Molecular biology of the cell
BIO 207

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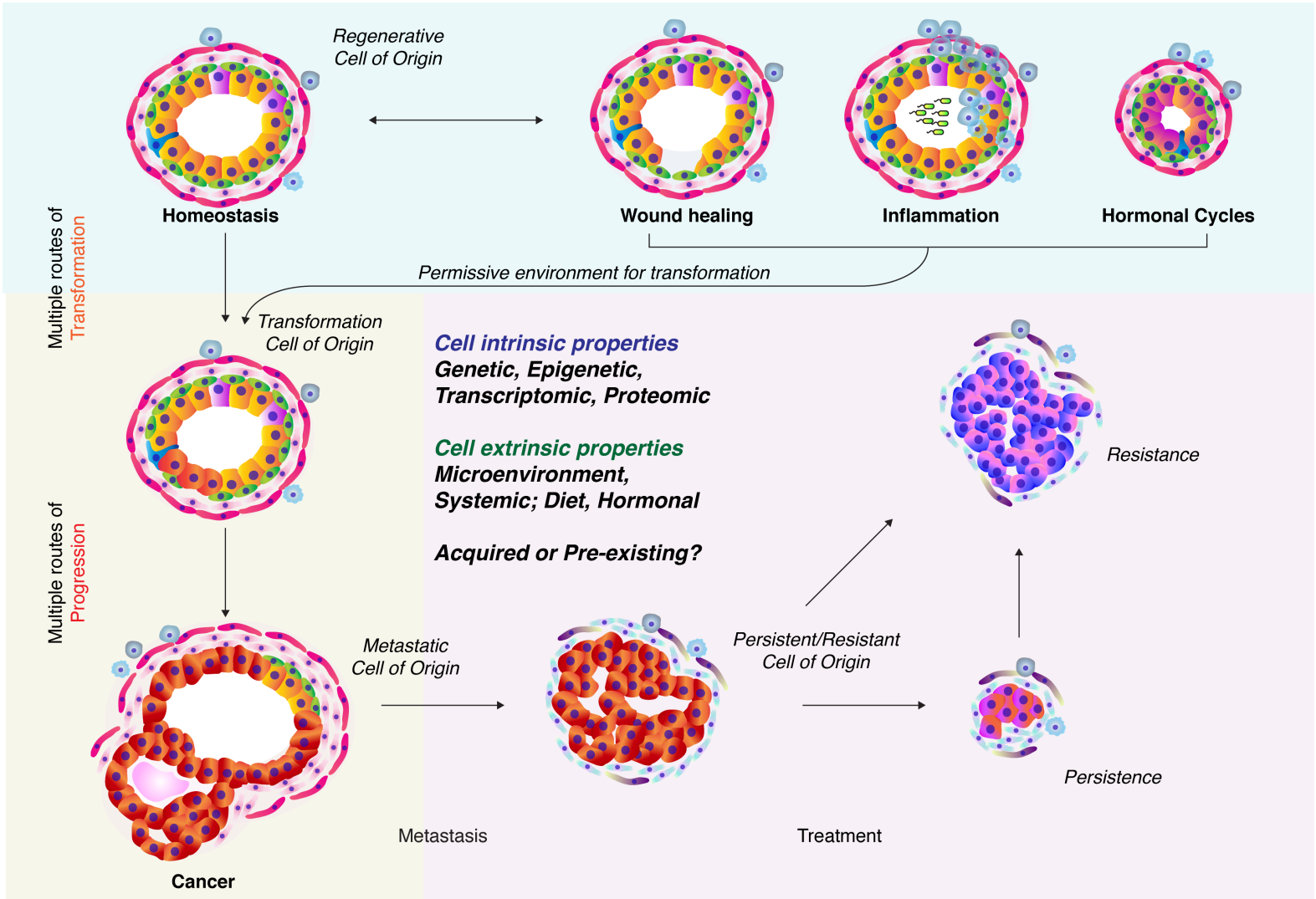
Research interests Karthaus Lab



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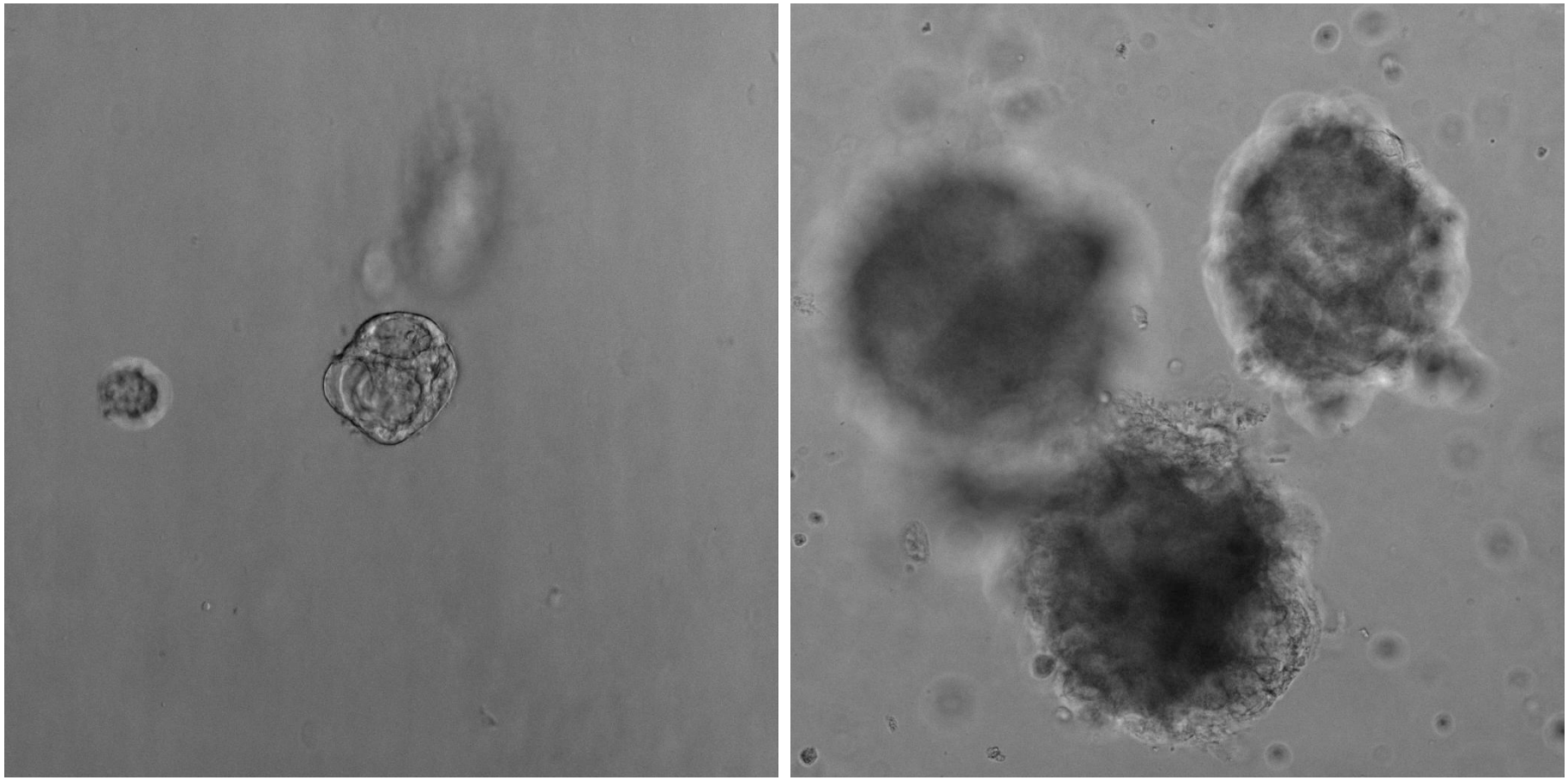


Organoids are mini organs in a dish. Are powerful model to study biology. The concepts discussed in this course are essential to understand if one works with cells!

Course objectives BIO 207

Develop an intuitive understanding of the organization and function of a eukaryotic cell

Why does a eukaryotic cell perform a function?
How does a eukaryotic cell perform a function?
What are the features of the molecules involved in this function?
How are these molecules organized in the cell?

The names of the molecules are important to know, they are part of the day-to-day vocabulary of a life scientist.

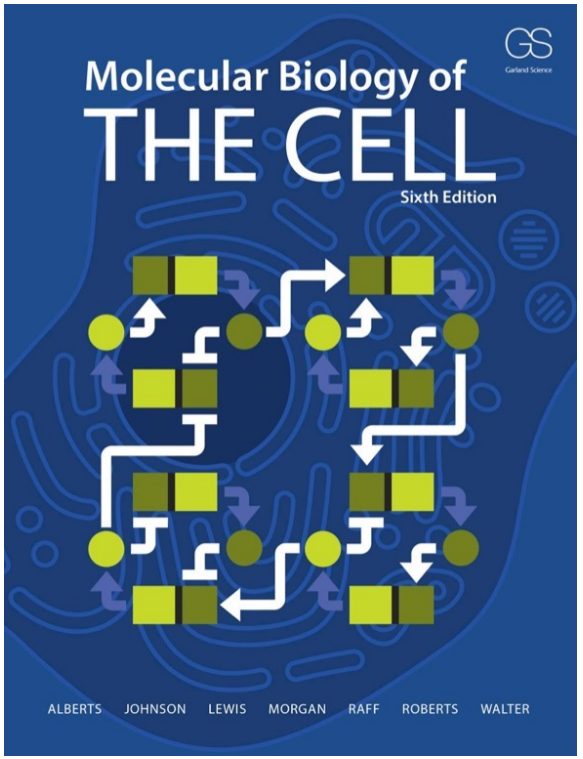
Course information BIO 207

19/02 Seminar & Exercises
26/02 Seminar & Exercises
05/03 Seminar & Exercises
12/03 Seminar & Exercises
19/03 Seminar & Exercises
26/03 Seminar & Exercises
02/04 Seminar & Exercises
09/04 Seminar & Exercises
16/04 Seminar & Exercises
23/04 Easter
30/04 Seminar & Exercises
07/05 Seminar & Exercises
14/05 Seminar & Exercises
21/05 Seminar & Exercises
28/05 Q&A

Course material

Molecular Biology of the cell

Chapter 10, 11, 12, 13, 15, 16, 19 and selection of 18 (Cell Death)



PDF of all chapters and seminars will be on MOODLE

Course information BIO 207

Questions:
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Announcements on MOODLE

Exam Open book

Topic of the day

Cell membranes

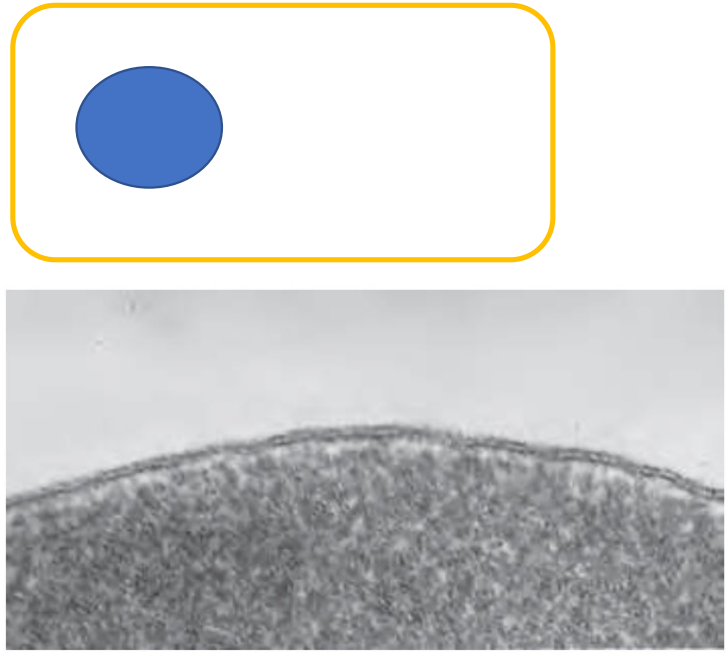
Plasma membrane (Outside of the cell)

Membranes of organelles
Golgi complex
Endoplasmic Reticulum
Nucleus
Mitochondrion

CHAPTER
10

Membrane Structure

Cell membranes an introduction



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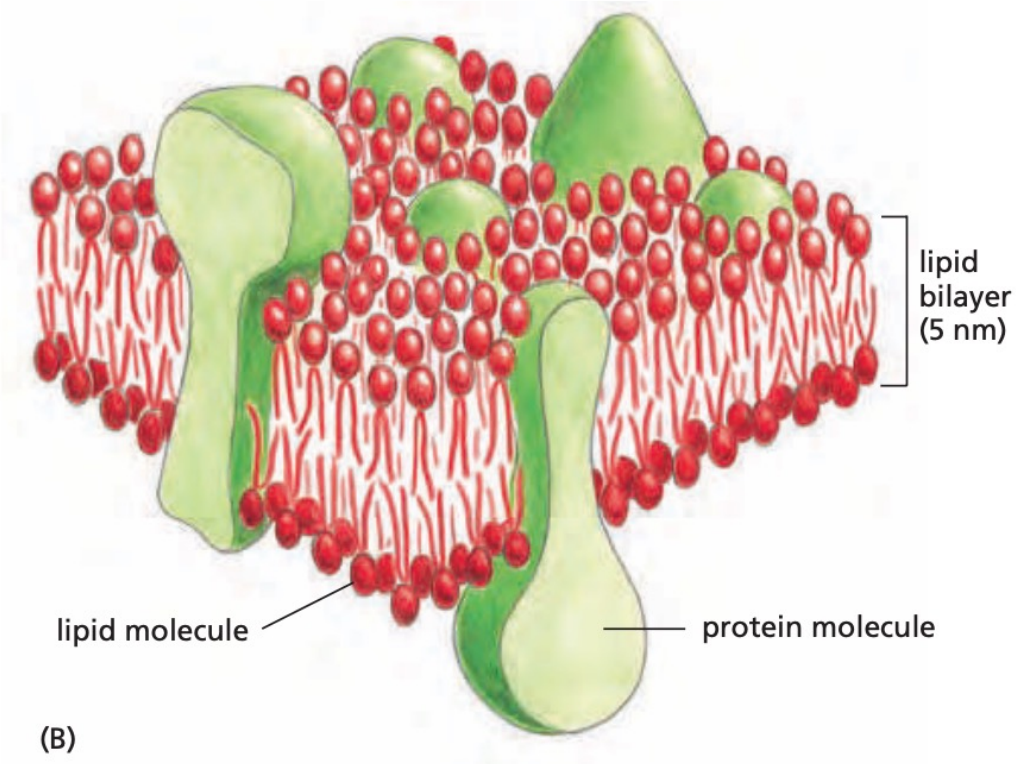


(B)

Figure 10–1 Two views of a cell membrane. (A) An electron micrograph of a segment of the plasma membrane of a human red blood cell seen in cross section, showing its bilayer structure. (B) A three-dimensional schematic view of a cell membrane and the general disposition of its lipid and protein constituents. (A, courtesy of Daniel S. Friend.)

The origin of cell membranes and the origin of life in water

Scientific American

Genesis Landscape

Hot springs, pools and geysers can kick-start chemical systems necessary for life on Earth to begin, according to one theory. The conditions set in motion seven steps, beginning with chemical synthesis, moving through cycles of increasing complexity and ending in colonization of new territory.

1 Synthesis
Many of life's basic building blocks, such as amino acids, are formed in space and fall to Earth.

2 Accumulation
In-falling organic compounds, along with others generated within hot springs on a volcanic landscape, accumulate in hydrothermal pools.

3 Concentration
The compounds are concentrated within tiny vesicles made of simple molecules called lipids. The close proximity, plus heat and chemical energy from the spring system, links them together to form more complex molecular chains.

4 Cycling
Pools go through repeated cycles of three phases: dry, wet and moist gels. Dry times help to synthesize polymers used to carry information, such as chains of nucleic acids. In a wet period, protocells can form, encapsulating these polymers and protecting them. Then, in the gel phase, protocells pack together in a system called a progenote and exchange sets of polymers, selecting those that enhance survival during many cycles.

5 Distribution
The best-adapted protocells spread to other pools or streams, moving by wind and water, and some develop the ability to use carbon dioxide for photosynthesis. After much trial and error, one protocell assembles the complicated molecular machinery that enables it to divide into daughter cells. This paves the way for the first living microbial community.

6 Adaptation
Some of these early microbes are pushed into saltwater estuaries, beyond their native freshwater ponds. The microbes that survive pass along useful traits that help descendants expand their range to oceans.

7 Colonization
Sea storms and tugging tides select for mats of rugged microbes able to cement themselves together using grains of minerals. These layers pile up into stacks called stromatolites. Life continues to expand into other niches, setting the stage for free-living cells. After billions of years, these organisms evolve into complex multicellular plants and animals.

When the pool refills, the films rehydrate and bud off trillions of protocells, membranes that encapsulate collections of random polymers.

Increasing complexity

Progenotes

The cycle repeats, again and again. Every time it does, protocells interact, compete for resources and evolve more complex functional polymers until a "progenote" community emerges that is able to exchange adaptive molecules, developing ever more sophisticated functions.

Gel phase

Gels

Protocells

Protocells

Protocells that survive the changing conditions then group together in a moist gel as the pool level drops.

Organic compounds, some forming membranes, collect in pools.

Films

Films

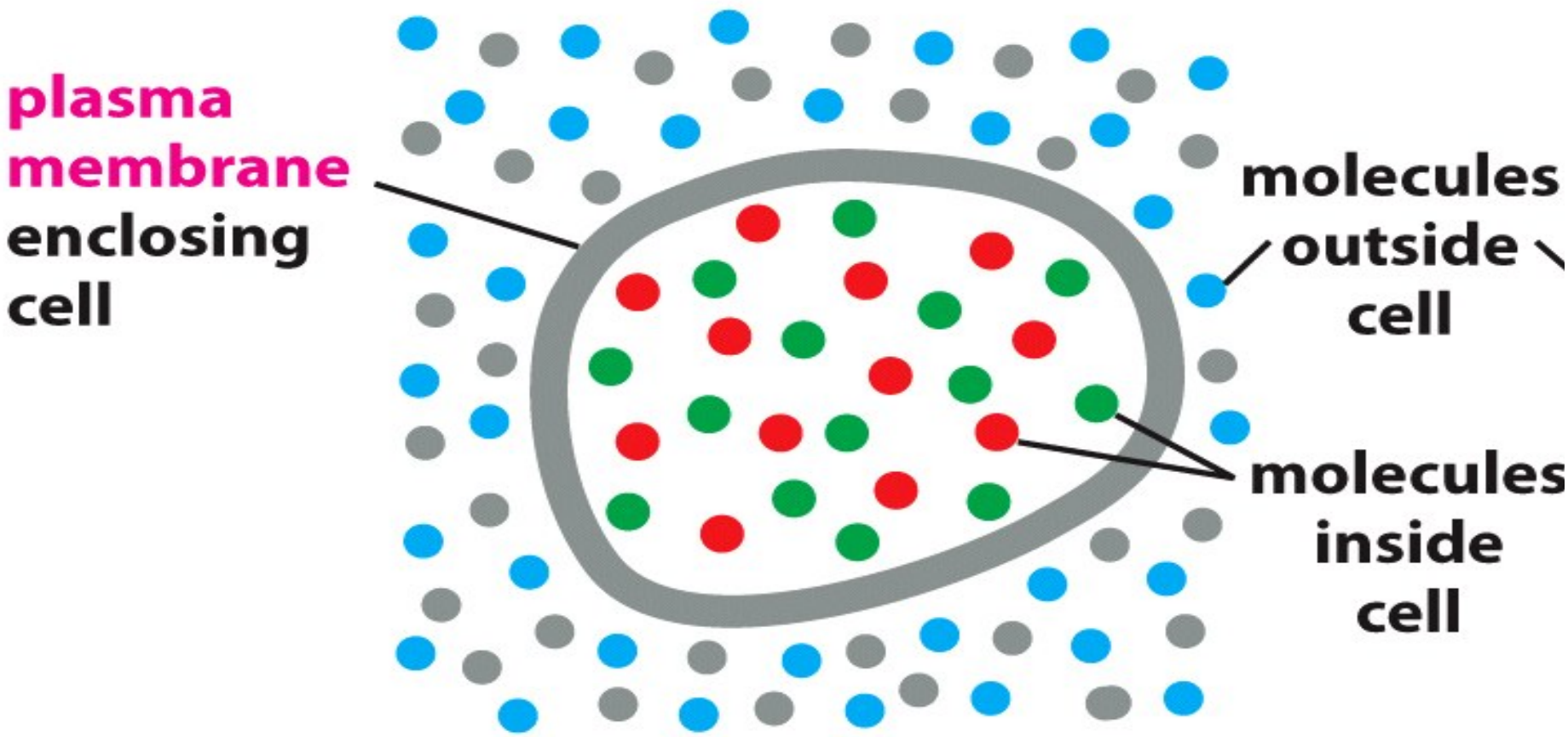
Membranes dry to form films. Between these layers, simple organic building blocks bond together to form polymers.

Wet

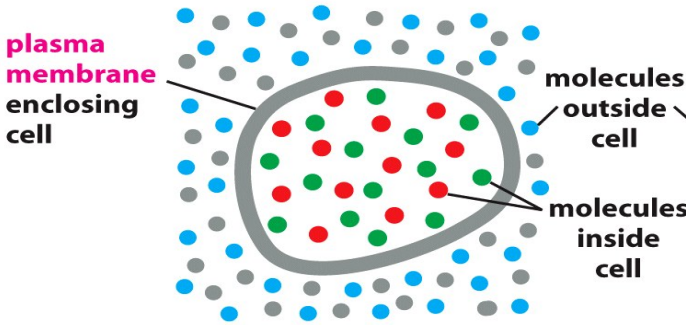
Dry

Illustration by José Miguel Mayo (landscape) and Jen Christiansen (cycling detail)

A plasma membrane protects the cytosol (inner parts of the cell) and their chemistry



The plasma membrane protects the cytosol and the chemistry of the cell



Outside of the cell

The plasma membrane
~ 5 nanometer across

Hydrophilic

Hydrophobic

Hydrophilic

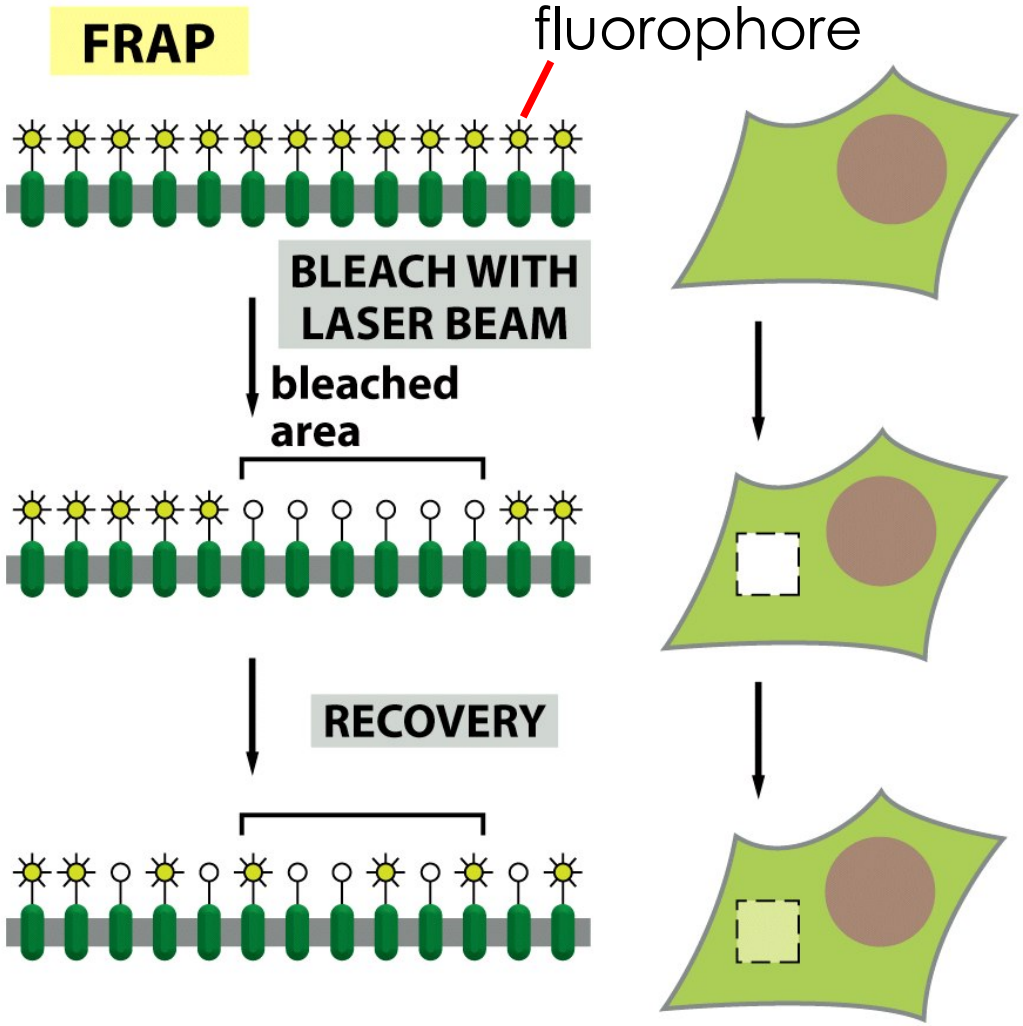
Inside of the cell

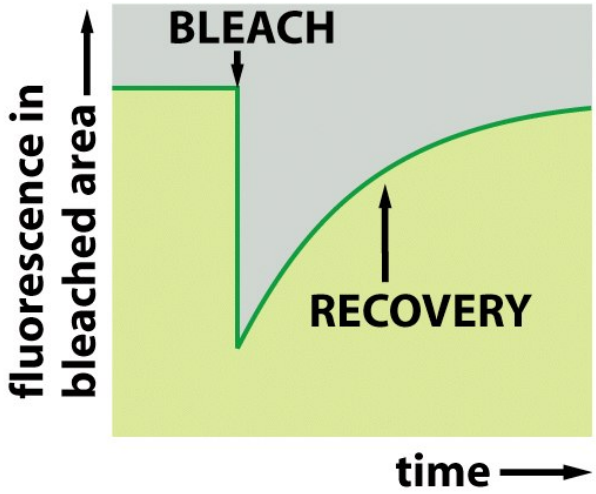
2 types of molecules

1: Lipids
2: Proteins

Cell membranes are liquid with similar properties as oils

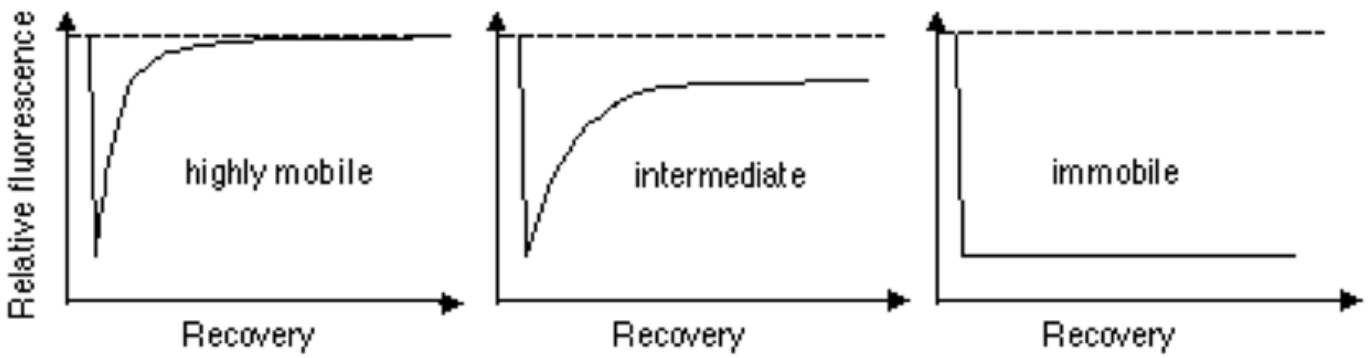
Cell membranes are a liquid



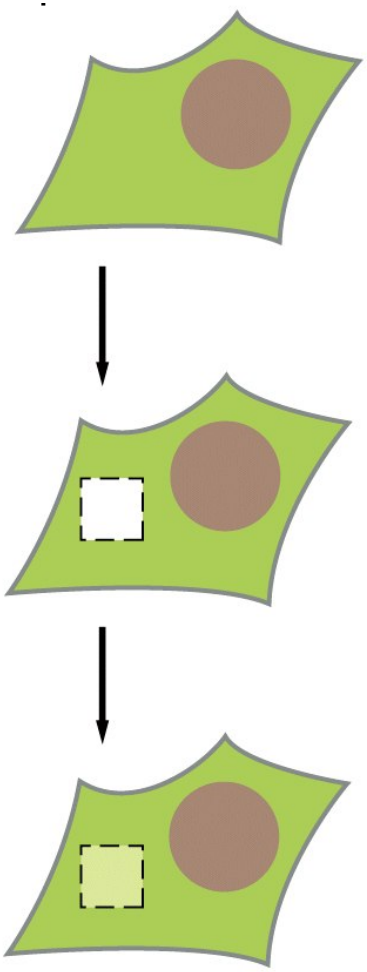


Photobleaching: Destruction of a fluorophore with a laser

Cell membranes are a liquid

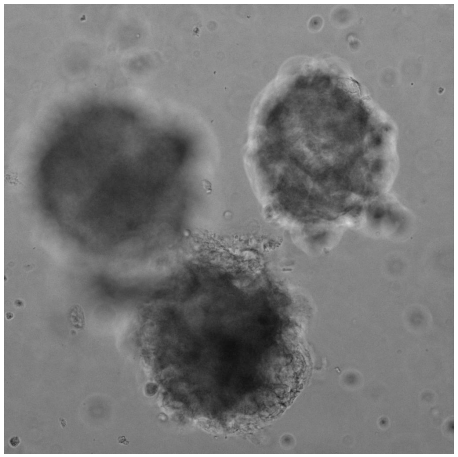


coefficient de diffusion



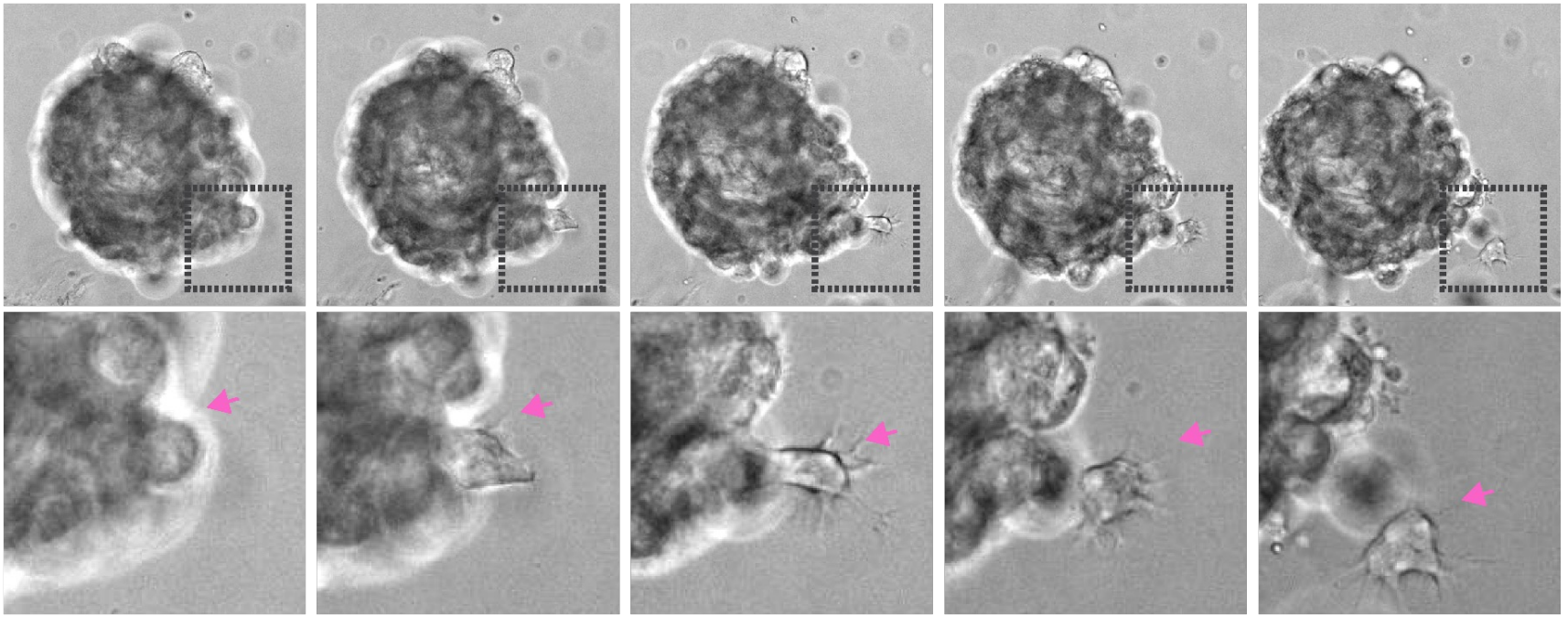
A liquid like the cell membrane will diffuse and the color will recover!

Cell membranes are a liquid

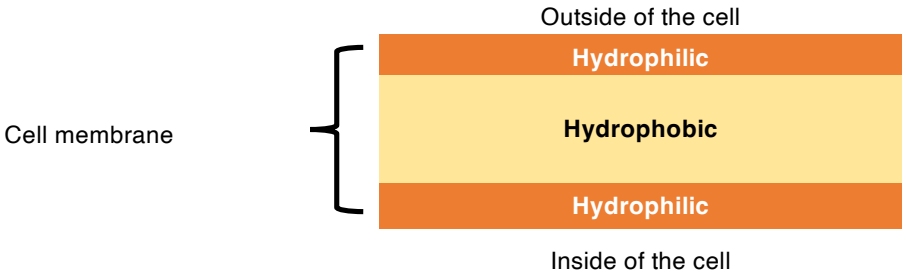


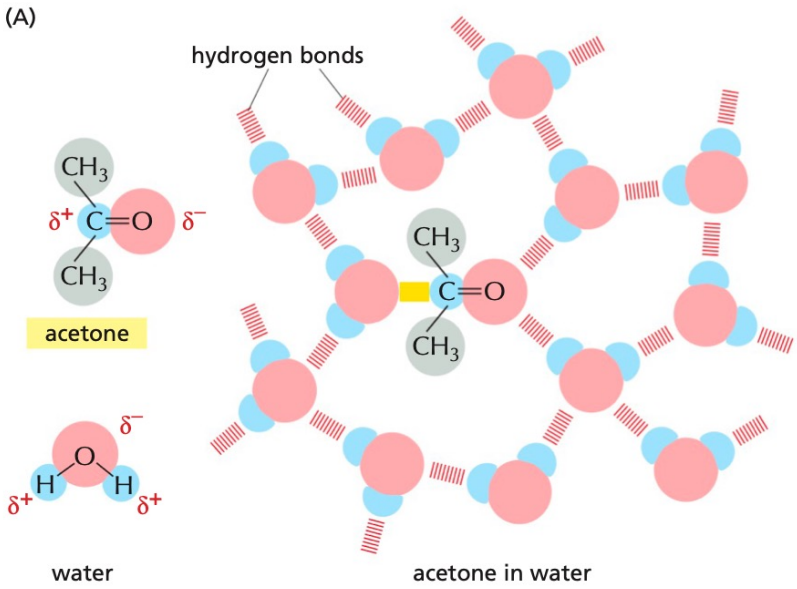
The liquid nature of the plasma membrane allows a cell deform it

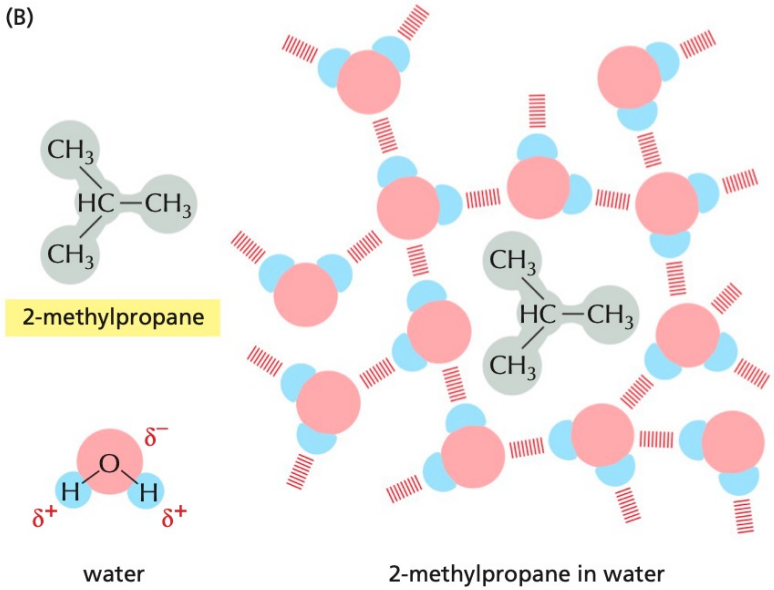
Deformation can be to the outside of the cell or inwards to the cytoplasm



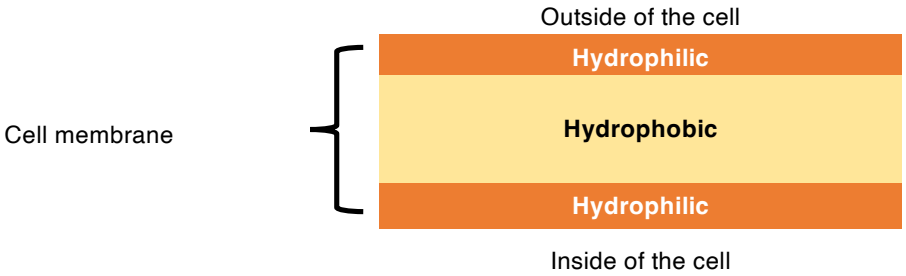
Hydrophobic vs Hydrophilic interactions

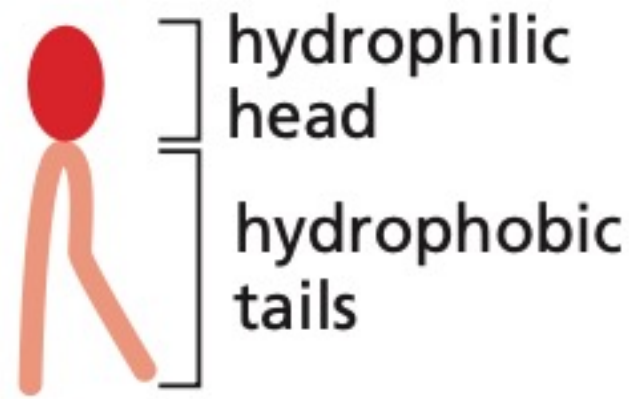


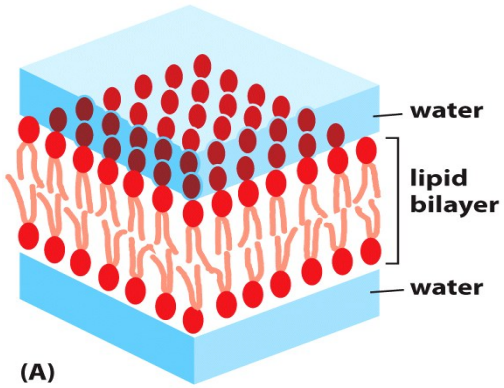


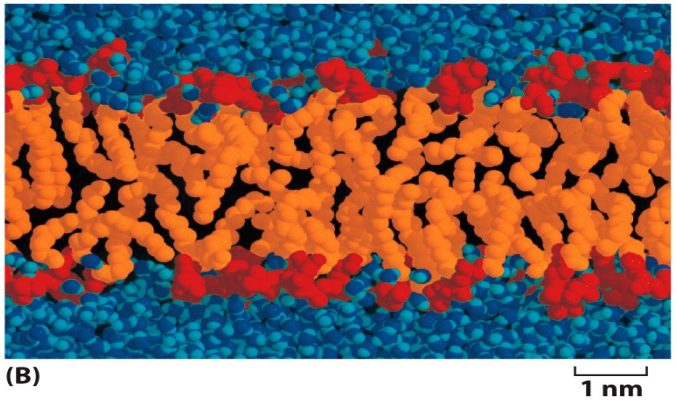


Cell membranes are composed of lipids 50:50 mass ratio



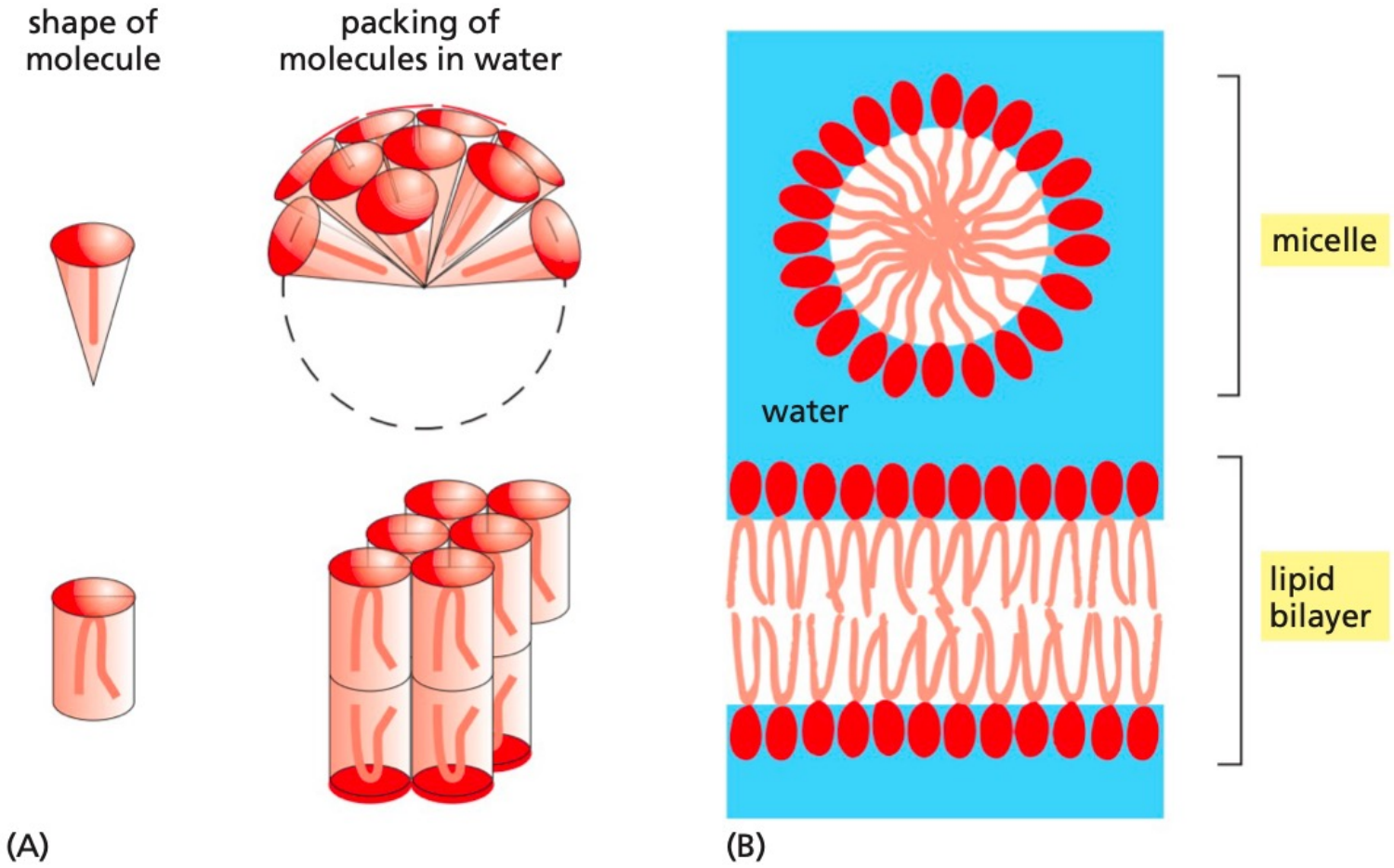




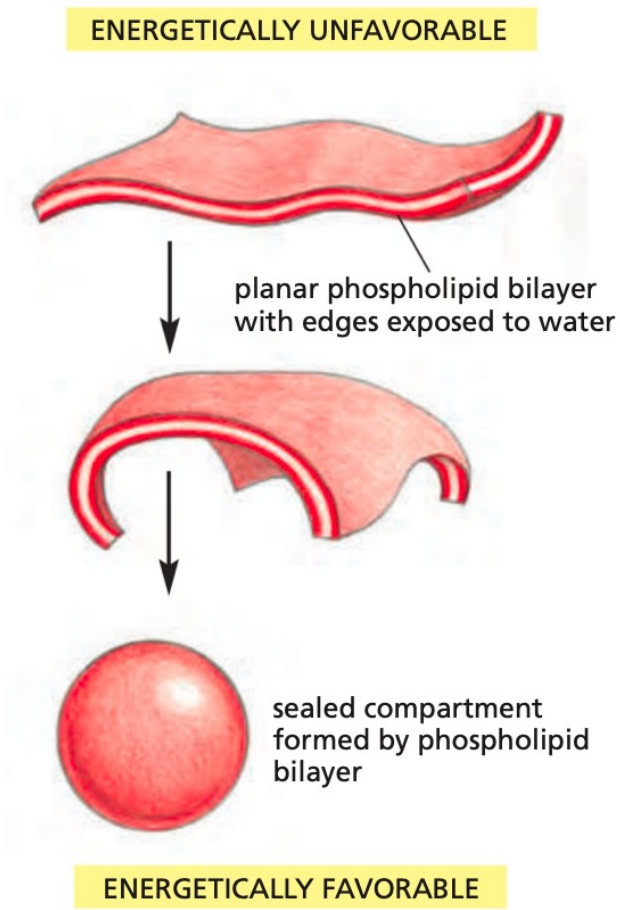


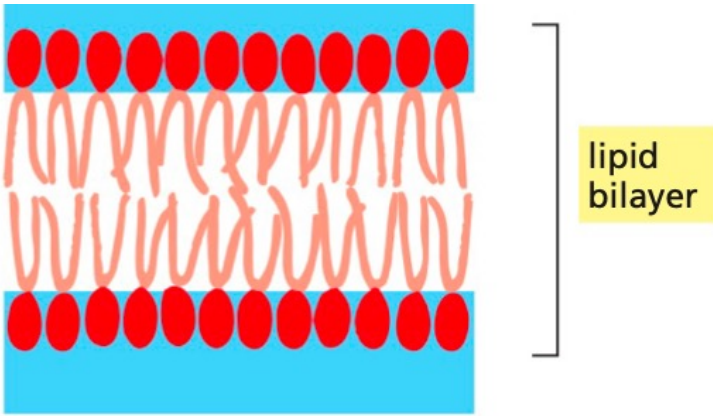
Phospholipids make up majority of lipids in the membrane
Phospholipids are **amphiphilic**: They have a hydrophilic head and hydrophobic tail

The molecular shape of lipids defines the behaviour in water

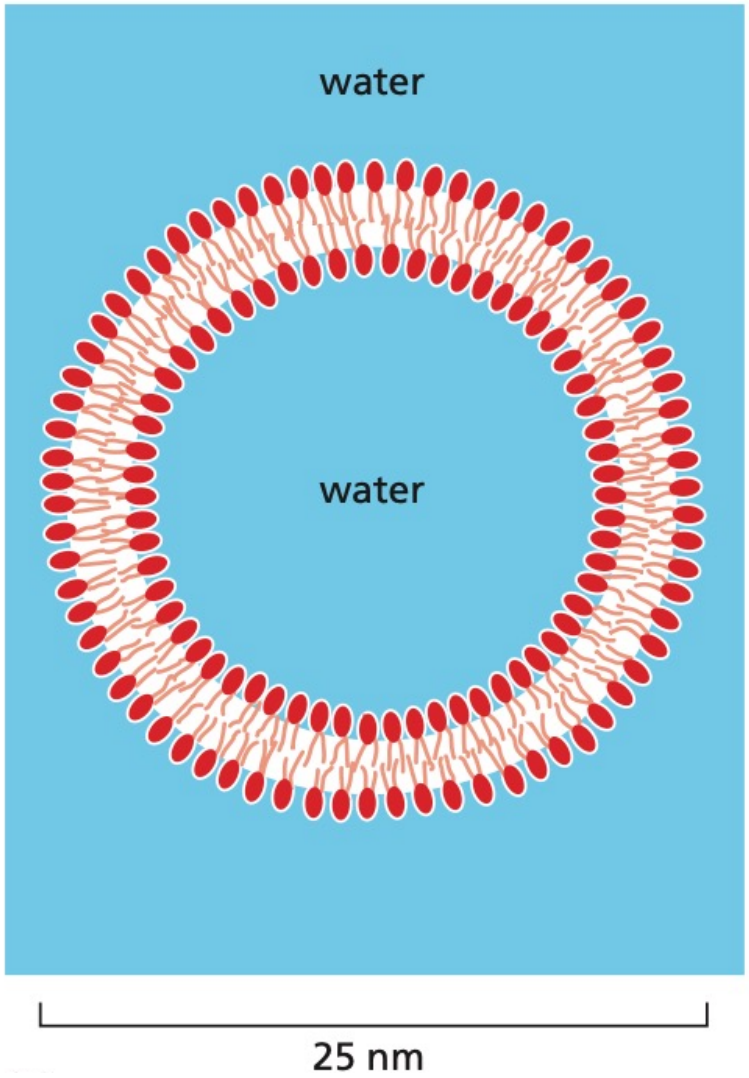


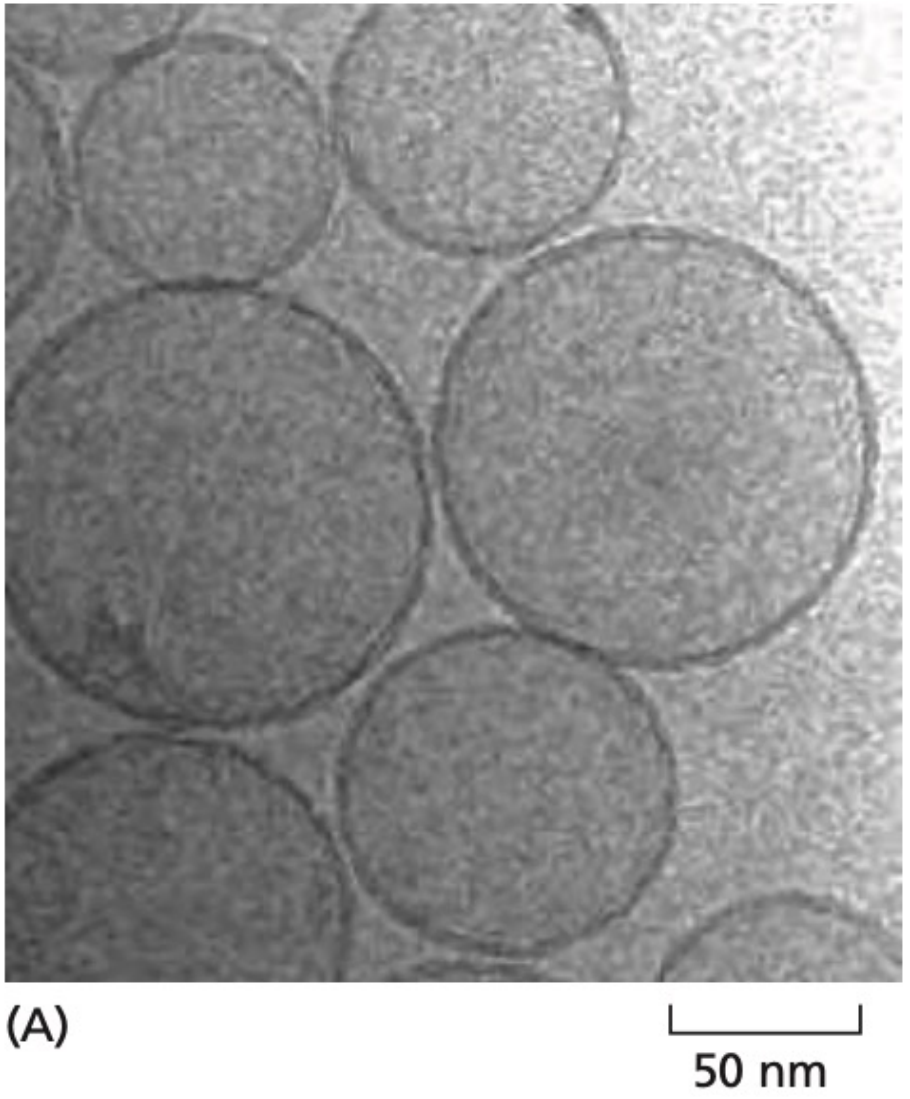
The phospholipid bilayer form a sealed compartment



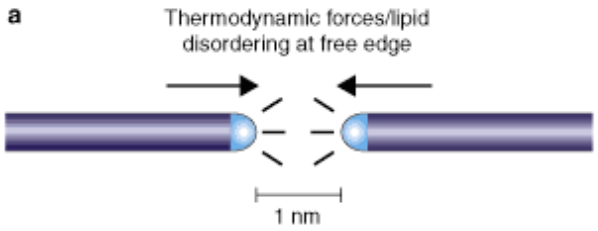


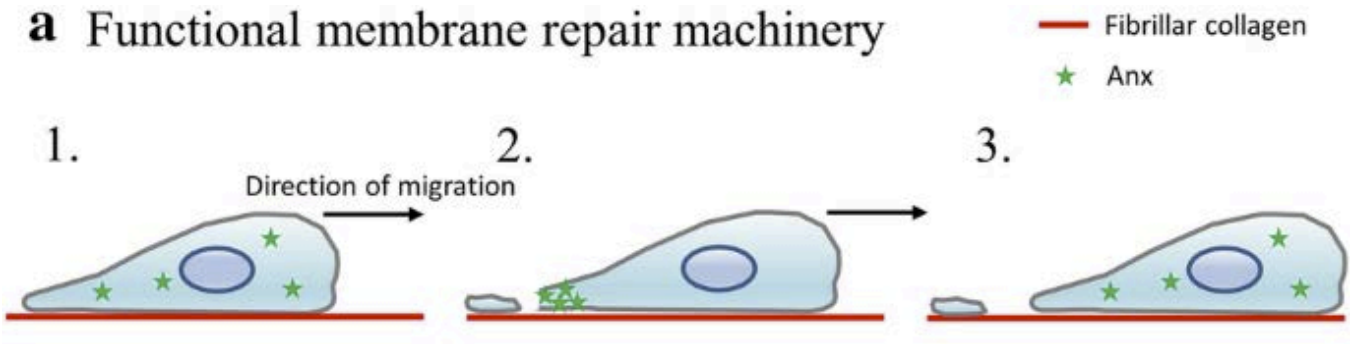
Cell membranes are composed of lipids





Cell membranes can self repair due to these properties





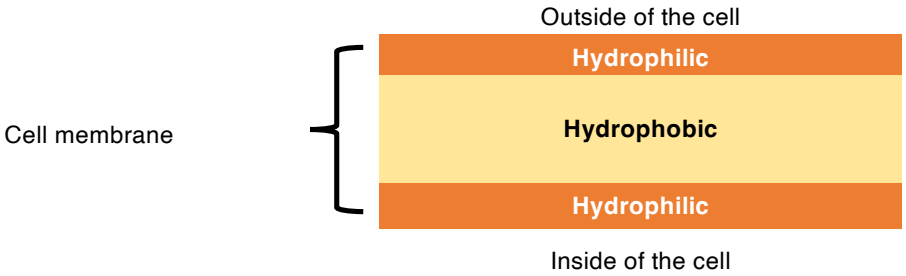
Cell membranes in summary

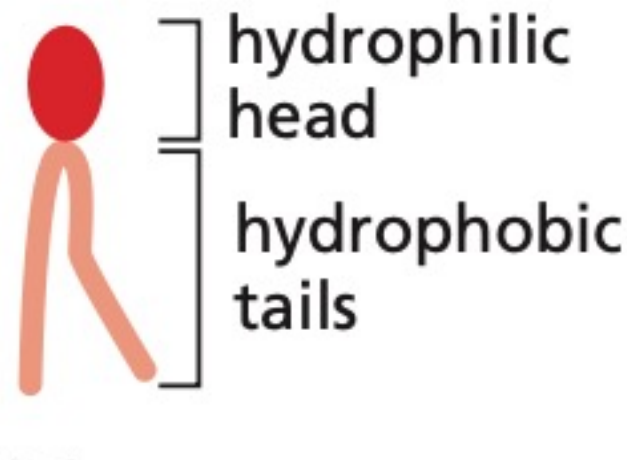
Cell membranes are fluids with features similar to oil
Cell membranes are composed of amphiphilic molecules
The main component are phospholipids and proteins
Cell membranes are self-repairing
The plasma membrane protects and controls the internal chemical composition of a cell

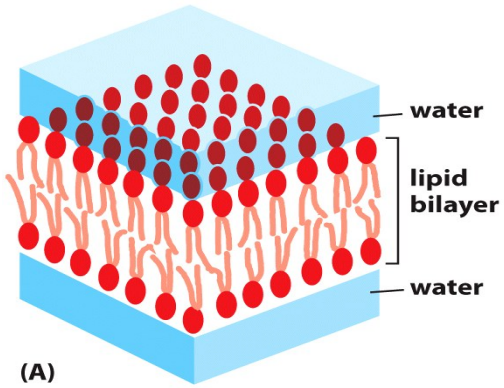
Additional functions
It can changes in composition and properties (fluidity, permeability,...) according to the need
It can change according in response temperature, the ionic composition of the medium, the presence of neighboring cells (friendly or not), ...
It transport of ions, molecules: Chapter 11
Allows for communication (transmission of information) between the outside and the inside, (signals: chapters 15, 19)

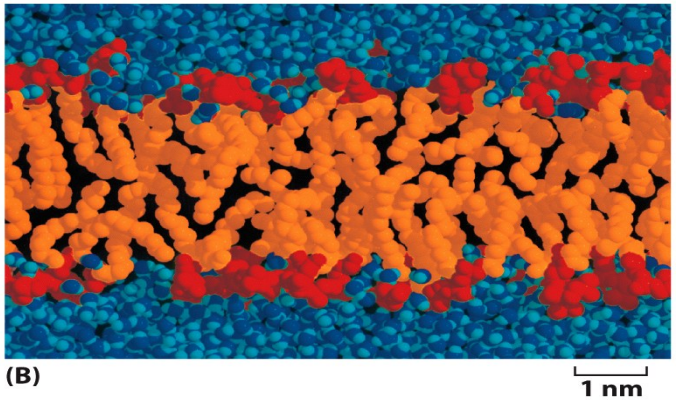
What kind of lipids are found in the membrane and how to they function in the membrane?

The lipids found in cell membranes



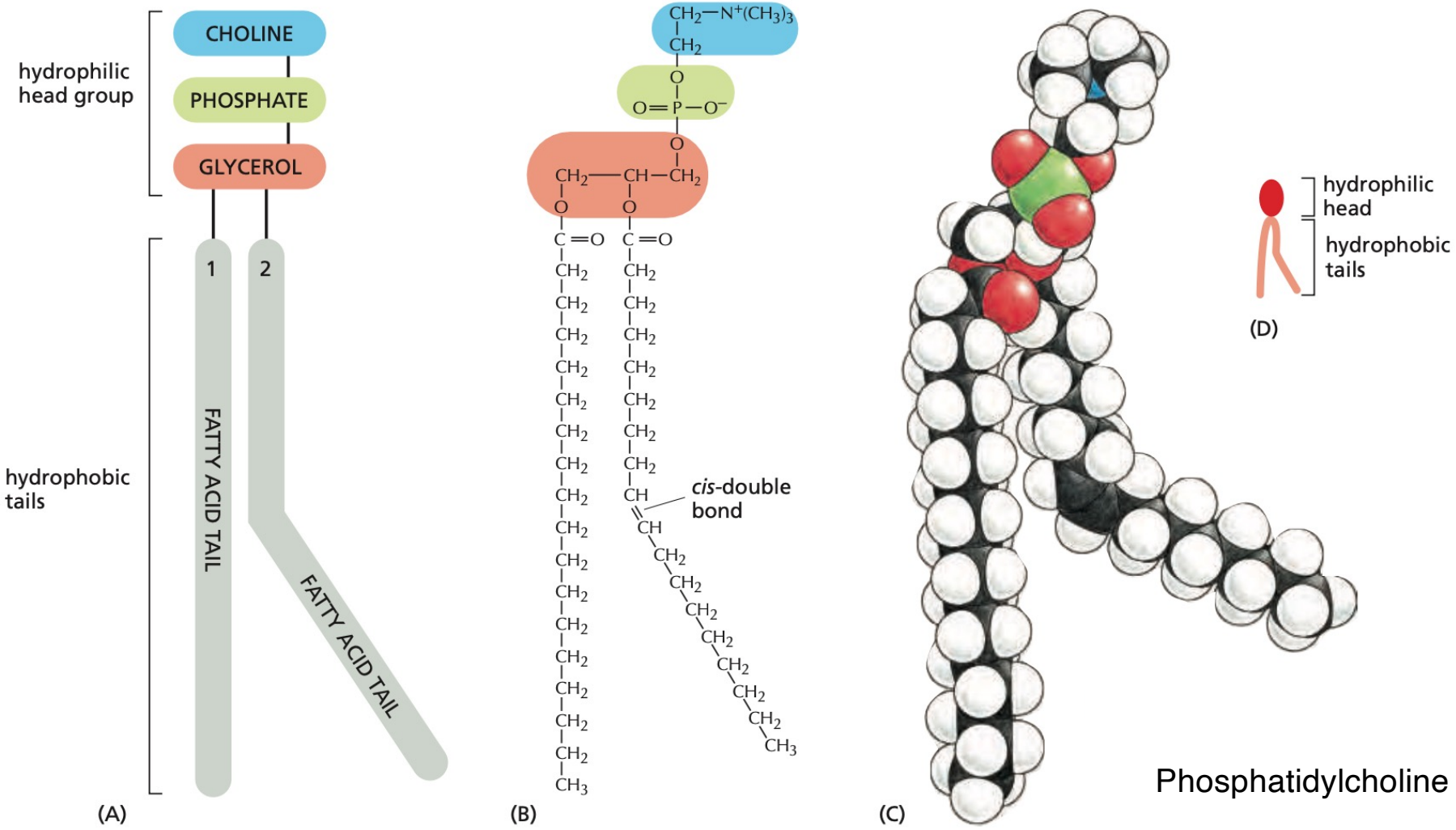




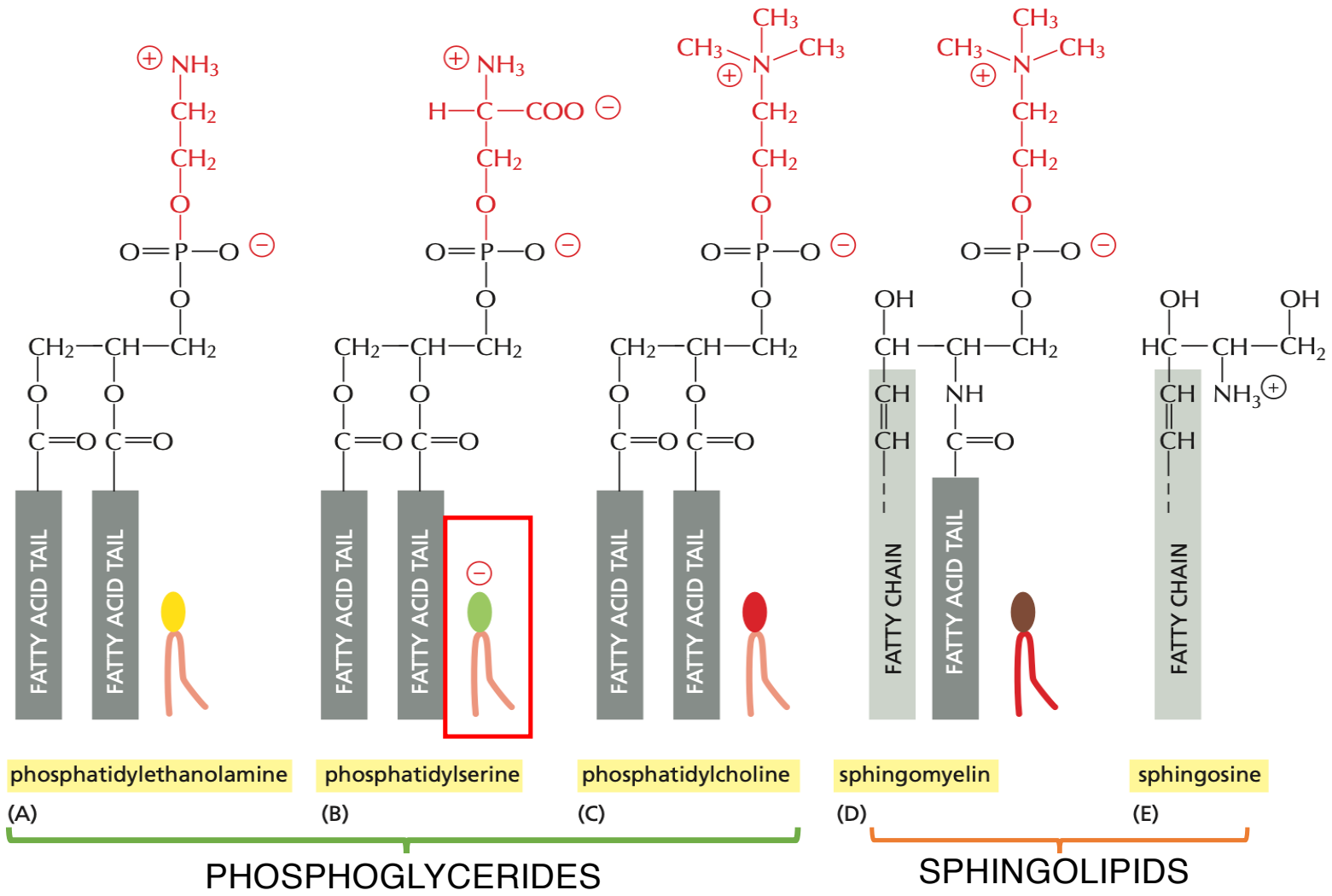


Phospholipids make up majority of lipids in the membrane
Phospholipids are amphiphilic: They have a hydrophilic head and hydrophobic tail

The parts of a typical phospholipid molecule

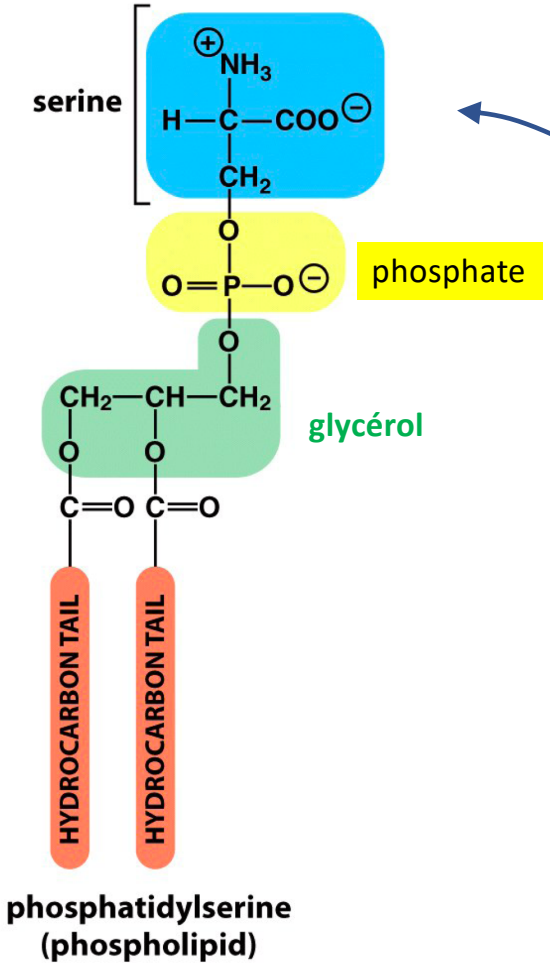


Four major phospholipids in mammalian plasma membranes

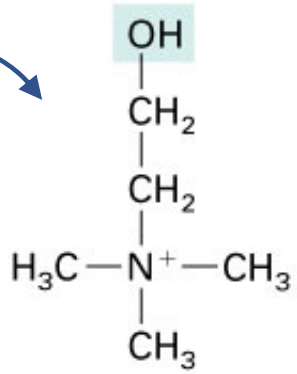


There are 3 main classes of lipids found in the cell membranes

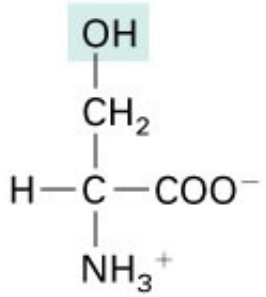
PHOSPHOGLYCERIDES



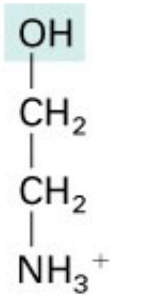
phosphatidylserine
(phospholipid)



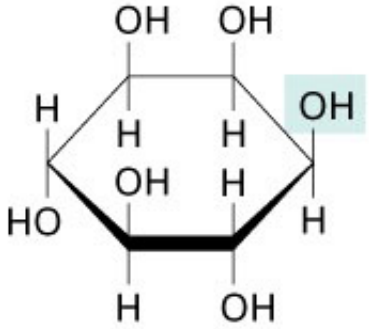
Choline



Serine



Ethanolamine



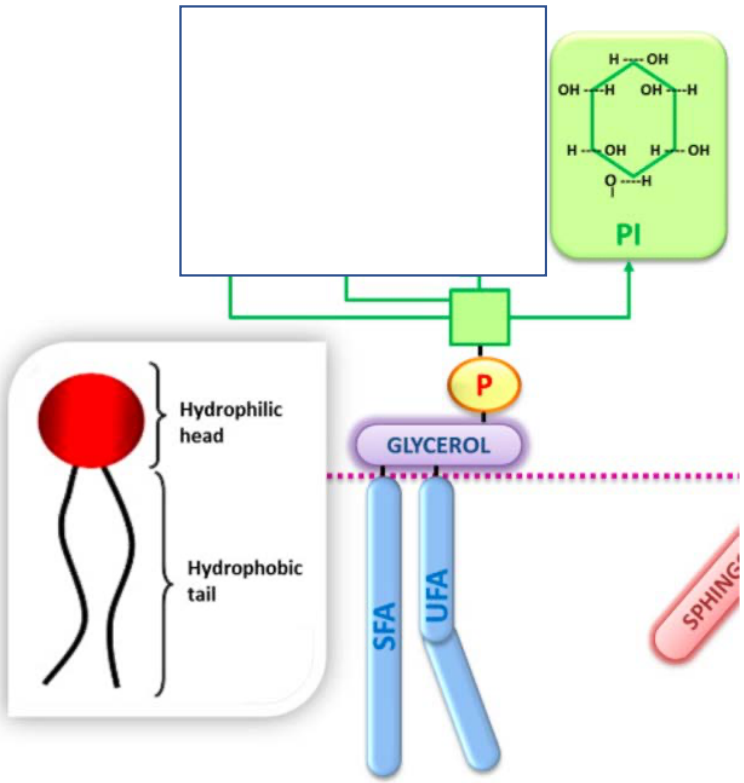
Inositol

These are alcohols that are covalently bound to the phosphate group

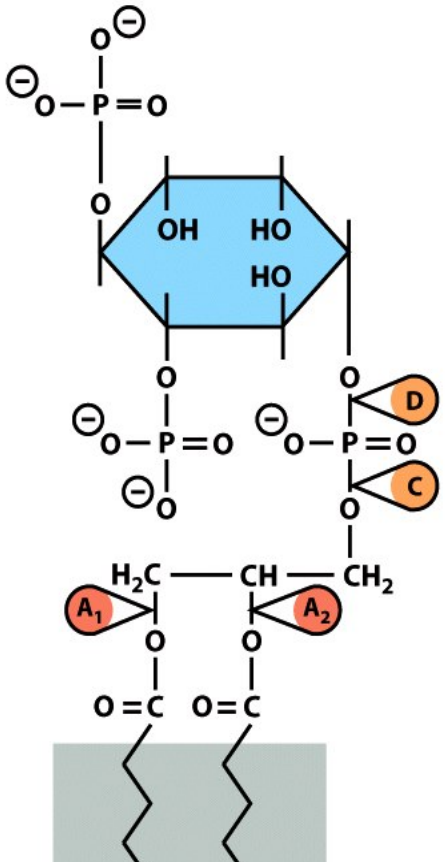
Ce n’est pas un sucre

Phosphatidylinositol a special phoshoglyceride

PI: Phosphatidyl-inositol



It can be phosphorylated

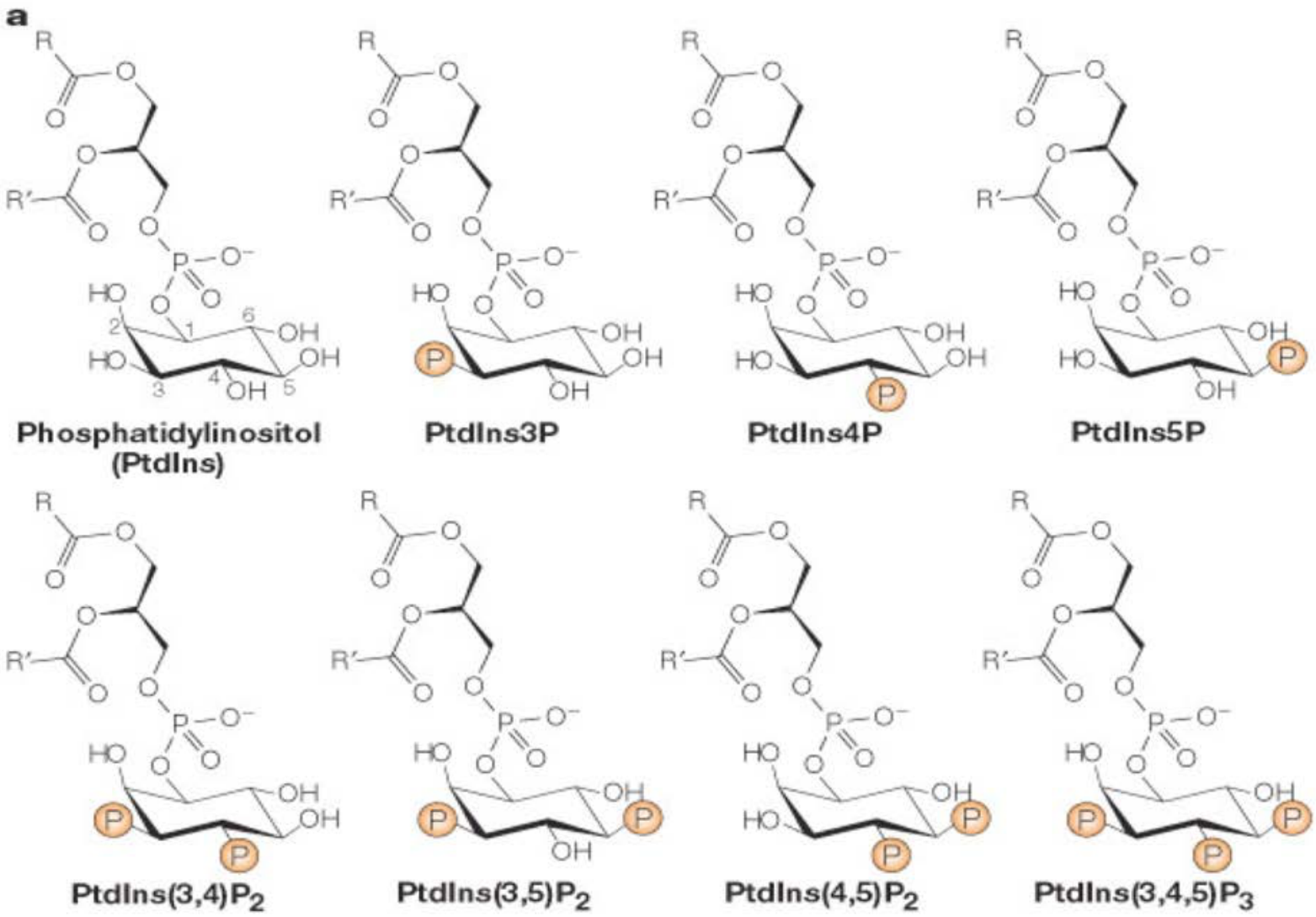


Phosphatidylinositol: 8 kinds based on the phosphorylation status

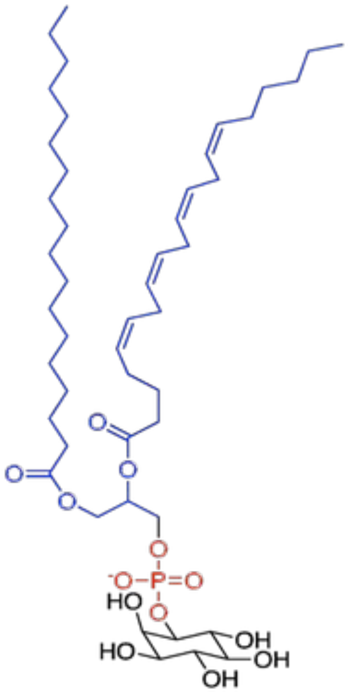
Addition and removal of phosphates is one of the fastest ways (seconds) to modify a membrane.

It is used in cellular communication, in biology called is is called cellular signalling

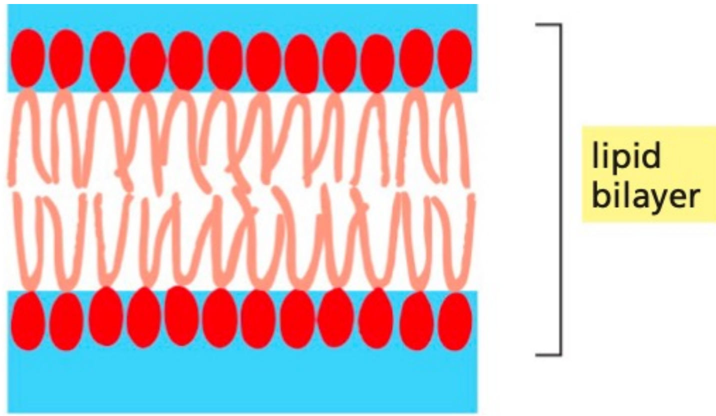
Phosphorylation is an enzymatic reaction done by Kinases (Adding) and Phosphatases (Substracting)



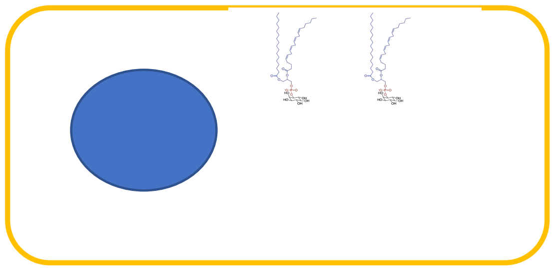
Phosphatidylinositol: 8 kinds based on the phosphorylation status



Extracellular (Outside of the cell)



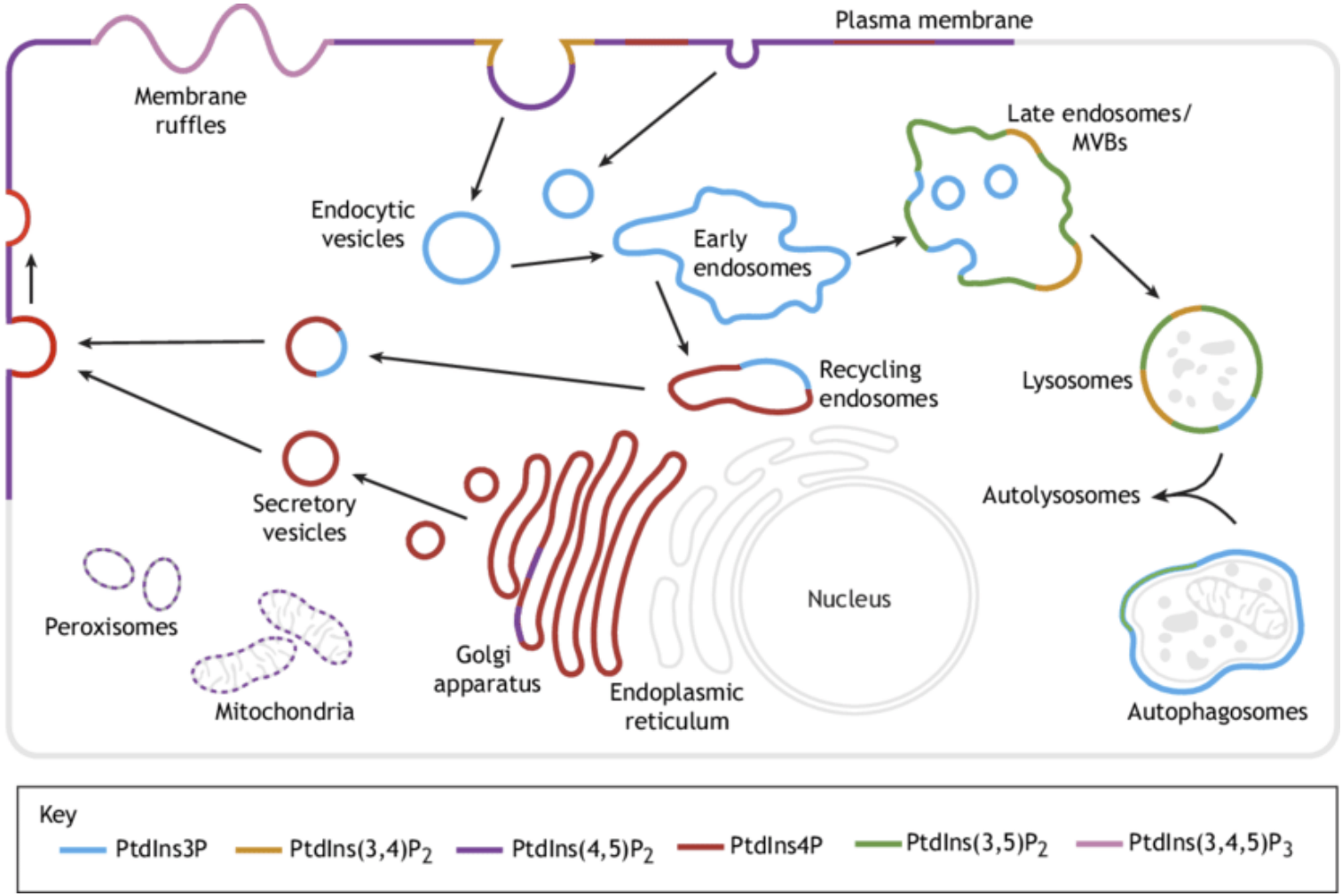
Cytosol (Intracellular / Inside of the cell)



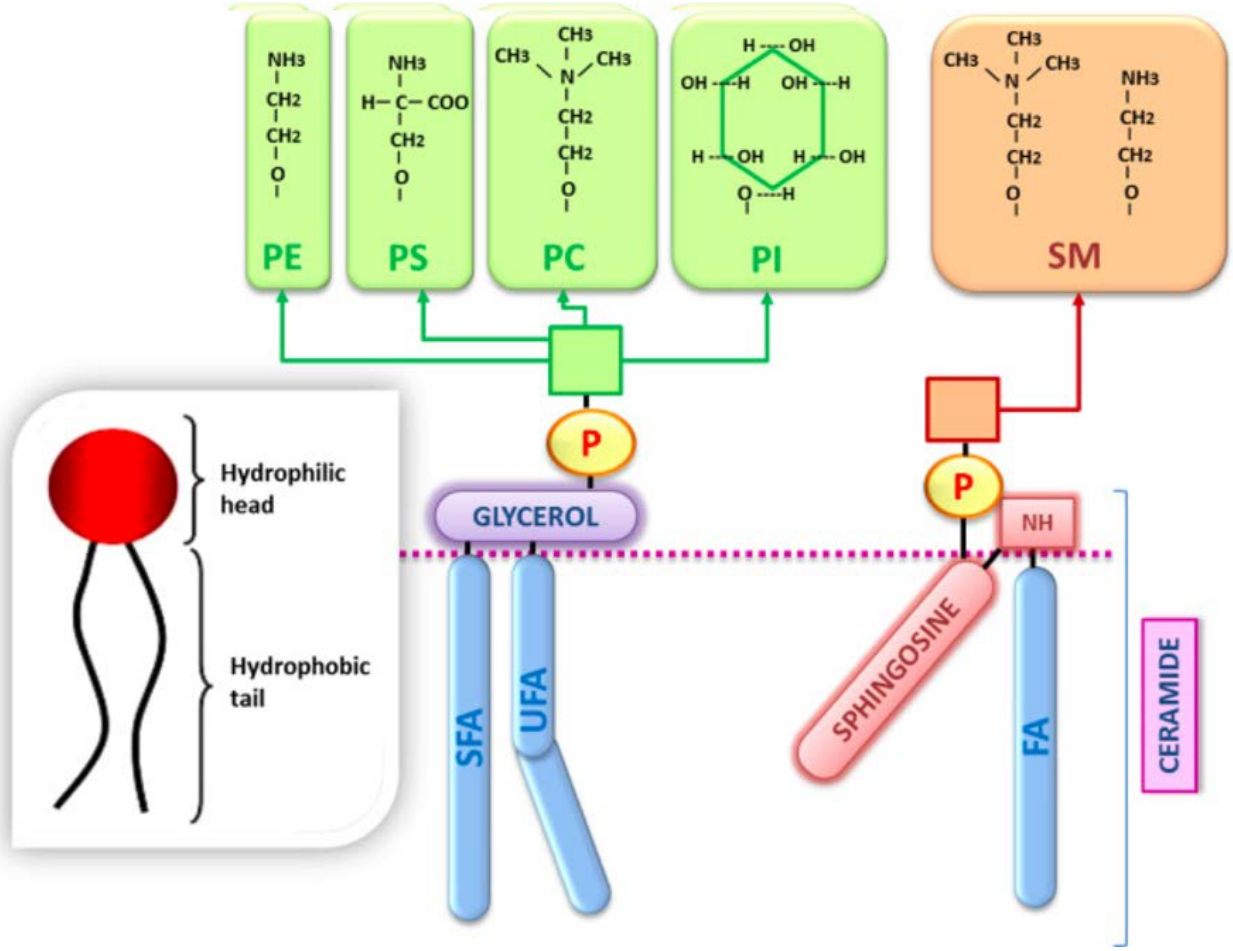
Phosphatidylinositols face intracellular

The position of PI allows cytosolic enzymes, Kinases and Phosphatases (Intracellular / Inside of the cell)

Specific locations in the cell of the phosphatidylinositols



Sphingolipids

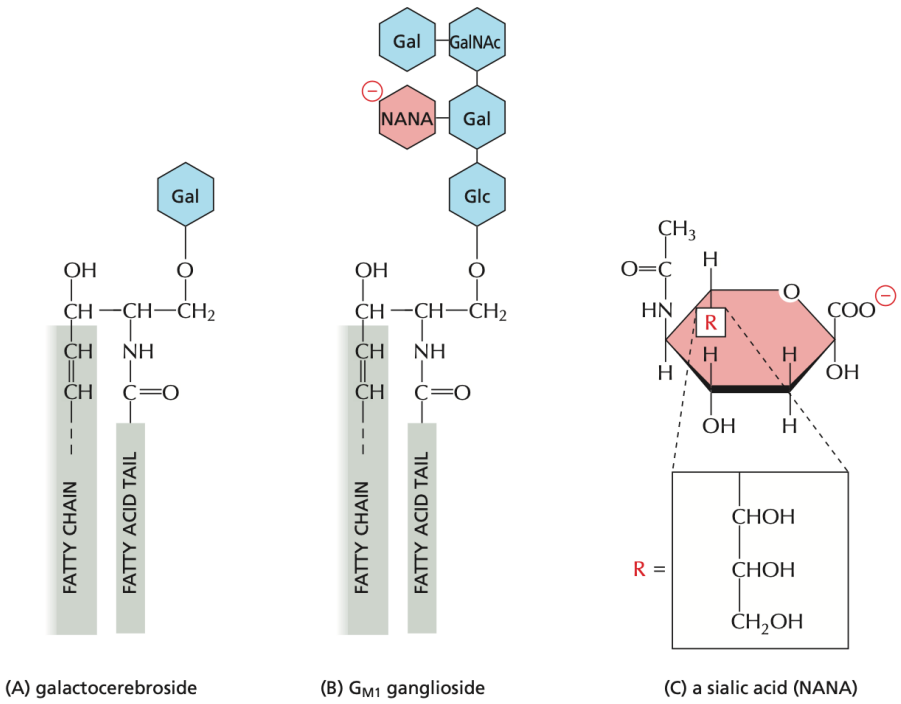


The “skeleton” of sphingolipids is different compared to phoshoglycerides

Sphingosine and a Ceramide (derived from palmitate)

Sphingolipids can be modified in two ways

Glycosphingolipids

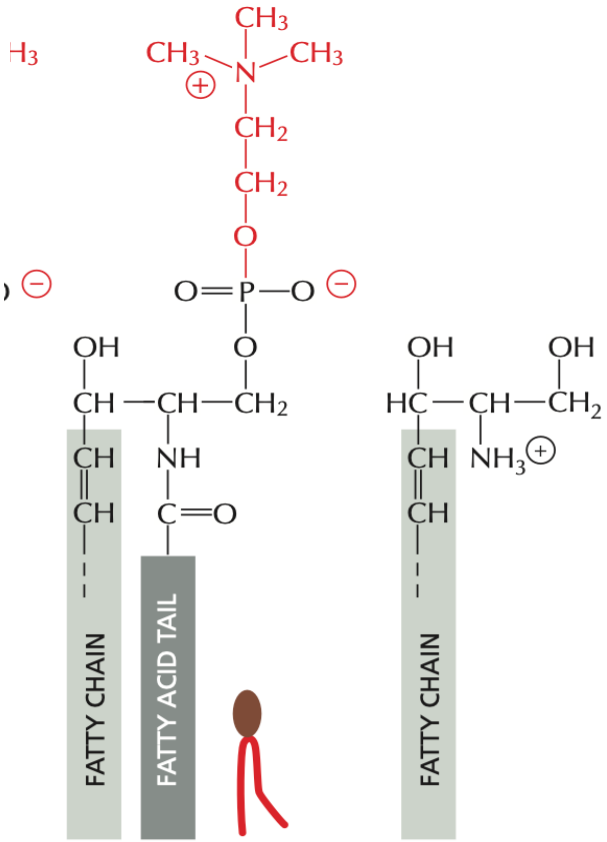


(A) galactocerebroside

(B) G_{M1} ganglioside

(C) a sialic acid (NANA)

Phosphosphingolipids



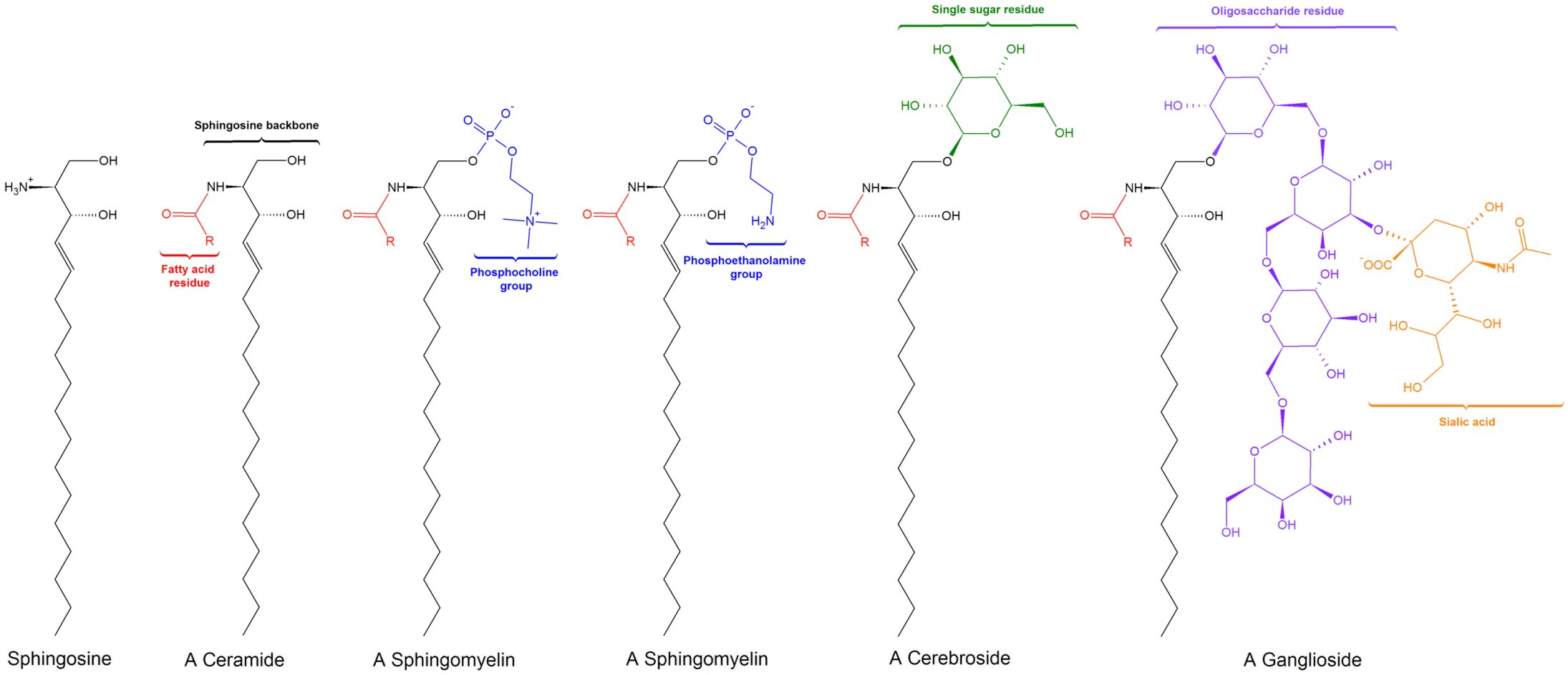
sphingomyelin

(D)

sphingosine

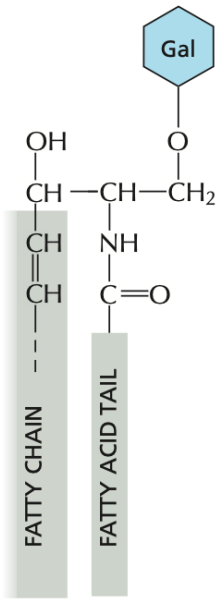
(E)

Sphingolipids can be modified in two ways

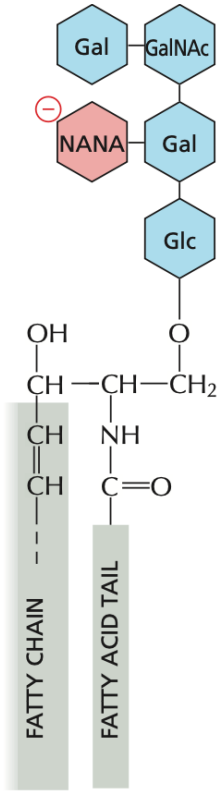


Glycolipids

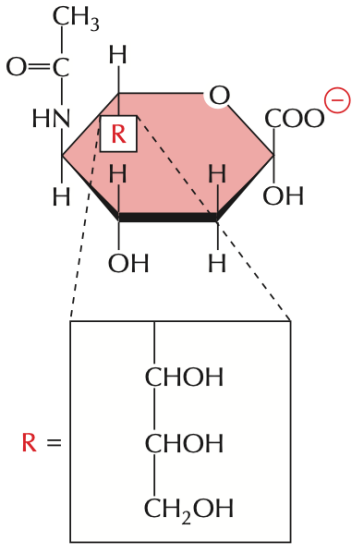
Glycolipids are always on the outer layer of a cell membrane!



(A) galactocerebroside

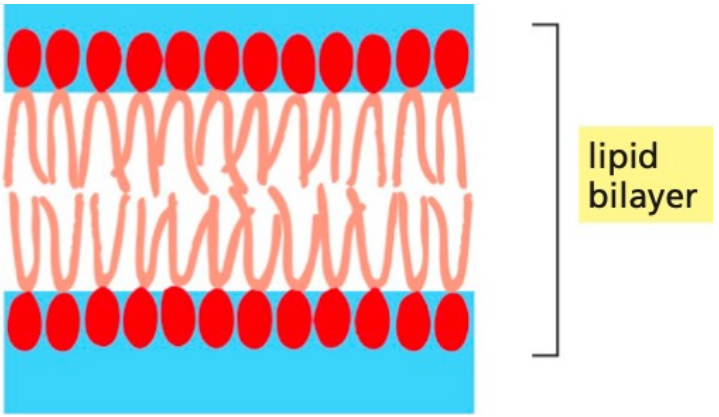


(B) G_{M1} ganglioside

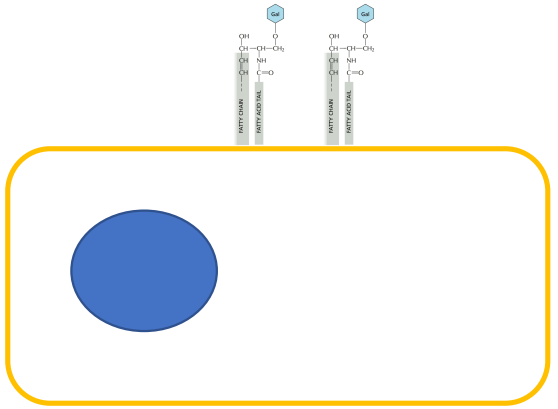


(C) a sialic acid (NANA)

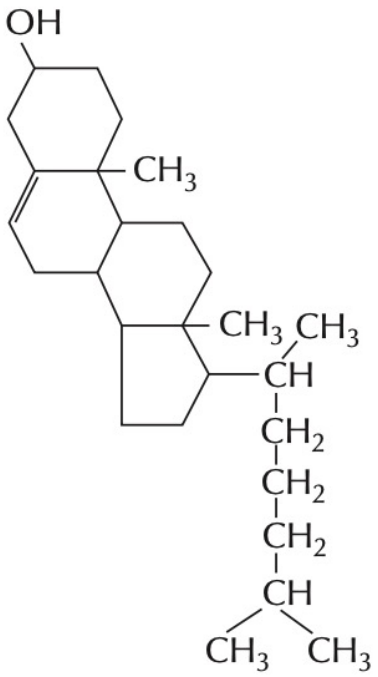
Extracellular (Outside of the cell)



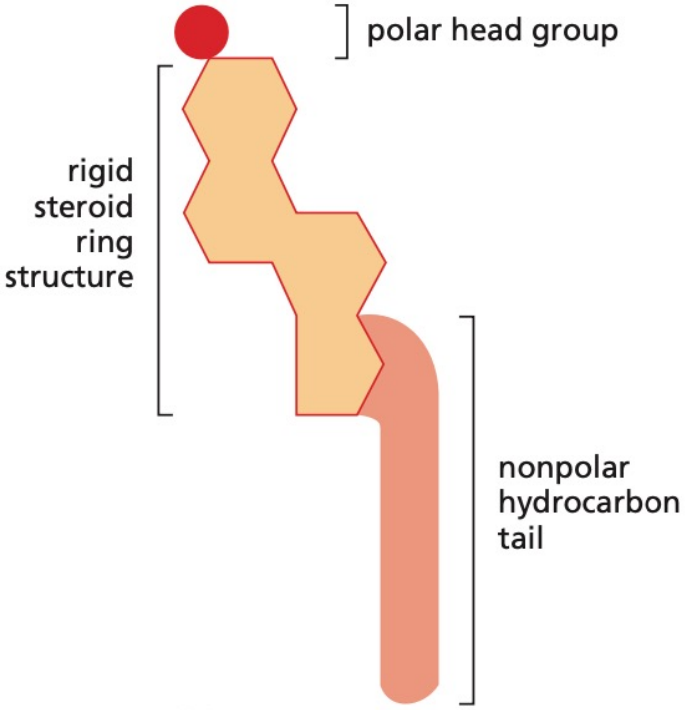
Cytosol (Intracellular / Inside of the cell)



Membrane lipid type 3: cholesterol



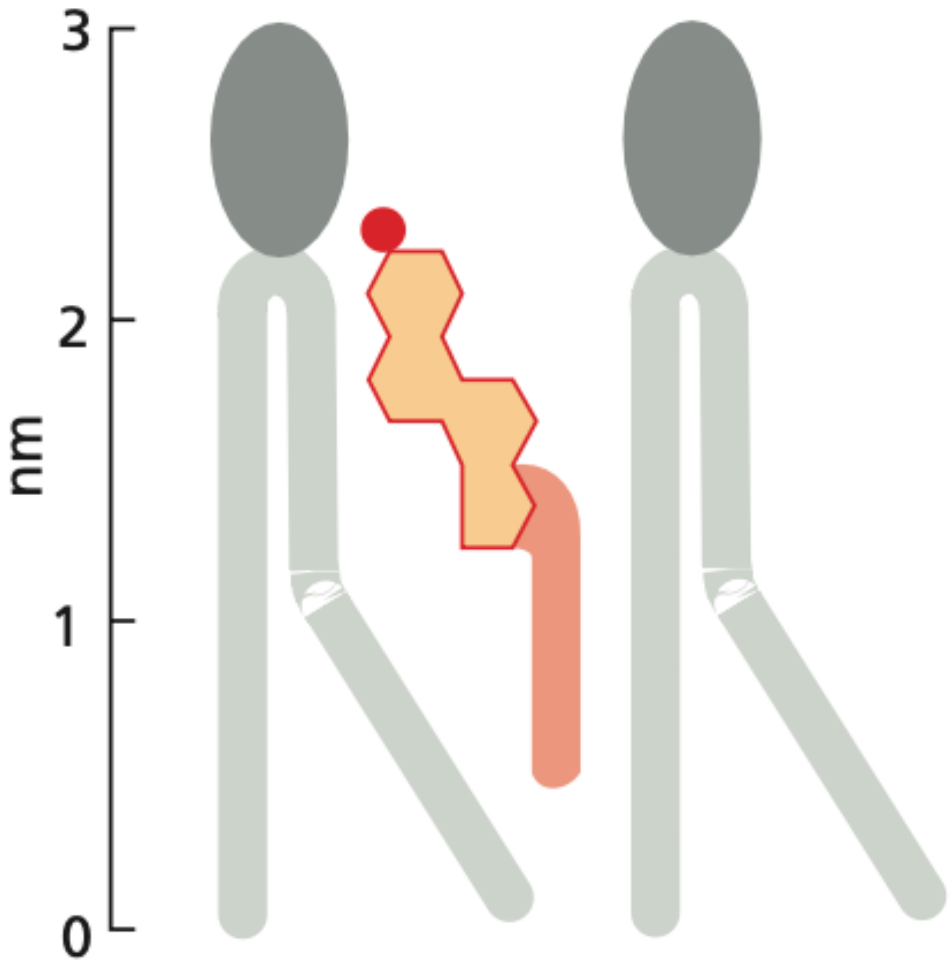
(A)



(B)

(C)

Cholesterol in a lipid bilayer



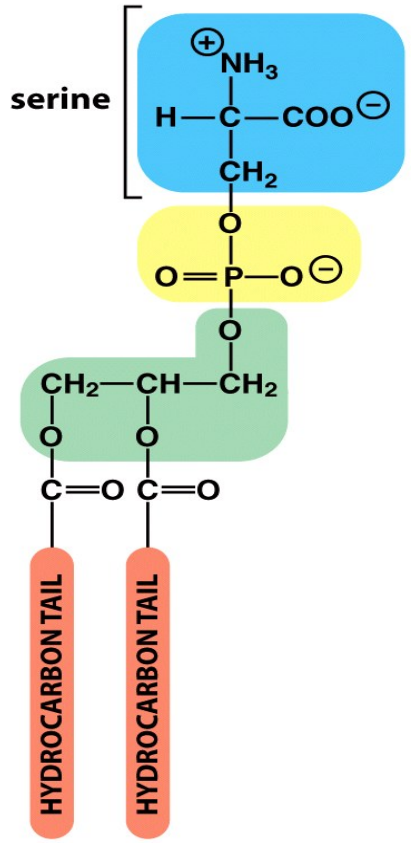
polar head groups

cholesterol-stiffened region

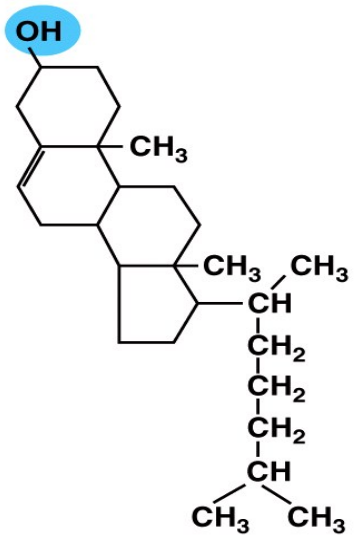
more fluid region

Cholesterol stiffens the cell membrane due to the rigid steroid rings

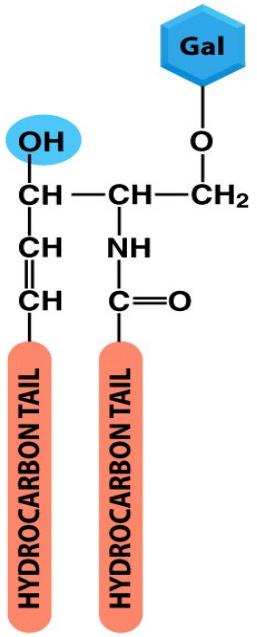
In summary, three major classes of lipids



phosphatidylserine
(phospholipid)

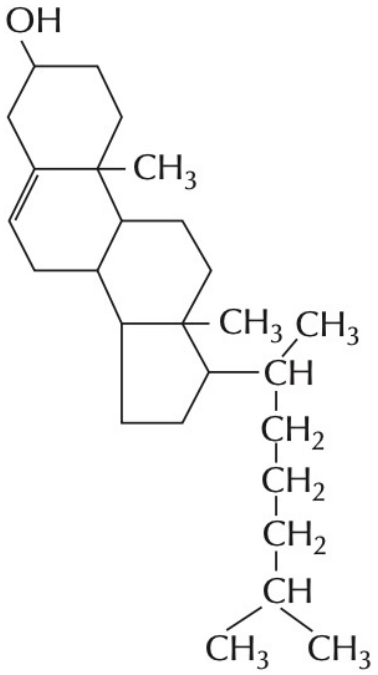


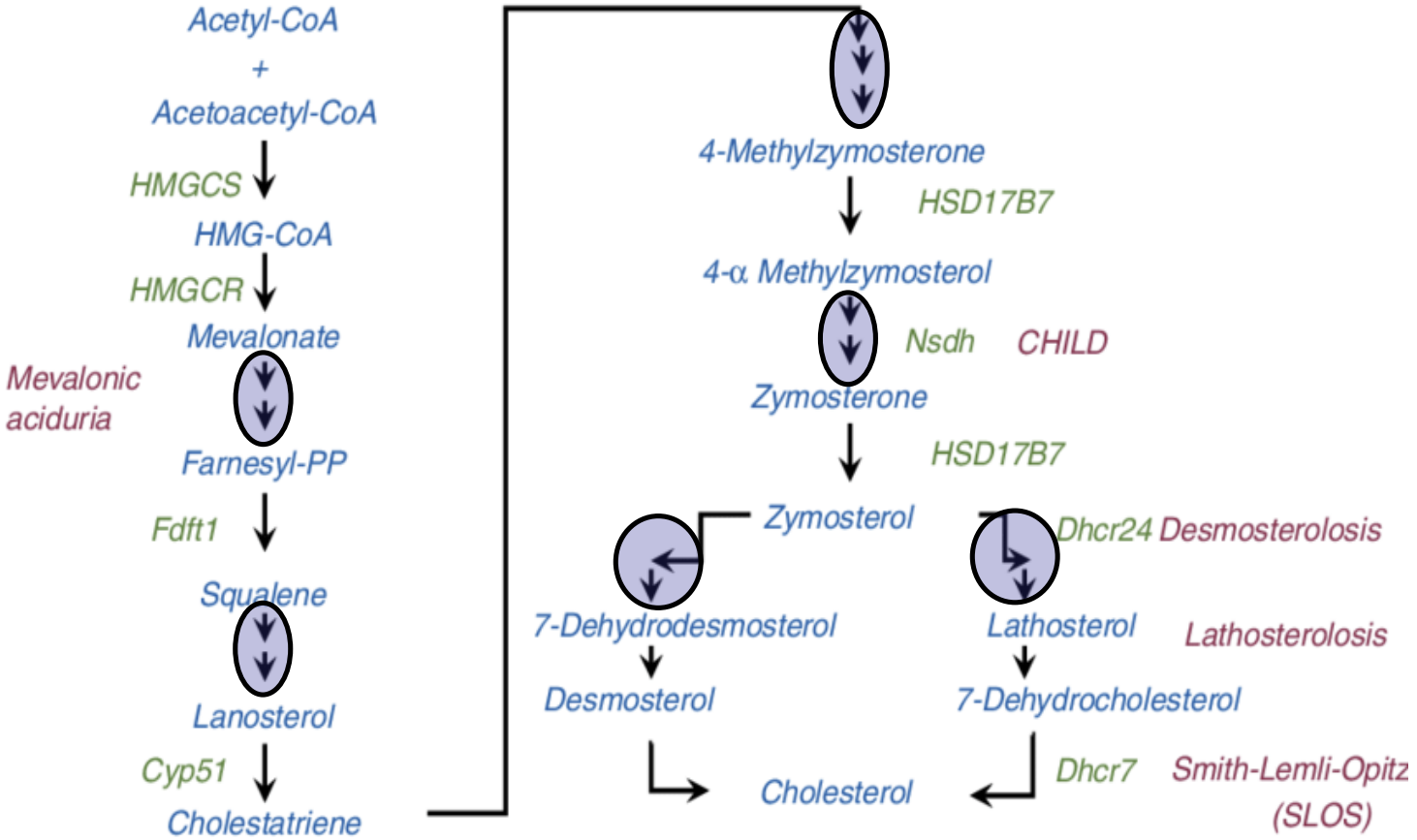
cholesterol
(sterol)



galactocerebroside
(glycolipid)

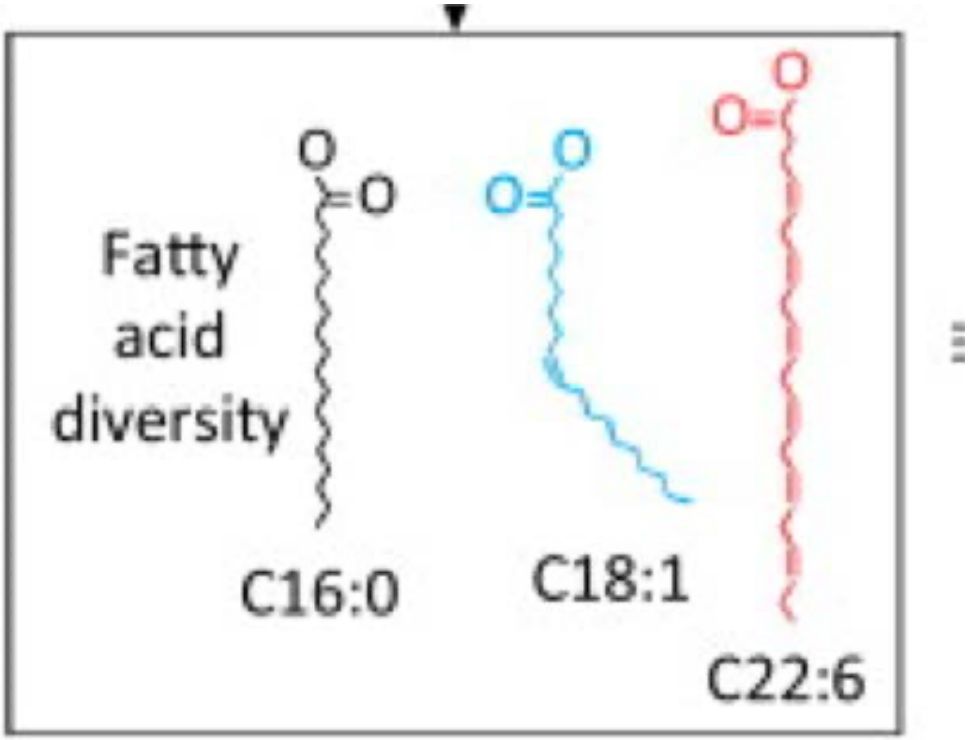
How are lipids made?



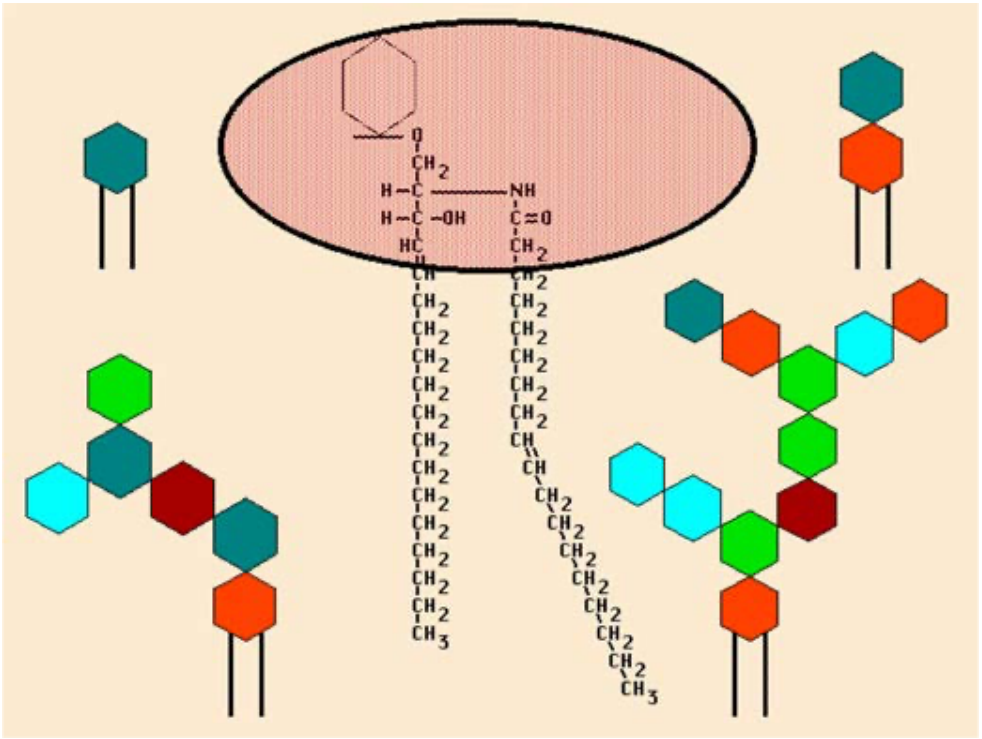


There are many enzymes involved in the synthesis of lipids, this is very different from protein synthesis (DNA -> RNA -> Protein)

Lipids are incredibly diverse



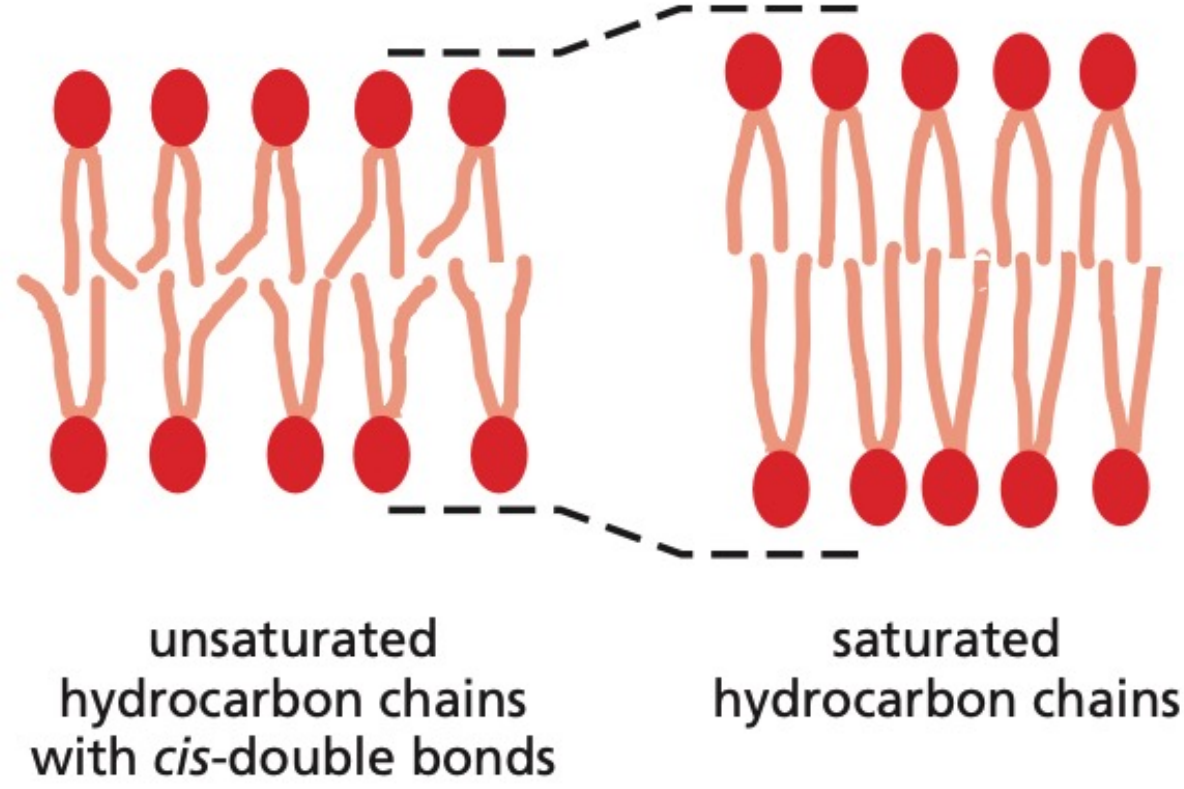
Variations in carbon tail length and saturation



Variations in polar head composition

What are some of the effects of these varieties on cell membrane?

The influence of *cis*-double bonds in hydrocarbon chains

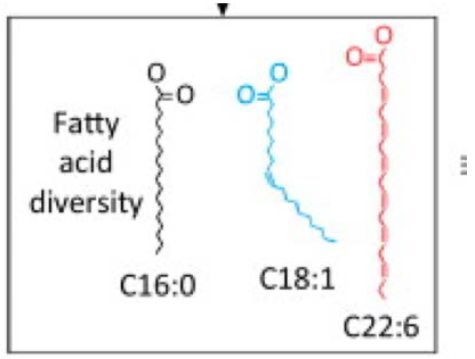


More satured hydrocarbons = more rigid membrane

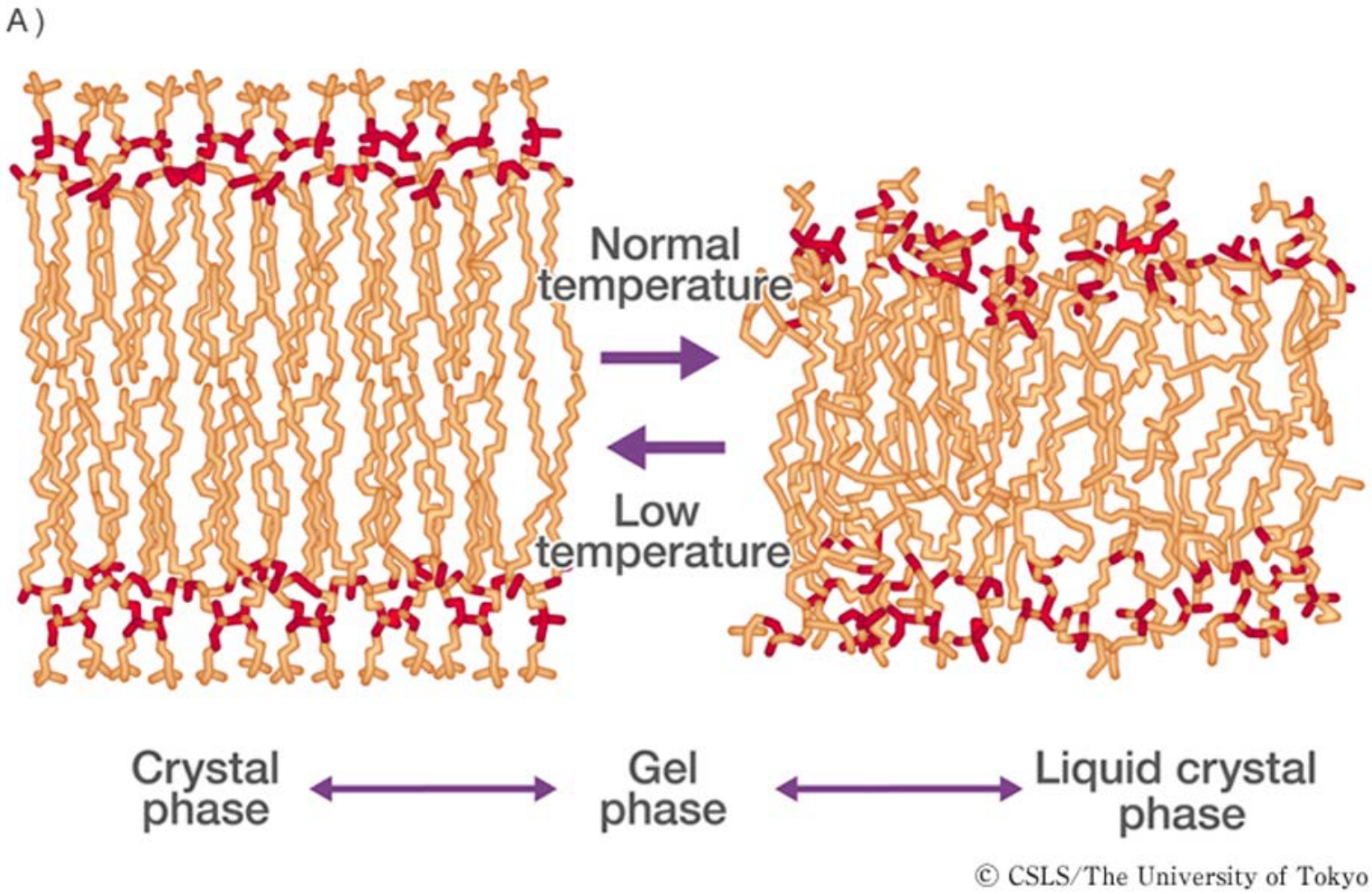
The length of the fatty acid tail influences viscosity

Tail Length	Double Bonds	Transition Temperature
12	0	-1
14	0	23
16	0	41
18	0	55
20	0	66
22	0	75
24	0	80

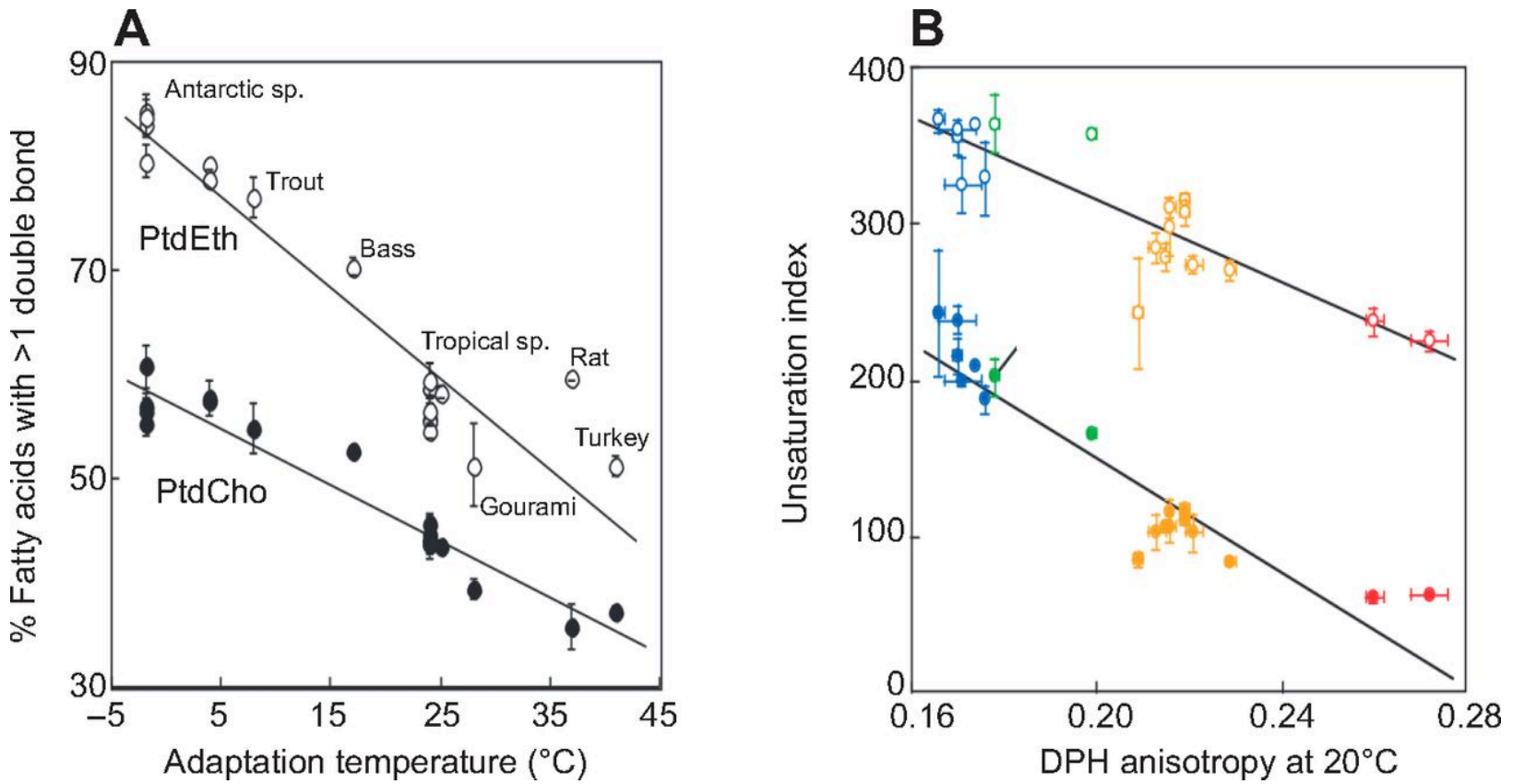
The longer the tail the more viscous the membrane will be, very long tails make a rigid substance.



Temperature changes the viscosity of the membrane



Animals living in cold have different membrane compositions!



Antarctic (blue), temperate (green), tropical (orange) and homeothermic (red).

Scott A. L. Hayward et al. J Exp Biol 2014;217:6-15

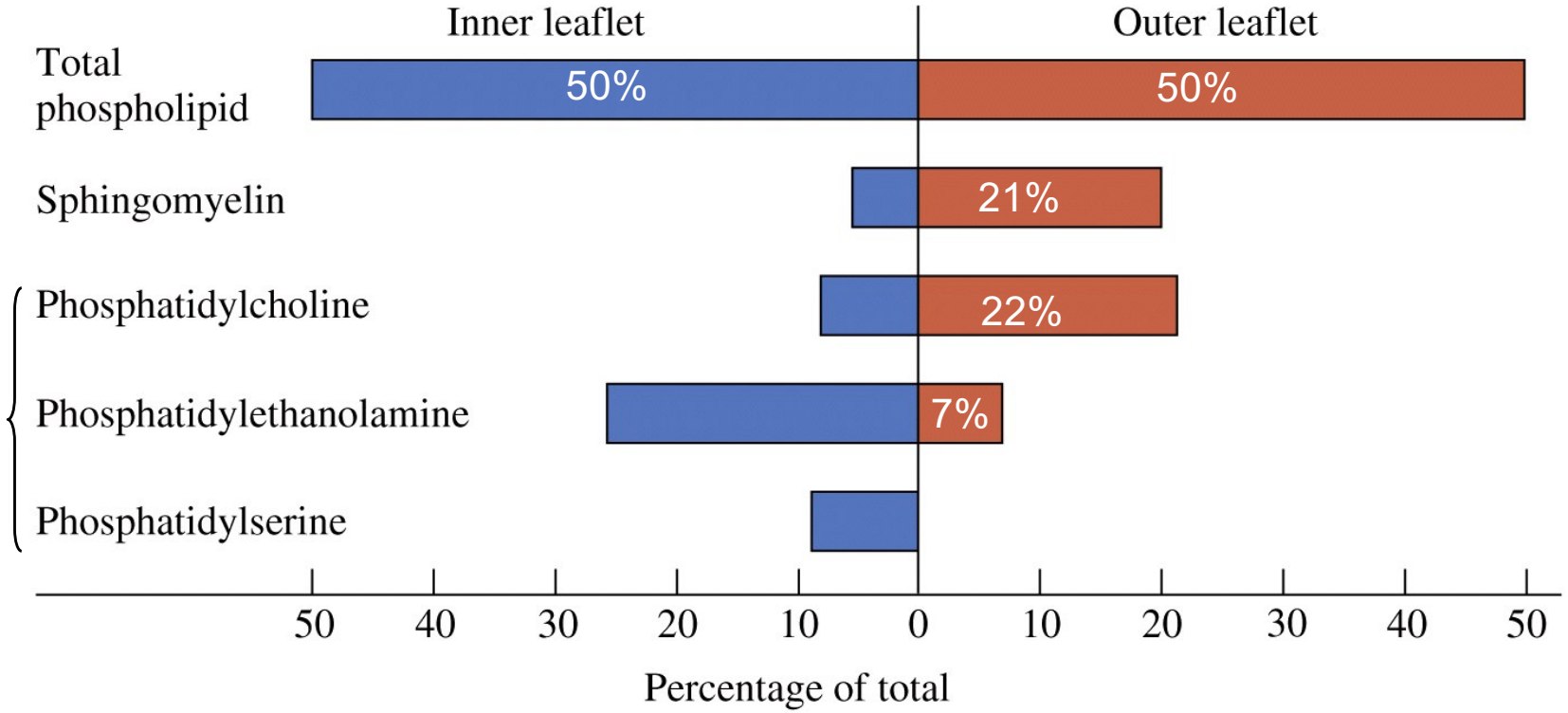
How are lipids distributed in the cell membrane?

Lipid Compositions of different cell 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	14	8	23	27	30

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



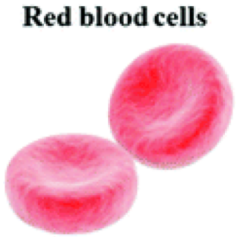


Figure 9-2 Concepts in Biochemistry, 3/e

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

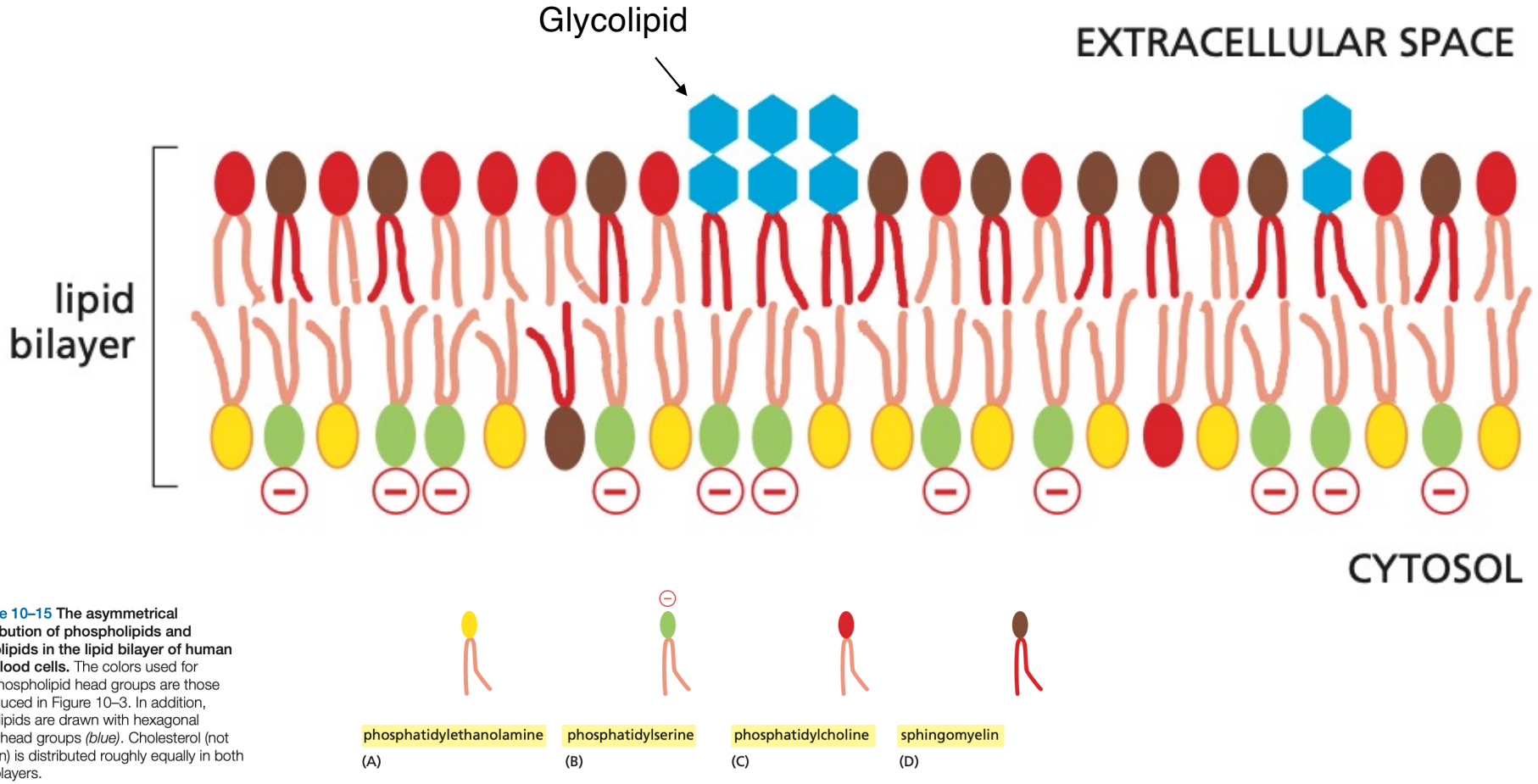
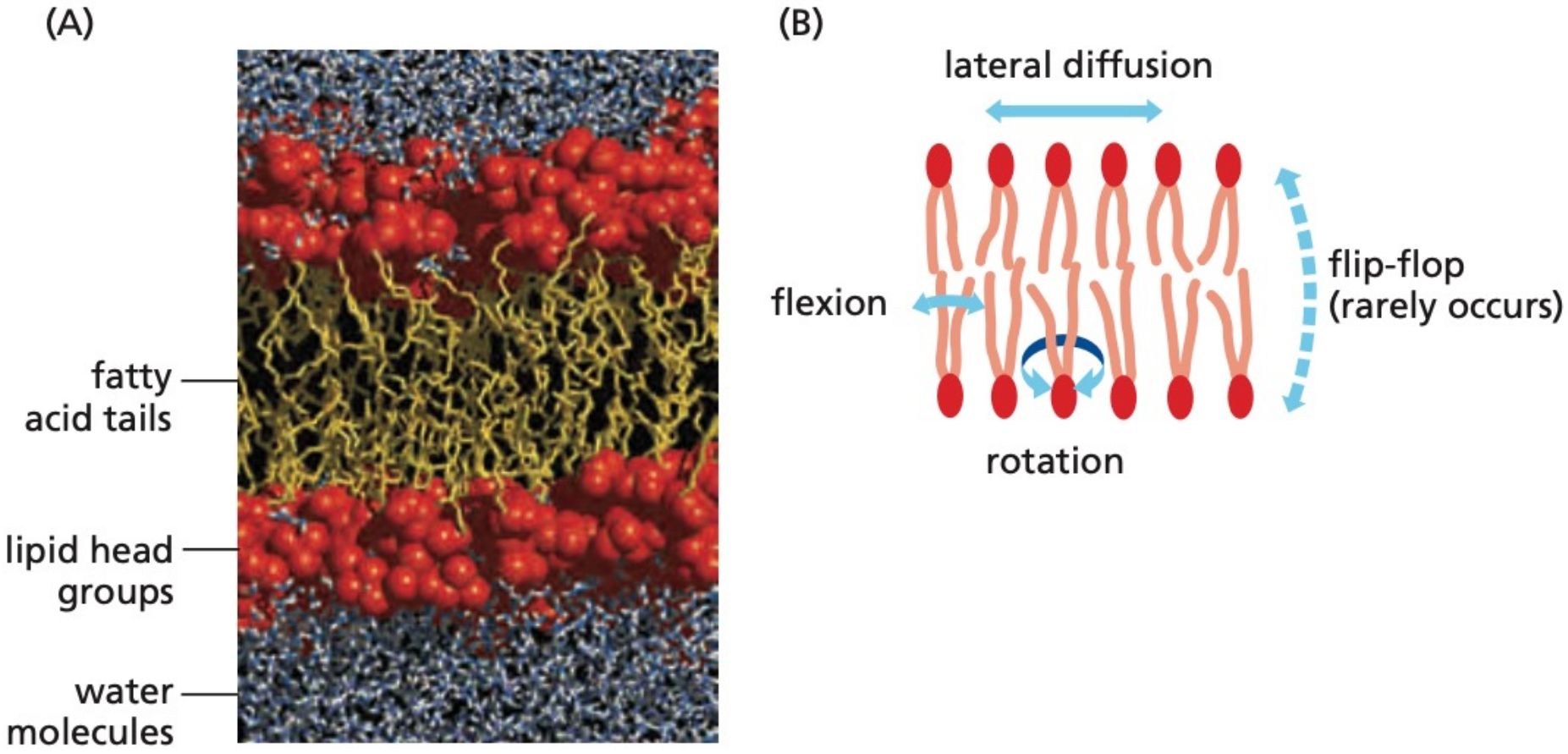


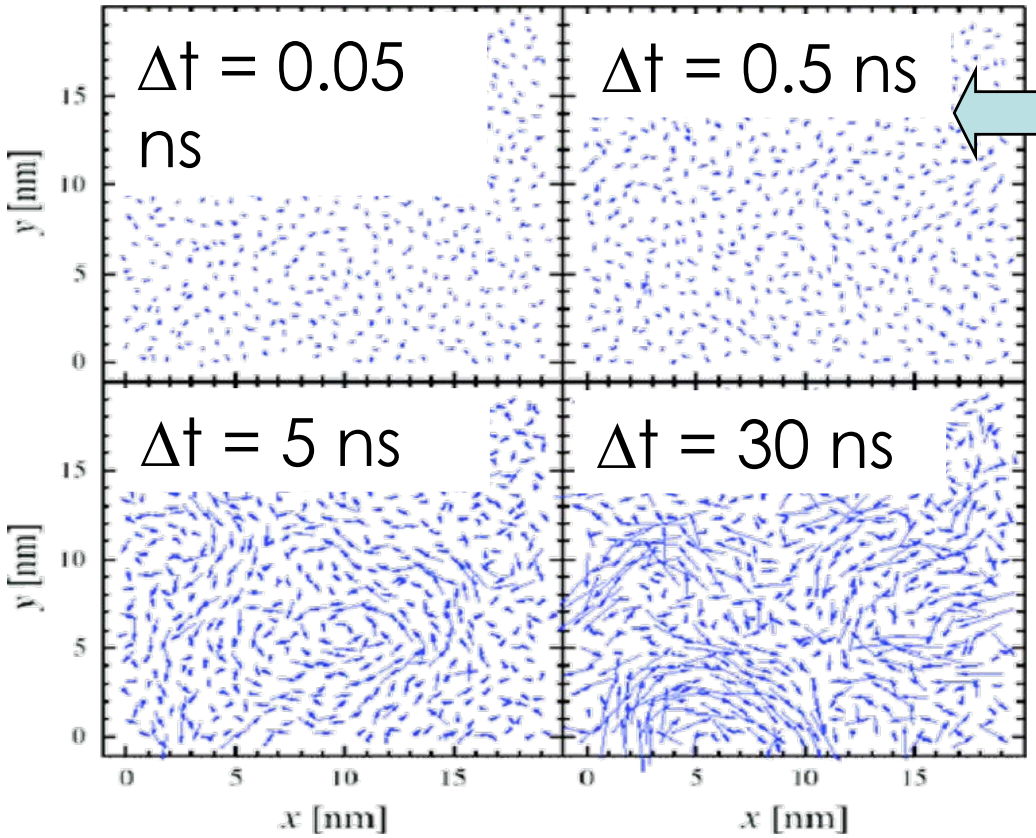
Figure 10–15 The asymmetrical distribution of phospholipids and glycolipids in the lipid bilayer of human red blood cells. The colors used for the phospholipid head groups are those introduced in Figure 10–3. In addition, glycolipids are drawn with hexagonal polar head groups *(blue)*. Cholesterol (not shown) is distributed roughly equally in both monolayers.

How do the lipids move through the cell membrane?

Lipids have several ways to move through and within a membrane



Lateral movement of lipids looks like a liquid flow



Lateral displacements of individual lipids during a period of Δt

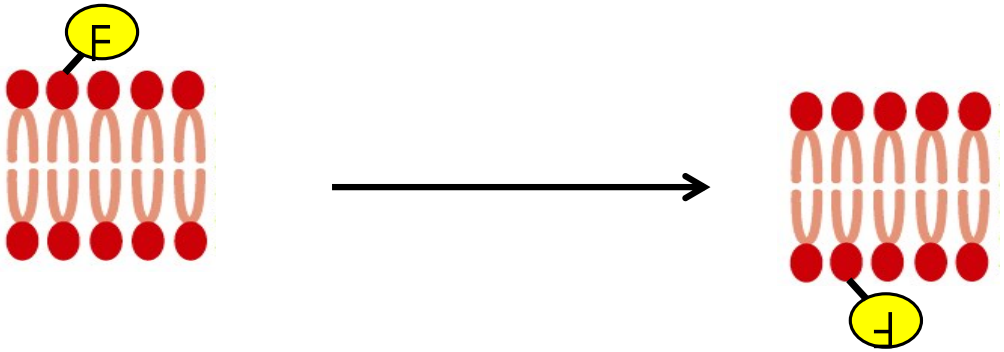
On a molecular scale, lipids move in unison as loosely defined clusters.

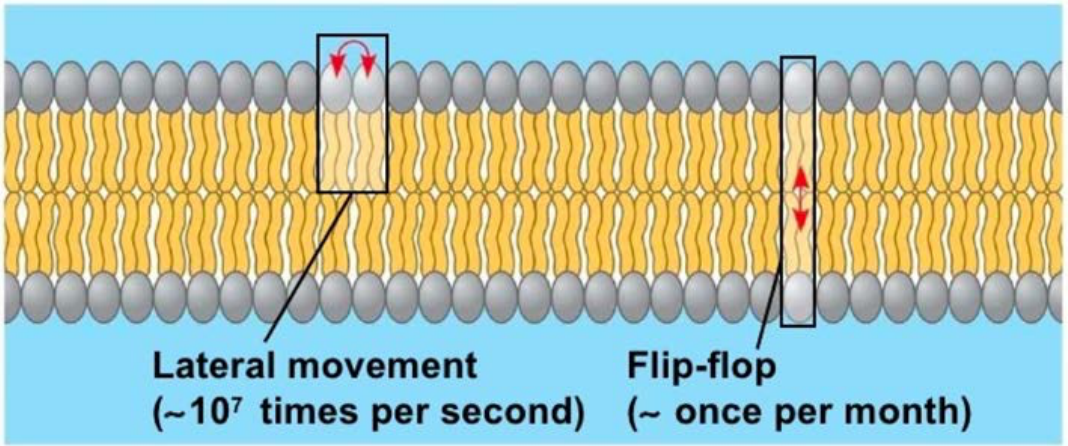
On larger scales, the intimately correlated motions of neighboring lipids manifest themselves as 2D flow patterns

Falck, Rog, Karttunen, Vattulainen, J Am Chem Soc 130, 44 (2008)

FLIP-FLOP of lipids

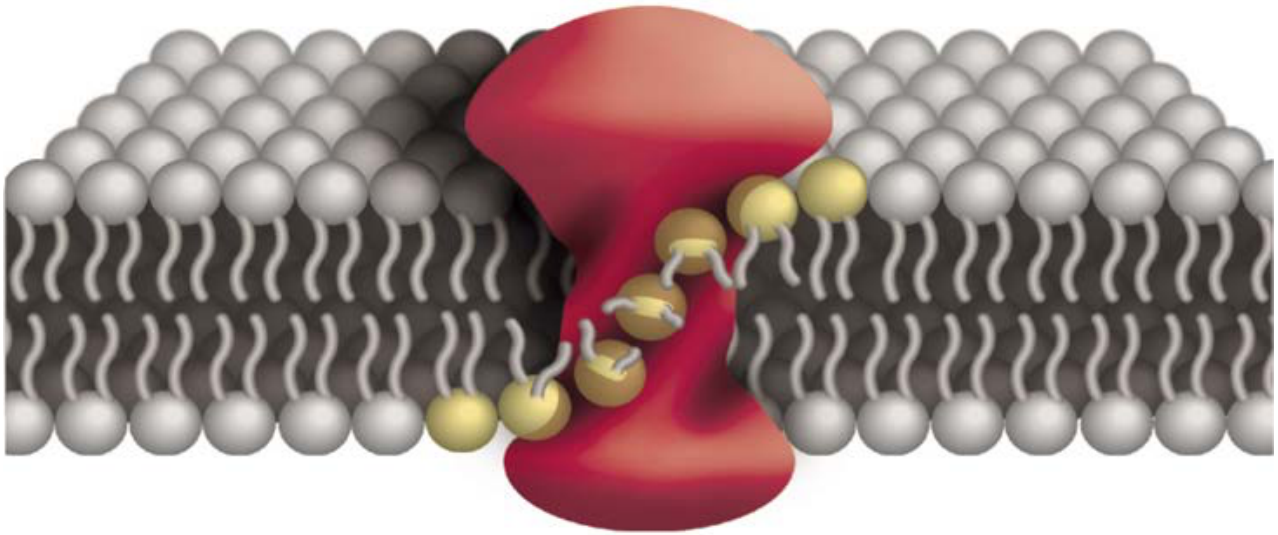
Flip-flop ?





Movement of phospholipids

FLIP-FLOP of lipids is an active process



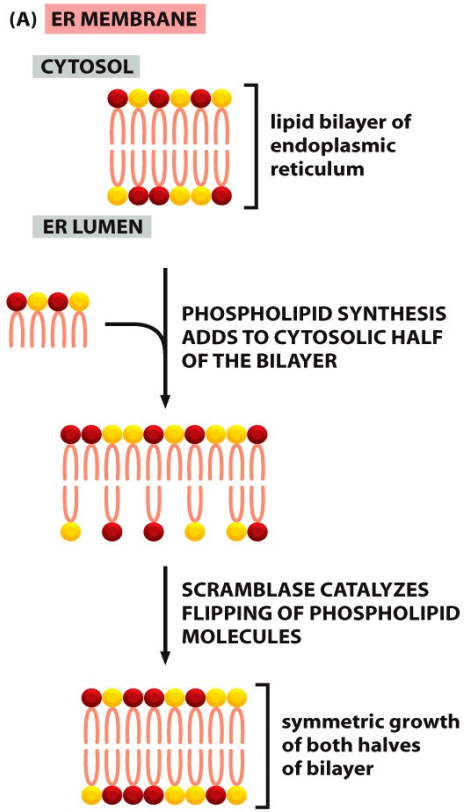
There are proteins whose role is to flip specific lipids from one sheet to another of the membrane, in a given direction: these are Flipases

There are also scramblases, which switch lipids in both directions

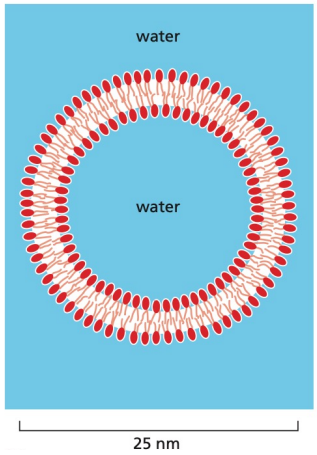
FLIP-FLOP of lipids is an important process

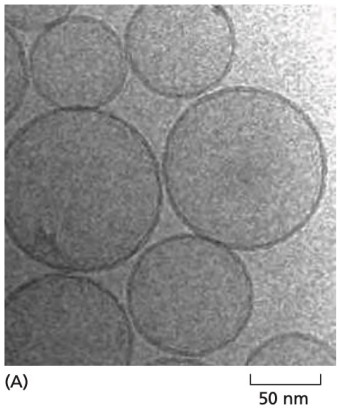
The enzymes responsible for lipid synthesis have well-defined locations in the cell, in particular their active site is on a specific side of the membrane: cytoplasmic side for some, opposite side (luminal) for others.

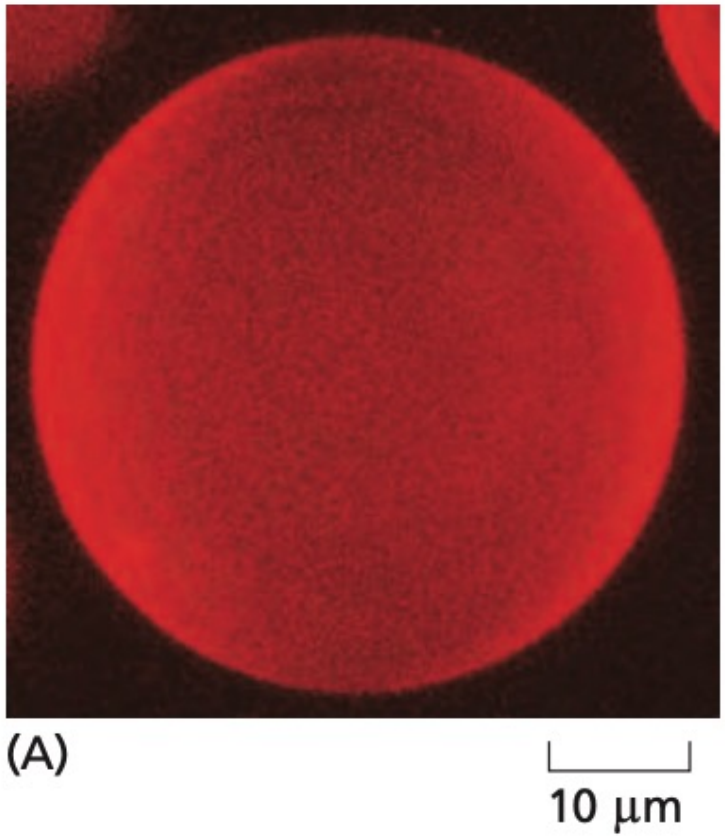
The synthesis of Phosphatidylcholine (PC) for example is done on the cytoplasmic side, in the endoplasmic reticulum (ER), but the two sheets are mostly formed of PC



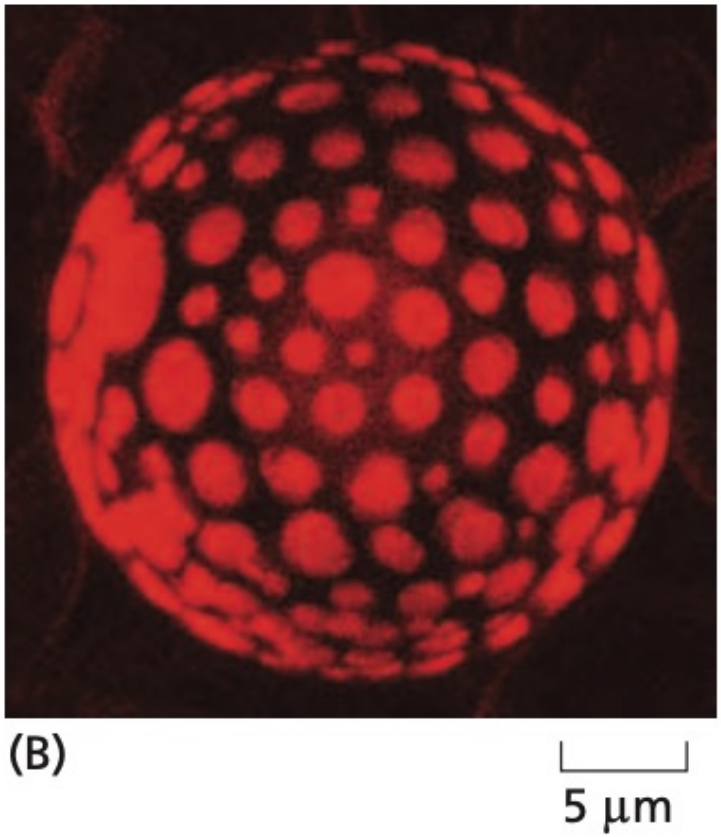
Lateral phase separation in artifical lipid bilayers







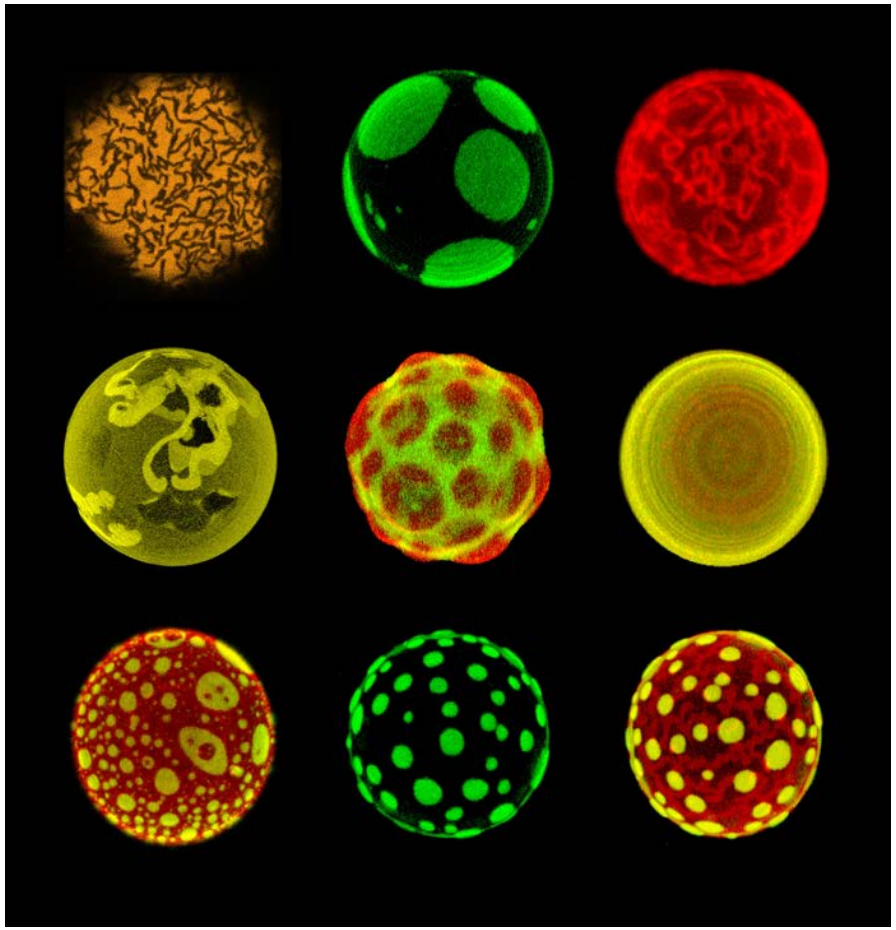
Phosphatidylcholine : Sphingomyelin
1:1



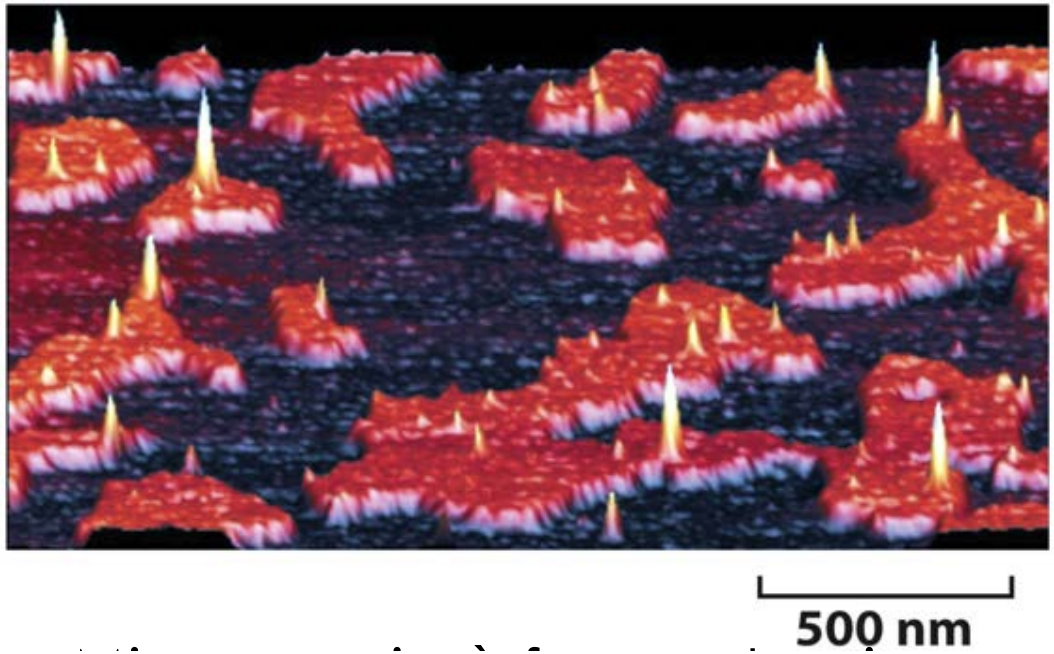
Phosphatidylcholine : Sphingomyelin : Cholesterol
1:1:1

These islands are called lipid rafts!

Does lateral phase separation happen in cells?

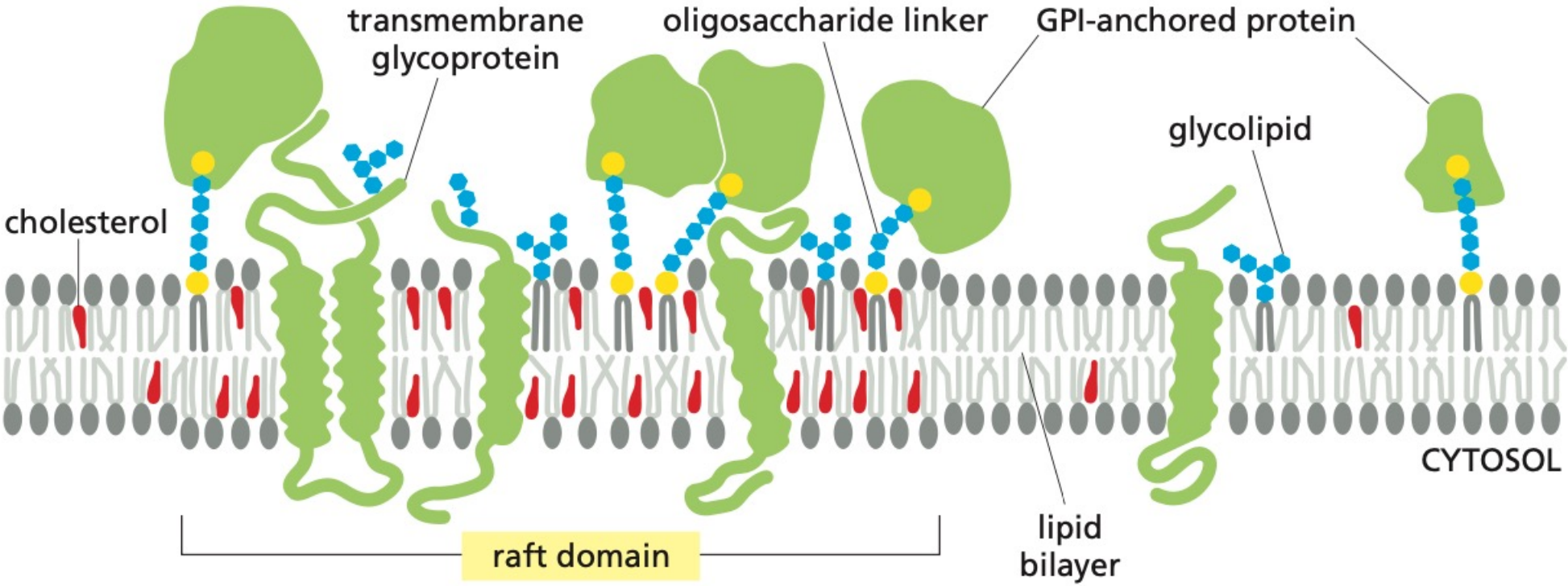


Lipid rafts appear to be present in cells but are much smaller than in laboratory settings



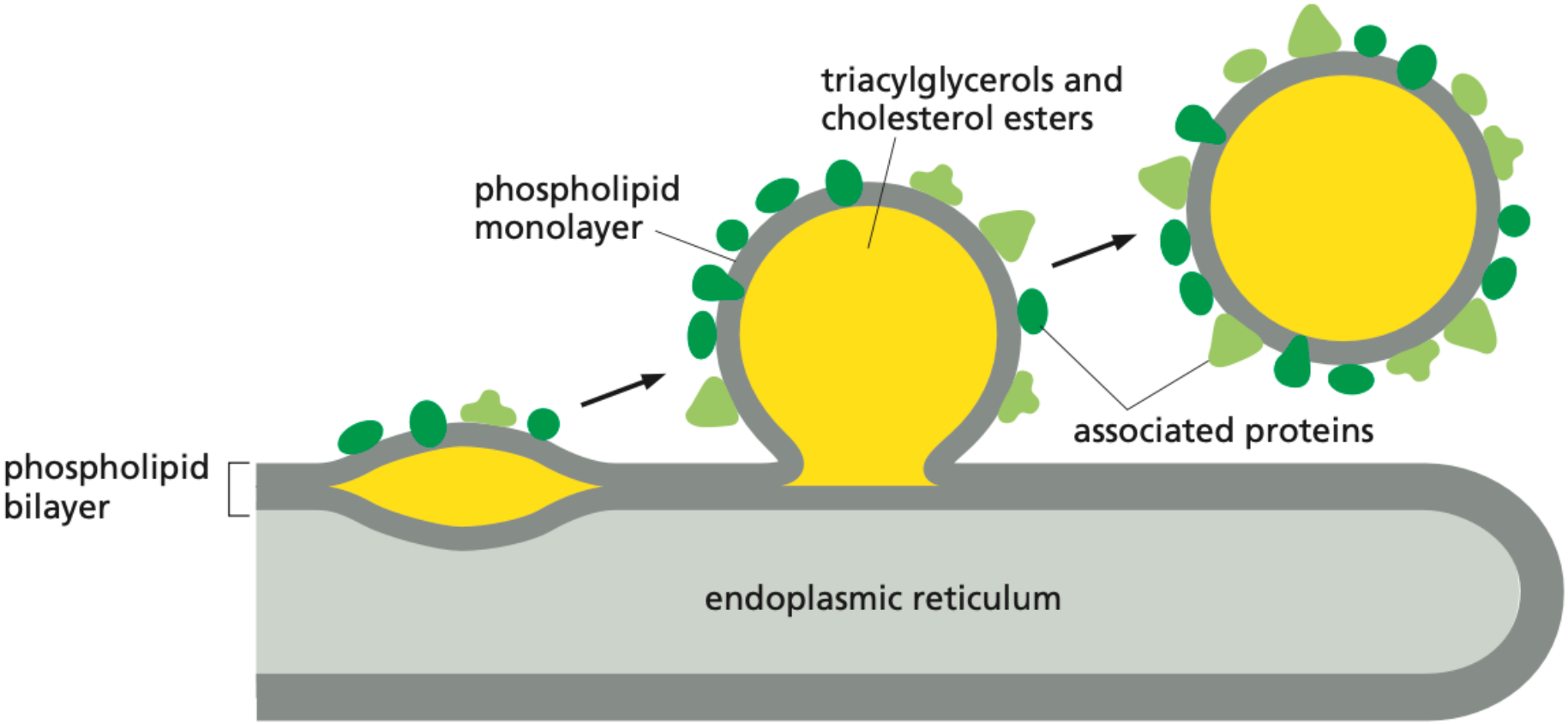
Atomic force microscopy image of a plasma membrane

The lipid raft



The lipid raft is hypothesized to play an important role in cell signaling

Making lipid droplets, a model



Key points

There are many kinds of membrane lipids (important not all lipids found in the cell are membrane lipids)
There are 3 main classes, phosphoglycerides, sphingolipids and sterols
Membrane lipids are amphiphilic
Membranes are fluids thanks to the molecular qualities of lipids

Functions of membrane lipids

Collective function:
impermeable barrier between the outside and inside of the cell - "solvent" for membrane proteins and other lipids

Semi-collective roles:
- Compartmentalization of 2D space into domains (lipid rafts) that may have specific functions (cellular interactions, signalling platforms, etc)

Individual roles
- Recognition point for other molecules (usually proteins). Ex: glycolipids towards the outside, phosphoinositides towards the inside

Many functions of lipids are unknown! membrane lipids may have "off-membrane" roles. Lipids are an researched by several labs here at EPFL! (Prof D'Angelo and Prof La Manno)

The knowledge of the cell membrane, essential during COVID19 pandemic

RNAse

Lipid
Nano
Particle