Molecular Organization of the Cell Membrane

A walk from molecules to a functional biostructure

Cell Membrane

- Definition

An ultrastructure

separating

connecting

the cell to the environment

Coarse chemical composition

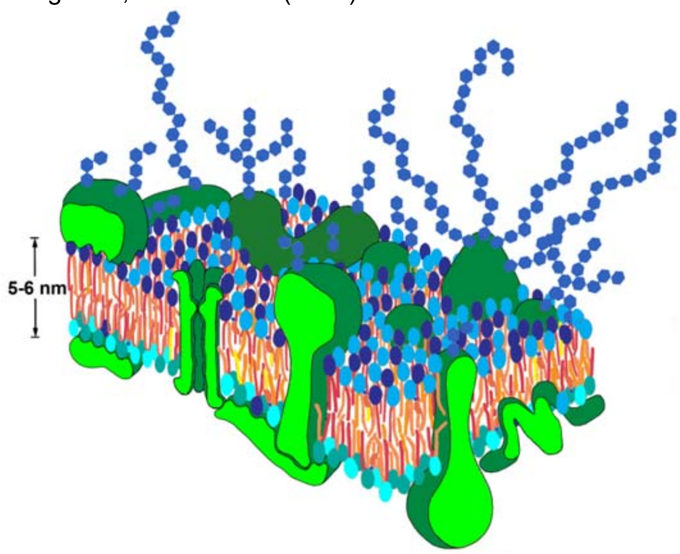
- Water: 20-30%
- Dry material: 70-80%
  - Minerals: ~1%
  - Organic compounds: ~99%
    - Lipids: 40-50%
    - Proteins: 50-60%
    - Sugar components: 1-10%

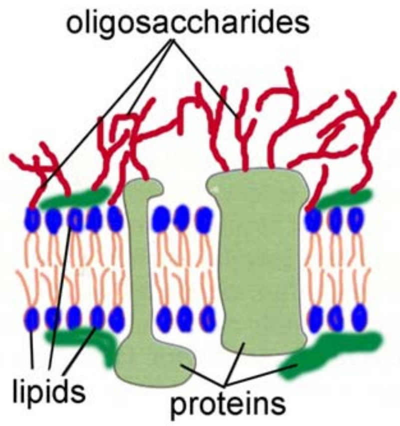
Why so low amount of water?

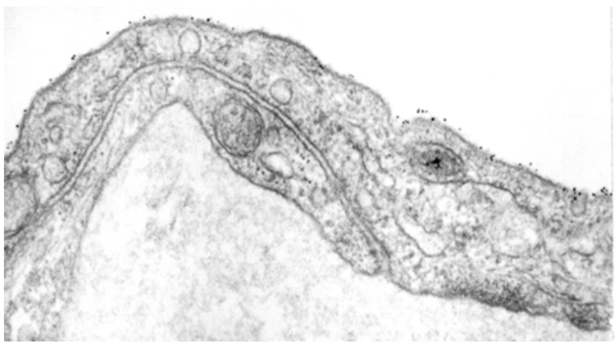
Mosaic Fluid Model

for Molecular Assembly of Biomembranes

Singer SJ, Nicolson GL (1972) The fluid mosaic model of the structure of cell membranes. *Science*. 175: 720-731.







Cell Membrane Functions

1. ***Barrier***
2. ***Metabolic***

Physical, (bio)chemical and biological features of cell membranes

- Heterogeneity
- Asymmetry
- Two-dimensional fluidity

- *Which are responsible components for these features?*
- *What's the biological significance of these features?*

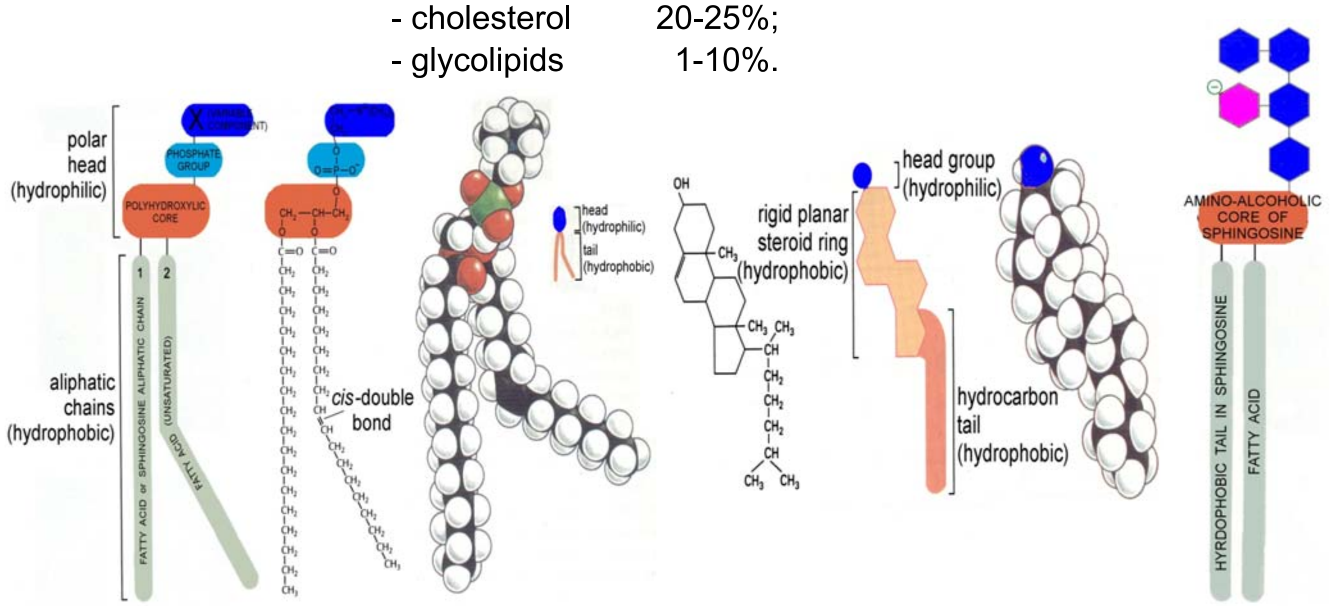
Heterogeneity

Lipids' contribution (more than 1000 molecular species)

Lipids' classification:

1. *According to* ***broad chemical structure***:

- phospholipids 70-75%;
- cholesterol 20-25%;
- glycolipids 1-10%.



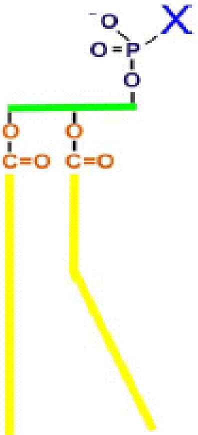
Heterogeneity

Lipids' contribution

(Phospho)lipid classification:

1. *According to* ***polyhydroxylic compound*** *in structure*:
   - phosphoglycerides (glycerophospholipids);
   - sphingolipids.

2. *According to X* ***(variable compound in polar head)***:



X - choline → phosphatidylcholines (PC); 20-25%
X - ethanolamine → phosphatidylethanolamines (PE); 20-25%
X - serine → phosphatidylserines (PS); 20-25%
X - inositol → phosphatidylinositols (PI); 10-15%
X - hydrogen → phosphatidic acids (PA); ~1%

More phospholipids:

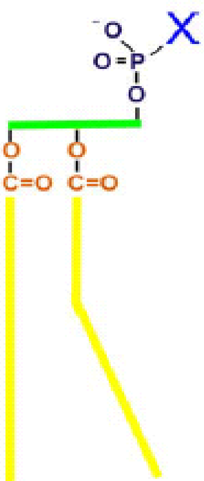
sphingomyelins (SM); 20-25%

cardiolipins: 1,3-diphosphatidylglycerol

plasmalogens (1-fatty alcohols instead of fatty acids)

More heterogeneity for membrane's lipids

Fatty acids' contribution



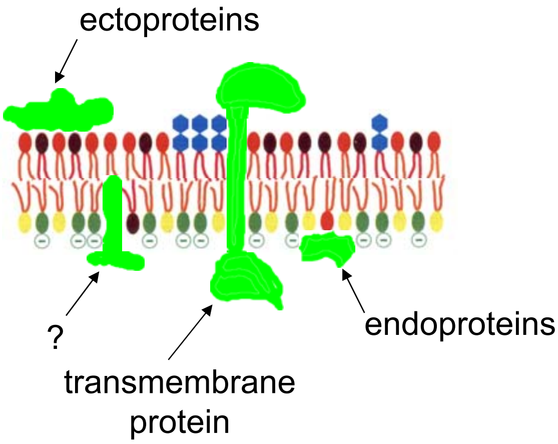
(a) 1st hydroxyl of glycerol: a saturated fatty acid (C_{14}, C_{16}, C_{18}); abundance order: $C_{16} > C_{18} > C_{14}$.

(b) 2nd hydroxyl of glycerol: an unsaturated fatty acid ($C_{18:1}$, $C_{18:2}$, $C_{18:3}$, $C_{20:4}$)

N.B. *No fatty acids below C_{12} or longer than C_{22}*

Heterogeneity

Proteins' contribution



According to position versus bilayer:

- peripheral (extrinsic) – ~25%;
- integral (intrinsic) – ~75%.

Extrinsic proteins:

- ectoproteins;
- endoproteins.

Intrinsic proteins:

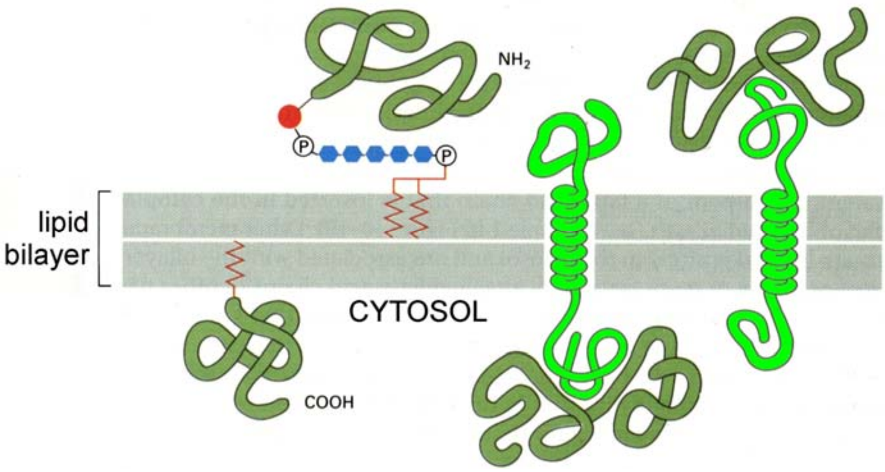
- transmembrane proteins;
- ?

Heterogeneity

Proteins' contribution

Physico-chemical features of peripheral proteins

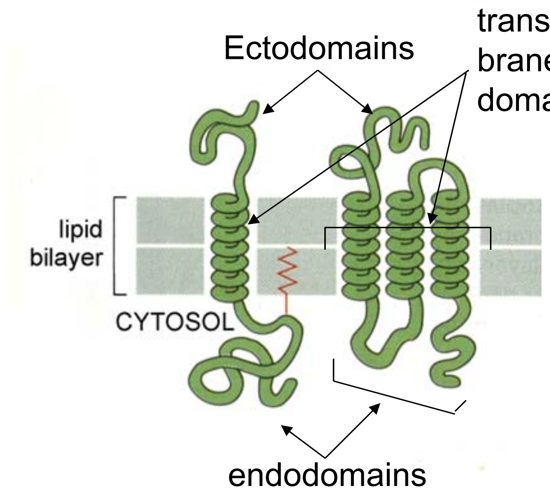
- Extractible with saline solutions, or chelating agents;
- Hydrophilic;
- No lipid attached, and water soluble after extraction;



Heterogeneity
Proteins' contribution

Physico-chemical features of transmembrane proteins
- Extractible by detergents only;
- Keep associated lipids permanently;
- Insolubile in water;
- Amphifilic.

Structural domains in transmembrane proteins



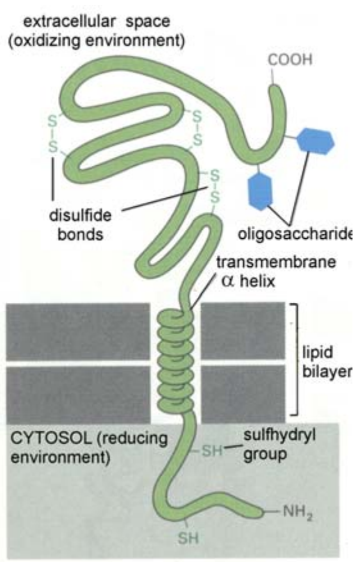
1. Extracellular domain (ectodomain);
2. Cytoplasmic domain (endodomain);
3. Transmembrane domain.

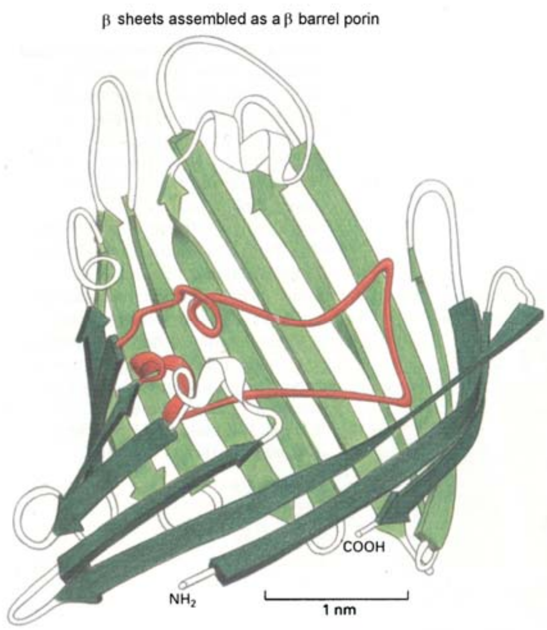
Transmembrane protein classification according to membrane-spanning segments:
1. single-pass;
2. multi-pass.

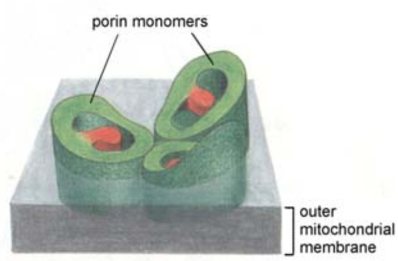
Transmembrane protein classification according to polypeptide chain orientation:
1. type I – NH_2-terminal end on ectodomain;
2. type II – NH_2-terminal end on endodomain.

Heterogeneity
Proteins' contribution

Structural assemblies for transmembrane domain





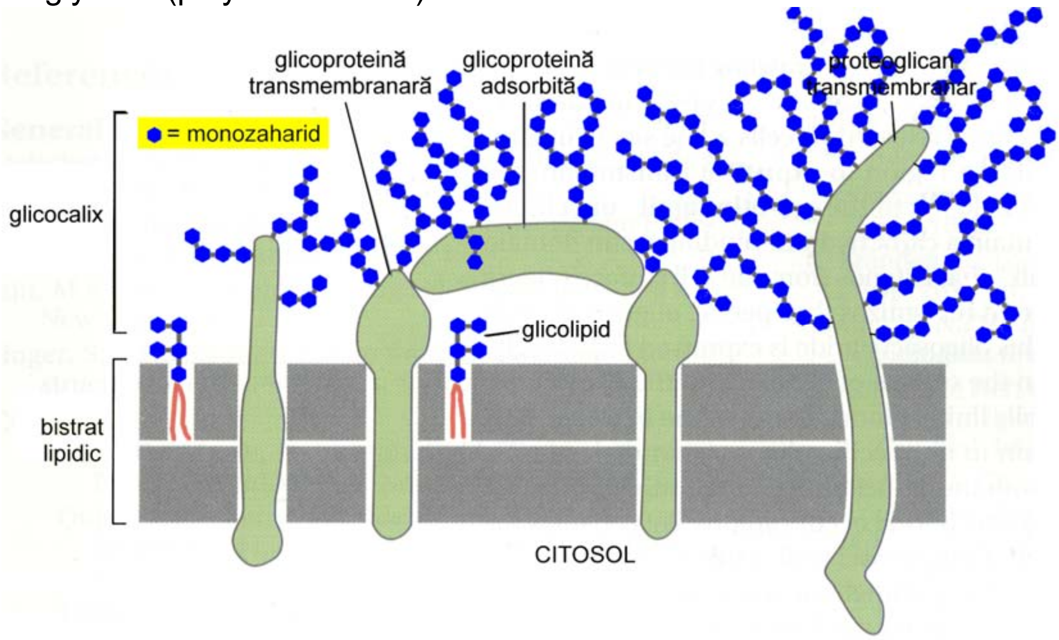


Heterogeneity

Sugar components' contribution

Glycoconjugates on the cell surface (glycocalyx)

1. Glycolipids (oligosaccharides);
2. Glycoproteins (oligosaccharides);
3. Proteoglycans (polysaccharides).

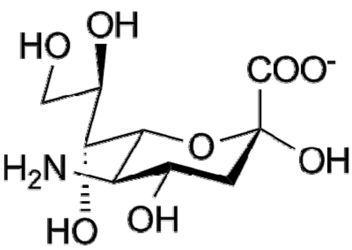


Heterogeneity

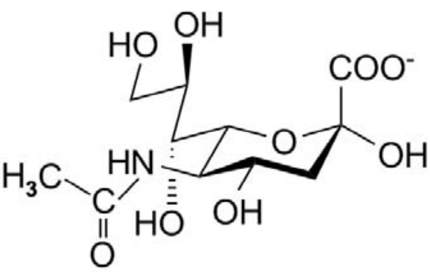
Sugar components' contribution

Generalities about sugar components of glycocalyx

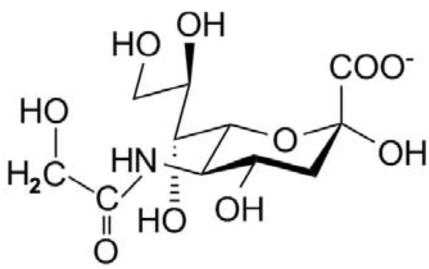
- Monosaccharides: Glc, Glc*N*Ac, Gal, Gal*N*Ac, Man, Fuc, sialic acids (SA)



Neuraminic acid



N-acetyl-neuraminic acid



N-glycolyl-neuraminic acid

Heterogeneity

Sugar components' contribution

Generalities about sugar components of glycocalyx

- Monosaccharides: Glc, Glc*N*Ac, Gal, Gal*N*Ac, Man, Fuc, sialic acids (SA)
- Glycolipids: 1 oligosaccharide chain, un-branched
- Glycoproteins: many chains, branched, inserted as ***N***-, or ***O***-glycosidic linkage
- Structural considerations concerning saccharide sequence: Glc never in a terminal position, sialic acids always in terminal positions

Asymmetry

Lipids' contribution

Asymmetrical distribution of lipids in the membrane

PC & SM – external leaflet of the lipid bilayer
PE, PS & PI – internal leaflet of the lipid bilayer
Cholesterol – about equally distributed in both monolayers
Glycolipids – exclusively in external monolayer

Asymmetry

Proteins' contribution

Peripheral (extrinsic) proteins

- Ectoproteins (some molecular species)
- Endoproteins (other molecular species)

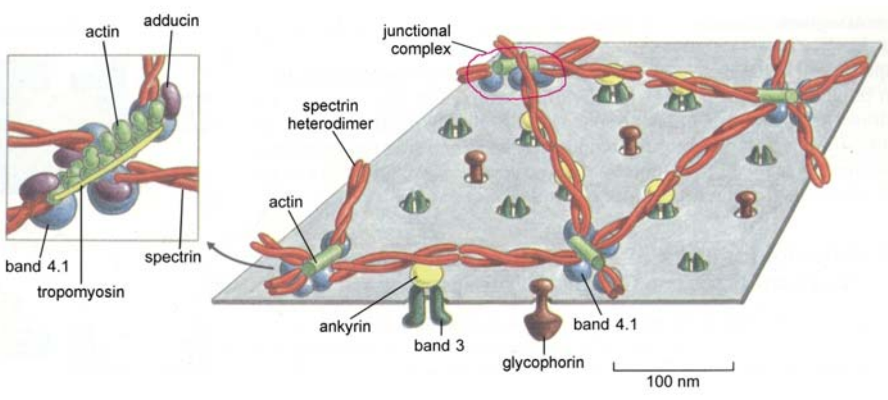
Integral (intrinsic) proteins

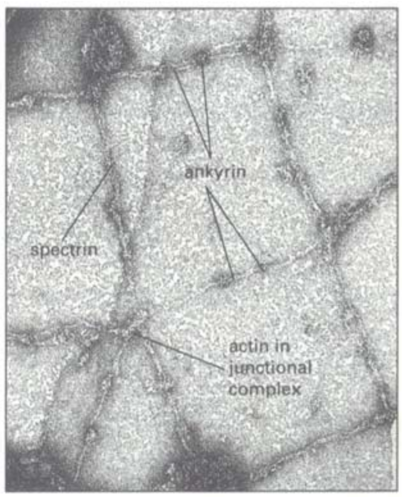
- Transmembrane
- ?

Asymmetry

Proteins' contribution

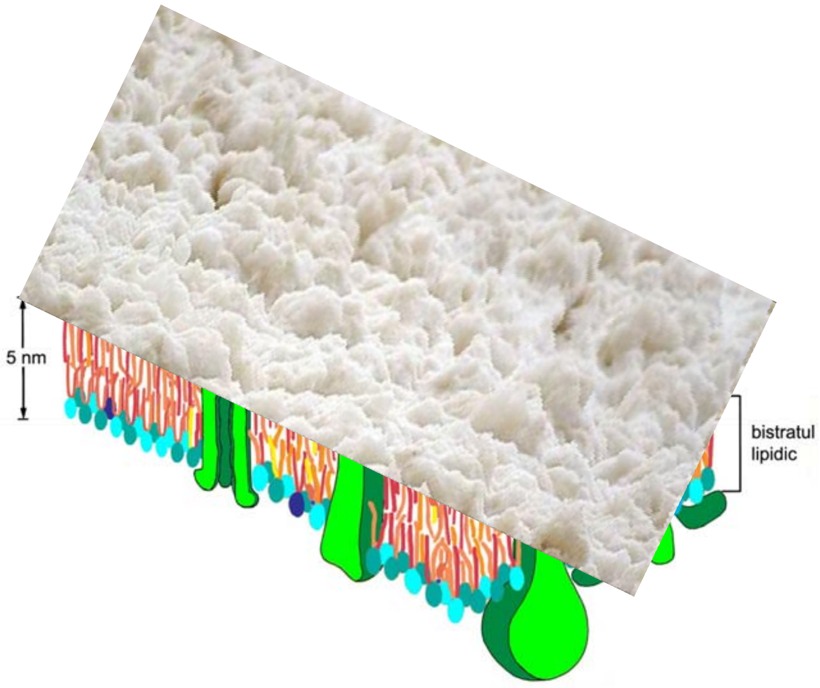
Assembly of membrane cytoskeleton (*only on the cytosolic face*)





Asymmetry

Sugar components’ contribution



Biological significances

- ***For heterogeneity***
  - High diversity of components – variety of function that can be assured
- ***For asymmetry***
  - Different events can occur on the two sides of the membrane
  - Events can be independent or correlated, depending on the cell need in various contexts

See you next week

Physical, (bio)chemical and biological features of cell membranes

- Heterogeneity
- Asymmetry
- Two-dimensional fluidity

Two-dimensional fluidity

How to understand it?

What is the biological significance of this feature of biomembranes?

Two-dimensional fluidity

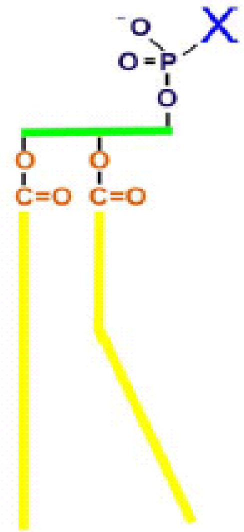
Physical state and dynamics of lipid bilayer and cell membrane

- Fluid structure showing a two-dimensional moving induced even by lipids of the bilayer

Lipid moving in bilayer

1. Intramolecular moving
2. Intermolecular moving

Lipids' Intramolecular Moving



1. Rotational moving 10^7-10^9 rotations/s

2. Tail flexing 10^6-10^8 flexions/s

Lipids' Intermolecular Moving

1. Translational moving 10^7 changes in direction/s

2. Flip-flop moving extremely rare

Membrane Fluidity Regulation

Factors that control and modulate the membrane fluidity

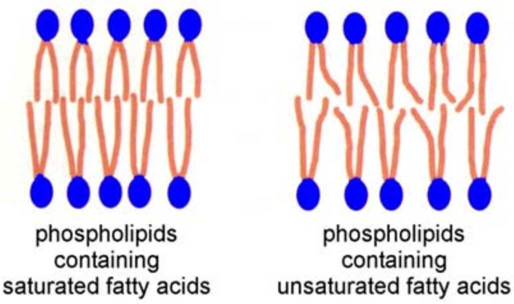
Physical factors
- Pressure
- Temperature

Chemical Factors
- Intrinsic
- Extrinsic

Intrinsic factors which control and regulate membrane fluidity

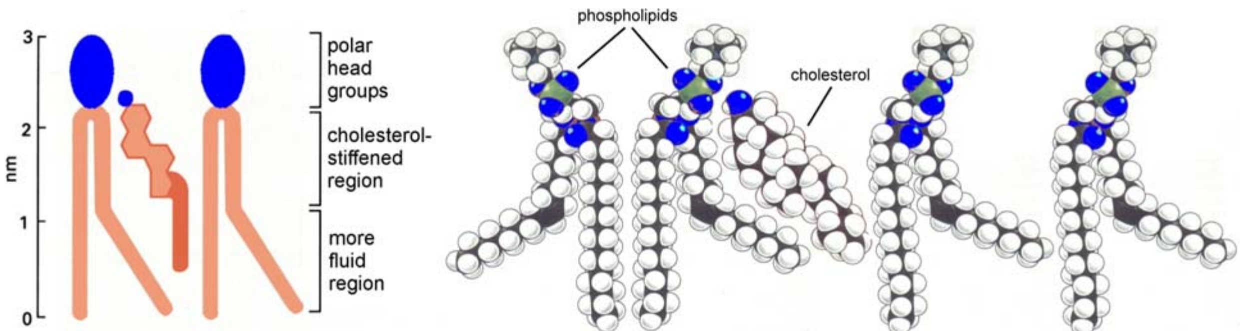
Unsaturated fatty acid effect

More crowded lipids,
more interactions,
less fluidity



Less crowded lipids,
less interactions,
more fluidity

Cholesterol effect



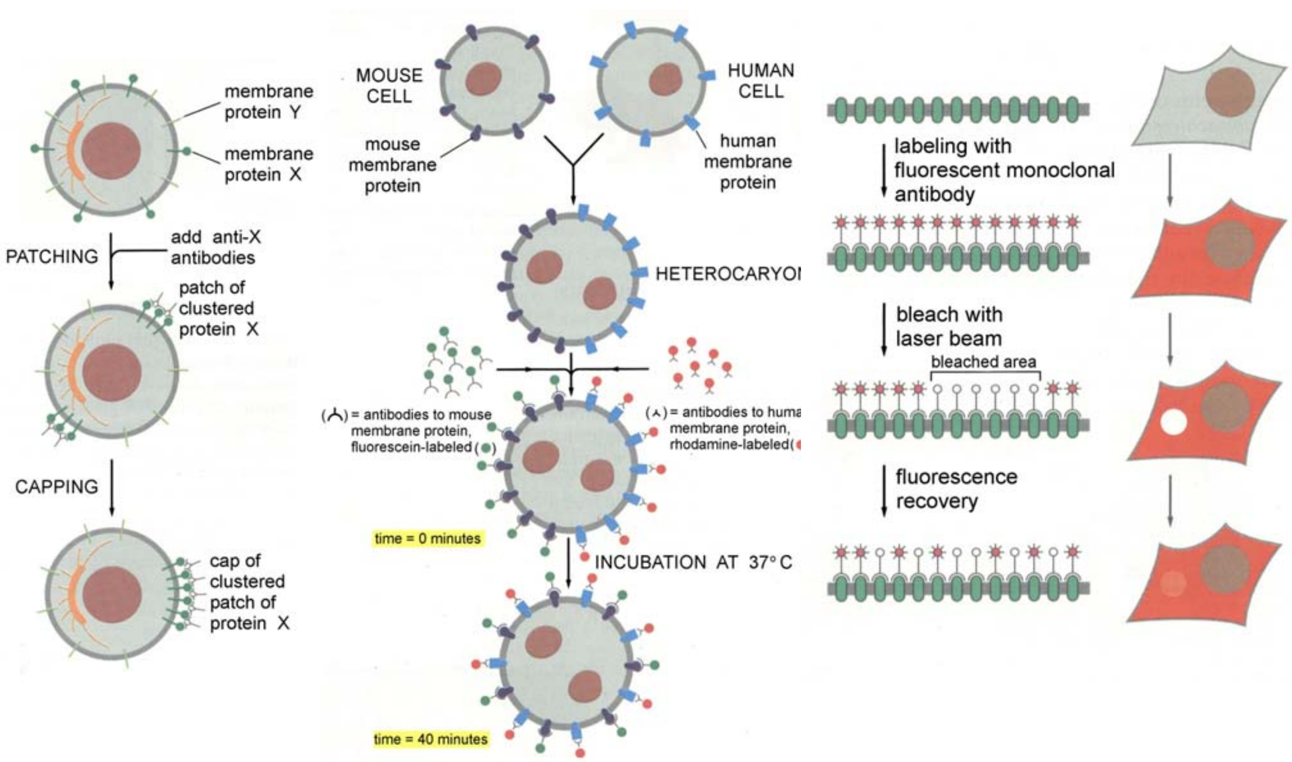
Cholesterol is filling spaces between phospholipids, increasing interactions, decreasing membrane fluidity

Extrinsic chemical factors for modeling the membrane fluidity

- Physiological
- Pathological
- Therapeutic

Two-dimensional fluidity

Membrane protein mobility



Two-dimensional fluidity

Mesomorphic character of the lipid bilayer

Membrane microdomains – specific associations of membrane components following physical-(bio)chemical rules, covering surfaces of micro/nano-meters, in order to increase the effectiveness of their functions

Examples: lipid rafts, caveolae/plasmalemmal vesicles

Lipid rafts' features: specific rations between membrane lipids (more cholesterol, more sphingolipids, few glycerophosphatides, few unsaturated fatty acids in the internal leaflet), specific proteins (acylated, carrying GPI anchors)

Biological significance of membrane's components dynamics

- Improve the effectiveness of membrane functions – various partners by movement can find one-another to interact and doing their best together
- Assure the dynamics of membrane microdomains
- Resulting in increase of the effectiveness of every component and increase of diversity of functions of the membrane as an integrative system

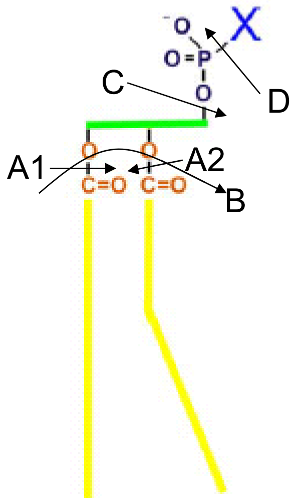
Cell membrane functions

- Barrier
- Metabolic functions (exchanges of substances and information)

Barrier: absolute ***versus*** selective
Metabolic functions: responsibility of proteins, but involve also the other molecular components, ingeniously exploiting their (bio)chemical complexity

Functions for membrane lipids

1. Structural function – assure the behavior as a barrier;
2. Metabolic functions:
   (i) Regulate membrane proteins activity (act on 3D organization of membrane proteins in the bilayer)
   (ii) Cell-to-cell recognition and intercellular signaling (glycolipids)
   (iii) Phospholipids and cell signaling (phospholipases)



- Phospholipase A1 (PLA1) – breakedowns FA at 1st glycerol OH;
- Phospholipase A2 (PLA2) – splits off FA at 2nd glycerol OH;
- Phospholipase B (PLB) – removes simultaneously both FA together;
- Phospholipase C (PLC) – cuts between glycerol and phosphate;
- Phospholipase D (PLD) – removes X component

Arachidonic acid
as a source of messenger molecules

1. Cyclooxygenase-dependent pathway →
   - *(i)* prostaglandins
   - *(ii)* prostacyclins
   - *(iii)* thromboxanes

2. Lipoxygenase-dependent pathway → leukotrienes

Phosphoinositide Cascade

phosphatidylinositol (PI)

↓ PI kinase (ATP → ADP)

phosphatidylinositol 4-phosphate (PIP)

↓ PIP kinase (ATP → ADP)

phosphatidylinositol 4,5-bisphosphate (PIP_2)

↓ phospholipase C-β *(phosphoinositide-specific PLC)*

diacylglycerol (DAG) + inositol 1,4,5-trisphosphate (IP_3)

(activate protein kinase C) *(release Ca^{2+} from endoplasmic reticulum)*

Membrane protein functions

Structural role in functional membrane assembly, but act in metabolic functions of membranes.

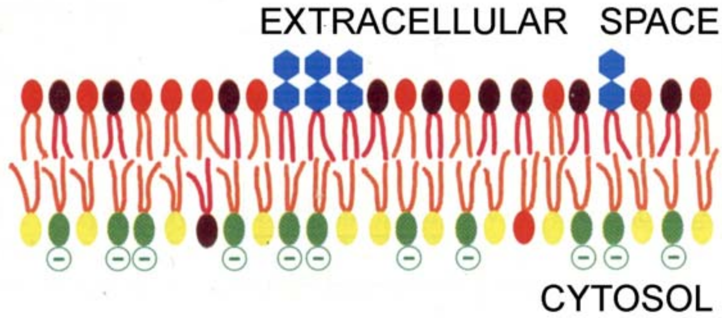
Membrane proteins function as:

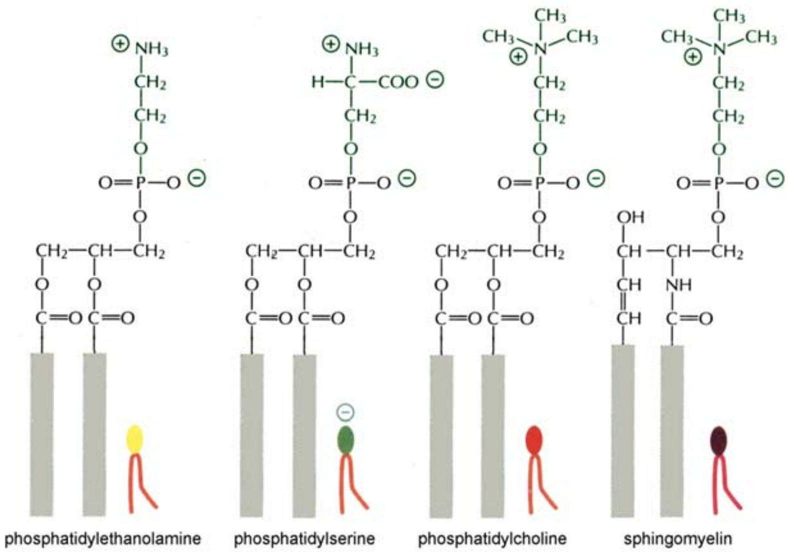
- Membrane transporters (channels, pumps, connexons);
- Proteins for vesicular transport (clathrin, caveolin);
- Receptors (for hormones, growth factors, cytokines chemokines);
- Adhesion molecules (integrins, cadherins);
- Enzymes (matrix metalloproteases, phospholipases);
- Signaling proteins;
- Structural proteins.

Role of membrane sugar components

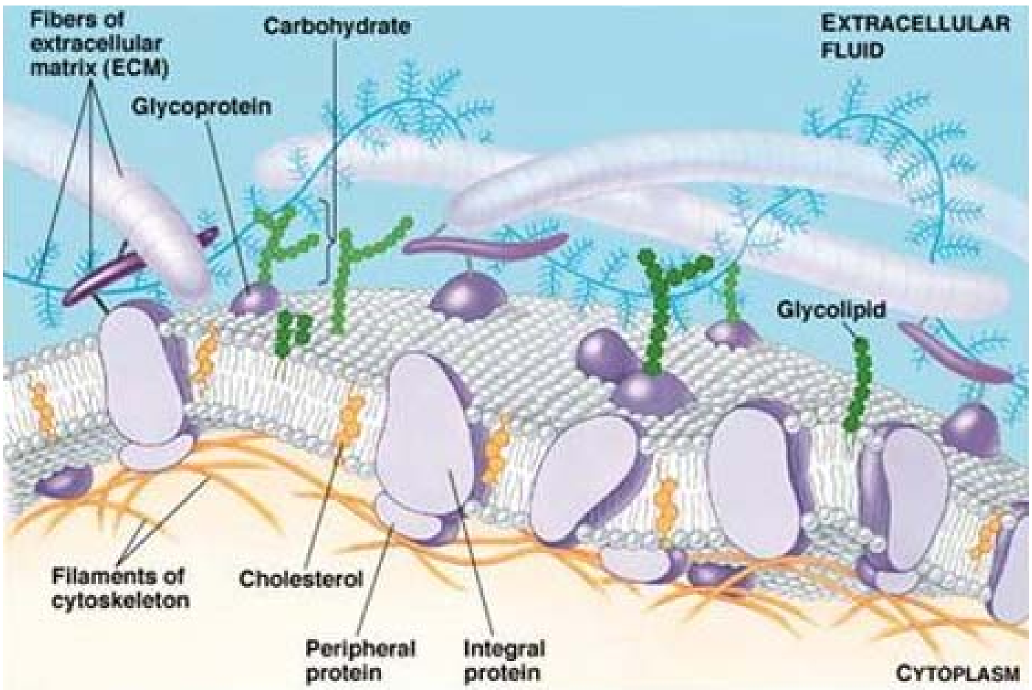
- Membrane protection
- Negative electric charge of cell surface
- Needed, but not properly sufficient for receptor functions
- Involved in cell recognition events:
  - Blood group system ABO
  - Leukocyte extravasation
  - Fertilization (sperm fusion with the egg)

Summary (I)





Summary (II)



https://sjcabiology.wikispaces.com/Cell+Membrane

Cell membrane: a heterogeneous, asymmetrical and dynamic ultrastructure containing lipids, proteins and sugars

membrane microdomains; membrane domains