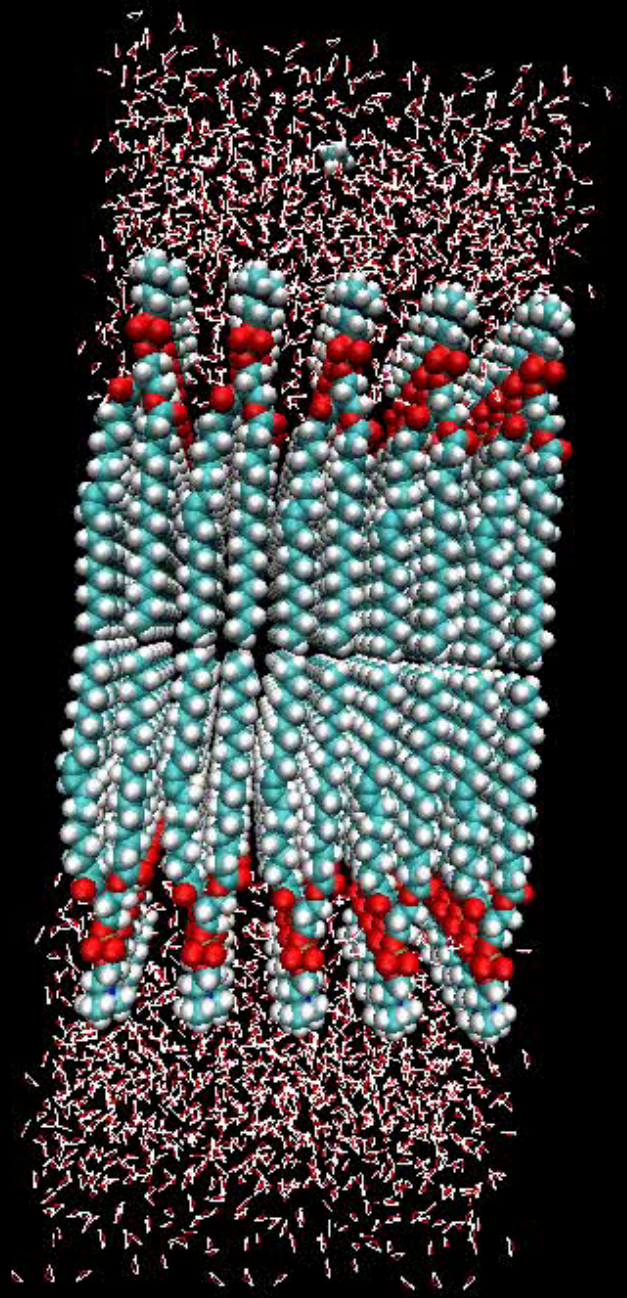
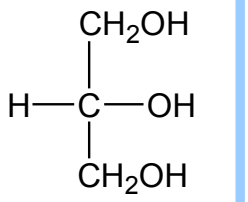


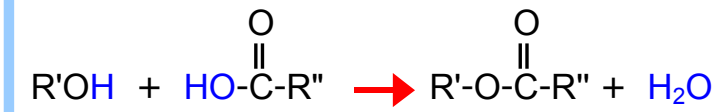
Lipid bilayer

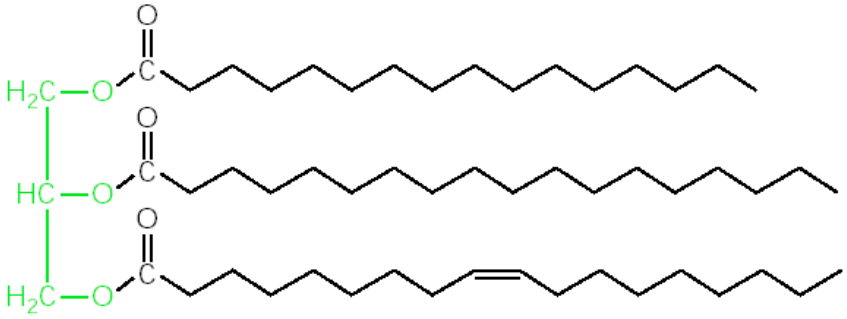
Glycerophospholipids

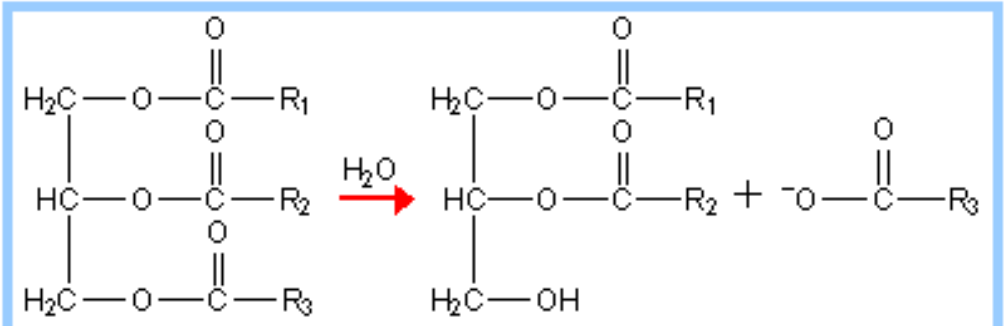


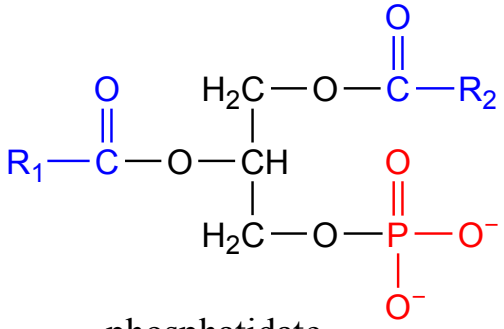
glycerol

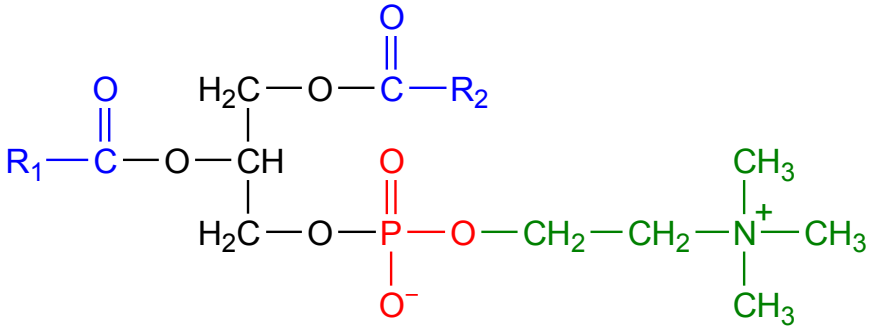
Formation of an ester:

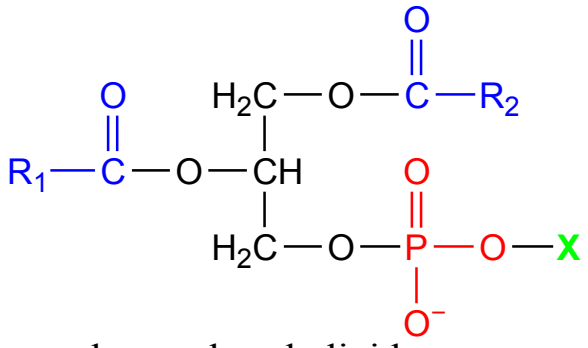


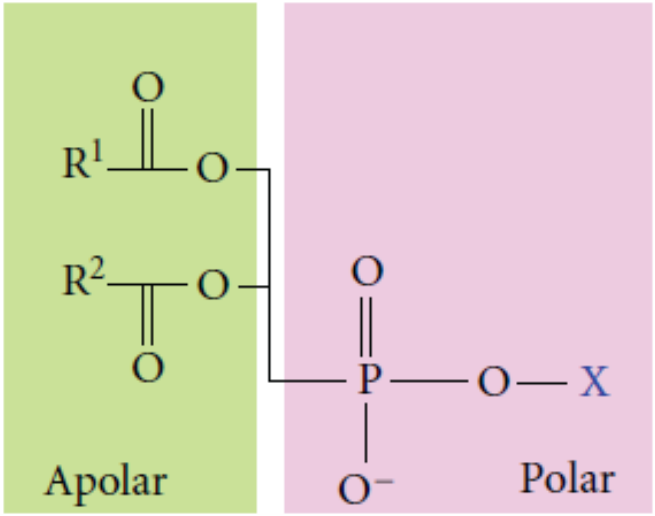





phosphatidate

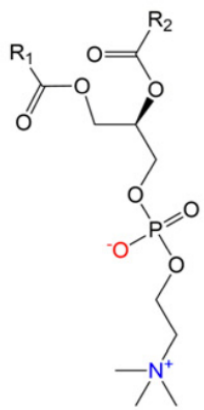

phosphatidylcholine


glycerophospholipid

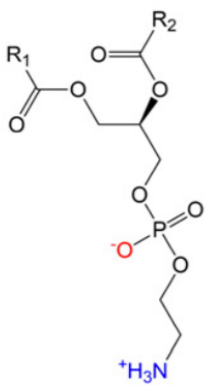


According to the head group X, there are several kinds of lipids.

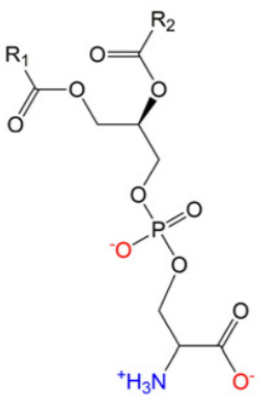
The structure of several common mammalian phospholipids that can be found in the plasma membrane along with their charge ranges under physiological conditions.



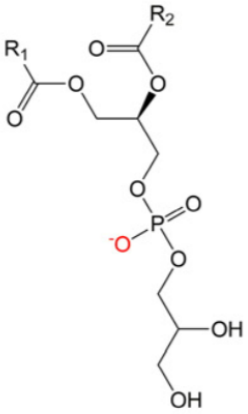
Phosphatidylcholine
Neutral



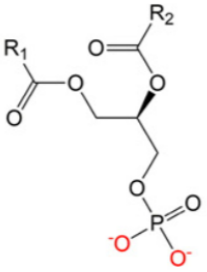
Phosphatidylethanolamine
Neutral



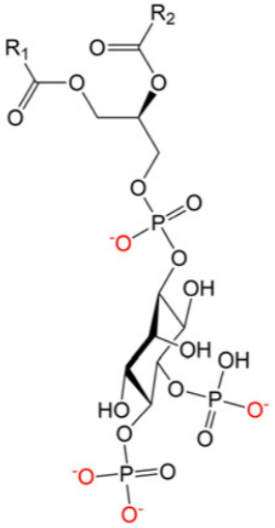
Phosphatidylserine
-1 at pH 7.0



Phosphatidylglycerol
-1 at pH 7.0



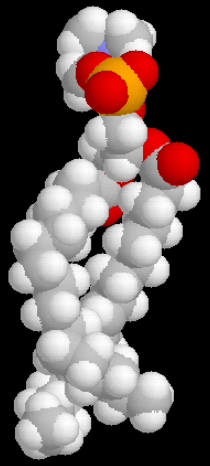
Phosphatidic acid
-1 to -2



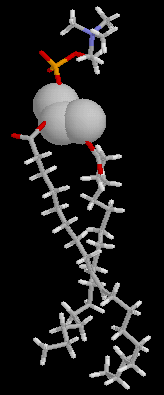
Phosphatidylinositol 4,5-bisphosphate
-3 to -5

Depends on
pH, hydrogen bonding, presence of counterions

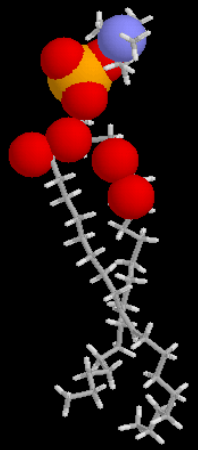
A phospholipid is an amphiphilic molecule

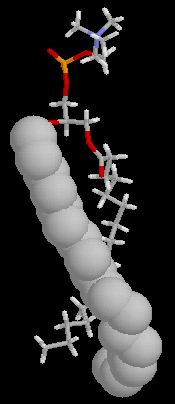


The hydrophobic regions



The polar regions

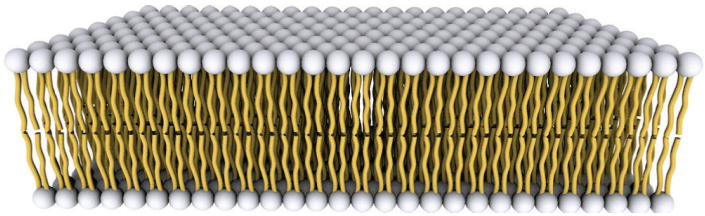


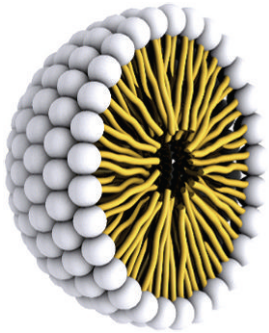


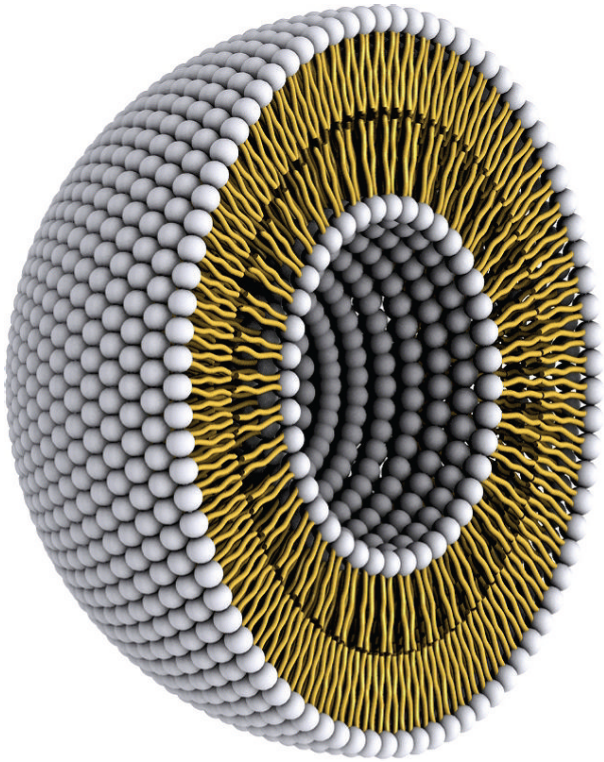
Lipid assembly is a water (entropy)-driven process.
The hydrophobic Effect

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

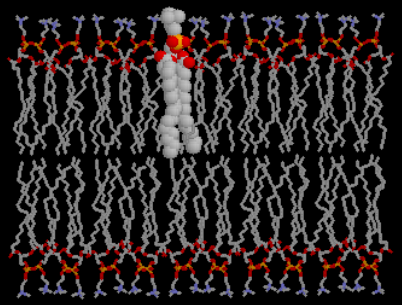
- Above 8 carbons, molecules bind strongly to a membrane or proteins with hydrophobic pockets.

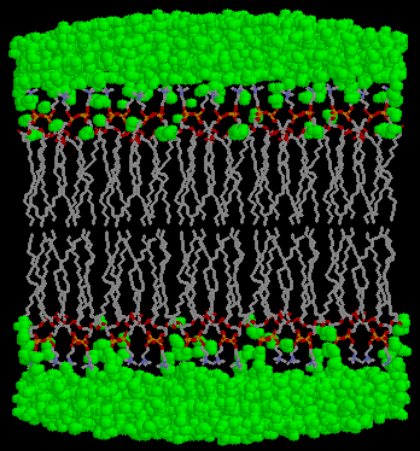


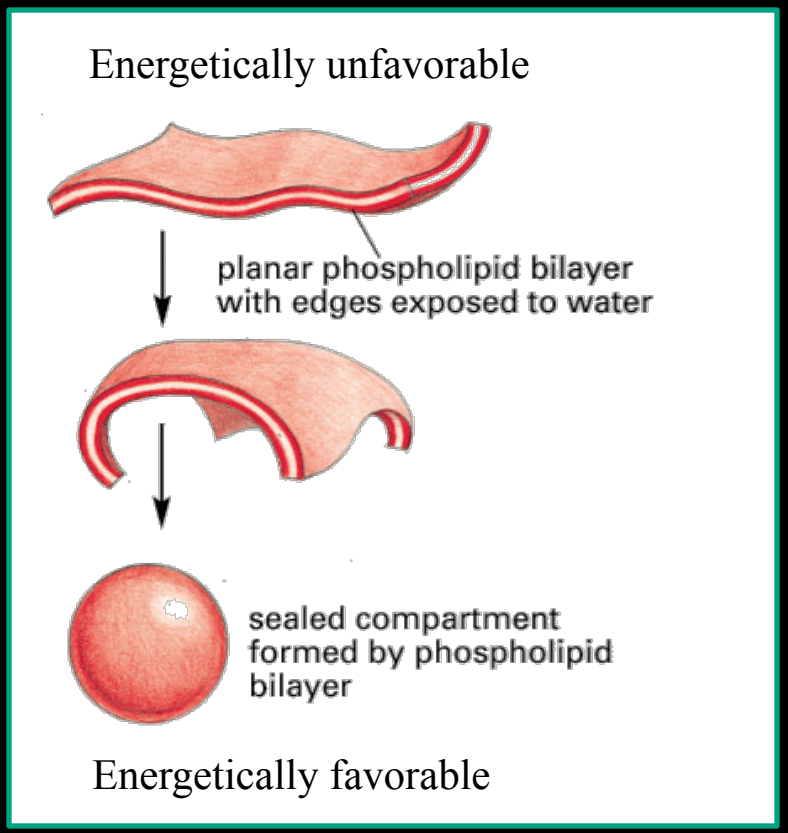


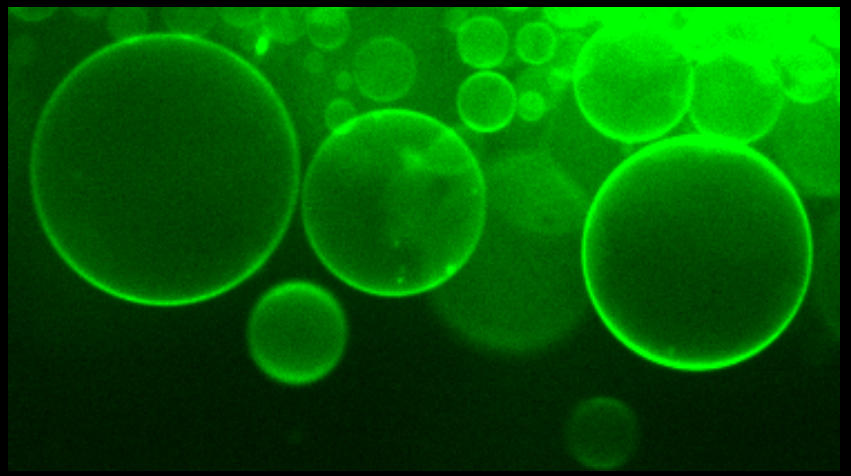


The lipid bilayer





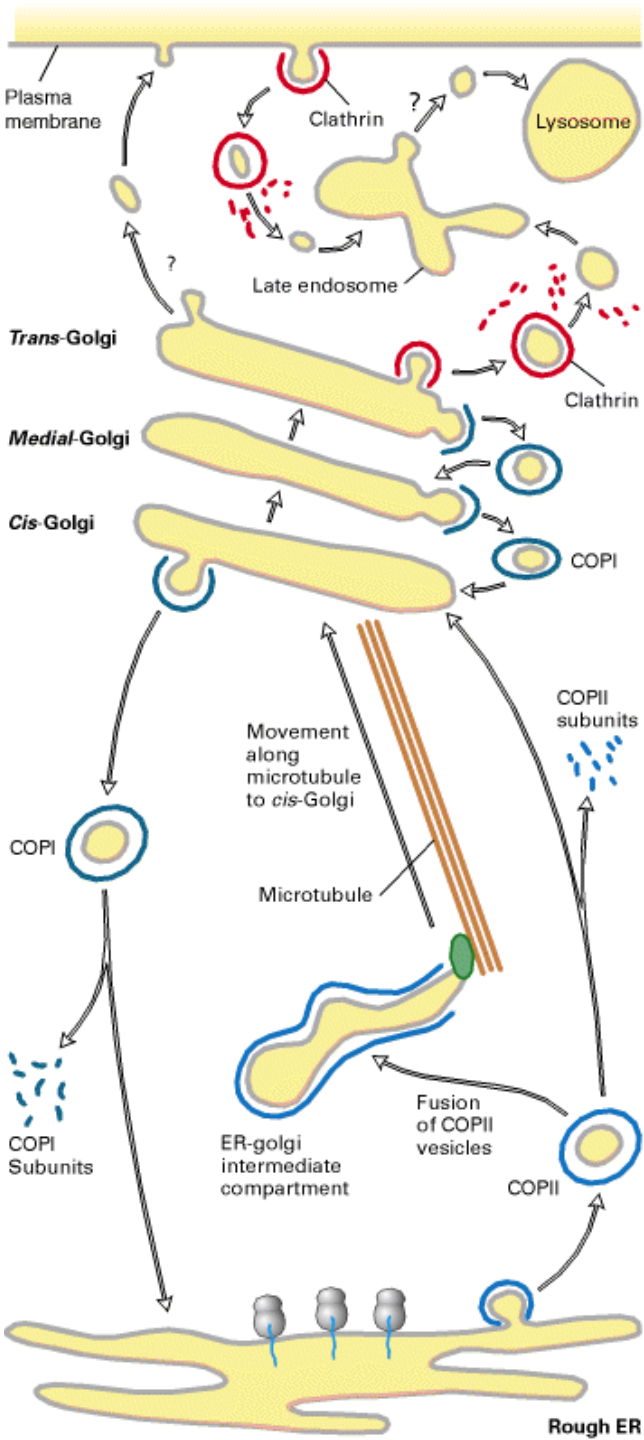




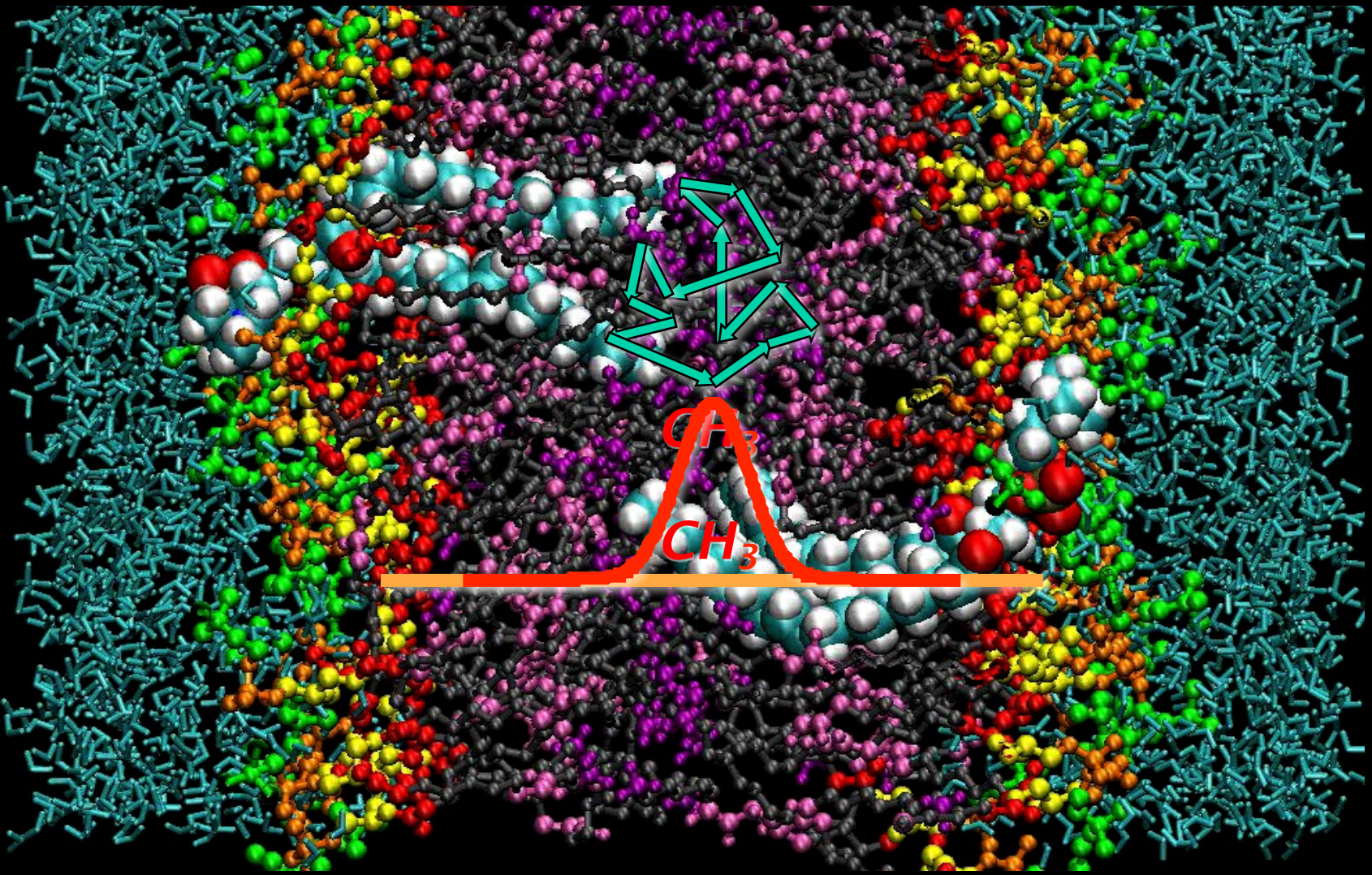
Giant vesicle with a diameter d=50 μm

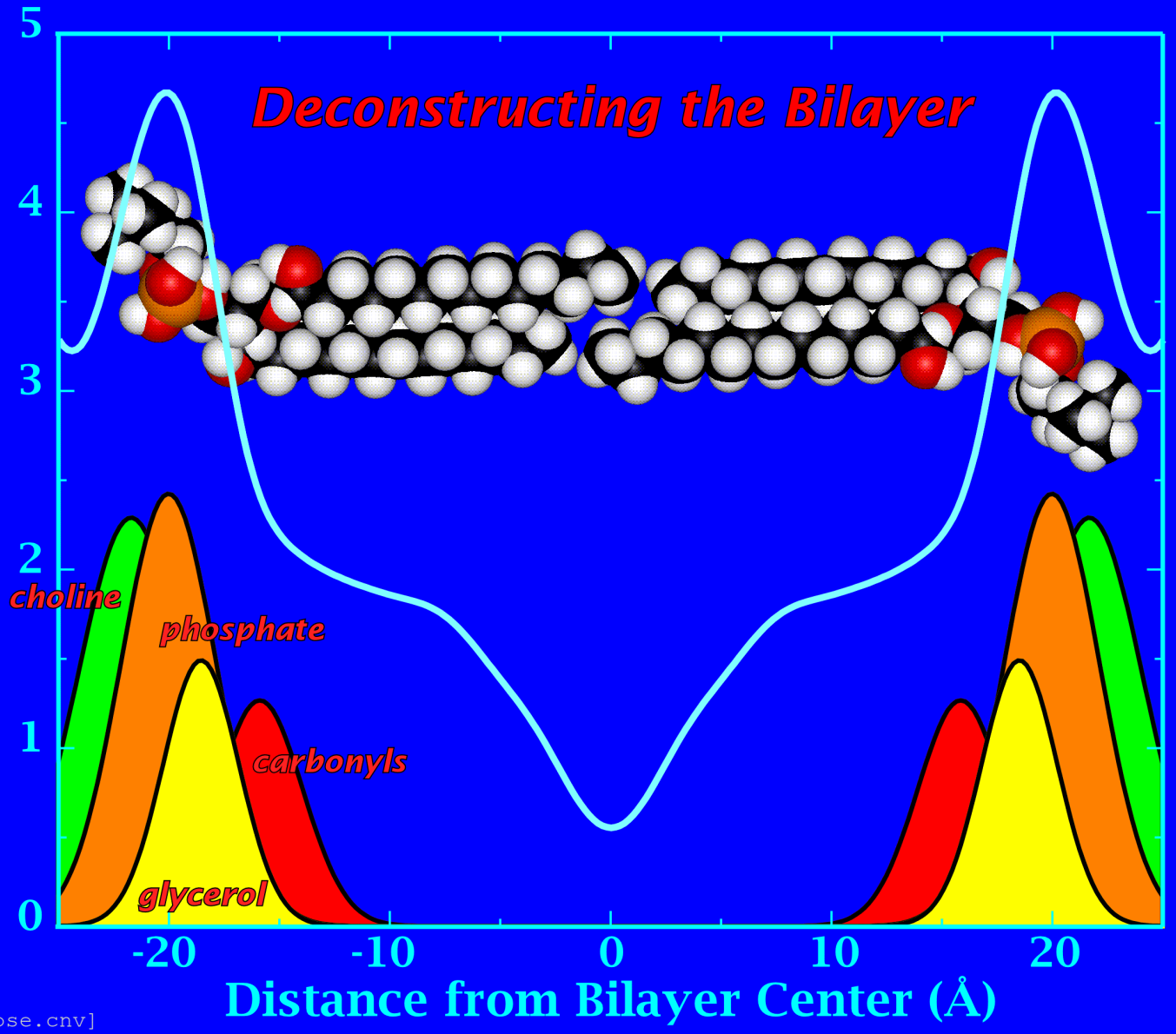
Lipid bilayers are excellent for cell membranes

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



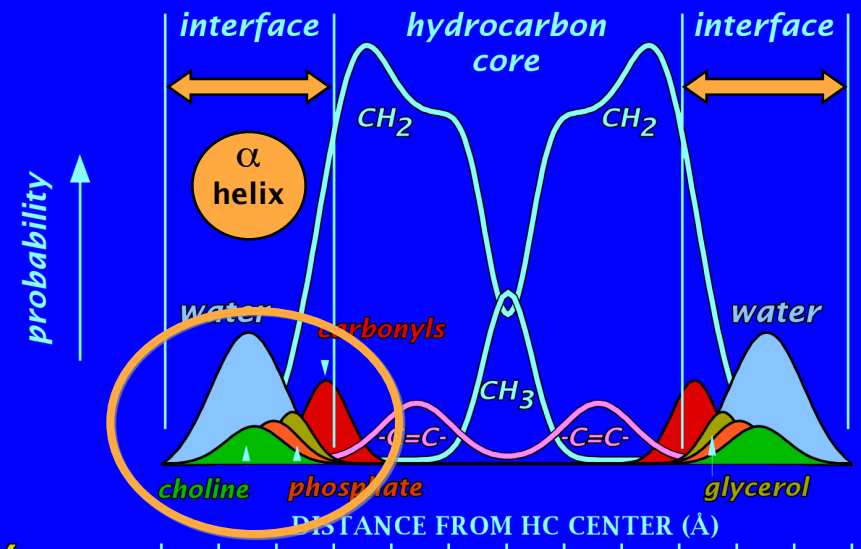
Defining "The Structure" of Fluid Bilayers





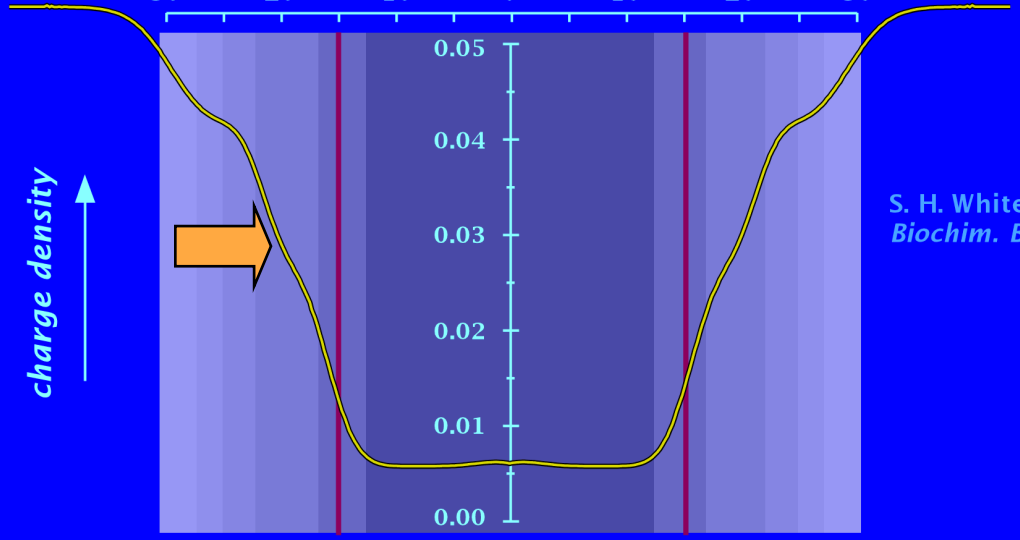
[bilayer_decompose.cnv]

DOPC Structure Summary



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

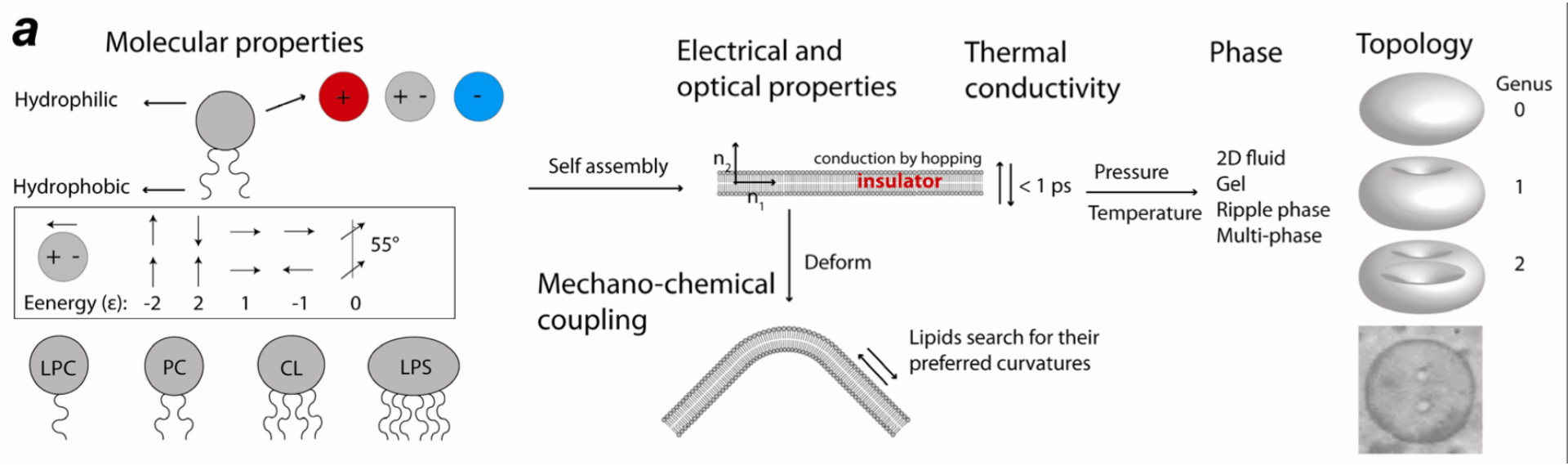
Bilayer Polarity Profile



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

[profiles_perturbed_10.cnv]

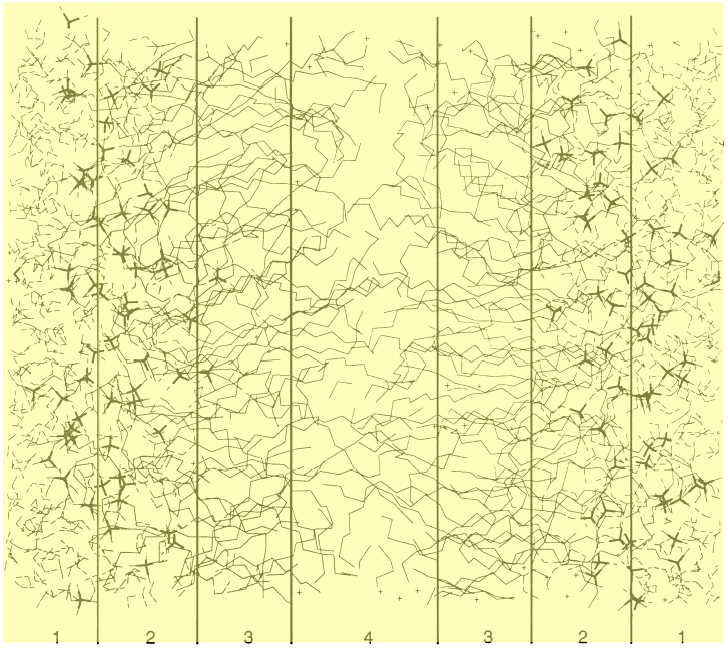
Physico-chemical properties of phospholipids



Physical properties of membranes

(based on Müller & Rudin "black lipid bilayer" model membrane)

	cell membrane	lipid bilayer
capacitance	~ 1 μF/cm^2	~ 1 μF/cm^2
resistance	~ 10^3 Ω cm^2	10^6–10^9 Ω cm^2
H_2O permeability	90–400 μm/s	17–104 μm/s
surface tension	0.3–1 dyne/cm	0.5–2 dyne/cm



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

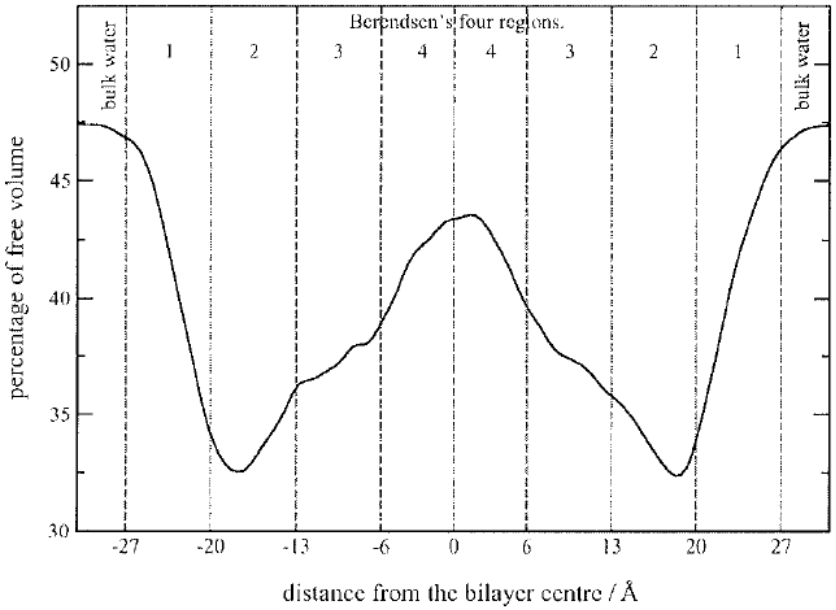
Region 3: soft polymer

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

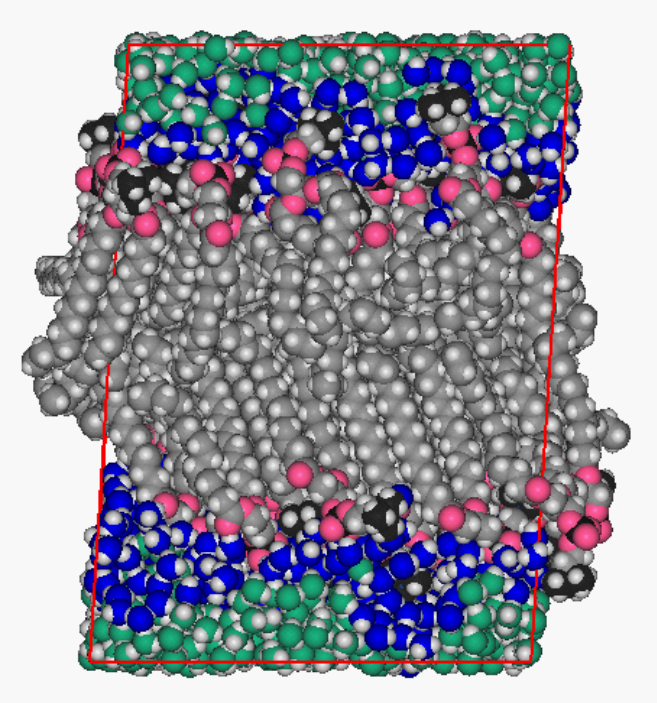
Region 4: decane

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

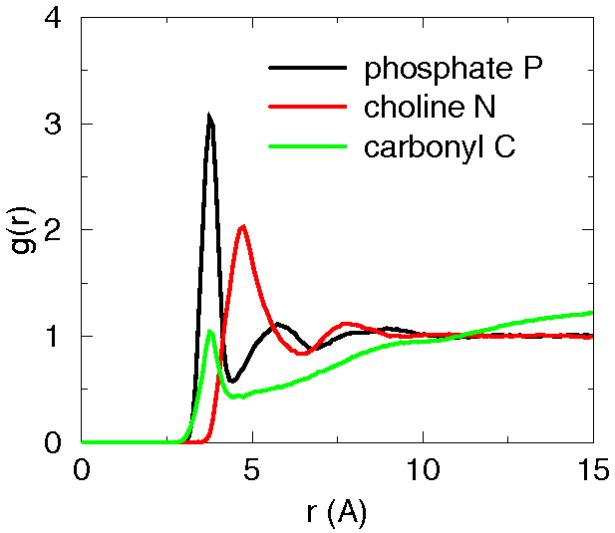
Free vilume distribution



"Bound" water

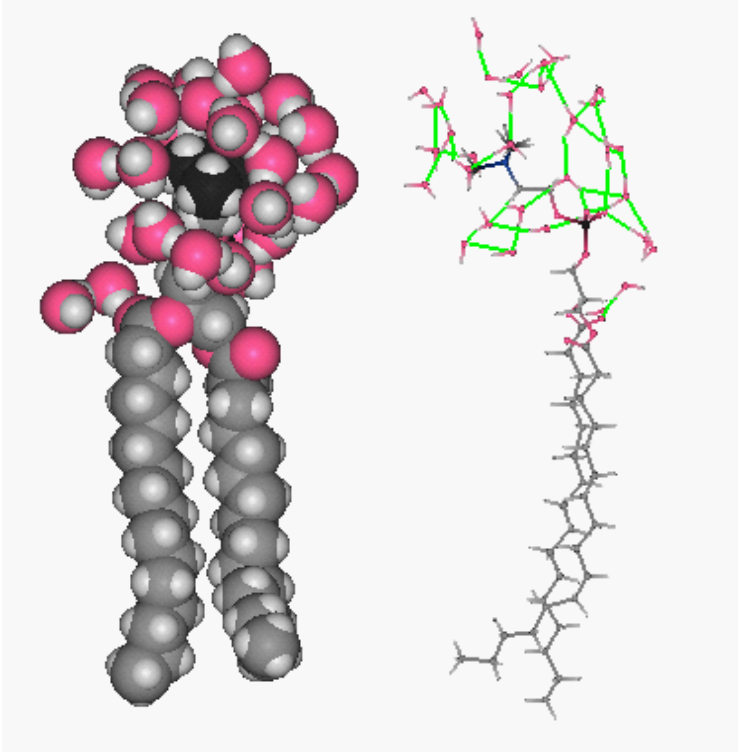


Radial distribution of water O



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

First solvation shell

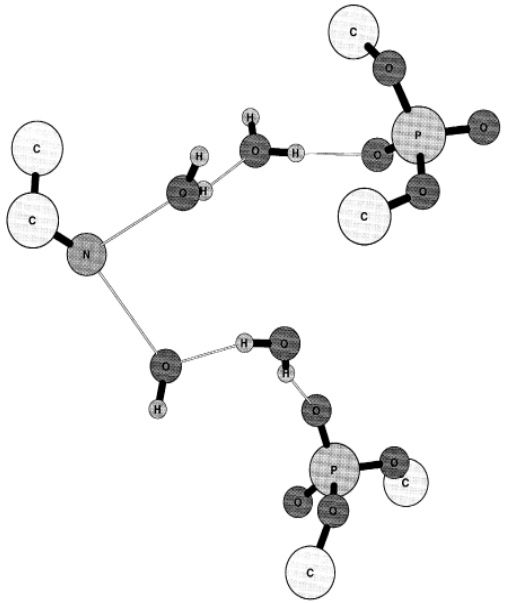


Diffusion constants of water

DPPC bilayer (nw = 28, 50˚C)

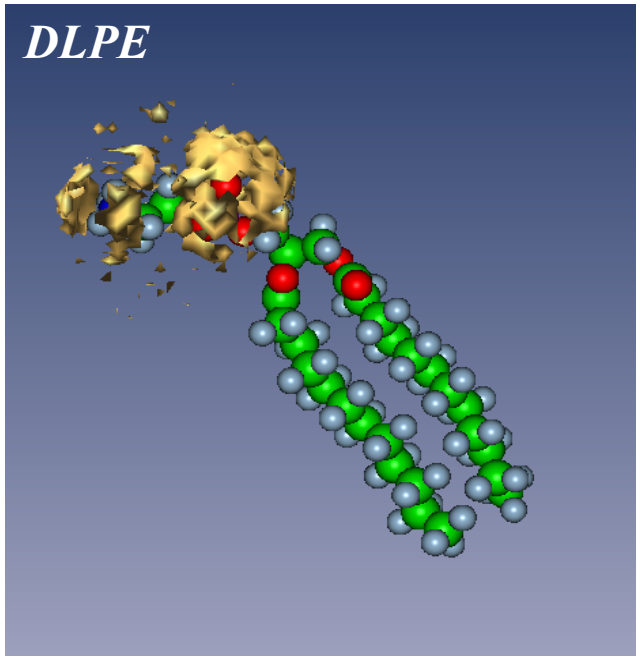
	D (10^{-5} cm^2/s)
bulk	6.2
N bound	4.1
P bound	3.0
CO bound	2.2

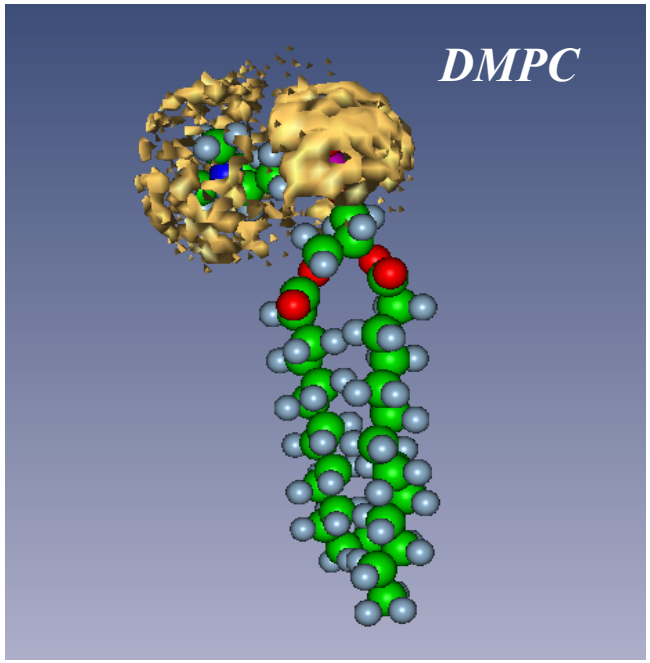
[Tobias, in "Hydration Processes in Biology," NATO ASI, ISO Press (1999)]

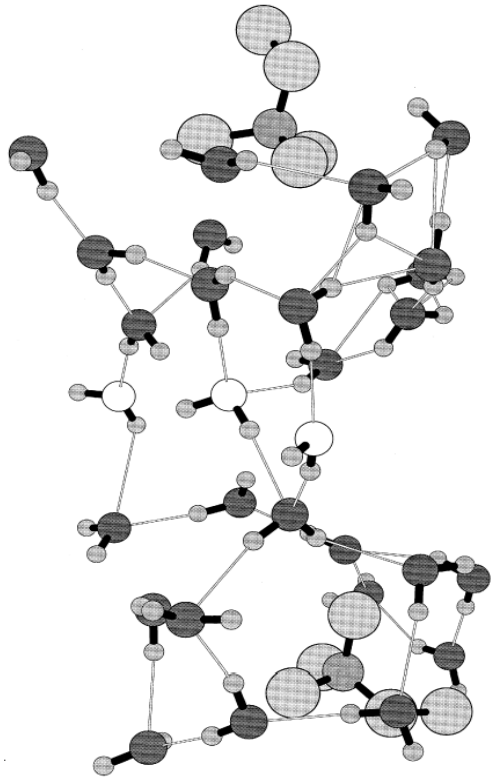


Water bridges between PE headgroups.

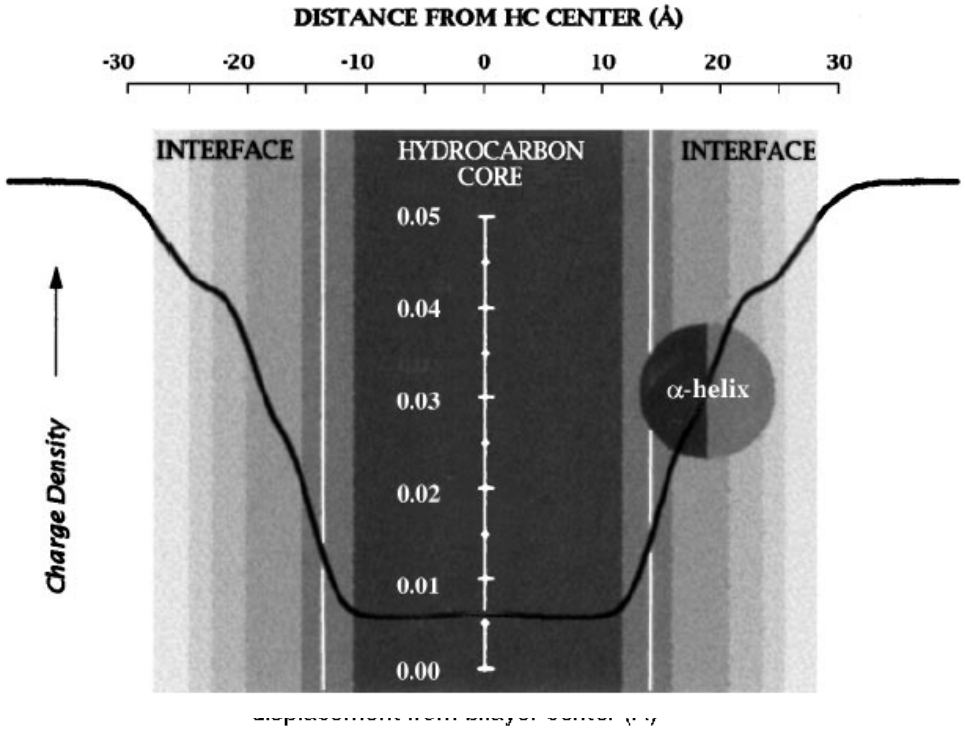
The clathrate cages around $N(CH_3)_3$ groups from two PC headgroups from opposing bilayers.

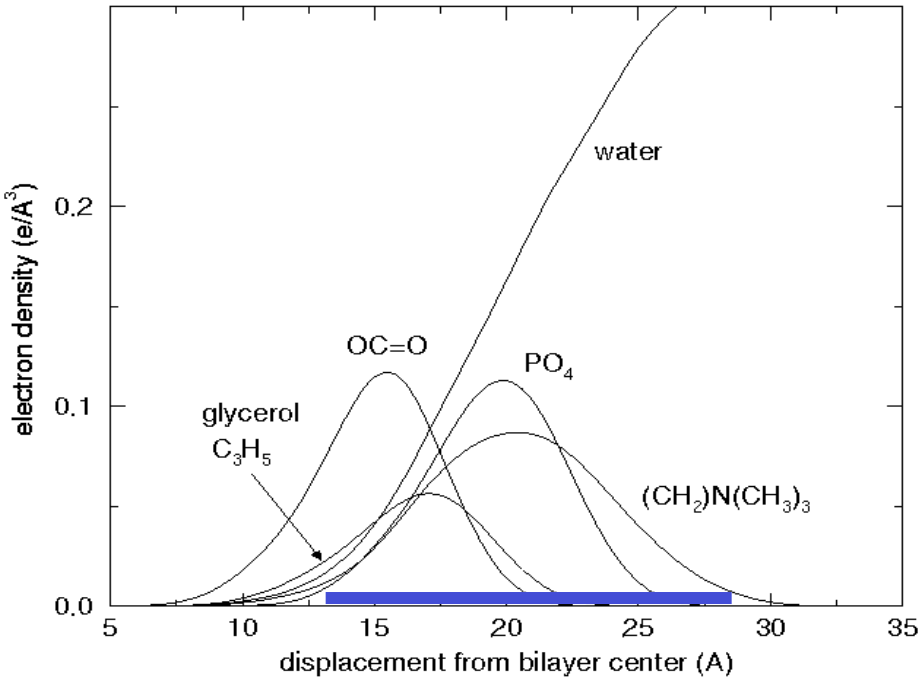






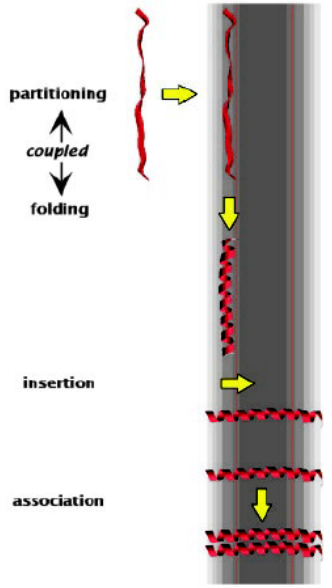
The membrane/water interface





Polarity profile

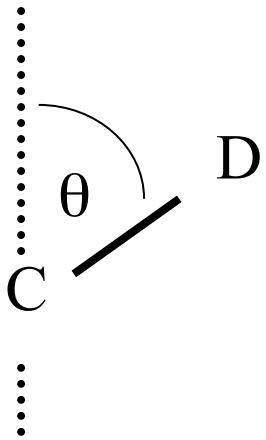
~ 40% of the membrane is interface

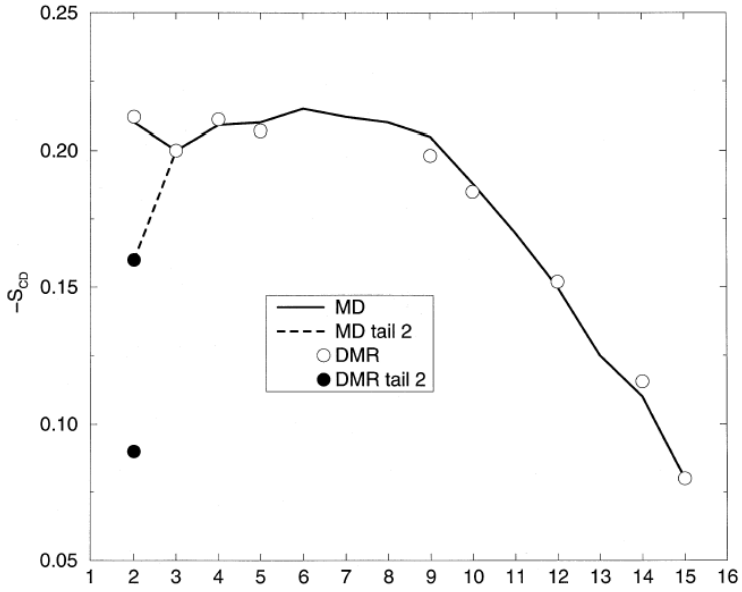


"Bilayer/water interface is a region of tumultuous chemical heterogeneity"

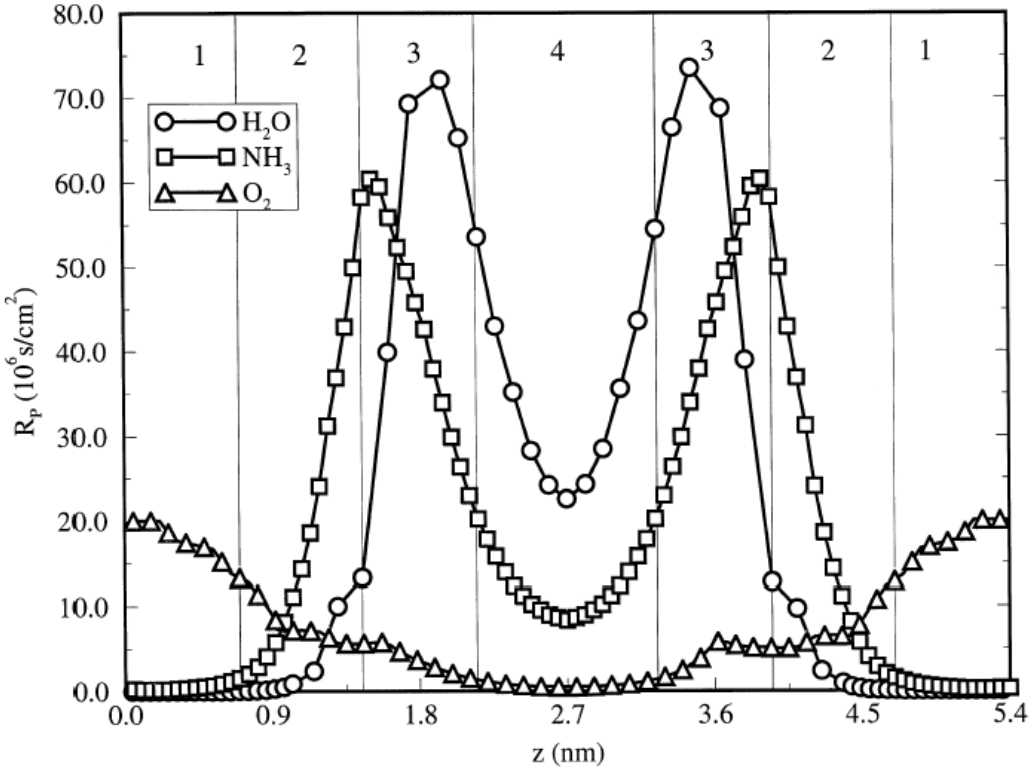
- The chain order parameters are at their plateau values.

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



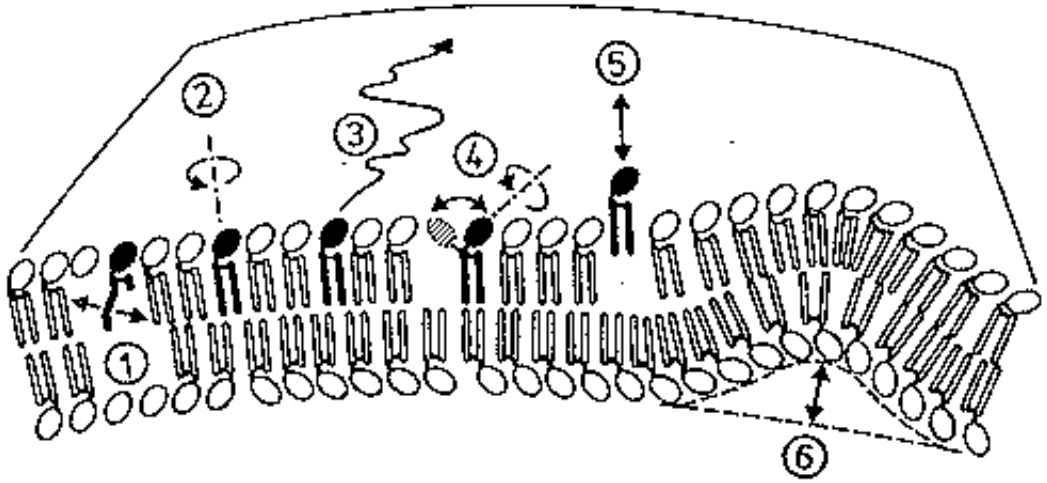


- The main barrier to permeation of small molecules.



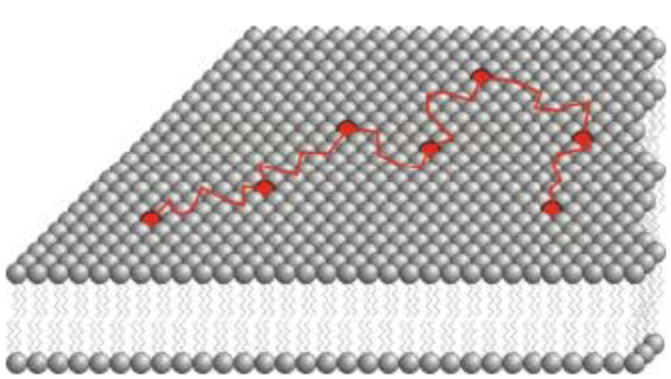
Motions in lipid membranes span a wide range of length and time scales.

Motion type	Diacyl phospholipid	Monoacyl fatty acid[a]
Trans-gauche isomerization	ps–ns	
Wobble	ns	
Axial rotation	ns	
Lateral diffusion	ns–ms	
Flip-flop	days	ms–s
Escape	days	s

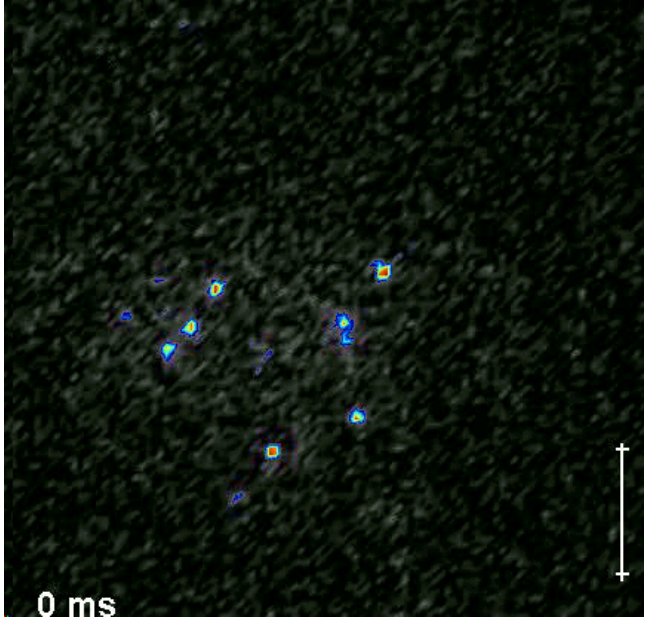


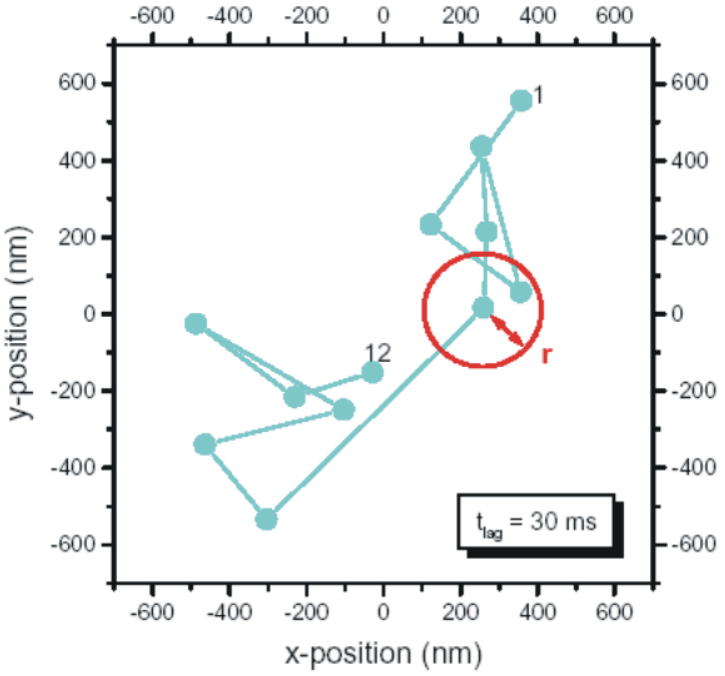
König & Sackmann, Curr. Opin. Coll. Int. Sci. 1, 78 (1996)

Single-molecule diffusion



thickness: 5 nm





Single dye-labeled lipids

Two dimensions diffusion coefficient

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

The average D for phospholipid = 1 x 10^{-8} cm^2/s

The average distance a free lipid molecule diffusing in 1 second;

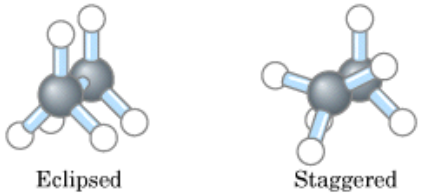
x = (4 x 10^{-8} cm^2/s x 1 s) ½ = 2 x 10^{-4} cm = 2 µm

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

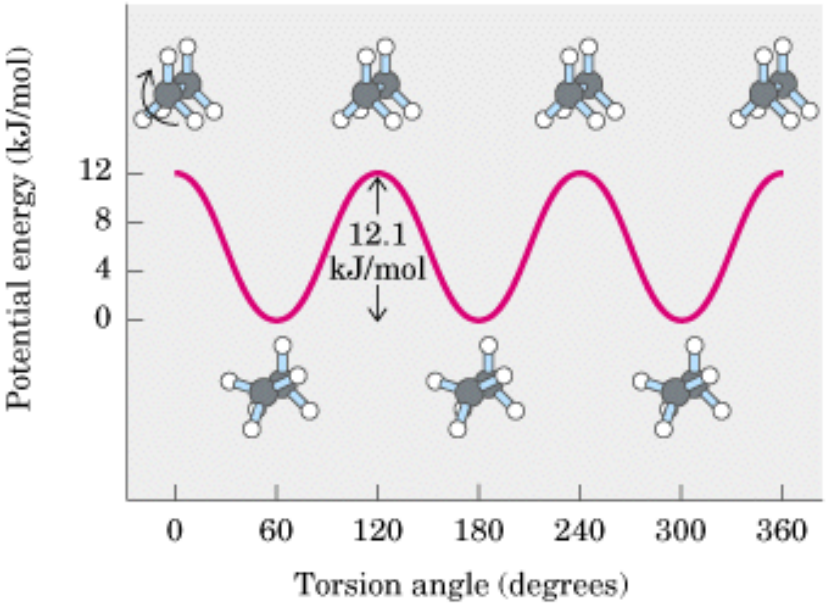
Lipid phase behavior

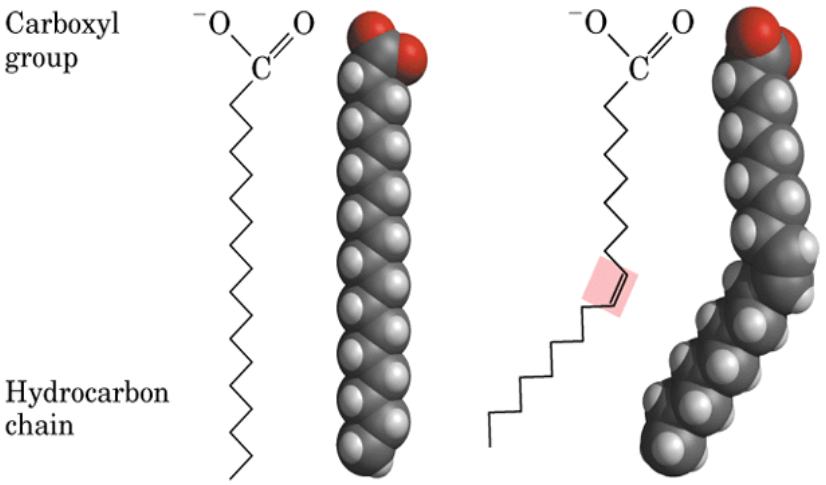
Lyotropic liquid crystals – the phases formed depend upon the nature of the molecules involved, the temperature and the type of solvent.

Thermotropic liquid crystals – the mesomorphic phase formed is characteristic of the temperature.



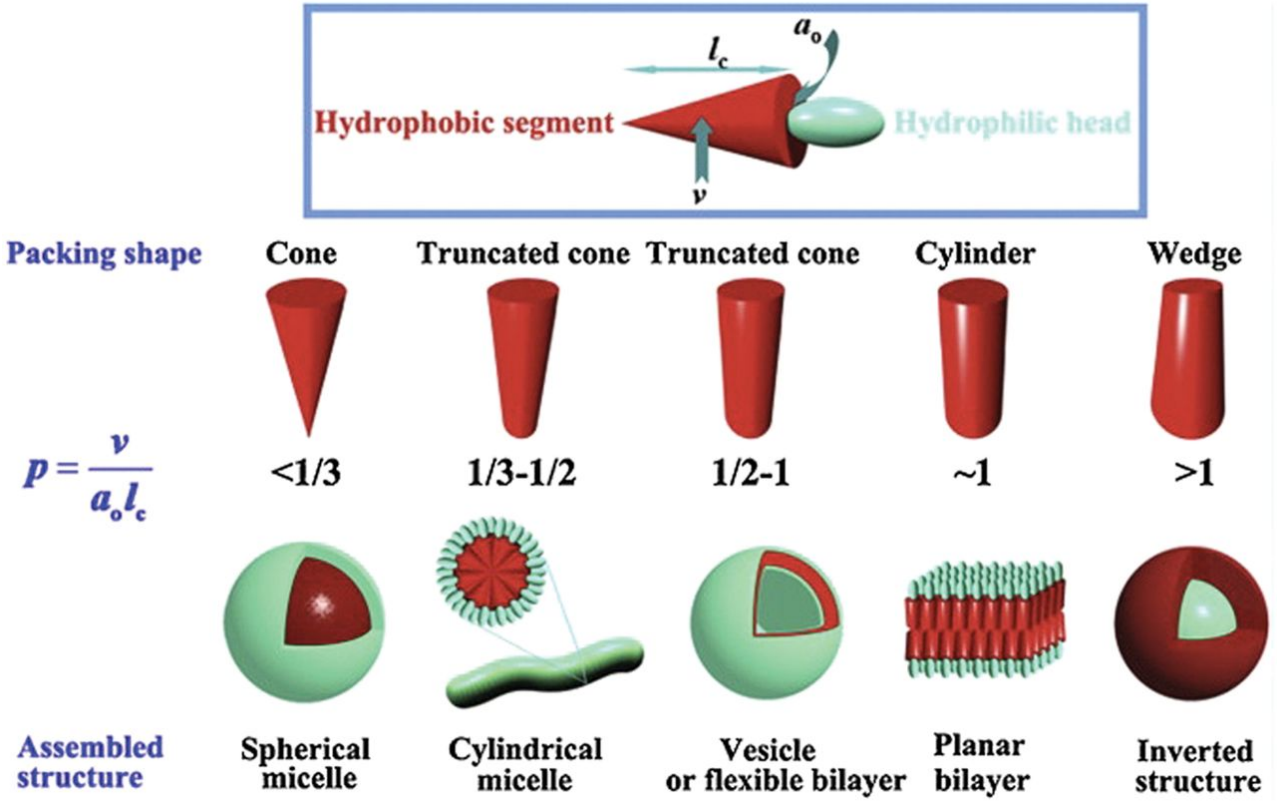
Acyl Chain Configuration





Graphic representation of individual surfactant geometry and the corresponding aggregate structure.

The molecular packing parameter, P.



$$P = \frac{v}{a_0 l_C}$$

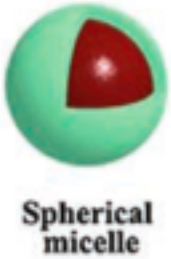
v - the volume occupied by the hydrophobic portion of the surfactant,
l_c - the critical chain length of the hydrophobic portion,
a_o - the representative surface area occupied by the surfactant.

Mosley G L et al. Journal of Laboratory Automation 2012;2211068212457161

Packing Parameter as a Geometric Constraint – Micelle

R - the radius of micelle,
N - the number of surfactant molecules in one micelle (i.e., the aggregation number).

For spherical micelles in an aqueous solution the surface area and spherical volume in terms of R and N is:



$$4\pi R^2 = a_0 N \qquad \frac{4}{3}\pi R^3 = \nu N$$

$$N = \frac{4\pi R^3}{3\nu} \qquad N = \frac{4\pi R^2}{a_0}$$

This results in individual surfactant molecules occupying space in the shape of shallow cones:

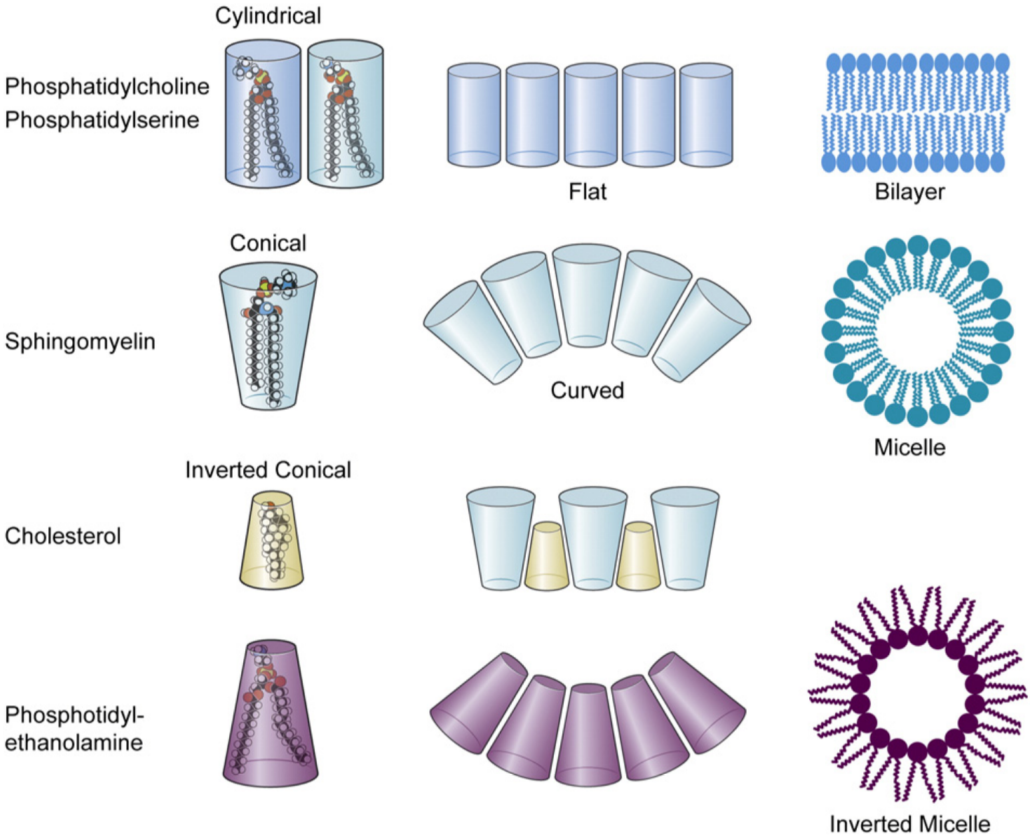
$$\frac{\nu}{a_0 R} = \frac{1}{3} \qquad \frac{\nu}{a_0 R} < \frac{1}{3}$$

The value of P can be used to predict the supermolecular self-assembled structures of a surfactant solution.

This molecular perspective of the geometric packing is related to parameters of the macroscopic aggregate structural geometry by

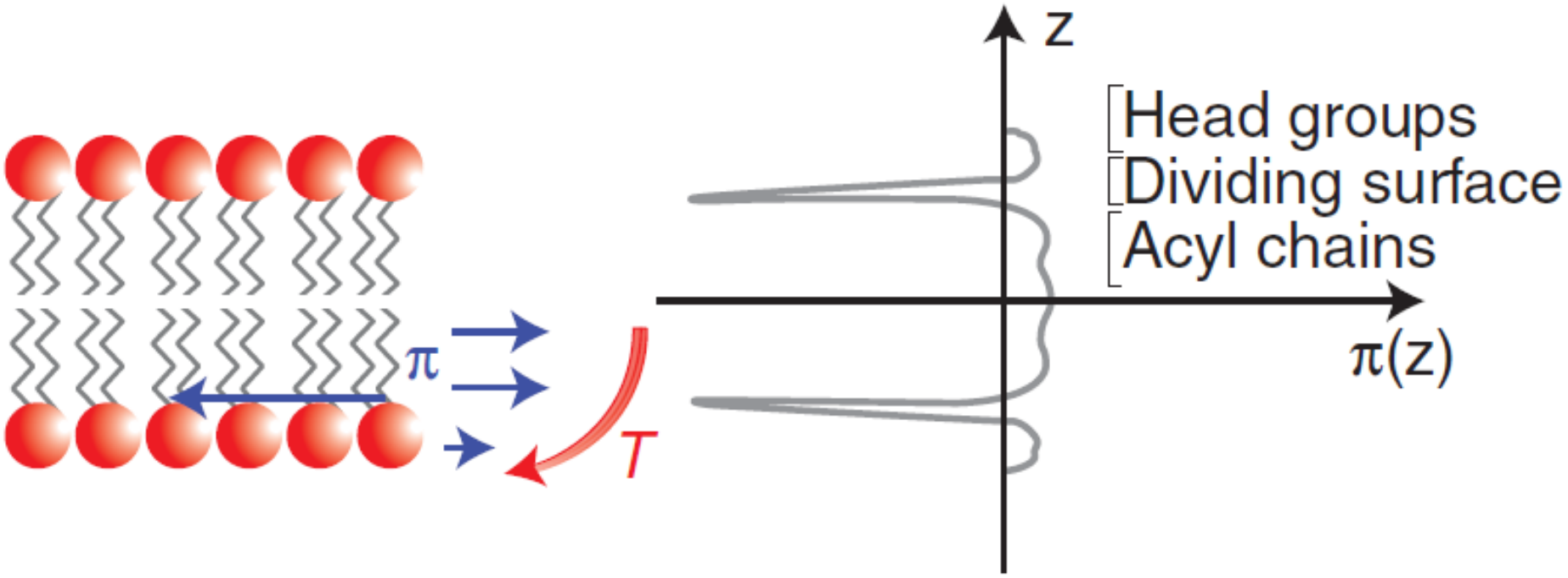
$$P = \frac{v}{a_0 l_C} = 1 + H l_C + \frac{K l_C^2}{3}$$

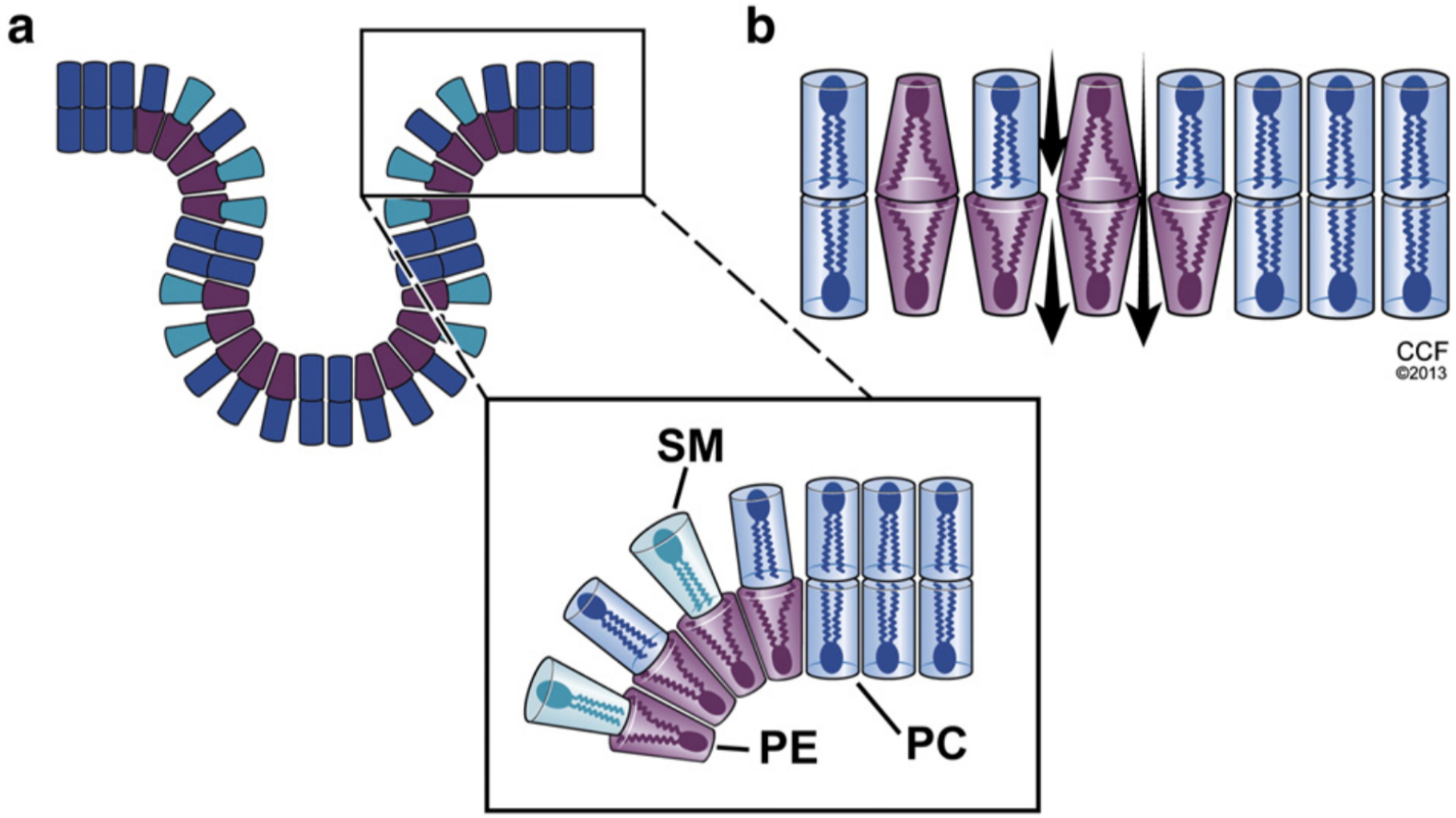
where H is the mean curvature and K is the Gaussian curvature.



The forces that act within the bilayer.

When the areas under the curves add to zero, the membrane is globally at rest.



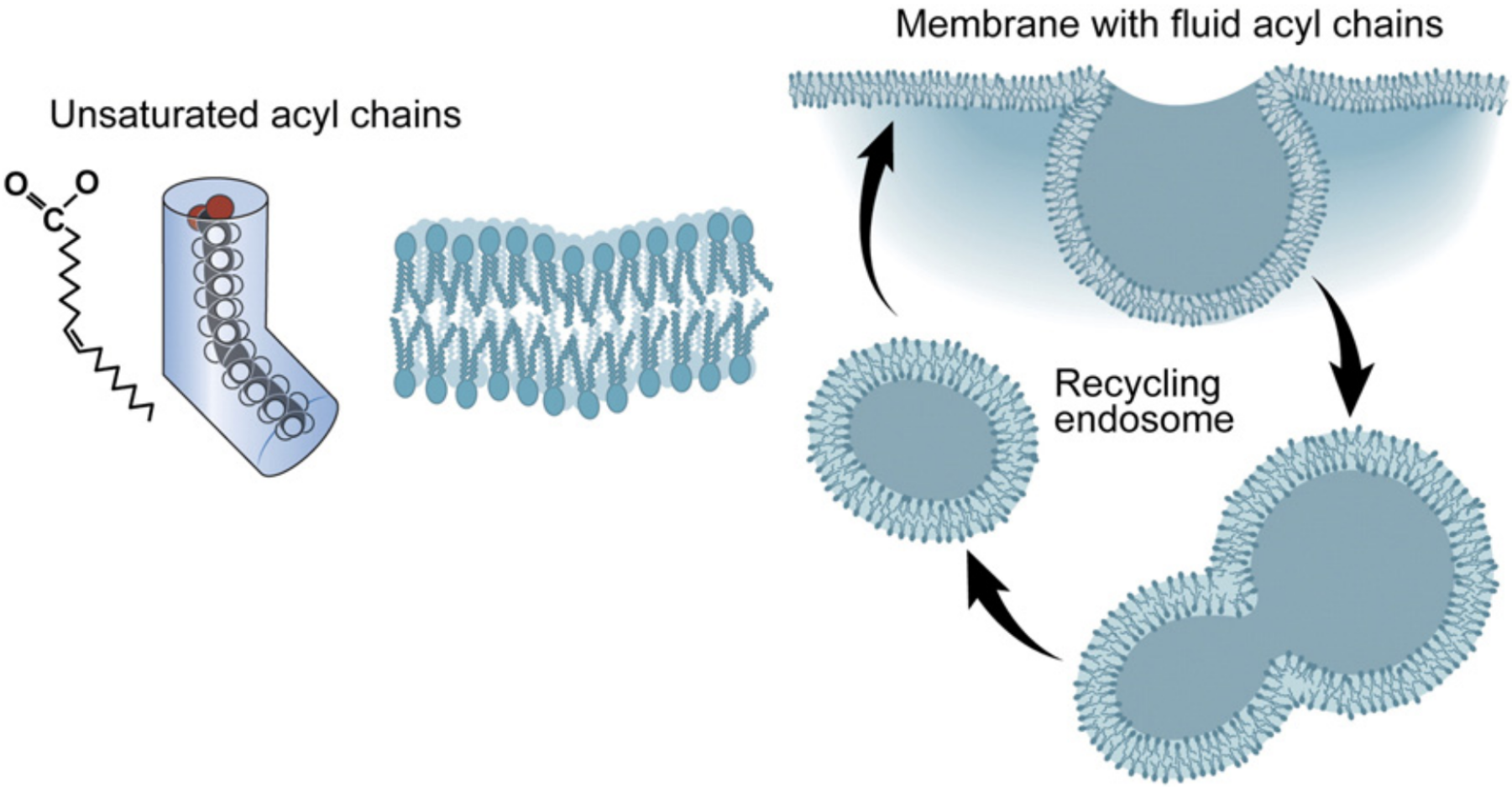


Effect of lipid composition on cell membrane, endocytic function, and transport.

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.

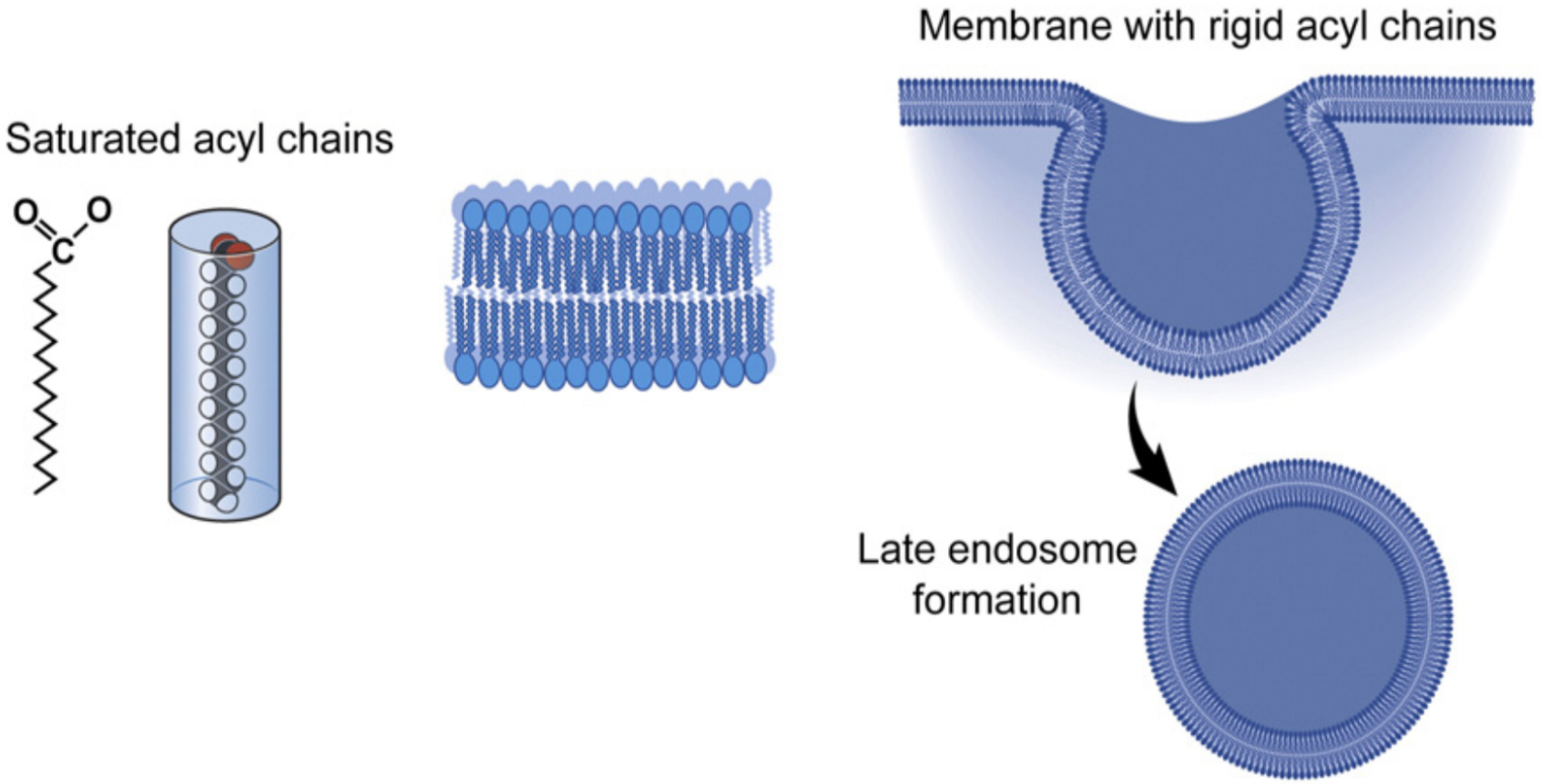
Effect of acyl chain of lipids on cell membrane barrier - endocytic function.

Phospholipid membranes with fluid acyl chains sort towards recycling vesicles

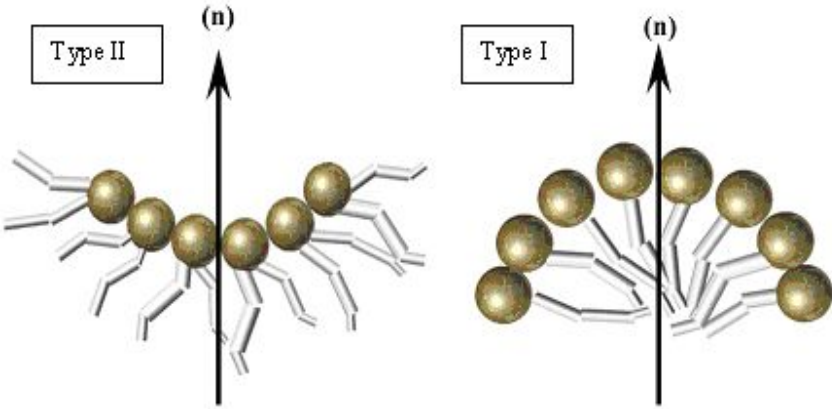


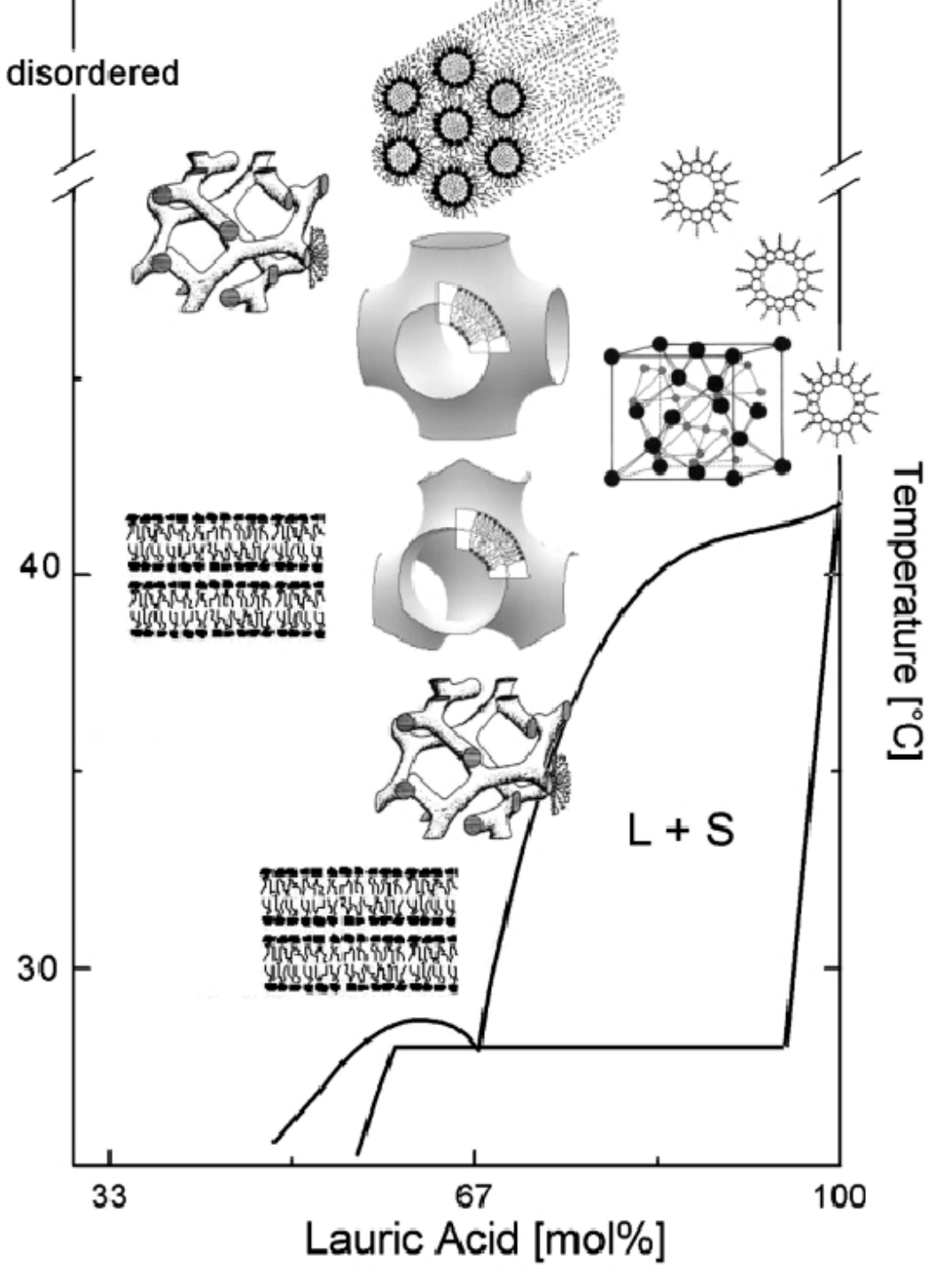
Effect of acyl chain of lipids on cell membrane barrier - endocytic function.

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



Lyotropic Phases

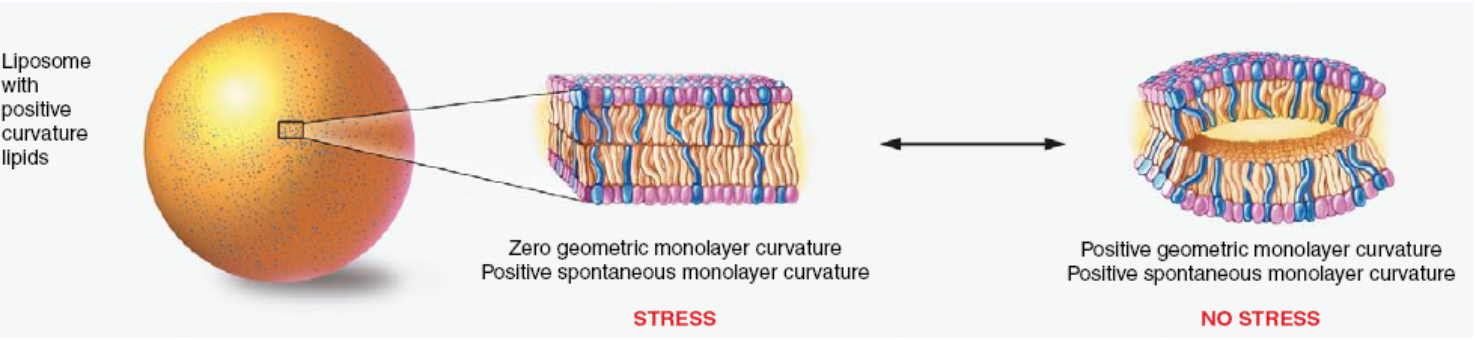


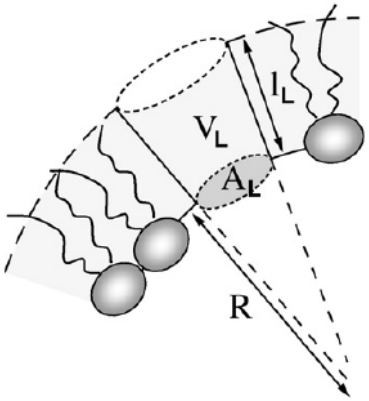


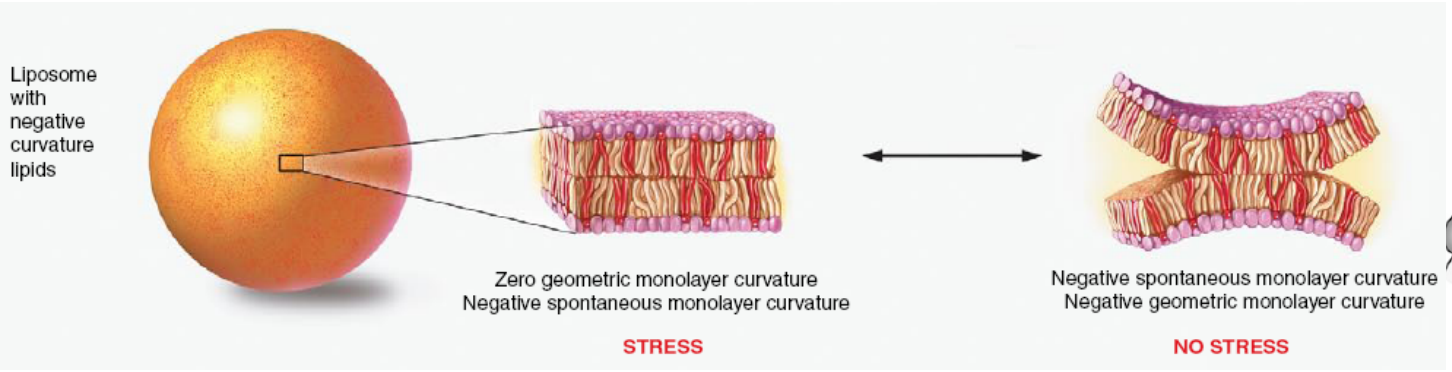
DLPC/LA pseudo-binary phase diagram.

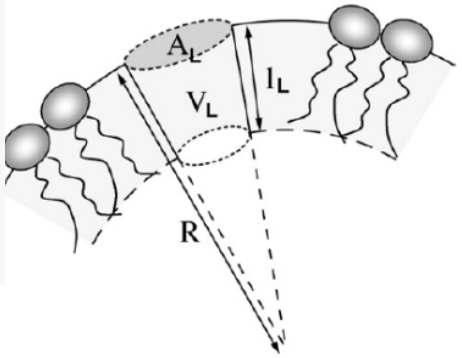
Spontaneous curvature of a lipid bilayer

When using lipid mixtures, it is possible to predict if liposomes will be formed by calculating the additive PP (i.e., the sum of the PP of each lipid component multiplied by its mole fraction). If the additive PP is in the range of 0.74–1.0, liposomes are likely to be formed

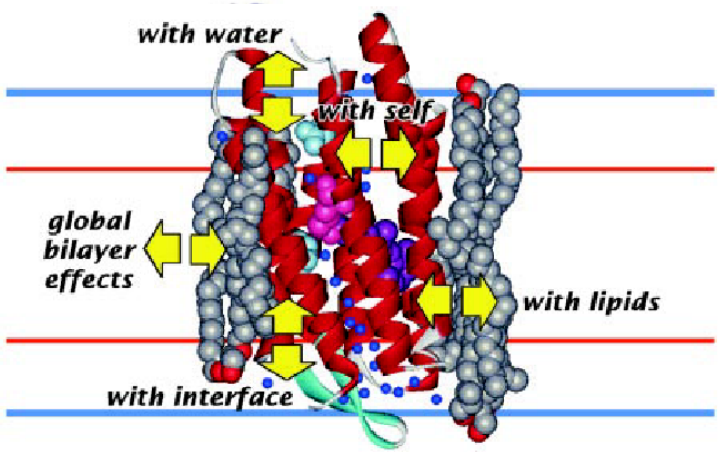


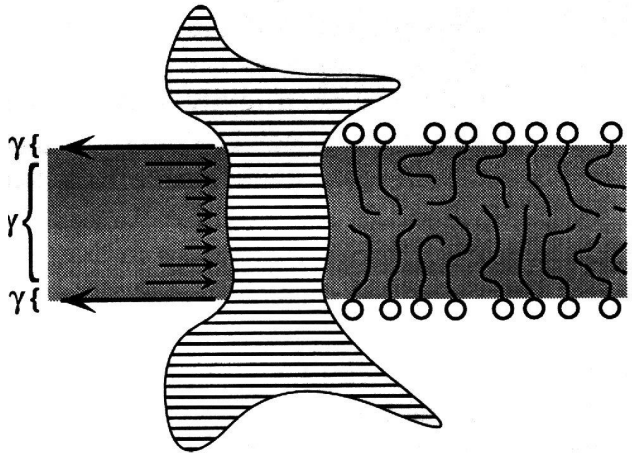


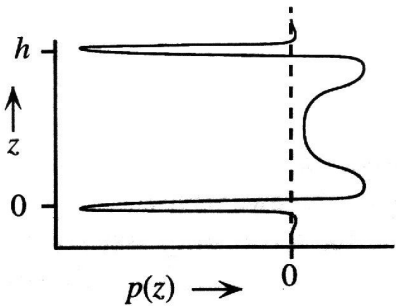




Lateral pressure in membranes
(a mechanism for modulation of protein function)



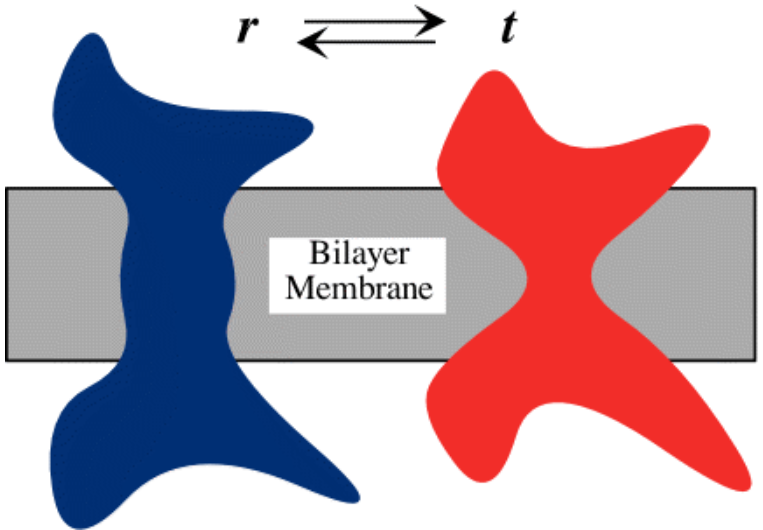


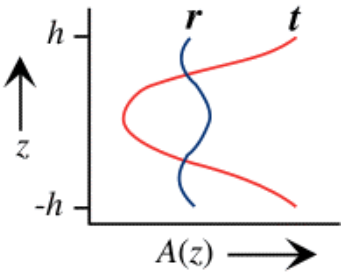


The membrane is self-assembled structure – there is no overall stress.

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

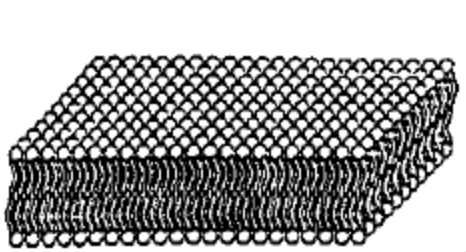
Many protein functions depend on a transition between conformational states.

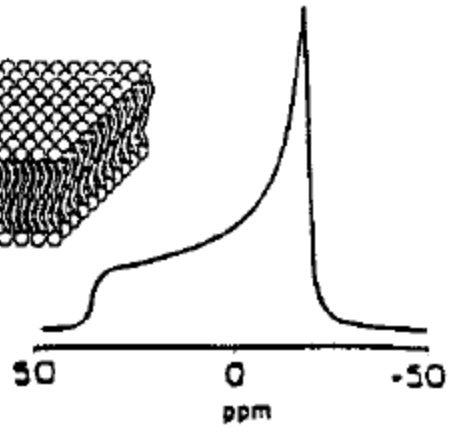




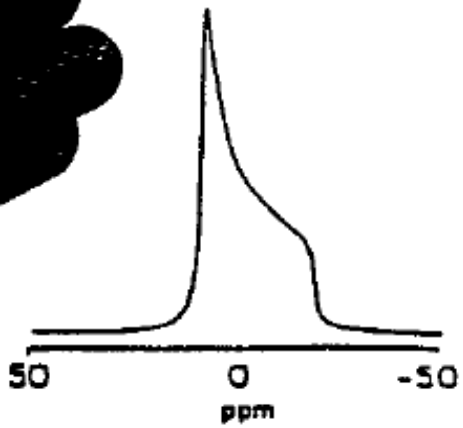
Lipid phases with corresponding ^{31}P NMR spectra

BILAYER

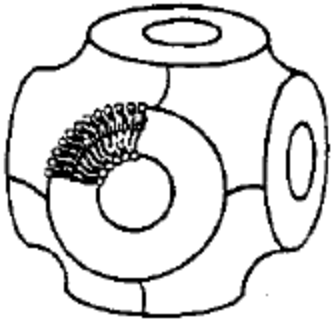


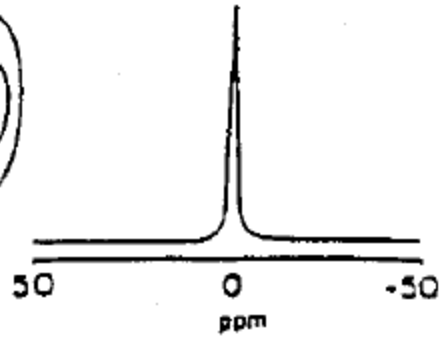


HEXAGONAL (HII)



CUBIC

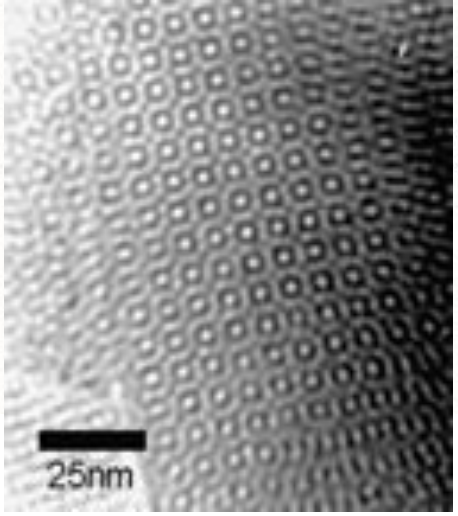


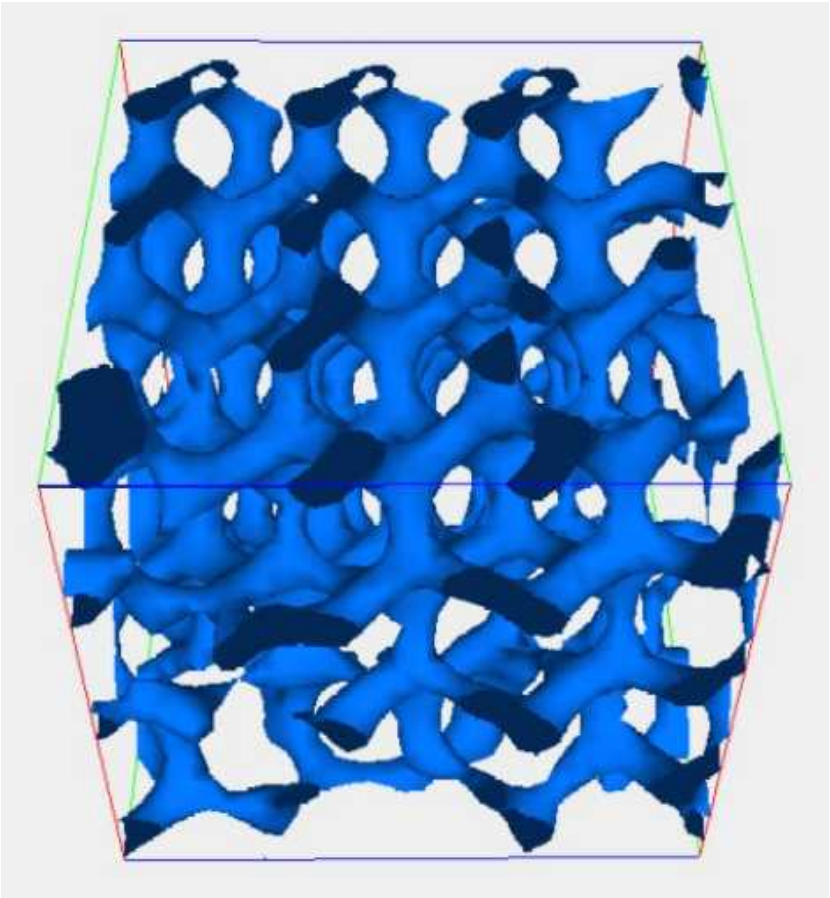


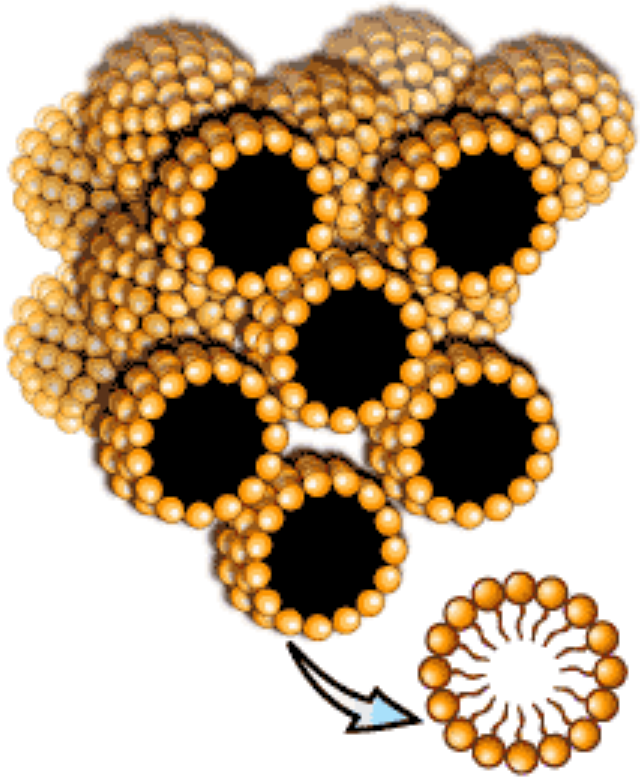
Cubic Phases

- These are the non-lamellar phases which have the least degree of curvature.

- The size of the unit cells ranges from 80Å up to 370Å.

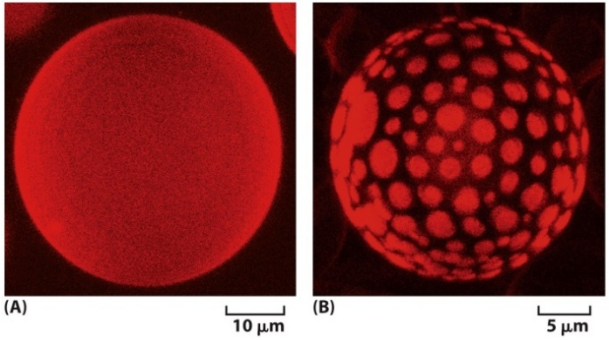


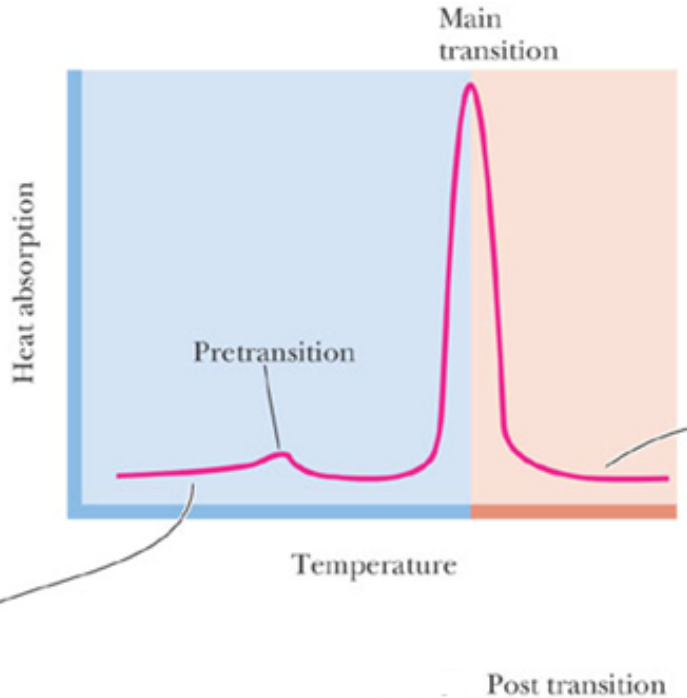


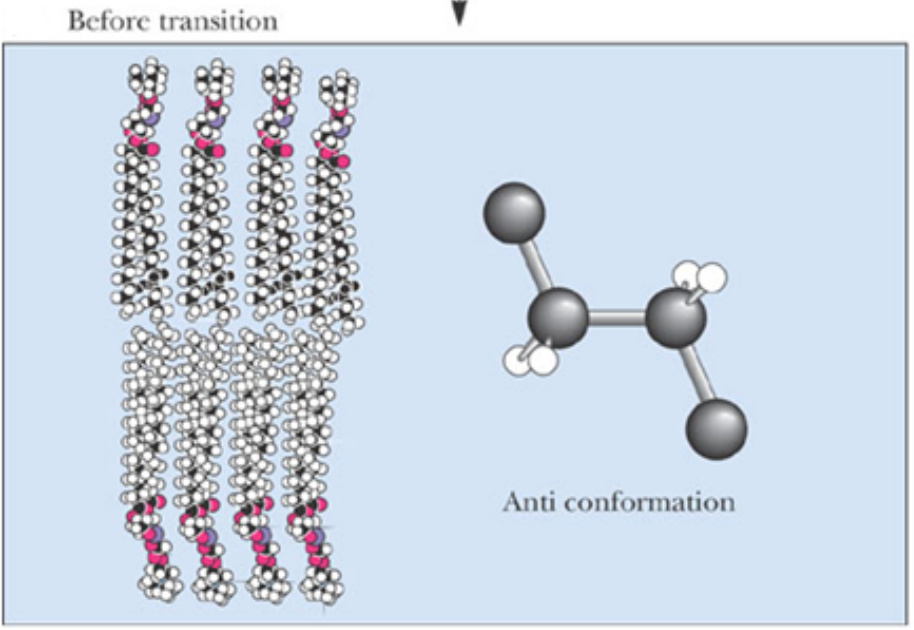


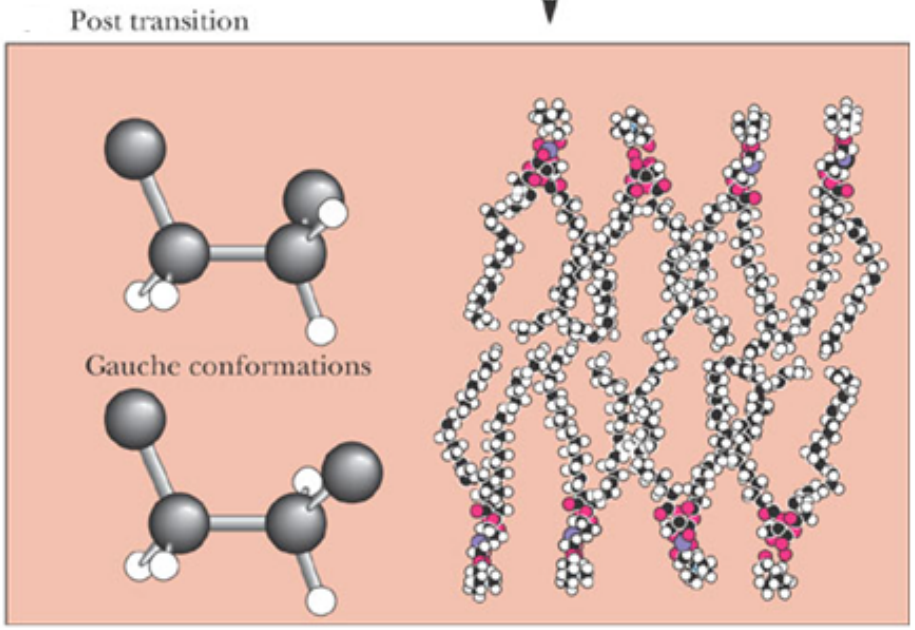
Example of a Cubic Phase

Thermotrophic phase transitions

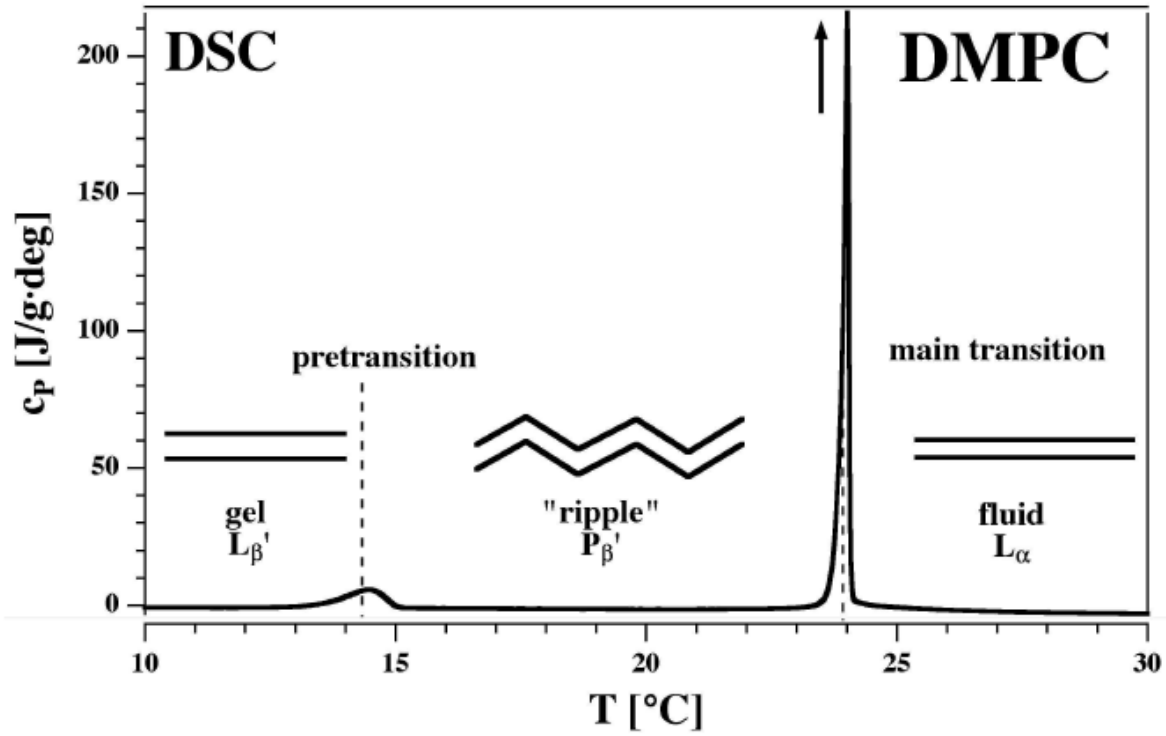


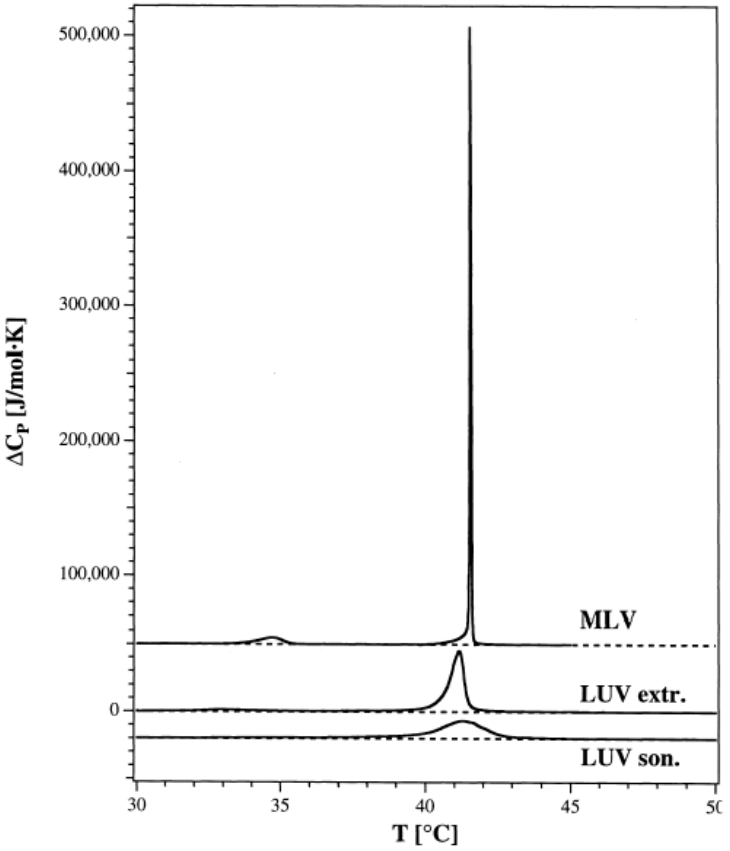






Phase transition



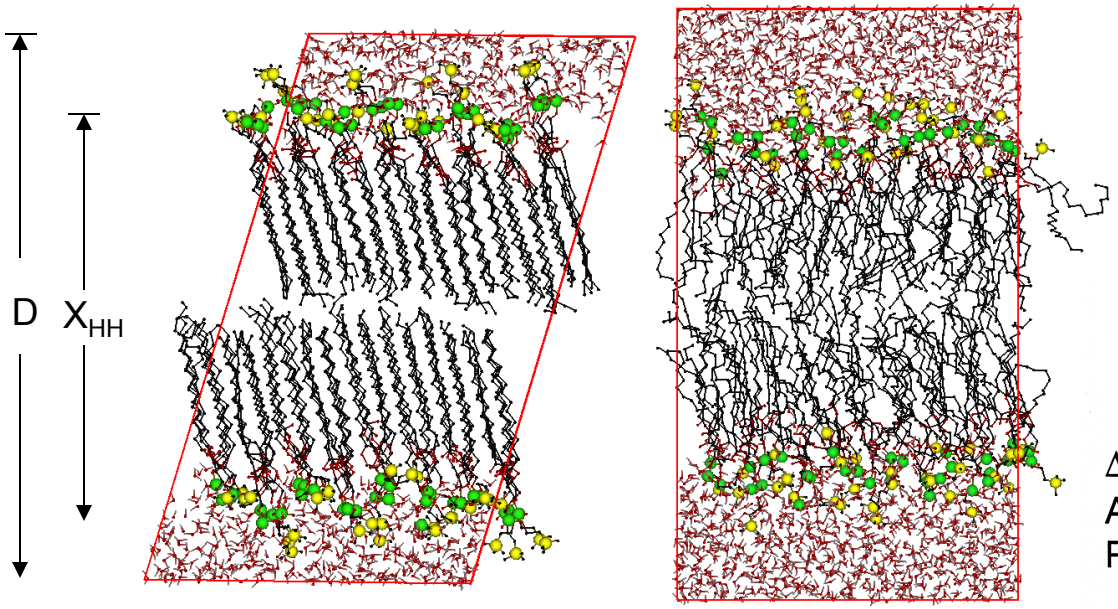


Experimental heat capacity profiles for DPPC; MLV, extruded LUV and sonicated SUV.

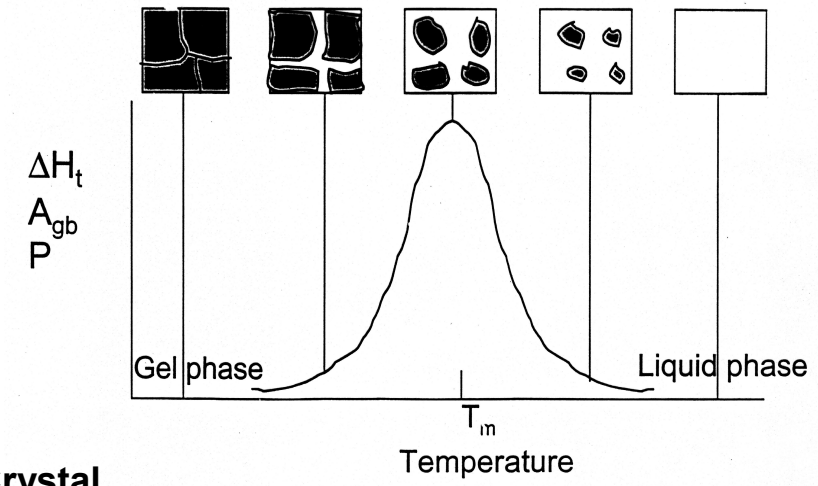
Thermotrophic phase transitions

Gel, 19˚C, n_w = 12

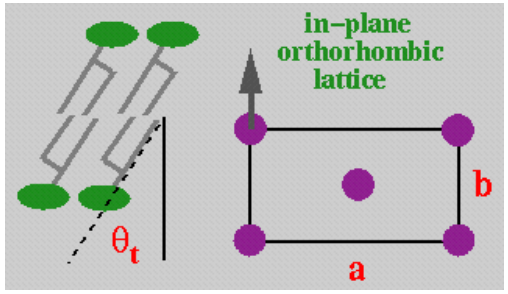
Liq. Cryst., 50˚C, n_w = 28



1. *Tu, Tobias, Blasie & Klein, Biophys. J. 70, 595 (1996)*
2. *Tristram-Nagle et al., Biophys. J. 64, 97 (1993)*
3. *Tu, Tobias & Klein, Biophys. J. 69, 2558 (1995)*
4. *Nagle et al., Biophys. J. 70, 1419 (1996)*



Quantity	Gel		Liquid Crystal	
	MD[1]	X-ray[2]	MD[3]	X-ray[4]
A (Å^2/lipid)	45.8	47.2	61.8	62.9
D (Å)	65.2	63.4	67.3	67.2
X_{HH} (Å)	45.6	45.0	37.2	36.4
θ (˚)	33.6	32.0		
a (Å)	8.6	8.5		
b (Å)	5.5	5.6		



Fatty acid composition of E. coli cells cultured at different tempertures

	Percentage of total fatty acids*			
	10 °C	*20 °C*	*30 °C*	*40 °C*
Myristic acid (14:0)	4	4	4	8
Palmitic acid (16:0)	18	25	29	48
Palmitoleic acid (16:1)	26	24	23	9
Oleic acid (18:1)	38	34	30	12
Hydroxymyristic acid	13	10	10	8
Ratio of unsaturated to saturated†	2.9	2.0	1.6	0.38

Source: Data from Marr, A.G. & Ingraham, J.L. (1962) Effect of temperature on the composition of fatty acids in *Escherichia coli. J. Bacteriol.* **84,** 1260.

*The exact fatty acid composition depends not only on growth temperature but on growth stage and growth medium composition.

†Ratios calculated as the total percentage of 16:1 plus 18:1 divided by the total percentage of 14:0 plus 16:0. Hydroxymyristic acid was omitted from this calculation.

The effect of lipid structure on phase behavior

- For a representative lipid such as phosphatidylcholine (PC), there is an increase in T_c by ~ 20 ^oC and ΔH by ~2-3 kcal/mol as each two carbon unit is added.

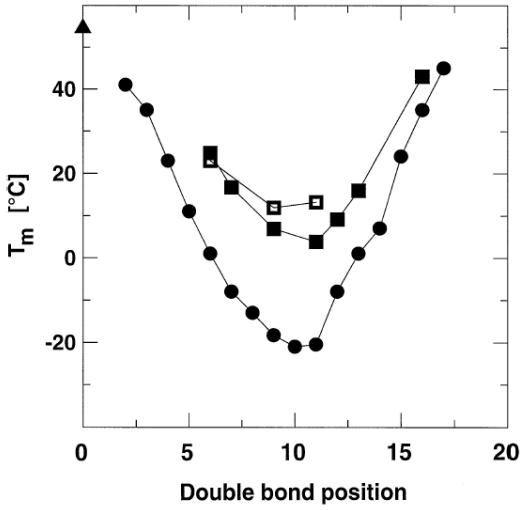
- Inclusion of a cis double bond at the C-9 position results in a large decrease in T_c.

- T_c and ΔH are sensitive to the head group constituent. For example, PE usually has T_c 20 ^oC higher than the corresponding PC species.

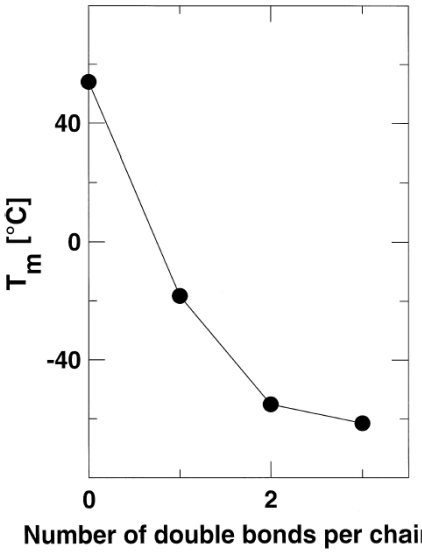
- Sensitive to the presence of solutes (cations, peptides, etc.).

Phase Transition Temperatures for Phospholipids in Water

Phospholipid	Transition Temperature (T_m), °C
Dipalmitoyl phosphatidic acid (Di 16:0 PA)	67
Dipalmitoyl phosphatidylethanolamine (Di 16:0 PE)	63.8
Dipalmitoyl phosphatidylcholine (Di 16:0 PC)	41.4
Dipalmitoyl phosphatidylglycerol (Di 16:0 PG)	41.0
Dilauroyl phosphatidylcholine (Di 14:0 PC)	23.6
Distearoyl phosphatidylcholine (Di 18:0 PC)	58
Dioleoyl phosphatidylcholine (Di 18:1 PC)	−22
1-Stearoyl-2-oleoyl-phosphatidylcholine (1-18:0, 2-18:1 PC)	3
Egg phosphatidylcholine (Egg PC)	−15

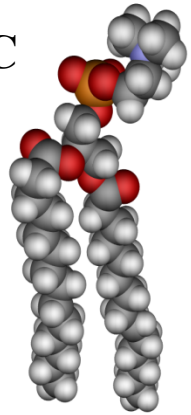


circle - 18:1cX/18:1cX PC
square - 18:0/18:1cX PC
frame - 18:1tX/18:1tX PC



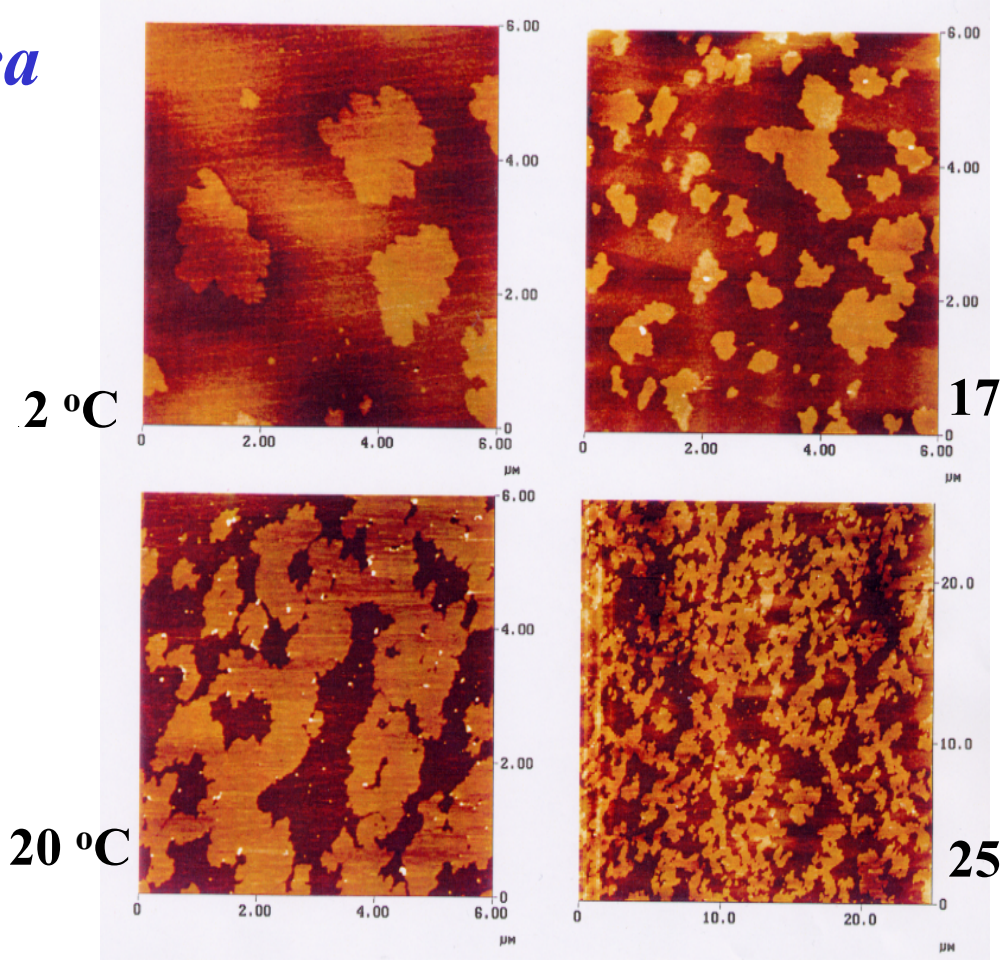
DMPC monolayer on mica

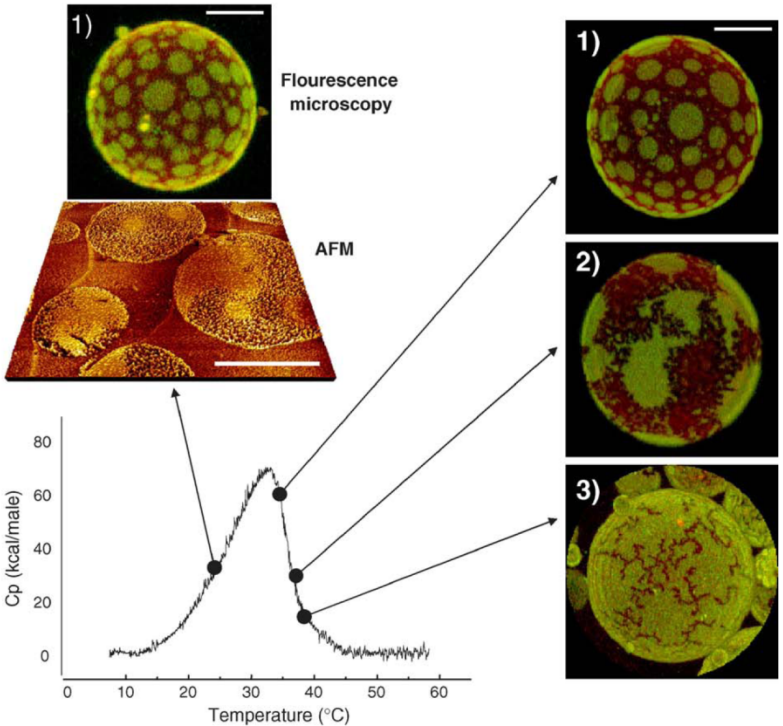
DMPC



$T_p = 15\ ^oC$

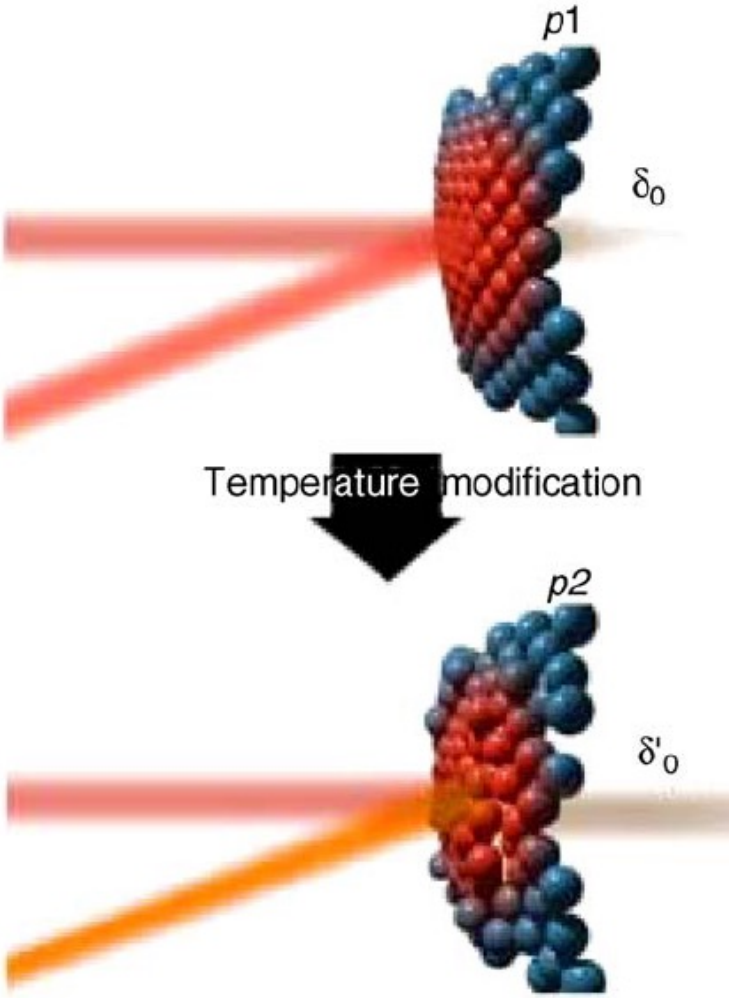
$T_m = 24\ ^oC$

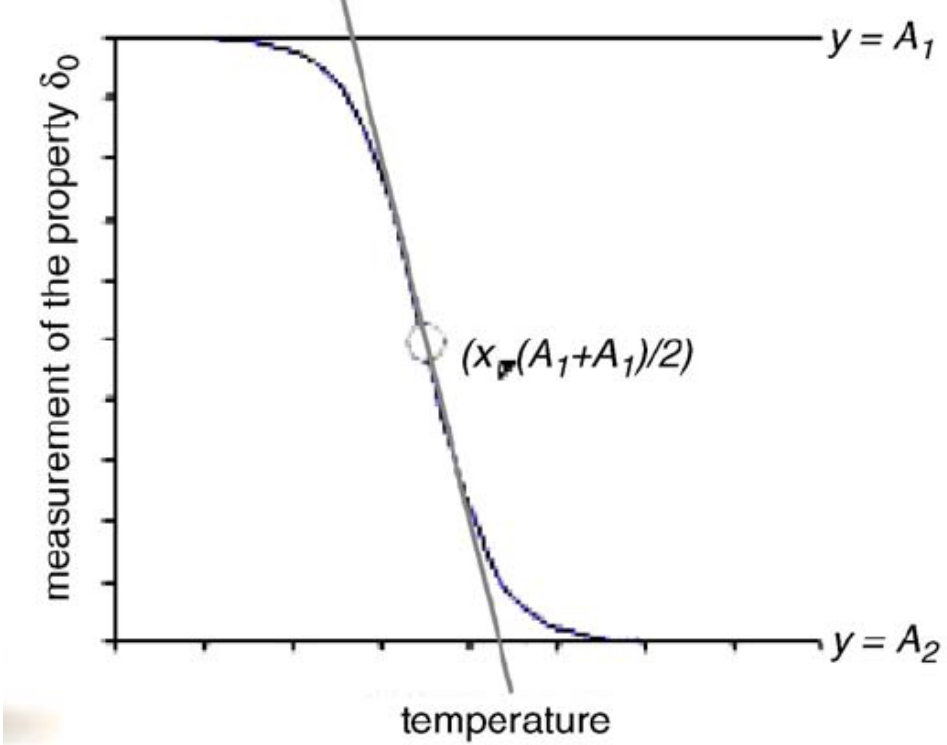




Native pulmonary surfactant membranes obtained using differential scaning calorimentry, DiIC18/ Bodipy-PC labeled GUV and AFM images.

Determination of phase transition temperatures of lipids by light scattering.





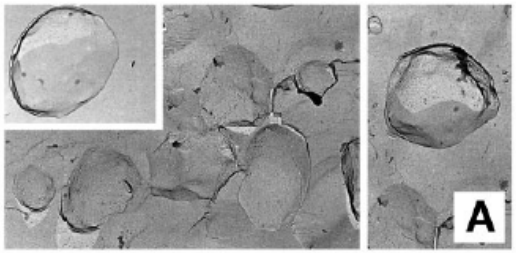
Boltzmann regression curves

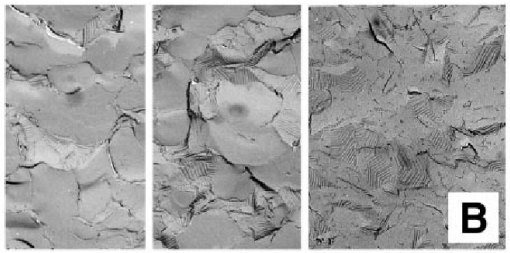
$$y = \frac{A_1 - A_2}{1 + e^{(x - x_0)/\Delta x}} + A_2$$

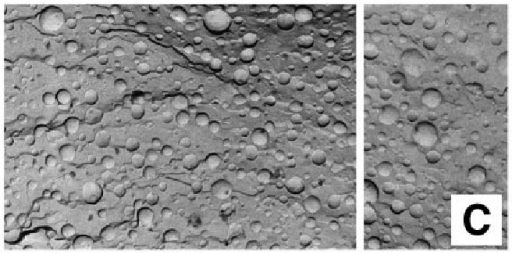
with A_1, the initial y value (initial count rate of lipids in Phase 1), A_2, the final y value (lipids in Phase 2), x_0, the centre of the distribution (y value at x_0 being half way between the two limiting values A_1 and A_2: $y(x_0) = (A_1 + A_2)/2$) and Δx, the width of the slope.

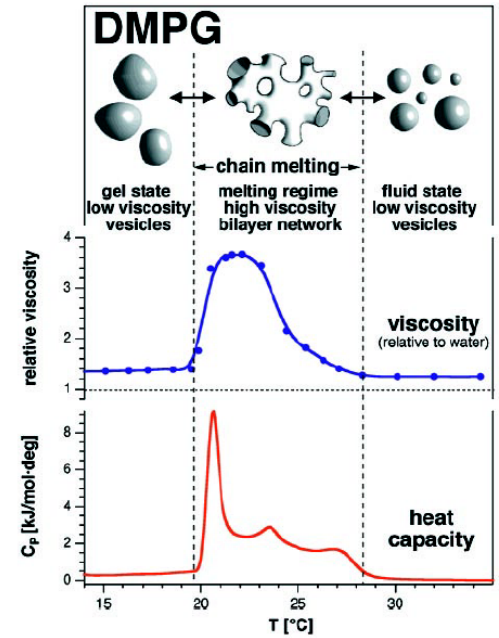
DMPG dispersion

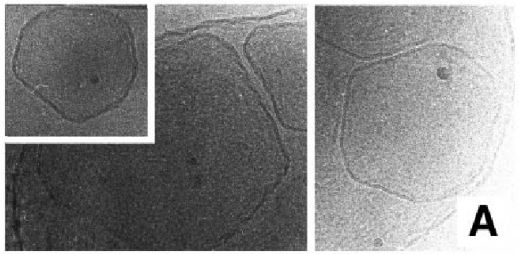
Freeze fracture electron micrographs

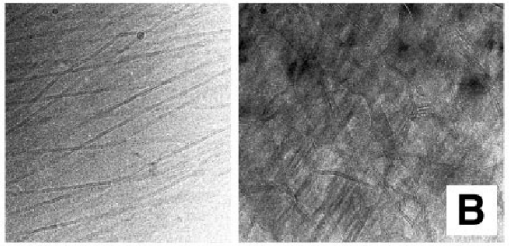


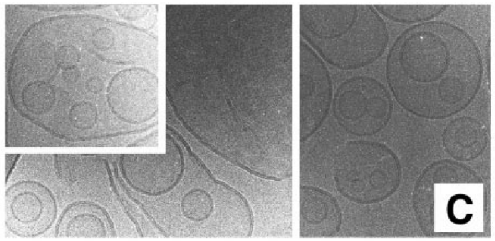






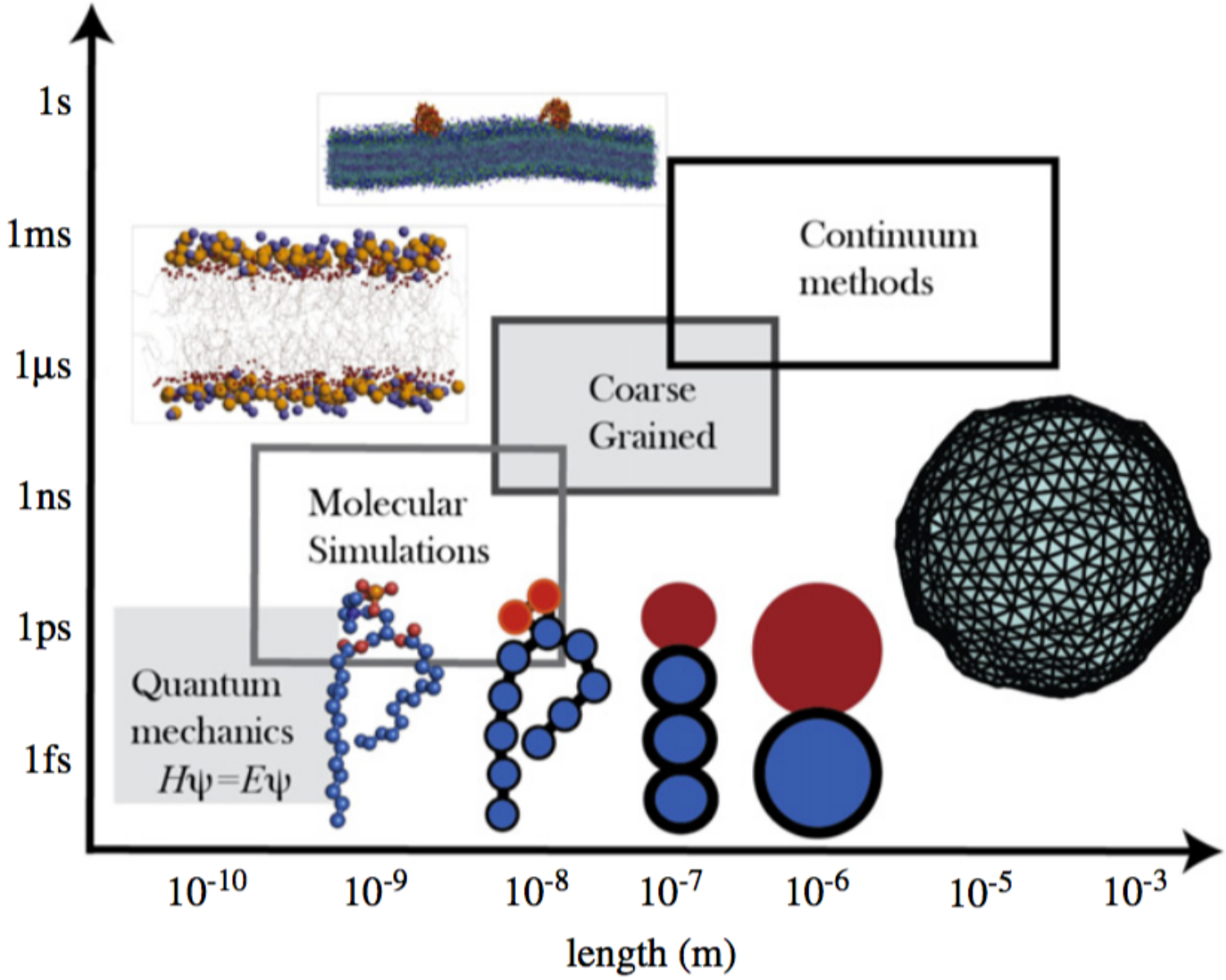




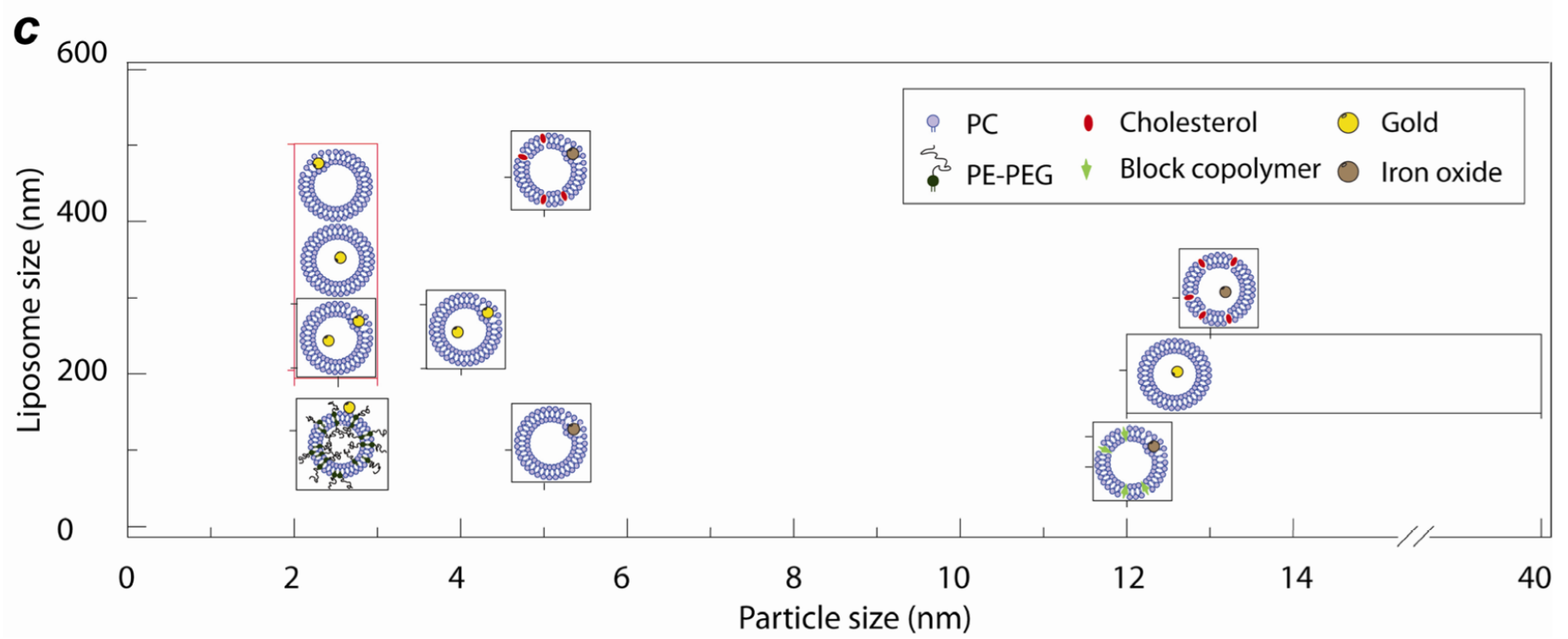


Cryo-TEM micrographs

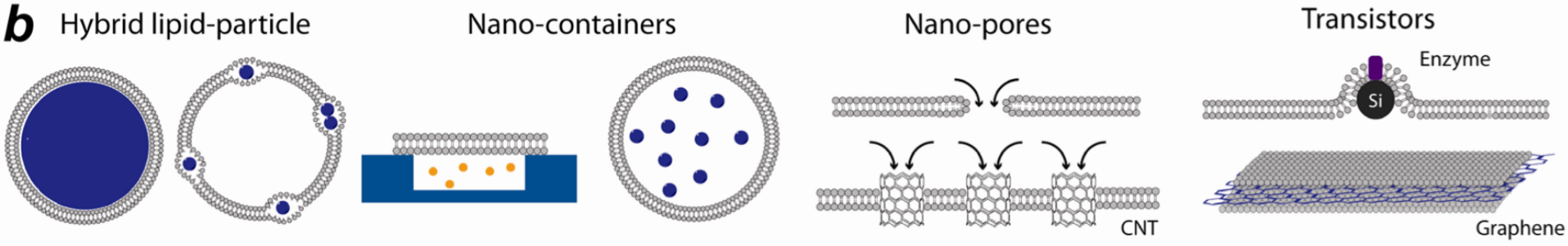
DMPC lipid molecules described at multiple resolutions.



Liposomes functionalized with nanoparticles allowing for radiation/ magnetic field triggered cargo release. The ticks on the box sides indicate the size or the size range of the synthesized particles.



Lipid based nano-devices.



Lipidomics – the systematic decoding of lipid-based information in biosystems, is composed of identifying and profiling lipids and lipid-derived mediators.

Lipidomics can be subdivided into

- architecture/membrane lipidomics
- mediator lipidomics.