

# Protein structure

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# Objectives:

- Understand the peptide bonding between amino acids.
- Explain the different levels of protein structure and the forces stabilizing these structures and what happens when the protein is denatured.
- Define the  $\alpha$ -helix and  $\beta$ -sheet as the most commonly encountered secondary structures in a protein molecule.
- Correlate the protein structure with function with hemoglobin as an example.
- Understand how the misfolding of proteins may lead to diseases like Alzheimer's or prion disease.

# What are proteins?



large, complex molecules

made up of hundreds or thousands of **smaller units called amino acids** which are attached to one another in long chains by a **peptide bond**

required for the structure, function, and regulation of the body's tissues and organs.

They do most of the work in cells

play many critical roles in the body.

# What are proteins?



There are mainly 20 different types of amino acids that can be combined to make a protein.

The **sequence of amino acids determines** :

1- each protein's unique three-dimensional (3D) structure

2- its specific function.

Proteins can be described according to their large range of functions in the body

Antibody

Enzyme

Messenger

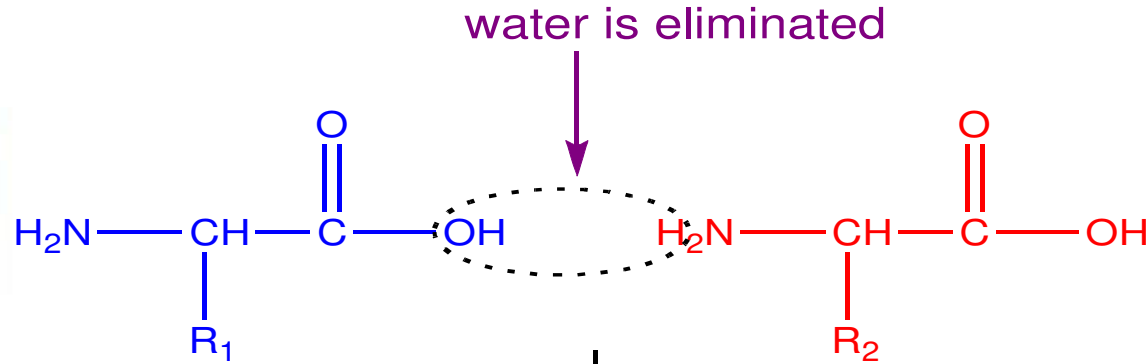
Structural component

Transport/  
storage

# Peptide Bond (Amide bond):

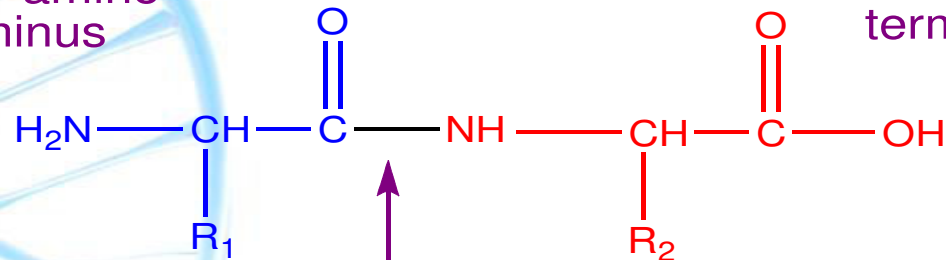
formed between  **$\alpha$ -carboxyl group** of an amino acid and  **$\alpha$ -amino group** of the other amino acid.

two amino acids condense to form...



...a dipeptide. If there are more it becomes a polypeptide. Short polypeptide chains are usually called peptides while longer ones are called proteins.

N or amino terminus



+ HOH

peptide bond is formed

residue 1

residue 2

## Notes :

Covalent bond formed by (dehydration ):

1- OH from COOH.

2- H from NH<sub>3</sub>.

“removal of water”

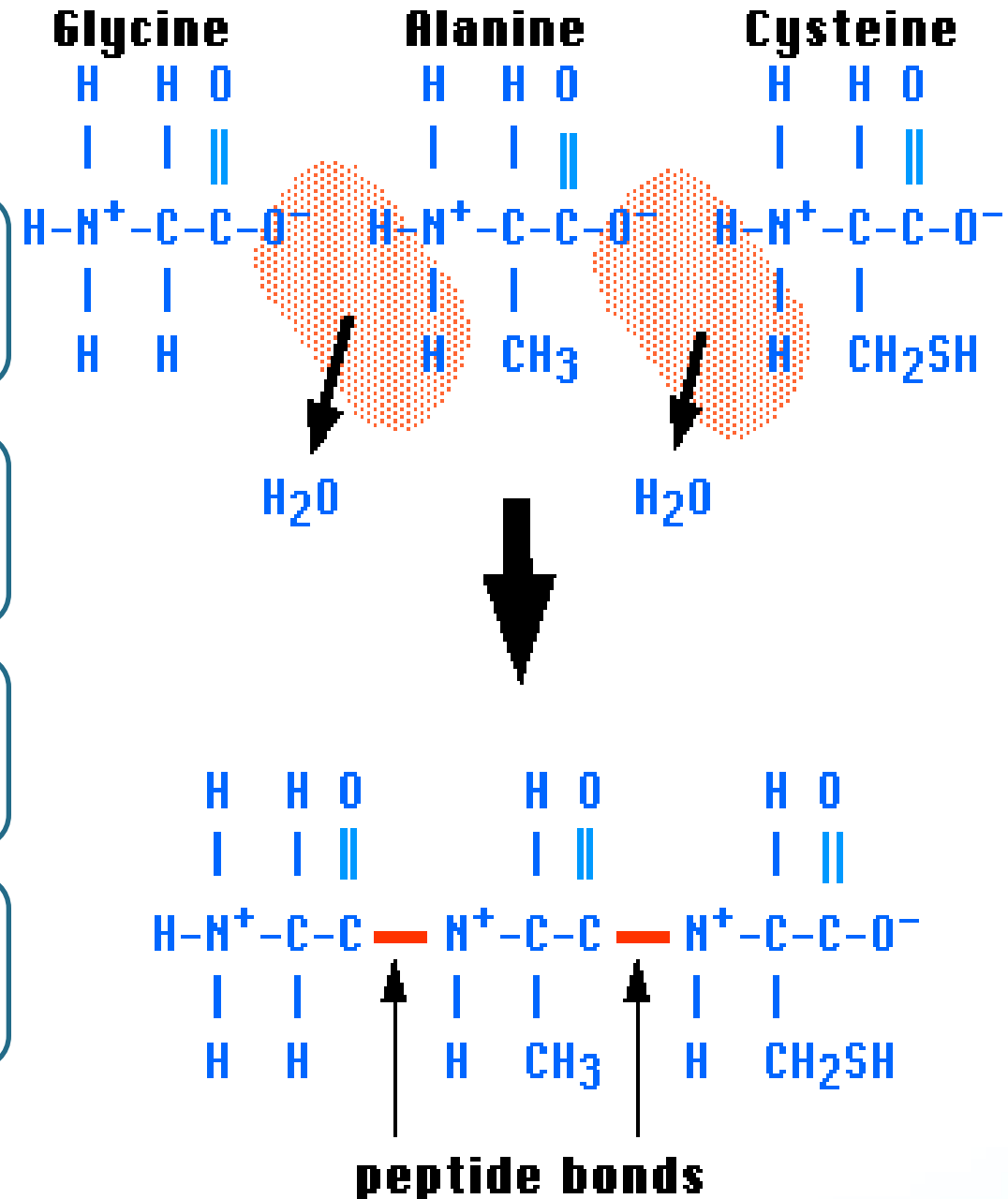
- Residue : amino acid in a peptide chain
- We always read from N-terminus to C-terminus.

❖ Each amino acids in a chain make **two** peptide bonds

❖ The amino acids at the two ends of a Chain make **only one** peptide bond

❖ The amino acid with a free amino group is called **amino terminus** or NH<sub>2</sub>-terminus

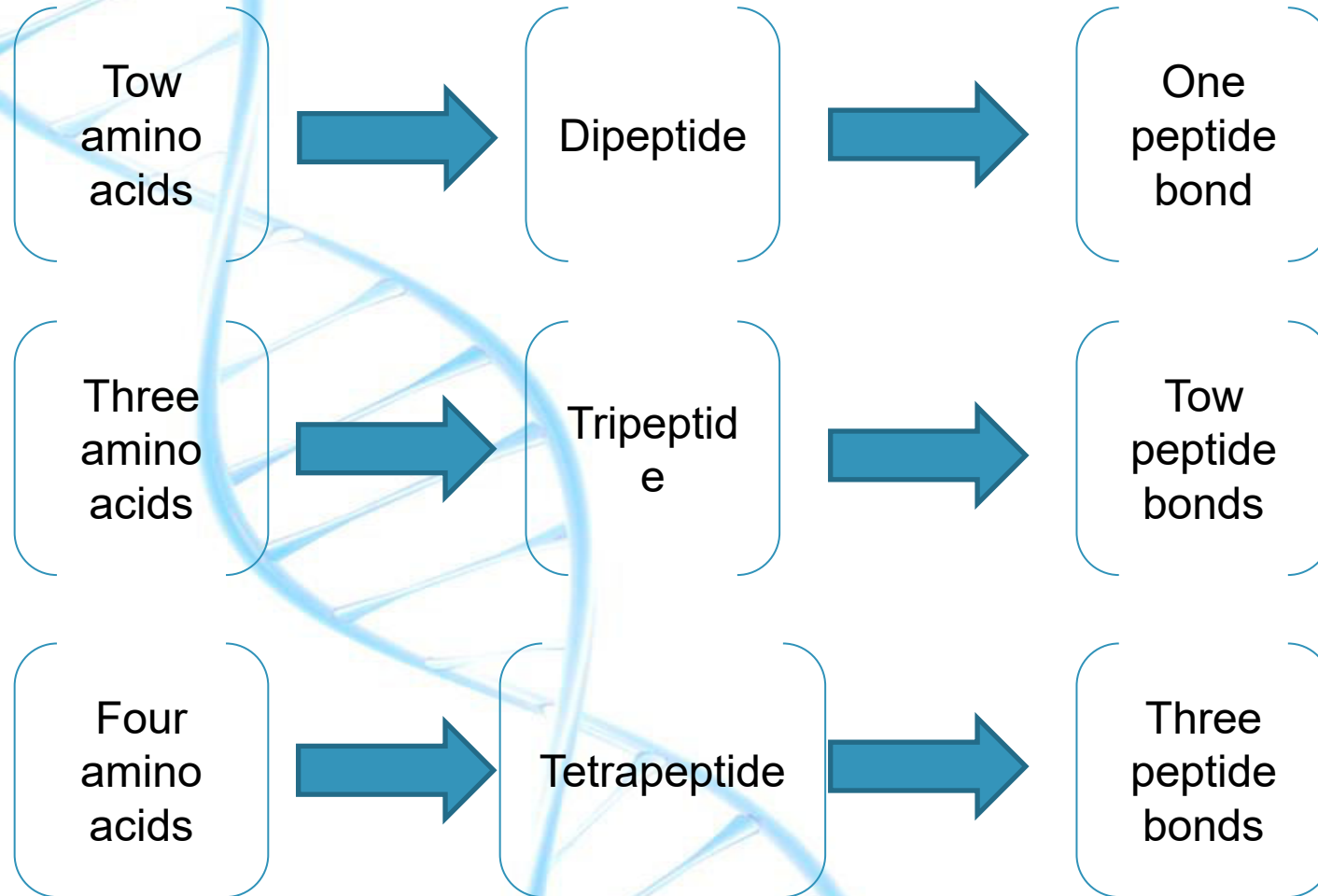
❖ The amino acid with a free carboxylic group is called **carboxylic terminus** or COOH-terminus





# Peptides

- Amino acids can be polymerized to form chains :



- Oligopeptide: 2-20 amino acids

- Polypeptide : more than 20 amino acids

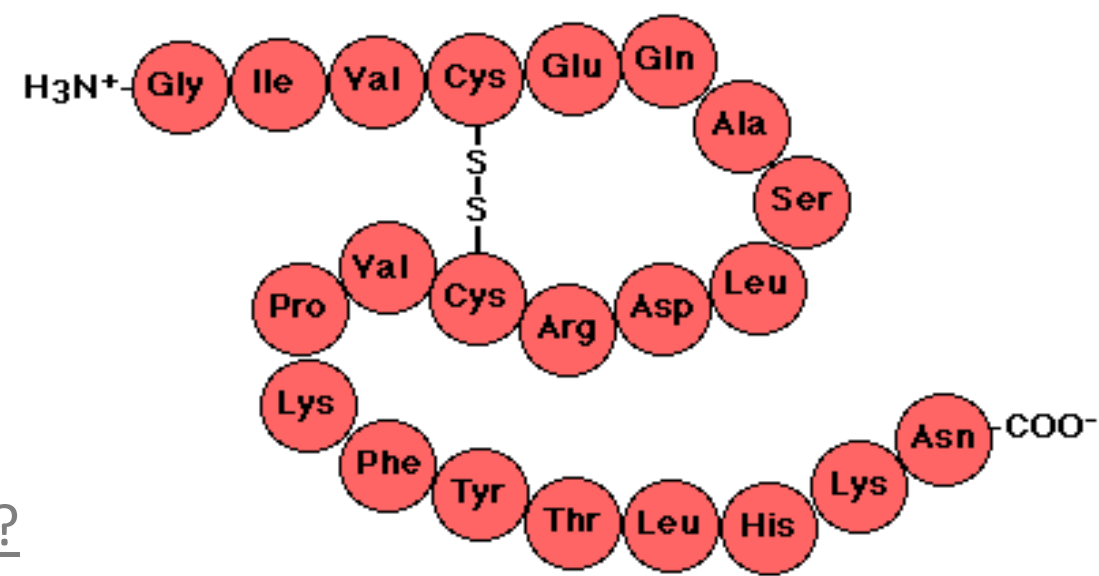
## Notes :

- Oligo means few
- Poly means many
- Number of peptide bonds:  
= number of amino acids - 1

# Primary Structure

the linear sequence of amino acids in a protein.

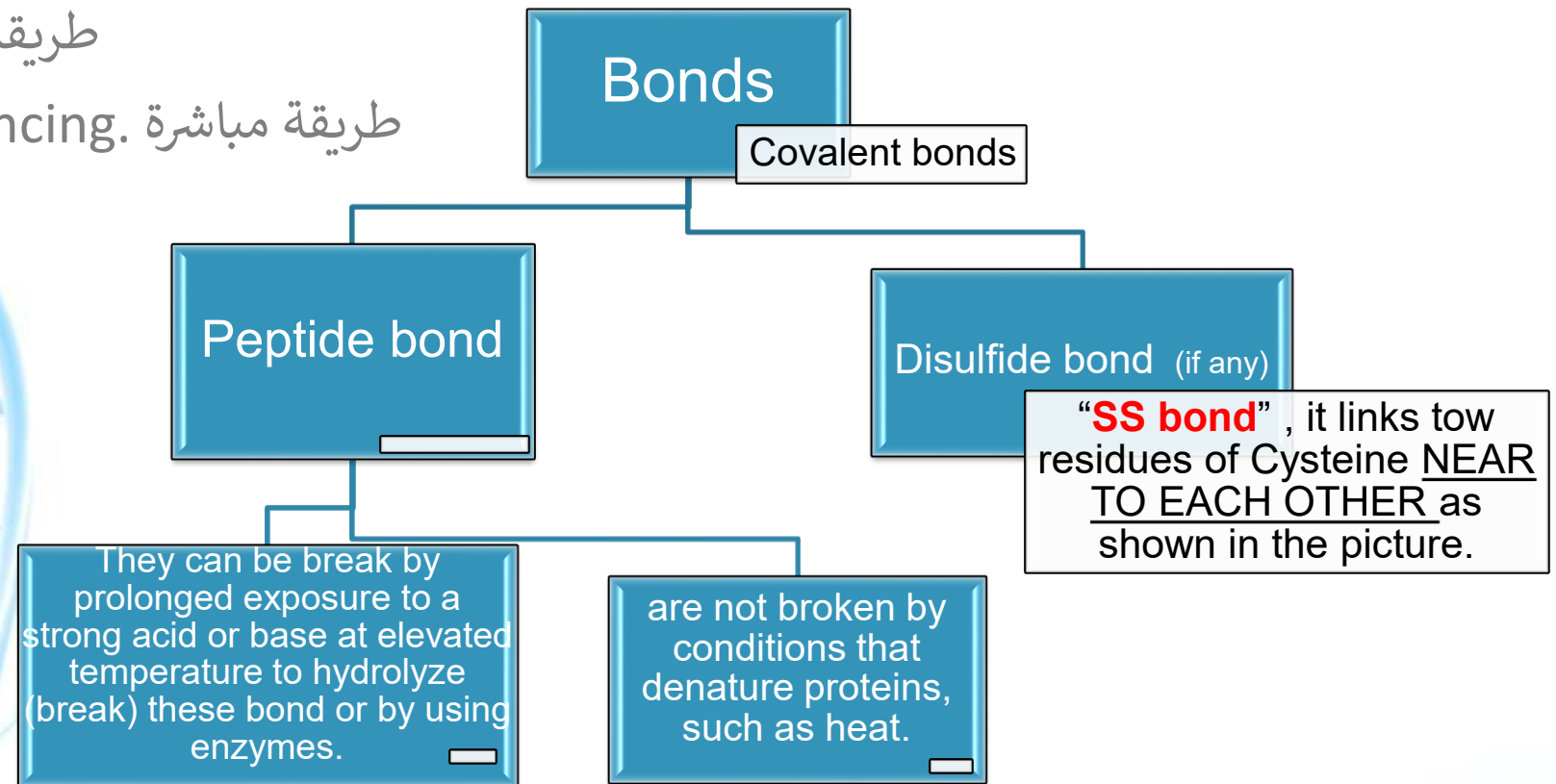
- How to determine the primary structure sequence ?
  1. DNA sequence. طريقة غير مباشرة
  2. Direct amino acids sequencing. طريقة مباشرة



\*\*Primary Structure proteins are not functional.

الفهم اكثر:

<https://youtu.be/NfMZLk-8r34>

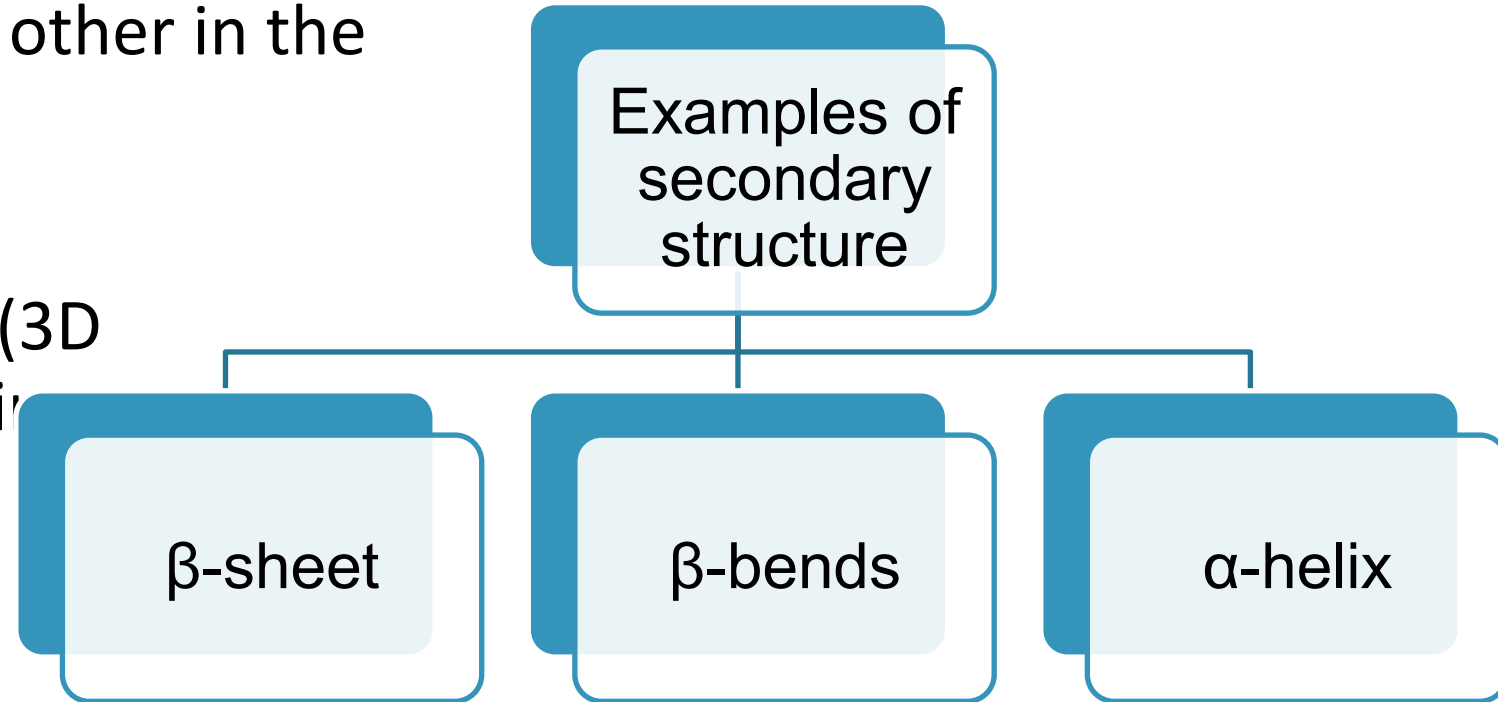




# Secondary structure

Not functional

- It is regular arrangements of amino acids that are located near to each other in the linear sequence.
- Excluding the conformations (3D arrangements) of its side chains



- Bonds that are found in it: Hydrogen bonds.
- for the secondary structure , we do not look at the R side chains nor do we look at the hydrophobic interactions that give it its 3D structure so we exclude that.. We only look at the hydrogen bonds.

# $\alpha$ -helix:

- It is a **right-handed spiral (clock wise)**, in which side chains of amino acids extended **outward**.
- **Hydrogen bonds: Stabilize the  $\alpha$ -helix.**  
“form between the peptide bond carbonyl oxygen and amide hydrogen.”
- **Amino acids per turn: Each turn contains 3.6 amino acids.**

$\alpha$ -helix forms between amino acids in the same strand

Ball-and-stick model of a portion of the  $\alpha$ -helical secondary structure of a protein molecule



This ribbon model shows the general arrangement of atoms in a portion of the  $\alpha$ -helical secondary structure of a protein molecule.



The two models superimposed



# Secondary structure

Amino acids that disrupt an  $\alpha$ -helix:

- **Proline** → imino group, interferes with the smooth helical structure.  
"لأنه تركيبه على شكل حلقة فبيخرب الشكل الحلزوني"
- **Glutamate, aspartate, histidine, lysine** or **arginine** → form ionic bonds.  
"these are all polar CHARGED amino acids so they would form ionic bonds thus it would change the shape"
- **Bulky side chain, such as tryptophan.**  
"حجمه كبير فبغير الشكل"
- **Branched amino acids at the  $\beta$ -carbon, such as valine or isoleucine.**

للفهم أكثر:

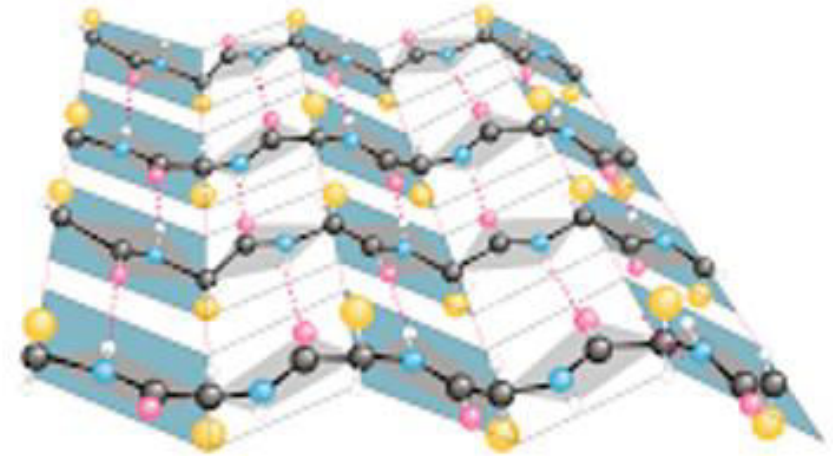
<https://www.youtube.com/watch?v=V3DgrOG1exY>

## $\beta$ -sheet

- **Two or more** polypeptide chains make hydrogen bonding with each other.

“beta sheet could be a long polypeptide while the helix is just one polypeptide chain”

- Also called pleated sheets because they appear as folded structures with edges.
- **Hydrogen bonds: Stabilize the  $\beta$ -sheet”**



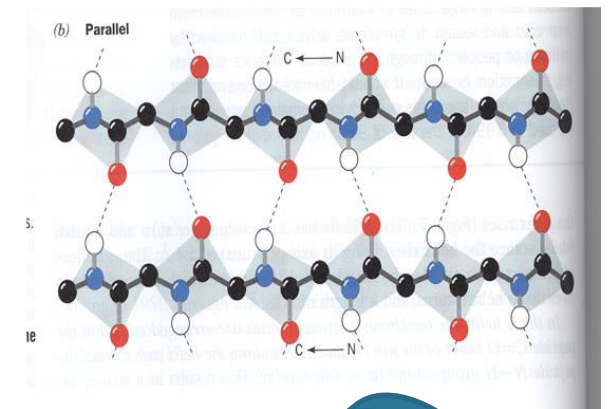
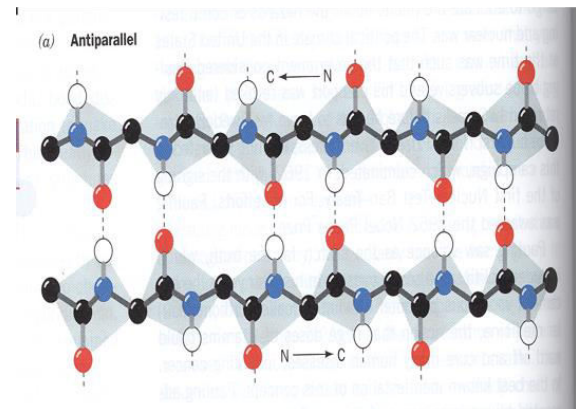
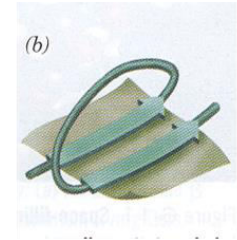
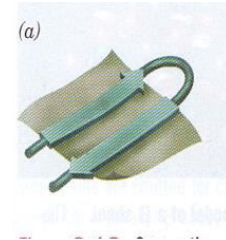
الفهم أكثر:

<https://www.youtube.com/watch?v=koyE9Nplacc>

# $\beta$ -sheet (Antiparallel and parallel sheets)

- Hydrogen bonds in the parallel direction are less stable than in the antiparallel

- “notice the dotted lines in the picture..in the antiparallel the lines are straight but in the parallel , they aren't”







**Other secondary structure examples:**

- **$\beta$ -bends (reverse turns):**
  - Reverse the direction of a polypeptide chain.
  - Usually found on the surface of the molecule and often include charged residues.
  - The name comes because they often connect successive strands of antiparallel  $\beta$ -sheets.
  - $\beta$ -bends are generally composed of four amino acid residues, proline or glycine are frequently found in  $\beta$ -bends.
- **Nonrepetitive secondary structure:**
  - e.g. loop or coil conformation.



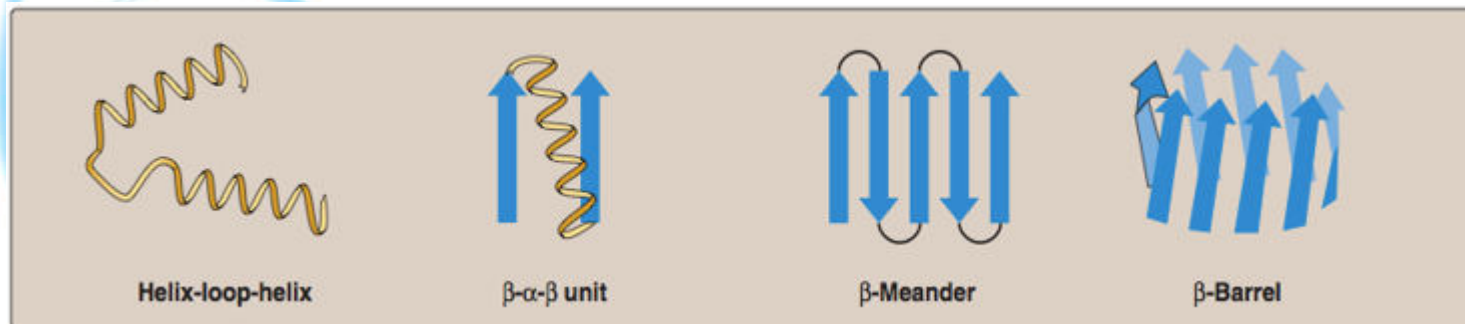
# Secondary structure

## Other secondary structure examples:

- Supersecondary structures (motifs):  
A combination of secondary structural elements.

“that is,  $\alpha$ -helices,  $\beta$ -sheets, and coils”

“These form primarily the core (interior) region of the molecule. They are connected by loop regions” .



$\alpha$   $\alpha$  motif: two  $\alpha$  helices together

$\beta$   $\alpha$   $\beta$  motif: a helix connects two  $\beta$  sheets

$\beta$  hairpin: reverse turns connect antiparallel  $\beta$  sheets

$\beta$  barrels: rolls of  $\beta$  sheets

For more understanding

<https://www.youtube.com/watch?v=4YbwjjZ>

WGPA

# Tertiary Structure

- **A functional protein** Sometimes the tertiary structure is the **end product** of some proteins.

What is it

It is the three-dimensional (3D) structure of an entire polypeptide chain including **side chains**.

Domains

- They are the fundamental functional and 3D structural **units** of a polypeptide. >200 amino acids fold into two or more **clusters**.

- The **core of a domain** is built from combinations of supersecondary structural elements (motifs) and their side chains.

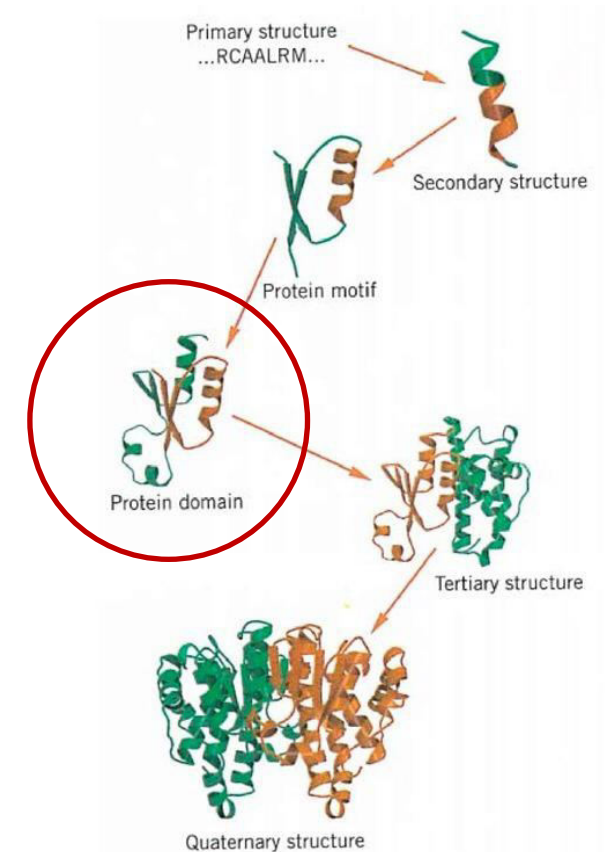
- Domains can be combined to form **tertiary structure**.

Supersecondary structural elements (motifs)

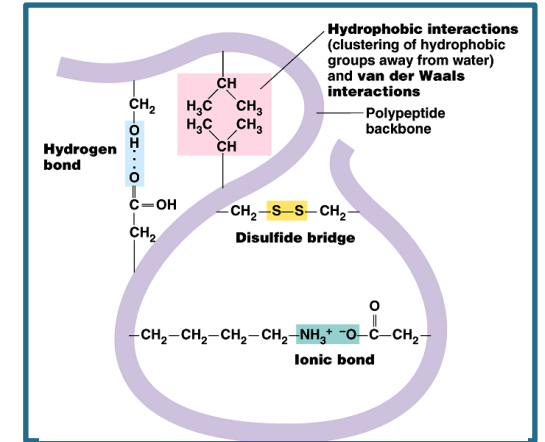
The core of a domain

Domain

Tertiary structure.



# Tertiary Structure



## Interactions stabilizing tertiary structure

### Disulfide bonds.

**Extra:** a covalent linkage formed from the sulfhydryl group ( $-SH$ ) of each of two cysteine residues to produce a cystine residue.

### Hydrophobic interactions

**Extra:** Amino acids with nonpolar side chains tend to be located in the interior of the polypeptide molecule, where they associate with other hydrophobic amino acid

### Hydrogen bonds

**Extra:** Amino acid side chains containing oxygen- or nitrogen-bound hydrogen

### Ionic interactions

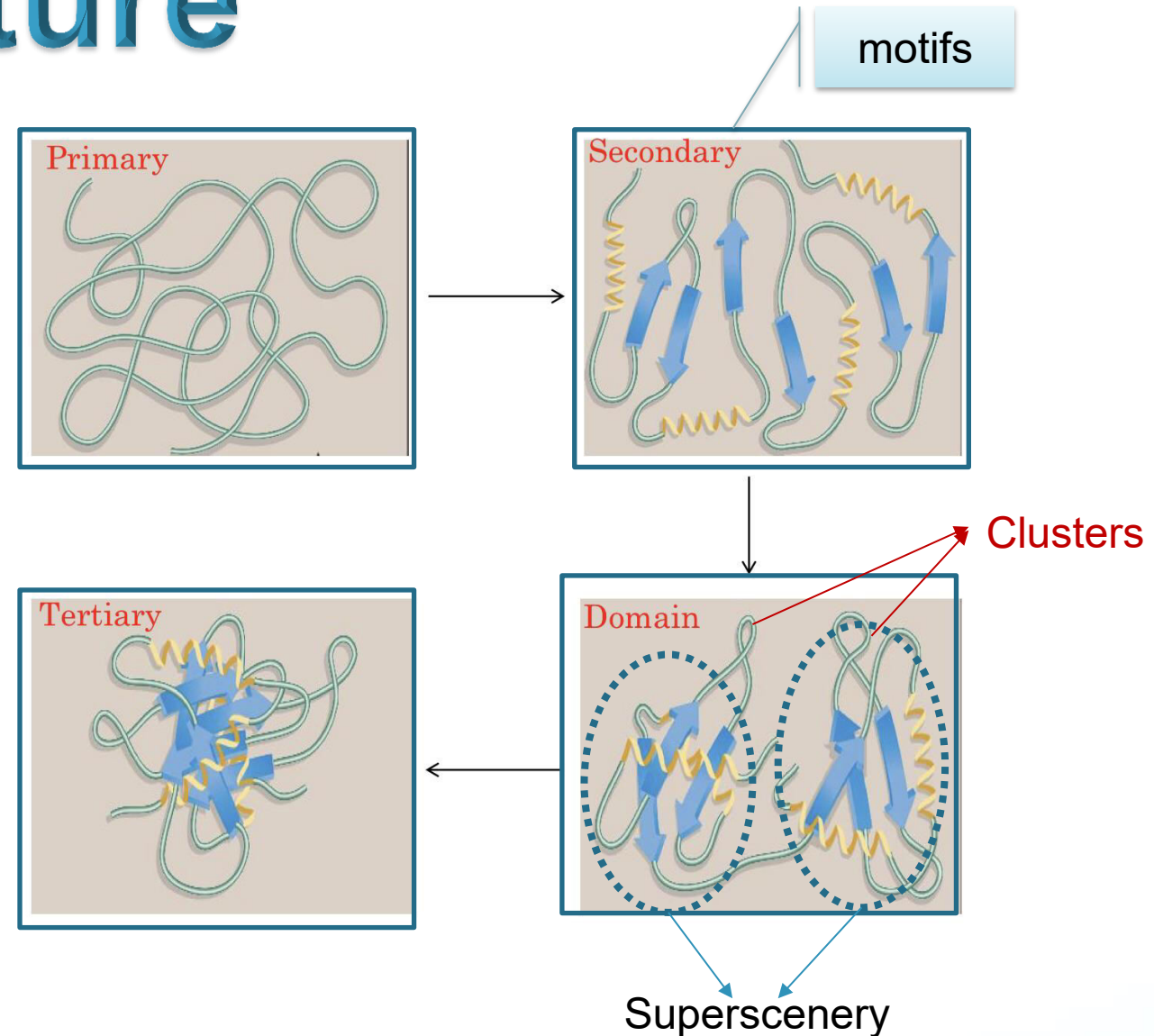
**Extra:** Negatively charged groups can interact with positively charged groups such as : carboxylate group ( $-COO^-$ ) in the side chain of aspartate and amino group ( $-NH_3^+$ )

• للفهم أكثر :

<https://youtu.be/ysPt1lllcs>

# Tertiary Structure

**Interactions** between the side chains of amino acids determine how a **long** polypeptide chain folds into the intricate three-dimensional shape of the functional protein.





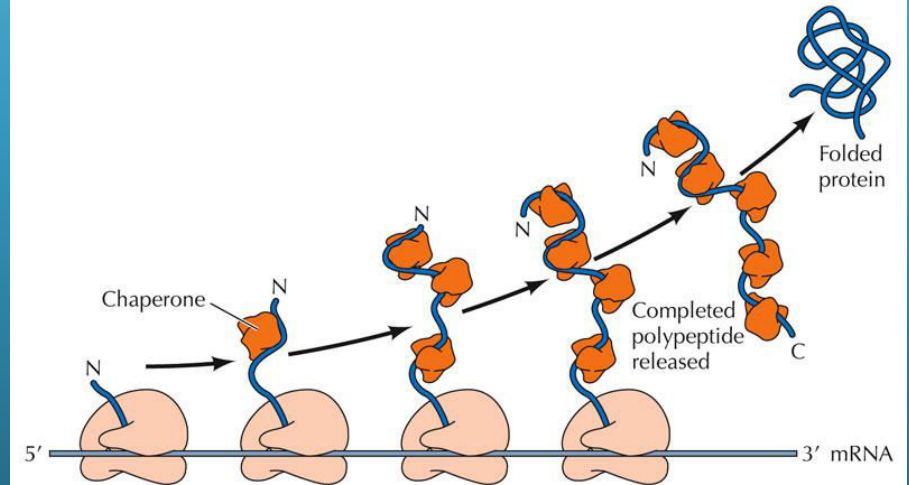
# Tertiary Structure

## Chaperons

They are a specialized group of proteins, required for the proper folding of many species of proteins. Role of chaperons, also known as “**Heat Shock**”,

in protein folding: They interact with polypeptide at various stages during the folding process. Examples of chaperons: **Hsp60** and **Hsp70**.

How Chaperons helps folding the protein:



# Quaternary structure

- Some proteins contain two or more polypeptide chains that may be structurally **identical** (**homomeric**) or totally **unrelated** (**heteromeric**).
- Each chain forms a 3D structure called **subunit**.

According to the number of subunits: dimeric, trimeric, ... or multimeric.

Subunits may either function independently of each other, or work cooperatively, e.g. **hemoglobin**.

## Hemoglobin: a globular protein.

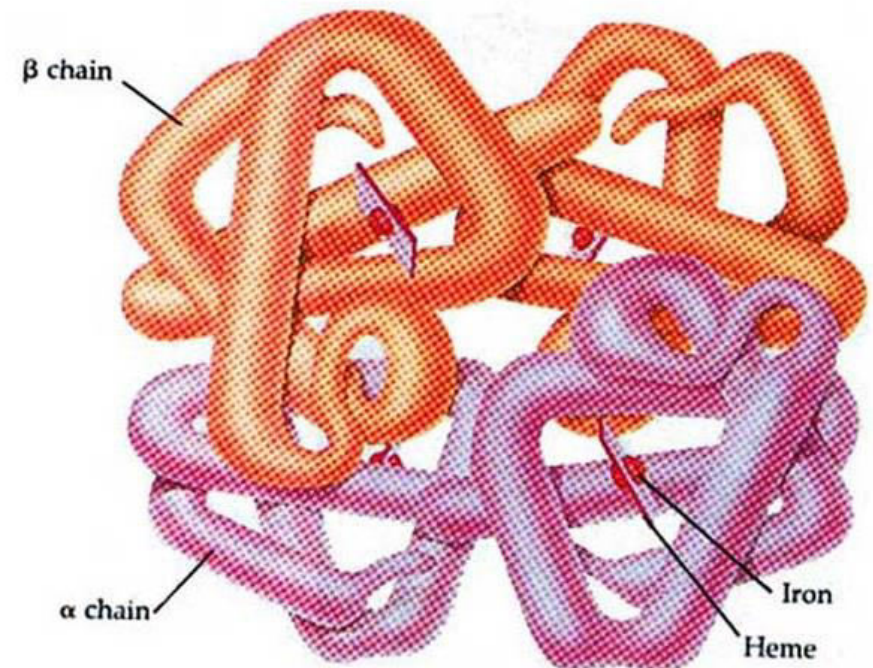
Spherical (“globe-like”) يعني ان لها شكل كروي

- A **multisubunit protein** is called **oligomer**.

(An oligomer usually refers to a macromolecular complex)

- Composed of  $\alpha_2 \beta_2$  subunits (4 subunits).
- Two same subunits are called **protomers**.

(a **protomer** is the structural unit of an oligomeric protein).



(b) Hemoglobin



## Denaturation of protein

unfolding and disorganization of the protein's **secondary and tertiary structures**.

## Denaturation agents

Heat

Organic solvents

Mechanical mixing.

Strong acids or bases

Detergents

Ions of heavy metals  
(e.g. lead and mercury)

- Most proteins, once denatured, remain permanently disordered.
- Denatured proteins are often insoluble and, therefore, **precipitate from solution**.

# Proteins misfolding:

- Every protein **must** fold to achieve its normal conformation and function.
- **Abnormal** folding of proteins leads to a number of diseases in humans.

## Alzheimer's disease

**$\beta$  amyloid** protein is a **misfolded** protein.

Amyloid is aggregates of misfolded proteins outside neurons, it interfere with neuron's ability of sending messages

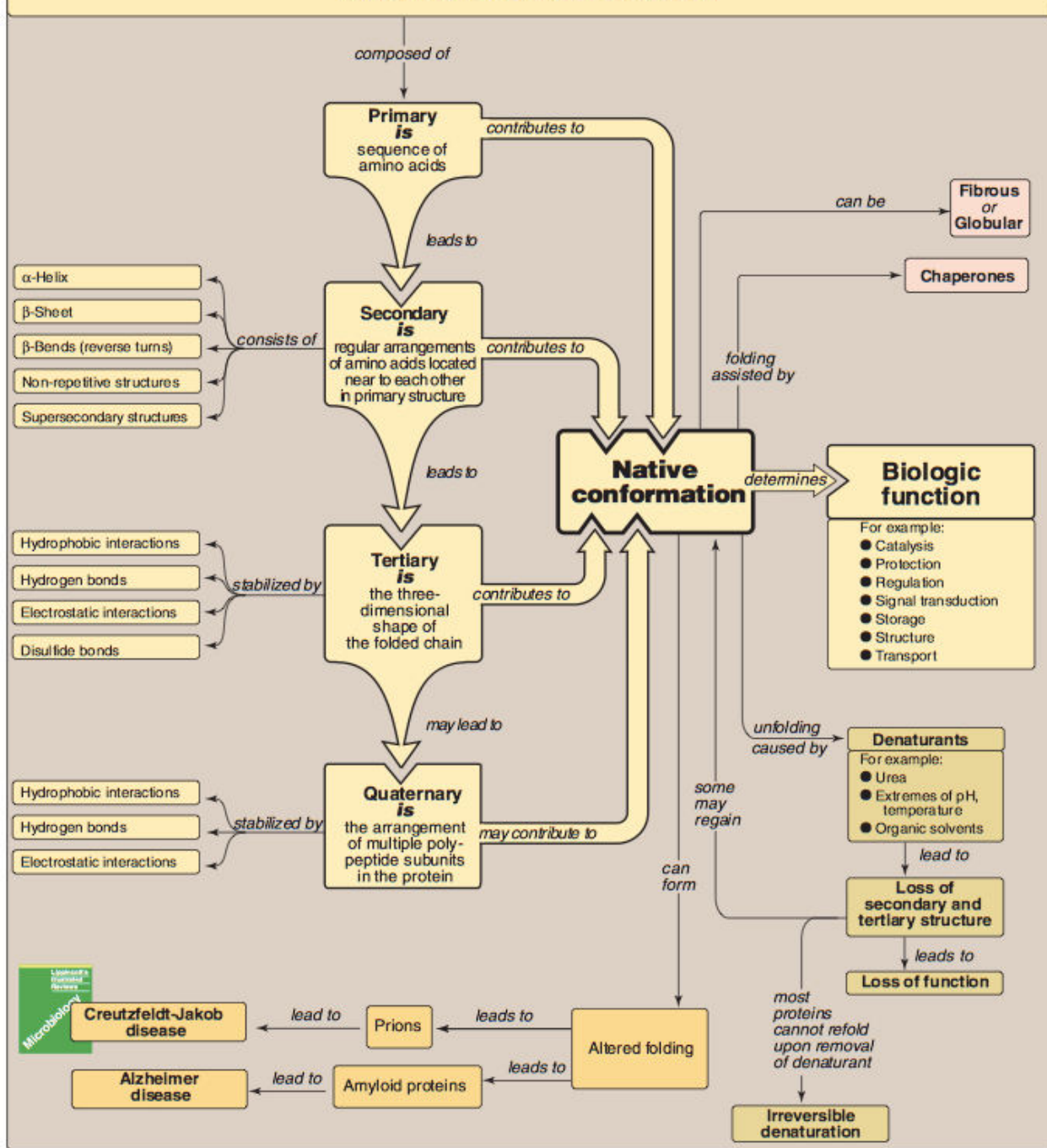
It forms fibrous **deposits or plaques in the brains** of Alzheimer's patients.

## Creutzfeldt-Jacob or prion disease

**Prion** protein is present in normal brain tissue , in diseased brains, the same protein is **misfolded**.

It, therefore, forms insoluble fibrous aggregates that damage brain cells.

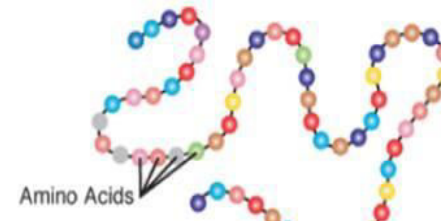
# Hierarchy of protein structure



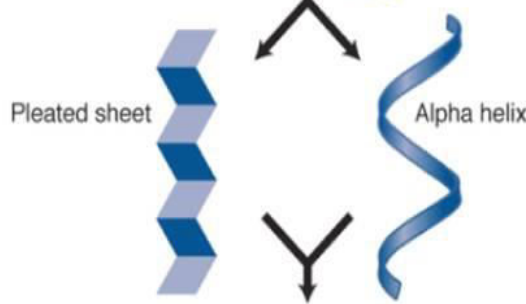
# Protein



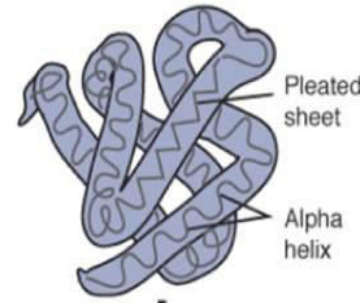
## Levels of protein organization



**Primary protein structure**  
is sequence of a chain of amino acids



**Secondary protein structure**  
occurs when the sequence of amino acids are linked by hydrogen bonds



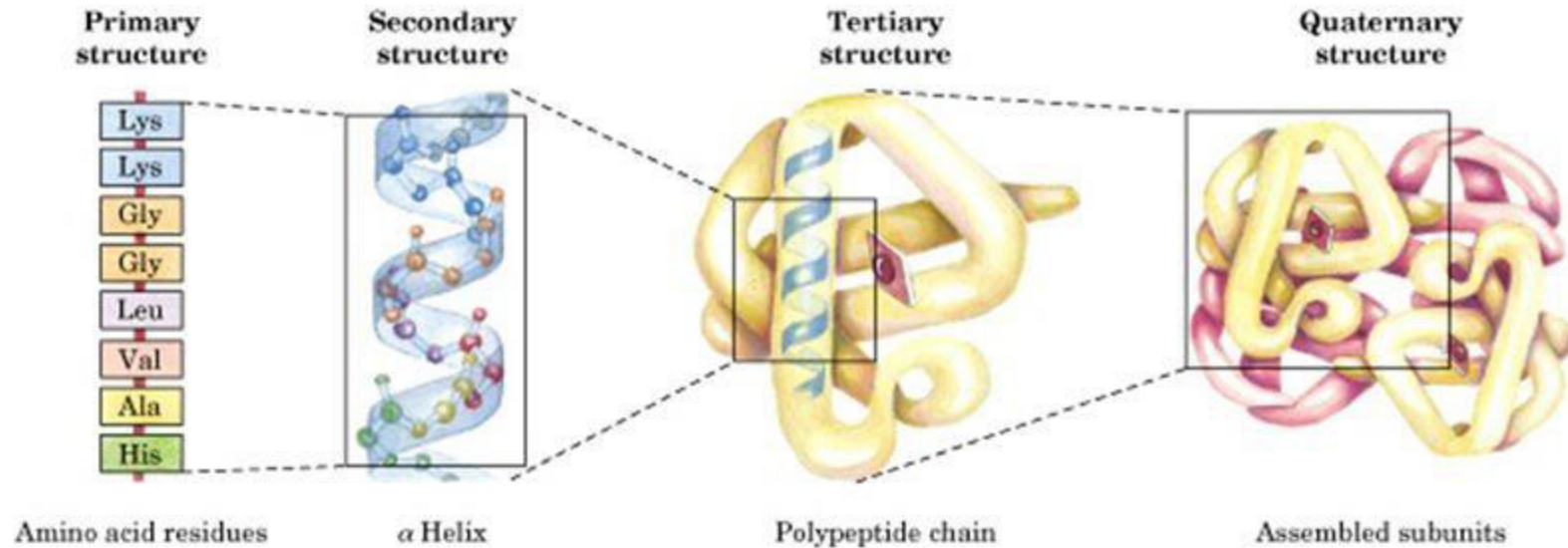
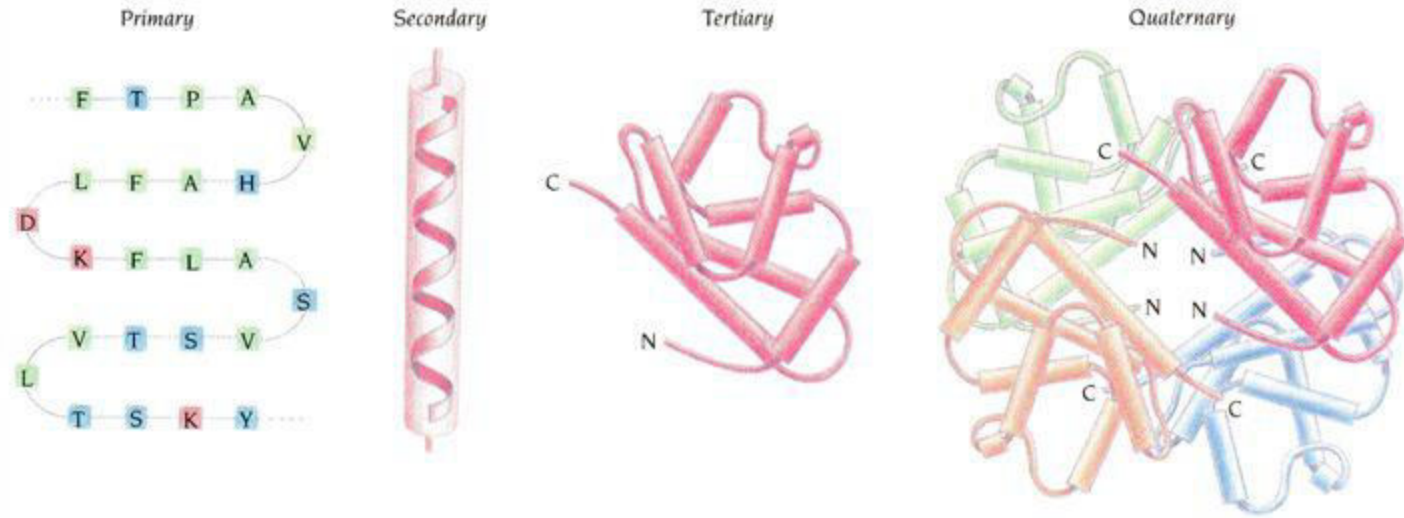
**Tertiary protein structure**  
occurs when certain attractions are present between alpha helices and pleated sheets.



**Quaternary protein structure**  
is a protein consisting of more than one amino acid chain.

# Review

# Levels of protein structure organization





# Take home messages

- ▶ Native conformation of the protein is the functional, fully folded protein structure
- ▶ The unique 3D structure of the native conformation is determined by its primary structure, i.e. the amino acid sequence
- ▶ Interactions of between the amino acid side chains guide the folding of the polypeptide chain to form secondary, tertiary and sometimes quaternary structures that cooperate in stabilizing the native conformation of the protein.
- ▶ Protein denaturation results in unfolding and disorganization of of the protein's structure, which are not accompanied by hydrolysis of peptide bonds.
- ▶ Disease can occur when an apparently normal protein assumes a conformation that is cytotoxic, as in the case of Alzheimer disease and Prion disease.

# MCQs

**Q1: the linear sequence of amino acids in protein is:**

- A) primary structure
- B) secondary structure
- C) tertiary structure
- D) quaternary structure

**Q3: which of the following structure is functional structure?**

- A) primary & secondary structure
- B) secondary & tertiary structure
- C) primary & quaternary structure
- D) quaternary & tertiary structure

**Q2: A tripeptide have:**

- A) 1 peptide bond
- B) 2 peptide bond
- C) 3 peptide bond
- D) 4 peptide bond

**Q4: It's a specialized group of protein, required for the proper folding:**

- A) Histones
- B) chaperones
- C) domains
- D) prion

**Answer key:**

- 1) A
- 2) B
- 3) D
- 4) B





## SAQs

1. Which protein is not affected by the denaturation process?
2. A disulfide bond links two residues near to each other. What are these residues?
3. How can we determine the primary structure sequence of protein?
4. In which protein structure we include the side chain (R)?
5. An example for a bulky side chain that disrupt the  $\alpha$ -helix is?
6. Compare the stability in hydrogen bonds between parallel direction and anti-parallel direction?
7. What is the structural unit of an oligomeric protein?

### **Answer key:**

1) Primary protein. 2) 2 Cysteine. 3) By DNA sequencing + direct amino acid sequencing. 4) In tertiary Structure. 5) Tryptophan. 6) H bonds are more stable in anti-parallel direction (or the parallel direction is less stable). 7) protomer.

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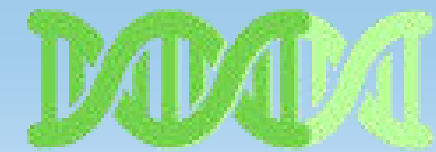
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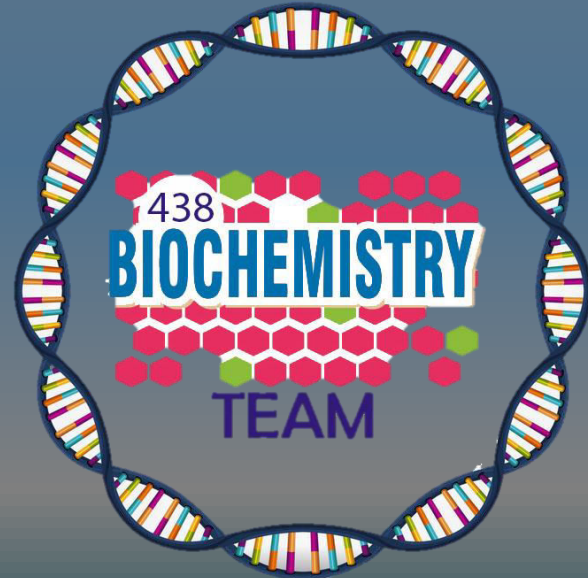
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- جود العتيبي
- سارة الهلال
- شهد السلامه
- طيف العتيبي
- عبير الخضير
- غيداء البريثن
- لينا العصيمي
- نورة التركي
- نورة المزروع
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- هيفاء الوايلي

## ❖ Boys team:

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- حميد حميد
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- عمر الغامدي
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