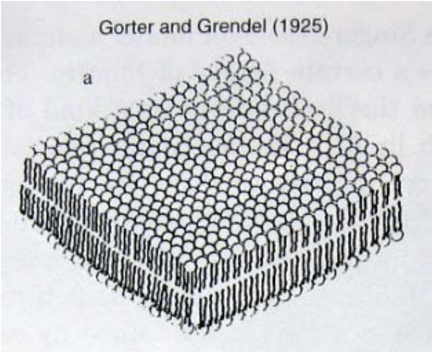
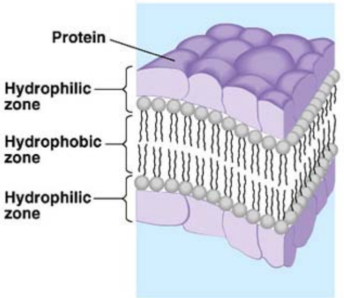
Lipids, lipid mixtures, and membranes

Voet & Voet Chapter 12
1, 2, 3A to C
Van Meer et al. 2008. Nature Reviews Mol.Cell.Bio. 9, 112

Early model of the erythrocyte membrane

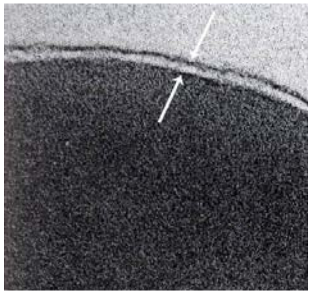


The structure of the cellular membrane



(a) The Davson-Danielli model

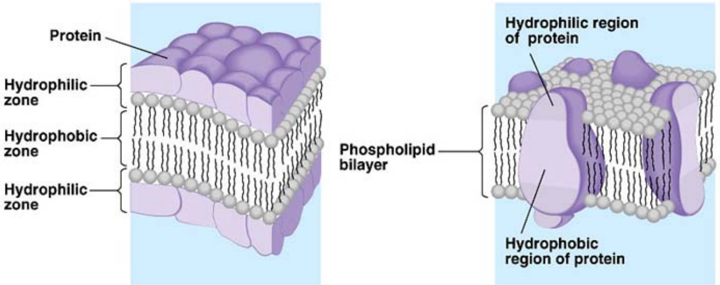
1935



Robertson

1966

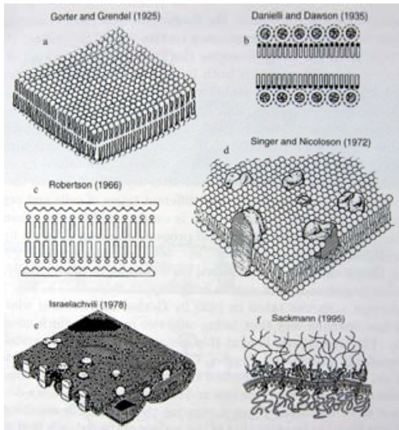
Singer and Nicolson 1972



(a) The Davson-Danielli model

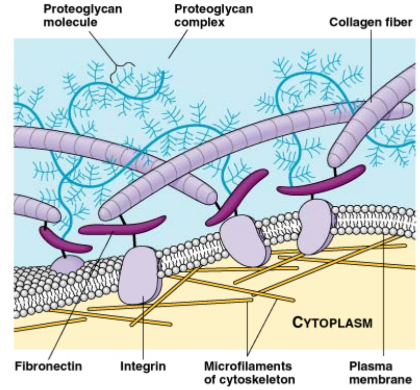
(b) Current fluid mosaic model

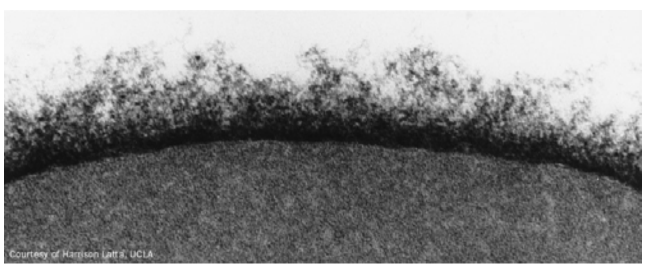
Historic picture gallery of membrane modelling



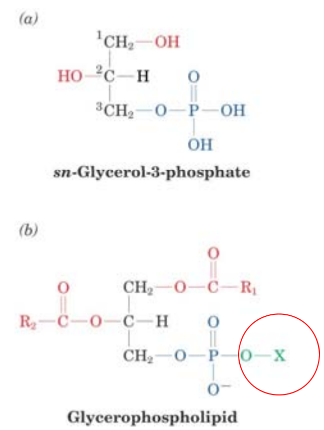
from the book
Life - as a matter of fat
O. Mouritsen
Springer 2005

Current model of the cellular membrane



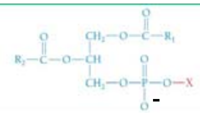


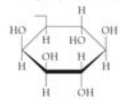
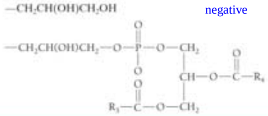
The erythrocyte glycocalyx as revealed by electron microscopy using special staining techniques.



Molecular formula of glycerophospholipids.

WILEY



Name of X—OH	Formula of—X	**Net charge**	Name of Phospholipid
Water	—H	negative	Phosphatidic acid
Ethanolamine	$—CH_2CH_2NH_3^+$	neutral	Phosphatidylethanolamine
Choline	$—CH_2CH_2N(CH_3)_3^+$	neutral	Phosphatidylcholine (lecithin)
Serine	$—CH_2CH(NH_3^+)COO^-$	negative	Phosphatidylserine
myo-Inositol		negative	Phosphatidylinositol
Glycerol	$—CH_2CH(OH)CH_2OH$	negative	Phosphatidylglycerol
Phosphatidylglycerol			Diphosphatidylglycerol (cardiolipin)

The Common Classes of Glycerophospholipids.

WILEY

Mole %

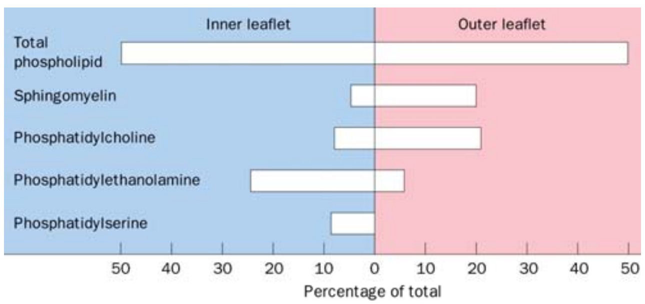
Lipid	Human Erythrocyte		Human Myelin	Beef Heart Mitochondria	*E. coli*
Phosphatidic acid	1.5	**1**	0.5	0	0
Phosphatidylcholine	19	**16**	10	39	0
Phosphatidylethanolamine	18	**16**	20	27	65
Phosphatidylglycerol	0	**0**	0	0	18
Phosphatidylinositol	1	**0.7**	1	7	0
Phosphatidylserine	8.5	**7**	8.5	0.5	0
Cardiolipin	0	**0**	0	22.5	12
Sphingomyelin	17.5	**15**	8.5	0	0
Glycolipids	10	**5**	26	0	0
Cholesterol	25	**40**	26	3	0

[a]The values given are weight percent of total lipid.

Source: Tanford, C., *The Hydrophobic Effect*, p. 109, Wiley (1980).

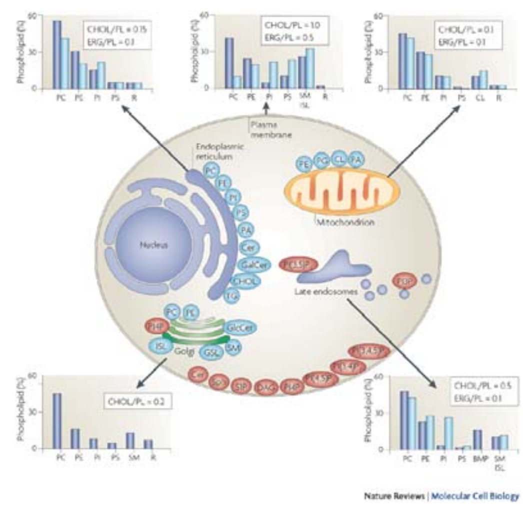
Lipid Compositions of Some Biological Membranes

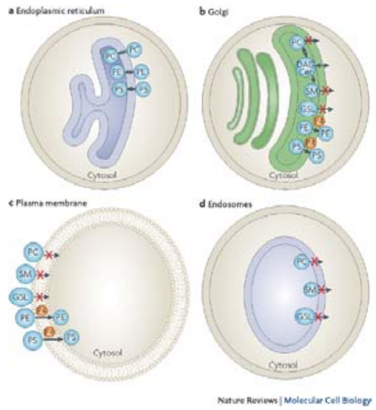
WILEY



Asymmetric distribution of phospholipids
in the human erythrocyte membrane.

WILEY





DPPC = di palmitoyl phosphatidylcholine
DMPC= Can you guess?

	Symbol[a]	Common Name	Systematic Name	Structure	mp (°C)
	Saturated fatty acids				
L	12:0	Lauric acid	Dodecanoic acid	$CH_3(CH_2)_{10}COOH$	44.2
M	14:0	Myristic acid	Tetradecanoic acid	$CH_3(CH_2)_{12}COOH$	52
P	16:0	Palmitic acid	Hexadecanoic acid	$CH_3(CH_2)_{14}COOH$	63.1
S	18:0	Stearic acid	Octadecanoic acid	$CH_3(CH_2)_{16}COOH$	69.6
	20:0	Arachidic acid	Eicosanoic acid	$CH_3(CH_2)_{18}COOH$	75.4
	22:0	Behenic acid	Docosanoic acid	$CH_3(CH_2)_{20}COOH$	81
	24:0	Lignoceric acid	Tetracosanoic acid	$CH_3(CH_2)_{22}COOH$	84.2

[a]Number of carbon atoms : number of double bonds. For unsaturated fatty acids, *n* is the number of carbon atoms, *n* *x* is the double-bonded carbon atom, and *x* is the number of that carbon atom counting from the methyl terminal (ω) end of the chain.

Source: Dawson, R.M.C., Elliott, D.C., Elliott, W.H., and Jones, K.M., *Data for Biochemical Research* (3rd ed.), Chapter 8, Clarendon Press (1986).

The Common Biological Fatty Acids.

	Symbol[a]	Common Name	Systematic Name	Structure	mp (°C)
	Unsaturated fatty acids (all double bonds are cis)				
	16:1*n* 7	Palmitoleic acid	9-Hexadecenoic acid	$CH_3(CH_2)_5CH=CH(CH_2)_7COOH$	−0.5
O	18:1*n* 9	Oleic acid	9-Octadecenoic acid	$CH_3(CH_2)_7CH=CH(CH_2)_7COOH$	13.4
	18:2*n* 6	Linoleic acid	9,12-Octadecadienoic acid	$CH_3(CH_2)_4(CH=CHCH_2)_2(CH_2)_6COOH$	−9
	18:3*n* 3	α-Linolenic acid	9,12,15-Octadecatrienoic acid	$CH_3CH_2(CH=CHCH_2)_3(CH_2)_6COOH$	−17
	18:3*n* 6	γ-Linolenic acid	6,9,12-Octadecatrienoic acid	$CH_3(CH_2)_4(CH=CHCH_2)_3(CH_2)_3COOH$	
	20:4*n* 4	Arachidonic acid	5,8,11,14-Eicosatetraenoic acid	$CH_3(CH_2)_4(CH=CHCH_2)_4(CH_2)_2COOH$	−49.5
	20:5*n* 3	EPA	5,8,11,14,17-Eicosapentaenoic acid	$CH_3CH_2(CH=CHCH_2)_5(CH_2)_2COOH$	−54
	22:6*n* 3	DHA	4,7,10,13,16,19-Docosahexenoic acid	$CH_3CH_2(CH=CHCH)_6CH_2COOH$	
	24:1*n* 9	Nervonic acid	15-Tetracosenoic acid	$CH_3(CH_2)_7CH=CH(CH_2)_{13}COOH$	39

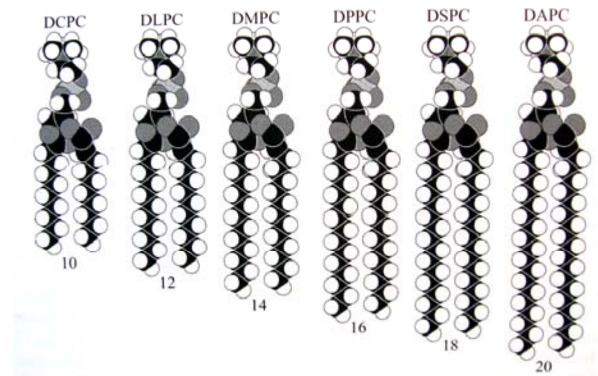
[a]Number of carbon atoms : number of double bonds. For unsaturated fatty acids, *n* is the number of carbon atoms, *n* *x* is the double-bonded carbon atom, and *x* is the number of that carbon atom counting from the methyl terminal (ω) end of the chain.

Source: Dawson, R.M.C., Elliott, D.C., Elliott, W.H., and Jones, K.M., *Data for Biochemical Research* (3rd ed.), Chapter 8, Clarendon Press (1986).

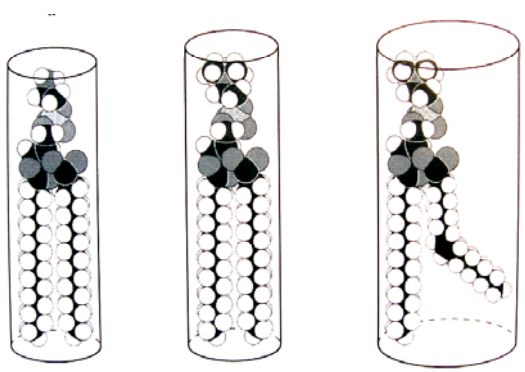
The Common Biological Fatty Acids.

Voet Biochemistry 3e Page 383
© 2004 John Wiley & Sons, Inc.

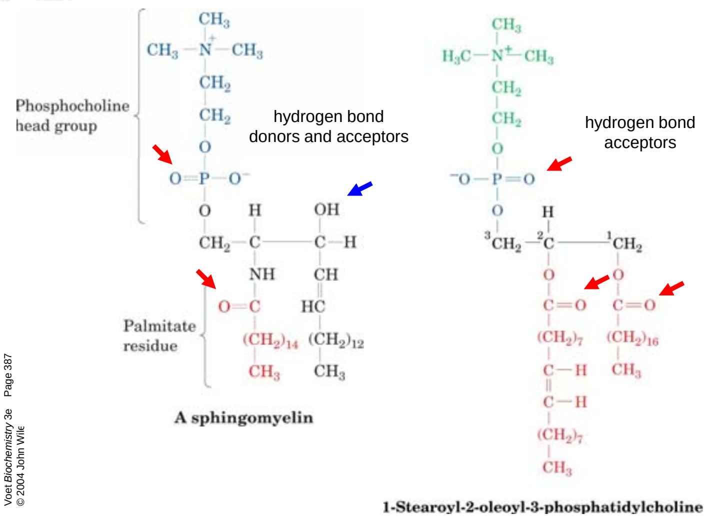
Phospholipids have different acyl chains

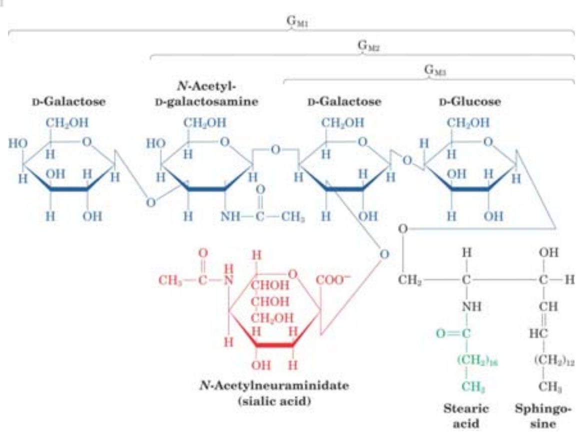


Dimensions of the phospholipids molecules



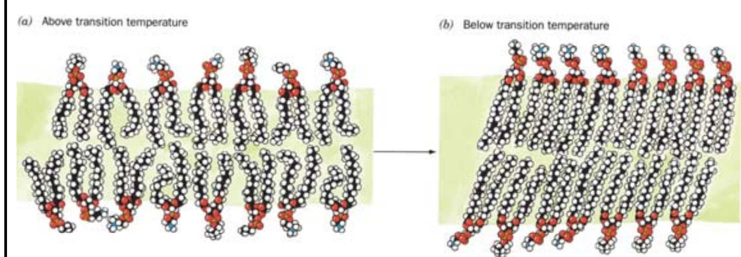
DSPE DSPC SOPC





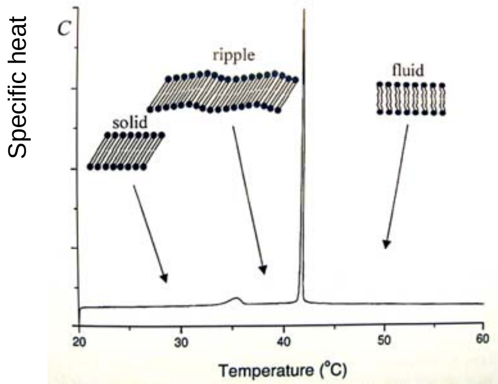
Ganglioside G_{M1}.

Exploring lateral heterogeneity in synthetic membranes



fluid or “liquid” solid or “gel”

Phase transition and phases in DPPC



Phase diagram of lipid bilayers of binary mixtures of PC lipids

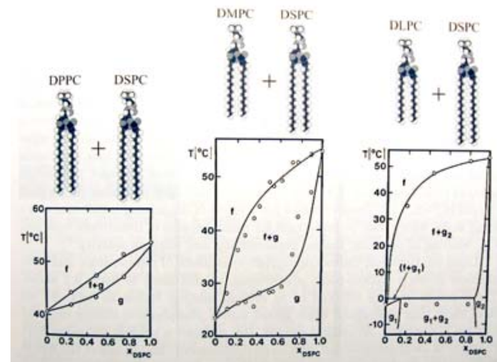
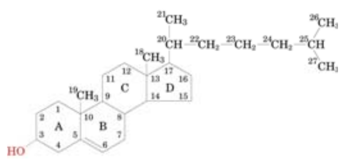
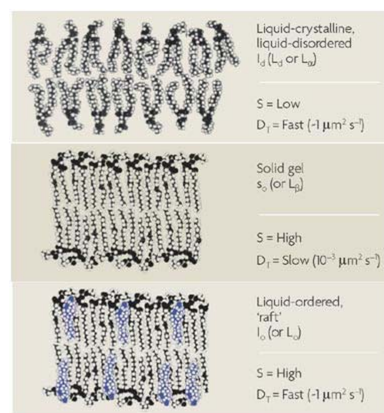


Fig. 9.7. Phase diagrams of lipid bilayers for three binary mixtures of PC lipids with different fatty-acid chain lengths. *f* denotes the liquid-disordered phase and *g* denotes solid-ordered phases

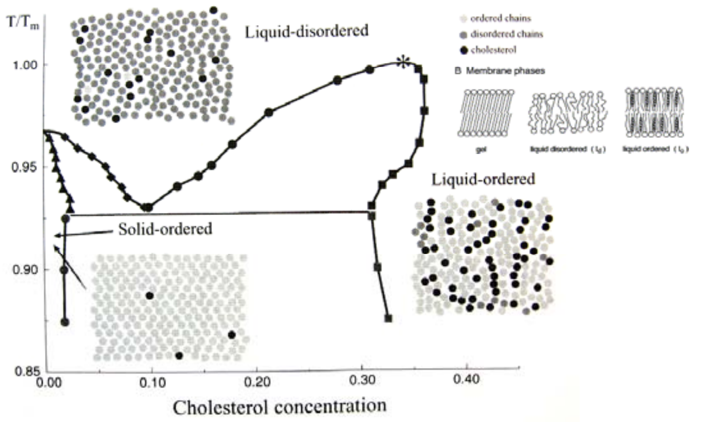
How does cholesterol affect the physical properties of lipids bilayers?

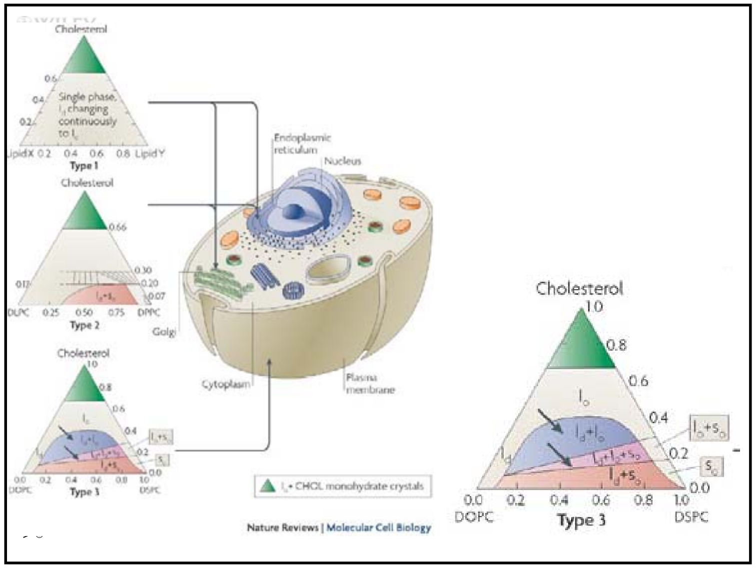




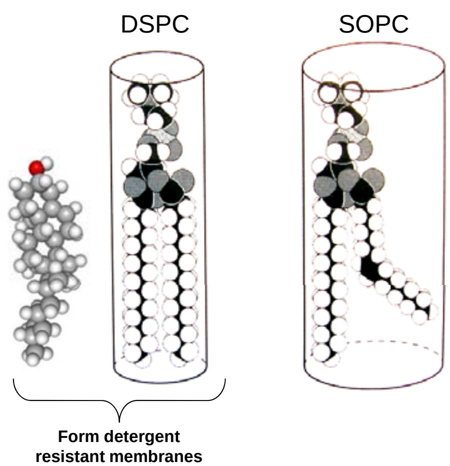
Nature Reviews | Molecular Cell Biology

Phase diagram of lipid bilayers with cholesterol

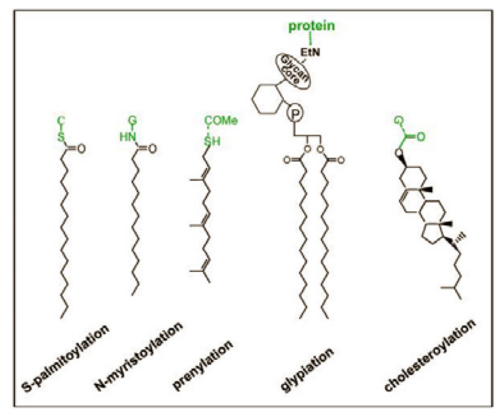




Dimensions of the phospholipids molecules

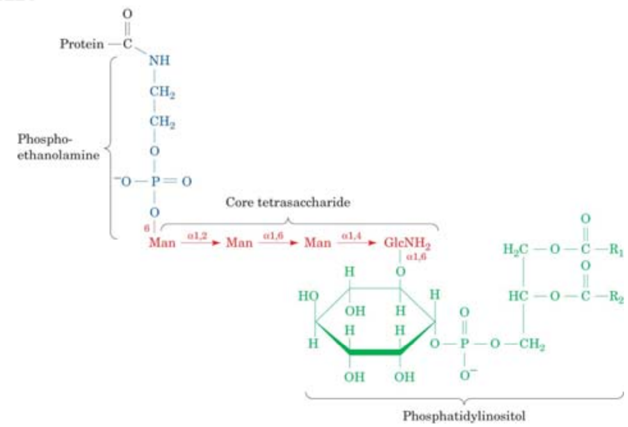


How to target proteins to membranes?



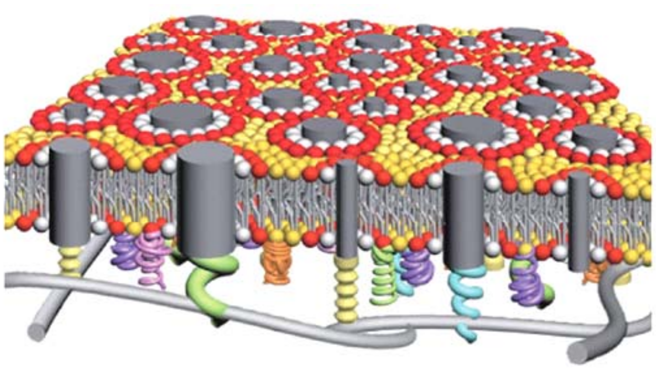
Covalent lipid modification of proteins

- Palmitoylation (16 C acyl chain)
  - (Cys) thioester bond
  - The most abundant
  - The only reversible (can be cleaved by thioesterases)
- N-myristoylation (14 C acyl chain)
  - In most cases not enough to anchor a protein to membrane
  - N-terminal Gly, amide bond
- Prenylation (farnesyl or geranylgeranyl)
  - Thioether linkage to a C-terminal Cys



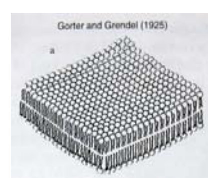
Core structure of the GPI anchors of proteins

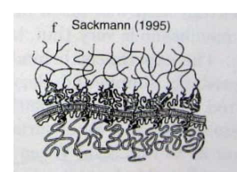
Density of membrane proteins in the ER and Golgi
30000 per μm^2



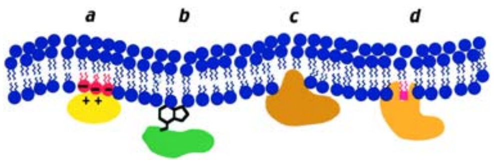
The membrane is a protein-lipid composite rather than a dilute solution of protein in a lipid solvent

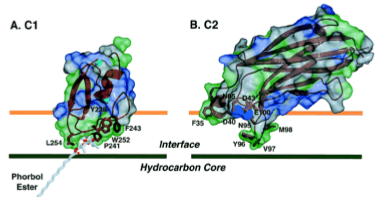
Biological membranes are different from synthetic membranes





Protein-lipid interactions



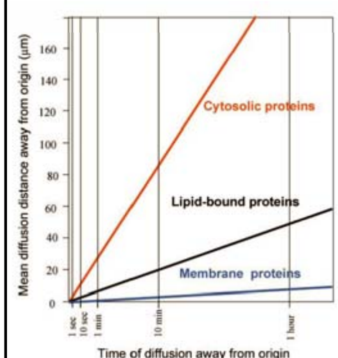


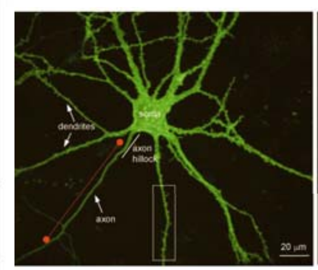
Protein binding domains

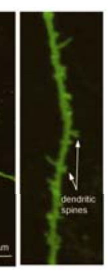
- Polybasic domains
  - Short cluster of basic amino acids (<30)
  - non-specific binding to acidic lipids
  - Act synergistically with lipid modifications
- Phospho inositides binding modules
  - Low affinity lipid interaction modules that regulate transient association w/cellular membranes
  - Examples:
    - PH, FERM, ENTH [PI(4,5)P_2]
    - FYVE, PX [PI(3)P]
- C1 and C2 domains

Table 1. Occurrence of Membrane Targeting Motifs in the Human Genome

Membrane Targeting Motif	Number of Motifs in the Human Genome
Lipid-based:	
Palmitoylation	?
Myristoylation	270
Prenylation (CaaX)	214
Protein-based:	
Polybasic	?
PH domains	448
ENTH domains	16
FYVE domain	66
PX domains	65
C2 domain	225
C1 domain	97

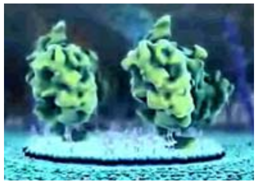






they targets in the cell?

What are lipid rafts?



Origin of the raft hypothesis

- glycosphingolypids cluster in Golgi before being sorted to the apical surface of polarized epithelial cell
  - Biochemistry 27, 6197 (1988)
- glycosphingolypids clusters are insoluble in Triton X-100 at 4 ºC, and the detergent resistant membranes are rich in cholesterol, and GPI-anchored proteins
  - (1994)
- synthetic membranes composed of glycosphingolipids and cholesterol recapitulate the detergent-resistant characteristics of the glycosphingolipid clusters
  - (2001)

Two lines of inquiry emerged from the early raft studies

- exploring lateral heterogeneity in synthetic membranes
- addressing the functionality of glycosphingolipid-cholesterol rich domains in biological membranes

This characterizations have proven to be frustratingly difficult

Provisional contemporary definition of rafts

- "**Membrane rafts are small (10-200 nm), heterogeneous, highly dynamic, sterol- and sphingolipid-enriched domains that compartmentalize cellular processes**"
  - 2006 Keystone Symposium

Suggested roles for Rafts

- Signal transduction pathways
- Apoptosis Cell adhesion and migration
- Synaptic transmission Organization of cytoskeleton
- Protein sorting during exo- and endocytosis
- Point of entry of viruses, bacteria, and toxins
- Site of viral assembly and formation of prion and Alzheimer amyloid

Conclusion

- The existence of lipid rafts cannot be taken as a established fact
- We should proceed with caution and open mind to alternative mechanisms for phenomena currently attributed to rafts