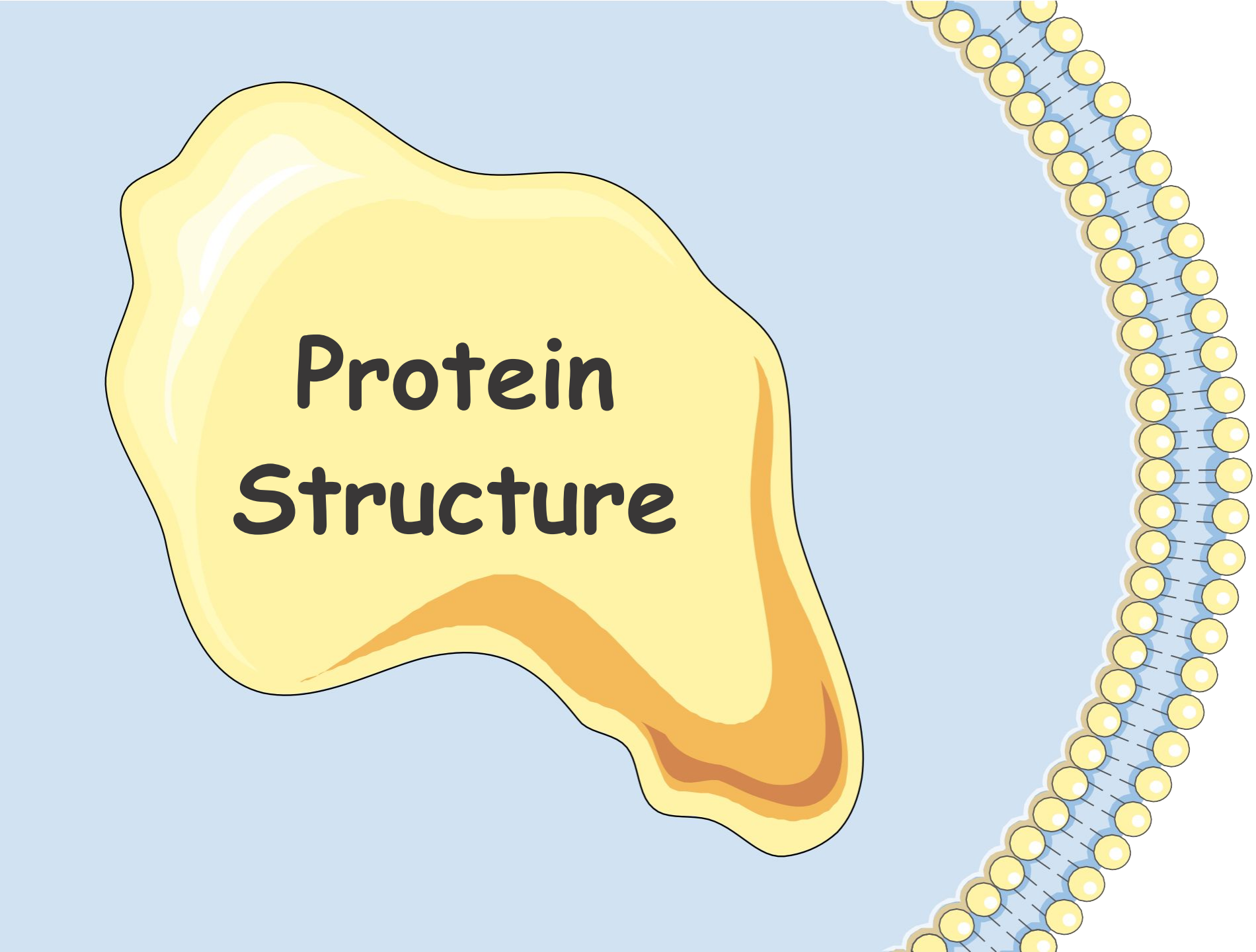
Protein Structure



MED441
KING SAUD UNIVERSITY

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2
V1

Foundation Block - KSU

Color Index:

- Main text
- Important
- Notes
- Boys slides'
- Girls slides'
- Extra

Editing File

Objectives

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

What are Proteins?

- **Proteins:** are large, complex molecules that play many critical roles in the body.
- Made up of: hundreds or thousands of amino acids (the smaller units - protein building blocks).
-
- Amino acids are attached to one another in long chains.
- There are mainly 20 different types of amino acids that can be combined to make a protein.

The sequence of amino acids determines

Protein's unique three dimensional (3D) structure

Protein's specific function.

What are Proteins?

The importance of proteins

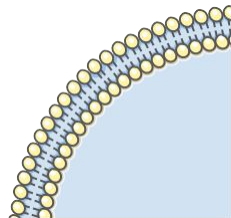
They do most of the work in cells .

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

Protein functions

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

- Antibody
- Enzyme
- Messenger
- Structural component
- Transport
- Storage



Primary Structure

- **Primary structure:** the linear sequence of amino acids.
- Not functional.

Notes 439:

- Disulfide (SS) bond links two residues of Cysteine near to each other.

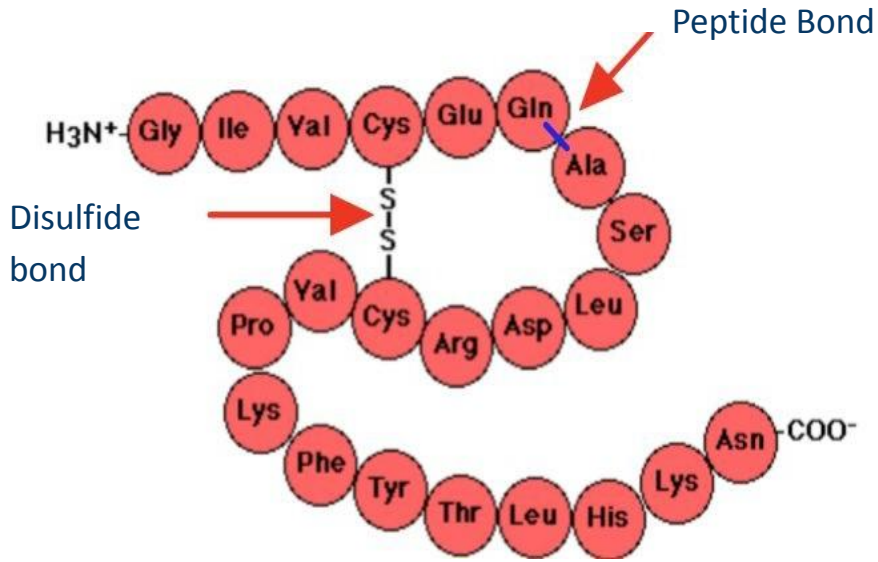
- The primary structure is the simplest and the first level of structure.
- Peptide bonds are very strong and they require enzymes to be broken.

Covalent Bonds in the Primary Structure

- Peptide bond
- Disulfide bond (if any)

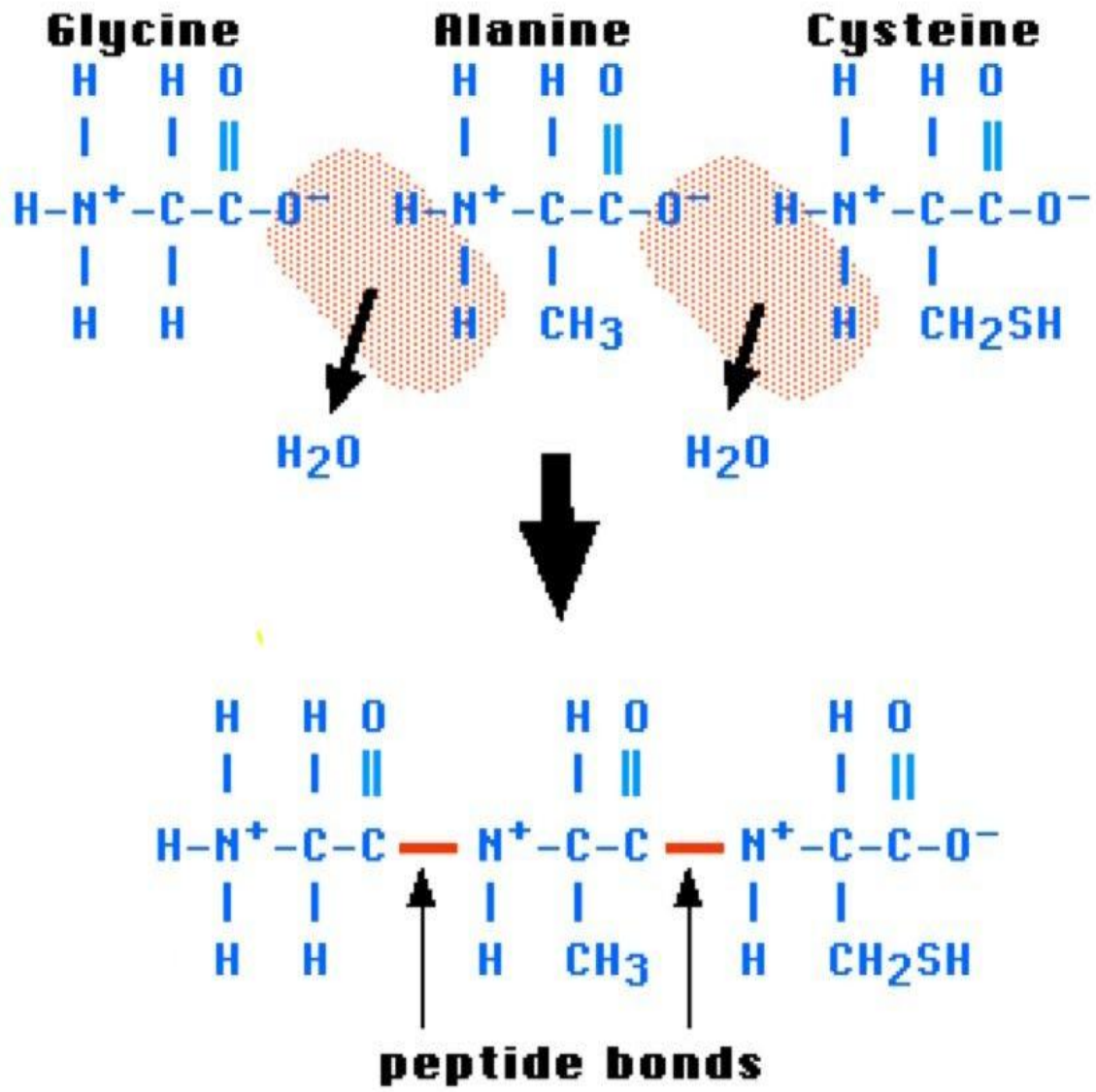
To Determine the Primary Structure Sequence

- DNA Sequencing (indirect)
- Direct amino acid sequencing

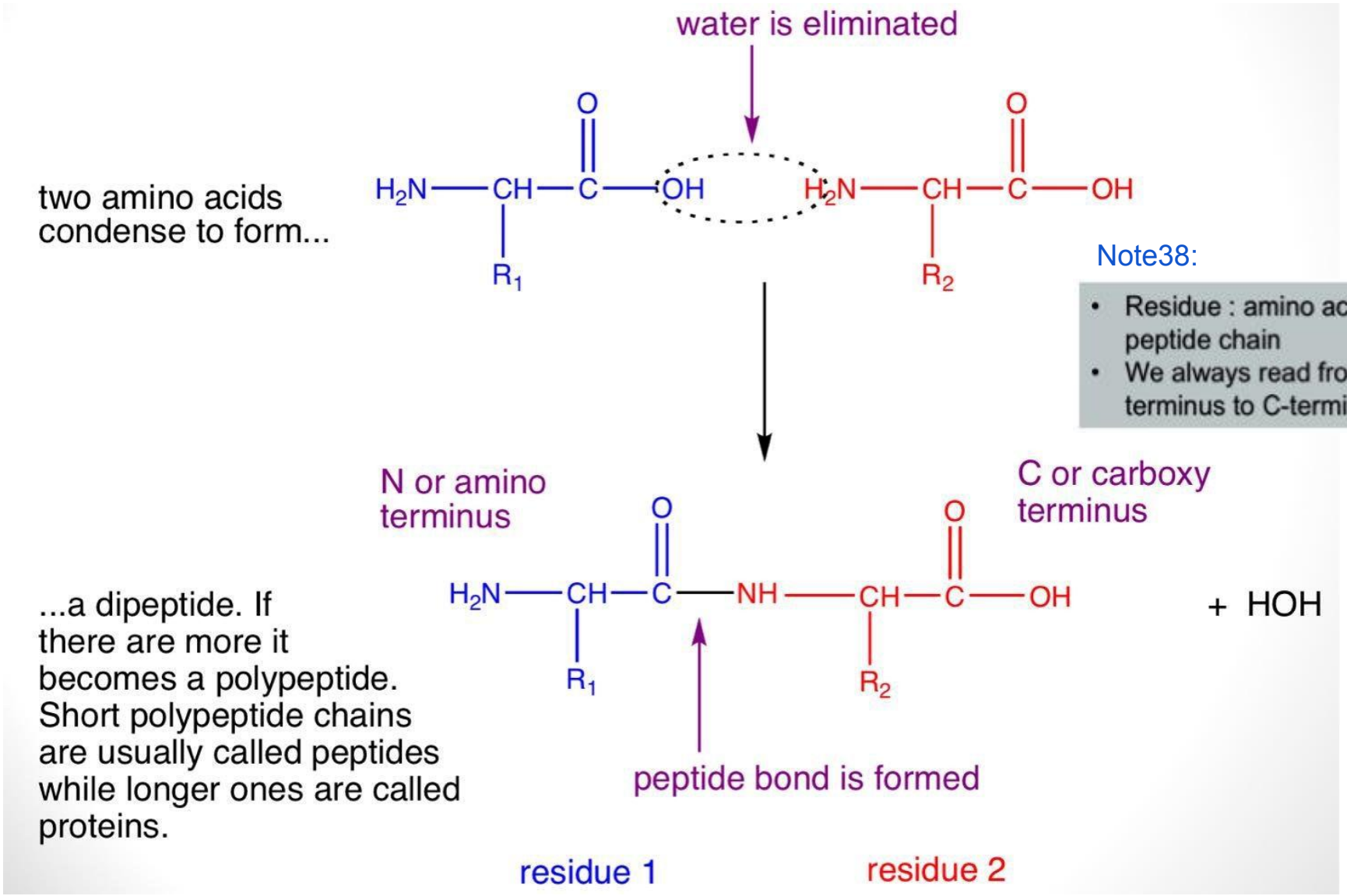


Peptide Bond (Amide Bond)

- Each amino acid in a chain makes 2 peptide bonds.
- The amino acids at the two ends of a chain make only 1 peptide bond.
- **Amino (NH_2-) terminus:** amino acid with a free amino group.
- **Carboxyl (COOH-) terminus:** amino acid with a free carboxylic group.



Peptide Bond (Amide Bond)

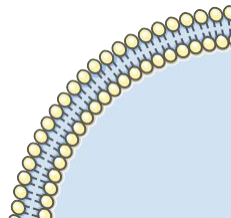


Peptides

Notes 438:

- Oligo: few
- Poly: more
- Number of peptide bonds = number of amino acid - 1

2 amino acids	Dipeptide	1 peptide bond
3 amino acids	Tripeptide	2 peptide bonds
4 amino acids	Tetrapeptide	3 peptide bonds
2 - 20 amino acids	Oligopeptide	
More than 20 amino acids	Polypeptide	

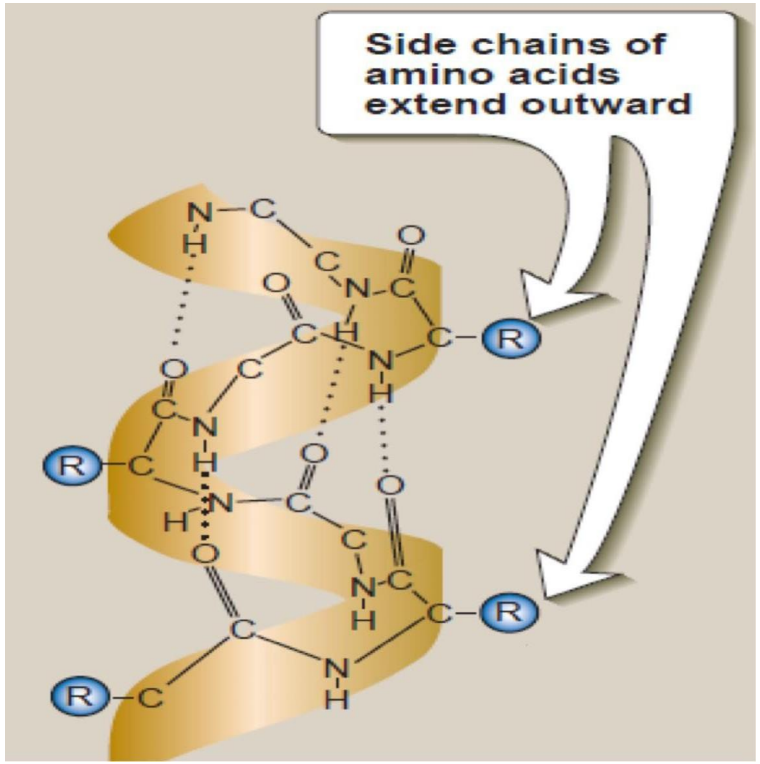


Secondary Structure

- It is regular arrangements of amino acids that are located near to each other in the linear sequence.
- Not functional.
- Excluding the conformations (3D arrangements) of its side chain.

Examples of Secondary Structure

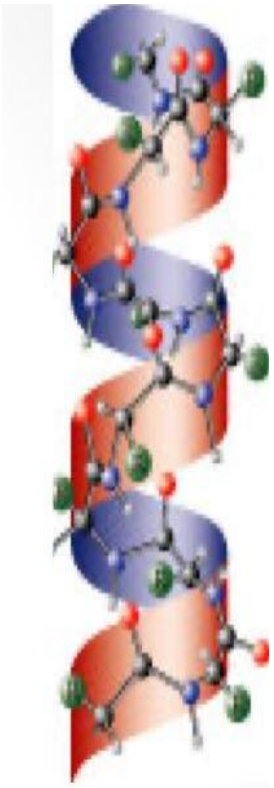
- α-helix
- β-sheet
- β-bends



α-Helix

α-helix is the most common and thus the most stable secondary structure.

- **α-helix:** a right-handed spiral, in which side chains of amino acids extended outward.
- Hydrogen bonds stabilize the α-helix.
    - H-bonds form between the peptide bond carbonyl oxygen and amide hydrogen.
- Amino acids per turn: each turn contains 3.6 amino acids.
- Amino acids that disrupt an α-helix:



01

Proline:

Has imino group ⟶ interferes with the smooth helical structure.
(Proline has a ring structure that disrupts the helical structure)

02

Glutamate - Aspartate - Histidine - Lysine - Arginine:

They form ionic bonds.

03

Tryptophan:

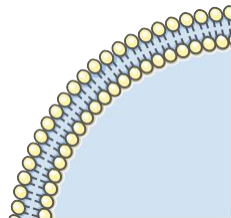
Because of the bulky side chain.

Note: there might be other amino acids but we only have Tryptophan.

04

Valine - Isoleucine:

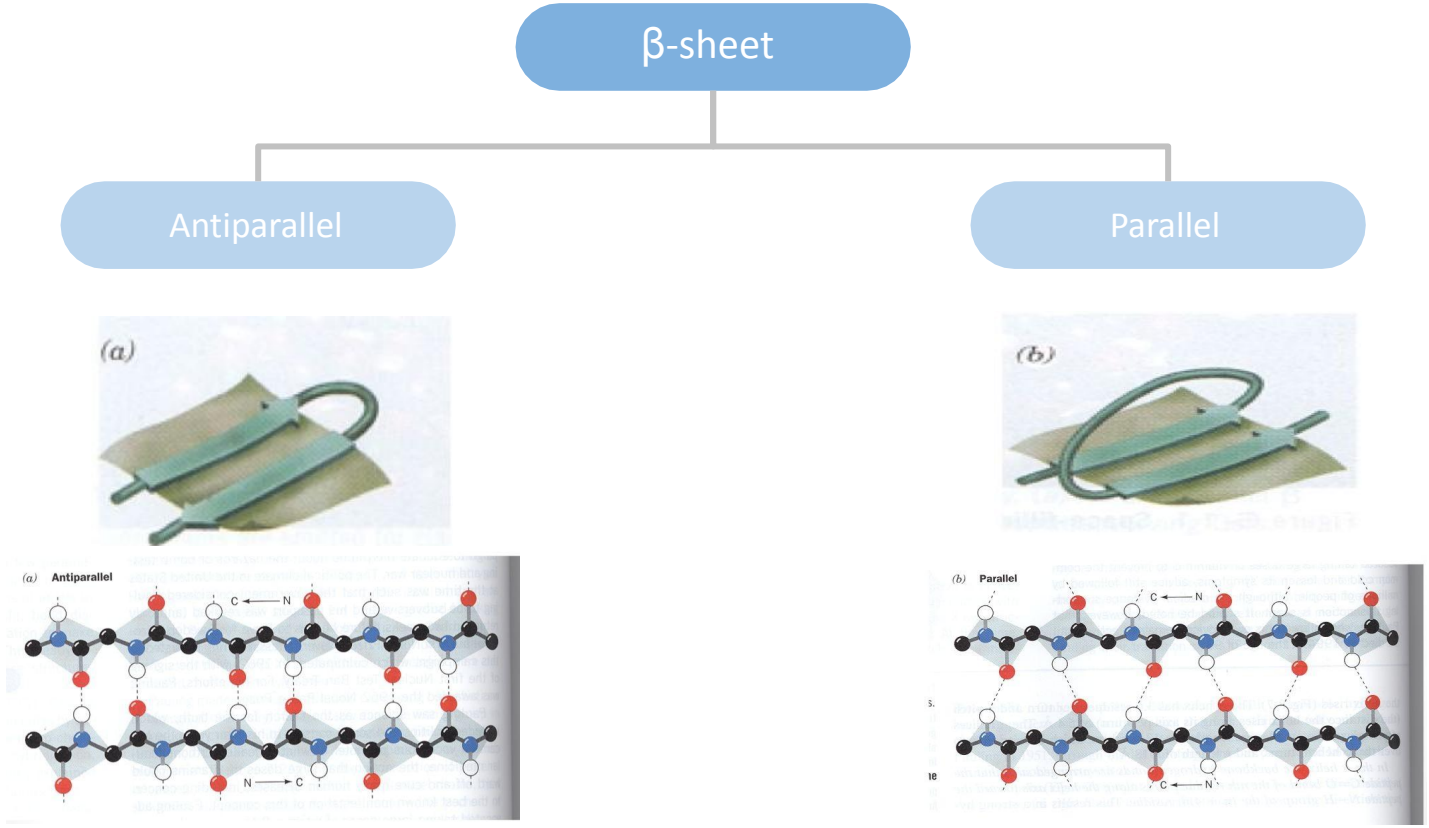
Branched amino acids at the β-carbon.



β-Sheet (Composition of a β-Sheet)

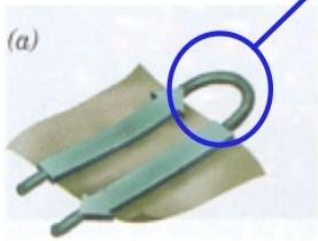
- The **tail** represents the **N- terminus.**
- The **head** represents the **C-terminus**.

- **β-sheet:** 2 or more polypeptide chains make hydrogen bonding with each other.
- Also called pleated sheets because they appear as folded structures with edges.



Hydrogen bonds in parallel direction is less stable than in antiparallel direction

Other Secondary Structure Examples?



1- β-bends (reverse turns):

Usually found on the surface of the molecule.

Generally composed of 4 amino acid residues.

Often include charged residues

Reverse the direction of a polypeptide chain.

The name comes because they often connect successive strands of antiparallel β-sheets.

Proline or glycine are frequently found in β-bends.

Note:

- **Glycine:** smallest amino acid which makes it easier to bend.
- **Proline:** due to bending and bending due to lack of hydrogen bonds.

2 Non Repetitive secondary structure:

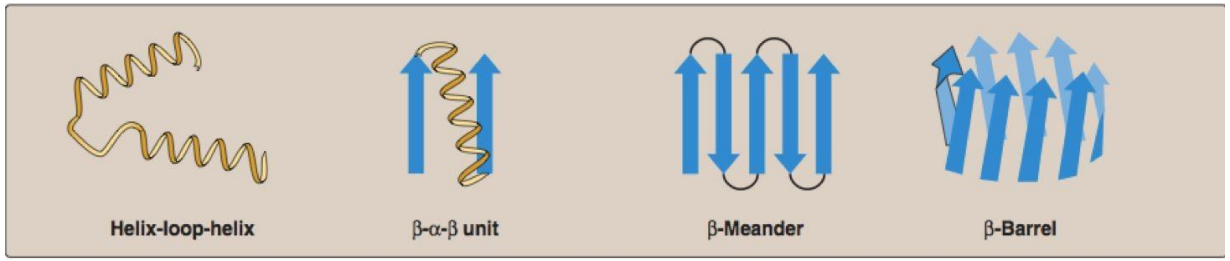
- e.g. loop or coil conformation.

Supersecondary Structures

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

Examples of Supersecondary Structure

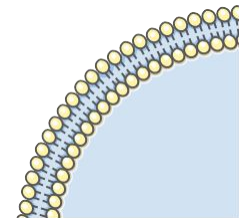
- **α α motif:** 2 α helices together.
- **β α β motif:** a helix connects 2 β sheets.
- **β hairpin:** reverse turns connect antiparallel β sheets.
- **β barrels:** rolls of β sheets.



A video to illustrate (click)

Tertiary Structure

- **Tertiary structure:** the three-dimensional (3D) structure of an entire polypeptide chain including side chains.
- **Domains:** the fundamental functional and 3D structural units of a polypeptide.
  - Core of a domain: built from combinations of supersecondary structural elements (motifs) and their side chains.
- Polypeptide chain that is greater than 200 amino acids in length --> generally consist of 2 or more domains.
- Domains combined ⟶ tertiary structure.



Interactions Stabilizing Tertiary Structure

Disulfide Bonds

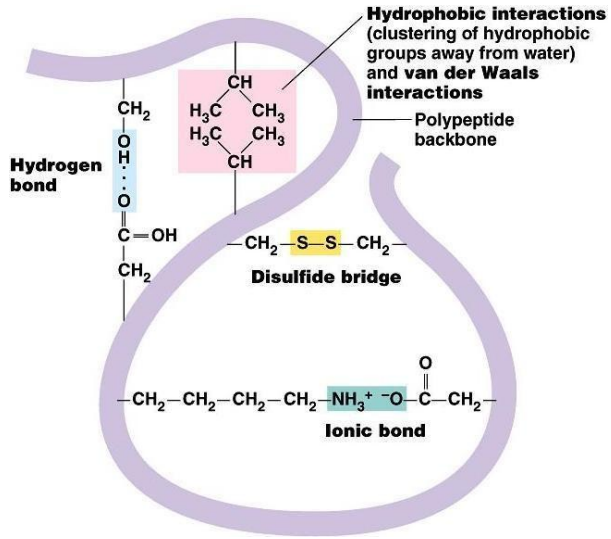
A covalent bond formed between the side chains of Cysteins.

Hydrophobic Interactions

Interactions between non polar amino acids in the interior of the polypeptide or it's the most important interaction that stabilizes the tertiary structure

The hydrogen bonds between the polar and hydrophilic side chains the surface with the water molecule

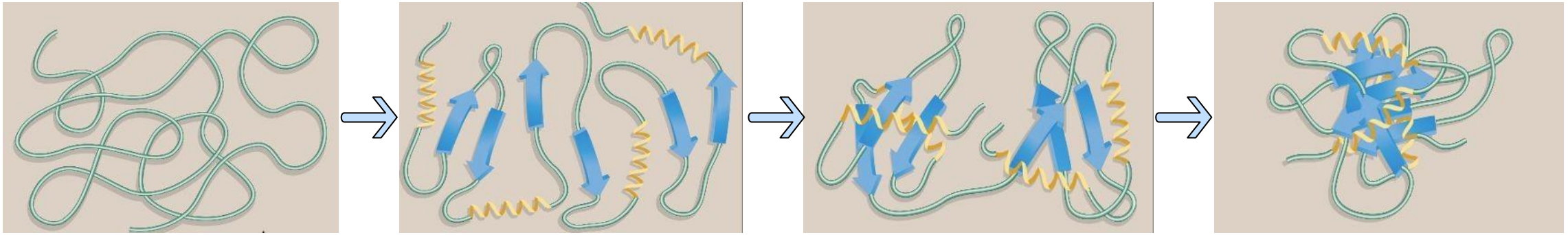
Oppositely charged side chains groups interact together.



[A video to illustrate (click)]

Levels of Folding

In some proteins, another level of folding (after the tertiary structure) is the quaternary structure.



Primary Structure | Secondary Structure | Domains | Tertiary structure

Chaperons (Heat Shock Proteins)

Chaperons are folded by other chaperons.

- **Chaperons:** a specialized group of proteins, required for the proper folding of many species of proteins.
- Chaperons interact with polypeptide at various stages during the folding process.

Quaternary Structure

Proteins with 2 or more polypeptide chains:

Structure of the chains:

- Identical
- Totally unrelated.

Each chain forms a subunit (3D structure)

According to the number of subunits

- Dimeric
- Trimeric
- Multimeric

How subunits work together

- Independently
- Cooperatively
  Example: Hemoglobin

- If the protein has one polypeptide chain ⟶ the protein has three levels of structure only (primary - secondary - tertiary).
- If the protein has more than one polypeptide chain ⟶ the protein has four levels of structure only (primary - secondary - tertiary - quaternary).
- **Nascent Protein:** the primary structure of a protein.
- **Native Protein:** the mature protein that has been folded.
- The quaternary structure is the last complexity level.

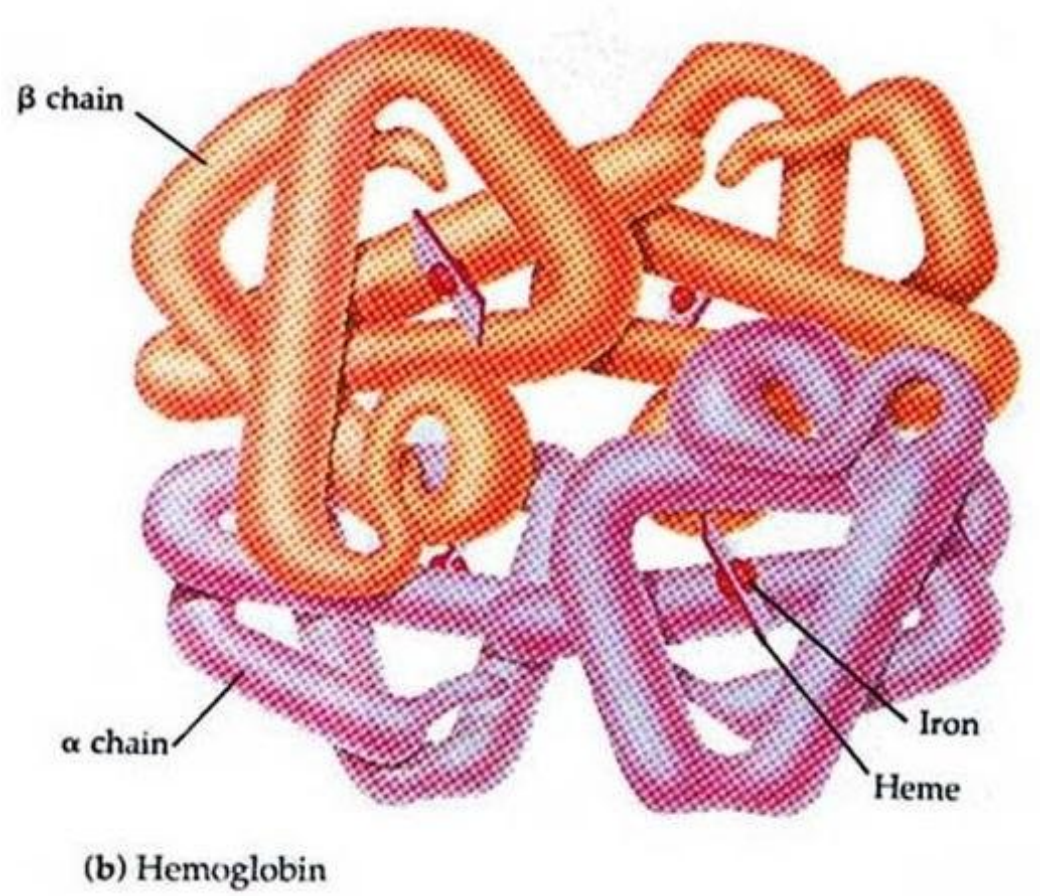
Hemoglobin

01 It is a **globular** protein.

02 Composed of **4** subunits: $\alpha_2 \beta_2$

03 Multisubunit protein called **oligomer.**

04 2 same subunits called **protomers.**



(b) Hemoglobin

Globular is round/spherical.

A video to illustrate (click)

Denaturation of Proteins

Denaturation of Proteins

Definition

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

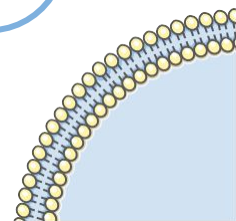
Notes

- Most proteins, once denatured, remain permanently disordered.
- Denatured proteins are often insoluble → precipitate.

Agents

- Organic Solvents
- Strong Acids/Bases
- Ions of Heavy Metals (Lead + Mercury)
- Heat
- Mechanical Mixing
- Detergents

A video to illustrate (click)

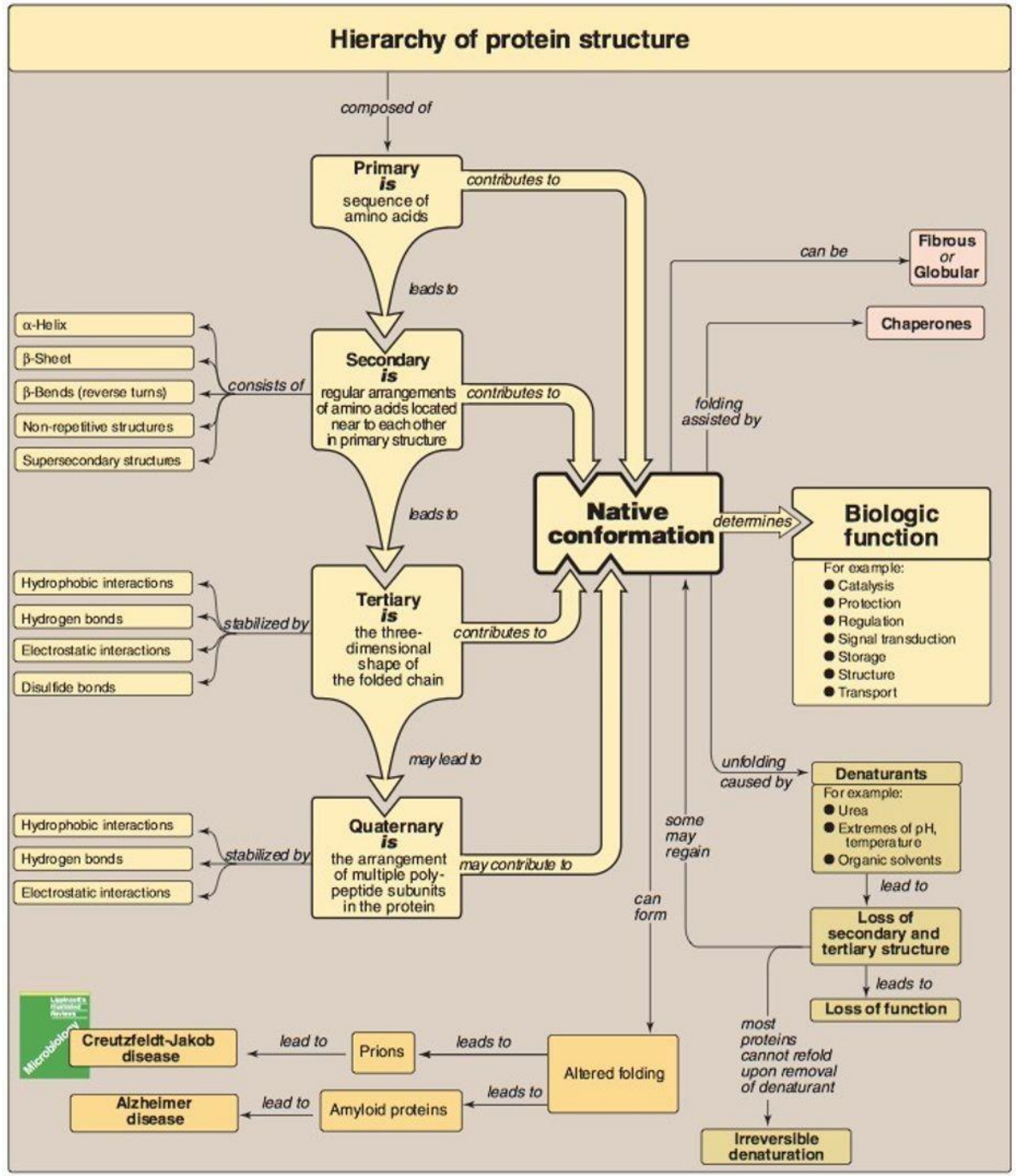


Protein Misfolding

- Every protein must fold to achieve its normal conformation and function.
- Abnormal folding of proteins leads to a number of diseases in humans (Example: Alzheimer's - prion diseases).

Alzheimer's disease		Creutzfeldt-Jakob (Prion) Disease
β amyloid	Misfolded Protein	Prion protein
Forms fibrous deposits or plaques in the brain.	Result	Forms insoluble fibrous aggregates that damage brain cells.
	Notes	Prion protein is present in normal brain tissue but it's not misfolded.

A video to illustrate (click)


Hierarchy of protein structure
composed of
Primary
is
sequence of amino acids
contributes to
leads to
can be
Fibrous
or
Globular
Chaperones
folding assisted by
α-Helix
β-Sheet
β-Bends (reverse turns)
Non-repetitive structures
Supersecondary structures
consists of
Secondary
is
regular arrangements of amino acids located near to each other in primary structure
contributes to
leads to
Native conformation
determines
Biologic function
For example:
Catalysis
Protection
Regulation
Signal transduction
Storage
Structure
Transport
Hydrophobic interactions
Hydrogen bonds
Electrostatic interactions
Disulfide bonds
stabilized by
Tertiary
is
the three-dimensional shape of the folded chain
contributes to
may lead to
unfolding caused by
Denaturants
For example:
Urea
Extremes of pH, temperature
Organic solvents
lead to
Hydrophobic interactions
Hydrogen bonds
Electrostatic interactions
stabilized by
Quaternary
is
the arrangement of multiple polypeptide subunits in the protein
may contribute to
some may regain
can form
Loss of secondary and tertiary structure
leads to
Loss of function
most proteins cannot refold upon removal of denaturant
Irreversible denaturation
Creutzfeldt-Jakob disease
lead to
Prions
leads to
Altered folding
Alzheimer disease
lead to
Amyloid proteins
leads to

Take Home Messages

01 **Native conformation of the protein:** the functional, fully folded protein structure.

02 The unique 3D structure of the native conformation is determined by its primary structure (amino acid sequence).

03 Interactions 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.

04 Protein denaturation results in unfolding and disorganization of of the protein's structure, which are not accompanied by hydrolysis of peptide bonds.

05 Disease can occur when an apparently normal protein assumes a conformation that is cytotoxic, as in the case of Alzheimer disease and Prion disease.

1) D 2) B 3) A 4) C 5) C

Quiz

Q1: A right-handed spiral, in which side chains of amino acids extended outward.

A	β - sheet	B	β - bend	C	α - sheet	D	α - helix

Q2: Reverse turns connect antiparallel β sheets.

A	β α β motif	B	β hairpin	C	β barrels	D	α α motif

Q3: The fundamental functional and 3D structural units of a polypeptide

A	Domain	B	Subunit	C	Motif	D	Chaperon

Q4: Which of the following amino acids is frequently found in β - bend?

A	Isoleucine	B	Methionine	C	Proline	D	Lysine

Q5: The three-dimensional structure of an entire polypeptide chain including side chains.

A	Primary Structure	B	Secondary Structure	C	Tertiary Structure	D	Quaternary Structure

Answer Key:

Q6: List two ways used to determine the primary structure sequence.

Q7: List the forces that stabilize the tertiary structure of proteins.

Q8: What causes Creutzfeldt-Jakob disease? How does it affect the patient's brain?

Q9: How many amino acids per turn

Q6:.

DNA Sequence - Direct Amino acid sequencing.

Q7:

Disulfide bonds - Hydrophobic interactions - Hydrogen bonds - Ionic interactions.

Q8:

Prion protein is misfolded. Thus, it forms insoluble fibrous aggregates that damage brain cells.

Q9:

Biochemistry 441

Girls

Leader: Ghadah Alarify

Members:

Yara Almufleh
Reema Alrashedi
Wareef Almousa
Joud Alangari
Fay Alluhaidan
Sarah Alhamlan
Arwa Almobeirek
Jumana AL-qahtani
Latifa Alkhdiri
Alanoud Alhaider
Futoon Almotairi
Manal Aldhirgham
Raaoum Jabor
Norah alawlah
Shahad Helmi
Rand Aldajani

Boys

Leader: Khalid Alhamdi

Members:

Ahmed Alayban
Sultan Alosaimi
Abdullah Alomran
Bassam Alghizzi
Ibrahim Aljurayyan
Mohammed Almutairi
Turki Alkhalifa
Malik Alshaya
Faisal Alhmoud
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