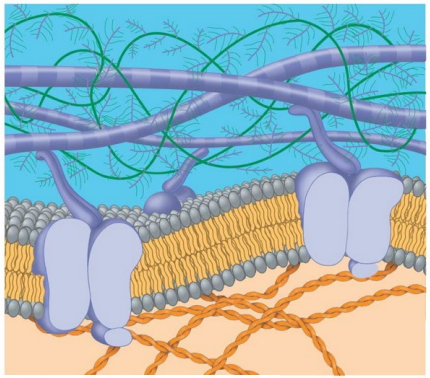
The Extracellular Matrix, Polymers and Biomimetic Materials

Jurica Bauer

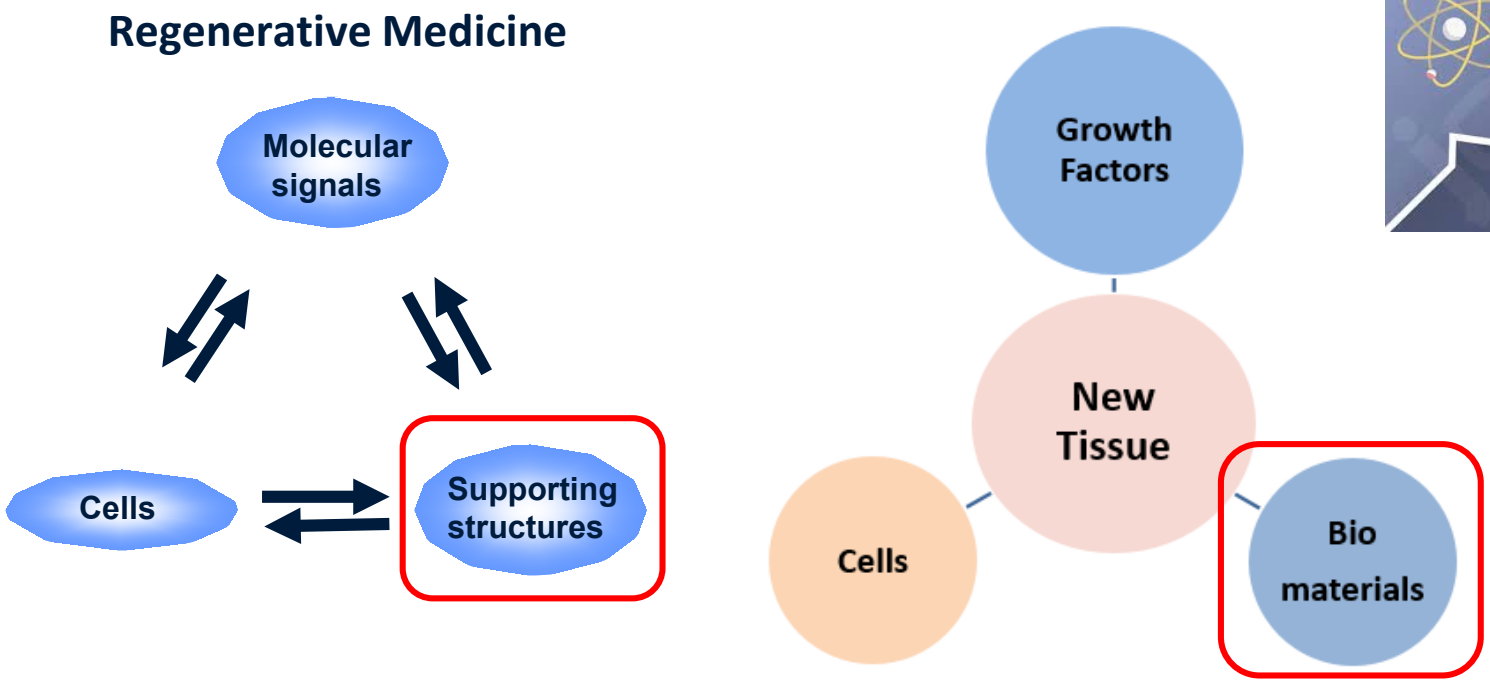
Bachelor RMT Experience Day

22nd November 2023

Maastricht



The Three "Pillars" of Regenerative Medicine (RM)



The Extracellular Matrix, Polymers and Biomimetic Materials

What is extracellular matrix (ECM)?

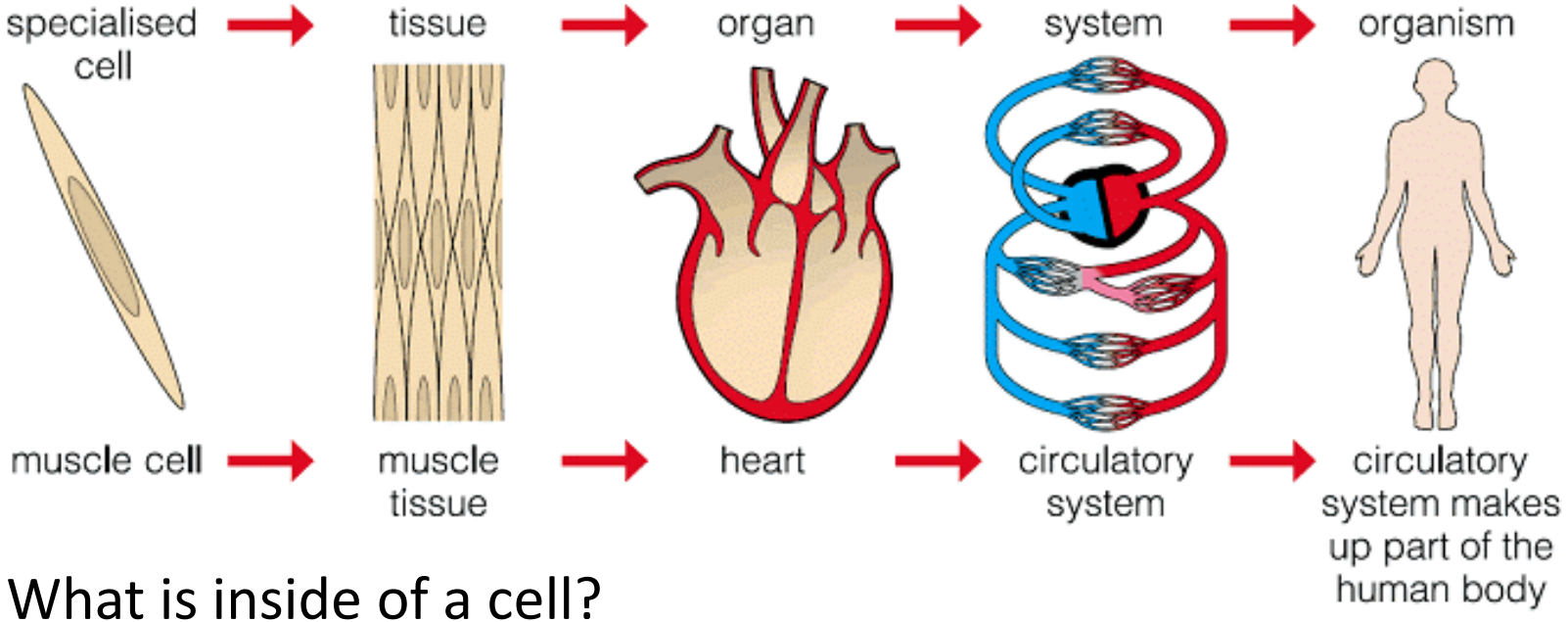
What are polymers?

What are biomimetic materials?

Objectives

- To explain the nature, structure, and function of the major components of the ECM
- To illustrate how these basic building blocks can create highly specialized environments
- To recognize polymer structures and properties
- To explain how materials scientists try to create ECM-like environments
- To identify current trends in ECM-like materials

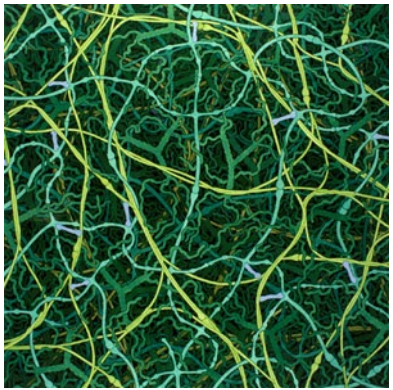
From Cells to Tissues and Organs

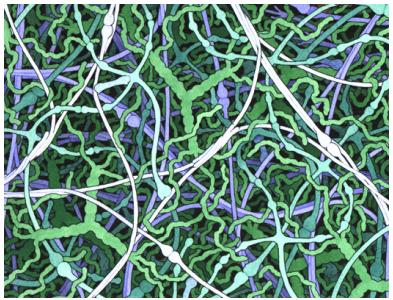


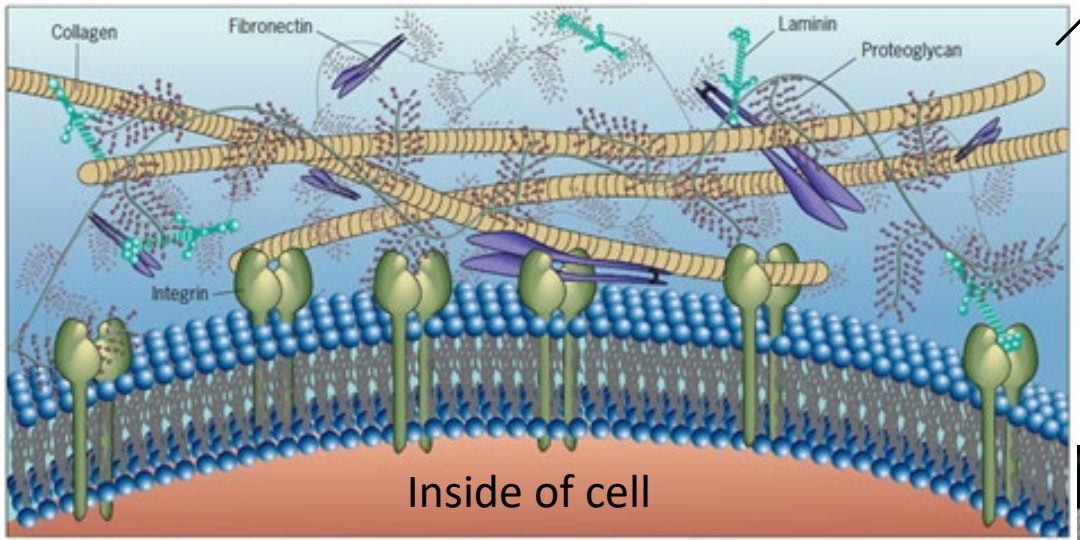
What is inside of a cell?

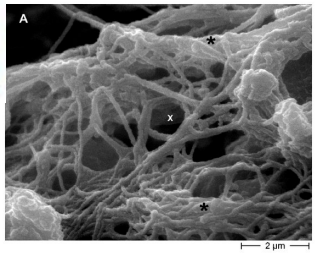
What is outside of a cell?

Cellular Environment





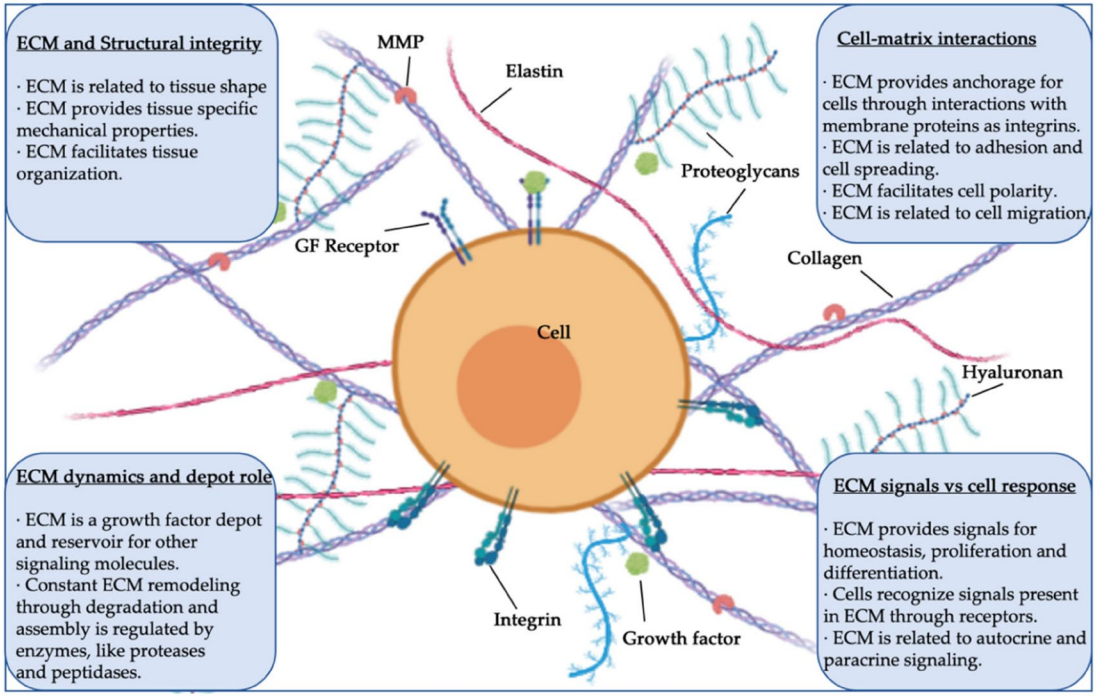




https://www.khanacademy.org/science/biology/structure-of-a-cell/cytoskeleton-junctions-and-extracellular-structures/v/extracellular-matrix; drawing © David Goodsell; diagram adapted from Cell and Molecular Biology Concepts and Experiments by Karp, 2010; SEM image: https://doi.org/10.1155/2015/542687

Extracellular Matrix

- Structural Support
- Cell Adhesion
- Cell Signalling
- Regulation of Cell Behavior
- Storage of Bioactive Molecules
- Tissue Development and Repair



Int. J. Mol. Sci. **2020**, *21*(15), 5447; https://doi.org/10.3390/ijms21155447

Extracellular Matrix

- A complex and dynamic network of proteins and carbohydrates that provides structural and biochemical support to the surrounding cells and enables survival and proliferation

  - Proteins (collagen, elastin)
  - Polysaccharides (hyaluronic acid)
  - Proteoglycans (aggrecan, perlecan, etc)
  - Large Glycoproteins (laminins, fibronectin, etc)

The exact nature and ratios of these molecules differ per tissue.

Composition of ECM

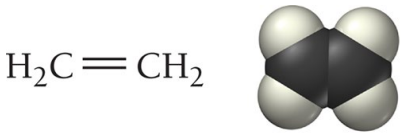
What are:

- proteins
- carbohydrates and polysaccharides
- glycoproteins
- proteoglycans

- **polymers**

Polymers

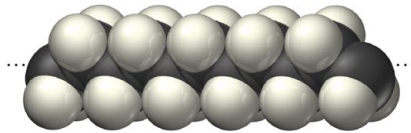
- **Polymers**—very large molecules made by repeated linking together of monomers
  - **Monomers**—small molecules



Monomer

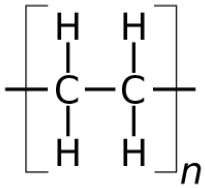
Ethene or ethylene

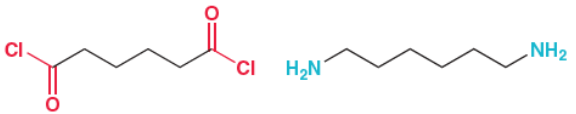
$\cdots CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2\cdots$



Polyethylene

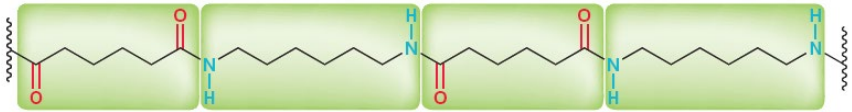
Polymer



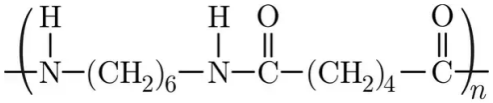


A diacid halide

A diamine



Nylon 6,6



Nylon 66

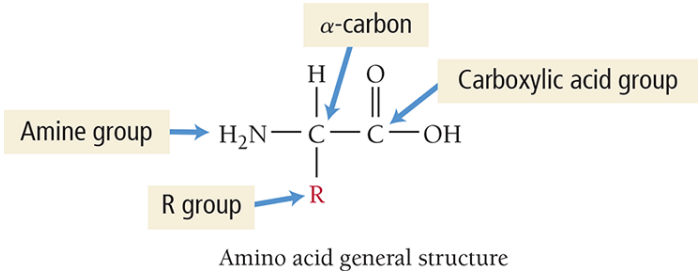
Polymers

- **Natural polymers** — polymers found in living organisms, like starches, proteins, and DNA
- **Synthetic polymers** — polymers made in a lab
  - Plastics, Styrofoam cups, nylon rope, Plexiglas

High molecular weights!

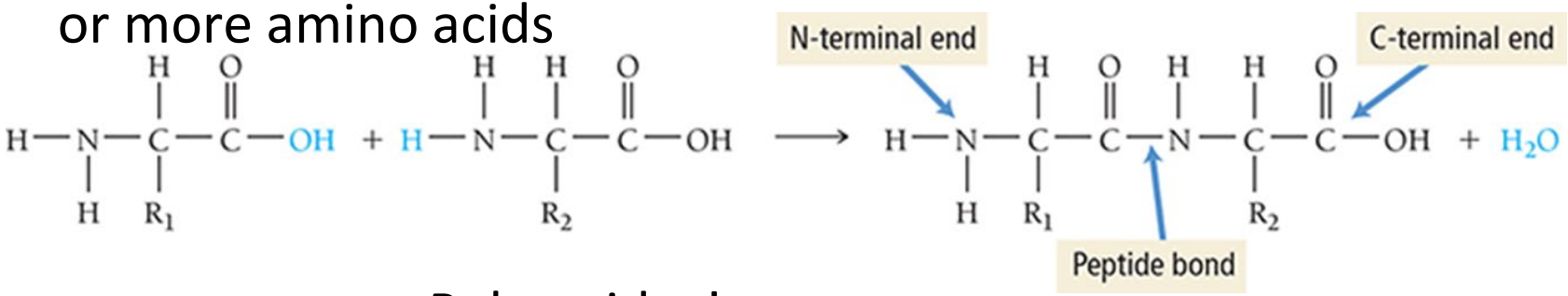
Peptides and Proteins

- **Amino acids** link together via reaction of the amine end of one amino acid with the carboxylic end of another—a **peptide** (amide) **bond .**



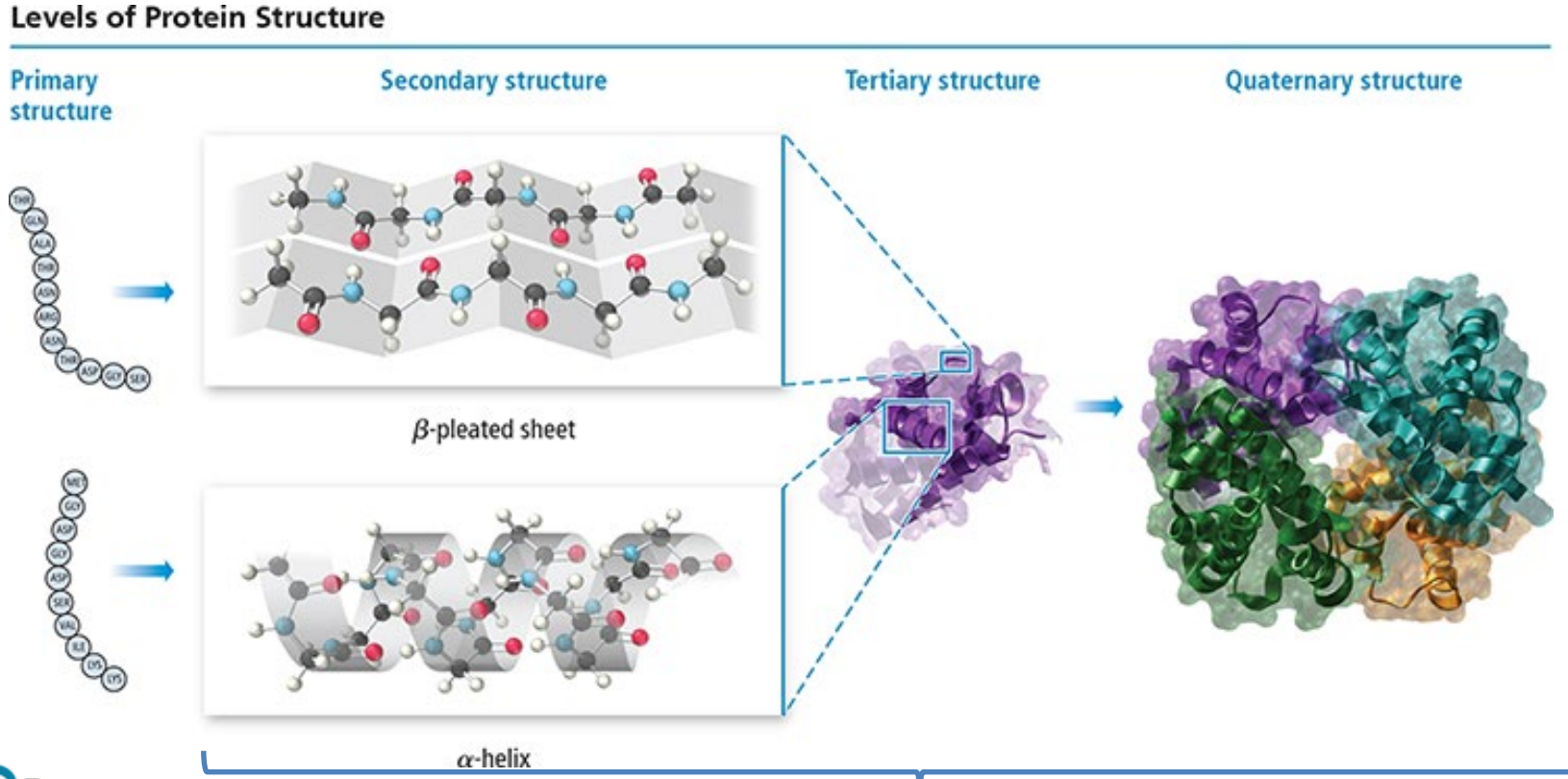
Amino acid general structure

- **Polypeptide**—molecule made of three or more amino acids



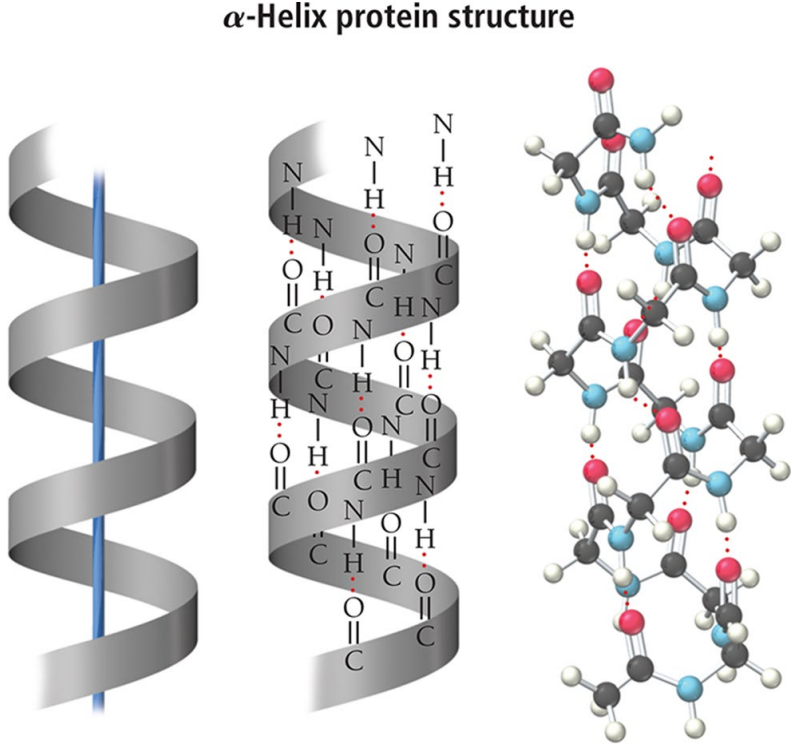
Polyamides!

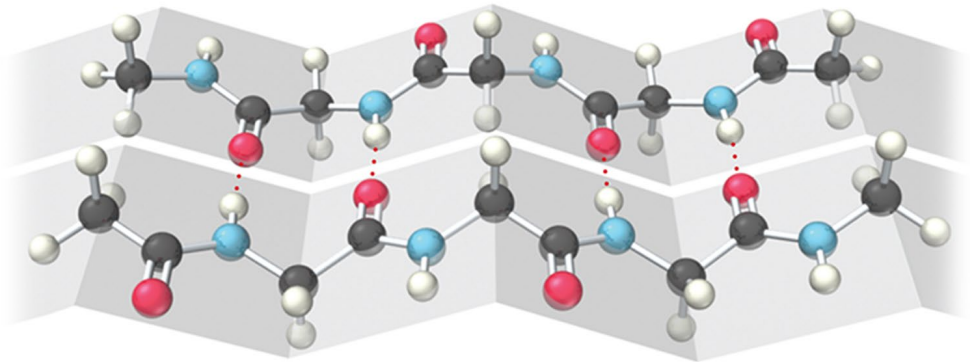
Protein Structure



Supramolecular interactions!

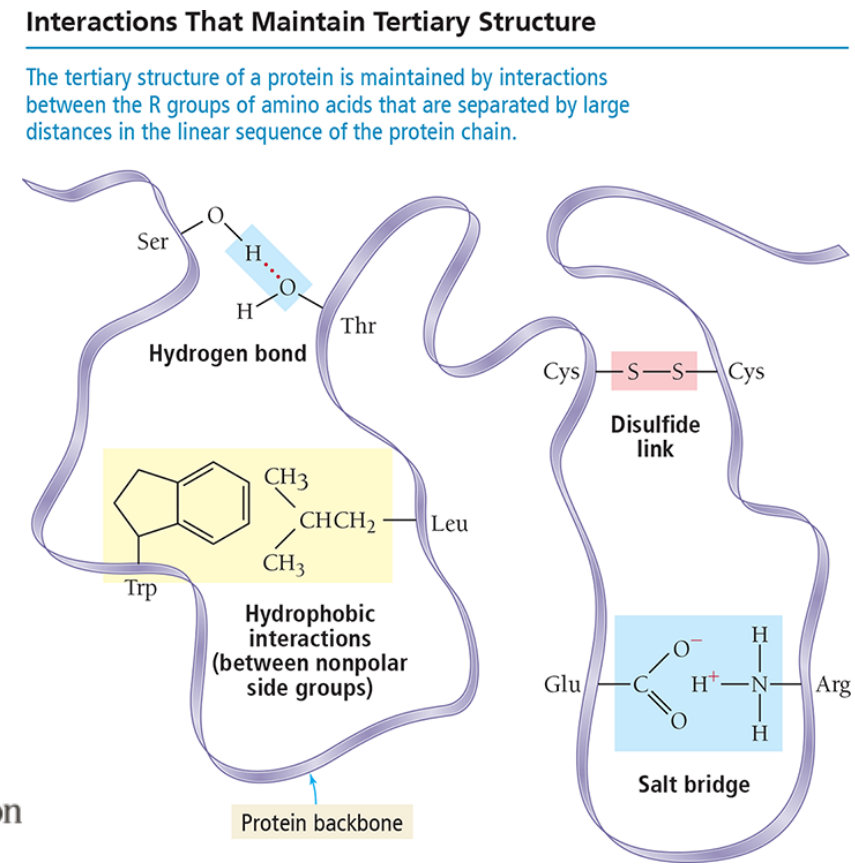
Protein Structure



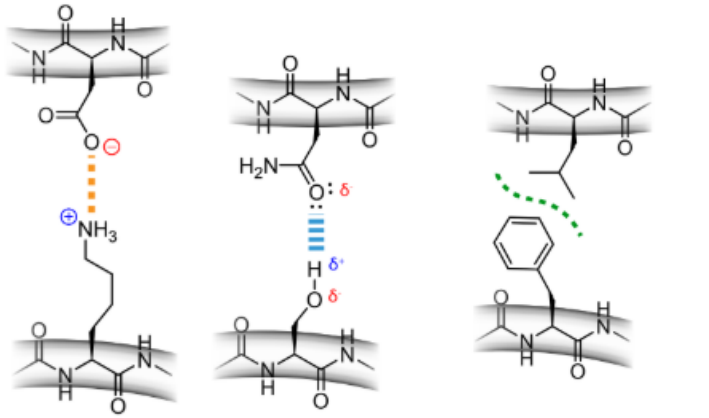


Hydrogen bonds!

Protein Structure

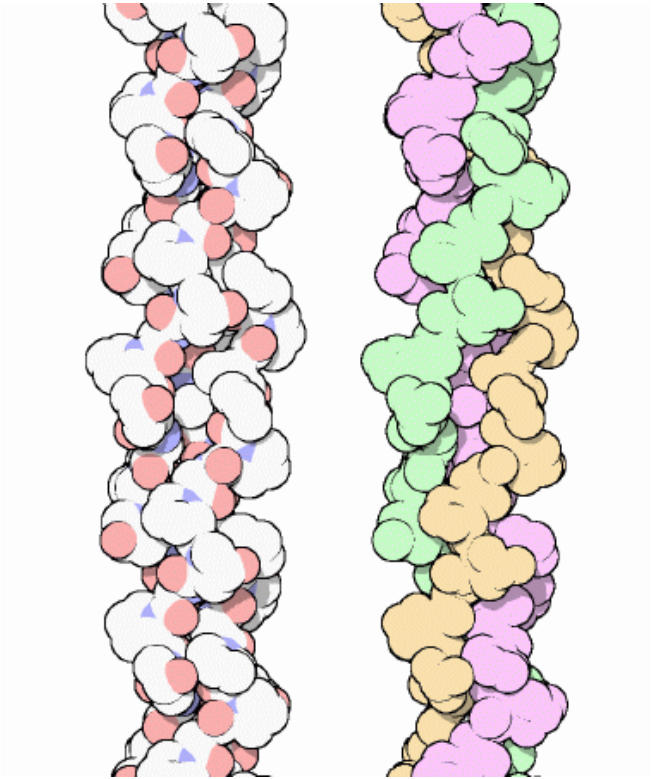


Supramolecular interactions



https://www.labxchange.org/library/items/lb:LabXchange:6b3379dd:html:1

Collagen in the ECM

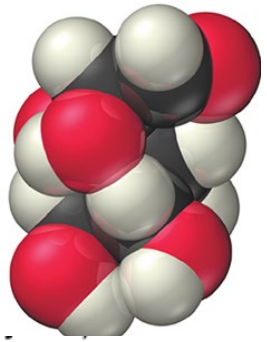


About 25% of all the protein in your body is collagen. Collagen is a major structural protein, providing strength to tendons, bone, and support to organs. It is the most abundant protein in the ECM.

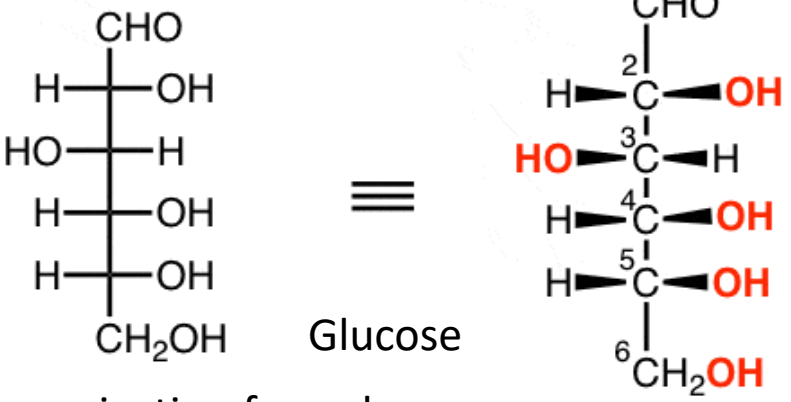
The “triple helix” structure of collagen is an excellent example of supramolecular organization.

Collagen when cooked, denatures and forms gelatin, a popular ingredient in cooking, and our most common hydrogel.

Carbohydrates



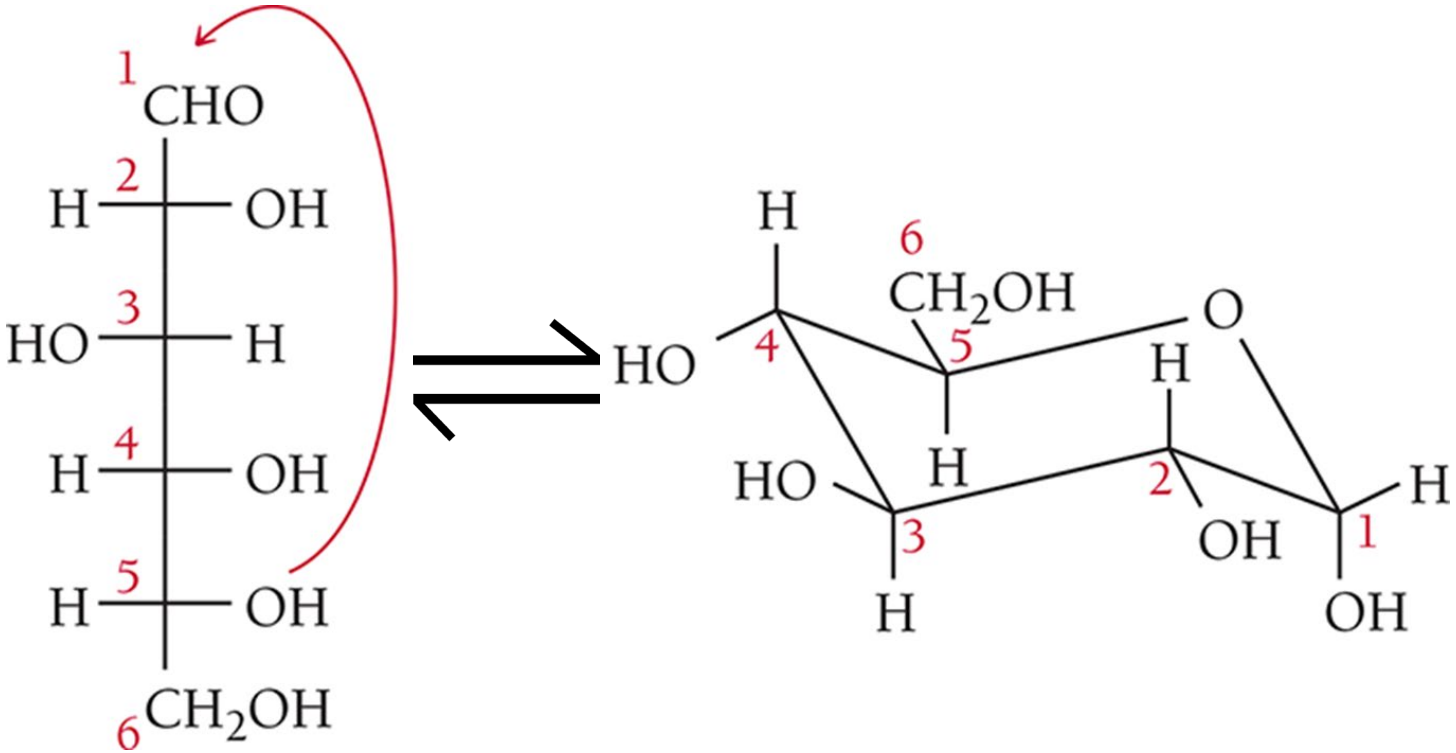
- Carbon, hydrogen, and oxygen $(CH_2O)_n$
- Polyhydroxycarbonyls that have many OH and one C=O
  - Aldose when C=O is aldehyde
  - Ketose when C=O is ketone
- The many polar groups make simple carbohydrates soluble in water
  - Blood transport



Fischer projection formula

https://www.masterorganicchemistry.com/2018/01/25/converting-a-fischer-projection-to-a-haworth-and-vice-versa/

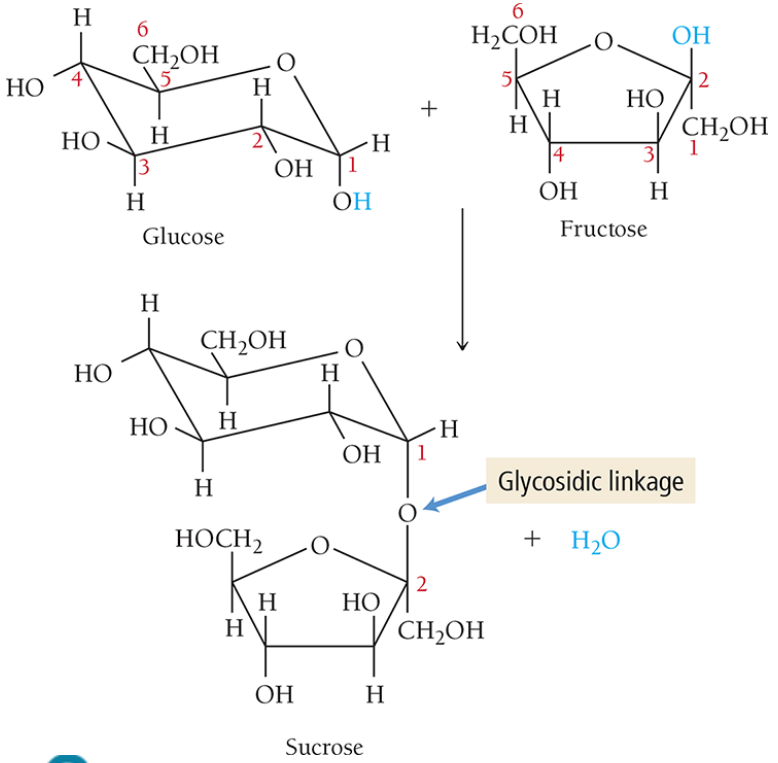
Carbohydrates

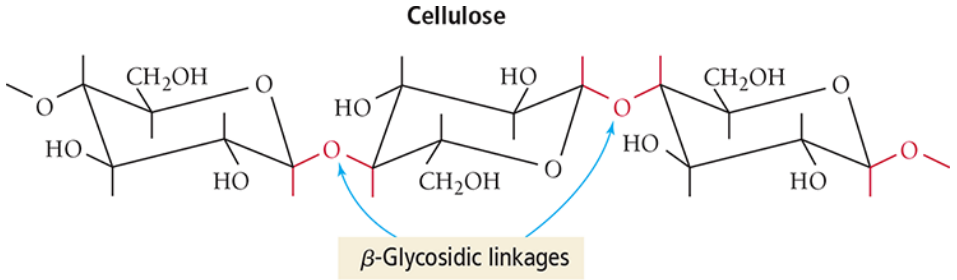


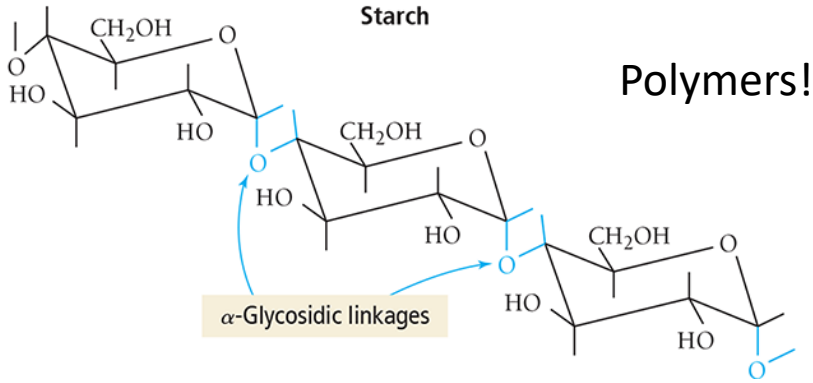
Carbohydrates

- **Monosaccharides** cannot be broken down into simpler carbohydrates.
- **Disaccharides** are two monosaccharides attached by a glycosidic link.
  - Glycosidic link forms with the condensation of H_2O between two monosaccharides.
- **Polysaccharides** are three or more monosaccharides linked into complex chains.
  - Starch, cellulose and glycogen are polysaccharides of glucose.

Disaccharides & Polysaccharides



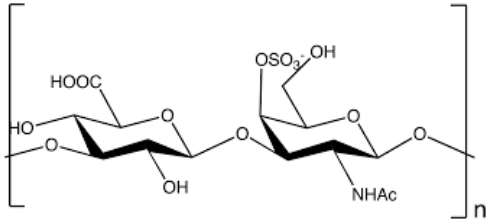


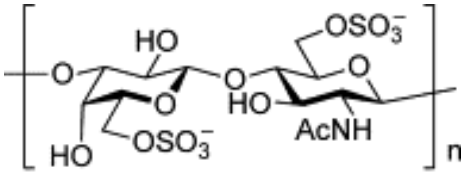


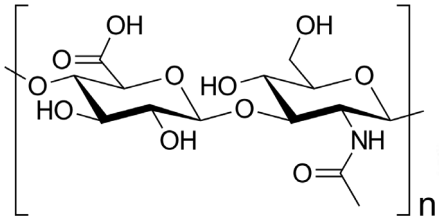
Polymers!

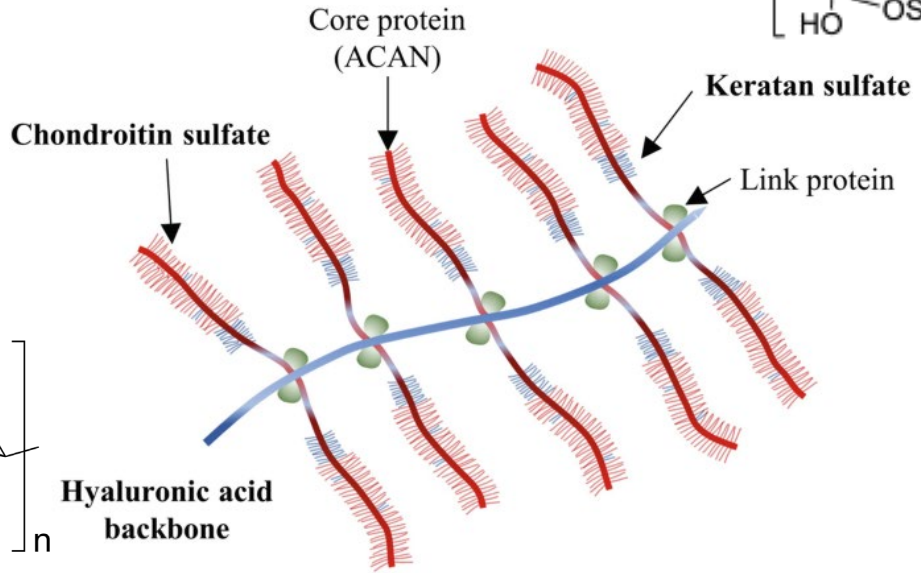
Aggrecan Molecule

Aggrecan (ACAN) is a high molecular weight **proteoglycan** in ECM. It exhibits a bottlebrush structure, in which chondroitin sulfate and keratan sulfate glycosaminoglycan (GAG) chains are attached to an extended protein core.







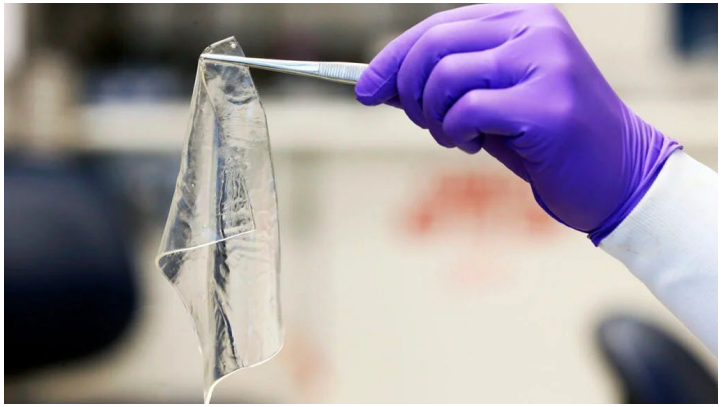


Knowledge Gap

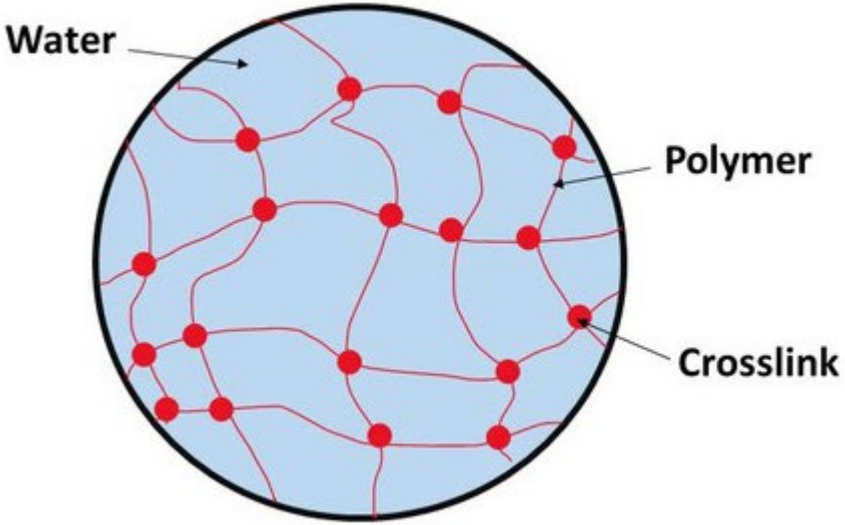
- How do we recreate the ECM?
- How do we control the ECM?
- How does the reciprocal interaction Cells-Matrix work?
- How can we mimic functions of the ECM with (synthetic) materials? (biomimetic materials)

Hydrogels

- 3D network of hydrophilic polymer chains capable of absorbing and retaining water or aqueous solutions



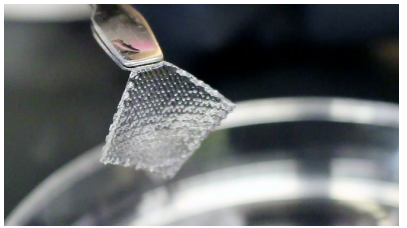
https://www.medicalnewstoday.com/articles/hydrogel-patches-could-prevent-melanoma-breast-cancer-and-colon-cancer-from-recurring

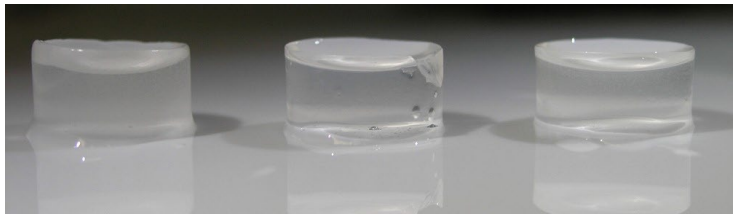


https://www.sciencebuddies.org/science-fair-projects/project_ideas/AgTech_p013/agricultural-technology/water-conservation-hydrogels

Hydrogels

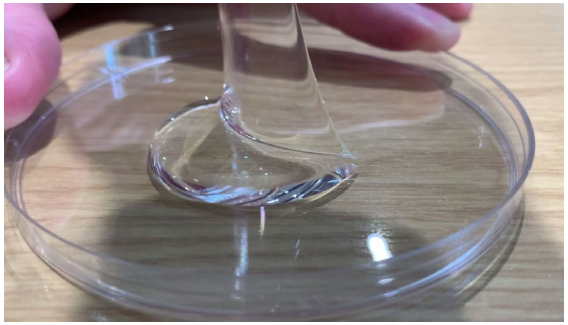
- Mostly water
- Water-soluble polymers
- Provide structural support and adhesion for cells
- Easy to change mechanical properties
- Preferred use of bio-sourced materials
  - Gelatin
  - Hyaluronic acid
- Most widely used 3D cell culture platform
- Most ECM materials are hydrogelish in behaviour
  - Collagen
  - Gelatin
  - Laminin
  - Fibrin
  - GAG's





Biomaterials in RM

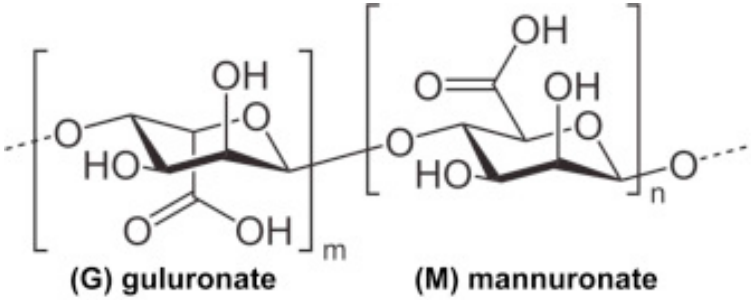
Alginate hydrogels for hosting cells



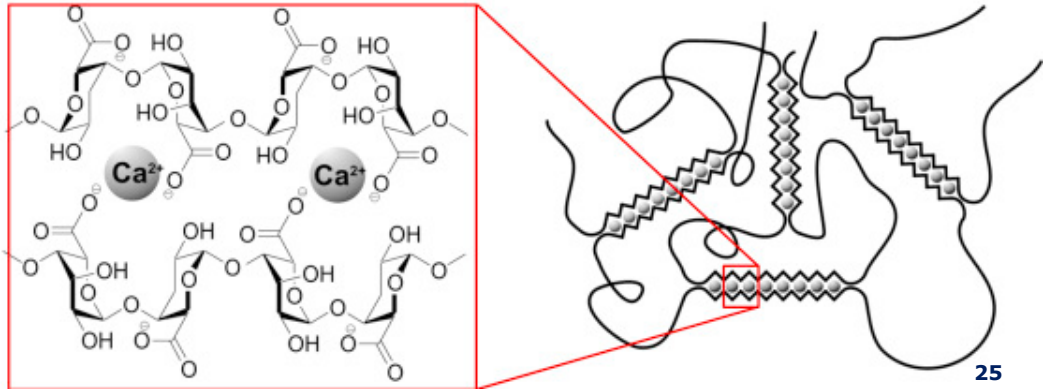
Potential controlled release of drugs, hormones, growth factors, cells, etc

→ **Practical & Case**

https://doi.org/10.1016/j.carbpol.2015.05.021

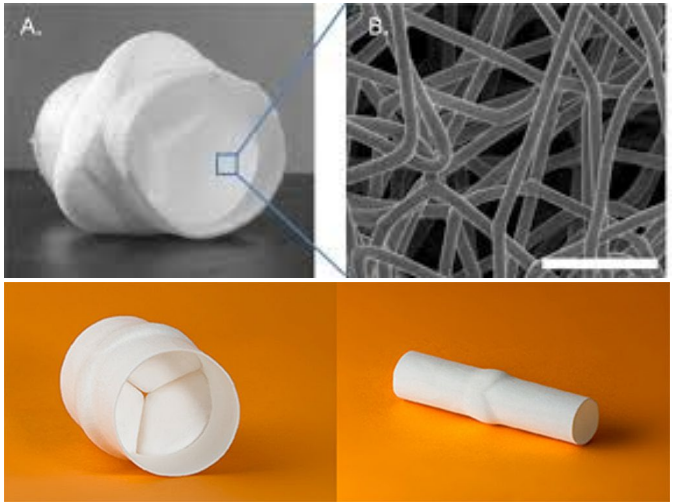


Ca^{2+} **Crosslinking the polymer chains!**



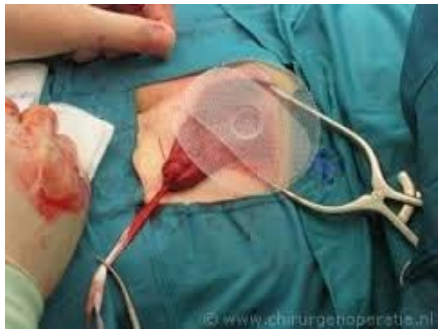
Supramolecular interactions!

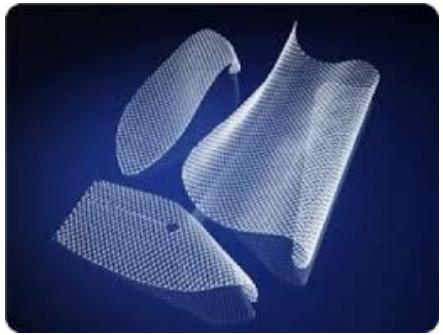
Fabrication



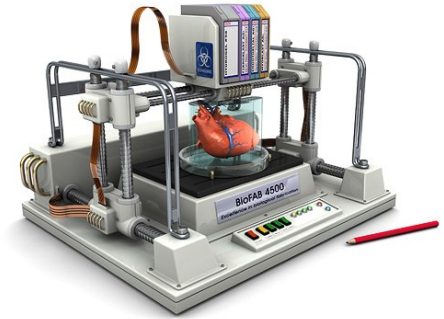
Van Loon et al. Cardiology and Cardiovascular Research 2013, Xeltis 2016

Electrospinning





Textile technologies



3D (Bio)Printing

Dynamic ECM-like Biomaterials

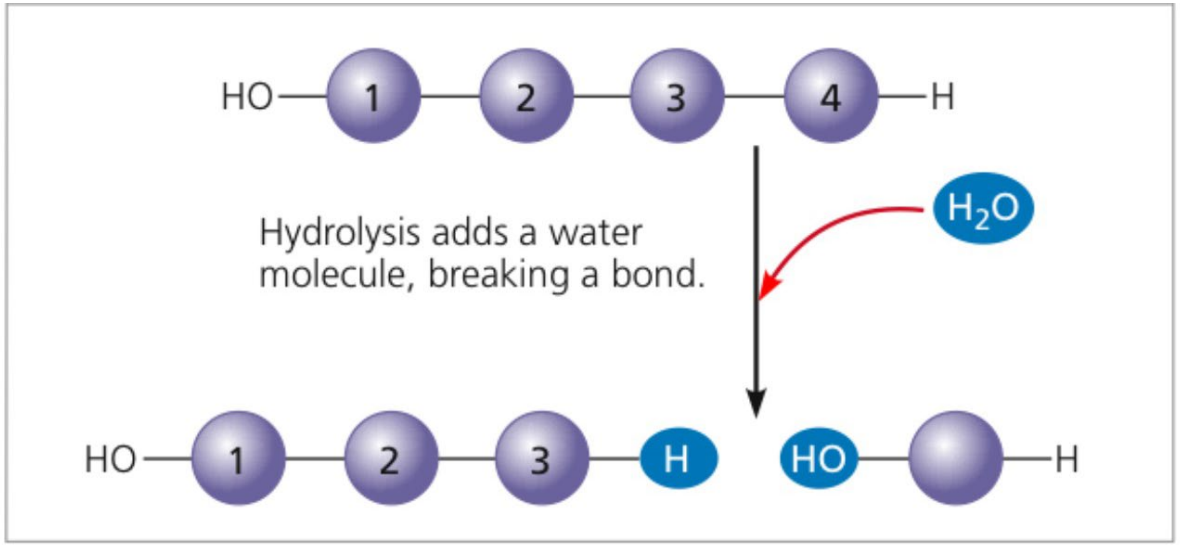
- Biomaterials should not be simply static
- Movement towards more dynamic or responsive systems
- Closer attempts at mimicking ECM functions

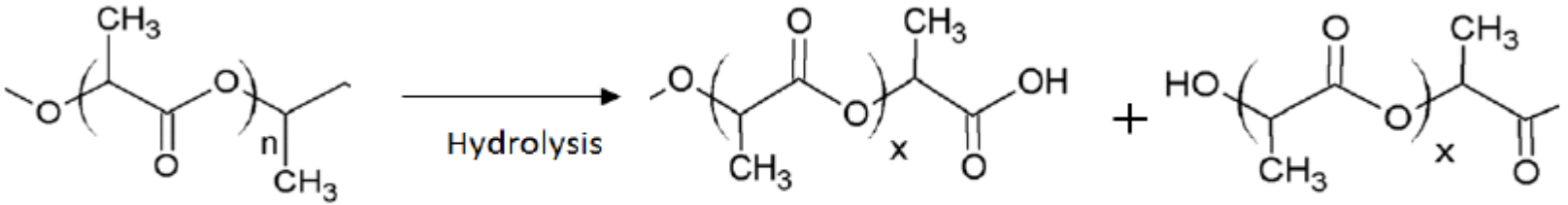
Biodegradability

When is polymer degradation desired and when is it not?

Biodegradability

Break down and decomposition of material under natural conditions



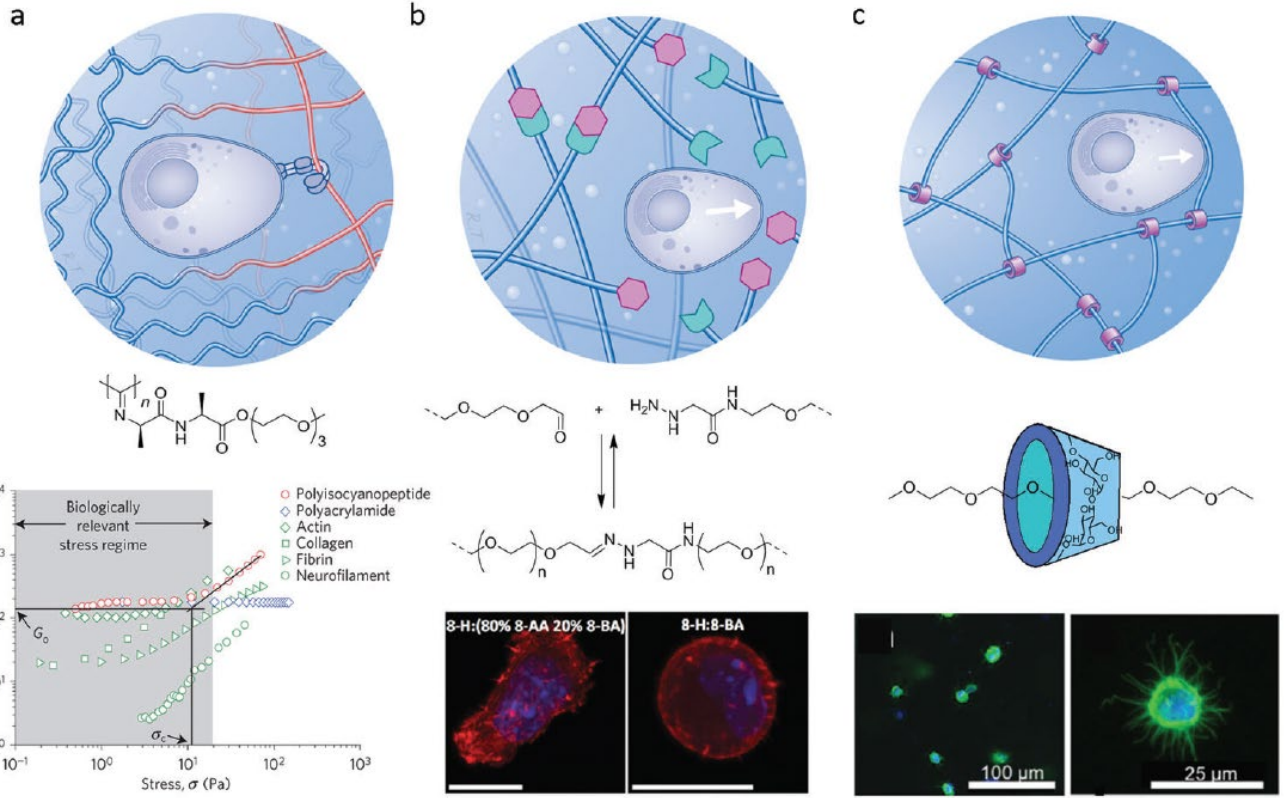


Poly (lactic acid)

Carboxyl End Group

Hydroxyl End Group

Responsive Biomaterials



Tunable:

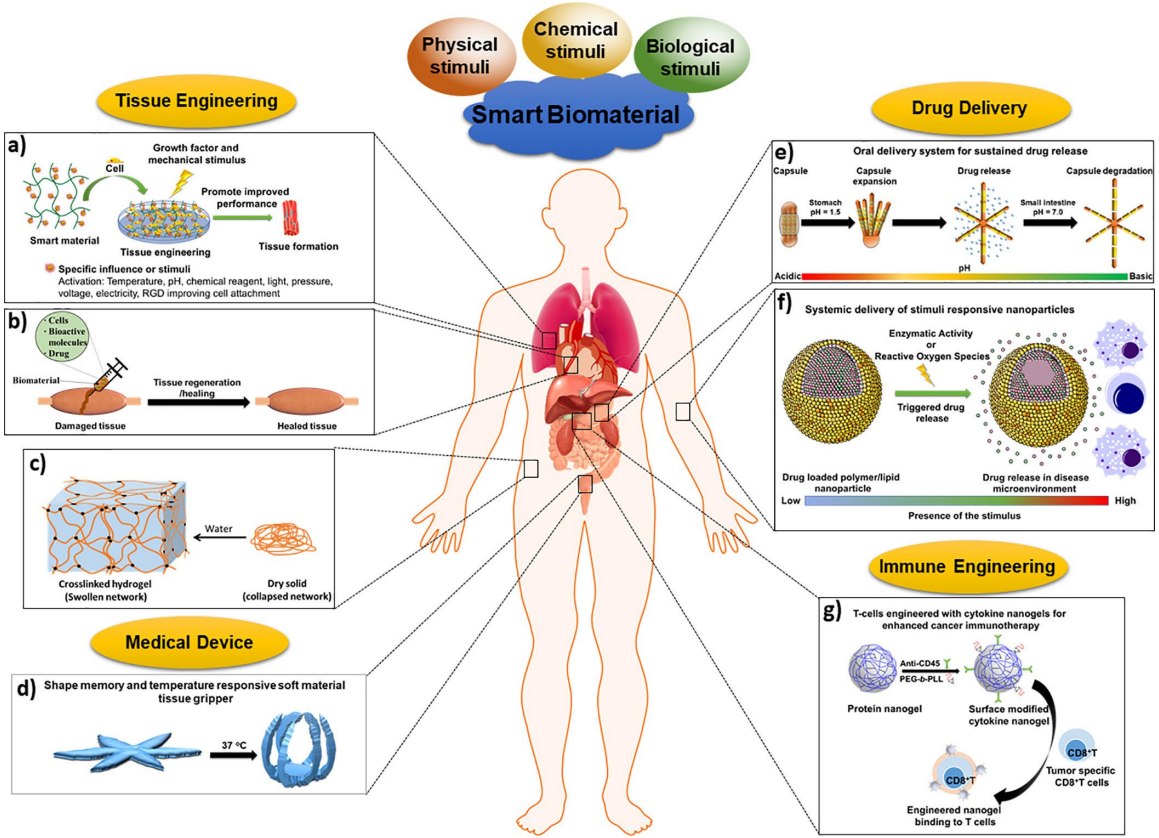
- mechanical properties
- biological activities
- molecule or cell release
- etc

Chemical equilibrium!

Mater. Horiz., **2017**, *4*, 1020.

Outlook Smart Biomaterials

- Responding to physiological and external stimuli
- Control over cell behavior
- Multifunctional
- Personalized



ACS Biomater. Sci. Eng. **2018**, *4*, 3809.

Objectives & Summary

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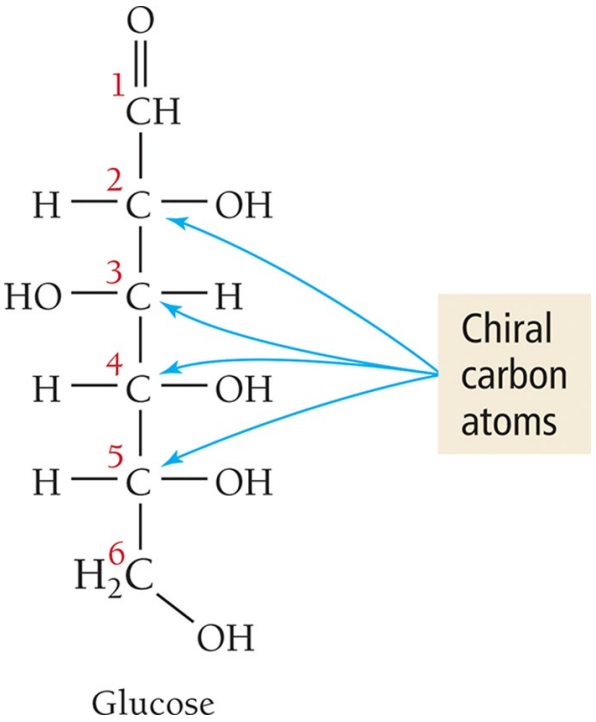
Q&A

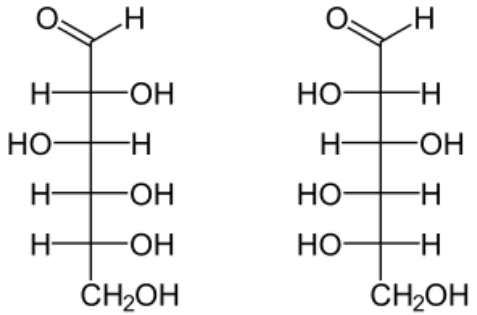
Back-up Slides

Carbohydrates



Glucose

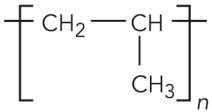
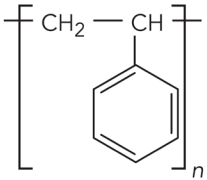
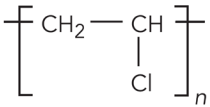
- Several chiral carbons in a carbohydrate, resulting in many possible stereoisomers



D-Glucose L-Glucose

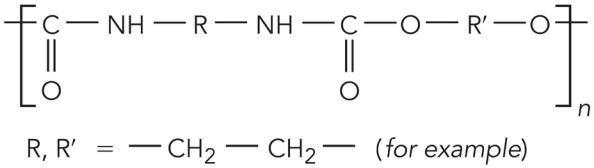
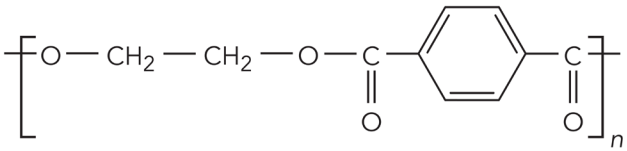
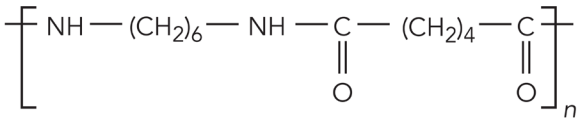
Natural sugars are always D-sugars!
(check the D/L notation yourself)

Polymers

Polymer	Structure	Uses
Addition Polymers		
Polyethylene		Films, packaging, bottles
Polypropylene		Kitchenware, fibers, appliances
Polystyrene		Packaging, disposable food containers, insulation
Polyvinyl chloride		Pipe fittings, clear film for meat packaging

Functional groups?

Polymers

Polymer	Structure	Uses
Condensation Polymers		
Polyurethane	 R, R′ = —CH_2—CH_2— (*for example*)	"Foam" furniture stuffing, spray-on insulation, automotive parts, footwear, water-protective coatings
Polyethylene terephthalate (a polyester)		Tire cord, magnetic tape, apparel, soda bottles
Nylon 6,6		Home furnishings, apparel, carpet fibers, fish line, polymer blends

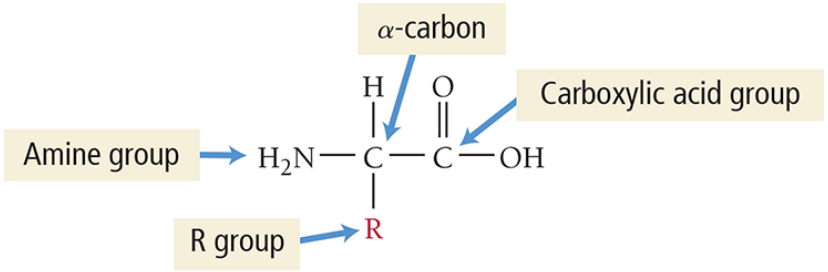
Functional groups?

Proteins

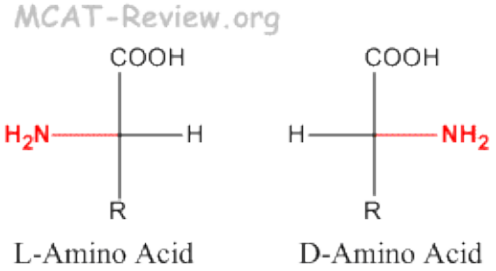
- Involved in practically every facet of cell function
- Structural elements of muscle, skin, and cartilage
- Different classes of proteins with varied function
- Polymers of amino acids

Amino Acids

- Consist of a carbon atom—called the α-carbon—bonded to four different groups: amine group, R group (or side chain), carboxylic acid group, and hydrogen atom
- —NH_2 group on carbon adjacent to COOH
- All amino acids except for glycine are chiral; all natural amino acids feature the L-chirality



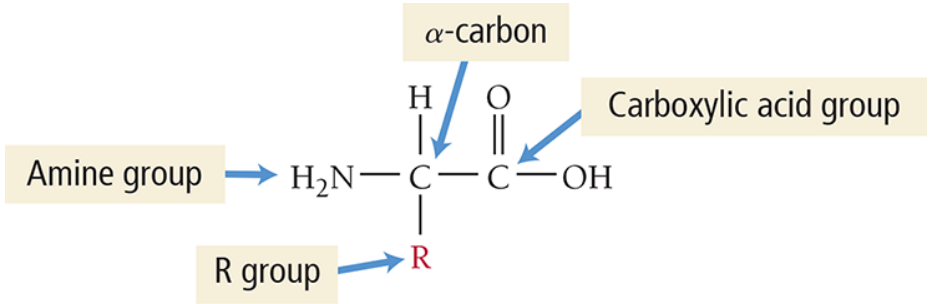
Amino acid general structure



L-Amino Acid D-Amino Acid

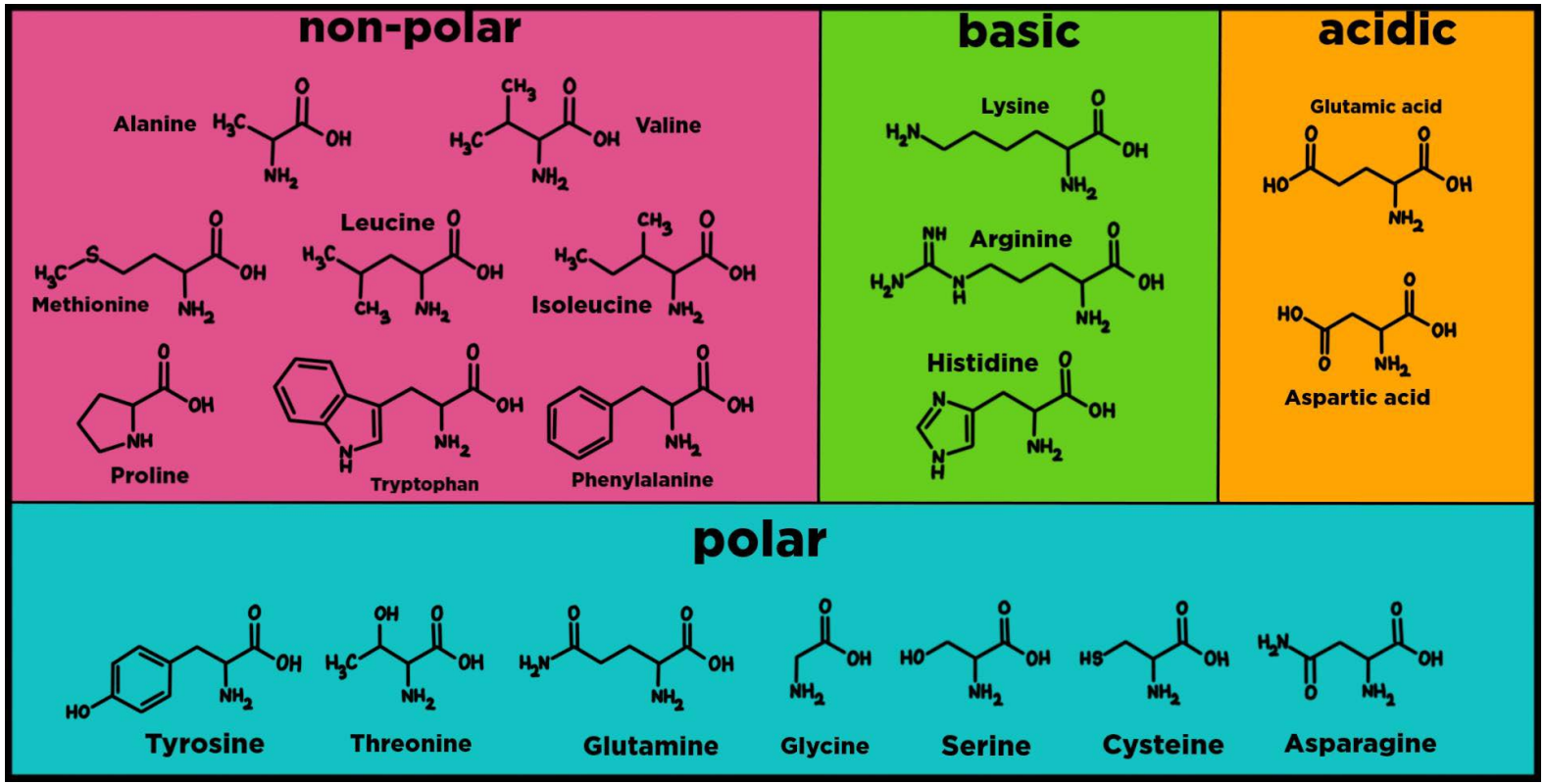
Amino Acids

- The main difference between amino acids is the side chain.
  - **R group**
- Some R groups are polar while others are nonpolar.
- Some polar R groups are acidic while others are basic.



Amino acid general structure

Amino Acids



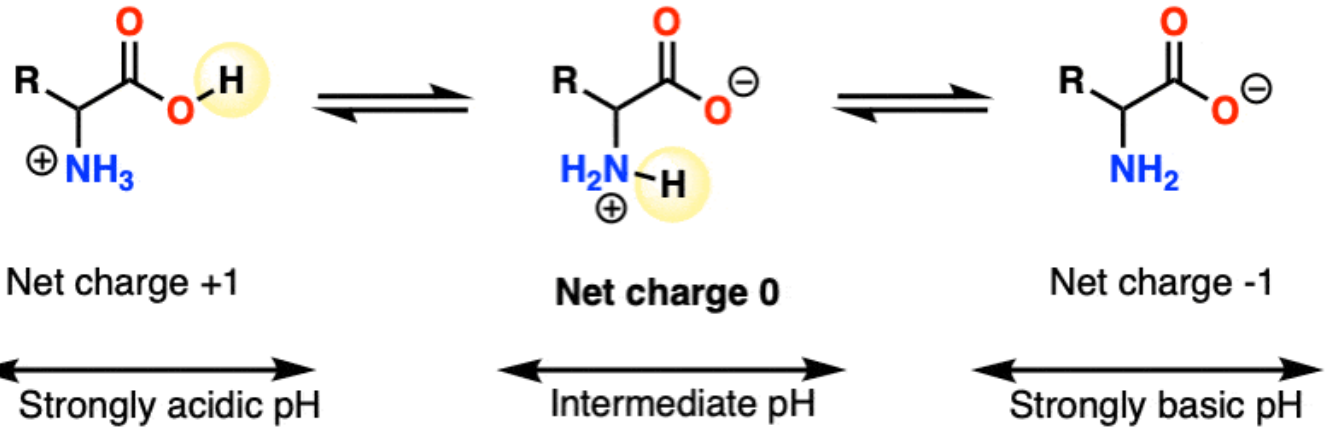
https://www.expii.com/t/amino-acids-overview-structure-10076

Amino Acids

The pH-dependent structures of a typical amino acid

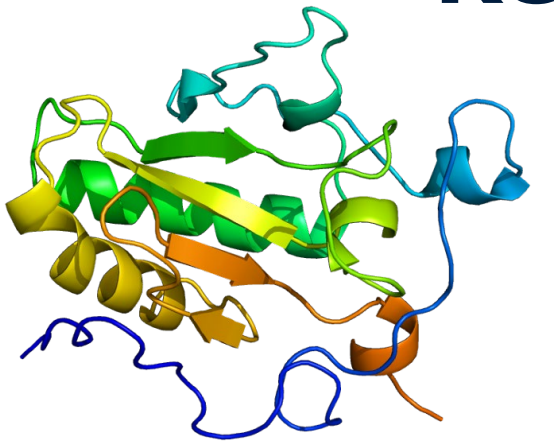
For a typical amino acid with a neutral sidechain **R** :

- the positively charged form (+1) dominates at low pH,
- the zwitterionic (neutral) form dominates at intermediate pH, and
- the negatively charged form (-1) dominates at high pH

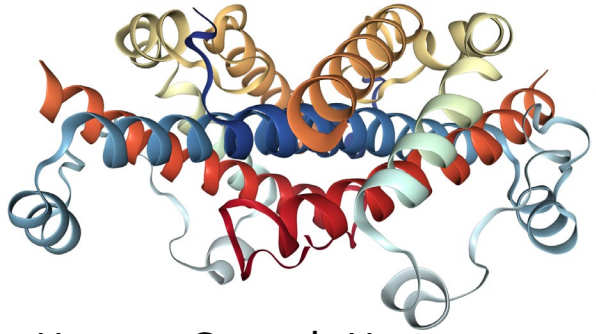


https://www.expii.com/t/amino-acids-overview-structure-10076

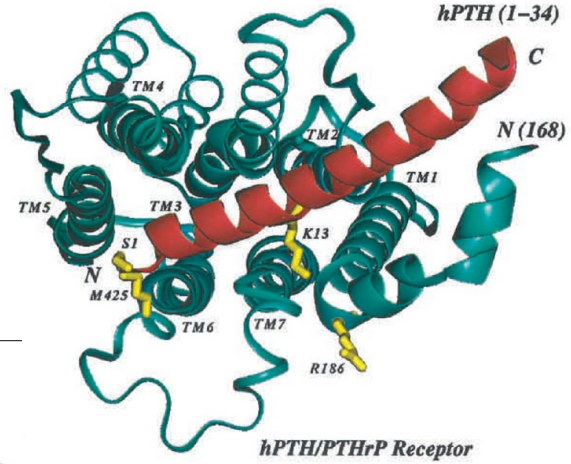
Relevant Proteins

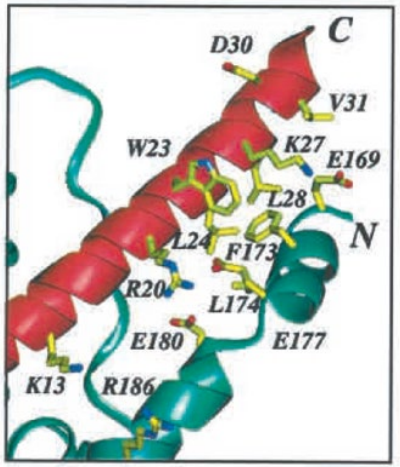


Indian Hedgehog Protein



Human Growth Hormone





hPTH-PTHrP Complex

https://doi.org/10.1016/S0021-9258(19)61502-4