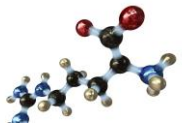
بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ



Biochemistry

وَلَقَدْ خَلَقْنَا الْإِنسَانَ وَنَعْلَمُ مَا تُوَسْوِسُ بِهِ نَفْسُهُ ۖ وَنَحْنُ أَقْرَبُ إِلَيْهِ مِنْ حَبْلِ الْوَرِيدِ

Final | Lecture 1

Protein Structure Pt.1

Written by : Raghad Farraj
Hala Marei

Reviewed by : Leen Khader

Color coding used in the modified:

- *Black: the original slides*
- *Blue: the doctor's explanation/words*
- *Gray: additional information and explanation*
- *Red: important information*

Protein structure

بسم الله الرحمن الرحيم، أول محاضرة من مادة الفاينل

Prof. Mamoun Ahram

Overview of proteins

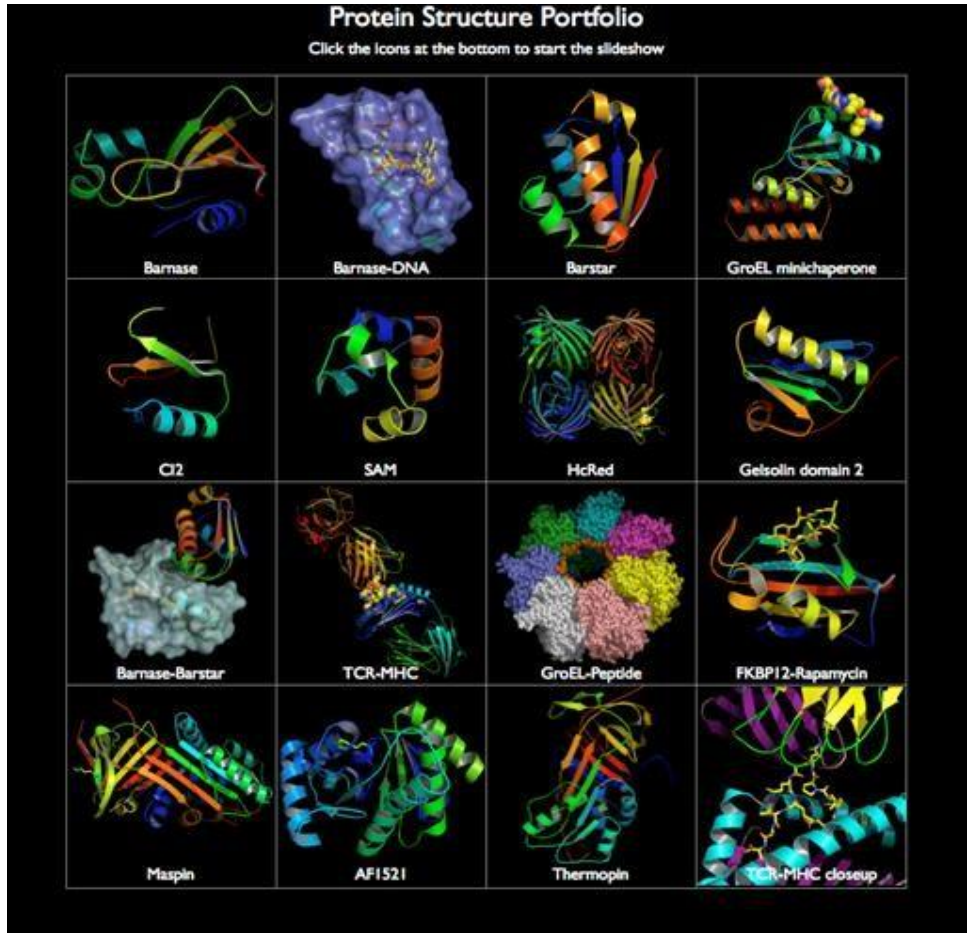
Proteins are polypeptides (a stretch of amino acids)

- Proteins have different structures, and some have repeating inner structures, other do not.
- A protein may have *gazillion* possibilities of structures, but a few would be active.

Same proteins have similar structure, if the structure is changed the protein can lose its function (or wouldn't be efficiently)

proteins tend to adopt the most energetically favorable (**lowest energy**) conformation, so although many structures are possible, only a few are stable and functional

- These active structures are known as native conformations (the 3-dimensional structure of a properly folded and functional protein).



Levels of protein structure

Protein structures are divided into the following 4 levels

Primary structure: the sequence (order) of amino acid residues

Secondary structure: the localized organization of parts of a polypeptide chain (helices, sheets and turns)

Tertiary structure: the three-dimensional structure and/or arrangement of all the amino acids residues of a polypeptide chain (organization in space)

Some proteins are made of multiple polypeptides crosslinked (connected) with each other. These are known as multimeric proteins.

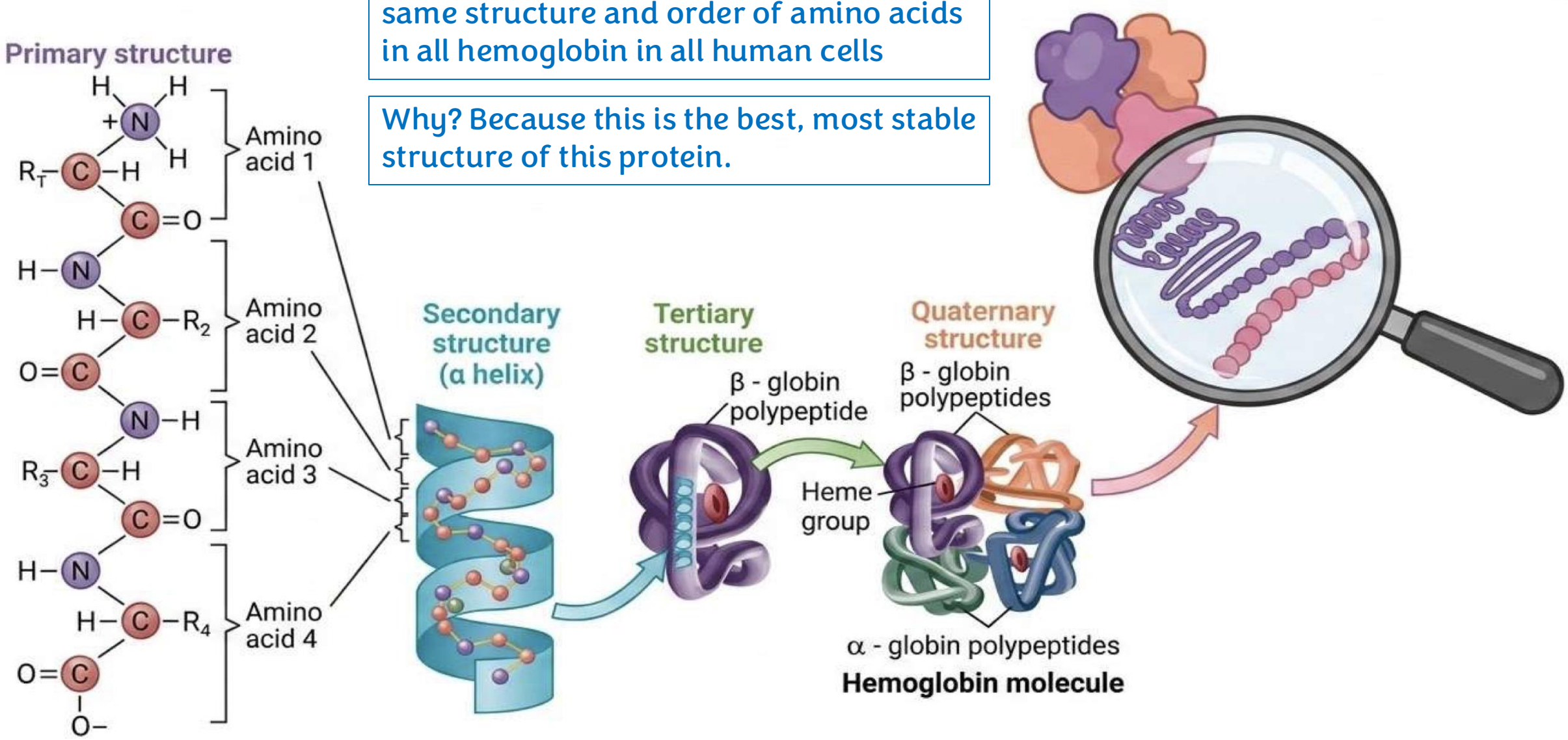
Quaternary structure describes the number and relative positions of the subunits in a multimeric protein (3D structure of a protein composed of more than one polypeptide)

This is an animation

We use hemoglobin as an example because it's the most studied protein

Hemoglobin is made of 4 polypeptides, same structure and order of amino acids in all hemoglobin in all human cells

Why? Because this is the best, most stable structure of this protein.



Primary structure

What is primary structure?

The pictures from this slide were moved to the next slide.

- The order in which the amino acids are covalently linked together.
  - Example: Leu—Gly—Thr—Val—Arg—Asp—His

Val 106 = Valine is the 106th amino acid
Val 106 Ala = Valine was replaced by Alanine (a mutation)

- The primary structure of a protein determines the other levels of structure.
- Protein isoforms are versions of products of one gene or multiple genes with small differences from each other in their amino acid sequences, their modifications or processing, and with different structural and functional properties.

Hemoglobin in our bodies is not one kind, we have:
Hemoglobin HbA (adult hemoglobin)
Hemoglobin gamma HbF (fetal hemoglobin)
The difference in structure has a **purpose** behind it

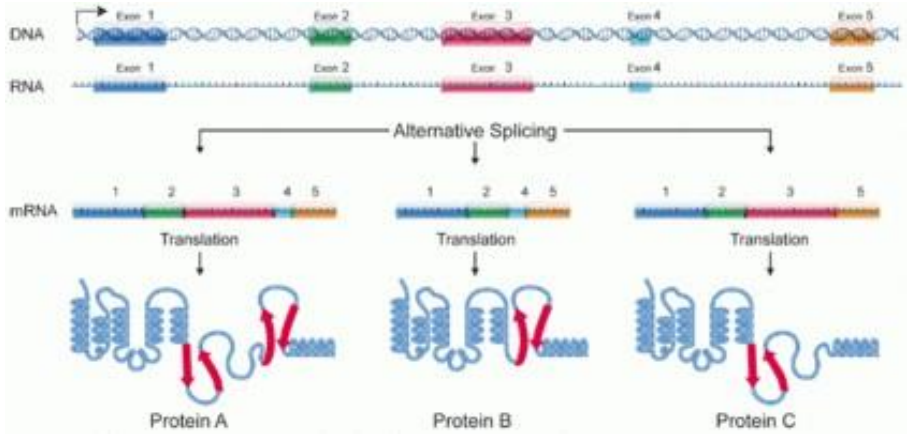
This difference is because the fetus depends on the mother for oxygen. While the mother can obtain oxygen whenever simply by breathing, the fetus, must **extract oxygen from the mother's blood.** After birth, HbF is gradually replaced by HbA.

What is primary structure?

The sequence alignment shows that serine is replaced by threonine at this position, which isn't a big difference. Both amino acids have polar, uncharged hydroxyl-containing side chains. However, threonine has an additional methyl group and is branched at the β-carbon

	1	5	10	15
Myoglobin	gly-----leu-ser-asp-gly-glu-trp-gln-leu-val-leu-asn-val-trp-gly-lys-val-			
β-chain hemoglobin	val-his-leu-thr-pro-glu-glu-lys-ser-ala-val-thr-ala-leu-trp-gly-lys-val-			
α-chain hemoglobin	val-----leu-ser-pro-ala-asp-lys-thr-asn-val-lys-ala-ala-trp-gly-lys-val-			
ζ-chain hemoglobin	met-ser-leu-thr-lys-thr-glu-arg-thr-ile-ile-val-ser-met-trp-ala-lys-ile-			
γ-chain hemoglobin	met-gly-his-phe-thr-glu-glu-asp-lys-ala-thr-ile-thr-ser-leu-trp-gly-lys-val-			

In order to understand human proteins, we can study them in other organisms because both proteins got the same function



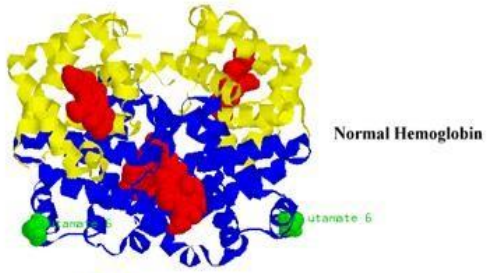
We can say that if a protein has almost the same order of amino acids as another protein then they have the same function

In the US, it was found that cancer cells were able to move from a fish to another, that is important to study because we can see if it is applicable on humans

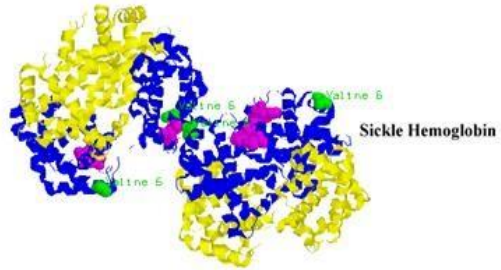
Enzyme GATA2 is identical in humans and mouses so we can study it in mouses

Why is the primary structure important?

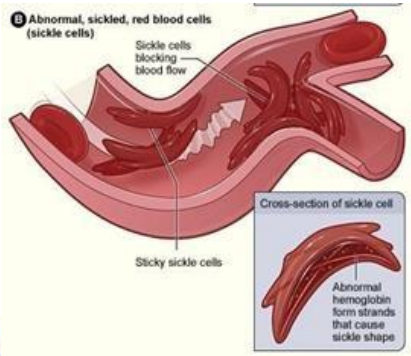
Knowing the primary structure can allow us to predict the function of the protein



Sickle hemoglobin (HbS) as an example

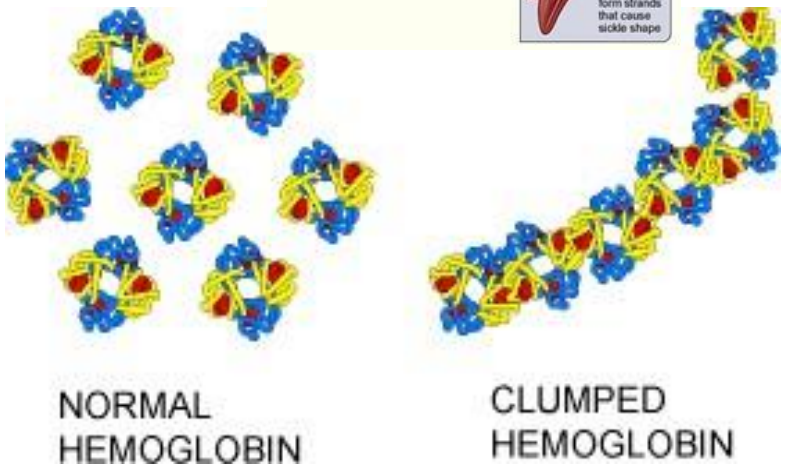


- A single amino acid substitution can give rise to a malfunctioning protein, as is the case with sickle-cell anemia.
- It is caused by a change of amino acids in the 6th position of β globin (Glu to Val).



Glu is negatively charged and Val is non-polar, this change causes hemoglobin to aggregate. We have millions of hemoglobin in each RBC so when they aggregate, they change the shape of the RBC

- The mutation results in:
- 1) arrays of aggregates of hemoglobin molecules.
- 2) deformation of the red blood cell.
- 3) clotting in blood vessels and tissues.



Secondary Structure

What is a secondary structure? How is it formed?

The peptide bond itself does not freely rotate

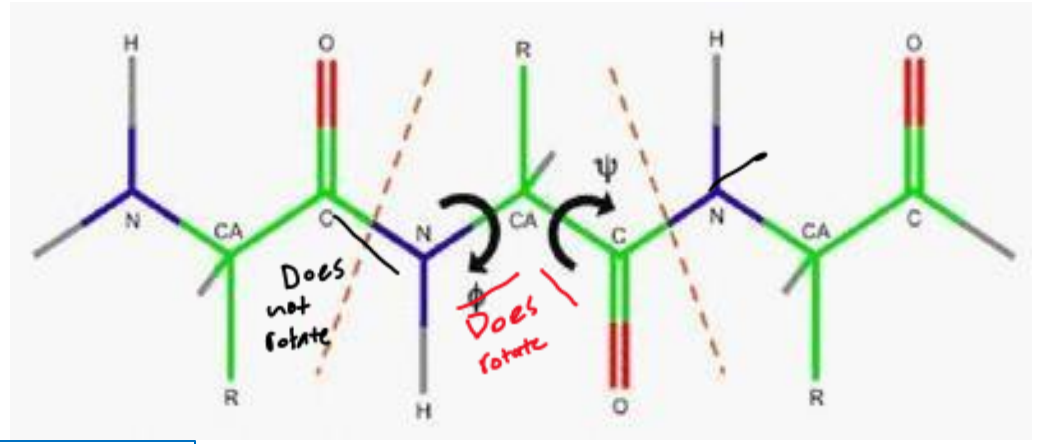
- Two bonds within each amino acid residue can freely rotate.
  - the bond between the α-carbon and the amino nitrogen
  - the bond between the α-carbon and the carboxyl carbon

- A secondary structure is hydrogen-bonded, locally arranged structures of the backbone of a polypeptide chain.
- Examples:
  - Alpha helix
  - Beta-pleated sheet
  - Turns
  - Loops
  - Bends
  - Coils

Regular secondary structures

Non-regular secondary structures

Secondary structure consists of **localized,** organized structures stabilized mainly by **hydrogen bonds between peptide backbone groups:**
C=O → H-bond acceptor
N-H → H-bond donor

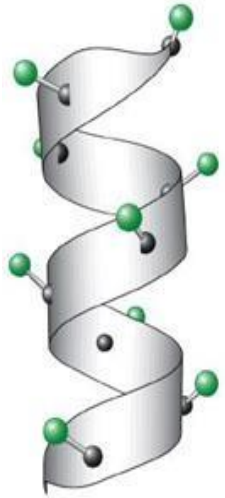


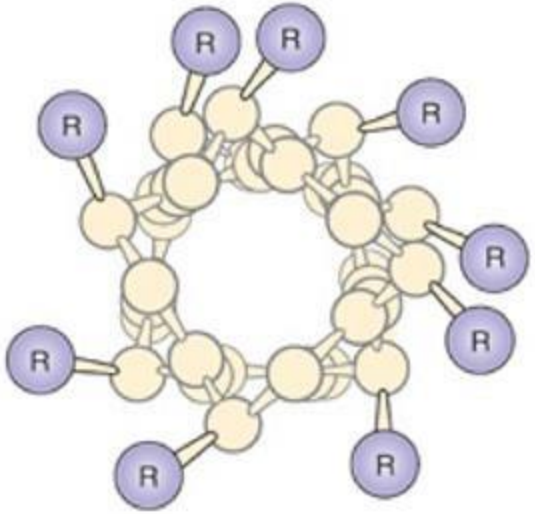
Regular = repeating pattern
Non-regular = irregular regions

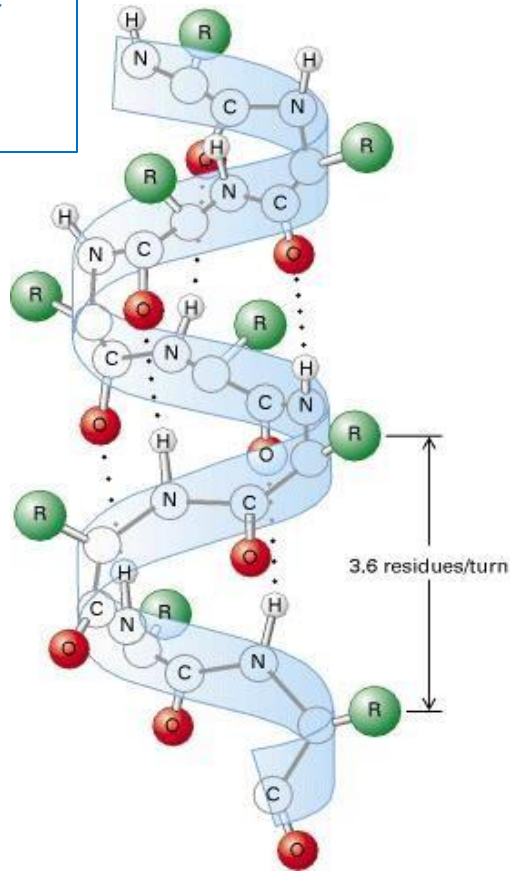
The α helix

- It looks like a helical rod.
- The helix has an average of 3.6 amino acids per turn.
- It is very stable because of the linear hydrogen bonds.
- The side chains of the amino acids project outward from the helix in order to avoid molecular congestion (known as steric hindrance because of the spatial organization of atoms in space) with the polypeptide backbone and with each other.

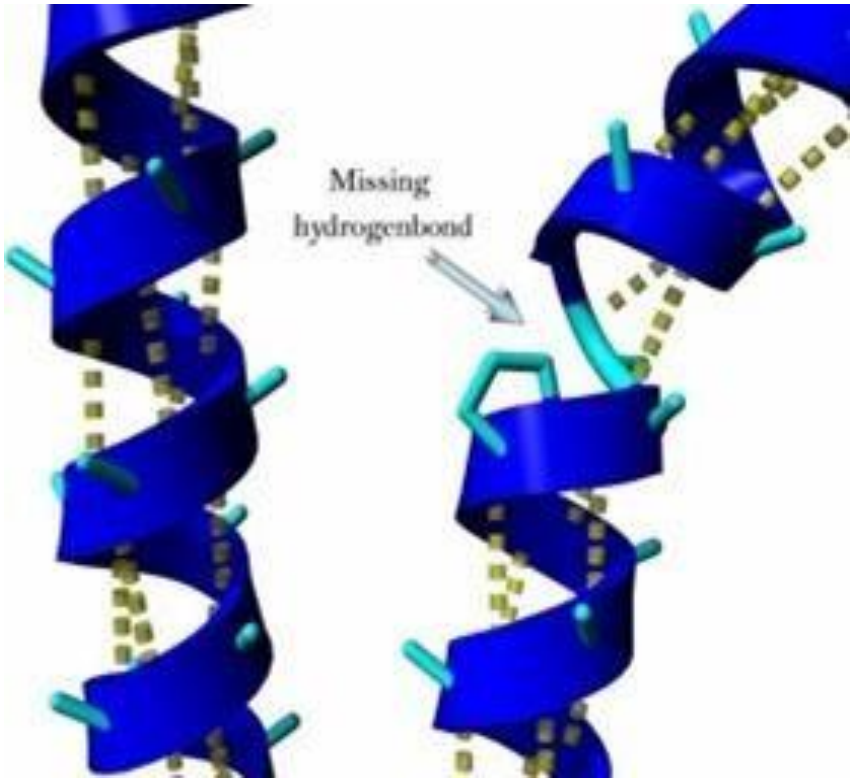
unlike DNA branches (bases) that extend inward







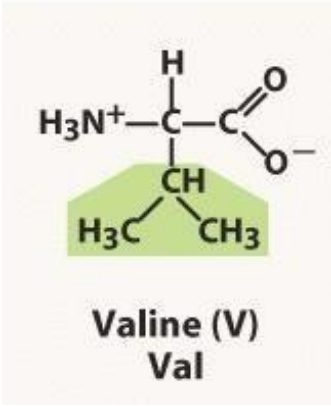
Amino acids NOT found in α-helix

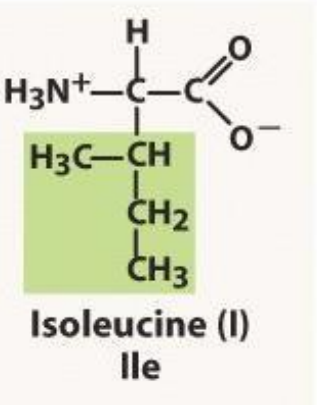


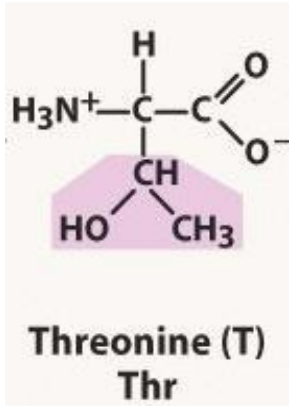
- Glycine: too small
- Proline we can see it in the end of the alpha helix
  - No rotation around N-C bond
  - No hydrogen bonding of α-amino group

Proline is a rigid amino acid, and the alpha helix depends on the hydrogen bones, which is formed between the peptide bond components and the proline doesn't have a hydrogen bond donor

- Close proximity of a pair of charged amino acids with similar charges (having two positively charged or two negatively charged amino acids close to one another leads to repulsion)
- Amino acids with branches at the β-carbon atom (the carbon under the central carbon) (valine, threonine, and isoleucine) We can see them in the end of the Alpha helix

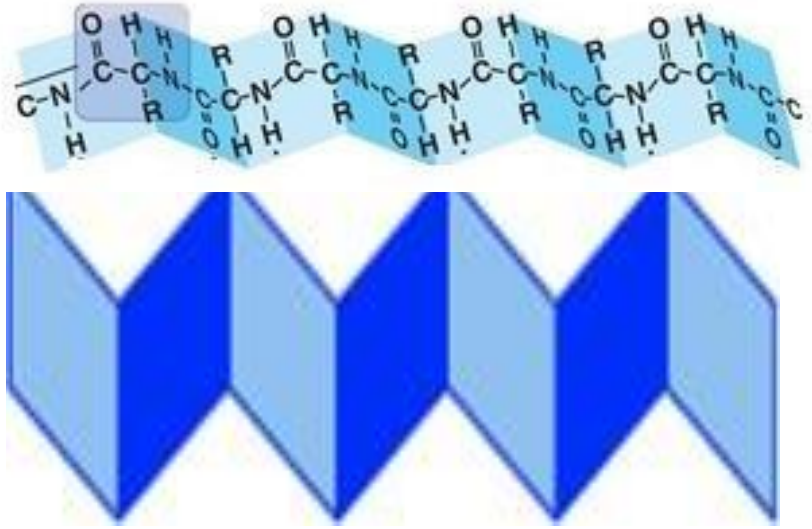






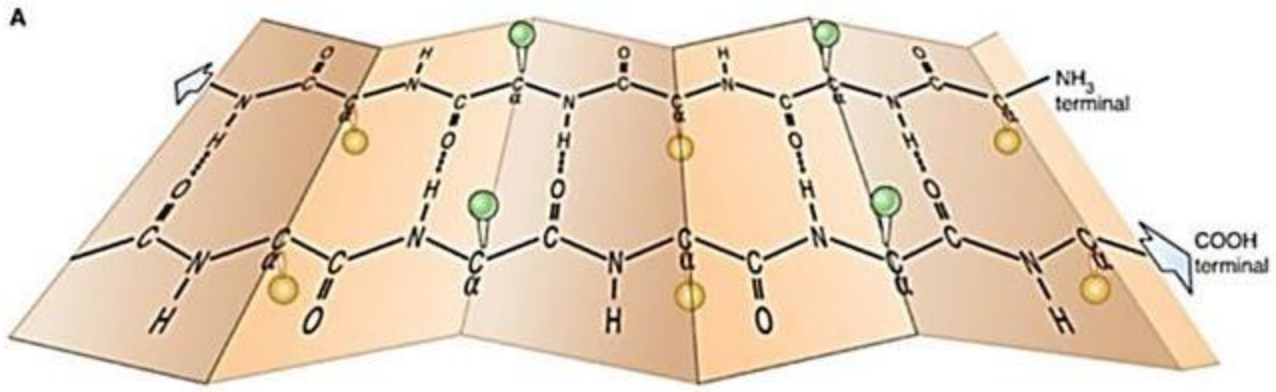
β-pleated sheet (β sheet)

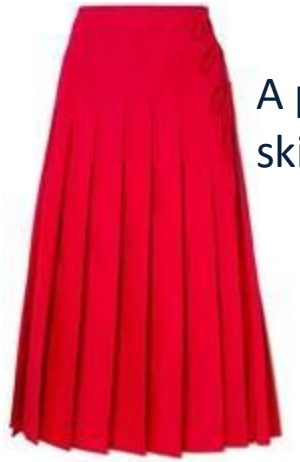
- They are composed of two or more straight chains (β strands) that are hydrogen bonded side by side (when they are above each other between the components of the peptide bond).



β strand

- Optimal hydrogen bonding occurs when the sheet is bent or folded (pleated) to form β-pleated sheets.



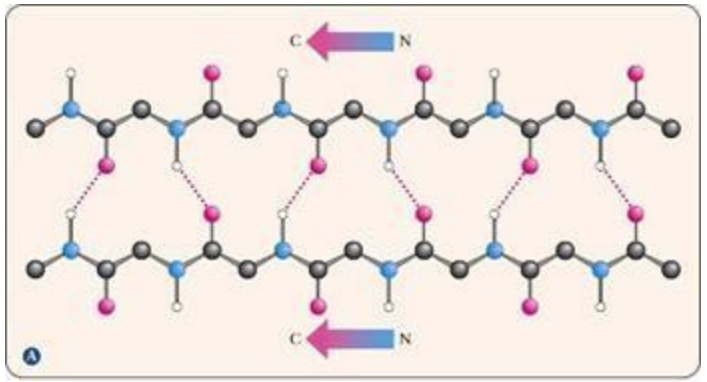


A pleated skirt

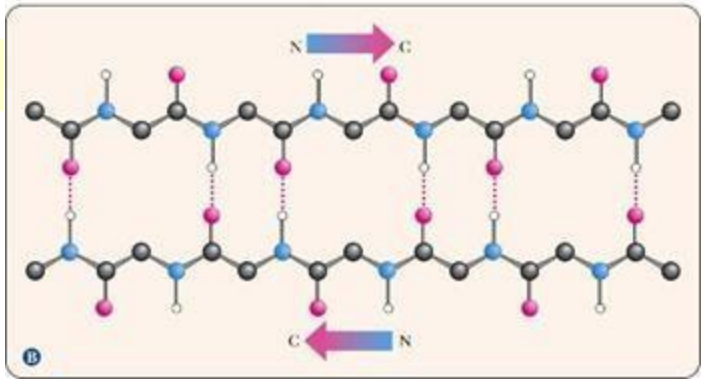
More on β-sheets

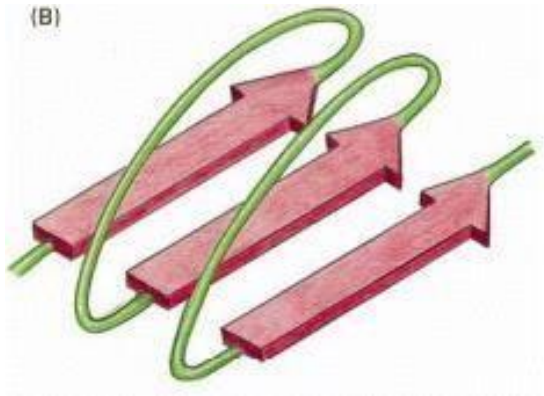
- β sheets can form between many strands, typically 4 or 5 but as many as 10 or more. We draw them as arrows that are hydrogen bonded with each each other when they are aggregates
- Such β sheets can be purely antiparallel, purely parallel, or mixed.
- Proline tends to disrupt β strands. Why?

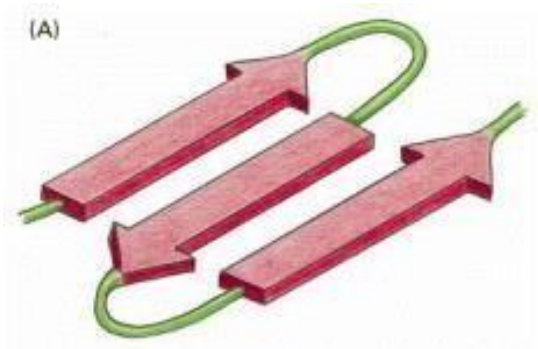
Parallel

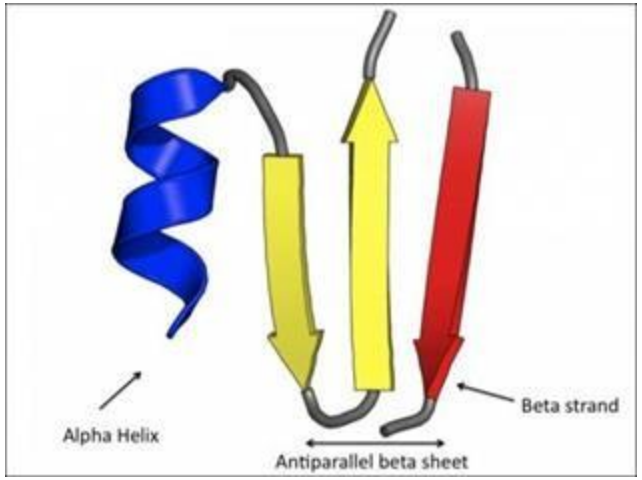


Antiparallel





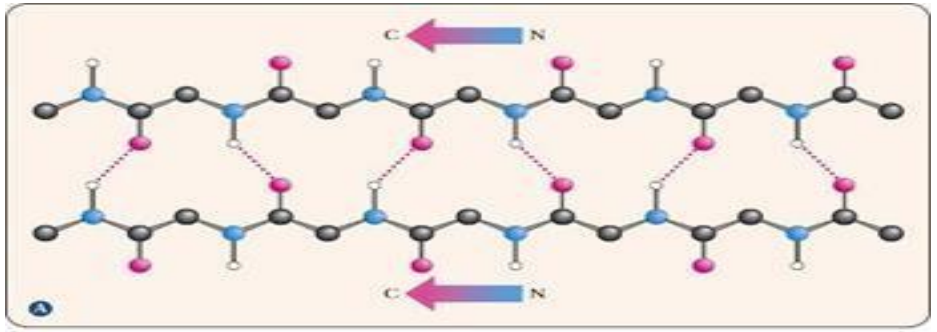




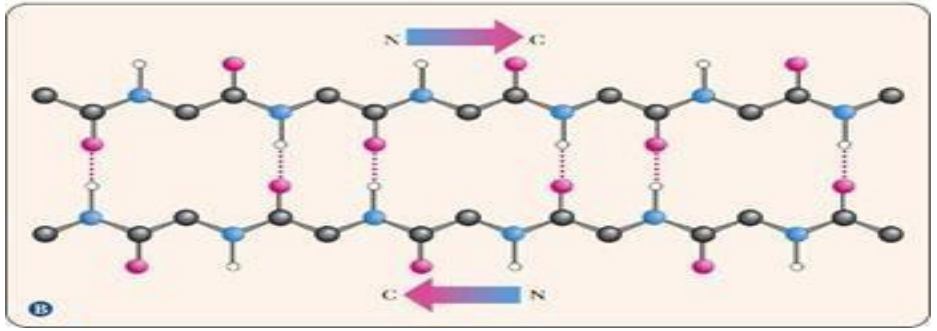
Based on hydrogen bonding pattern, which do you think is more stable: parallel or anti-parallel sheets?

The anti parallel sheets

Parallel means that the two strands are in the same direction from the N terminus to the C terminus for example



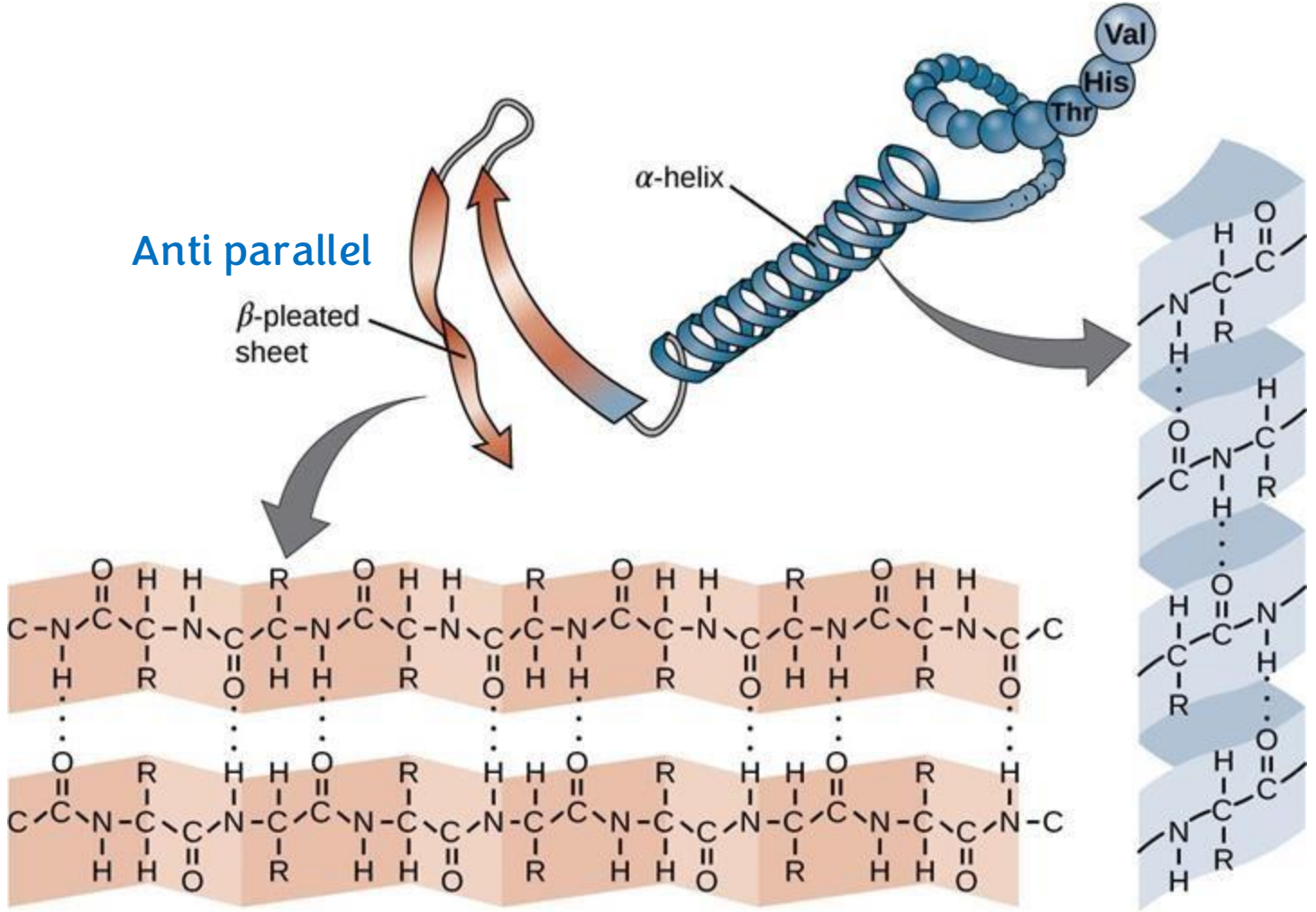
Anti-parallel means that the strands are not in the same direction. One of them begins with the N terminus , and the other one begins with a C terminus.



Notice also that both proline and glycine also breaks the beta strands.
Pro->Can't do H-bonds
Gly->Too small
However, the amino acids with branches at the β-carbon atom that ruins the alpha helix likes to be in the beta strands.

How are they illustrated/drawn?

Notice that between the helix and the strand, we have a random structure and between the two strands, we also have a random structure

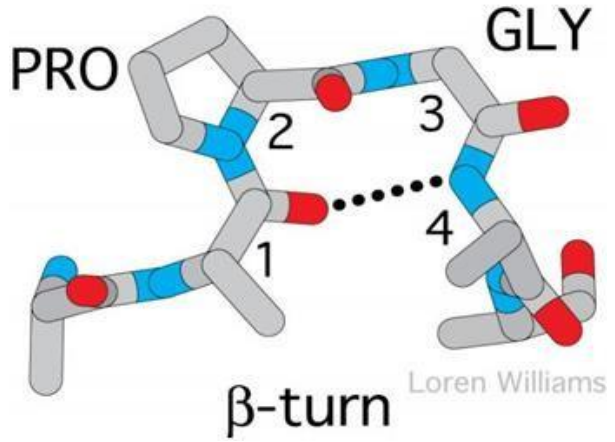


Turns

- Turns are compact, U-shaped secondary structures.
- They are also known as hairpin bends.
- The most common is a β-turn, which is made of 4 residues where glycine and proline are commonly present. Why?
- What are they used for? How are they stabilized?

We have proline because it causes a sharp turn and glycine because it allows more rotation around the two bonds that are beside the alpha C because Gly doesn't have an R group that can cause repulsion.

- The turns are stabilized by hydrogen bonds between the peptide bonds components of the first and forth amino acids.



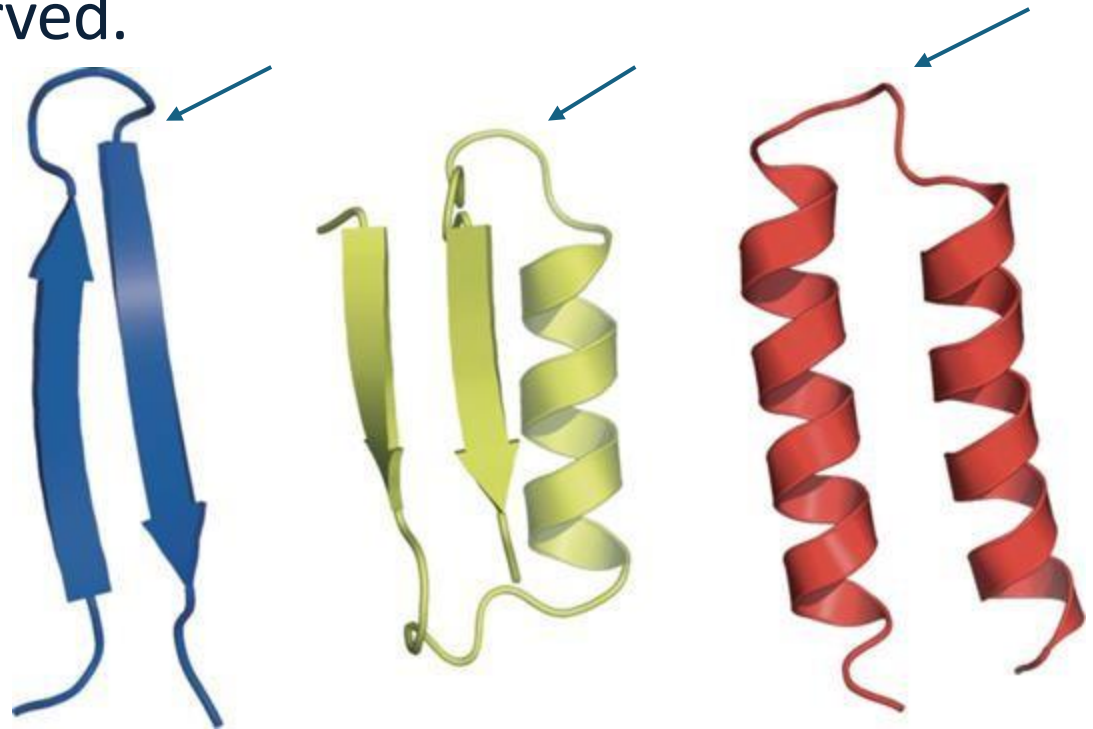
Loops and coils

- Loops are a diverse class of secondary structures in proteins with irregular structure and that connect the main secondary structures.
- They are found on surface of molecule and provide flexibility to proteins

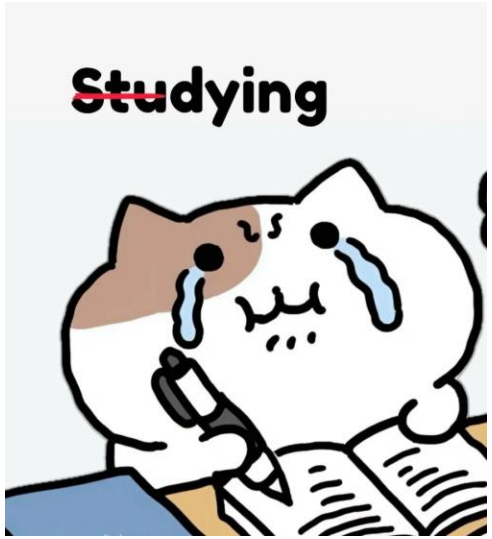
(it allows the protein to rotate and bend , it gives the protein a 3D structure and it makes the protein compact)

- Amino acids in loops are often not conserved.

We can see the loops between the alpha helixes and between the different structures



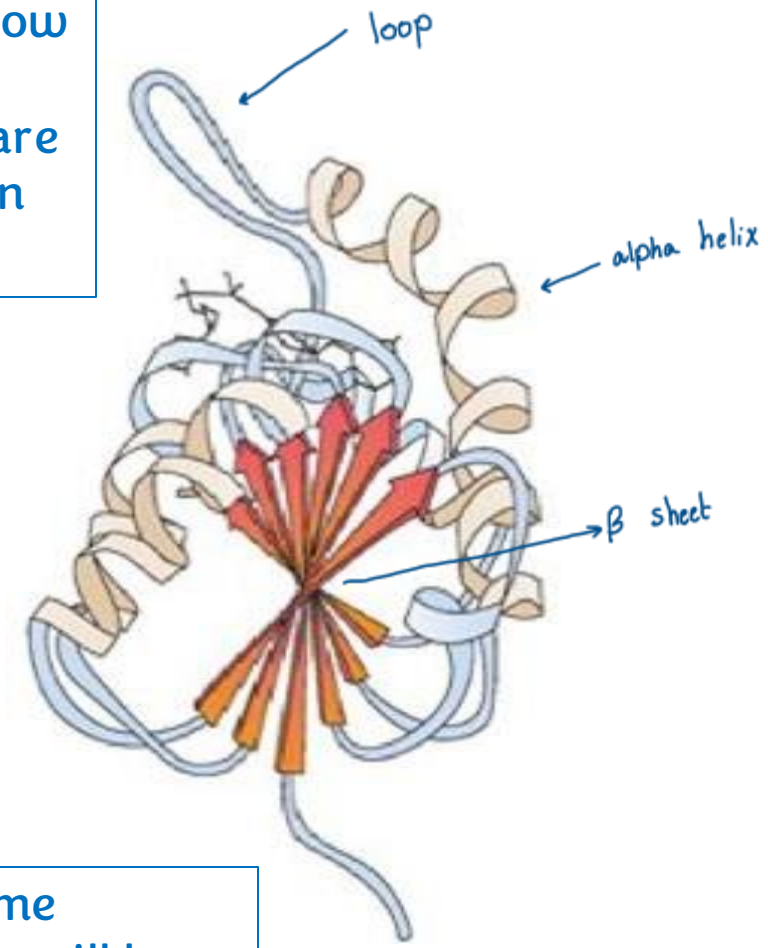
Tertiary structure



What is a tertiary structure?

- The overall conformation of a polypeptide chain
- The three-dimensional arrangement of all the amino acids residues In space
- The spatial arrangement of amino acid residues that are far apart in the sequence this means that, for example I can find the 15 and the 111 amino acid besides each other because of the folding amino acids in space

Basically it is how amino acids and how Secondary structures are organized in space

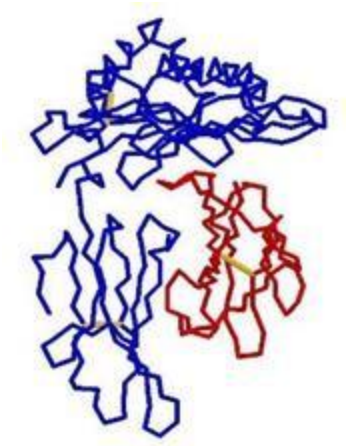


For the same protein, we will have the same structure always in the same place.

How to look at proteins...

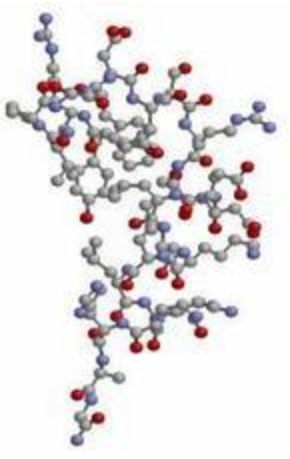
The 3D structure can be presented in different ways
Each way shows me something

Trace structure



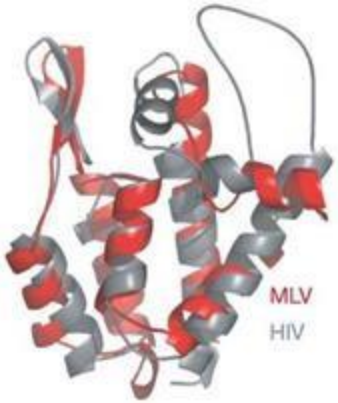
It is like you are holding a pencil and following the backbone
It doesn't show me the R groups

Ball and stick structure



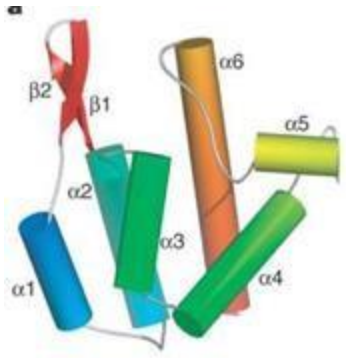
It shows the atoms, for example: C=black,O=red,N=blue,H=white

Ribbon structure



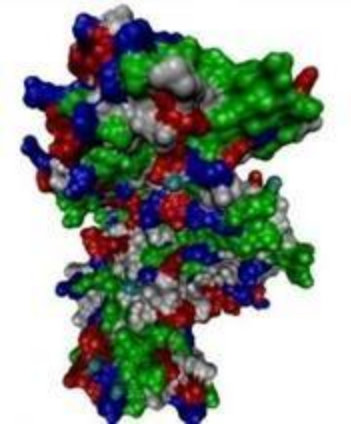
It shows me the secondary structures

Cylinder structure



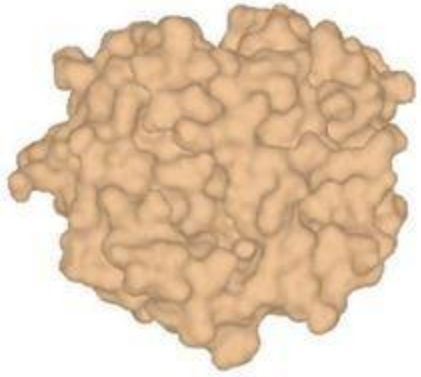
Instead of showing the alpha helix as a helix it's represents it with a cylinder

Space-filling structure



It shows me the organization of atoms

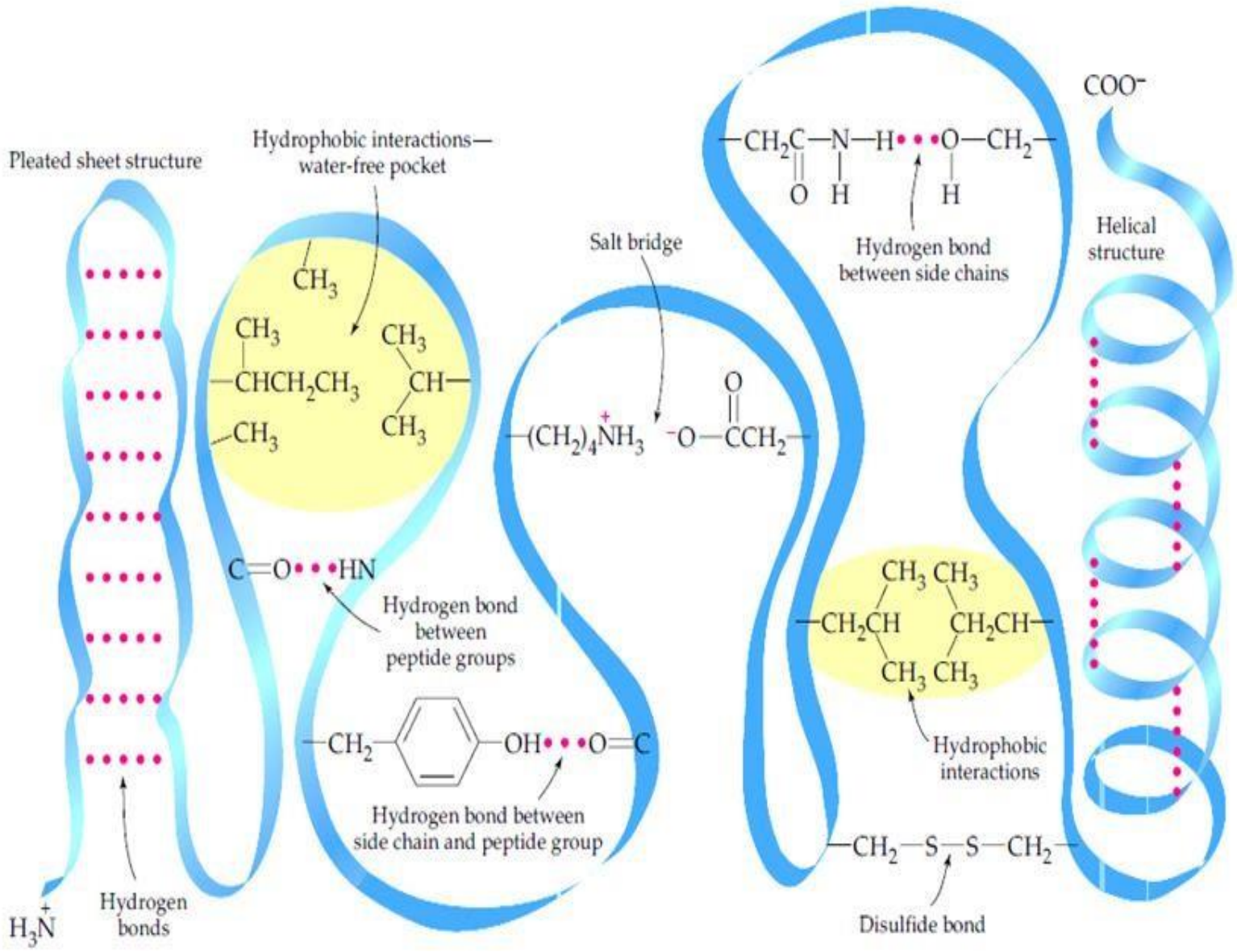
Protein surface map



This is relatively new It's only shows me the surface of the protein the curves and so on it is important because the drug will bind to the surface of the protein

It helps me understand the reason why specific amino acids are near each other. When I want to invent a drug, I will know that there is a specific space between specific atoms so I can make the drug fit in that space

Shape-determining forces



The tertiary structure is determined by the R groups. Exactly by the non-covalent interactions between the other groups (hydrophobic interactions, Van der waals interactions, electrostatic, interactions, and hydrogen bonds)

The secondary structure is written in mind by the hydrogen bonding between the peptide bones

For example, two polar amino acids beside each other or lysine next to a glutamate make electrostatic interactions

Valine and alanine should be at a distance because of repulsion of the Van der waals interaction , but not too far away because there will be no interaction between them

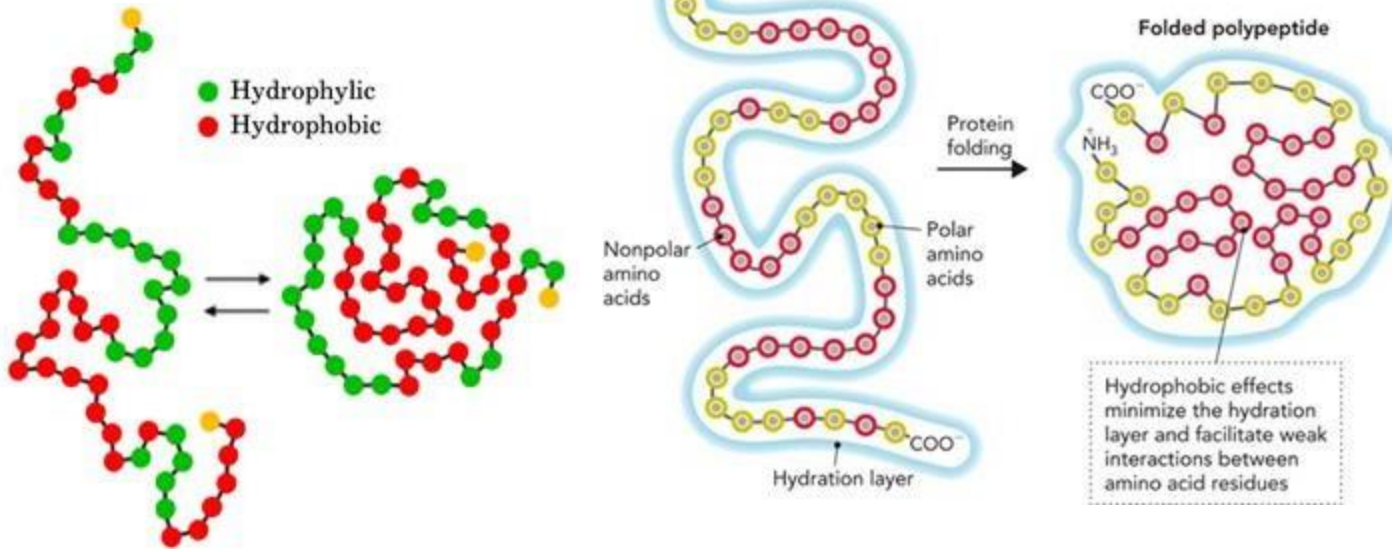
The hydrogen bonds as well are formed between the R groups

Localization of amino acids

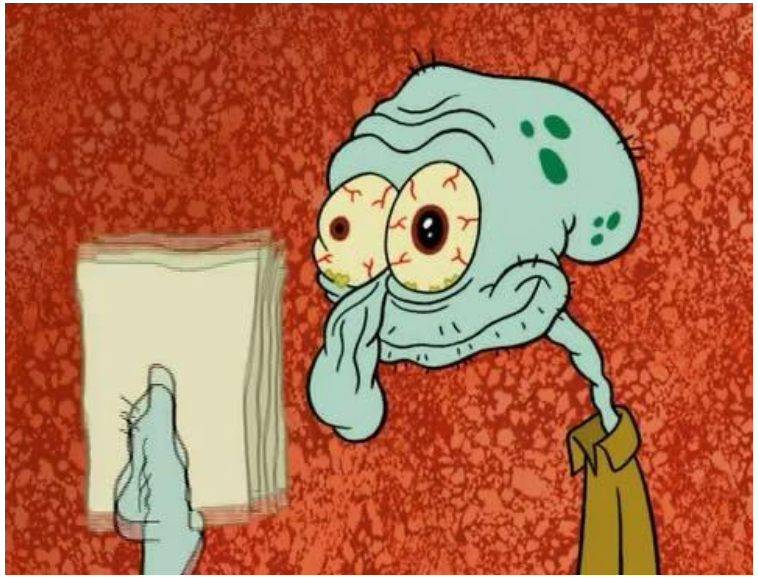
- Polar amino acids can be found in the interior of proteins
- In this case, they form hydrogen bonds to other amino acids or to the polypeptide backbone
- They play important roles in the function of the protein

Can polar amino acids be found in the interior?...YES

Usually, the hydrophilic amino acids are on the surface because they can interact with water and hydrophobic amino acids are in the core to avoid water



Quiz time !



Additional Resources:

رسالة من الفريق العلمي:

Reference Used:
(numbered in order as cited in the text)

1. Dr. Mamoun Ahram lecture

لا تنسونا من صالح دعائكم

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	26	For example, two polar amino acids beside each other or lysine next to a glutamate make **hydrostatic** interactions	For example, two polar amino acids beside each other or lysine next to a glutamate make **electrostatic** interactions
V1 → V2			