EPFL

BIO-212 - Lecture 2
Carbohydrates

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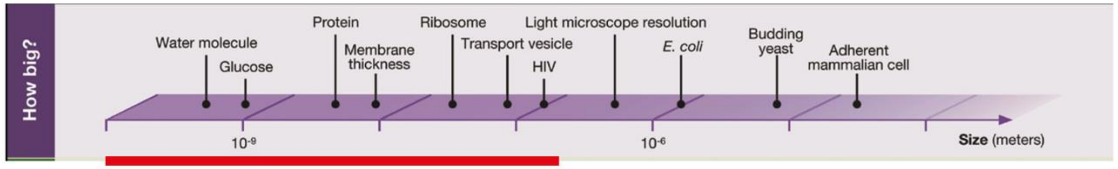
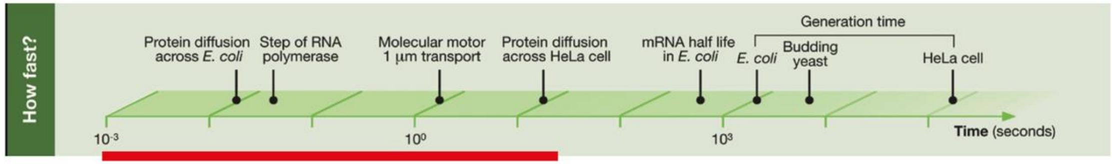
Lecture 1 – Quick Summary

- Biomolecules on the scales of life:

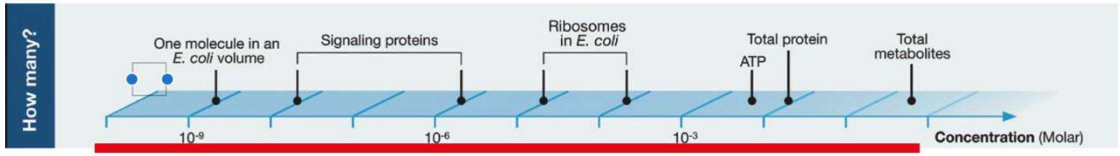


0.1nm — 100nm

1Å= 0.1nm



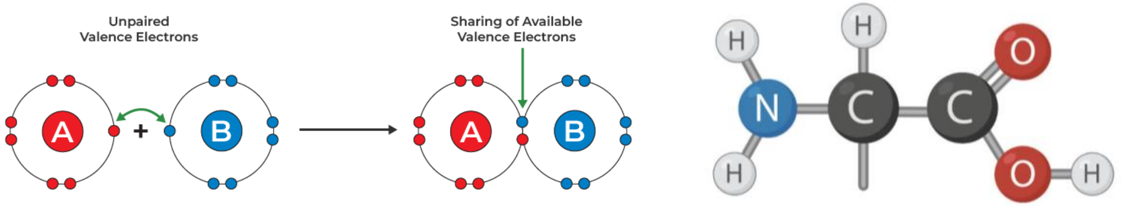
ns — s



nM — M

- Atomic and molecular interactions in biomolecules

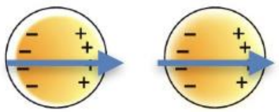
Covalent bonds



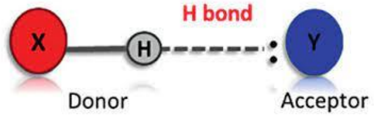
~100-800kJ/mol

Non-covalent interactions

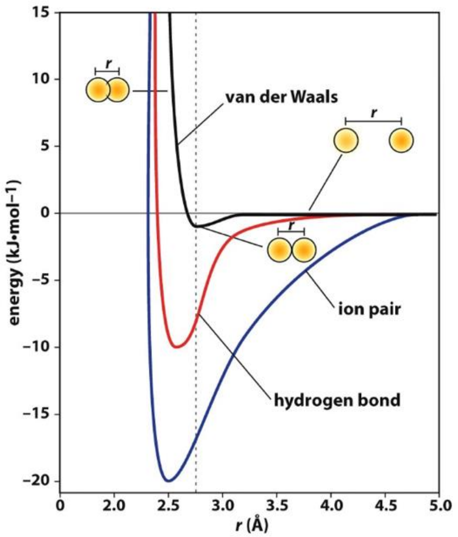
van der Waals interactions



Hydrogen bonds



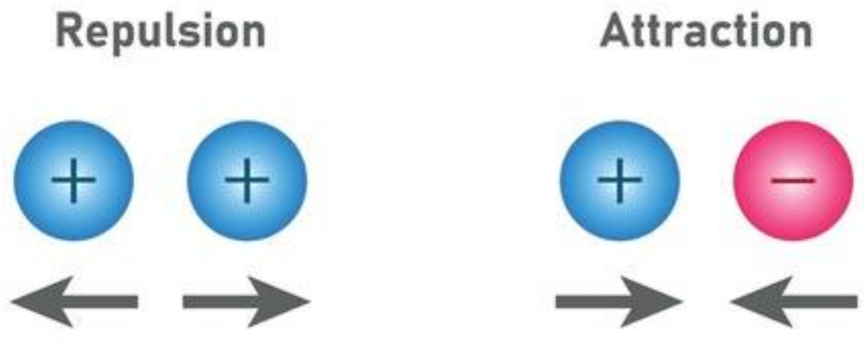
Ionic interactions



Lecture 1 - Extra Clarifications

• Origin of interactions

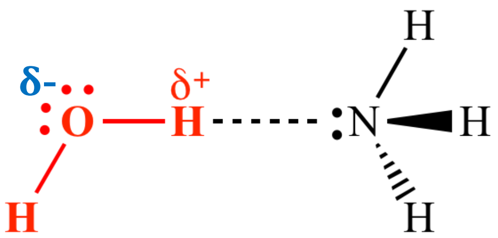
It is always about (partial) electrostatic charges:



If permanent disrete charges: **Electrostatic**

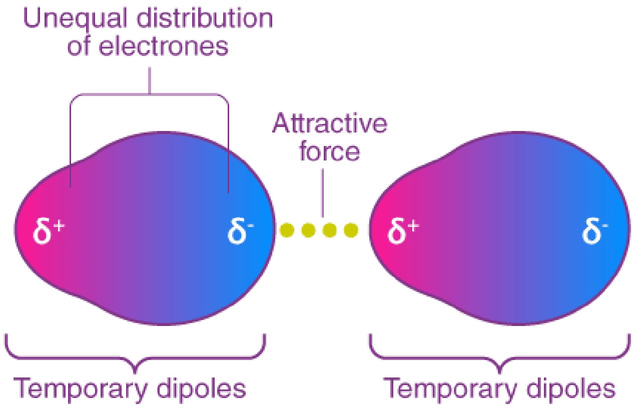
If temporary or permanent dipoles: **van der Waals**

Polarized bonds with suitable donors and acceptors: **H-bond**

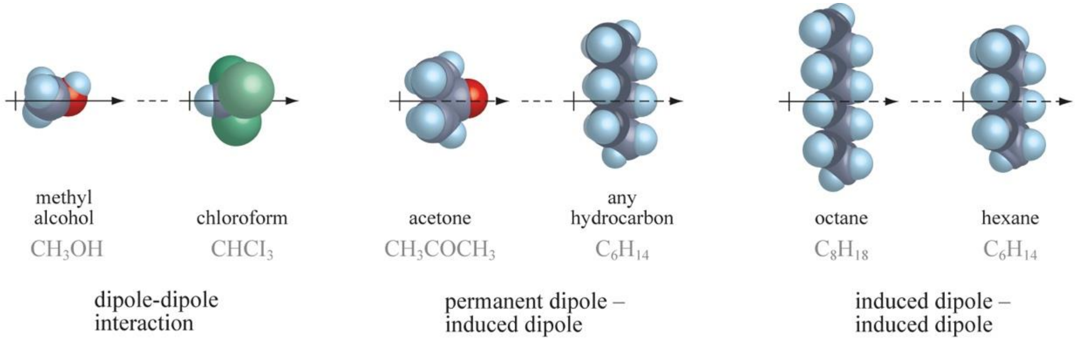


• van der Waals forces

Chemical groups and atoms are dipoles consisting of partial positive and negative charges.



Dipoles will interact with each other when sufficiently close and also induce dipoles in other groups

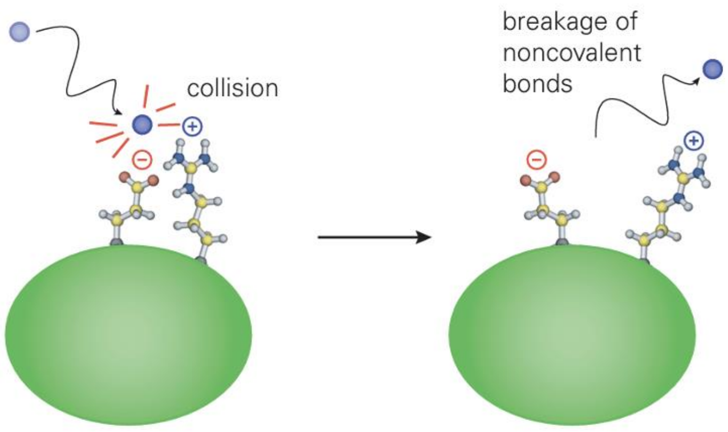


Lecture 1 - Extra Clarifications

• Impact of thermal energy

Thermal energy corresponds to the average kinetic energy of molecules as they diffuse through space.

It always has a **positive sign** and depends on temperature (~ $k_B \cdot T$)



If the energy of a collision (~$k_B \cdot T$) is greater than the stabilizing energy of the bond (**negative sign**), it can break it.

• Energy units

Energy units (Joule or Calories) were defined for macroscopic processes: mechanical work and heat

$$J = N \cdot m$$

However when using them to describe interaction energy, we end up with numbers that are <10^{-20}J in most cases.

To normalize, we calculate the energy for 1 mole of such interactions, equal to Avogardo's number of $6.02 \cdot 10^{23}$.

$$E\ (J/mol) = E\ (J) \cdot N_A\ (mol^{-1})$$

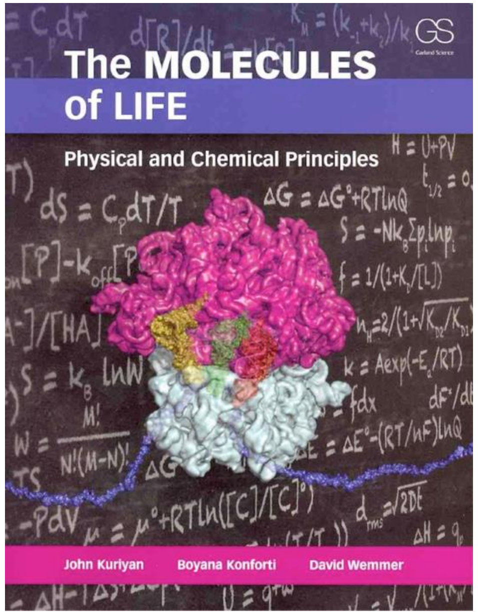
Lecture 2 - Outline

Today:

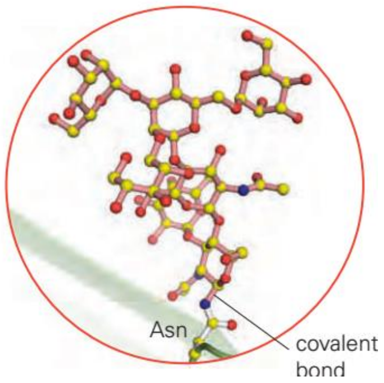
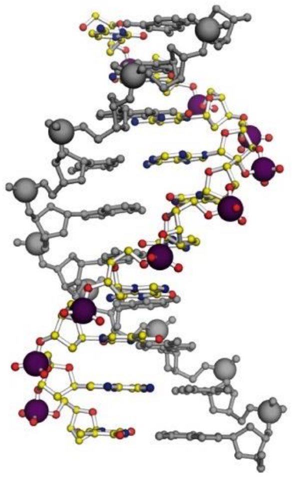
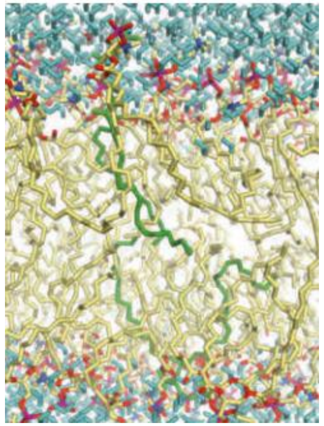
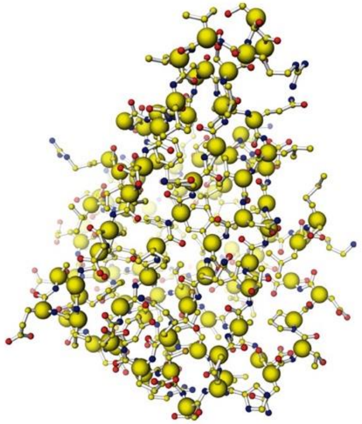
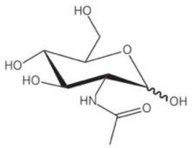
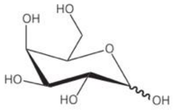
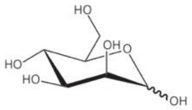
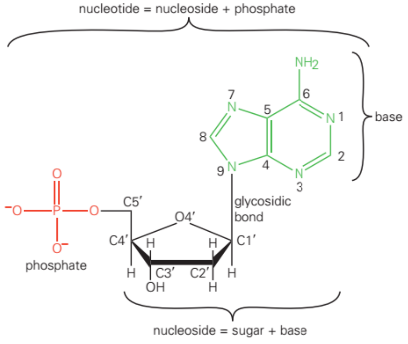
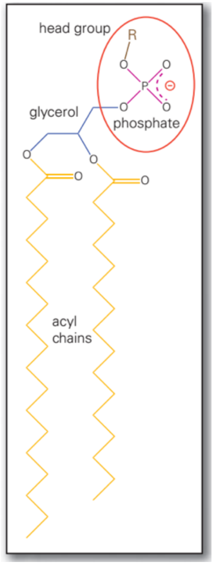
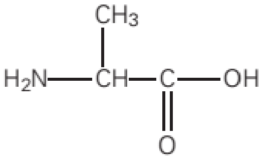
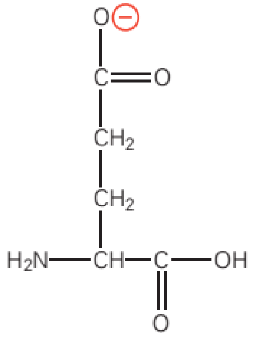
- Carbohydrate composition and assembly
- Relevant molecules and bonds
- Biological functions

Reading suggestions:

- The Molecules of Life (Chapter 3)



The molecules of Life

	Carbohydrates	Nucleic Acids	Lipids	Proteins
Macromolecular Structure				
Building Block	 N-acetylglucosamine (GlcNAc)  galactose (Gal)  mannose (Man)			 

Carbohydrates - Intro

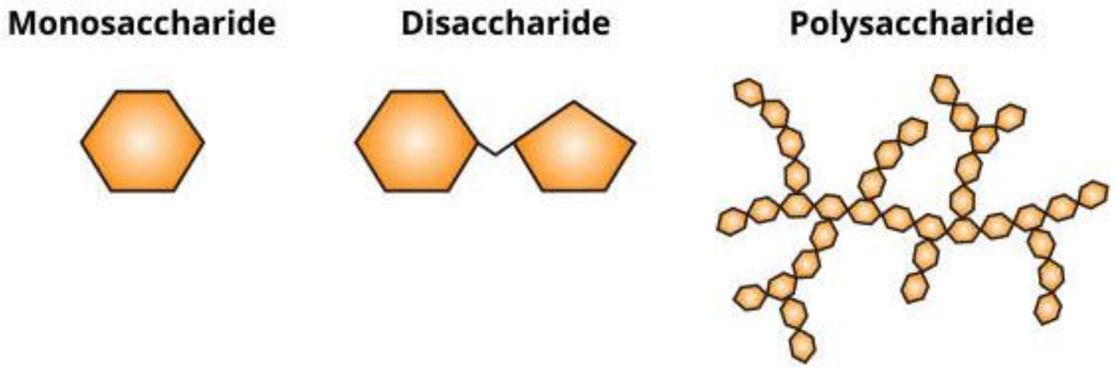
- **Carbohydrates, glycans, sugars or saccharides** are a diverse group of biomolecules that represent 2-10% of dry matter in humans and as high as 60-90% in plants (depending on the source).

- They serve many roles in cells:
  - energy metabolism and storage (e.g., glucose, glycogen, and amylose)
  - markers of cellular identity (e.g., glycolipids and glycoproteins),
  - structural components (e.g., cellulose in plants),
  - constituents of nucleotides (e.g., ribose in RNA, deoxyribose in DNA)

Greek: **γλυκύς** (glykys) = sweet
Sanskrit: **śarkarā** = sugar

- General Formula: $\mathbf{C_nH_{2n}O_n}$
(due to the 1:1 ratio of C to H_2O, the name **carbohydrates** was proposed)

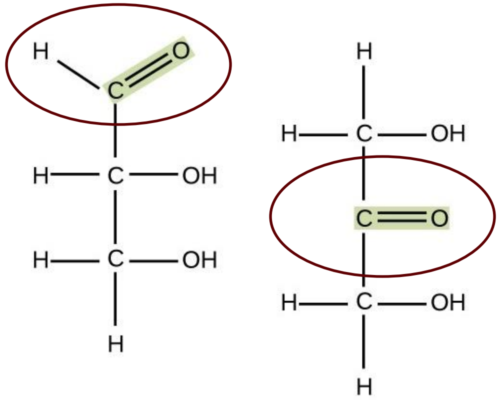
- Like nucleic acids they also form polymers from smaller building blocks (**monosaccharides**)



Monosaccharides

aldose | ketose

glyceraldehyde | dihydroxyacetone

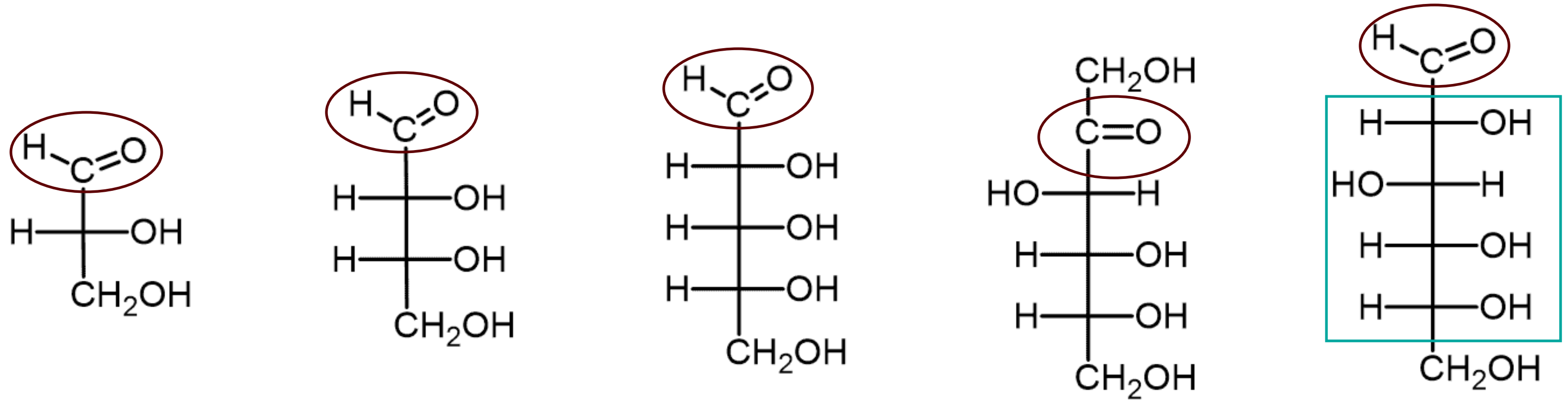


- Smallest groups – building blocks for larger carbohydrates
- Chain of 3 or more carbons, one carrying a carbonyl (C=O), and others with hydroxyl groups (OH)
- Their names carry the extension **"ose"**
- There are 2 primary chemical groups: **aldehyde** and **ketone**

- Aldoses have an aldehyde group: HC=O
- Ketoses have a keto group: C=O

- Categorized based on the length of sugar chain and the primary chemical group:

Triose | Tetrose | Pentose | Hexose | Hexose



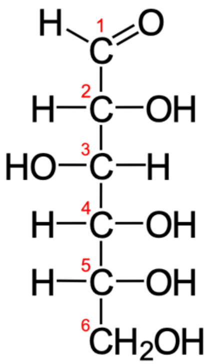
Aldotriose | Aldotetrose | Aldopentose | Ketohexose | Aldohexose

The diversity comes from the locations of H and OH groups around each carbon

Monosaccharides – Some important examples

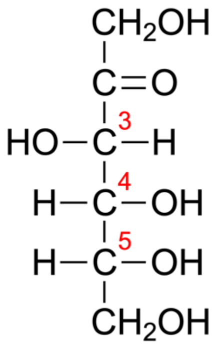
- For most of them **historic names** have been preferentially used, rather than the exact chemical names

• Glucose



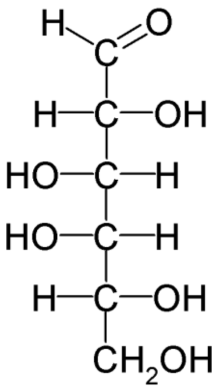
- The most abundant monosaccharide
- Important in metabolism, energy storage, structural assembly etc.

• Fructose



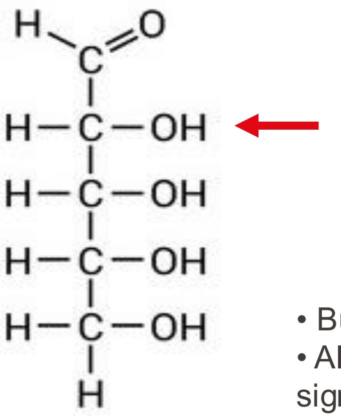
- Fruit sugar
- Component of sucrose

• Galactose



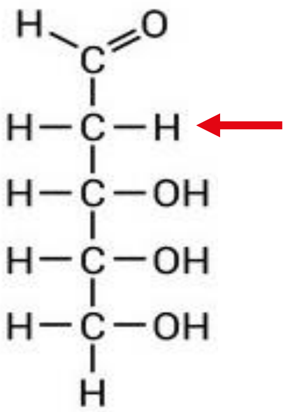
- Component of lactose (milk sugar)
- Present in glycoproteins and glycolipids (e.g., blood group antigens)

• Ribose



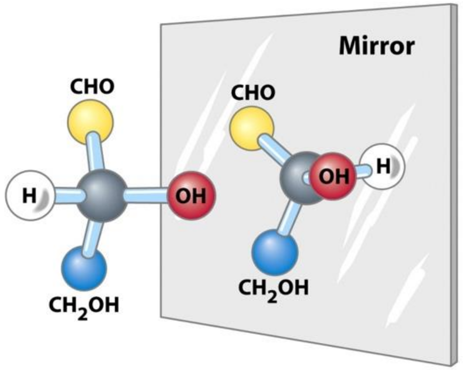
- Building blocks of nucleic acids
- Also important for intracellular signaling and metabolism

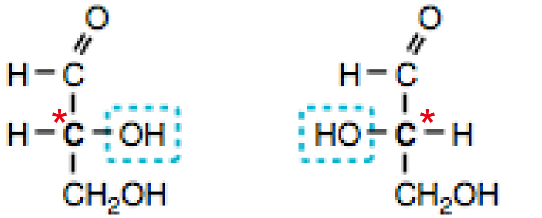
• Deoxyribose



These are very important structures to memorize!!!

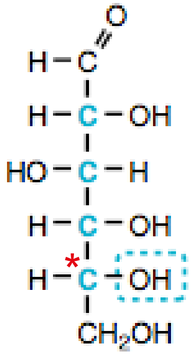
Chirality of monosaccharides - Stereoisomerism





D–Glyceraldehyde L–Glyceraldehyde

<u>The main chiral center is always the first asymmetric carbon from the distal end (*).</u>

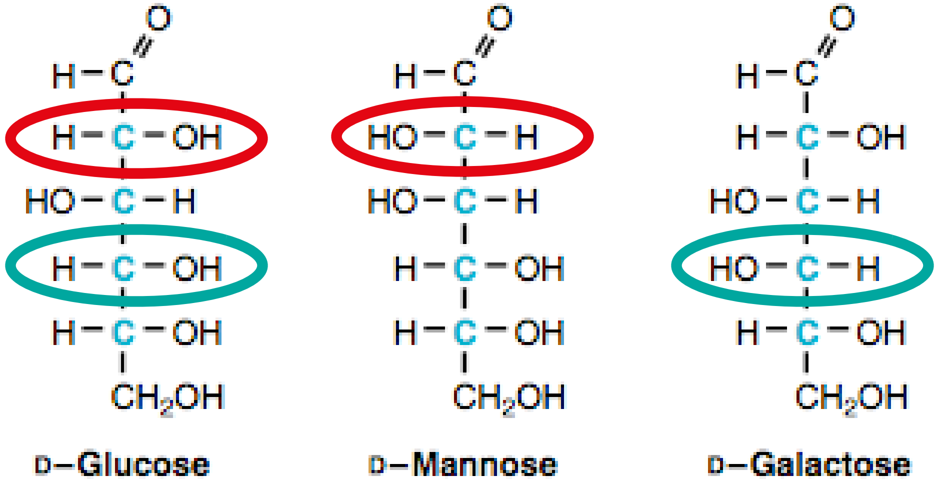


D–Glucose

- Chiral center appears when there are **4 different substituents**
- D and L mirror images (nomenclature based on rotation of polarized light, D=dexter, L=laevus)
- Glyceraldehyde has **a single chiral center**, while **longer sugars have multiple chiral centers**.
- Other sugars defined with respect to the asymmetric carbon in glyceraldehyde
- **The great majority of human (or natural) sugars are D**

D-glucose also called **dextrose** in the clinic

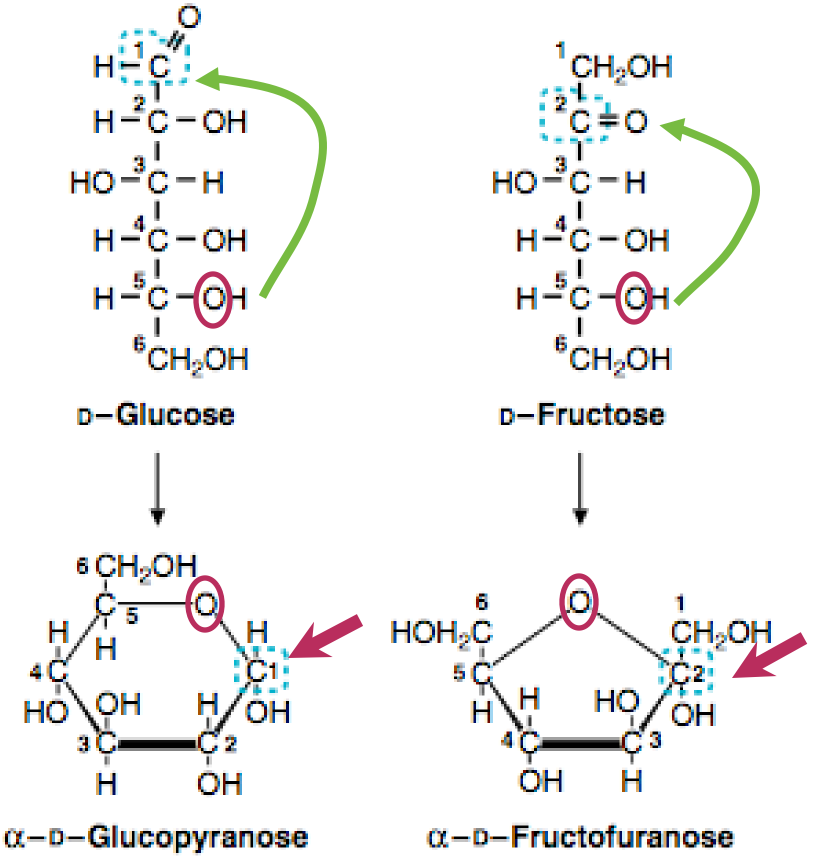
Stereoisomers and epimers



D-Mannose and D-Galactose are **epimers** of D-Glucose

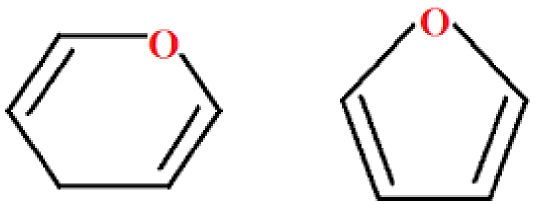
- **Stereoisomers**: same formula ($C_6H_{12}O_6$ in this example) but differ in position of OH at one or more chiral carbons
- **Enantiomers**: stereoisomers that differ at the main chiral carbon (i.e., D- versus L-glucose)
- **Epimers**: stereoisomers that differ at only one chiral carbon (compare glucose, mannose and galactose)
- Epimers interconverted by enzymes called **epimerases** (i.e. the OH changed to other chiral position)

Formation of cyclic structures in solution



- In solution monosaccharides form ring structures (C=O group is attacked by the OH group of the chiral carbon)
- C=O becomes anomeric carbon (i.e. **a new stereo center**)
- This is **only possible for sugars with 5 or more carbons**
- Resulting products carry the extension **pyranose** or **furanose**

Naming scheme based on:



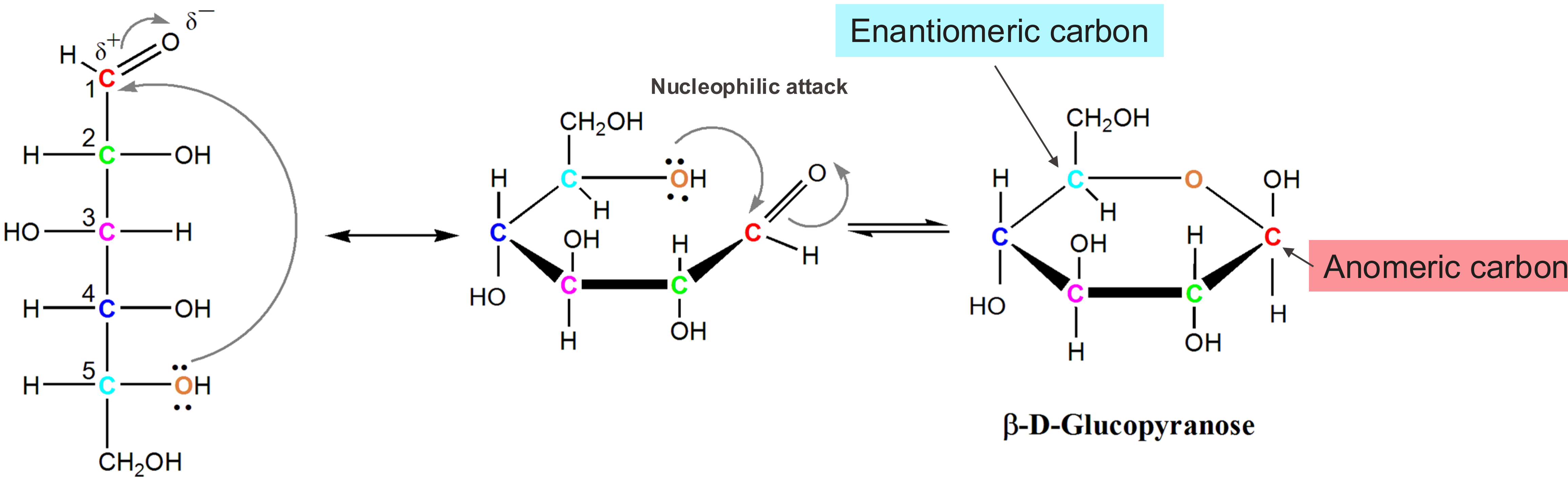
Pyran Furan

Aldose -> Hemiacetal form
Ketose -> Hemiketal form

Although note that there are no double bonds in actual sugars

Formation of cyclic structures in solution

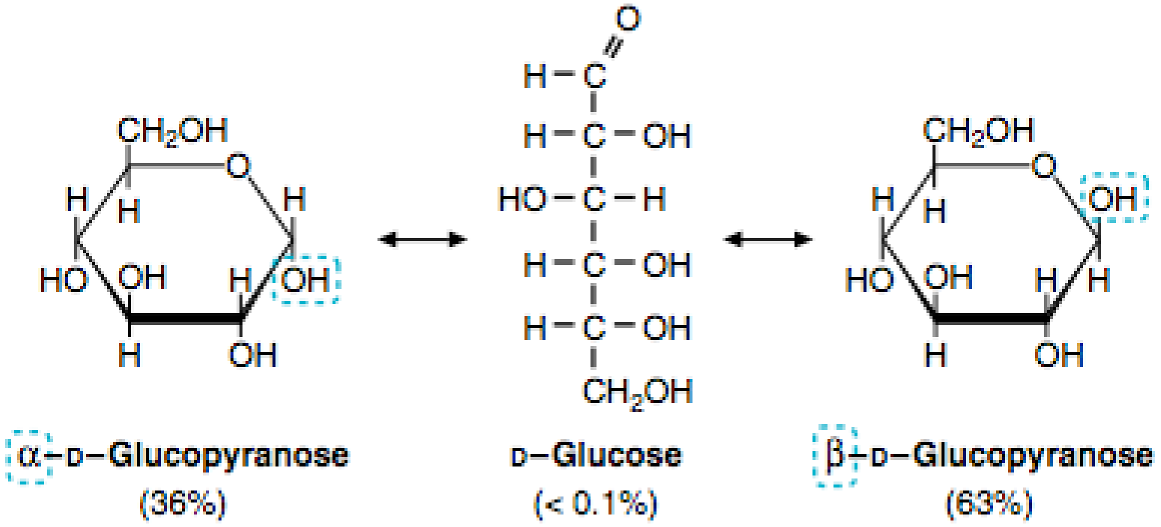
• An **autocatalysis reaction** enabled by the **electrophilic** nature of aldehyde carbon and **nucleophilic** properties of OH groups

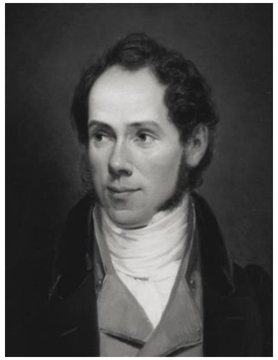


• For longer sugars (6+ carbons) the reaction can take place using any OH group attached to C5, C6 or beyond.

• The **pyran** and **furan** forms (6- or 5-membered rings) are **energetically favorable** compared to larger chains.

Mutarotation around the anomeric carbon





Augustin-Pierre Dubrunfaut
(1797 - 1881)

- In solution there is an equilibrium between 3 forms (**alpha, beta and linear**)
- Different anomeric forms have **different optical properties** (light polarization) which is how they were originally characterized
- **Mutarotases**: enzymes that catalyze mutarotation (i.e. speed up reaction)
- **Enzymes often react with only one stereoisomer (alpha or beta)**

Emil Fischer
(1852 - 1919)

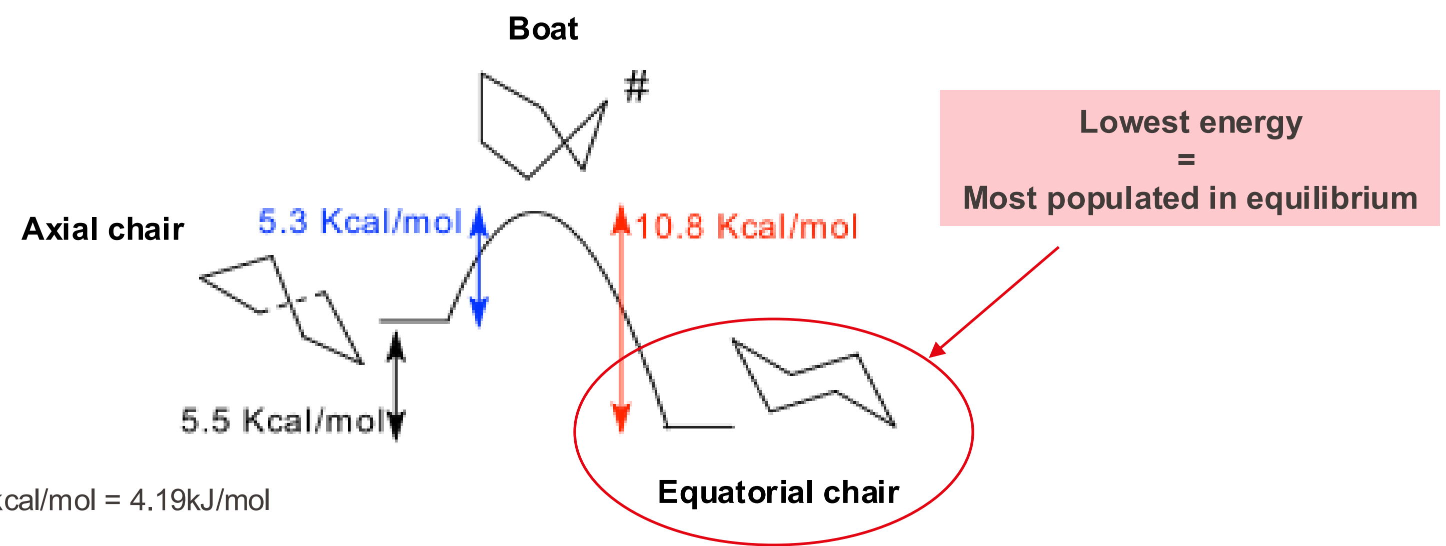
The cyclic molecules are not planar

• In the absence of double bonds, the chain of carbons features **sp3 hybridization** which leads to **non-planar** structure of sugar rings

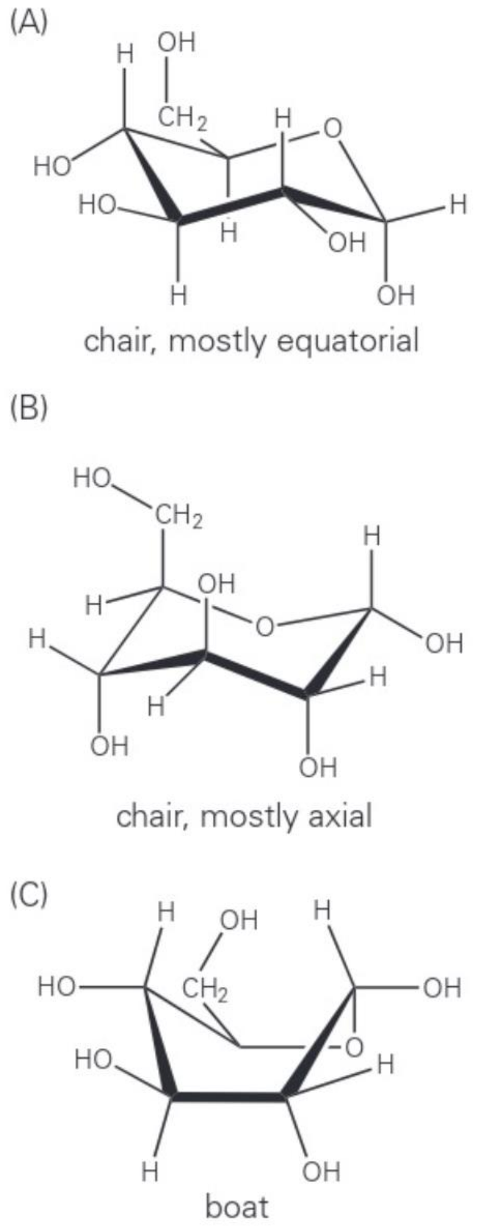
• The groups around each carbon will be at a tetrahedral angle (~109˚)

• The ring forms of sugars can interconvert between **3 conformational states** (2 **chair** and 1 **boat**) with relatively small energy differences

• The boat conformation is the highest in energy and is the least populated state, while the two chair conformations are featured by more particles in equilibrium.



1kcal/mol = 4.19kJ/mol

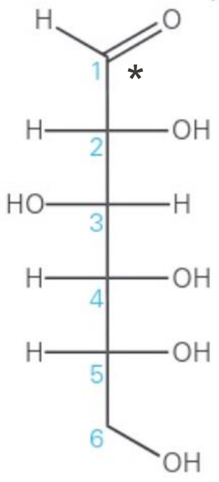


Different representations of monosaccharides

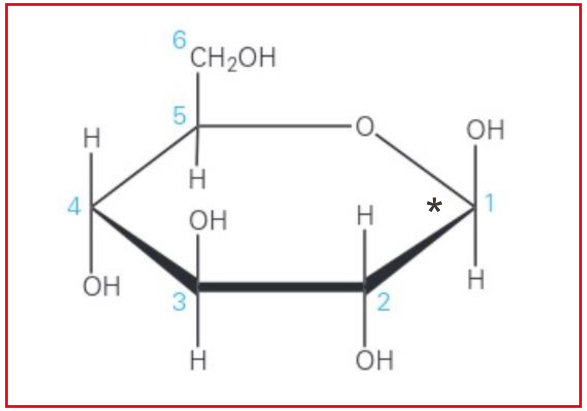
- Please learn how to convert from linear to simple cyclic representation

(A)

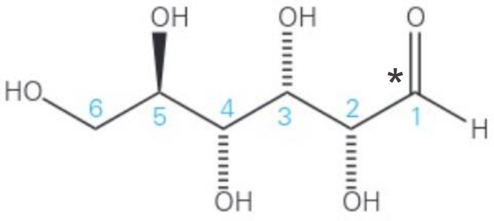
β-D-glucose = aldohexose

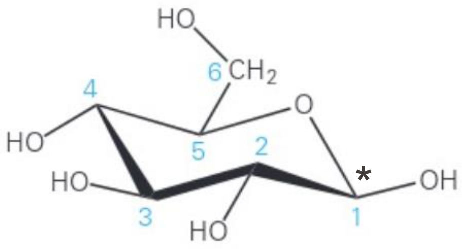


Fischer



Haworth





If you are comfortable with stereospecific representations, please use them (not necessary)

Some tips:

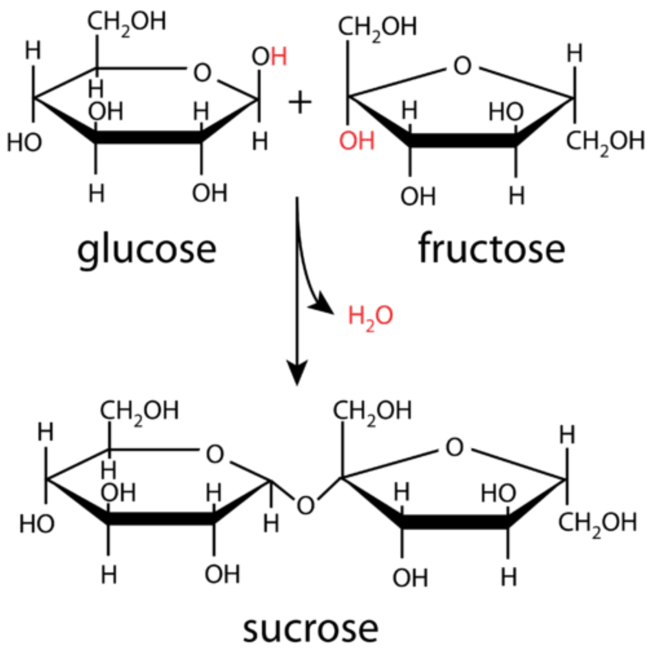
- Use planar representation since it is easier.
- Pay attention to the C numbering and be systematic about clockwise or counter-clockwise organization in cyclic form.
- If C number increases clockwise then the group (H or OH) that is on the left side in linear structure will be above the plane in circular structure. Right side -> Below the plane
- Anomeric carbon always denoted by asterisk. Anomeric state needs to be correct.
- Avoid flipping the structure without a good reason -> Small mistakes can crawl in.
- If even a single OH group is on the wrong side after conversion -> You made a different sugar

Corrected from the original version

Assembly of larger carbohydrates and their biological roles

Formation of larger carbohydrate chains

- Monosaccharides may be covalently linked to form longer chains
- This reaction is catalyzed by an enzyme group called **synthases**
- Water molecule is generated from the leaving H and OH groups
- The linkage between glycans is called “**glycosidic**”
- The inverse reaction (sugar breakdown) is called **hydrolysis**

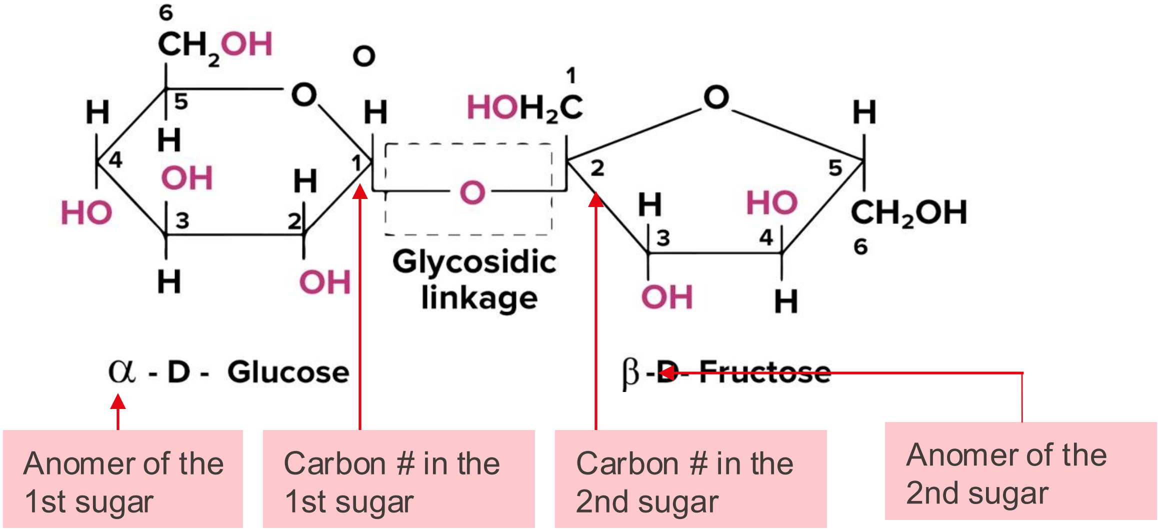


Glycosidic bond naming:

α1 -> **β**2 O-glycosidic bond

or

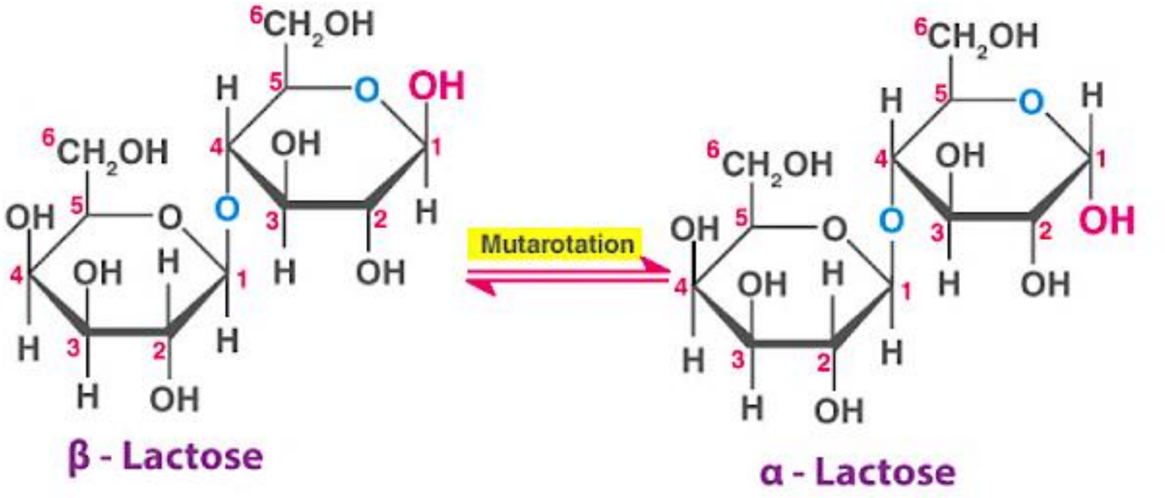
α(1-2)**β** O-glycosidic bond



Anomeric state of the terminal carbohydrate

• Often, the anomeric form of the terminal monosaccharide in sequence is left unspecified when defining the glycosidic bond (i.e., just **α**(1-4) instead of **α**(1-4)**α** or **α**(1-4)**β**)

• This is because in the absence of other chemical bond restraints, the terminal carbohydrate will be able to freely change anomeric states and, consequently, exist in both anomeric states with some distribution



Polymeric carbohydrates will have **α** and **β** forms

• What is the exception to this rule? When will we know definitively the anomeric state of the 2nd sugar?

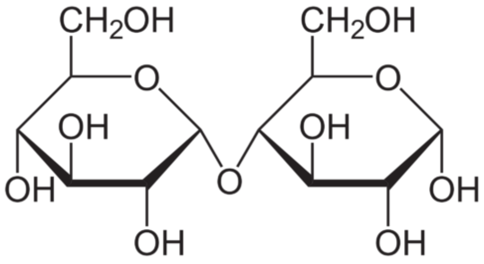
Categories of larger carbohydrate chains

- Disaccharide: **2 monosaccharides** linked by O-glycosidic bond (e.g. sucrose lactose)

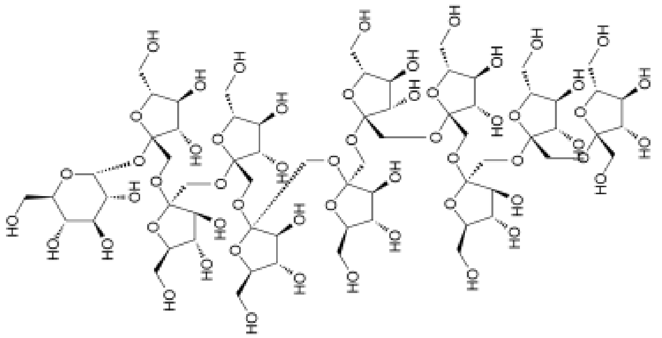
- Oligosaccharides: **3-30 monosaccharides** linked by O- or N-glycosidic bonds (e.g. glycoprotein or glycolipid moieties)

- Polysaccharides: **very large number of linked monosaccharides** (e.g. starch, cellulose)

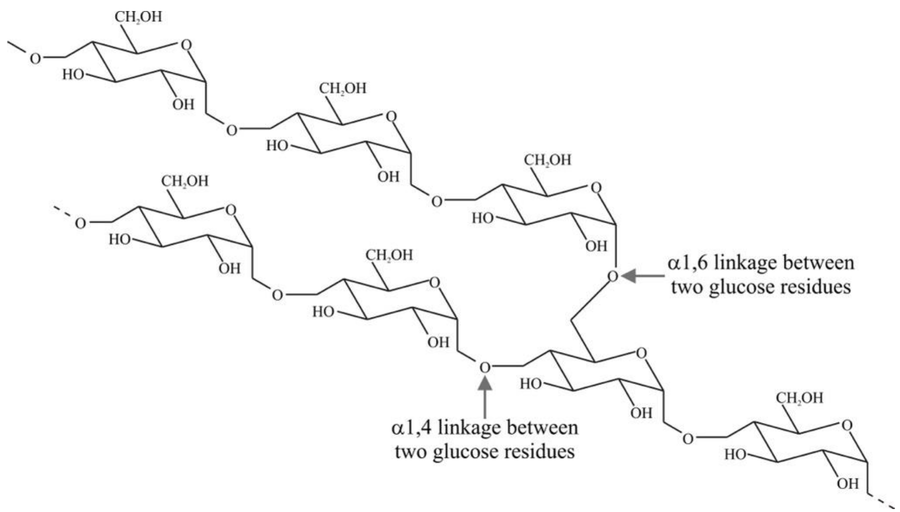
Disaccharide
(Maltose)



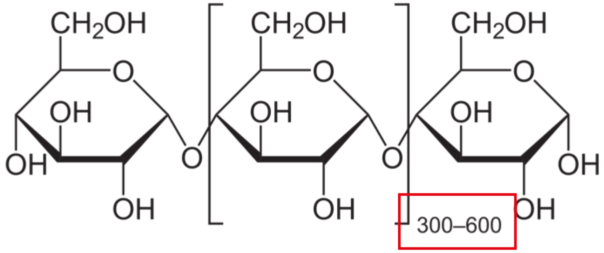
Oligosaccharide
(Oligofructose)



Branched polysaccharide
(Amylopectin)



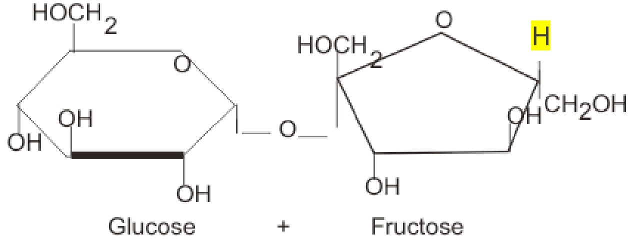
Linear polysaccharide
(Amylose)



Components of starch

Common disaccharides

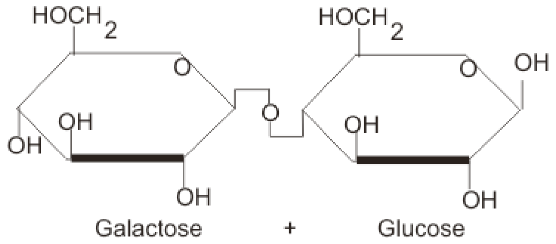
Corrected from the original version



Sucrose

Glucose + Fructose
α(1-2) linkage

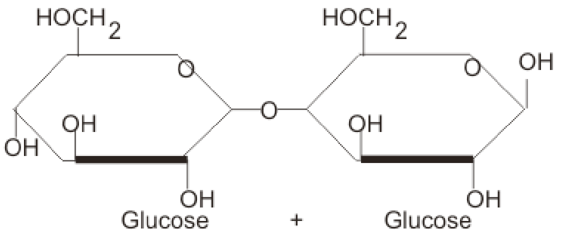
Table sugar



Lactose

Galactose + Glucose
β(1-4) linkage

Milk sugar



Maltose

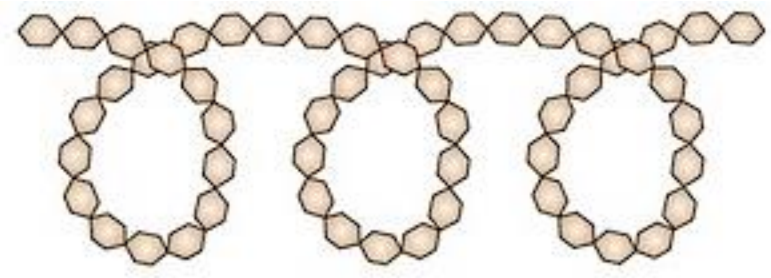
Glucose + Glucose
α(1-4) linkage

Malt sugar
(breakdown product of starch)

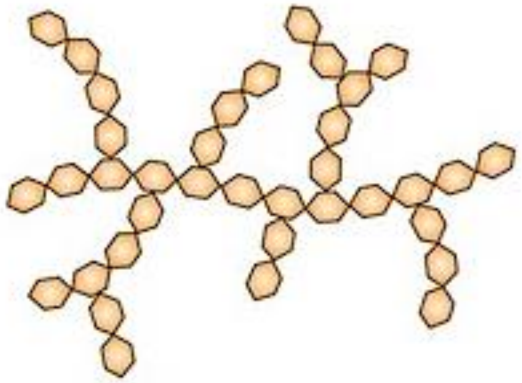
Common polysaccharides - Starch

- Poly-glucose synthesized in plants and one of the primary sources of dietary carbohydrates in animals
- The main roles are storage of energy and source of carbon for photosynthesis
- 2 components:
  - Amylose: **α(1-4)** glucose linkage
  - Amylopectin: **alpha(1-4)** and **alpha(1-6)** glucose linkage

Amylose

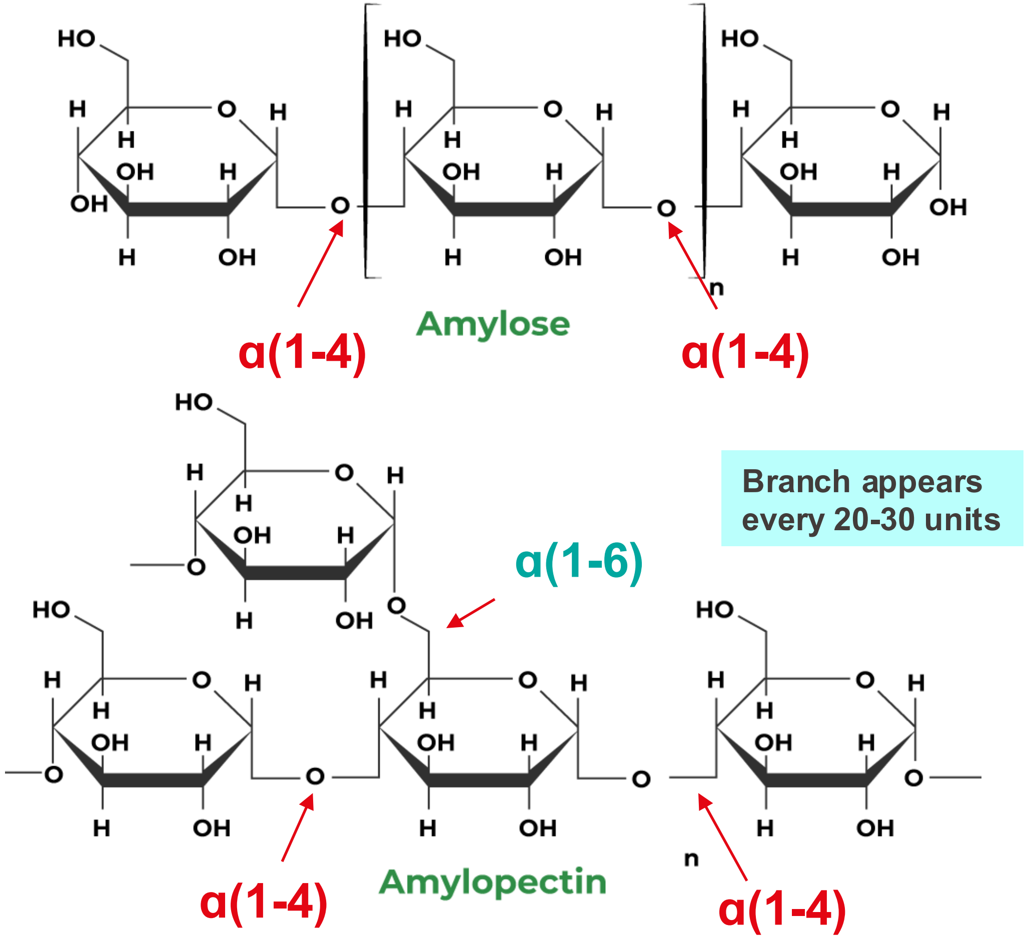


Amylopectin



Linear (helical) assembly
(~200-20'000 glucose units)

Branched assembly
(>1'000'000 glucose units)

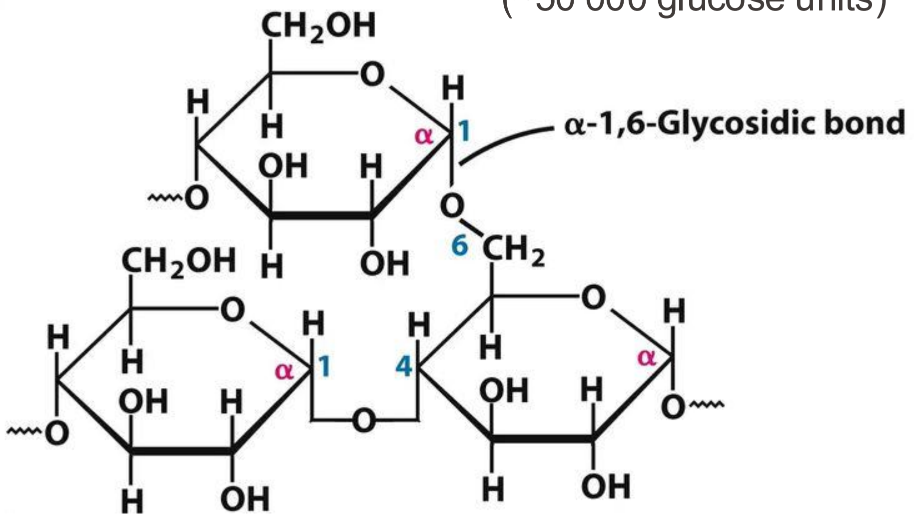


Common polysaccharides - Glycogen

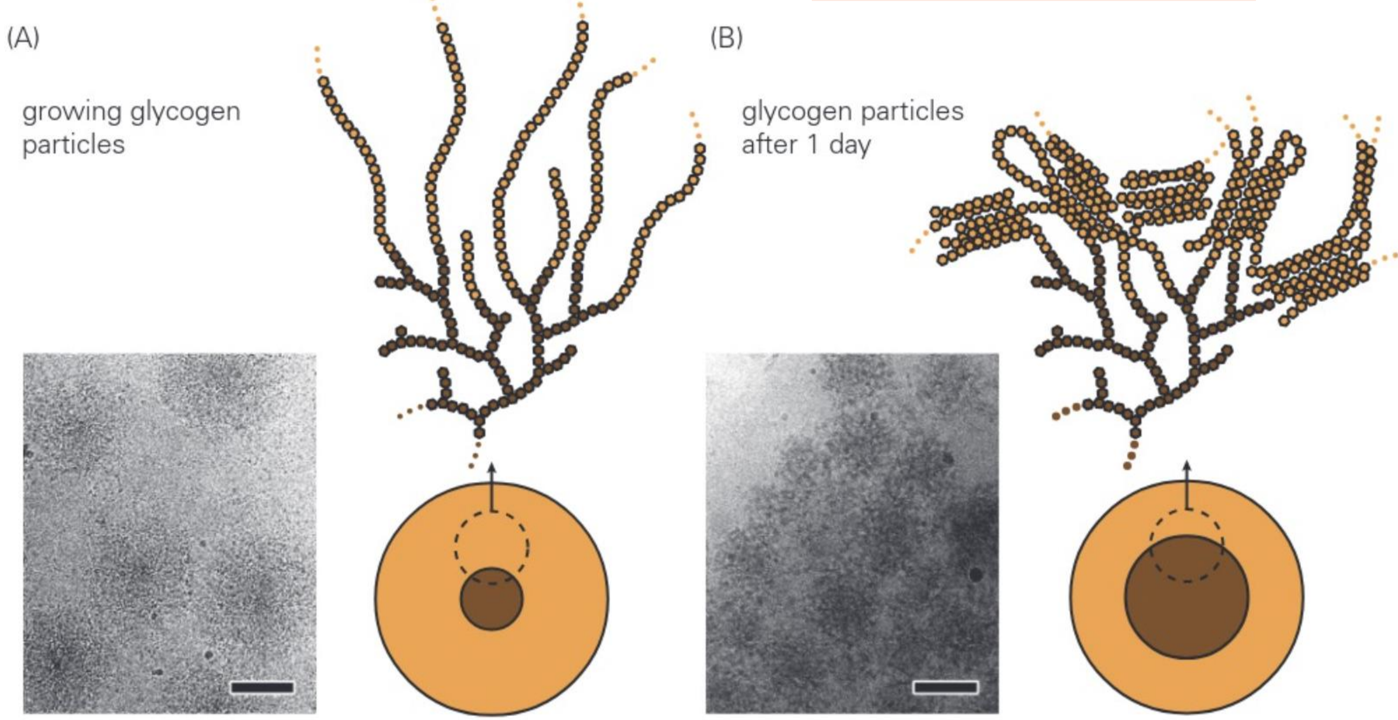
- Poly-glucose found in animals. It is the animal analog to starch, serving as a short-term energy storage.
- After feeding, human bodies have ~80-100g of glycogen in the **liver** and ~300-400g in **skeletal muscles**
- **Insulin** is the key anabolic hormone that promotes glycogen storage after a meal
- The lysis of glycogen into glucose units is controlled by the **glucagon** and **epinephrine** hormones
- The structure is similar to amylopectin but with more **alpha(1-6)** linkages

Increased branching and non-covalent interactions reduce molecule size

Branched assembly
(~50’000 glucose units)



Branch appears every ~12 units

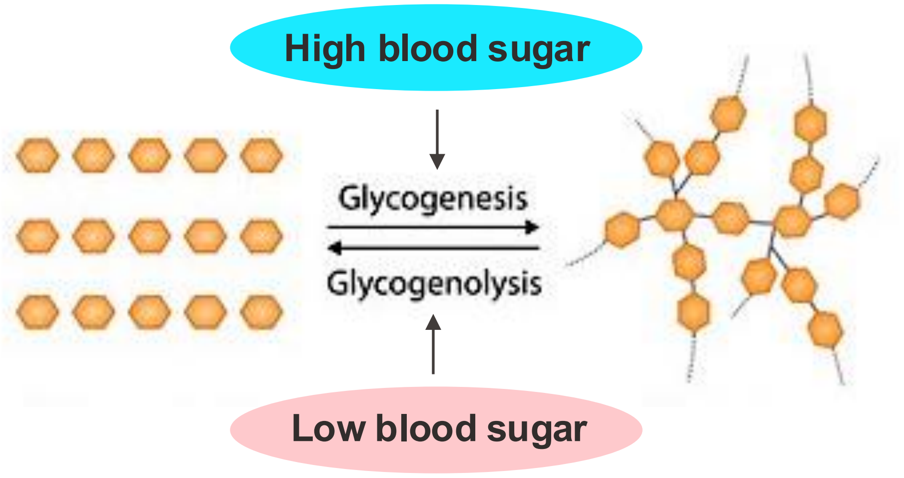


Metabolic use of glucose and glycogen

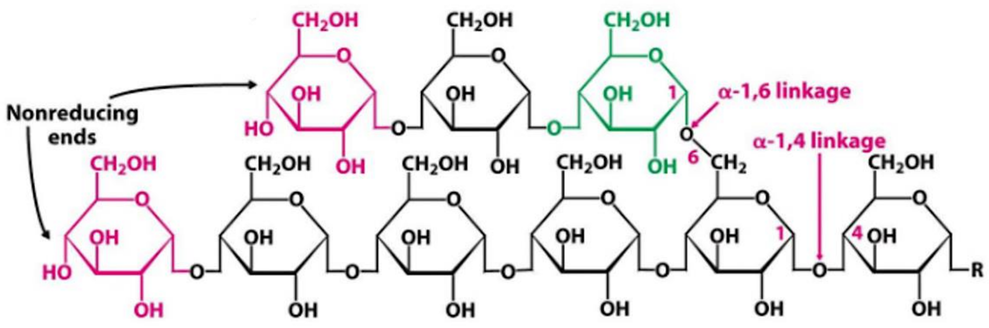
- Each molecule of glucose goes through **glycolysis, Krebs cycle** and **oxidative phosphorylation** generating **30-32 ATP** molecules

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O + ATP\ (energy)$$

- One of the main reasons carbohydrate metabolism is the main cellular supply of energy is the ability to rapidly store glucose molecules through polymerization, and mobilize them when needed:



Glucose addition and removal is via **nonreducing** ends



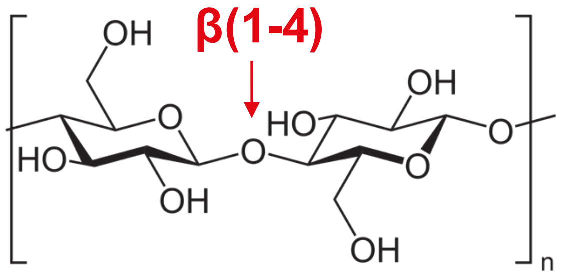
# of branches in glycogen = # of nonreducing ends

- Greater branching frequency improves glycogen packing into smaller volume and **increases the speed of synthesis and lysis steps** since all nonreducing ends can be modified **simultaneously**.

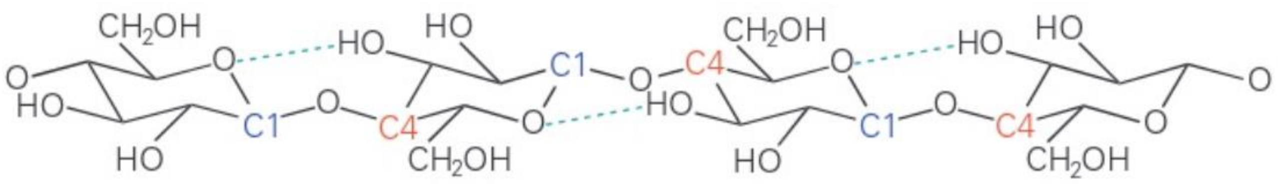
To be covered in more detail in BIO-213

Common polysaccharides - Cellulose

- Poly-glucose found in plants where it assembles the cell wall
- The most abundant biomolecule on the planet
- Glucose linked by **β(1-4) bonds**
- Component of food, paper, clothing, filters etc.

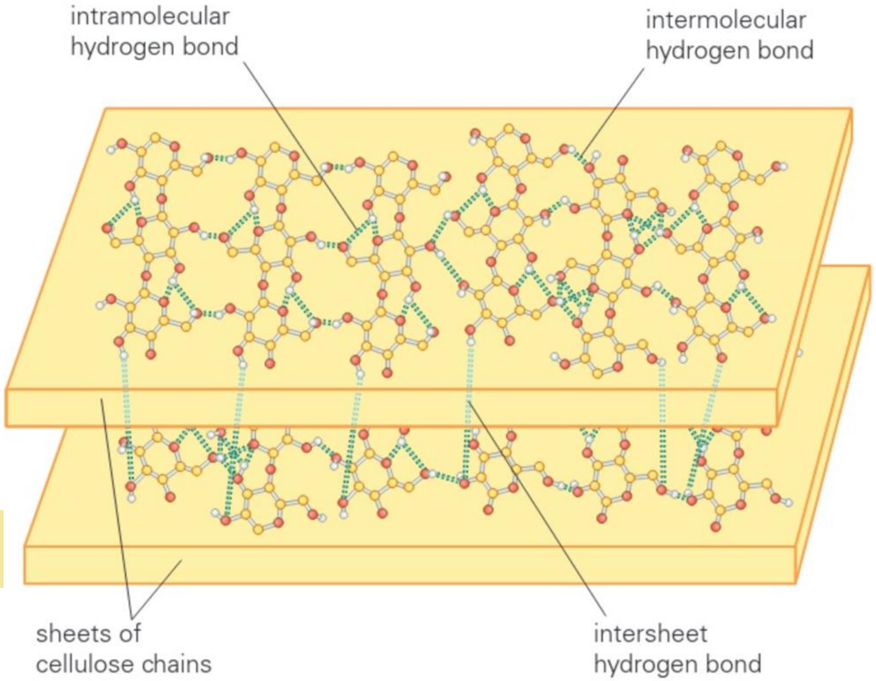


Hydrogen bonding improves stability of a single strand



cellulose = poly(glucose-β(1→4)glucose)

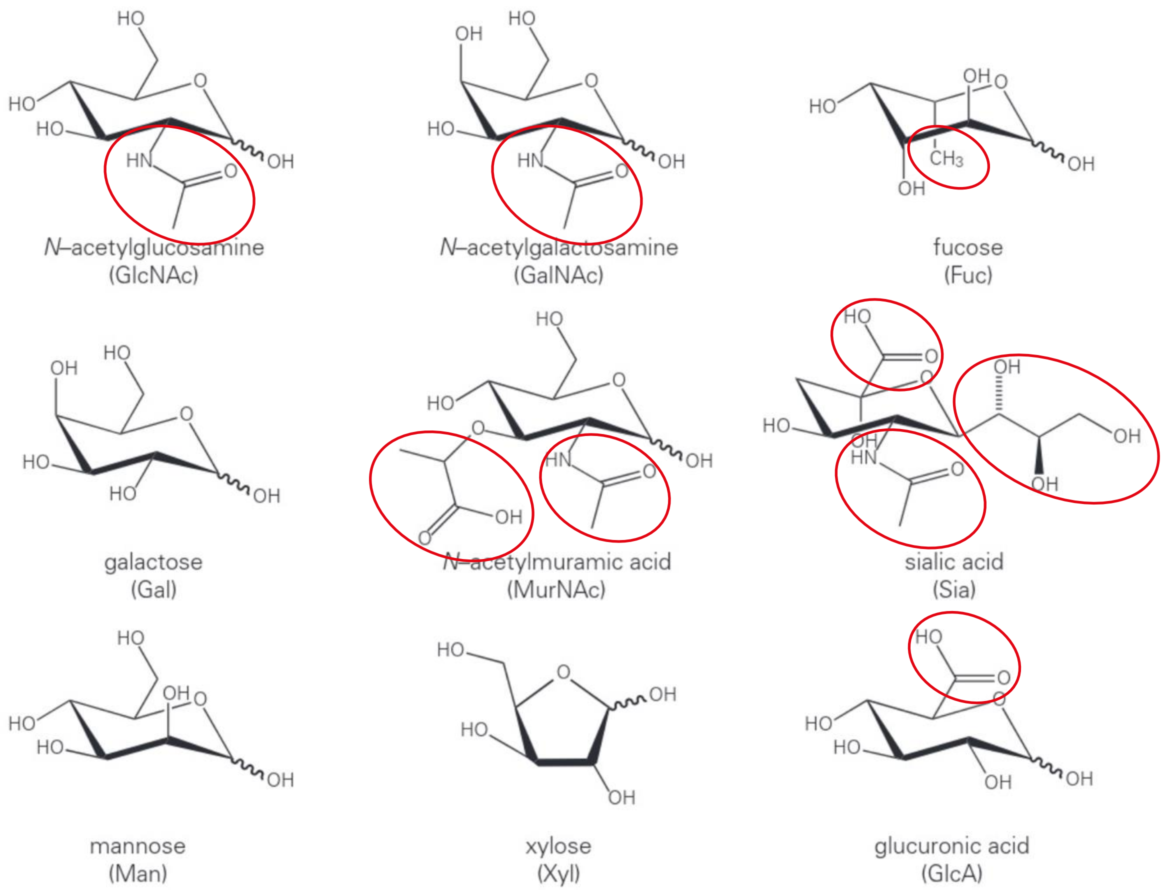
Cellulose chains assemble into sheets providing mechanical stability



Expanding the chemical diversity and roles of carbohydrates

Sugars with non-standard chemical groups

- Typically **generated through covalent modifications** (e.g., N-acetylation, methylation, sulfation etc.) of existing carbohydrate building blocks.
- The oligo- and poly-saccharides containing these units are typically not used as metabolic fuel inside the cell but for structural roles, signaling or covalent modifications of lipids and proteins



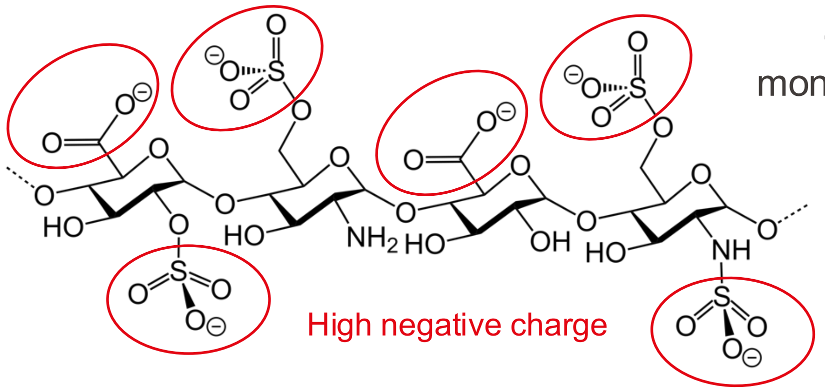
Glucose	Glc
Mannose	Man
Galactose	Gal
Fucose	Fuc
Xylose	Xyl
Sialic acid	Sia
N-Acetylglucosamine	GlcNAc
N-Acetylgalactosamine	GalNAc
N-Acetylmuramic acid	MurNAc
Glucuronic acid	GlcA

These are not essential structures to remember.

Glucosaminoglycans

- Glycosaminoglycans (GAGs) are long, unbranched, negatively charged polysaccharides made of repeating disaccharide units, found in the extracellular matrix and on cell surfaces
- Major types of GAGs include hyaluronic acid, heparin, heparan sulfate, chondroitin sulfate, and keratan sulfate.

• Heparin (similar to heparan sulfate)

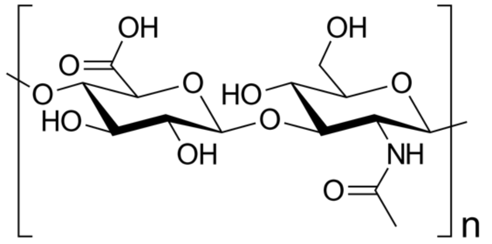


~ 20 - 60 monosaccharides

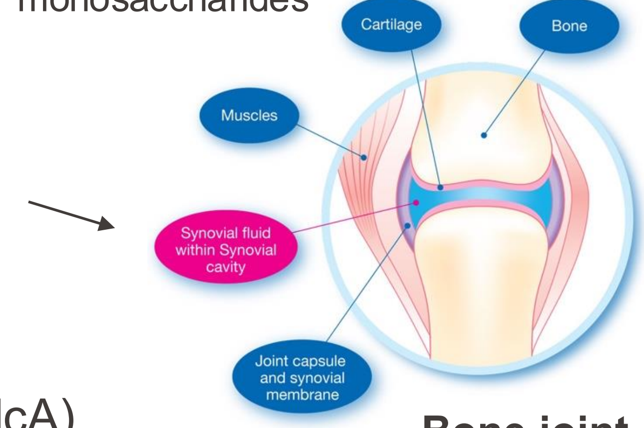
Composition:
- α-L-iduronic acid (IdoA) - O-sulfated
- α-D-glucosamine (GlcN) - O and N sulfated

Role:
- Produced by mast cells to reduce inflamatory response
- Used as anticoagulant in clinic (reduces blood clotting)

• Hyaluronic acid



~ 50 - 50'000 monosaccharides



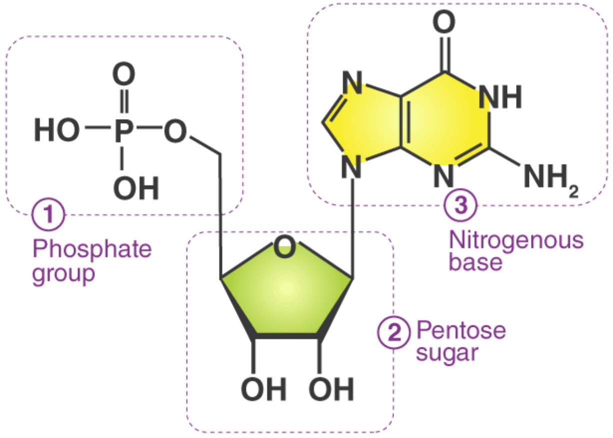
Bone joint

Composition:
- β-D-glucuronic acid (GlcA)
- β-N-acetyl-D-glucosamine (GlcNAc)

Role:
- Major component of extracellular matrix (ECM)
- Tissue elasticity, joint lubrication, turgor pressure...

Carbohydrates can be attached to other biomolecules

Nucleotides

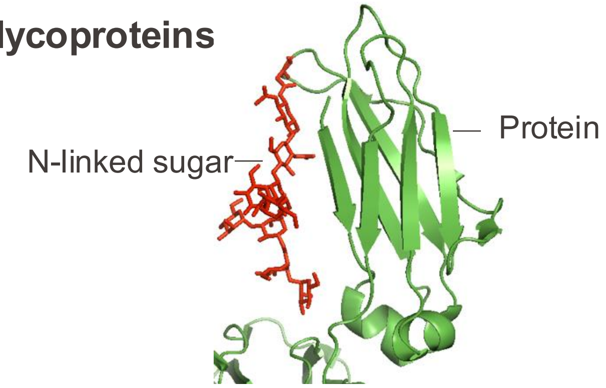


(2) - Ribose or Deoxyribose

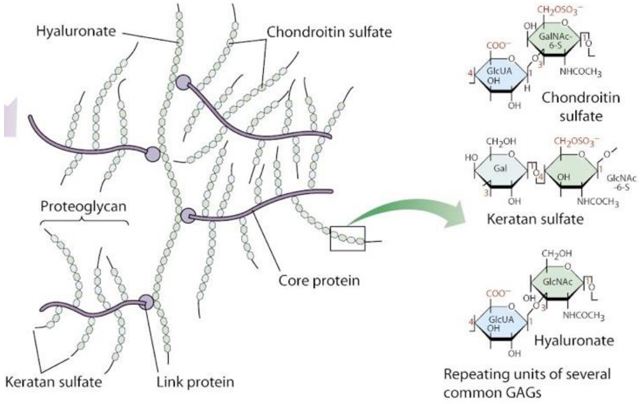
The sugar moiety defines the type and role of nucleic acid molecule

Proteins

Glycoproteins

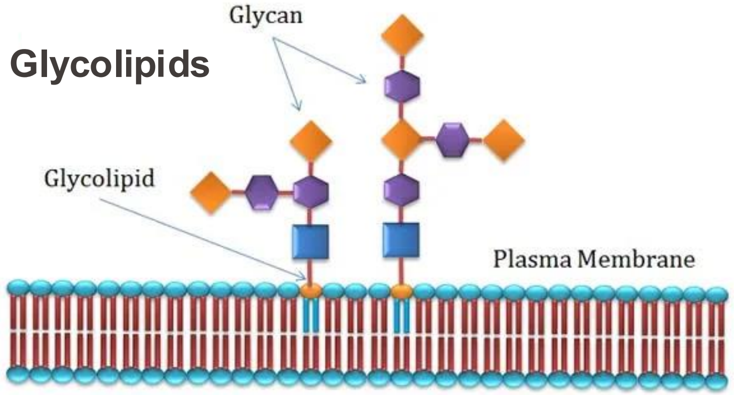


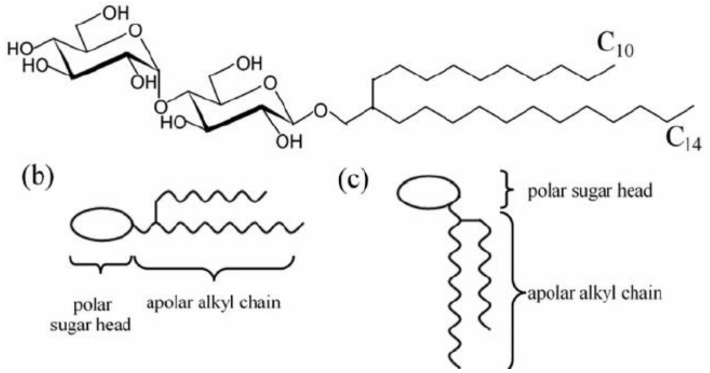
Proteoglycans



Lipids

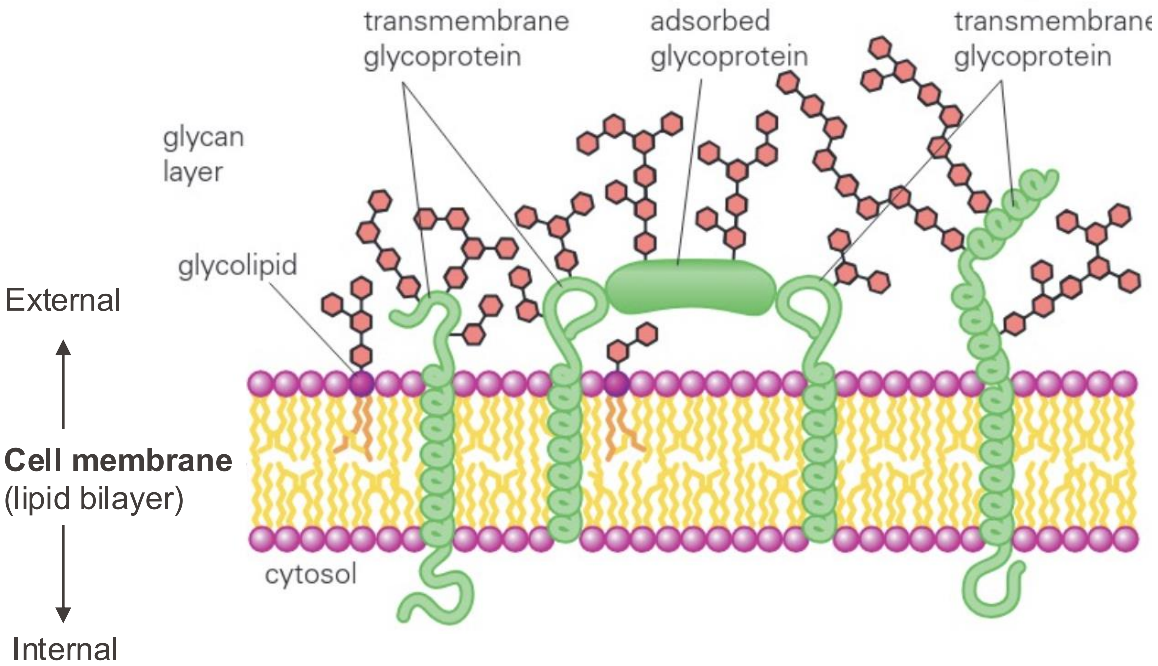
Glycolipids

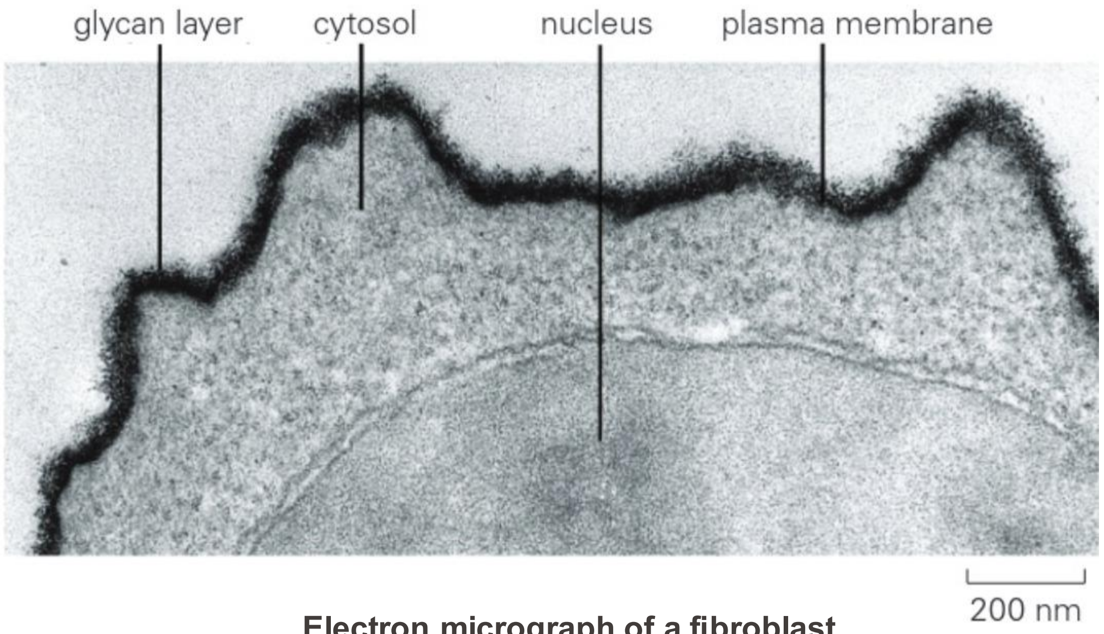




Glycolipids and glycoproteins as cell markers

- Both glycoproteins and glycolipids are **primarily present on the cell membrane** facing the extracellular space.
- Their **synthesis** and **export** to the cell membrane is dependent on **endoplasmic reticulum (ER)** and **Golgi apparatus**.





Electron micrograph of a fibroblast

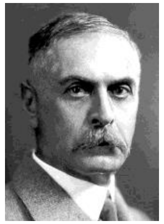
- The type and content of glycan groups depends on the type of cell and plays an important role in **cellular recognition by other cells, signaling and immune molecules, or viruses**.

Blood group antigens are determined by glycolipids

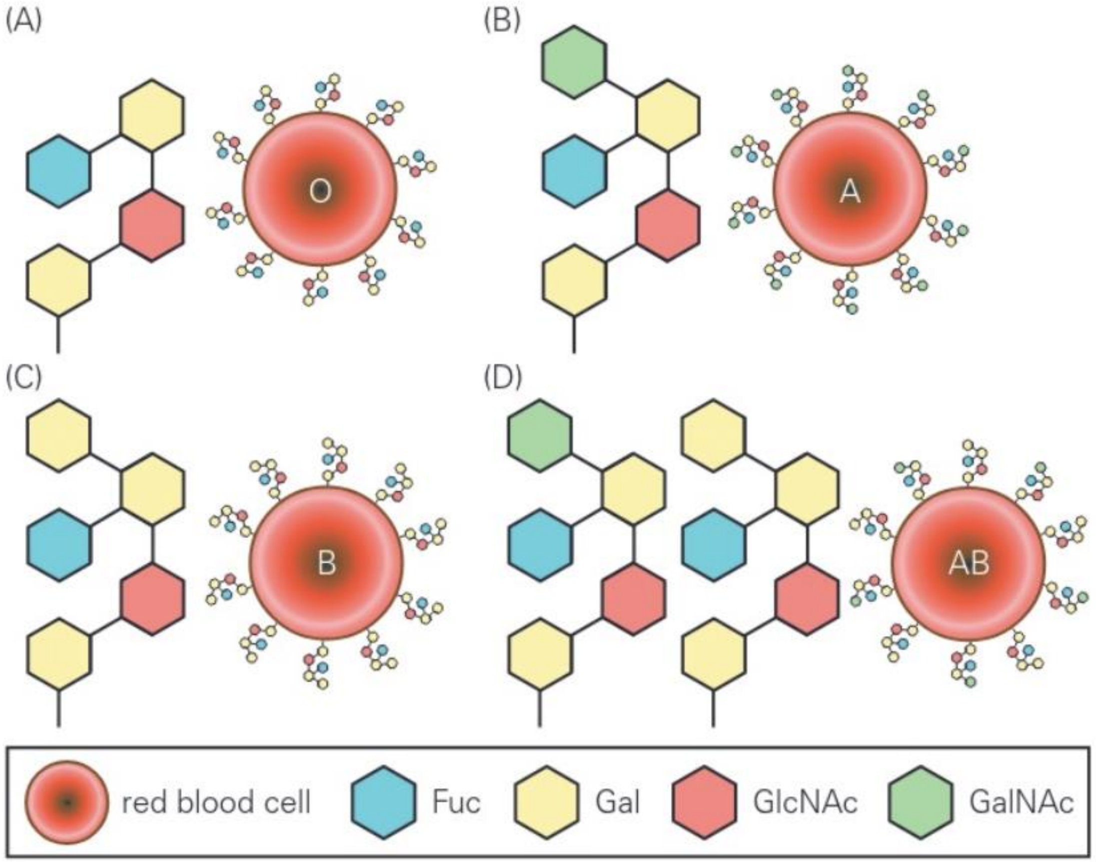
- The human blood groups (ABO) are determined by the **oligosaccharide head groups of glycolipids** present in the outer leaflet of the **red blood cell membrane**
- Subtle variations arose from genetic differences in enzymes that control glycosylation

- All blood group antigens contain the same core of monosaccharides (O group marker), but A and B antigens also contain an additional terminal residue which could be:
  - N-acetyl-galactosamine (A)
  - Galactose (B)

- The immune system develops tolerance to “self” glycolipids from the early age. However, it will treat different glycolipids as foreign if encountered (e.g., through transfusion of the wrong blood type).

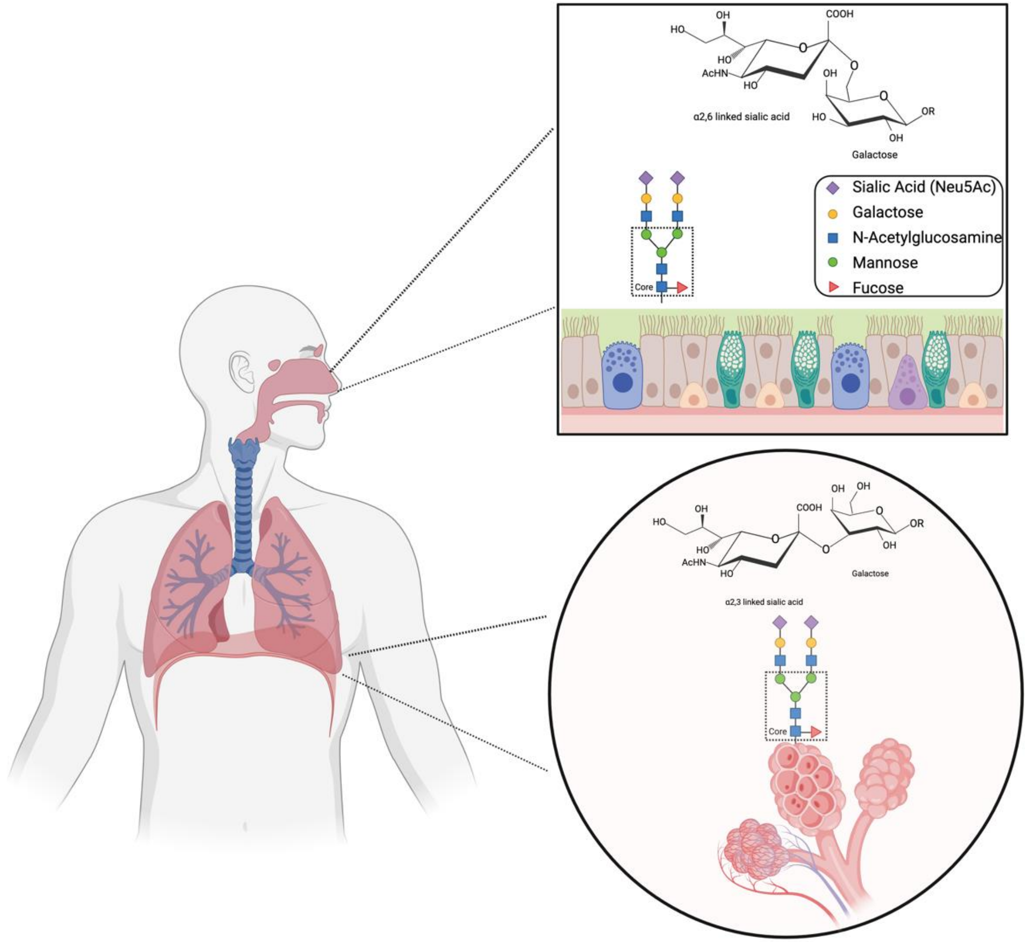


Karl Landsteiner
(1868 - 1943)

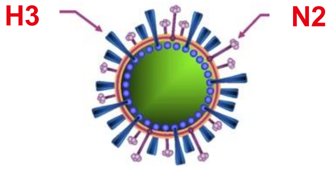


Influenza (flu) virus targets cells with specific glycans

- Influenza virus recognizes and infects target cells based on the specific glycan receptors (sialyl-lactose) present as glycolipids or glycoprotein conjugates



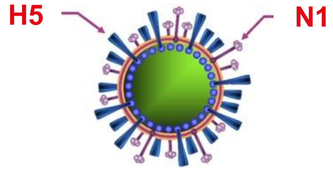
α(2-6) Sialyl-lactose ← Seasonal Flu (e.g., H3N2)



Upper respiratory tract (nose, throat, trachea)

Result: Mild respiratory infection of nose and throat

α(2-3) Sialyl-lactose ← Bird Flu (e.g., H5N1)



Lower respiratory tract (lung alveoli)

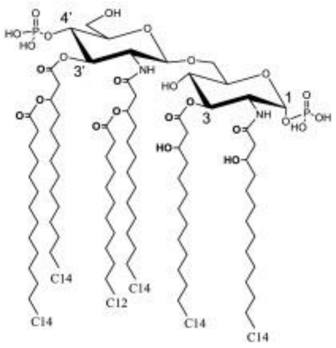
Result: Severe respiratory infection commonly leading to pneumonia and complications

- The only difference between these sugars is **one covalent bond**

Carbohydrates in bioengineering

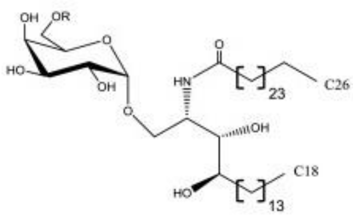
• Vaccines and adjuvants

Bacterial glycolipids (LPS)

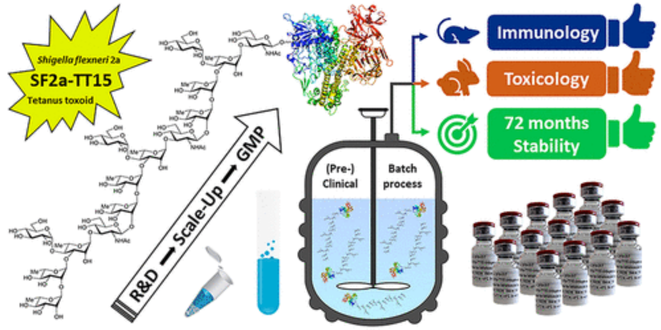


E. Coli Lipid A

α-Galactosylceramide

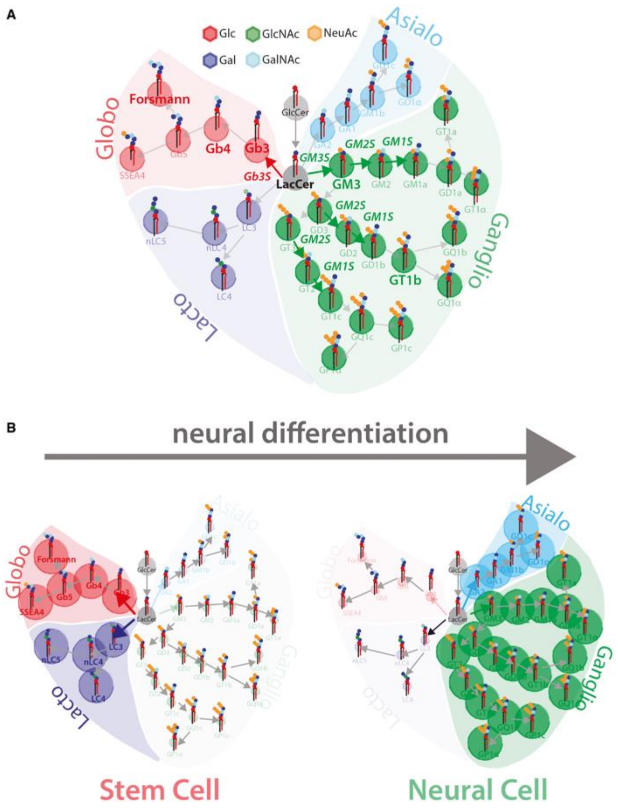


Fully synthetic glycan vaccine for Shigella



https://research.pasteur.fr/fr/team/chemistry-of-biomolecules/

• Glycolipids and cell fate



https://www.epfl.ch/labs/dangelo-lab/

• Nutrition and Cancer

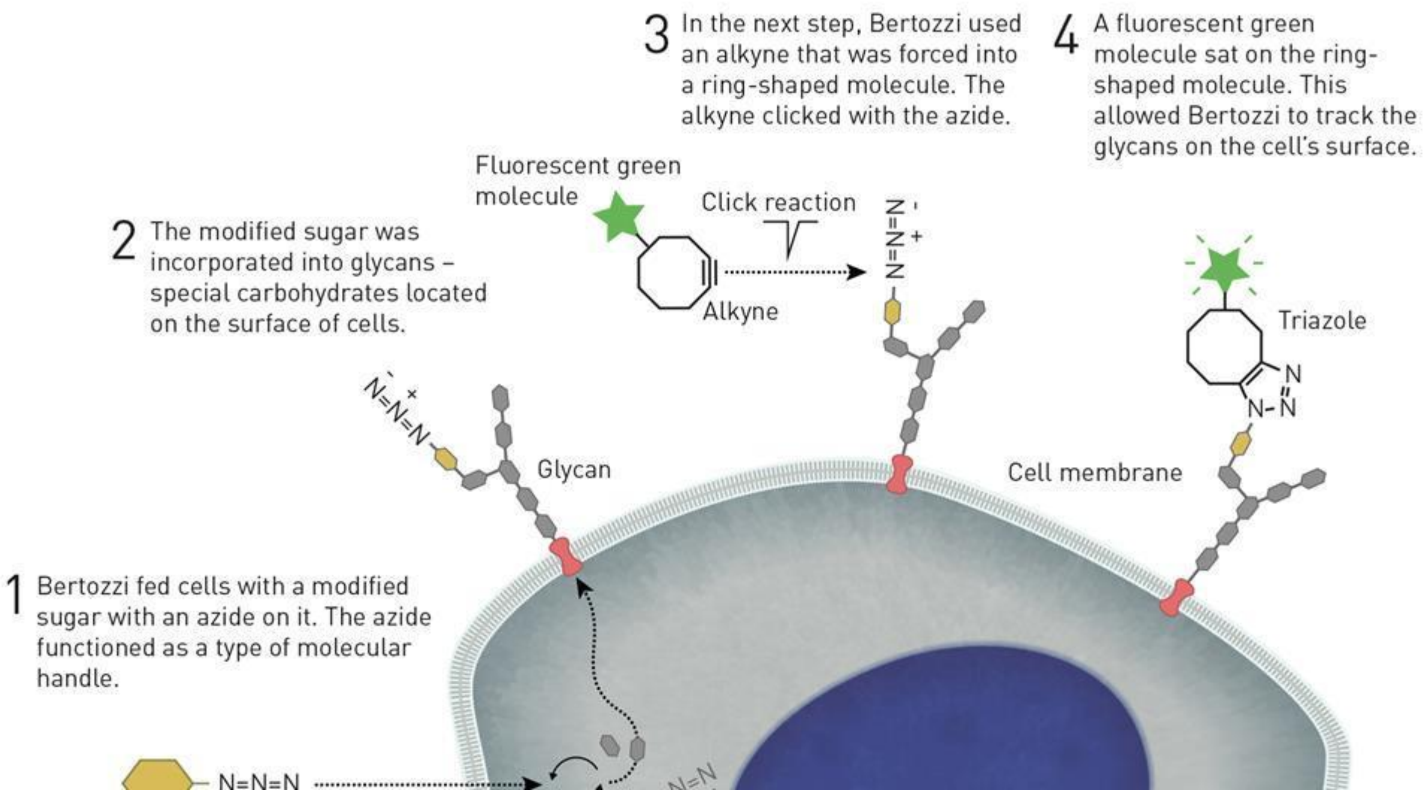
AI in food and nutrition

Track your individual response to food and help advance science

https://www.epfl.ch/labs/salathelab/
https://meylan-lab.com/lung-cancer-resistance-the-key-is-glucose/

Carbohydrates in bioengineering

- Biorthogonal chemistry approaches to label and track carbohydrates in cells



Carolyn Bertozzi

Nobel Prize in Chemistry, 2022

https://bertozzigroup.stanford.edu/

Carbohydrates - Take home messages

- Carbohydrates are a diverse family of biomolecules with primary function in energy storage and metabolism.
- Monosaccharide represent the smallest building blocks of carbohydrates with the general formula of $\mathbf{C_nH_{2n}O_n}$ but can include other groups (e.g., sulfate, amino, and carboxylic acid)
- Monosaccharides with 5 or more carbons exist as cyclic molecules in solution
- Longer carbohydrate chains are built from monosaccharide units connected via glycosidic bonds. Their primary role is metabolic (e.g., glycogen) or structural (e.g., cellulose).
- Carbohydrate polymers are very dynamic and lack a structured 3D assembly but some local organization can occur (i.e., cellulose sheets)
- They can also be conjugated to proteins and lipids and presented on cell surface (signaling role) or as part of extracellular matrix (structural role)