Today's class:

Glycans and lipids

This lecture largely follows the chapter 3 in the book
'The Molecules of Life' by Kuriyan, Konforti & Wemmer, 1st Ed, 2013

Biomolecules of life not coded by DNA

Glycans

Glycans are sugars or sugar derivatives, and their polymers. The simplest individual subunits of glycans have roughly the formula $(HCOH)_n$ with n between 3 and 9, but most commonly 5, 6, or 7. Many glycans also have sugars with additional functionality relative to these simplest subunits. Glycans are also known as carbohydrates.

Lipids

Lipids are amphipathic molecules (also called amphiphilic, that is, part hydrophobic and part hydrophilic). Lipids are the primary components of biological membranes. Although membranes contain embedded proteins, most of the critical properties of membranes arise from the lipid components.

Glycans

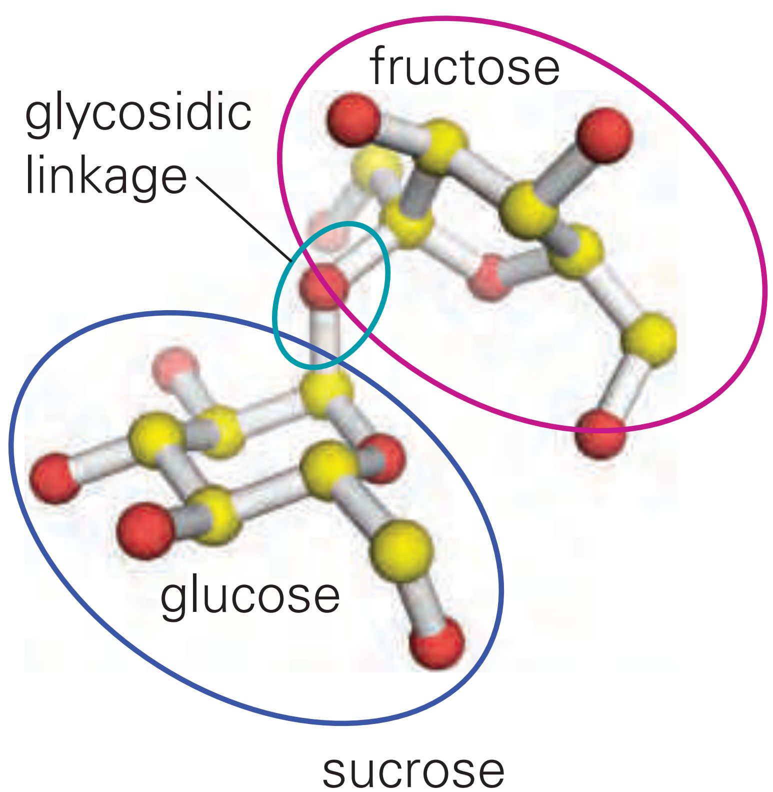
Simple sugars are made of hydroxylated carbon

Carbohydrate = hydrated carbon

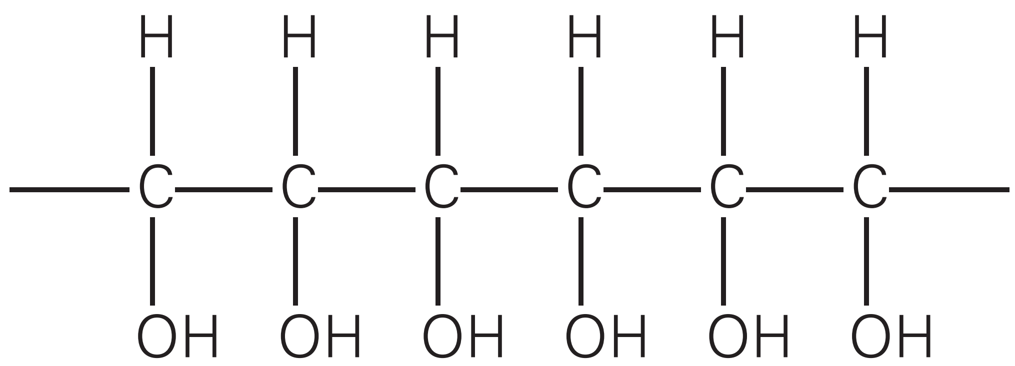
sugars are made of adding water molecules to carbon $\Longrightarrow$ $(CH_2O)_n$

Simple sugars are those with small n

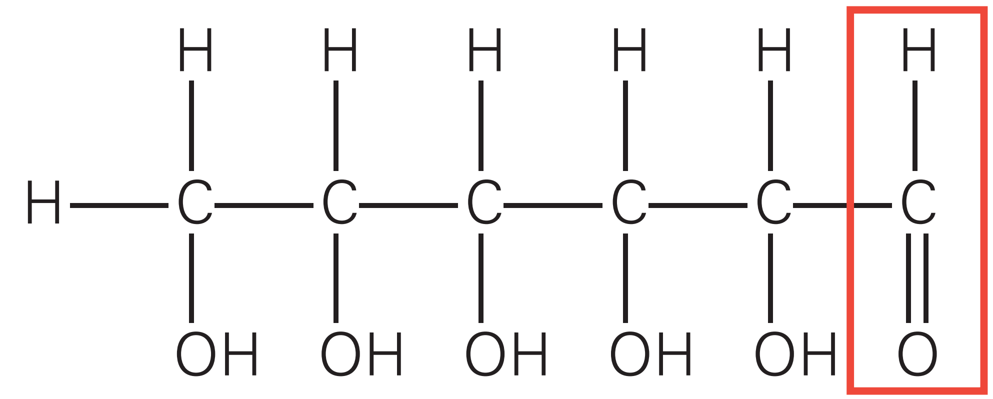
Simple sugars combine via glycosidic bonds to make homo- and heteropolymers



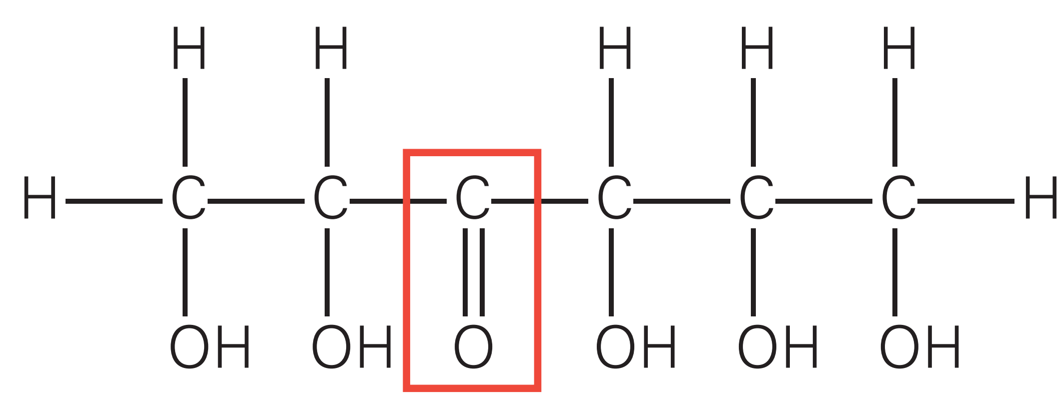
Simple sugars can be aldehyde or ketones



A simple chain of HCOH leaves bonding unsatisfied at the ends



Aldehyde



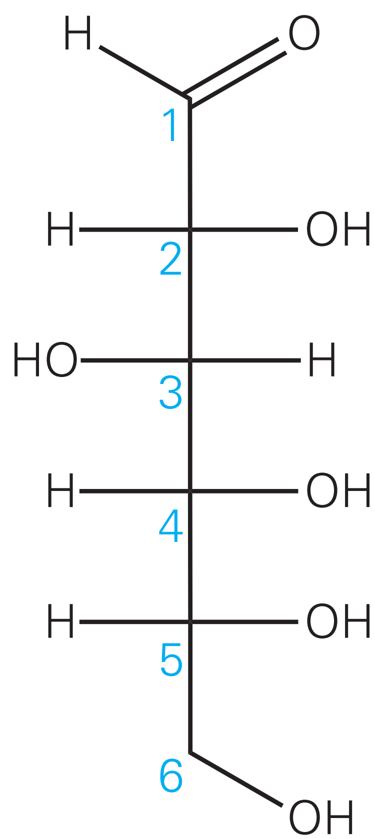
Ketone

Glucose = an aldehyde sugar, also called an aldohexose

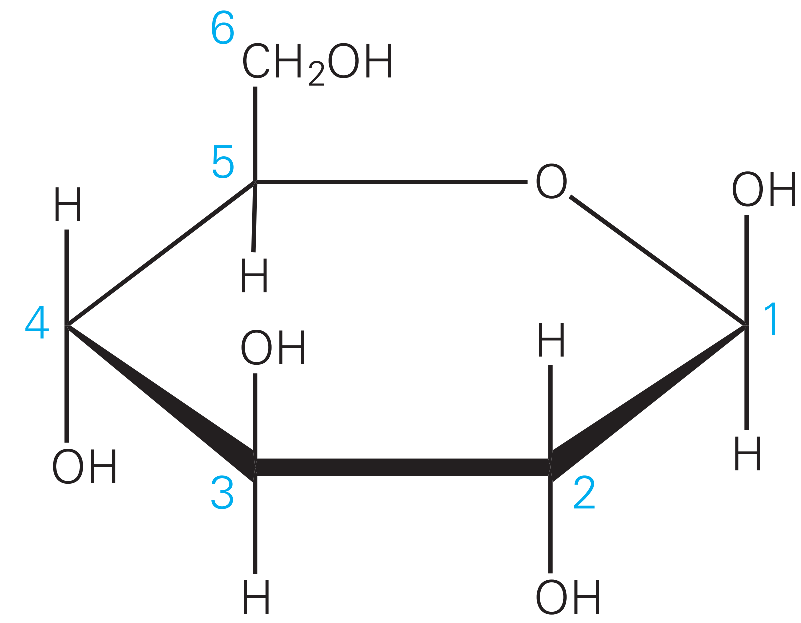
Fructose = a ketone sugar, also called an ketohexose

Sugars can be drawn differently

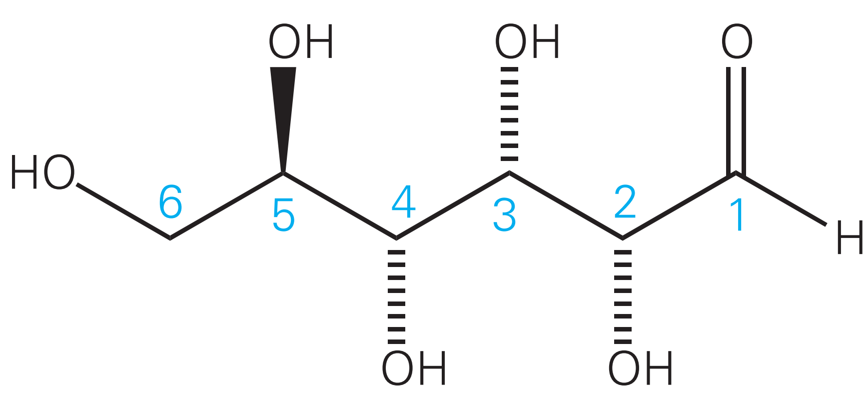
β-D-glucose = aldohexose

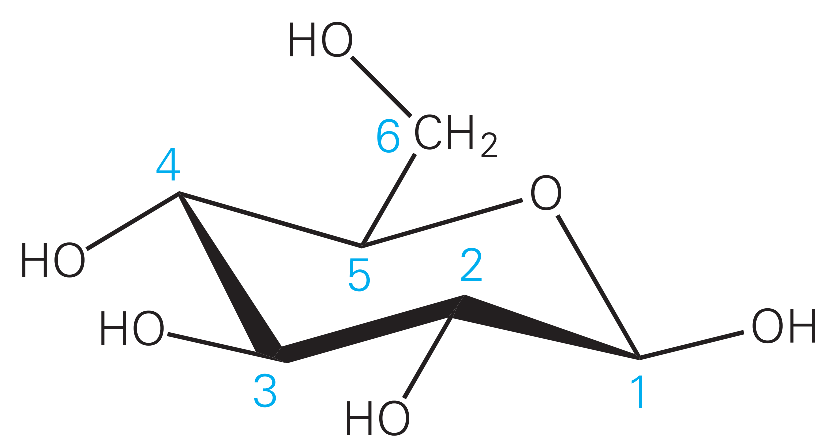


Fischer



Haworth





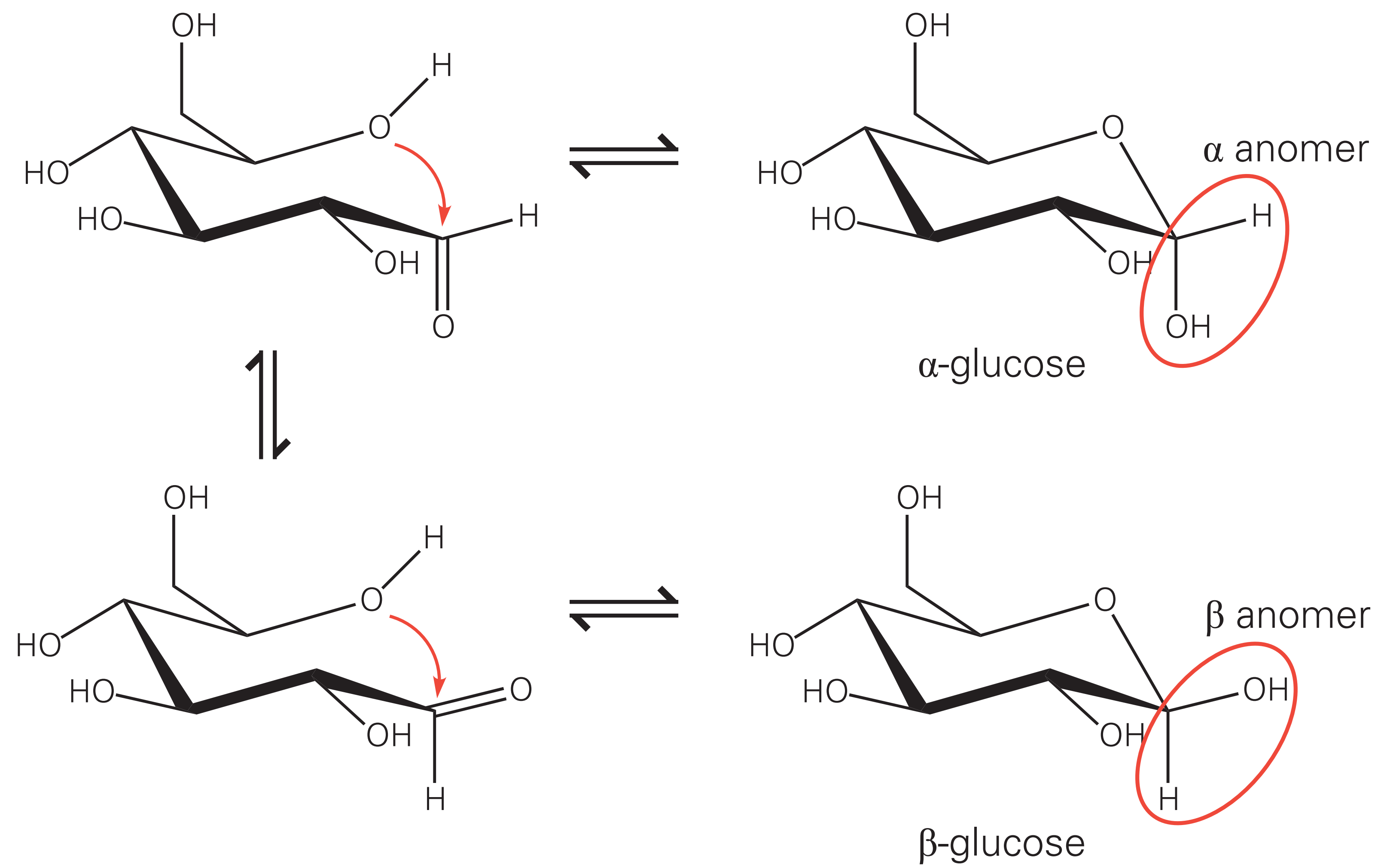
Sugars can exist in linear and cyclized forms

Anomers

Anomers are forms of sugars that differ only in the equatorial or axial position of the hydroxyl at the position of ring closure.

Axial and equatorial

Axial and equatorial are terms that define the directions of substituents of rings such as sugars, relative to the plane of the ring.



Here α & β forms have different chemical properties and interconvert

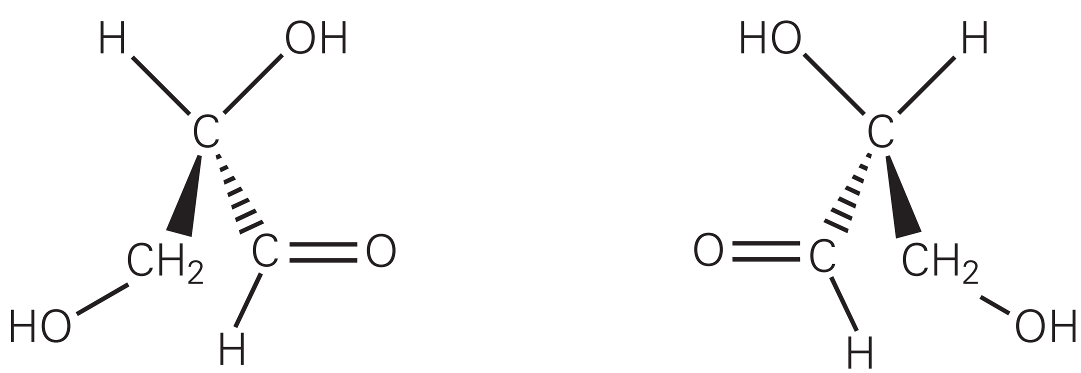
In glucose, $\alpha : \beta \approx 1 : 2$

β-form has lower conformational energy than the α-form

Chirality in sugars

Most carbon atoms in sugars are “chiral”—four chemically distinct substituents.

glyceraldehyde



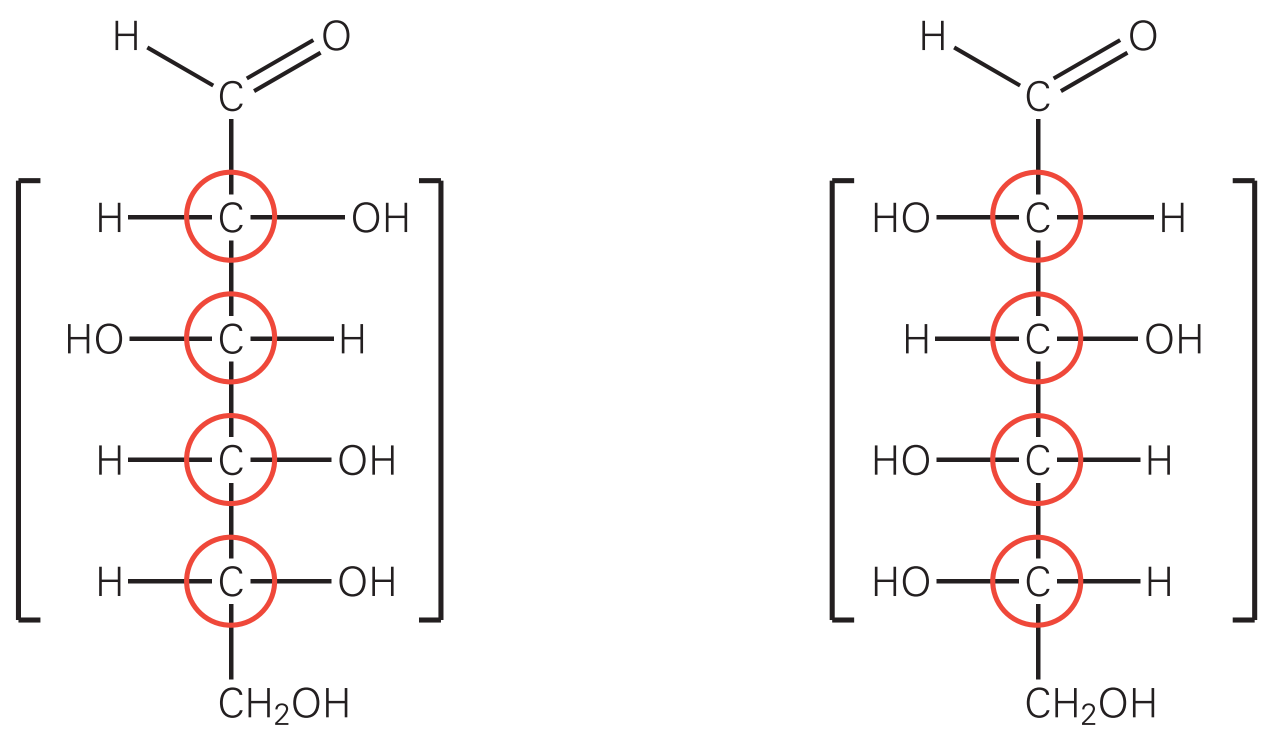
D ***L***

- Solutions of chiral molecules exhibit optical activity - rotation of plane polarized light
- The two configurations of atoms about the chiral center are denoted D (dextrorotatory - clockwise rotation) and L (levorotatory - anti-clockwise rotation).
- All chiral centers are then named acc to similarity with D- or L-glyceraldehyde
- For simple sugars D or L is decided based on the chirality of the C-atom furthest from the aldehyde

- A molecule with one chiral center can exist in two non-superimposable mirror image configurations, known as **enantiomers**.
- In hexose sugars, the four central carbon atoms are chiral
- Enantiomers have same physical and chemical properties

But there is a difference!

D-glucose L-glucose

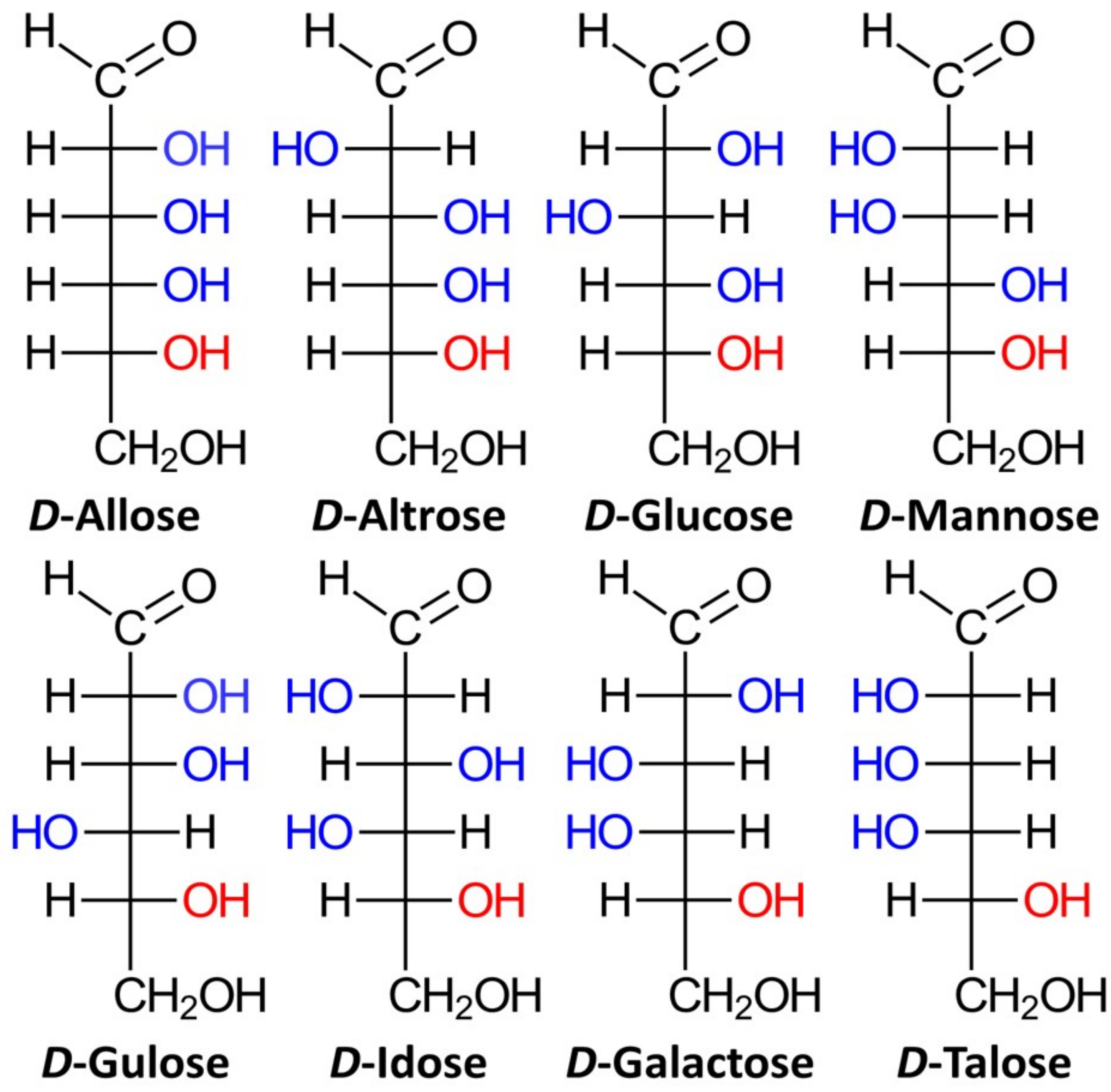


4 chiral carbons

mirror images

Enantiomers of glucose

Structural isomers hexose family



- There are 16 possible isomers of hexose sugars.
- So, there are 8 sets of enantiomers which have distinct properties
- Only D-forms of aldohexoses occur in nature
- Of 8 possible D-aldohexoses, only glucose, mannose and galactose are found commonly in biological systems

Sugars with other chemical functionalities

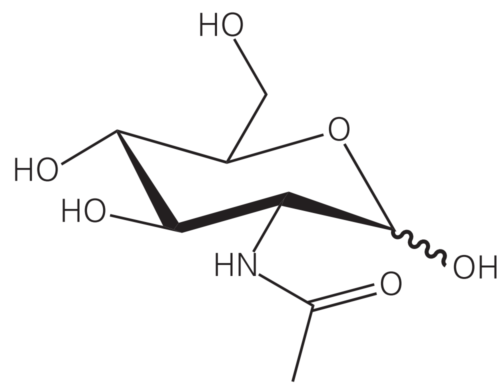
Oligosaccharide and polysaccharide

Oligosaccharides are glycans that are polymers of sugars. Specific small polymers are usually designated by the number of sugar units, such as monosaccharide, disaccharide, trisaccharide, etc. The term polysaccharide is usually used when there are more than about 30 sugar units in the polymer.

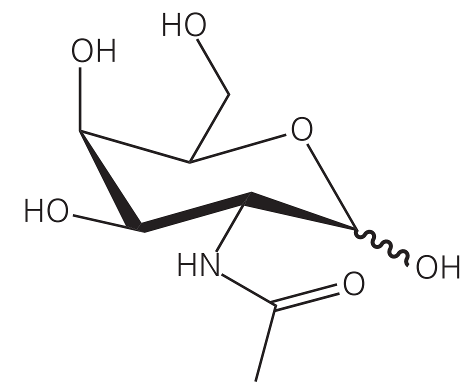
Table 3.1 Abbreviations used for the names of the sugars that commonly occur in oligosaccharides.

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

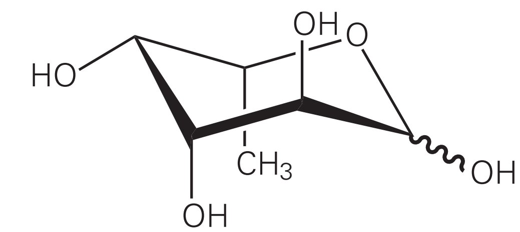
These sugars commonly occur in oligosaccharides attached to proteins



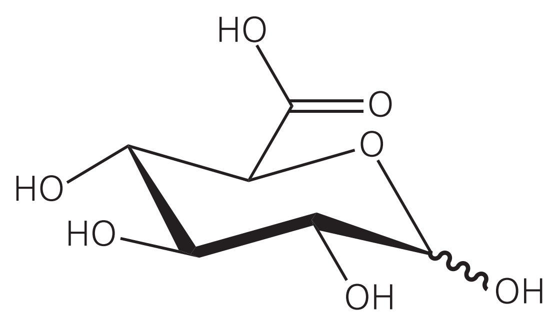
N–acetylglucosamine
(GlcNAc)



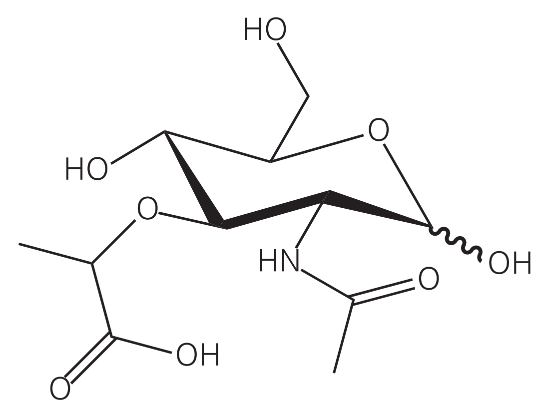
N–acetylgalactosamine
(GalNAc)



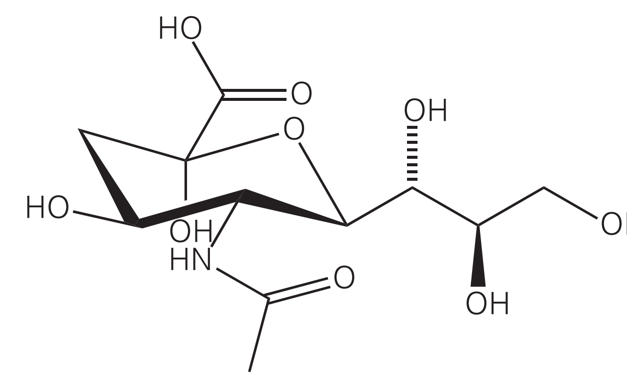
fucose
(Fuc)



glucuronic acid
(GlcA)



N–acetylmuramic acid
(MurNAc)

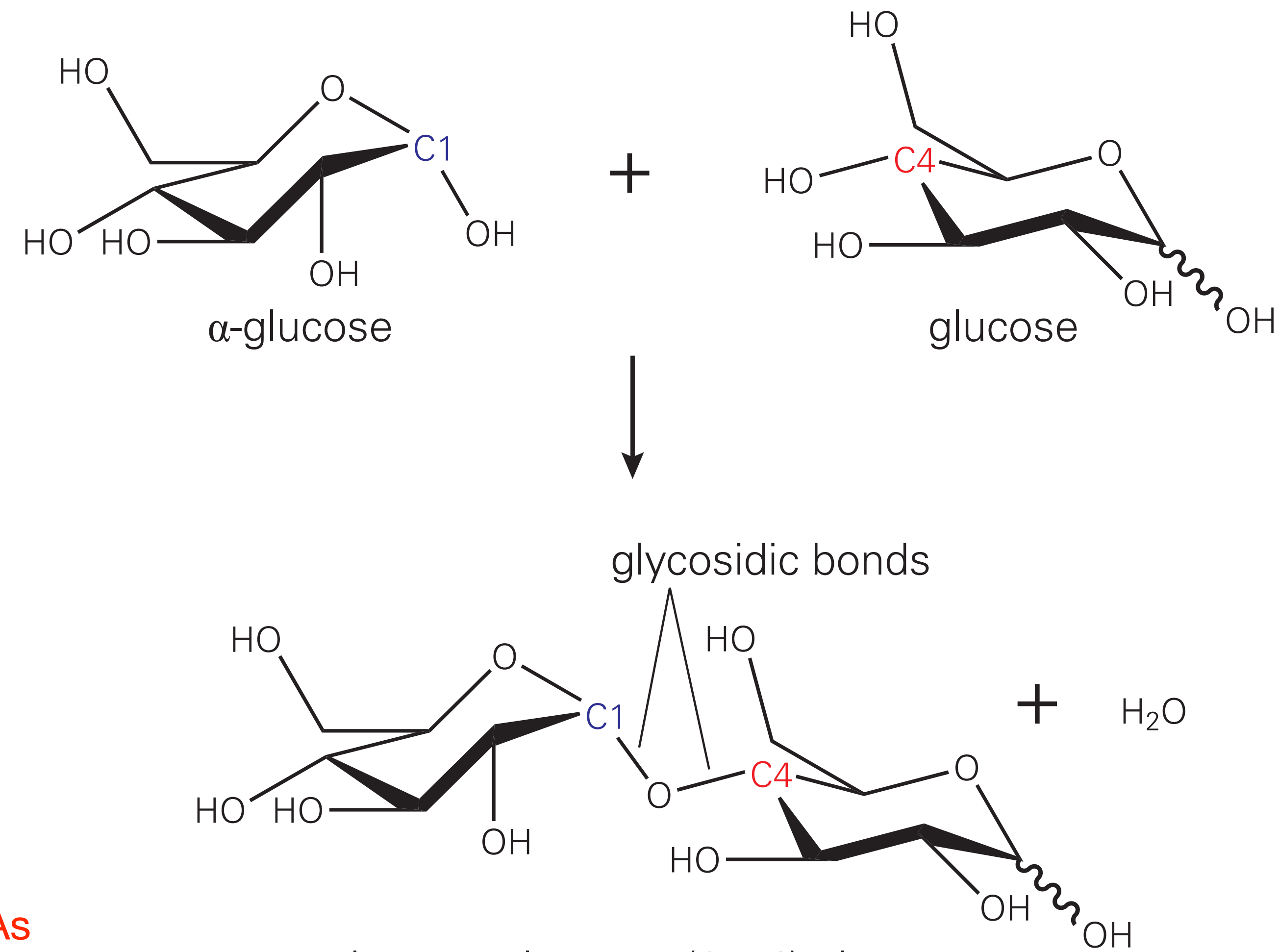


sialic acid
(Sia)

Glycans form polymeric structures that can have branched linkages

Glycosidic linkage

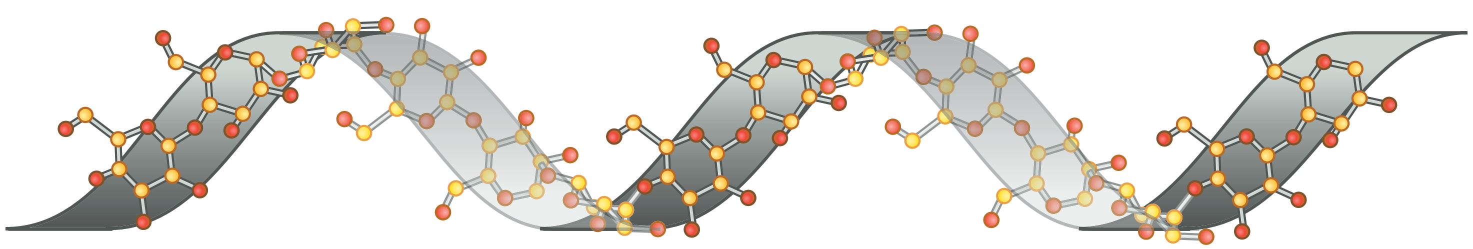
Glycosidic linkages are the attachments between sugars in polysaccharides. They are specified by the atom linked on each sugar and the orientation of the bond to the ring (when needed). These linkages are often called glycosidic bonds.



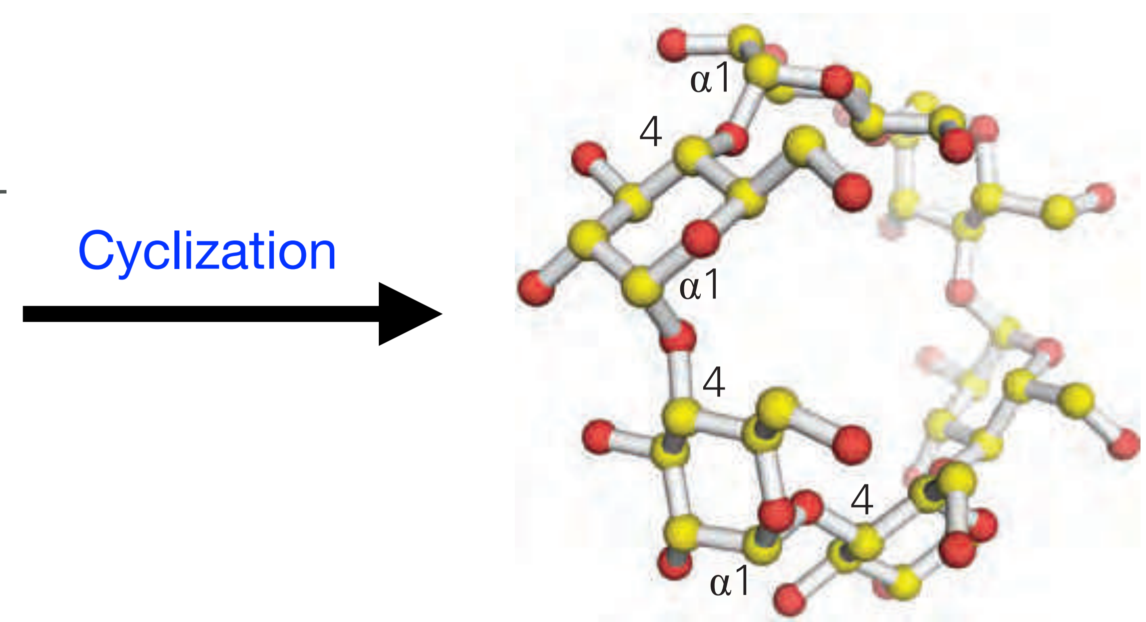
maltose = glucose-α(1→4)-glucose

All these O-H groups can be involved in a glycosidic linkage

A distinction of glycans from proteins/NAs where polymerization only happens through back-bond linkages



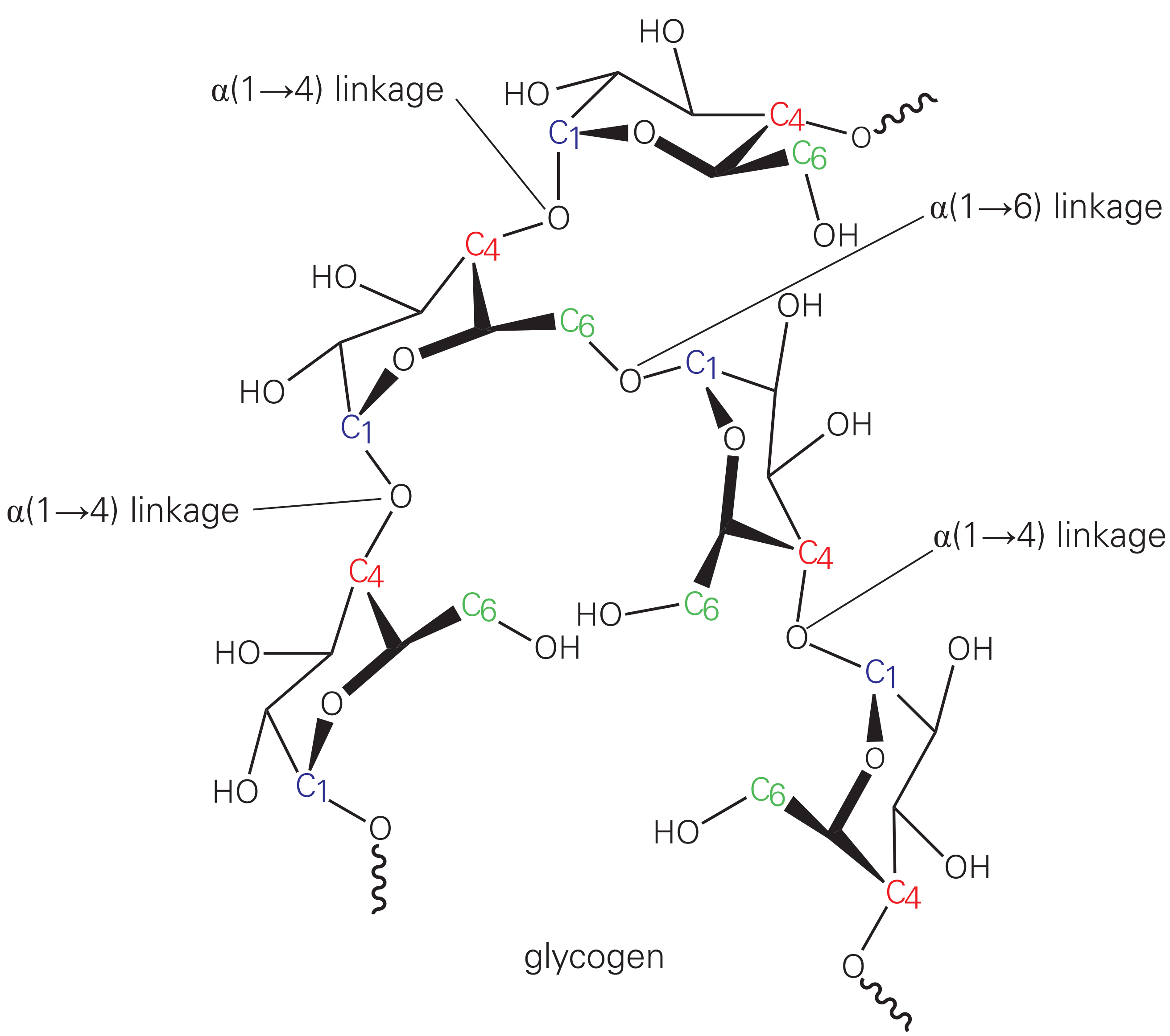
amylose

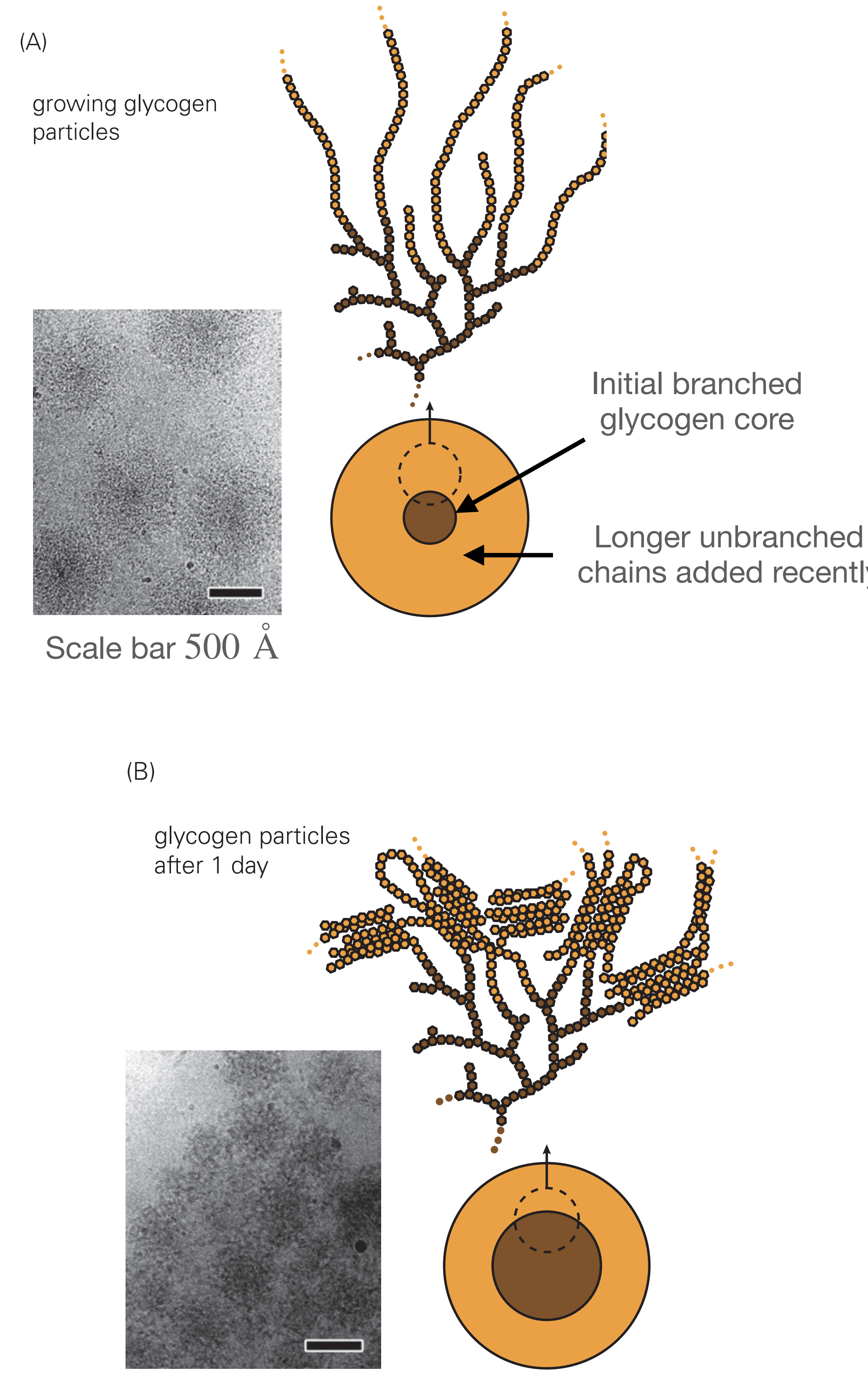


cyclodextrin

Sequential monomers linked by glycosidic bonds creates a spiral polymer

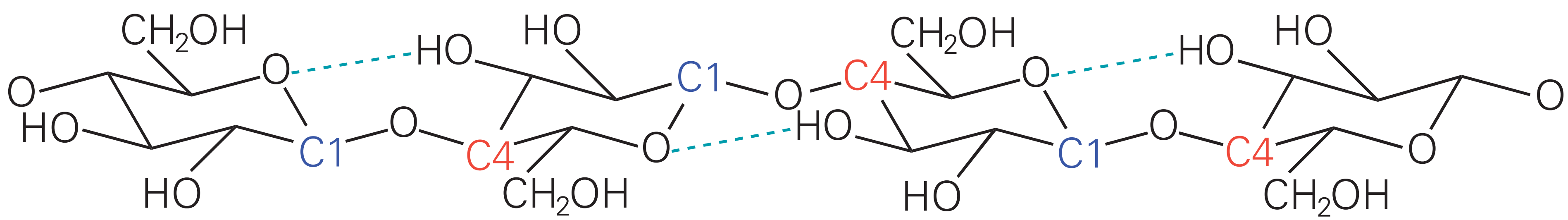
Dramatic polymeric forms of glucose: glycogen





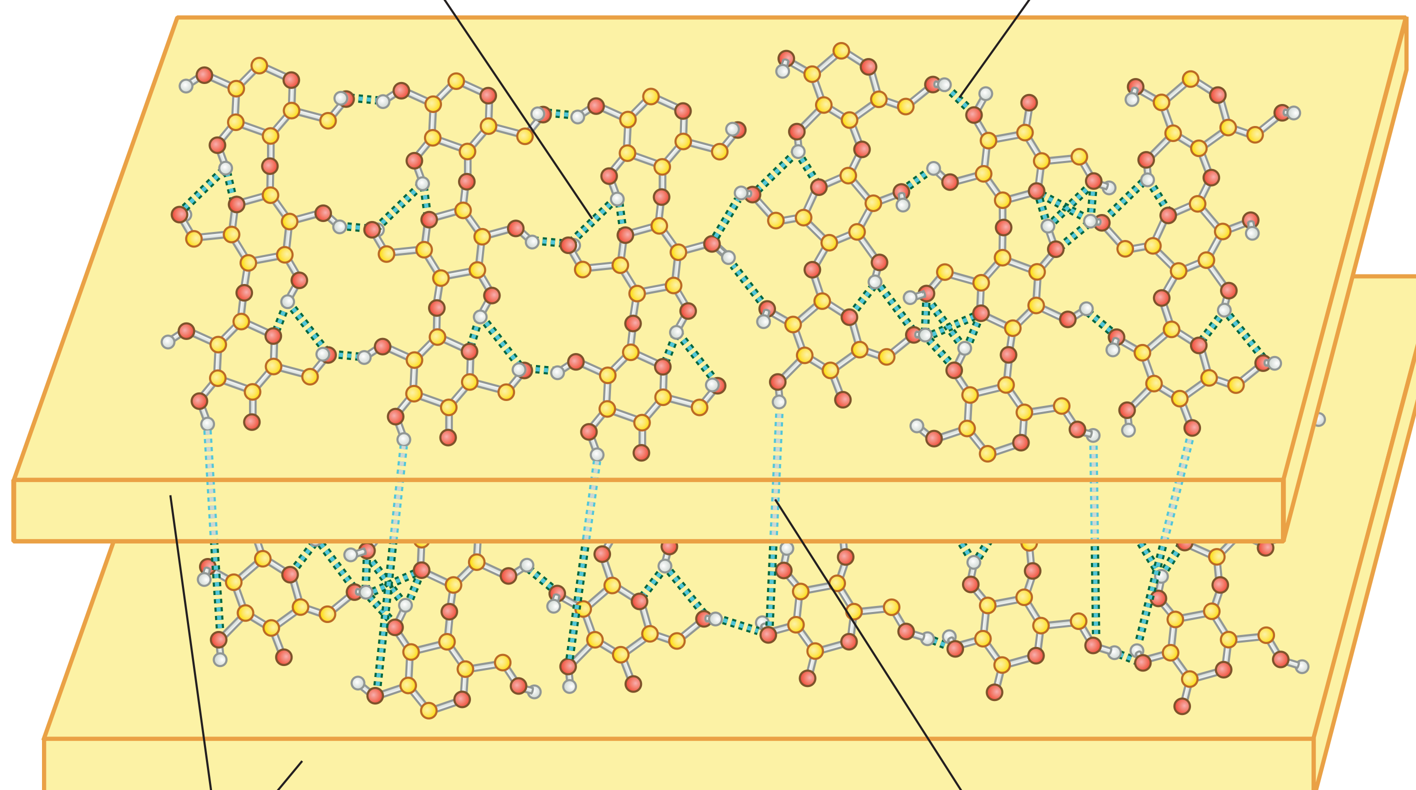
- Primary energy storage compound in animal cells
- glycogen has both $1 \rightarrow 4$ & $1 \rightarrow 6$ linkages
- one glucose residue in every 12 has a branch
- One polymer has about 50000 glucose units
- Chain growth is controlled by enzymes

Dramatic polymeric forms of glucose: cellulose



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

- Cellulose is made through $\beta-$anomer of glucose
- This changes the properties dramatically!
- Cellulose has a sheet-like structure stacked on top of another while glycogen is gel-like
- Cellulose is stabilized by both intra- and intermolecular as well as inter-sheet H-bonds
- Glycogen is easily metabolized while cellulose is almost unbreakable and supports cell walls in plants
- Cellulose is the most abundant biopolymer in nature



Glycans may be attached to proteins

The process of attaching carbohydrate to a protein is called protein glycosylation

N-linked glycosylation

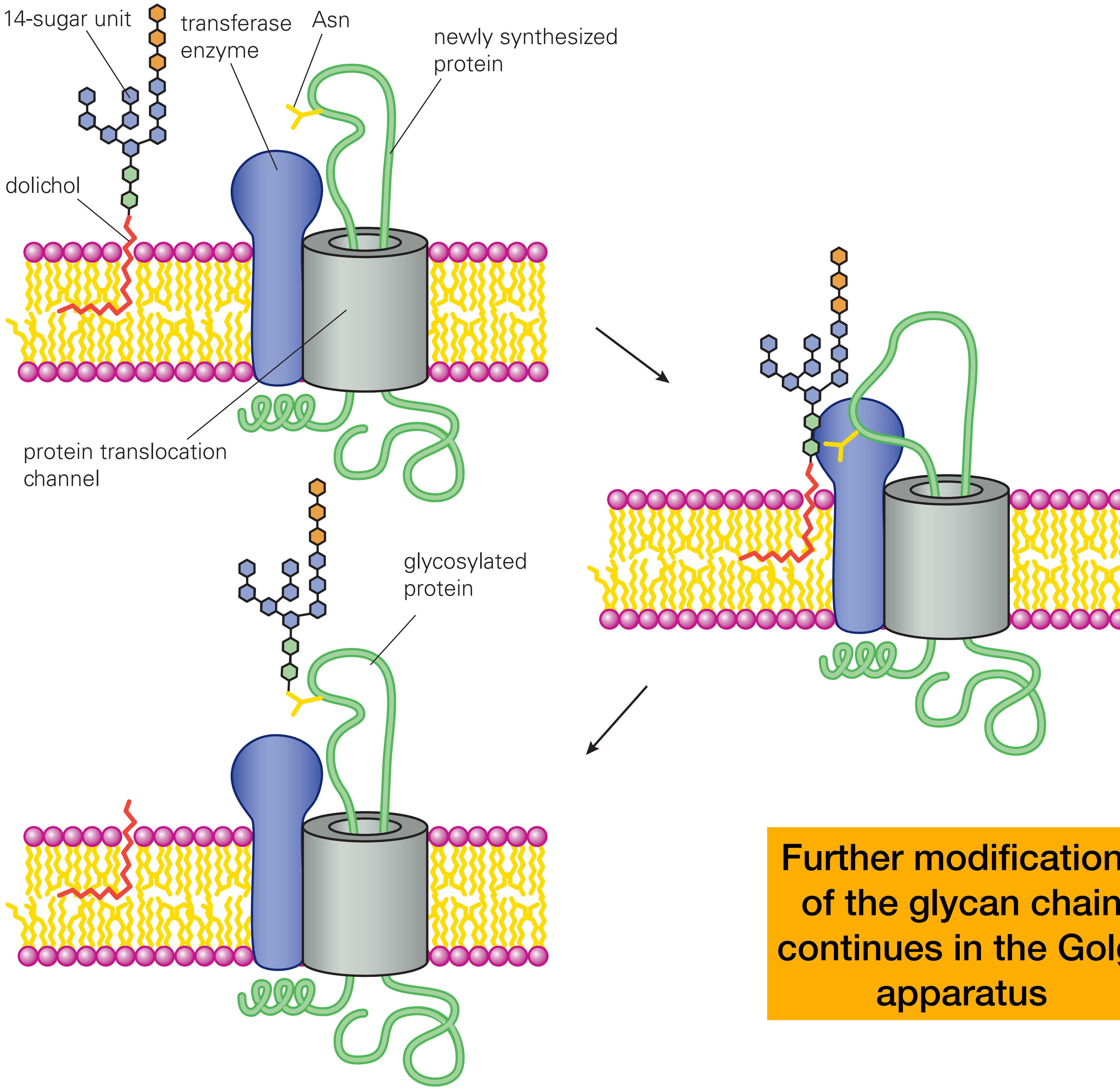
glycan linked to the sidechain amide of Asn

O-linked glycosylation

glycan linked to the sidechain hydroxyl of Ser or Thr

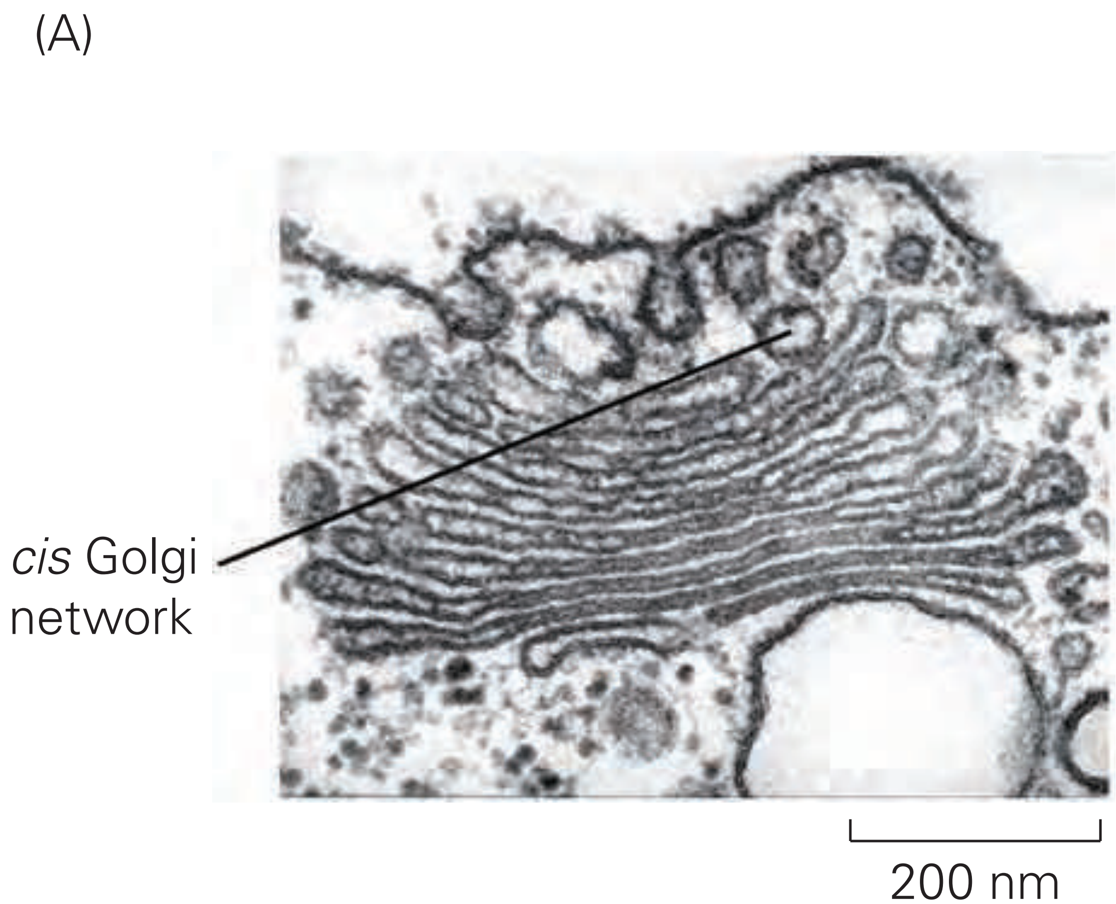
- All secreted or membrane-bound proteins are glycosylated through polysaccharides
- Cytosolic proteins are rarely glycosylated and then mostly by monosaccharides
- About 90% glycosylation are N-linked
- Initial step of N-glycosylation starts as the protein moves through a translocating channel on the ER membrane

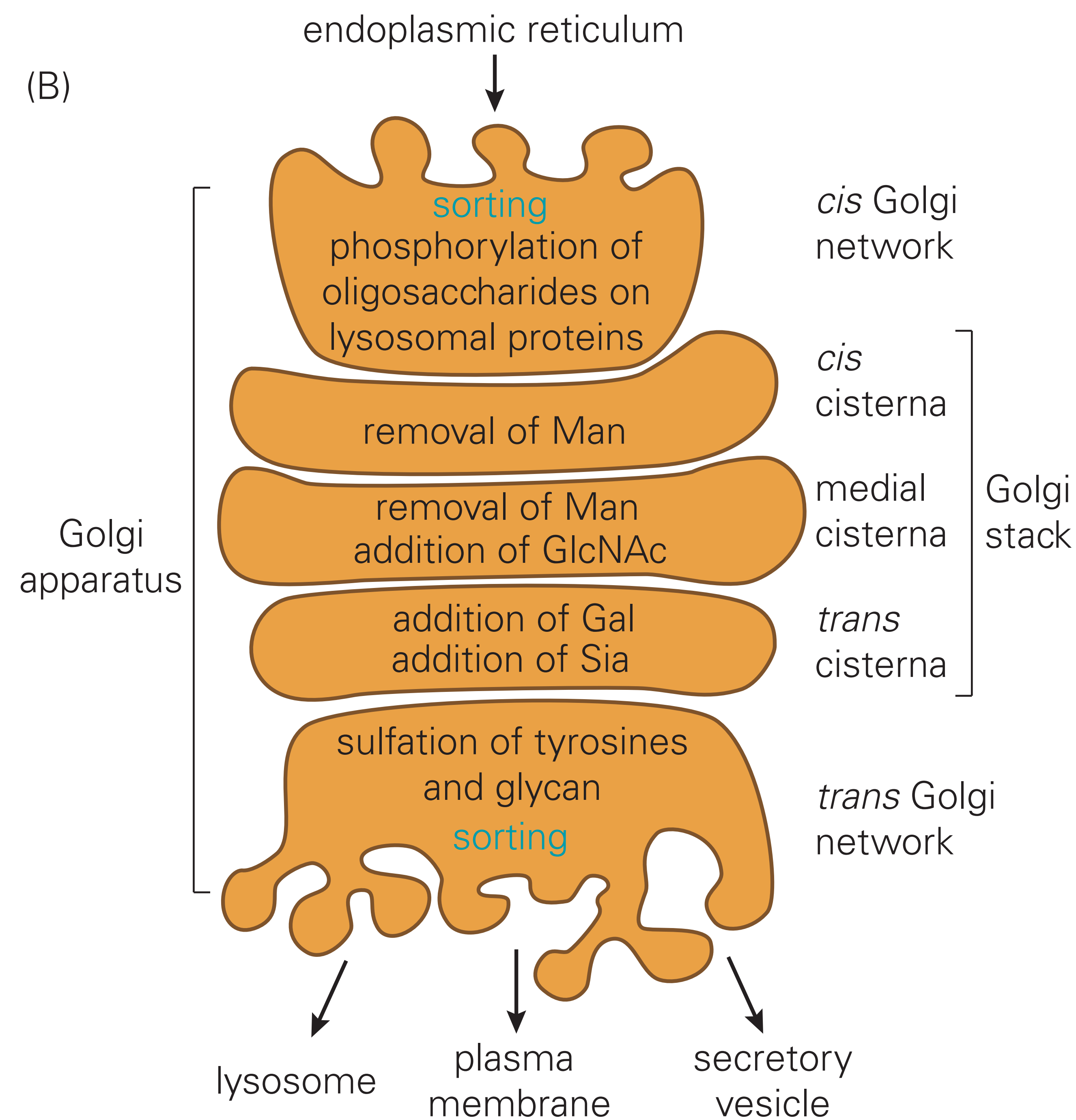
Glycosylation of a membrane protein starts at ER



Further modifications of the glycan chain continues in the Golgi apparatus

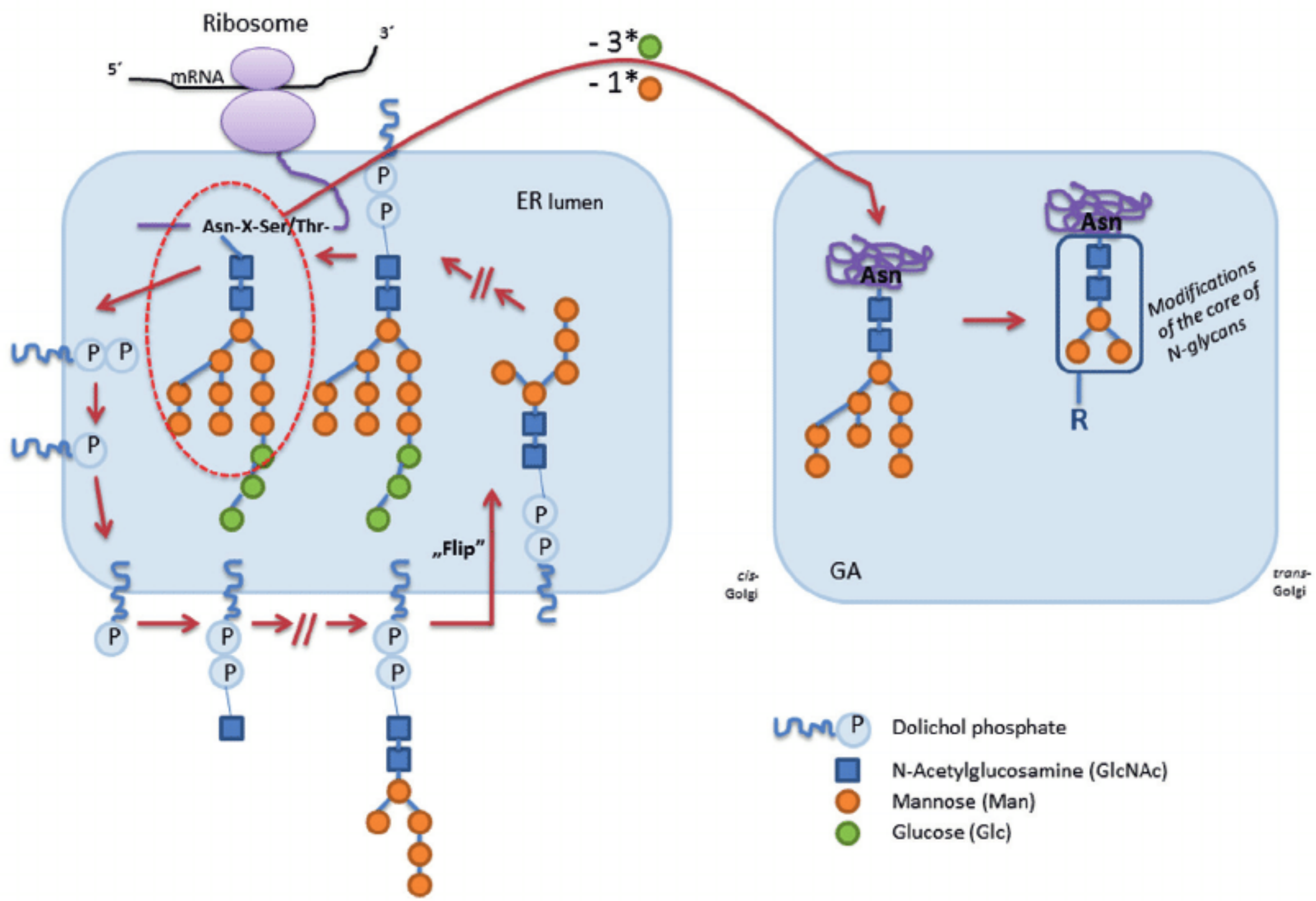
Glycoprotein processing in the Golgi apparatus





- O-linked oligosaccharides are formed almost entirely in the Golgi apparatus
- The class of enzymes carrying out the glycosylation—the glycosyl transferases
- They enzymes catalyze the addition of simple sugar monomers, like glucose or mannose to Ser or Thr residues
- The sugar chain then grow by one sugar at a time

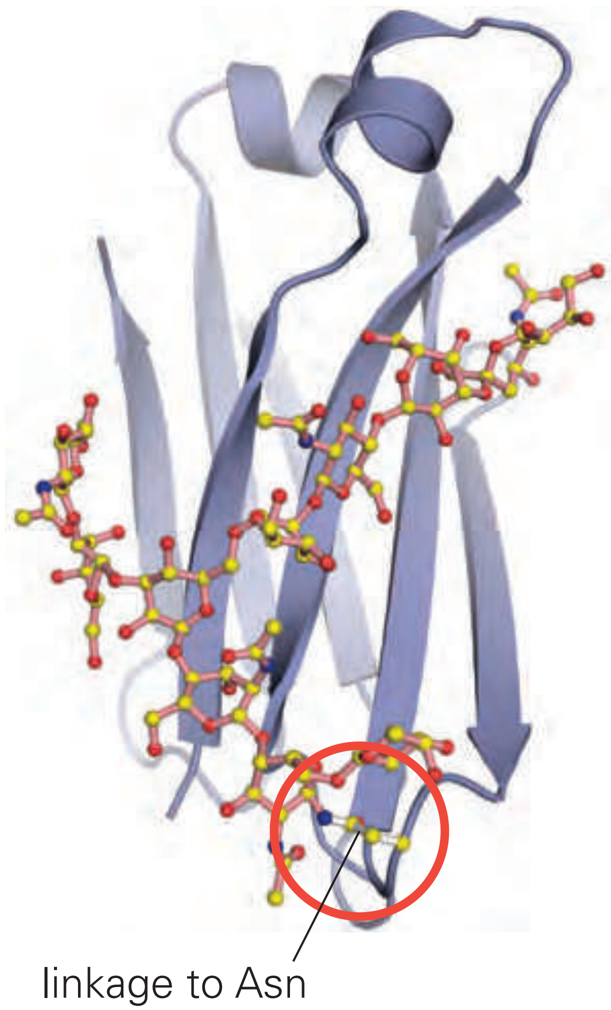
The decoration of proteins with glycans is not templated



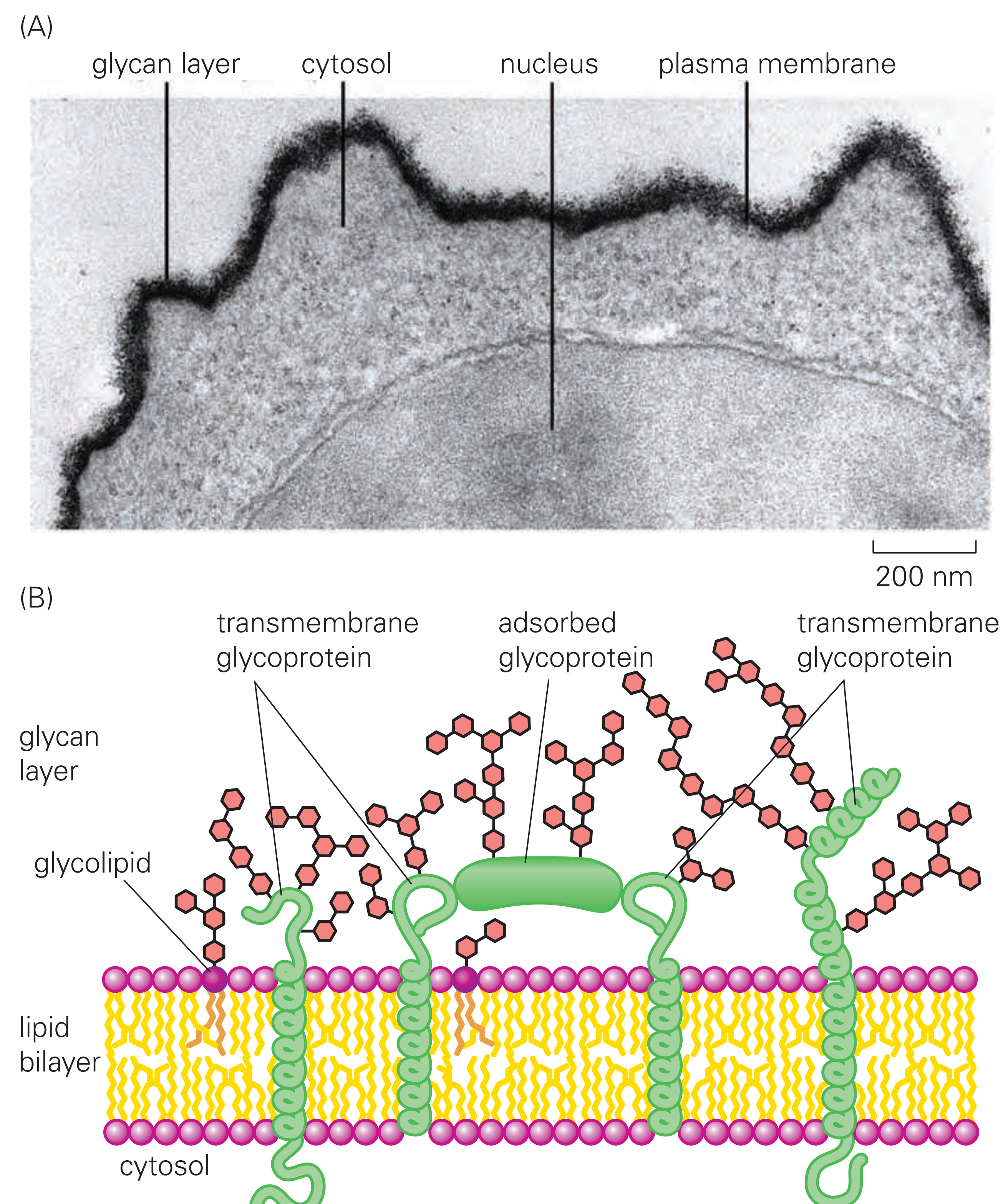
- No stored code for glycan synthesis - unlike protein or nucleic acids
- Structures of oligosaccharides synthesized by any particular cell at any given time is determined by enzyme type, concentrations, substrate specificities, and spatial localization
- Glycans synthesized in a particular location share the same core structure but vary in the finer details of their structure
- The control of enzyme identity and localization does lead to reproducible products under defined conditions, but fine structure variations still occur.

Glycosylated proteins are quite heterogeneous

Glycan modifications alter the properties of proteins



- Glycan chain can cover a large surface area on the protein
- Most of the cell surface proteins are glycosylated that are part of the glycan layer also called *glycocalyx* in some cells
- Majority of the cell surface presented to the surroundings is made of glycan
- Cell-cell interactions are mediated through protein-glycan interactions



Glycan modifications alter the properties of proteins

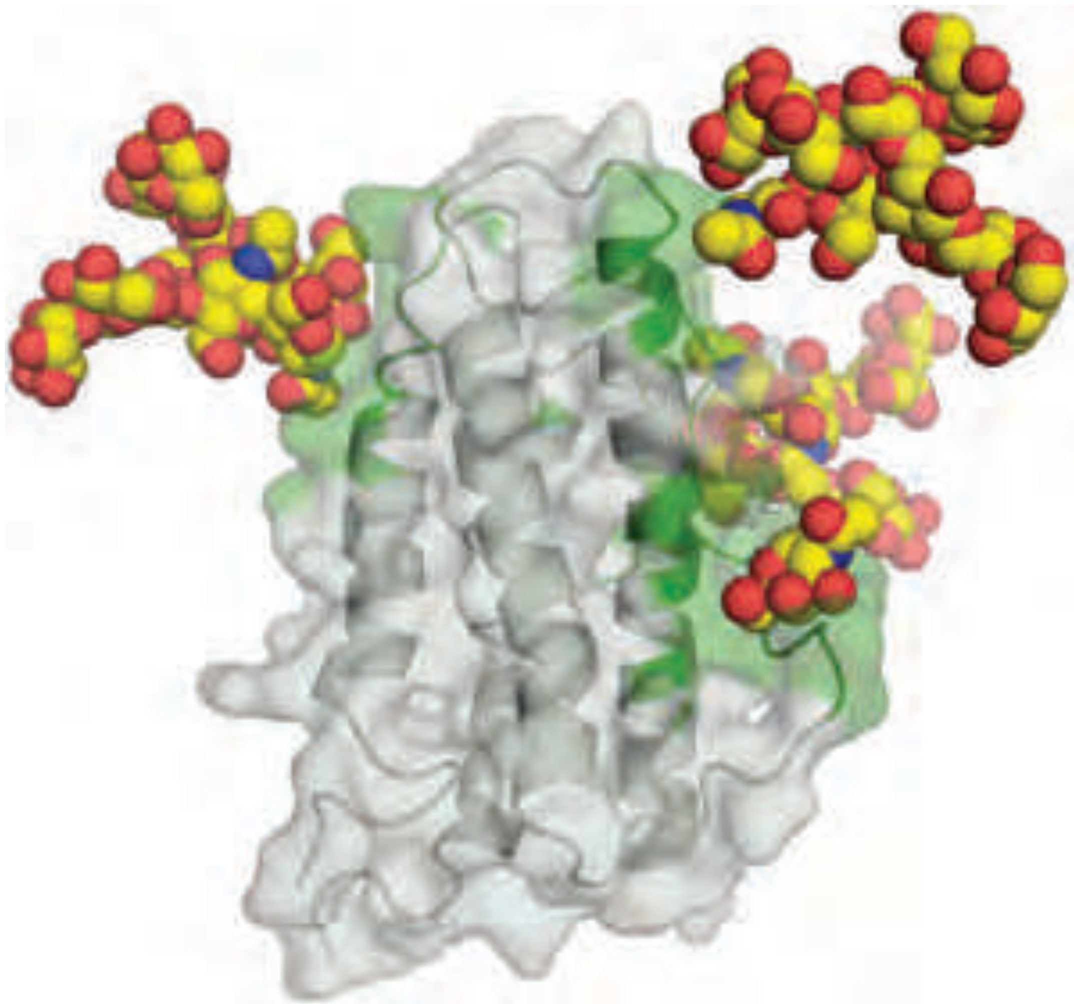


Figure 3.24 The structure of the human protein hormone erythropoietin. Each erythropoietin molecule has three N-linked complex carbohydrates and one O-linked GalNAc residue. Regions of the protein surface that interact with the sugars are colored *green*. (PDB code: 1BUY; glycans modeled by R.J. Woods.)

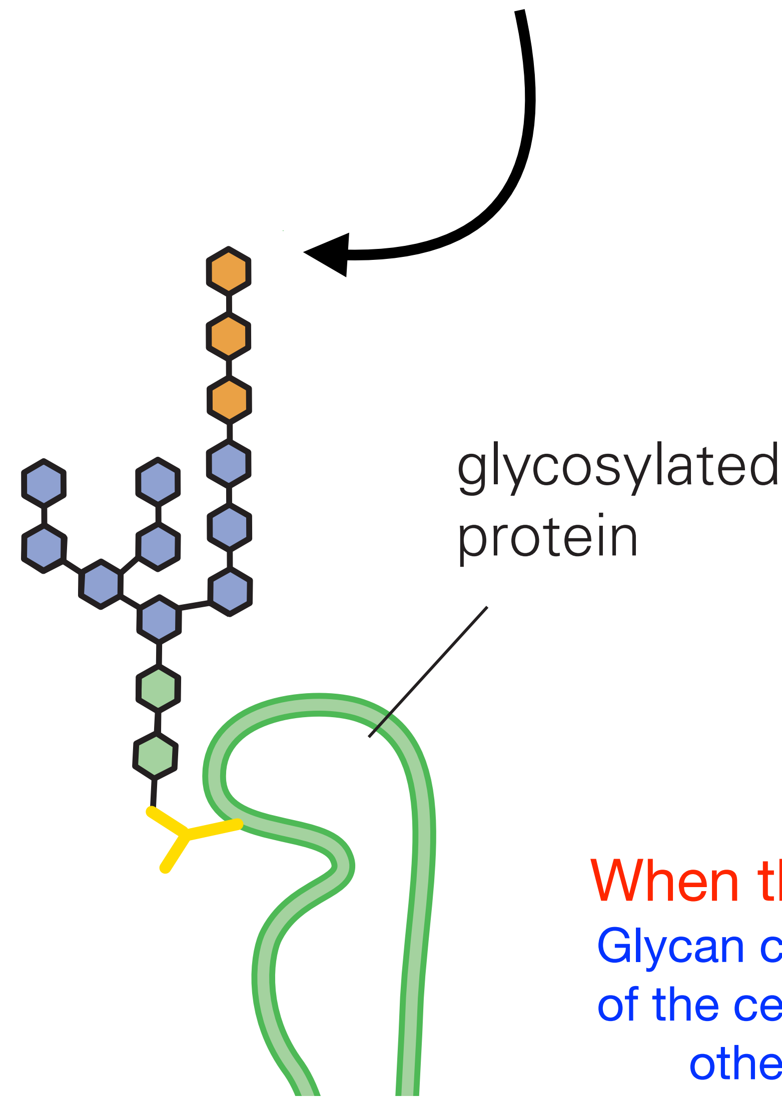
Activity of proteins, like erythropoietin increases with extent of glycosylation

The 'big' glycan chains protect the protein against degradation

The protease enzymes 'struggle' to access the protein backbone for cleaving it!

Glycosylation is important for intracellular trafficking of proteins

The glycan chain acts as an "address label"



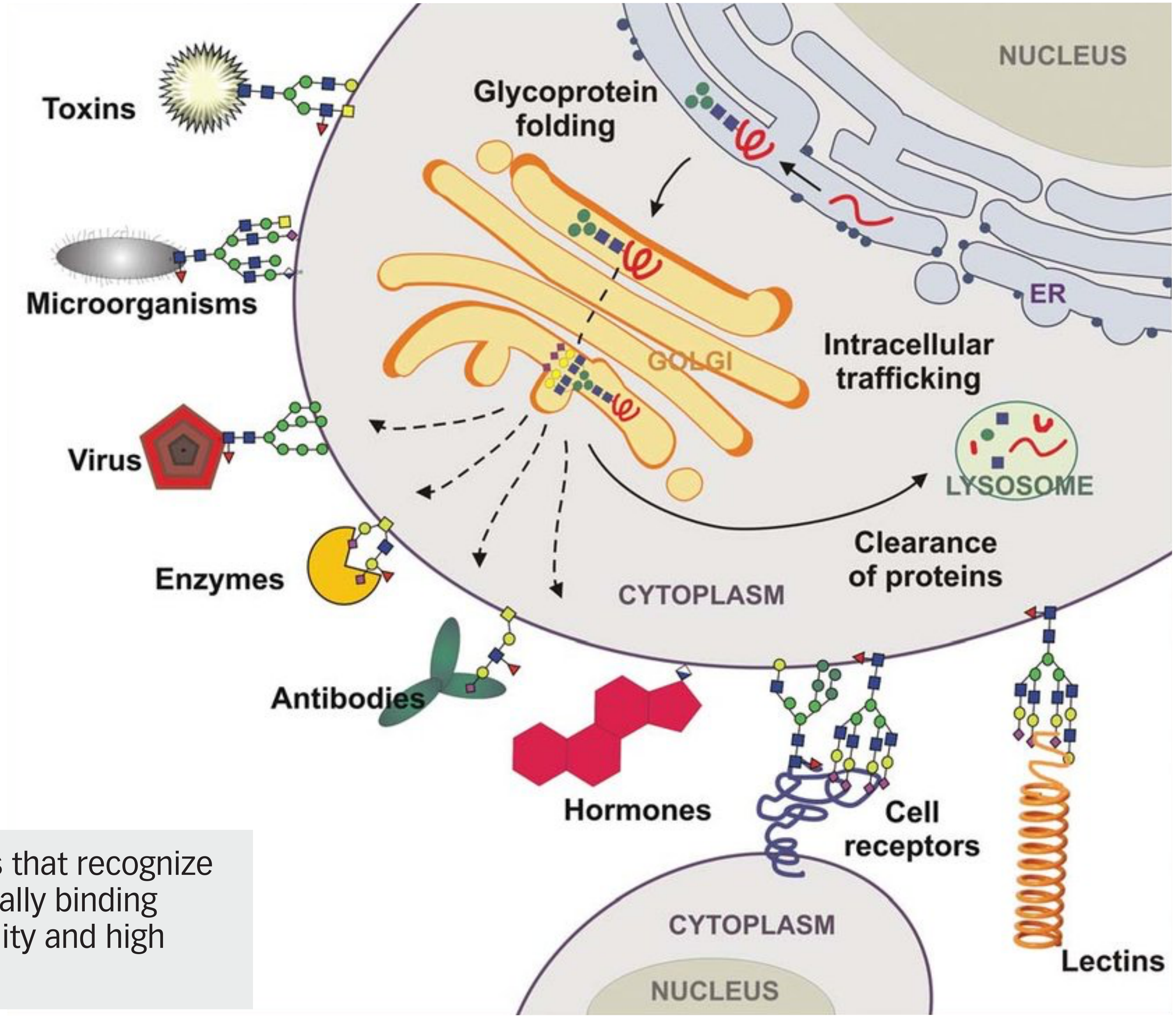
Inside ER

Glycan chain is an indicator of progress of folding of the protein and determines when a protein is allowed to move to the next destination

When the protein is ready to move

Glycan chain is an indicator of which part of the cell the protein needs to go - some other organelle or the membrane

Protein-glycan interactions are important in cellular recognition



Lectins

Lectins are proteins that recognize specific sugars, usually binding with moderate affinity and high specificity.

The affinity is boosted by multivalent interactions with many glycan chains

Glycans present on red blood cells define the "blood groups"

Cell-surface glycoproteins can also be recognized by antibodies in the immune system

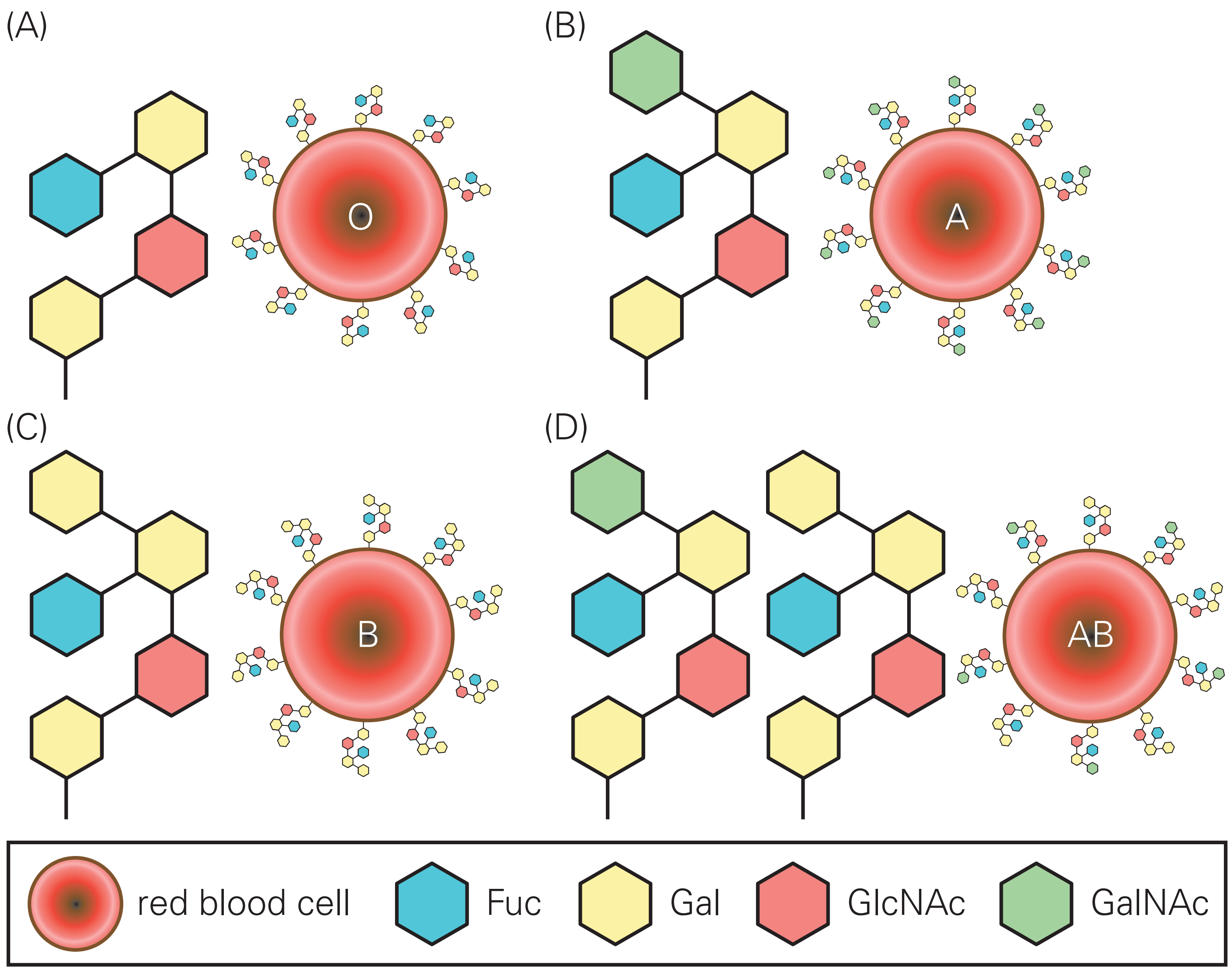


Figure 3.26 Glycans that are attached to proteins on the surface of red blood cells. These glycosylation patterns define an individual's blood type. (A) The O blood type has a non-antigenic tetrasaccharide that is common to the surface antigens of the other blood groups. A-type (B) and B-type (C) individuals produce oligosaccharides with an additional Gal or GalNAc residue, respectively. (D) AB-type individuals produce a mixture of the A- and B-type oligosaccharides.

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Glucuronic acid	GlcA