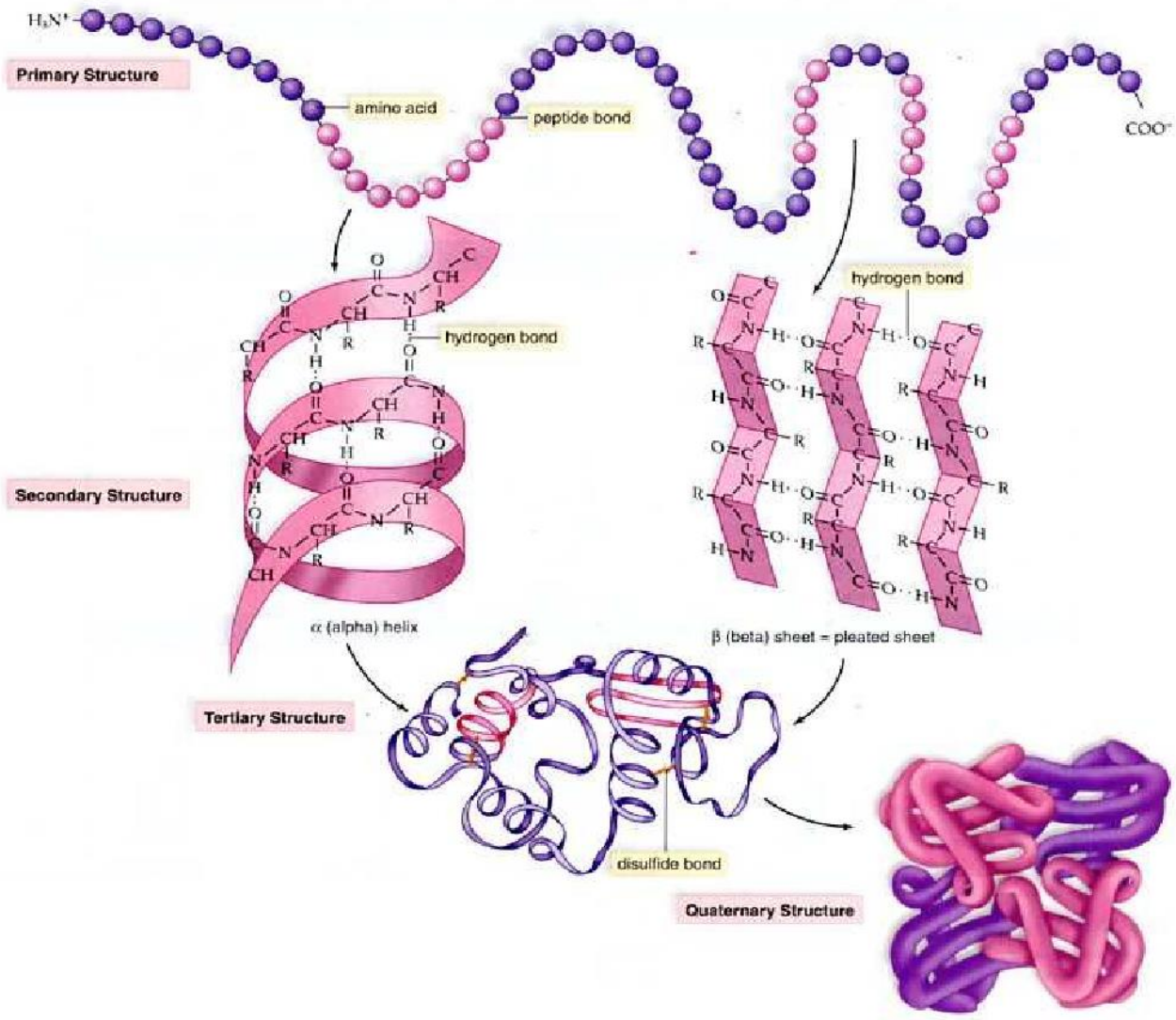
Protein Folding Mechanism



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Introduction to protein structure

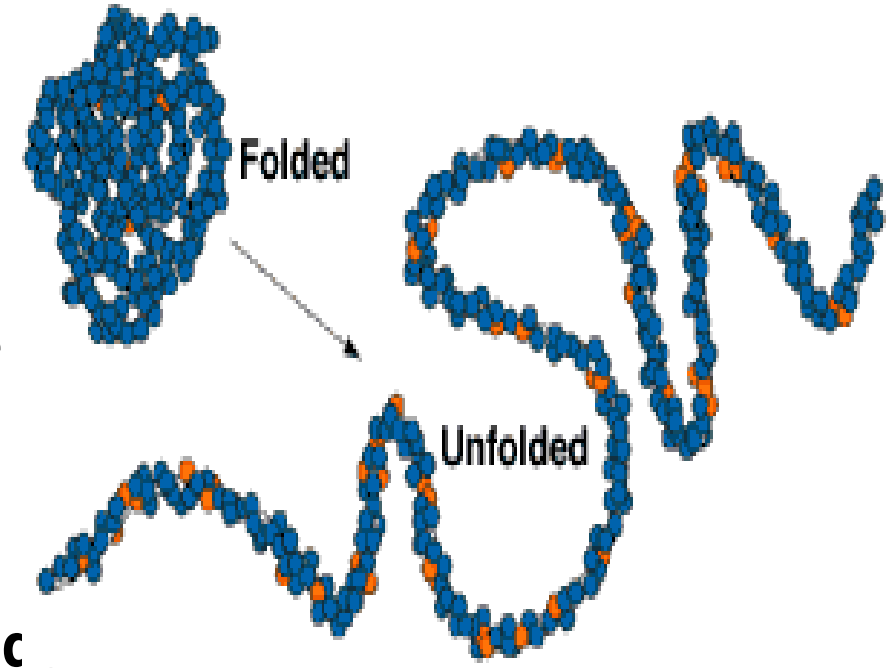
Proteins *are large molecules that our cells need to function properly. They consist of amino acids. The structure and function of our bodies depend on proteins. The regulation of the body's cells, tissues, and organs cannot happen without them. Proteins have several layers of structure each of which is important in the process of protein folding.*

- The first most basic level of protein structure is the sequence of amino acids themselves.(**primary structure)**
- The next layer in protein structure is the **secondary structure. Secondary structure** includes **α-Helixes and β-sheets.**
- The **tertiary structure** is the next layer in protein structure. This takes the α-Helixes and β-sheets and allows them to fold into a three dimensional structure.
- Protein **folding** is essential for a polypeptide chain to acquire its proper structure and function.

Protein Folding

- **Protein folding** is a remarkably complex physicochemical process via which a **polymer of amino acids** that samples many, many conformations in its unfolded state adopts a well-packed and essentially unique native fold. (Methods in Enzymology, 2007)
- Proteins are folded and held together by several forms of **molecular interactions.**

  The molecular interactions include the **thermodynamic Stability** of the complex, the **hydrophobic interactions and the disulfide bonc** formed in the proteins.



History of Protein Folding

- In **1972, Christian Anfinsen** received a **Nobel Prize** for discovering in the 1950s that proteins assume their three-dimensional conformations and therefore gain their catalytic potential, exclusively based on primary instructions in their intrinsic amino acid sequence. This insight forged the link between the genetic code and protein function, but it emerged from simple denaturation-renaturation experiments involving a small number of isolated, pure enzymes, which at that time were rather **simple and small**.
- As more **complex genes** have been analyzed and expressed over time, it has become common knowledge that most complex proteins are notoriously difficult to refold at concentrations present in cells and at the bulk concentration of protein that prevails in cells. Indeed, many proteins even fold poorly when expressed inside cells from distant species.

Protein Folding

- Proteins must fold to their active native state when they emerge from the ribosome and when they repeatedly unfold and refold during their lifetime
- Protein folding is assisted by HSP called chaperones. Multimeric complexes that form hollow structures, called chaperonins, also participate in protein folding.
- The folding process is difficult and potentially dangerous .
- Biological health depends on its success and disease on its failure.
- However, more than 50 y after the formative demonstration that protein folding is a straightforward biophysical process , there is not general agreement on the overarching questions of how proteins fold and why they fold in that way.
- Given this uncertainty, one is not sure how to even think about many related biophysical and biological problems.

❖ The nature of protein folding pathways ,S. Walter Englander and Leland Mayne, PNAS November 11, 2014 111 (45) 15873-1588.

Protein folding contd…

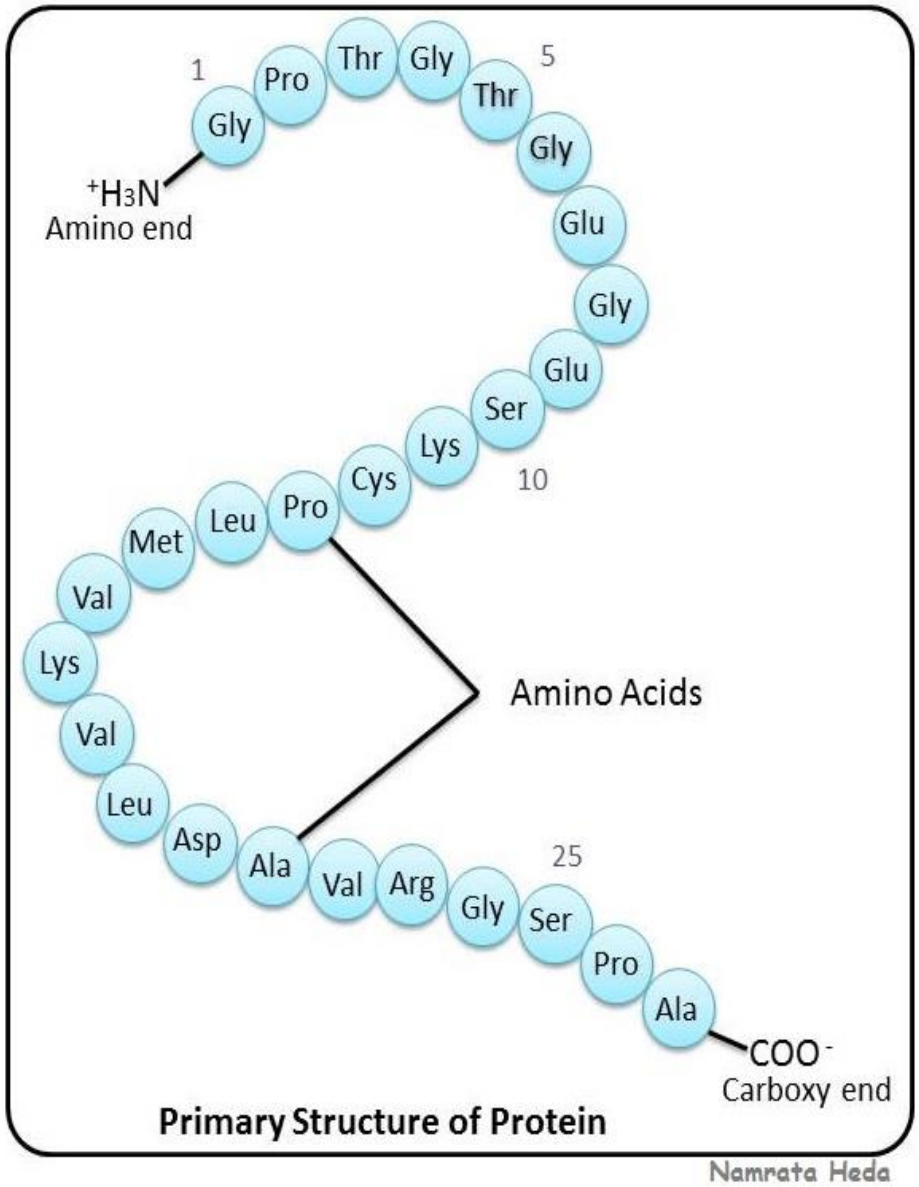
The process depends upon:

- The solvent (water or lipid bilayer)
- The concentration of salt
- The PH
- The temperature
- The possible presence of cofactor
- Molecular chaperones

Primary Structure

The primary structure of a protein, its linear amino-acid sequence, determines its native conformation. he specific amino acid residues and their position in the polypeptide chain are the determining factors for which portions of the protein fold closely together and form its three-dimensional conformation. The amino acid composition is not as important as the sequence.

- Voet D, Voet JG, Pratt CW (2016).*Principles Of Biochemistry* (Fifth ed.). Wiley. ISBN 978-1-118-91840



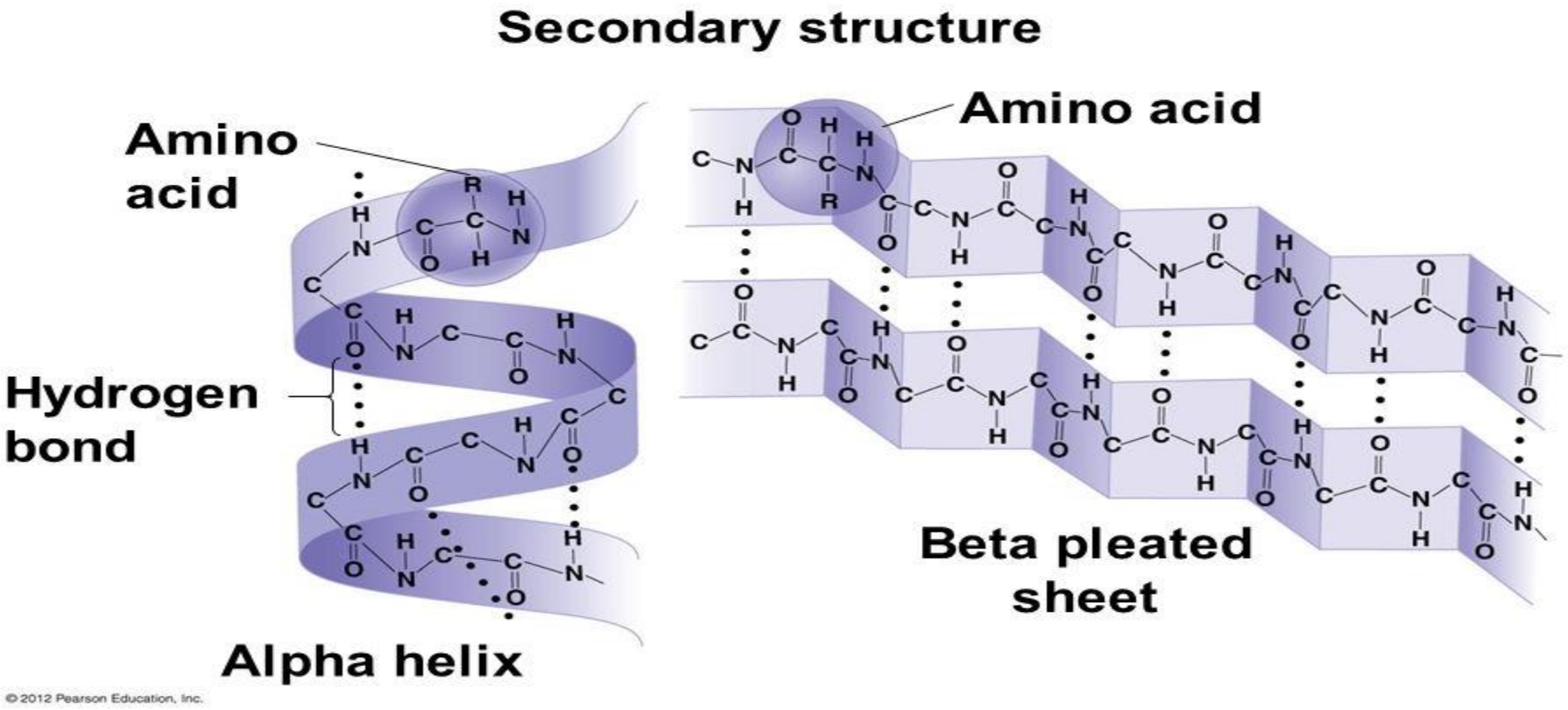
Secondary Structure

- Formation of a secondary structure is the first step in the folding process that a protein takes to assume its native structure. Characteristic of secondary structure are the structures known as alpha helices and beta sheets that fold rapidly because they are stabilized by intramolecular hydrogen bonds, as was first characterized by Linus Pauling.
- Formation of intramolecular hydrogen bonds provides another important contribution to protein stability.
- Protein secondary structure takes on the three forms

➢ Alpha helix

➢ Beta sheet

➢ Turn , coil or loop



✓α-helices are formed by hydrogen bonding of the backbone to form a spiral shape .

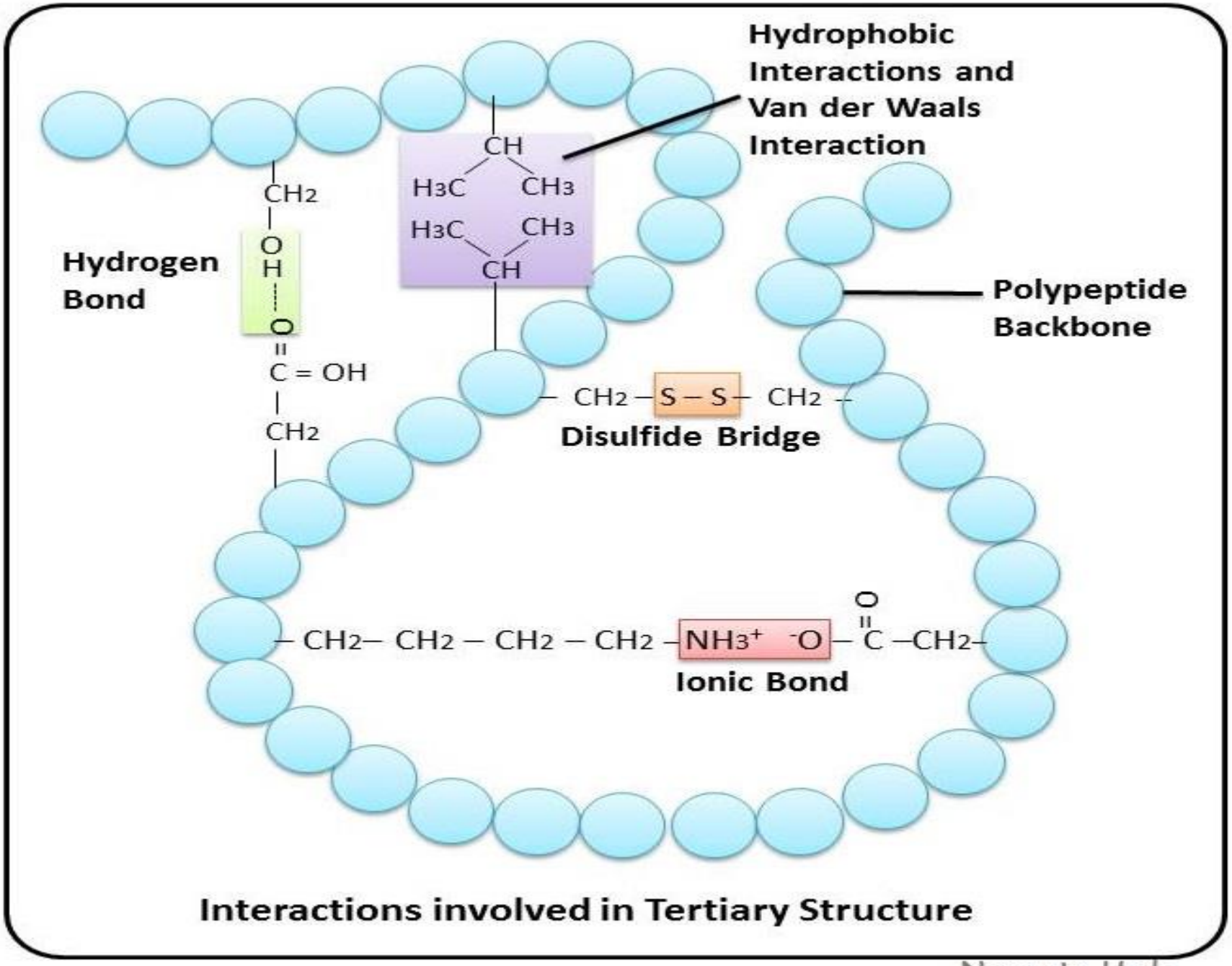
✓β pleated sheet is a structure that forms with the backbone bending over itself to form the hydrogen bonds .

Tertiary structure

The alpha helices and beta pleated sheets can be **amphipathic in nature,** or contain a **hydrophilic** portion and a **hydrophobic** portion. This property of secondary structures aids in the tertiary structure of a protein in which the folding occurs so that the hydrophilic sides are facing the aqueous environment surrounding the protein and the hydrophobic sides are facing the hydrophobic core of the protein.

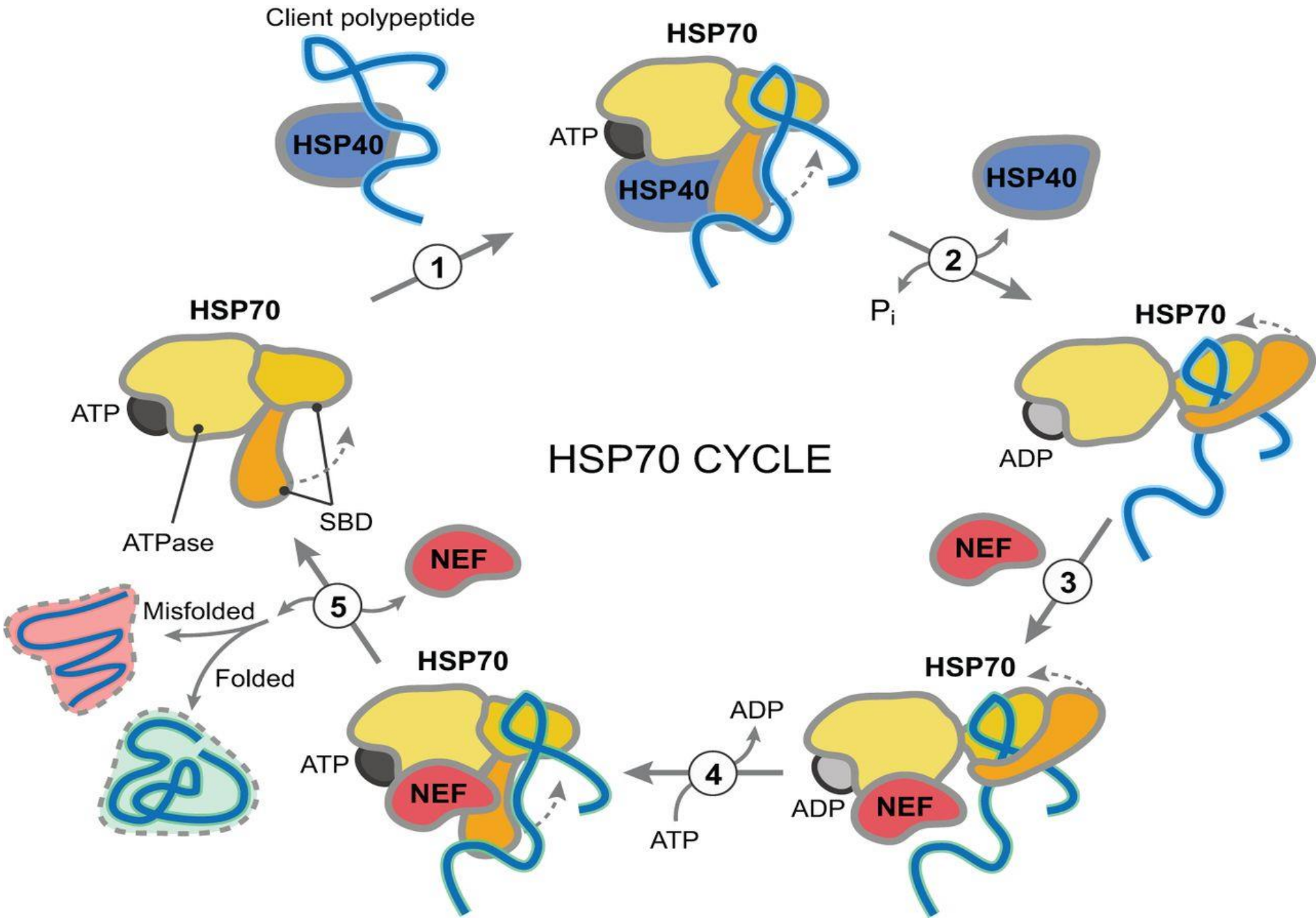
STABILITY FACTORS

- ✓ Peptide bond
- ✓ Terminal electrostatic interaction
- ✓ H-Bonding
- ✓ Hydrophobic interaction
- ✓ Disulphide bond


Hydrophobic Interactions and Van der Waals Interaction
Hydrogen Bond
Polypeptide Backbone
Disulfide Bridge
Ionic Bond
Interactions involved in Tertiary Structure
Namrata Heda

Driving forces of protein folding

- **Molecular chaperones** provide the solution to this paradox. In many cases, chaperones, such as the **Hsp70** chaperone system, stabilize aggregation-prone (i.e., hydrophobic) intermediates. In more difficult cases, tube-like chaperones, such as the **GroEL/Hsp60** chaperone system, funnel the polypeptide into the protected internal space of giant ring-based structures.
- These two strategies represent the basic principles that permit proteins to fold in the cell, and the establishment of the mechanisms and pathways involved represents, in our time, an advance comparable to that made by Anfinsen in his time.


Client polypeptide
HSP40
1
HSP70
ATP
HSP40
2
Pi
HSP40
HSP70
ADP
3
NEF
HSP70
ATP
NEF
4
ADP
ATP
HSP70
ATP
ATPase
SBD
5
NEF
Misfolded
Folded
HSP70 CYCLE

Driving forces of protein folding

- **Hydrophobic effect:** Protein folding must be thermodynamically favorable within a cell in order for it to be a spontaneous reaction. Since it is known that protein folding is a spontaneous reaction, then it must assume a negative Gibbs free energy value.
- Minimizing the number of hydrophobic side-chains exposed to water is an important driving force behind the folding process.

Driving forces of protein folding

- The hydrophobic effect is the phenomenon in which the hydrophobic chains of a protein collapse into the core of the protein (away from the hydrophilic environment).
- The multitude of hydrophobic groups interacting within the **core of the globular folded protein** contributes a significant amount to protein stability after folding, because of the vastly accumulated vander Waals forces (specifically London Dispersion forces).