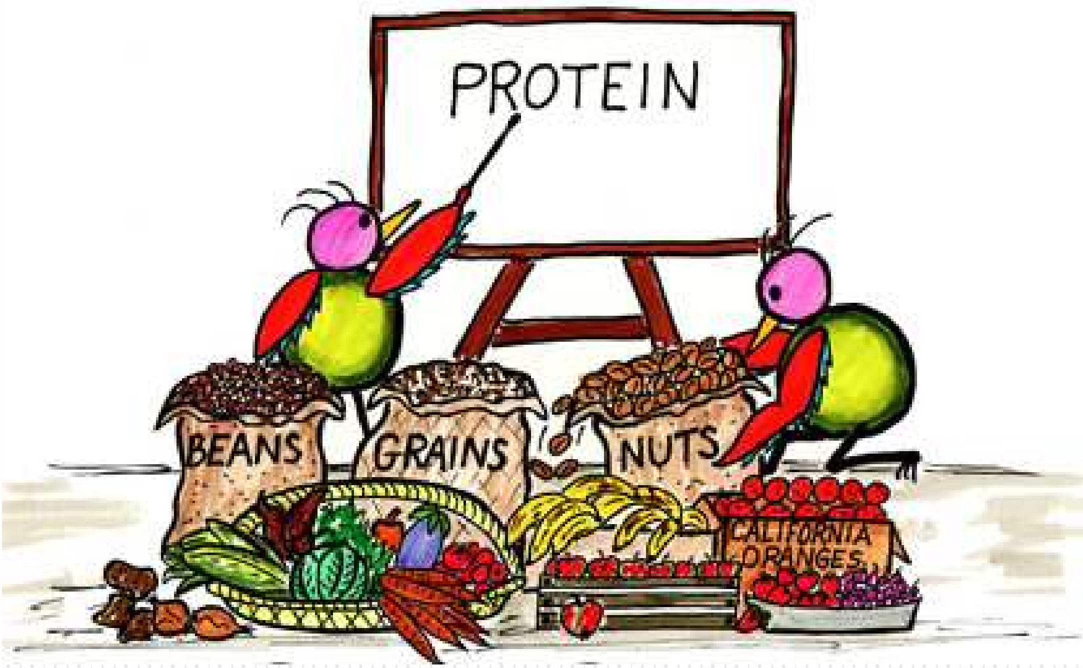
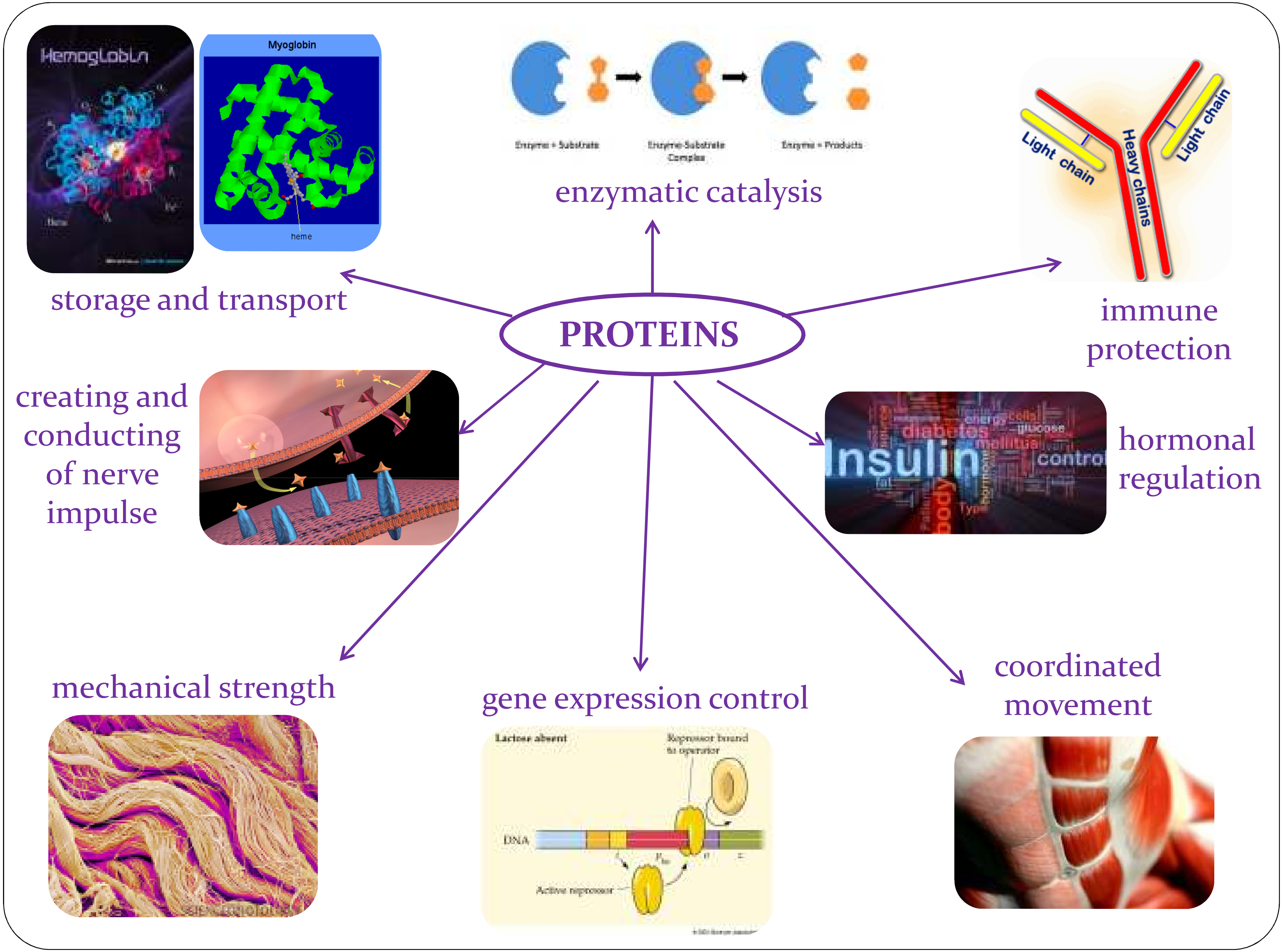
Proteins: higher orders of structure. Myoglobin and hemoglobin; collagen

Vedrana Čikeš Čulić




PROTEINS
storage and transport
Hemoglobin
Myoglobin
heme
enzymatic catalysis
Enzyme + Substrate
Enzyme-Substrate Complex
Enzyme + Products
immune protection
Light chain
Heavy chains
Light chain
creating and conducting of nerve impulse
hormonal regulation
Insulin
diabetes
glucose
control
mechanical strength
gene expression control
Lactose absent
Repressor bound to operator
DNA
Active repressor
coordinated movement

CONFIGURATION

VS

CONFORMATION

Characteristics of proteins

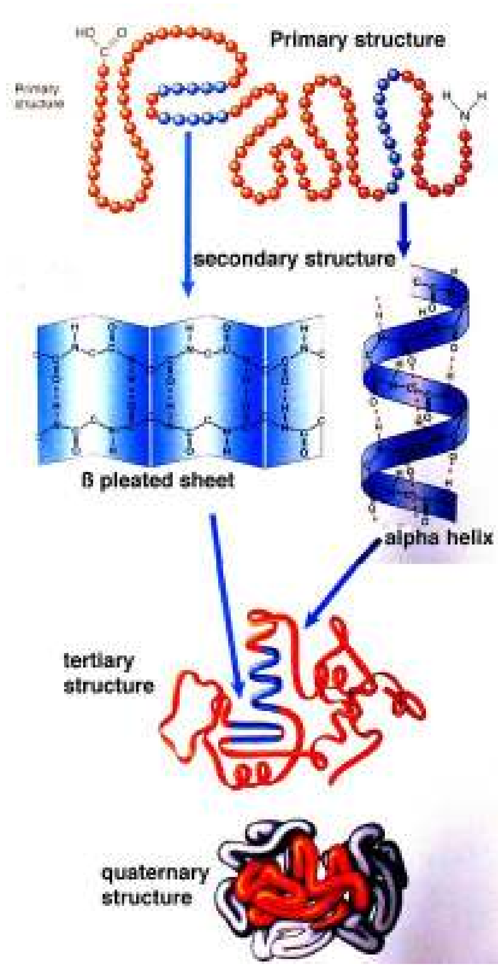
- SOLUBILITY at physiologic pH:
  SOLUBLE vs NON-SOLUBLE

- SHAPE:
  GLOBULAR vs FIBROUS

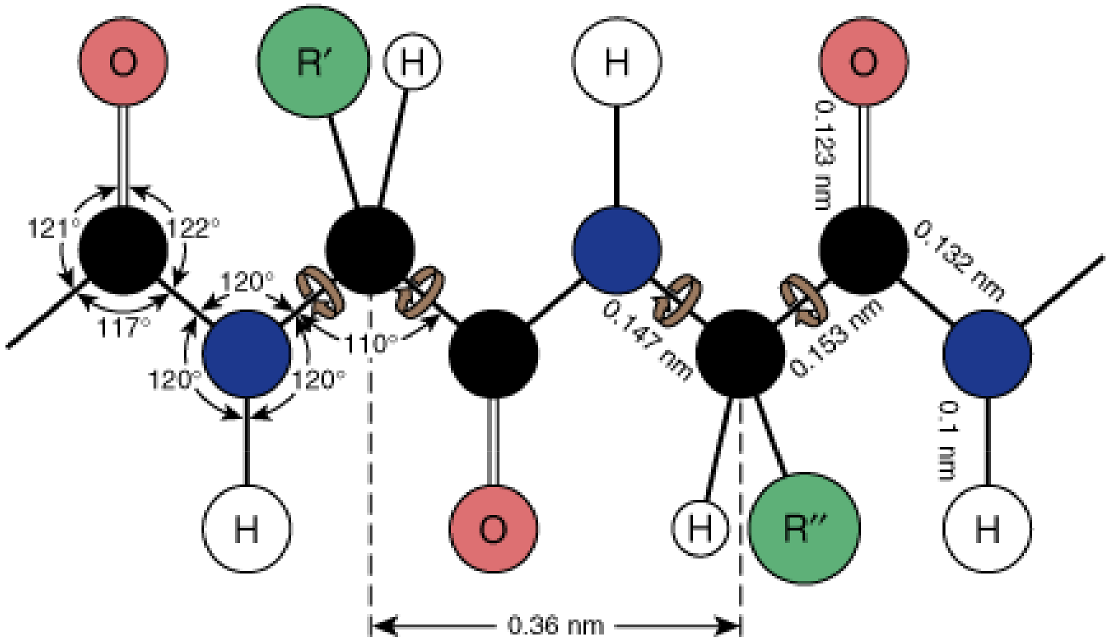
- NONPROTEIN GROUPS:
  LIPOPROTEINS, GLYCOPROTEINS, METALLOPROTEINS

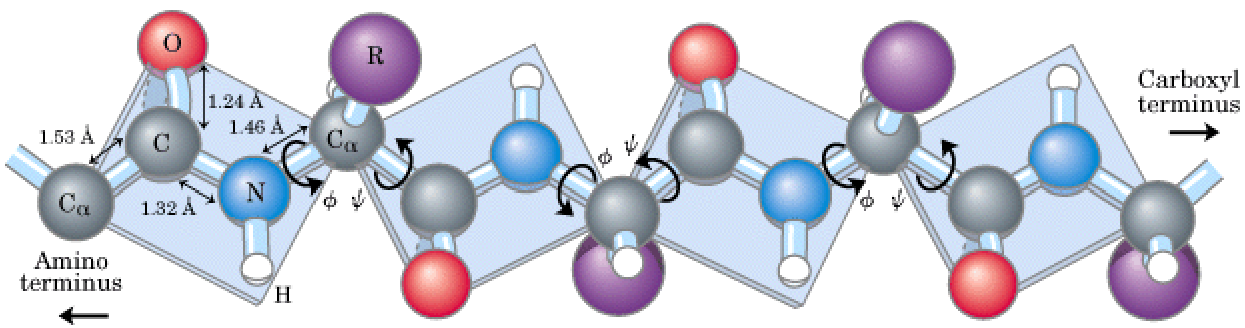
Levels of the protein structure

- PRIMARY STRUCTURE—the sequence of the amino acids
- SECONDARY STRUCTURE—geometrically ordered units
- TERTIARY STRUCTURE—the assembly of secondary structural units into larger functional units
- QUATERNARY STRUCTURE—the number and types of polypeptide units of oligomeric proteins and their spatial arrangement

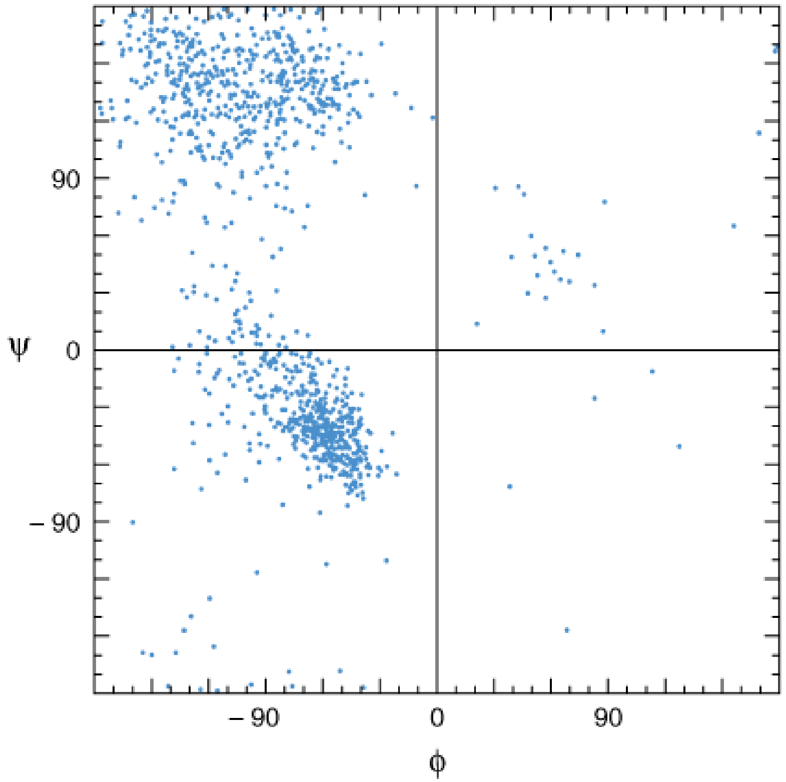


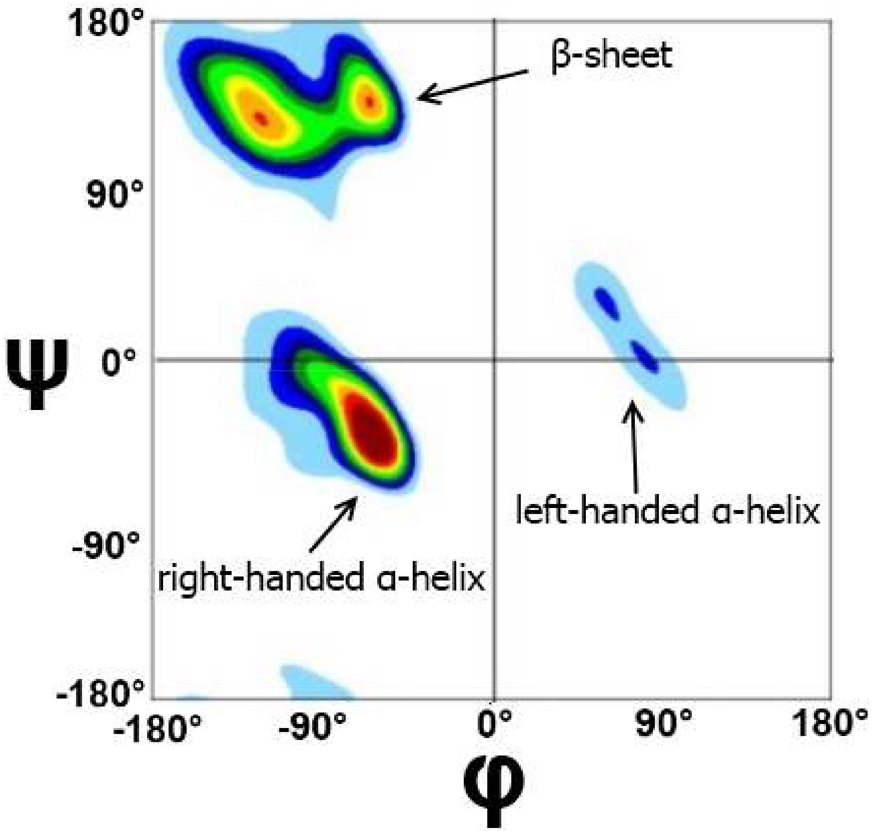
Secondary Structure





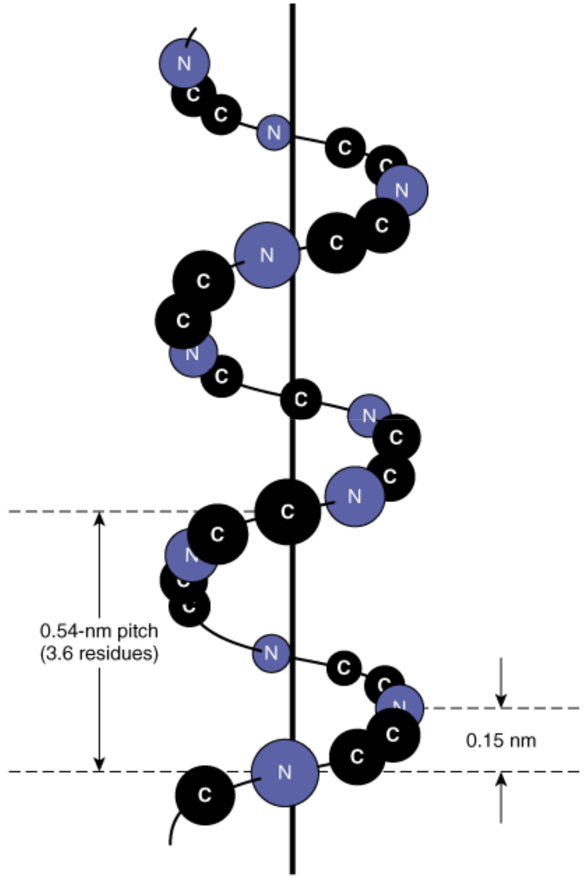
Ramachandran plot shows allowed and non-allowed phi (Φ) and psi (Ψ) values

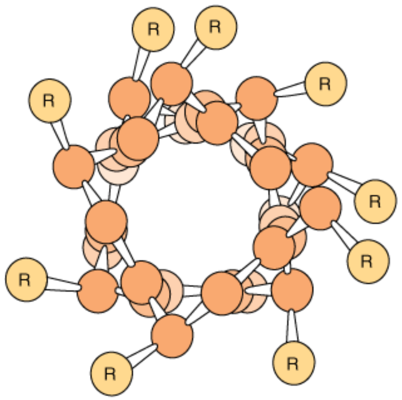




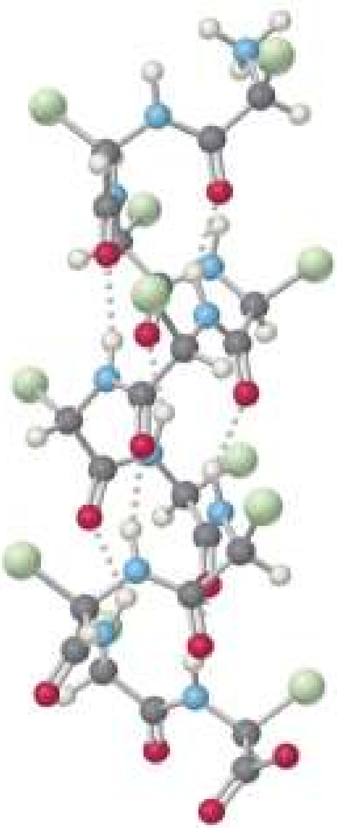
α-Helix

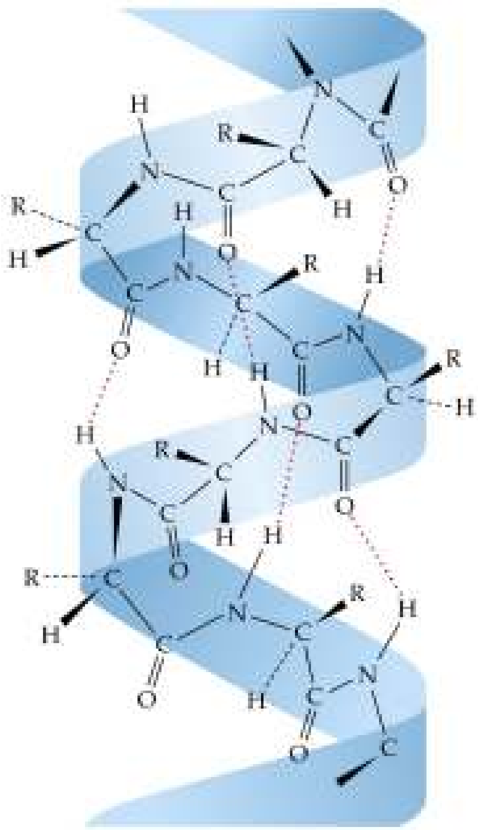
- constant Φ and Ψ angels
- average of 3.6 amino-acyl residues per pitch
- R groups face outward
- only L-amino acids
- only right-handed helices





α-Helix





- HYDROGEN BONDS - between the oxygen of the peptide bond carbonyl and the hydrogen atom of the peptide bond nitrogen of the fourth residue down the polypeptide chain
- amphipathic helices

β-Sheet

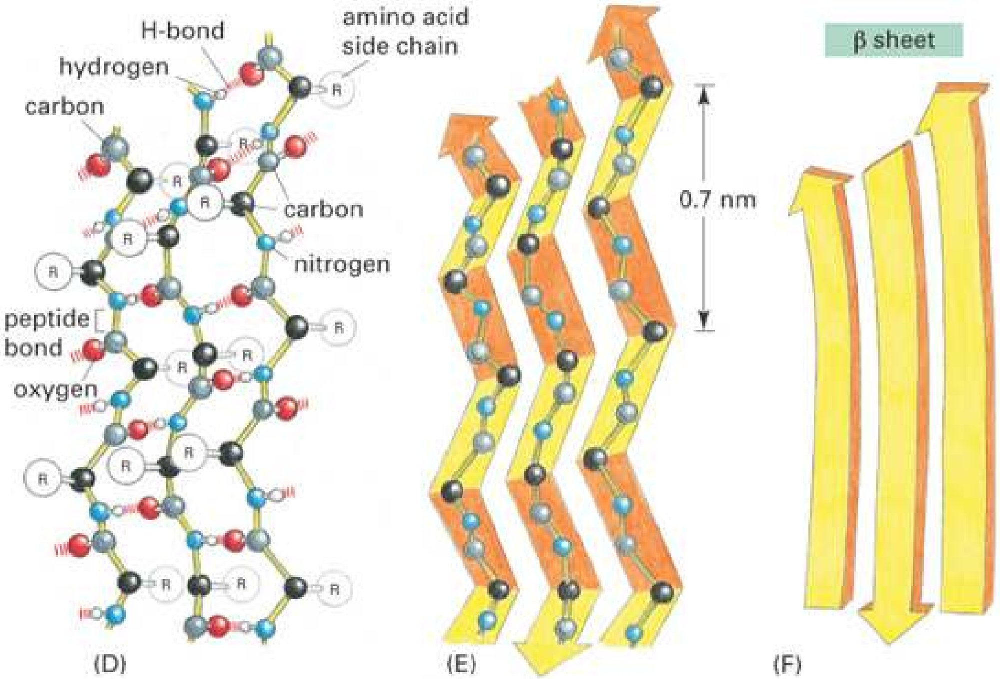
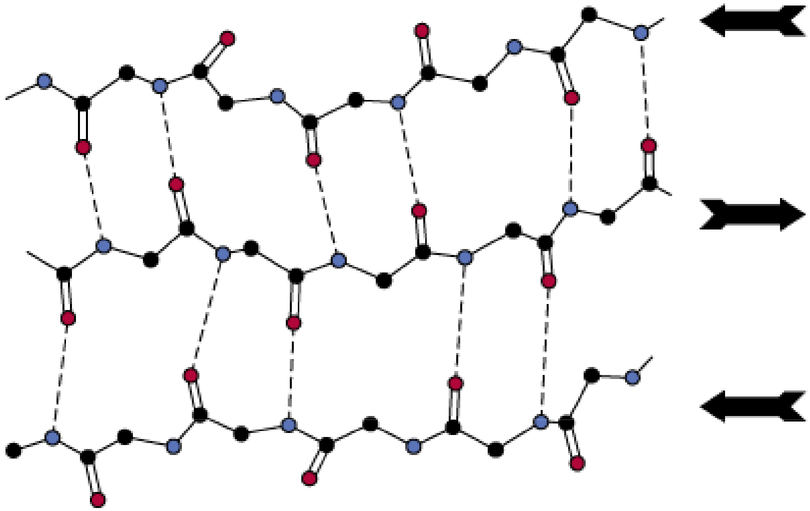


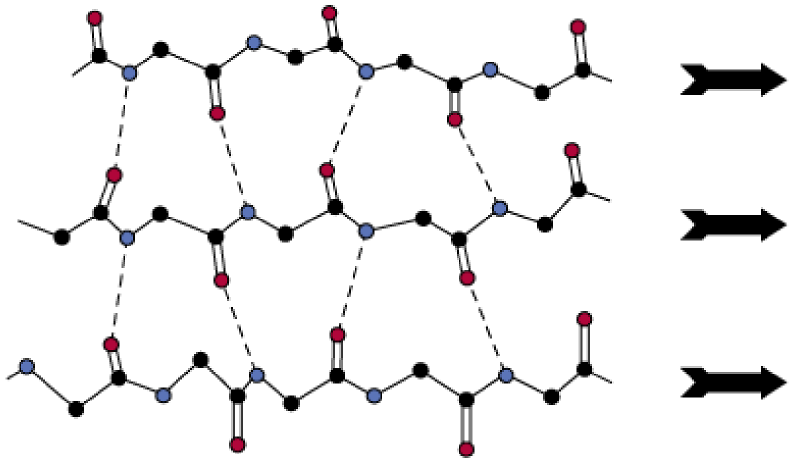
Figure 4-10 part 2 of 2 Essential Cell Biology, 2/e. (© 2004 Garland Science)

- zig-zag pattern
- R groups of adjacent residues point in opposite directions
- the peptide backbone is highly extended
- hydrogen bonds - adjacent segments of the sheet

β-Sheet

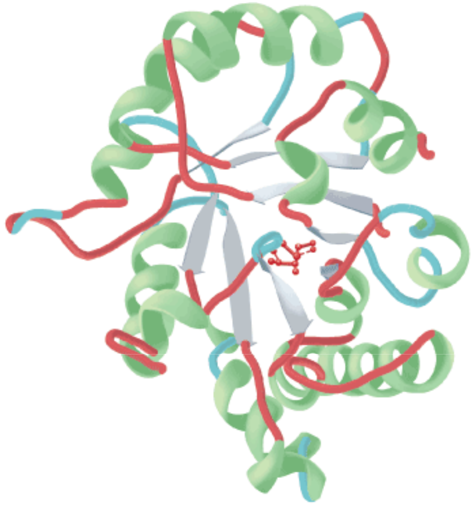


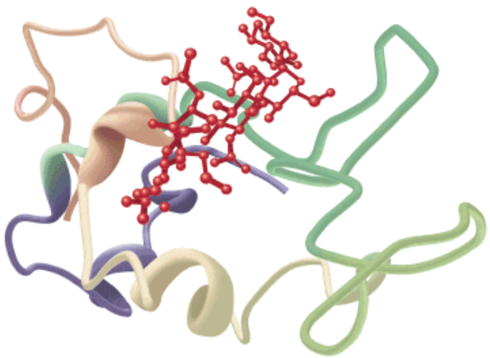
ANTIPARALLEL
β-SHEET

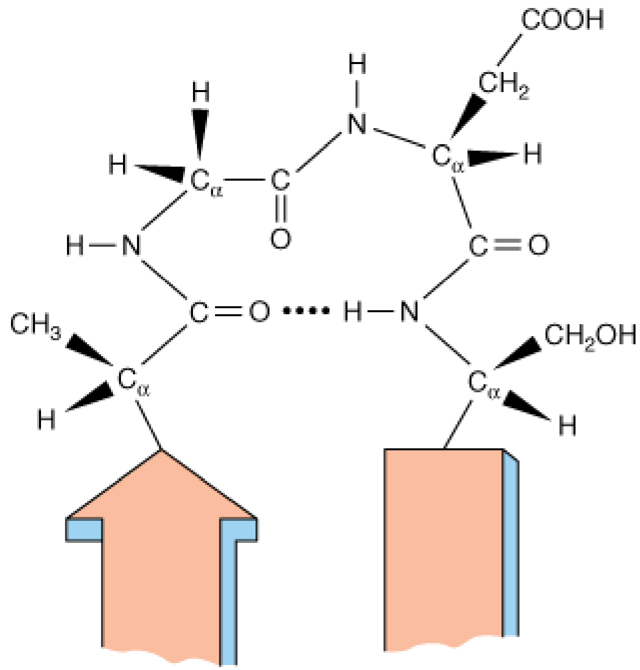


PARALLEL
β-SHEET

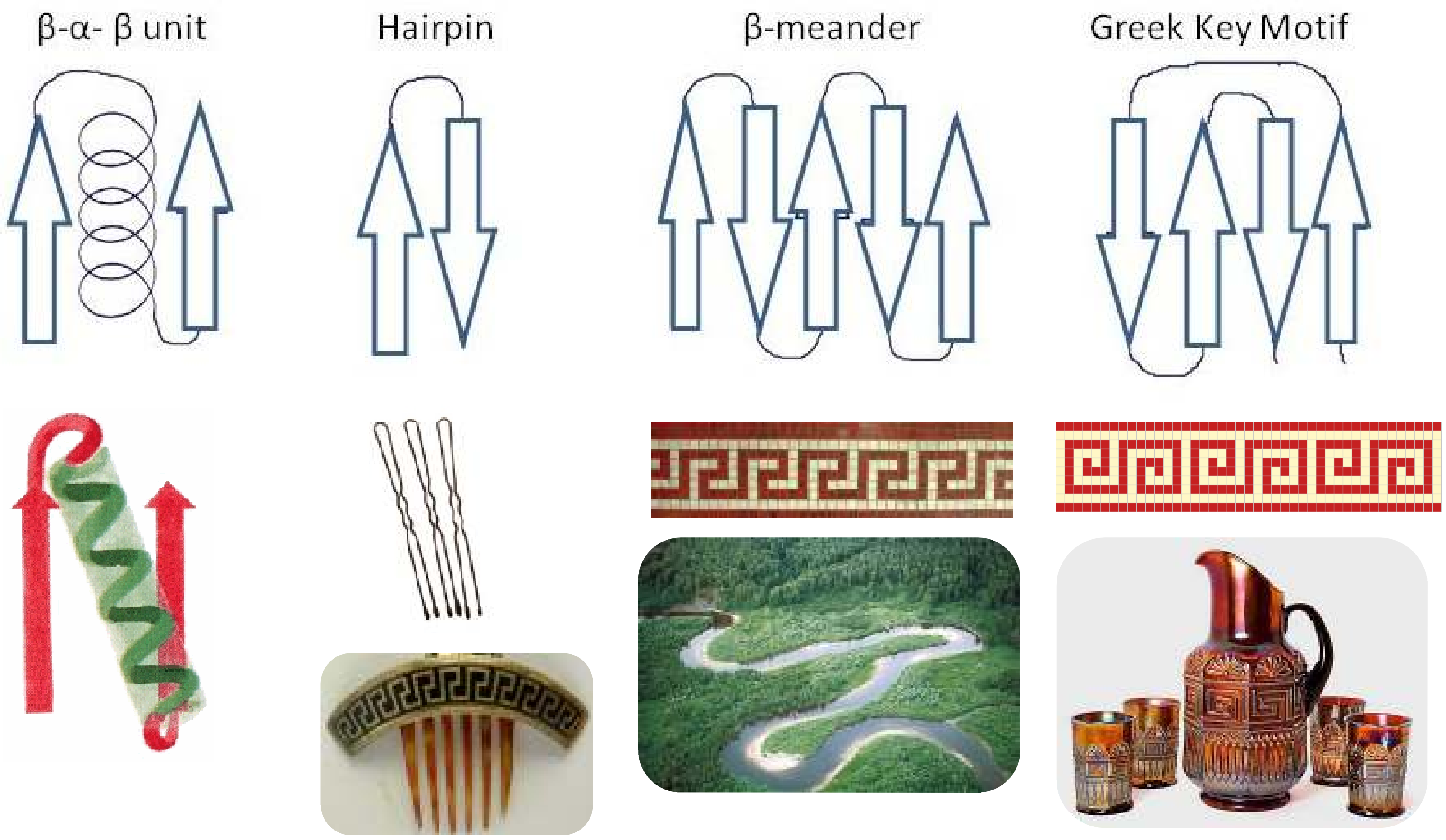
Loops & Bends



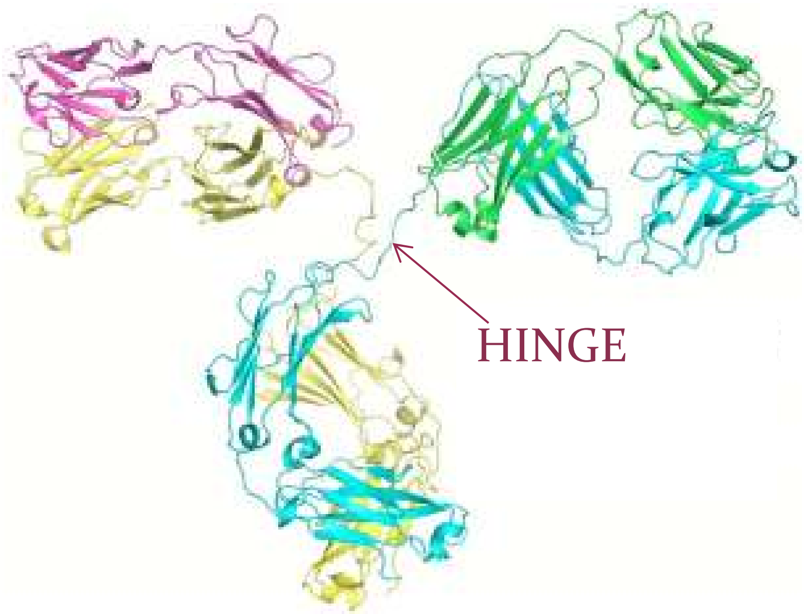




Supersecondary structures

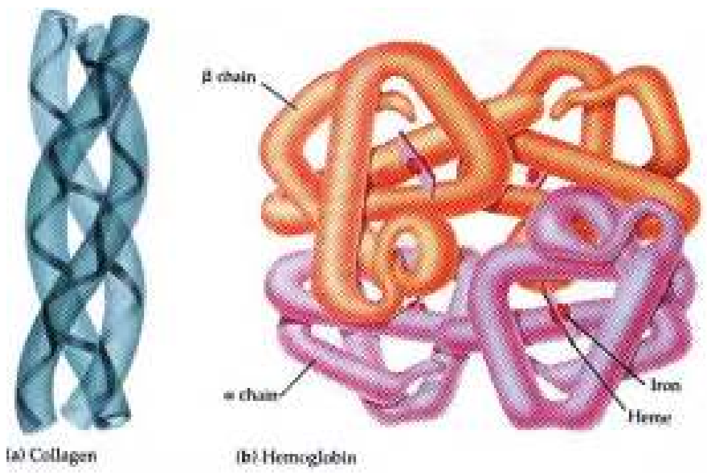


Tertiary Structure



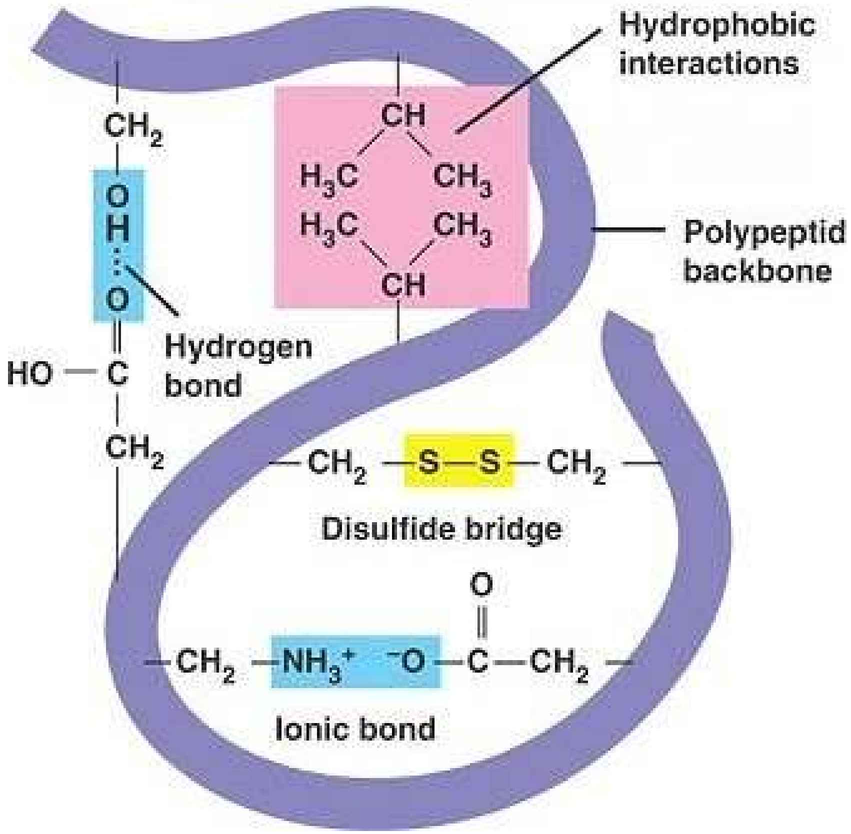
- 3D conformation of a polypeptide
- The sequence of amino acids determines the tertiary structure
- DOMAINS – formation of assembled secondary structural features (helix, sheet, bend, turn, loop) – functional unit of protein

Quaternary structure



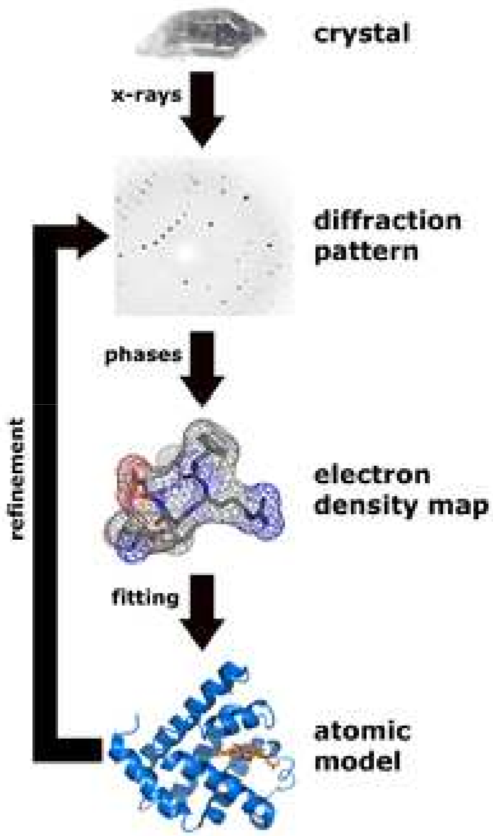
- Two or more polypeptide chains (protomers)
- MONOMERIC, DIMERIC etc.
- HOMODIMER vs HETERODIMER

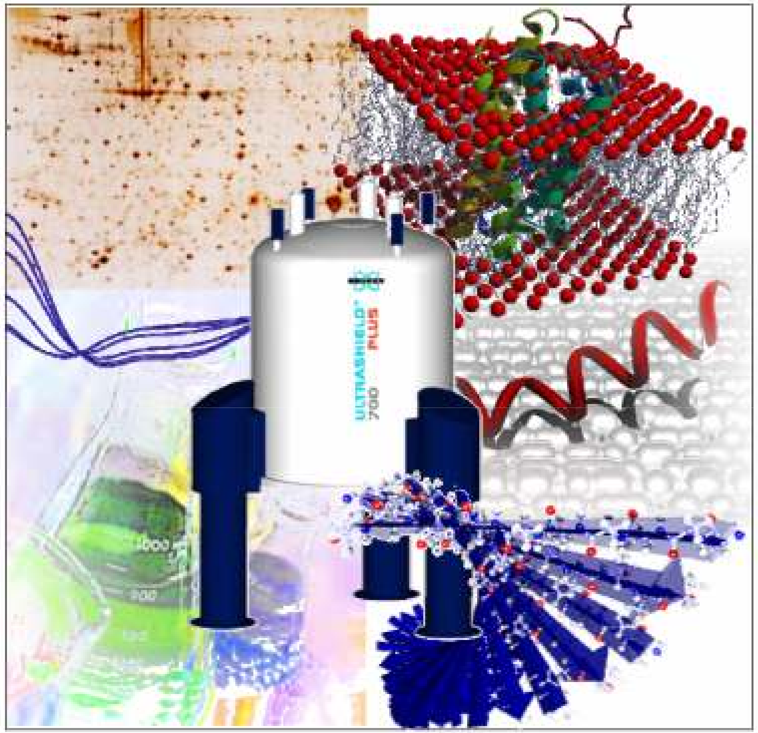
Stabilization of the Tertiary & Quaternary Structure



- noncovalent interactions
- hydrophobic interactions
- hydrogen bonds
- disulfide bonds

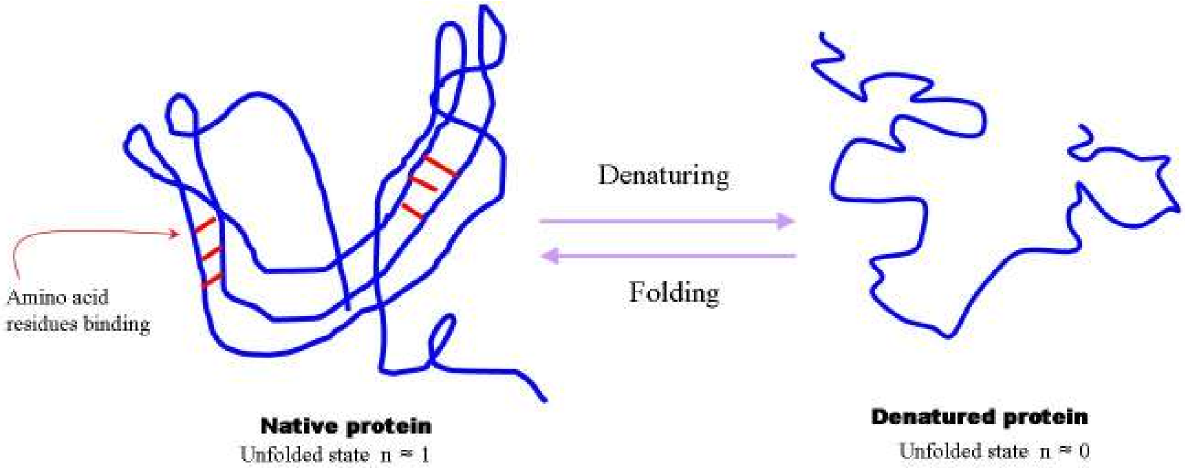
X-Ray Crystallography
NMR spectroscopy

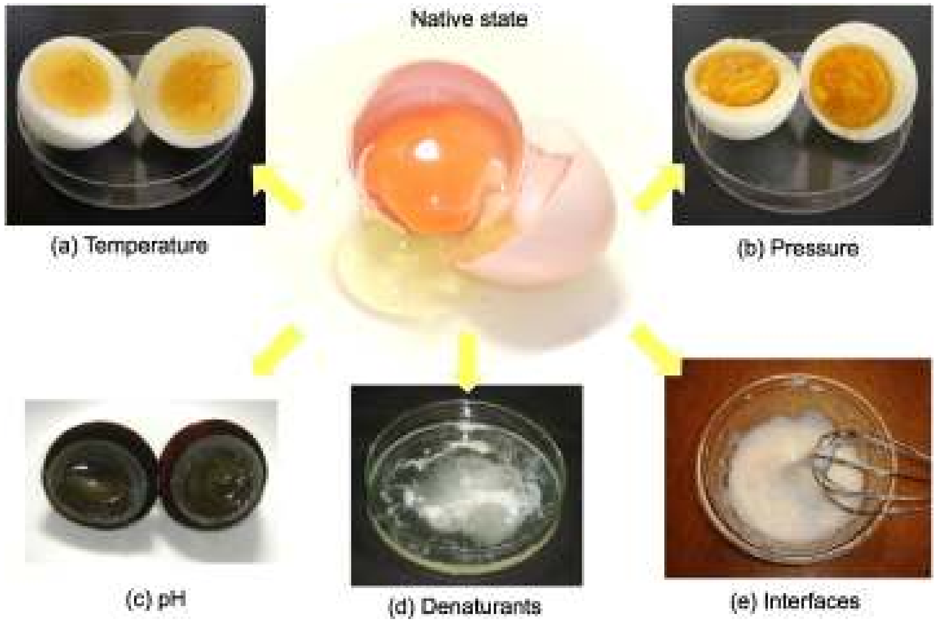




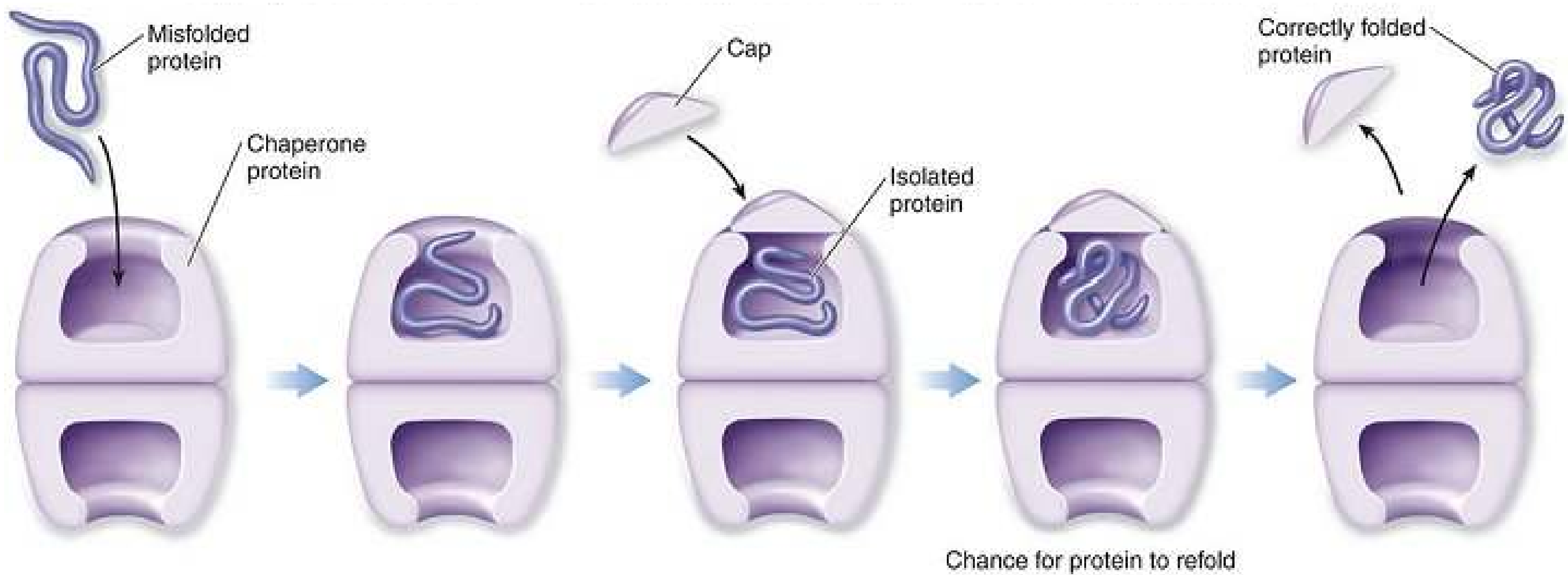
- determination of protein 3D structure

Folding ↔ Denaturation



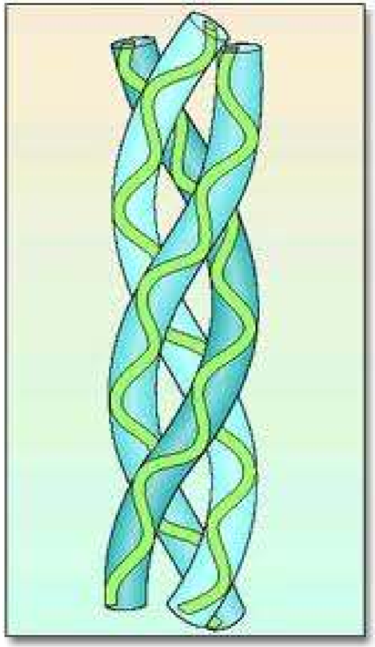


Chaperones



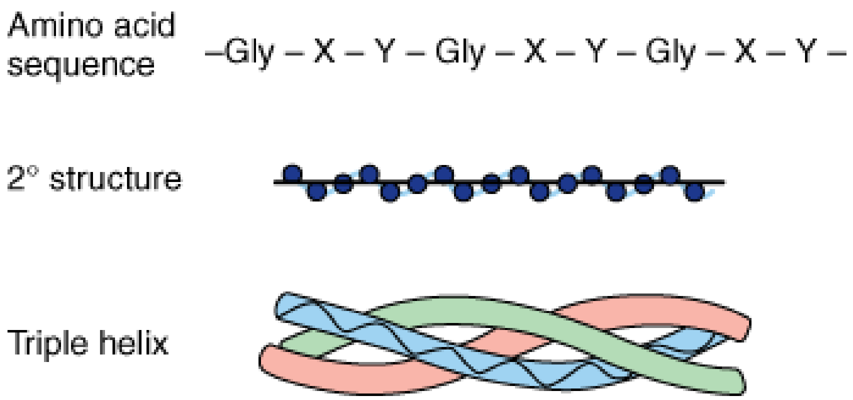
Misfolded protein
Chaperone protein
Cap
Isolated protein
Correctly folded protein
Chance for protein to refold

Collagen

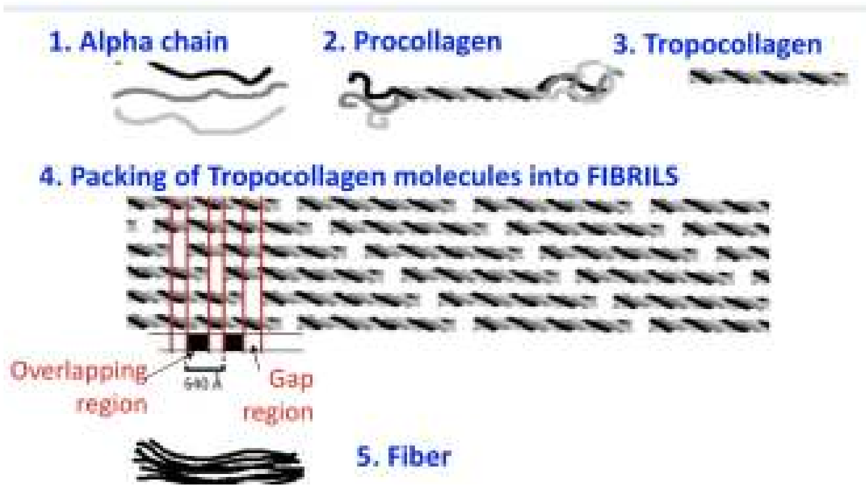


- FIBROUS protein
- structural strength for cells and tissues
- constituent of skin, bones, teeth, ligaments, tendons

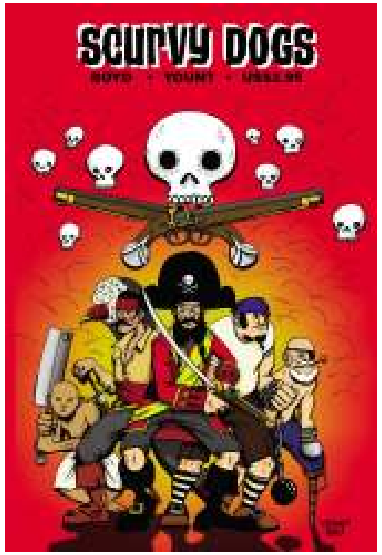
Collagen



- triple helix
- TROPOCOLLAGEN
- every third amino acid residue is GLYCINE
- rich in proline and hydroxyproline

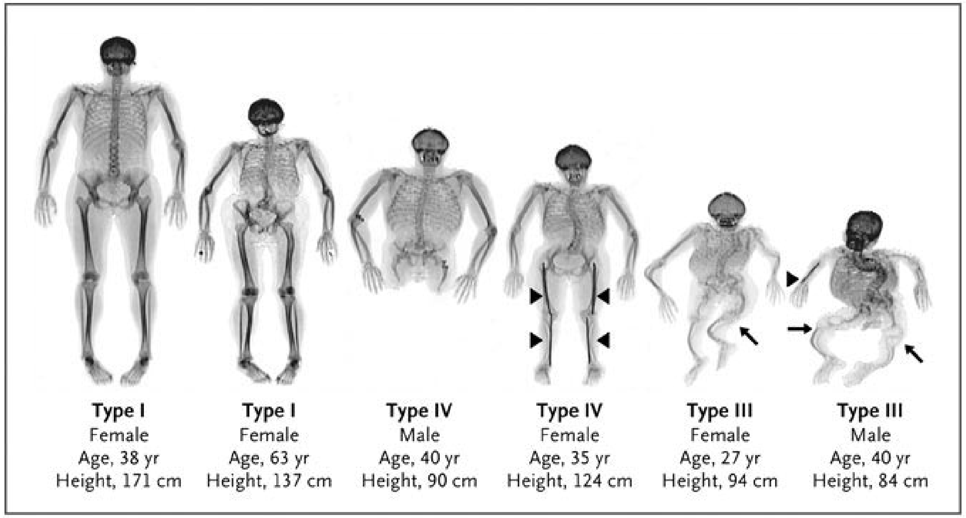


Collagen



SCURVY

OSTEOGENESIS IMPERFECTA




Myoglobin
Hemoglobin
JACOB

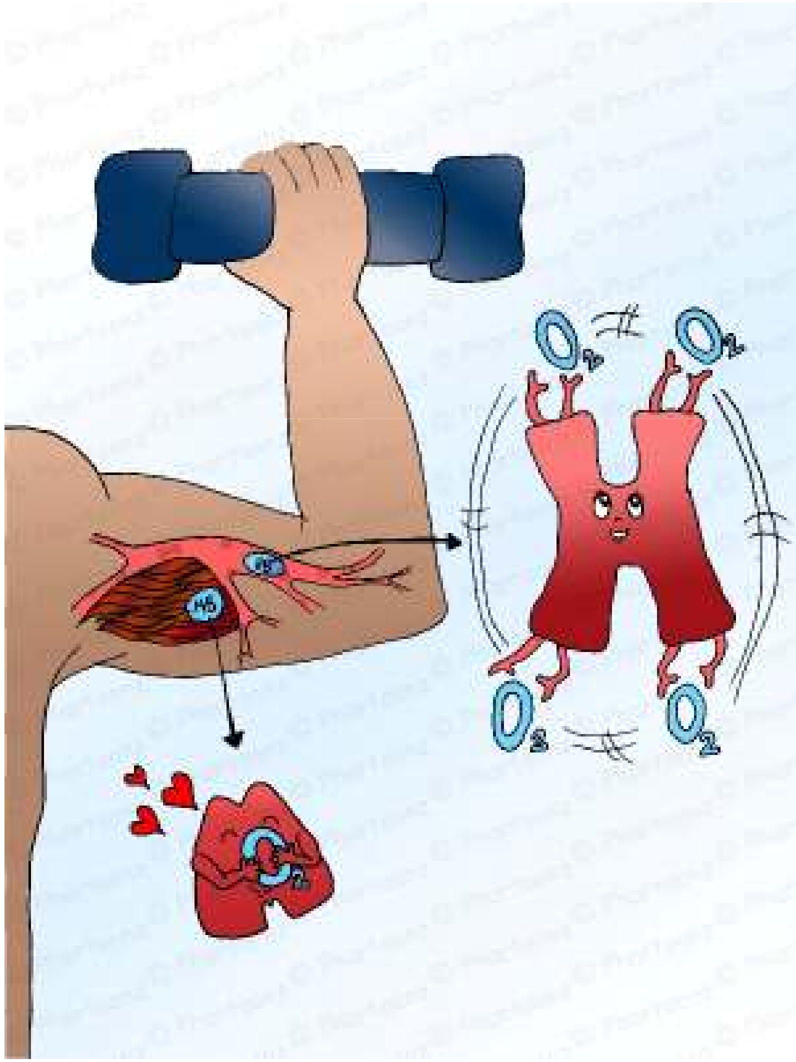
Myoglobin & Hemoglobin

• HEME proteins

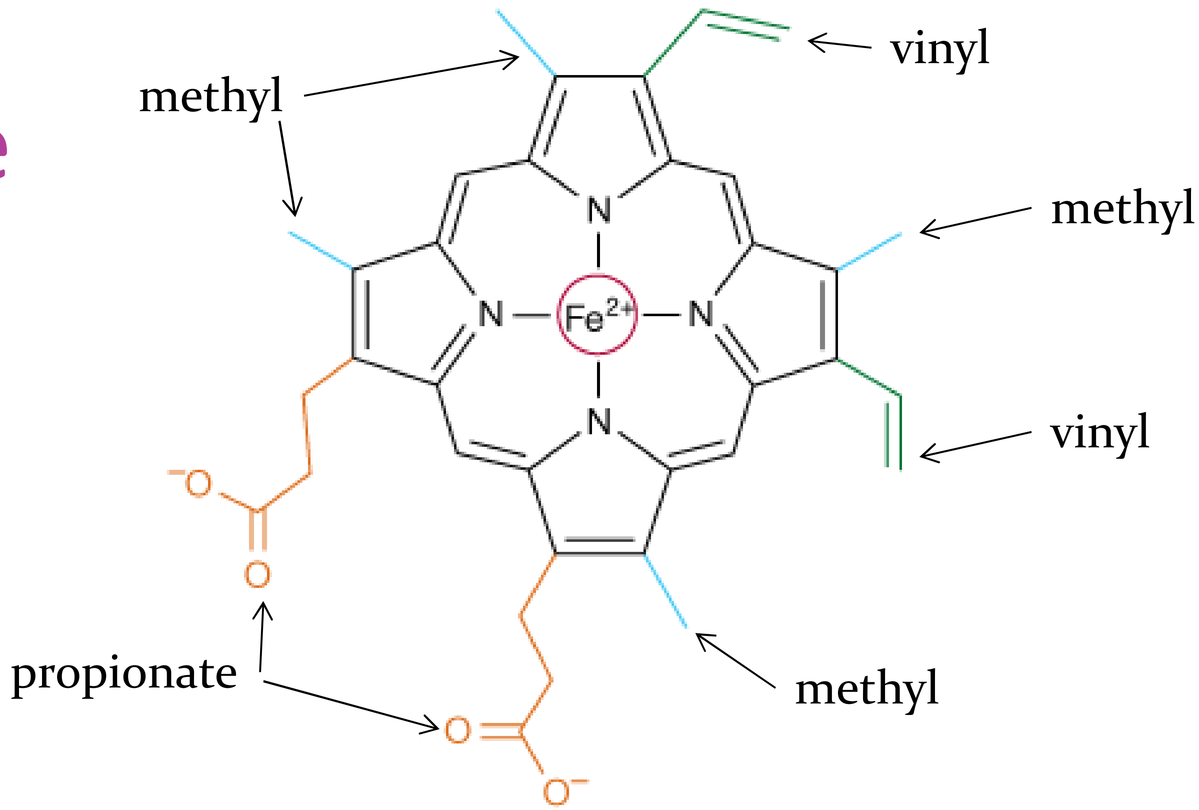
•Supply of OXYGEN:

✓ Myoglobin → red muscle

✓ Hemoglobin → erythrocytes

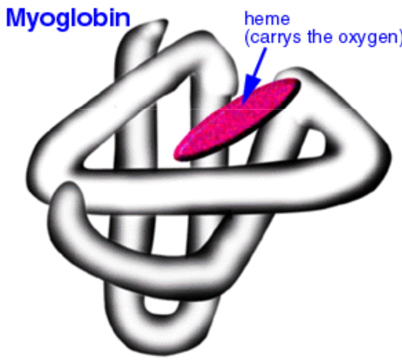


Heme



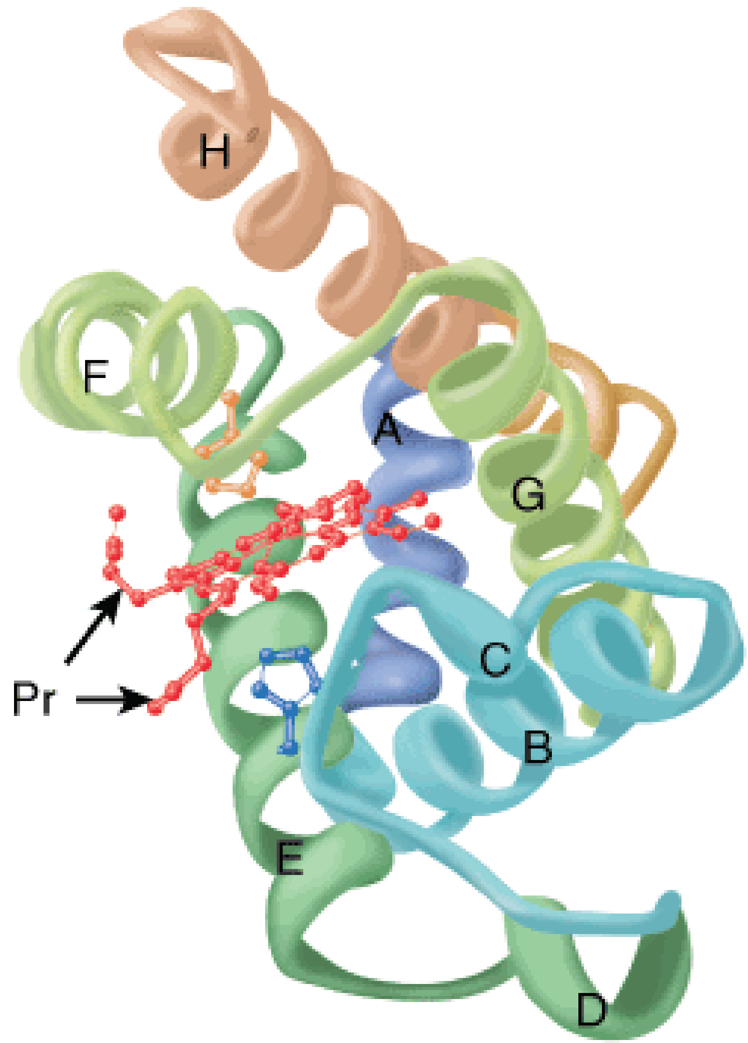
- prosthetic group of: Hb and Mb (Fe^{2+})
  cytochromes (Fe and Cu)
  chlorophyll (Mg)
- cyclic tetrapyrrole

Myoglobin



- oxygen storage in red muscle
- responsible for RED COLOR of tissues
- ONE polypeptide chain + ONE Heme
- GLOBULAR protein
- sea mammals = lots of myoglobin in muscle

Myoglobin



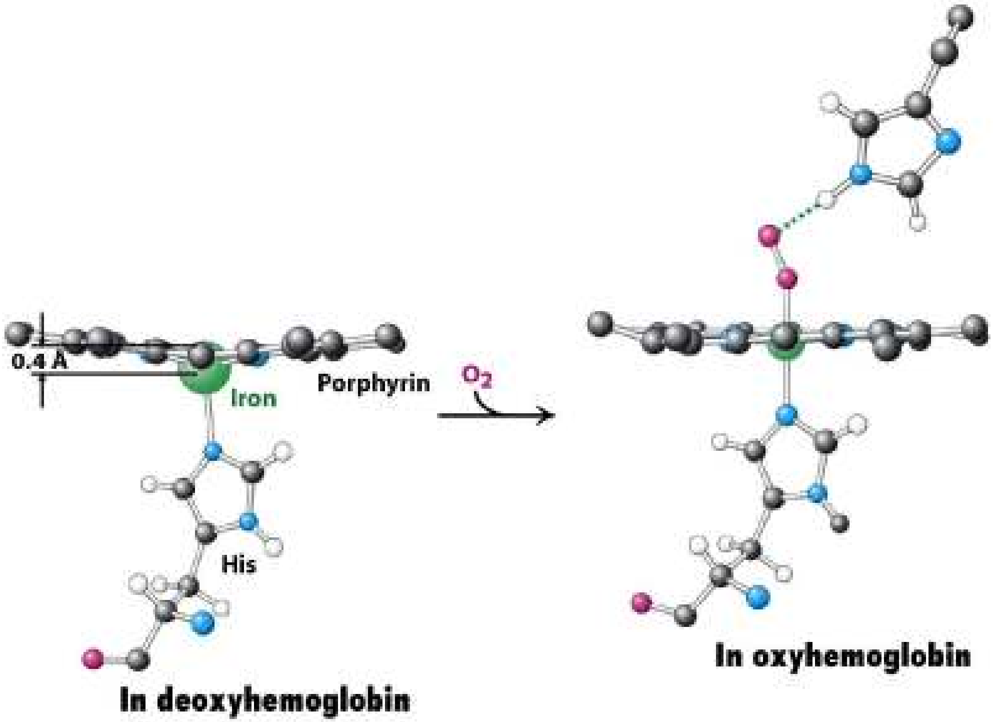
distal histidine

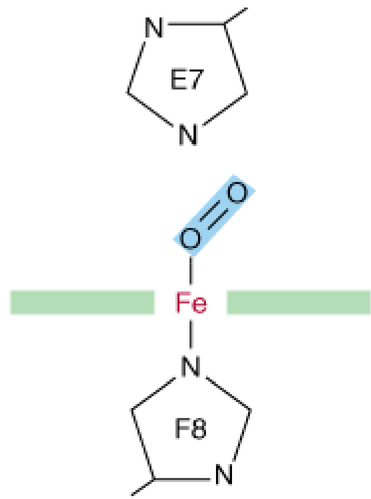
proximal histidine

heme

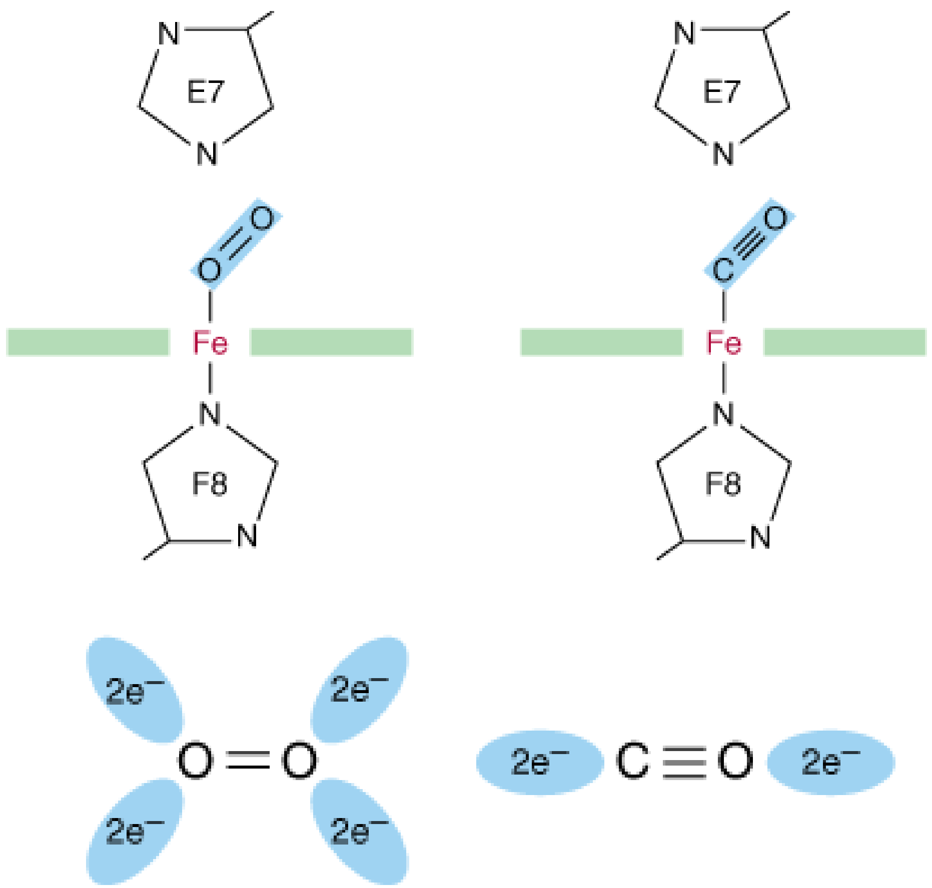
Pr = propionate

The Iron Moves Toward the Plane of the Heme When Oxygen Is Bound





CO and O_2 are competing for the same binding site on heme

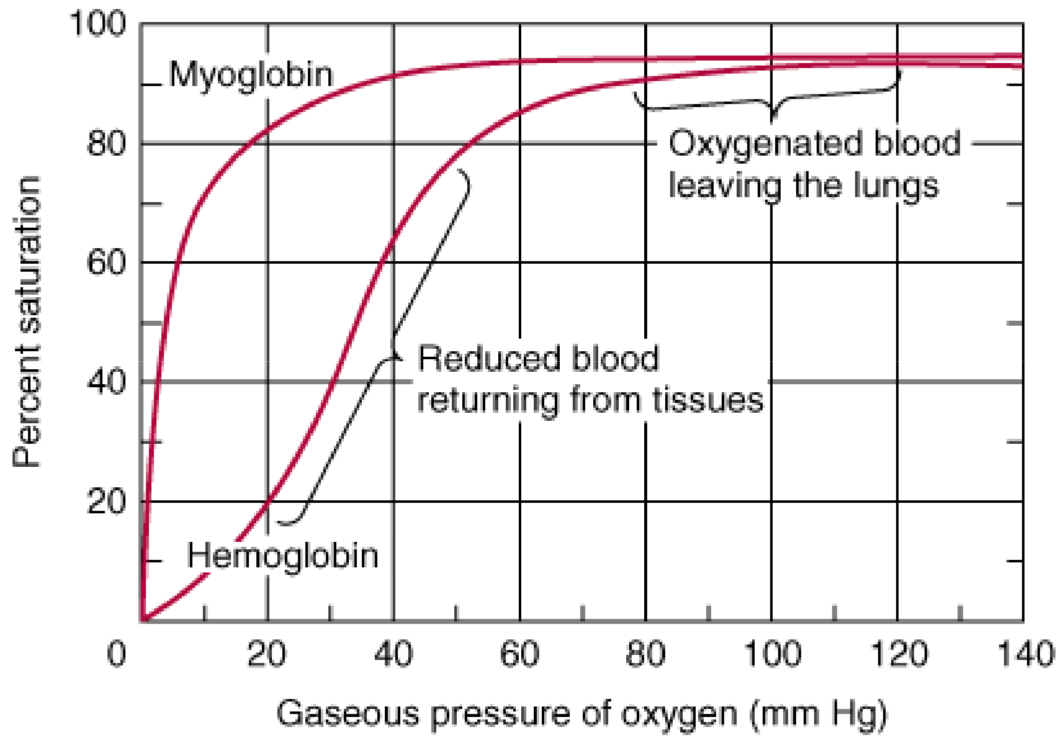


- Isolated heme binds CO 25,000 times more strongly than O_2

- Distal His weakens the binding of CO:
  - forcing it to links an angle and not perpendicular
  - enhances the binding of O_2

- Hb and Mb bind CO 200 times more strongly than O_2

The Oxygen Dissociation Curves



- Myoglobin (monomer)

$Mb + O_2 \rightarrow MbO_2$

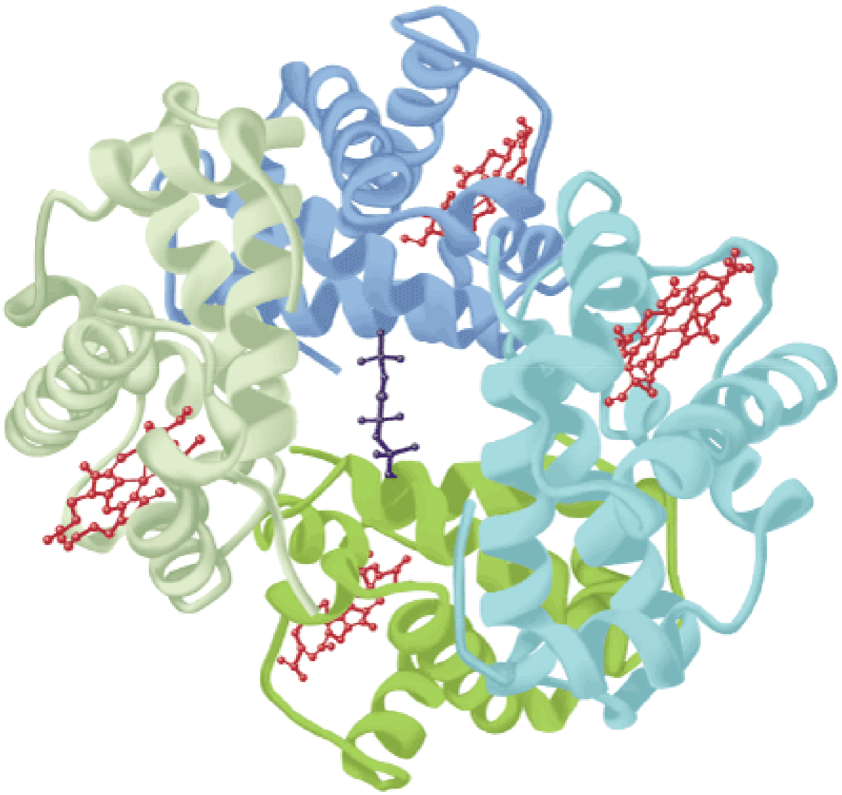
hyperbolic curve

- Hemoglobin (tetramer)

$Hb + 4O_2 \rightarrow Hb(O_2)_4$

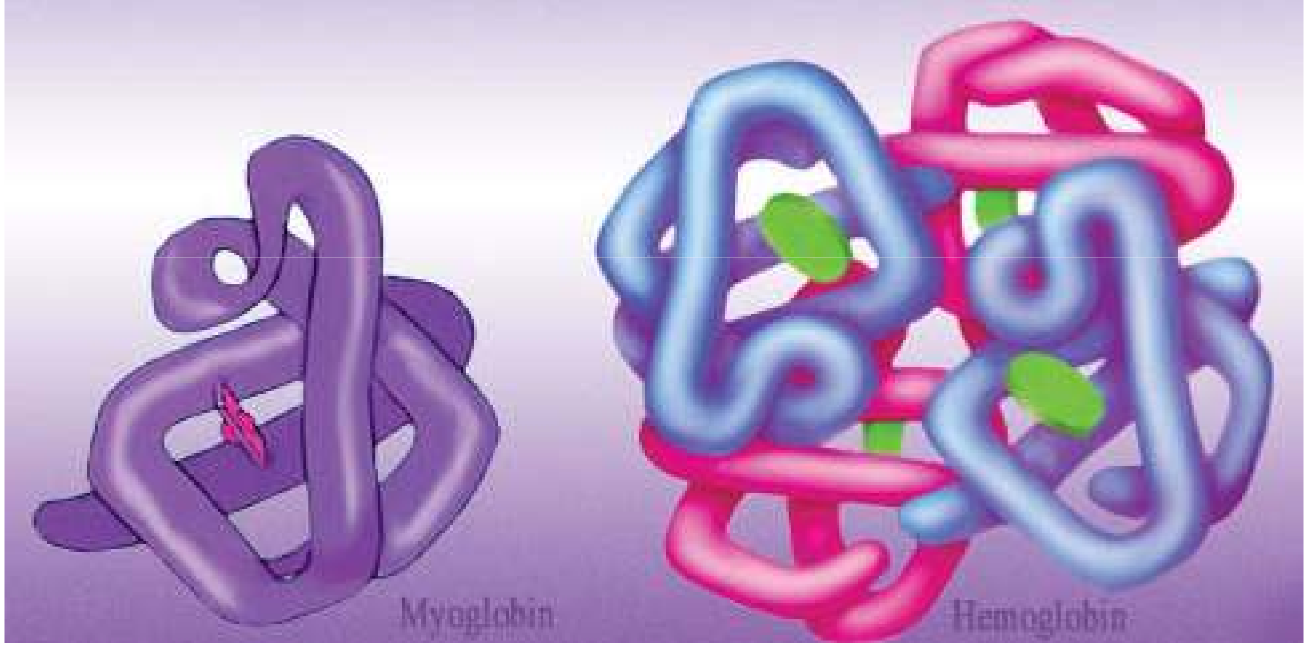
sigmoid curve

Hemoglobin quaternary structure

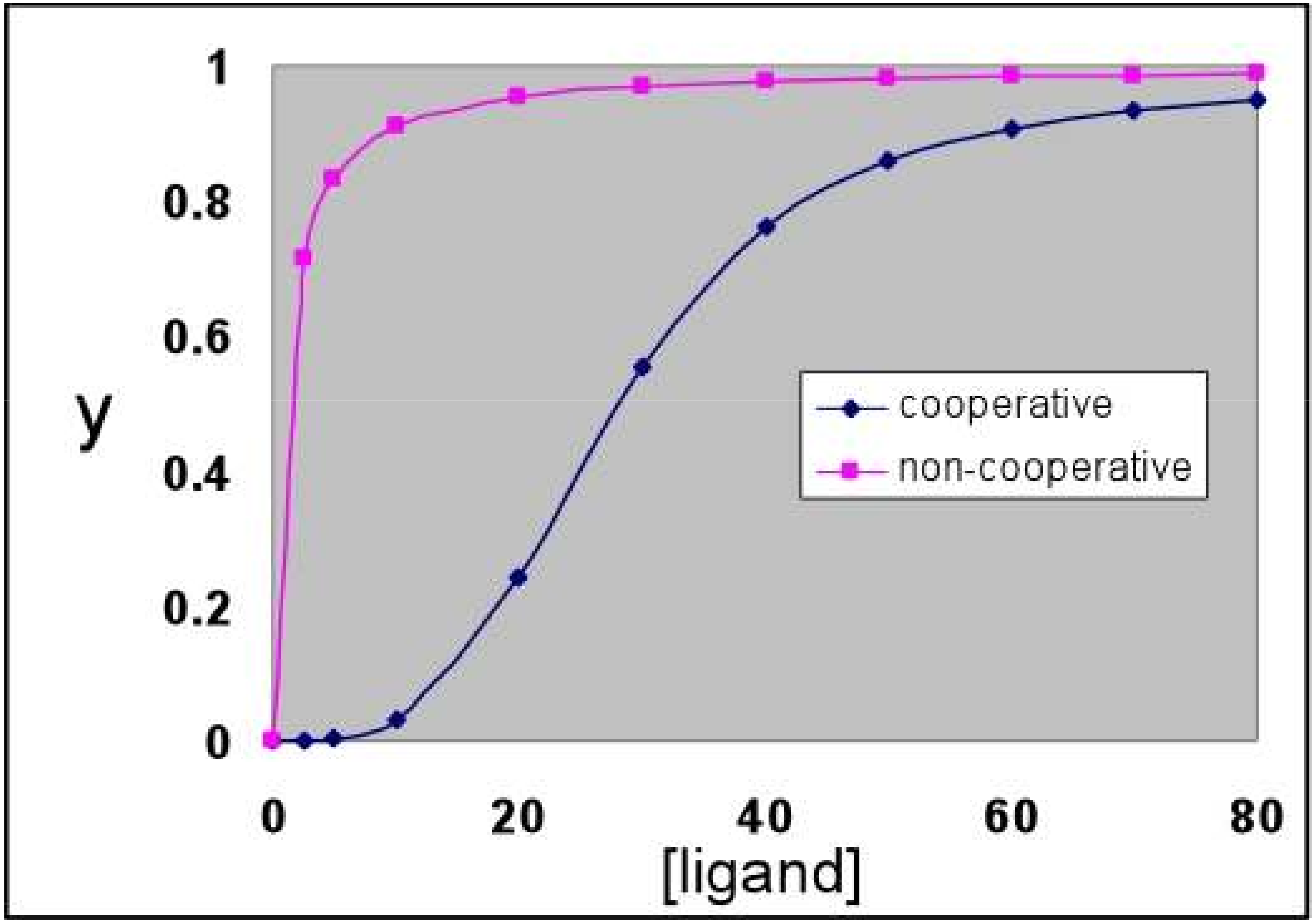


- ALLOSTERIC protein
- TETRAMERIC - pairs of two different polypeptide subunits: $\alpha_1\alpha_2\beta_1\beta_2$
- Covalent bonds between subunits

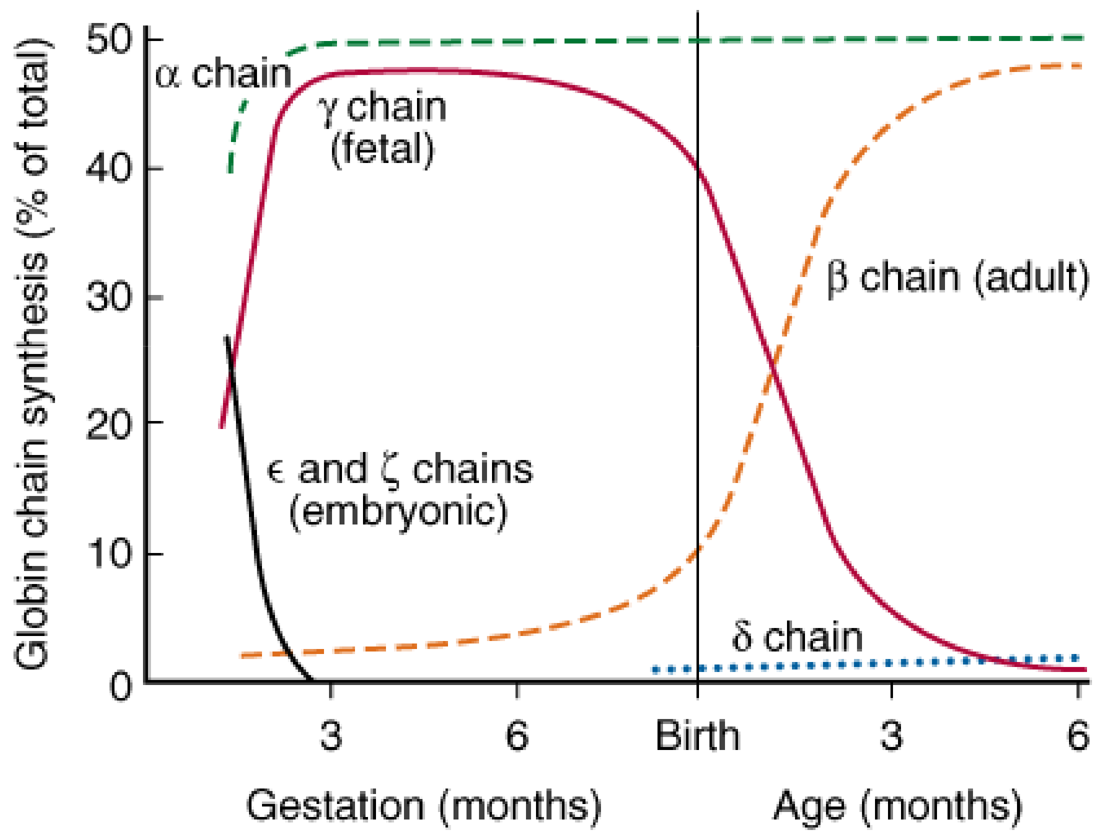
Myoglobin & the Subunits of Hemoglobin Share Almost Identical Secondary and Tertiary Structures



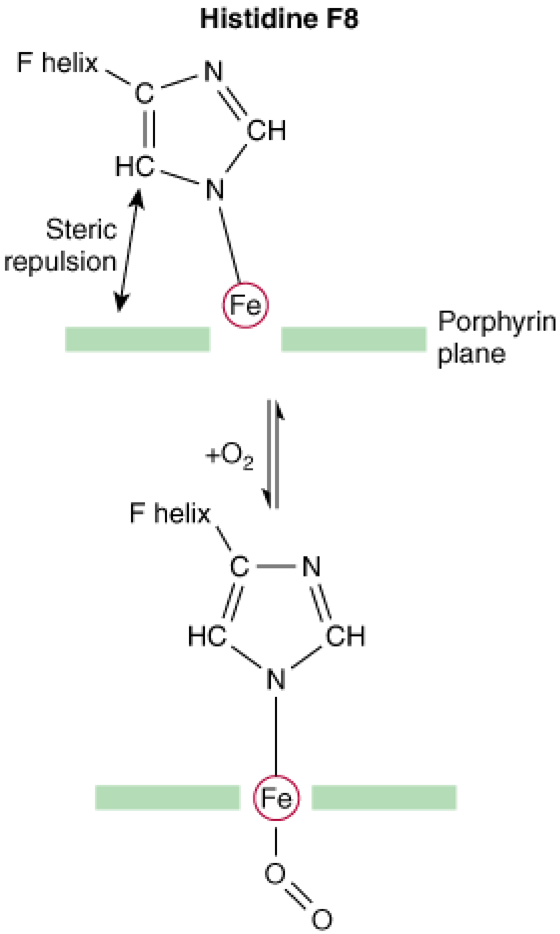
Cooperative binding

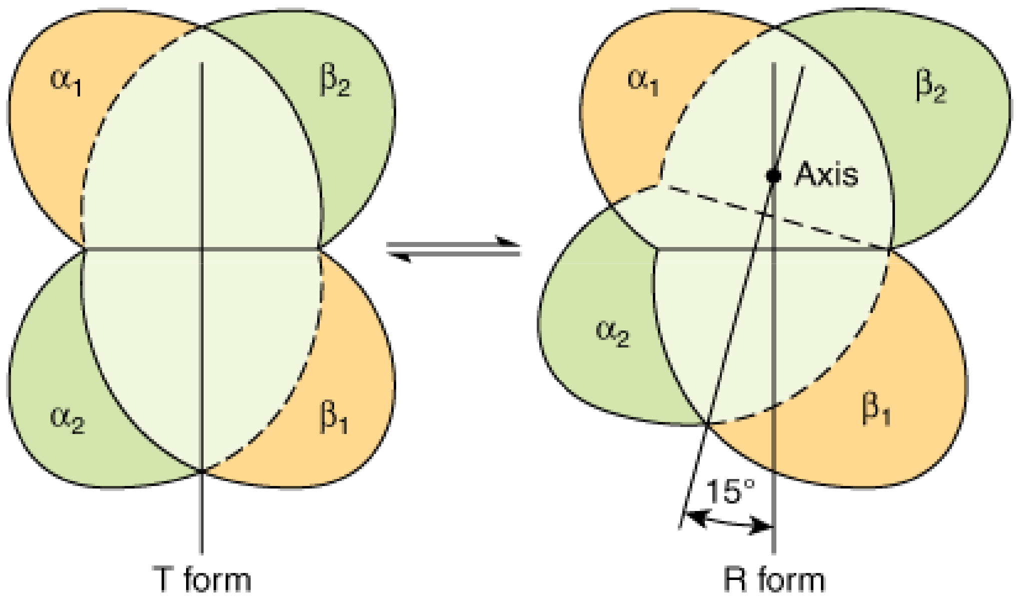


Fetal hemoglobin HbF ($\alpha_2\gamma_2$)



Oxygenation of Hemoglobin Is Accompanied by Large Conformational Changes

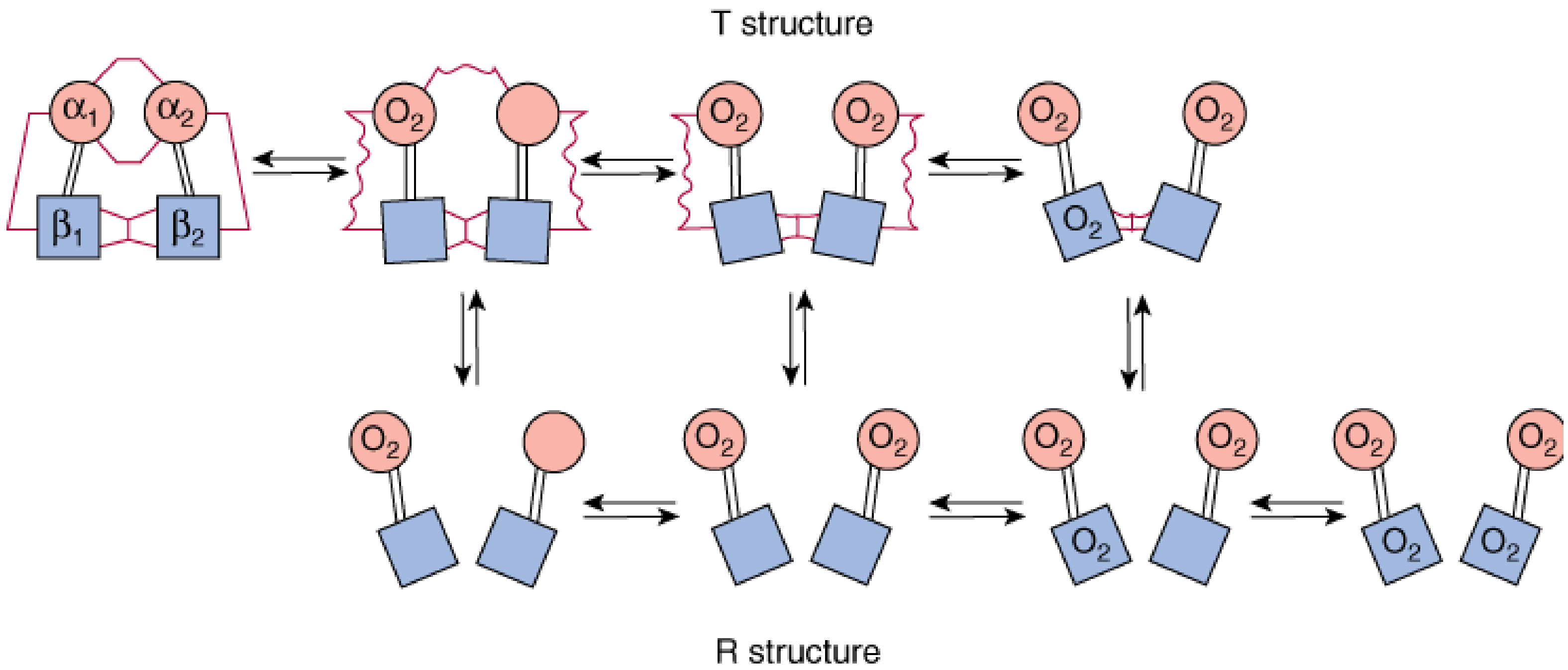




T = Taut
low affinity for O_2

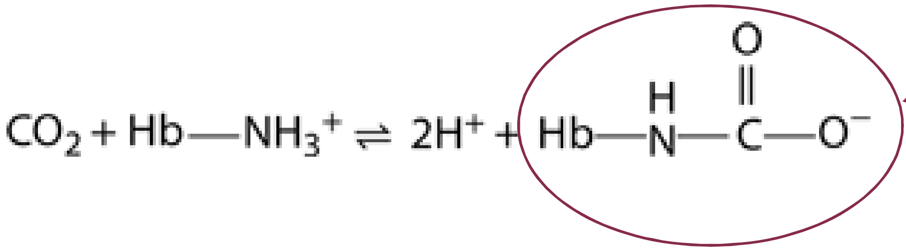
R = Relaxed
high affinity for O_2

Transition from the T structure to the R structure



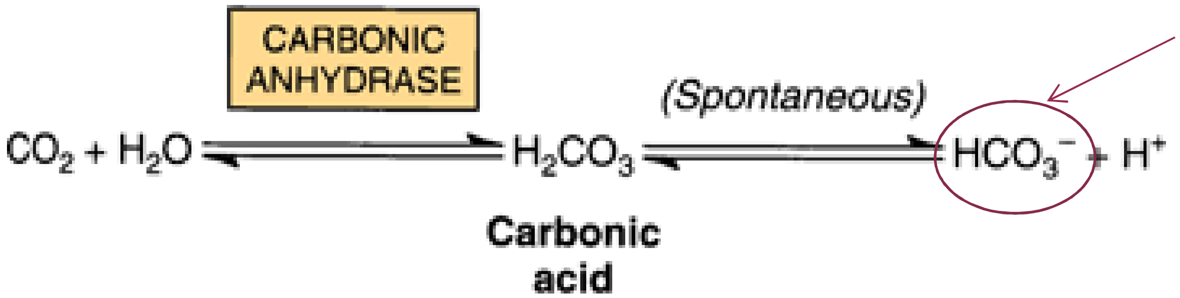
- all subunits of deoxyHb are in T structure
- successive O_2 binding makes R structure more probable
- first molecule O_2 binds to T structure, and fourth molecule to R structure

Hemoglobin transports CO_2 and protons to the lungs



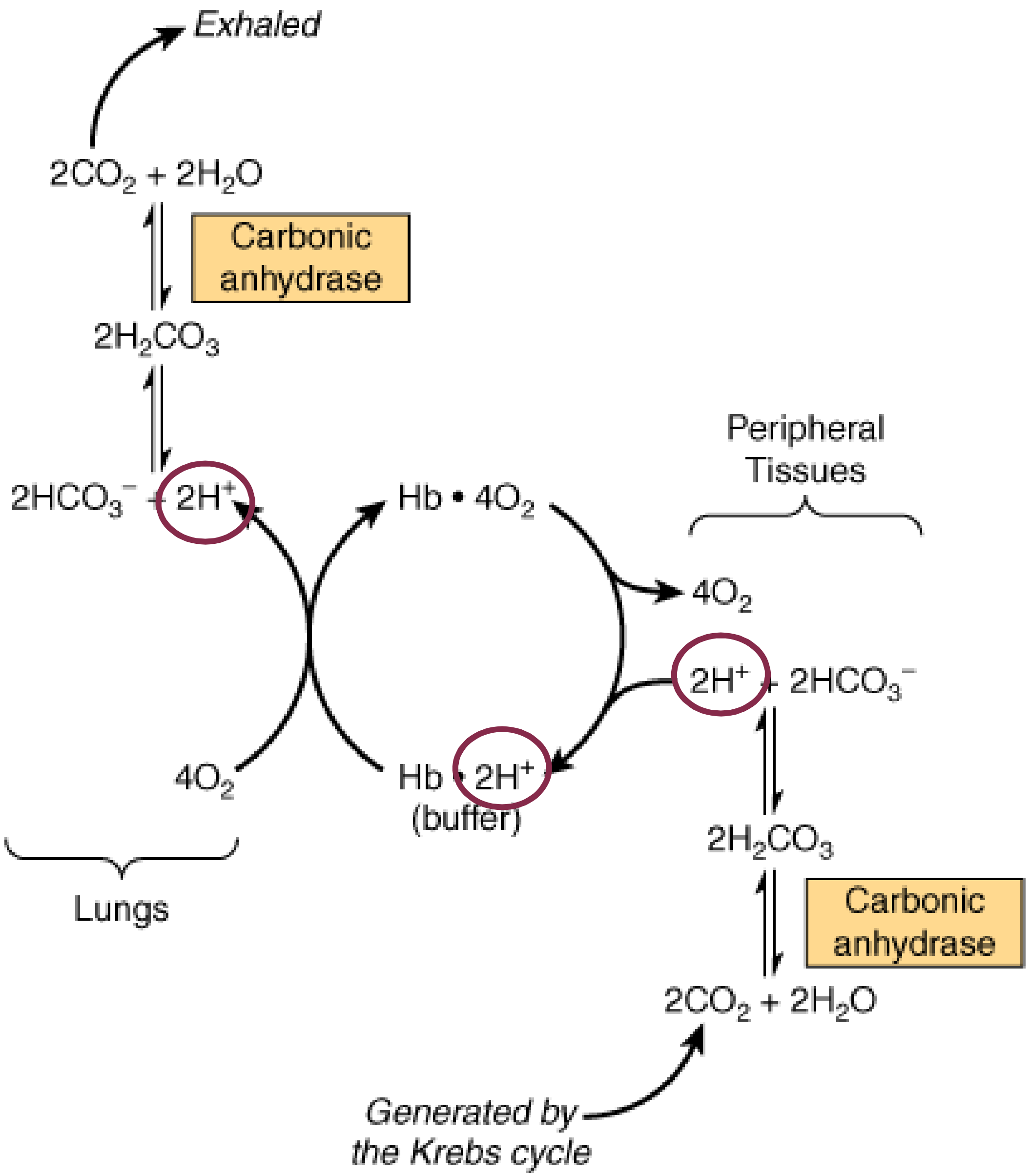
CARBAMATE

- + to –
- salt bridge formation
- 15% CO_2 in venous blood



BICARBONATE

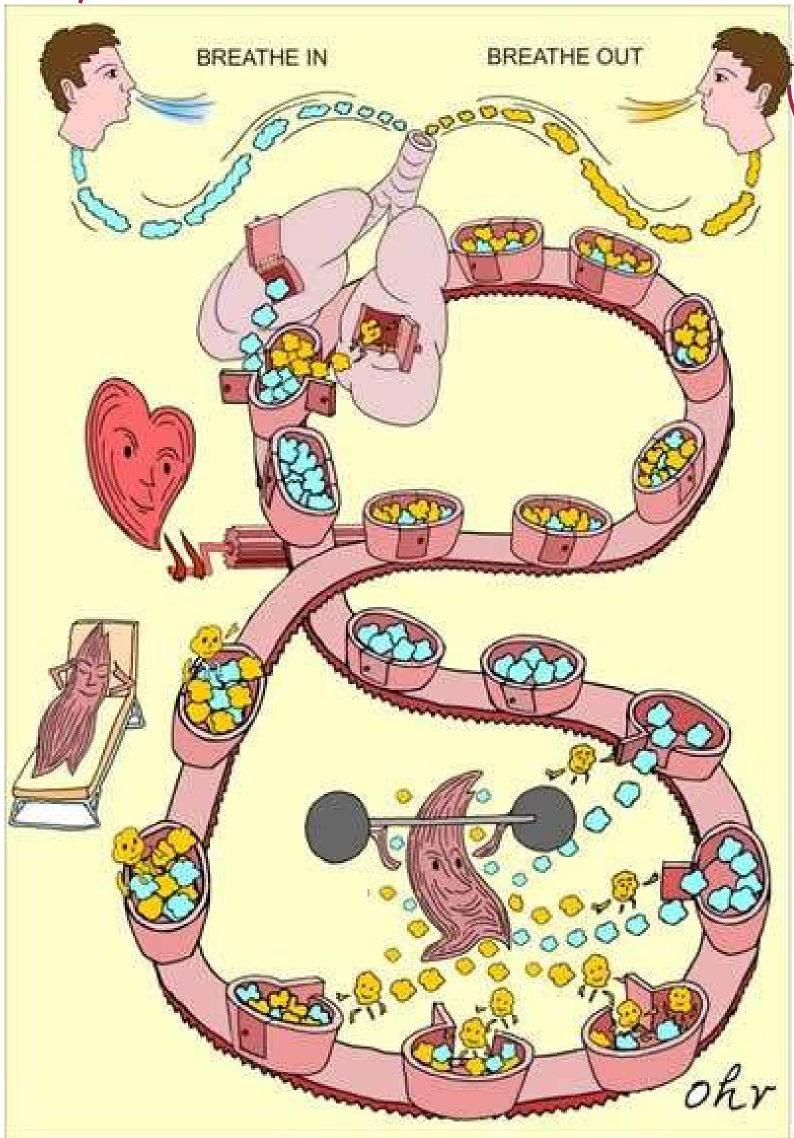
- ~80% CO_2 in venous blood

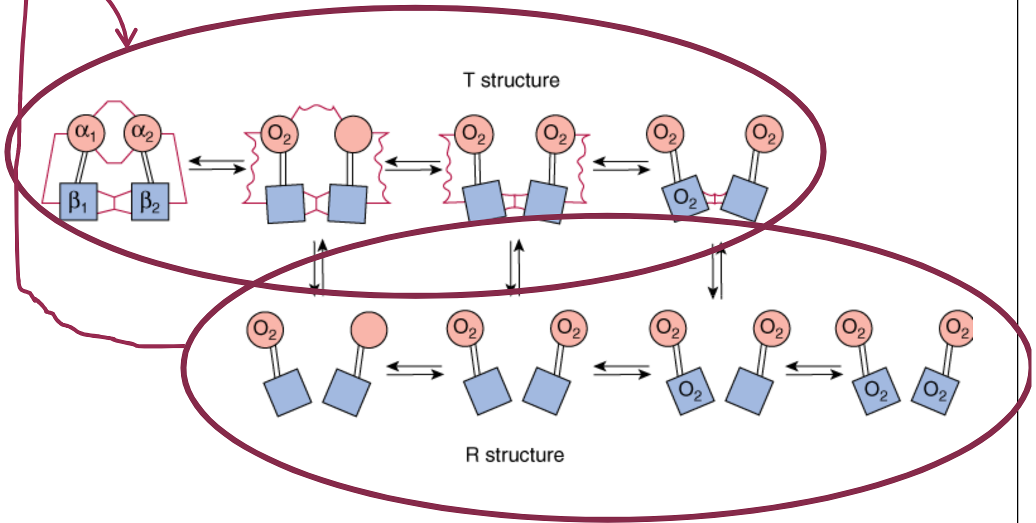


Bohr effect

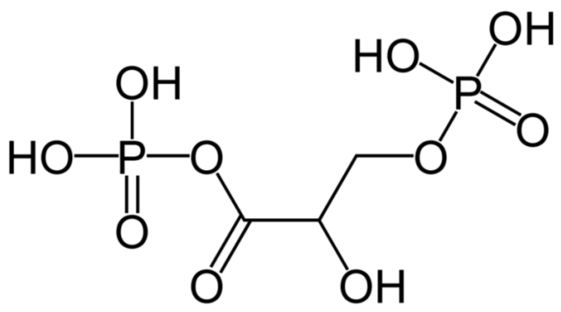
- Reciprocal coupling of proton and O_2 binding
- Mechanism of oxygen delivering to the cells according to their needs
- Metabolically active cells, which need lot of oxygen, produce lot of waste products: H^+ and CO_2

Bohr effect

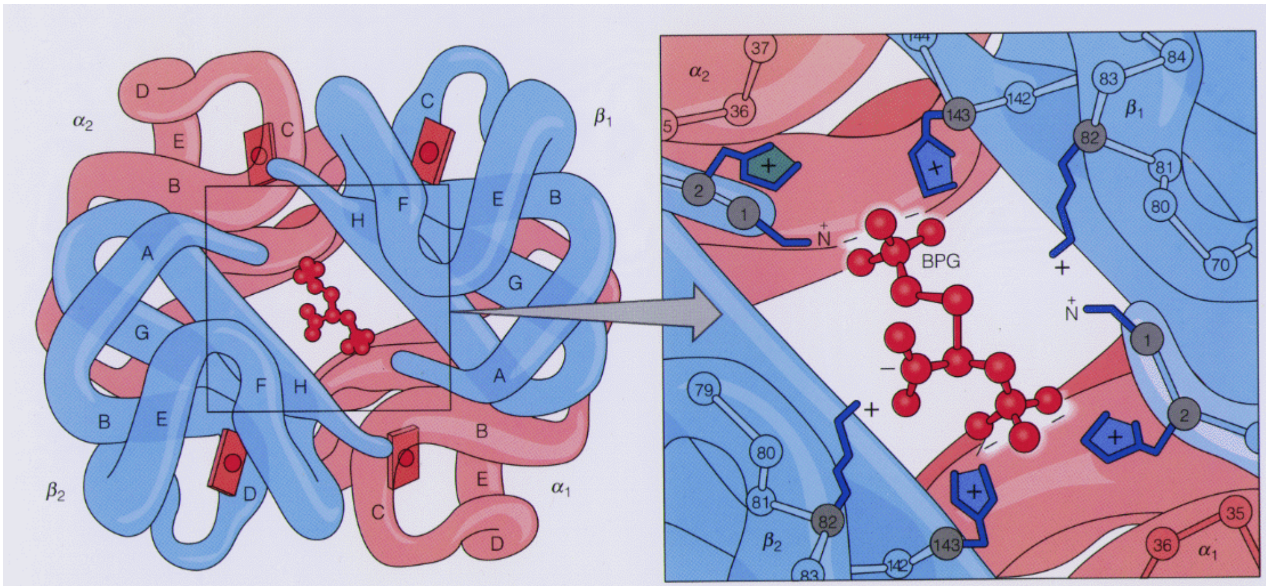

BREATHE IN
BREATHE OUT
ohr


T structure
α_1
α_2
β_1
β_2
O_2
R structure

2,3- bisphosphoglycerate (BPG) stabilizes the T structure of hemoglobin

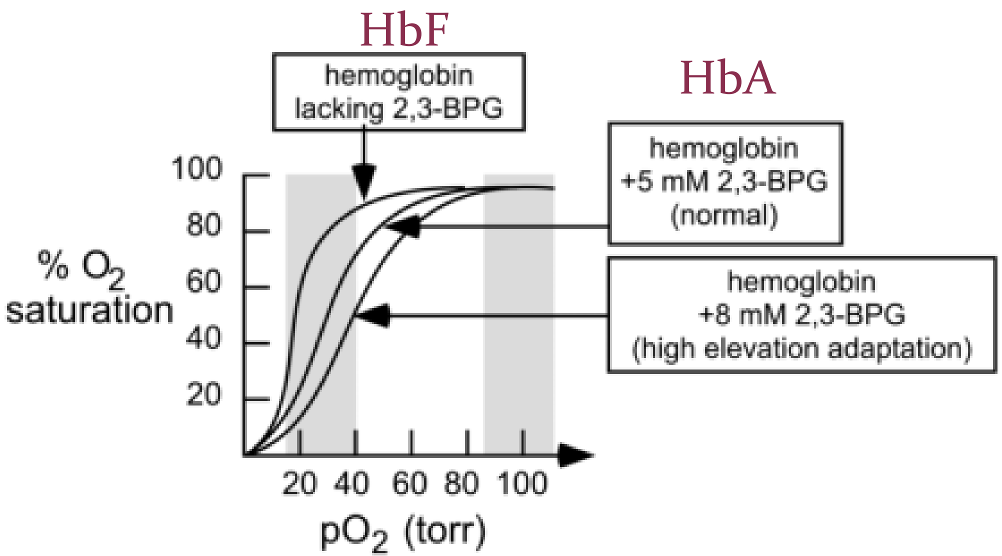


- BPG forms salt bridges with the terminal amino groups of β chains
- BPG binds more weakly to HbF than to HbA → HbF having a higher affinity for O_2 than HbA.



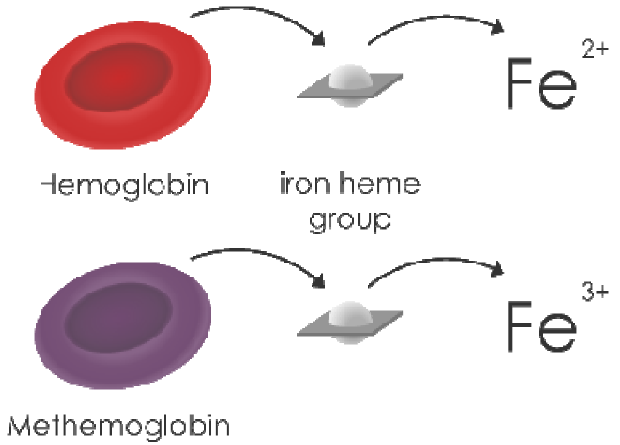
Adaptation to high altitude

- increased number of erythrocytes
- increased concentration of Hb and BPG

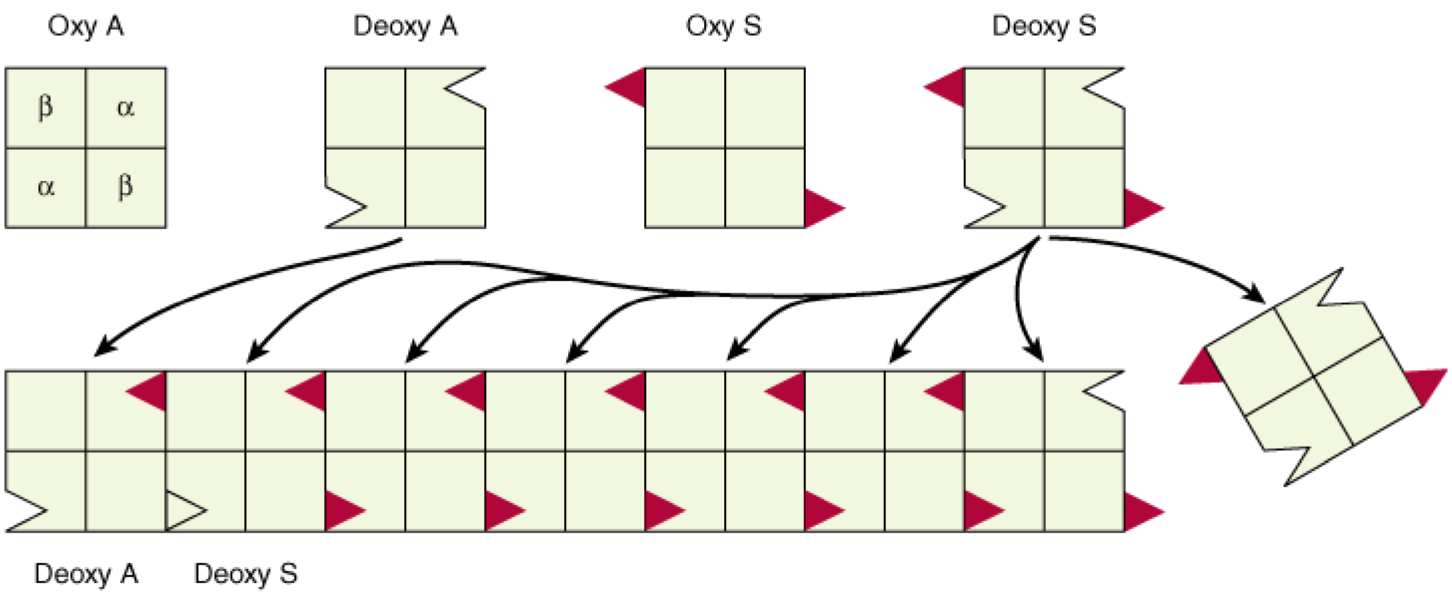


Methemoglobin

- Heme iron is ferric (Fe^{3+}) rather than ferrous (Fe^{2+})
- Fe^{3+} doesn't bind O_2
- is coordinated by H_2O molecule on 6th coordination site
- Causes the brown color of dried blood or old meat
- Enzyme methemoglobin reductase reduces the Fe^{3+} of methemoglobin to Fe^{2+}
- The resulting tissue hypoxia leads to **polycythemia,** an increased concentration of erythrocytes



Hemoglobin S – sickle cell anemia



Biomedical implications of Hb

- Myoglobinuria - myoglobin in urine
- Anemia - reduction in the number of red blood cells or of hemoglobin in the blood
- Thalassemia - partial or total absence of one or more or chains of hemoglobin
- Glycated Hemoglobin (HbA_{1c})