BCMB 3100 – Lipids
(Text Chapters 11, 12, 13)

• Definition
• Major classes
• Fatty acids
• Triacylglycerol
• Glycerophospholipids
• Sphingolipids
• Cholesterol

_________________ : water insoluble organic compounds in living organisms

Lipids are hydrophobic or amphipathic

In BCMB3100 we will emphasize
* phospholipids
* glycolipids
* cholesterol (steroid)

_________________ : main lipids in most biological membranes

_________________ : 2nd most abundant lipid in membranes (abundant in CNS) from animals and plants
Structural relationships of major lipid classes

Structure and nomenclature of fatty acids
### Table 9.1 Some common fatty acids (anionic forms)

<table>
<thead>
<tr>
<th>Number of carbons</th>
<th>Number of double bonds</th>
<th>Common name</th>
<th>IUPAC name</th>
<th>Melting point, °C</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>0</td>
<td>Laurie</td>
<td>Dodecanoate</td>
<td>44</td>
<td>CH₁₉(CH₂)₁₉COO⁻</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>* Myristate</td>
<td>Tetradecanoate</td>
<td>52</td>
<td>CH₁₄(CH₂)₁₄COO⁻</td>
</tr>
<tr>
<td>16</td>
<td>0</td>
<td>* Palmitate</td>
<td>Hexadecanoate</td>
<td>63</td>
<td>CH₁₅(CH₂)₁₅COO⁻</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>* Stearate</td>
<td>Octadecanoate</td>
<td>70</td>
<td>CH₁₆(CH₂)₁₆COO⁻</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>Arachidate</td>
<td>Eicosanoate</td>
<td>75</td>
<td>CH₁₈(CH₂)₁₈COO⁻</td>
</tr>
<tr>
<td>22</td>
<td>0</td>
<td>Behenate</td>
<td>Docosanoate</td>
<td>81</td>
<td>CH₂₀(CH₂)₂₀COO⁻</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>Lignocerate</td>
<td>Tetracosanoate</td>
<td>84</td>
<td>CH₂₂(CH₂)₂₂COO⁻</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>Palmitoleate</td>
<td>cis-Δ⁹-Octadecenoate</td>
<td>−0.5</td>
<td>CH₁₅(CH₂)₁₅CH=CH(CH₂)₉COO⁻</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>* Oleate</td>
<td>cis-Δ⁹-Octadecenoate</td>
<td>13</td>
<td>CH₁₆(CH₂)₁₆CH=CH(CH₂)₉COO⁻</td>
</tr>
<tr>
<td>18</td>
<td>2</td>
<td>* Linoleate</td>
<td>cis,cis-Δ⁹,12-Octodecadienoate</td>
<td>−9</td>
<td>CH₁₅(CH₂)₁₅CH=CH(CH₂)₉CH₉COO⁻</td>
</tr>
<tr>
<td>18</td>
<td>3</td>
<td>* Linolenate</td>
<td>all cis-Δ⁹,12,15-Octadecatrienoate</td>
<td>−17</td>
<td>CH₁₅(CH₂)₁₅OH=CH(CH₂)₉CH₉CH(CH₂)₉COO⁻</td>
</tr>
<tr>
<td>20</td>
<td>4</td>
<td>Arachidonate</td>
<td>all cis-Δ⁵,8,11,14-Octadecatrienoate</td>
<td>−49</td>
<td>CH₁₈(CH₂)₁₈CH=CH(CH₂)₈(CH₂)₄COO⁻</td>
</tr>
</tbody>
</table>

**common name**
- 18:0 stearate
- 18:1 oleate
- 18:2 linoleate

**IUPAC name**
- Octadecanoate
- cis-Δ⁹-Octadecenoate
- cis,cis-Δ⁹,12-Octadeceadienoate

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[Unsaturated FA - at least one C-C double bond](a)

[ Unsaturated FA - at least one C-C double bond](b)

[ Unsaturated FA - at least one C-C double bond](c)

[Saturated FA - no C-C double bonds](a)

Oleate

Linolenate

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You must be able to draw the structure of those marked *
Structural relationships of major lipid classes

**LIPIDS**
- Fatty acids
- Triacylglycerols
- Waxes
- Sphingolipids
  - Steroids
  - Lipid vitamins
  - Terpenes
  - Isoxepanoids

**Glycero phospholipids**
- Plasmalogens
- Phosphatidates
- Sphingomyelins
- Other phospholipids
  - Phosphatidyl-
  - Phosphatidyl-
  - Phosphatidyl-
  - Phosphatidyl-
- Eicosanoids

**Ceramides**
- Cerebrosides
- Gangliosides
- Other glycosphingolipids
- Glycosphingolipids

Structure of a triacylglycerol

(a) Glycerol backbone

(b) Triacylglycerol

_________________ are a neutral storage form of fatty acids

See Pg. 193
An EXAMPLE

A triglyceride molecule. Left: glycerol; right (top to bottom): palmitic acid, oleic acid, alpha-linolenic acid

Note: the types of fatty acyl groups present in any given triacylglycerol may vary.

Figure 1  Adipose tissue fatty acid composition in 4258 and 3096 healthy men and women from 19 studies. Data are shown for individual studies (panels A–L) and collated values are shown in the histogram (panel M). Data are expressed as mean (mol%) and error bars represent SD.

Leanne Hodson, C. Murray Skeaff, Barbara A. Fielding
Fatty acid composition of adipose tissue and blood in humans and its use as a biomarker of dietary intake
MEMBRANE LIPIDS: 3 major types = phospholipids, glycolipids, & cholesterol

_________________: most abundant class of lipids in membranes (note: triacylglycerols most abundant on mass basis in mammals); derived from glycerol or sphingosine

*lipids from glycerol = phosphoglycerides (also called glycerophospholipids)

* phosphoglycerides consist of glycerol backbone, two fatty acids & a phosphorylated alcohol

See Fig. 11.5

Fatty acids in biological organisms

Fatty acid chains (long aliphatic tails) in phospholipids & glycolipids contain even # of carbons (12-20) with 16 and 18 being most common

Fatty acids can be ______________ or ______________

Under physiological conditions fatty acids are ionized (pKa 4.5-5.0)
Fig 9.1 Structural relationships of major lipid classes

(a) Glycerol 3-P and (b) phosphatidate

See Fig. 11.6
Phospholipases hydrolyze phospholipids

__enzymes__ that catalyze hydrolysis of triacylglycerols

__catalyze__ hydrolysis of glycerophospholipids

See Fig. 11.7
Structural relationships of major lipid classes

(a) ____________:
structural backbone of sphingolipids

(b) ___________:
sphingosine + fatty acid at C2

See Fig. 11.8
(c) **Sphingomyelin:** present in plasma membrane & myelin sheath around neurons

See Fig. 11.8

**Example of a Cerebroside:** abundant in nerves

- **Sugar-**Sphingosine
- Fatty acid

- **Structure of a galactocerebroside**

See Pg. 196
Example of a Ganglioside $G_{M2}$ (NeuNAc in blue)

Abundant in the brain and nervous system; Cell surface, cell-cell interactions (e.g. blood group antigens)

Hexosaminidase A cleaves here

Mutation $\rightarrow$ Tay-Sachs disease

Structural relationships of major lipid classes

LIPIDS

- Fatty acids
- Eicosanoids
- Triacylglycerols
- Waxes
- Sphingolipids
- Sphingomyelins
- Ceramides
- Cerebrosides
- Gangliosides
- Other glycosphingolipids
- Glycosphingolipids
Structure of the steroid cholesterol.
Steroids are polyrenyl compounds

In eukaryotes but NOT in most prokaryotes

Other steroids: steroid hormones (estrogen → estradiol, testosterone, corticosteriods), bile salts, sterols in plants, yeast, fungi

See Pg. 197

• Cholesterol modulates the fluidity of mammalian cell membranes
• It is also a precursor of the steroid hormones and bile salts
Stereo view of cholesterol

- Polar OH (red), fused ring system nearly planar

Waxes: esters of long-chain monohydroxylic alcohols and long-chain fatty acids (nonpolar)

Waxes are very water insoluble and high melting point

They are widely distributed in nature as protective waterproof coatings on leaves, fruits, animal skin, fur, feathers and exoskeletons

Myricyl palmitate, a wax

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{(CH}_2\text{)}_{14} \quad \text{C} \quad \text{O} \quad \text{(CH}_2\text{)}_{29} \quad \text{CH}_3 \\
\end{align*}
\]

\begin{itemize}
  \item Palmitate portion
  \item Myricyl alcohol portion
\end{itemize}
**Eicosanoids**: oxygenated derivatives of C20 polyunsaturated fatty acids (e.g. arachidonic acid)

(a) Arachidonic acid

(b) Prostaglandin E2
can cause constriction of blood vessels
(aspirin inhibits prostaglandin synthesis)

(c) Thromboxane A2
involved in blood clot formation

(d) Leukotriene D4
mediator of smooth-muscle contraction and bronchial constriction seen in asthmatics

Arachidonic acid and three eicosanoids

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**Some vitamins are Lipid Vitamins**

• Four lipid vitamins: A, D, E, K
• (All contain rings and long, aliphatic side chains
• All are highly hydrophobic
• The lipid vitamins differ widely in their functions

* Examples of isoprenoids

See Fig. 15.19 for structures
BCMB 3100 - Lipids

- Biological Membranes
- Micelles
- Lipid Bilayer
- Peripheral membrane proteins
- Integral membrane proteins
- Lipid-anchored
- Transport across membranes
- Signal Transduction
Structure of a typical eukaryotic plasma membrane

See Fig. 12.1; 12.8

• Highly selective permeability barriers that surround cells & cellular compartments

• Sheetlike structures of ~60-100Å

• Consists mostly of lipids & proteins in ratio of 1:4 to 4:1 (typical 40% lipid; 60% protein). Lipids & proteins may be glycosylated.

• Lipids in biological membranes are ______________: hydrophilic (polar) head group & hydrophobic tail. Spontaneously form bilayers in aqueous solution.

Lipids in biological membranes are ______________: hydrophilic (polar) head group & hydrophobic tail. Spontaneously form bilayers in aqueous solution.
Membrane lipid and bilayer

Lipids in biological membranes include phospholipids, sphingolipids, cholesterol (in some eukaryotes)
Stereo view of cholesterol

- Polar OH (red), fused ring system nearly planar
Amphipathic nature of cerebroside

Amphipathic lipids can take two different forms in aqueous media: _________ or ______________

______________: a globular structure in which polar head groups are on the surface and hydrocarbon tails are on the inside

Salts of fatty acids tend to form micelles. Micelles usually are < 200 μm in diameter.
Structure and nomenclature of fatty acids

---

favored structure for phospholipids & sphingolipids since lipids with two fatty acyl chains are too large to fit into the center of a micelle. Bilayers can have large dimensions (10^7 Å, 1mm) (recall diameter = ~60-100Å)

Lipid bilayers self-assemble due to hydrophobic interactions between hydrocarbon tails (main force), van der Waals attractive forces between hydrocarbon tails, & electrostatic & H-bonding forces between polar head groups and water

Bilayers are extensive, closed, and self-sealing

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A liposome  Fig. 12.2

Preparation of liposomes  Fig. 12.3
Lipid bilayers are permeability barriers to ions & polar molecules

**Lipid vesicles (liposomes):** aqueous compartments enclosed by lipid bilayers. Small vesicles (~ 500 Å), large vesicles (~10⁴ Å, 1 μm)

Use lipid vesicles to measure membrane permeability
1. Form vesicles in solution containing A
2. Separate vesicles from free A
3. Measure flux of A out of vesicles

Results

Permeability coefficient (cm/s)

Na⁺ 10⁻¹²; Trp 10⁻⁷; indole ~5x10⁻⁴; water ~5x10⁻³

**Water & hydrophobic molecules readily traverse membranes while ions & most polar molecules do not**

![Figure 12.4](image-url)
Lipid Bilayers and Membranes Are Dynamic Structures

(a) Lateral diffusion is very rapid
(b) Transverse diffusion (flip-flop) is very slow

Experiment showing that lateral diffusion occurs in biological membranes via use of heterokaryons (Frye & Edidin)

- Diffusion of membrane proteins
**Fluorescence recovery after photobleaching (FRAP) evidence for fluid membrane. Fig. 12.14**

![Diagram of FRAP](image)

From such data rate is determined as diffusion coefficient.

**Biological Membranes (cont.)**

- Contain _______ both embedded in the bilayer & on its surface. _______ may function as pumps, gates, receptors, energy transducers & enzymes.
- Held together by noncovalent interactions
- Asymmetric: the two surfaces (faces) differ in properties
- Two dimensional fluids - lipids & proteins rapidly diffuse in plane of membrane but NOT across membrane
- ___________ - membrane proteins and lipids can rapidly diffuse laterally or rotate within the bilayer (Singer & Nicolson, 1972)
- Compositions of biological membranes vary considerably among species and cell types
Freeze-fracture electron microscopy, shows the distribution of membrane proteins

1. Quick freeze liquid N
2. Fracture
3. Remove ice by vacuum
4. Layer thin layer C
5. Shadow with platinum vapor
6. Digest away organic matter
7. TEM of carbon-metal replica

Phase transition of a lipid bilayer

- Fluid properties of bilayers depend upon the flexibility of their fatty acid chains

- **Ordered state:** a rigid state in which all C-C bonds have trans conformation (all trans)
- **Disordered liquid-crystalline phase:**

- **Fluid state:** a relatively disordered state in which some of the C-C bonds are in the gauche conformation
Phase transition of a lipid bilayer

Transition from rigid to partly fluid state occurs at $T_M$, the __________

$T_M$ depends on ______ of fatty acyl chains & on degree of __________

Rigid state favored by saturated fatty acyl chains

Disordered state favored by cis double bound(s) (i.e. $T_M$ is lowered)

Prokaryotes regulate membrane fluidity by varying # of double bonds & length of fatty acyl chains. As temperature changes from 42ºC to 27ºC ratio of saturated:unsaturated changes from 1.6 to 1
Packing of fatty acid chains in membrane is disrupted by double bounds and lowers Tm.

In eukaryotes membrane fluidity is largely regulated by cholesterol. Cholesterol moderates the fluidity of membranes (prevents tight packing of fatty acyl chains & blocks large motions)

Addition of 20 mol% cholesterol broadens phase transition

Fig. 12.6
Cholesterol modulates fluidity of the membranes. Also, association with sphingolipids leads to cholesterol-rich regions called lipid rafts that may effect specific membrane-protein function.

http://en.wikipedia.org/wiki/Lipid_raft
Three types membrane associated proteins

______________________: loosely bound to membrane by H-bonds or electrostatic forces, generally water soluble once released from membrane using high salt or pH. Often bound to integral membrane proteins

______________________: proteins firmly bound to membrane by hydrophobic interactions. Solubilized with detergents. Most have one or more membrane spanning domains (e.g. $\alpha$-helix with $\sim$20 amino acids).
Integral and peripheral membrane proteins

Fig. 12.8

Stereo view of bacteriorhodopsin: an integral membrane protein

light-driven proton pump

[member of 7TM receptor family of proteins]

See Fig. 12.9

Bacterial porin

molecular filters for hydrophilic compounds

[family of proteins from the outer membrane of Gram-negative bacteria]

Fig. 12.10
**Lipid-anchored membrane proteins:** proteins covalently linked to lipid membrane

**Types of links:**

*direct amide or ester bond* between amino acid and fatty acyl group such as myristate or palmitate

*prenylation:* link to an isoprenoid chain (e.g. farnesyl or geranylgeranyl) via the S of a Cys near the C terminus of the protein

*glycosylphosphatidylinositol anchor:* C-terminal α-carboxyl of protein-phosphoethanolamine-glycan-phosphatidylinositol
Characteristics of membrane transport

Small uncharged and hydrophobic molecules can diffuse across membranes. Other molecules require protein assisted movement.

<table>
<thead>
<tr>
<th>TABLE 9.3 Characteristics of different types of membrane transport</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein carrier</td>
</tr>
<tr>
<td>Simple diffusion</td>
</tr>
<tr>
<td>Channels and pores</td>
</tr>
<tr>
<td>Passive transport</td>
</tr>
<tr>
<td>Active transport</td>
</tr>
<tr>
<td>Primary</td>
</tr>
<tr>
<td>Secondary</td>
</tr>
</tbody>
</table>
**Membrane transport through a pore or channel**

Central passage through water-filled pore allows specific molecules to transverse the membrane (e.g. porin in mitochondria outer membrane)

There are many types of channels; ion channels can transport ions much faster than pumps

[e.g. Transient receptor potential channels]

Examples: voltage-gated channels, ligand-gated channels, transient receptor potential channels

**Types of passive and active transport**

See Fig. 12.18
Active & passive transporters undergo a conformational change to drive transport

**Primary active transporter:**
\[ \text{Na}^+ - \text{K}^+ \text{ ATPase} \]

**Secondary active transporter:**

**Active transporters** move molecules against a concentration gradient: 1º transporters use 1º energy source (e.g. light, ATP, electron transport); 2º transporters driven by ion gradient

**Primary active transporter:**

**Secondary active transporter:**

\[ \text{glucose transporter} \]

Extracellular space:
- \([\text{K}^+] = 5 \text{ mM}\)
- \([\text{Na}^+] = 145 \text{ mM}\)

Cytosol:
- \([\text{K}^+] = 140 \text{ mM}\)
- \([\text{Na}^+] = 5 \text{–} 15 \text{ mM}\)

See Fig. 12.16 / 12.19
Active transport in *E. coli*

- Oxidation of $S_{\text{red}}$ generates a transmembrane proton gradient
- Movement of $H^+$ down its gradient drives lactose transport (lactose permease)

Potassium ion channel (1) Fig. 12.22
Potassium ion channel (2) Fig. 12.23
Selectivity filter of K+ ion channel

Potassium ion channel (3) Fig. 12.24
Energetic basis of ion selectivity in K+ ion channel
Potassium ion channel (4) Fig. 12.24
Energetic basis of ion selectivity in K+ ion channel.

Potassium ion channel (5) Fig. 12.25
Rapid rate of K+ movement due to structure of channel and electrostatic repulsion of incoming K+.
Molecules and complexes that are too large to be transported via transport proteins are transported in lipid vesicles out of the cell via \textit{exocytosis}, and into the cell via \textit{endocytosis}. We will not cover these processes in this course.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{signal_transduction.png}
\caption{Signal transduction through a membrane}
\end{figure}
Three general classes of membrane receptor proteins:

- seven-transmembrane-helix receptors
- Dimeric receptors that recruit protein kinases
- Dimeric receptors that are protein kinases

General mechanism of signal transduction across a membrane:

(e.g. hormones)

- *G proteins
- Tyrosine kinase
- Adenylate cyclase
- Phospholipase C

*detect
*amplify
signal external

To generate response
(e.g. changes in gene expression, enzyme activity, ion channel, etc.)
Common secondary messengers Fig. 13.2

G-protein cycle

- G proteins are activated by binding to a receptor-ligand complex
- G-proteins are inactivated slowly by their own GTPase activity
  (kcat about 3/min)
Understanding G Proteins:
Hydrolysis of GTP to GDP and $P_i$

Three general classes of membrane receptor proteins:

Seven-transmembrane-helix receptors (7TM)

Dimeric receptors that recruit protein kinases

Dimeric receptors that are protein kinases
Three general classes of membrane receptor proteins:

**Seven-transmembrane-helix receptors (7TM)**

*All 7TM appear to be G-protein-coupled receptors (GPCRs)*

Dimeric receptors that recruit protein kinases

Dimeric receptors that are protein kinases

**Summary of the adenyl cyclase signaling pathway**

*Example of seven-transmembrane-helix (7TM) receptor*

See Fig 13.6, 13.7; 13.8
Production, inactivation of cAMP

(continued)
• Activation of protein kinase A by cAMP

See Fig. 13.7

Caffeine & theophylline inhibit cAMP phosphodiesterase

• Inhibition of cAMP phosphodiesterases prolongs the effects of cAMP

• This increases the intensity and duration of stimulatory hormones
• Inositol-phospholipid signaling pathway

See Fig. 13.11, 13.12

Phospholipases hydrolyze phospholipids

Lipases: enzymes that catalyze hydrolysis of triacylglycerols

Phospholipases: catalyze hydrolysis of glycerophospholipids
Phosphatidylinositol 4,5-bisphosphate (PIP$_2$) produces IP$_3$ and diacylglycerol

See Fig. 13.11

(continued)
• Activation of receptor tyrosine kinases by ligand-induced dimerization

Three general classes of membrane receptor proteins:
- Seven-transmembrane-helix receptors
- Dimeric receptors that recruit protein kinases
- Dimeric receptors that are protein kinases

See Fig. 13.15

(continued)

• Phosphorylated dimer phosphorylates cellular target proteins
(continued)

- Each domain catalyzes phosphorylation of its partner

Insulin receptor and tyrosine kinase activity

- Insulin binds to 2 extracellular α-chains
- Transmembrane β-chains then autophosphorylate
- Tyrosine kinase domains then phosphorylate insulin-receptor substrates (IRSs) (which are proteins)
Insulin-stimulated formation of PIP₃

A different type of tyrosine kinase signal transduction:
Growth hormone receptor for which binding brings together associated proteins with tyrosine kinase domains

Three general classes of membrane receptor proteins:
Seven-transmembrane-helix receptors
*Dimeric receptors that recruit protein kinases
Dimeric receptors that are protein kinases

Fig. 13.13
Cross-phosphorylation of two JAK2 induced by hormone receptor dimerization

Small G proteins (small GTPases)
are a large superfamily of signalling proteins

They include: Ras, Rho, Aft, Rab, and Ran

Small GTPases cycle between an active GTP-bound form and an inactive GDP-bound form

Small GTPases are smaller (20-25kd) and monomer compared to the larger (30-35 kd) and trimeric G proteins
Structure and nomenclature of fatty acids

- **Saturated** FA - no C-C double bonds
- **Unsaturated** FA - at least one C-C double bond
- **Monounsaturated** FA - only one C-C double bond
- **Polyunsaturated** FA - two or more C-C double bonds

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</table>
Another method to measure membrane permeability

Mueller & Rudin: dip paint brush into lipid membrane solution & paint across 1 mm diameter hole partitioned between two aqueous media. → macroscopic bilayer membrane

Measure electrical conductance from one media to the other