Master’s Degree in Cellular and Molecular Biology
Curriculum in Advances Cellular Studies

Metabolic Biochemistry

(6+1 CFU, 48 + 12 hours)

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3 CFU (24 hours)
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Phone. 070-6754507

Prof. Francesca Pintus
3CFU (24 hours) +1 CFU lab (12 hours)
E-mail: fpintus@unica.it
Phone. 070-6754522

Department of Life and Environmental Sciences

Prof.ssa Alessandra Olianas

Department of Life and Enviromental Sciences
Biomedical Section (Biochemistry Laboratory)

Dip. Scienze della Vita e dell’Ambiente
Sezione Biomedica (laboratorio di Biochimica)
Tel. 0706754507
Students reception: by appointment

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I° SEMESTER

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
9-11am			**Metabolic Biochemistry** (classroom 7 Block H - D2)	**Metabolic Biochemistry** (classroom 105 Block F)		
11am-1pm		**Metabolic Biochemistry** (classroom 3 Block H - D1)				

SLIDES

Prof. Olianas

-

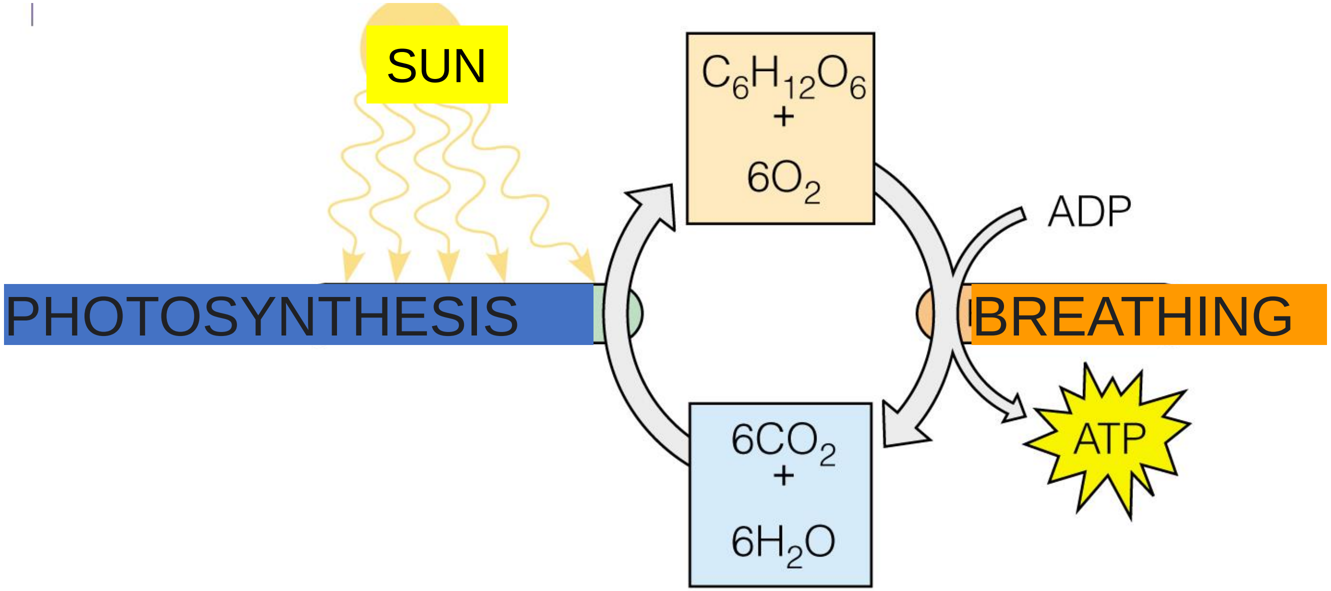
The slides of the lessons will be on personal link the day after
(Alessandra Olianas unica: materiale didattico)

Carbohydrates = saccharides (Greek: sakcharon, sugar)

Essential components of all living organisms

- **Most abundant class of biological molecules**

Main energy cycle of the biosphere it is based on the metabolism of carbohydrates



Carbohydrates Functions

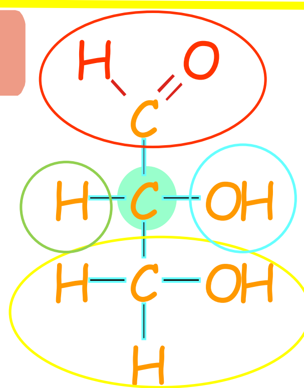
- **Supply chemical energy**
- **Support (vegetable cell wall)**
- **Protection (bacterial wall)**
- **Skeletal joint lubricants**
- **Inter-cell adhesion**
- **Cellular "recognition"**

Carbohydrates

- Monosaccharides (glucose)
- Oligosaccharides **glycosides**
- Polysaccharides **glycans**

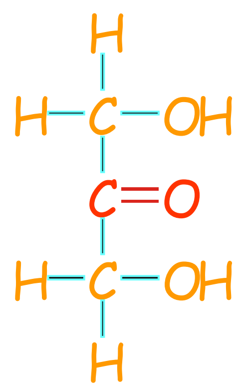
Monosaccharides
Polyalcohol
with a aldehyde or ketone group

aldose



Glyceraldehyde

ketose



dihydroxyacetone

Monosaccharides

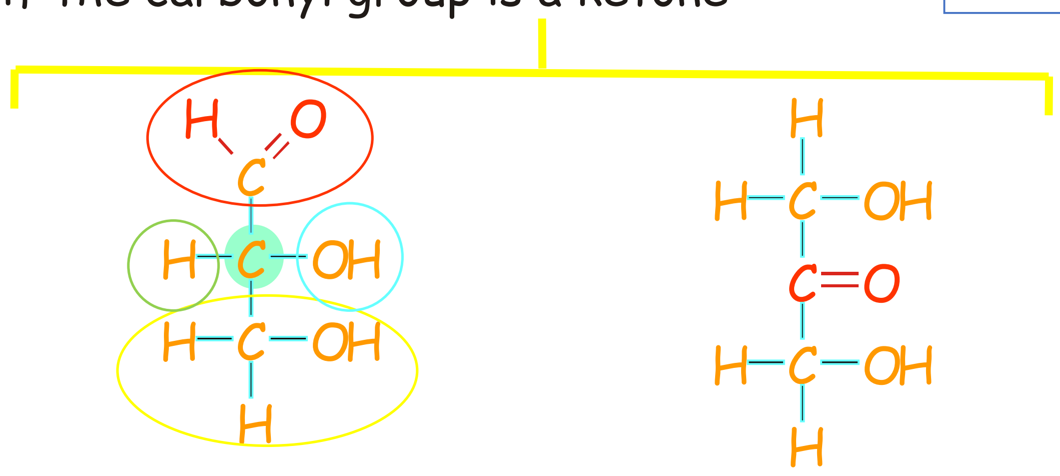
Aldehyde or ketone derivatives of straight-chain polyhydroxy alcohols containing at least three carbon atoms.

Classification:

Chemical nature of their carbonyl group and the number of their C atoms

- Aldoses: if the carbonyl group is an aldehyde
- Ketoses if the carbonyl group is a ketone

The Two Families of Monosaccharides Are Aldoses and Ketoses



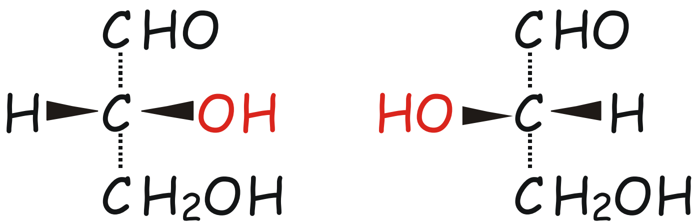
aldoses

ketoses

Glyceraldehyide

dihydroxyacetone

(Fischer projection)



D-Glyceraldehyde L -Glyceraldehyde

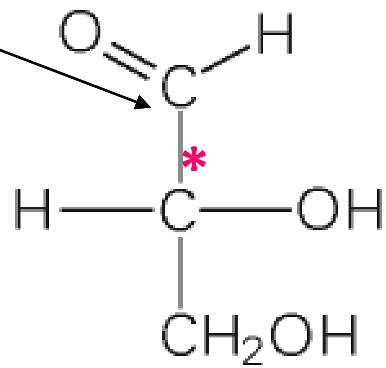
- Glyceraldehyde contains one asymmetric carbon atom and forms two enantiomers

D or L sugar is defined according to the configuration of the last chiral center (i.e. the chiral center farthest from the C-carbonyl).

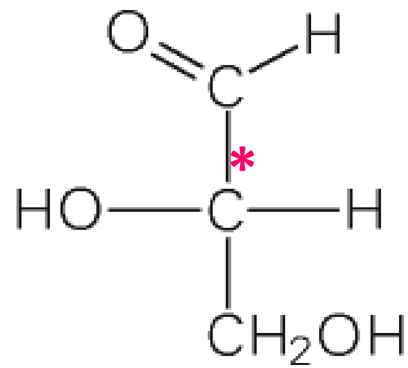
-OH linked to last chiral center on the right in D-sugar
-OH linked to last chiral center on the left in L-sugar

Most oxidized carbon :

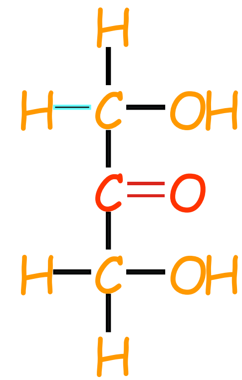
Fisher's projection



D -Glyceraldehyde
$(C_3H_6O_3)$



L-Glyceraldehyde
$(C_3H_6O_3)$

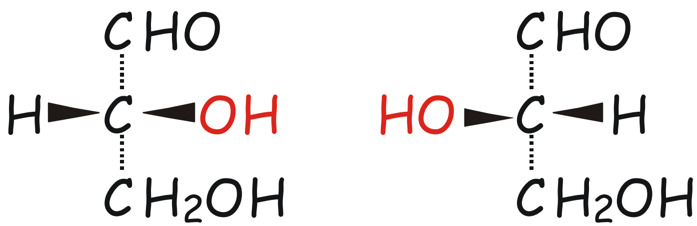


dihydroxyacetone

they have similar chemical reactivity but different physical properties and biological roles.
They have different interact with polarized light, are optically active (they can rotate the plane of polarized light to the right (+) or to the left (-))

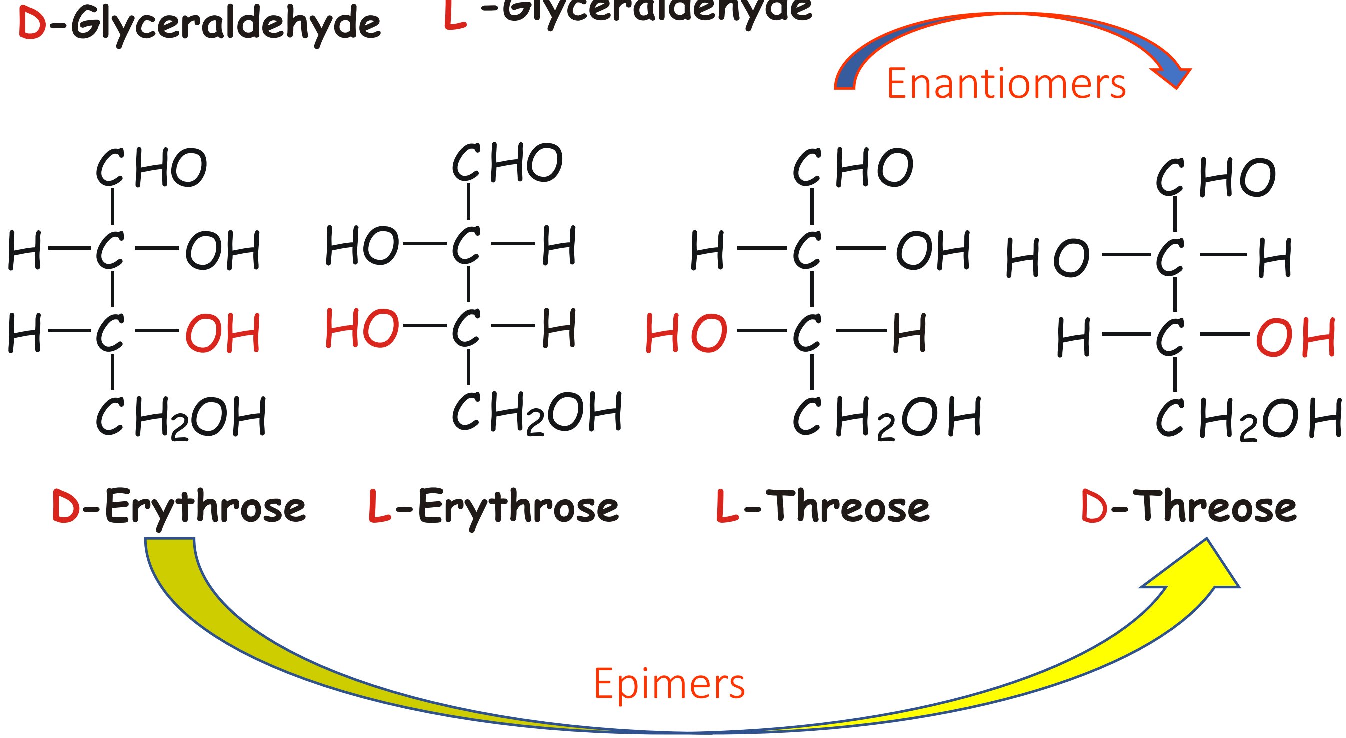
With the exception of dihydroxyacetone, all other monosaccharides are chiral compounds:

(Fischer projection)



D-Glyceraldehyde L -Glyceraldehyde

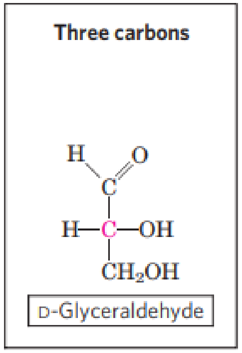
- Glyceraldehyde contains one asymmetric carbon atom and forms two enantiomers



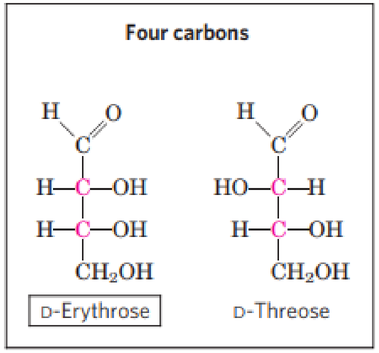
- the asymmetric carbon farthest from the aldehyde group determines the configuration (D or L series)

ALDOSES

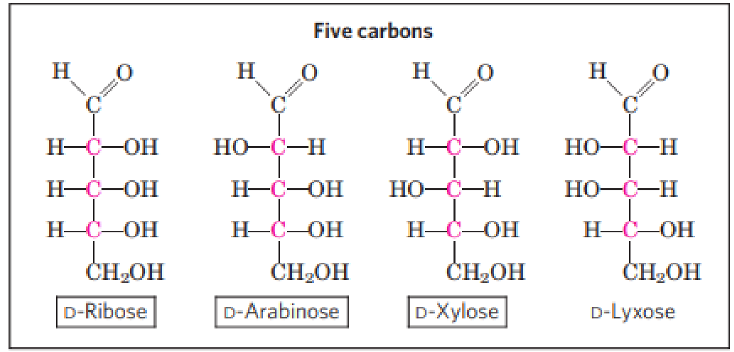
TRIOSE

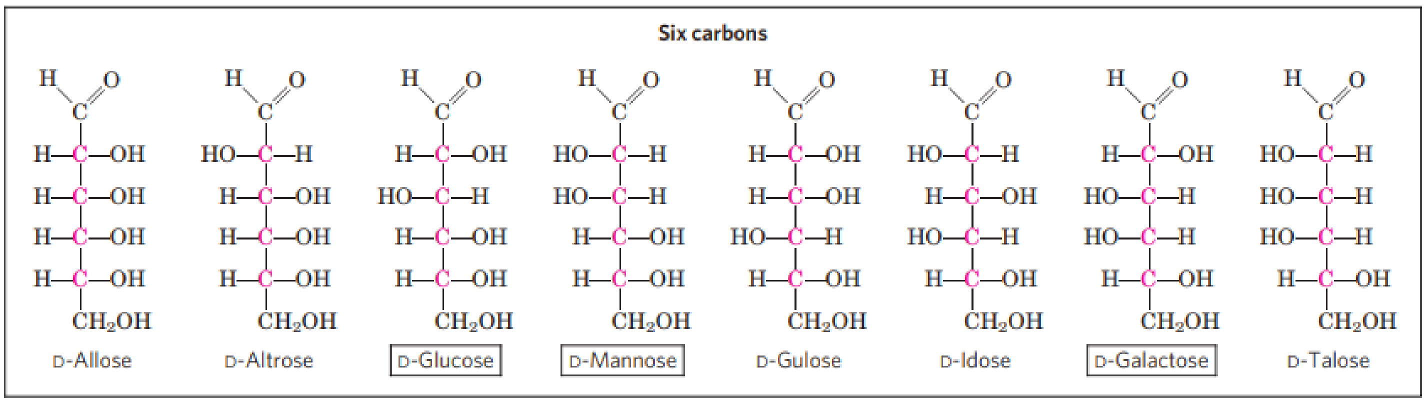


TETROSES



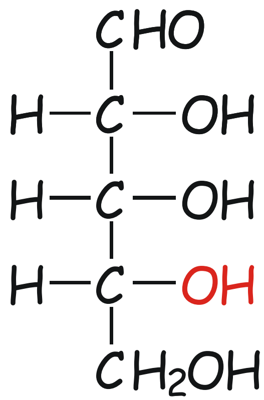
PENTOSES



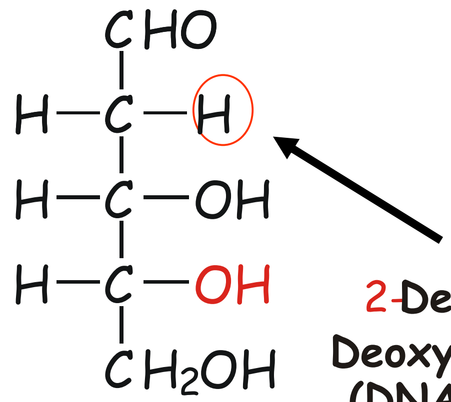


HEXOSES

PENTOSES

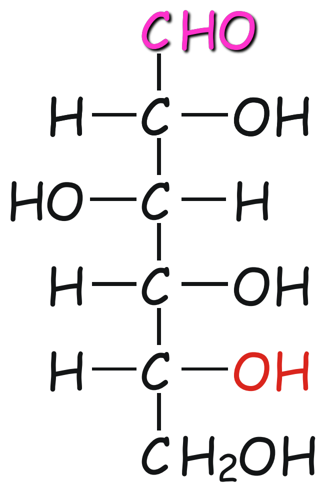


D-Ribose
Ribonucleic acid (RNA)

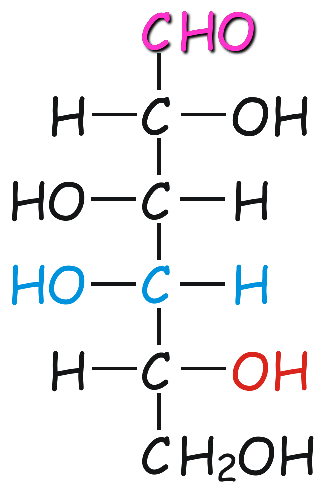


2-Deoxy-D-ribose
Deoxyribonucleic acid (DNA)

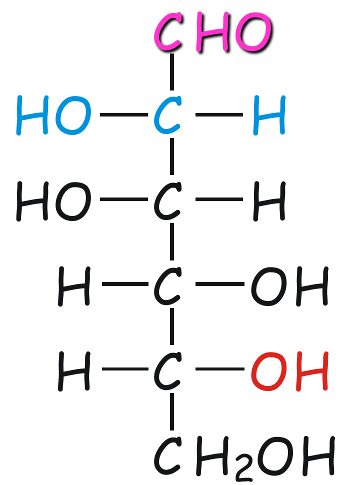
HEXOSES



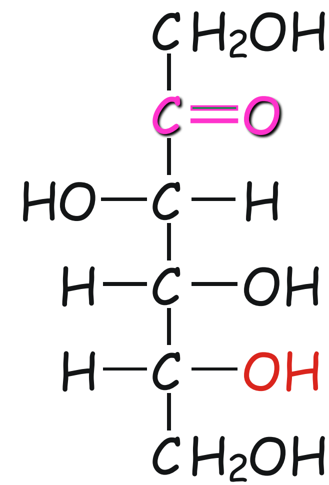
D-Glucose



D-Galactose



D-Mannose



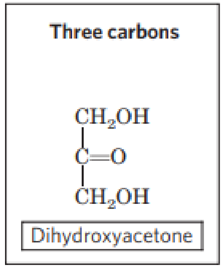
D-Fructose

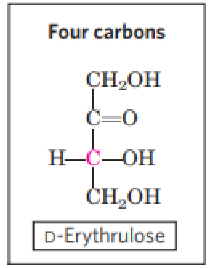
- epimers = sugars that differ in the configuration at one chiral center

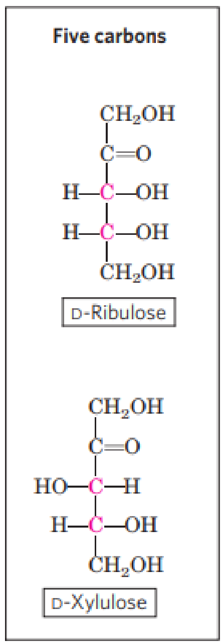
KETOSES

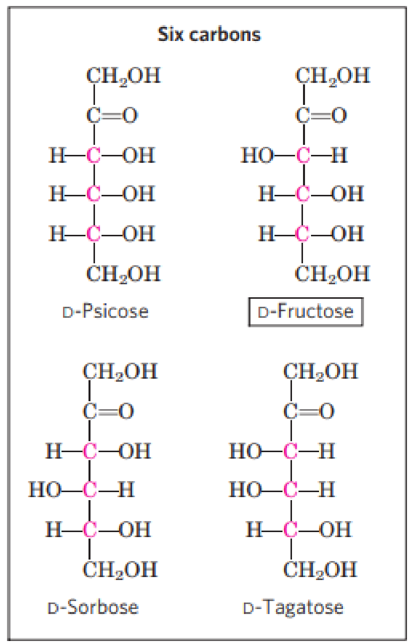
TRIOSE

TETROSES





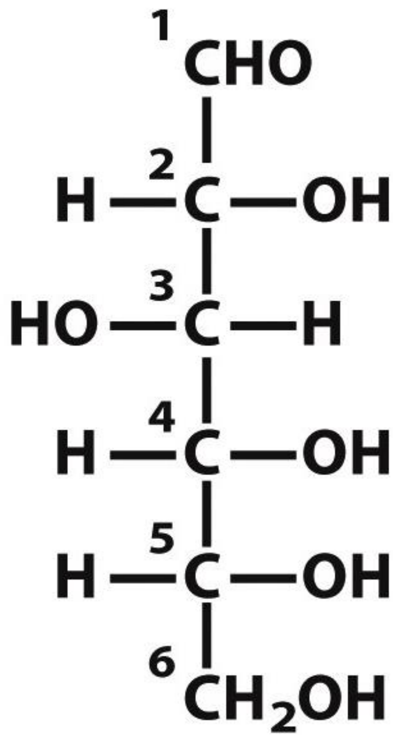




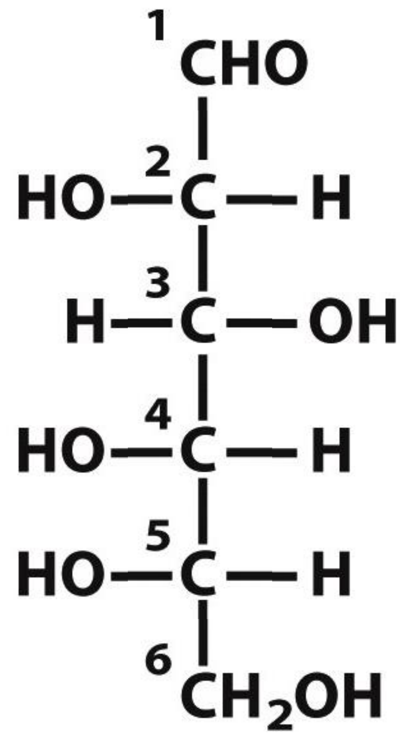
PENTOSES

HEXOSES

D-glucose



L-glucose



The configuration of each chiral center must be reverse

Lehninger Principles of Biochemistry, Fifth Edition
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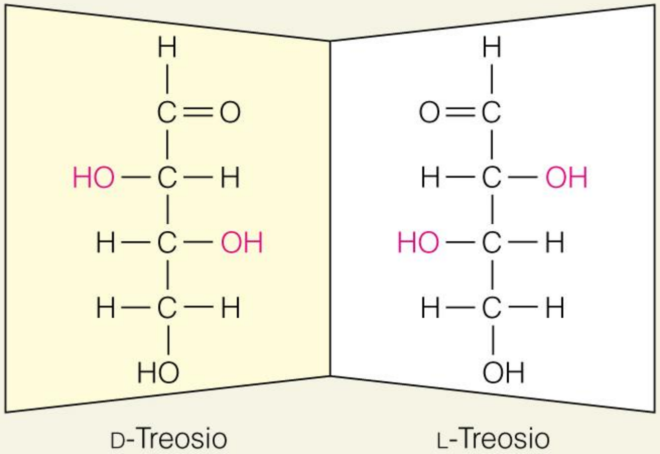
Enantiomers

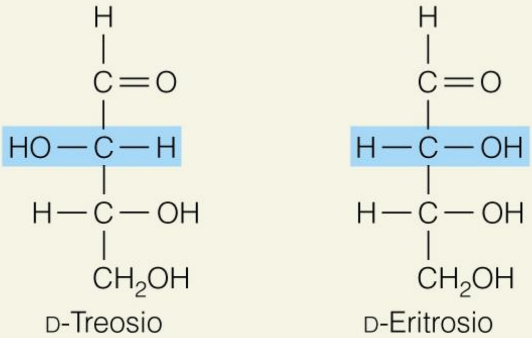
they are mirror images of each other that are non-superimposable

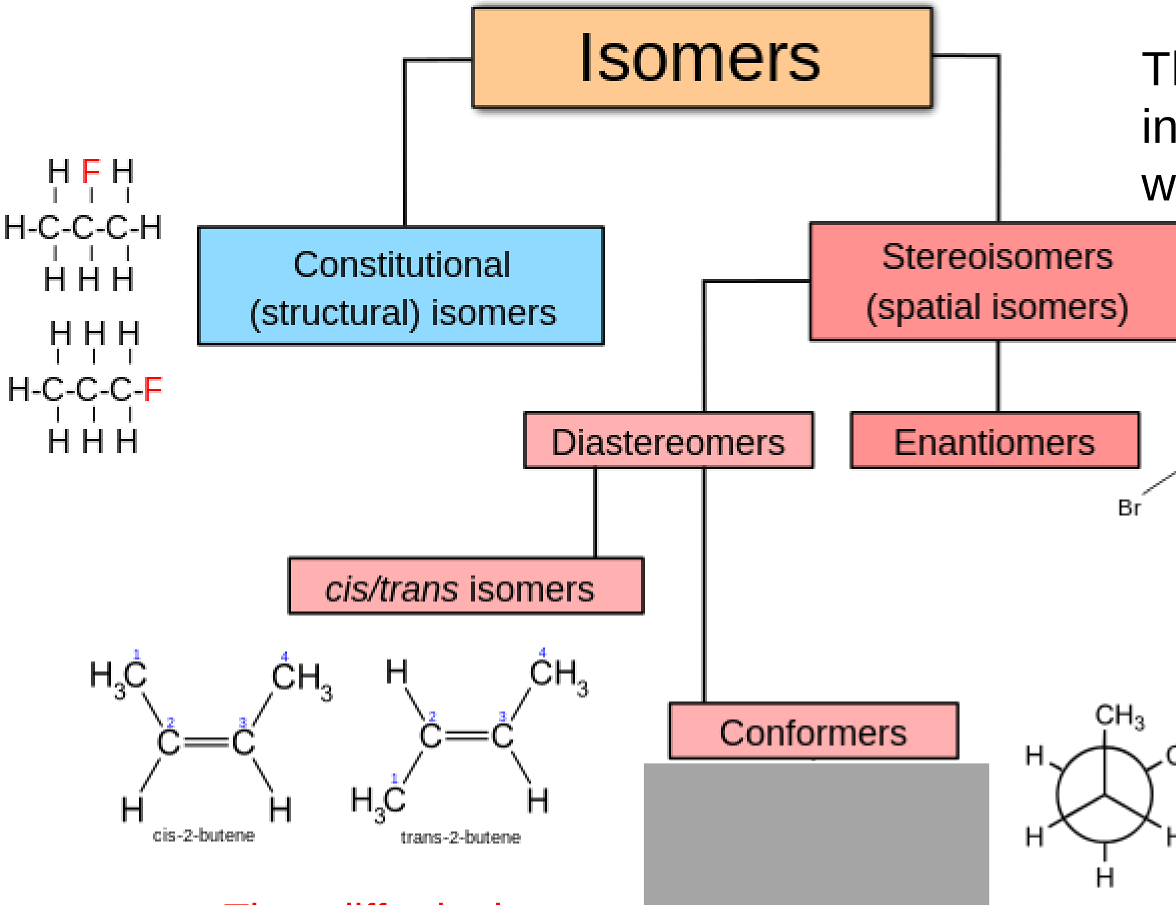


Epimers

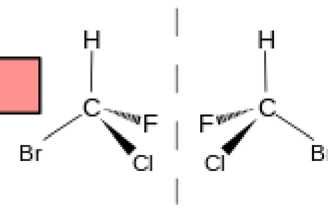
they are not mirror images of each other

They have opposite configuration at only one chiral carbon



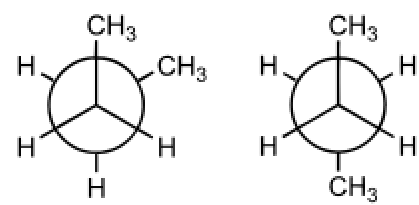


The stereoisomers cannot be interconverted into each other without breaking covalent bonds



They differ in the configuration around a chiral carbon
Optical properties
Racemes

They differ in the configuration around a double bond

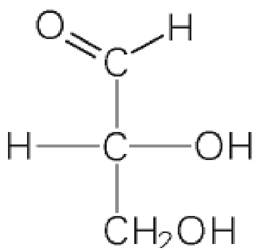


Conformation: spatial arrangement of atoms which is obtained without breaking covalent bonds

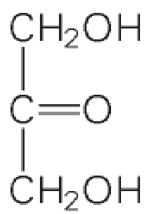
STEREOISOMERY

Isomers

Isomers constitutional



-Glyceraldehyde



Dihydroxyacetone

STEREOISOMERI
Gli atomi sono legati
nello stesso ordine ma differiscono
nel riordinamento spaziale

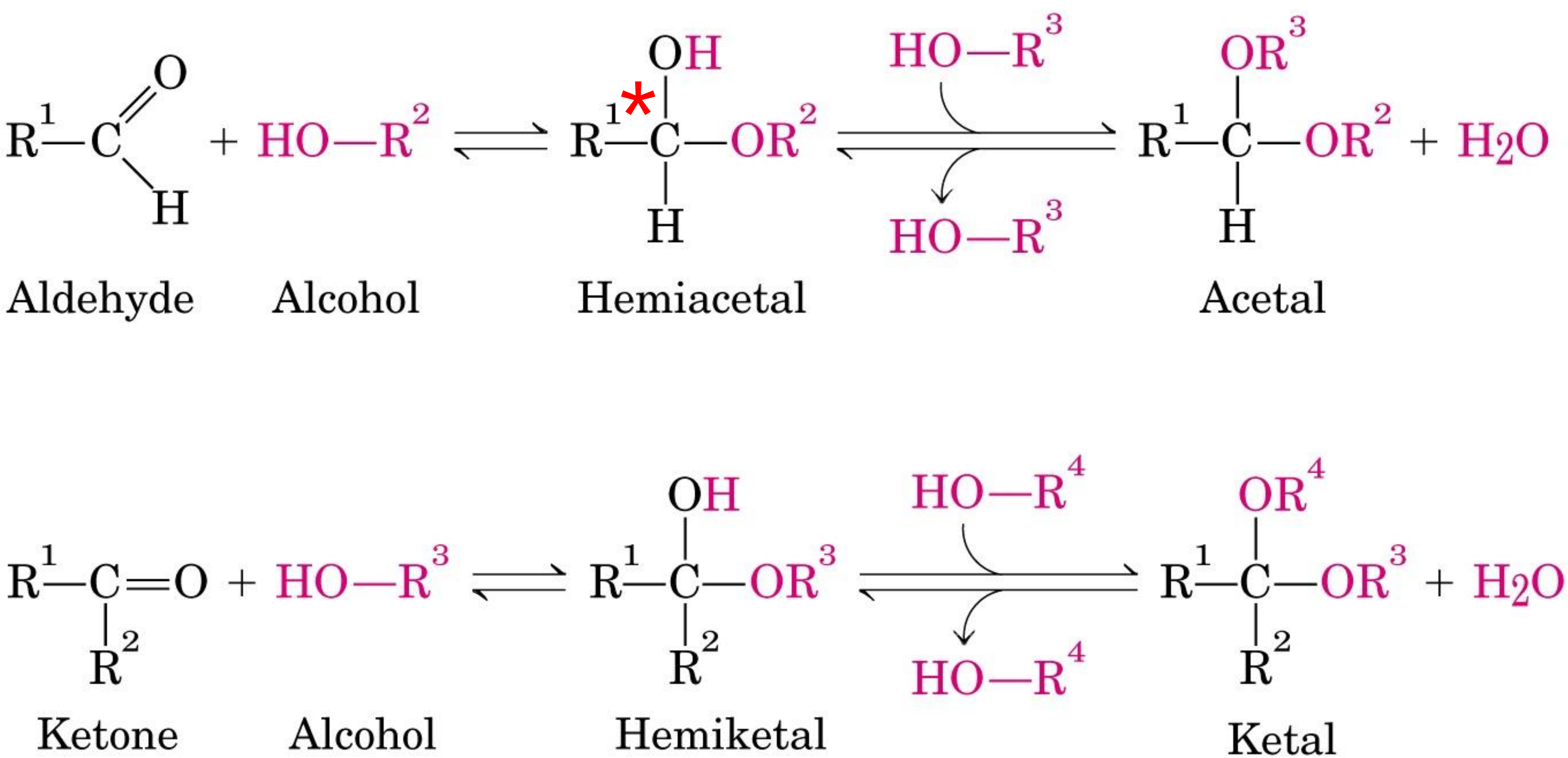
Molecules with the same chemical bond but different CONFIGURATION.
There are two types of stereoisomers in the carbohydrate class:

ENANTIOMERS

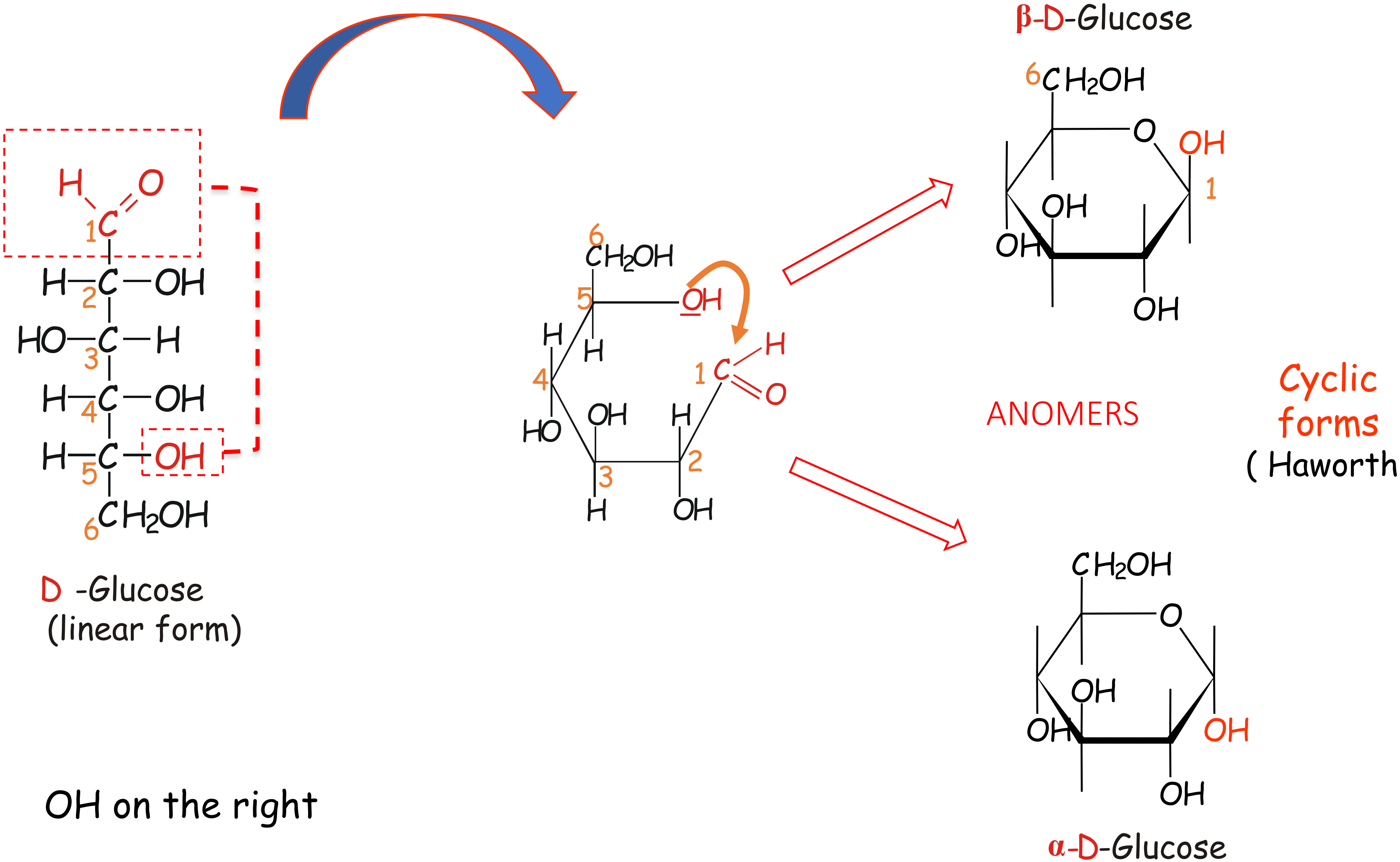
DIASTEREOISOMERS

1 or more ASYMMETRIC tetrahedral carbon atoms (CHIRAL)

PENTOSES AND HESOSES MAY ASSUME CYCLIC STRUCTURES (CYCLIC POLYHYDROXY HEMIACETALS OR HEMIKETALS)

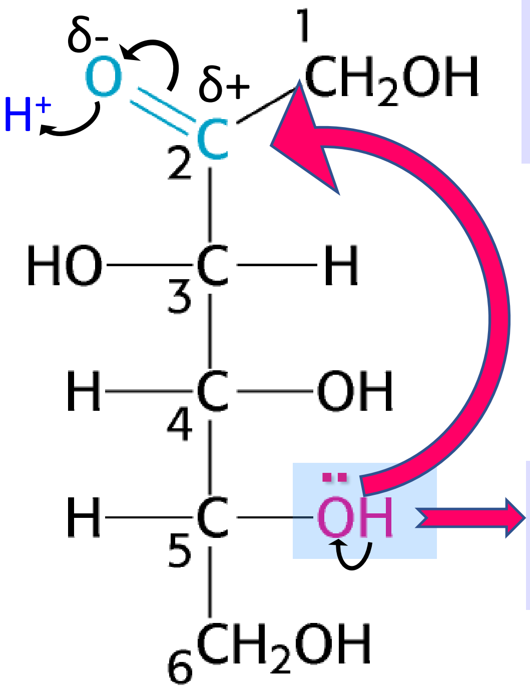


Glucose forms a ring by reaction between the aldehydic group and the oxydril C5



OH on the right

Fructose: hemiketal
carbonyl carbon in C-2 and the alcoholic group in C-5--→ 5-atom ring

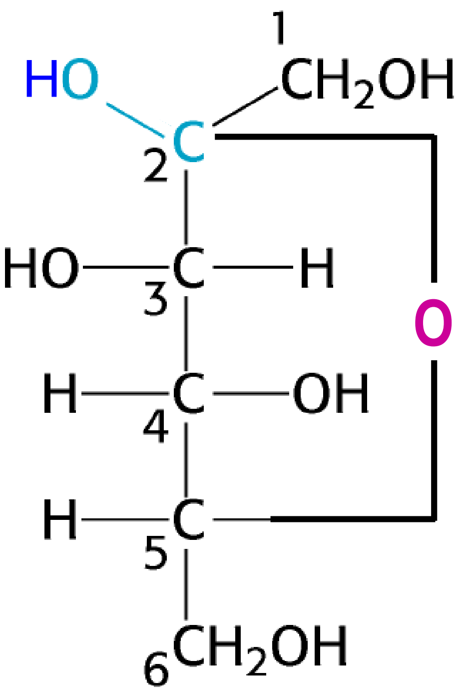


Nucleophilic attack of oxygen on C2

Hydrogen released as H +

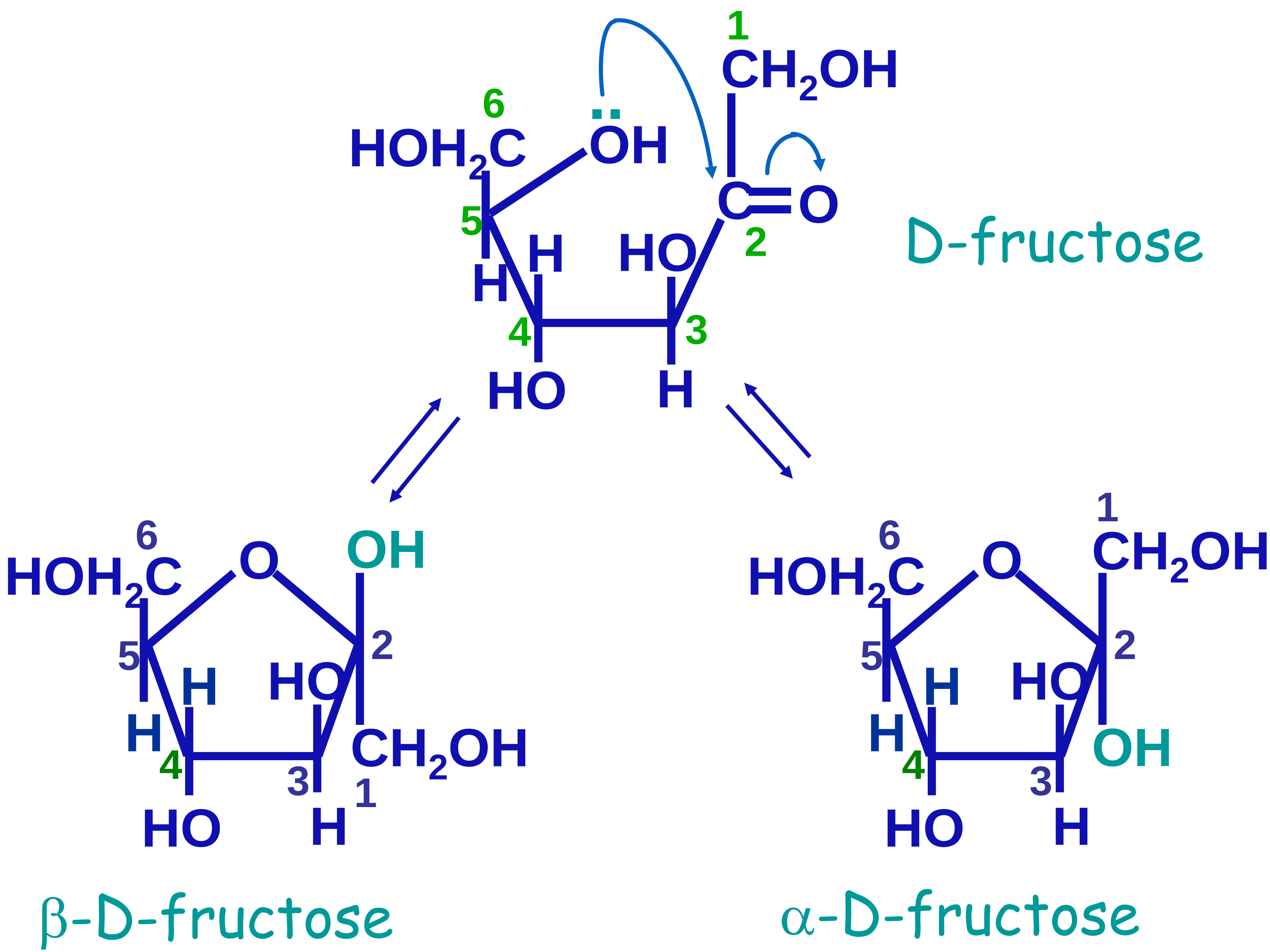
D-Fructose:

Carbon atom of fructose at C-2, becomes a chiral Carbon (sp3)

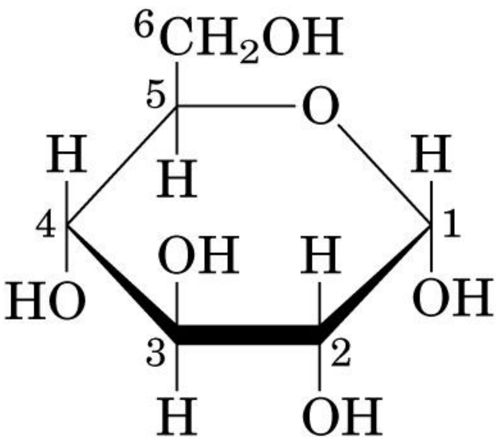


Tymoczko et al., PRINCIPI DI BIOCHIMICA zanichelli editore S.p.A Copyright © 2010

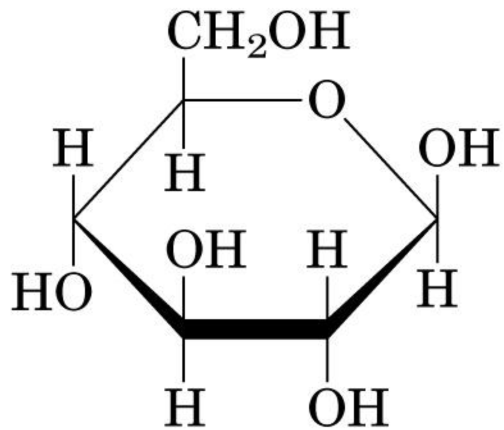
FRUCTOSE



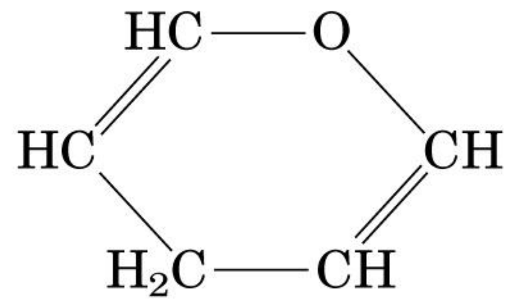
Haworth



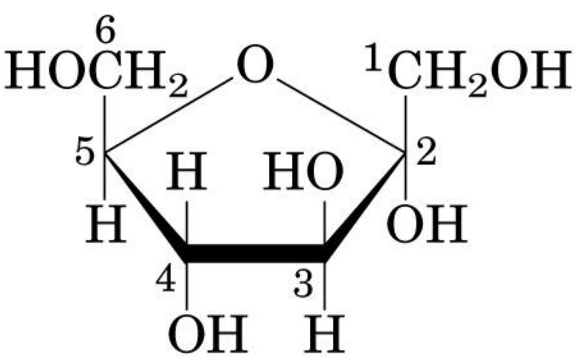
α-D-Glucopyranose



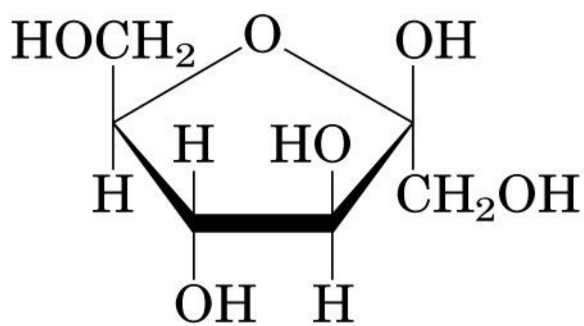
β-D-Glucopyranose



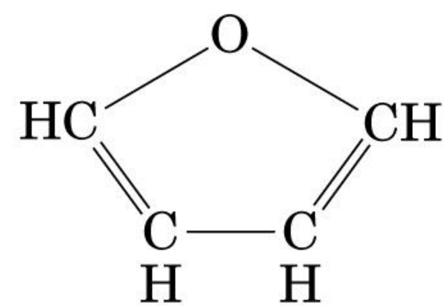
Pyran



α-D-Fructofuranose

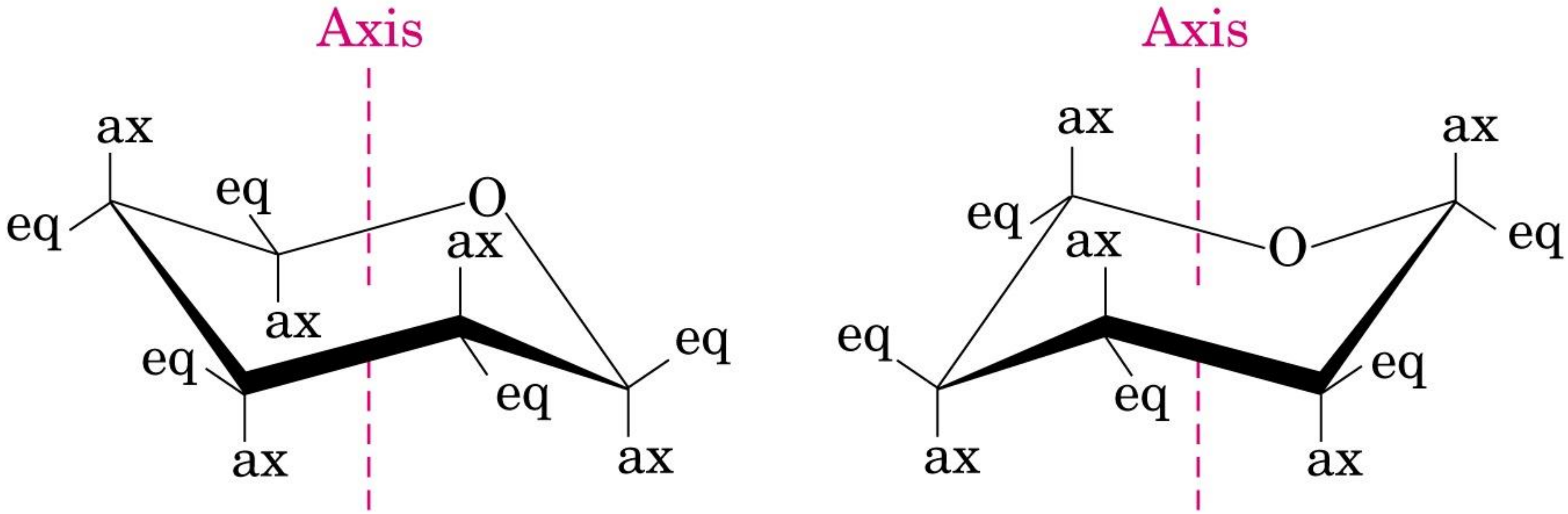


β-D-Fructofuranose



Furan

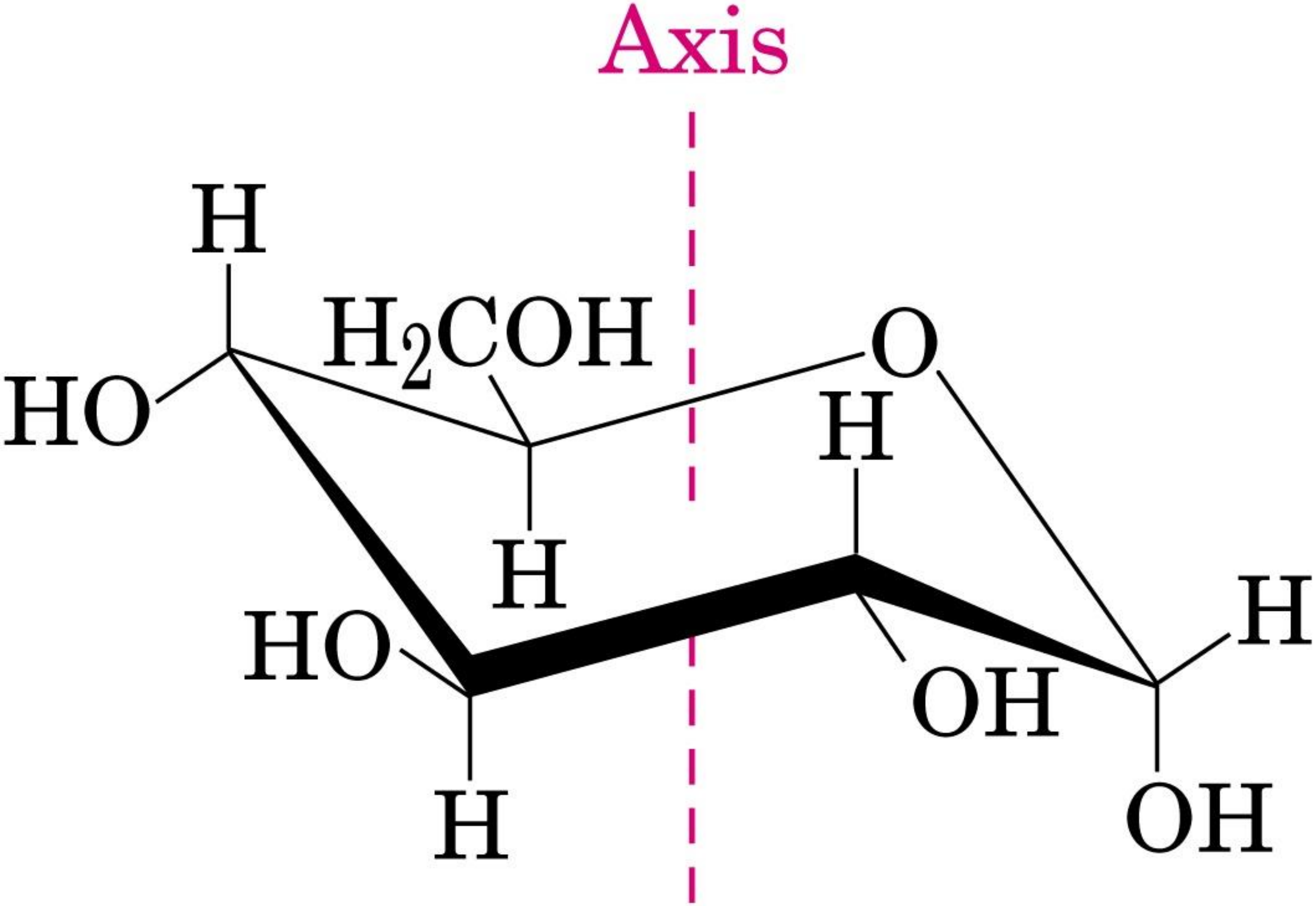
The six-membered pyranose ring is not exactly planar



Two possible chair forms
(a)

β-D GLUCOPYRANOSE without breaking of the bond

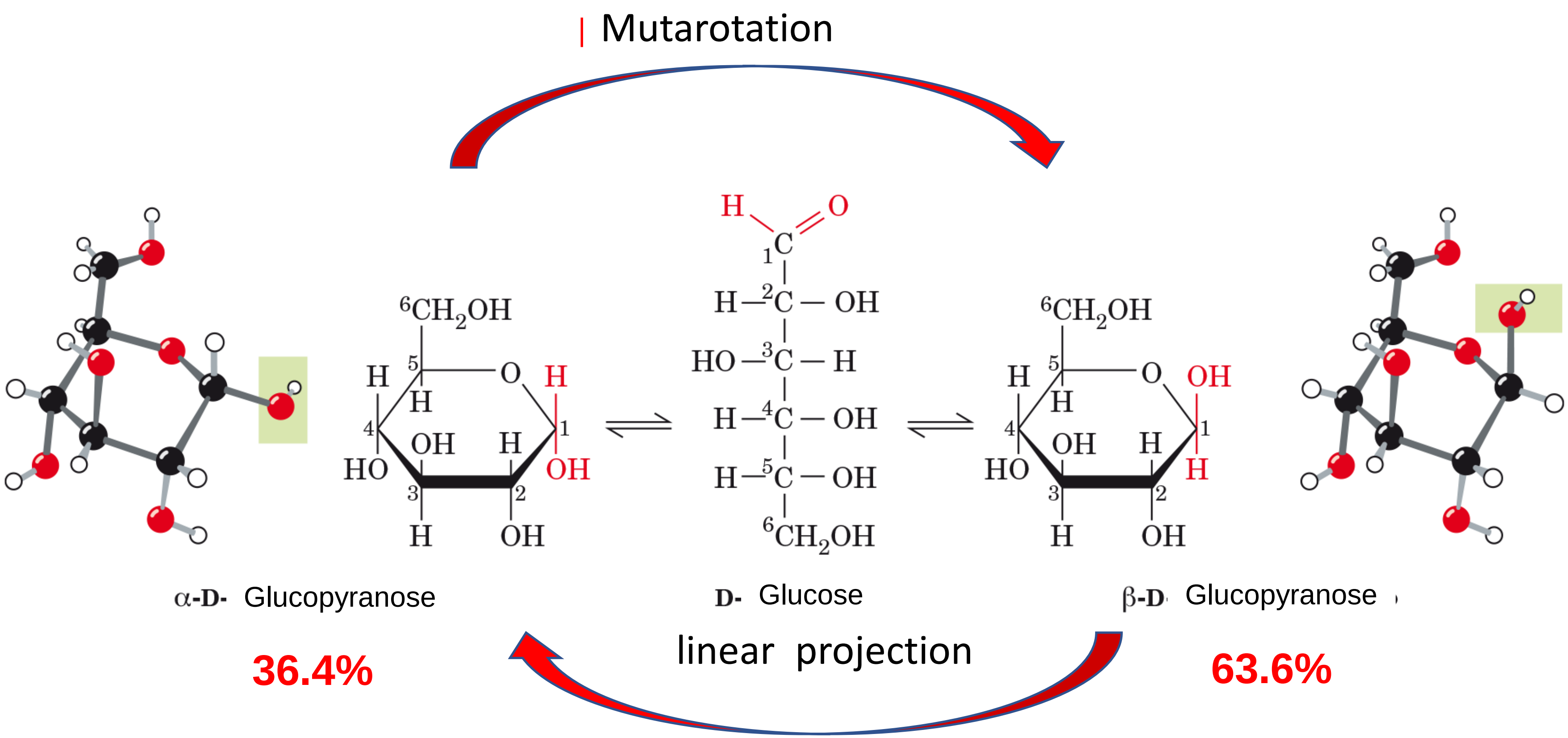
The most substituents are in equatorial position



α-D-Glucopyranose

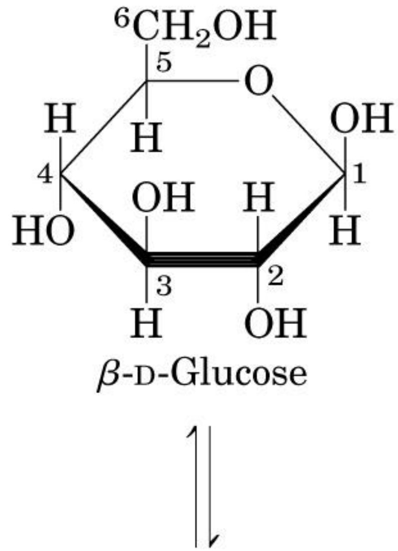
(b)

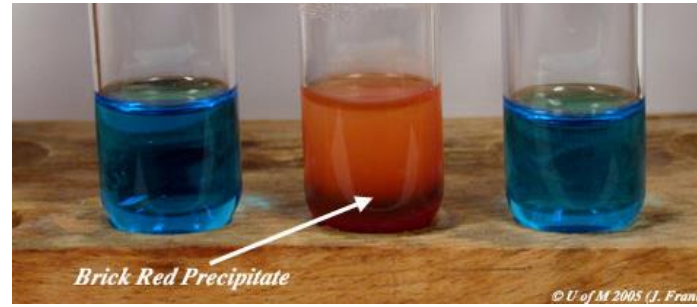
Monosaccharides interconvert throught the linear form



Monosaccharides are reducing:

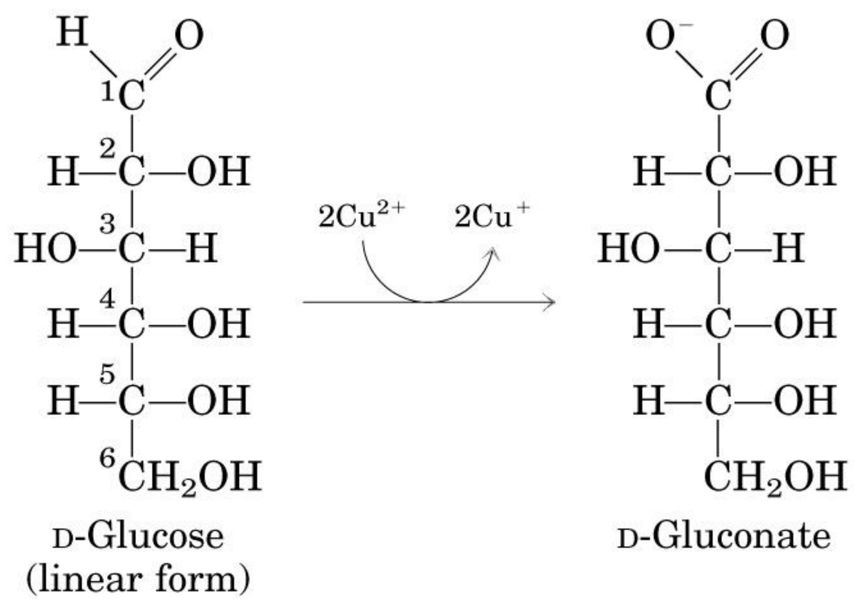
Quantitative determination of sugars





Fehling Reaction

Anomeric carbon is oxidized to carboxyl group and the Cu^{2+} ion is reduced to Cu^{+}

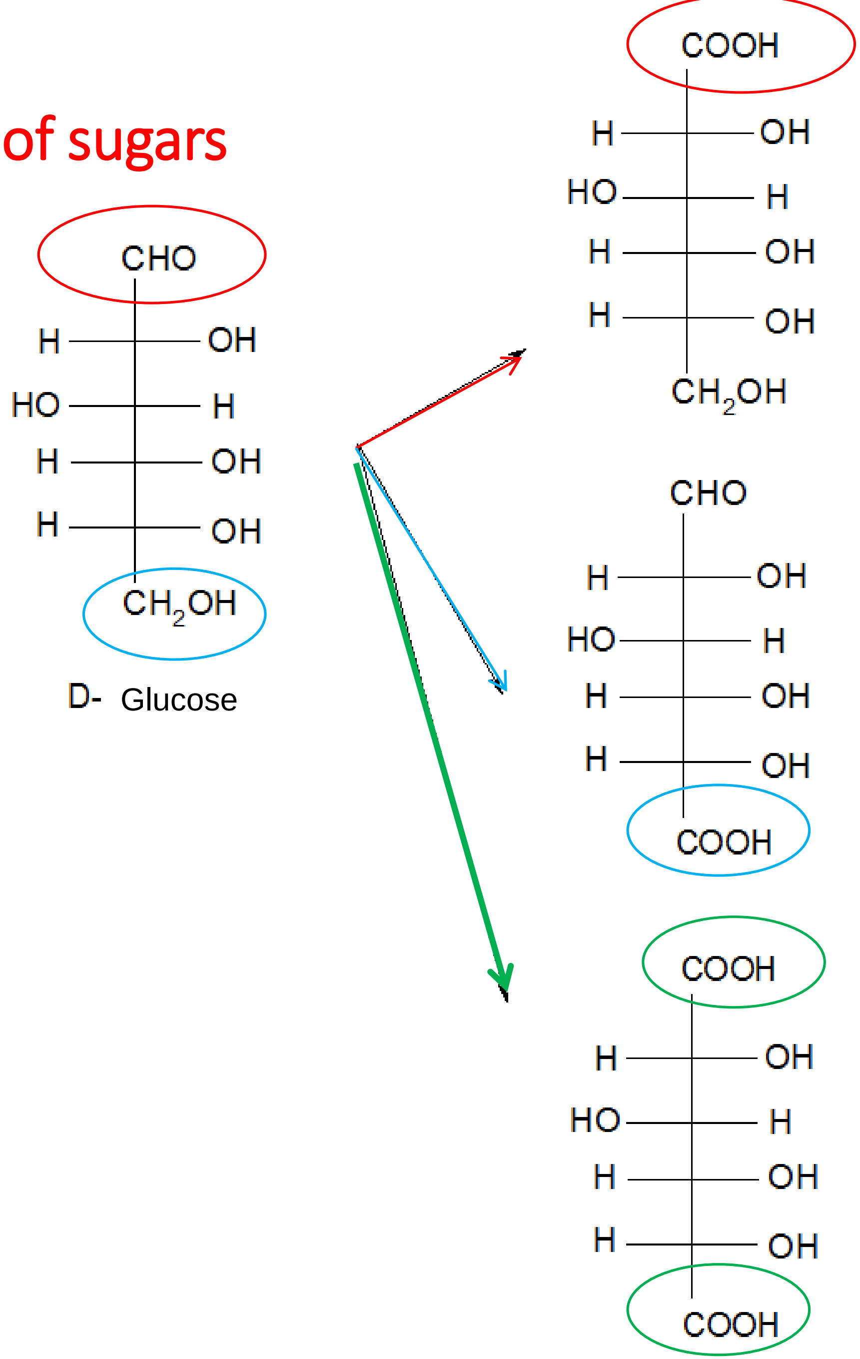


(a)

Biological derivatives of sugars

Chemical oxidation of aldose

ACIDS



D- Glucose

ALDONIC Acid

Gluconic acid

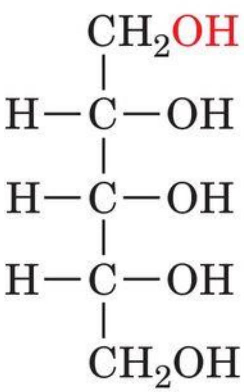
URONIC Acid

Glucuronic acid

ALDARIC Acid

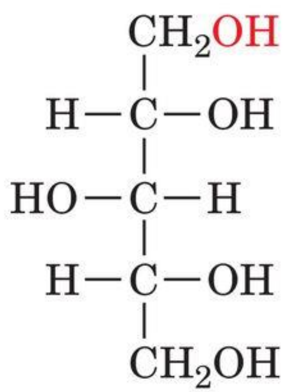
Glucaric acid

Biological derivatives of sugars



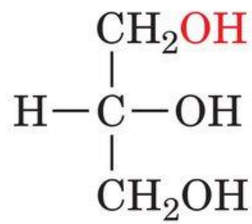
Ribitol

(ribose)

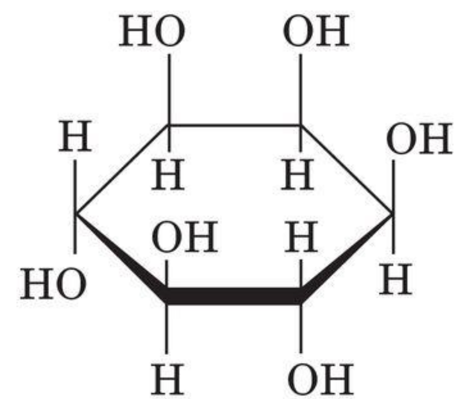


Xylitol

(xilulose)



Glycerol



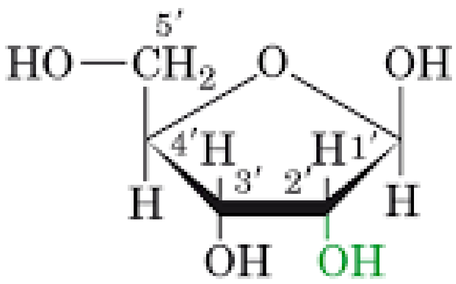
***myo*-Inositol**

Reduction of aldose or ketose

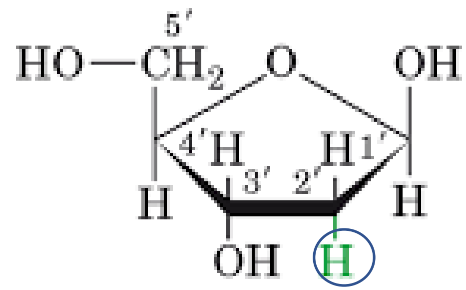
↓

ALDITOL (polyalcohol)

Biological derivatives of sugars



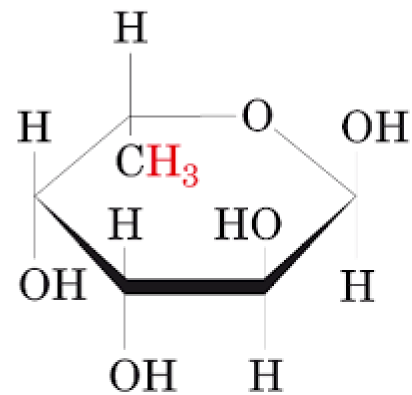
Ribose



Deoxyribose

Substitution of –OH with -H

DEOXY-SUGARS

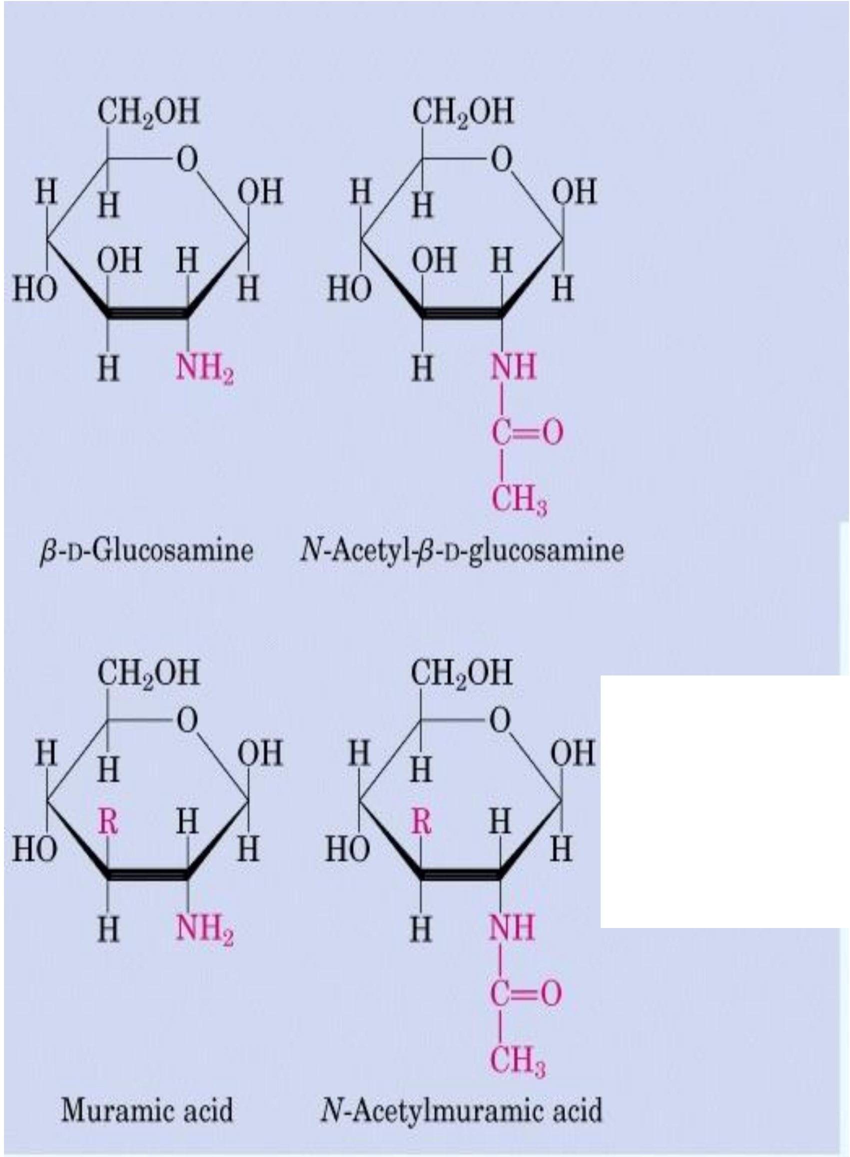


α-L Fucose

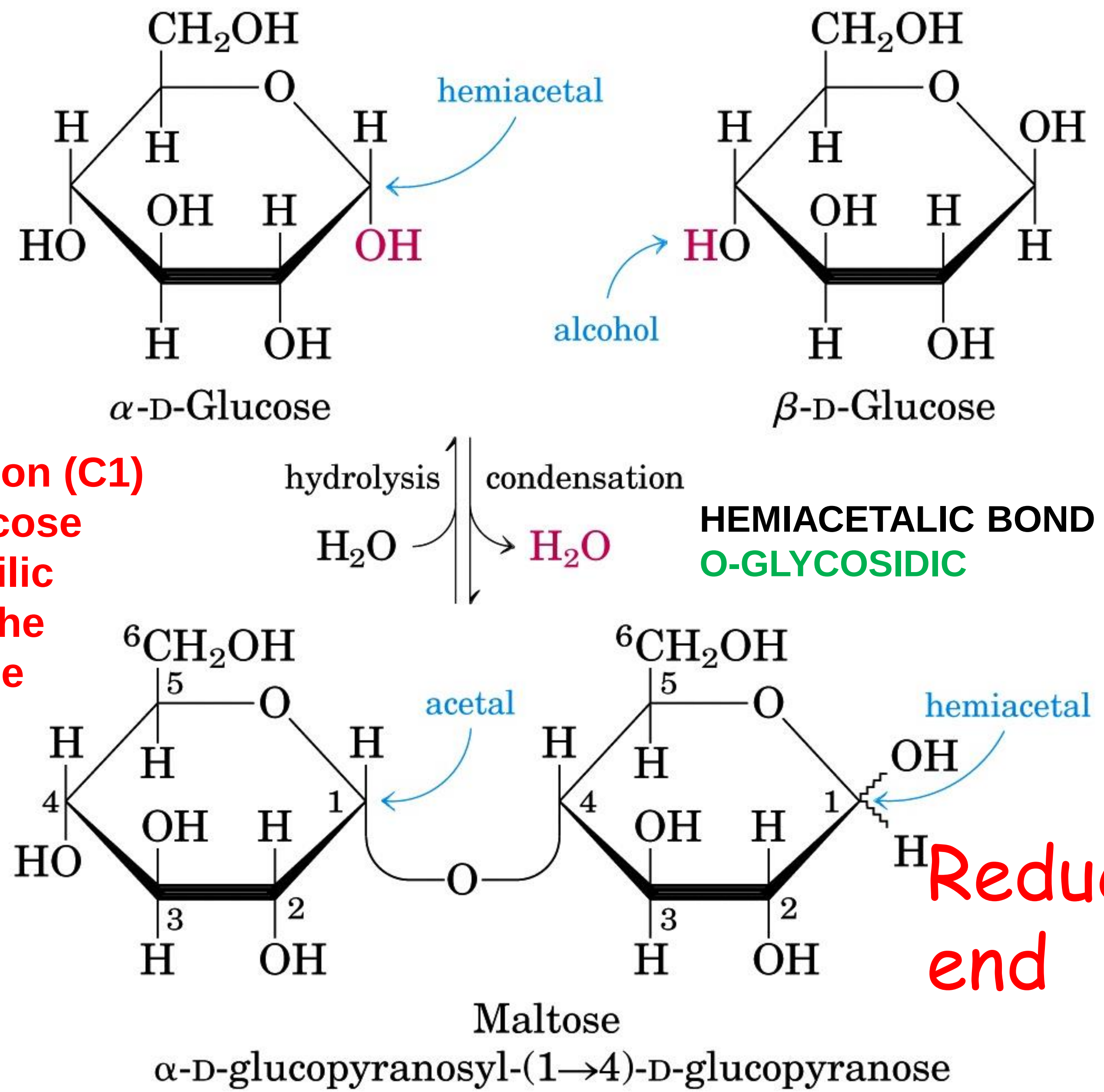
Biological derivatives of sugars

Substitution of –OH with aminic group (often acetylated)

Aminosugars



DISACCHARIDES (GLYCOSIDES)

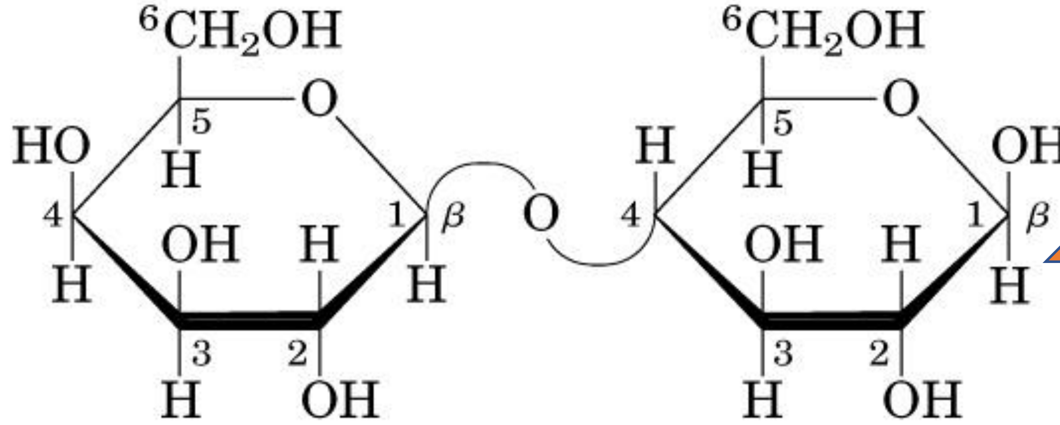


Anomeric carbon (C1) of the first glucose binds to oxydrilic group (C4) of the second glucose

HEMIACETALIC BOND = O-GLYCOSIDIC

Reducing end

Lactose:
β-galactose + β-glucose

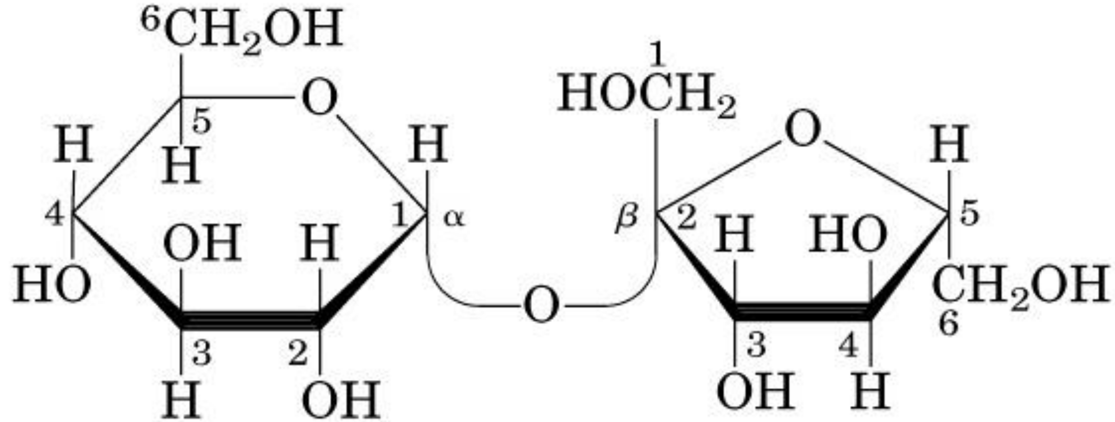


Lactose (*β* form)
β-D-galactopyranosyl-(1→4)-*β*-D-glucopyranose
Gal(*β*1→4)Glc

Lactose or milk sugar occurs naturally only in milk , where its concentration range from 0 to 7% depending on the species.

Lactose is a reducing sugar because it presents a free anomeric carbon of its glucose residue

Sucrose:
β-D-fructose + α-D-glucose
Non-reducing



Sucrose
β-D-fructofuranosyl α-D-glucopyranoside
Fru(β2↔1α)Glc

Sucrose: the most abundant disaccharide occurs throughout the plant kingdom and is familiar to us as common table sugar.

Sucrose is not a reducing sugar because anomeric carbon atoms (C1 of the glucose and C2 of the fructose) make glycosidic bond

POLYSACCHARIDES

Monosaccharides linked by glicosidic bonds

Medium to high molecular weight (Mr .20,000).

Polysaccharides, also called glycans,

Monosaccharide units differ,

- in the length of their chains,
- in the types of bonds linking the units,
- in the degree of branching.

POLYSACCHARIDES

Monosacchaides linked by glicosidic bonds

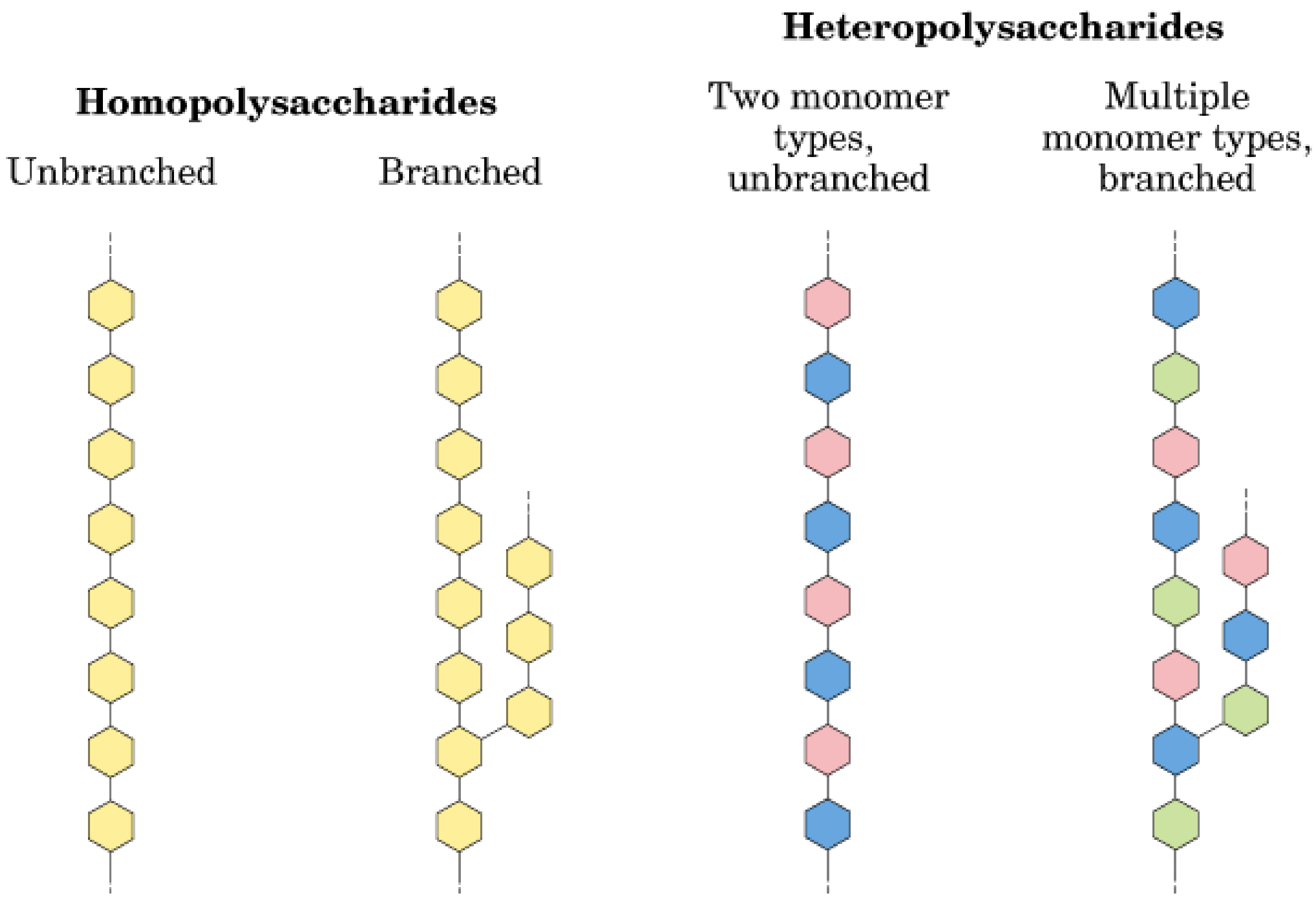
HOMOPOLYSACCHARIDES

1 type of monosaccharides residues

contain only a single monomeric species

HETEROPOLYSACCHARIDES

2 or more type of monosaccharides residues



HOMOPOLYSACCHARIDES

FUNCTIONS

Some homopolysaccharides serve as structural elements in plant cell walls and animal exoskeletons.

Some homopolysaccharides serve as storage forms (used as fuels)

STRUCTURAL

Cellulose (plants)

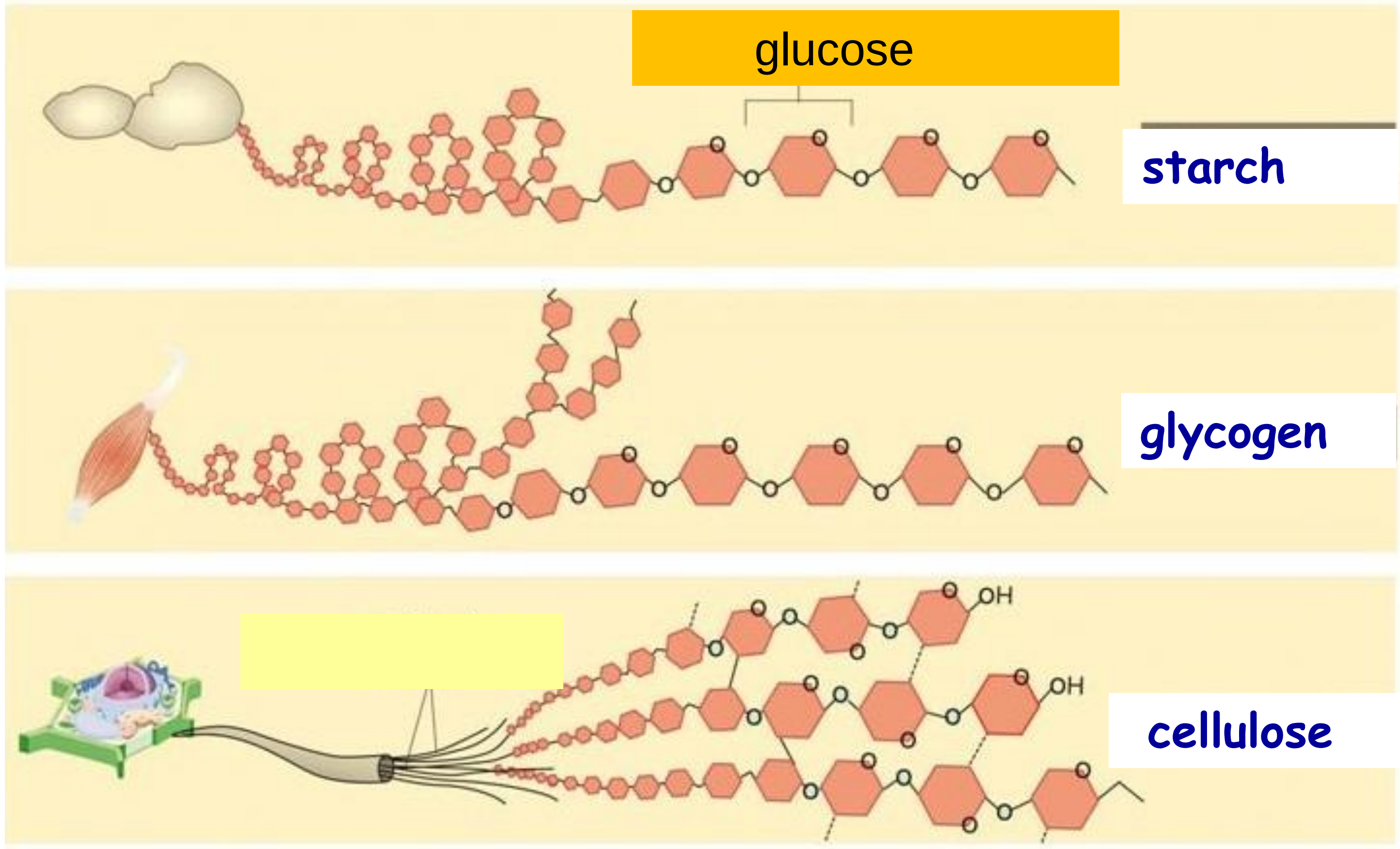
Chitin (insects)

STORAGE

Starch (plants)

Glycogen (animals)

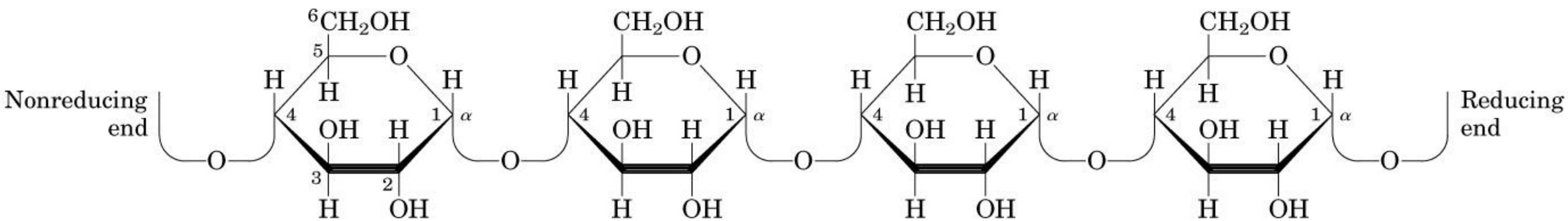
HOMOPOLYSACCHARIDES



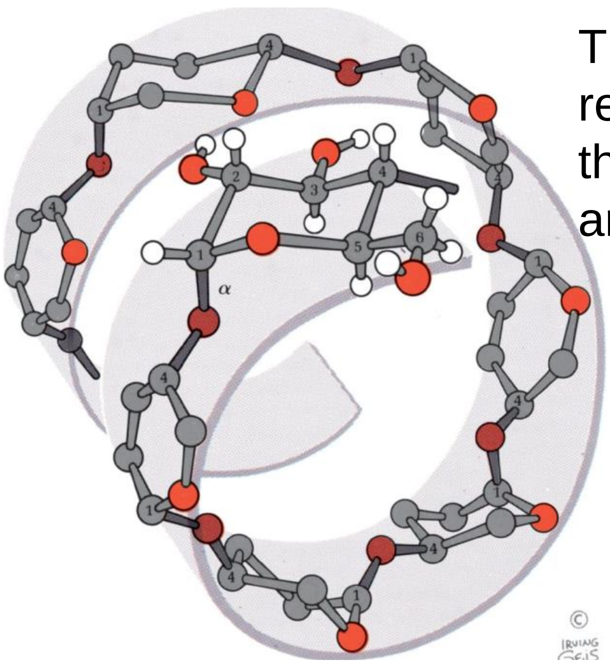
Starch (α-glucose)

contains two types of glucose polymer, amylose and amylopectin

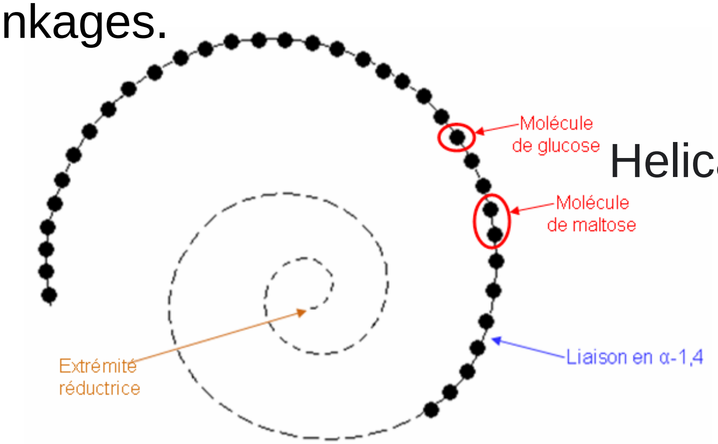
Amylose is a linear chain and consists of long, unbranched chains of D-glucose residues connected by (α1->4) linkages (as in maltose).
Molecular weight: from a few thousand to more than a million.



Amylopectin



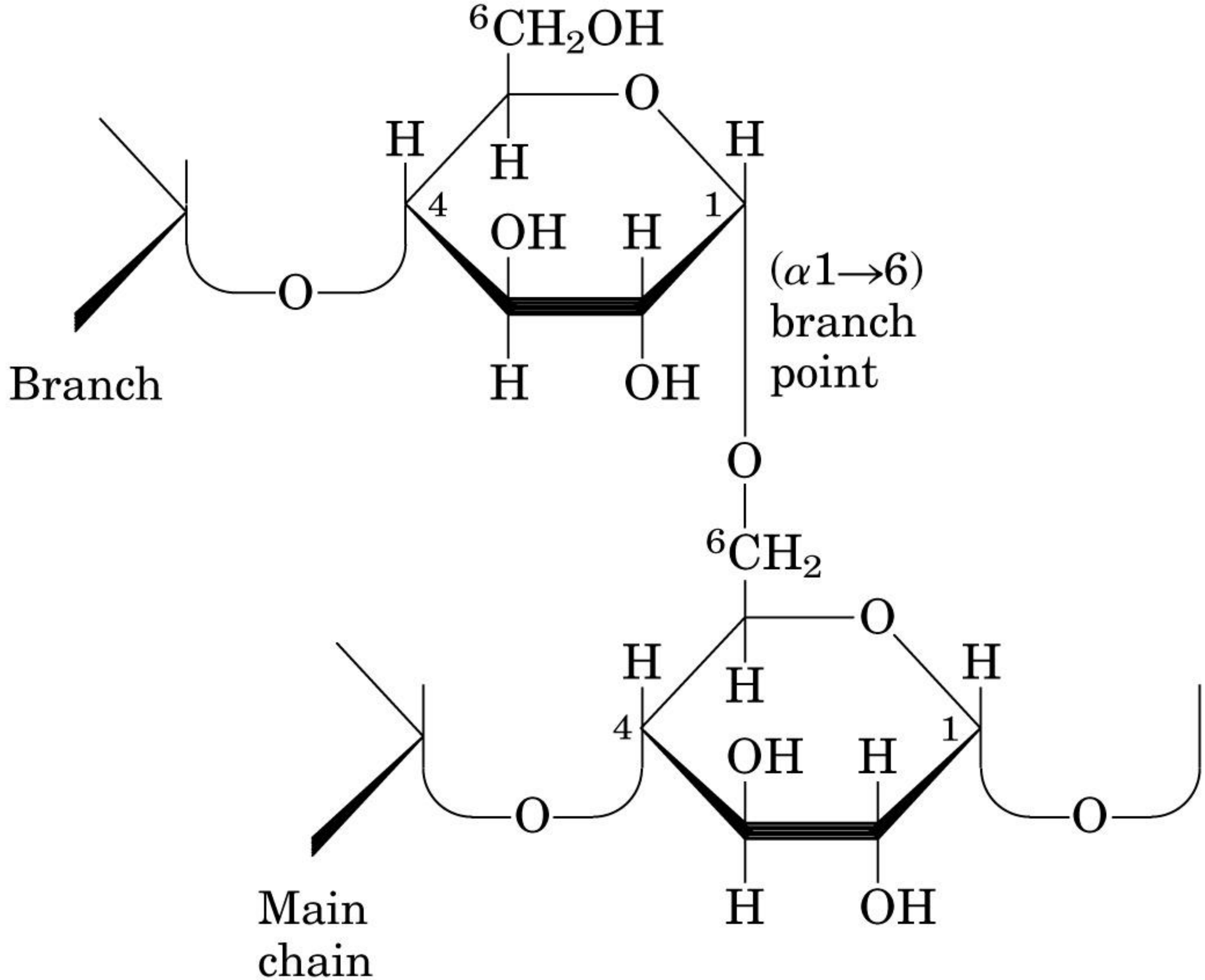
The glycosidic linkages joining following glucose residues in amylopectin chains are (α1->4) ;
the branch points (every 24 to 30 residues) are (α1->6)) linkages.



Helical shape

Storage function: CHLOROPLASTS PLANTS

A branching point of amylopectin approximately every 20 to 30 residues



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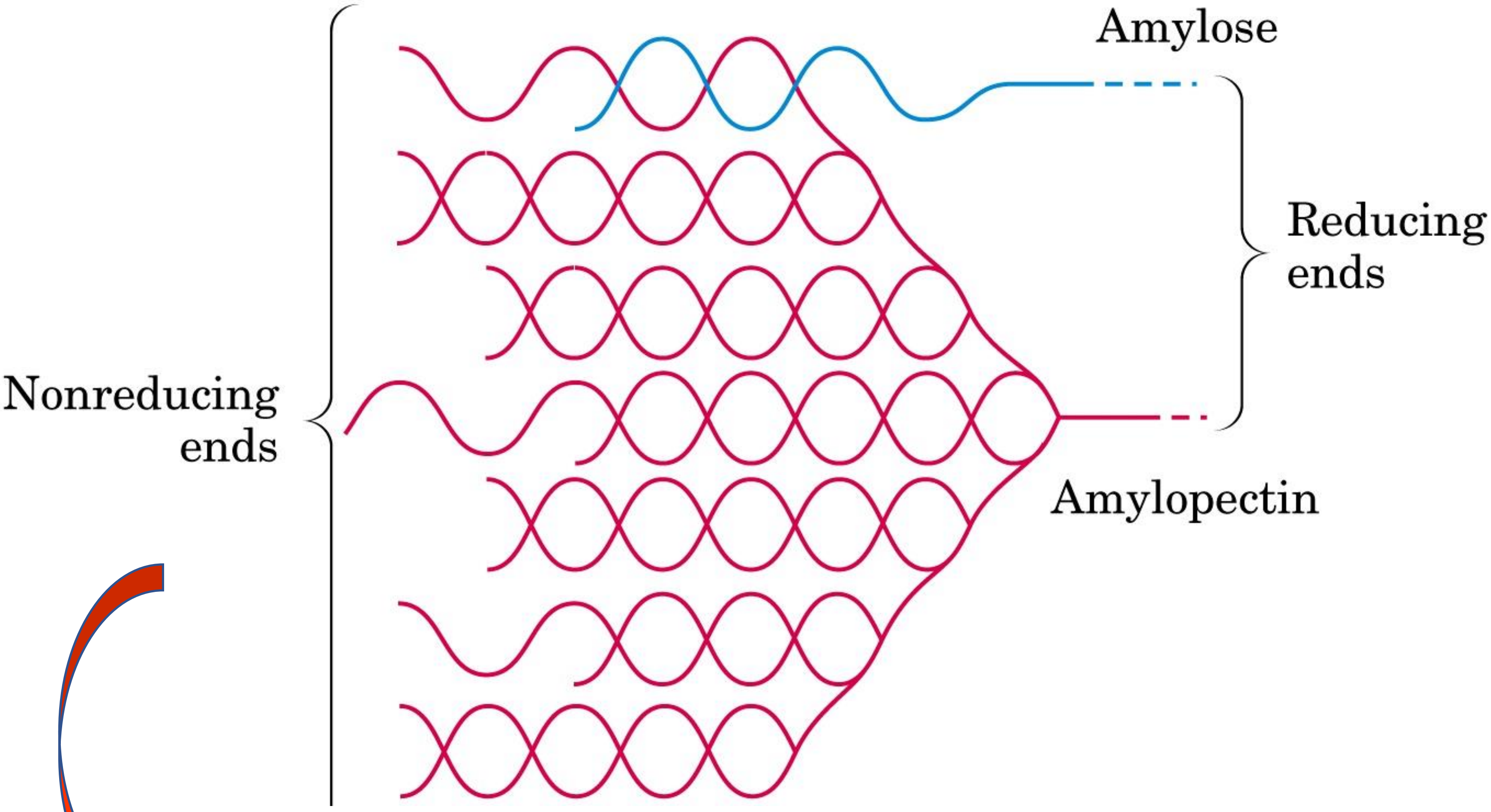
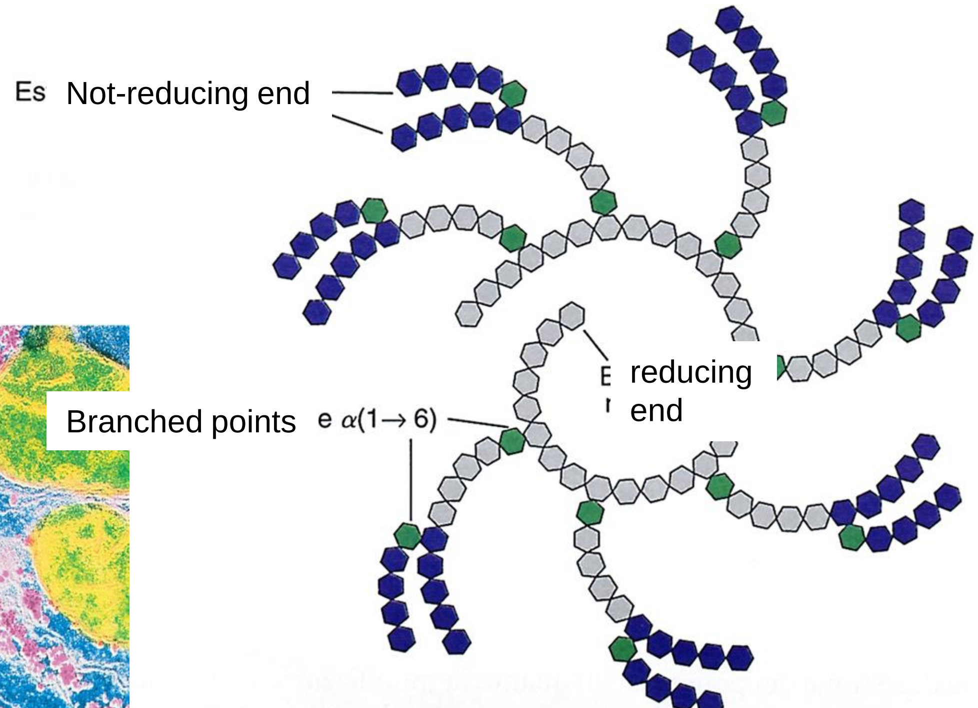
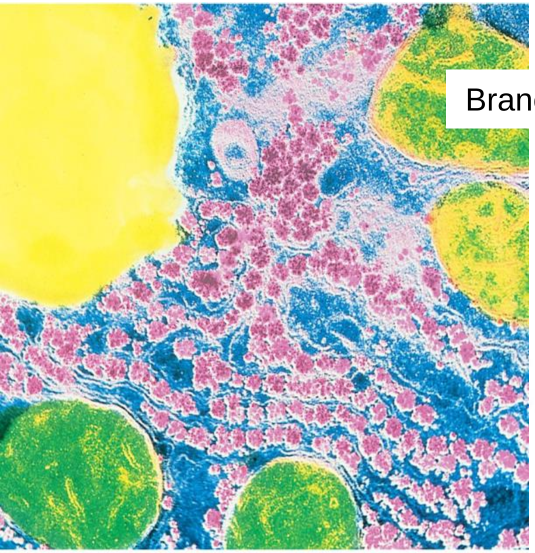


Starch digestion takes place by AMYLASE enzyme

Glycogen (α-glucose)

The structure of glycogen is similar to the amylopectin but glycogen is more extensively branched (every 8 to 12 residues)




CNRI/Science Photo Library/Photo Researchers

Glycogen

Abundant in the liver (about 7% of the wet weight) and in skeletal muscle.

In hepatocytes glycogen is found in large granules that contain, in tightly bound form, the enzymes responsible for the synthesis and degradation of glycogen.

Why glucose must store in glycogen?

Hepatocytes store glycogen equivalent to a glucose concentration of 0.4 M.

The concentration of glycogen, which is insoluble and contributes little to the osmolarity of the cytosol, is about 0.01 M.

If Glucose were 0.4 M, the osmolarity would be elevated, leading to osmotic entry of water that might rupture the cell.

The polysaccharide chains can assume a three-dimensional structure, by the rotation that can occur freely around the glycosidic bond.

The glucose chains of amylose, amylopectin and glycogen tend to wind themselves in a spiral, assuming a helical conformation. These spiralized chains aggregate to form deposit granules.

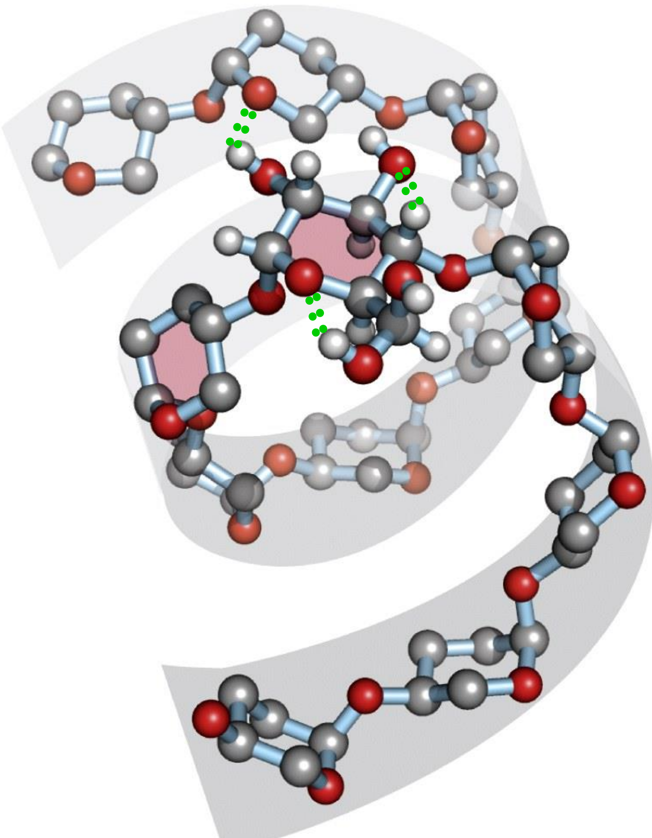


Figure 7-20b
Lehninger Principles of Biochemistry, Fifth Edition
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The polysaccharide helices are stabilized by H bonds between the OH groups of the glucose residues

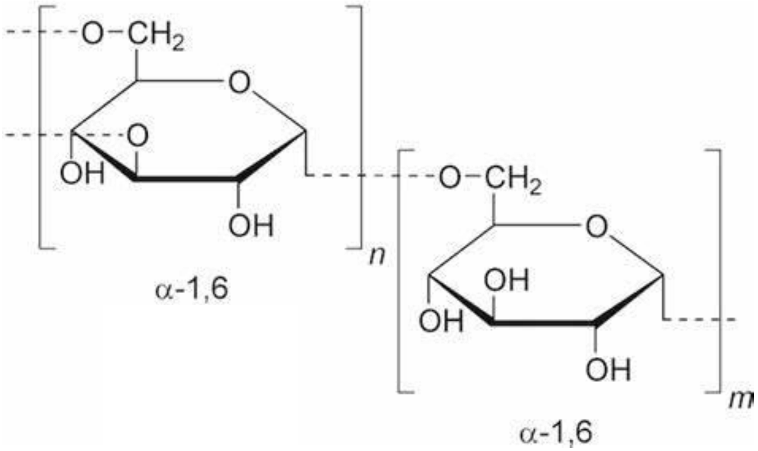
Dextrans

bacterial and yeast polysaccharides

(α1->6)-linked poly-D-glucose

(α1->4) branches

(α1->4) or (α1->2) branches



Dental plaque, formed by bacteria growing on the surface of teeth, is rich in dextrans, which are adhesive and allow the bacteria to stick to teeth and to each other.

Dextrans also provide a source of glucose for bacterial metabolism.

Synthetic dextrans are used in several commercial products (for example, Sephadex) that serve in the fractionation of proteins by size-exclusion chromatography

.

Homopolysaccharides with Structural Roles

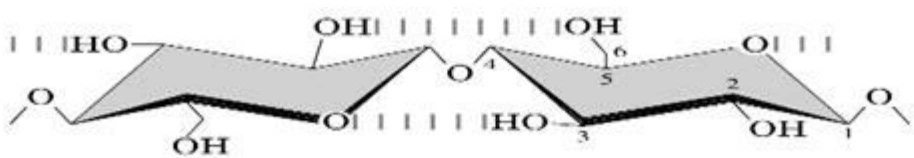
Cellulose:

Cell walls of plants (stalks, stems, trunks, and all the woody portions of the plant body)

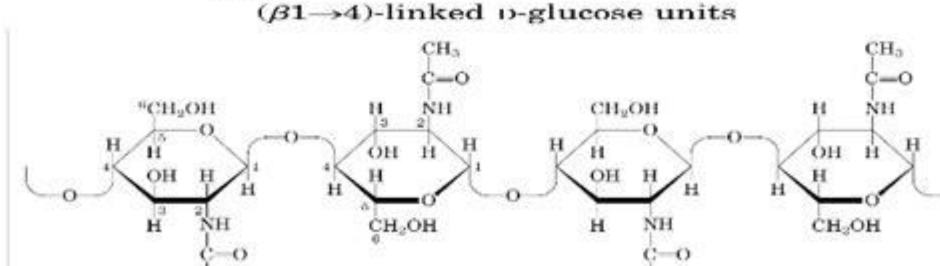
Unbranched

10,000 to 15,000 D-glucose units.

Glucose residues have the configuration β

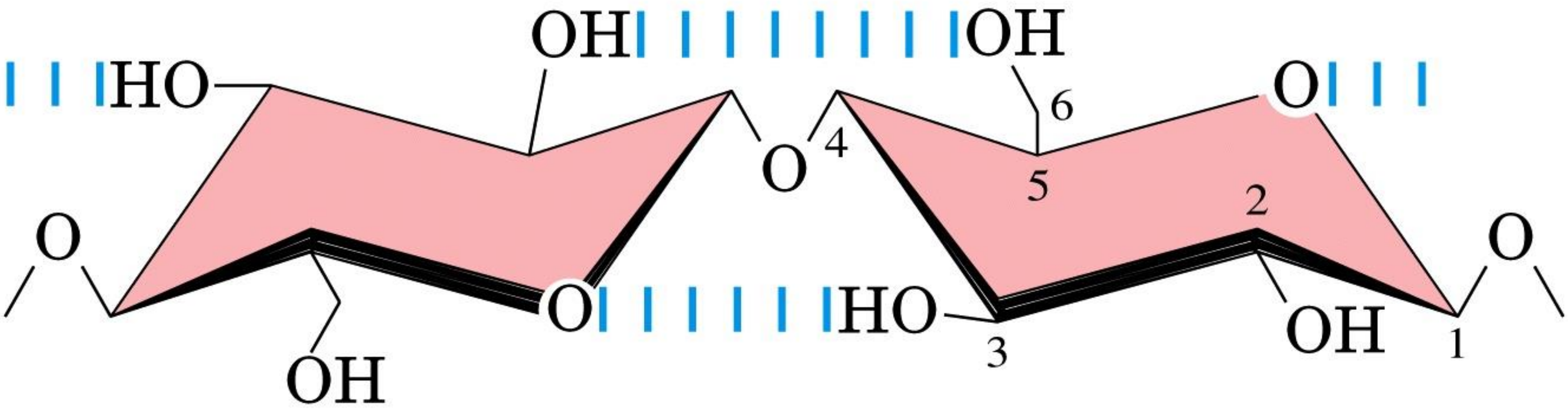


(β1→4)-linked D-glucose units



Structural polysaccharides:

Two units of D-glucose in a cellulose chain



(β1→4)-linked D-glucose units

Glycogen and starch, ingested in the diet, are hydroyzed by α-amylases and glycosidases, enzymes in saliva and the intestine that break (α1->4) glycosidic bonds between glucose units.

Most vertebrate animals cannot use cellulose as a fuel source, because they lack an enzyme to hydrolyze the (β1->4) linkages.

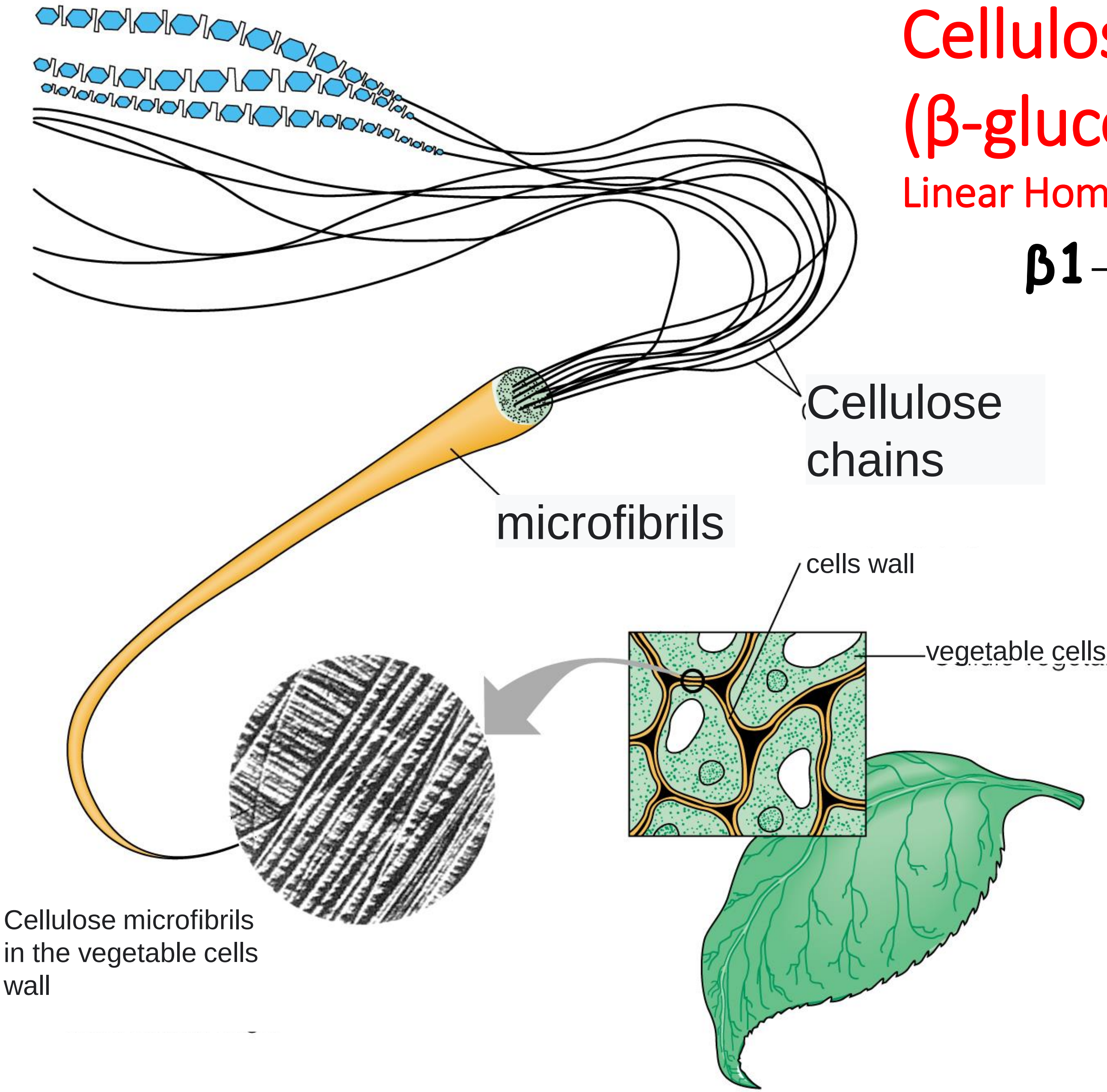
Termites readily digest cellulose (and therefore wood), but only because their intestinal tract harbors a symbiotic microorganism, Trichonympha, that secretes cellulase, which hydrolyzes the (β1->4) linkages.

STRUCTURAL Homopolysaccharides

Cellulose: (β-glucose)

Linear Homopolymer

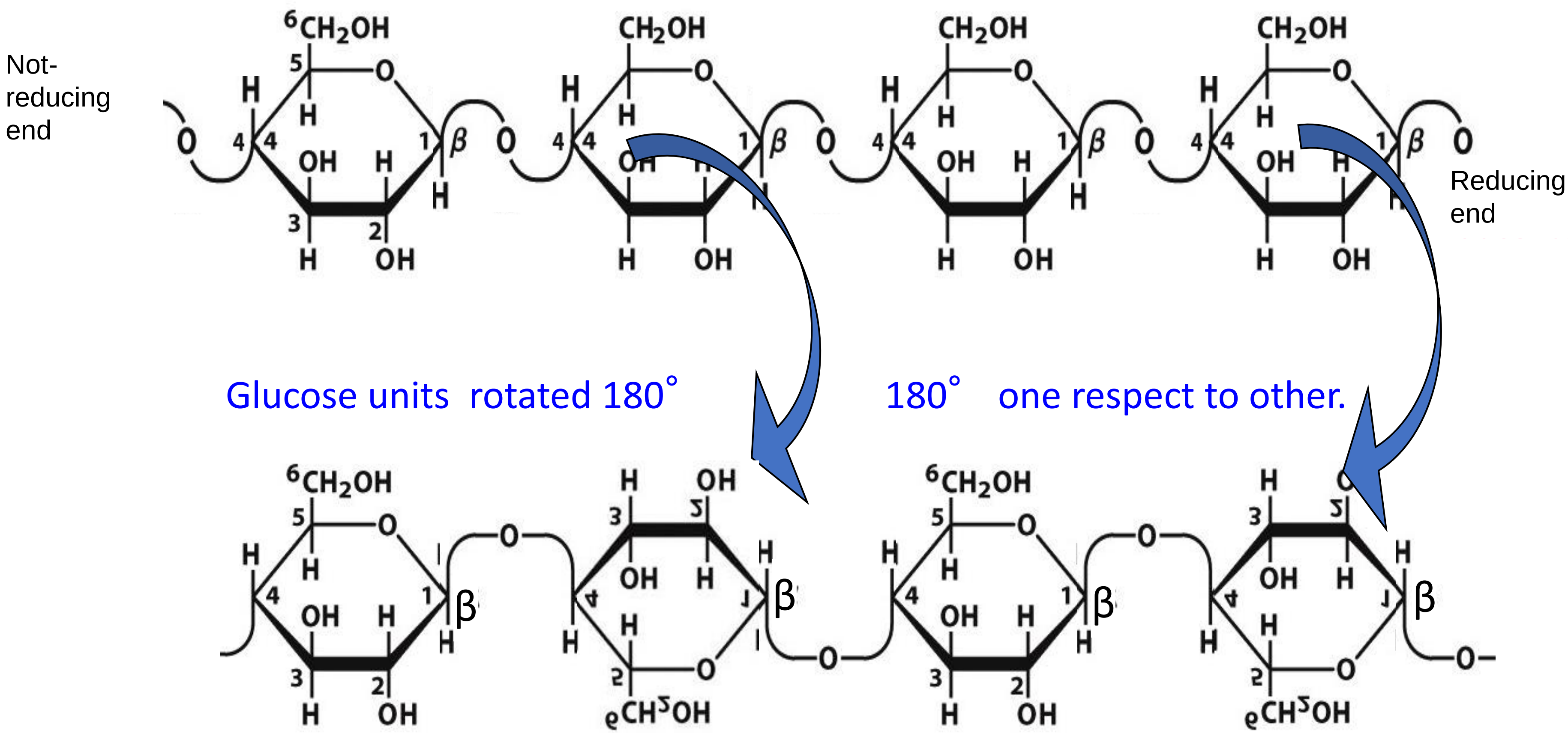
β1→4



Ruminant animals (sheep, and goats) harbor symbiotic microorganisms in the rumen (the first of their four stomach compartments) that can hydrolyze cellulose, allowing the animal to degrade dietary cellulose from soft grasses, but not from woody plants.

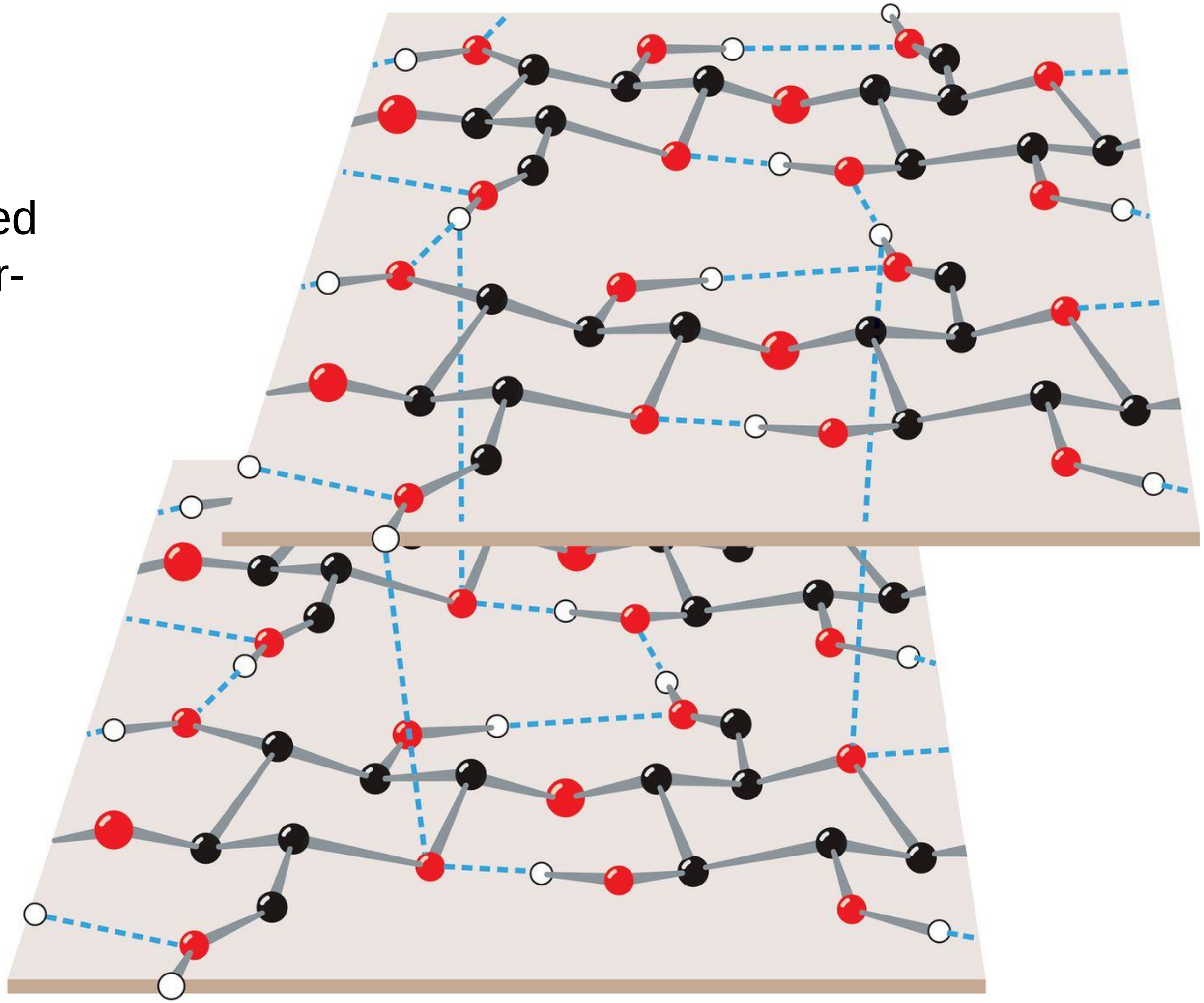
Fermentation in the rumen yields acetate, propionate, and β-hydroxybutyrate, which the animal uses to synthesize the sugars in milk

CELLULOSE: linear forms of polysaccharide from D-glucose units with **β-(1→4) O-glycosidic bond**



Cellulose:

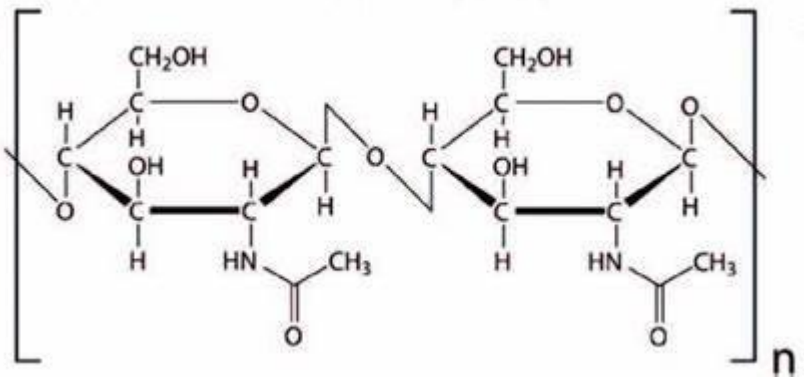
The structure is stabilized by hydrogen bonds inter-molecular that make it insoluble in water.



Illustration, Irving Geis. Image from the Irving Geis Collection, Howard Hughes Medical Institute. Reprinted with permission.

Chitin

is the principal component of the hard exoskeletons of arthropods—insects, lobsters, and crabs,



A linear homopolysaccharide composed of N-acetylglucosamine in (β1->4) linkage

Chemical difference from cellulose is the replacement of the hydroxyl group at C-2 with an acetylated amino group.

Chitin forms extended fibers similar to those of cellulose, and like cellulose cannot be digested by vertebrates.

Abbreviations

Arabinose	Ara
Fructose	Fru
Fucose	Fuc
Galactose	Gal
Glucose	Glc
Mannose	Man
Rhamnose	Rha
Ribose	Rib
Xylose	Xyl

Glucuronic acid	GlcA
Galactosamine	GalN
Glucosamine	GlcN
N-Acetylgalactosamine	GalNAc
N-Acetylglucosamine	GlcNAc
Iduronic acid	IdoA
Muramic acid	Mur
N-Acetylmuramic acid	Mur2Ac
N-Acetylneuraminic acid (a sialic acid)	Neu5Ac

POLYSACCHARIDES

Monosacchaides linked by glicosidic bonds

HOMOPOLYSACCHARIDES

1 type of monosaccharides residues

contain only a single monomeric species

HETEROPOLYSACCHARIDES

2 or more type of monosaccharides residues

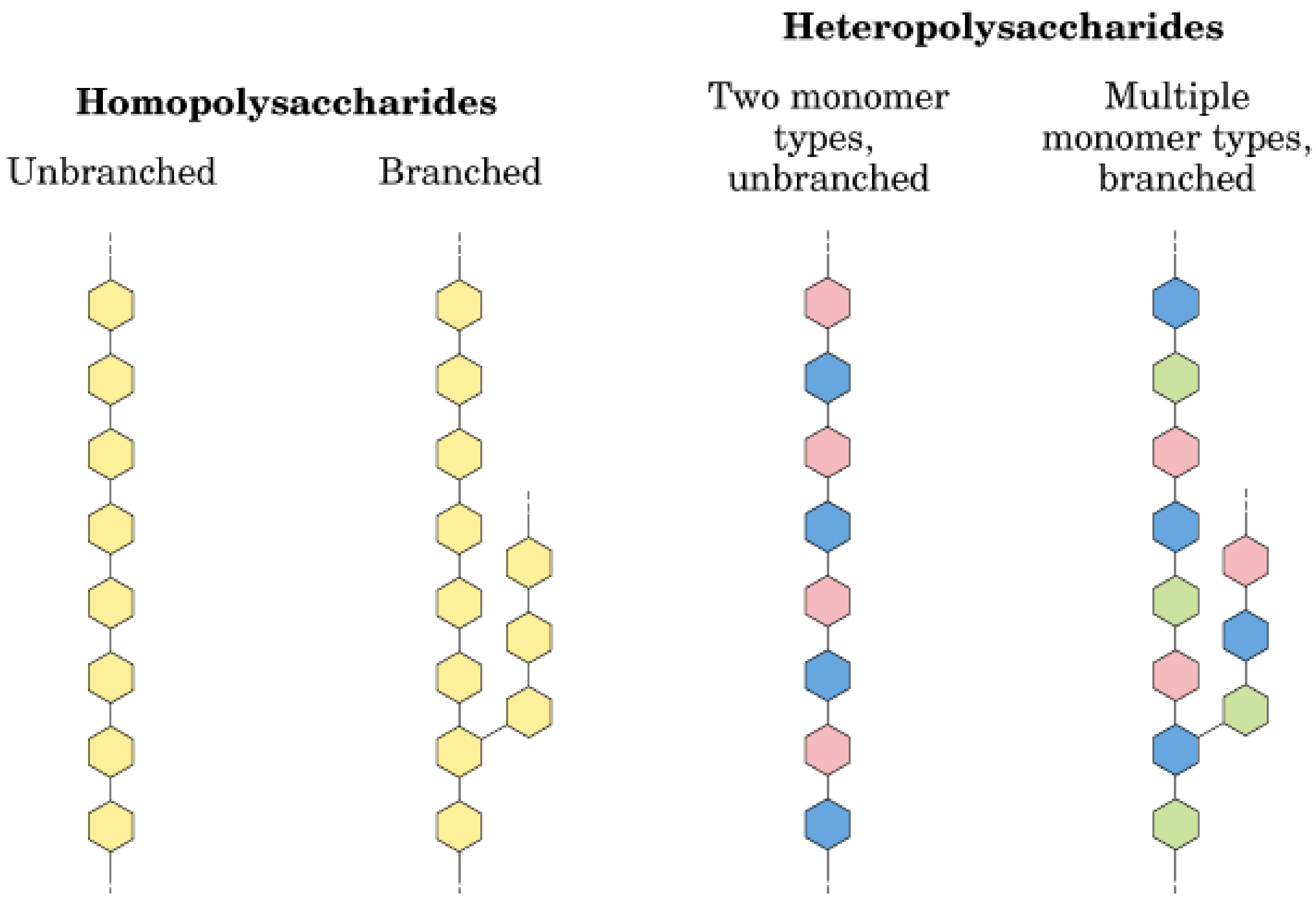


TABLE 7–1 Symbols and Abbreviations for Common Monosaccharides and Some of Their Derivatives

Abequose	Abe	Glucuronic acid	GlcA
Arabinose	Ara	Galactosamine	GalN
Fructose	Fru	Glucosamine	GlcN
Fucose	Fuc	*N*-Acetylgalactosamine	GalNAc
Galactose	Gal	*N*-Acetylglucosamine	GlcNAc
Glucose	Glc	Iduronic acid	IdoA
Mannose	Man	Muramic acid	Mur
Rhamnose	Rha	*N*-Acetylmuramic acid	Mur2Ac
Ribose	Rib	*N*-Acetylneuraminic 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).

HETEROPOLYSACCHARIDES

Heteropolysaccharides are polysaccharides constituted by the union of different monosaccharides, through glycosidic bonds.

They differ from homopolysaccharides which are composed of the monomeric repetition of the same sugar

.

GLYCOSAMINOGLYCANS

Cell matrix (animals)

PEPTIDOGLYCANS

Cell wall (bacteria)

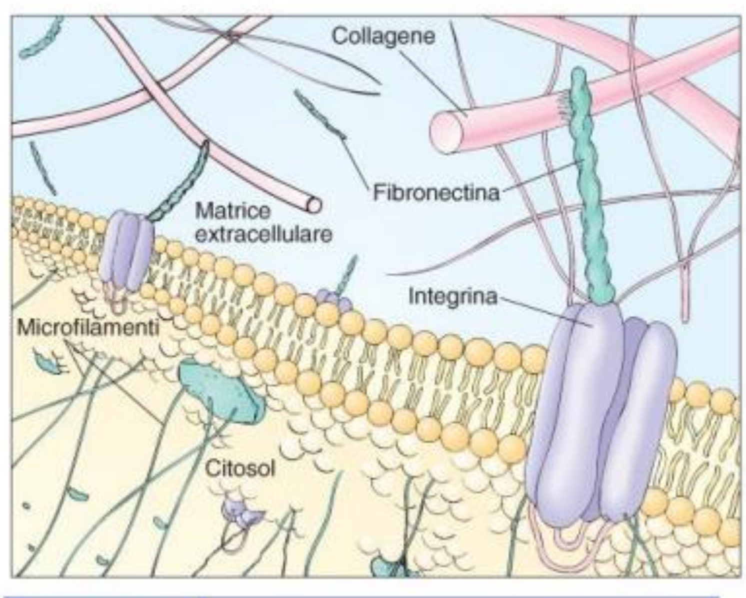
Polymers formed by different monomers are a very complex category of compounds, both for the variety of monomers and the type of bonds that can be formed

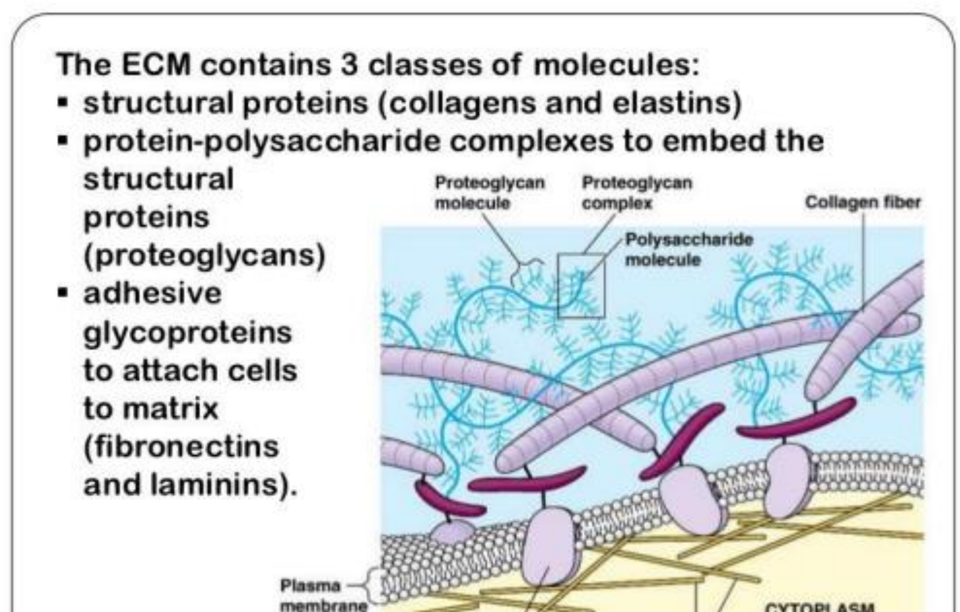
Glycosaminoglycans Are Heteropolysaccharides of the Extracellular Matrix

The extracellular space in the tissues of multicellular animals is filled with a gel-like material, the extracellular matrix (ECM),
(also called ground substance)

- ECM holds the cells together

- ECM provides a porous pathway for the diffusion of nutrients and oxygen to individual cells.





HETEROPOLYSACCHARIDES

GLYCOSAMINOGLYCANS
Cell matrix (animals)

(1 uronic acid and 1 N-acet. amino-sugar Repeated and linear)

PEPTIDOGLYCANS
Cell wall (bacteria)
(rigid component , linear repeat)

Mur2Ac(β1->4)GlcNac

They are not found in plants

N-Acetylglucosamine	GlcNAc
N-Acetylmuramic acid	Mur2Ac

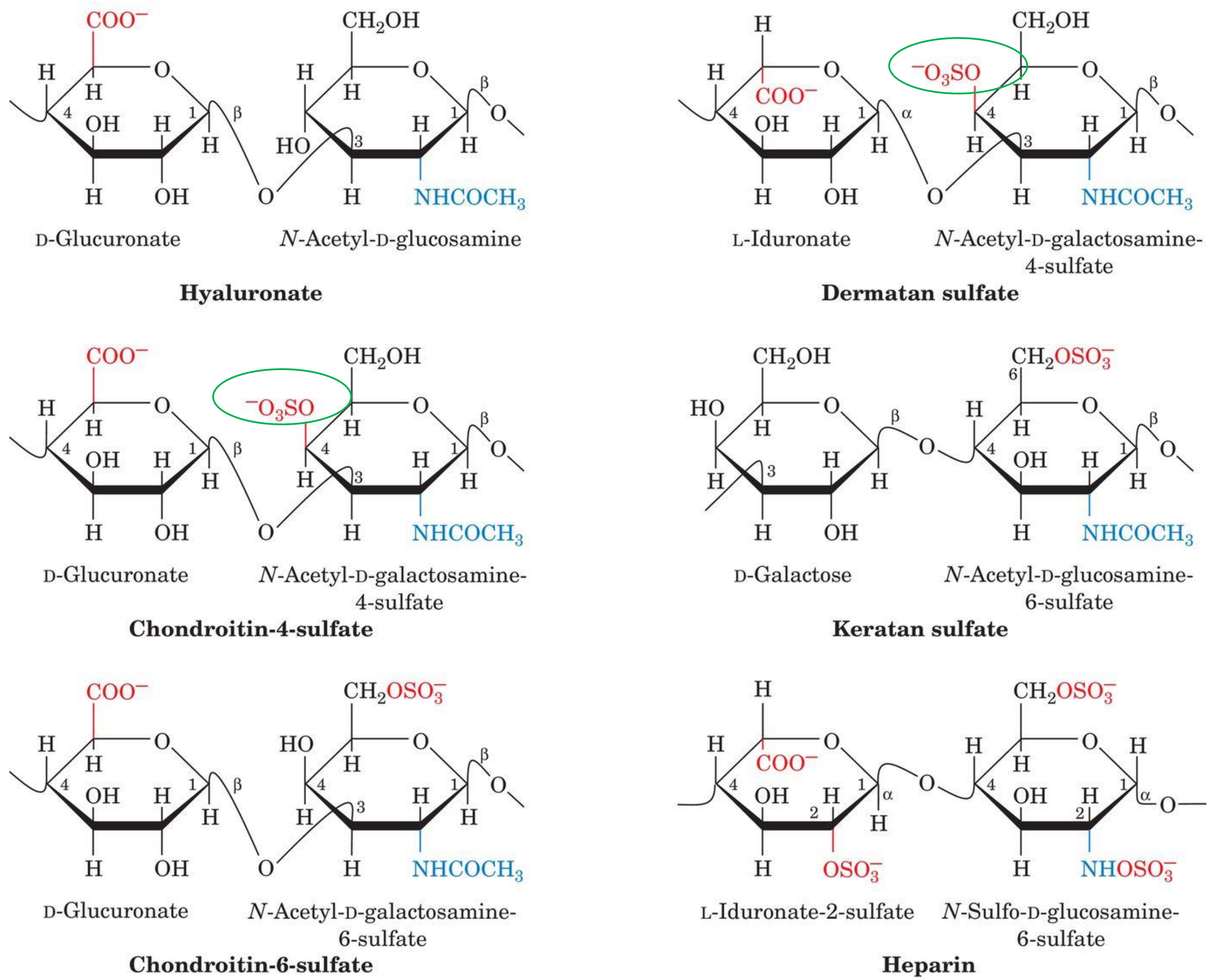
Glycosaminoglycans:

They are a family of linear polymers composed of repeating disaccharide units .

N-Acetyl-D-Glucosamine/ Galactosamine

Uronic acid

Often solphorated



- <u>GLYCOSAMINOGLYCANS</u>

SIX CLASSES :

Hyaluronic acid (also called hyaluronan)

Chondroitin-4-sulfate (Greek: chondros, cartilage)

Chondroitin-6-sulfate

Dermatan sulfate

Keratan sulfate

Heparin

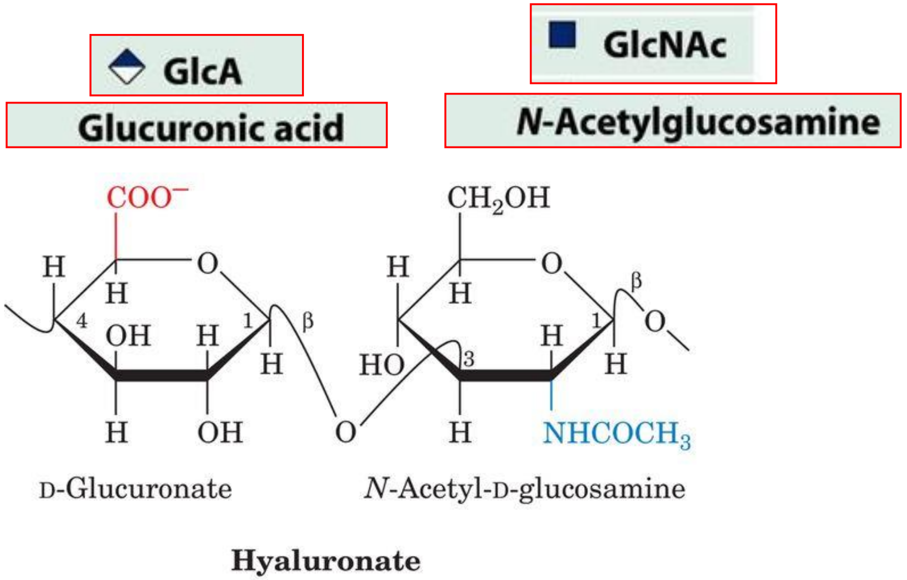
Heparan sulfate

Structural function:

They form an extracellular gelatinous matrix capable of holding together the protein components of the skin and connective tissue

Hyaluronic acid (also called hyaluronan)

Greek hyalos means “glass”; hyaluronan can have a glassy or translucent appearance



Component of synovial fluid (the fluid that lubricates the joints) and the vitreous humor of eye.

Contains residues of D-glucuronic acid and N-acetylglucosamine

Hyaluronan is also a component of the extracellular matrix of cartilage and tendons

Disaccharides units β1-4 linked

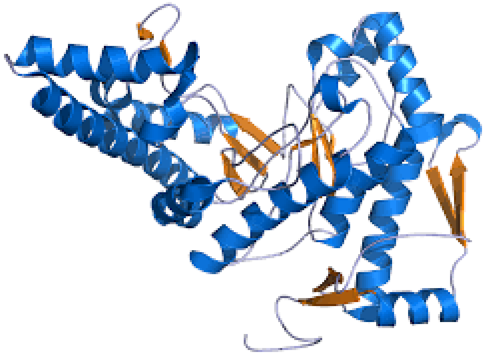
Up to 50,000 repeats of the basic disaccharide unit,

Contributes to elasticity

Strong noncovalent interactions with other components of the matrix.

Hyaluronidase

Enzyme secreted by pathogenic bacteria



Can hydrolyze the glycosidic linkages of hyaluronan

↓

tissues will be more susceptible to bacterial invasion.

In many animal species

↓

in sperm hydrolyzes an outer glycosaminoglycan coat around the ovum, allowing sperm penetration

Hyaluronic acid (HUA) is a popular dermal filler material.

Hyaluronidase use to dissolve the excess or defects of a hyaluronic acid-based filler.

SIX CLASSES :

Hyaluronic acid (also called hyaluronan)

Chondroitin-4-sulfate (Greek: chondros, cartilage)

Chondroitin-6-sulfate

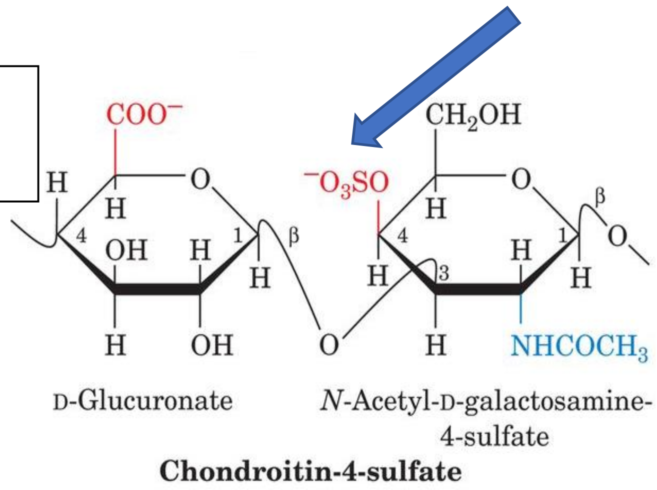
Dermatan sulfate

Keratan sulfate

Heparin

Heparan sulfate

Chondroitin-4-sulfate
(Greek: chondros, cartilage)



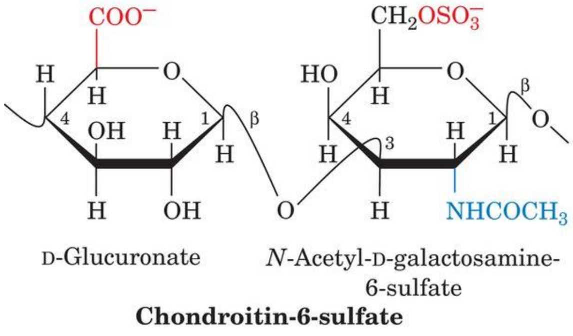
Major component of cartilage, tendons, ligaments, and the walls of the aorta and other connective tissue

Constituting of D-glucuronic acid and N-acetyl-D-galactosamine (in place of hyaluronate's N-acetyl-D-glucosamine residues)

N-acetyl-D-galactosamine is sulfated at the C4 position

Chondroitin-6-sulfate

N-acetyl-D-galactosamine is sulfated at the C6 position



SIX CLASSES :

Hyaluronic acid (also called hyaluronan)

Chondroitin-4-sulfate (Greek: chondros, cartilage)

Chondroitin-6-sulfate

Dermatan sulfate

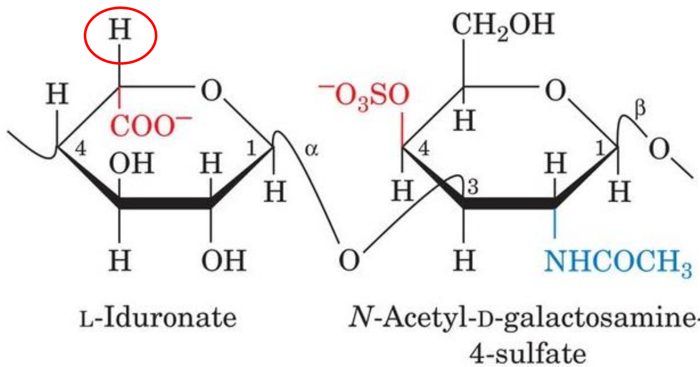
Keratan sulfate

Heparin

Heparan sulfate

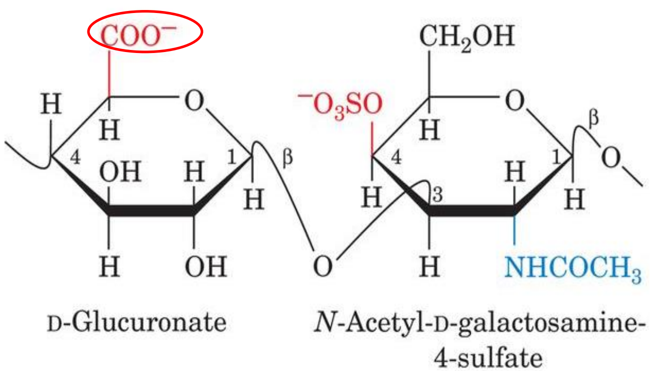
Dermatan sulfate (Greek derma, “skin”)

So named because of its prevalence in skin



Dermatan sulfate

Differs from chondroitin-4-sulfate only by an inversion of configuration about C5 of the β-D-glucuronate residues to form L- iduronate.



Chondroitin-4-sulfate

Dermatan sulfate contributes to the pliability of skin and it is also present in blood vessels and heart valves

SIX CLASSES :

Hyaluronic acid (also called hyaluronan)

Chondroitin-4-sulfate (Greek: chondros, cartilage)

Chondroitin-6-sulfate

Dermatan sulfate

Keratan sulfate

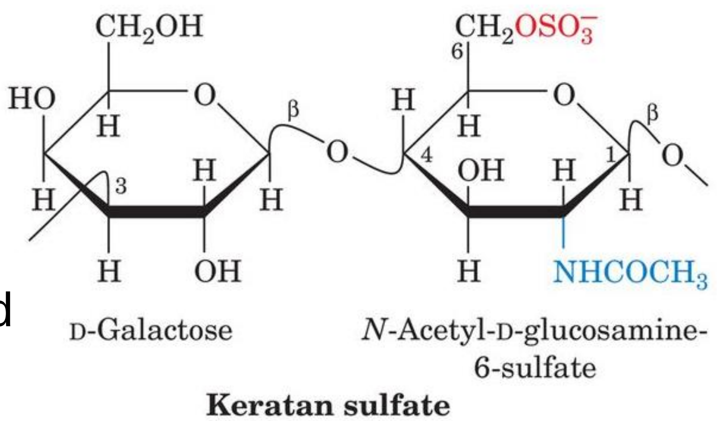
Heparin

Heparan sulfate

Keratan sulfate

(Greek keras, “horn”)

It is especially present in cornea, cartilage and bone.
Synthesized also in the central nervous system and in structures formed of dead cells: horn, hair, hoofs, nails, and claws



Contains D-galactose and N-acetyl-D-glucosamine 6-sulfated β(1-4) linked

SIX CLASSES :

Hyaluronic acid (also called hyaluronan)

Chondroitin-4-sulfate (Greek: chondros, cartilage)

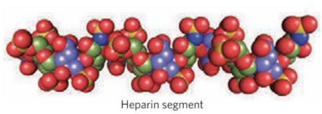
Chondroitin-6-sulfate

Dermatan sulfate

Keratan sulfate

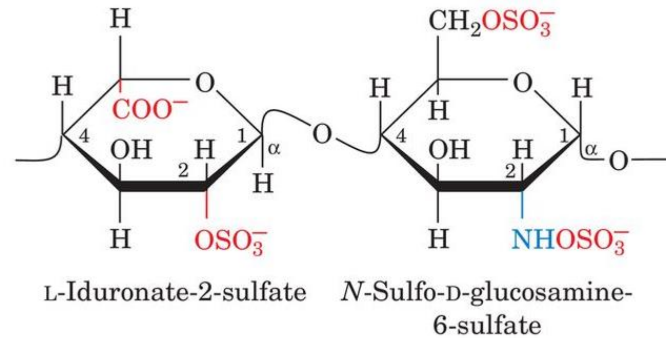
Heparin and Heparan sulfate

Heparin



It is contained in many tissues.
It binds to plasma protein (prothrombin III).

Exclusively in the intracellular granules of the mast cells that line arterial walls, especially in the liver, lung and skin.



Heparin

Inhibits the clotting of blood, and its release, through injury, is thought to prevent runway clot formation

Its main characteristic is the high degree of sulfation.

Therefore, heparin has a wide clinical use to inhibit blood clotting in postsurgical patients

Heparan sulfate

(Greek hepar, “liver”);

It was originally isolated from dog liver

Contains a similar disaccharide repeat unit as heparin but it has more N-acetyl groups, fewer N-sulfate goups, and a lower degree of O-sulfate groups.

Extracellular or an integral components
Ubiquitous of the cell surface in many tissue, such as blood vessel walls and brain.

Mucopolisaccharidoses

They are a group of metabolic disorders caused by the absence or malfunctioning of lysosomial enzyme.

Lysosomial enzymes are necessary for degradation of dermatan and heparan sulfate.

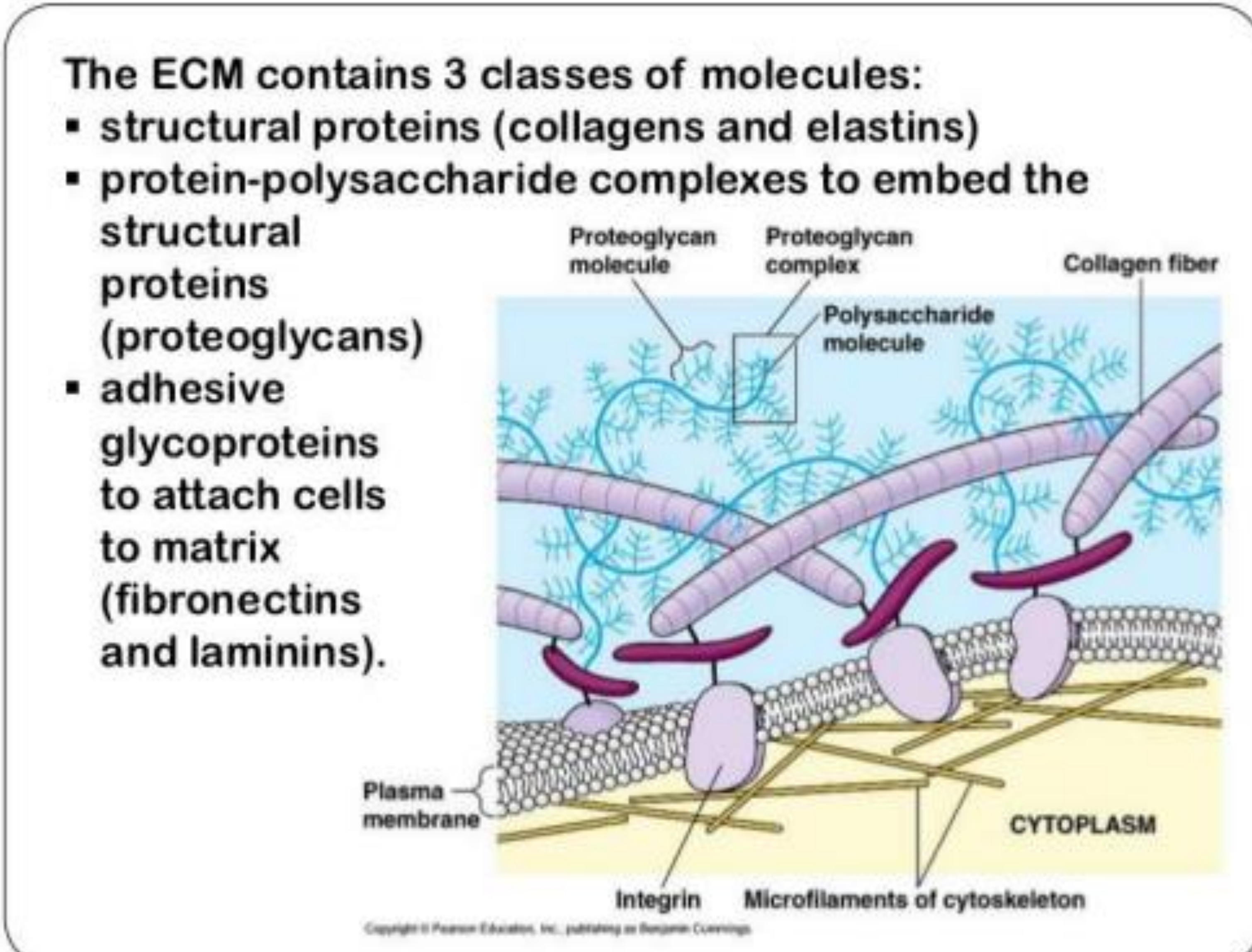
GAGs accumulate in various organs and tissues causing complex clinical manifestations:

- Mental retardation
- Skeletal changes
- Enlargement of the liver, spleen
- Respiratory and heart disease

Sanfilippo Syndrome
Hurler Syndrome
Hunter Syndrome

Proteoglycans

They are Glycosaminoglycan-Containing Macromolecules of the Cell Surface and Extracellular Matrix



Proteoglycans

Functions:

Structural support and hydration:
They are the main component of the extracellular matrix, forming hydrated gels that provide volume and resistance to compression.

Cellular communication and regulation:
They act as ligands and receptors for growth factors, cytokines, and other signaling molecules.

Lubrication:
They have a lubricating role, especially in joints.

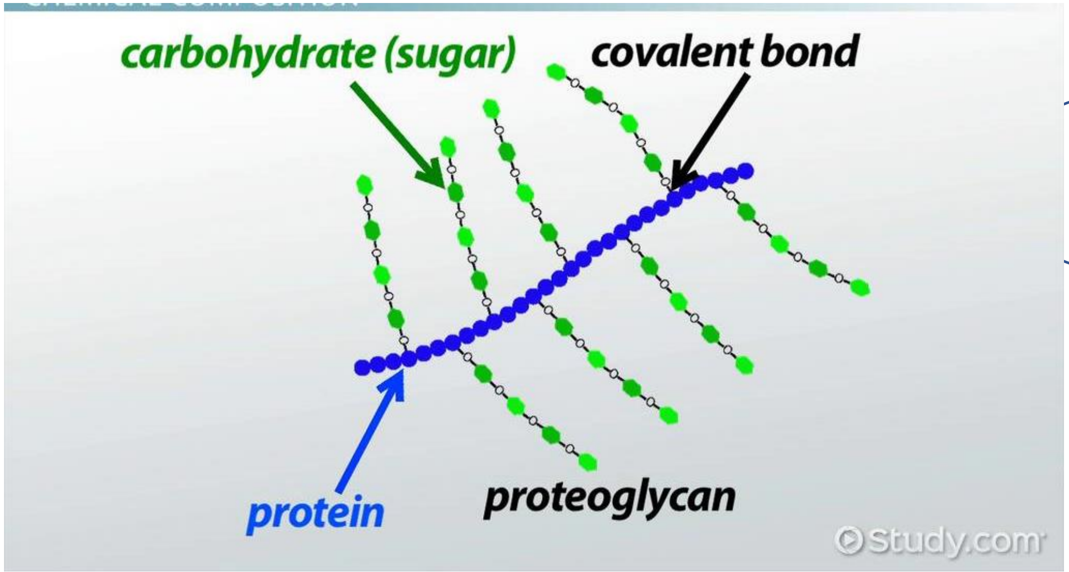
They are involved in cell recognition and the regulation of cell proliferation and differentiation.

Proteoglycans

Mammalian cells can produce 40 types of proteoglycans.

Proteins + Glycosaminoglycans

Glycosaminoglycans bind to proteins to form proteoglycans,

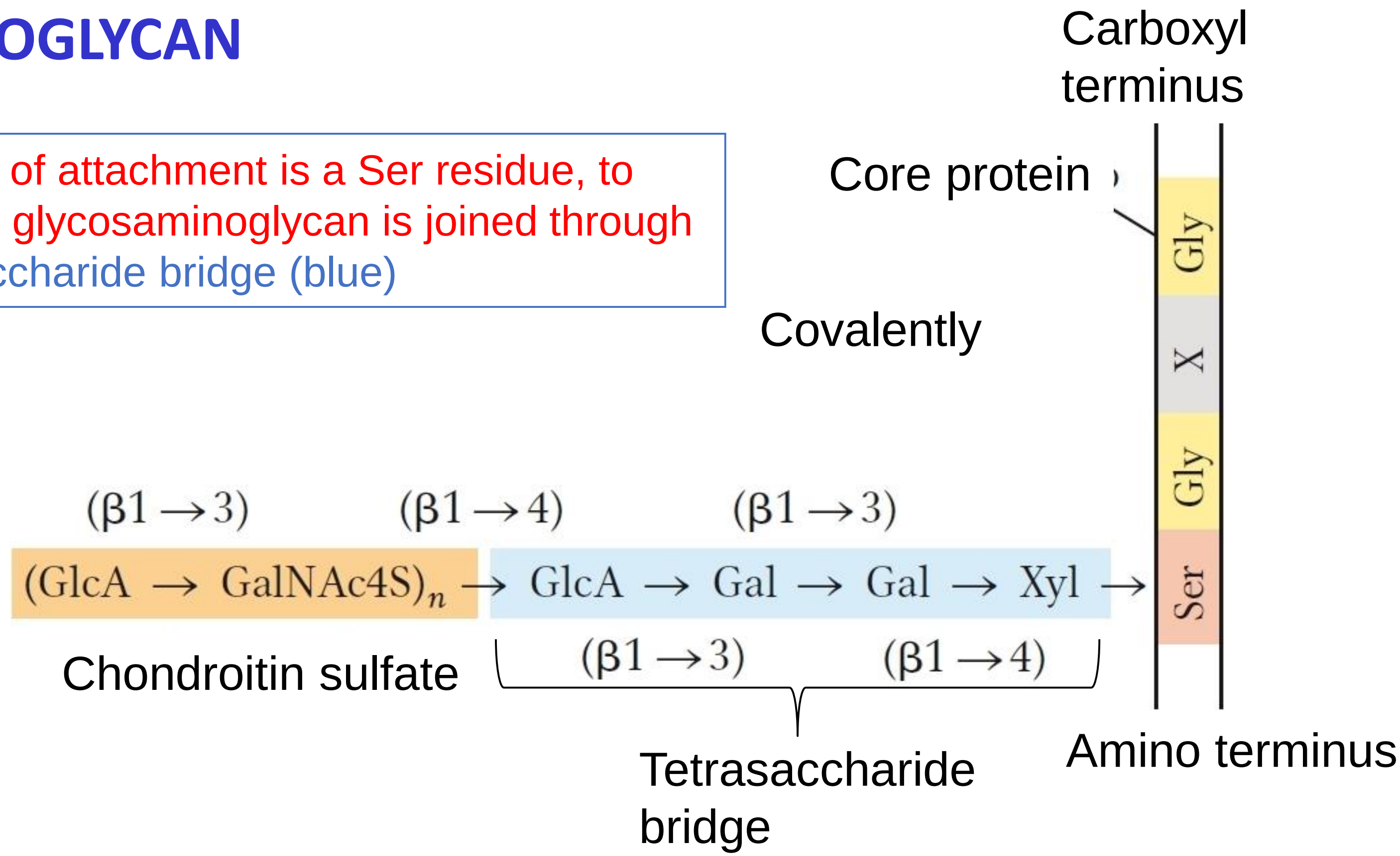


They form an extracellular gelatinous matrix capable of holding together the protein components of the skin and connective tissue

The basic proteoglycan unit consists of a "core protein" with covalently attached glycosaminoglycan(s).

PROTEOGLYCAN

The point of attachment is a Ser residue, to which the glycosaminoglycan is joined through a tetrasaccharide bridge (blue)



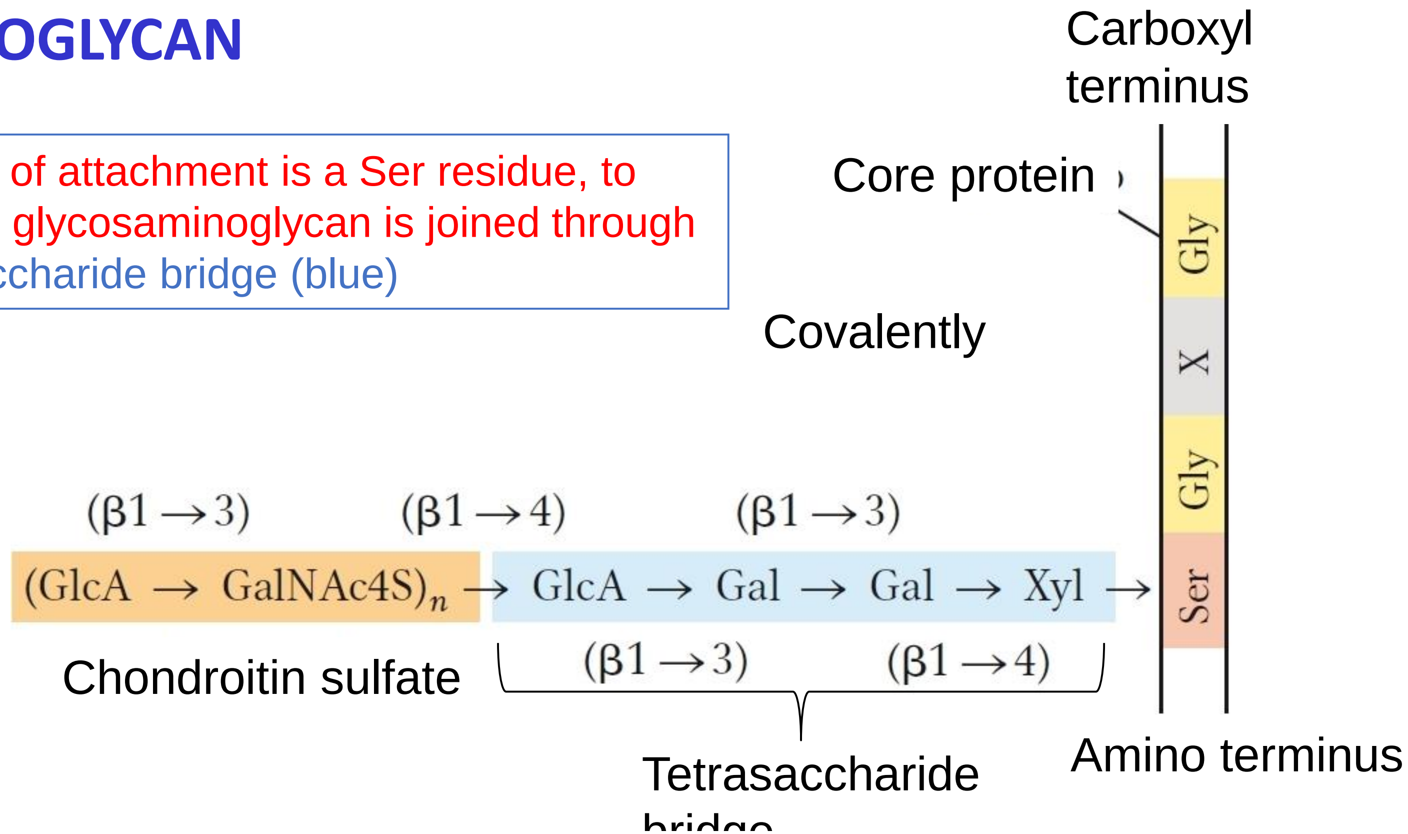
sequence –Ser–Gly–X–Gly–

terminus

FIGURE 7–25 Proteoglycan structure, showing the tetrasaccharide bridge. A typical tetrasaccharide linker (blue) connects a glycosaminoglycan—in this case chondroitin 4-sulfate (orange)—to a Ser residue in the core protein. The xylose residue at the reducing end of the linker is joined by its anomeric carbon to the hydroxyl of the Ser residue.

PROTEOGLYCAN

The point of attachment is a Ser residue, to which the glycosaminoglycan is joined through a tetrasaccharide bridge (blue)

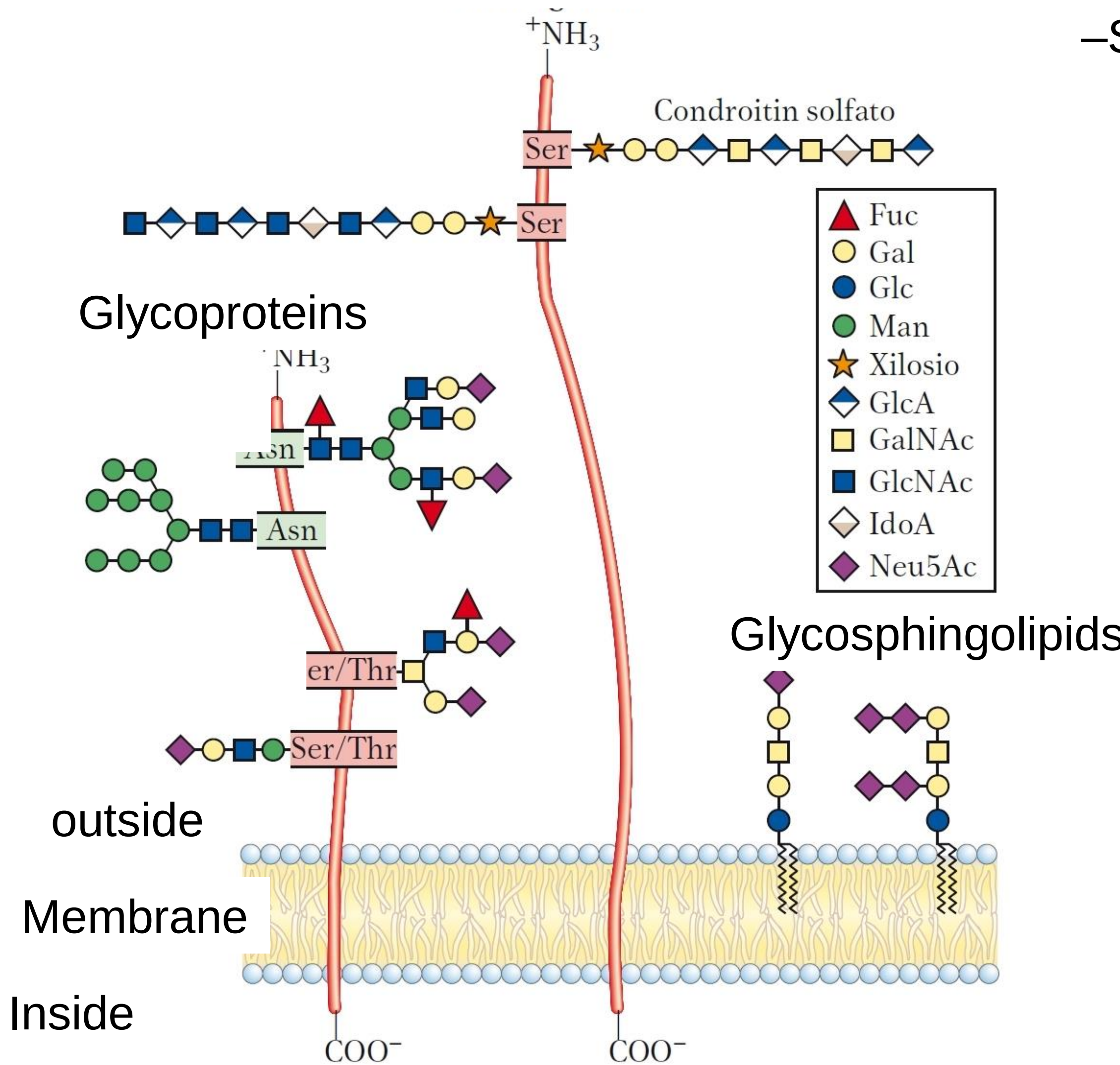


sequence –Ser–Gly–X–Gly–

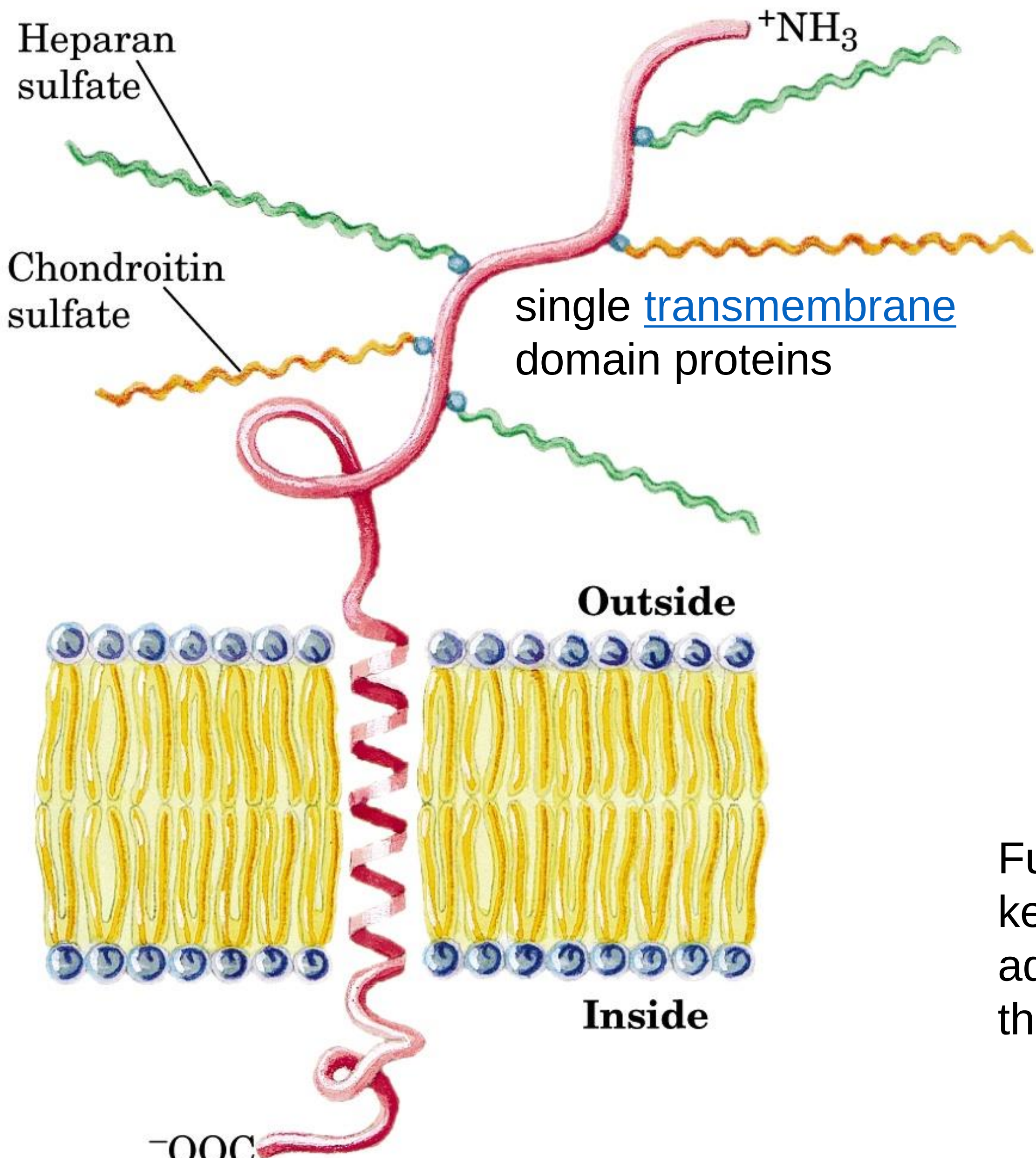
The Ser residue is generally in the sequence –Ser–Gly–X–Gly– (where X is any amino acid residue), although not every protein with this sequence has an attached glycosaminoglycan

Proteoglycans

–Ser–Gly–X–Gly–



Proteoglycan structure: Syndecans have a single trans-membrane domain



single transmembrane domain proteins

Syndecans have a single transmembrane domain and an extracellular domain bearing three to five chains of heparan sulfate and in some cases chondroitin sulfate

consisting of four members:
syndecan-1,
syndecan-2,
syndecan-3,
syndecan-4.

Functionally, syndecans play key roles in cell signaling, adhesion, and interactions with the extracellular matrix (ECM).

Syndecan-1 is predominantly expressed in epithelial cells,

syndecan-2 in mesenchymal and neuronal tissues,

syndecan-3 is the major syndecan of the nervous system,

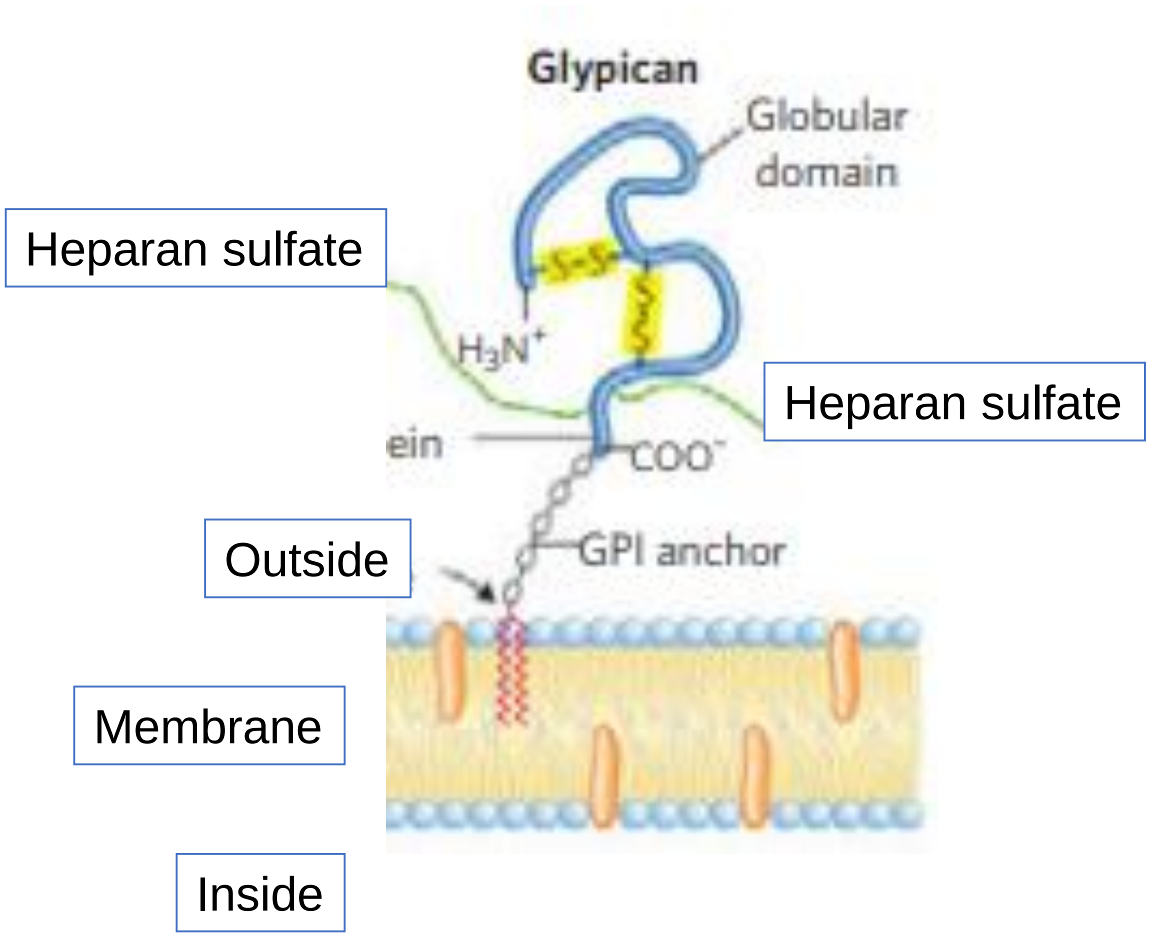
syndecan-4 is present in many cells forming stable adhesions,

Syndecan-2 and syndecan-3

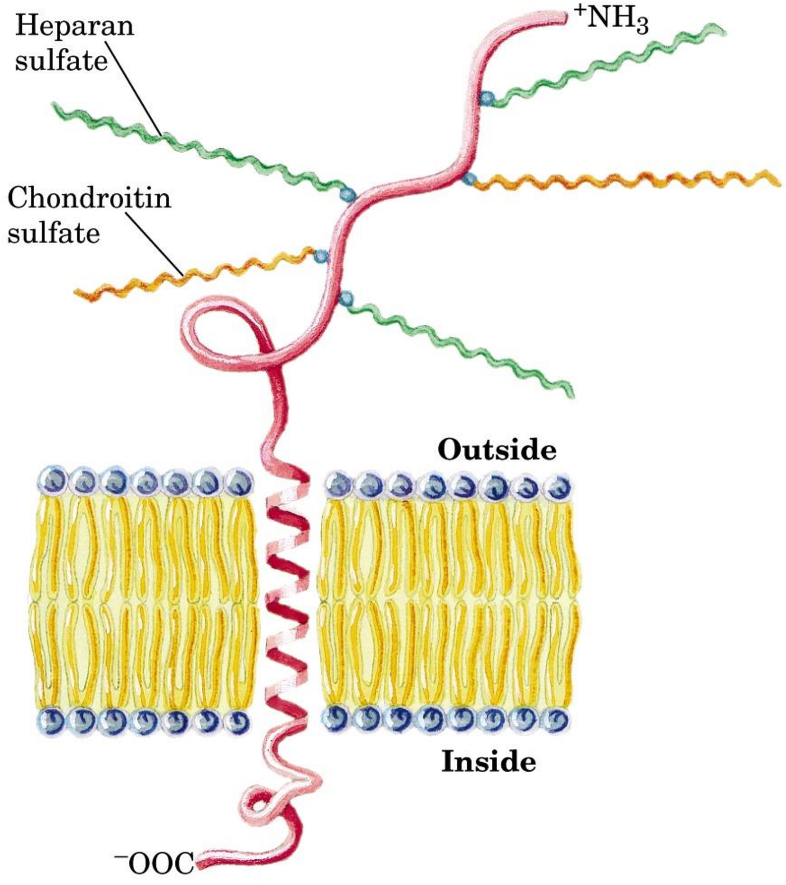
expressed in the brain

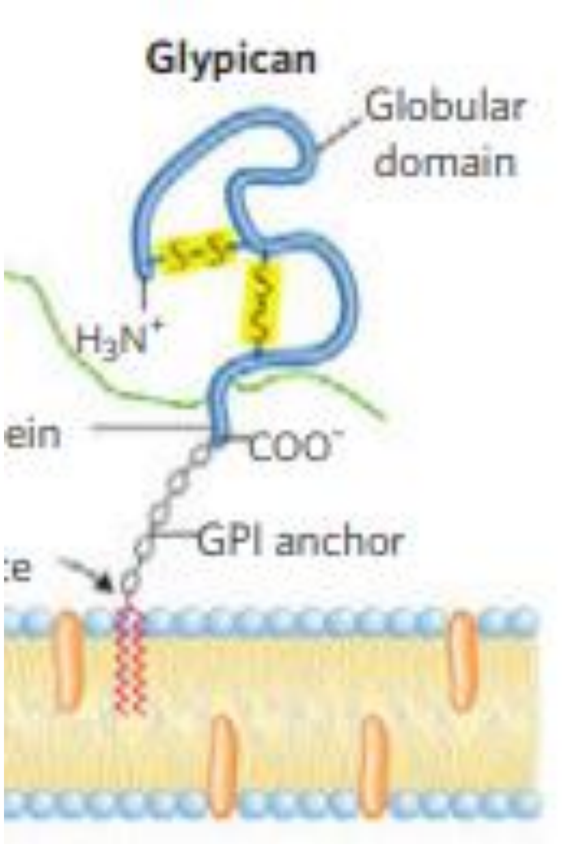
play important roles in neuronal development and dendritic spine formation and structure.

Glypicans are attached to the membrane by a lipid anchor, a derivative of the membrane lipid phosphatidylinositol



Syndecans and glypicans can be shed into the extracellular space.





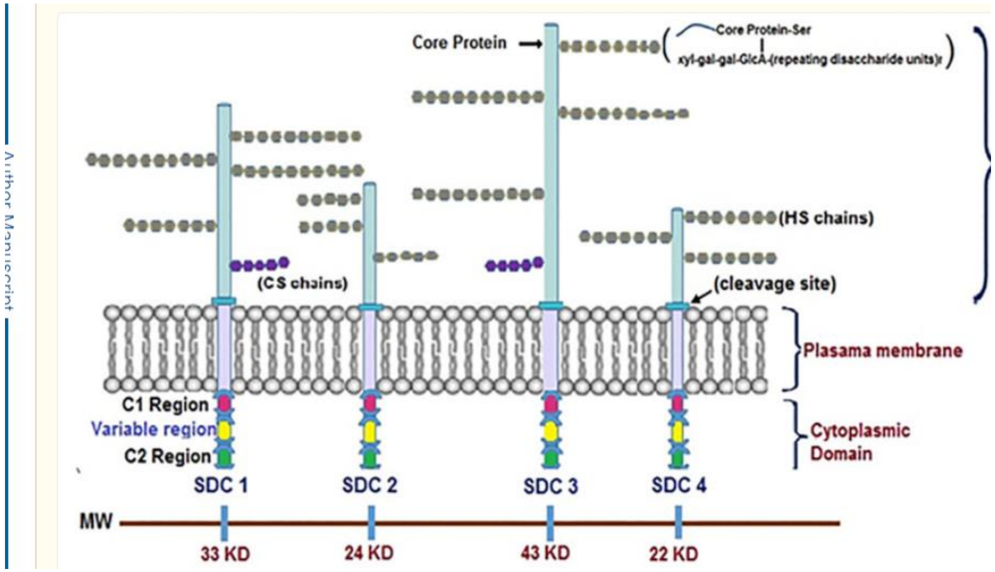
Syndecan diseases

involve the dysregulation of syndecans, in various conditions like cancer, inflammation, and liver disease

Syndecan-1 is implicated in multiple myeloma and liver cancer, where its elevated levels can indicate a poor prognosis.

J Cell Physiol. 2018 Mar 25;233(9):6346–6358. doi: 10.1002/jcp.26388

Syndecans in chronic inflammatory and autoimmune diseases: Pathological insights and therapeutic opportunities



Peripheral Leukocyte Syndecan-3 Is Elevated in Alzheimer’s Disease: Evidence from a Human Study

Int. J. Mol. Sci. **2025**, *26*(14), 6587; https://doi.org/10.3390/ijms26146587

SDC3 was significantly elevated in AD patients

Neurocan is a chondroitin sulfate proteoglycan,

it is a component of the extracellular matrix of the central nervous system

It can bind to various structural extracellular matrix components, such as hyaluronate, heparin

It is thought to be involved in the modulation of cell adhesion and neurite outgrowth during development.

˙Its possible role in various symptoms of bipolar disorder.

Mol Neuropsychiatry. 2018 Jun; 4(1): 30–34.
Published online 2018 May 17. doi: 10.1159/000488590

PMCID: PMC6032033
PMID: 29998116

Further Evidence of an Association between *NCAN* rs1064395 and Bipolar Disorder

Versican is a large chondroitin sulfate/dermatan sulfate proteoglycan.

It is involved in development, guiding embryonic cell migration in the formation of the heart and outlining the path for neural crest cell migration.

In adults, serves as a structural macromolecule of the extracellular matrix in the brain and large blood vessels.

In contrast, it is transiently expressed at high levels during development and under pathological conditions when the extracellular matrix dramatically changes, including in the inflammation and repair process.

There are many reports showing the upregulation of versican in cancer, which correlates with cancer aggressiveness.

Phosphacan is a chondroitin sulphate that binds to neurons and neural cell adhesion molecules;

modulates neural-glial interactions associated with neural differentiation.

Brevican is expressed in the terminally differentiated CNS, particularly in perineuronal nets.

Serum Brevican as a Biomarker of Cerebrovascular Disease in an Elderly Cognitively Impaired Cohort

2024 Biomolecules Jan 7;14(1):75. doi: 10.3390/biom14010075.

A decrease may be associated with early cerebrovascular damage

Aggrecan is a large proteoglycan that forms giant hydrated aggregates with hyaluronate in the extracellular matrix (ECM).

Aggrecan is a critical component to cartilage structure and the function of joints.

The extraordinary resistance of these aggregates to compression explains their abundance in articular cartilage of joints where they ensure adequate load-bearing.

In brain, they provide mechanical buffering and contribute to formation of perineuronal nets, which regulate synaptic plasticity.

Aggrecan is also present in cardiac jelly, developing heart valves, and blood vessels during cardiovascular development.

Journal of Histochemistry & Cytochemistry JHC

J Histochem Cytochem. 2020 Nov; 68(11): 777–795.
Published online 2020 Sep 1. doi: 10.1369/0022155420952902

Aggrecan in Cardiovascular Development and Disease

Monitoring Editor: Liliana Schaefer and Charles W. Frevert

Christopher D. Koch, Chan Mi Lee, and Suneel S. Apte

Mutation in the Aggrecan gene

(AGC1, locus 15q26.1) . transmitted as an autosomal dominant trait.

Spondyloepiphyseal dysplasia, Kimberley type

•

Disease with characteristics of short stature and premature degenerative arthropathy.

It has been described in one multigenerational South African family of English white descent.

The main clinical features may include proportionate short stature (less than fifth percentile for age), stocky habitus and early-onset progressive osteoarthropathy of the weight-bearing joints.

Radiographic features are flattened vertebral bodies with sclerosis and prominent endplate irregularity and flattened femoral epiphyses

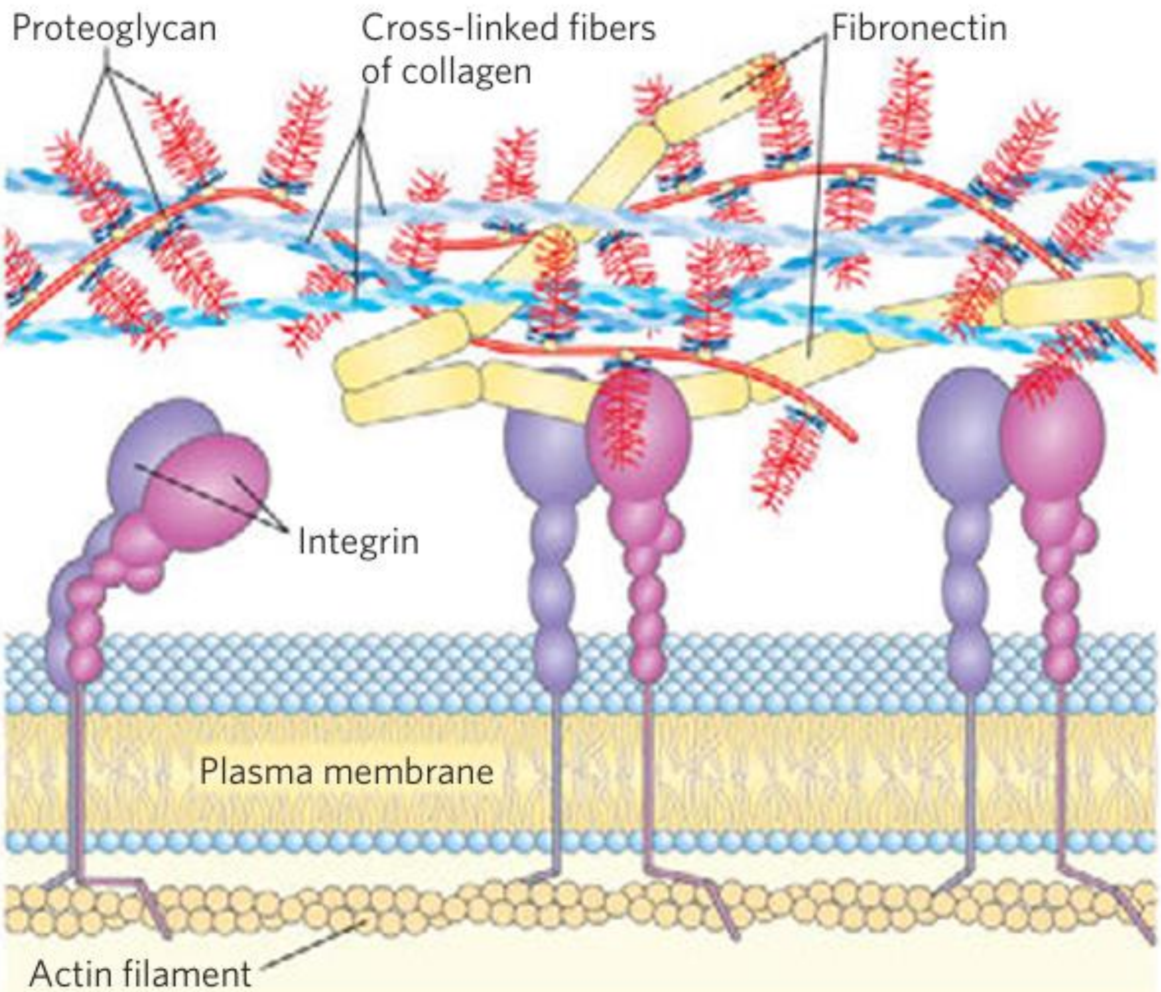
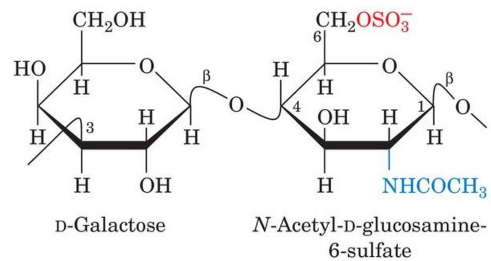


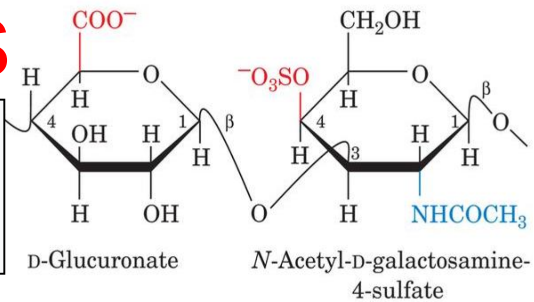
FIGURE 7–29 Interactions between cells and the extracellular matrix. The association between cells and the proteoglycan of the extracellular matrix is mediated by a membrane protein (integrin) and by an extracellular protein (fibronectin in this example) with binding sites for both integrin and the proteoglycan. Note the close association of collagen fibers with the fibronectin and proteoglycan.

Proteoglycans

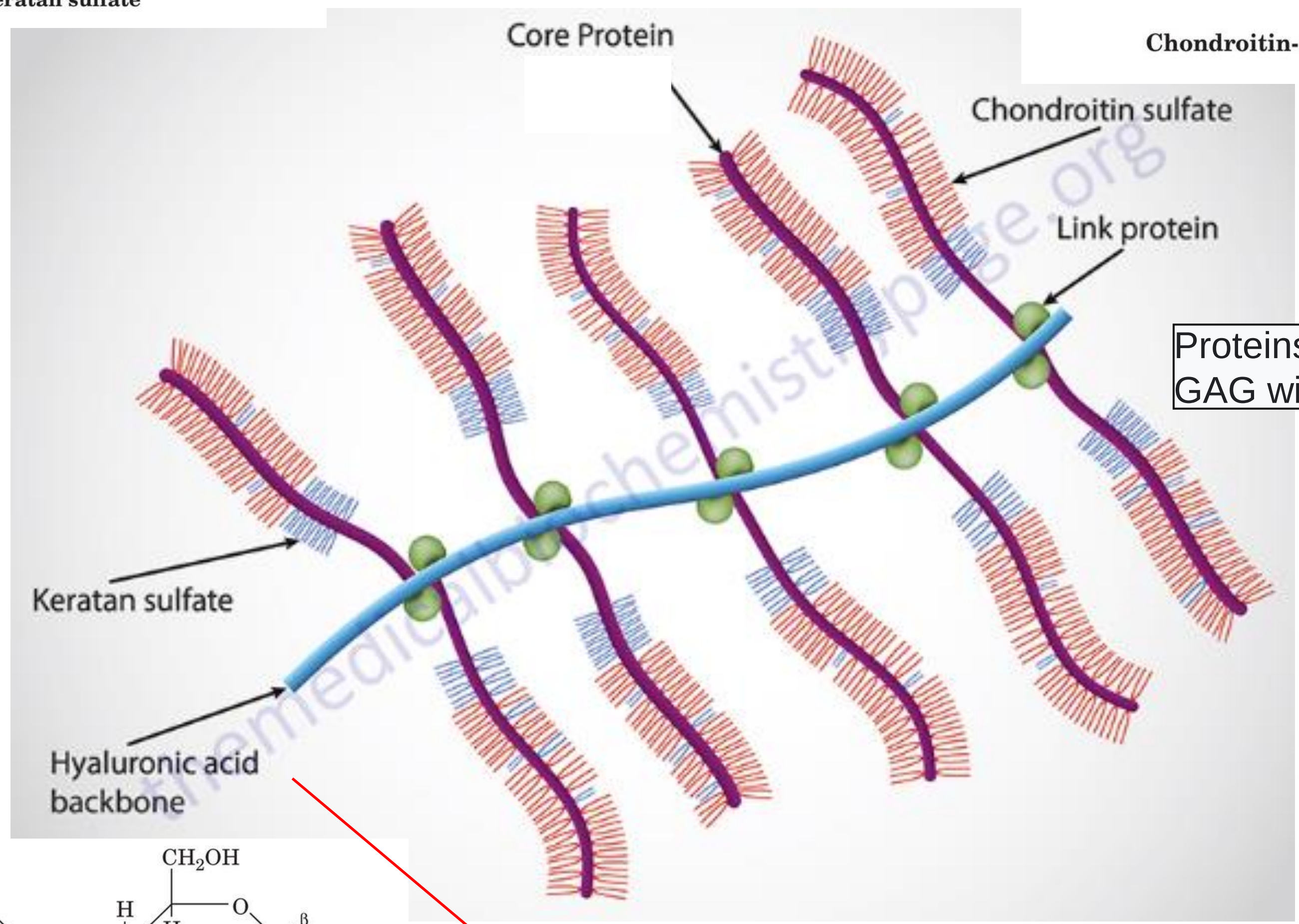


Keratan sulfate

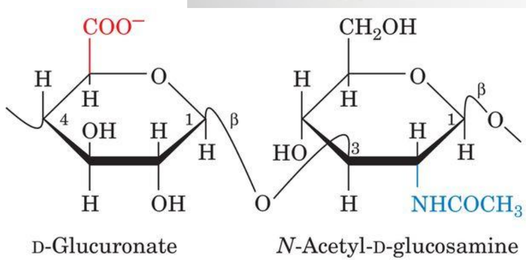
In the cartilage bind to collagen by electrostatic bond between solfate and carboxylate of proteoglycan and basic residue of collagen



Chondroitin-4-sulfate



Proteins covalently bind to GAG with Ser residues



Long Single chain → non-covalently linked protein chains branch off from hyaluronic acid

Structures and Roles of Some Polysaccharides

Polymer	Type*	Repeating unit[†]	Size (number of monosaccharide units)	Roles
Starch				Energy storage: in plants
Amylose	Homo-	$(\alpha 1 \rightarrow 4)$Glc, linear	50–5,000	
Amylopectin	Homo-	$(\alpha 1 \rightarrow 4)$Glc, with $(\alpha 1 \rightarrow 6)$Glc branches every 24 to 30 residues	Up to 10^6	
Glycogen	Homo-	$(\alpha 1 \rightarrow 4)$Glc, with $(\alpha 1 \rightarrow 6)$Glc branches every 8 to 12 residues	Up to 50,000	Energy storage: in bacteria and animal cells
Cellulose	Homo-	$(\beta 1 \rightarrow 4)$Glc	Up to 15,000	Structural: in plants, gives rigidity and strength to cell walls
Chitin	Homo-	$(\beta 1 \rightarrow 4)$GlcNAc	Very large	Structural: in insects, spiders, crustaceans, gives rigidity and strength to exoskeletons
Peptidoglycan	Hetero-; peptides attached	4)Mur2Ac$(\beta 1 \rightarrow 4)$ GlcNAc$(\beta 1$	Very large	Structural: in bacteria, gives rigidity and strength to cell envelope
Hyaluronate (a glycosamino-glycan)	Hetero-; acidic	4)GlcA$(\beta 1 \rightarrow 3)$ GlcNAc$(\beta 1$	Up to 100,000	Structural: in vertebrates, extracellular matrix of skin and connective tissue; viscosity and lubrication in joints

* Each polymer is classified as a homopolysaccharide (homo-) or heteropolysaccharide (hetero-).

[†]The abbreviated names for the peptidoglycan and hyaluronate repeating units indicate that the polymer contains repeats of this disaccharide unit, with the GlcNAc of one disaccharide unit linked $\beta(1 \rightarrow 4)$ to the first residue of the next disaccharide unit.

GLYCOCONIUGATES

PROTEOGLYCANS

Present in the extracellular matrix, consisting of several molecules of glycosaminoglycans (hetero-polysaccharides) covalently joined to a membrane or secreted protein.

They mediate the activity of growth factors,regulate the assembly of collagen fibers with which they interact, contribute to the mechanical strength of the connective tissue, modulate the development of various tissues (cartilage, tendons)

GLYCOPROTEINS

Proteins bond to oligosaccharide chains
They are present in the plasma membrane, blood, biological fluids and the extracellular matrix.
They constitute recognition sites for other proteins on the cell surface, are involved in cellular communication mechanisms and in many other functions.

GLYCOLIPIDS

Membrane lipids bound to oligosaccharides and serve as recognition sites for several proteins