

CHEM 153A Week 5

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Carbohydrates

- **Carbohydrates** = aldehydes or ketones with at least two hydroxyl groups, or substances that yield such compounds on hydrolysis
- many carbohydrates have the empirical formula $(CH_2O)_n$
- **monosaccharides** = simple sugars, consisting of a single polyhydroxy aldehyde or ketone unit
 - Example: D-glucose
- **disaccharides** = oligosaccharides with two monosaccharide units
 - Example: sucrose (D-glose and D-fructose)
- **Oligosaccharides** = short chains of monosaccharide units, or residues, joined by glycosidic bonds
- **Polysaccharides** = sugar polymers with 10+ monosaccharide units
 - Examples: cellulose (linear), glycogen (branched)

Functions of Carbohydrates

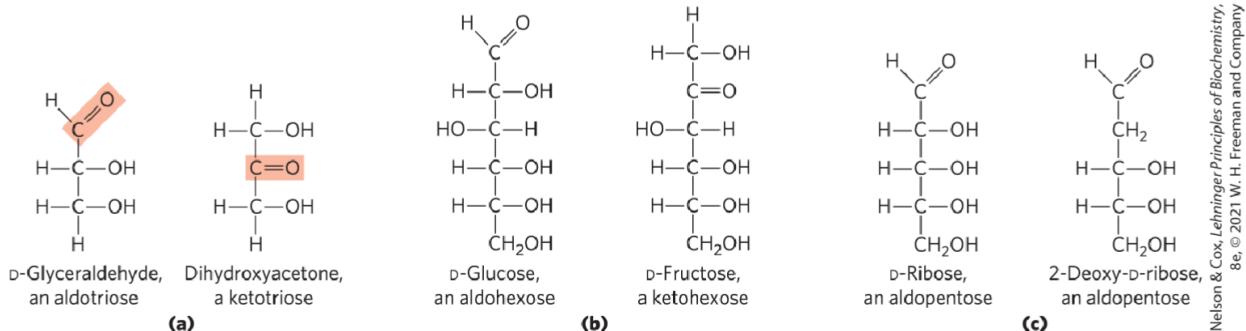
- Energy sources (e.g., large polymers for energy storage)
- Protein targeting
- Cell identification/recognition (e.g., determination of blood type)
- Protection/structure (e.g., call walls and insect shells)
- Components of other biomolecules (e.g., antibiotics, enzyme cofactors, nucleic acids, etc.)
- Other (e.g., lubrication in joints)

From previous courses:

- What a carbohydrate is
- Different kinds of sugars (mono-, di-, poly-)
- Basic structures of a few monosaccharides
- Basic nomenclature
 - Aldoses vs. Ketoses (functional group)
 - C₃ = triose
 - C₄ = tetraose
 - C₅ = pentose
 - C₆ = hexose

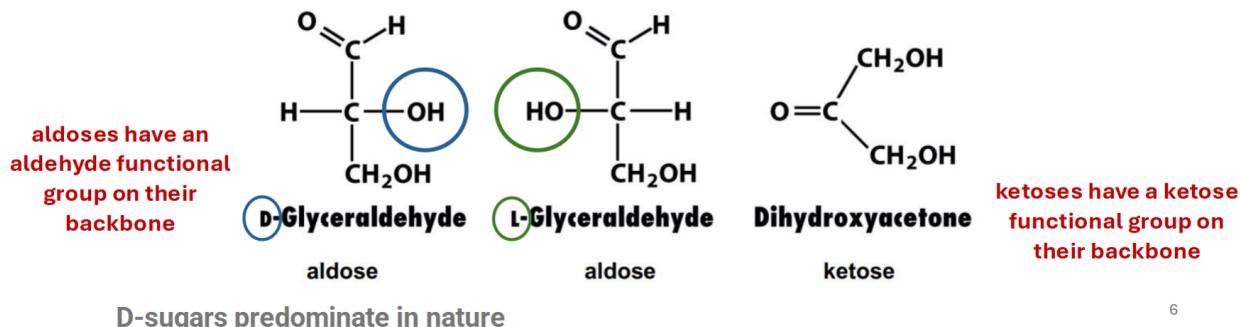
Aldoses and Ketoses

- **aldose** = carbonyl group is at an end of the carbon chain (in an aldehyde group)
- **ketose** = carbonyl group is at any other position (in a ketone group)



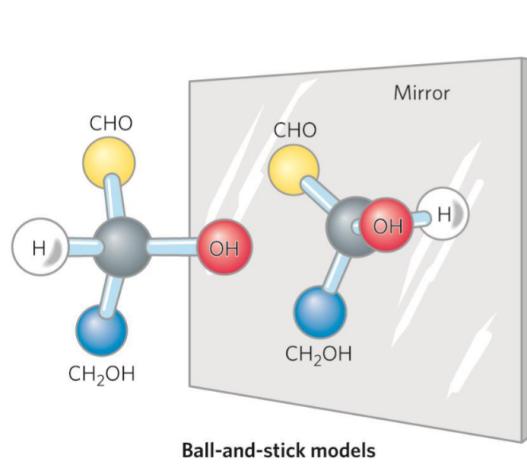
Basic Trioses - D and L

- The below structures are all **trioses** (three carbon sugars) - basically the simplest sugars possible
- For n stereocenters, there are 2 possible stereoisomers (making 2^n stereoisomers total)
- Glyceraldehyde has 1 stereocenter, hence 2 stereoisomers, notated as D and L
 - If the OH on the last chiral carbon points to the right, the sugar is D
 - If the OH on the last chiral carbon points to the left, the sugar is L



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Enantiomers of Glyceraldehyde



Fischer projection formulas



Perspective formulas

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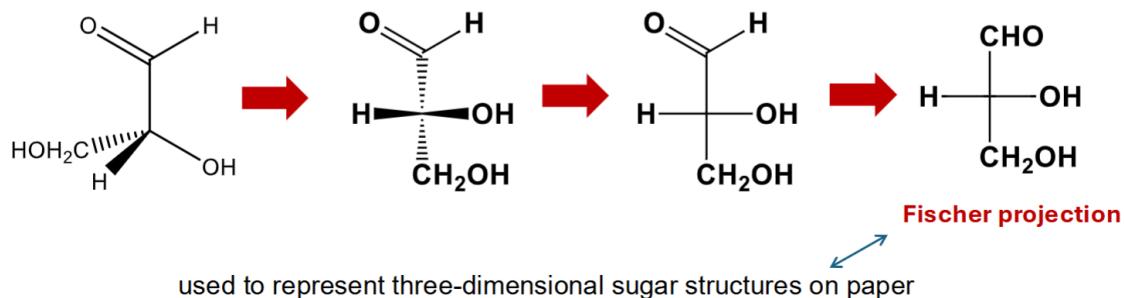
D Isomers and L Isomers

- **reference carbon** = chiral center *most distant* from the carbonyl carbon
- two groups of stereoisomers:
 - D isomers = configuration at reference carbon is the same as D-glyceraldehyde
 - * on the right (dextro) in a projection formula
 - * most hexoses of living organisms
 - L isomers = configuration at reference carbon is the same as L-glyceraldehyde
 - * on the left (levo) in a projection formula

Fischer Projection Review

- Fischer projections are the preferred representation of linear carbohydrates
- Vertical lines represent dashes angled away from you
- Horizontal lines represent wedges angled towards you
- Fischer projections of longer sugars are set up in such a way as to easily transition to cyclic molecules

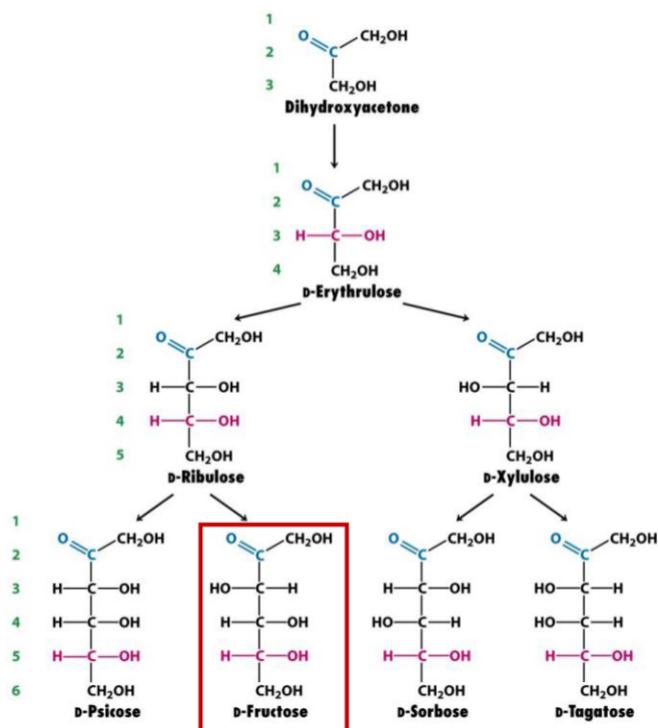
D-(+)-glyceraldehyde



Ketose Family

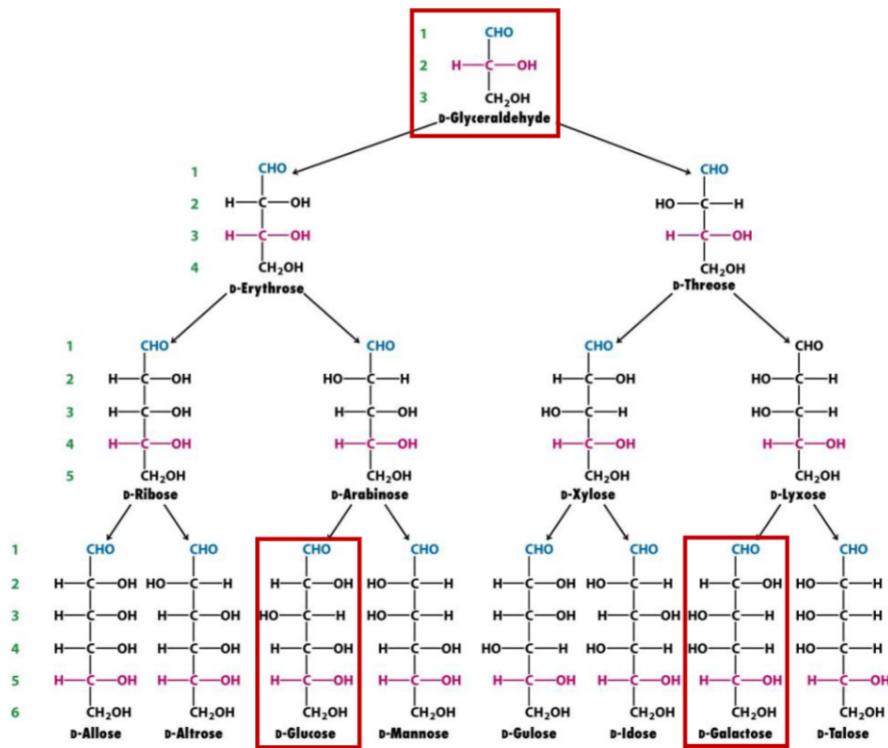
The carbons of a sugar are numbered beginning at the end of the chain nearest the carbonyl group

- C₃ = triose
- C₄ = tetraose
- C₅ = pentose
- C₆ = hexose



3 stereocenters, so 2^3 stereoisomers, but we're excluding L sugars so $8/2 = 4$.

Aldose Family

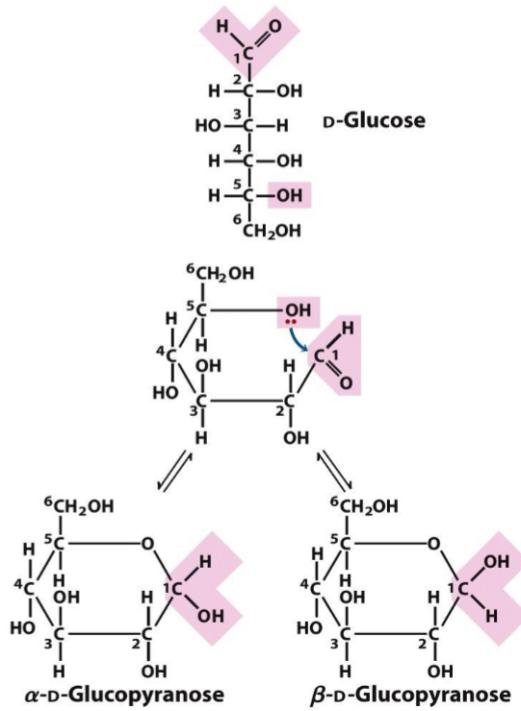


The Common Monosaccharides Have Cyclic Structures

- in aqueous solution, aldotetroses and all monosaccharides with 5+ backbone carbon atoms occur as cyclic structures
 - covalent bond between the carbonyl group and the oxygen of a hydroxyl group → cyclic hemiacetal
- Linear sugars cyclize via intramolecular hemiacetal formation
- Favored ring sizes: 5- and 6-membered rings (furanoses and pyranoses)

Formation of the Two Cyclic Forms of D-Glucose

- Reaction between the aldehyde group at C-1 and the hydroxyl group at C-5 forms a **hemiacetal linkage**
- mutarotation** = the interconversion of α and β anomers



Mutarotation is the interconversion of α and β anomers

Cyclization of Monomeric Sugars

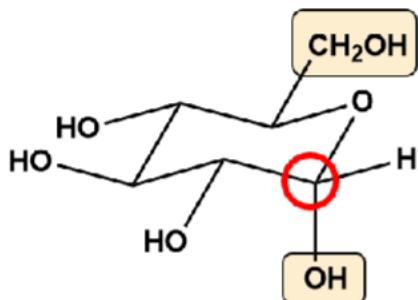
- Previous linear molecule had four stereocenters
 - Cyclization generates a new stereocenter at C_1
- Two possibilities can form, α and β anomers
 - Notation denotes whether -OH is on the same side of ring as C_6
 - * α is opposite side
 - * β is same side
- For D-sugars, C_6 is above the ring so always the same behavior
 - α , -OH is down (trans)
 - β , -OH is up (cis)
- Cyclization is a reversible process
 - This means anomers can interchange
 - * This is called **mutarotation**
 - C_1 is now the anomeric carbon

Mutarotation

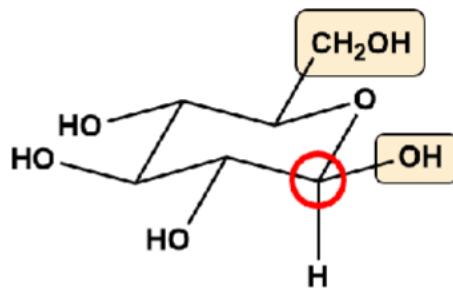
- In aqueous solution, cyclic sugars like glucose exist in equilibrium with their open-chain form.
- When a sugar molecule opens up, the **hemiacetal bond at the anomeric carbon is broken**, forming the linear aldehyde (or ketone) form.
- This open-chain form can then reclose to form either the α - or β -anomer.

- The direction from which the hydroxyl group attacks the carbonyl carbon determines whether the -OH at the anomeric carbon ends up in the axial (α) or equatorial (β) position. Under acidic or basic conditions, this equilibrium is established more rapidly, but it occurs spontaneously even in pure water. Thus, mutarotation is the chemical process by which the configuration at the anomeric center interconverts, switching the α - and β -anomeric forms.

Cyclization of monomeric sugars produces either of two stereoisomeric configurations: α and β



If $-\text{CH}_2\text{OH}$ and $-\text{OH}$ are *trans*: α

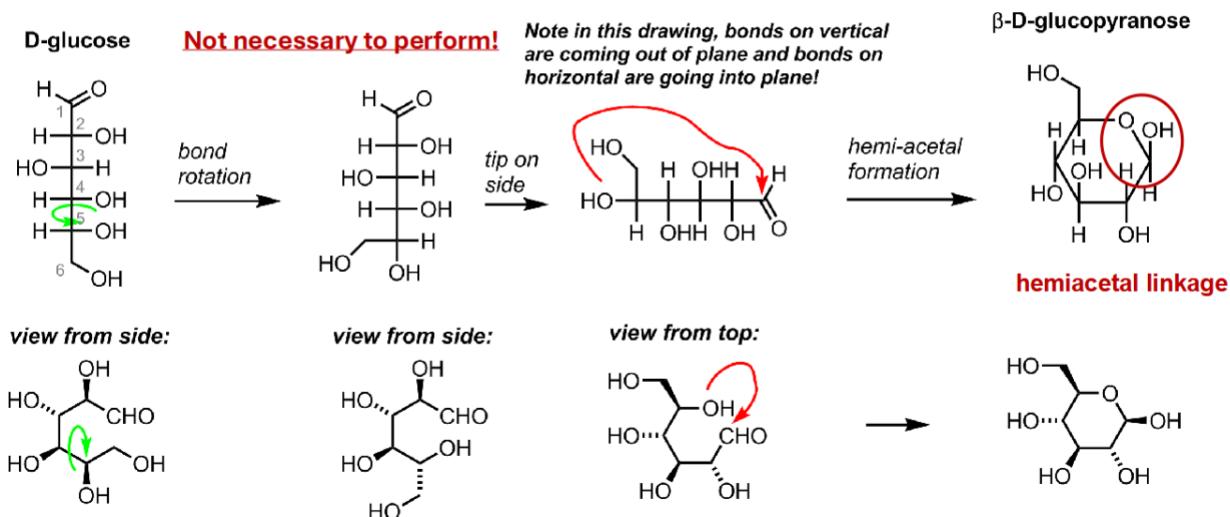


If $-\text{CH}_2\text{OH}$ and $-\text{OH}$ are *cis*: β

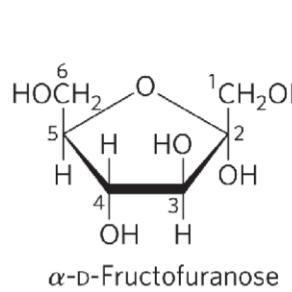
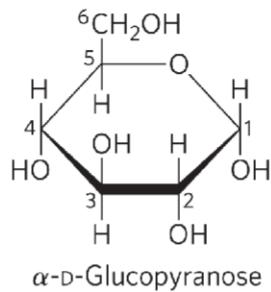
The anomeric carbon serves as the **connection** to other monosaccharides

The **anomeric carbon** is highly reactive because it retains some of the original reactivity of the carbonyl group from the linear form. This makes it ideal for forming **glycosidic bonds**, which are the covalent linkages between sugars or between a sugar and another molecule (such as a protein or lipid)

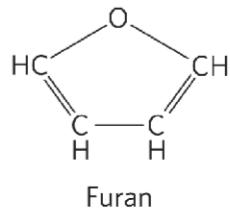
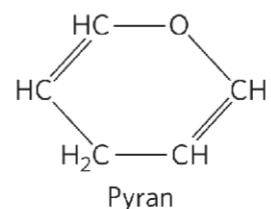
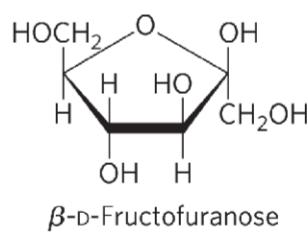
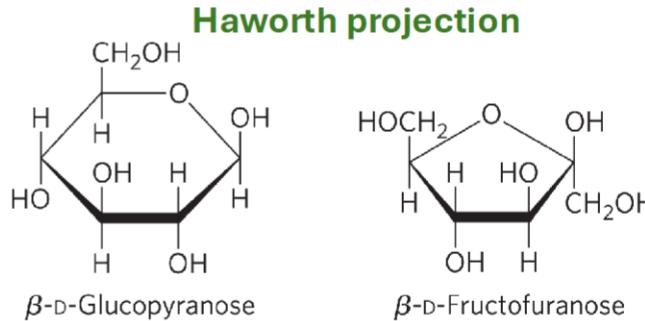
Cyclization of Linear Monosaccharides Mechanism



Pyranoses and Furanoses



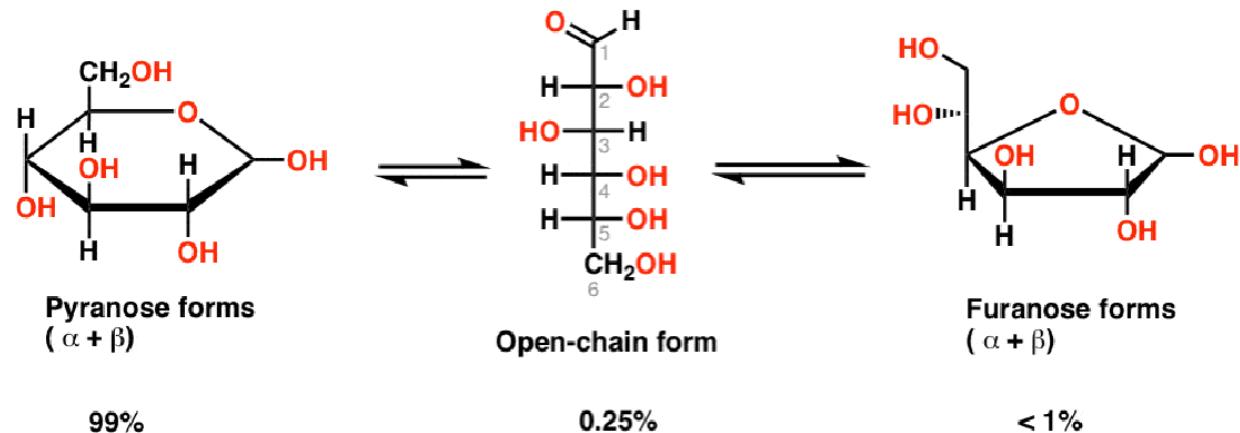
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- Six-membered ring compounds are called **pyranoses** because they resemble the six-membered ring compound pyran. The systematic names for the two ring forms of D-glucose are therefore α -D-glucopyranose and β -D-glucopyranose
- Ketohexoses (such as fructose) also occur as cyclic compounds with α and β anomeric forms. In these compounds, the hydroxyl group at C-5 (or C-6) reacts with the keto group at C-2 to form a **furanose** (or pyranose) ring containing a hemiketal linkage.
- D-Fructose readily forms the furanose ring the more common anomer of this sugar in combined forms or in derivatives is β -D-fructofuranose

Furanoses can exist in equilibrium with pyranoses

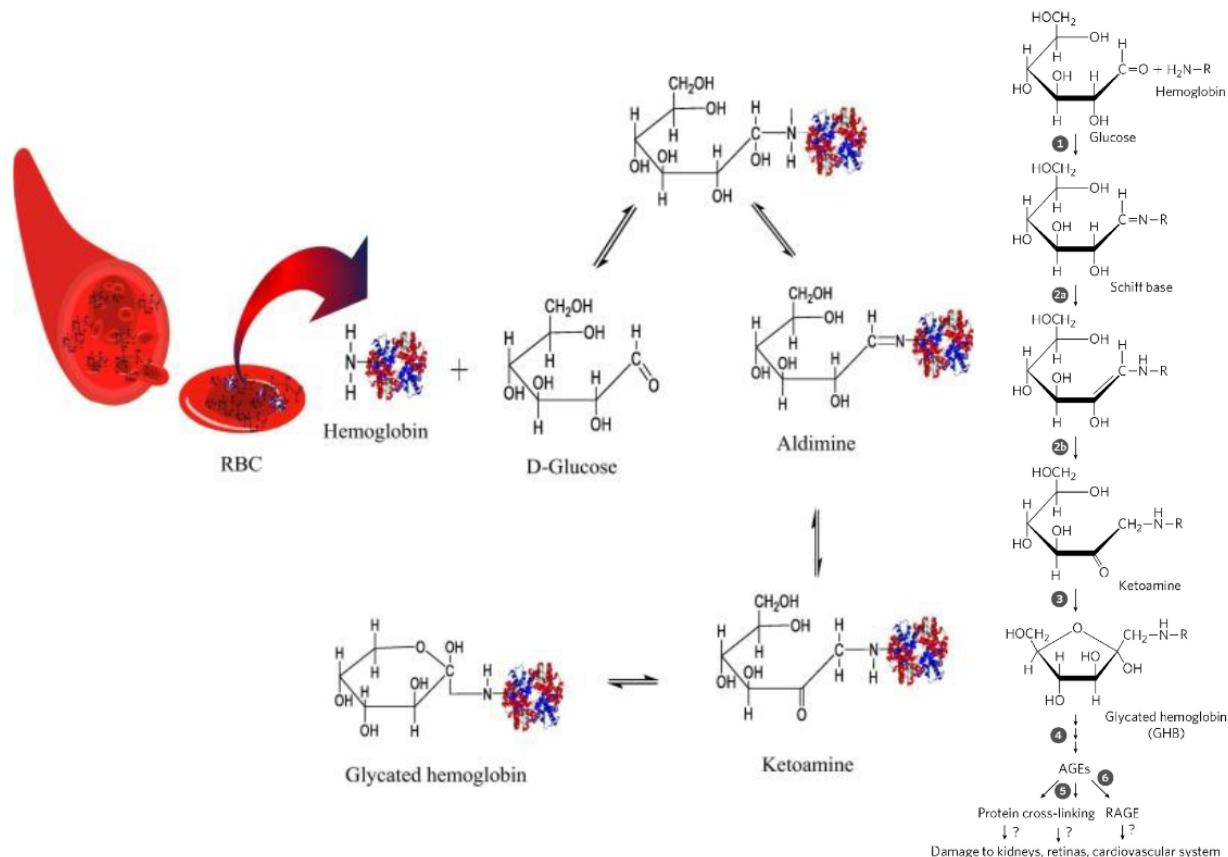
The pyranose form of glucose dominates (>99%) at equilibrium in aqueous solution



Hemoglobin Glycation

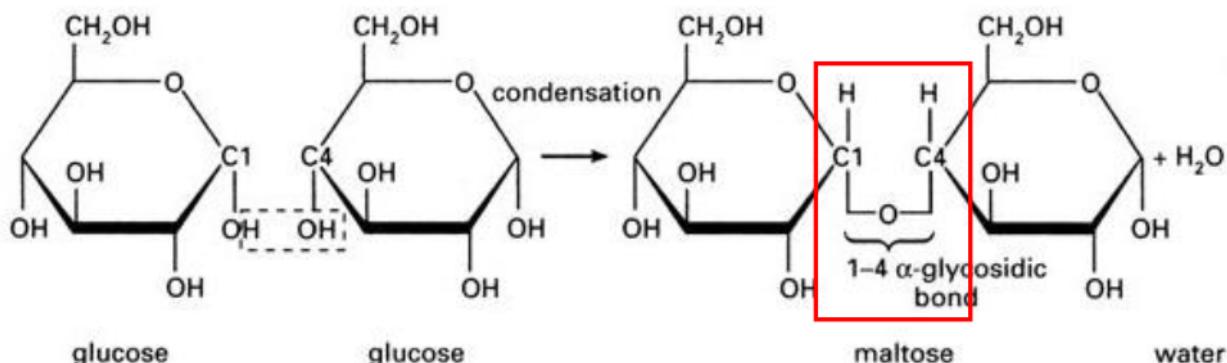
(so named to distinguish it from glycosylation, the enzymatic transfer of glucose to a protein)

- A person's glycated hemoglobin fraction (HbA1c) reflects the average concentration of glucose in the blood (AG) over the past 2-3 months and is the gold standard measure for establishing risk for diabetes-related complications in patients with type 1 or type 2 diabetes



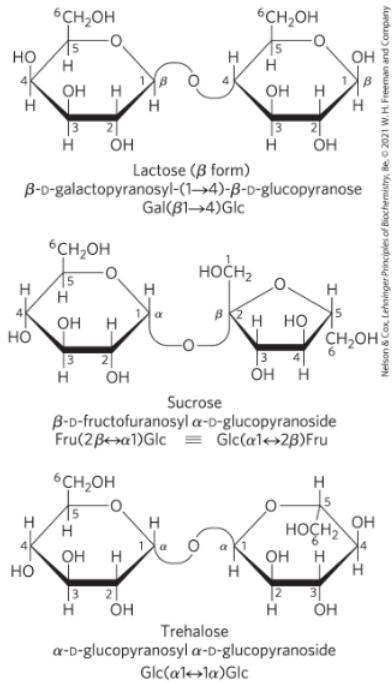
Glycosidic Bond Formation

- Glycosidic bonds are covalent bonds that form between the hemiacetal group of a carbohydrate and a hydroxyl group on another compound (for us, other carbohydrates)
- This is how disaccharides, oligosaccharides, and polysaccharides form
 - Glycosidic bonds are noted with: The carbon they come from, the carbon they're going to, and the α/β arrangement (determined by the anomeric carbon)



Nomenclature for Glycosidic Bonds

- Anomeric Configuration:
 - α : In a Haworth projection of a D-pyranose, the -OH on the anomeric carbon is positioned on the side opposite the CH_2OH group (typically shown "down" or in an axial orientation)
 - β : The -OH on the anomeric carbon is on the same side as the CH_2OH group (typically shown "up" or in an equatorial orientation)
- Linkage Positions:
 - The notation (e.g., 1 \rightarrow 4) indicates that the bond forms between the anomeric carbon (C1) of one sugar and a specific carbon (e.g., C4) on the adjacent sugar
 - Other common linkages include:
 - * 1 \rightarrow 6: For example, in glycogen, the main chain is formed by $\alpha(1\rightarrow4)$ linkages with branch points at $\alpha(1\rightarrow6)$ bonds
 - * 1 \rightarrow 2: In sucrose, the glycosidic bond links the anomeric carbon of glucose to the anomeric carbon of fructose (commonly described as α -D-glucopyranosyl-(1 \rightarrow 2)- β -D-fructofuranoside)
- Examples:
 - Amylose (starch): Composed of $\alpha(1\rightarrow4)$ glycosidic bonds
 - Cellulose: Consists of $\beta(1\rightarrow4)$ glycosidic bonds
 - Glycogen: Features $\alpha(1\rightarrow4)$ bonds in its main chain with $\alpha(1\rightarrow6)$ bonds at branch points
 - Sucrose: Has an $\alpha(1\rightarrow2)$ glycosidic bond linking the two monosaccharides



Note that the glycosidic bond can be alpha or beta, and that the second carbohydrate can be linked at any of the carbon atoms that contain an -OH. The glycosidic bond is named as alpha or beta, followed by numbers that correspond to the locations of the carbons involved in the glycosidic bond.

Polysaccharides

Monomeric subunits, monosaccharides, serve as the building blocks of large carbohydrate polymers. The specific sugar, the way the units are linked, and whether the polymer is branched determine its properties and thus its function

- Most carbohydrates in nature occur as polysaccharides ($M_r > 20000$)
- also called **glycans**

TABLE 7-1
Symbols and Abbreviations for Common Monosaccharides and Some of Their Derivatives

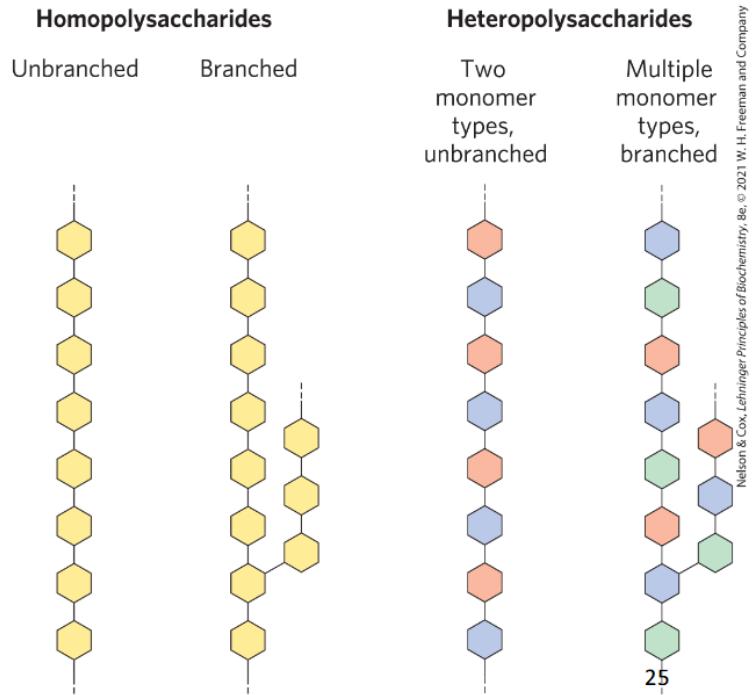
Abequose	Abe	Glucuronic acid	GlcA
Arabinose	Ara	Galactosamine	GalN
Fructose	Fru	Glucosamine	GlcN
Fucose	Fuc	<i>N</i> -Acetylgalactosamine	GalNAc
Galactose	Gal	<i>N</i> -Acetylglucosamine	GlcNAc
Glucose	Glc	Iduronic acid	IdoA
Mannose	Man	Muramic acid	Mur
Rhamnose	Rha	<i>N</i> -Acetylmuramic acid	Mur2Ac
Ribose	Rib	<i>N</i> -Acetylneurameric acid (a sialic acid)	Neu5Ac
Xylose	Xyl		

Note: In a commonly used convention, hexoses are represented as circles, *N*-acetylhexosamines as squares, and hexosamines as squares divided diagonally. All sugars with the "gluco" configuration are blue, those with the "galacto" configuration are yellow, and "manno" sugars are green. Other substituents can be added as needed: sulfate (S), phosphate (P), *O*-acetyl (OAc), or *O*-methyl (OMe).

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Homopolysaccharides and Heteropolysaccharides

- **Homopolysaccharides** = contain only a single monomeric sugar species
 - Serve as storage forms and structural elements
- **Heteropolysaccharides** = contain 2+ kinds of monomers
 - provide extracellular support



Polsaccharides Generally Do Not Have Defined Lengths or Molecular Weights

- This distinction between proteins and polysaccharides is a consequence of the mechanisms of assembly
- There is no template for polysaccharide synthesis
- The program for polysaccharide synthesis is intrinsic to the enzymes that catalyze the polymerization of monomer units

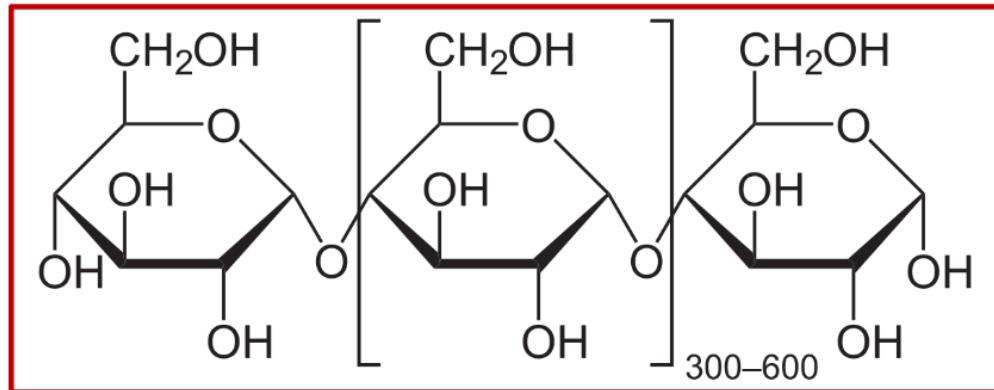
The sequences of complex polysaccharides are determined by the intrinsic properties of the biosynthetic enzymes that add each monomeric unit to the growing polymer.

Some Homopolysaccharides are storage forms of fuel

- storage polysaccharides = starch in plant cells and glycogen in animal cells
- **starch and glycogen molecules are heavily hydrated because they have many exposed hydroxyl groups available to hydrogen bond**

Starch (Amylose)

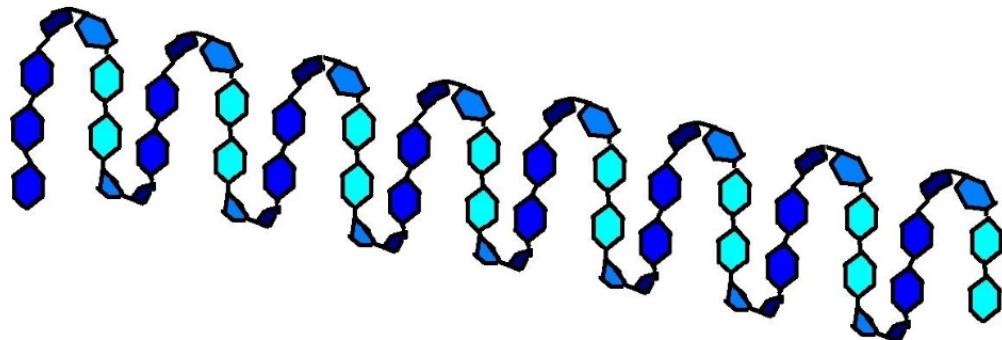
- **Amylose (starch) is a polysaccharide if α -D-glucose that's used for energy storage in plants**
- Standard 1,4 linkage, no branches
- Human enzymes can break down α linkages and utilize for energy



α -1,4-glycosidic bond

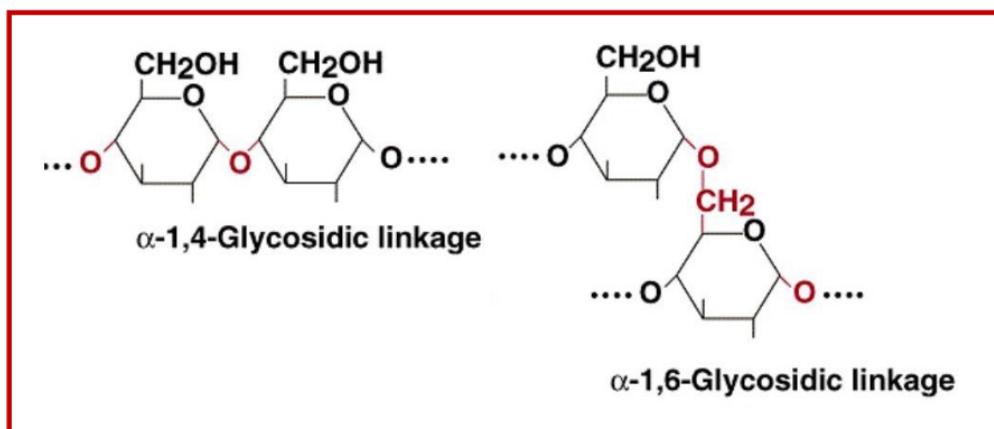
Starch (amylose) isn't a straight chain!

- On average, 8 glucose residues per turn.

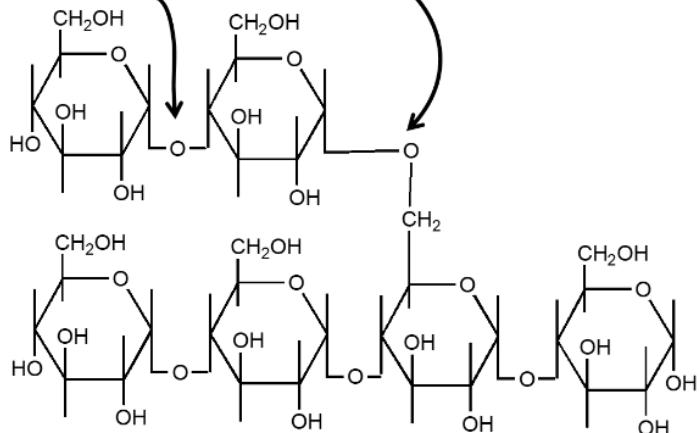


Glycogen

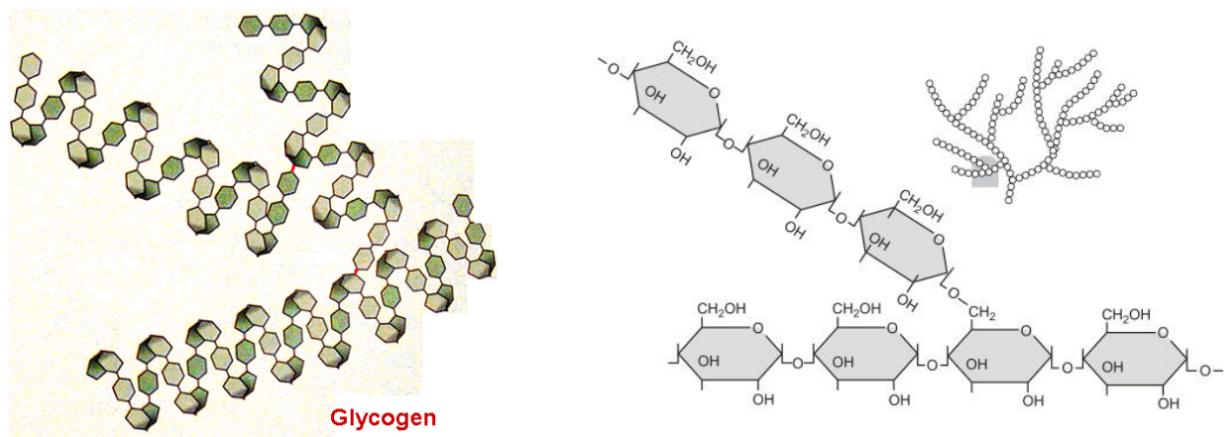
- Glycogen is a polysaccharide of α -D-glucose that's used for **energy storage in animals**
- Main linkage is 1,4 but after 8-10 residues there's a 1,6 linkage as well
- Multiple branches reduce time it takes for breakdown and utilization
- Human enzymes can more easily break down α linkages



Linear: $\alpha 1 \rightarrow 4$
Branches: $\alpha 1 \rightarrow 6$



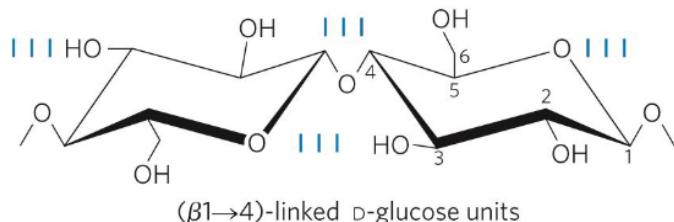
Glycogen isn't a straight chain either!



Some Homopolysaccharides Serve Structural Roles

Cellulose = tough, fibrous, water-insoluble substance

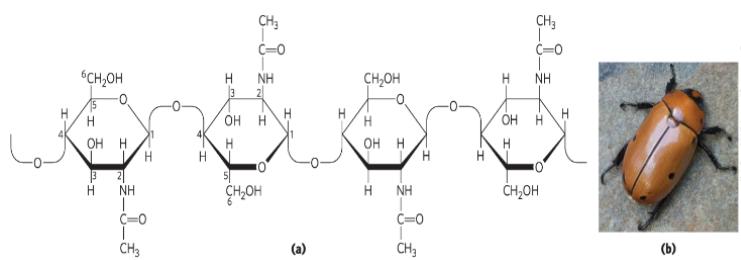
- linear, unbranched homopolysaccharide, consisting of 10000 to 15000 D-glucose units
- glucose residues have the β configuration
- linked by $(\beta 1 \rightarrow 4)$ glycosidic bonds
- animals do not have the enzyme to hydrolyze $(\beta 1 \rightarrow 4)$ glycosidic bonds



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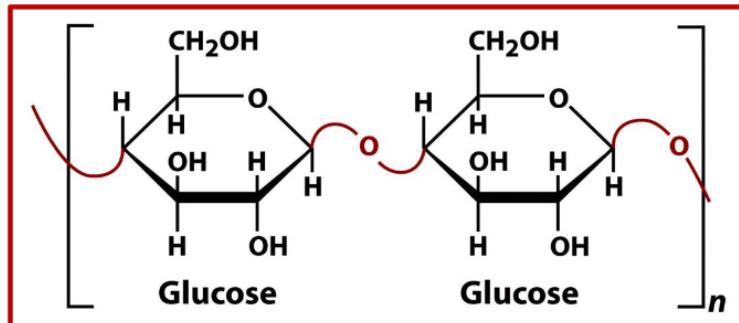
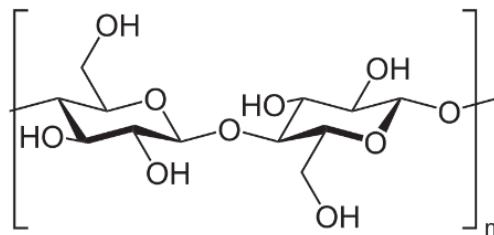
Chitin = linear homopolysaccharide composed of n -acetylglucosamine residues in $(\beta 1 \rightarrow 4)$ linkage

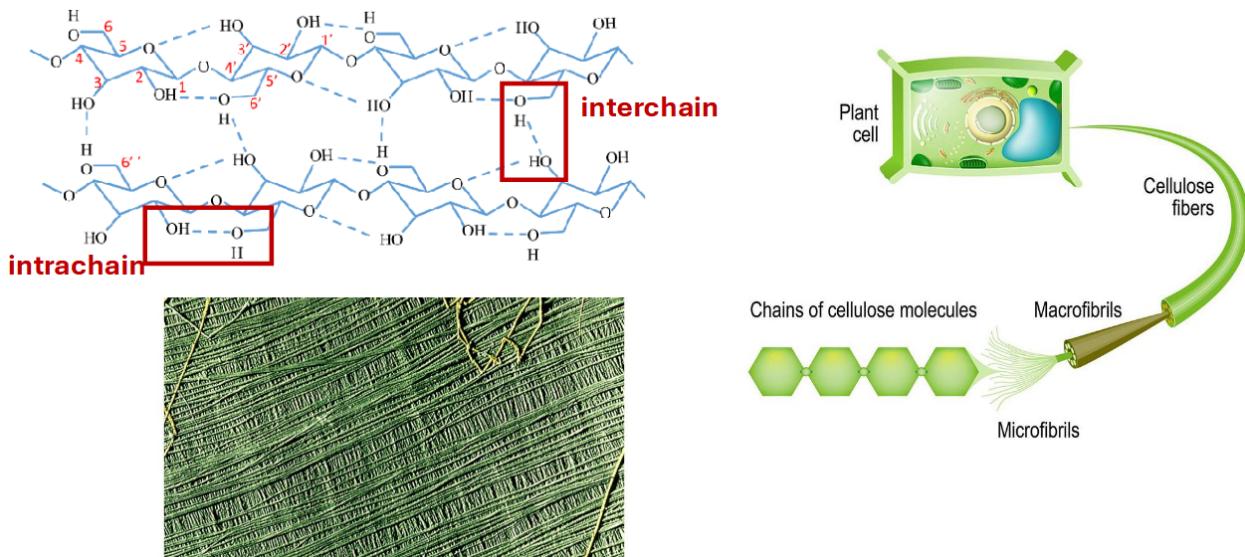
- Acetylated amino group makes chitin more hydrophobic and water-resistant than cellulose



Cellulose

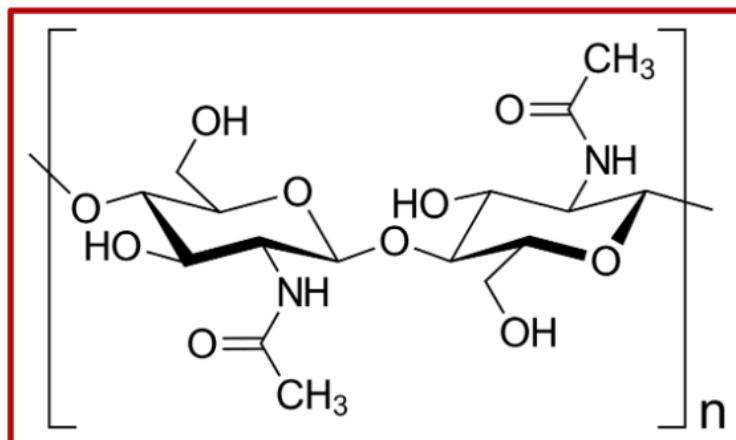
- Cellulose is a polysaccharide of β -D-glucose that's used **for structure** in plants
- Human enzymes can't break down β linkages! No way to use for energy
- **Cellulose has an alternating structure!** (every other glucose is inverted)
- Cellulose chains can form strong intrachain and interchain hydrogen bonds: High tensile strength





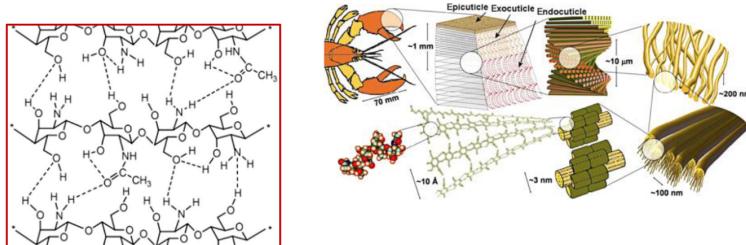
Chitin

- Chitin is a polysaccharide of N-acetyl-D-glucosamine connected through a $\beta(1 \rightarrow 4)$ linkage
- Structure of chitin differs from cellulose because of acetamide groups
- Also has alternating structure and strong interchain/intrachain hydrogen bonding

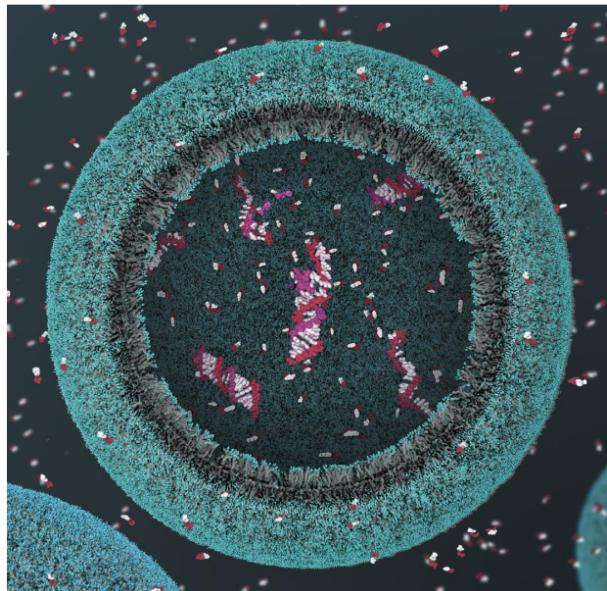


β -1,4-glycosidic bond

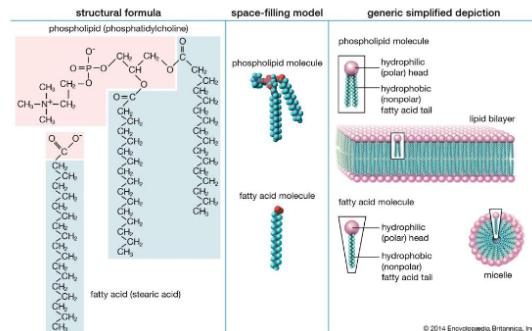
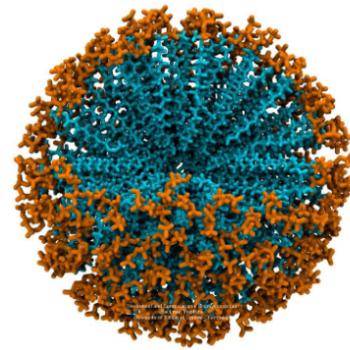
It is a **structural polysaccharide** found in the exoskeletons of **insects**, **crustaceans** (like crabs and shrimp), and the **cell walls of fungi**. Chitin is the second most abundant polysaccharide in nature after cellulose.



Lipids and Membranes



<https://animationlab.utah.edu/projects>



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Lipids

- Lipids are a class of organic compounds that are **insoluble in water**, and soluble in organic solvents
 - Note that this is a definition based around solubility, not so much structure
- Energy storage: Longer term in comparison with carbohydrates (hydrocarbon tails store lots of energy)
- Structural components: Cell membranes! (e.g., phospholipid bilayer)
- Signaling molecules: Both intracellular and intercellular (e.g., testosterone)

Lipidomics Seeks to Catalog All Lipids and their Functions

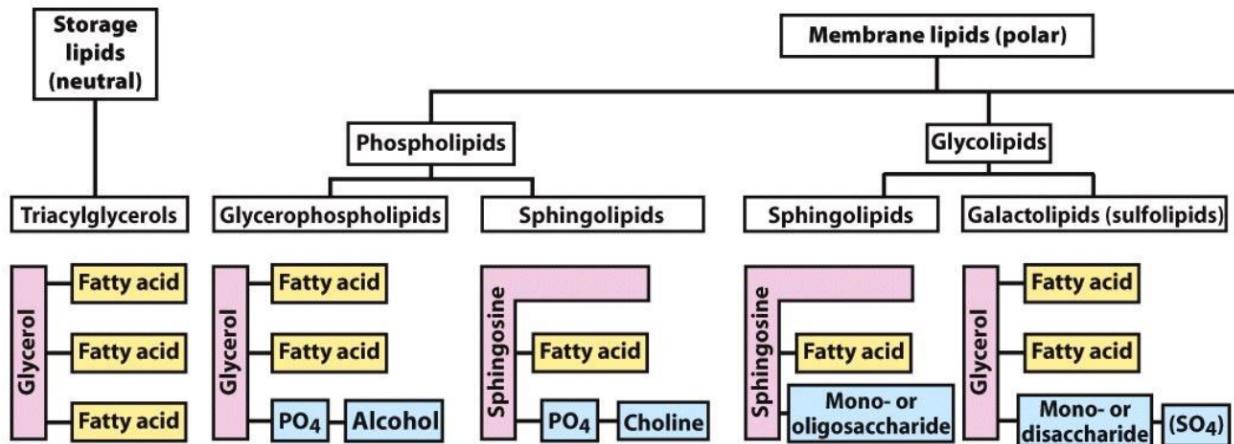
LIPID MAPS Lipidomics Gateway = database analogous to the Protein Data Bank

- has its own classification system of eight chemical categories

Table 10-2 Eight Major Categories of Biological Lipids

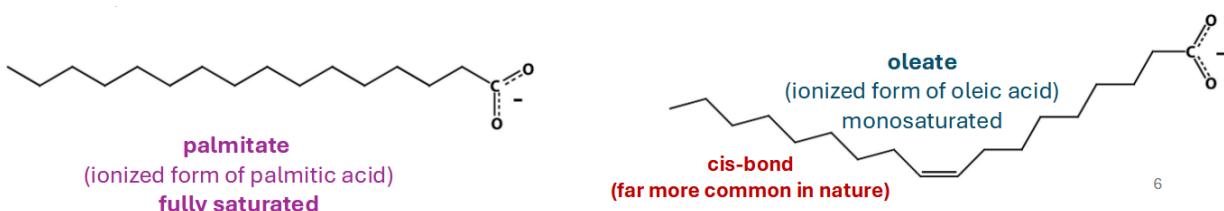
Category	Category code	Examples
Fatty acids	FA	Oleate, stearoyl-CoA, palmitoylcarnitine
Glycerolipids	GL	Di- and triacylglycerols
Glycerophospholipids	GP	Phosphatidylcholine, phosphatidylserine, phosphatidyethanolamine
Sphingolipids	SP	Sphingomyelin, ganglioside, GM2
Sterol lipids	ST	Cholesterol, progesterone, bile acids
Prenol lipids	PR	Farnesol, geraniol, retinol, ubiquinone
Saccharolipids	SL	Lipopolysaccharide
Polyketides	PK	Tetracycline, erythromycin, aflatoxin B ₁

Lipids Overview

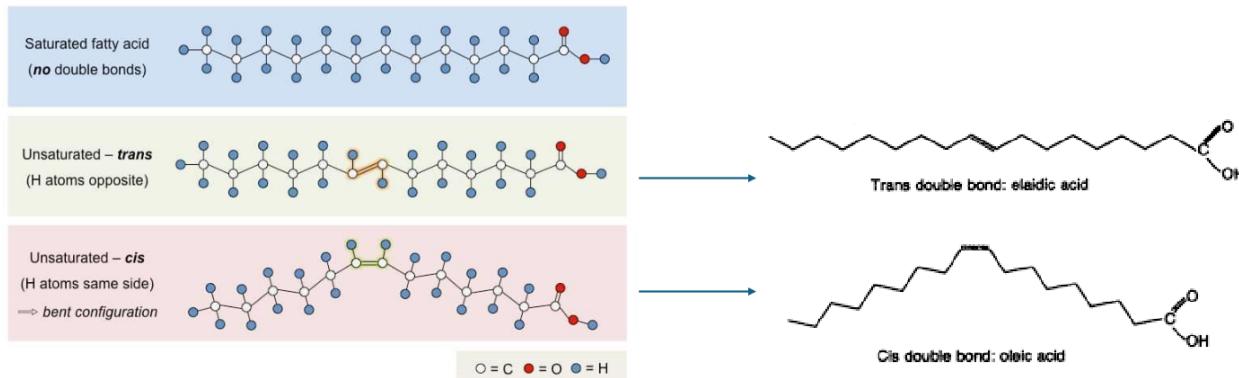


Fatty Acids

- **Fatty acids** are carboxylic acids with aliphatic chains (hydrocarbon chains) ranging from 4 to 36 carbons long (C₄ to C₃₆)
- In some fatty acids, this chain is unbranched and fully saturated (contains no double bonds)
- In others, the chain contains one or more double bonds. A few contain three-carbon rings, hydroxyl groups, or methyl-group branches
- A **polyunsaturated** fatty acid contains **more than one double bond** in its backbone
- Naturally occurring components of triacylglycerols and phospholipids



Cis and Trans Configuration



Unsaturated fats have one or more **double bonds** between carbon atoms. These double bonds can exist in two configurations:

- **Cis configuration:** The hydrogen atoms attached to the carbon atoms of the double bond are on the **same side** of the molecule. This creates a kink in the fatty acid chain, making it more difficult for the fats to pack together tightly. Cis fats are generally liquid at room temperature (e.g., oils)
- **Trans configuration:** The hydrogen atoms are on **opposite sides** of the double bond, resulting in a straighter chain, similar to saturated fats. This straight structure allows trans fats to pack together tightly, making them more solid at room temperature

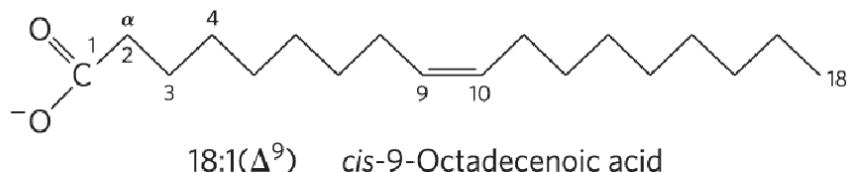
Common Patterns in Fatty Acids

Several naming schemes exist for fatty acids:

- most common fatty acids have even numbers of carbon atoms in an unbranched chain of 12 to 24 carbons: **the mode of synthesis, which involves successive condensations of two-carbon (acetate) units**
- In **monosaturated** fatty acids, the double bond is usually between **C-9 and C-10 (Δ^9)**
- in **polyunsaturated** fatty acids:
 - the double bonds are usually Δ^{12} and Δ^{15}
 - double bonds are usually separated by a methylene group
- double bonds are usually in the **cis** configuration

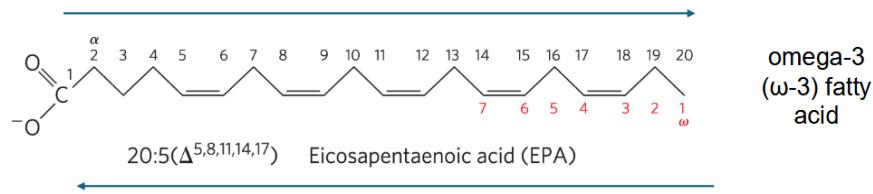
Nomenclature for Unbranched Fatty Acids

- the chain length and number of double bonds, separated by a colon
- numbering begins at the carboxyl carbon
- positions of double bonds are indicated by Δ and a superscript number



Polyunsaturated Fatty Acids (PUFAs)

- polyunsaturated fatty acids (PUFAs) = contain more than one double bond in their backbone
 - omega-3 ($\omega - 3$) fatty acids = double bond between C-3 and C-4 relative to the most distant carbon (ω)
 - omega-6 ($\omega - 6$) fatty acids = double bond between C-6 and C-7 relative to ω



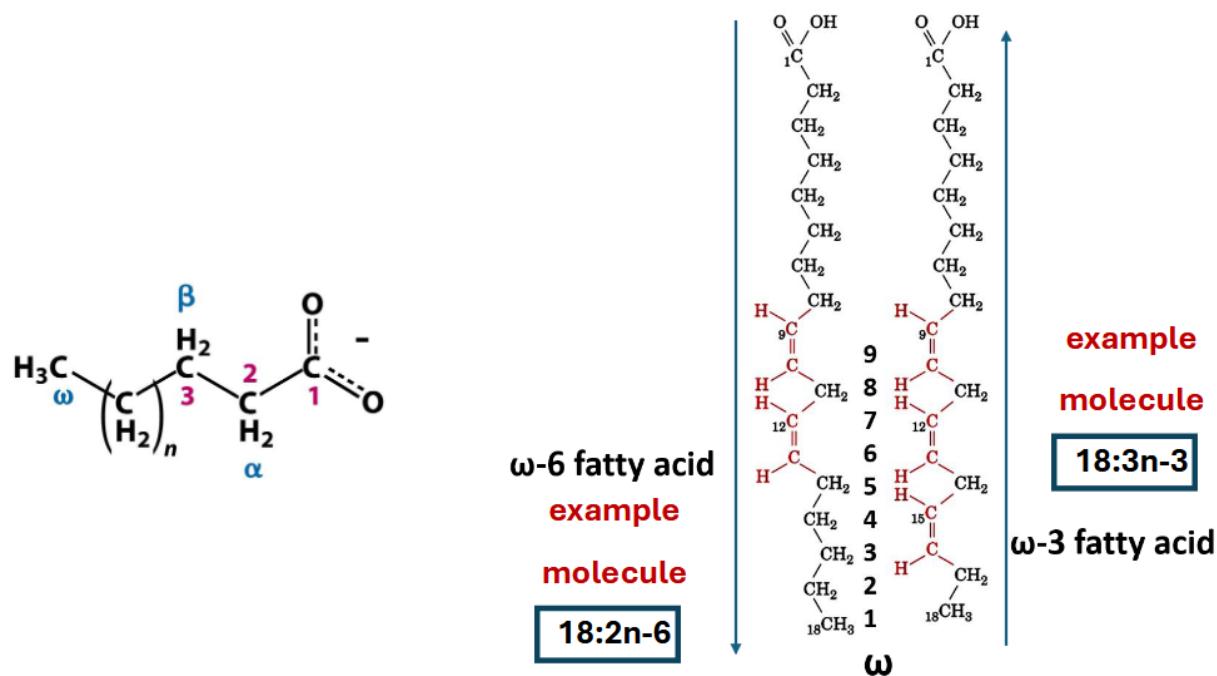
PUFAs and Human Nutrition

- humans must obtain the omega-3 PUFA α -linolenic acid (ALA; 18:3($\Delta^{9,12,15}$)) from their diet
- humans use ALA to synthesize:
 - eicosapentaenoic acid (EPA; 20:5($\Delta^{5,8,11,14,17}$))
 - dicosahexaenoic acid (DHA; 22:6($\Delta^{4,7,10,13,16,19}$))
- the optimal dietary ratio of omega-6 and omega-3 PUFAs is between 1:1 and 4:1

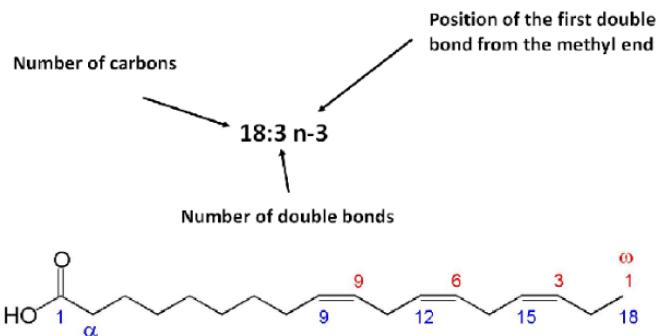
EPA and **DHA** are essential omega-3 fatty acids that play critical roles in **reducing inflammation**, supporting **cardiovascular health**, **brain function**, **eye health**, and **immune regulation**. DHA is particularly important for brain development and structure, while EPA is more involved in reducing inflammation and maintaining heart health.

Naming Fatty Acids

- Several naming schemes exist for fatty acids
 - **Omega Naming:**
 - The # of carbons in the fatty acid (e.g., 18)
 - The # of double bonds (2 or 3, for our examples)
 - The position of the first double bond from the methyl end (e.g., 6 and 3)
 - * Omega (ω) carbon is the final carbon in the fatty acid chain. We'll count backwards from ω to the first carbon in the double bond.



Omega Naming



Symbol	Common name	Systematic name	Structure
Saturated Fatty Acids			
12:0	lauric acid	dodecanoic acid	$\text{CH}_3(\text{CH}_2)_{10}\text{COOH}$
16:0	palmitic acid	hexadecanoic acid	$\text{CH}_3(\text{CH}_2)_{14}\text{COOH}$
18:0	stearic acid	octadecanoic acid	$\text{CH}_3(\text{CH}_2)_{16}\text{COOH}$
Unsaturated Fatty Acids			
16:1n-7	palmitoleic acid	9-hexadecenoic acid	$\text{CH}_3(\text{CH}_2)_5\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$
18:2n-6	linoleic acid	9,12-octadecadienoic acid	$\text{CH}_3(\text{CH}_2)_4(\text{CH}=\text{CHCH}_2)_2(\text{CH}_2)_6\text{COOH}$
20:4n-6	arachidonic acid	5,8,11,14-eicosatetraenoic acid	$\text{CH}_3(\text{CH}_2)_4(\text{CH}=\text{CHCH}_2)_4(\text{CH}_2)_2\text{COOH}$
20:5n-3	EPA	5,8,11,14,17-eicosapentaenoic acid	$\text{CH}_3\text{CH}_2(\text{CH}=\text{CHCH}_2)_5(\text{CH}_2)_2\text{COOH}$
22:6n-3	DHA	4,7,10,13,16,19-docosohexenoic acid	$\text{CH}_3\text{CH}_2(\text{CH}=\text{CHCH}_2)_6\text{CH}_2\text{COOH}$

Fatty acid MPs - Length

Table 9-1 The Common Biological Fatty Acids

Symbol ^a	Common Name	Systematic Name	Structure	mp (°C)
Saturated fatty acids				
12:0	Lauric acid	Dodecanoic acid	<chem>CH3(CH2)10COOH</chem>	44.2
14:0	Myristic acid	Tetradecanoic acid	<chem>CH3(CH2)12COOH</chem>	53.9
16:0	Palmitic acid	Hexadecanoic acid	<chem>CH3(CH2)14COOH</chem>	63.1
18:0	Stearic acid	Octadecanoic acid	<chem>CH3(CH2)16COOH</chem>	69.6
20:0	Arachidic acid	Eicosanoic acid	<chem>CH3(CH2)18COOH</chem>	77
22:0	Behenic acid	Docosanoic acid	<chem>CH3(CH2)20COOH</chem>	81.5
24:0	Lignoceric acid	Tetracosanoic acid	<chem>CH3(CH2)22COOH</chem>	88
Unsaturated fatty acids (all double bonds are cis)				
16:1n-7	Palmitoleic acid	9-Hexadecenoic acid	<chem>CH3(CH2)5CH=CH(CH2)7COOH</chem>	-0.5
18:1n-9	Oleic acid	9-Octadecenoic acid	<chem>CH3(CH2)7CH=CH(CH2)8COOH</chem>	12
18:2n-6	Linoleic acid	9,12-Octadecadienoic acid	<chem>CH3(CH2)4(CH=CHCH2)2(CH2)6COOH</chem>	-5
18:3n-3	α-Linolenic acid	9,12,15-Octadecatrienoic acid	<chem>CH3CH2CH=CHCH2CH3(CH2)6COOH</chem>	-11
18:3n-6	γ-Linolenic acid	6,9,12-Octadecatrienoic acid	<chem>CH3(CH2)4(CH=CHCH2)3(CH2)3COOH</chem>	-11
20:4n-6	Arachidonic acid	5,8,11,14-Eicosatetraenoic acid	<chem>CH3(CH2)4(CH=CHCH2)4(CH2)2COOH</chem>	-49.5
20:5n-3	EPA	5,8,11,14,17-Eicosapentaenoic acid	<chem>CH3CH2CH=CHCH2CH5(CH2)2COOH</chem>	-54
22:6n-3	DHA	4,7,10,13,16,19-Docosohexenoic acid	<chem>CH3CH2CH=CHCH2CH6CH2COOH</chem>	-44
24:1n-9	Nervonic acid	15-Tetracosenoic acid	<chem>CH3(CH2)13CH=CH(CH2)13COOH</chem>	39

^aNumber of carbon atoms:Number of double bonds. For unsaturated fatty acids, the quantity "n-x" indicates the position of the last double bond in the fatty acid, where n is its number of C atoms, and x is the position of the last double-bonded C atom counting from the methyl-terminal (ω) end.

Source: LipidBank (<http://www.lipidbank.jp>)

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why are MPs going up?

Longer chains: stronger van der Waals forces

The **melting point** of a substance is the temperature at which it transitions from a **solid** to **liquid** state.

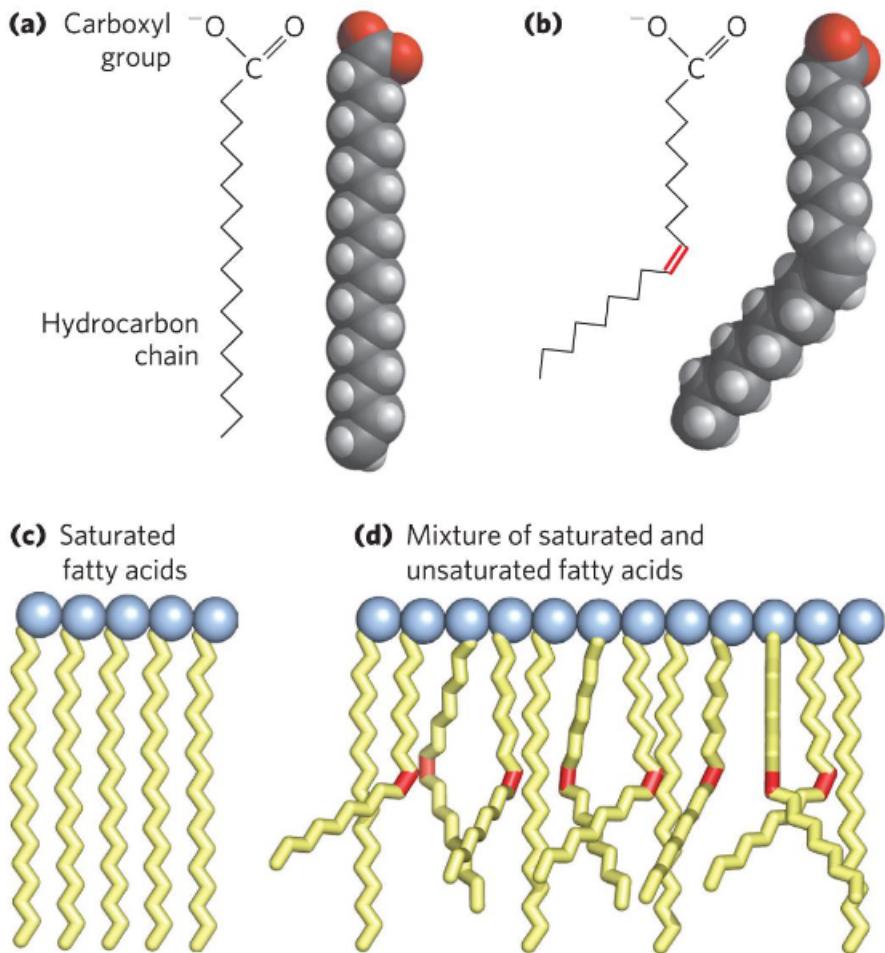
- The same phenomenon happens in hydrocarbons

Melting Points of Fatty Acids

At room temperature:

- saturated fatty acids have a waxy consistency
- unsaturated fatty acids are oily liquids
- extent of packing depends on degree of saturation: kinks disrupt packing

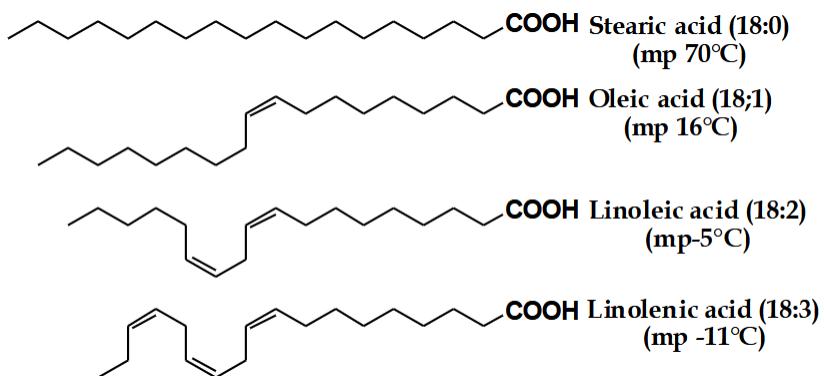
Fully saturated fatty acids in the extended form pack into nearly crystallizing arrays, stabilized by extensive hydrophobic interaction. The presence of one or more fatty acids with *cis* double bonds (red) interferes with this tight packing and results in less stable aggregates.



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Fatty acid MPs - Unsaturation

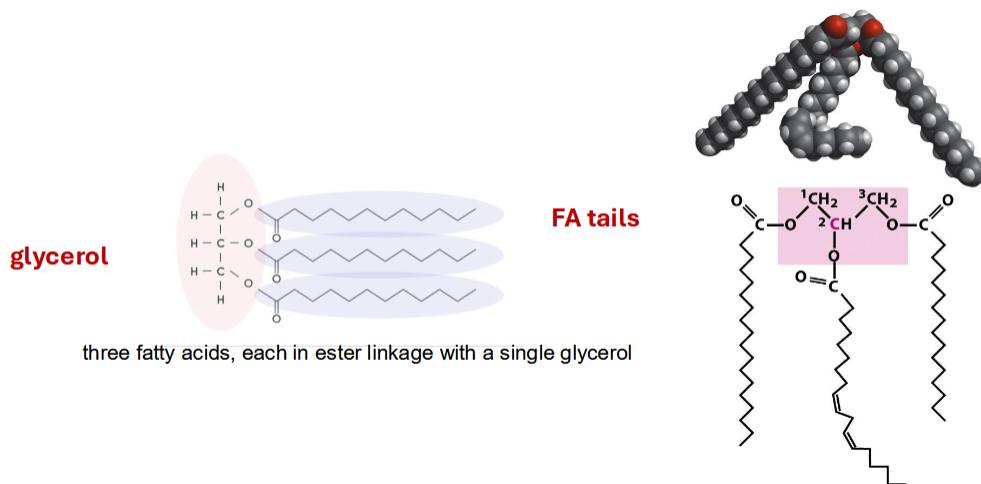
- Melting points decrease as we increase unsaturation
- Has implications for biological regulation of membranes



Triacylglycerols (TAGs)

- Triacylglycerols are esters derived from glycerol and three fatty acids
- Constitute ≈ 90% of dietary lipids, and the vast majority of fat in the body

- Major form of metabolic energy storage in humans:
 - Glycogen (the storage form of glucose in the body) < 200 grams of in most people
 - Human body fat is measured in whole percentages (**kilograms**)

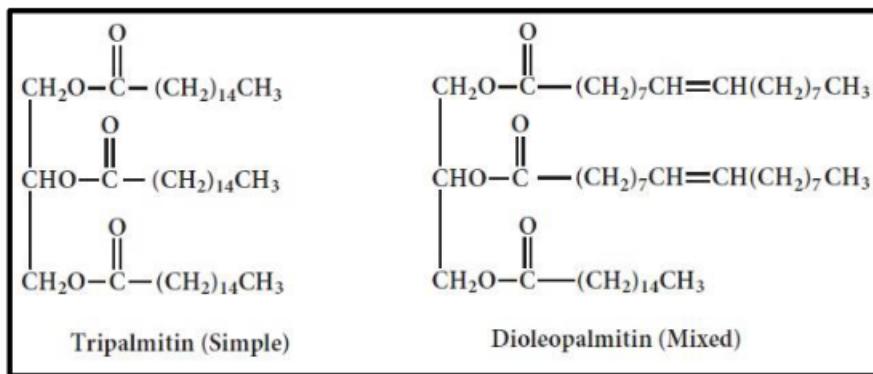


Triacylglycerols Provide Stored Energy

- vertebrates store triacylglycerols as lipid droplets in adipocytes (fat cells)
- plants store triacylglycerols in the seeds
- Carbohydrates (like glycogen) are **short-term** storage, TAGs are **long-term** storage.

More on TAGs

- Less oxidized than carbohydrates and amino acids (more reduced → better energy storage)
 - CH₄ (most reduced) → CO₂ (most oxidized)
- AG Composition:
 - Simple TAGs: All three fatty acids are identical
 - Mixed TAGs: Contain different fatty acids



In biochemistry, a molecule that is more reduced carries a greater number of electrons that can be transferred to another acceptor (for instance, in an oxidation reaction). When such a molecule is oxidized, those electrons are released, allowing the cell to harness energy (e.g., through cellular respiration). Therefore, a more reduced molecule has a higher potential to yield energy upon oxidation.

TAG Catabolism

- TAGs are broken down during **lipolysis**, generating glycerol and three fatty acids
- The resulting fatty acids are then fed into **beta oxidation** (catabolic cycle that oxidizes the fatty acid - reducing NAD^+ / FAD^- and generates acetyl-CoA)
 - During beta-oxidation, fatty acids are sequentially broken down through a series of reactions. **These reactions shorten the fatty acid chain by two carbons each cycle.**
 - Fatty acids go through cycles until they are spent (i.e., the longer the fatty acid, the more energy it can produce: **more carbons = more oxidation cycles → More ATP**)

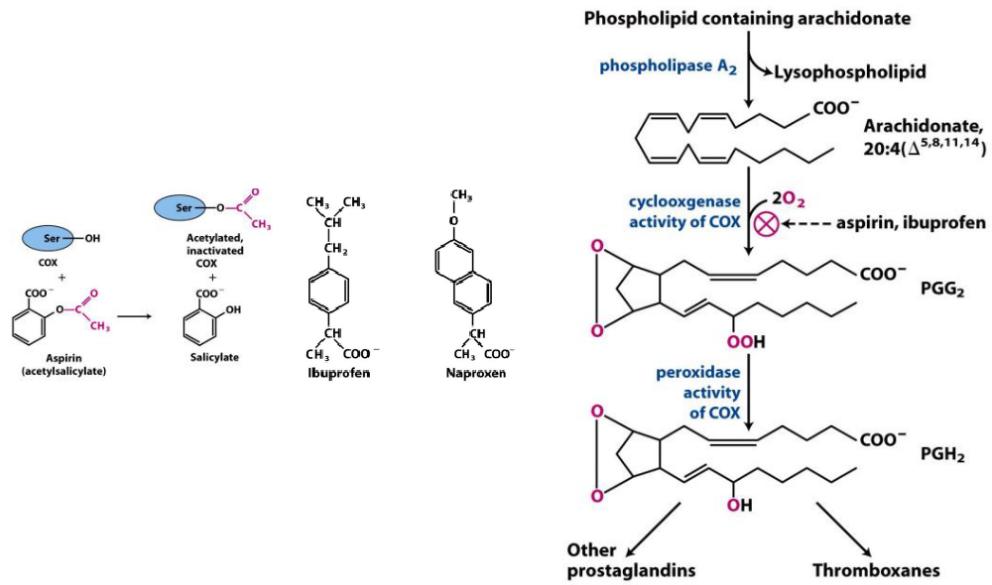
Lipids vs. Polysaccharides

Feature	Lipids	Polysaccharides
Energy Density	High	Lower
Storage Form	Triglycerides in adipose, oils in plants	Glycogen in animals, starch in plants
Accessibility	Slower to mobilize	Rapidly accessible
Oxygen Requirement	Requires oxygen (aerobic only)	Can function anaerobically
Water Balance	Hydrophobic, does not bind water	Hydrophilic, binds water
Primary Use	Long-term, sustained energy	Short-term, immediate energy

- **Lipids** are ideal for **long-term energy storage** in a compact, water-free form, but they are slower to access and require oxygen to be metabolized.
- **Polysaccharides** are better for **short-term, quick energy** due to their rapid mobilization, ability to function anaerobically, and role in immediate energy needs, despite their lower storage efficiency.
- **Polysaccharides** are stored as large polymers to avoid increasing osmotic pressure; however, when broken down into glucose units, they can increase osmotic pressure, especially if rapidly mobilized.
- **Lipids** do not affect osmotic pressure due to their hydrophobicity and storage in non-aqueous environments, making them ideal for high-capacity energy storage without impacting cellular water balance.

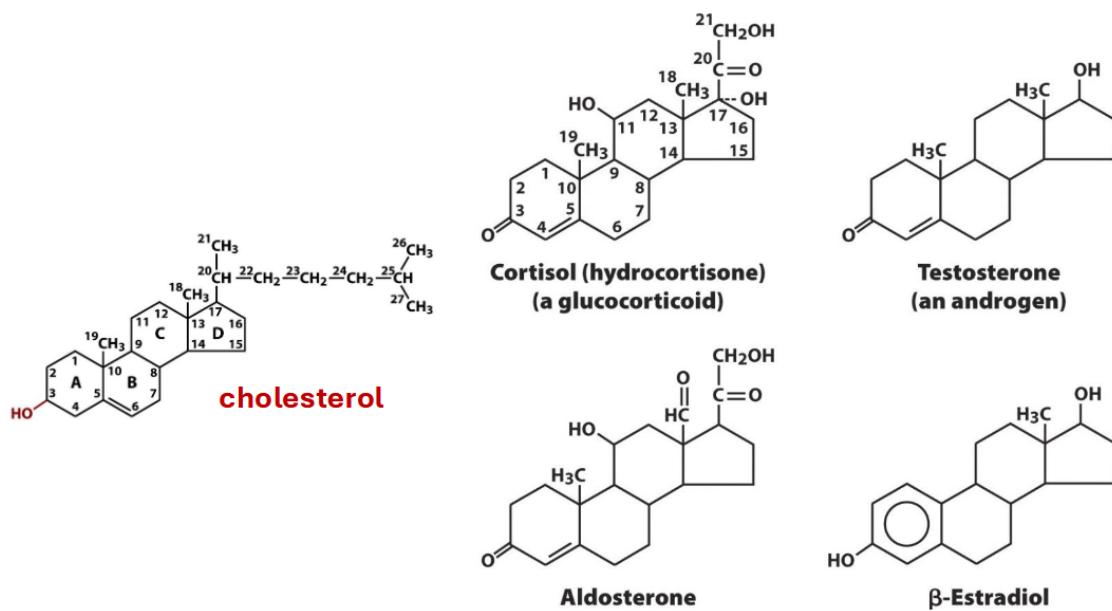
Eicosanoids - Local Hormones

- **Eicosanoids** are a family of biologically active molecules derived from arachidonic acid (specifically an arachidonate phospholipid)
- Considered "local" hormones - all autocrine and paracrine signaling:
 - **Paracrine Signaling:** Hormone acts on **neighboring cells** (prostaglandins released in response to tissue damage act on nearby cells to mediate inflammation)
 - **Autocrine Signaling:** Hormones act on the **same cell** that produced them (certain **growth factors** can act on the cells that secrete them to regulate cell growth or survival)



Sterols - Global Hormones

- Sterols are a subset of steroids that play several roles in eukaryotes
 - Components of membranes
 - Signaling compounds
- "Global" hormones, also known as **endocrine hormones**: signaling molecules that are released into the **bloodstream** and travel throughout the body to exert their effects on **distant target organs** or tissues
- Bind to nuclear receptors



A diet rich in certain types of fatty acids, particularly saturated fats and trans fats, can contribute to cardiovascular diseases and lead to vein or artery clogging due to several factors, including:
Build-Up of Plaque in Arteries (Atherosclerosis):

- **Saturated fats** (commonly found in animal products like butter, cheese, and fatty meats) and **trans fats** (found in processed and fried foods) can raise levels of **low-density lipoprotein (LDL)** cholesterol in the blood
- High levels of **LDL cholesterol** can lead to the formation of **plaque** (a mixture of cholesterol, fats, calcium, and other substances) on the walls of arteries
- This plaque build-up narrows the arteries and **restricts blood flow**, which is called **atherosclerosis**. Over time, this can cause the arteries to harden and lose flexibility, making it difficult for blood to flow through smoothly.

Cholesterol

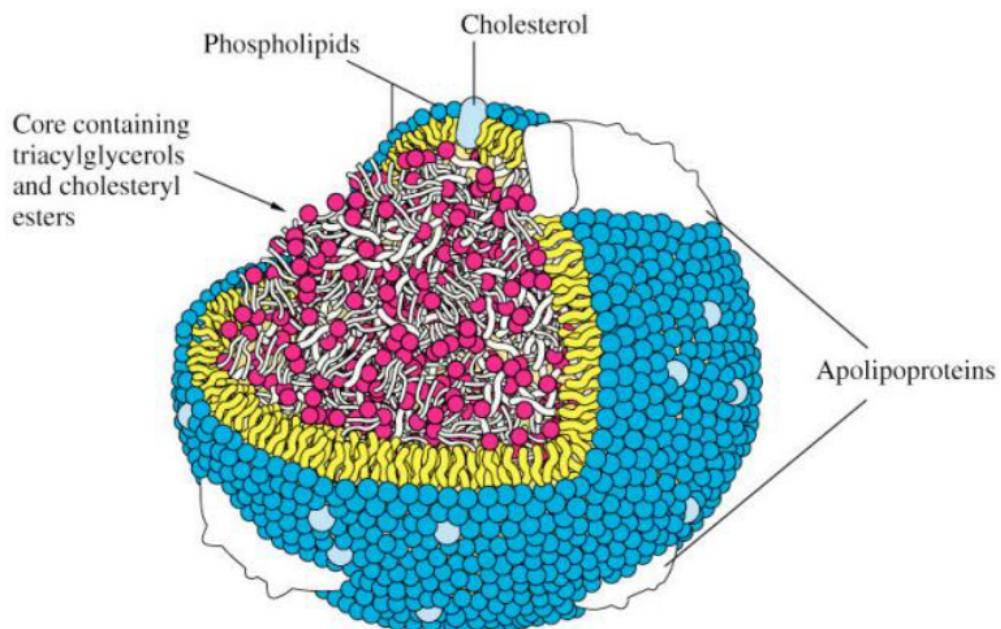
Cholesterol and triglycerides are insoluble in water and therefore these lipids must be transported in association with proteins as lipoproteins. The two main types of lipoproteins that carry cholesterol are:

- **Low-Density Lipoprotein (LDL)**: Often referred to as "bad cholesterol" because high levels of LDL can lead to cholesterol accumulation in the arteries
- **High-Density Lipoprotein (HDL)**: Referred to as "good cholesterol" because it helps remove excess cholesterol from the bloodstream and takes it back to the liver for elimination

Lipoproteins are complex particles with a central core containing cholesterol esters and triglycerides surrounded by free cholesterol, phospholipids, and apolipoproteins, which facilitate lipoprotein formation and function.

Lipoproteins

- How do we transport all those lipids through our aqueous transportation networks? (circulatory system and lymph)
- **Lipoproteins** are a composite structure, a phospholipid monolayer with several apolipoproteins (specialized proteins that bind lipids to form and regulate lipoproteins)
- Inside is packed with various lipids - TAGs and cholesterol for the most part



Classes of Lipoproteins

Table 20-1 Characteristics of the Major Classes of Lipoproteins in Human Plasma

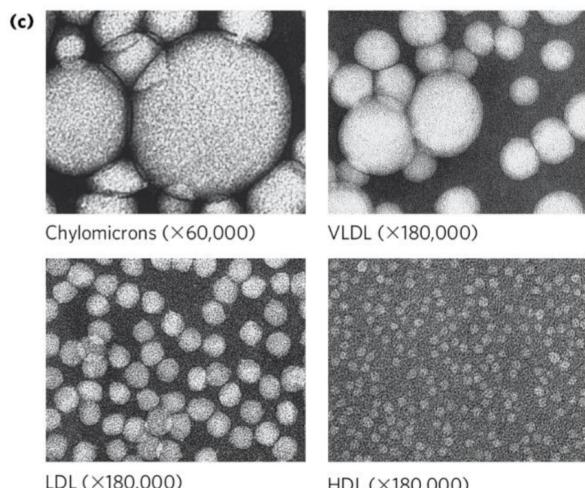
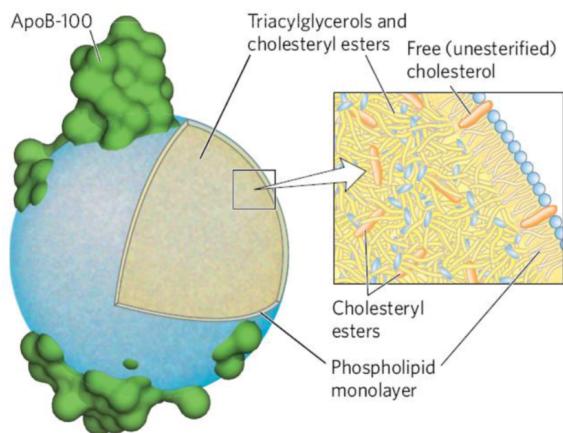
	Chylomicrons	VLDL	IDL	LDL	HDL
Density ($\text{g} \cdot \text{cm}^{-3}$)	<0.95	<1.006	1.006–1.019	1.019–1.063	1.063–1.210
Particle diameter (\AA)	750–12,000	300–800	250–350	180–250	50–120
Particle mass (kD)	400,000	10,000–80,000	5000–10,000	2300	175–360
% Protein ^a	1.5–2.5	5–10	15–20	20–25	40–55
% Phospholipids ^a	7–9	15–20	22	15–20	20–35
% Free cholesterol ^a	1–3	5–10	8	7–10	3–4
% Triacylglycerols ^b	84–89	50–65	22	7–10	3–5
% Cholesteryl esters ^b	3–5	10–15	30	35–40	12
Major apolipoproteins	A-I, A-II, B-48, C-I, C-II, C-III, E	B-100, C-I, C-II, C-III, E	B-100, C-I, C-II, C-III, E	B-100	A-I, A-II, C-I, C-II, C-III, D, E

^aSurface components

^bCore lipids.

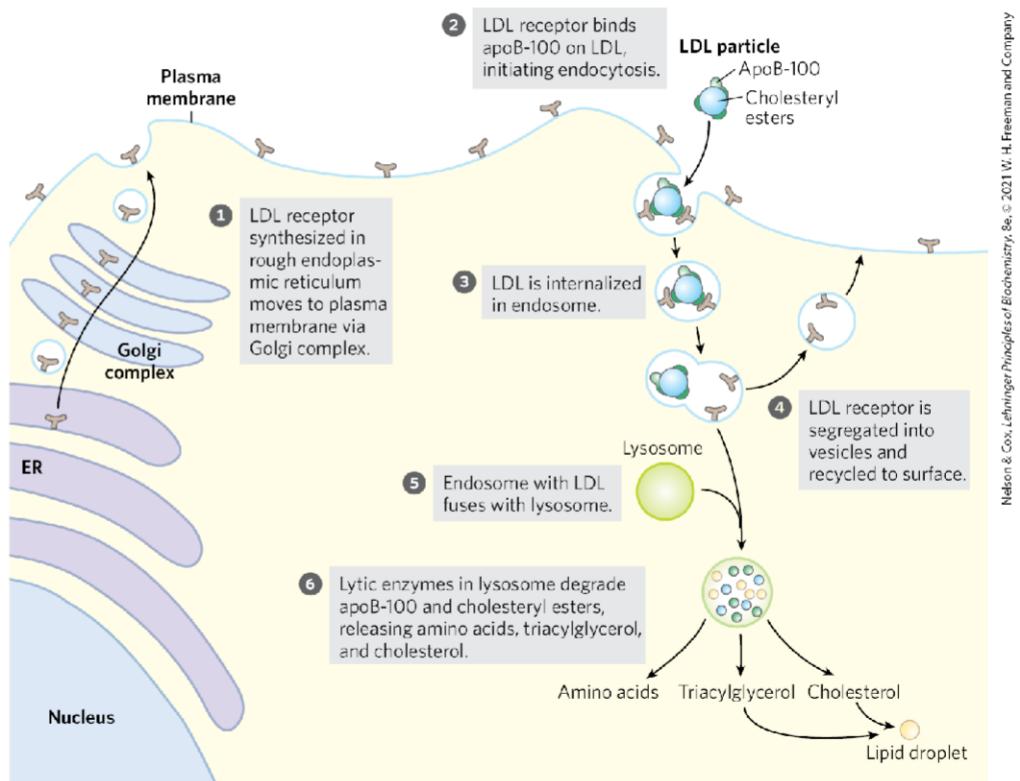
Lipoproteins

(b) Low-density lipoprotein (LDL)



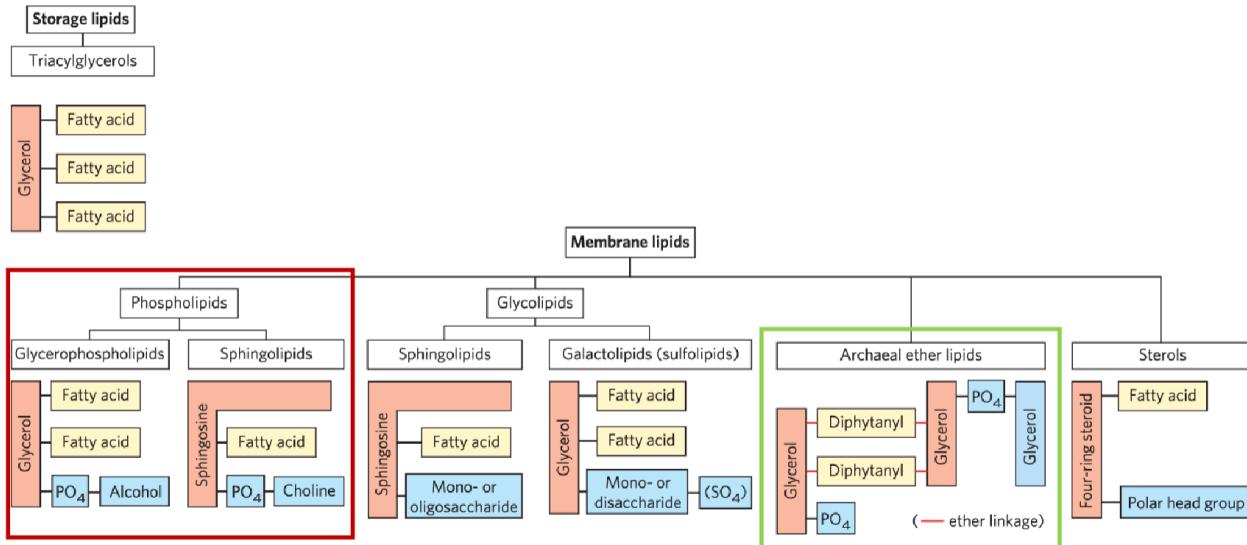
Receptor-Mediated Endocytosis

apoB-100 of LDL is recognized by receptors in the plasma membrane.



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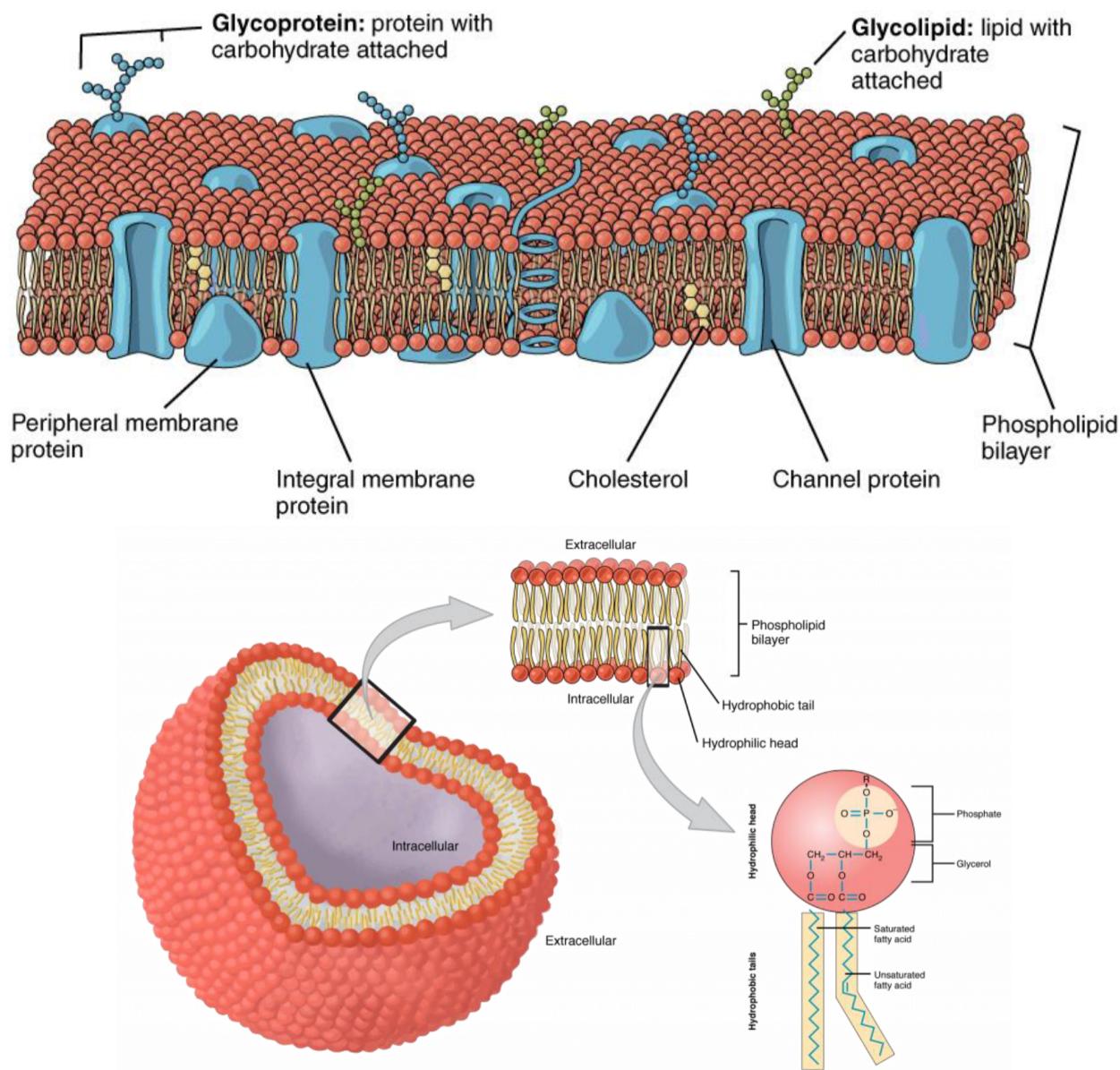
Some Common Types of Storage and Membrane Lipids



More on archeal lipids:

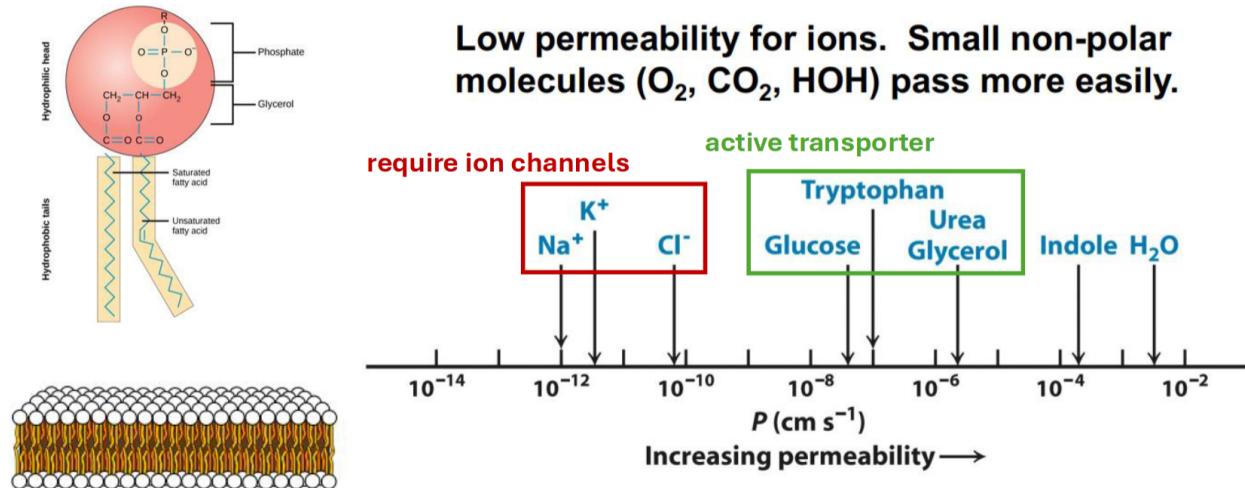
<https://doi.org/10.1016/j.bbali.2016.12.006>

Cell Membrane: Fluid Mosaic Model

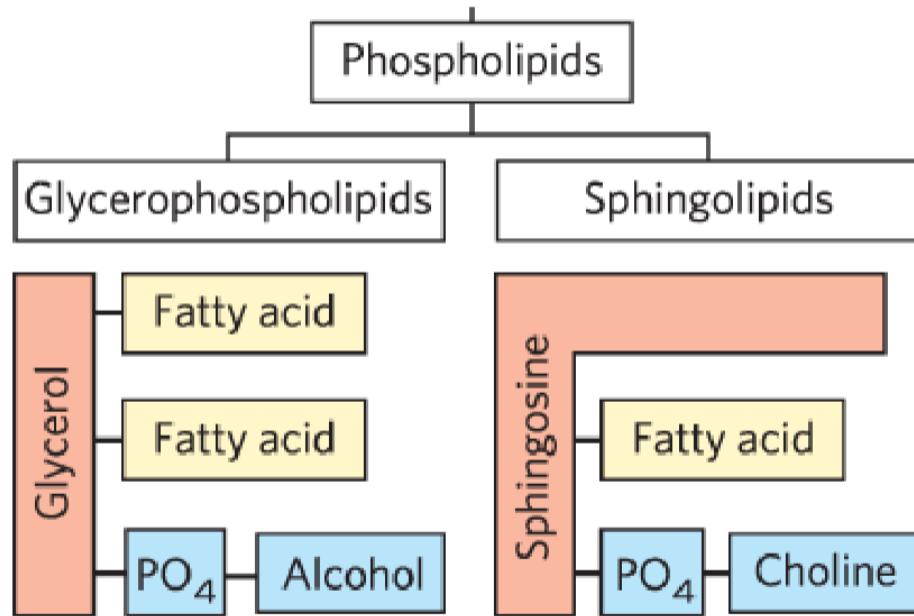


Membrane Permeability

- Low permeability for ions.
- Small non-polar molecules (O_2 , CO_2 , H_2O) pass more easily.



Types of Phospholipids



Glycerophospholipids

- Backbone: Glycerol
- Structure: Two fatty acids attached to the glycerol backbone, a phosphate group (PO_4) linked to an alcohol (e.g., choline or ethanolamine)
- Function: In cell membranes, it has a role in structural integrity and signaling

Sphingolipids:

- Backbone: Sphingosine
- Structure: One fatty acid attached to the sphingosine backbone, a phosphate group (PO_4) linked to choline or another alcohol group

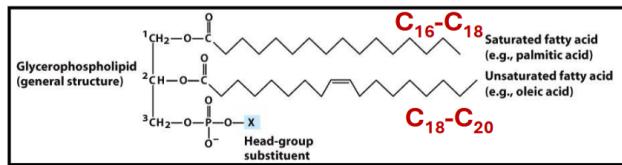
- Function: In cell membranes, particularly in neural tissues, they contribute to signaling and cellular recognition

Glycerophospholipids

precursor to the other glycerophospholipids

common membrane components

part of several signaling pathways



Name of glycerophospholipid	Name of X	Formula of X	Net charge (at pH 7)
Phosphatidic acid	—	—H	-1
Phosphatidylethanolamine	Ethanolamine	—CH ₂ —CH ₂ —NH ₃ ⁺	0
Phosphatidylcholine	Choline	—CH ₂ —CH ₂ —N(CH ₃) ₃ ⁺	0
Phosphatidylserine	Serine	—CH ₂ —CH—NH ₃ ⁺ COO ⁻	-1
Phosphatidylglycerol	Glycerol	—CH ₂ —CH(OH)—CH ₂ —OH	-1
Phosphatidylinositol 4,5-bisphosphate	myo-Inositol 4,5-bisphosphate		-4
Cardiolipin	Phosphatidyl-glycerol		-2

Structure: Glycerophospholipids are based on a glycerol backbone, with two fatty acids and a phosphate group attached. The phosphate group is further linked to a polar "head group" (e.g., ethanolamine, choline, serine, glycerol).

Roles:

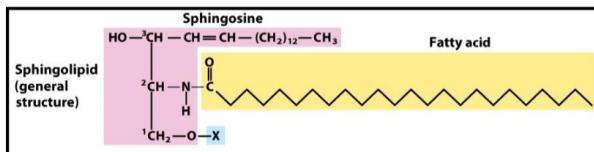
- Precursor function:** Phosphatidic acid serves as the precursor to other glycerophospholipids
- Membrane components:** Glycerophospholipids like phosphatidylethanolamine, phosphatidylcholine, and phosphatidylserine are crucial for membrane structure and function
- Signaling pathways:** Specialized glycerophospholipids (e.g., phosphatidylinositol 4, 5-bisphosphate) participate in intracellular signaling, regulating processes like calcium release and enzyme activation
- Cardiolipin:** Vital for mitochondrial membrane integrity and function

Sphingolipids

precursor to the other sphingolipids

common membrane component

glycolipids



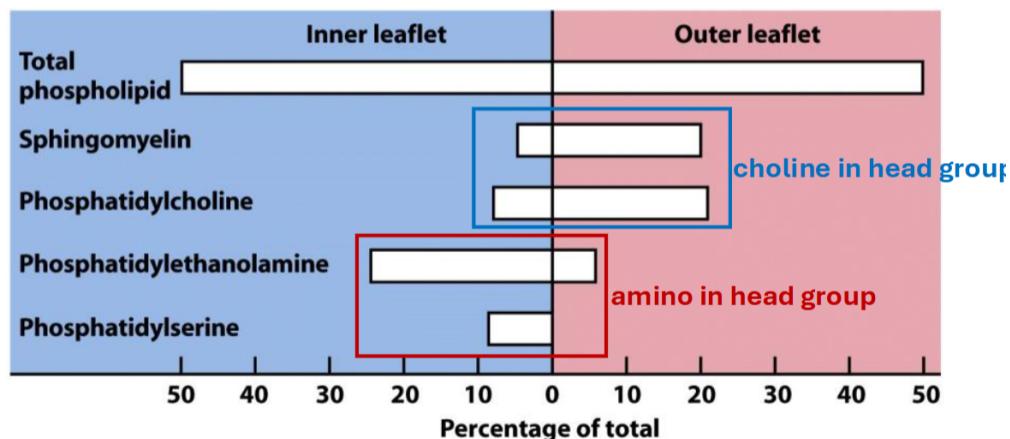
Name of sphingolipid	Name of X—O	Formula of X
Ceramide	—	—H
Sphingomyelin	Phosphocholine	
Neutral glycolipids Glucosylceramide	Glucose	
Lactosylceramide (a globoside)	Di-, tri-, or tetrasaccharide	
Ganglioside GM2	Complex oligosaccharide	

Structure: Sphingolipids are built on a sphingosine backbone (rather than glycerol), with a single fatty acid and a polar head group. The head groups can vary, producing different sphingolipid types **Roles:**

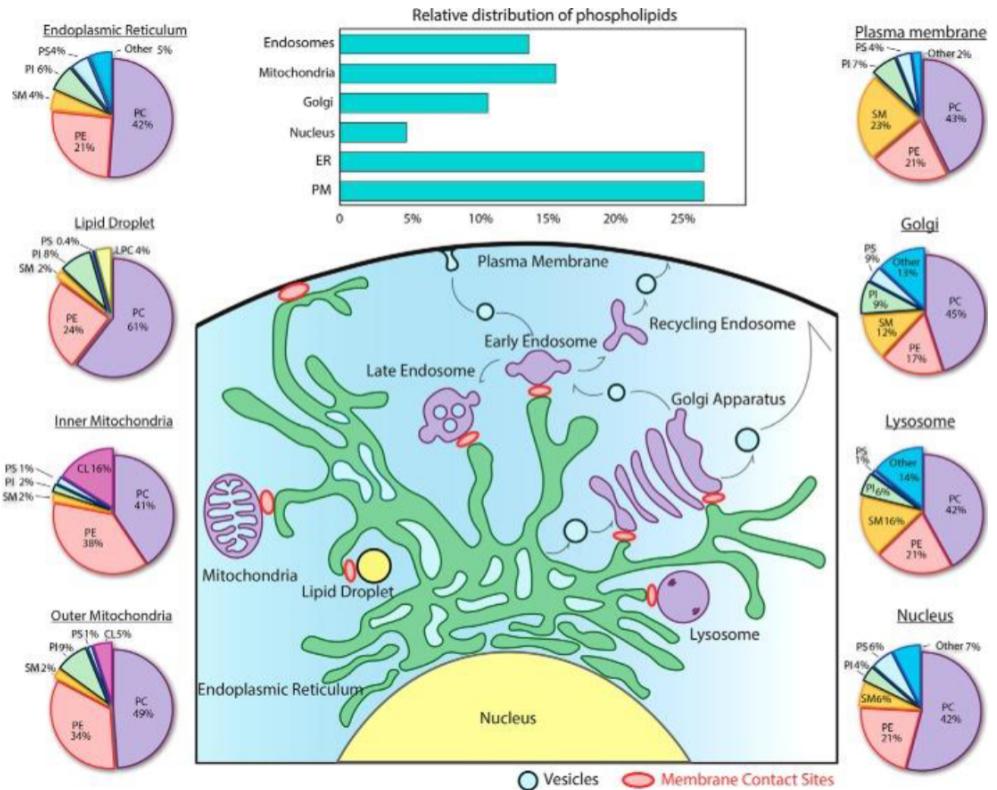
1. **Precursor function:** Ceramide acts as a precursor for more complex sphingolipids
2. **Membrane components:** Sphingomyelin is a major component of myelin sheaths in nerve cells
3. **Glycolipids:** These include neutral glycosphingolipids (e.g., glucosylceramide) and more complex gangliosides. These glycolipids play roles in cell recognition, signaling, and interactions.

Phospholipid Asymmetry

- Cell membranes maintain asymmetry in phospholipid content
- Why? Likely helps maintain different electric environments and contribute to structure - also relevant for biological regulation
- If phosphatidylserine (PS) is seen on the outer membrane, it's targeted for phagocytosis
 - In platelets, this triggers aggregation



Lipids in Organelles



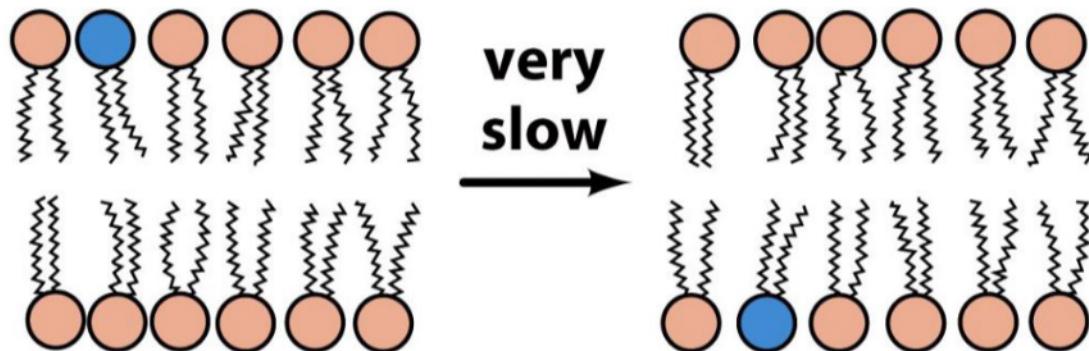
doi:10.1074/jbc.R117.000582

Abbreviations for the pie charts:

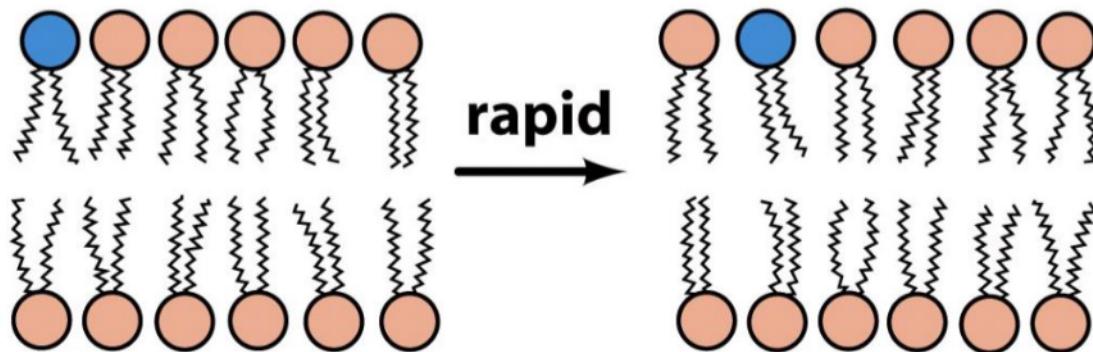
- Phosphatidylcholine (PC)
- Phosphatidylethanolamine (PE)
- Phosphatidylserine (PS)
- Phosphatidylglycerol (PG)
- Cardiolipin (CL)
- Sphingomyelin (SM)
- Other - Includes Phosphatidic Acid (PA)
- Diacylglycerol (DAG) and Lysolipids
- Lipids show distinct distributions and functions across different organelles, with specific abundances in organelles/compartments such as the **endoplasmic reticulum (ER)**, **mitochondria**, **lysosomes**, **nucleus**, **Golgi apparatus**, **plasma membrane (PM)**, **endosomes**, and **lipid droplets**.

Phospholipid Diffusion

Transverse diffusion



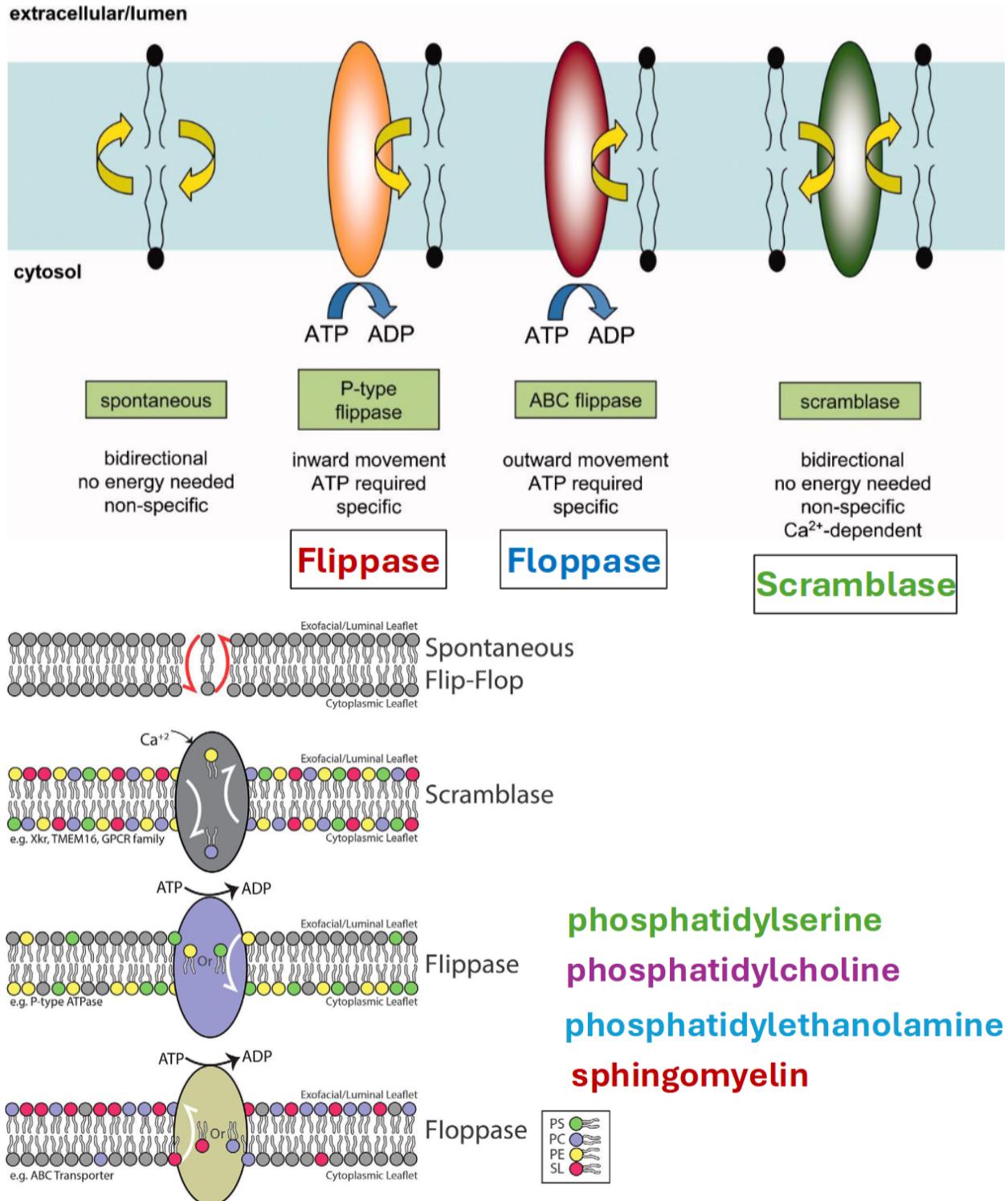
Lateral diffusion



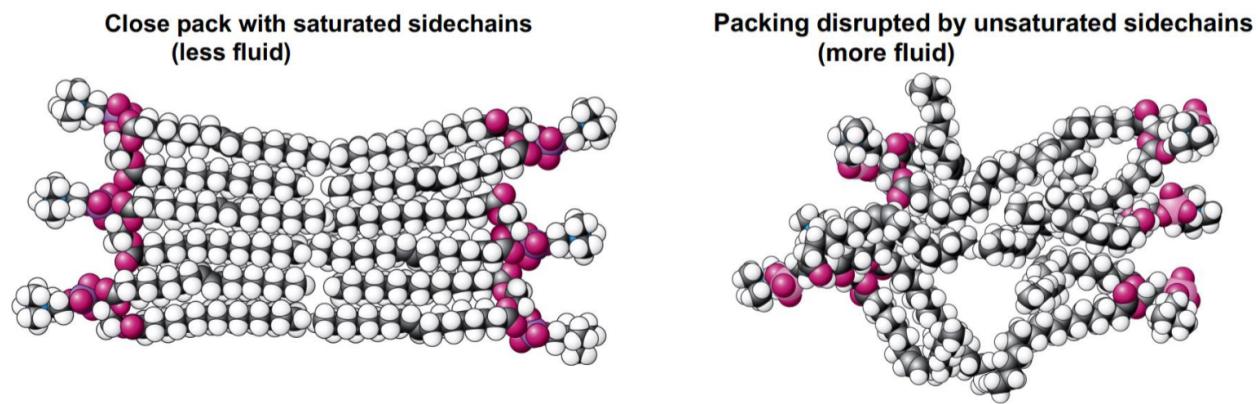
Changes in lipid organization can affect various cellular functions, such as membrane trafficking or signal transduction. These membrane-related effects can cause disease in living organisms due to genetic alterations, environmental factors (e.g., high dietary intake of saturated fats), or both

Flippase, Floppase, and Scramblase

- **Flippase and Floppase** maintain asymmetry by putting phospholipids where they're "supposed" to be
- **Scramblase** indiscriminately flips phospholipids both directions - what would happen if scramblase dominated?
 - Phospholipid content would **even out** (50:50 equilibrium)
 - This would include PS
- **Scramblase** is activated by levels of Ca^{2+} signaling that trigger in case of damage - beginnings of apoptosis (conversely flippase and floppase are inhibited)



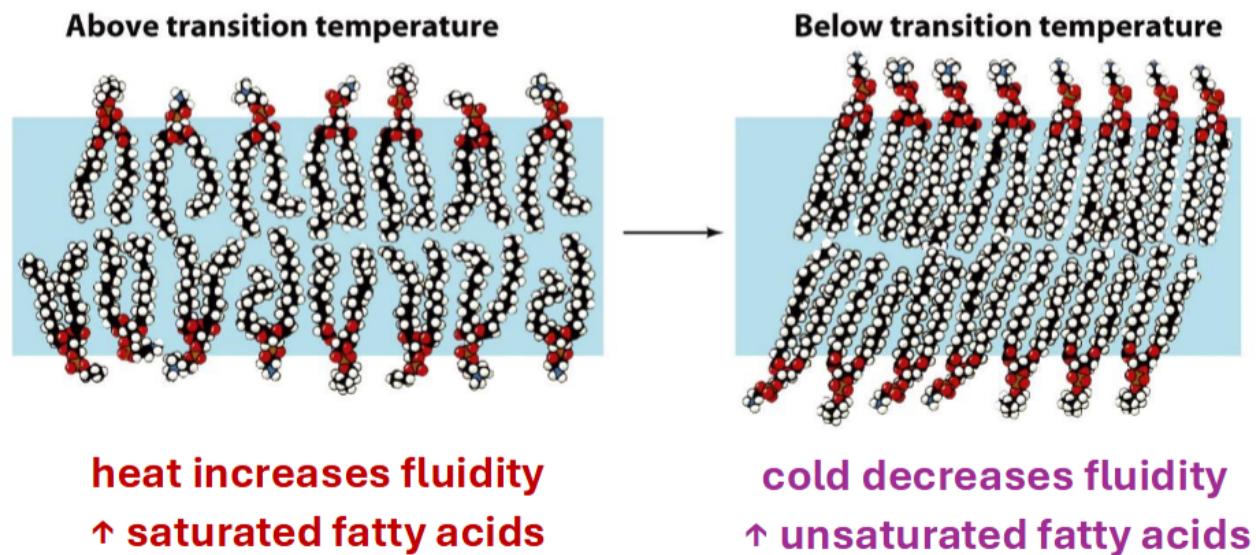
Saturated and Unsaturated Phospholipid Structure



- Saturated phospholipids generate more rigid structures (Left).
- Unsaturated phospholipids generate more fluid structures (Right).

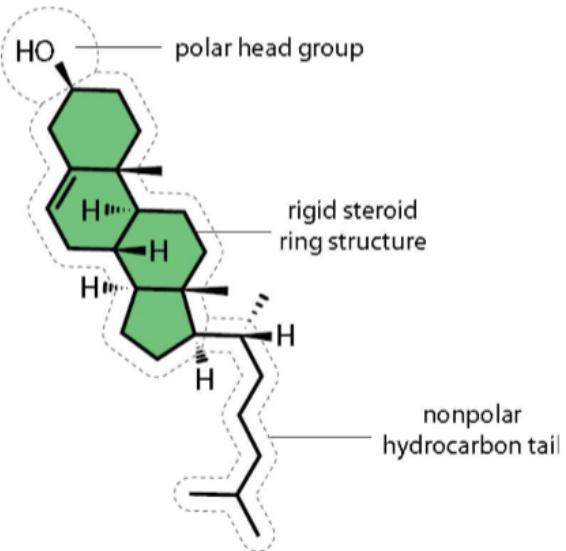
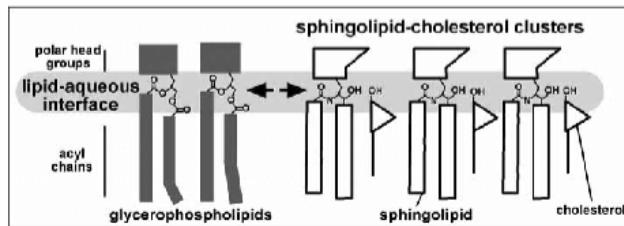
Phospholipids - Cell Regulation

Cells can regulate their own lipid composition to maintain membrane fluidity (called **homeoviscous adaptation**)

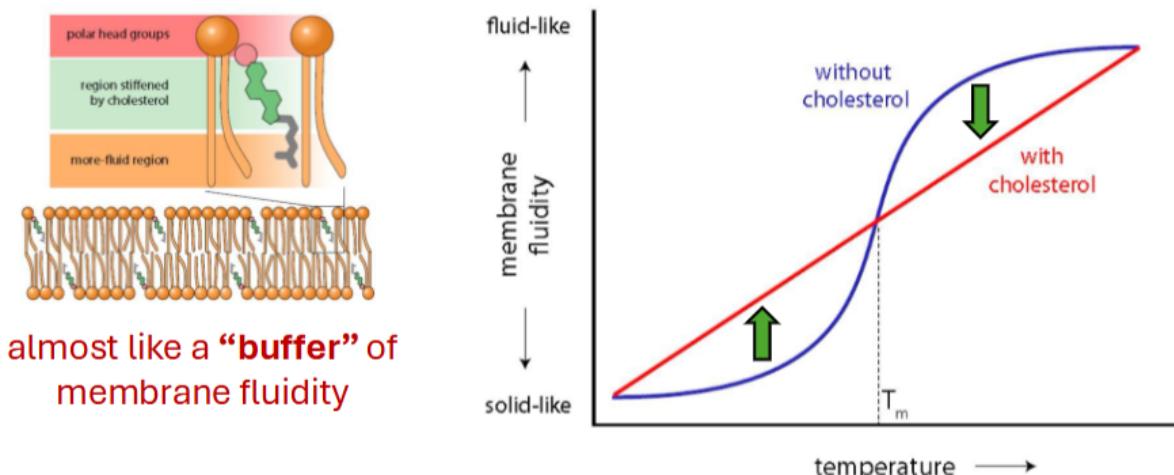


Moderation of membrane fluidity by Cholesterol

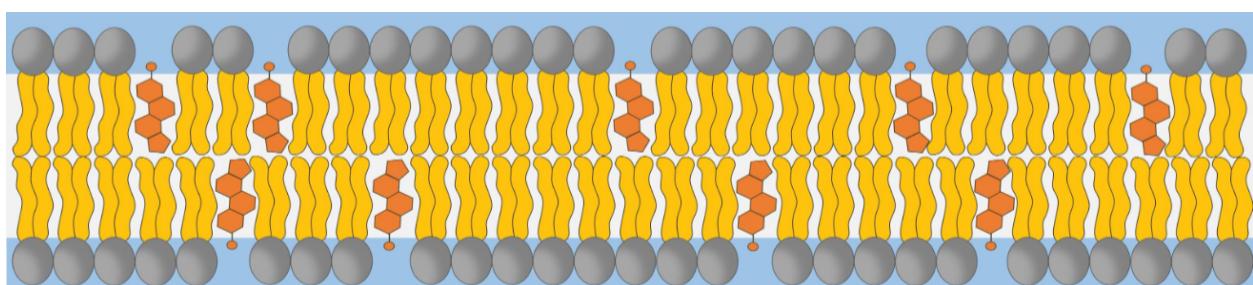
- As we've already discussed, cholesterol serves as a biosynthetic precursor to sterol hormones
- Also serves as an important membrane structural component
- Polar head group (-OH) creates hydrogen bonding with sphingolipids, creating **lipid rafts**



- At low temperatures, phospholipids pack tightly, but cholesterol's rigid four ring structure reduces extent of packing
- At high temperatures, phospholipids pack loosely, but the intermolecular interactions with cholesterol keeps phospholipids somewhat closer together
- All in all, this means that cholesterol moderates membrane fluidity.



- The mammals have evolved sophisticated and complex mechanisms to maintain plasma cholesterol levels, as well as cell membrane cholesterol levels, within a narrow physiological range.



Cholesterol Homeostasis

- Animal cells maintain cholesterol homeostasis by transporting cholesterol from one membrane to another. Cholesterol derived from low-density lipoprotein (LDL) is taken into cells through endocytosis mediated by LDL receptors (LDLRs)
- The LDL-derived cholesterol is released in lysosomes and then transported to the plasma membrane (PM), where it plays a structural role, and to the endoplasmic reticulum (ER) membrane.

Membrane Proteins Redux

- We've dealt with how proteins use their primary/secondary structures to associate with membranes, but not with any lipid-based solutions.
- Enter **lipid-anchored proteins**, proteins located on the surface of the cell membrane that are covalently attached to lipids embedded within the cell membrane

