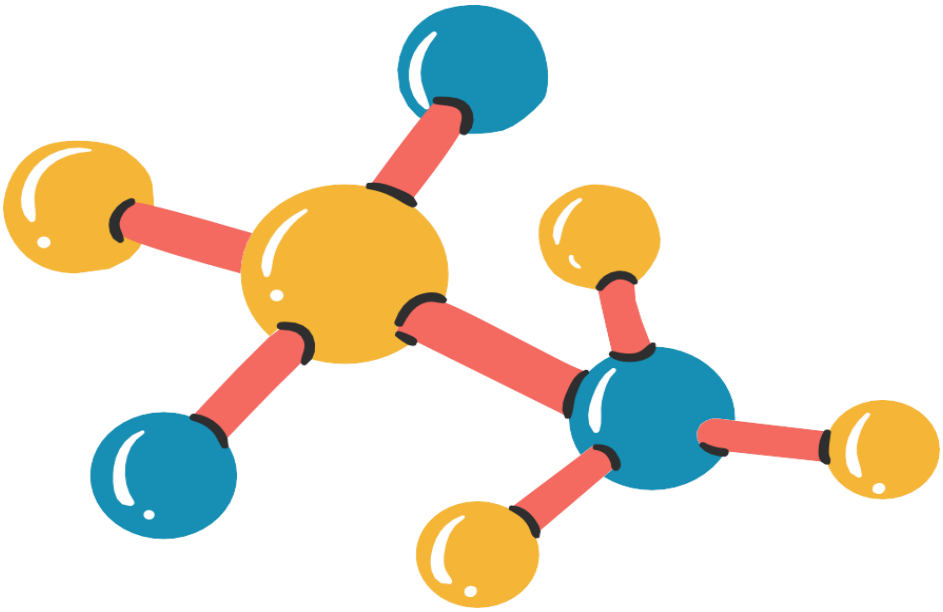
Sheet no.18

Biochemistry



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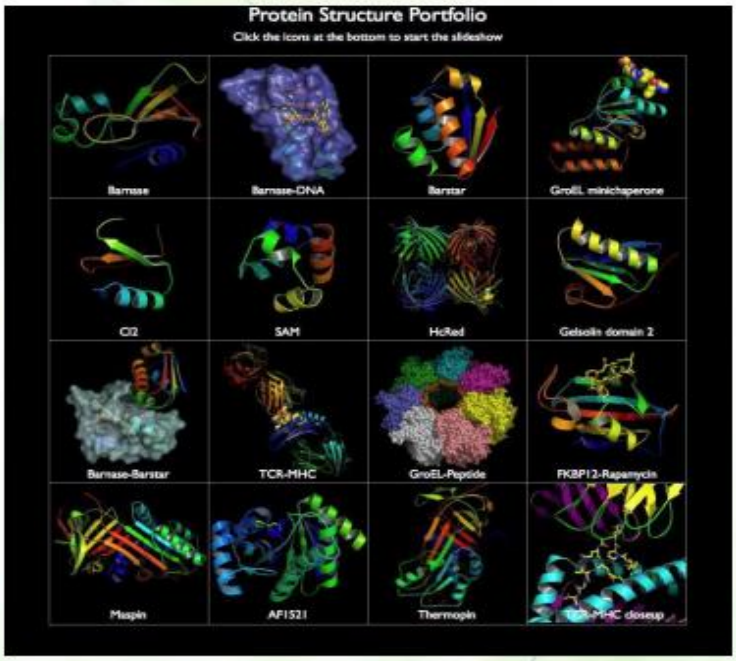
Proteins Structure

Protein Structure

Overview of proteins

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



Nature of proteins:

A. Composition:

1. Proteins are macromolecules formed of amino acids united together by peptide bonds (peptide bond is actually amide bond) .

2. Amino acids are commonly found in proteins in different proportions (we have huge variety in the order of proteins , can describe through number of proteins = 20^n ,

n : the number of residues in the protein > multi multi different proteins.

3. Some proteins are formed of 2 or more polypeptide chains.

B. Size of proteins.

1. Proteins having a very high molecular weight, ranging from 5,000 to several millions.

*There are 4 stages in the formation of proteins :

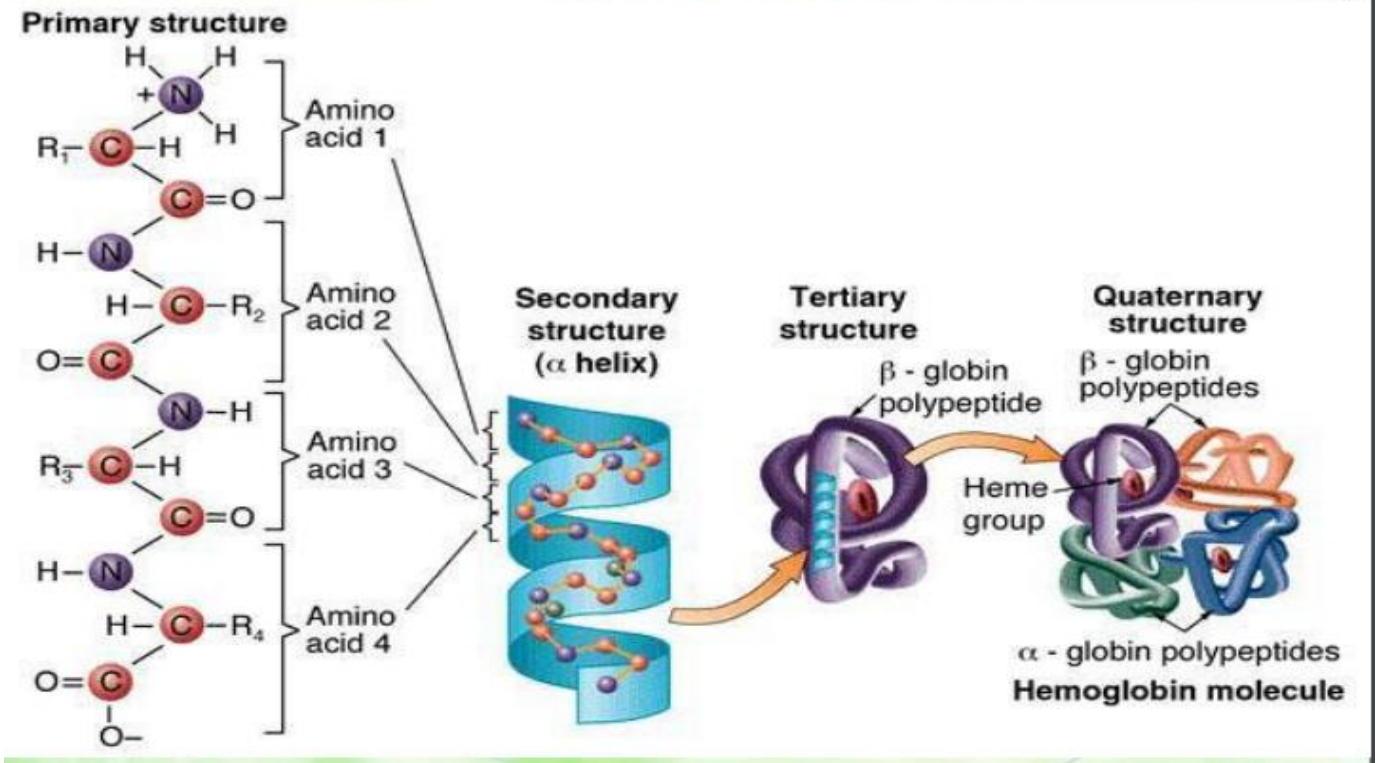
Primary , secondary , tertiary , quaternary .

In each stage we can obtain details of the proteins in the following manner :

Levels of protein structure

- Primary structure: the sequence of amino acid residues
- Secondary structure: the localized organization of parts of a polypeptide chain
- Tertiary structure: the three-dimensional structure and/or arrangement of all the amino acids residues of a polypeptide chain
- 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

Protein structure



Primary structure

What is primary structure?

- The order in which the amino acids are covalently linked together.

  Example: Leu—Gly—Thr—Val—Arg—Asp—His
- The primary structure of a protein determines the other levels of structure.
- A single amino acid substitution can give rise to a malfunctioning protein, as is the case with sickle-cell anemia.

- ***Conformation of proteins = (protein structure):***

A* Primary structure:

In this stage we have the inherited information of forming proteins. Also we can the see the sequence of the amino acid from the N terminus to the C terminus.

- Definition: *It is the arrangement of amino acids in the polypeptide chain.*

- Bonds responsible for the primary structure: The peptide bonds "covalent".

The R groups are outward to reduce steric hindrance.

- Mechanism:

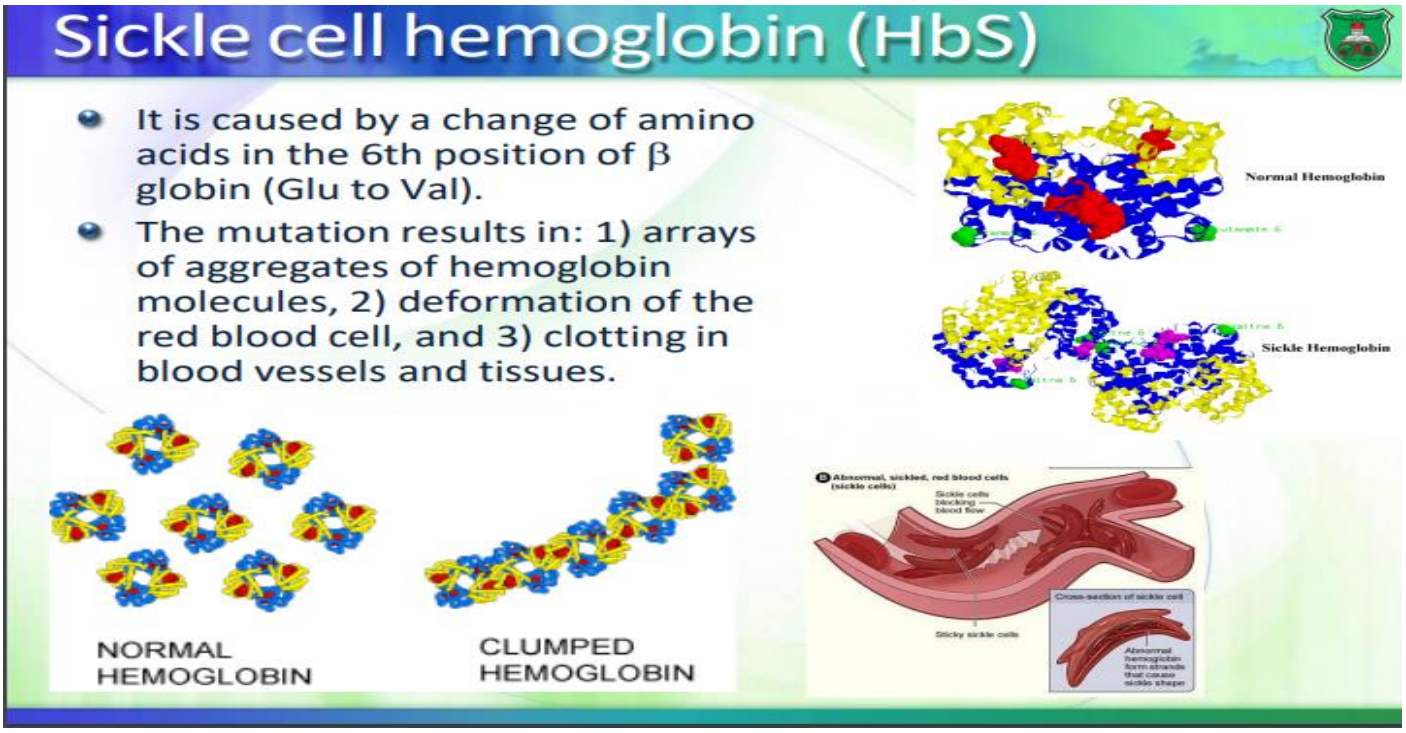
1. Each polypeptide chain starts on the left side by free amino group of the first amino acid, It is termed N-terminal (or N-terminus) amino acid.

2. Each. polypeptide chain ends on the right side by free carboxyl group last amino acid, It is termed C-Terminal (or C-terminus) amino acid.

3-The types and arrangement of amino acid in each protein is determined by the genetic information present in DNA.

The importance of the primary conformation:

A single amino acid substitution can give rise to a malfunctioning protein, as is the case with



sickle-cell anaemia:

Mutation: It is caused by a change of amino acids in the 6th position of β globin (Glu to Val).

Results: This mutation results in:

1) Arrays of aggregates of hemoglobin molecules (cause the Val is hydrophobic a.a so in this case it will face the environment which is unfavourable situation . In order to be more stable , it will aggregate to each other (same principle in the Micelle formation)

2) Deformation of the red blood cell . This leads to convert the shape of RBC from concave into the sickle shape that will reduce the *affinity to carry* O_2 .

3) Clotting in blood vessels and tissues.

Cystic fibrosis:

Just from non polar to non polar amino acid changes.

It's an inherited disease results from a mutation CFTR gene which will change a protein that regulates *the movement of salt (as Cl^-) in and out of cells*. The result is thick, **sticky mucus in the respiratory, digestive systems. as well as increased salt in sweat**.

This affects the movement of chloride in and out of cells. With this defect , chloride stay trapped inside the cells and this decrease water movement toward outside because chloride is pulling the water by osmatic pressure.

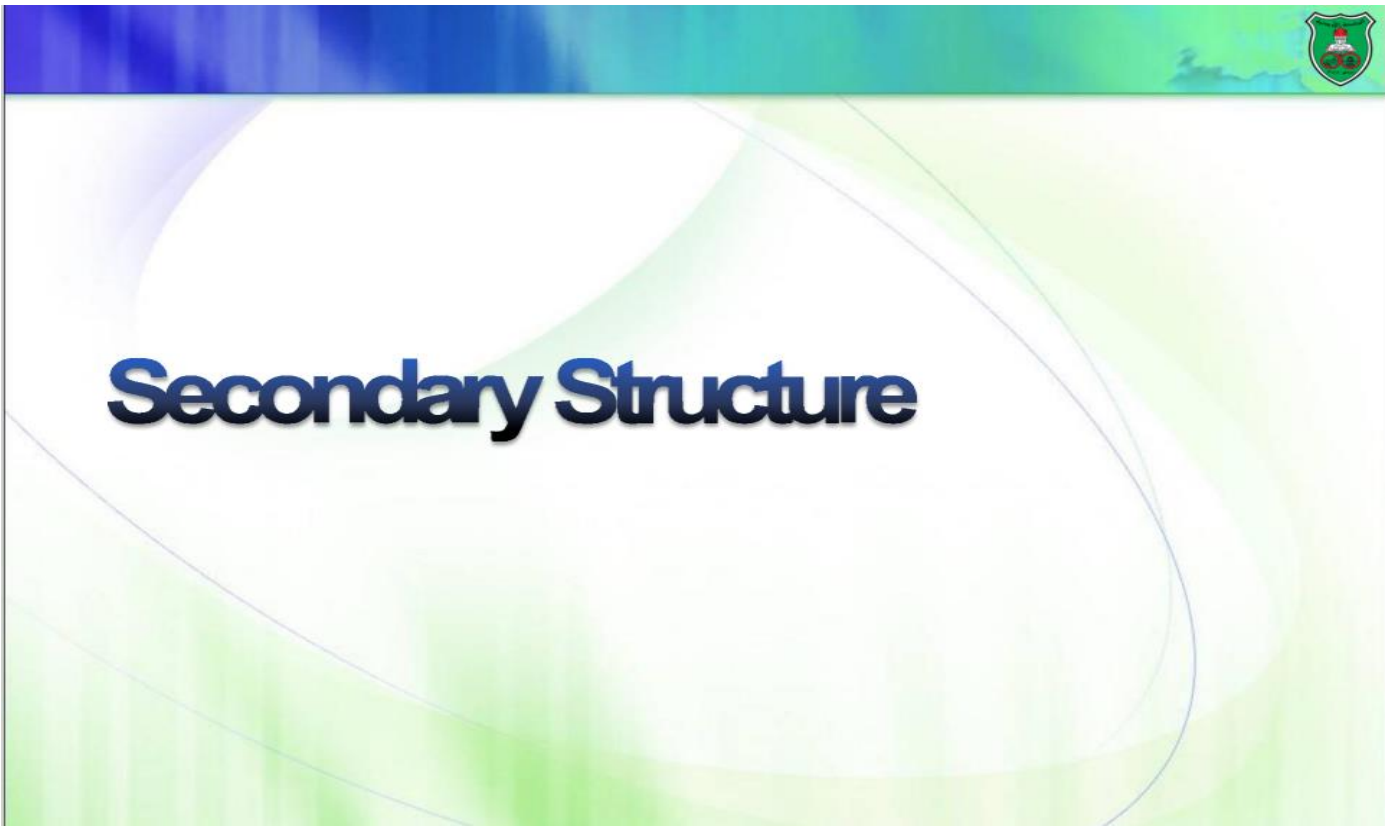
Hence this lower the amount of water in these secretions making them thick and sticky not acting as lubricant (ملين)

Digestive

The thick mucus can also block tubes that carry digestive enzymes from your pancreas to your small intestine. Without these digestive enzymes, your intestines aren't able to completely absorb the nutrients in the food you eat.

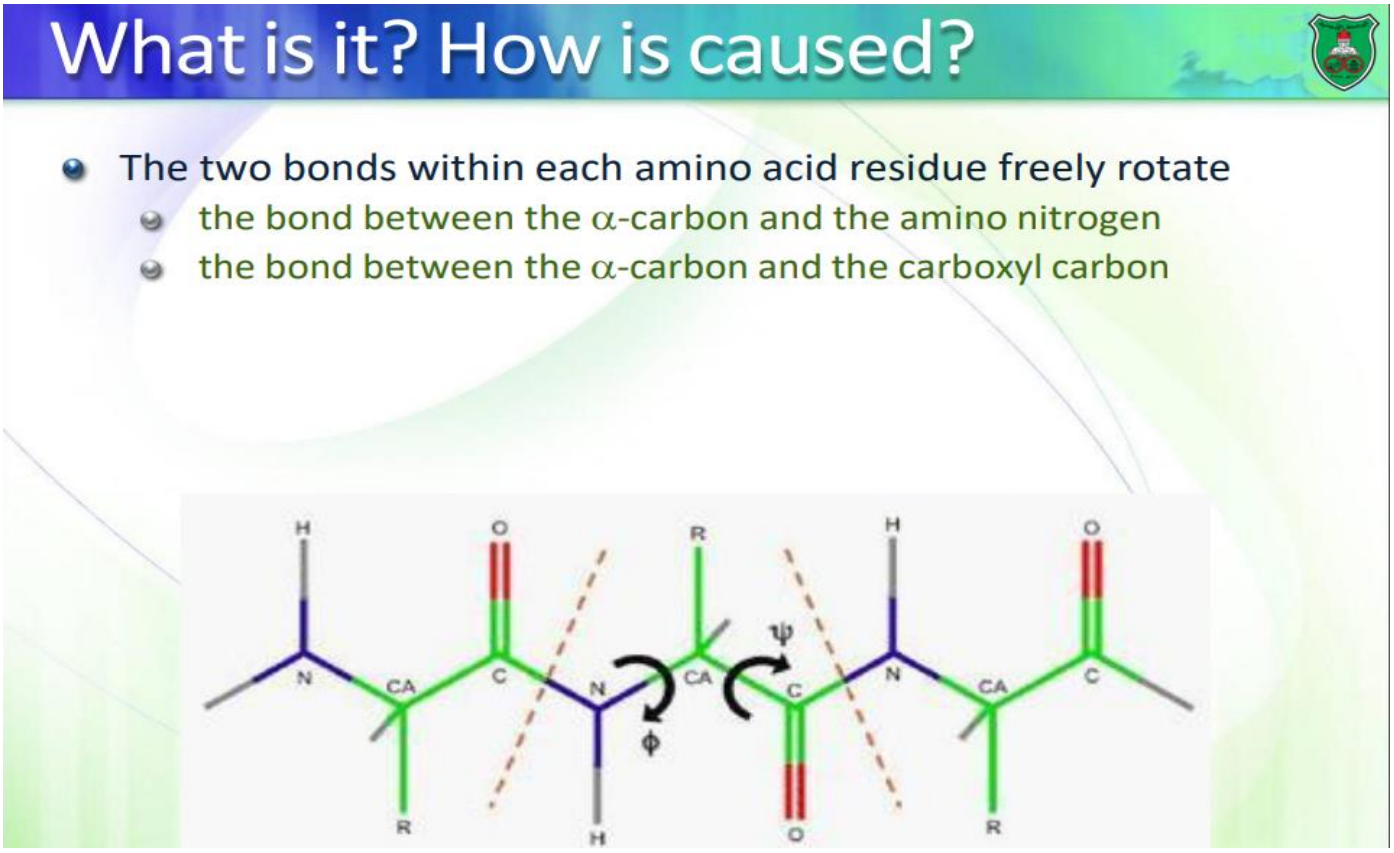
Respiratory

The mucus that is secreted will be very thick and close the tubes that carry air in and out of your lungs. It may be a medium for a bacteria to grow.



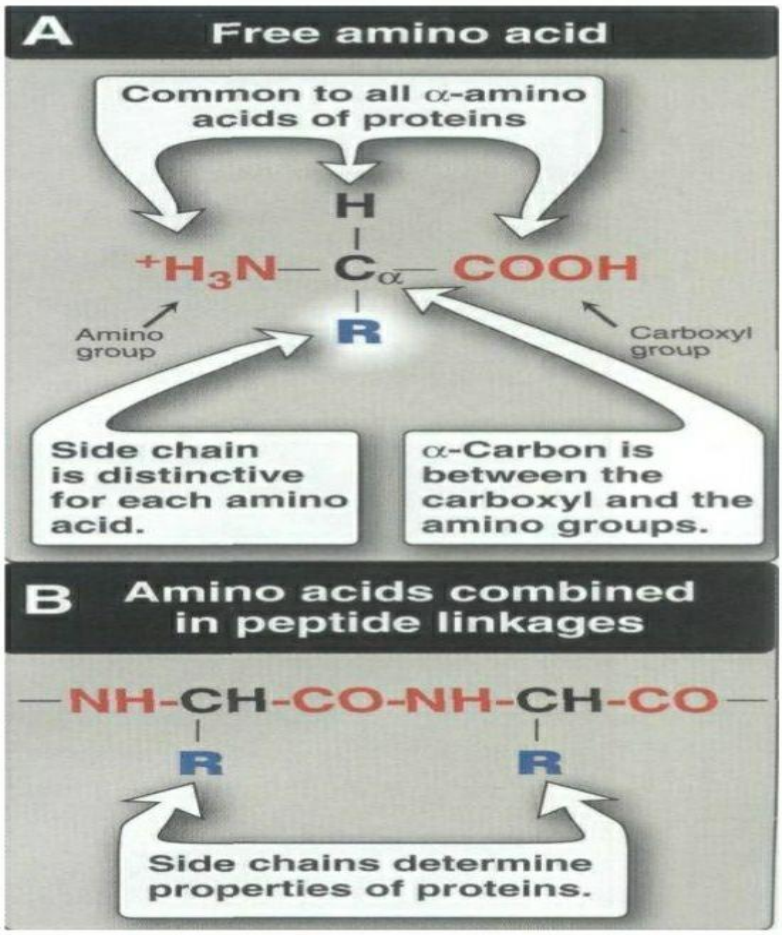
B*Secondary structure:

Here we have interactions between backbone atoms (one difference of tertiary form) we can define it as : It is the spatial relationship of adjacent amino acid residues.



Bonds responsible: *Hydrogen bonds*.

It is the bond between the hydrogen of -NH group of one amino acid residues and the carbonyl oxygen (C=O) of the fourth one .



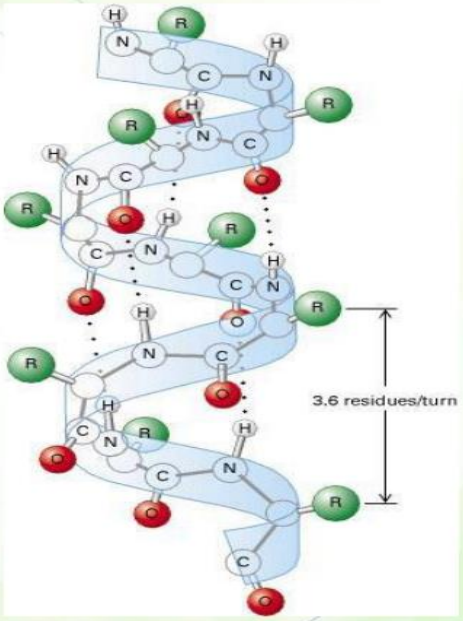
****Secondary structure results from interaction of adjacent amino acid residues (first and fourth).**

Common secondary structures

- A hydrogen-bonded, local arrangement of the backbone of a polypeptide chain.
- Polypeptide chains can fold into regular structures such as:
  - Alpha helix
  - Beta-pleated sheet
  - Turns
  - Loops

The α helix

- It looks like a helical rod.
- The helix has an average of 3.6 amino acids per turn.
- The pitch of the helix *(the linear distance between corresponding points on successive turns)* is 5.4 Å
  - 1 Å = 10^{-10} m
- It is very stable because of the linear hydrogen bondings.



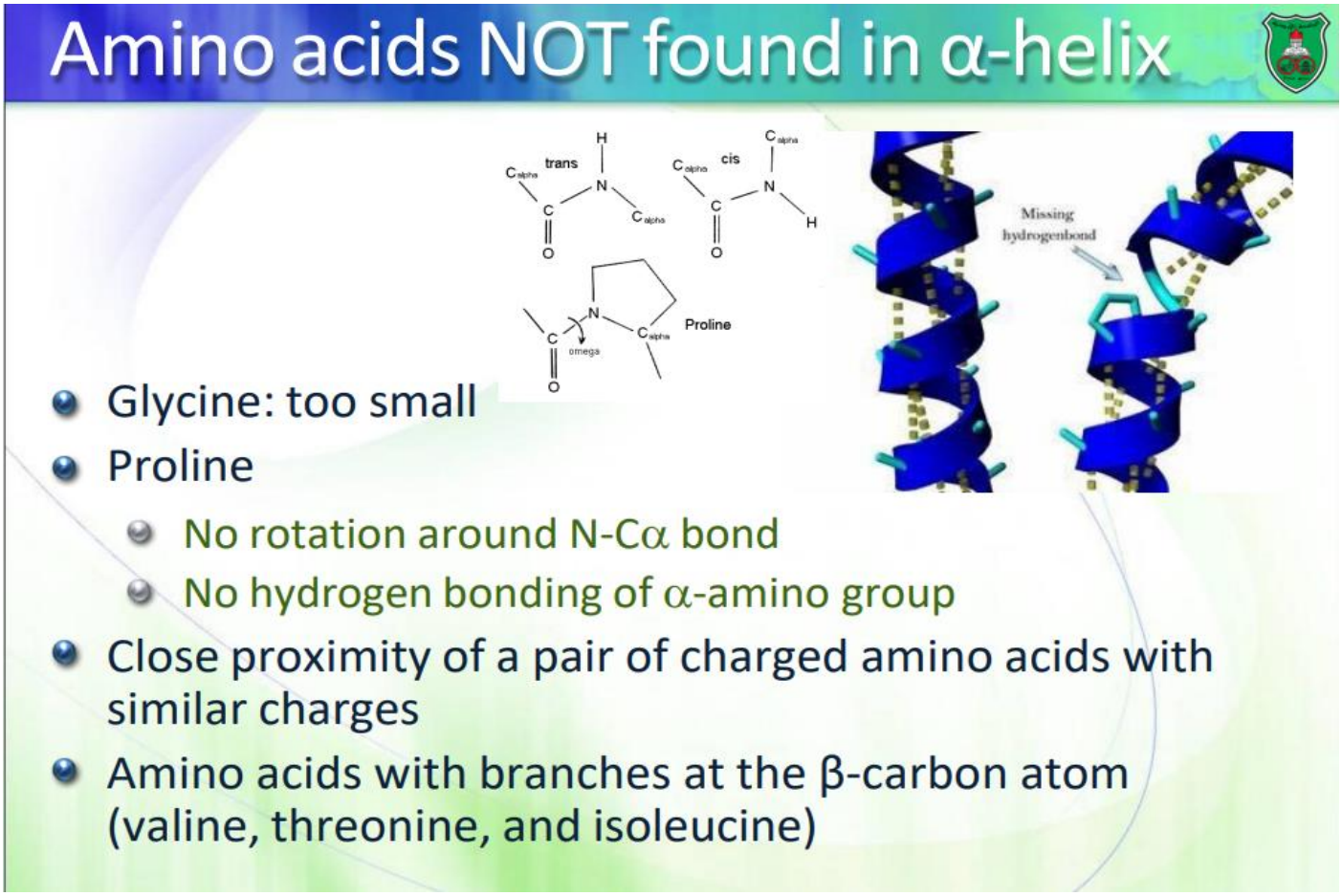
***Alpha helix :**

Shape & formation:

It is a rod like structure with the peptide bonds coiled tightly inside and the side chains of the residues (R) extending outward from the chain.

The helix has an average of 3.6 amino acids per turn. The pitch of the helix (the linear distance between corresponding points on successive turns) is 5.4 Å

(1 Å = 10^{-10}m) .It is very stable since of the linear hydrogen bonding.



Amino acids NOT found in α-helix (TROUBLES WE FACE IN THE PRIMARY STRUCTURE) :

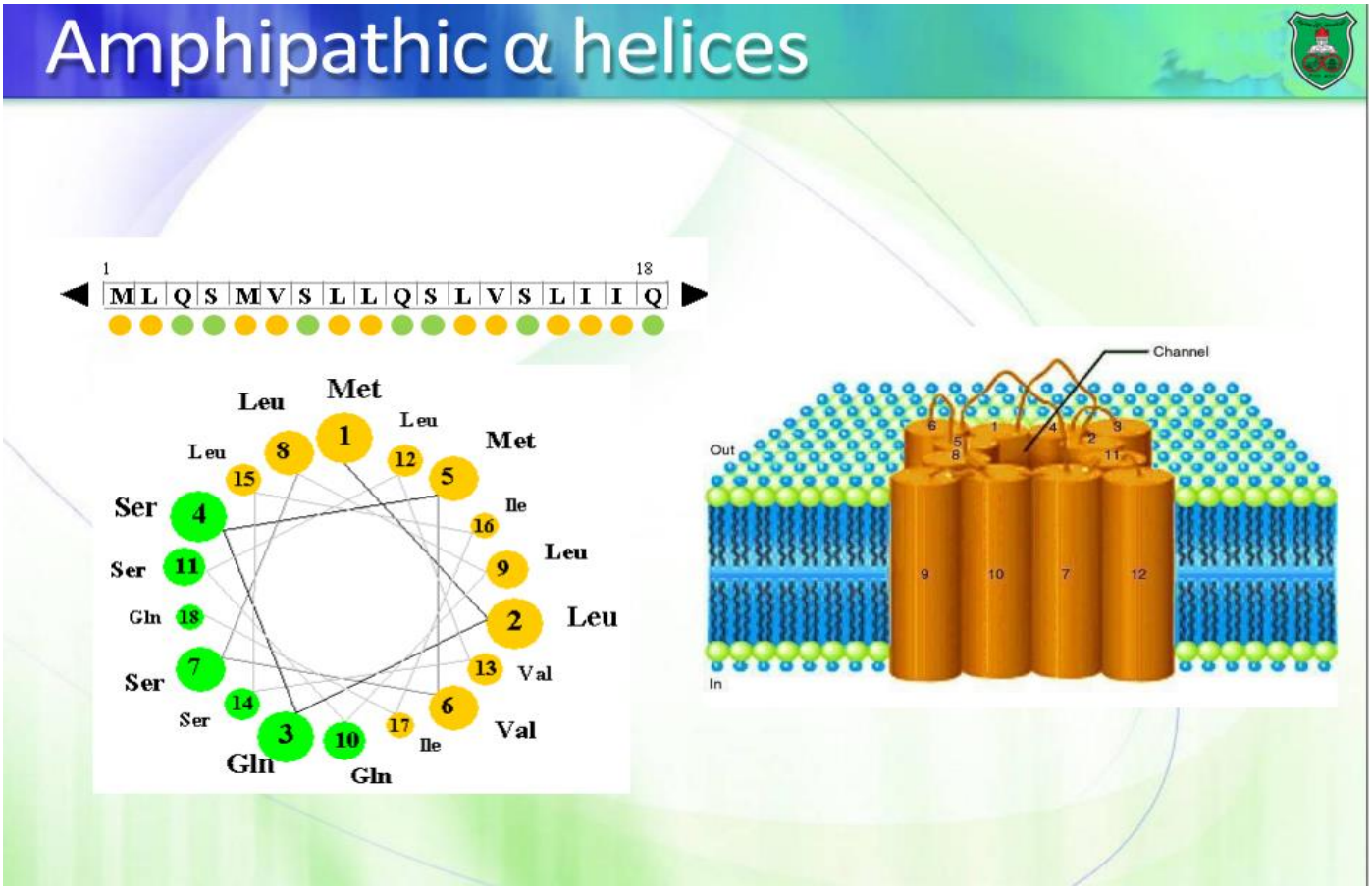
1-*Glycine*: too small and very movable

2-Proline: two reasons

a-No rotation around N-Cα bond

b-No hydrogen bonding of α-amino group

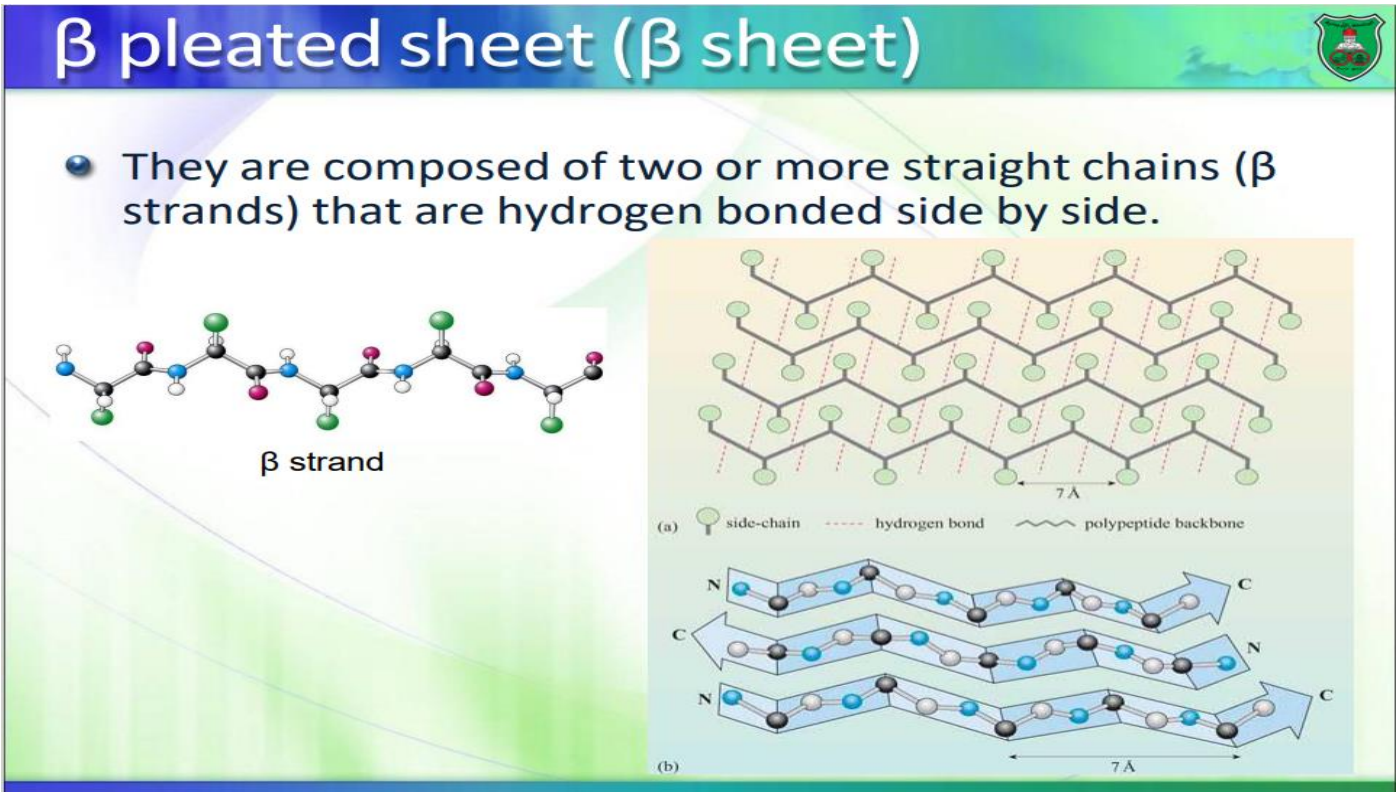
3-Close proximity of a pair of charged amino acids with similar charges , or two bulky ones adjacent to each other.Amino acids with branches at the β-carbon atom (valine, threonine, and isoleucine) , by its branching it becomes wider more and more to fill space.



Amphipathic α helices:

Channels in the cell membrane as an example. We see there are two domains : one faces the hydrophobic region of the membrane so it should be consisted of non-polar (hydrophobic) amino acids . Where inside the channel we need polar amino acids to facilitate movement of molecules. We call it amphipathic nature . This trans membrane domain is critical in forming the passage of molecules.

Note : not necessary for all proteins to have this ability , it depends on the function.

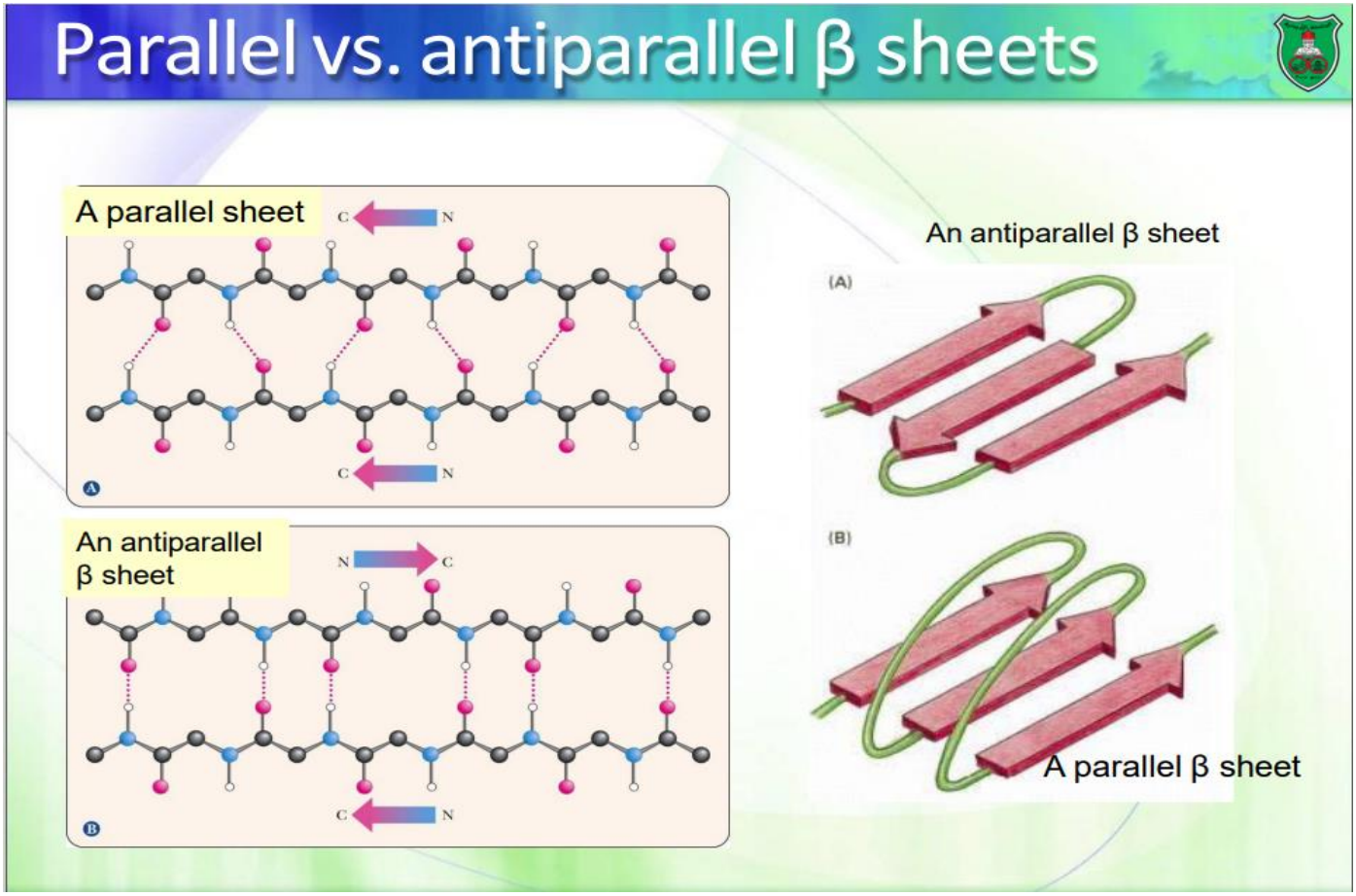


Beta-pleated Sheet

This structure is formed between two or more separate polypeptide chains. It may also be formed between segments of the same polypeptide chain.

Hydrogen bond is also responsible for its formation. It occurs between (-NH) group of one chain (or segment) and (C=O) of group of adjacent chain (or segment).

We have more space for groups to orientate , so the difficulties we find in the a helix not found here.



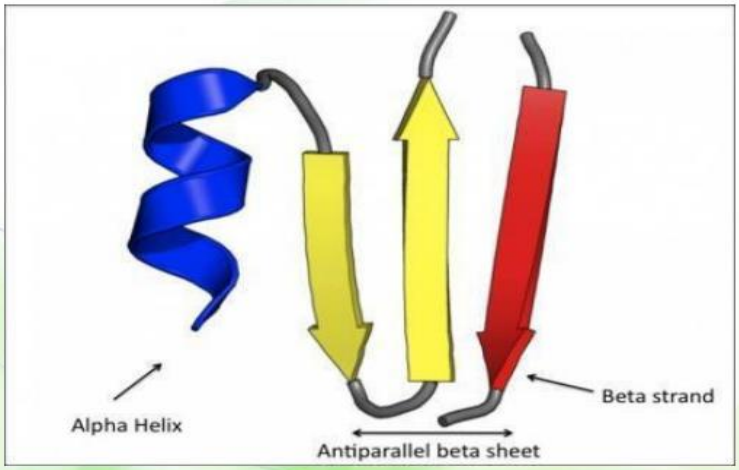
Two types of β-sheets are present:

1) Parallel β-sheets: in which the two polypeptide chains run in the same direction. Here we have *loops* to connect the sheets with each other. We recognize the N terminus and C terminus in the same direction as shown in the picture. some amino acid without forming sheets (doesn't participate)

2) Antiparallel β-sheets: in which the two polypeptide chains run in opposite direction here we find *turns*.

How many β strands can a β sheet have?

- β sheets can form between many strands, typically 4 or 5 but as many as 10 or more.
- Such β sheets can be purely antiparallel, purely parallel, or mixed.



How many β strands can a β sheet have?

β sheets can form between many strands, typically *4 or 5* but as many as *10 or more*. Such β sheets can be purely antiparallel, purely parallel, or mixed. Using many techniques to determine the changes in proteins shape to understand the function to make drugs in a disease case.

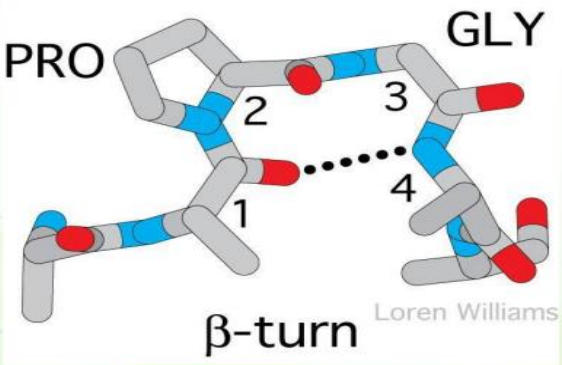
-Each amino acids forming the structure of 2nd stage depending on the inherited information that stored in the *primary structure*. Each protein has its own 3D shape , so by the eventual of the folding process we get that functional shape.

Effect of amino acids in β-sheets

- Valine, threonine and Isoleucine with branched R groups at β-carbon and the large aromatic amino acids (phenylalanine, tryptophan, and tyrosine) tend to be present in β-sheets.
- Proline tends to disrupt β strands

β-turns

- Turns are compact, U-shaped secondary structures
- They are also known as β turn or hairpin bend
- What are they used for? How are they stabilized?
- Glycine and proline are commonly present in turns
- Why?

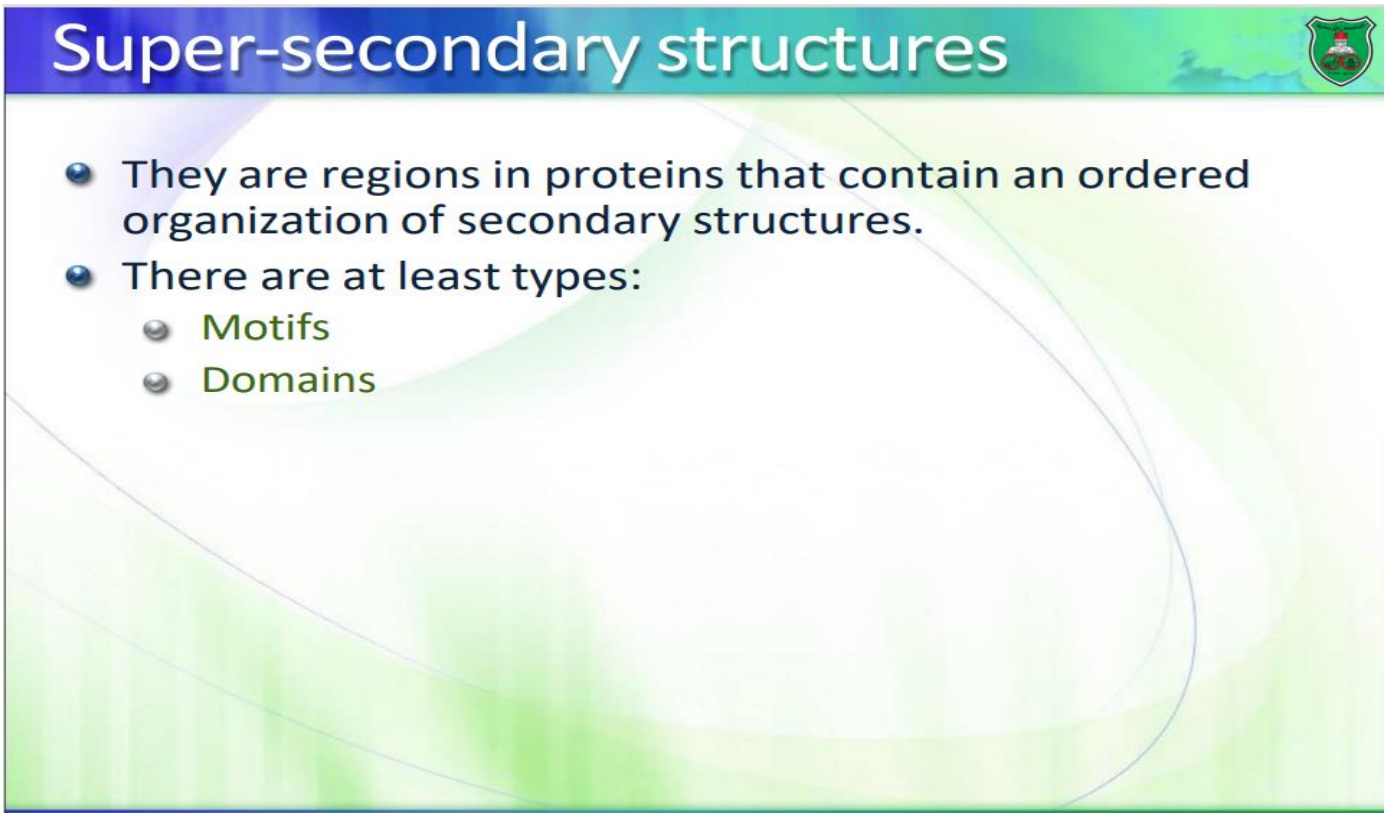


Turns

Turns are compact, U-shaped secondary structures

They are also known as β turn or hairpin bend

-Gly and Pro are favourable in the turns because of the small size and flexibility of Gly and the cyclic structure of the Pro. The benefit of the turns is to change the direction of the peptide backbone by nearly 180°, allowing the peptide chain to fold back onto itself (as in anti-parallel B sheets) , we see loops in the parallel one.



Super (up)-secondary structures

*They are regions in proteins that contain an ordered organization of secondary structures. We consider them between the secondary and tertiary structure.

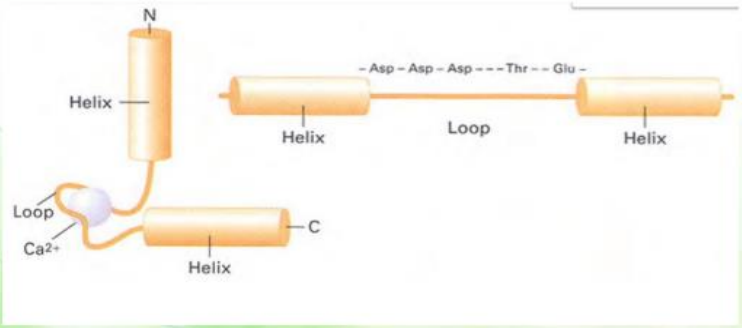
*Generally, occur when the protein chain needs to change direction in order to connect two other elements of secondary structure.

One method for stabilizing a β-turn structure is to create a disulfide bridge between side chains.

*Pro and Gly residues are favoured in β-turns mainly due to the cyclic structure of Pro and the flexibility of Gly.

A motif (a module)

- A motif is a repetitive supersecondary structure, which can often be repeated and organized into larger motifs.
- It usually constitutes a small portion of a protein (typically less than 20 amino acids).
- In general, motifs may provide us with information about the folding of proteins, but not the biological function of the protein.

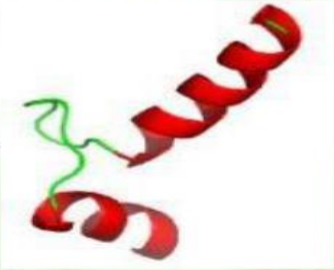


A motif is a repetitive units ,need of secondary structure. Motif (helix , sheets , turns , loops ,…) It can be very short (made up of 20 amino acids) and it can be long (complex). Not related to protein function.

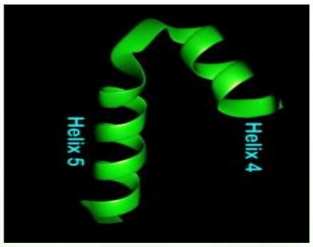
Examples of motifs

Very simple

Helix-loop-helix is found in many proteins that bind DNA. It is characterized by two α-helices connected by a loop.

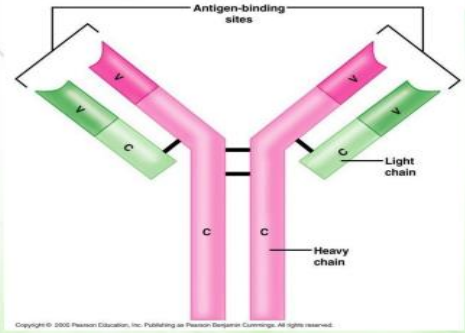


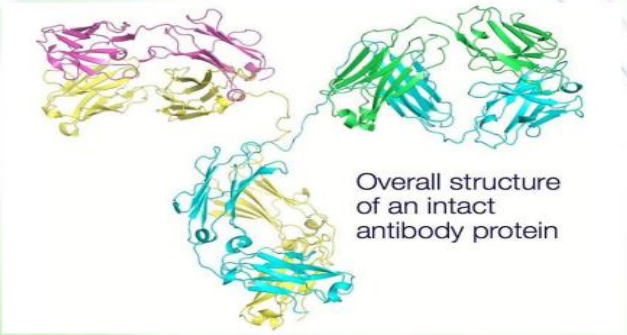
Helix-turn-helix is a structural motif capable of binding DNA. It is composed of two α helices joined by a short strand of amino acids

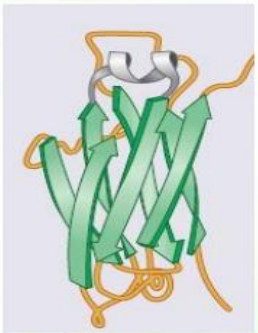


A more complex motif is...

- The immunoglobulin fold or module that enables interaction with molecules of various structures and sizes. **In antibodies**



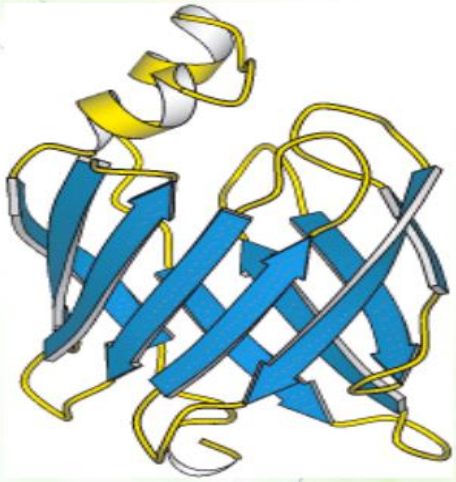




This fold can be found in another protein, but this does not mean that they are similar in function, it is only similar in shapes.

A domain

- A domain is a compactly folded region of polypeptide found in proteins with similar function and/or structure.
- Domains with similar conformations are associated with the particular function.
- A structural domain may consist of 100–200 residues in various combinations of α helices, β sheets, turns, and random coils.
- They fold independently of the rest of the protein.
- Domains may also be defined in functional terms
  - enzymatic activity
  - binding ability (e.g., a DNA-binding domain)



It is usually larger, associated with a specific function.

The main difference between domain and motif:

**** Domain is not super secondary structure, it is functional unit. They are similar in sequence, so they are similar in function and shape between different proteins.**

***Domains may also be defines in functional terms :**

-Enzymatic activity (catalytic domain →the amino acids responsible of running of the reaction .

-Binding ability : It contains a specific sequence of amino acids that has the ability to bind to DNA, so it is known through this that this protein is a transcription factor that has the ability to bind to DNA.

Tertiary structure

What is tertiary structure?

- The overall conformation of a polypeptide chain
- The three-dimensional arrangement of all the amino acids residues
- The spatial arrangement of amino acid residues that are far apart in the sequence

**The tertiary structure (3D shape of the molecule) the functional form contains only one polypeptide chain

*In the secondary structure , It has 5 helix and 2 sheets

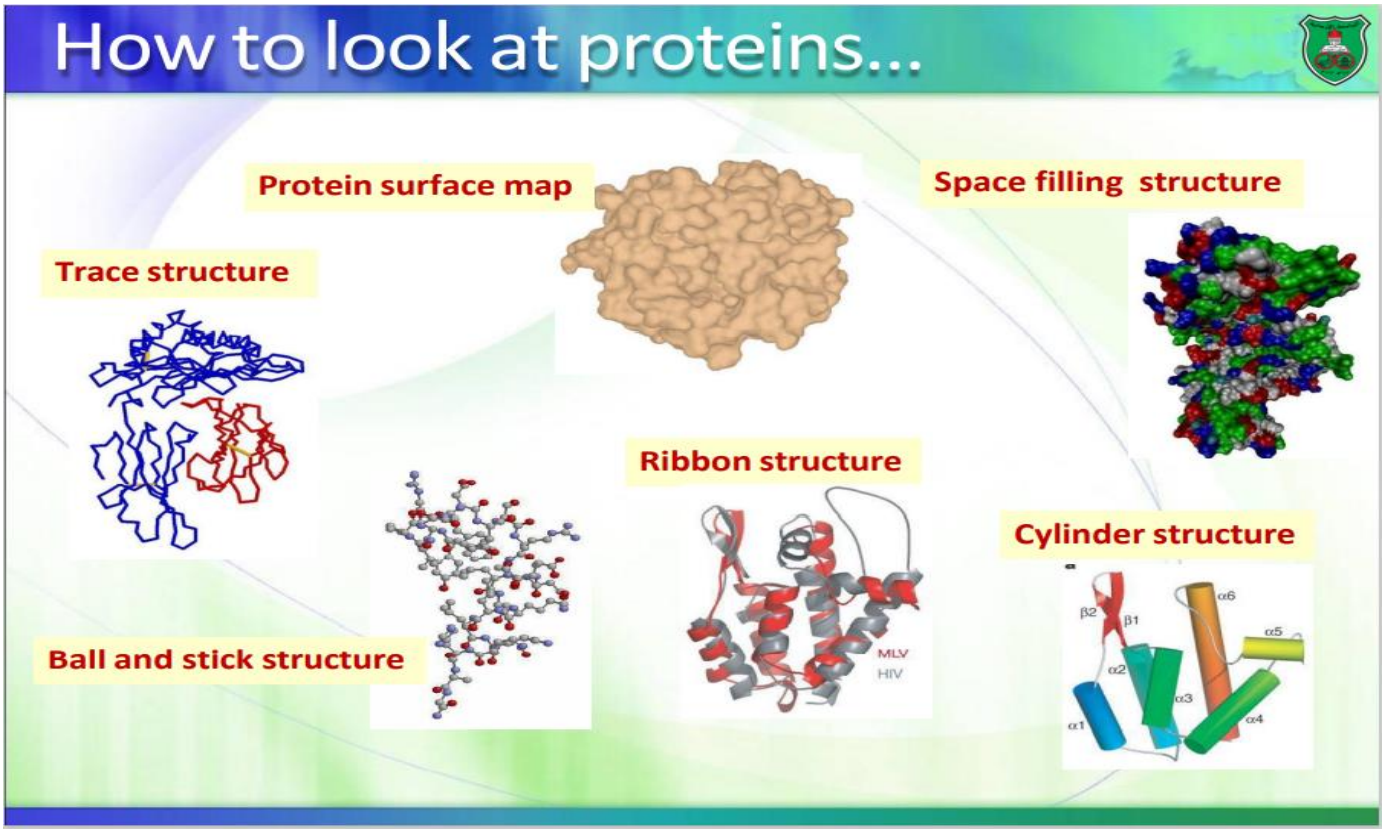
*In tertiary structure, We would like to know how they are arranged in relation to each other and the distances

and angles between them and are they parallel or perpendicular and are the sheets between the helixes or not.

This is the final shape of our conformation of the polypeptide chain + any additions to the protein such as sugar (glycoprotein), heme group (heme protein) or lipid (lipoprotein) are added at this stage (tertiary structure).

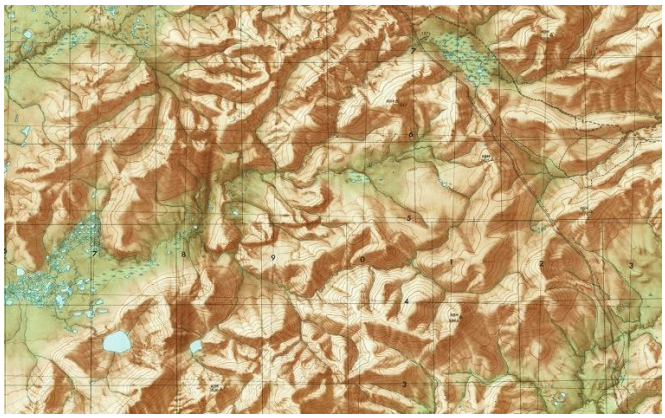
If a protein consists of only one peptide chain, then this is the maximum form (tertiary structure) it will receive.

If a protein consists of more than one peptide chain, it will form quaternary structure. It is formed as a result of interactions between R groups.



The tertiary structure is represented in different ways:

1*Protein surface map : Like a topographic map



2*Space filling structure: colorful shape (Each color represents an atom)

Red → oxygen. Blue → nitrogen.

Green → R group Gray → carbon

*it Expresses the volume of the size of the atoms

3*Cylinder structure → It represents a helix in the form of a cylinder and shows the relationship of a helix with another helix(parallel, perpendicular , etc ..)

-loops and turns → lines -Sheets → arrows …

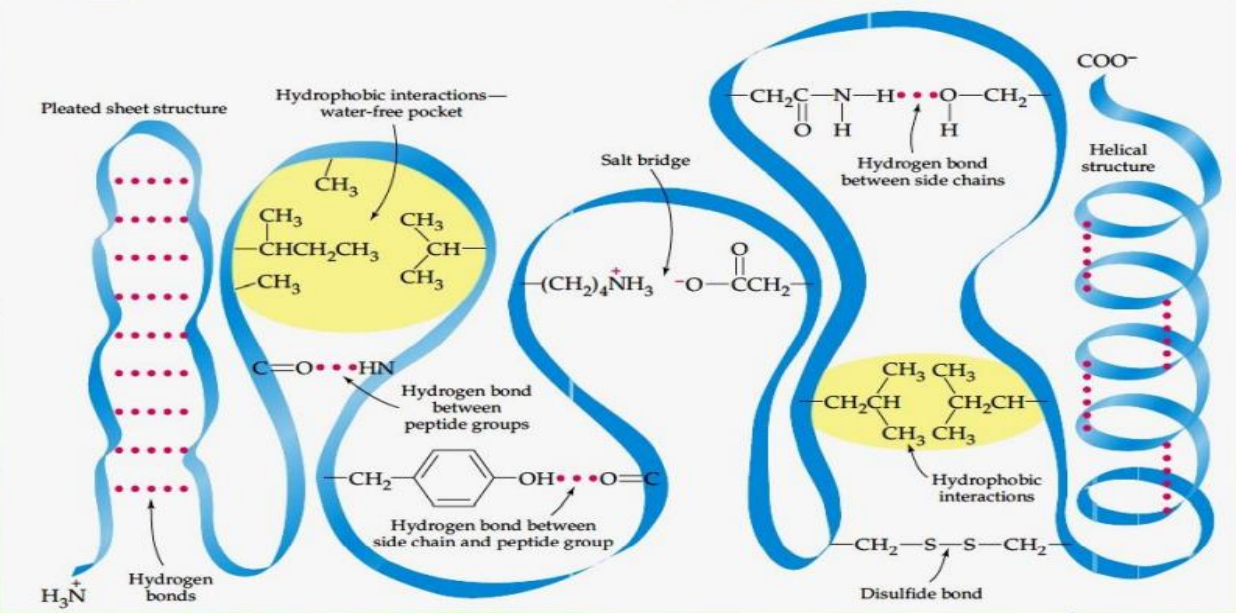
4*Ribbon structure …

5*Ball and stick structure.

Atoms → balls Bonds → lines

6*Trace structure

Shape determining forces



The tertiary structure is determined by the interactions between the side chains

***For example,**

1* the hydrophobic side chains combined together and form hydrophobic pocket and a large number of hydrophobic interactions between them.

2* salt bridges → (ionic interactions) between positively charged amino acids and negatively charge amino acids' side chains

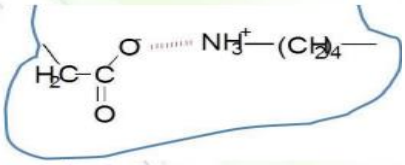
3* hydrogen bonds between side chains

4* hydrogen bonds between the side chain and the back bone.

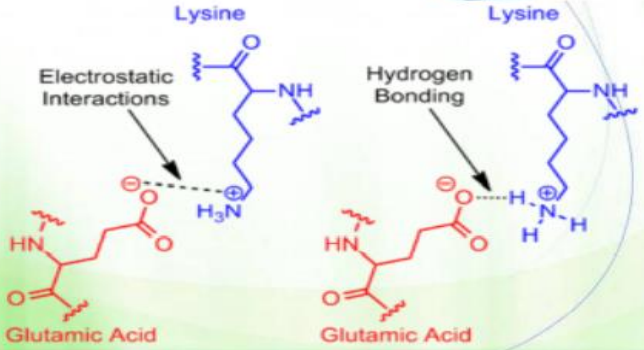
5* disulfide bond (covalent bonds) contributes in tertiary structure between cysteine.

Non-covalent interactions

- Hydrogen bonds occur not only within and between polypeptide chains but with the surrounding aqueous medium.
- Charge-charge interactions (salt bridges) occur between oppositely charged R-groups of amino acids.
- Charge-dipole interactions form between charged R groups with the partial charges of water.



The same charged group can form either hydrogen bonding or electrostatic interactions



**Salt bridges:

- Full charge — full charge

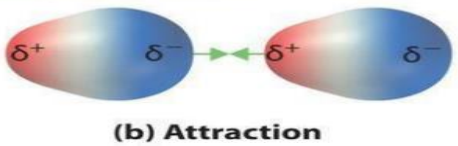
-Full charge — partially

- Partially — partially

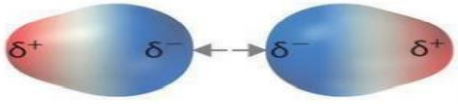
-All possibilities exist and all contribute to reaching the final shape and its stability

van der Waals attractions

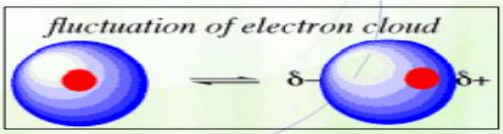
- There are both attractive and repulsive van der Waals forces that control protein folding.
- Although van der Waals forces are extremely weak, they are significant because there are so many of them in large protein molecules.



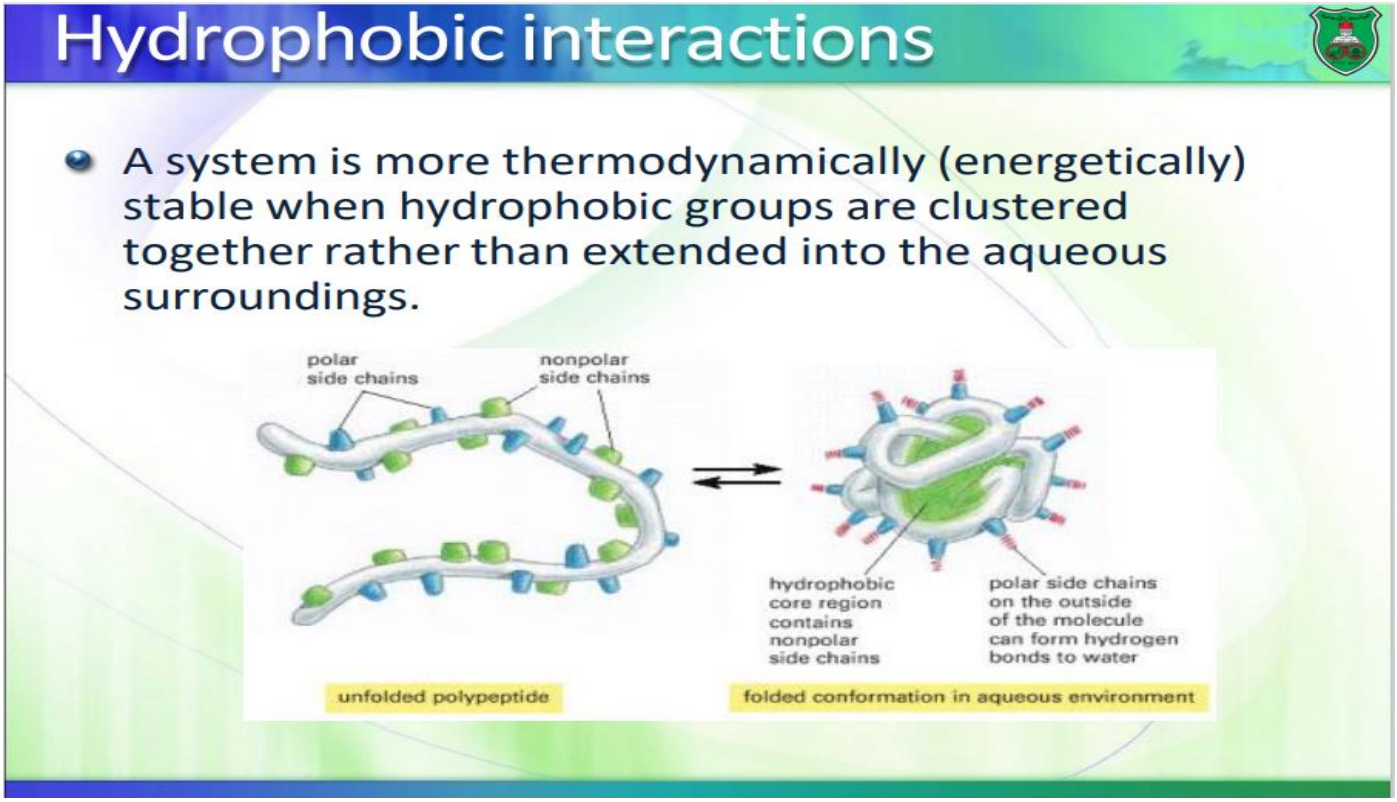
(b) Attraction



(d) Repulsion



Van der Waals is found between atoms contributes in protein folding.



When the shape is like a rope, it is unstable. Immediately it will enter the folding process. When the three-dimensional structure is formed, the polar parts are on the surface (outside) and the non-polar parts are on the inside to reach a stable state, but this does not mean that there are no polar parts inside the protein. For example, We can find a protein that acts as an enzyme and an active site that is inside (containing polar amino acids) because they contribute to the catalysis process, and this process consists of many temporary steps until the final shape is obtained.

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

- 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