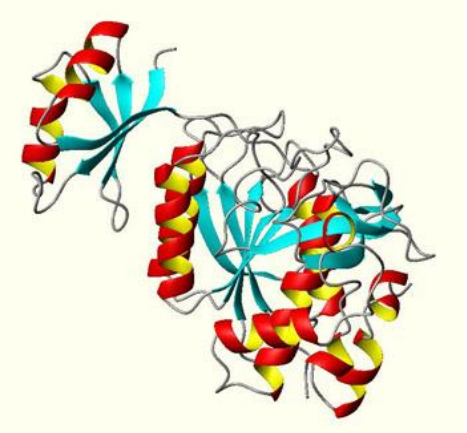
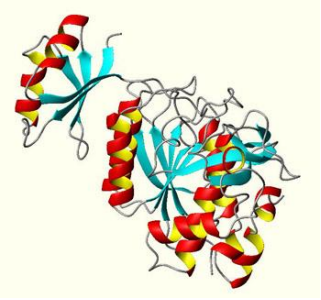


PROTEIN PHYSICS

A. V. Finkelstein &

O. B. Ptitsyn

LECTURE 1



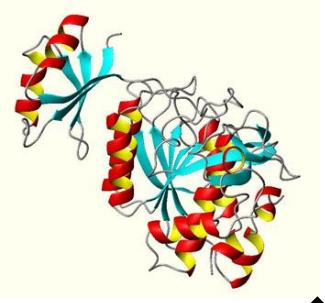
PROTEINS

Functions in a Cell

MOLECULAR MACHINES
BUILDING BLOCKS of a CELL
ARMS of a CELL

- **ENZYMES** - enzymatic catalysis of biochemical reactions
- REGULATORY PROTEINS - regulation of gene expression
- STRUCTURAL PROTEINS - form microtubules and microfilaments (actin, tubulin)
- TRANSFER PROTEINS - transfer other molecules (myoglobin, hemoglobin,
  - electron transport)
- RECEPTOR PROTEINS - accept and transmit intra(extra)cellular signals (insulin)
- STORAGE PROTEINS - store other molecules
- IMMUNO PROTEINS – bind foreign substances and target them for destruction
- MOTOR PROTEINS - capable of generating mechanical forces
  (myosin - its movement causes muscle contraction)

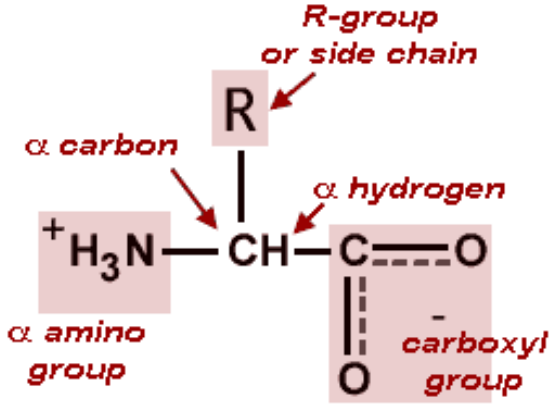
KEY & LOCK relation
with the interacting molecules



PROTEINS

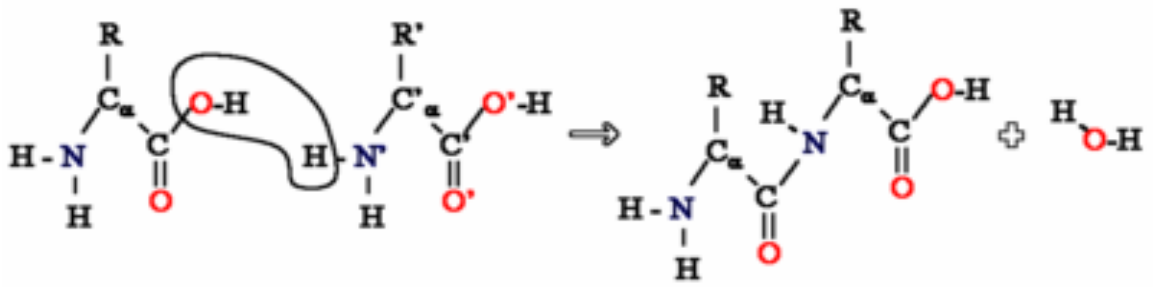
Structure

- Proteins are polymers
- Amino acids linked into a peptide chain
- E. Fisher beginning of 20th century



AMINO ACID

- Formation of a peptide bond (dehydration synthesis)

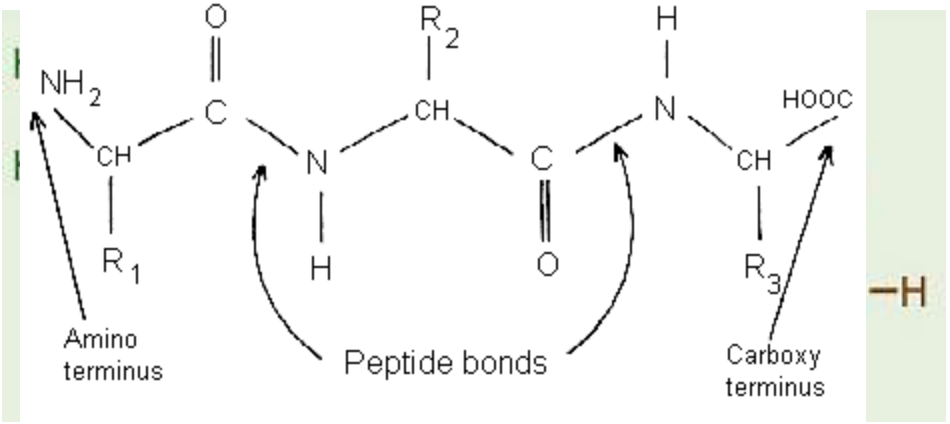


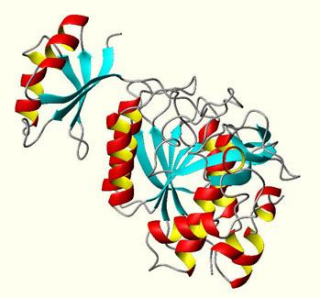
metastable bonds

- How to brake a peptide bond?

Amide hydrolysis - adding water

Polypeptide Chain





AMINO ACIDS

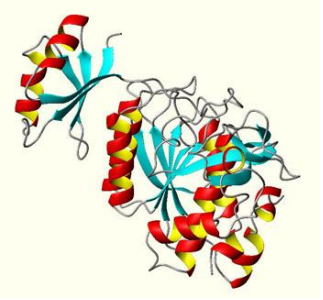
The number of amino acid residues and
their position in the sequence is
GENE ENCODED

- CODON – triplet of nucleotide (A, G, C T, U)
- 64 possible conformations from the four nucleotides
- 20 amino acids used generally

• Every protein has a unique sequence of amino acid (Frederick Sanger, 1955)
•Protein modification may contribute additionally to the variety of proteins
•Posttranslational modifications: Phosphorylation, glycosylation,…..)
•Some proteins require bonding of cofactors

•An opreating protein the chain is folded in a strictly specified structure.
•In the late 50s Perutz and Kendrew solved the first protein structure.
•The 3D structure of proteins has been shown already in 1860 by Hoppe-Zeiler.
•Hemoglobin crystals: in a crystal each atom occupies a unique place.

•The question whether the structure of a protein in a crystal is the same as in
•solution has been solved by NMR. Where proteins can be seen live in solution.

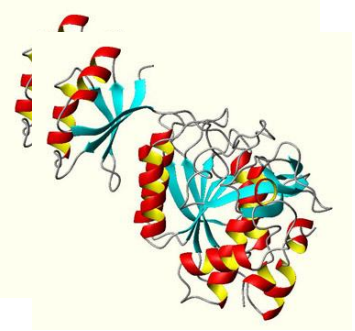


AMINO ACIDS

According to their environmental conditions and their general strucrture proteins can be divided into 3 classes:

1) **Fibrous Proteins**: form vast, water deficient aggregates. Hydrogen bonded, regular maintained by interactions between chains.
2) **Membrane proteins**: water deficient environment, restricted in size by the membrane thickness
3) **Water-soluble:** globular proteins, less regular, maintained by interchain interactions

Acidic side chain: Asp, Glu
Basic side chain: Lys, Arg, His
Sulfur containing side chains: Met, Cys
Polar, **uncharged** side chain: Ser, Thr, Tyr, Asn, Gln
Non polar side chain: Gly, Ala, Val, Leu, Ile, Phe, Trp, Pro, Met, Cys
Special cases: Gly, Pro, Cys



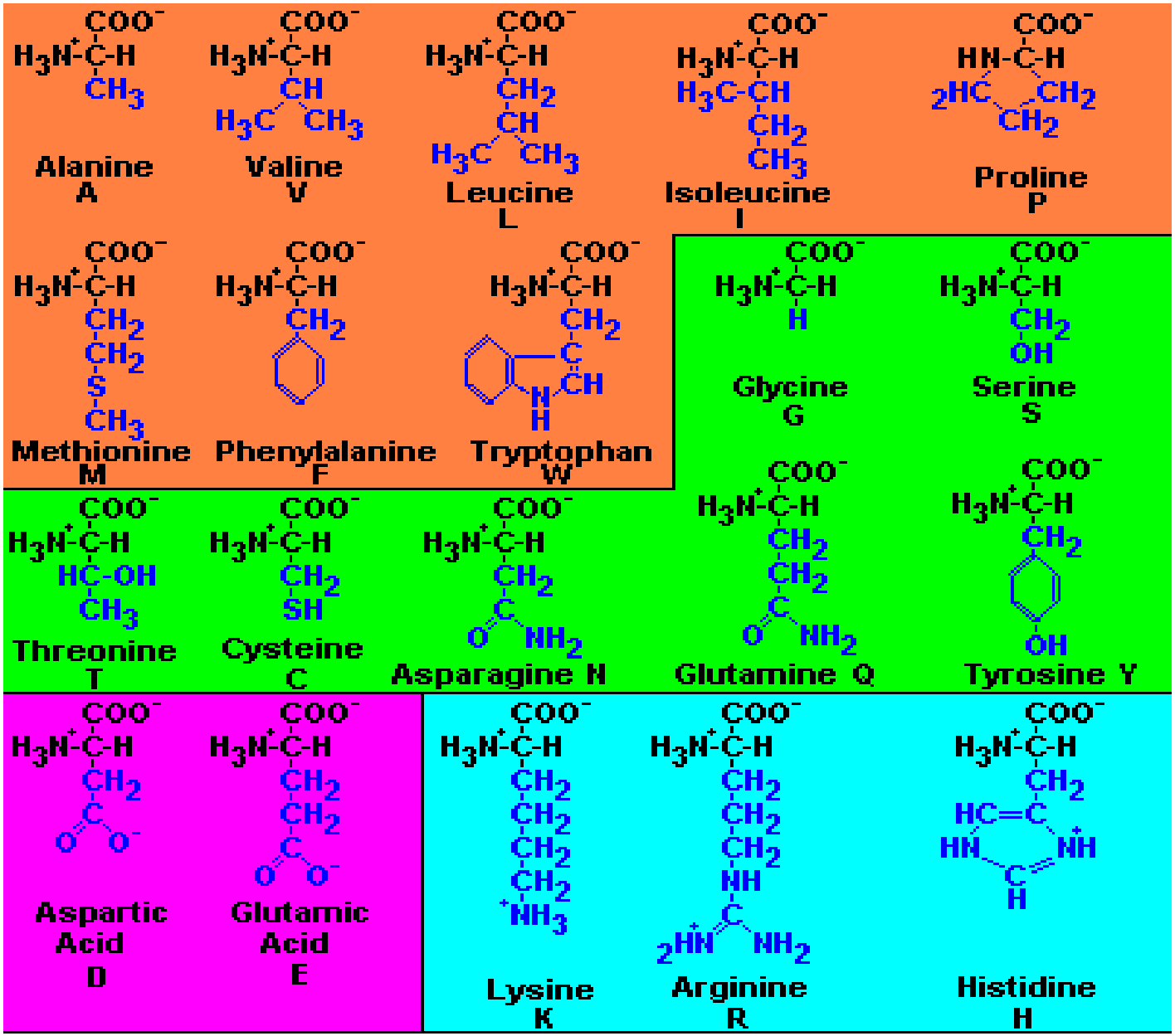
AMINO ACIDS

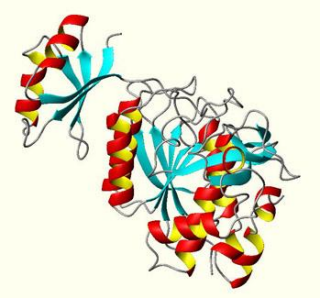
1. Non polar, hydrophobic

2. Polar, hydrophilic

   a. Basic

   b. Acidic





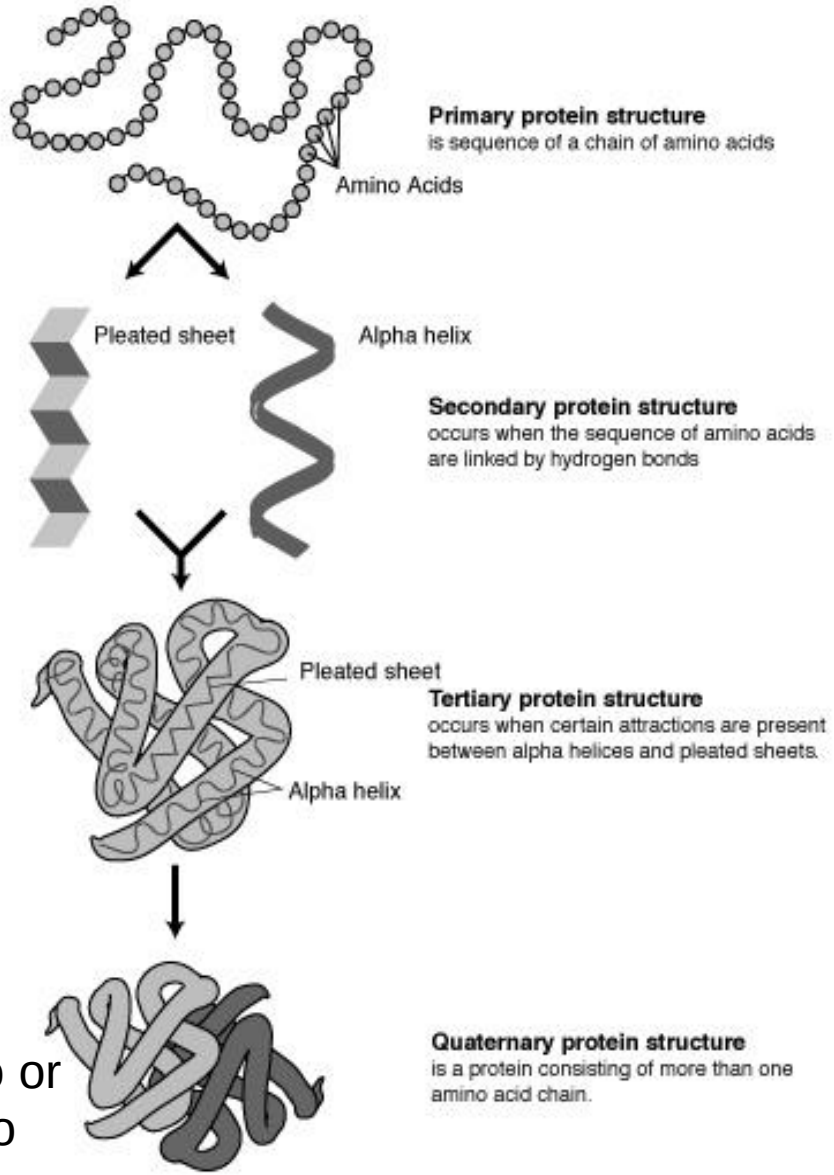
STRUCTURE LEVELS

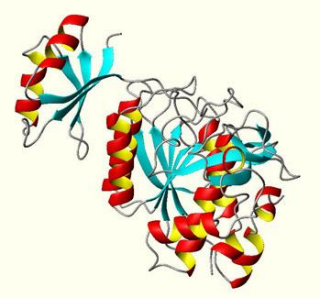
1. Primary structure
   The amino acid sequence

2. Secondary structure
   Local folding into stable structures: alpha-helices, beta-pleated sheets

3. Tertiary structure
   Complete 3D folding of a protein (domains)

4. Quaternary structure
   Regular association of two or more polypeptide chains to form a complex

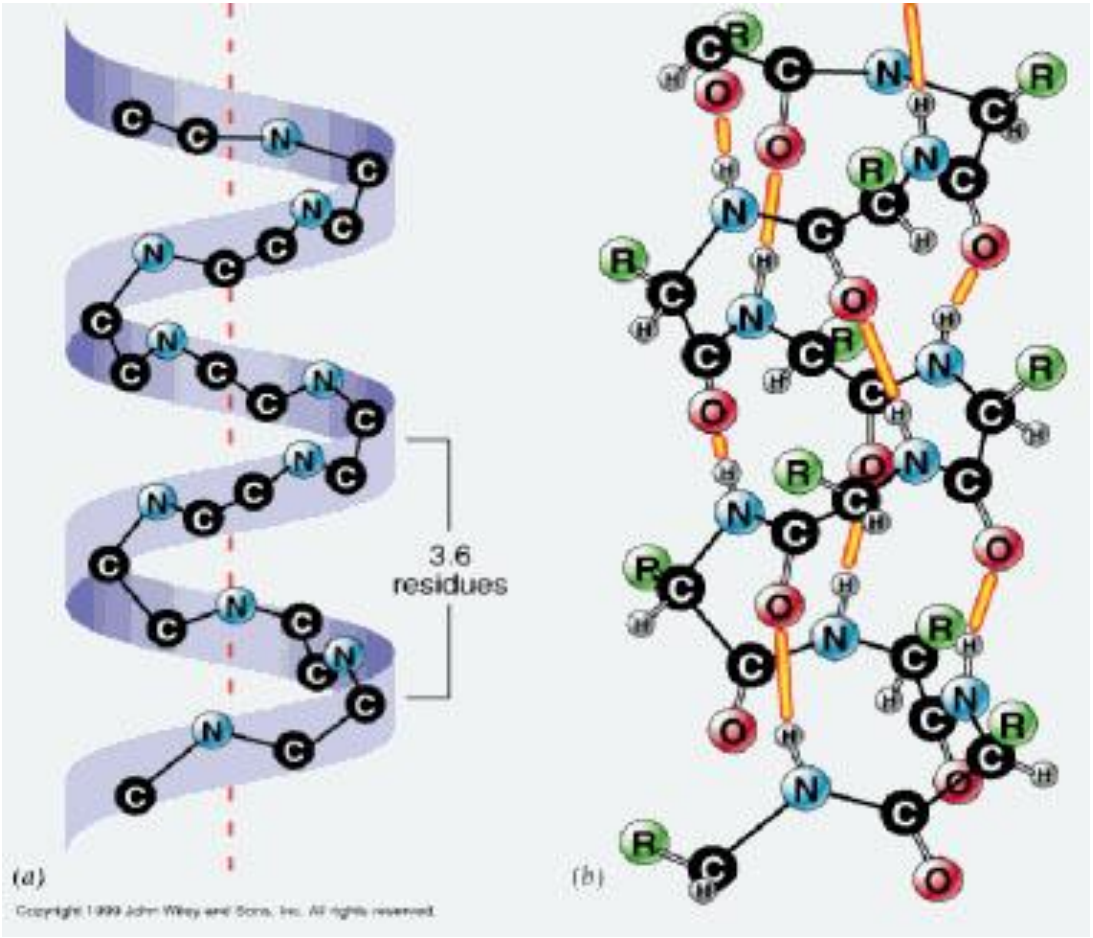


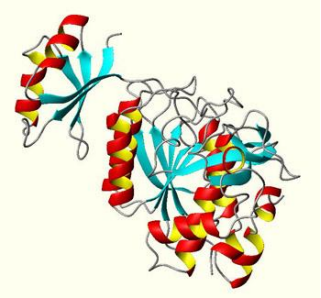


SECONDARY STRUCTURES

Alpha-helix

- The backbone follows a helical path (right, left), flexible
- Hydrogen bonds between backbone amino and carbonyl groups and those in the next turn of the helix
- The R-groups protrude out from the helix
- Proline tends to interrupt an alpha-helix





SECONDARY STRUCTURES

Beta-sheet

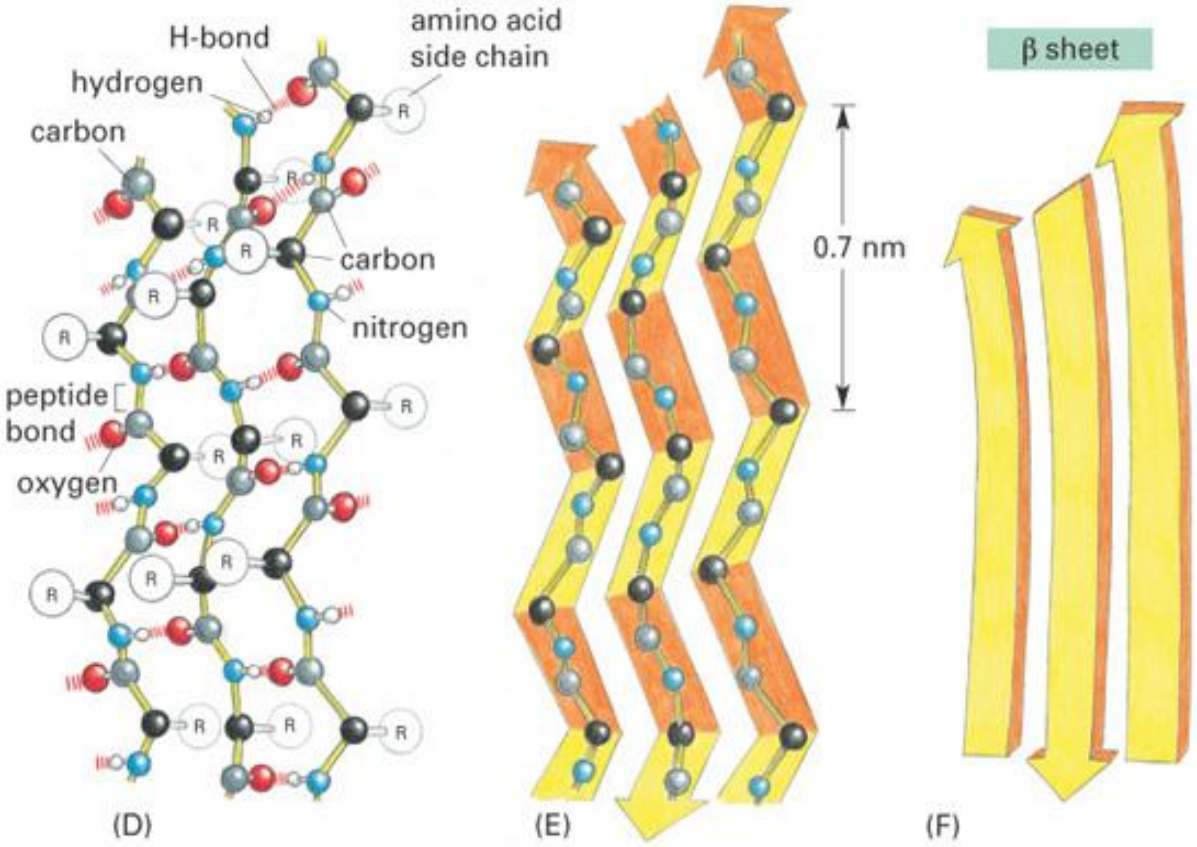
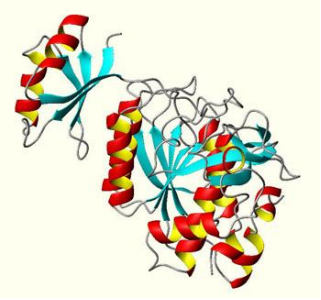


Figure 4-10 part 2 of 2 Essential Cell Biology, 2/e. (© 2004 Garland Science)

- Strands of protein lie adjacent to one another, interacting laterally via hydrogen bonds, between carbonyl oxygen and amino H atoms.

- Succesive side chains point straight up, then straight down.

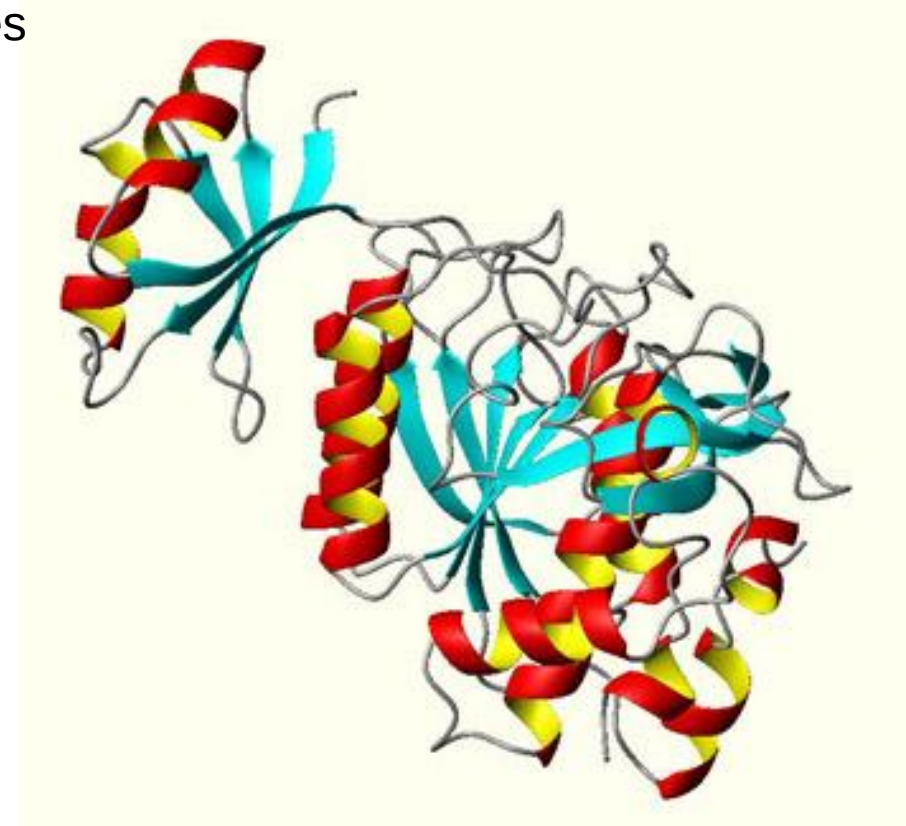


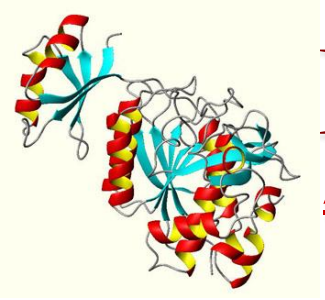
TERTIARY STRUCTURES

The packing of the secondary structures
Into a compact globule is called the
Tertiary structure.

Some tertiary structures can be
distinguished as most typical.
These will be considered later.
They often only comprise domains,
A domain comprises of 100-200 aa.

The arrangement of tertiary structures
In 3D is called quarternary structure.
(Hemoglobin, Myoglobin)





PROTEIN CLASSES

According to their environmental conditions

1. FIBROUS PROTEINS

- insoluble and strong, highly regular
- often found as an aggregate,
- their structure is highly H-bonded (classes: keratins, collagens, elastins)

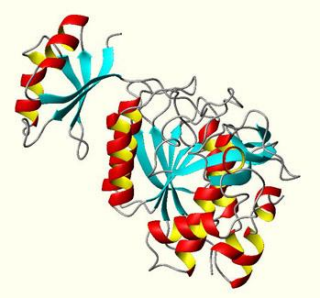
2. MEMBRANE PROTEINS

- reside in water-deficient membrane environment
- attached to, or associated with the membrane of a cell

3. GLOBULAR PROTEINS

- water soluble proteins, less regular
- interactions of the chain with itself and sometimes with co-factors

PHYSICS of SMALL PROTEINS! (200-300 AAs)
PHYSICS of SMALL WATER-SOLUBLE GLOBULAR PROTEINS!



PROTEIN'S FUNCTION

AMINO ACID SEQUENCE

Self-organization ↓ ↑ !? **Anfinsen (1960)**

?

3D FOLDED STRUCTURE

Key & Lock ↓ ↑

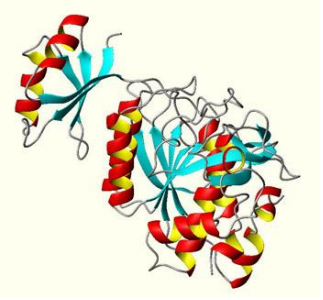
PROTEIN'S FUNCTION

❖ Renaturation – refolding of an unfolded protein chain

❖ Post-translational modifications
add or remove chemical groups; cleavage of the protein chain, phosphorylation,

❖ Co-factors, involved in functioning sometimes in protein formation
Small molecules, ions, sugars, nuclotides

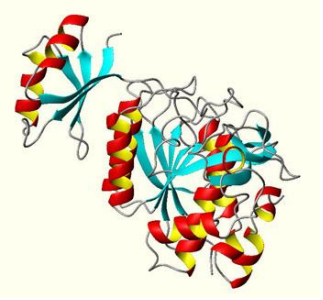
Is a protein hard or soft?



PROTEIN MODIFICATIONS

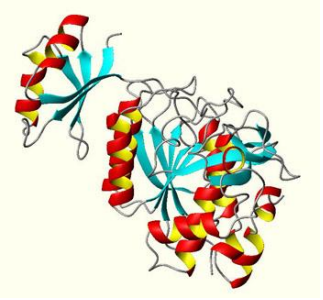
- Posttranslational modifications:
- Chemical modifications: provided by special enzymes rather than self organised

- Cleavage of the protein chain
- Modification of chain termini: Acetylation, Amidation,
- Glycosylation,
- Lipid binding to certain points,
- phosphorylation



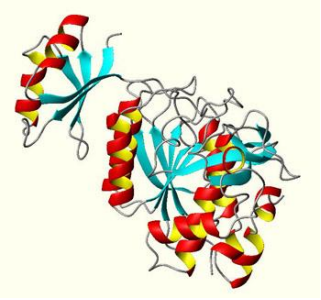
PROTEIN MODIFICATIONS

- Disulfide formation:
- Between Cys residues. Occurs intermolecular
- Proper S-S bonds are capable of self organisation under ideal conditions.
- In vivo they are formed by an enzyme disulfide isomerase.
- S-S bonds are mainly found in secreted proteins, since there is no Oxygen available intercellularly and hence no favorable oxidation potential.
- S-S bonds contribute to the structural stability of proteins



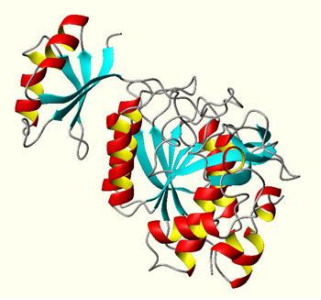
PROTEIN MODIFICATIONS

- Improper S-S bonds
- Improper S-S bonds prevent protein renaturation.
- Boiled egg does not unboil
- High temperature deos not only denature proteins, but breaks S-S bonds and reforms them between random Cys residues.
- Therefore S-S bonds can also be formed intramolecular.
- These new S-S bonds will prevent the polypeptide chains to renature.



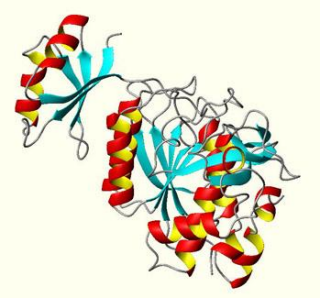
PROTEIN STRUCTURE FUNCTION

- First: AA sequence determines structure, determines function
- 3D strucure of a protein shows empty spaces in the interior
- Protein soft or hard?
- Protein is a hard structure
- Chains are packed tightly atom against atom
- The space filling model shows the tight packing, but does not give any clues about its organisation, but its physico-chemical properties fo the surface. These determine the specificity.
- The protein skeleton is responsible for the creation and maintenance of this surface.



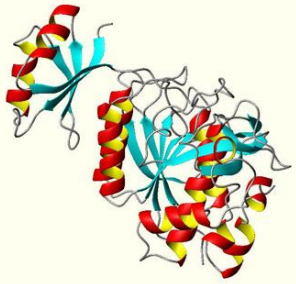
PROTEIN FUNCTION

- Second: apart from the polypeptide chain proteins often bind cofactors:
- Cofactors: Iron, Heme, Mg^{2+}, Ca^{2+}, sugars, nucleotides,
- Non-peptide molecules involved in function and formation of protein structure.
- Co factors can be chemically linked or packed in cavities
- Water molecules are tightly bound to the protein surface.
- Third: a solid protein behaves like a crystal
- It is firm and then suddenly melts.
- Like a light bulb: all or nothing model. Not gradually.

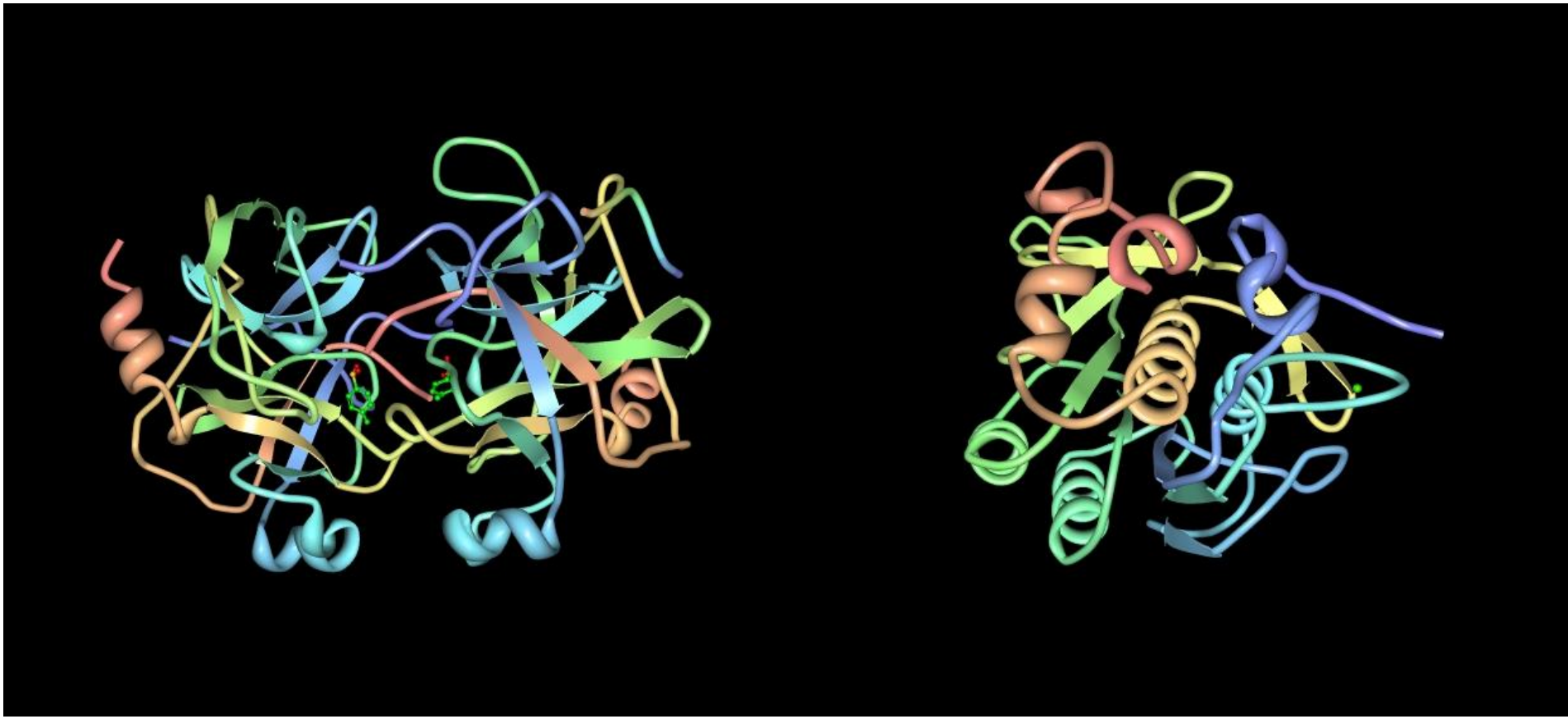


PROTEIN HARDNESS

- One needs to distinguish between single domain proteins.
- They are really hard
- One compact globule
- Larger proteins:
- Either multidomain organisation or quarternary structure
- The component subglobules are hard like a sigle domain protein
- But they can move relative towards each other.
- All globules can become deformed during enzyme action.



PROTEIN FUNCTION



Study questions

- 1) How many charged amino acids do you know?
- 2) which amino acids are the acidic amino acids? (name and structure)
- 3) Which are the basic amino acids? (name and structure)
- 4) wat are the pKa values of these amino acids?
- 5) Which amino acids do fluoresce? Name and structure) Which gives the highest quantum yield?
- 6) What are the levels of protein organisation?
- 7) How does structure and function relate?
- 8) Does function induce structure?
- 9) How are amino acids linked into a protein chain?
- 10) What are the conditions to form a peptide bond?