M.SC Semester III
Core Course XI
Bio-InorganicChemistry

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TOPIC:-Unit III Oxygen Transport

PROPERTIES OF O_2

- pO_2 at 1 atmosphere = 150-160 mmHg

- pO_{2max} of arterial blood is 100 mmHg (= 0.13mmol/L dissolved O_2)

- Limited solubility in aqueous solutions

- Transported in blood in complex with hemoglobin, which results in an ~60-hold increase in the O_2 content of blood (8.6 mmol/L)

- Stored in skeletal and striated muscle in complex with myoglobin (in the cytoplasm)

Delivered as needed to the mitochondria for electron transport

Heme

- Incorporated into proteins during synthesis

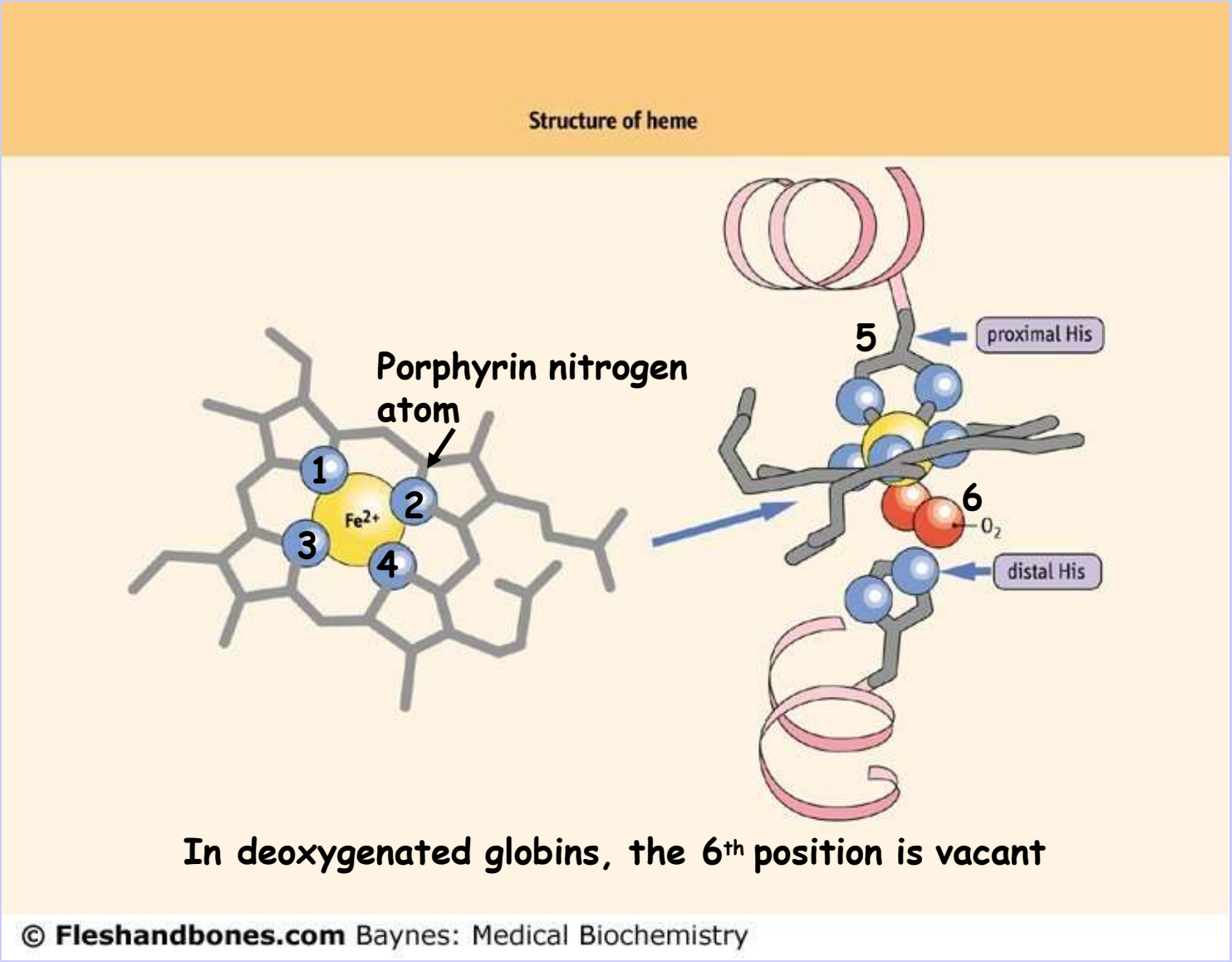
- Stabilized by hydrophobic residues found in interior of the protein: protective environment that prevents oxidation of Fe^{2+} to Fe^{3+} or "rusting". In this state it can not react with O_2.

- Iron is normally chelated by 6 atoms: 4 N atoms in the porphyrin ring; and two histidines in the heme binding pocket

    *Proximal histidine has an imidazole nitrogen that is close enough to bond directly to the Fe^{2+} atom

    *Distal histidine is important for allowing binding of Oto the Fe^{2+} atom

Heme (cont.)


Structure of heme
Porphyrin nitrogen atom
1
2
3
4
Fe^{2+}
5
proximal His
6
O_2
distal His
In deoxygenated globins, the 6th position is vacant
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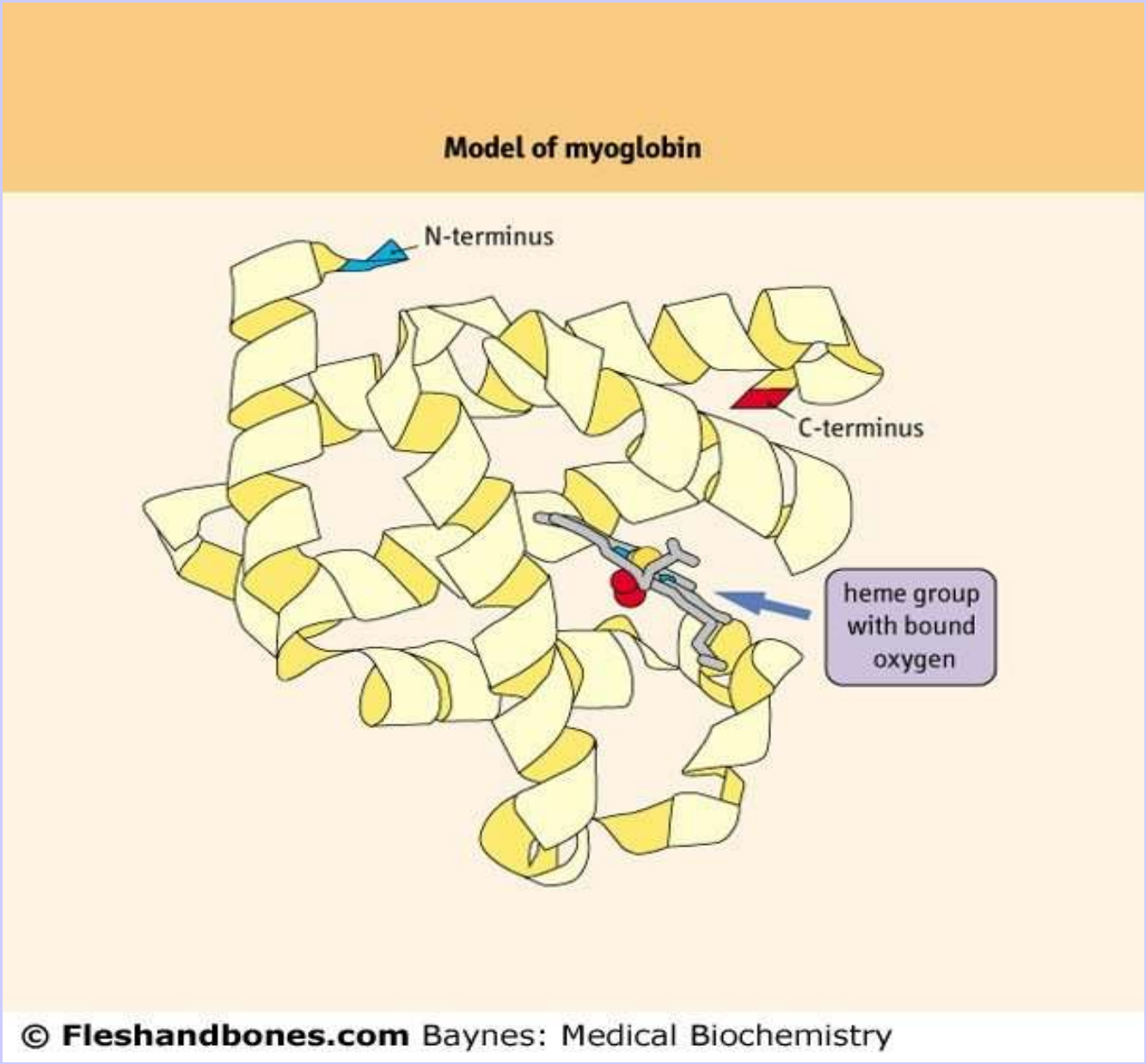
CHARACTERISTICS OF GLOBIN PROTEINS

- Single polypeptide chain of ~150 amino acids
- High proportion of α-helix: 75% of the amino acids are associated with 8 α-helices
- α-helices are organized into a tightly packed, nearly spherical, globular tertiary structure
- Highly soluble: polar amino acids on the exterior surface of the protein
- Each globin contains one noncovalently bound heme group

Myoglobin


Model of myoglobin
N-terminus
C-terminus
heme group with bound oxygen
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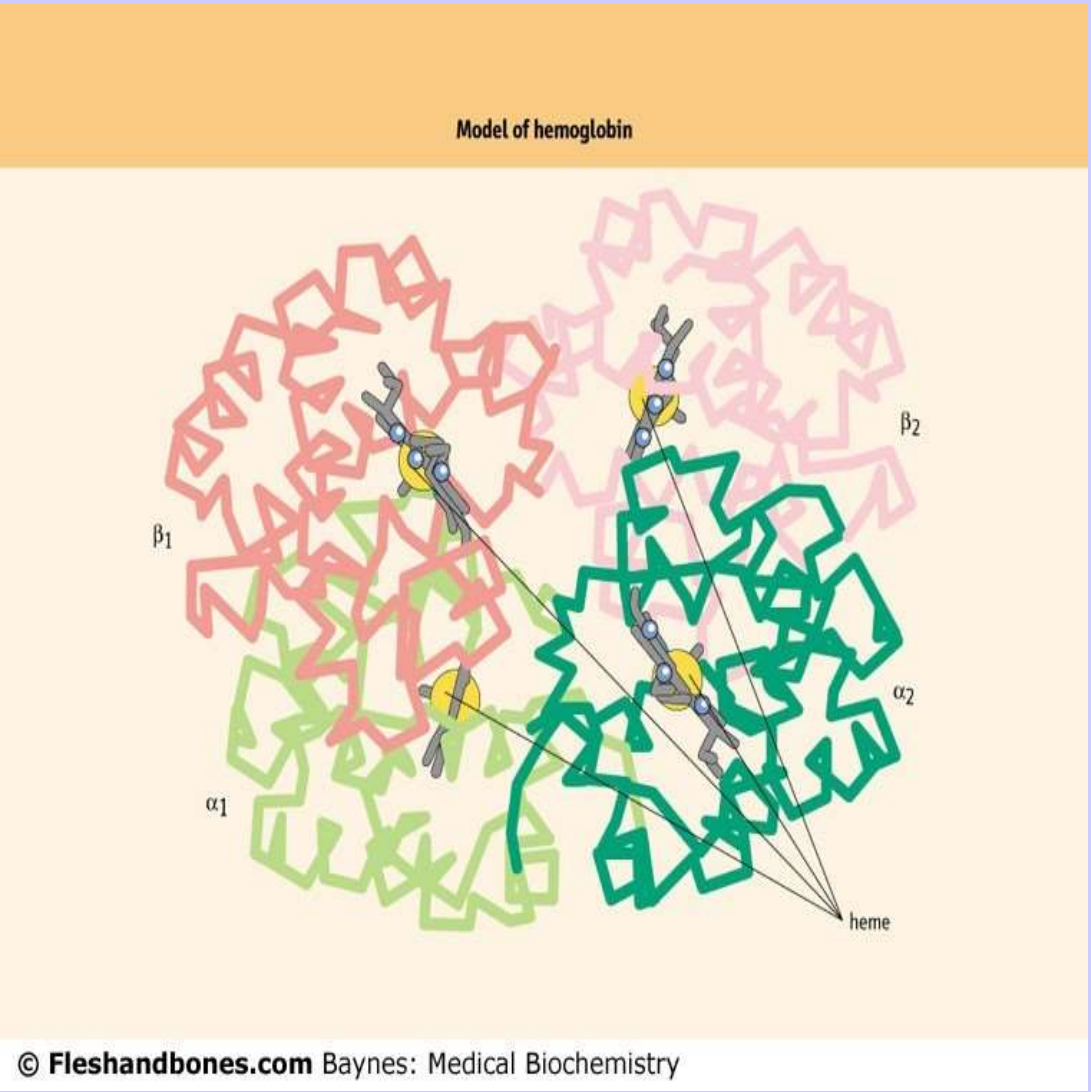
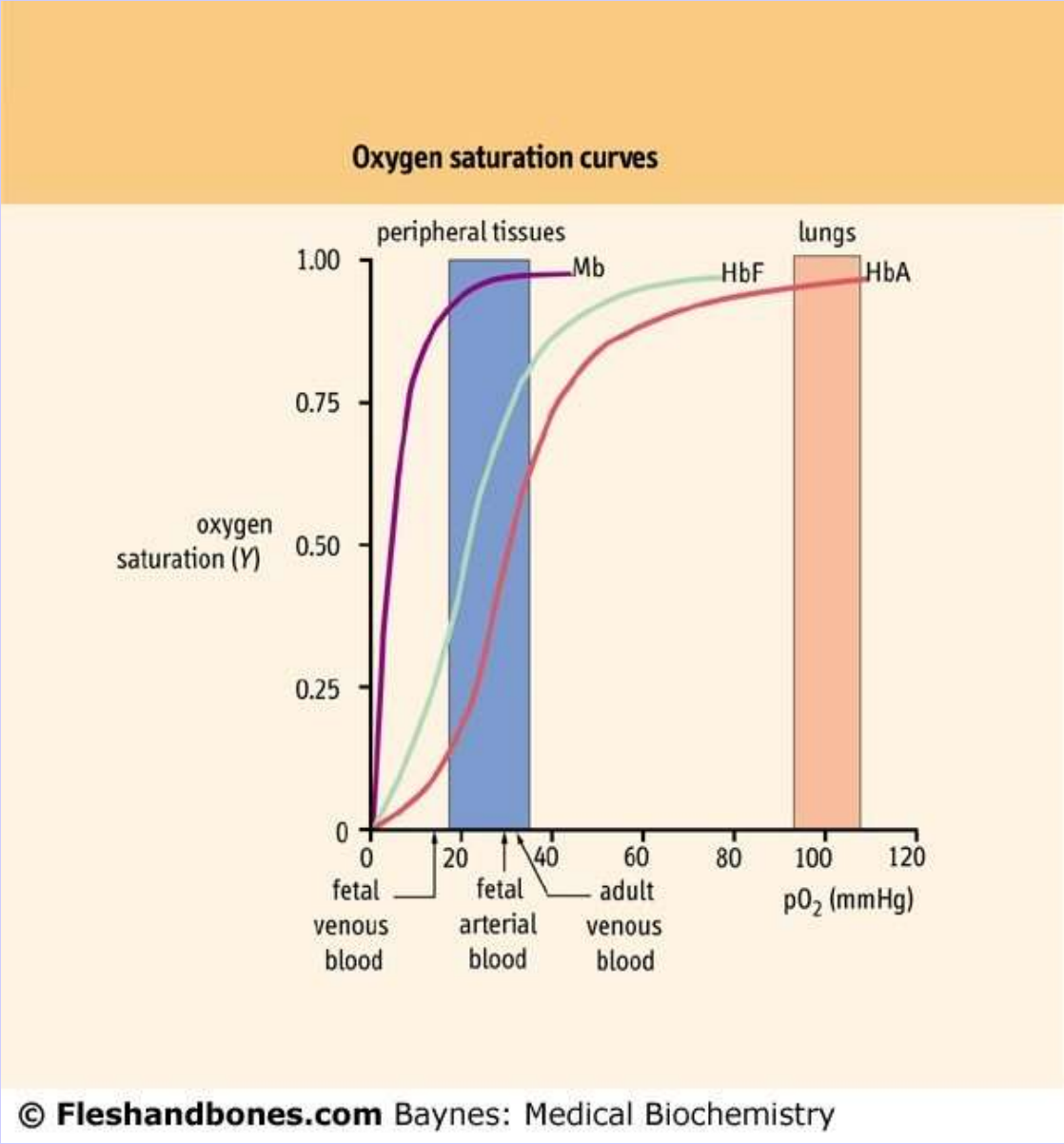
Hemoglobin



- Synthesized in RBC precursor cells: reticulocytes and erythroblasts
- Synthesis is tightly controlled and dictated by the concentration of heme
- Tetramer of 2 α-globin and 2 β-globin chains
- Best described as a dimer of the heterodimer ($\alpha\beta$)

INTERACTIONS WITH O_2



*Can bind up to 4 O_2 molecules

*Binding of O_2 is cooperative: the binding of 1 O_2 influences the binding of another

DEOXYGENATED VS. OXYGENATED HEMOGLOBIN

- As deoxygenated hemoglobin becomes oxygenated, significant structural changes take place
  - the proximal hisitidine and its helix shift
  - one heterodimer rotates and slides relative to the other
  - existing noncovalent bonds are broken and replaced by new ones

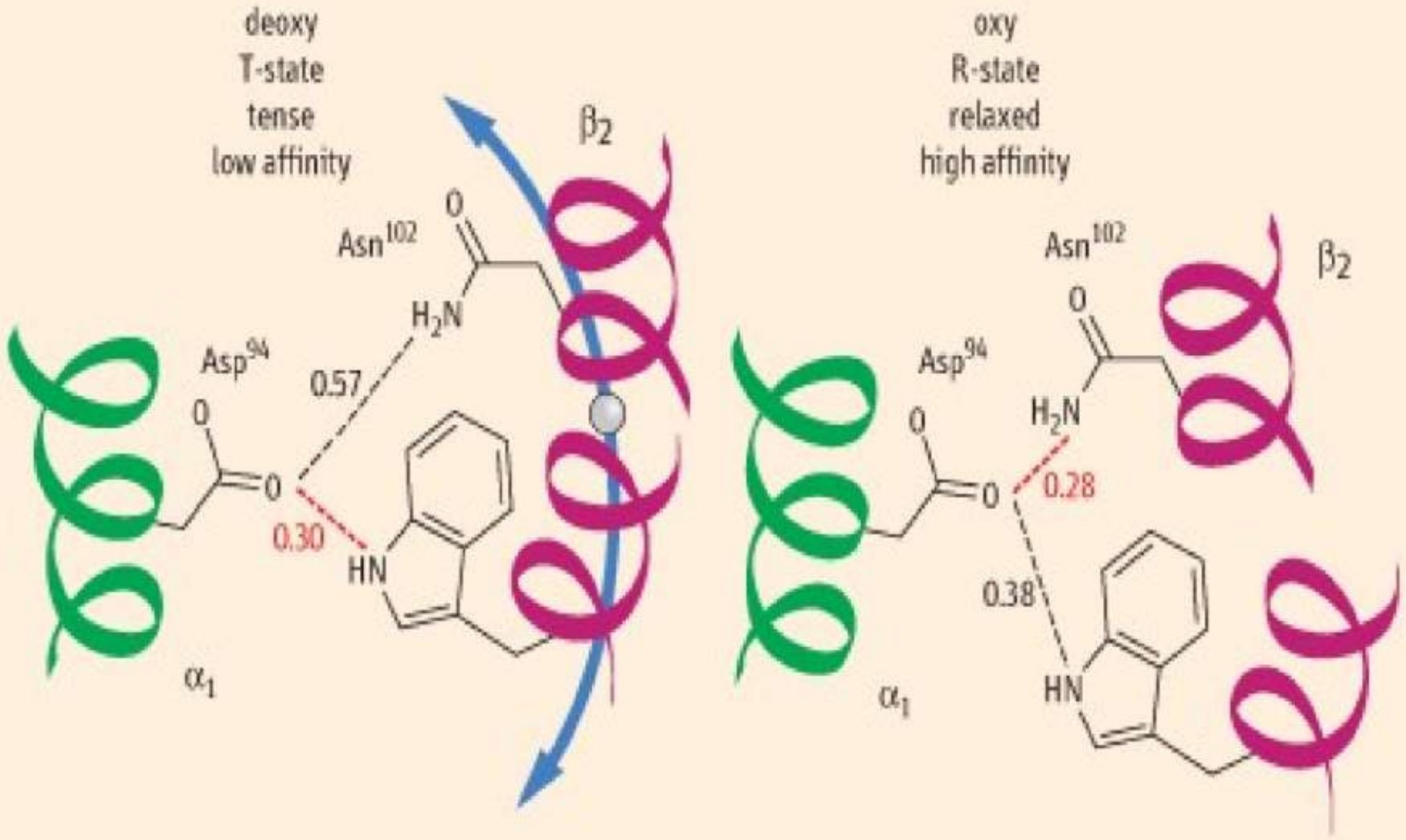
- Approximately 30 amino acids participate in the noncovalent (hydrogen and/or electrostatic) interactions between the 2 heterodimers

- Interactions between the two heterodimers are stronger in the T (tense)-state = deoxygenated hemoglobin

- These interactions are weaker in the R (relaxed)-state = oxygenated hemoglobin

- The R-state has a higher affinity for O_2 than the T-state

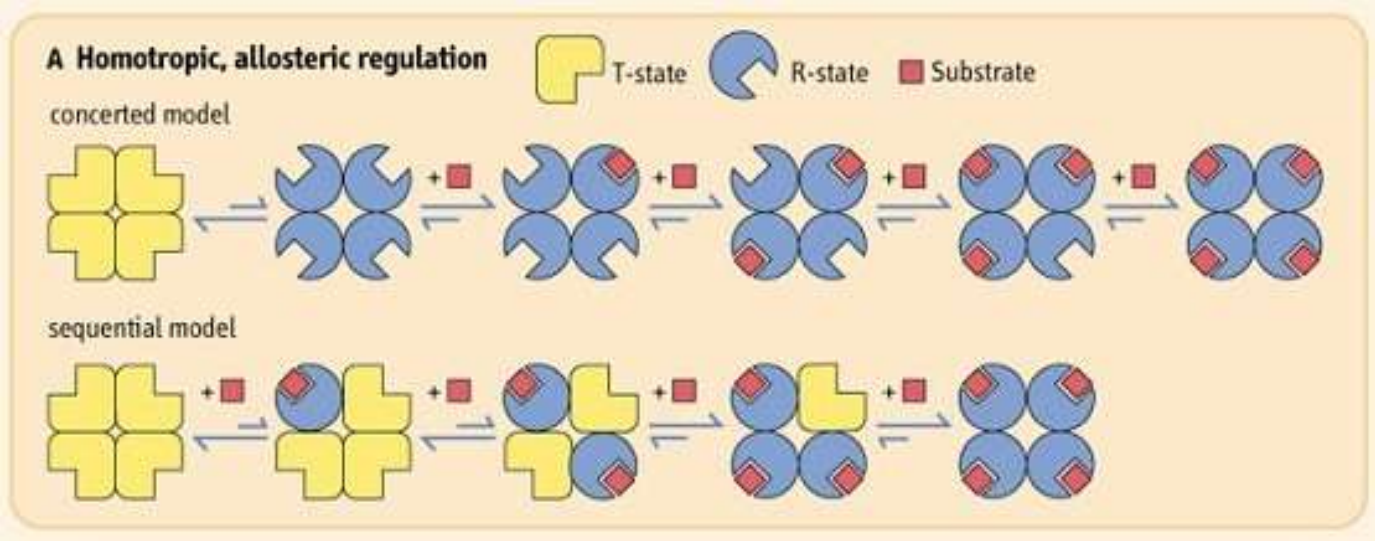
Differences between deoxygenated and oxygenated hemoglobin



DEOXYGENATED VS. OXYGENATED HEMOGLOBIN (CONT.)

- The transition of hemoglobin from the T- to the R-state is not well-defined

- Best explained as a combination of a sequential and a concerted model



- It is unknown whether the α and β subunits differ in O_2 affinity and which subunit binds to (or releases) O_2 first.

INTERACTIONS WITH ALLLOSTERIC EFFECTORS

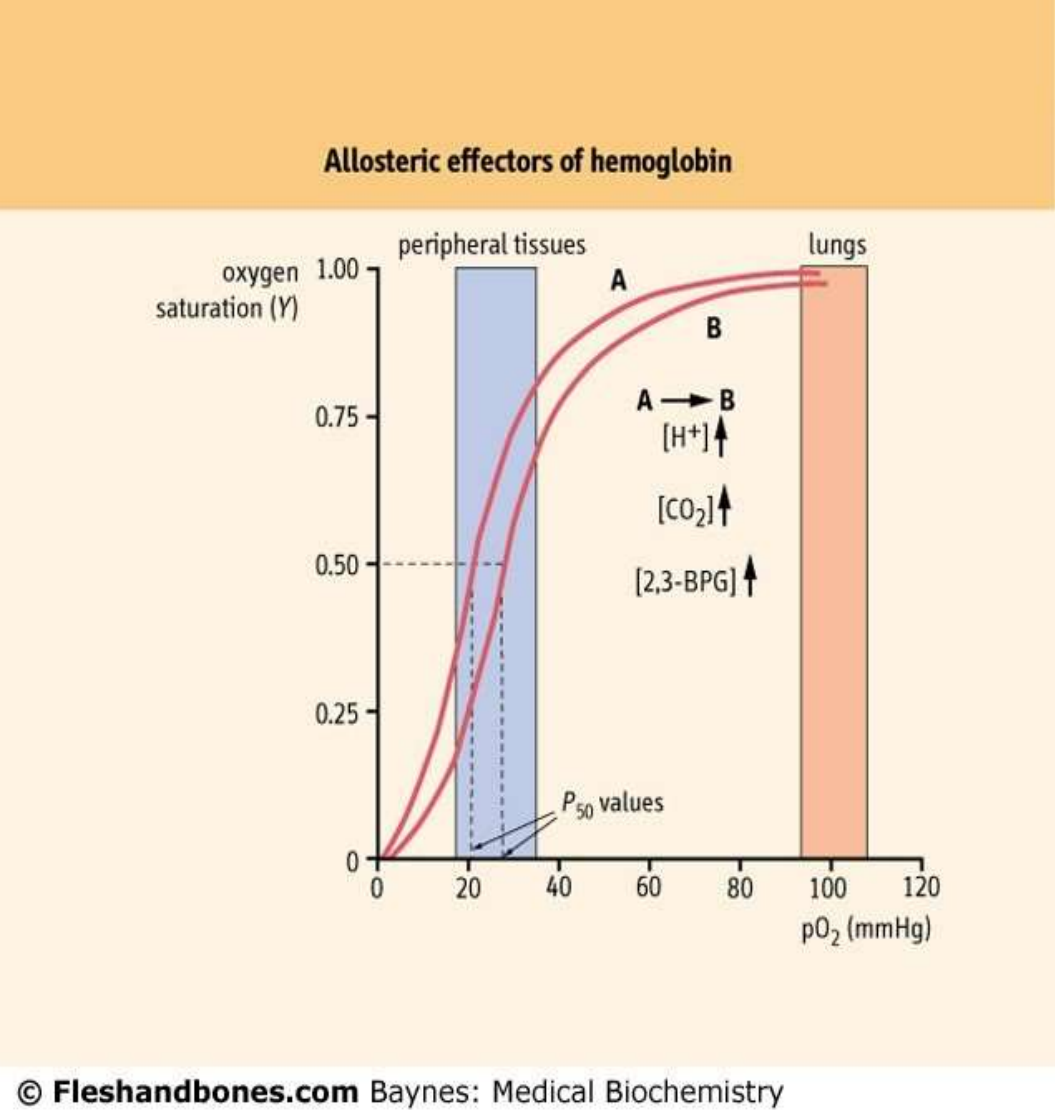
- Allosteric proteins are typically multisubunit proteins

- Small molecules know as allosteric effectors bind to the protein at sites that are spatially distinct from the ligand binding site and exert either a positive or negative effect on ligand binding

- These effects are accompanied by changes in tertiary and/or quaternary structure

- Hemoglobin is modified negatively (i.e. decreased affinity for O_2) by a number of allosteric effectors including H^+, CO_2 and 2,3-bisphosphoglycerate (2,3-BPG)

INTERACTIONS WITH ALLLOSTERIC EFFECTORS (CONT.)



- As the curve shifts from A to B the affinity for O_2 decreases
- The effects of these molecules appears to be additive
- Increasing temperature will also shift the curve to the right

Effect of CO_2: increased pCO_2 in venous capillaries decreases the affinity for O_2

1. CO_2 reacts reversibly with the unprotonated N-terminal amino groups of the globin polypeptides to form carbamino-hemoglobin

2. In peripheral tissues, carbamination (H_2CO_3) followed by hydration/dissociation ($H^+ + HCO_3^-$) generates additional protons available to participate in the Bohr Effect and facilitate CO_2-O_2 exchange (more O_2 can be released)

- Shifts the equilibrium towards the T-state thereby promoting the dissociation of O_2

Working Muscles…

Produce H^+ and CO_2 via aerobic metabolism and liberate heat

As the binding of O_2 is exothermic, affinity of O_2 decreases as temperature increases

More efficient release of O_2 to the surrounding tissue

Transport and Removal of CO_2

- Blood transports two forms of CO_2 to the lungs: carbamino-hemoglobin and H_2CO_3/HCO_3^- (carbonic acid-conjugate base pair)

1. Carbamino-hemoglobin: exposure to low pCO_2 results in the reversal of the carbamination reaction by mass action and O_2 binding is again favored. CO_2 is expelled by the lungs.

2. H_2CO_3/HCO_3^-: in the pulmonary capillaries RBC carbonic anhydrase converts H_2CO_3 into CO_2 and H_20, which are expelled in their gaseous forms into the atmosphere

Effect of 2,3-Bisphosphoglycerate

- Byproduct of anaerobic glycolysis in the RBC

- It is found at high concentrations (~4-5 mM) in RBCs nearly equal to the concentration of hemoglobin

- Reacts with only deoxygenated hemoglobin in a positively charged cavity where the two β-subunits juxtapose - stabilizes the T-state

- Its concentration is responsive to various physiological and pathological conditions.

  For example, when pO_2 is decreased, as in chronic tissue deprivation of O_2, the level of 2,3-BPG increases. This results in a stabilization of the T-state and further rightward shift of the curve facilitating O_2 release to the deprived tissues.

- Usually the rightward shift of the O_2 saturation curve has an insignificant effect on the O_2 saturation in the lungs

CARBON MONOXIDE (CO) POISONING

- Affinity of globin bound heme for *CO* is 10^4 times more then that for O_2; thus, it will bind preferentially

- Like O_2, it binds to the 6^{th} position if the heme iron

- Bound *CO* allosterically activates hemoglobin (shifts O_2 saturation curve to the left)

- Hemoglobin becomes trapped in the R-state

- Any O_2 already bound cannot be released so its transport to tissues becomes seriously compromised

- Prolonged exposure would be virtually irreversible ($t_{1/2}$ = 4-5 hr) and leads to highly toxic levels of carboxyhemoglobin

- Hyperbaric O_2 therapy (administration of 100% O_2) is used to treat *CO* poisoning

- This results in arterial and tissue pO_2 of 2000 and 4000 mmHg, respectively, displacing the bound *CO*, and resulting in a reduction in the $t_{1/2}$ to less then 20 min