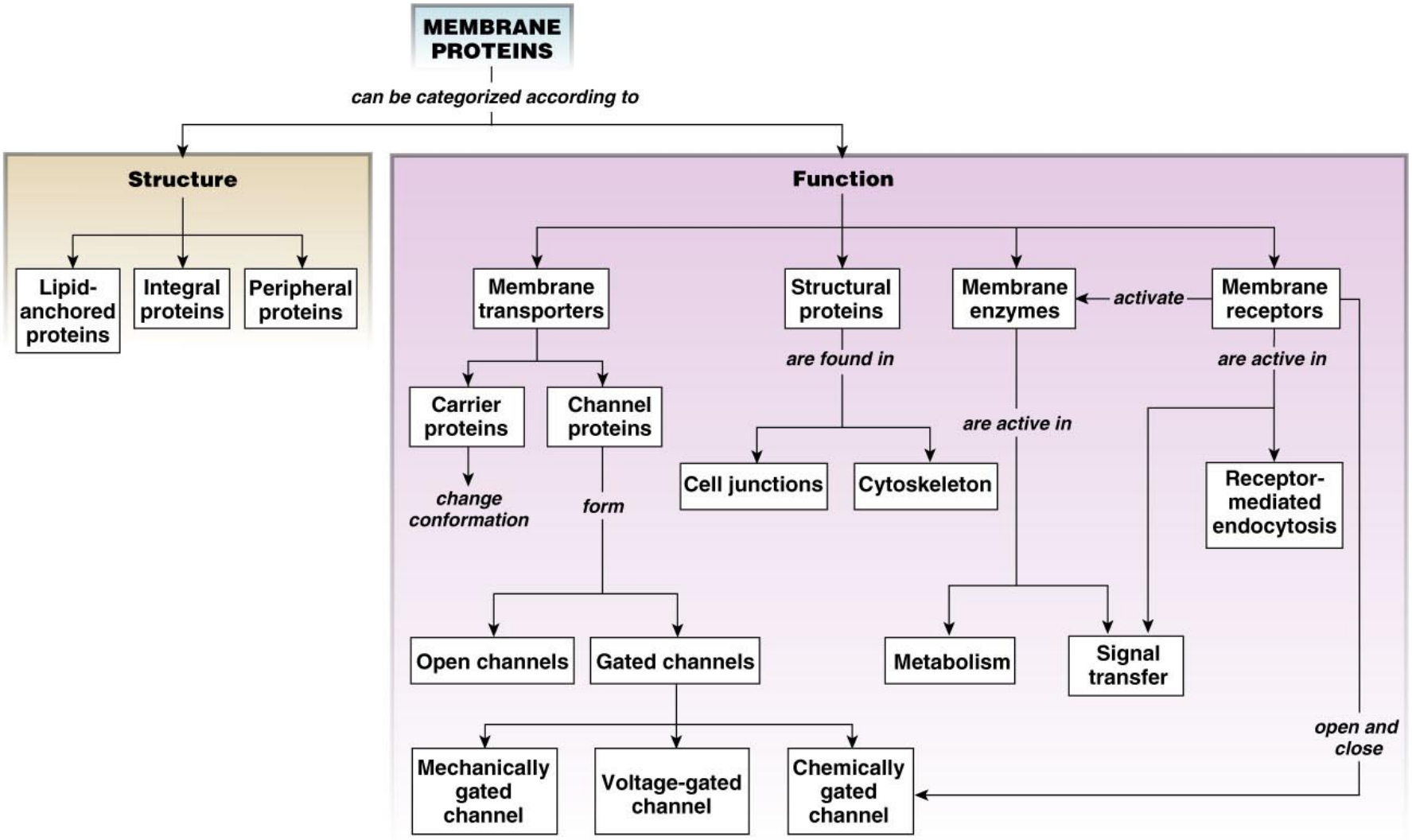
Figure 11.34 Physical Biology of the Cell (© Garland Science 2009)

Within cells, lipid composition differs depending on membrane type.

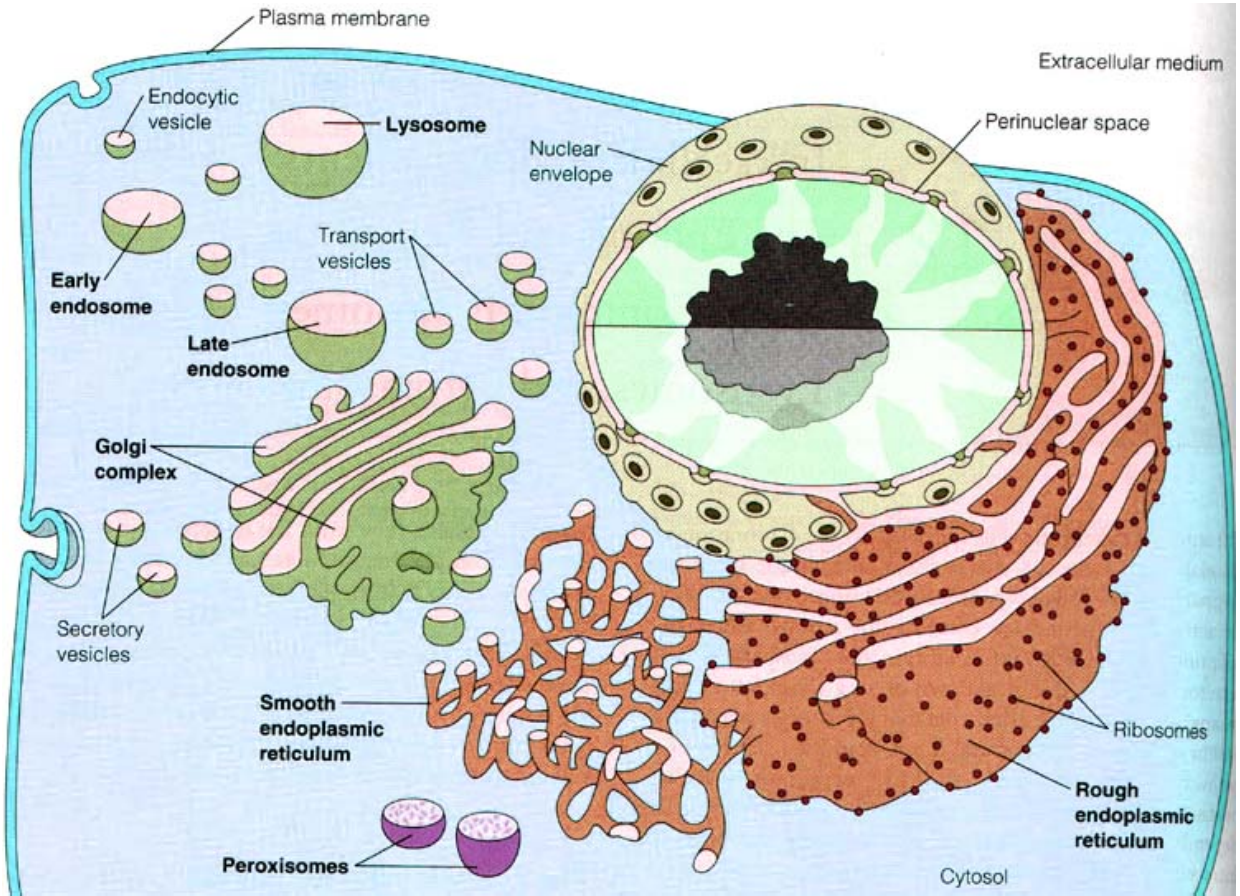




Membrane Proteins



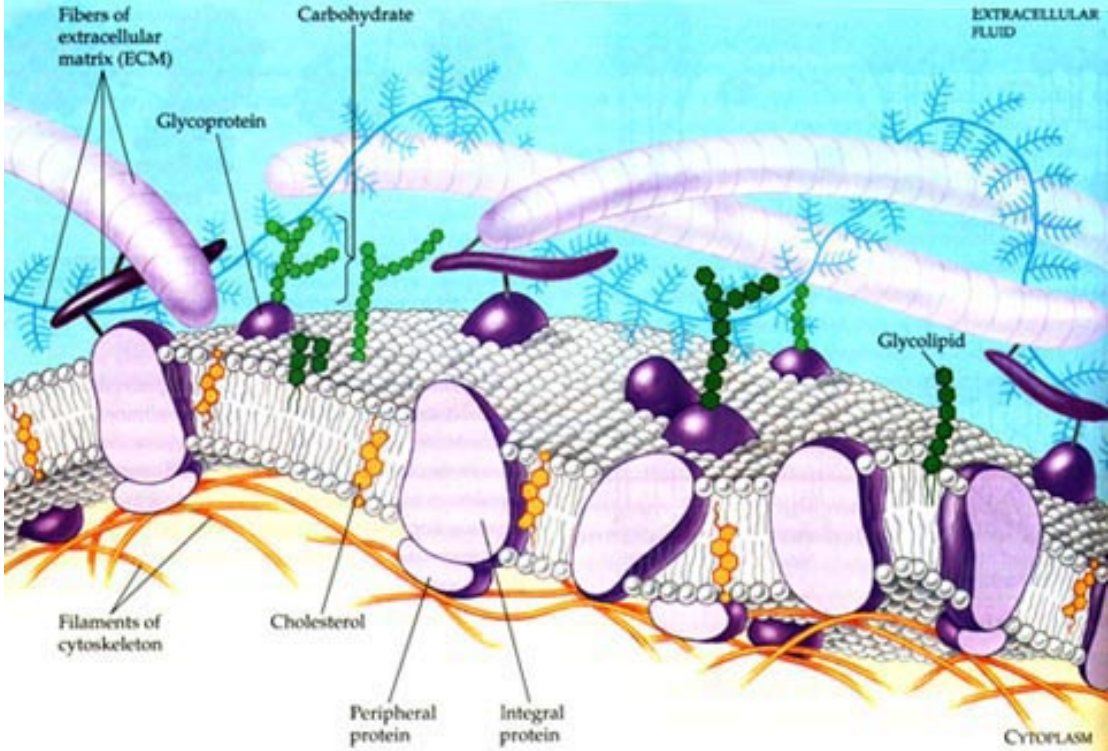
The asymmetrical distribution of proteins, lipids and associated carbohydrates in the plasma membrane is determined when the membrane is built by the ER and Golgi apparatus.



Membrane asymmetry

Types of asymmetry

- ***lipids***
- ***proteins***
- ***carbohydrate***
- ***salt composition***
- ***function***

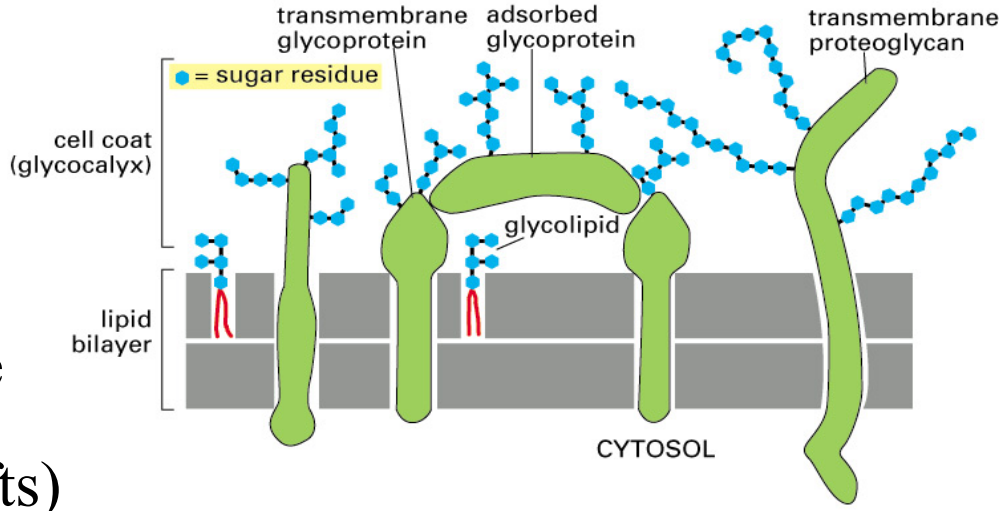


The detailed structure of an animal cell's plasma membrane, in cross section.

asymmetric functions ⇒ asymmetric structures

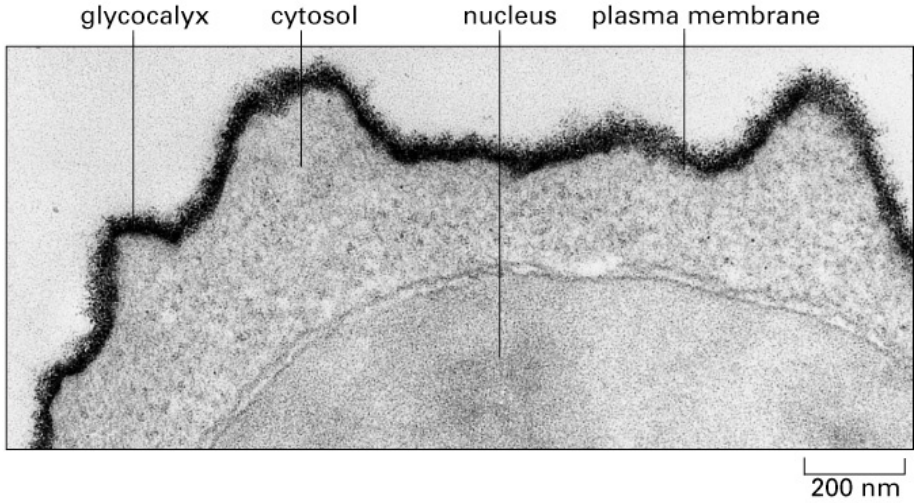
Carbohydrates

- Surface-associated sugers
- Exclusively on noncytosolic side
- Tend to self-associate (lipid rafts)



Functions

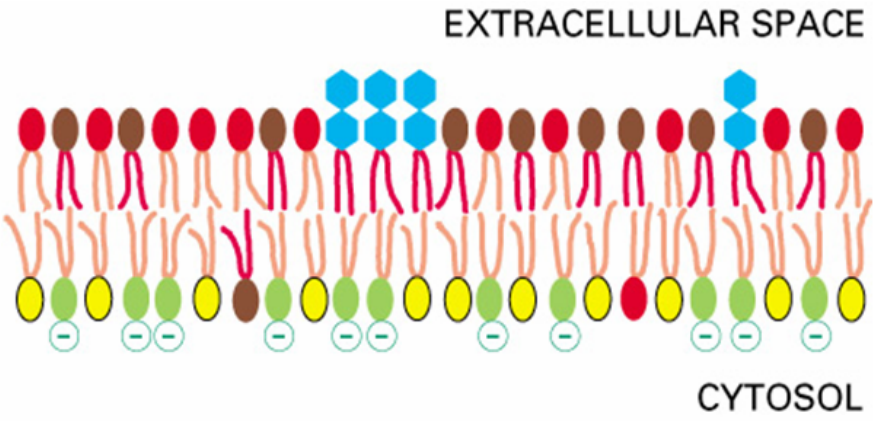
- Protection of cell surface
- Electrical effects
- Cell recognition and adhesion



- Lectins, or carbohydrate-binding proteins, are also involved in this layer

The diversity of carbohydrate chains is enormous, providing each individual with a unique cellular "fingerprint".

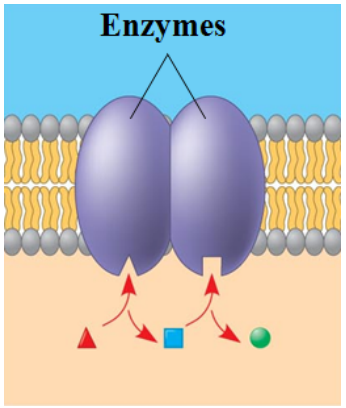
Lipid asymmetry

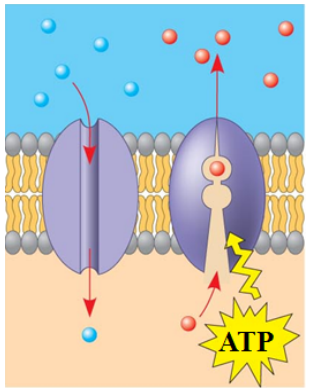


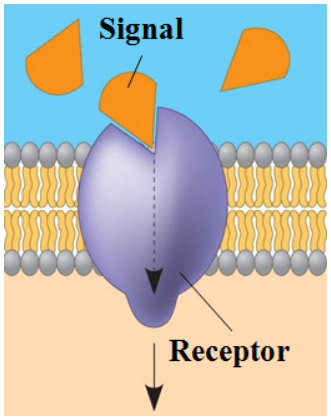
Membrane phospholipid	Percent of total membrane phospholipid	Distribution in membrane
Phosphatidylethanolamine	30	
Phosphatidylcholine	27	
Sphingomyelin	23	
Phosphatidylserine	15	
Phosphatidylinositol	5	
Phosphatidylinositol 4-phosphate		
Phosphatidylinositol 4,5-bisphosphate		
Phosphatidic acid		

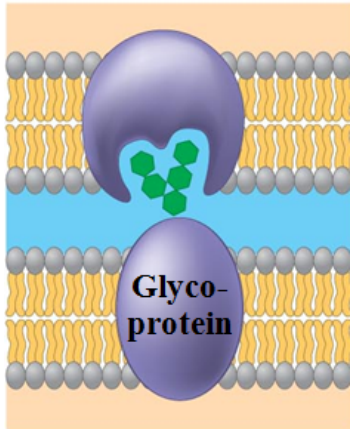
Major functions and asymmetry of membrane proteins:

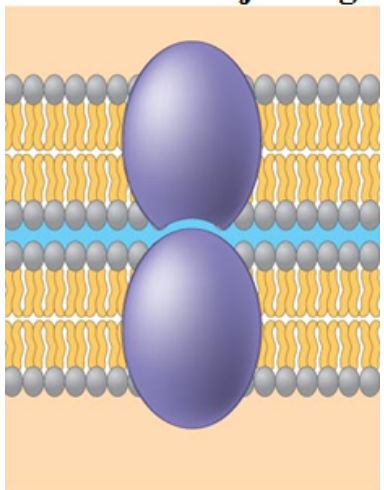
- *Transport*
- *Enzymatic activity*
- *Signal transduction*
- *Cell-cell recognition*
- *Intercellular joining*
- *Attachment to the cytoskeleton and extracellular matrix (ECM)*

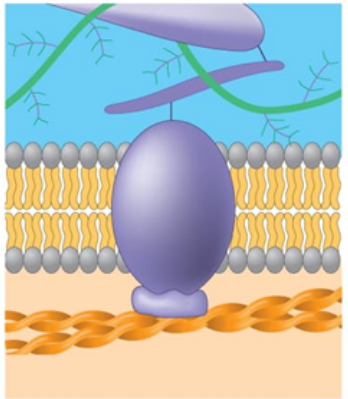




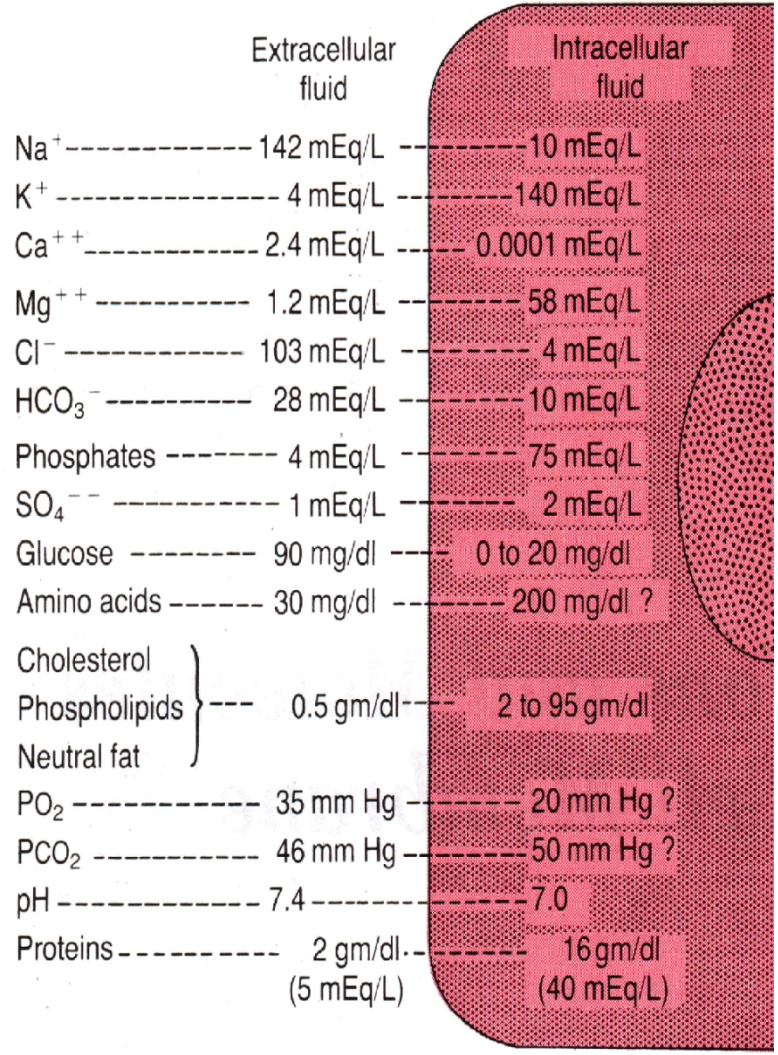








Attachment to the cytoskeleton and extra-cellular matrix (ECM)

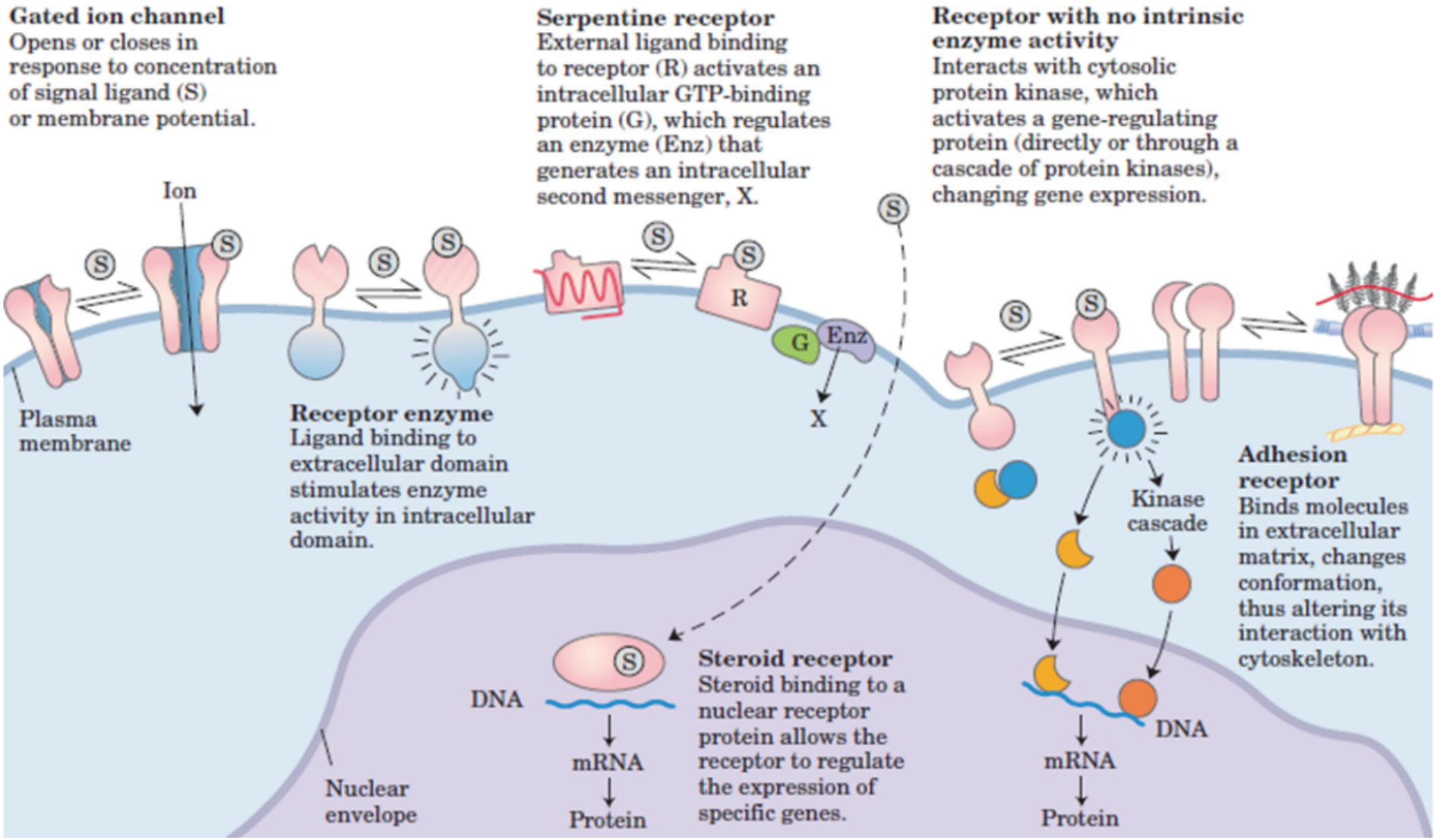


Mammalian cell intracellular and extracellular aqueous phases composition

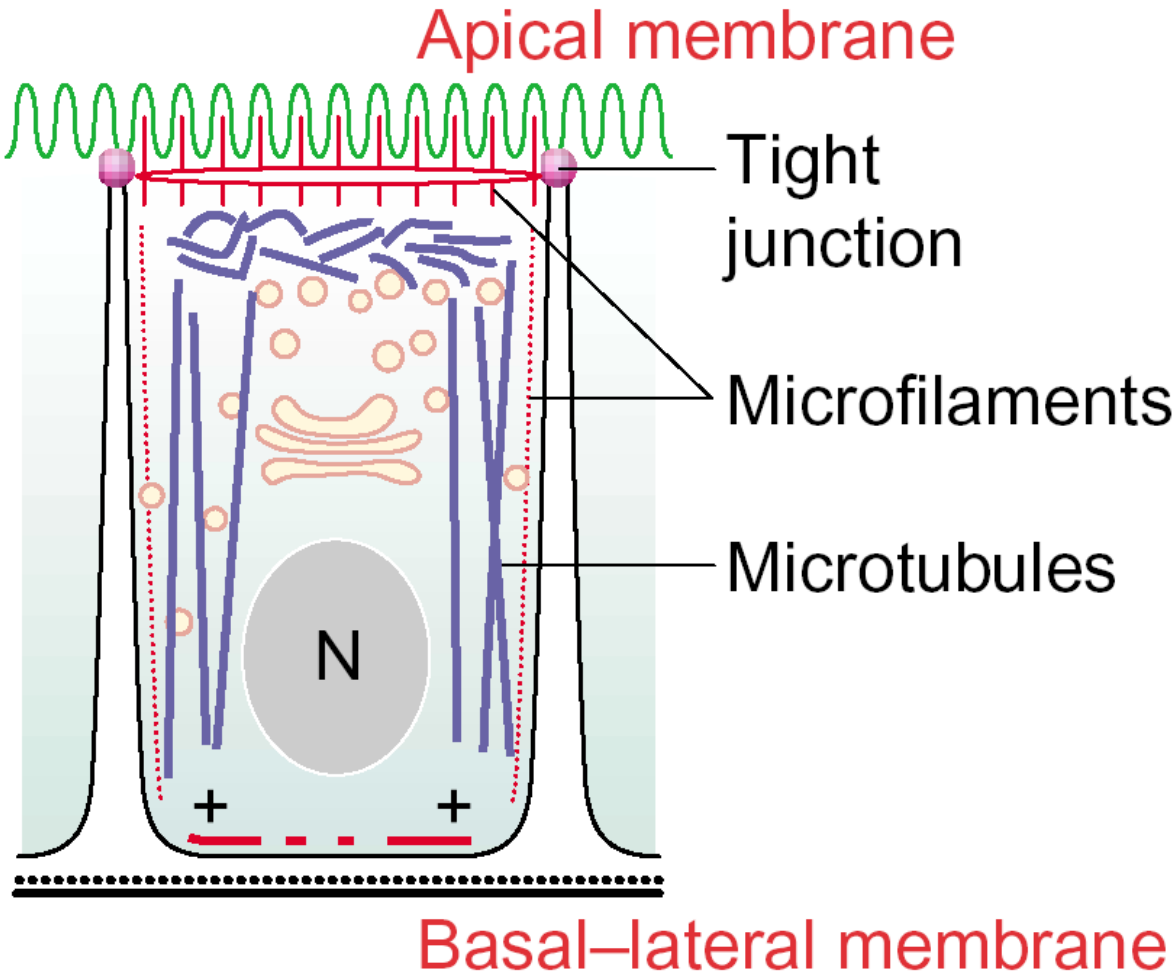
MAMMALIAN CELL

Ion	Cell (mM)	Blood (mM)
K^+	139	4
Na^+	12	145
Cl^-	4	116
HCO_3^-	12	29
X^-	138	9
Mg^{2+}	0.8	1.5
Ca^{2+}	<0.0002	1.8

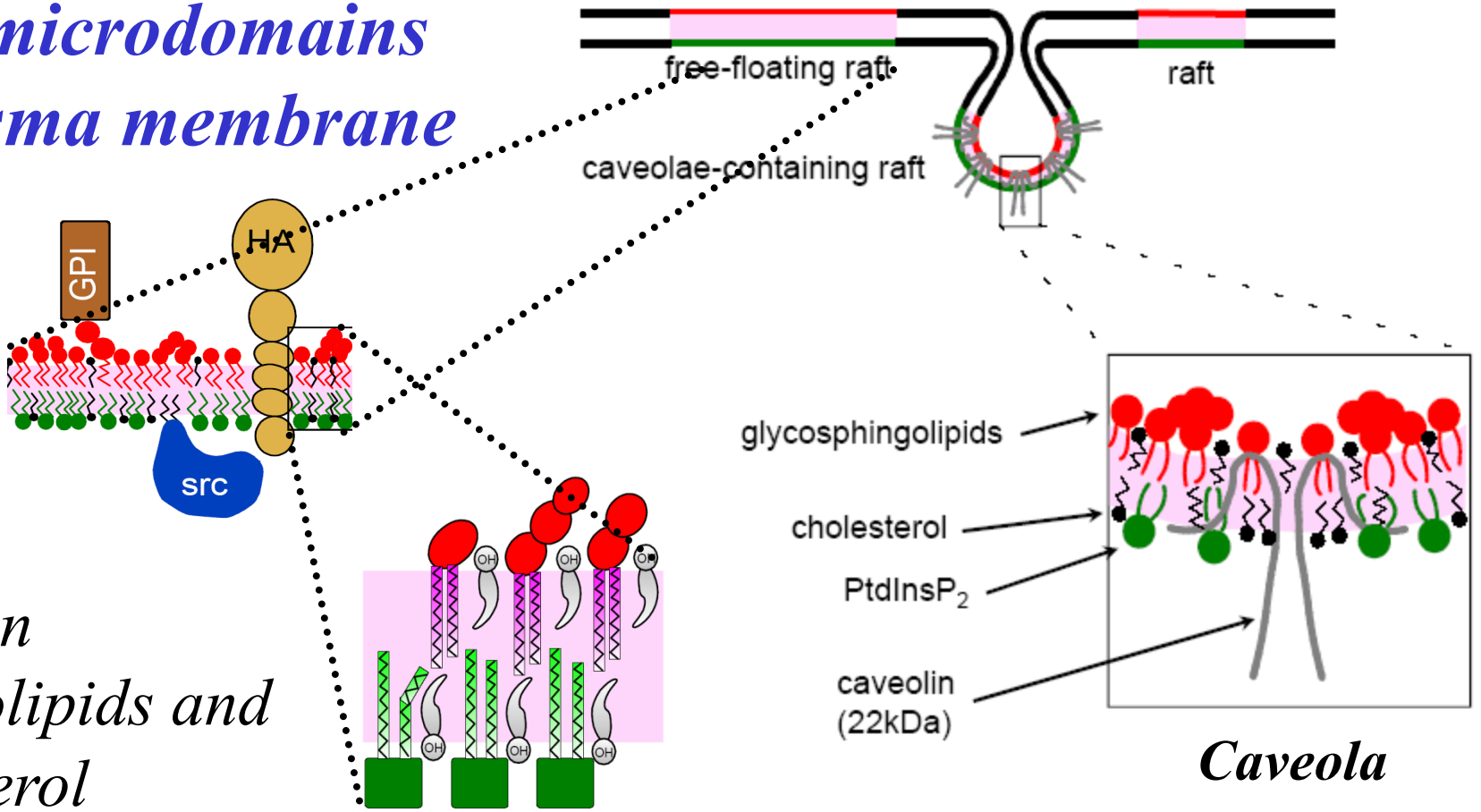
Asymmetry of events



Different plasma membrane regions in endothelial cell



Lipid microdomains in plasma membrane

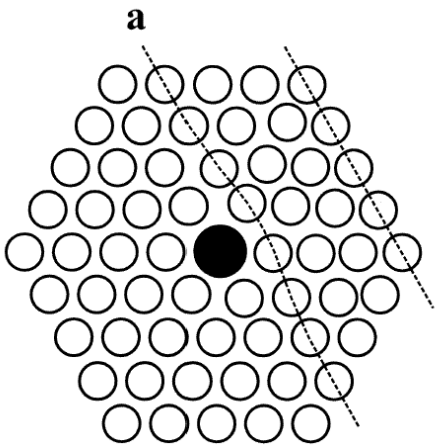


- *Rich in sphingolipids and cholesterol*

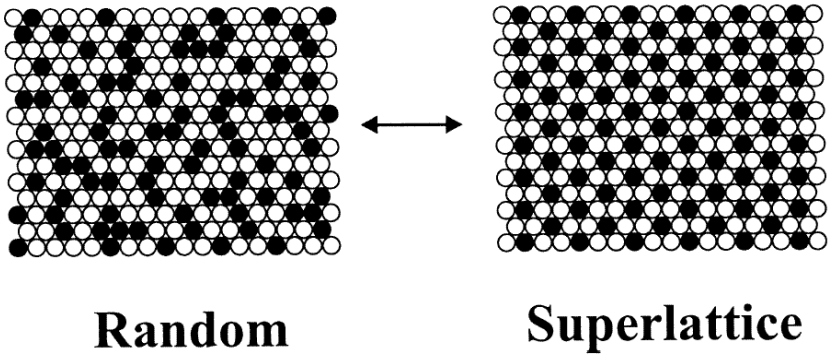
- *Longer, saturated chains of sphingolipids cause membrane thickening*

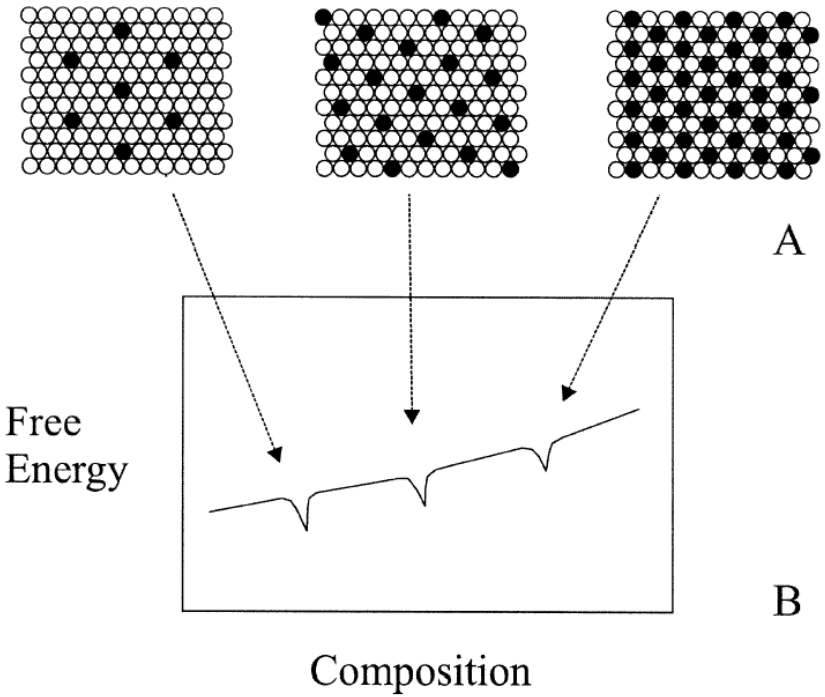
- *Such lipid arrangement recruits particular proteins and facilitates their transport or function as a group*

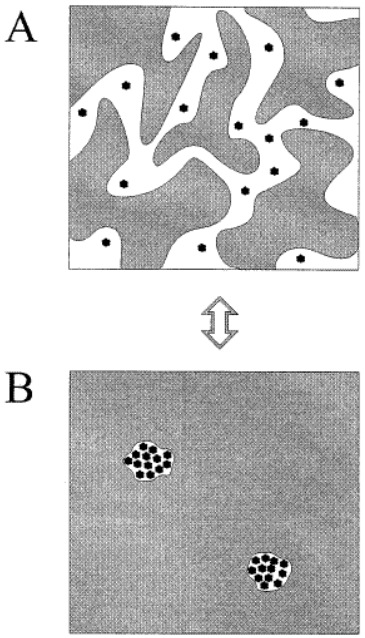
The superlattice



Lateral lattice strain caused by a bulkier guest molecule.

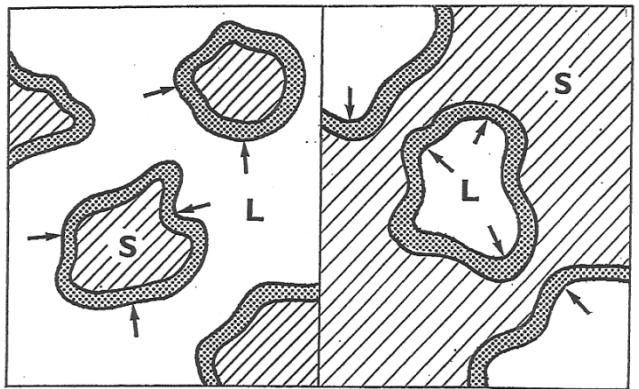






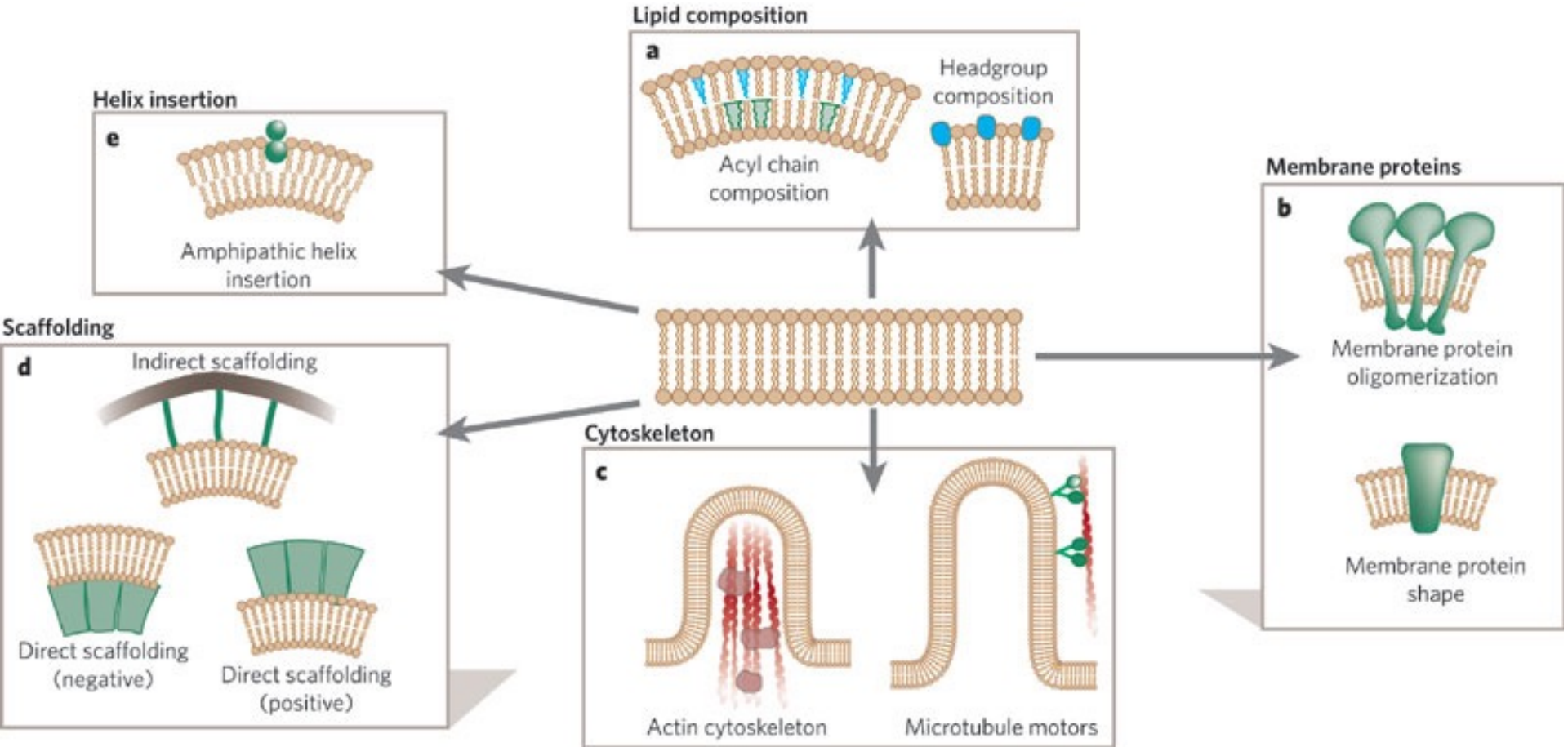
Control of membrane associated enzymes

„Percolation"



Curvature is a key property of functional membranes

Influences on membrane curvature



The induced shape changes

- after 30 h of metabolic depletion,
- instantaneously if lyso-PC or phosphatidylcholine with short chains is added,
- temporarily after the addition of phosphatidylserine or phosphatidylethenolamine

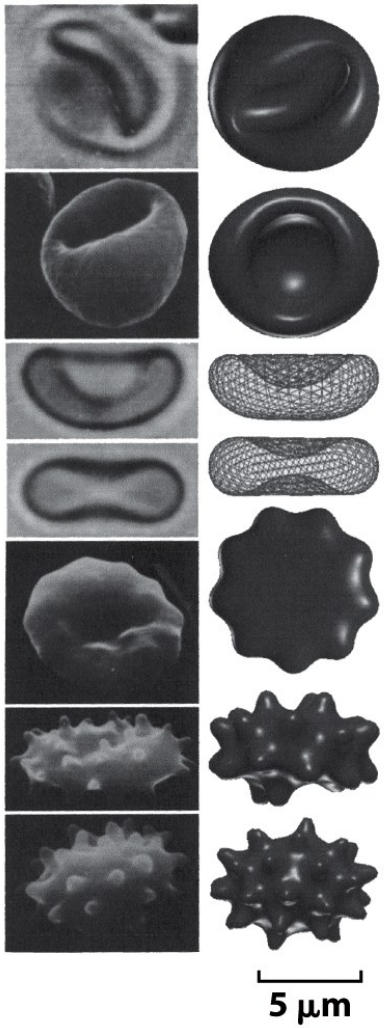
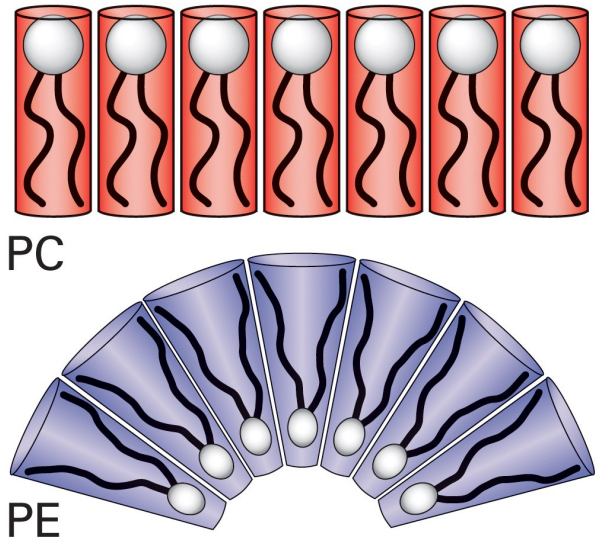
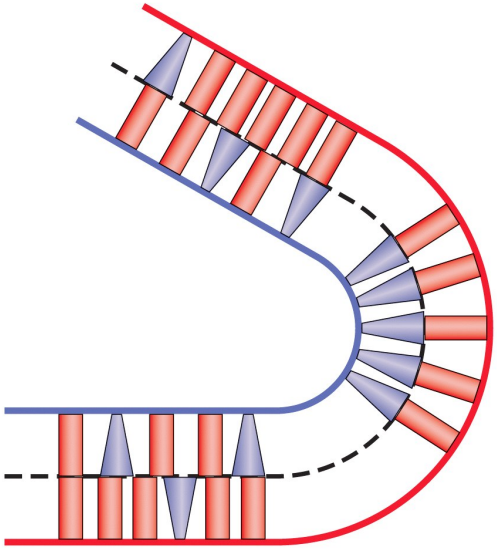


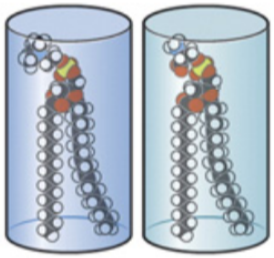
Figure 11.38 Physical Biology of the Cell (© Garland Science 2009)

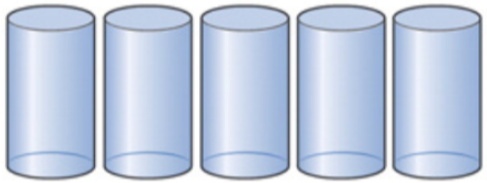




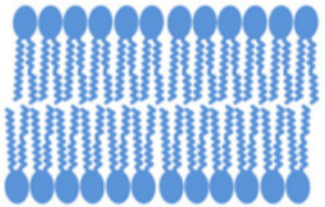
Cylindrical

Phosphatidylcholine
Phosphatidylserine





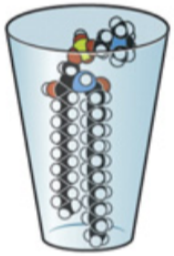
Flat

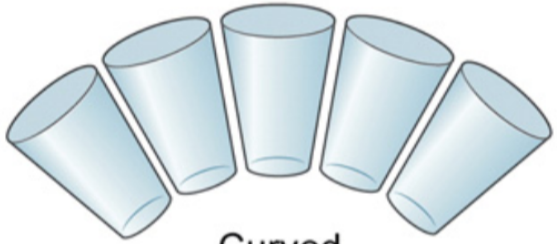


Bilayer

Conical

Sphingomyelin



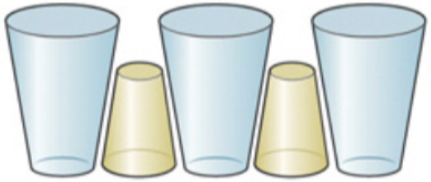


Curved

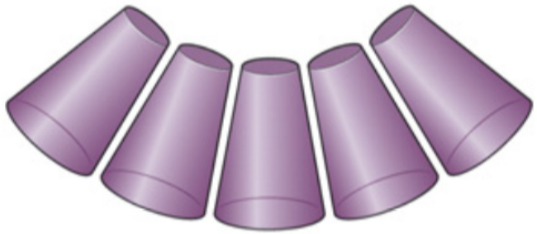
Micelle

Inverted Conical

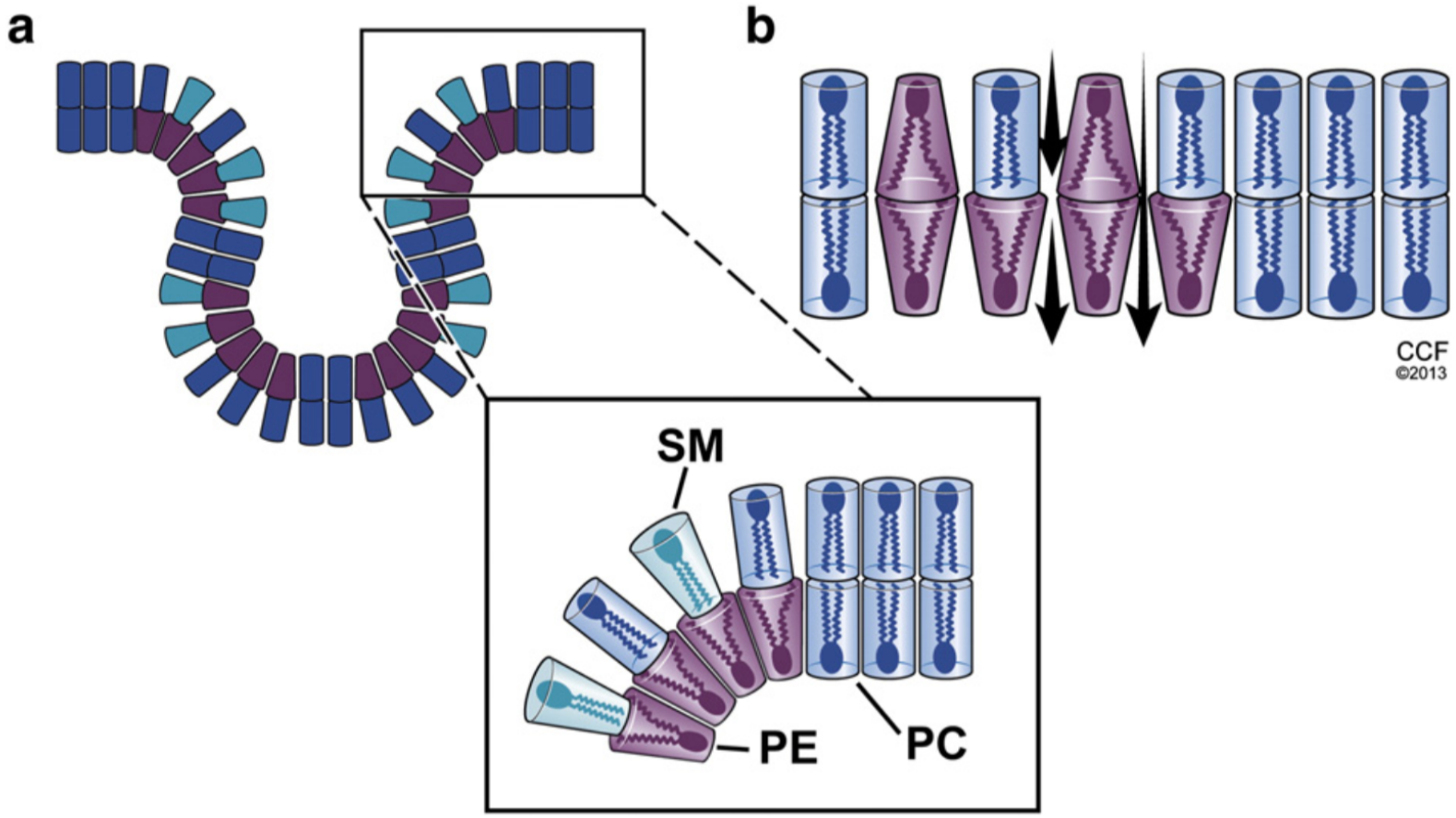
Cholesterol



Phosphotidyl-
ethanolamine



Inverted Micelle

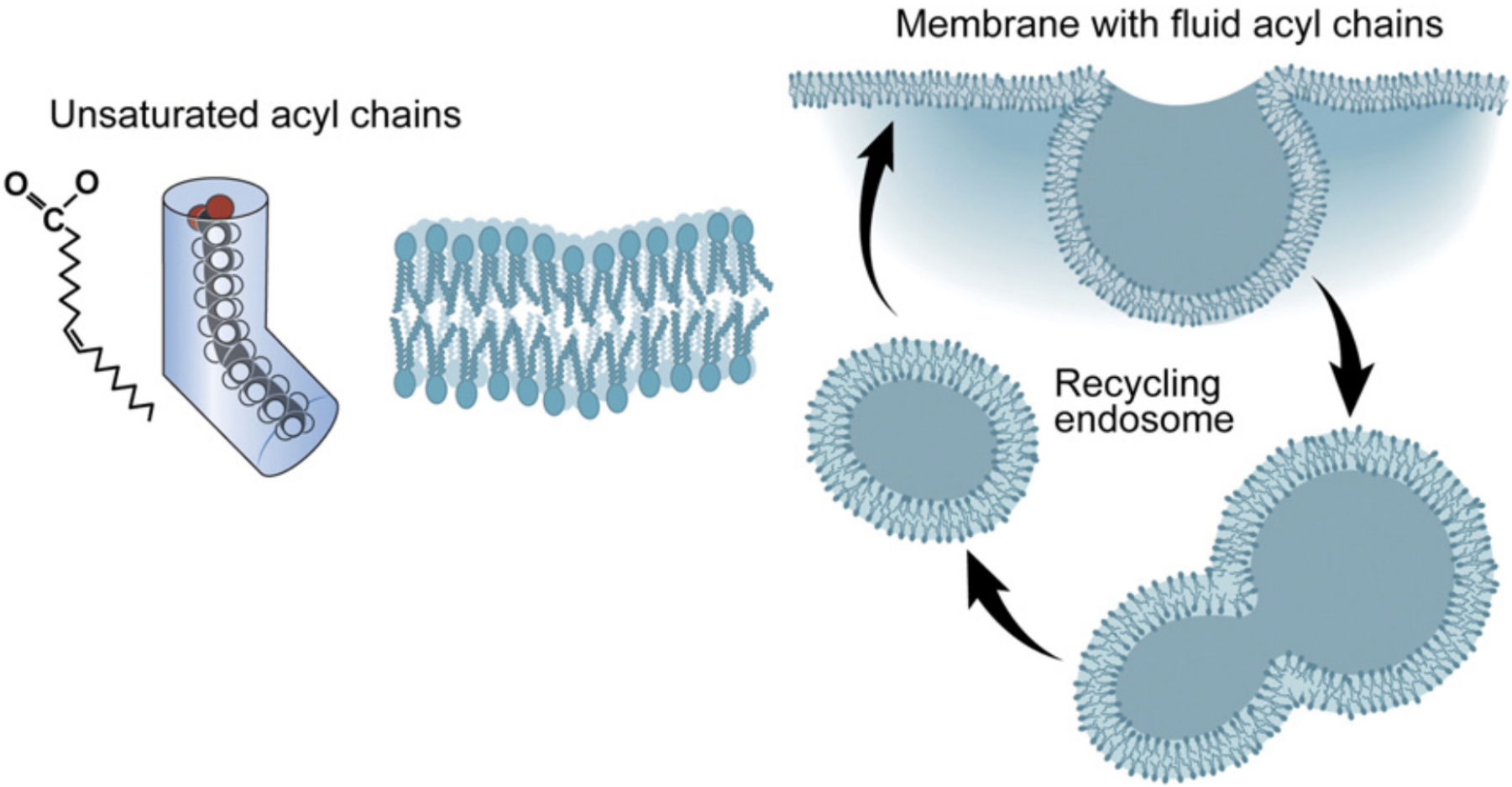


Effect of lipid composition on cell membrane, endocytic function, and transport.

a) Conical shape of PE facilitates membrane invagination during endocytosis.
b) High concentration of PE at outer leaflet could alter the membrane lipid arrangement and increase membrane permeability.

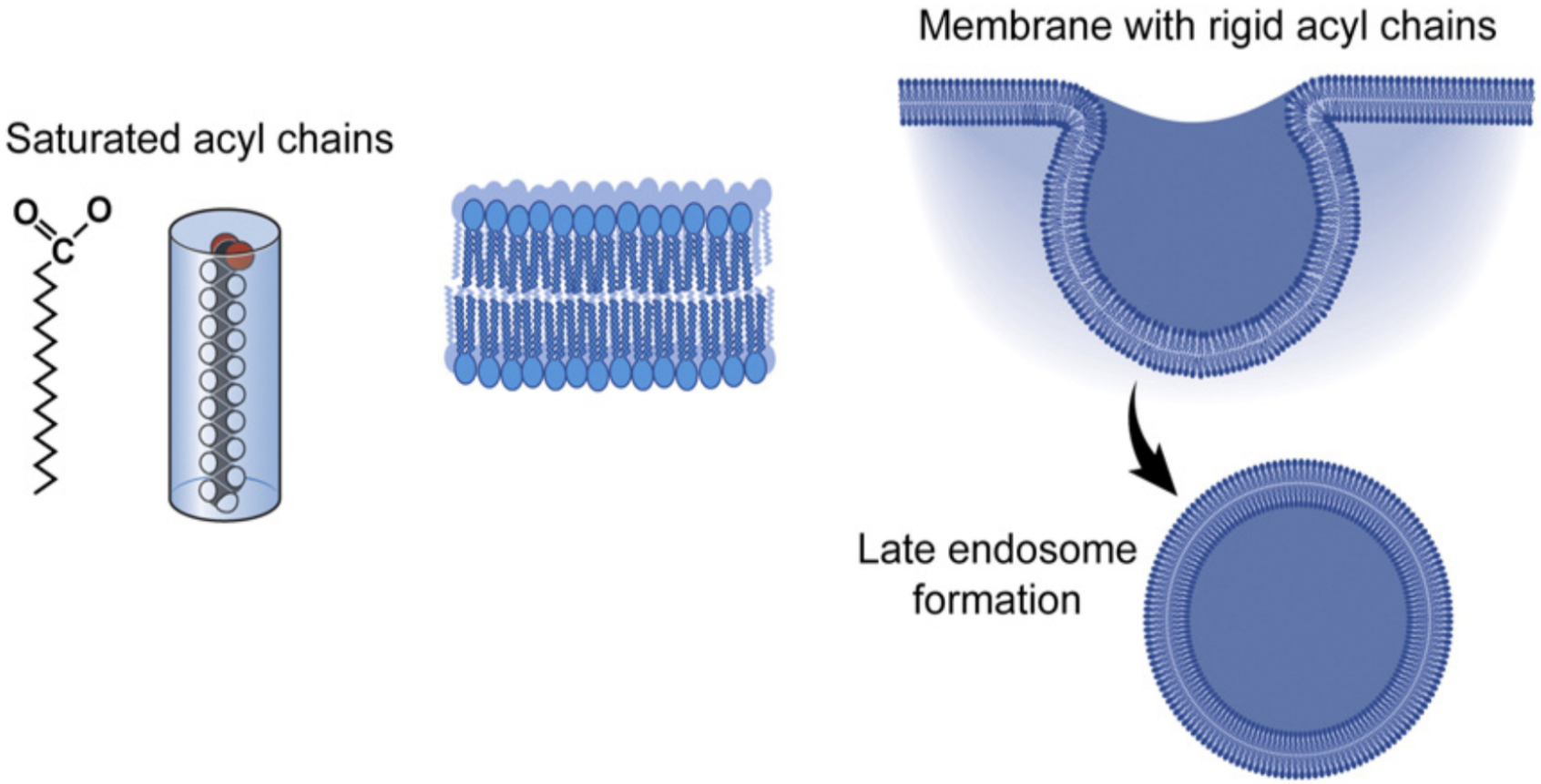
Effect of acyl chain of lipids on cell membrane barrier - endocytic function.

Phospholipid membranes with fluid acyl chains sort towards recycling vesicles



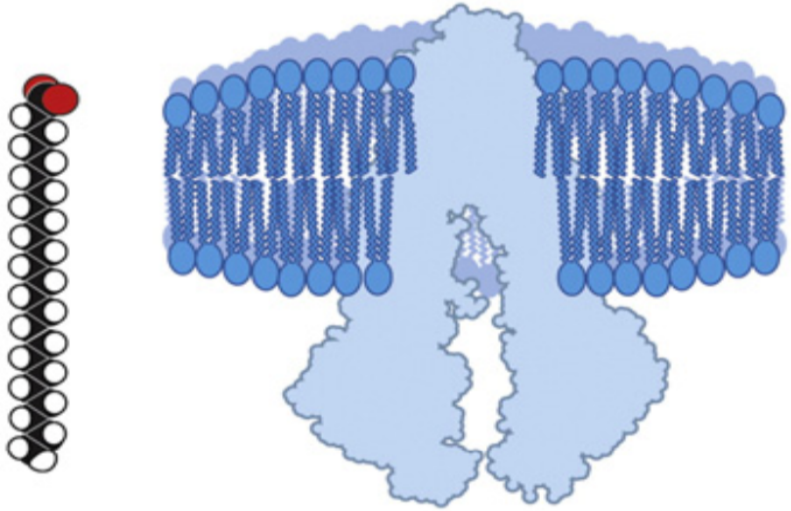
Effect of acyl chain of lipids on cell membrane barrier - endocytic function.

Phospholipids with saturated acyl chains sort towards late-endosome formation.

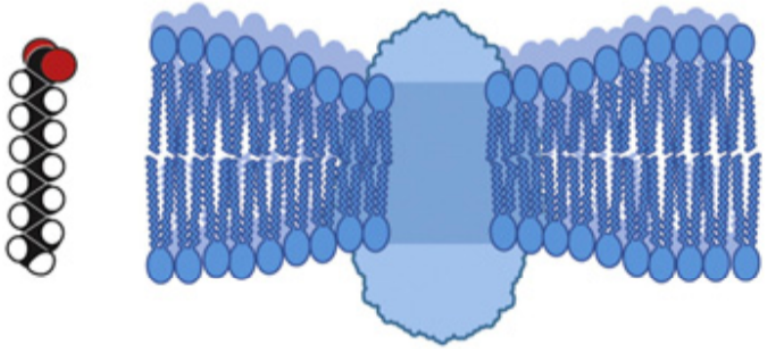


Effect of acyl chain of lipids on cell membrane barrier - trans-membrane protein organization.

Proteins with long trans membrane are associatedwith long acyl chain length



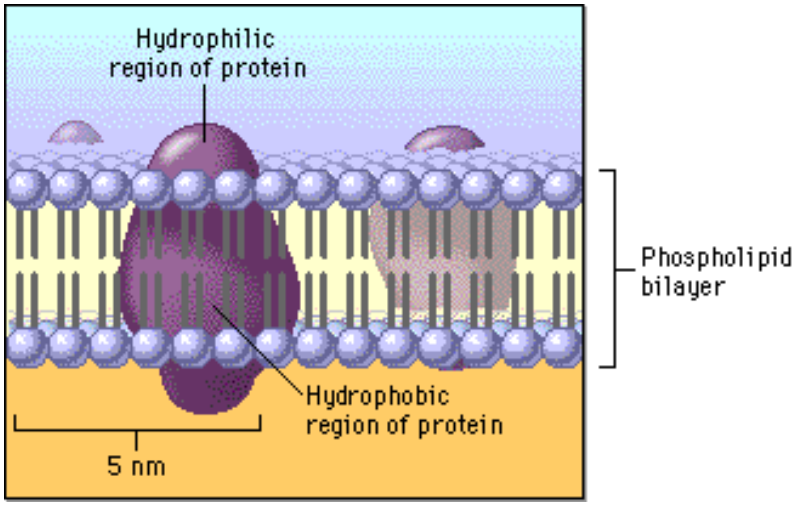
Proteins with short trans membrane are associated with short acyl chain length

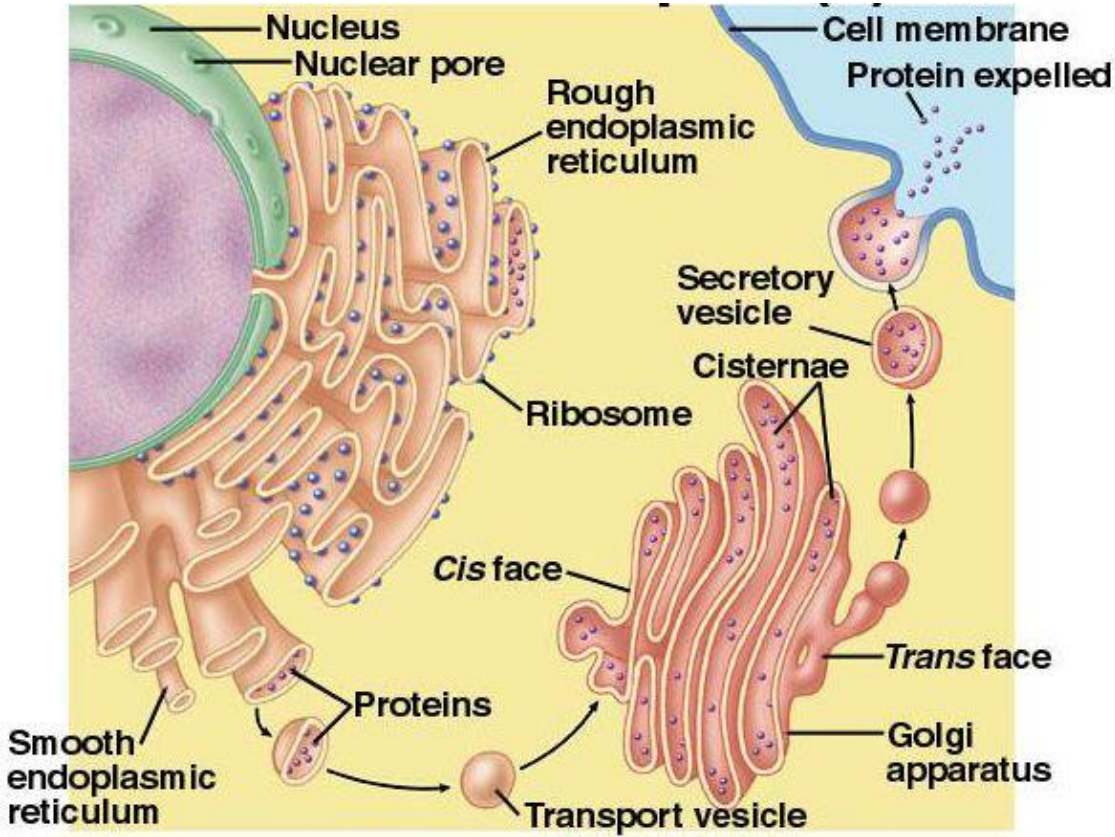


Membrane fluidity

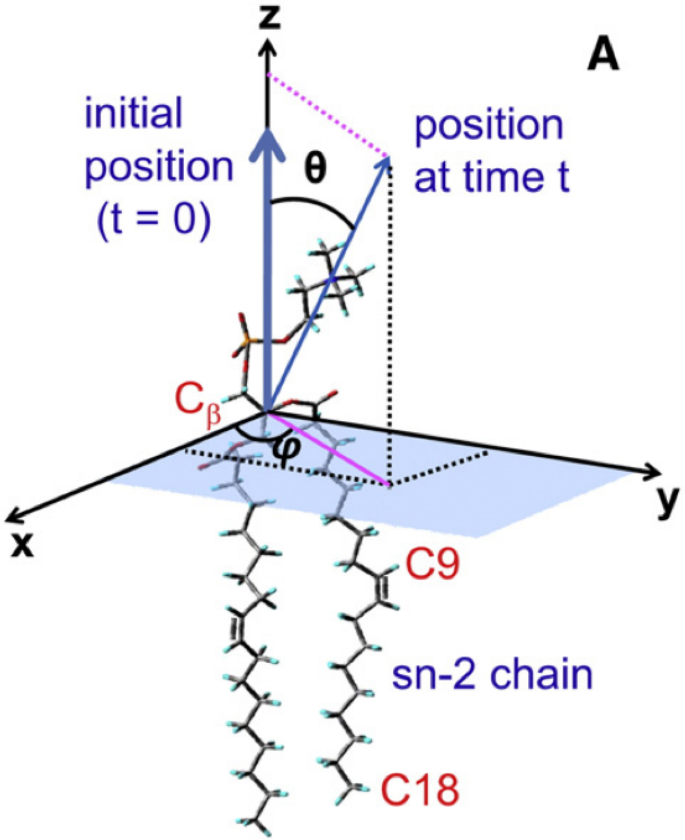
is necessary because

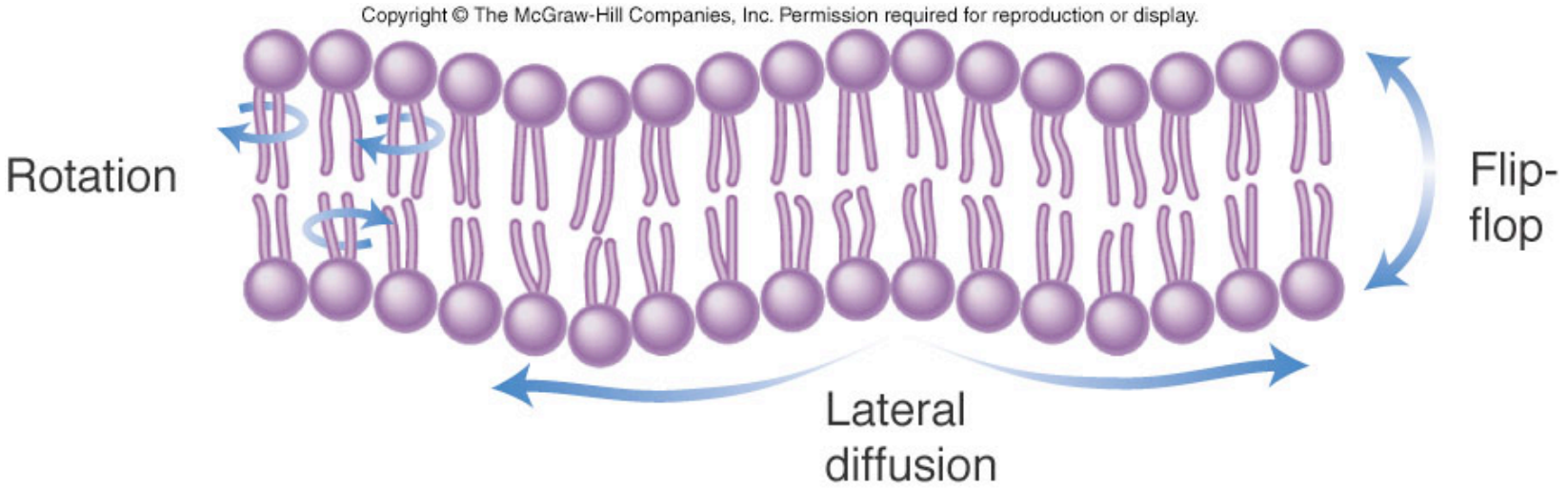
- Membranes must form barriers
- Turn corners
- Seal membrane proteins
- Form vesicles
- Fusion of vesicles





Lipid bilayer dynamics





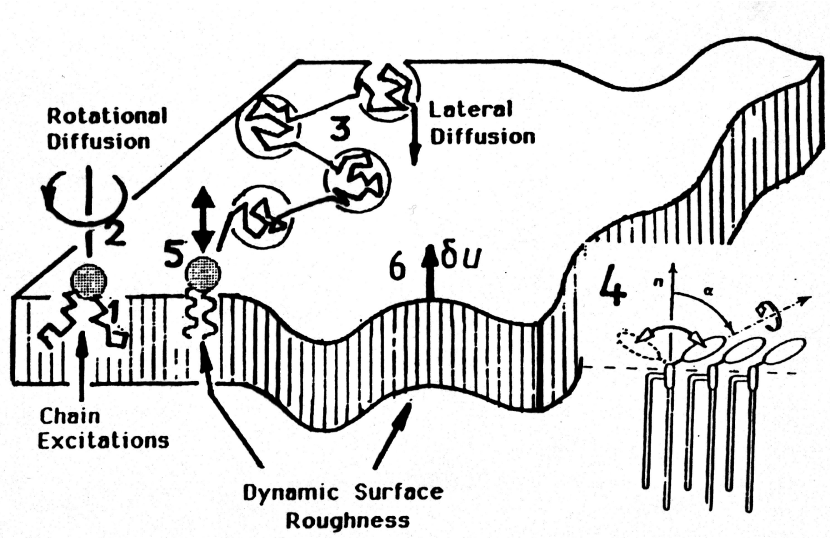
Molecular dynamics of membraane lipids

Lateral diffusion

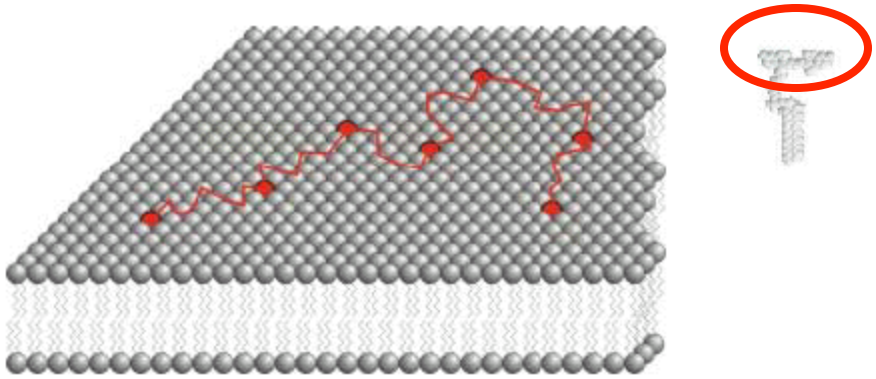
- Movement of lipids in plane of bilayer - FAST - lipid exchanges places with nearest neighbour every 10^{-7} sec

- A phospholipid can move several μm per second at 37°C, *e.g.* from one end of bacterium to other in <1 sec (animal cell, <1 min)

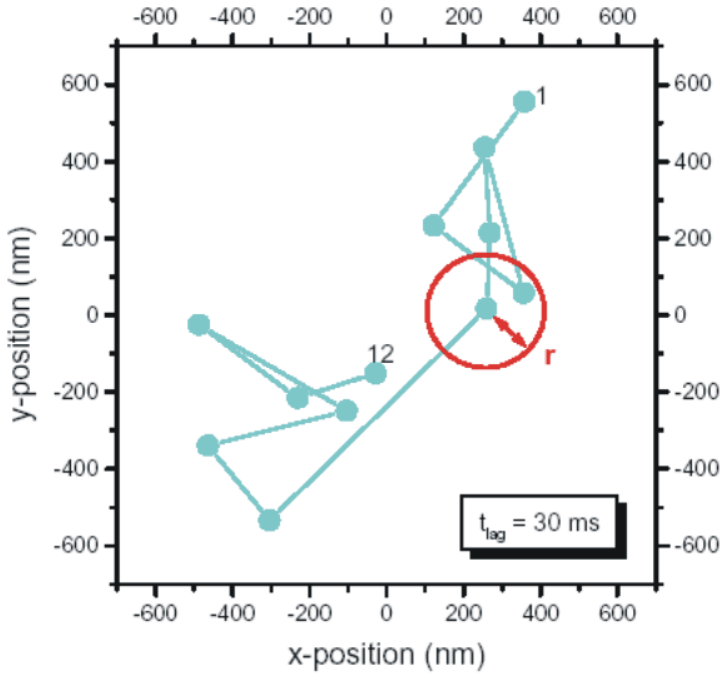
König & Sackmann, Curr. Opin. Coll. Int. Sci. 1, 78 (1996)

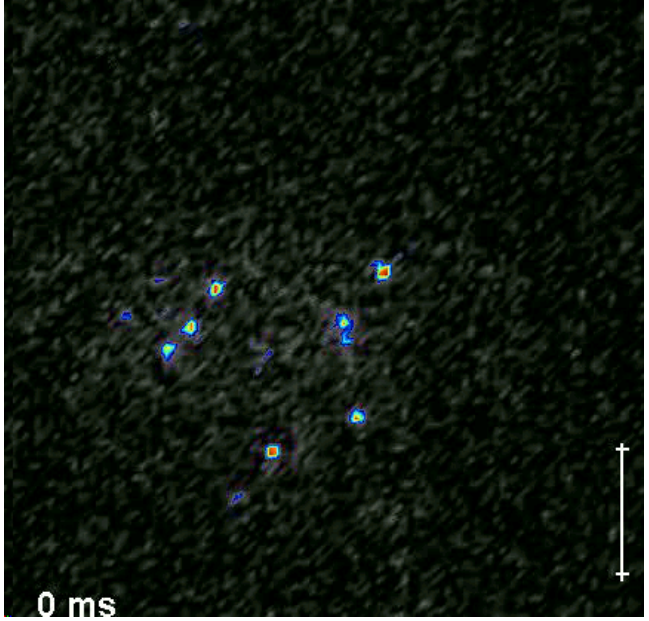


Single-molecule diffusion



thickness: 5 nm





Single dye-labeled lipids

Diffusion coefficient

Two dimensions

$$4D_2t = \left\langle \Delta x^2 + \Delta y^2 \right\rangle$$

GJ Schütz, H Schindler & **TS**, Biophys.J. 73 (1997) 1073

Axial rotation **- spinning about the long axis - FAST**

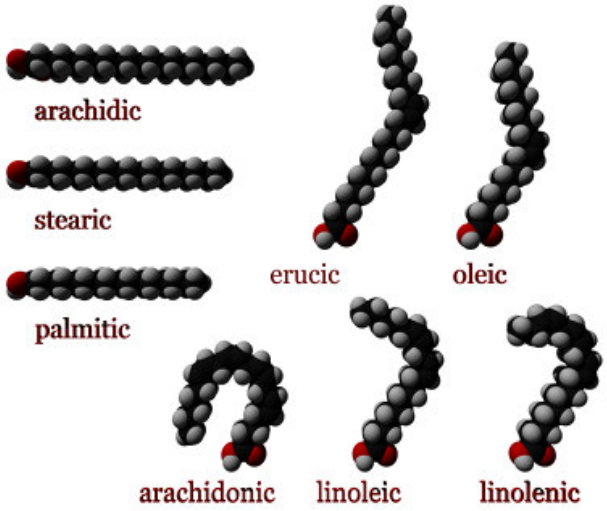
Intrachain motion **- flexing, kink formation**

Two different types of conformation for acyl chains:

- all-trans - straight, extended
- gauche - formed by 120° rotations about C = C bonds, short-lived kinks; lifetime ~ 10^{-9} sec

cis-double bond - very large, permanent kink in acyl chain

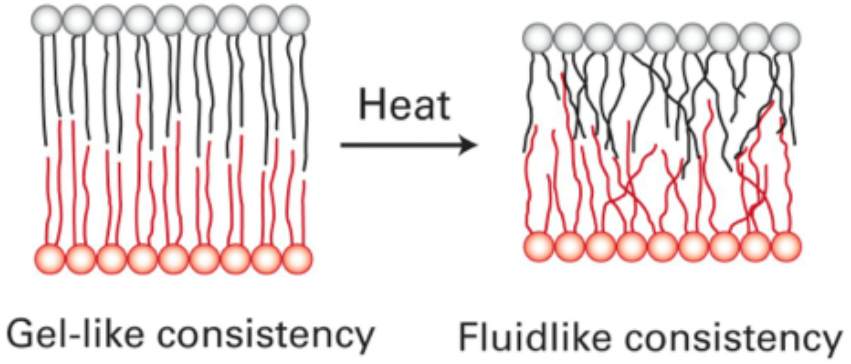
Kinks from gauche conformations and cis double bonds couse disorder in hydrocarbon region, disrupt packing.



All membranes undergo phase transitions.

First level: fatty acid melting temperatures

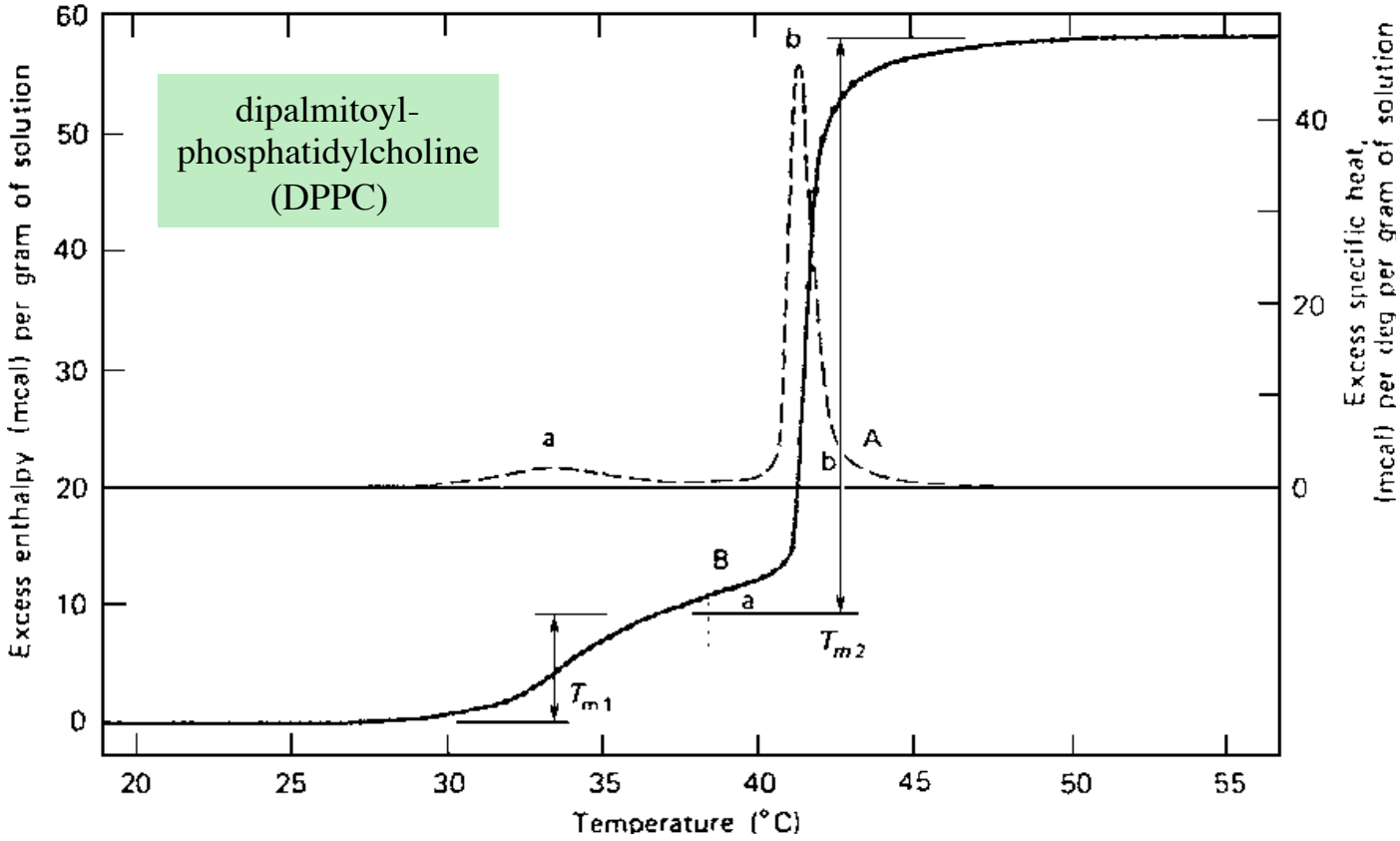
- increase with chain length
- decrease as add double bonds
- many organisms respond to temperature change by changing their fatty acids



Poikilotherms

Organisms that cannot regulate their own temperature must regulate membrane fluidity by changing fatty acid composition of membranes (called homeoviscous adaptation).

Pure lipids have sharp melting transitions



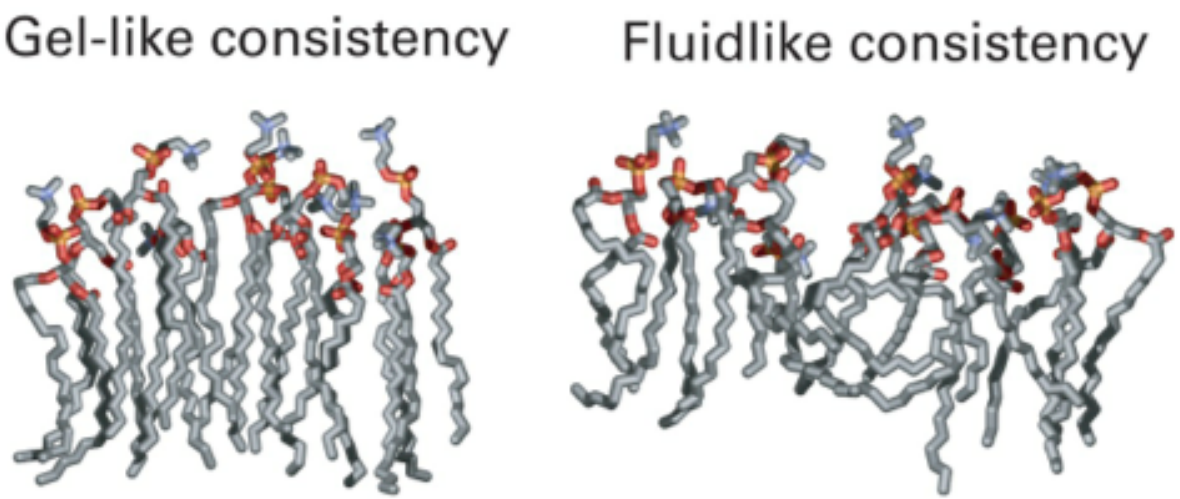
Phase transition in lipid bilayer

- **phospholipid bilayers behave as 2-D crystals**
- **single type of acyl chain**
- **melting occurs over 1-2°C temperature range; highly cooperative**

gel phase	liquid crystalline phase
ordered acyl chains	disordered acyl chains
all-trans conformation, tilted	gauche conformations
closly packed crystalline array	loosely packed
little molecular motion	lots of molecular motion
very slow lateral diffusion	fast lateral diffusion
little intrachain motion	rapid intrachain motion
thicker	thinner

Second level: properties of headgroups

- interactions with neighbors affect lipid mobility
- lateral diffusion
- rotation
- flip-flop
- interactions affected by head-group's charge & ability to H-bond



Effect of headgroup on T_m:

DPPC (di-16:0)	**42°C**
DPPS (di-16:0)	**55°C**
DPPE (di-16:0)	**63°C**

real membranes contain a large variety of chain lengths, unsaturation and headgroups → very broad melting transition, may cover 20°C

Prokryotes: *e.g.* E. coli

- Must be able to grow at different temperatures
- Fatty acids incorporated into membrane lipids are changed → membrane fluidity same at different temps

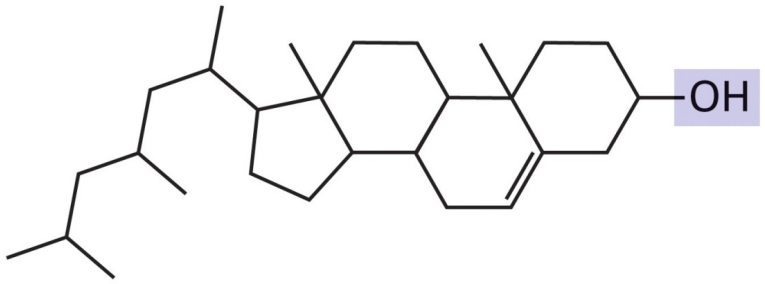
  - **42°C saturated/unsaturated = 1.6**
  - **27°C saturated/unsaturated = 1.0**

Third level – sterols

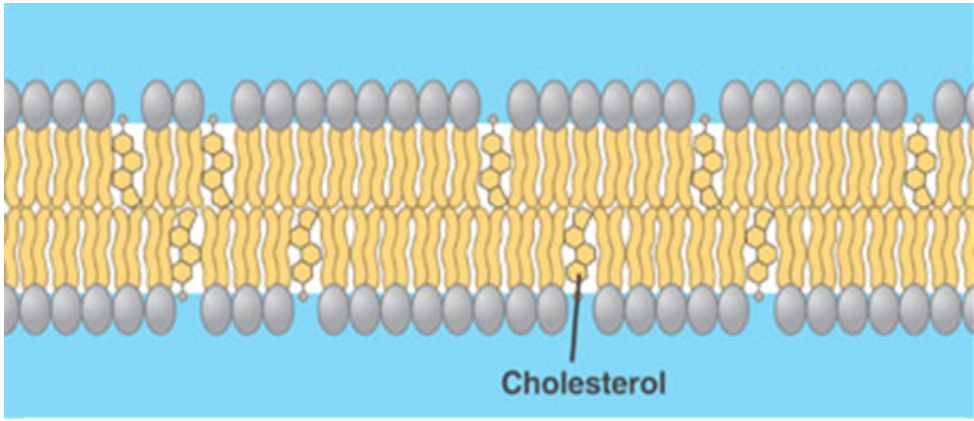
- cholesterol intercalates between phospholipids and "buffers" fluidity
- decreases intensity of gel – liquid transition

- long axis of cholesterol is parallel to acyl chains
- OH group interacts with polar headgroups

(c) Cholesterol



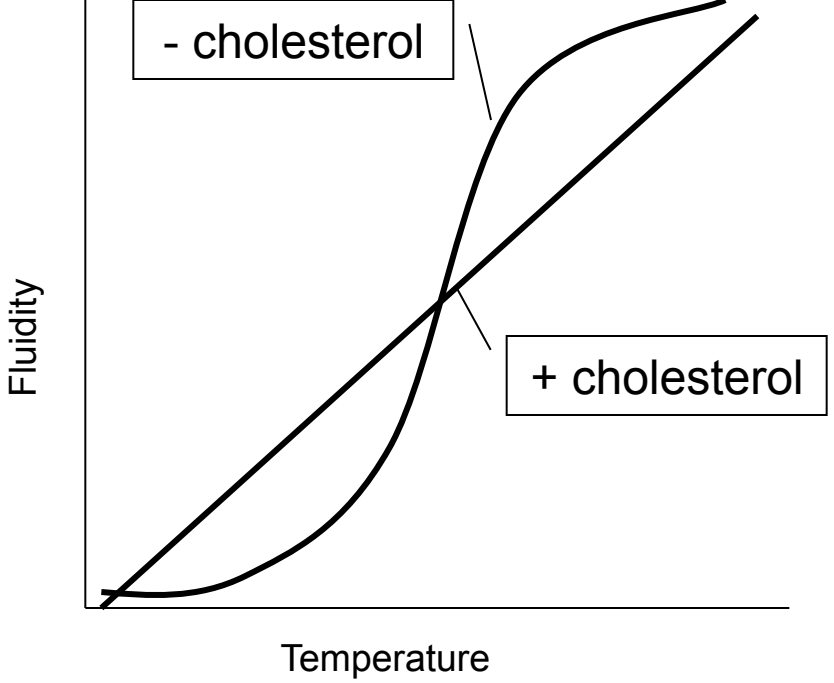
Makes membrane less permeable to small molecules.



Phospholipids show different degrees of affinity to cholesterol;

SM > PS > PC > PE

(phospholipid affinity toward cholesterol also depends on the molecular shape of the lipids)



Stabilizes fluidity

1. Below T_m (gel phase) - it increases fluidity, prevents close packing of acyl chains, inhibits crystallization, destabilizes the gel phase, so bilayer starts to melt at a lower temperature

2. Above T_m (liquid crystalline phase)

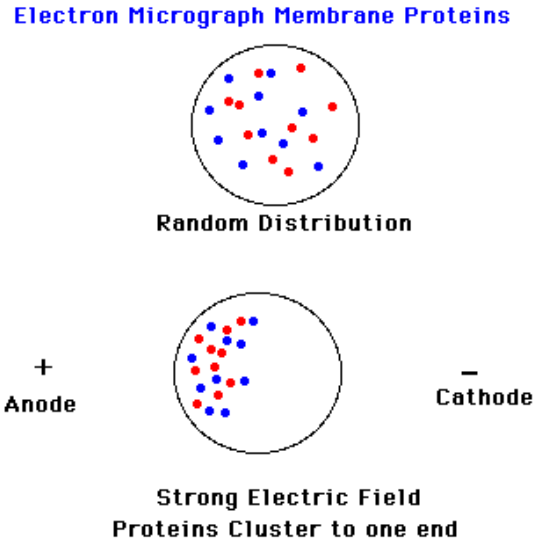
- it decreases fluidity, restricts chain motion – fewer kinks from gauche conformations
- has a condensing effect → more ordered structure, so bilayer finishes melting at a higher temperature
- > 30 mol % cholesterol eliminates phase transition
- a "buffer" to changes in membrane fluidity

Fourth level = proteins

lipid/protein ratio ⇒ increases at lower temperatures

Mmembrane protein dynamics

1. Lateral diffusion - rate is variable
2. Rotational diffusion - fast
3. Flip-flop - non-existent; polar domains cannot move through bilayer interior



Measuerd diffuiosn rate m^2sec^{-1}

Lipids	**1×10^{-8}**	**FAST**
Rhodopsin	**4×10^{-9}**	**FAST (unusual)**
many proteins	**$1\text{-}5 \times 10^{-10}$**	**MEDIUM**
Band 3	**1×10^{-12}**	**IMMOBILE**

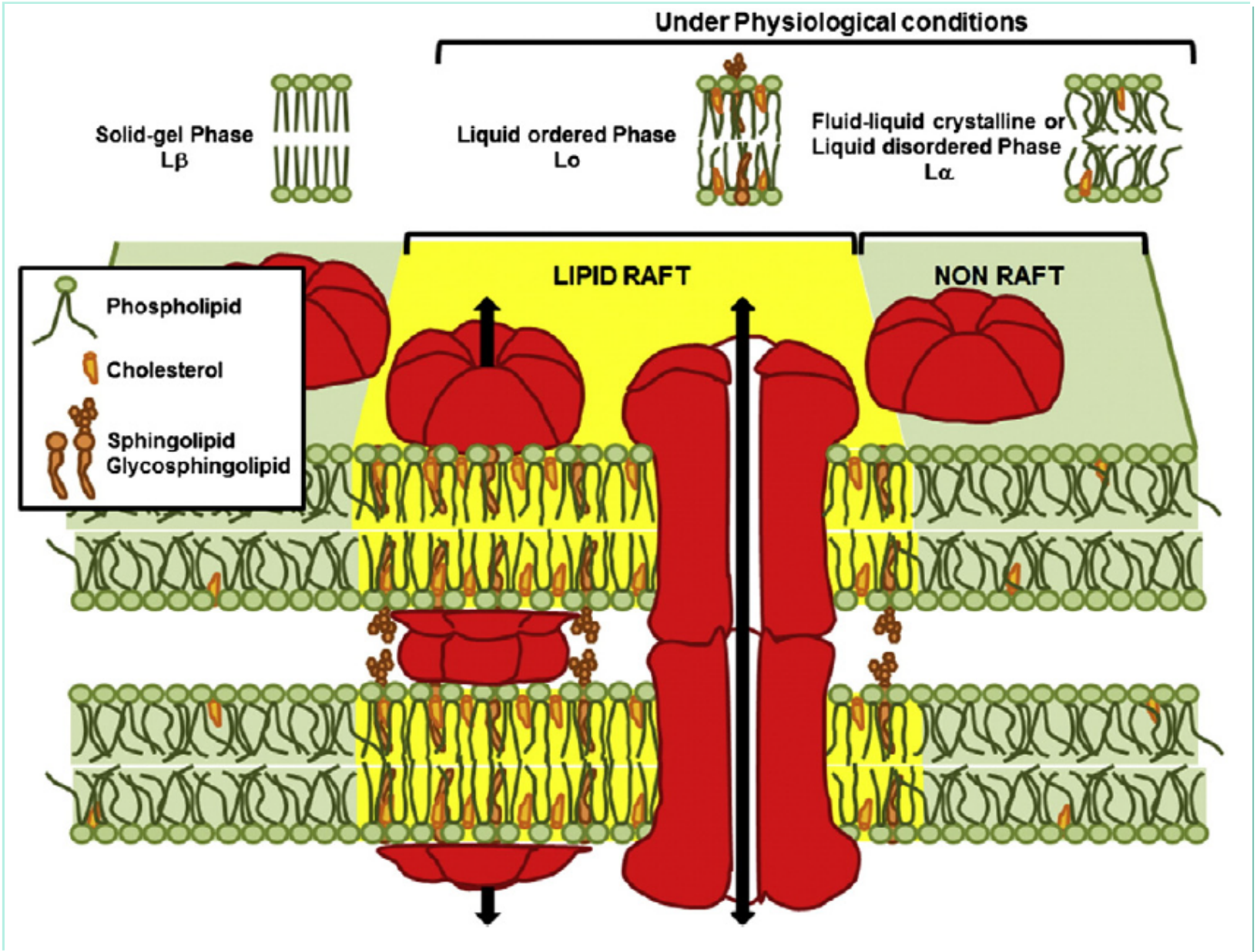
Reason for lateral immobility of proteins

1. Aggregate formation *e.g.* bacteriorhodopsin
2. Attachment to cytoskeleton *e.g.* Band 3
3. Binding of large peripheral proteins at inner/outer surface

Lipid-protein interactions

- Hydrophobic interactions - between lipid acyl chains and protein transmembrane α-helices
- Ionic/H-bonding interactions - between lipid headgroups and polar protein domains
- Each protein molecule interacts with an annulus (ring) of lipid annular or boundary lipid

The three major phases of lipid bilayer organization in biological membranes.



Properties of boundary lipids

1. Protein surface reduces flexing of acyl chains by factor of 10-20; lipid is less fluid, has restricted motion

2. Not static - a boundary lipid exchanges every 10^{-6} sec, rather than every 10^{-7} sec, ~10 × slower than normal

3. All proteins perturb one lipid layer, second and third layers are affected to lesser extent

- glycophorin perturbs 30 lipids with single spanning segment
- Band 3 ~700 lipids bundle of 14 spanning segments

4. Some proteins attract specific lipids into their boundary layer

- They may be required for protein function; can think of as being allosteric effectors
- Other lipids may be excluded from the boundary layer, *e.g.* cholesterol exclusion is seen for many proteins

5. Integral proteins usually retain tightly bound annular lipid even in detergent solution (mild conditions); often present after purification, *e.g.* P-glycoprotein transporter retains 55 lipids around it

Removal (using strong detergents or harsh conditions) often causes complete loss of activity (denaturation)

Lipid asymmetry in membranes - mechanisms

1. Slow flip-flop helps, but cannot maintain asymmetry for >24 hours

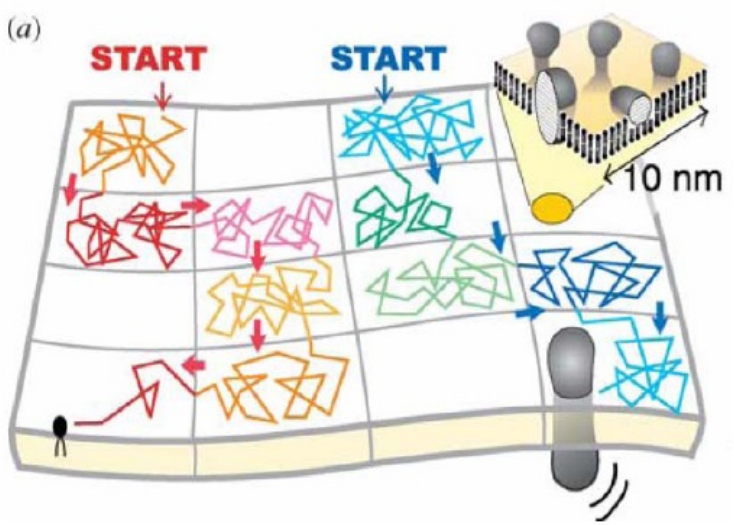
2. "Flippase" (phospholipid translocase)

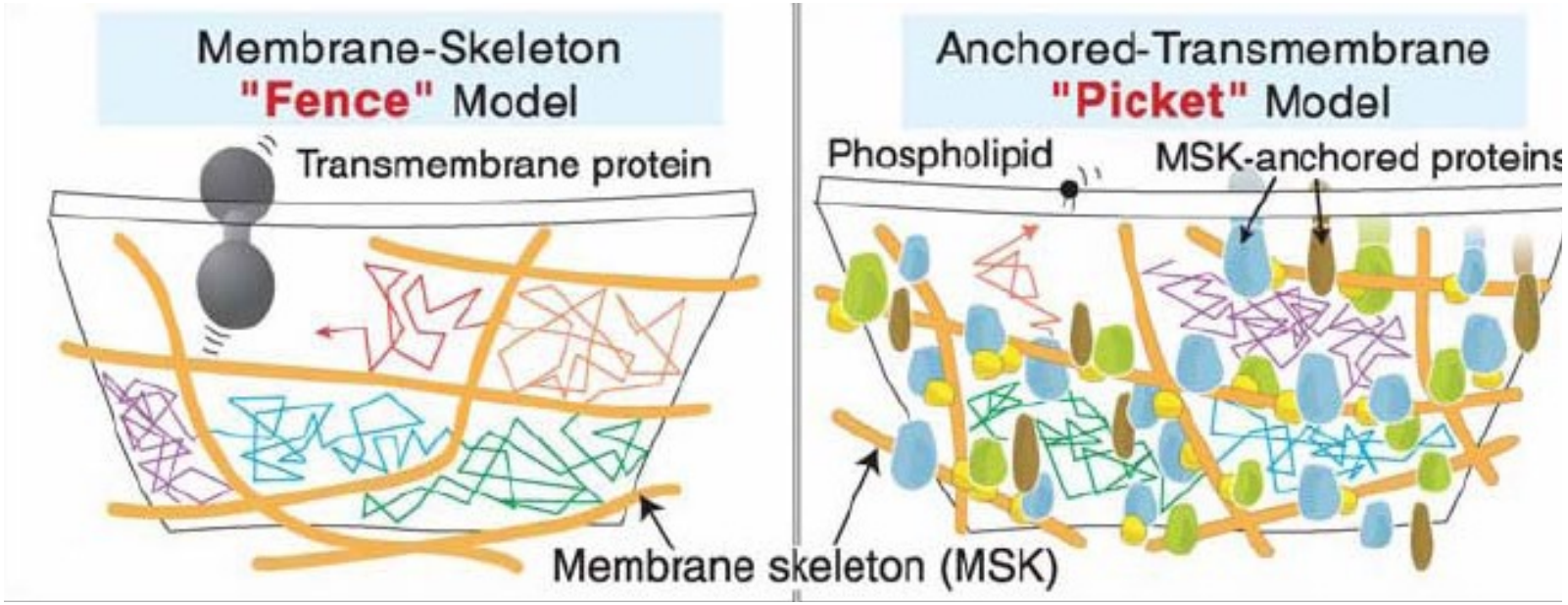
- plasma membrane-bound protein, low abundance
- uses ATP to move PE and PS from outer to inner leaflet
- selective; it does not translocate PC or SM

3. Cytoskeletal interactions

- some erythrocyte cytoskeletal proteins bind "amino" lipids with high affinity
- helps to keep PS and PE in the inner leaflet

The cell appears to have developed during evolution the means to control the long-range diffusion of membrane molecules.

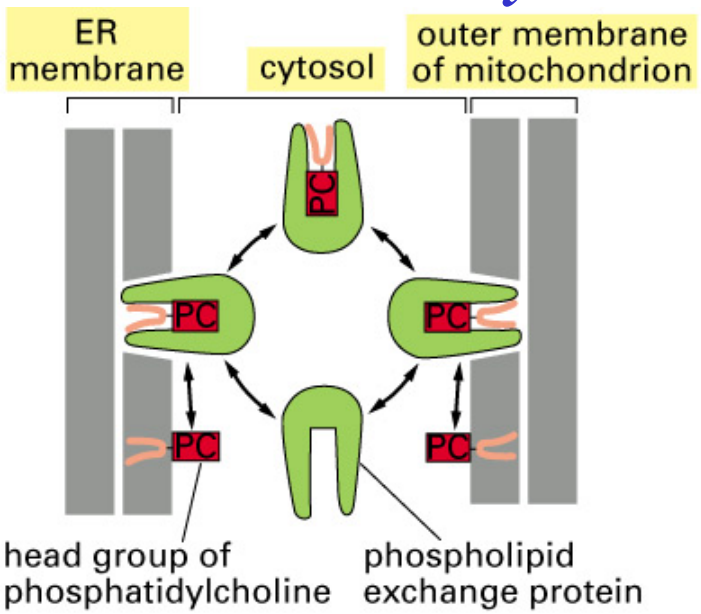




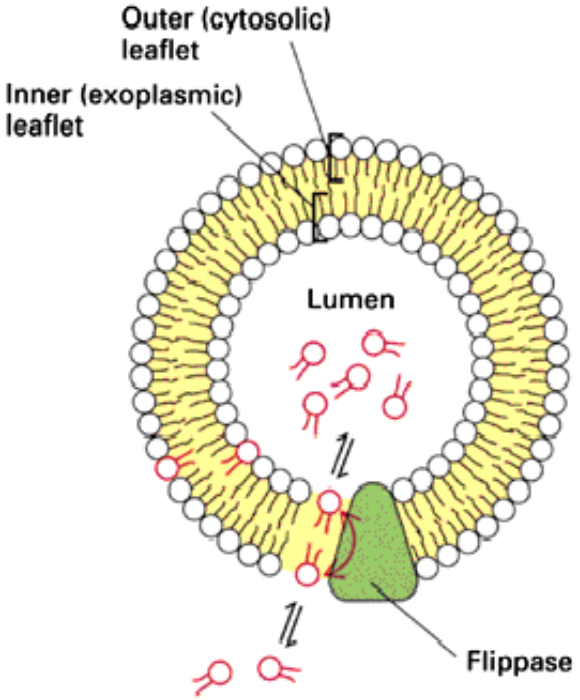
Transverse diffusion or Flip-Flop

- Movement from one side of bilayer to the other -VERY SLOW - 10^9 times slower than lateral diffusion.
- It takes 12-24 hours for half the phospholipid to exchange into the opposite leaflet.
- Large activation energy barrier to movement of polar headgroup through hydrophobic interior.

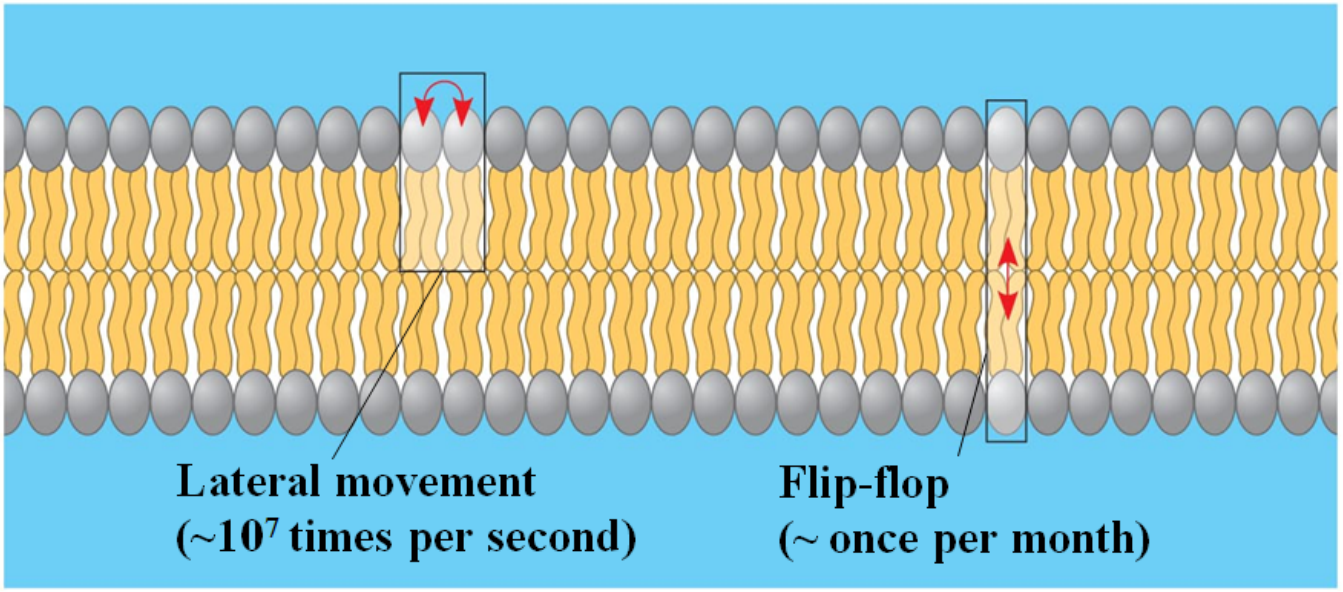
Slow flip-flop helps to maintain lipid asymmetry



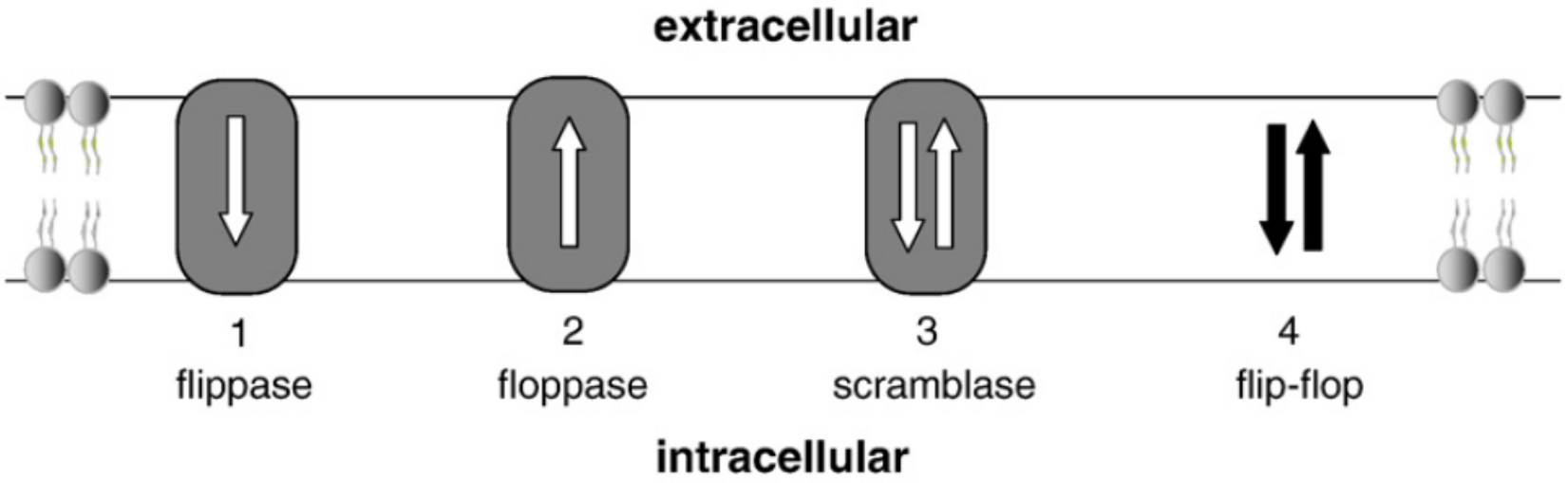
Phospholipid exchange proteins



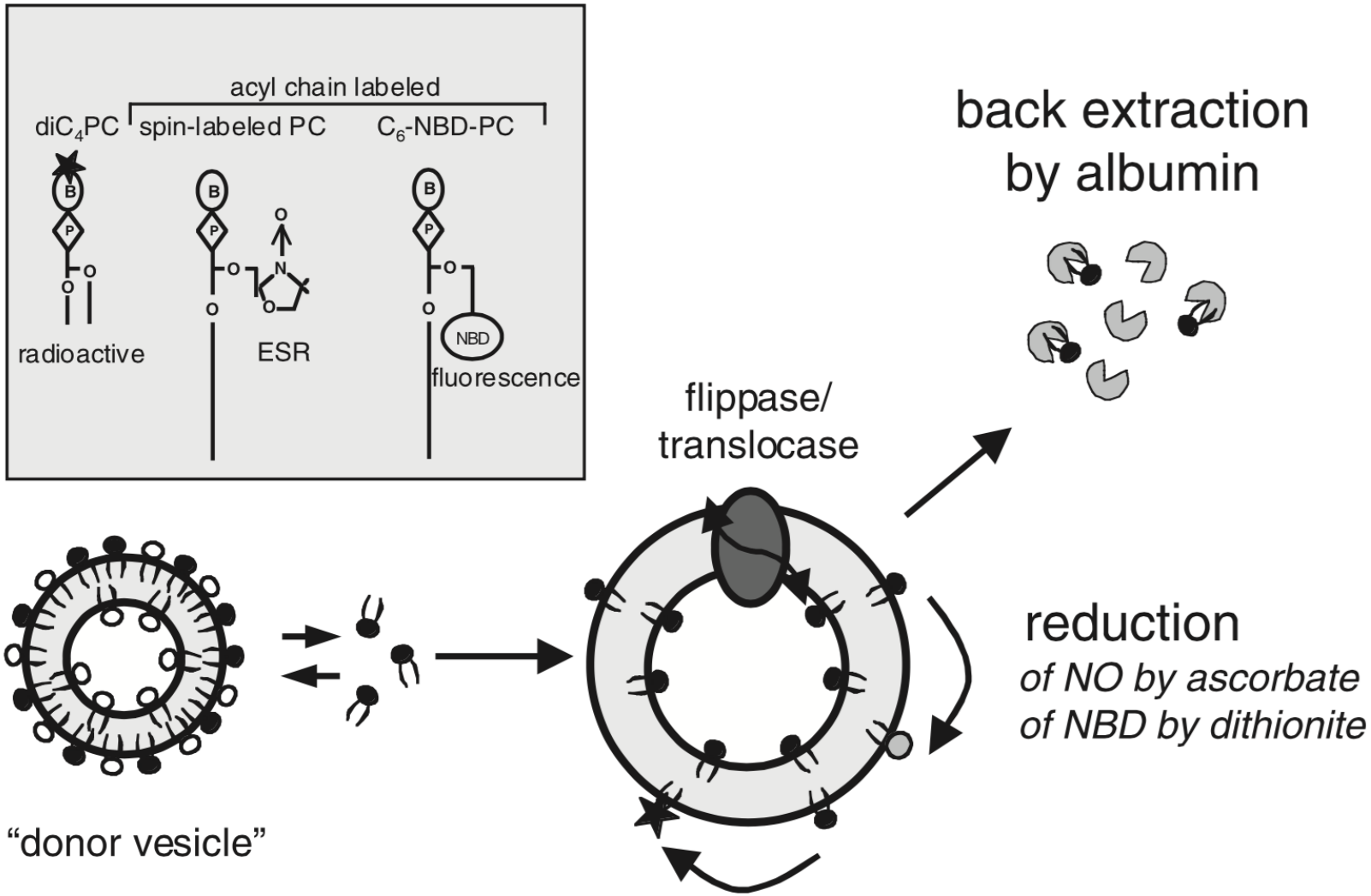
Lipid Flippases

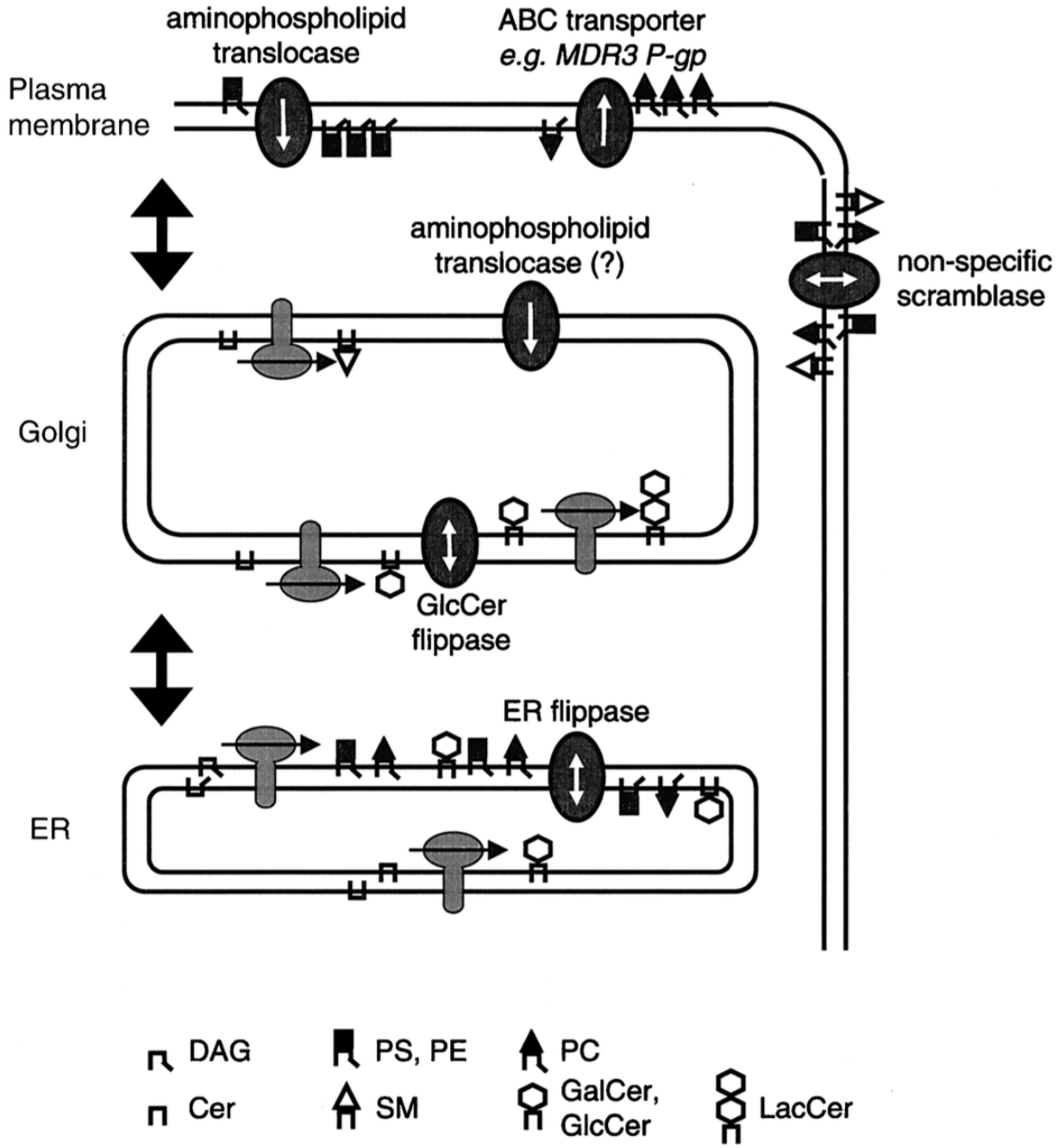


Movement of phospholipids



The techniques used for monitoring transbilayer movement of lipid.





Various proteins control lipid sidedness across cellular membranes.