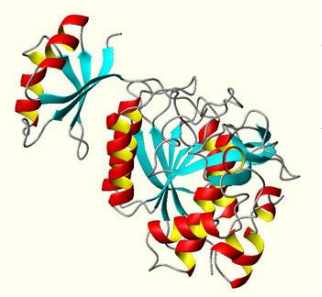


# PROTEIN PHYSICS

A. V. Finkelstein &

O. B. Ptitsyn

LECTURE 1



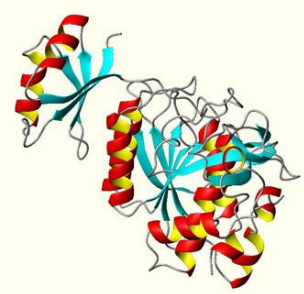
# PROTEINS

## 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**

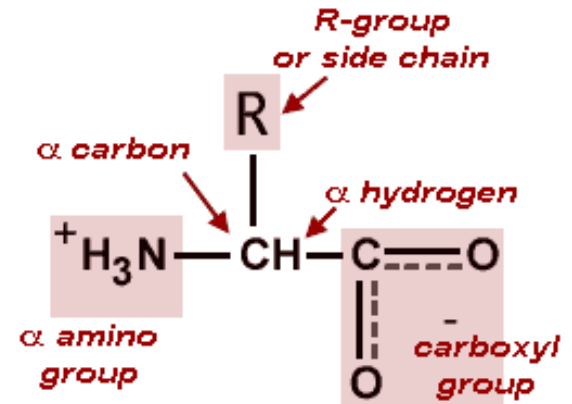
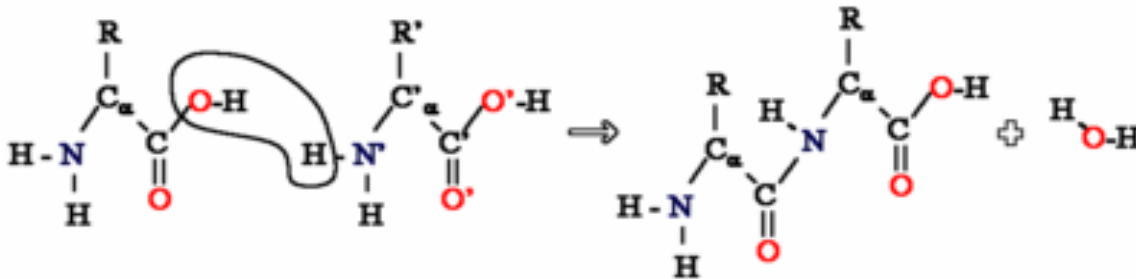


# PROTEINS

## Structure

- ❖ Proteins are polymers
- ❖ Amino acids linked into a peptide chain
- ❖ E. Fisher beginning of 20<sup>th</sup> century

- Formation of a peptide bond (dehydration synthesis)

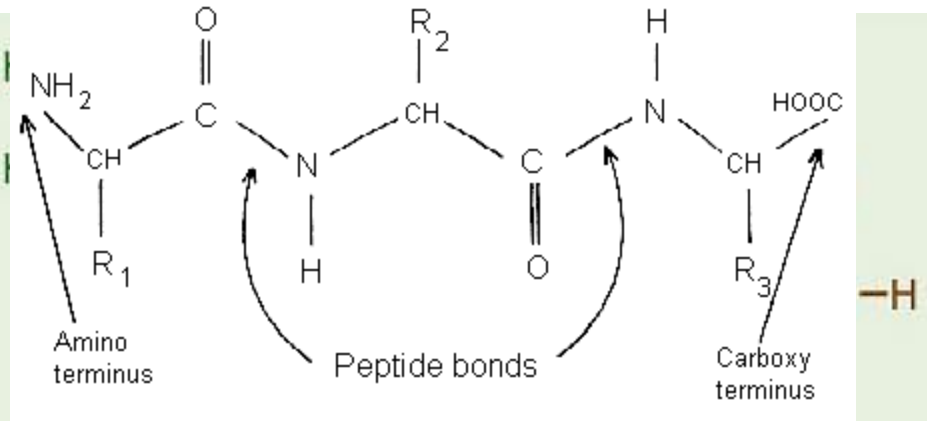


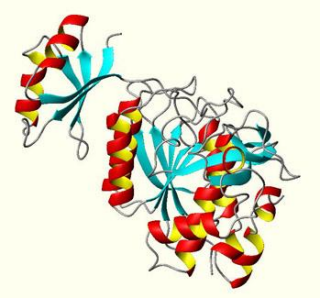
**AMINO ACID**

### metastable bonds

- How to brake a peptide bond?  
Amide hydrolysis - adding water

### Polypeptide Chain



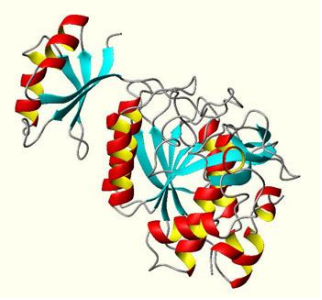


# AMINO ACIDS

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 operating 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 structure 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

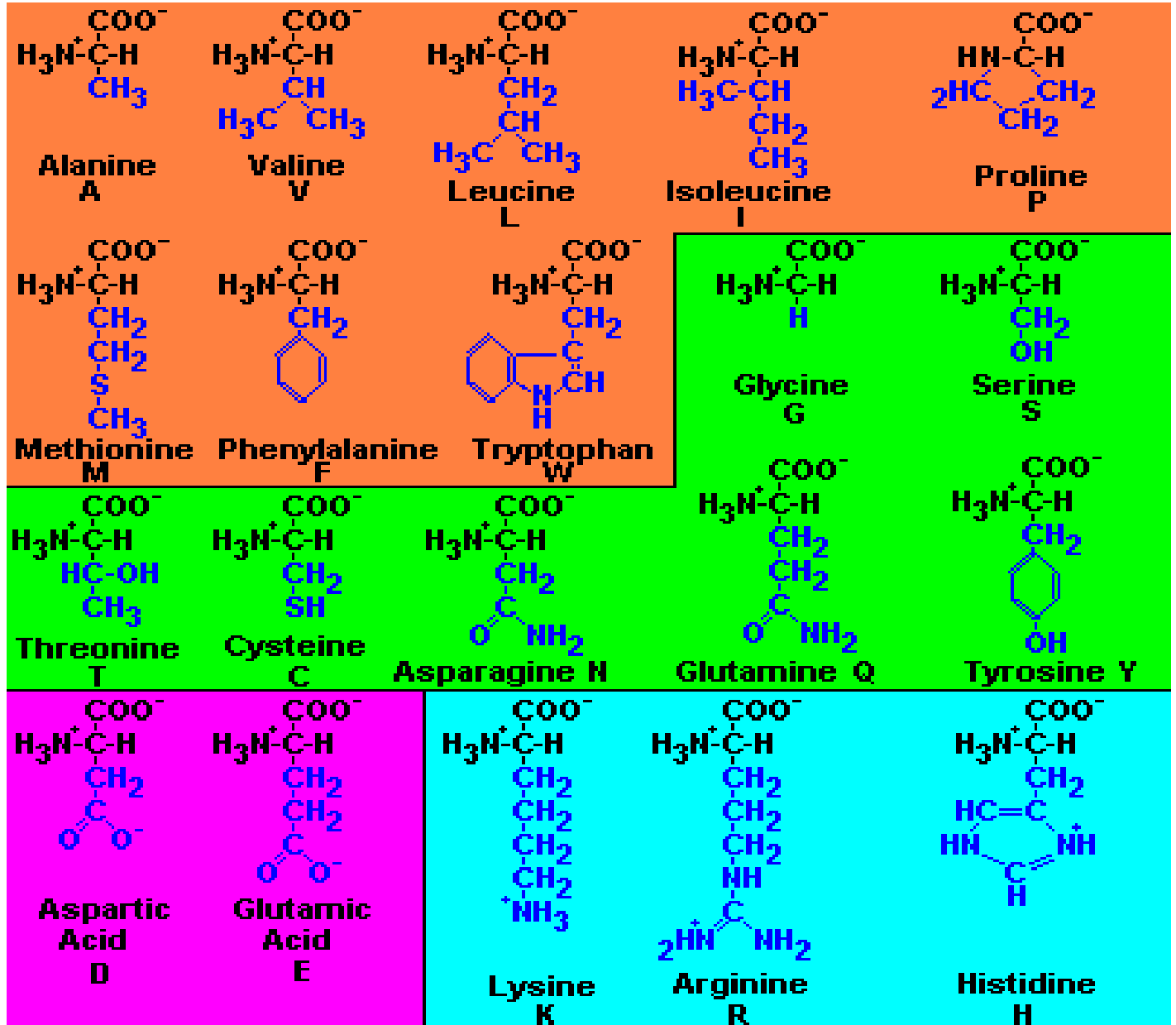
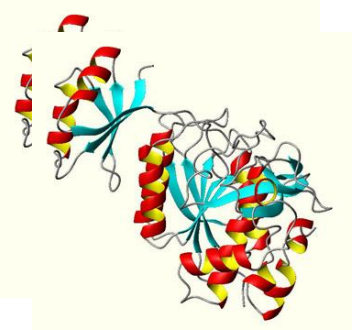
**Sulfur** containing side chains: Met, Cys

**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

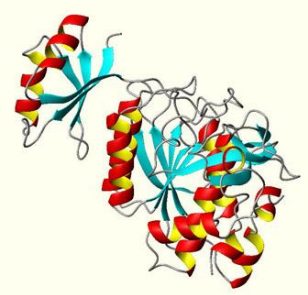


1. Non polar,  
hydrophobic

2. Polar,  
hydrophilic

a. Basic

b. Acidic



# STRUCTURE LEVELS

## 1. Primary structure

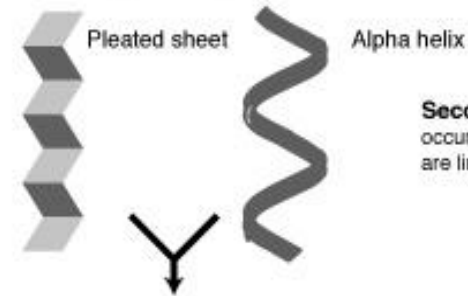
The amino acid sequence



**Primary protein structure**  
is sequence of a chain of amino acids

## 2. Secondary structure

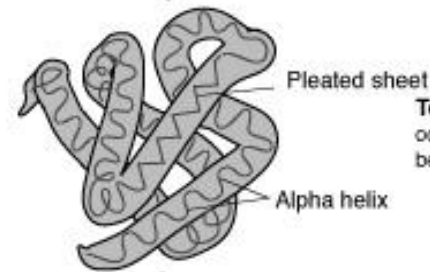
Local folding into stable structures: alpha-helices, beta-pleated sheets



**Secondary protein structure**  
occurs when the sequence of amino acids are linked by hydrogen bonds

## 3. Tertiary structure

Complete 3D folding of a protein (domains)



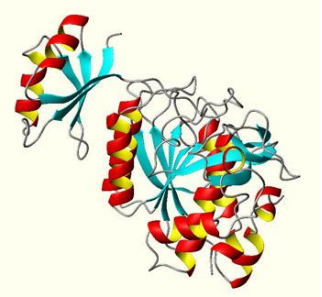
**Tertiary protein structure**  
occurs when certain attractions are present between alpha helices and pleated sheets.

## 4. Quaternary structure

Regular association of two or more polypeptide chains to form a complex



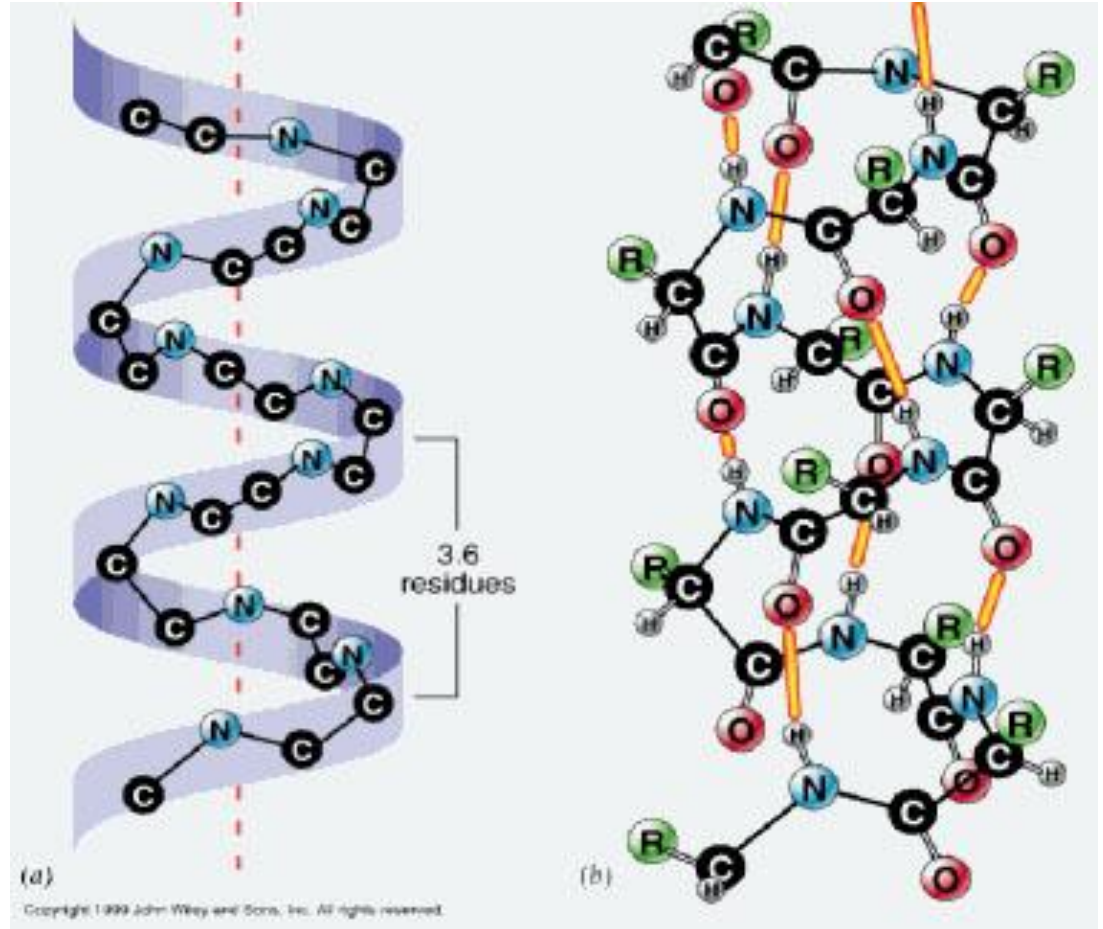
**Quaternary protein structure**  
is a protein consisting of more than one amino acid chain.



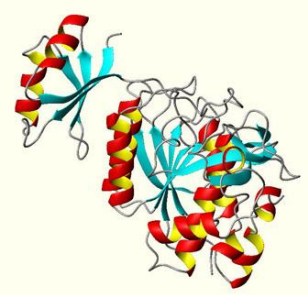
# SECONDARY STRUCTURES

## 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

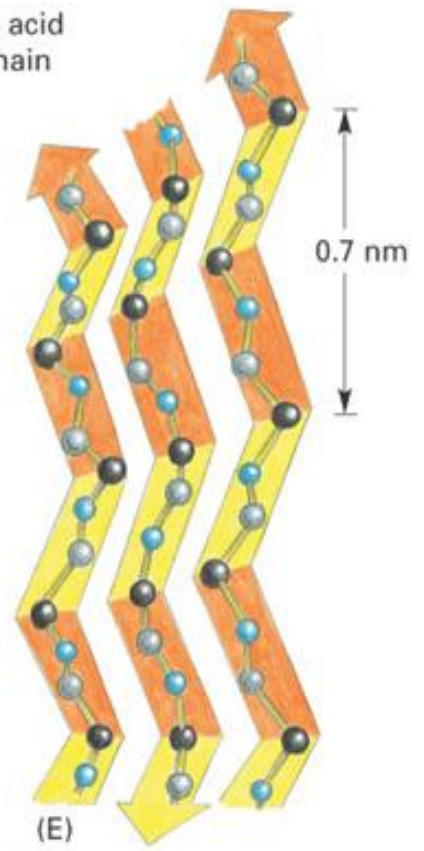
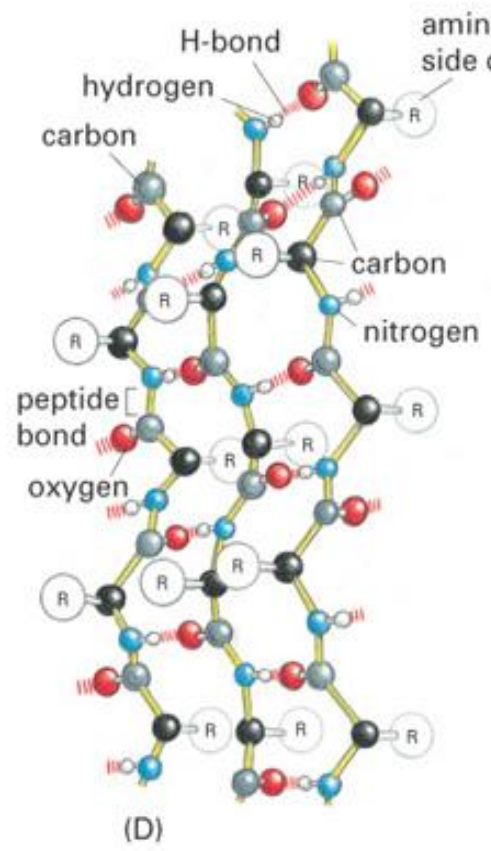




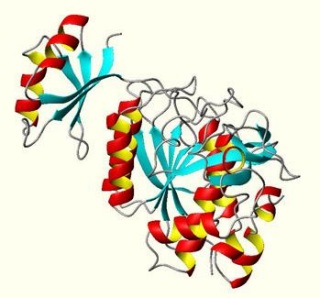


# SECONDARY STRUCTURES

## Beta-sheet



- Strands of protein lie adjacent to one another, interacting laterally via hydrogen bonds, between carbonyl oxygen and amino H atoms.
- Successive side chains point straight up, then straight down.

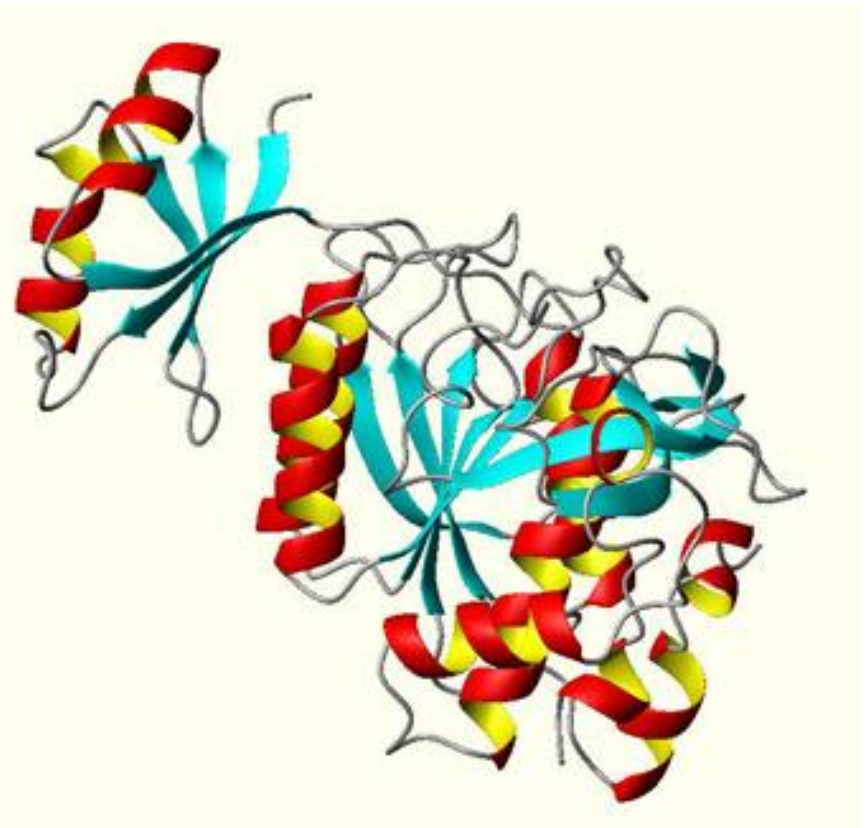


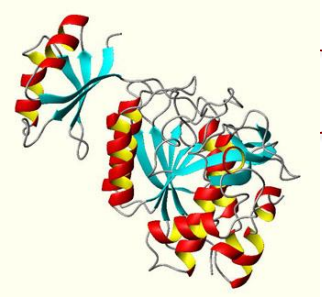
# TERTIARY STRUCTURES

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 quaternary 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)

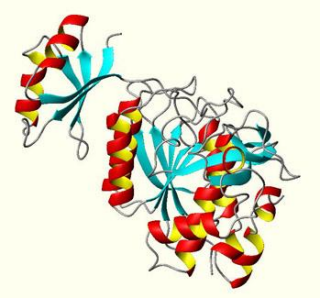
### 2. MEMBRANE PROTEINS

- 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  $\downarrow$   $\uparrow$ !?

Anfinsen (1960)

?

3D FOLDED STRUCTURE

Key & Lock  $\downarrow$   $\uparrow$

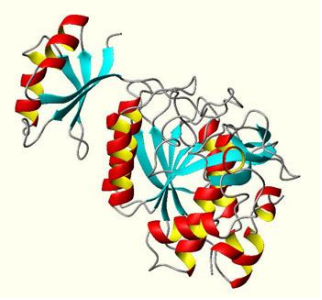
PROTEIN'S FUNCTION

❖ Renaturation – refolding of an unfolded protein chain

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

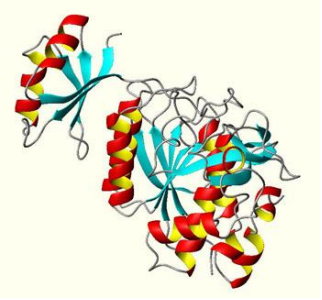
❖ Co-factors, involved in functioning sometimes in protein formation  
Small molecules, ions, sugars, nucleotides

Is a protein hard or soft?



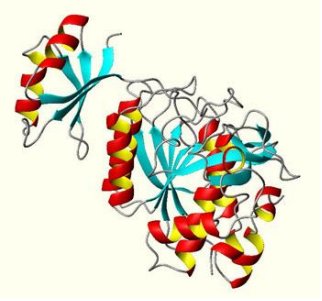
# PROTEIN MODIFICATIONS

- **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



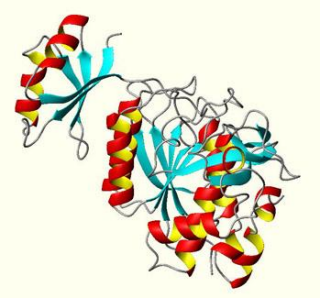
# PROTEIN MODIFICATIONS

- **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

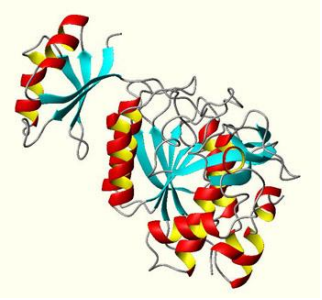
- **Improper S-S bonds**
- Improper S-S bonds prevent protein renaturation.
- Boiled egg does not unboil
- High temperature does not only denature proteins, but breaks S-S bonds and reforms them between random Cys residues.
- Therefore S-S bonds can also be formed intramolecular.
- These new S-S bonds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



# PROTEIN STRUCTURE FUNCTION

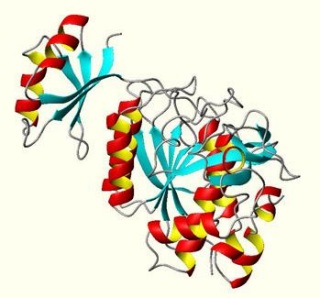
- First: AA sequence determines structure, determines function
- 3D structure of a protein shows empty spaces in the interior
- Protein soft or hard?
- Protein is a hard structure
- Chains are packed tightly atom against atom
- The space filling model shows the tight packing, but does not give any clues 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.





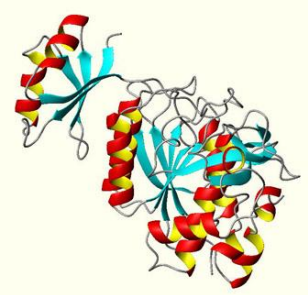
# PROTEIN FUNCTION

- 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.

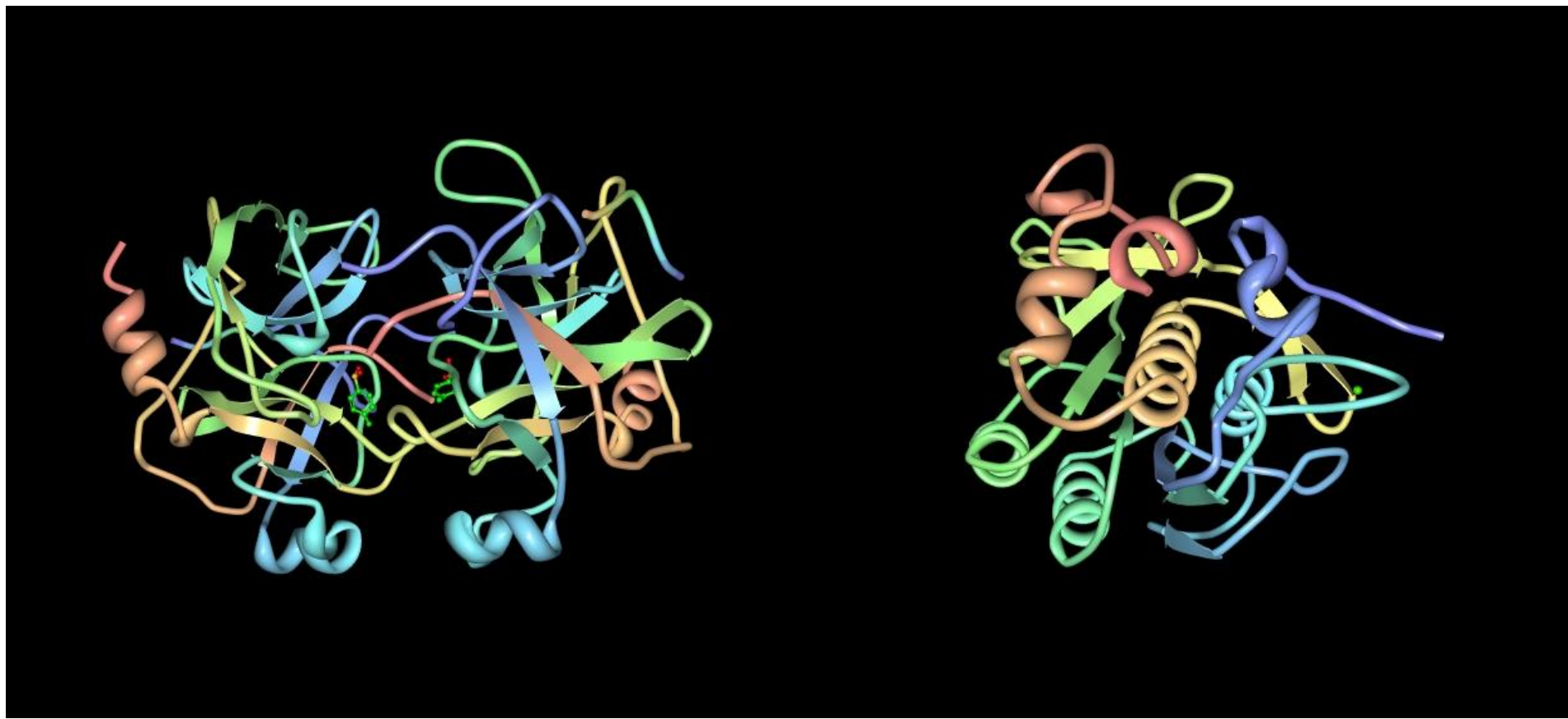


# PROTEIN HARDNESS

- One needs to distinguish between single domain proteins.
- They are really hard
- One compact globule
- Larger proteins:
- Either multidomain organisation or quaternary structure
- The component subglobules are hard like a single 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) what 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?