

Computational Cell Biology

Smooth
endoplasmic
reticulum

Mitochondrion

Rough
endoplasmic
reticulum

Golgi apparatus

Microfilament

Centriole

Nucleus

Ribosomes

Autumn 2025

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EPFL

Source: <http://www.daviddarling.info>

Lysosome

Core Concepts

Dimension dominates behaviour

Asking what “is” something is often useless, better to ask what does something “do”?

Membranes are not static nor are they random, they are a complex fluid



<https://sacgeologymuseum.files.wordpress.com/2013/09/gneiss.jpg>

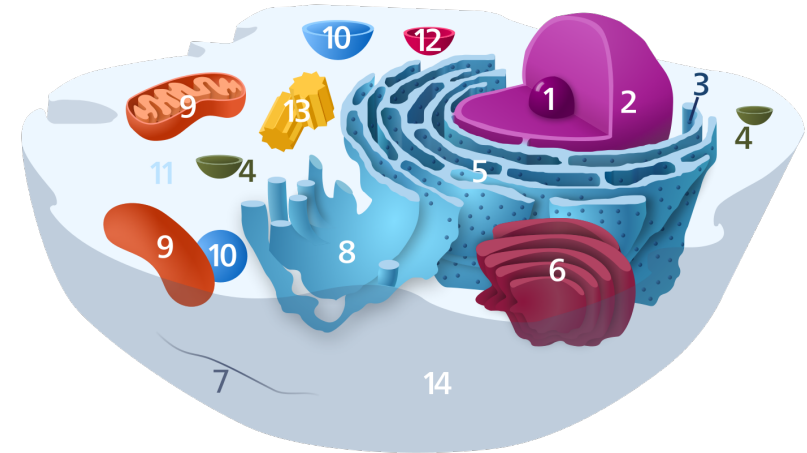


<http://hawriver.org/wp-content/uploads/2015/04/April-09-upper-bynum-res.-rapids.jpg>

Membranes are more than a barrier

Lipid membranes provide the cell with:

Structure - elastic, fluid, flexible 2d surface, forms smooth spheres as well as long, thin tubules in the ER, and flattened disks in the Golgi



Stability - self-heals small pores, relieves local tension by surface tension gradients

Controlled permeation - prevents ions and large molecules crossing, allows water and small molecules to pass

Functional protein environment - proteins need a specific mechanical and chemical environment to function

Lipids on the Frontier: a century of cell membrane bilayers,
M. Edidin, Nature 4:414 (2003)

Our present picture of cell membranes as lipid bilayers is the legacy of a century's study that concentrated on the lipids and proteins of cell-surface membranes. Recent work is changing the picture and is turning the snapshot into a video.

Membrane provides a stable regulatory environment for:

Channels and pores - selective permeability, gating open/closed, blockers

Receptors - bind ligands to transmit a signal across the membrane

G-Proteins - coupled to channels and receptors to transduce signals

Transmembrane proteins are affected by:

membrane thickness

fluidity or diffusion rates

rigidity or order/disorder of the lipids

trans-membrane lateral tension or pressure profile

Diversity implies **organization** at the molecular scale: **structural** (material properties, phase stability, formation/dissolution, e.g., cell division) and **dynamic** (transient domains around proteins, binding/unbinding of ligand/receptors, pore formation and vesicle fusion, etc.)

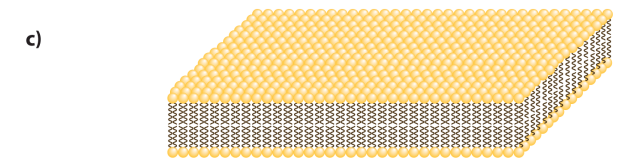
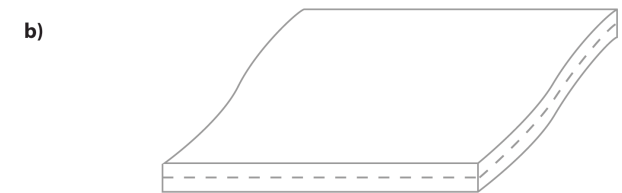
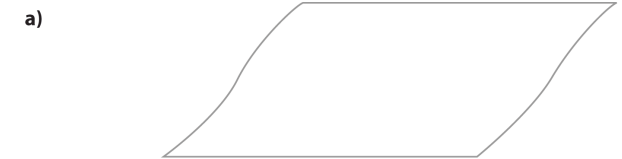
Membranes on different scales

How we describe a membrane mathematically depends on the scale of the question of interest:

Macroscopic - 2d surface, elasticity theory (sufficient for red blood cells), triangulated network “fish net”, model of the membrane, pore formation

Mesososcopic - adds physical properties involving thickness (e.g. lipid “shape” lateral stress profile/protein conformational changes), geometric asymmetry but no molecular details, pore formation

Molecular - lipids, proteins, protein channel dynamics, permeation, molecular rearrangements, pore formation, fusion



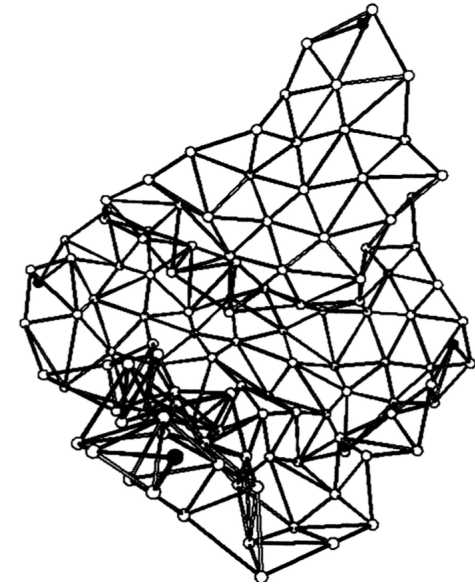
Each scale contributes more insight (and complexity) into the behaviour of biological membranes.

Membranes as random surfaces

In 1980s, a lot of interest in random surfaces, usually triangulated networks.

Quoting Kantor, Kardar and Nelson, PRL 57:791 (1986)

There is presently considerable understanding of properties of random walks and polymers, obtained through many experimental and theoretical methods.¹ It is therefore natural to generalize the problem from one-dimensional polymers to two-dimensional (2D) surfaces, and there are indeed many recent studies of random surfaces.²⁻⁶ However, in contrast to polymers, there is not a single universality class encompassing all types of surfaces.⁵ Most studies have focused on ran-



If the surface is self-avoiding, its radius of gyration is:

$$R_g \sim L^\nu$$

where Flory theory gives: $\nu = 4 / (d + 2)$ cp. $3 / (d + 2)$ for RWs

Flory theory gives: $\nu = D + 2 / (d + 2)$ for D-dim. objects embedded in d-dim. space.

Statistical Mechanics of Membranes and Surfaces, eds. D. Nelson, T. Piran, S. Weinberg, World Scientific Publishing, Singapore, 2004

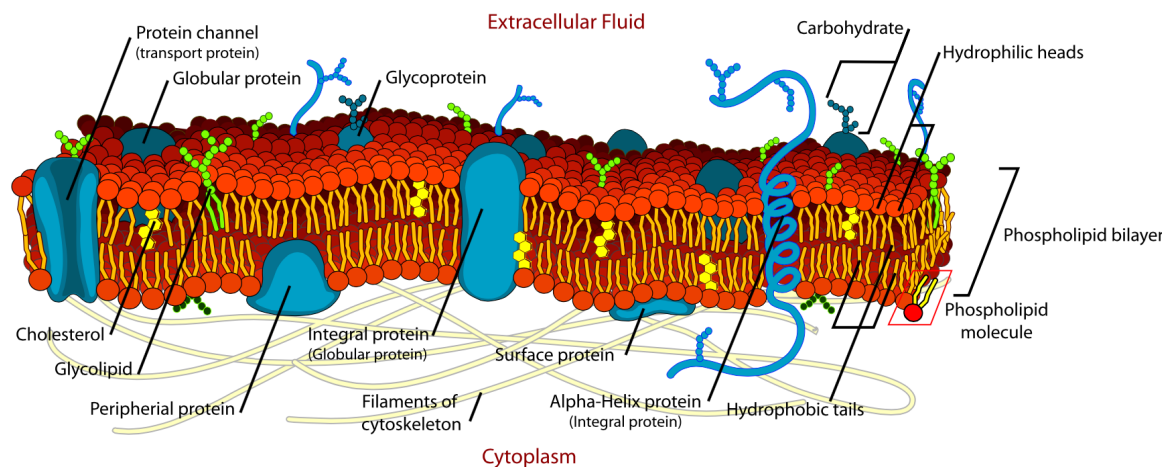
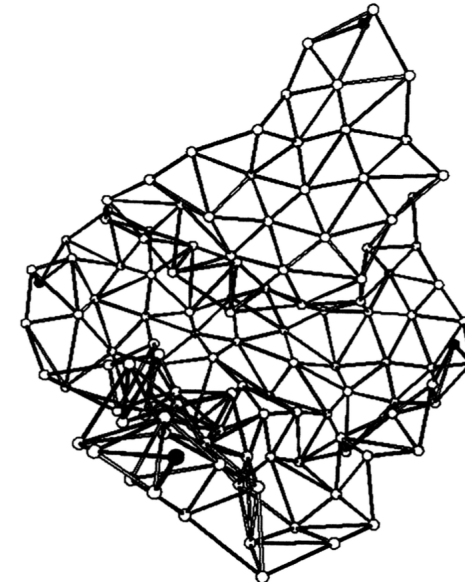
A phantom membrane model?

A phantom membrane or random surface is the generalisation of a phantom polymer to 2d - it is entropy dominated.

It has some unusual properties ...

... it can collapse ...

... it is non-volume preserving
(auxetic - a negative Poisson ratio)



Question 5 mins
While RWs are a good model for (long) polymers, why are random surfaces **not** a good model for biomembranes

Elastic theory of membranes

To go beyond a random surface model, we need to include the **energy** of membrane conformations: biological membranes do not self intersect!- Canham-Helfrich Hamiltonian gives the energy cost of smoothly curved surfaces in terms of two parameters: a **bending stiffness** κ and **spontaneous curvature** c_0

$$H = \kappa/2 \iint dA (c_1 + c_2 - c_0)^2$$

where $c_1(x,y) = 1/R_1$, $c_2(x,y) = 1/R_2$ are the local curvatures at any point (x,y) of the surface. If $c_0 = 0$, the preferred membrane conformation is planar. For a sphere $R_1 = R_2 = R$ at all points, and both curvatures are $1/R$.

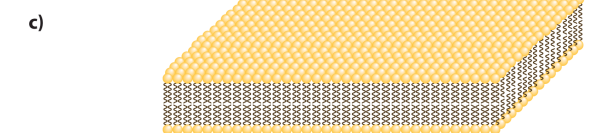
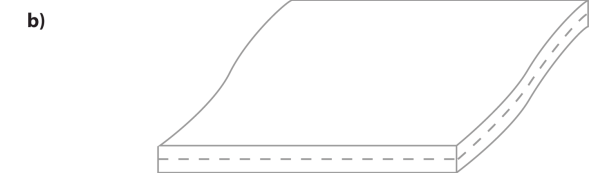
For symmetric lipid membranes $\kappa \sim 10 - 25 k_B T$, $c_0 \sim 0$

This is the first term in an expansion of the energy in powers of the curvature, recall definition of curvature: let a curve be defined parametrically by $\mathbf{r}(s)$ and the local tangent $\mathbf{t}(s)$

$$\mathbf{c}(s) = d\mathbf{t} / ds = d^2\mathbf{r}(s) / ds^2$$

P. B. Canham, The minimum energy of bending as a possible explanation of the biconcave shape of the human red blood cells, *J. Theor. Biology* 26:61-81 (1970)

W. Helfrich, Elastic properties of lipid bilayer membranes: theory and possible experiments, *Z. Naturforschung C* 28:693-703 (1974)



Red blood cells are dominated by symmetry **EPFL**

RBCs take up a wide variety of shapes controlled by physical constraints arising from environment and the energy of deforming the PM:

Inner volume is fixed
Plasma membrane area is fixed (# lipids constant)

(at constant temperature, osmolarity)

$$H = \kappa/2 \iint dA (c_1 + c_2 - c_0)^2$$

If $c_0 = 0$, the bilayer is symmetric and prefers to be flat;
if $c_0 \neq 0$, the two monolayers are different and the membrane prefers to be bent in its lowest energy state.

c_0 captures effects like: unequal numbers of lipids, different lipids, lipid tilt, in general any structural difference between the monolayers that cannot relax to a symmetric state in equilibrium

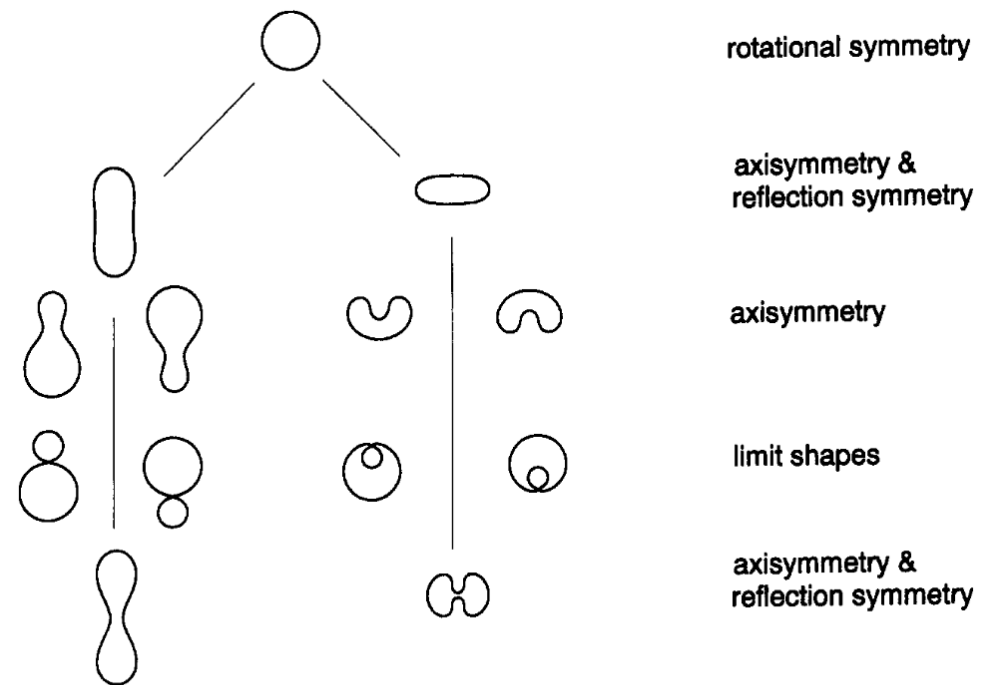


Figure 11. Bifurcation scheme with stationary shapes and their symmetry.

U. Seifert, *Advances in Physics*, 46:13-137 (1997)

Summary of elastic theories of membranes

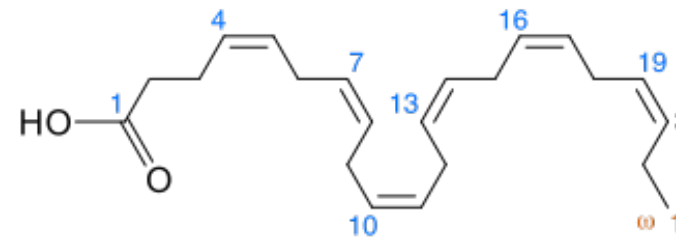
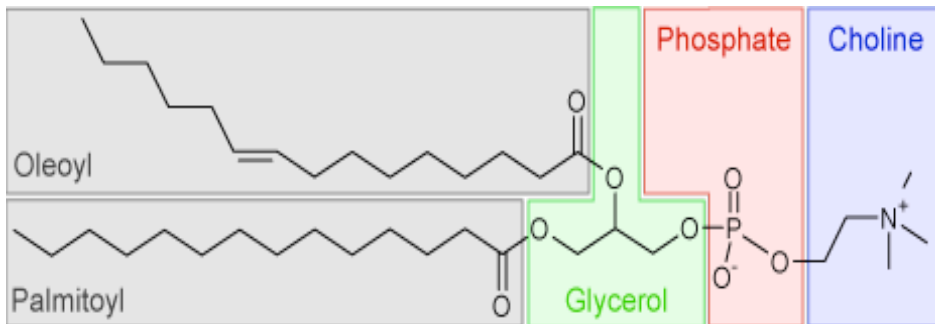
Elastic theories are *continuum* models and are limited to idealised cases like RBCs or toy models:

- They have properties that vary from point to point (shape, composition, thickness, orientation, stiffness) but they do so via differential equations
- They can incorporate two monolayers by defining properties on opposite sides of the surface
- They provide a first approximation to the equilibrium structure in a biological context
- But they don't allow discrete molecules, so they cannot describe phenomena on length scales of $\sim 1\text{nm}$ (typical lipid size), cp. hydrodynamics of fluid flow has *fluid elements* not molecules.
- They cannot deal with large curvatures
- For molecular details we need simulations

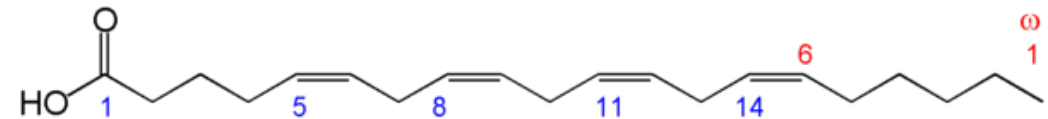
Membrane lipids

How do the types of lipid in cells differ? Headgroup - Tails (number, length, unsaturation)

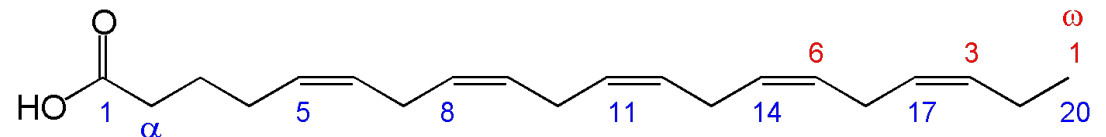
Most lipids look like DOPC below (Di-oleoyl palmitoyl phosphatidylcholine), that make bilayers and vesicles and are in the fluid phase at body temperature. Others like PE cannot form bilayers alone.



Docosahexaenoic acid in the brain - 6 double bonds, 22 C

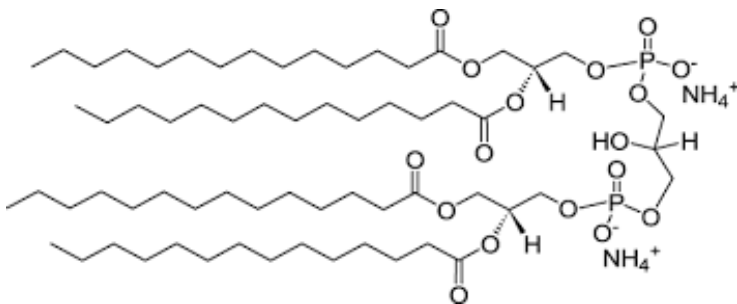


Arachidonic acid in the brain - 4 double bonds, 20 C



Eicosapentaenoic acid in the brain - 5 double bonds, 20 C

But our bodies have more exotic lipids:



Cardiolipin in the heart - 4 tails

Most cell membranes contain substantial amounts of unsaturated lipids - especially the brain as more than half its lipids are DHA, AA, and EA which are poly-unsaturated.

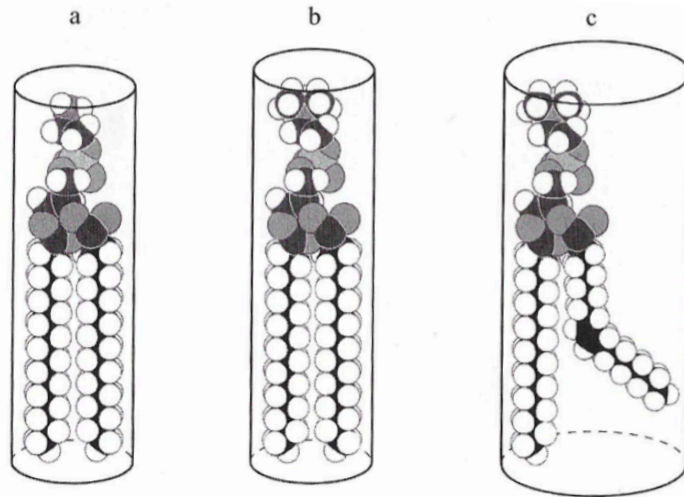


Fig. 4.1a–c. Schematic illustration of the dimensions of lipid molecules. (a) Di-stearoyl phosphatidylethanolamine (DSPE). (b) Di-stearoyl phosphatidylcholine (DSPC). (c) Stearoyl-oleoyl phosphatidylcholine (SOPC)

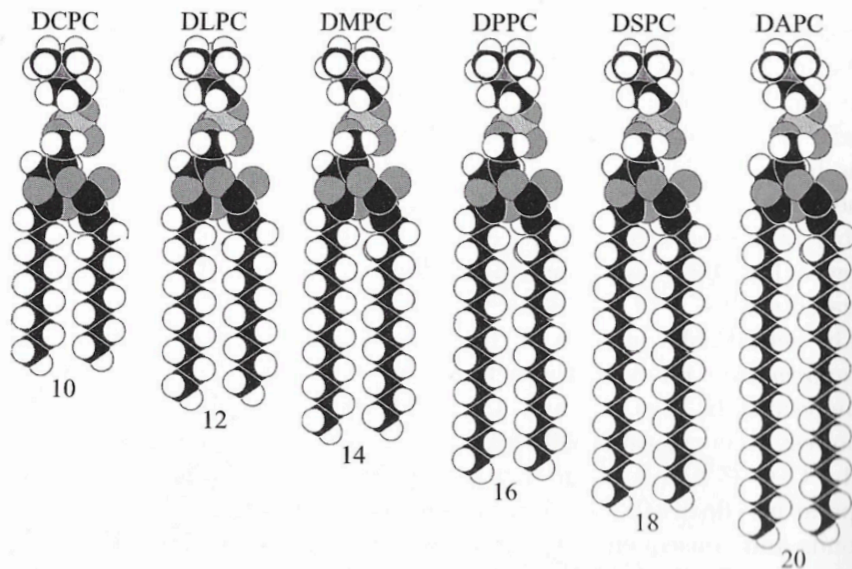


Fig. 4.2. The homologous family of di-acyl PC lipids with two identical saturated chains. The figure also serves to define the acronyms traditionally used for these lipids. The numbers at the bottom denote the number of carbon atoms in the fatty-acid chains

Recall the *packing parameter* $p = v / a_0 l_c$

v = equilibrium volume

a_0 = equilibrium cross-sectional area

l_c = maximum extension of the chains

But note that volume and headgroup area are affected by temperature, salt, etc, and curvature stress of membrane modifies them:

lipids affect membrane shape

membrane influences lipid shape

Life as a Matter of Fat, O. Mouritsen, Frontiers Collection, (Springer 2007)

Opposing forces between lipids in membranes

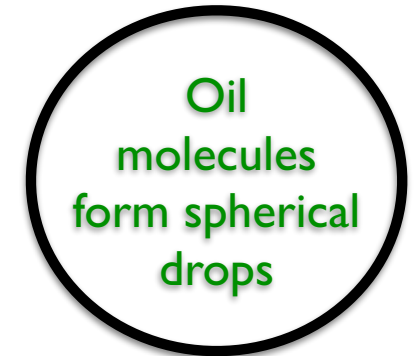
Oil molecules separate into an infinite phase because of the hydrophobic effect:

tiny spheres \Rightarrow spherical droplets (**what else could they do?**)

Lipids are asymmetric (hence - *amphiphiles*) \sim cannot form (filled) spheres.

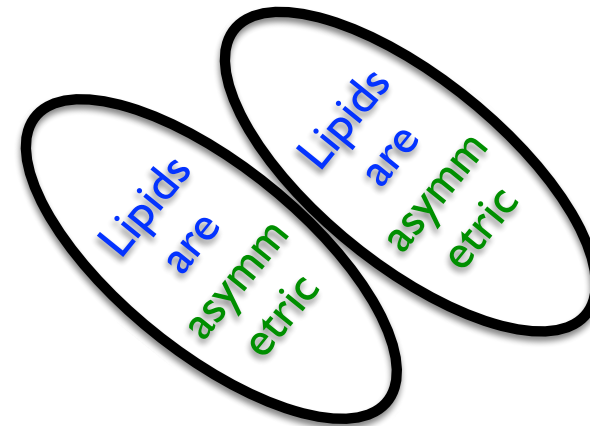
We know they form: micelles, bilayers, vesicles, etc. Can we describe this?

We try to hide the complexity of the molecular interactions into two terms:



Headgroup properties - typically repulsive due to:

- steric repulsion
- charge or dipole interactions
- mobility (protrusion from membrane)



Hydrocarbon tail properties - typically attractive due to:

- hydrophobic repulsion from water
- high flexibility/many conformational states within membrane interior, van der Waals

Israelachvili's packing parameter is a zeroth-order approximation to this complexity.

Membrane proteins

What is your picture of the plasma membrane?

Proteins make up a large fraction of membrane constituents.

In E. Coli, for example, there are > 1000 distinct trans-membrane helical proteins.

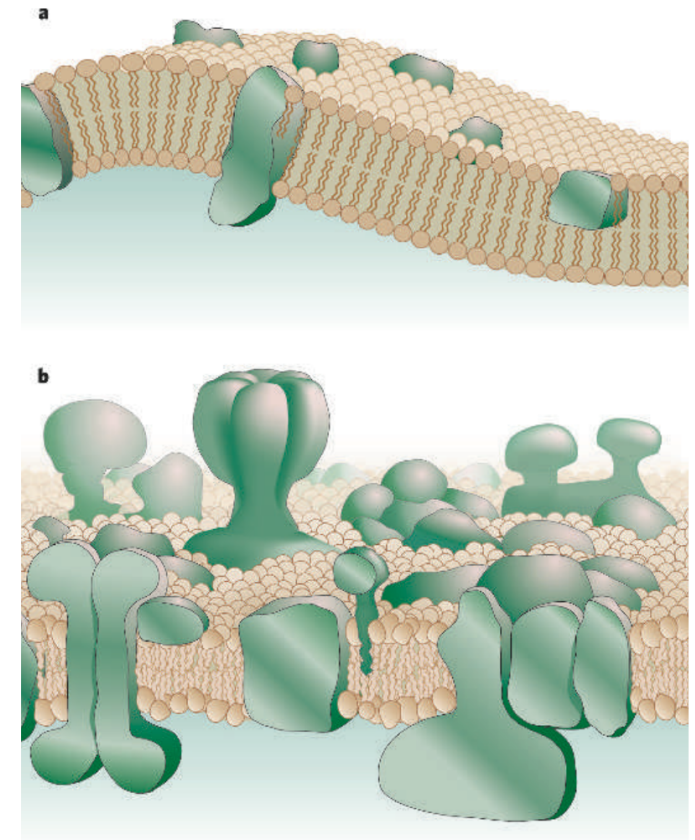
In general, 20-30% of all genes code for trans-membrane proteins and the fraction increases with genome size (bacteria, C. Elegans, humans, ...)

Genome-wide analysis of integral membrane proteins from eubacterial, archaean, and eukaryotic organisms

Protein Science 7:1029-1038 (1998)

Engelman DM Membranes are more mosaic than fluid Nature 438:578-580 (2005)

Proteins can locally dominate the surface; endo-exocytosis changes number/type of lipids constantly through trafficking.



Cholesterol

Cholesterol makes up 30-50% of typical mammalian membrane constituents.

But prokaryotes have 0% cholesterol in their membranes.

Mitochondria have almost no cholesterol, supporting the idea that they are an ancient prokaryote that merged with an ancient eukaryote.

Paradoxically, adding cholesterol to a lipid membrane has two apparently contradictory effects:

makes fluid membranes less fluid

makes solid phase membranes more fluid

Lipid bilayer has distinct phases as temperature increases:

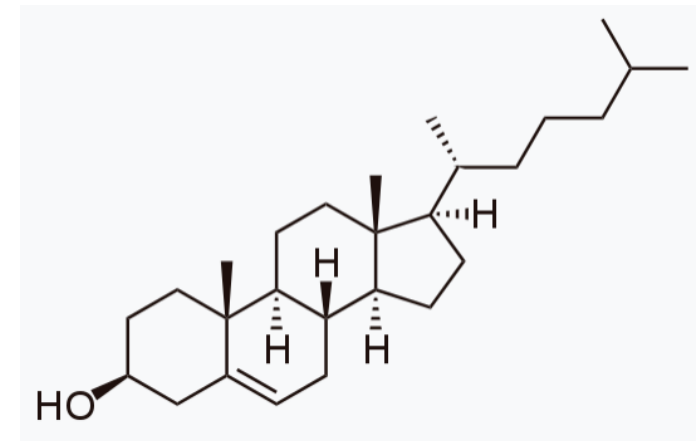
Gel (crystalline)

Liquid ordered (semi-fluid, liquid crystalline)

Liquid disordered (fluid)

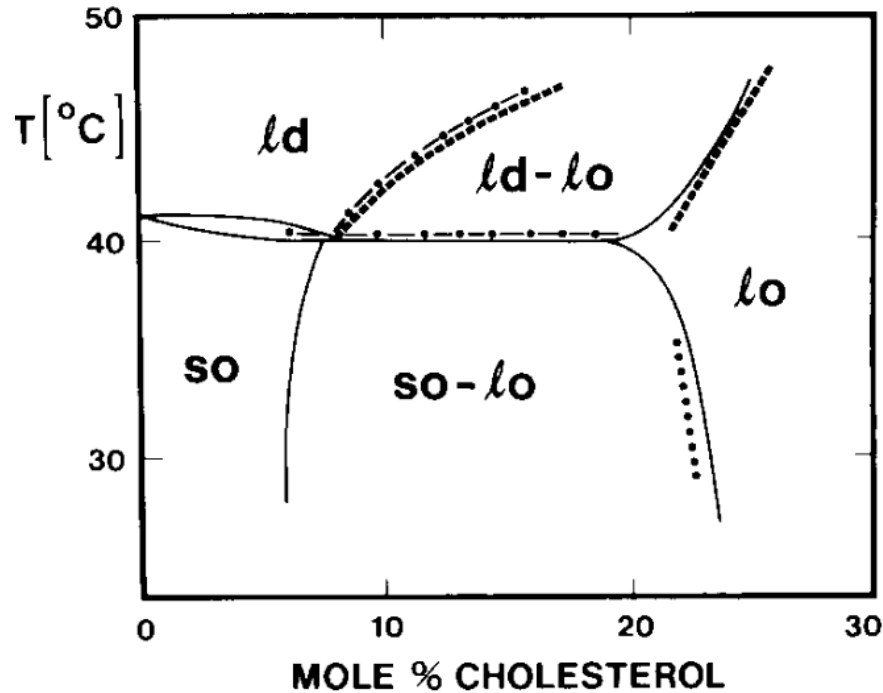
but the differences are subtle, not like:

Steam - Water - Ice



Wikipedia

Liquid ordered phase of lipids



Membranes are fluid

but not a simple fluid ...

J. H. Ipsen et al. Phase equilibria in the phosphatidylcholine cholesterol system, *Biochim. Biophys. Acta.* 905:162-172 (1987)

L_D - Liquid disordered phase has high lateral mobility (large diffusion of lipids), large disorder in chains (rotations and bends, not straight), headgroups also bounce up and down. The membrane thickness is decreased because of increased chain disorder.

L_O - Liquid ordered phase is more rigid, tails are all-trans, rotational mobility but slower lateral diffusion thought to be one of the factors leading to lipid “rafts” or domains of interacting proteins that carry out specific signalling tasks. Existence of “rafts” *in vivo* is disputed...

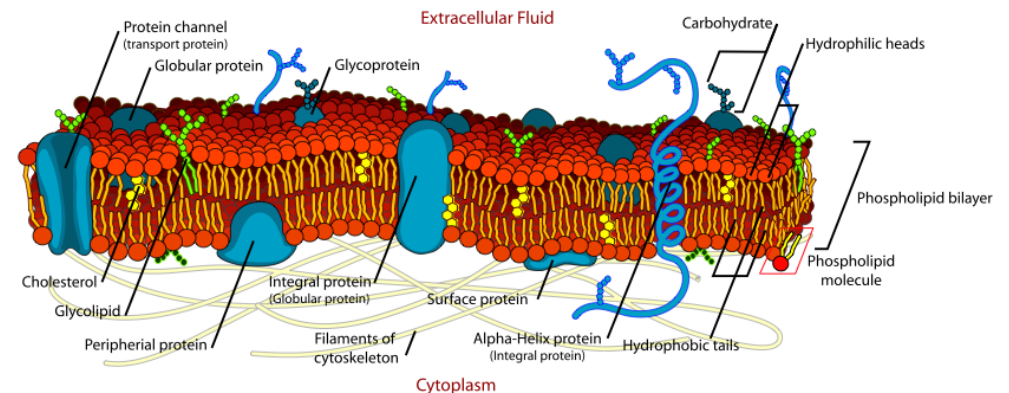
K. Simons and E. Ikonen, Functional rafts in cell membranes, *Nature* 387:569-572 (1997)

Membrane composition

Why are there so many different types of lipid in the body?

- If all nature needed was a barrier, a few lipid types would be sufficient - but there are 1000s of different types of lipid in cell membranes (cp. 4 bases in DNA and 20 amino acids in proteins)
- Membrane is a fluid so all components should diffuse freely - but different proteins need distinct environments due to thickness, tension, and their function depends on local lipid composition
- Different organs have different compositions: > 50% of neural membrane lipids are poly-unsaturated

Life as a Matter of Fat, O. Mouritsen, Frontiers Collection, (Springer 2007)



This diversity is expensive to maintain so it must have a reason: maybe membrane proteins need specific environments to function

Phospholipid headgroups govern area per lipid and emergent elastic properties of bilayers

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INTRODUCTION

Biological membranes are characterized by a strikingly large assortment of different lipid species (1–3) that may be related to the functions of their protein constituents. Variation of the lipids can have wide-reaching effects over the entire membrane structure on account of the highly collective intermolecular interactions. It has become well established that the lipid environment can substantially alter the functions and energetics of membrane proteins (4–9)

through the involvement of both the lipid polar headgroups and acyl chain substituents (3,10–13). One hypothesis is that lipids control membrane protein activity by allosteric modulation due to binding to specific recognition sites, as for diacylglycerol and protein kinase C (14,15), viral membrane proteins (16), and G-protein-coupled receptors (GPCRs) (17,18). Alternatively, the interactions may be nonspecific and entail modification of physical properties of the entire bilayer, including phase behavior, membrane thickness, molecular packing, surface charge density, lipid shape (19,20), and curvature stress (7). Recent literature has confirmed the asymmetric segregation of membrane lipids such as phosphatidylethanolamine (PE) and phosphatidylcholine (PC) in cellular plasma membranes, with PE being much more

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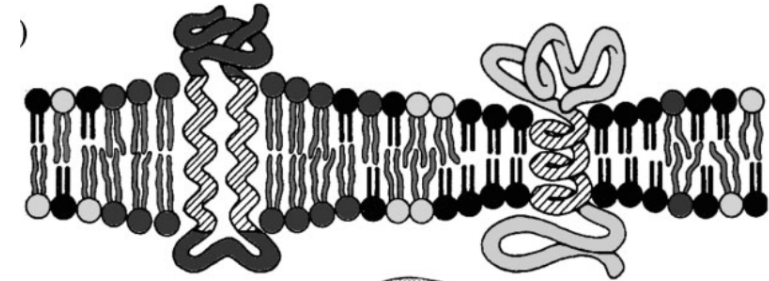
<https://doi.org/10.1016/j.bpj.2022.09.005>

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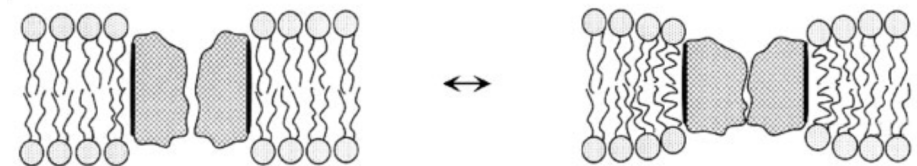
T. R. Molugu et al. *Biophys. J.* <https://doi.org/10.1016/j.bpj.2022.09.005> (2022)

Thickness, bending modulus, stretch modulus, fluidity - vary from point to point

Protein hydrophobic region must match the membrane **thickness (or pay high energy cost)**, hence they prefer to be surrounded by lipids with matching thickness



Channel proteins can have their open/closed equilibrium changed by **local membrane constituents**



Membrane **bending stiffness** (or degree of saturation of lipids) controls their shape; flexible lipids can form curved membranes, vesicles, tubes, rigid lipids form flat bilayers;

Stretch modulus is high which maintains surface area constant

Fluidity of membrane components allows cell to create/remove lipids that associate by diffusion; transient domains can form to aid signalling, tension can be relieved by lipid flow

Fatty acids, lipids, and being smart

Lipids are made from precursor fatty acids that are also converted into hormones.

Animals have to get so-called essential polyunsaturated fatty acids (PUFAs) in their diet as they cannot synthesize them:

Linoleic acid - C18:2n-6, 18 carbon chain with 2 double bonds starting at C6 from the end

α -linolenic acid -C18:3n-3 18 carbon chain with 3 double bonds starting at C3 from the end

Linoleic acid (n-6 family)



α -linolenic acid (n-3 family)

Arachidonic acid (AA)

Eicosapentanoic acid (EPA)

Docosahexaenoic acid (DHA)

These families cannot be interconverted, but can be made in the liver from the precursors, but it is less costly to eat them.

AA, Linoleic acid is found in seeds, corn; linolenic acid in green plants and algae.

DHA is found in algae, eggs, meat, cold-water fish and shell fish that eat algae.

Polyunsaturated lipids in the brain

60% of dry weight of brain is lipids, and 50% of this fraction are polyunsaturated lipids.

Mammals, reptiles and fish have different lipids in their muscles, livers, other organs but their brain lipids are similar: **why?**

Where do these exotic lipids come from? Fish - 50% of all fatty acids in salmon are DHA, while it is only 0.2% in cows.

Michael Crawford's hypothesis:

Human brain mass /body mass is high

PUFA composition of human brain is high

This can only happen where DHA and AA are plentiful, i.e., near the sea or eating brain/tissue of other animals

Why aren't fish smart? They have only the DHA present in egg, but mammals have a continuous supply from mother during gestation and breast milk.

Animal	Brain/Body ratio (%)
Mouse	2
Chimp	0.5
Gorilla	0.25
Cow	0.1
Human	2.1
Dolphin	1.5

Why polyunsaturated lipids in the brain?

1) DHA may provide membrane conditions optimal for trans-membrane G-proteins and the membrane fragility needed for plasticity in neuron membranes, as well as electrical properties. DHA is a non-lamellar forming lipid (Meyer Bloom)

2) Connectivity is a key factor - how easy is to for synapses to grow/shrink?

In the embryo, tight control of the growth/shrinkage of new synapses is crucial, which requires tight regulation of the production of AA and DHA in the growth zones. This requires enzymes (acyl-transferases, phospholipase A2 and C, etc), lipoproteins that transport fatty acids to the synapses.

If AA, DHA increase due to excess phospholipase activity \Rightarrow manic depression

AA, DHA decrease due to reduced acyl-transferase \Rightarrow schizophrenia

Possibility of schizophrenia arises with the appearance of the biochemical machinery that produces the connectivity and plasticity that makes humans human.

Only then (50 - 200, 000 years ago) could H. Sapiens evolve.

Myer Bloom, Evolution of membranes from a physics perspective, in In Search of a New Biomembrane Model, OG. Mouritsen and O. S. Andersen eds.) Biol. Skr. Dan. Vid. Selsk. 49:13-17 (1998)

Summary

At first sight, membranes are an impermeable barrier to protect the cell

But ... membranes are:

- **diverse** - 1000s types of lipid in them, lipidomics seeks to classify this
- **dynamic/fluid** - a constant traffic of lipids/proteins/vesicles to and from them
- **inhomogenous/complex fluid** - domains form and dissolve; properties vary in space/time
- **permeabilised** under cellular control (endo-, exo- cytos)
- **able to influence** protein function (ion channels, pumps)

Dimension dominates behaviour

1d - RW - Lecture 6

2d - membrane - Lecture 9

3d - protein droplets in cytoplasm - Lecture 12

Break

10 mins.