بسم الله الرحمن الرحيم

BIOCHEMISTRY

Lecture 15

Protein Structure (pt. 2)

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Some information about the previous lecture:-

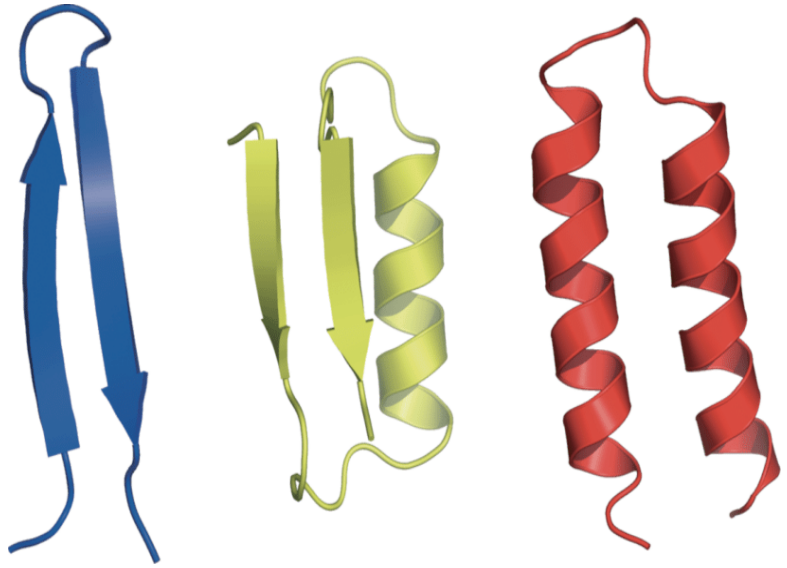
- In Beta-sheet structure, the R groups are in trans orientation, (meaning the first R group is above, the next R group is down, and so on), so we have low steric hindrance.

- Primary structure (sequence of amino acids) will determine what is the structure of protein (secondary, tertiary and quaternary), and any change in the primary structure leads to change in the whole structure.

Loops and coils

- Loops and turns make the kink (fold) that connect peptide chains (in case of secondary structure) to make a three-dimensional shape of the protein.
- Loops are a diverse class of secondary structures in proteins with irregular structure and that connect the main secondary structures (helices , strand , etc...)
- They are found on surface of molecule and provide flexibility to proteins.
- Loops are not organized structure such as a-helix and B-sheet.
- Short but longer than a turn.
- Amino acids in loops are often not conserved.

In a-helix and B-sheet structures there are rules in the amino acids sequence to give me these structures. And AI uses these rules to predict what kind of structure it might be.
That's means a-helix and B-sheet structures are conserved.
But loop's structure doesn't have any rule in the amino acids sequence, so it isn't conserved.



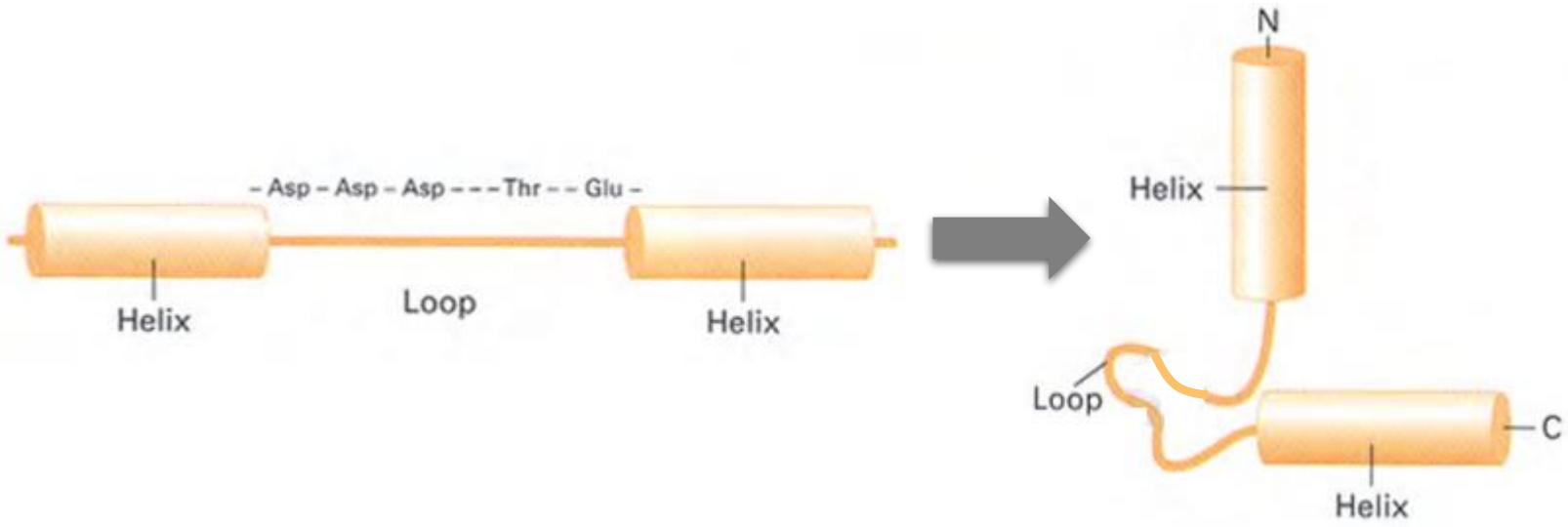
Super-secondary structures

- They are regions in proteins that contain an ordered organization of secondary structures (A collection of secondary structures).
- Examples:
  - Motifs
  - Domains

Usually in proteins there are no consecutive secondary structure, for example you may find a-helix then long sequence of amino acid (not considered as loop or turn) then another a-helix or B-sheet.
But if we found **consecutive secondary structures**
without any breaks or random structure, such as
(a-helix --- loop --- a-helix), we called it motif, a type of super-secondary structure.

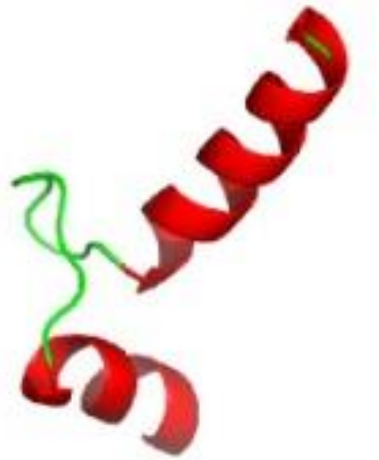
A motif (a module)

- A motif is made of multiple, repetitive or consecutive (connected) secondary structures, that can be small or large.
- They usually constitute 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.



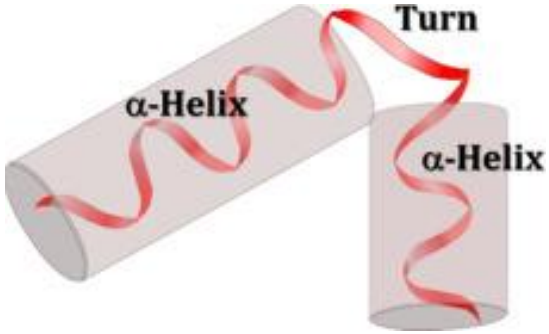
Examples of motifs

Helix-loop-helix: Two α-helices connected by a loop. It is found in DNA-binding proteins.



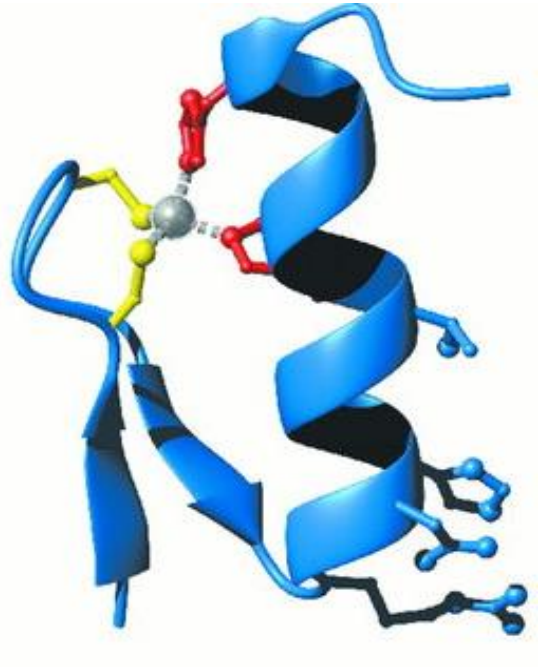
DNA-binding proteins wrap around the two strands of DNA stabilizing them.

Helix-turn-helix: Two α helices joined by a short strand of amino acids. It is found in DNA-binding proteins.



Zinc finger: Two beta strands with an alpha helix end folded over to bind a zinc ion. Important in DNA binding proteins. An example is steroid receptors.

Beta hairpin: Two antiparallel beta strands connected by a turn.

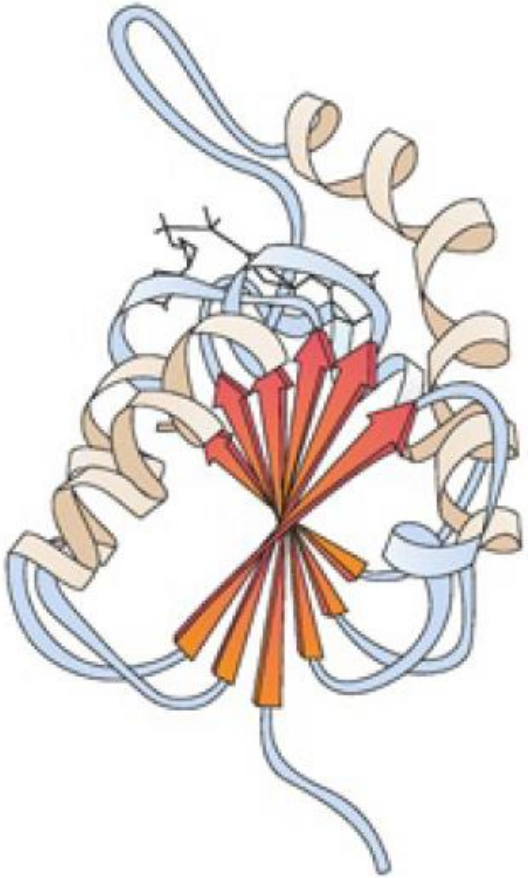


Tertiary Structure

What is tertiary structure?

Form the N to C termini

- The overall conformation of a polypeptide chain
- The three-dimensional arrangement of all the amino acids residues (how secondary structures are folded on each other)
- The spatial arrangement and location of amino acid residues that are far apart in the sequence



Try to walk with the direction of the polypeptide chain and describe the different structures that amino acids construct.

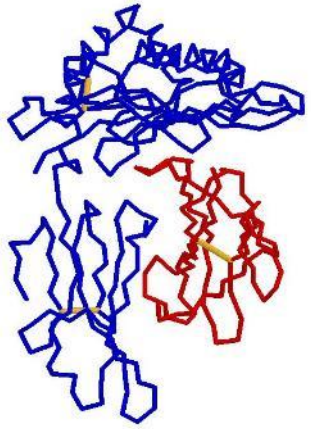
The connections between different secondary structures in a single polypeptide is part of the tertiary structure.

Each protein always has the same structure, and the tertiary structure deals with how amino acids are located after the folding of the polypeptide chain as shown in the figure on the right.

How to look at proteins (Model Systems)

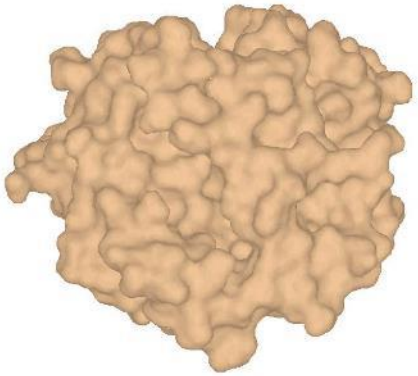
Possible Q:
How many alpha helices?
Are the beta strands parallel of antiparallel?
Answers are from clear images such as ribbon models

Trace structure



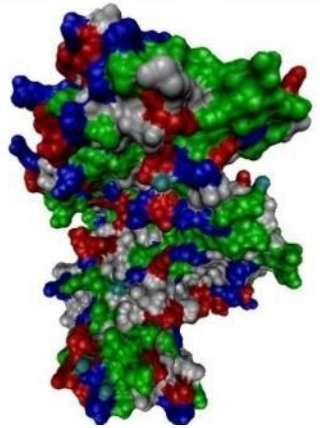
Simplest of all. Traces the backbone. N → C_{alpha} → C. neglecting R groups.

Protein surface map



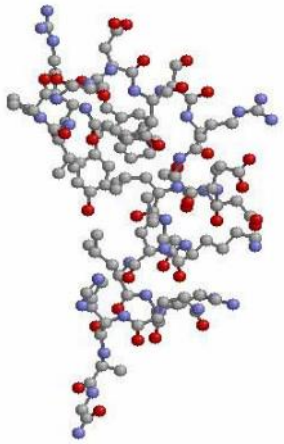
Only shows the surface. Shows the interaction between protein surface and external structure such as water. **Important in drug discovery and study.**

Space-filling structure



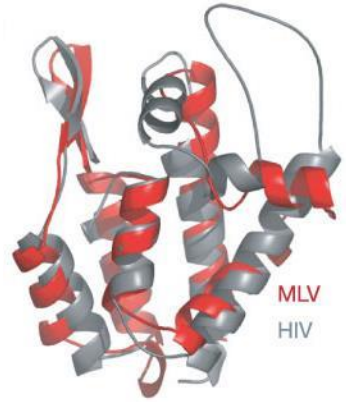
Similar to ball-and-stick, but the "balls" are filling the 3D space and **no spaces** between atoms are shown.

Ball and stick structure



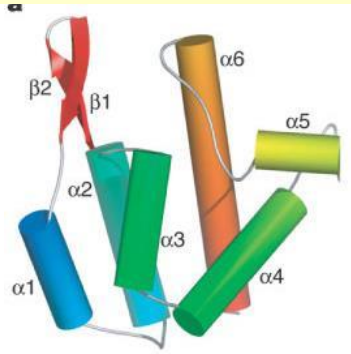
Also traces the backbone, but distinct atoms are represented by "balls" with "sticks" in between them.

Ribbon structure



So called because alpha helices are illustrated by ribbons.
Beta strands are illustrated by arrows where the head is directed from the N terminus to the C terminus.

Cylinder structure



Alpha helices are illustrated by cylinders.
Beta strands are illustrated by arrows (same as ribbon was).

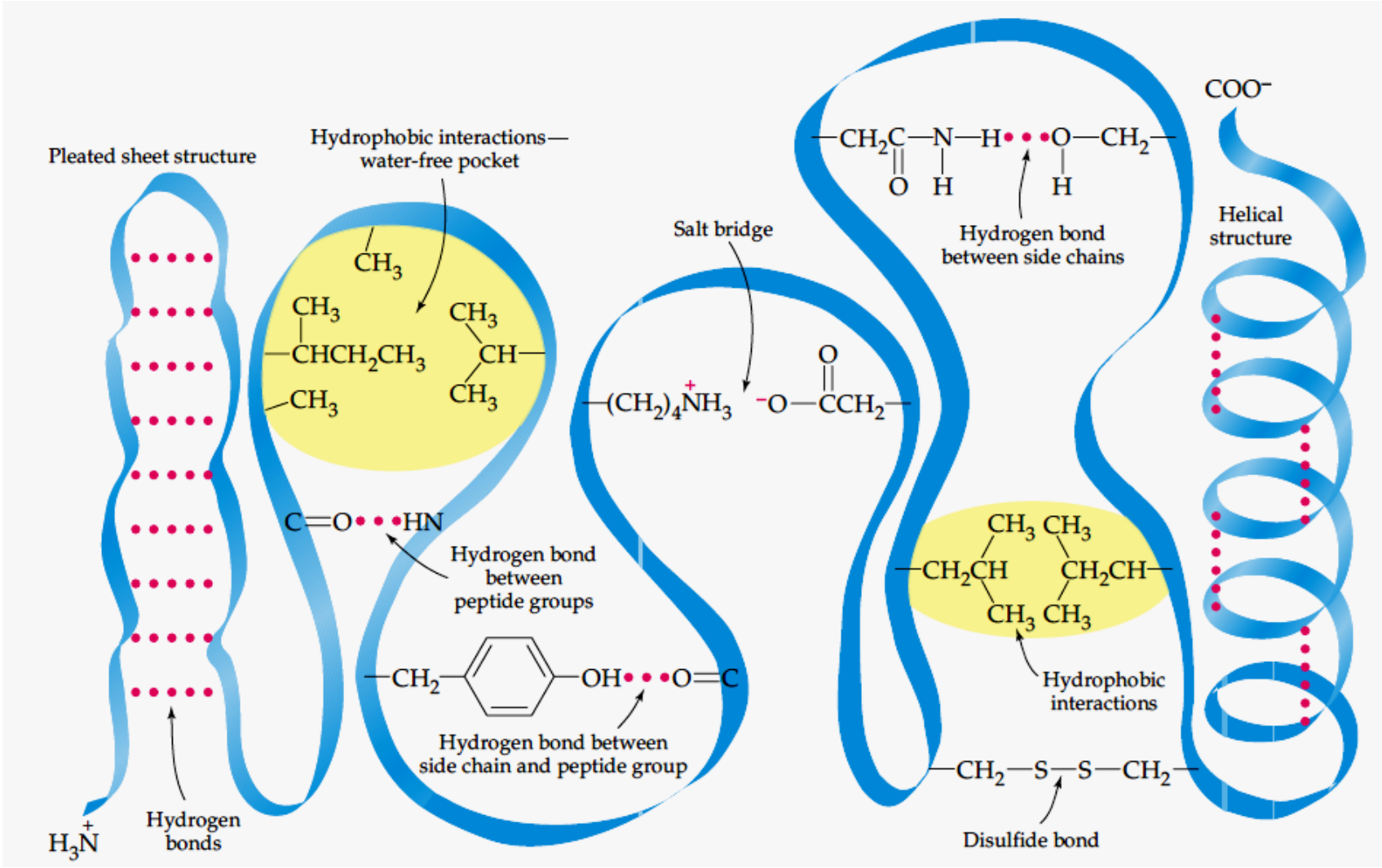
Shape-determining forces

As we said before, secondary structure is determined and stabilized by H-bonds between the components of the peptide bond in the backbone (the Carbonyl and Amino groups).

The tertiary structure is **determined** by non-covalent interactions by the R groups.

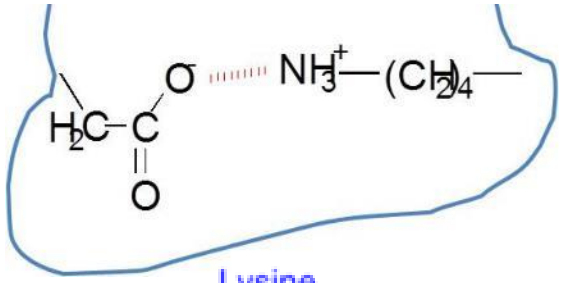
The tertiary structure is **stabilized** by other forces (discussed later in the lecture).

Recall the 4 non-covalent interactions in lecture 1.

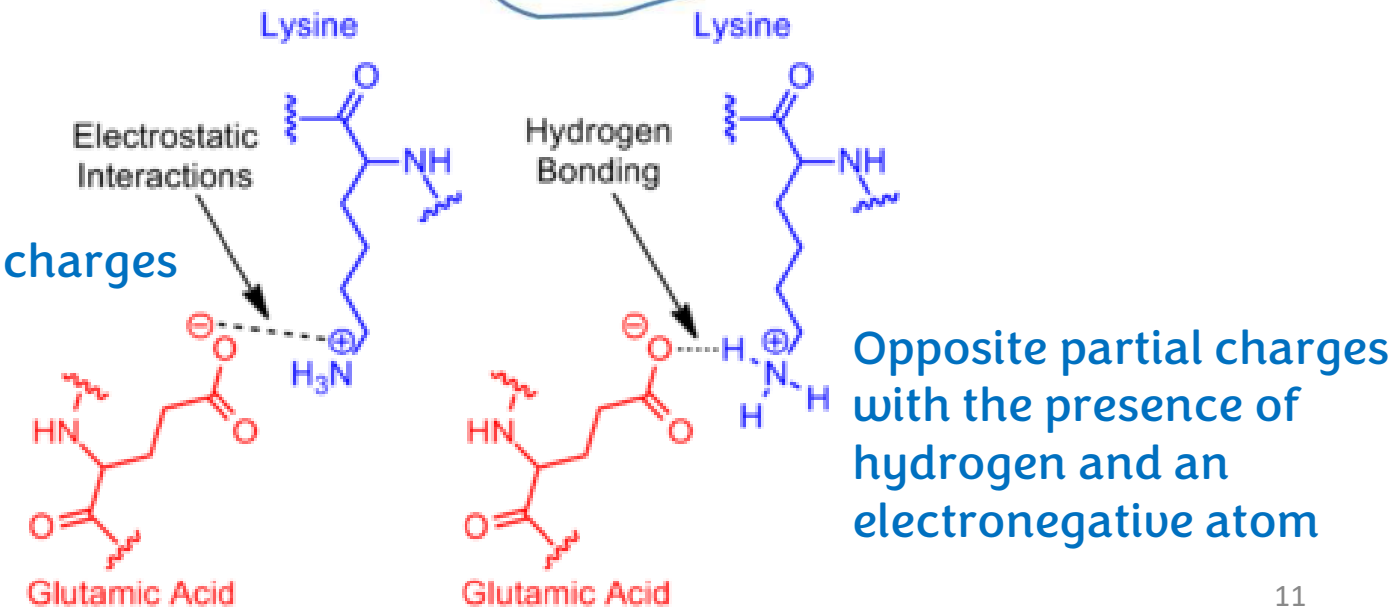


Non-covalent interactions

- 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



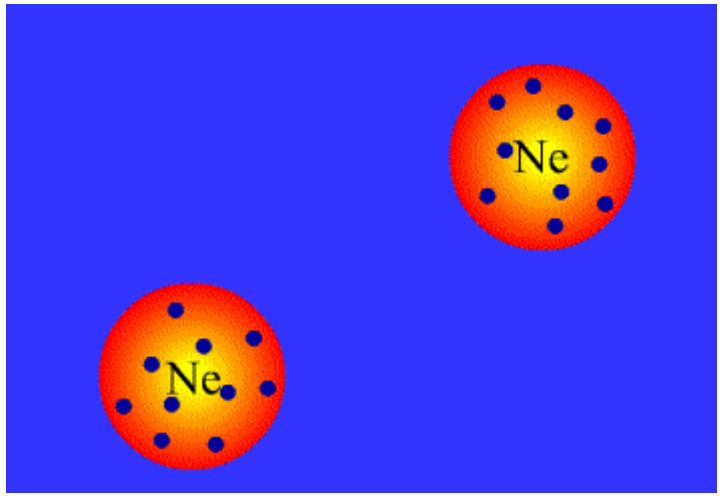
Opposite full charges

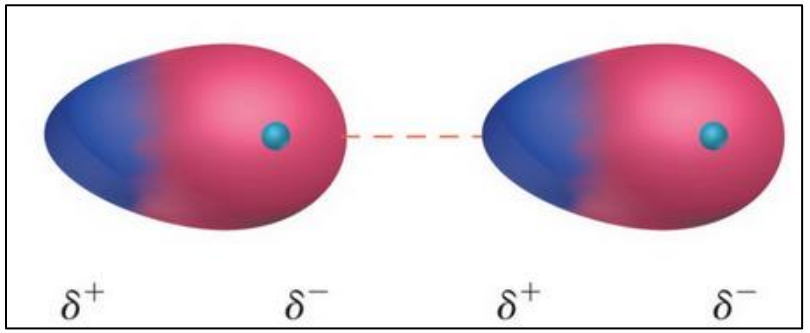
Opposite partial charges with the presence of hydrogen and an electronegative atom

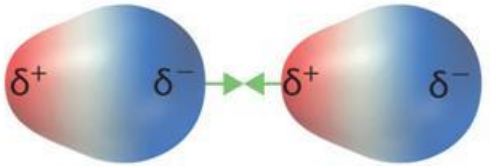
Van der Waals attractions

Induced dipoles caused by the temporal clustering of electrons on one side and can collectively cause considerable forces.

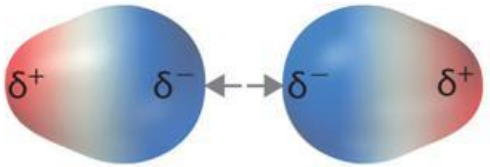
- There are both attractive and repulsive van der Waals forces that control protein folding.
- Although van der Waals forces are extremely weak, they are significant because there are so many of them in large protein molecules.



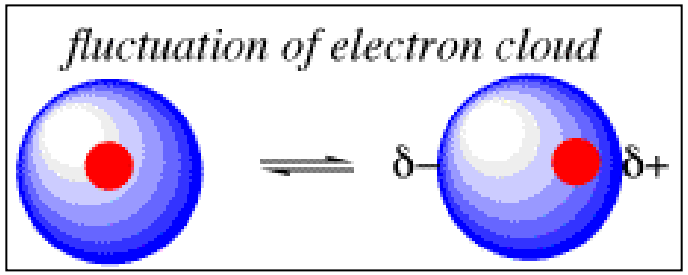




(b) Attraction



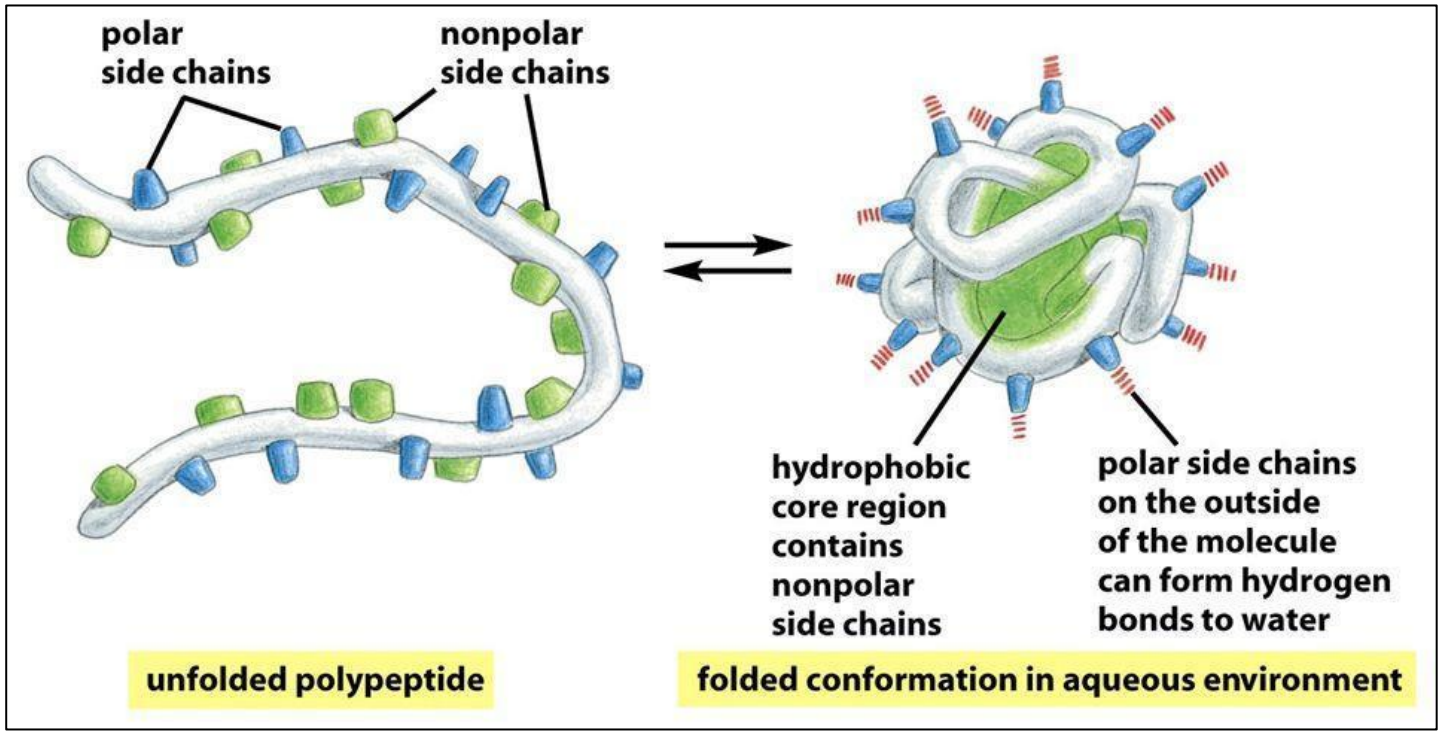
(d) Repulsion

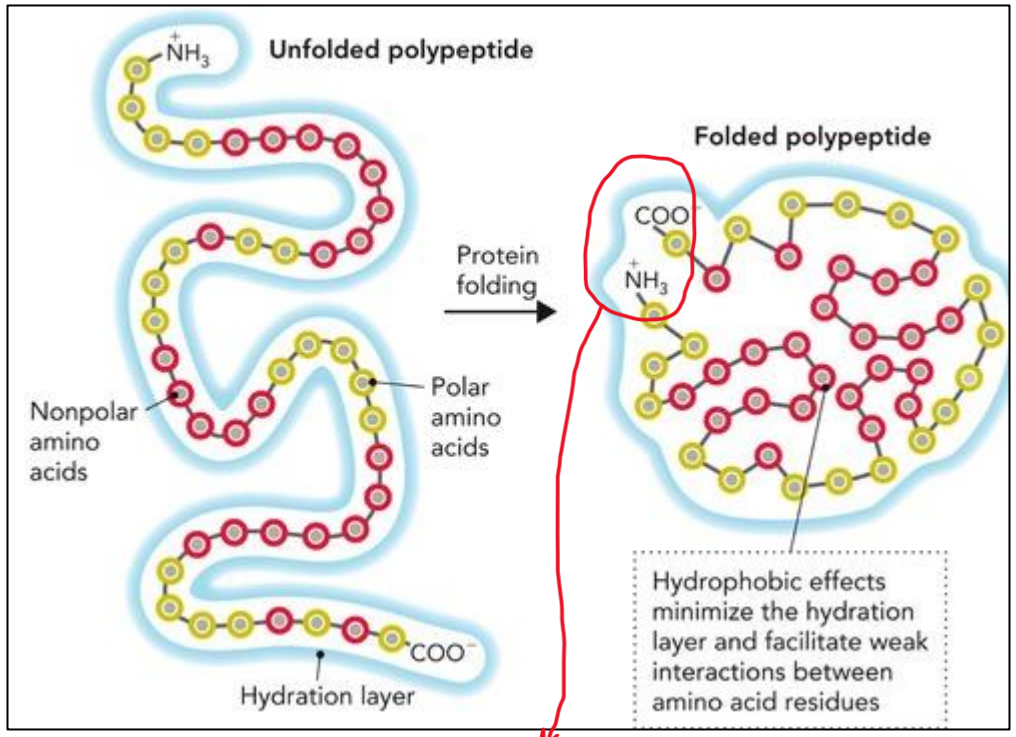


Hydrophobic interactions

Probably the most important interactions.

- A system is more thermodynamically (energetically) stable when hydrophobic groups are clustered together rather than extended into the aqueous surroundings; it happens directly after translation.





Hydrophobic amino acids → interior (usually)

Hydrophilic amino acids → exterior (usually)

N and C termini can be close to each other after folding

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

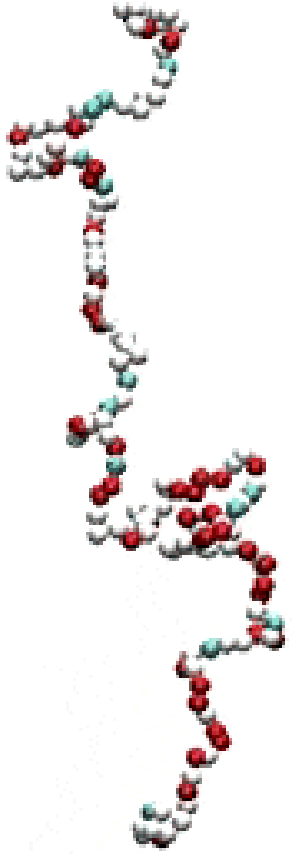
- Polar amino acids can be found in the interior of proteins
- In this case, they form hydrogen bonds to other amino acids or to the polypeptide backbone
- They play important roles in the function of the protein

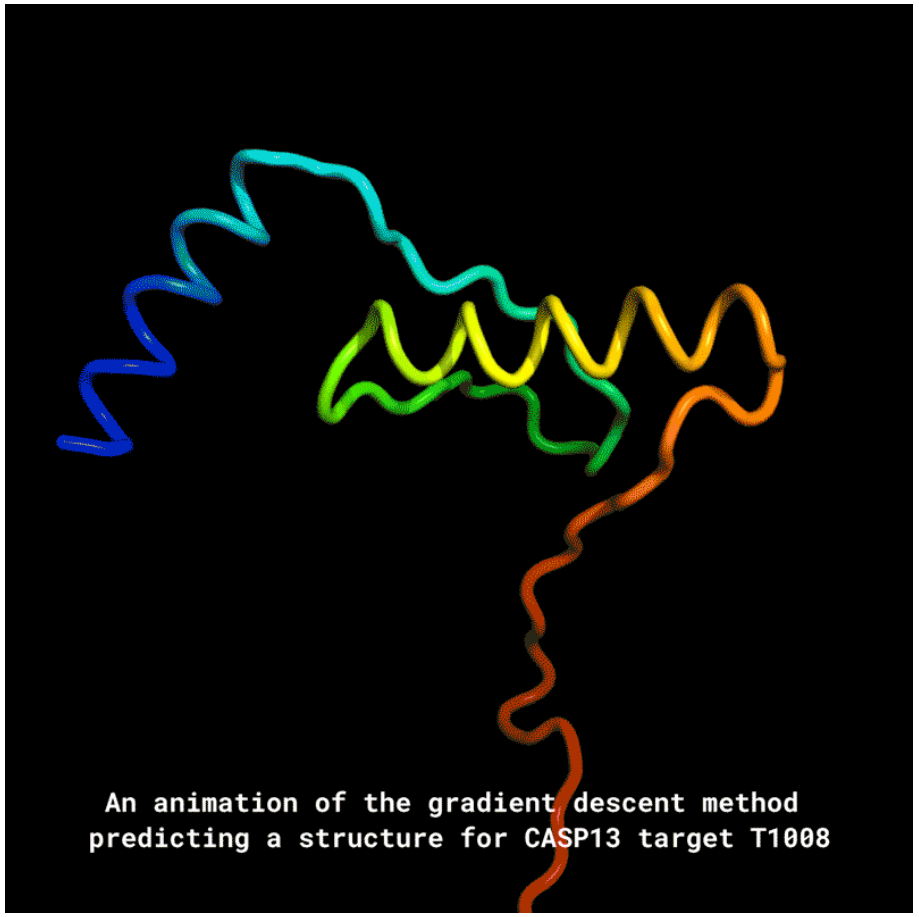
For example, in hemoglobin there are polar and even charges amino acids in the interior, so we can conclude that there is a special function behind this conformation.

If the polypeptide chain is put in a hydrophobic solvent such as benzene, the hydrophobic amino acids will fold out and hydrophilic with fold in changing the shape and causing the loss of biological function of the protein.

A hypothetical look at protein folding

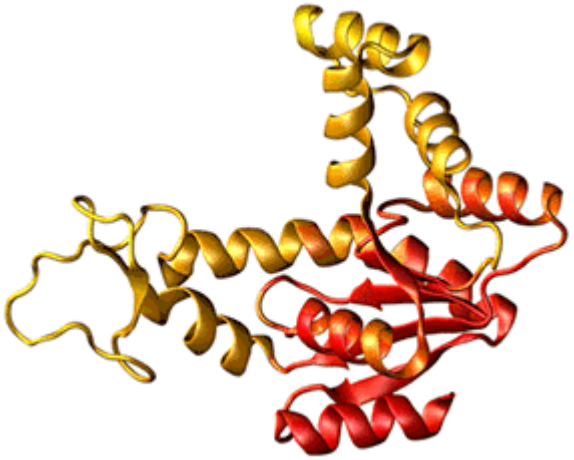
Folding is gradual, and this folding is governed by rules.

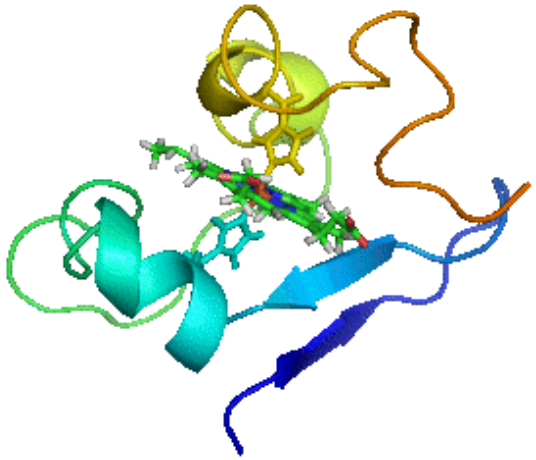


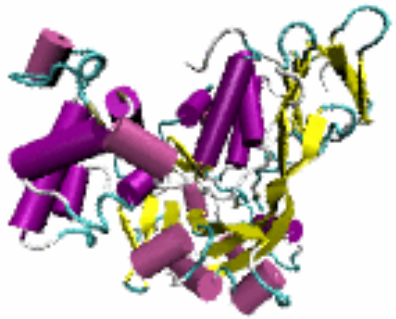


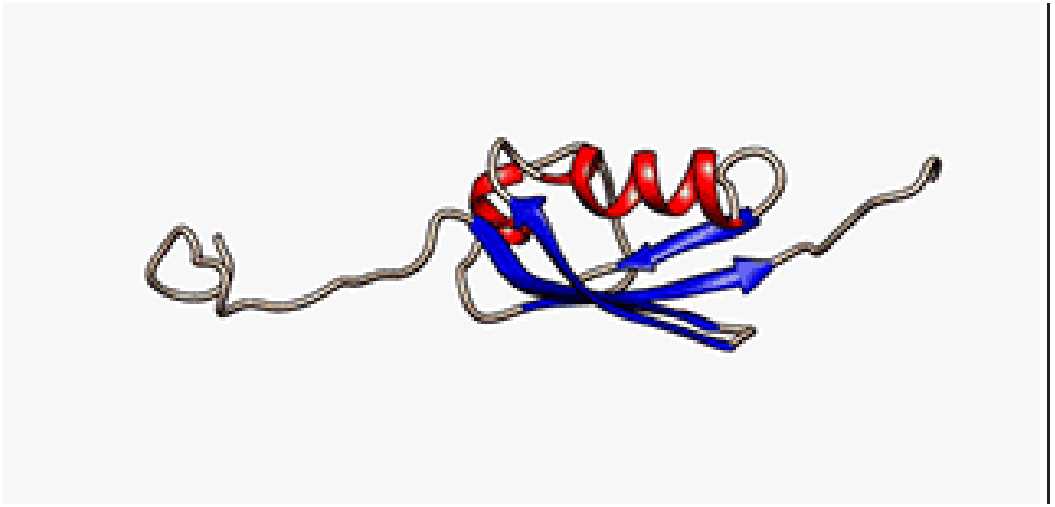
Protein are NOT static

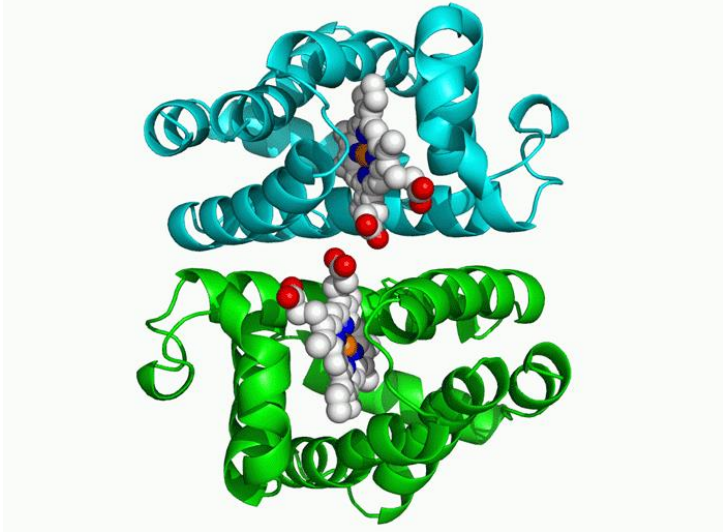
They are in constant movement (dynamic), and they collide with one another in the cytosol.











Stabilizing factors

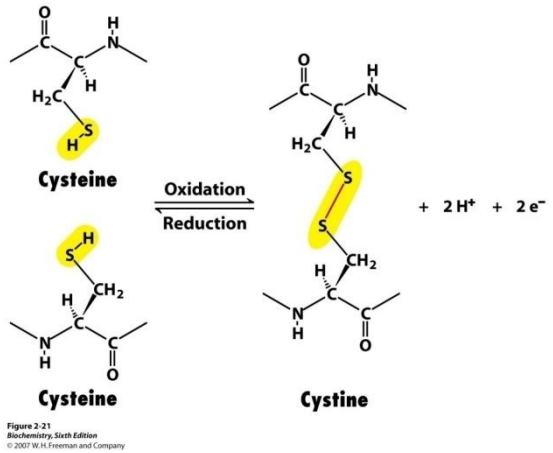
- There are two forces that do not determine the three-dimensional structure of proteins, but stabilize these structures:
  - Disulfide bonds
  - Metal ions

They **do not** determine the tertiary structure, but they help maintain and stabilize the structure after it had already formed.

Disulfide bonds

- The side chain of cysteine contains a reactive sulfhydryl group (—SH), which can oxidize to form a disulfide bond (—S—S—) to a second cysteine.
- The crosslinking of two cysteines to form a new amino acid, called **cystine**.

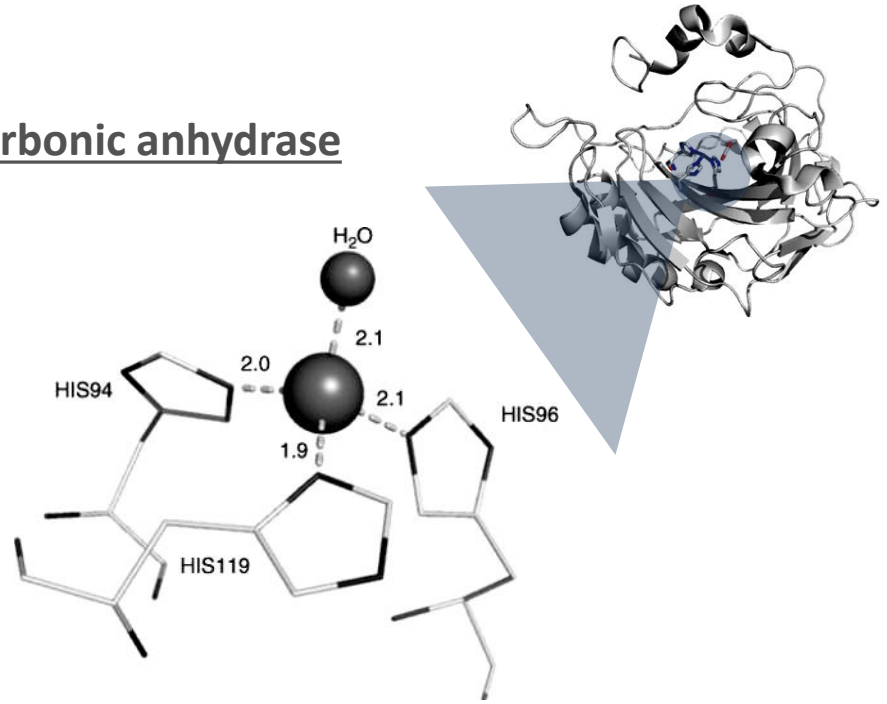
Such as in vasopressin



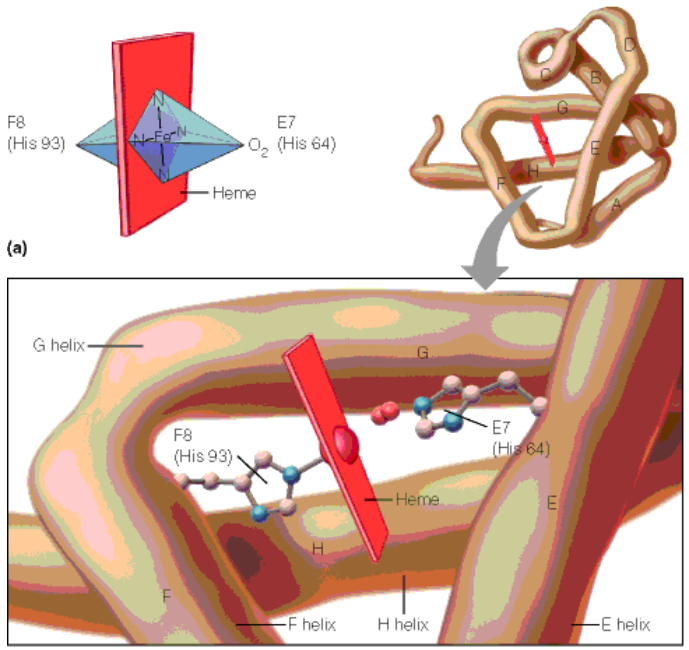
Metal ions

- Several proteins can be complexed to a single metal ion that can stabilize protein structure by forming:
  - **Covalent** interaction (myoglobin) between iron (in heme) and amino acids
  - **Salt bridges** (carbonic anhydrase) between zinc and amino acids around it.

Carbonic anhydrase



Myoglobin



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

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V1 → V2	10; second paragraph	stabilized	determined
	10	-----	Added the third paragraph
	INSIGNIFICANT ERRORS		
	9; space filling structure	No spaces … is shown	No spaces … are shown
	12; top right text	Clustering of electrons on on side	Clustering of electrons on one side
	14; first blue paragraph	Interion	Interior
V2 → V3			

Additional Resources Used:

1. Campbell Textbook:
   Sec. 4.3
   (Secondary Structure of Proteins)
   Sec. 4.4
   (Tertiary Structure of Proteins)

رسالة من الفريق العلمي:

اللهم انصر أهل غزة،
وأمدهم بجند من عندك،
واقهر أعداءهم واخذلهم ودمرهم

لا تنسوا إخوانكم من صالح الدعاء