Medicinal Chemistry

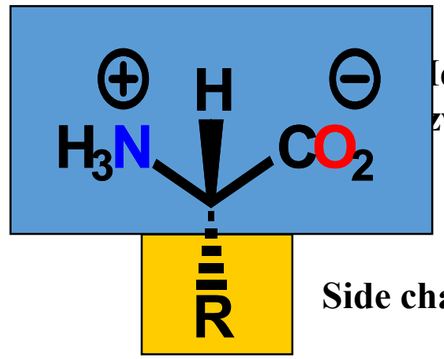
Chapter 3

DRUG TARGETS: PROTEINS

Contents

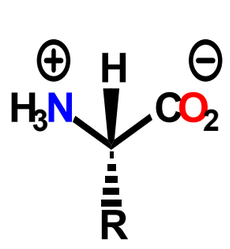
THE BUILDING BLOCKS FOR PROTEINS

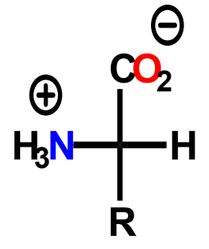
- Proteins are macromolecules made up of amino acid building blocks
- There are 20 common amino acids in human proteins
- Each amino acid has an identical head group
- Amino acids are chiral molecules (except glycine, R=H)
- Only L-amino acids are present in human biochemistry
- The L-amino acids are S-enantiomers (except cysteine; R = CH_2SH)



lead group
zwitterion)

Side chain



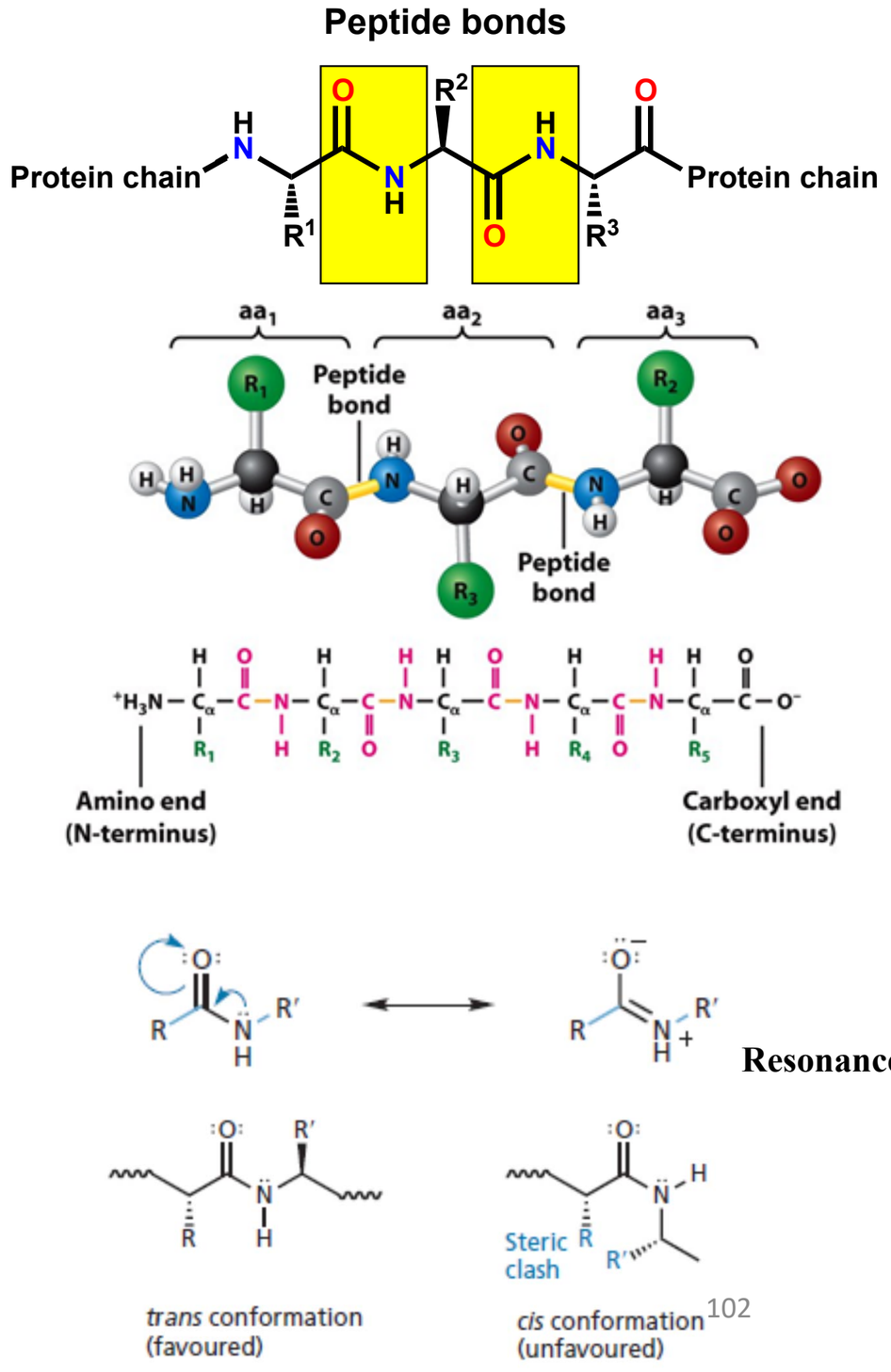


Fischer diagram

THE PRIMARY STRUCTURE OF PROTEINS

The primary structure of a protein refers to its amino acid sequence. Amino acids in peptides and proteins are joined together by peptide bonds (amide bonds) between the carboxyl and amino groups of adjacent amino acids. The backbone of all proteins consists of a [-N-Cα(R)-C(O)-] repetitive unit. Only the R-group side-chains vary. Written from left-to-right, from the protein's N- to C-terminus. The average yeast protein contains 466 amino acids.

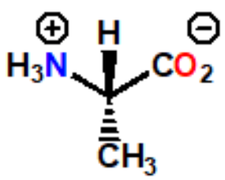
There are two possible conformations for the peptide bond, The trans conformation is the one that is normally present in proteins as the cis conformation leads to a steric clash between the residues.



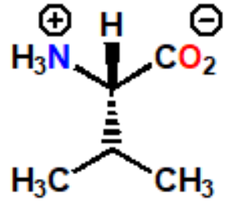
- **Codes for amino acids**

Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Cysteine	Cys	C
Glutamic acid	Glu	E
Glutamine	Gln	Q
Glycine	Gly	G
Proline	Pro	P
Serine	Ser	S
Tyrosine	Tyr	Y

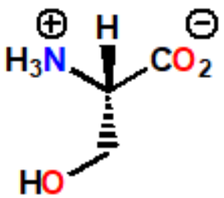
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Threonine	Thr	T
Tryptophan	Trp	W
Valine	Val	V



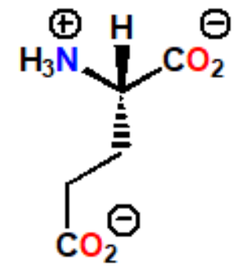
Alanine



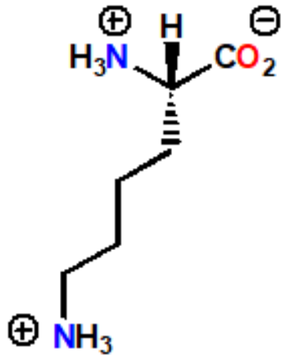
Valine



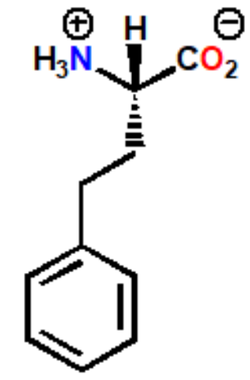
Serine



Aspartate



Lysine

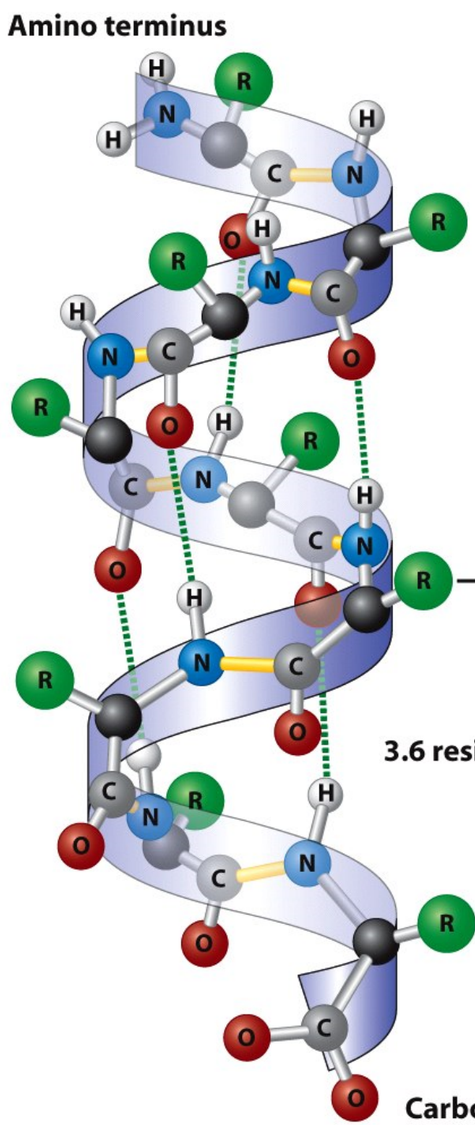


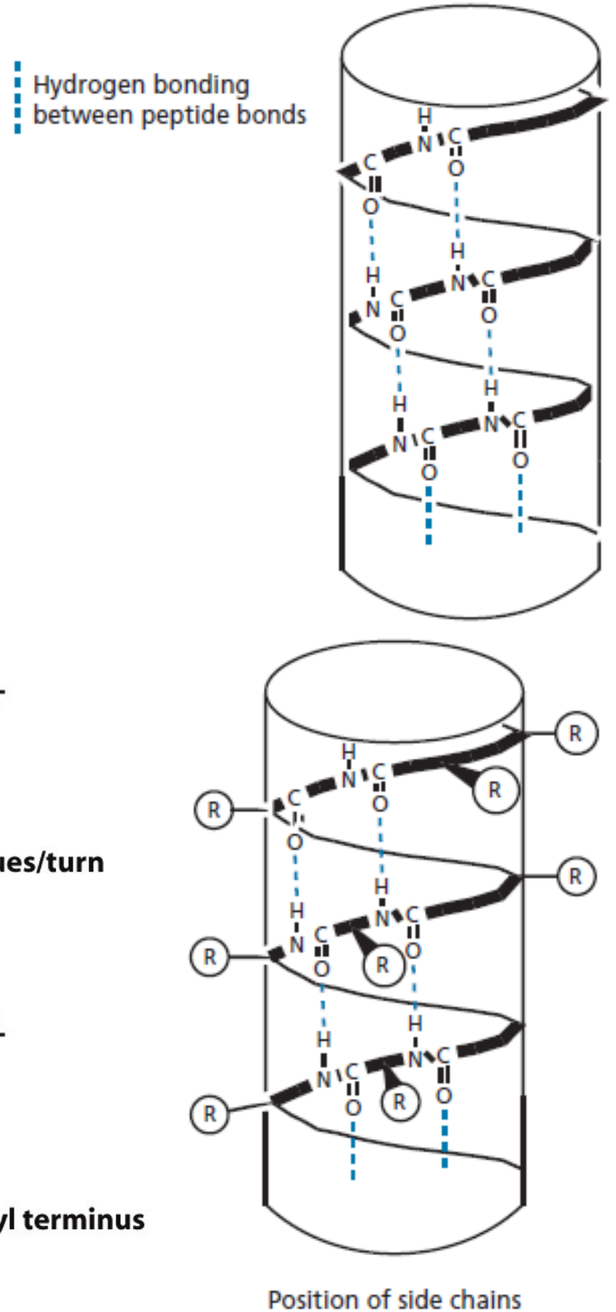
Phenylalanine

THE SECONDARY STRUCTURE OF PROTEINS

Secondary structure refers to short-range, periodic folding elements that are common in proteins. These include the α helix, the β sheet, and turns.

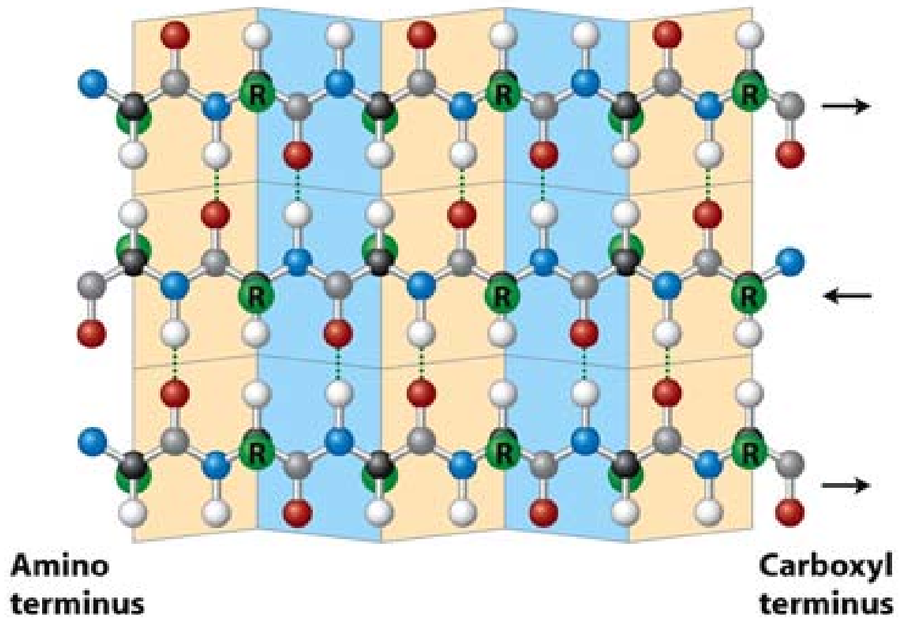
In the α helix, the backbone adopts a cylindrical spiral structure in which there are 3.6 aac per turn. The R-groups point out from the helix, and mediate contacts to other structure elements in the folded protein. The α helix is stabilized by H-bonds between backbone carbonyl oxygen and amide nitrogen atoms that are oriented parallel to the helix axis.

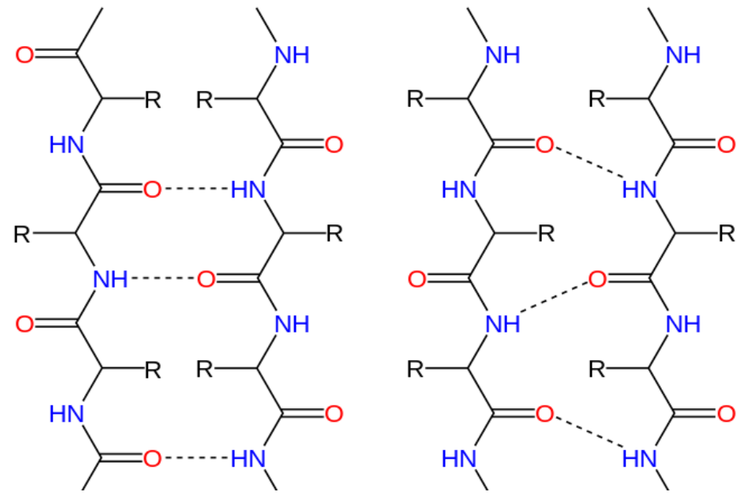




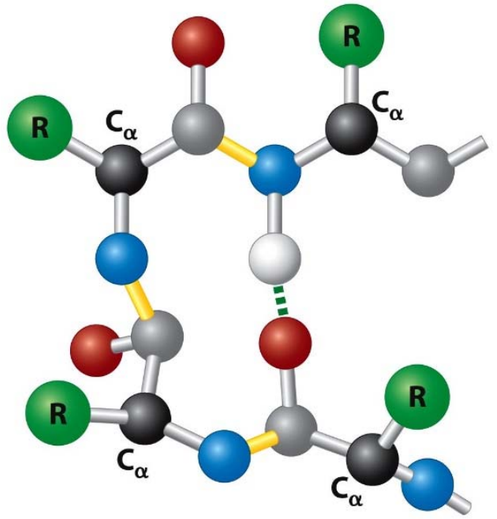
In β sheets (“pleated sheets”), each β strand adopts an extended conformation. ß strands tend to occur in pairs or multiple copies in ß sheets that interact with one another via H-bonds directed perpendicular to the axis of each strand. Carbonyl oxygens and amide nitrogen's in the strands form the H-bonds.

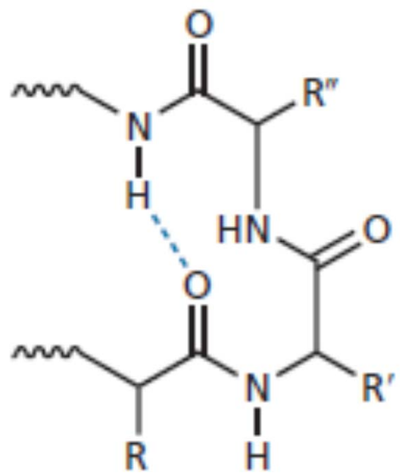
Strands can orient antiparallel or parallel to one another in β sheets. R-groups of every other amino acid point up or down relative to the sheet. Most ß strands in proteins are 5 to 8 aac long.





A β-turn allows the polypeptide chain to turn abruptly and go in the opposite direction. This is important in allowing the protein to adopt a more globular compact shape. A hydrogen bonding interaction between the first and third peptide bond of the turn is important in stabilizing the turn. Less abrupt changes in the direction of the polypeptide chain can also take place through longer loops, which are less regular in their structure, but often rigid and well defined.



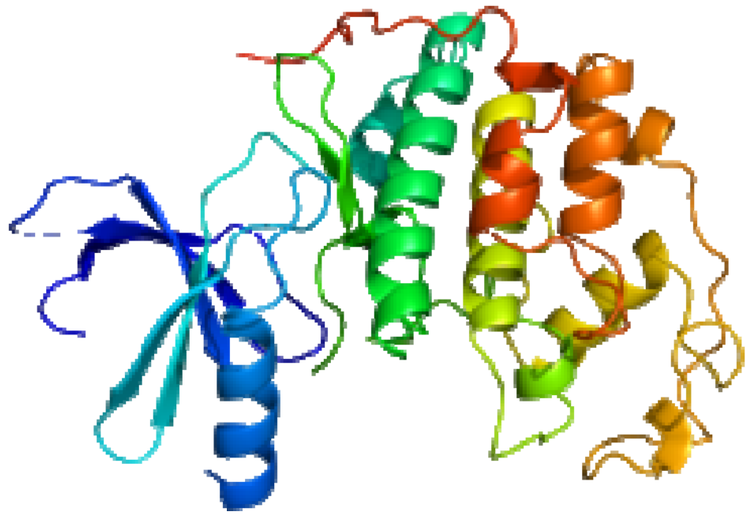


THE TERTIARY STRUCTURE OF PROTEINS

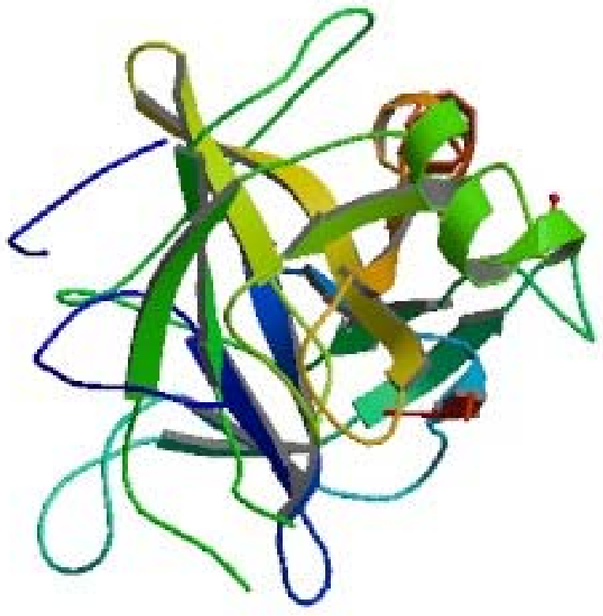
Tertiary structure refers to the folded 3D structure of a protein. Structural proteins are quite ordered in shape, whereas globular proteins, such as enzymes and receptors, fold up to form more complex structures.

Globular proteins often contain regions of ordered secondary structure, the extent of which varies from protein to protein, as cyclin-dependent kinase 2, has several regions of α helices and β-pleated sheets.

Chymotrypsin has very little secondary structure

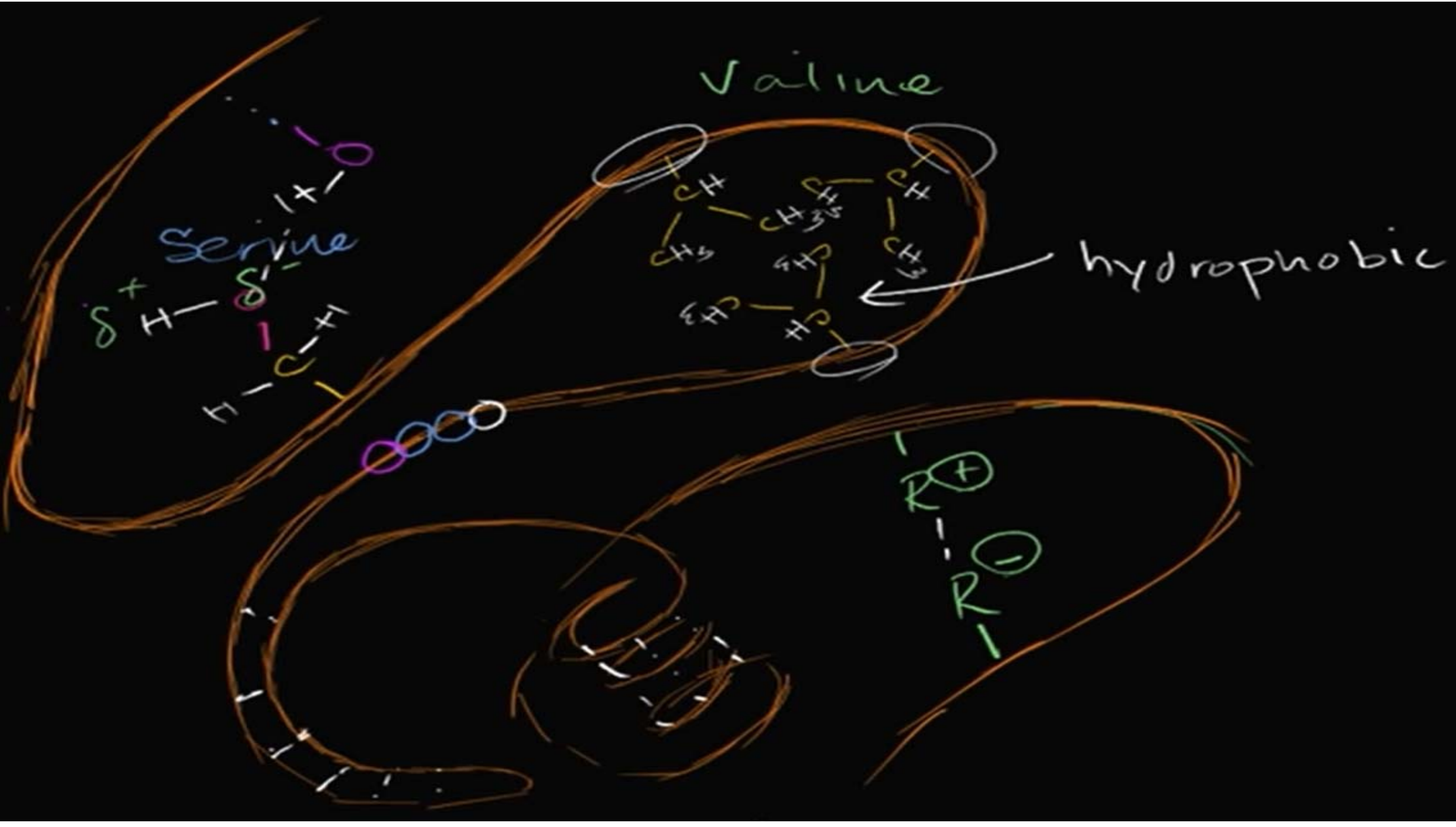


cyclin-dependent kinase 2



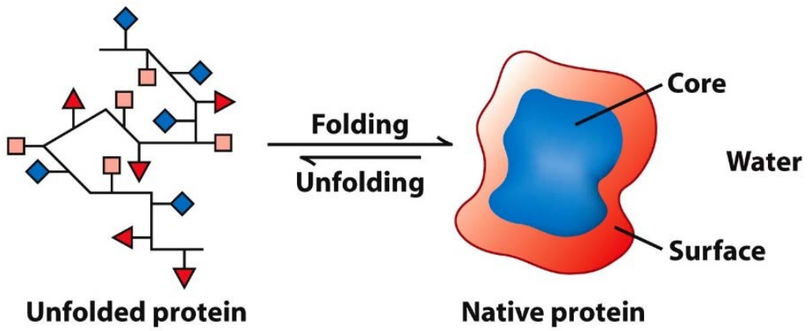
Chymotrypsin

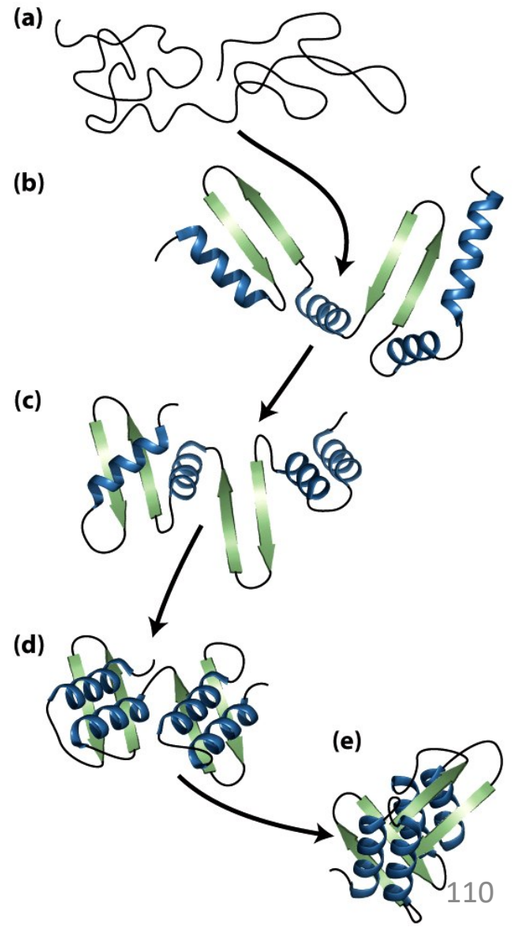

Serine


Valine
Serine
hydrophobic

The 3D structure of protein looks like a ball of string after a cat has been at it. The 3D proteins fold up to form a complex by a range of different chemical functional groups along its length not only peptide links, but also the side chains of each aac formed several of attractive or repulsive interaction. Thus, the protein minimize the unfavorable and maximize the favorable interactions until the most stable shape or conformation is found.

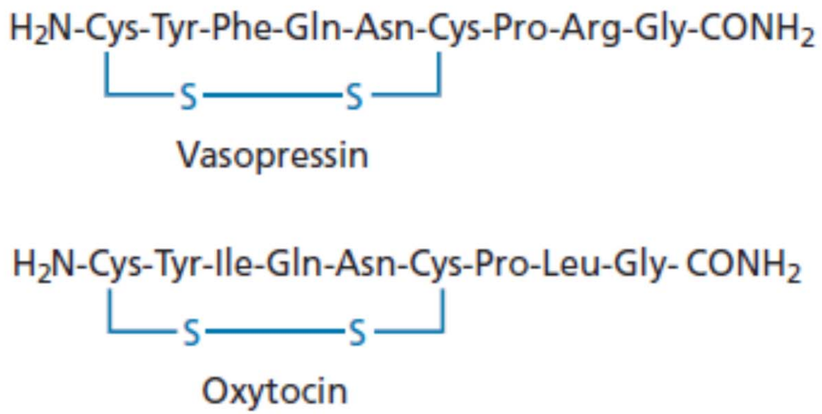
Folding tends to occur via successive conformational changes leading to secondary and then tertiary structure elements, The native conformation of a protein typically is its lowest free energy, so the most stable structure. The unfolded conformation of a protein can be generated by heating or treatment with certain organic solvents.



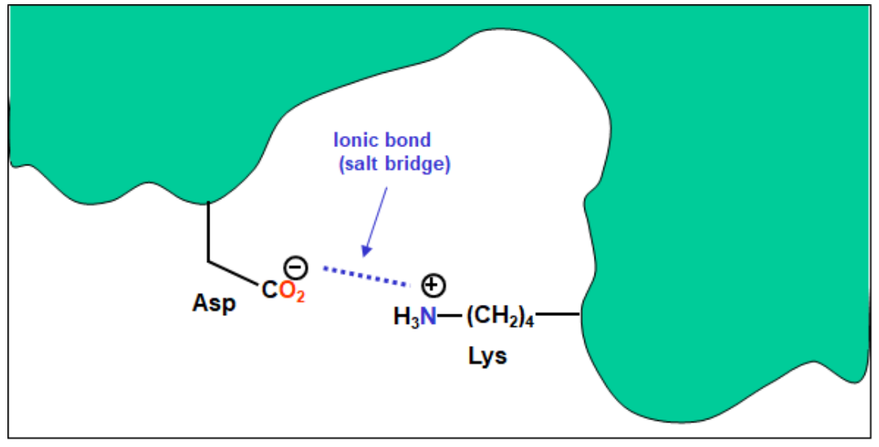


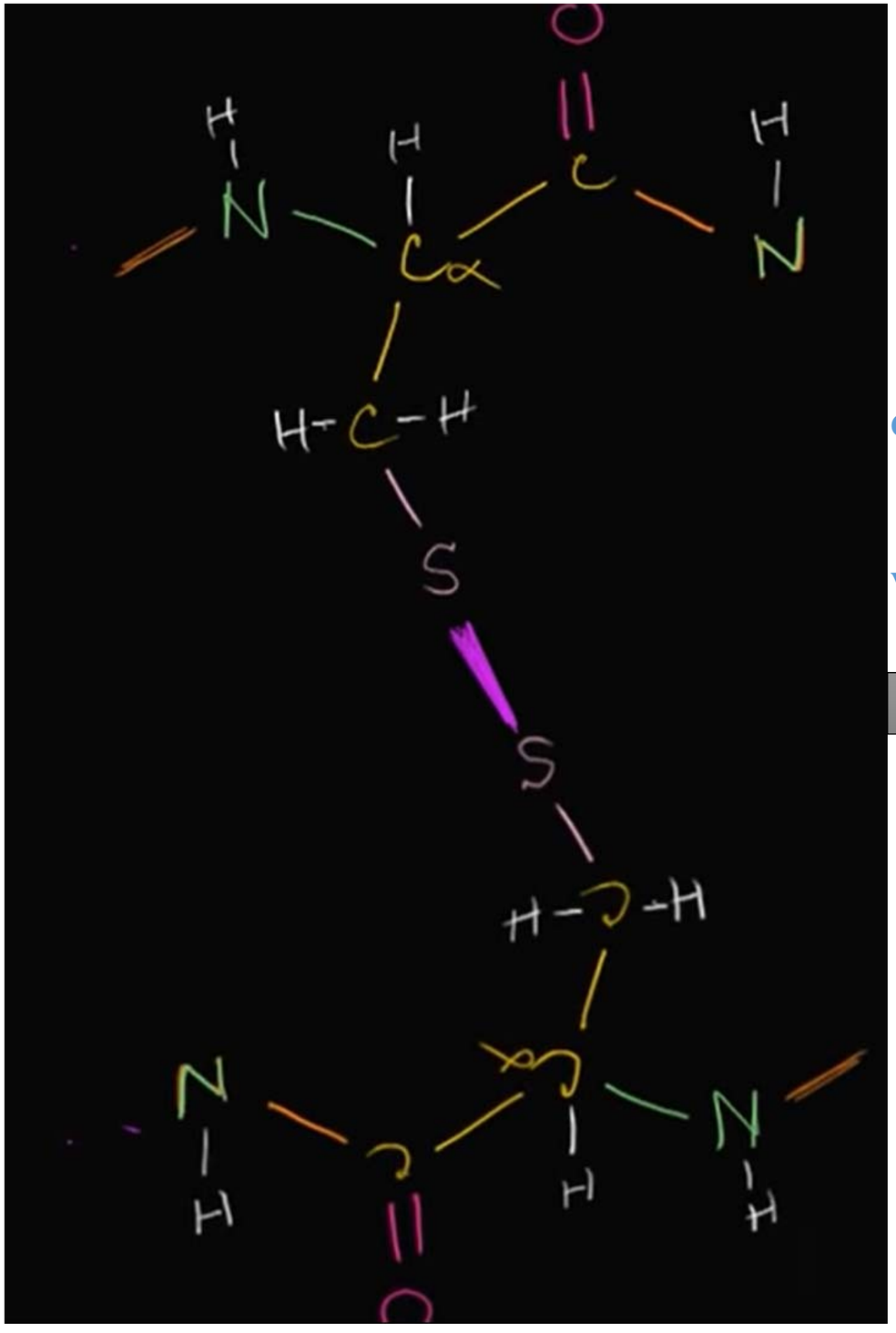
The relative importance of the bonding interactions in protein tertiary structure to follow the same order as their strengths: covalent, ionic, hydrogen bonding, and, finally, van der Waals.

Usually, the most important bonding interactions are those due to van der Waals interactions and hydrogen bonding,

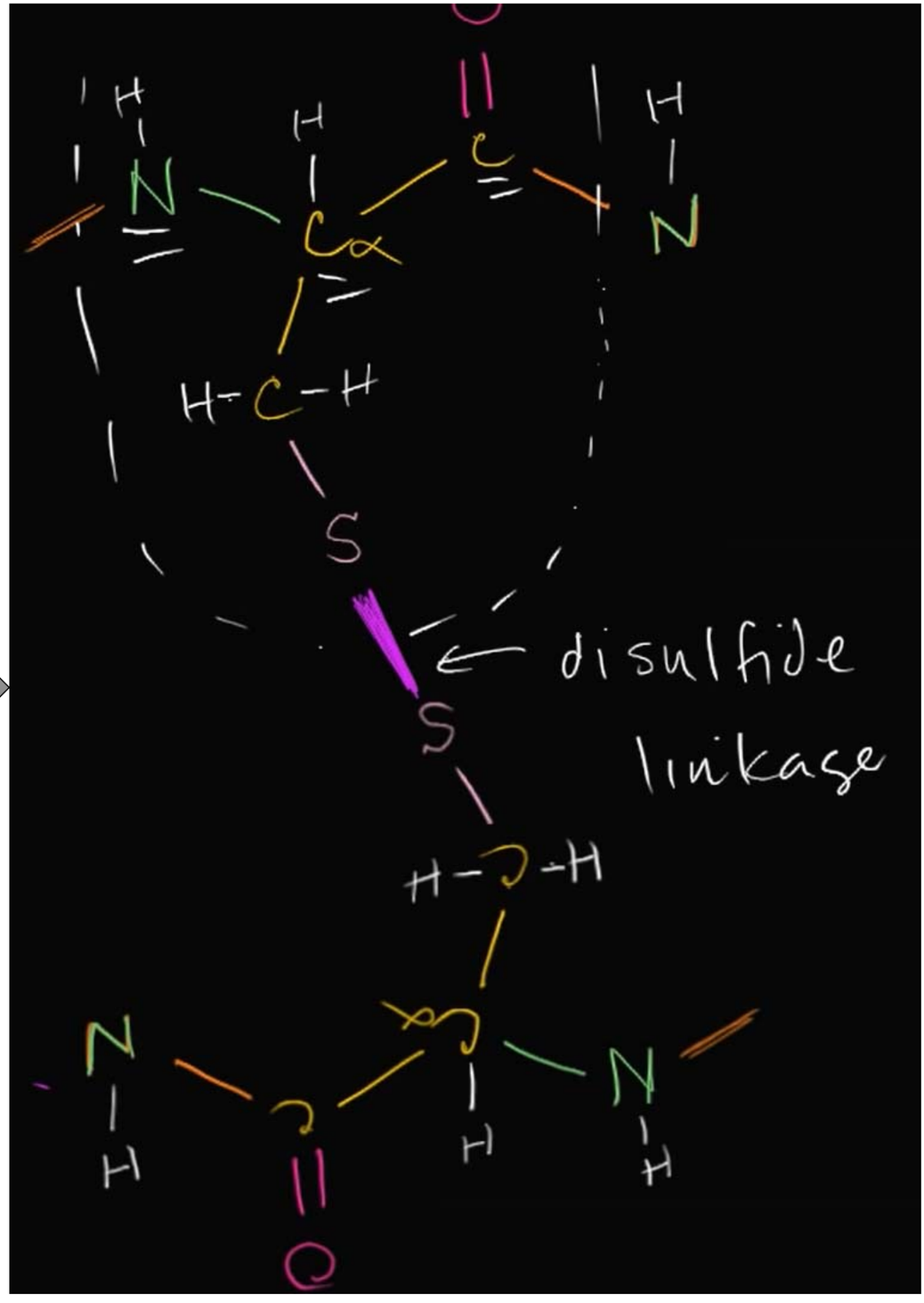


The only aac that can form a covalent disulphide bond is cysteine, such as the peptide hormones vasopressin and oxytocin. As far as ionic bonding also a limited number of aac capable of forming salt bridge between the carboxylate ion of an acidic residue, such as aspartic acid or glutamic acid, and the ammonium ion of a basic residue, such as lysine, arginine, or histidine

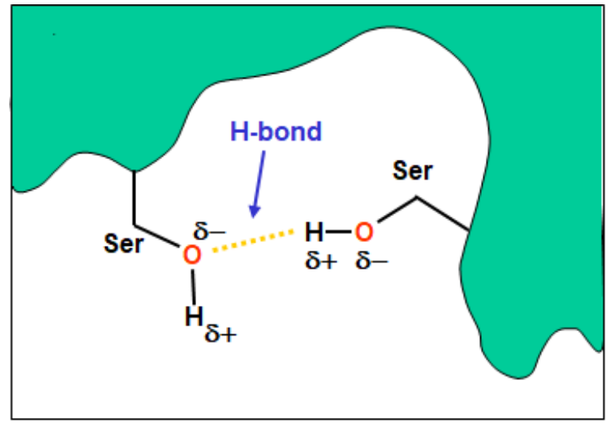


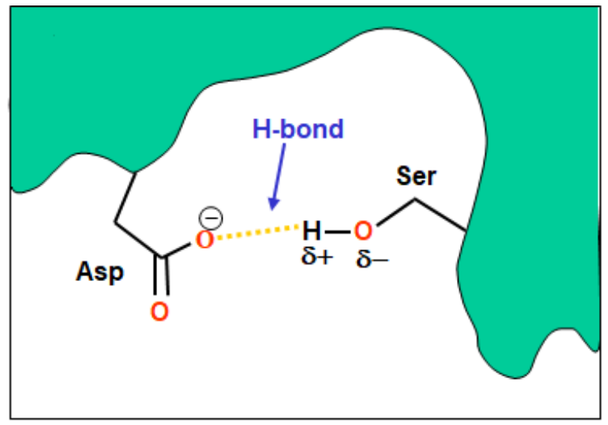


covalent disulphide bond is cysteine, such as the peptide hormones vasopressin and oxytocin

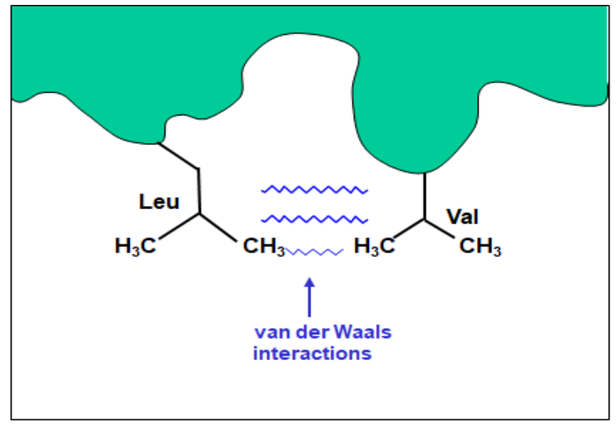


H-bond can be formed between a large number of amino acid side chains, such as serine, threonine, aspartic acid, glutamic acid, glutamine, lysine, arginine, histidine, tryptophan, tyrosine, and asparagine.

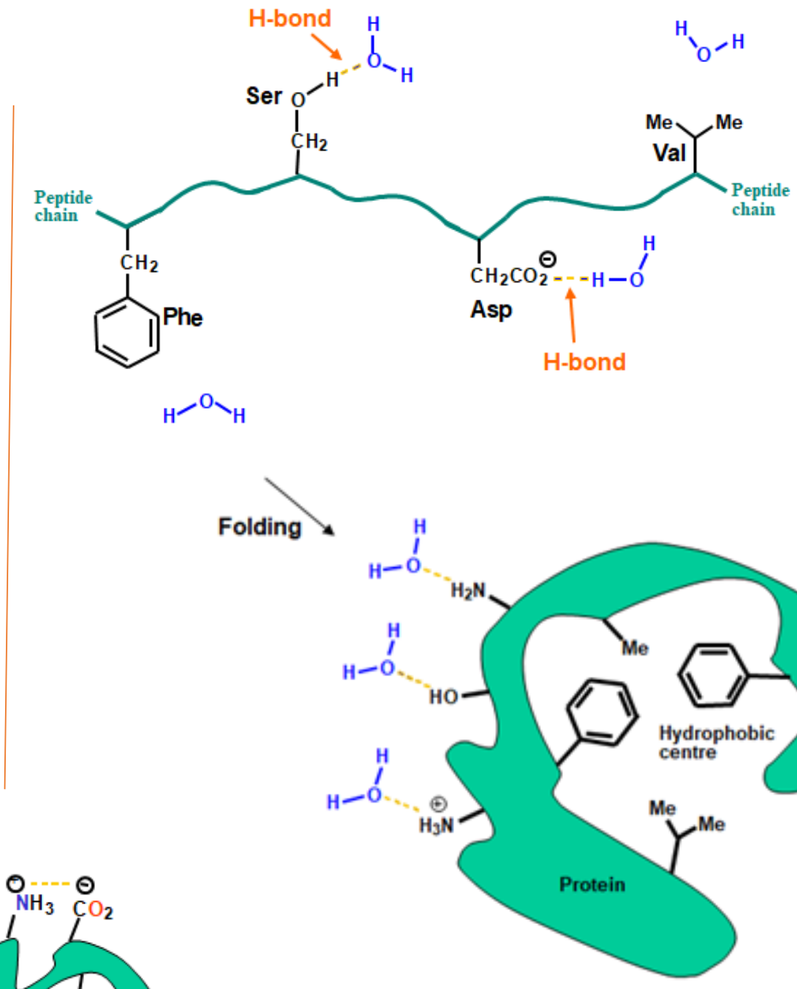


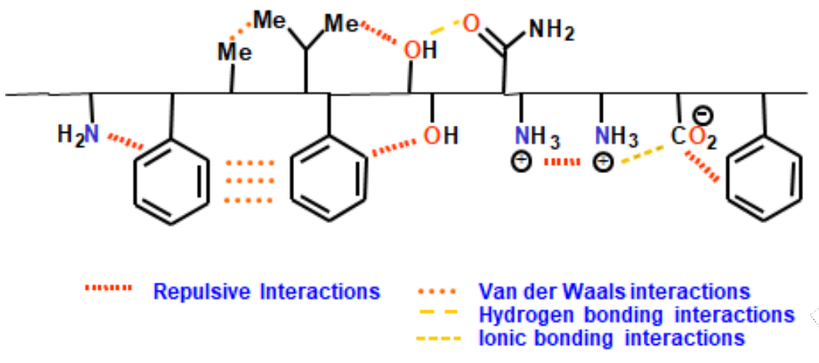


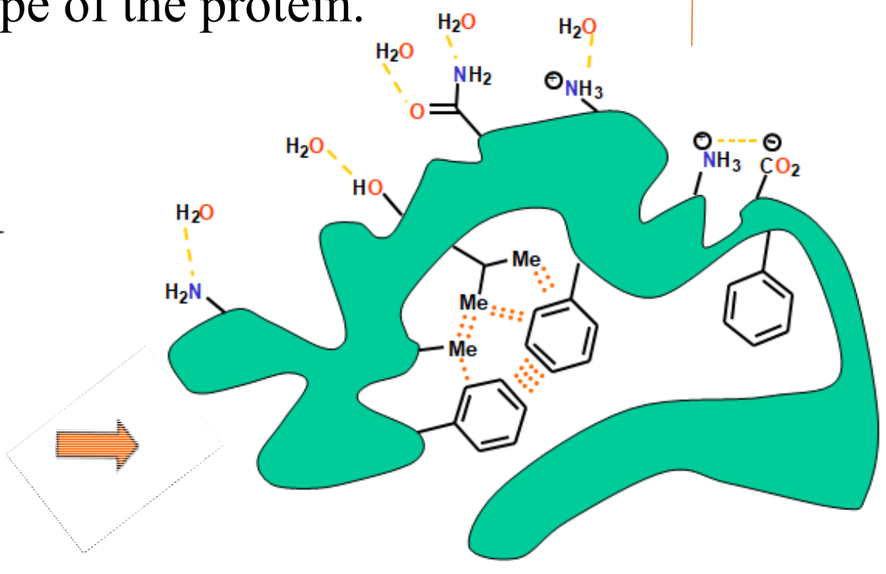
Hydrophobic interactions are the most important bonding interactions in aac, all aac have hydrophobic side chains capable of interacting with each other by van der Waals interactions. As alanine, valine, leucine, isoleucine, phenylalanine all have alkyl groups.



Van der Waals interactions are normally the most important form of bonding in tertiary structure. Proteins surrounded by water that it's interacts readily with polar, hydrophilic aac residues capable of forming hydrogen bonds on the surface, and that most of the hydrophobic groups are in the center so that they avoid water and interact with each other, were van der Waals interactions to largely determine the three-dimensional shape of the protein.



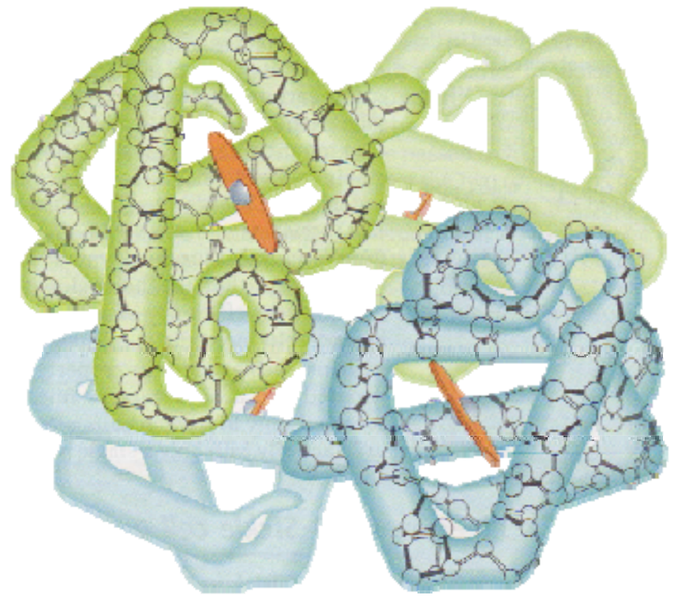




QUATERNARY STRUCTURE OF PROTEINS

QS. Consist of more than one pollpeptide chain, dimers (two subunits), tetramers (four subunits), and hexamers (six subunits) are fairly common. The proteins that comprise the individual subunits may be identical, or they may be different.

The QS. of hemoglobin consists of four peptide subunits. Two of the subunits are identical and are called the alpha subunits, and two subunits, called the beta subunits, are identical to each other but different from the alpha subunits.



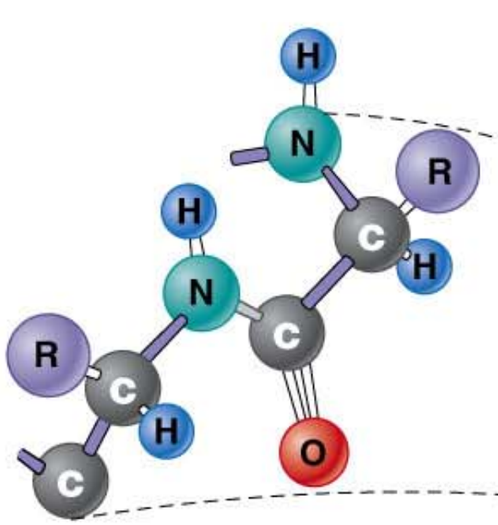
The four subunits of hemoglobin interlocked in a compact globular structure held together by ionic and hydrogen bonds between the amino acid side chains of the polypeptide subunits.

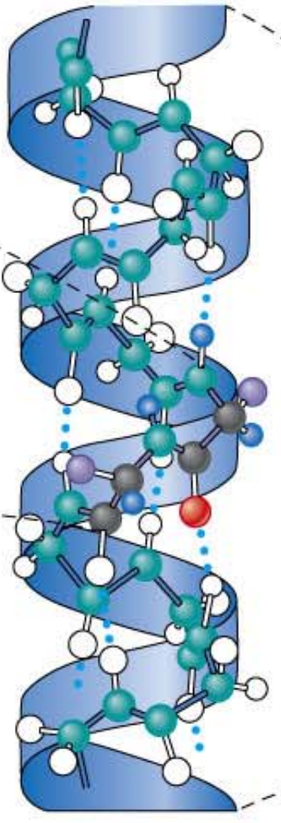
(a) Primary structure. The primary structure of a protein is a sequence of amino acids linked together by peptide bonds, forming a polypeptide.

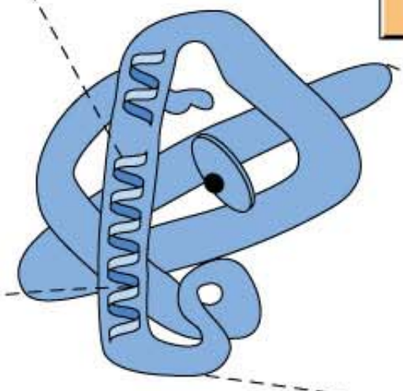
(b) Secondary structure. Local regions of the resulting polypeptide can then be coiled into an α helix, one form of secondary structure.

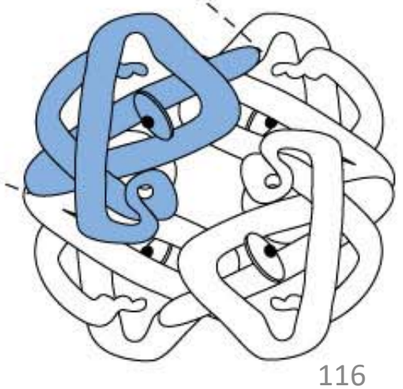
(c) Tertiary structure. Regions of secondary structure associate with each other in a specific manner to form the tertiary structure, which describes the final folding of the polypeptide.

(d) Quaternary structure. For multimeric proteins, the quaternary structure describes the association of two or more polypeptides as they interact to form the final, functional protein.









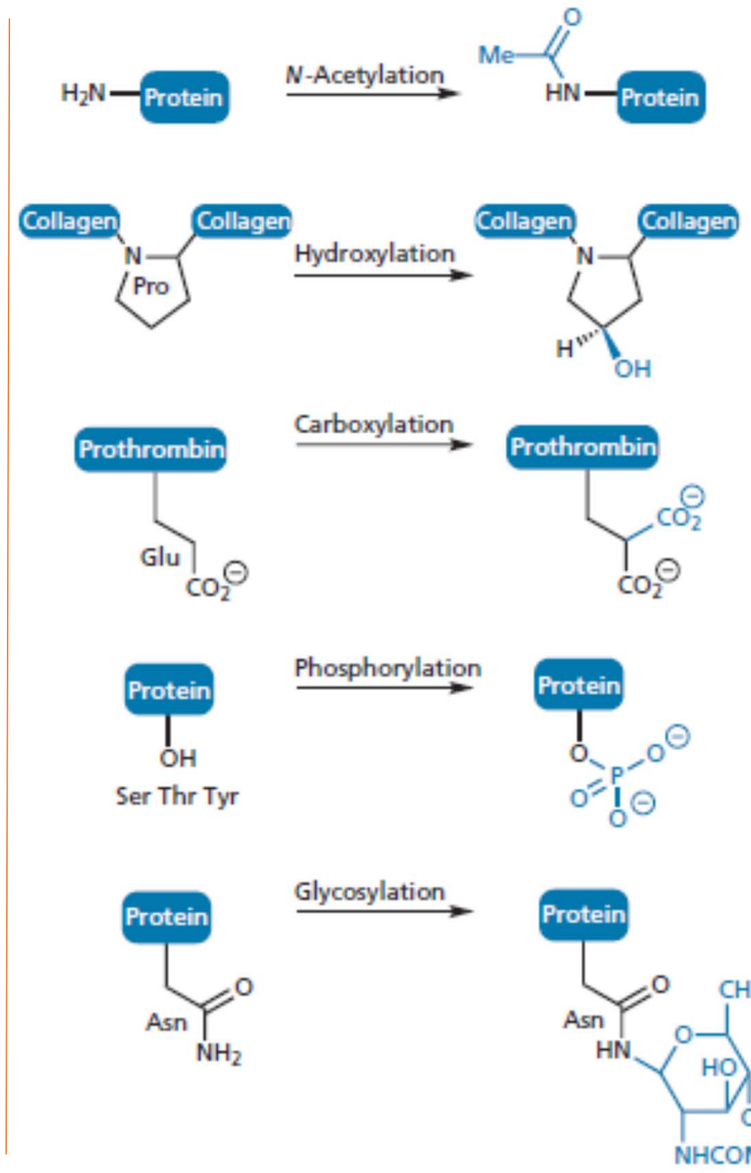
TRANSLATION AND POSTTRANSLATIONAL MODIFICATIONS

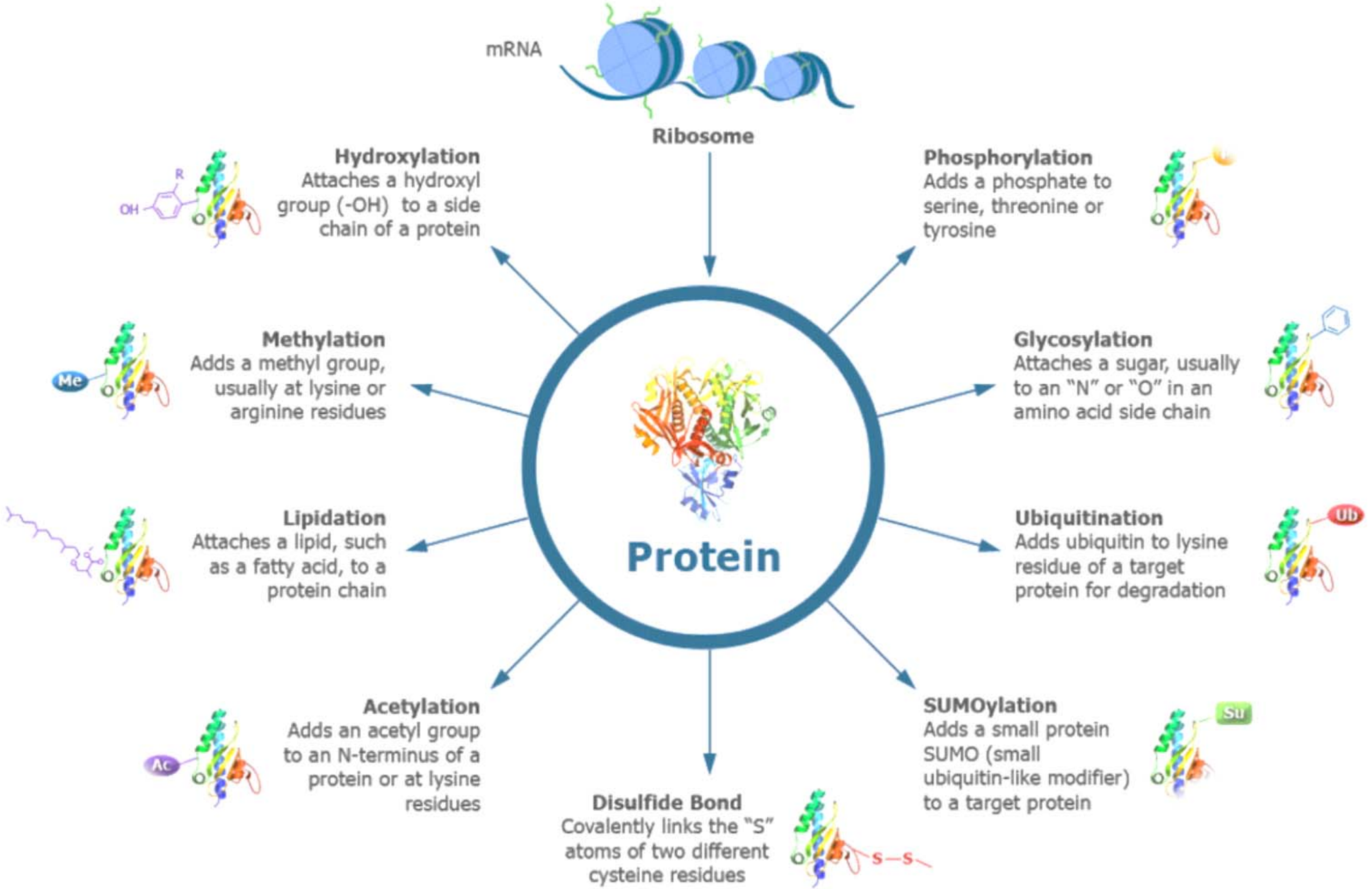
Translation: The process by which a protein is synthesized in the cell. Many proteins are modified following translation, and these modifications - Post-Translational Modifications (PTMs)- can have wide-ranging effects the protein activity, stability, localization and/or interacting partner molecules.

Chemical alterations that usually occur during the post translational modification of proteins include phosphorylation, methylation, acetylation, ubiquitination, nitrosylation, glycosylation, and lipidation.

Ex: Acetylation of proteins also has a role to play in the control of transcription, cell proliferation, and differentiation.

EX: Insufficient hydroxylation of proline residues results in scurvy

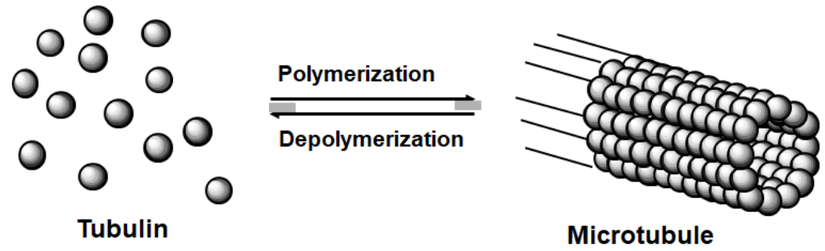


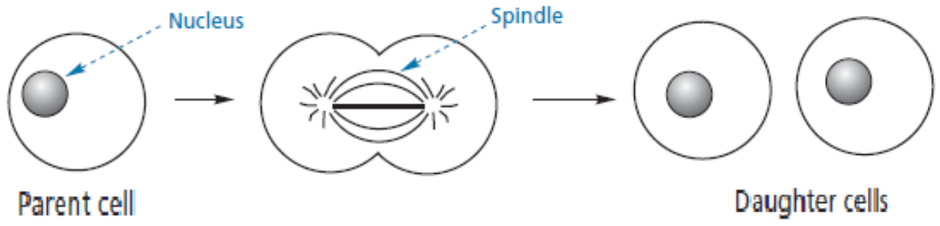

mRNA
Ribosome
Protein
Hydroxylation
Attaches a hydroxyl group (-OH) to a side chain of a protein
Phosphorylation
Adds a phosphate to serine, threonine or tyrosine
Methylation
Adds a methyl group, usually at lysine or arginine residues
Glycosylation
Attaches a sugar, usually to an "N" or "O" in an amino acid side chain
Lipidation
Attaches a lipid, such as a fatty acid, to a protein chain
Ubiquitination
Adds ubiquitin to lysine residue of a target protein for degradation
Acetylation
Adds an acetyl group to an N-terminus of a protein or at lysine residues
SUMOylation
Adds a small protein SUMO (small ubiquitin-like modifier) to a target protein
Disulfide Bond
Covalently links the "S" atoms of two different cysteine residues
R
OH
Me
Ac
Ub
Su
S—S

PROTEIN FUNCTION

Structural proteins do not normally act as drug targets. However, the structural protein tubulin is an exception. Tubulin molecules polymerize to form small tubes called microtubules in the cell's cytoplasm. These microtubules have various roles within the cell, including the maintenance of shape, exocytosis , and release of neuro transmitters.

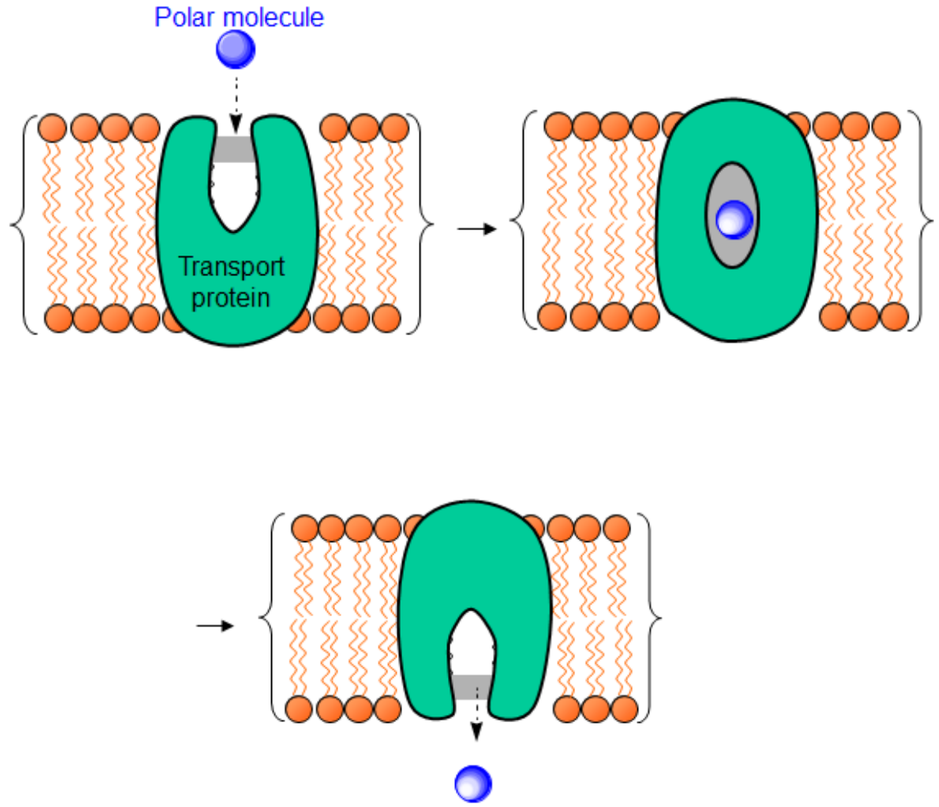
When a cell is about to divide, its microtubules depolymerize to give tubulin. The tubulin is then re polymerized to form a structure called a spindle which then serves to push apart the two new cells and to act as a framework on which the chromosomes of the original cell are transferred to the nuclei of the daughter cells





Transport proteins are proteins that transport substances across biological membranes. Transport proteins are found within the membrane itself, where they form a channel, or a carrying mechanism, to allow their substrate to pass from one side to the other.

These molecules can't pass through the hydrophobic membrane by themselves as polar structures. The transport proteins can float freely within the cell membrane because they have hydrophobic residues on their outer surface which interact favorably with the hydrophobic center of the cell membrane. The portion of the transport protein that is exposed on the outer surface of the cell membrane contains a binding site that can bind a polar molecule, stow it away in a hydrophilic pocket, and ferry it across the membrane to release it on the other side



Enzymes

- Act as catalysts for reactions within the cell
- Present on the inner surface of the cell membrane or within the cell
- Bind the substrates for a reaction and release products

Receptors

- Present in the cell membrane or within the cell
- Act as the cell's 'post boxes'
- Receive chemical messages from neurotransmitters and hormones
- Initiate or inhibit chemical signalling processes within the cell

Please find the book chapter and All chapter 3 attachment through the link:

http://u.pc.cd/mfzrtalK

Homework assignment: please answer questions 1, 2, and 3 at the end of the chapter