Classification of Lipids

- **Fatty acids**: are long chain linear (unbranched) hydrocarbon carboxylic acids
- **Triglycerides**: are fatty acid esters of glycerol
- **Phospholipids**: are lipids that contain one or more phosphate groups
- **Glycolipids**: have a carbohydrates component
- **Eicosanoids**: are a family of derivatives of Arachidonic acid
- **Steroids**: have a basic structure of a perhydrocyclo-pentanophenanthrene ring system
- **Lipoproteins**: are complexes of lipids and proteins that circulate in the blood.

Fatty Acids

- long chain linear hydrocarbons carboxylic acids
- Usually have an even number of C atoms (usually 12 to 20)
- The carbons are numbered starting from the carboxylic C.
- They are amphiphilic; they have a polar end and rest of the molecule is nonpolar
- Fatty acids may be saturated (no double bonds) or unsaturated (one or more double bonds)
- All naturally occuring double bonds have a cis-configuration
- 2 or more double bonds exist as non-conjugated double bonds
- Longer chain and saturation increases melting point of FA
- FAs are ionized at physiological pH

ω-3 Fatty Acids

- the highest numbered C is called the ω-C
- Sometimes FA are classified according to the position of the first double bond from the ω-end
- Most polyunsaturated fatty acids are ω-6 fatty acids
- ω-3 fatty acids are found mainly in fish and fish products. Also found in flax seeds
- ω-3 FAs inhibit formation of thromboxane A_2 (an eicosanoid) required for platelet aggregation and clot formation. Thus, ω-3 FAs decrease the risk of heart disease

Some Fatty Acids

Palmitic acid (hexadecanoic acid): 16:0

Stearic acid (Octadecanoic acid) : 18:0

Oleic Acid (9-octadecenoic acid): 18:1 (Δ^{9})

Linoleic Acid (9,12- octadecadienoic acid): 18:2 ($\Delta^{9,12}$)

α-Linolenic Acid (9,12,15-octadecatrienoic acid): 18:3 ($\Delta^{9,12,15}$)

γ-Linolenic Acid (6,9,12-octadecatrienoic acid): 18:3 ($\Delta^{6,9,12}$)

Arachidonic Acid (5,8,11,14-eicosatetraenoic acid) 20:4 ($\Delta^{5,8,11,14}$)

EPA (5,8,11,14,17-Eicosapentaenoic acid) 20:5 ($\Delta^{5,8,11,14,17}$)

TABLE 12.1 Some naturally occurring fatty acids in animals

Number of carbons	Number of double bonds	Common name	Systematic name	Formula
12	0	Laurate	*n*-Dodecanoate	$CH_3(CH_2)_{10}COO^-$
14	0	Myristate	*n*-Tetradecanoate	$CH_3(CH_2)_{12}COO^-$
16	0	Palmitate	*n*-Hexadecanoate	$CH_3(CH_2)_{14}COO^-$
18	0	Stearate	*n*-Octadecanoate	$CH_3(CH_2)_{16}COO^-$
20	0	Arachidate	*n*-Eicosanoate	$CH_3(CH_2)_{18}COO^-$
22	0	Behenate	*n*-Docosanoate	$CH_3(CH_2)_{20}COO^-$
24	0	Lignocerate	*n*-Tetracosanoate	$CH_3(CH_2)_{22}COO^-$
16	1	Palmitoleate	*cis*-Δ^9-Hexadecenoate	$CH_3(CH_2)_5CH{=}CH(CH_2)_7COO^-$
18	1	Oleate	*cis*-Δ^9-Octadecenoate	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COO^-$
18	2	Linoleate	*cis,cis*-Δ^9,Δ^{12}-Octadecadienoate	$CH_3(CH_2)_4(CH{=}CHCH_2)_2(CH_2)_6COO^-$
18	3	Linolenate	all-*cis*-$\Delta^9,\Delta^{12},\Delta^{15}$-Octadecatrienoate	$CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6COO^-$
20	4	Arachidonate	all-*cis*-$\Delta^5,\Delta^8,\Delta^{11},\Delta^{14}$-Eicosatetraenoate	$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2COO^-$

Triglycerides

- In Triacylglycerol (TG) all 3 –OH of glycerol are esterified by FAs. Monoacylglygerol and diacylglycerol have, respectively, 1 and 2 FAs
- Naturally occurring glycerol is L-glycerol.
- TG are the storage form of FA; most dietary fats are triglycerides
- Physiologically, TG are digested in the small intestine by the enzyme pancreatic lipase
- Monoacylglycerols are absorbed through the intestinal cells, re-converted to TG and assembled into lipoproteins

Phospholipids

- These are lipids that contain one or more phosphate groups
- PL are the primary components of biomembranes. Other lipids in biomembranes are glycolipids and cholesterol. Surfactants are phopsholipids, mostly phosphatidylcholine
- PL are subclassified based on their parent lipid; phopshoglycerides or sphingomyelins
- Phosphatidic acid: basic glycerophopholipid. 1,2-diacylglycerol joined to phosphoric acid by an ester link. This phosphate can form another ester linkage with an alcohol. Serine :phosphatidylserine; Choline: phosphatidylcholine

  Ethanolamine: phosphatidylethanolamine; Inositol: phosphatidylinositol; Glycerol: diphosphatidylglycerol (cardiolipin)

Sphingolipids

- Sphingosine is a derivative of glycerol but it has $–NH_2$ instead of -OH at C2 and has a -OH as well as a long chain hydrocarbon on C3
- The $–NH_2$ forms an amide bond with a long chain FA to form a ceramide.
- sphigomyelin is formed when a phosphodiester bridge links the C1 -OH of ceramide to ethanolamine or choline
- Sphingomyelins are found abundantly in the myelin sheath that surrounds the nerve fibers

Glycolipids

- Glycolipids are lipids that contain carbohydrates
- Cerebrosides have a monosaccharide attached to the C1 -OH of ceramide
- Gangliosides have an oligosaccharide attached to the C1 -OH of ceramide
- Cerebrosides and gangliosides are found in the brain and nervous tissue
- In biomembranes, glycolipids are oriented asymmetrically with the sugar units always on the extracellular side of the membrane

Cholesterol

- Cholesterol is an essential component of biomembranes and imparts stability to the fluid structure.
- Cholesterol is a steroid. All steroids have the same basic structure consisting of 4 hydrocarbon rings linked together
- Cholesterol has a –OH group which provides the polarity and a hydrocarbon group at the other end which adds to its hydrophobic nature
- In biomembranes, the –OH of cholesterol is aligned with the head group (phosphate) of phospholipids
- Steroids are important metabolically (cholesterol), for digestion (bile salts), as hormones (human sex hormones)

Biomembranes

- Make up boundaries of cells and intracellular organelles (nucleas, golgi, mitochondria, ER, etc.)
- Membranes are dynamic fluid structures
- Composed of a lipid bilayer with proteins embedded within the bilayer
- Lipids responsible for semipermeability of biomembranes; hydrophobic chemicals can penetrate, but most polar molecules are excluded
- Membrane proteins are transporters, channels and pumps for the selective entry of specific molecules

Lipid Bilayers

- Phospholipids are amphipathic: They have both hydrophilic and hydrophobic regions
- The two hydrocarbon chains are parallel to each other, the polar group is extended in the opposite direction.
- In aqueous solutions, amphipathic molecules arrange themselves as micelles, bilayers or liposomes.
- These structures are stabilized by hydrophobic interactions between hydrocarbon chains and hydrogen bonds between polar head groups and H_2O.
- Phospholipids and glycolipids favor the lipid bilayer over micelles because the interior of a micelle cannot accommodate 2 hydrocarbon chains of each molecule. Salts of fatty acids (soaps) prefer to organize as micelles.

Properties of Lipid Bilayers

- They form spontaneously. The bilayer structure is inherent in the structures of the constituent lipids.
- They are cooperative structures stabilized by hydrophobic interactions and hydrogen bonding.
- They are extensive / continuous without beginning or end.
- They are enclosed: do not have edges with exposed hydrocarbons. Thus, they form compartments
- They are non-leaky and self-sealing. Accounts for their permeability barrier.

Membrane Proteins

- Membrane proteins include pumps, channels, transporters, receptors and enzymes. Their function include transport and cellular communication.
- Membrane proteins are classified as peripheral or integral.
- Peripheral proteins are associated to polar head groups of the lipid bilayer by electrostatic interactions. They can be easily dissociated by high salt or altering pH.
- Integral proteins are embedded within the bilayer by hydrophobic interactions with hydrocarbon chains. Their embedded domains contain aa with hydrophobic side chains.
- Proteins that form channels and transporters have multiple transmembrane domains
- Certain proteins may be anchored to the bilayer by covalent bonds between aa of proteins and head groups on lipids

The Fluid-Mosaic Model of Membrane Structure

- The Fluid-Mosaic model for membrane structure was proposed by Singer and Nicolson in 1972
- States that biomembranes are fluid and dynamic. The membrane lipids are a solvent for the proteins. Thus, membranes are a solution of oriented lipids and proteins. They are constantly flowing or in motion.
- Lateral diffusion or movement of membrane components is rapid and constant. Transverse diffusion (flip-flop) between the two layers of the bilayer is slow and occasional.

Fluid-Mosaic Model (Continued)

- The FM model also states that membranes are like a mosaic because they are assembled from various components which includes lipids, proteins and carbohydrates.
- Oligosaccharide chains usually float outward toward the extracellular matrix rather than being exposed to the cytoplasm.
- The orientation of proteins and carbohydrates and the slow flip-flop rate causes the membrane bilayer to be assymetrical

Membrane Fluidity

- The degree of fluidity is determined by the fatty acid composition and cholesterol content.
- Unsaturation increases fluidity. The cis-configuration introduces a bend in hydrocarbon structure which interferes with close packing and hydrophobic interactions
- The fluidity is inversely related to fatty acid chain length. Longer the hydrocarbon chains, stronger the interaction between them.
- Cholesterol decreases membrane fluidity because of its bulky irregular structure. Cholesterol also restricts the dynamic movement of membrane lipids by specifically interacting with certain phospholipids

Double Membranes

- Certain cells and organelles are enclosed by double membranes. Eg: Bacteria, Mitochondria.
- The outer membrane is permeable to small molecules due to the presence of membrane channels made up membrane proteins called porins.
- The inner membrane is highly impermeable and contains pumps and transporters that regulate movement of small molecules across the membrane

Membrane Receptors

- Entry of large molecules and proteins into cells is mediated by membrane proteins called receptors
- Receptors are highly specific and have a high affinity for their ligands. Ligands may be hormones, growth factors etc
- Entry into cells is by the process of endocytosis.
- In endocytosis, a region of the bilayer containing the receptor-ligand complex invaginates, fuses and buds out as an enclosed vesicle containing the ligand.
- The vesicle continues to fuse with other internal vesicles till it is transported to its target
- Receptors control key biological processes and rely on membrane fluidity.

Protein Targeting: Example of Membrane Function

- The protein distribution amongst different cellular organelles is highly variable.
- Proteins are synthesized with specific signal sequences that target them to the appropriate location
- Eg: peroxisomal proteins contain a C-terminal SKL sequence, nuclear proteins contain an internal stretch of 5 basic aa, mitochondrial proteins have an N-terminal amphipathic helix.
- The signal sequences are recognized by specific receptors present on target membranes