Chapter 7

Heme proteins

Cooperativity

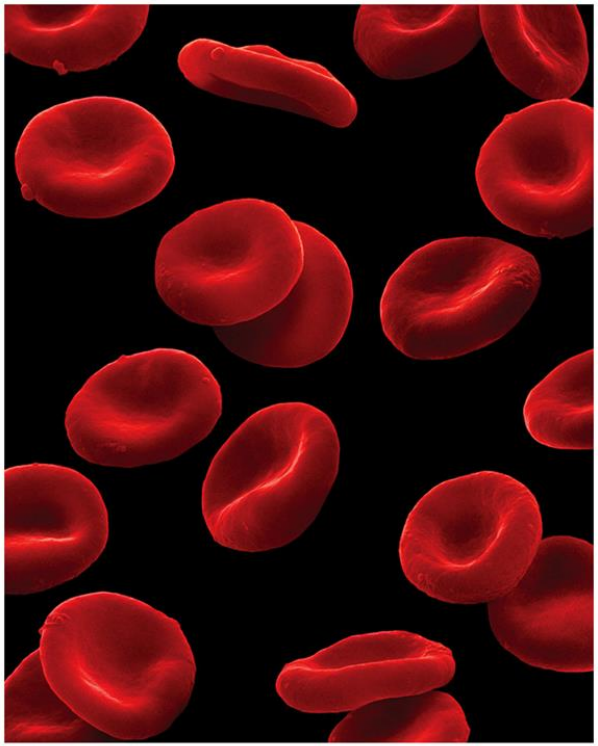
Bohr effect

Hemoglobin is a red blood cell protein that transports oxygen from the lungs to the tissues.

Hemoglobin is an allosteric protein that displays cooperativity in oxygen binding and release.

Myoglobin binds oxygen in muscle cells. The binding of oxygen by myoglobin is not cooperative.

Oxygen binding is measured as a function of the partial pressure of oxygen (pO2).



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The ability of myoglobin and hemoglobin to bind oxygen depends on the presence of a heme group.

The heme group consists of an organic component called protoporphyrin and a central iron ion in the ferrous (Fe2+) form, the only form that can bind oxygen.

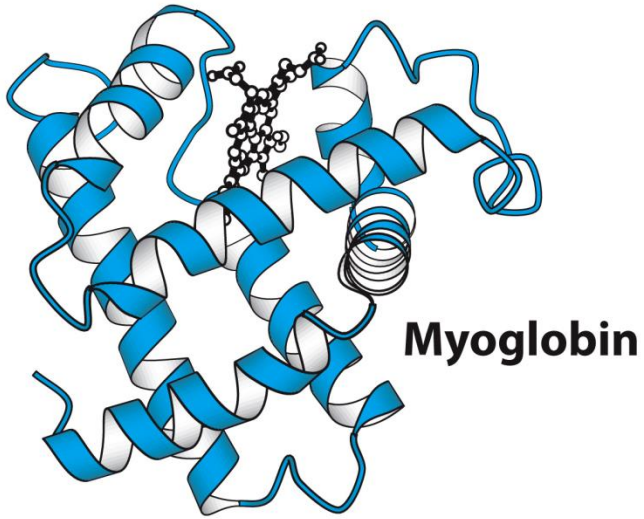
The iron lies in the middle of the protoporphyrin bound to four nitrogen atoms in porphyrin ring.

Iron can form two additional bonds, at the fifth and sixth coordination sites.

The fifth coordination site is occupied by an imidazole ring of a histidine called the proximal histidine.

The sixth coordination site binds oxygen.

Upon oxygen binding, the iron moves into the plane of the protoporphyrin ring.



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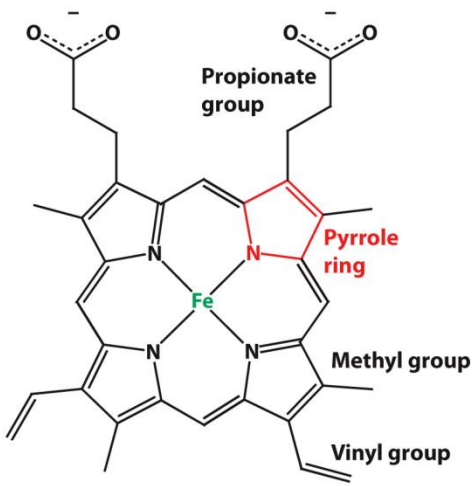

Heme
(Fe-protoporphyrin IX)

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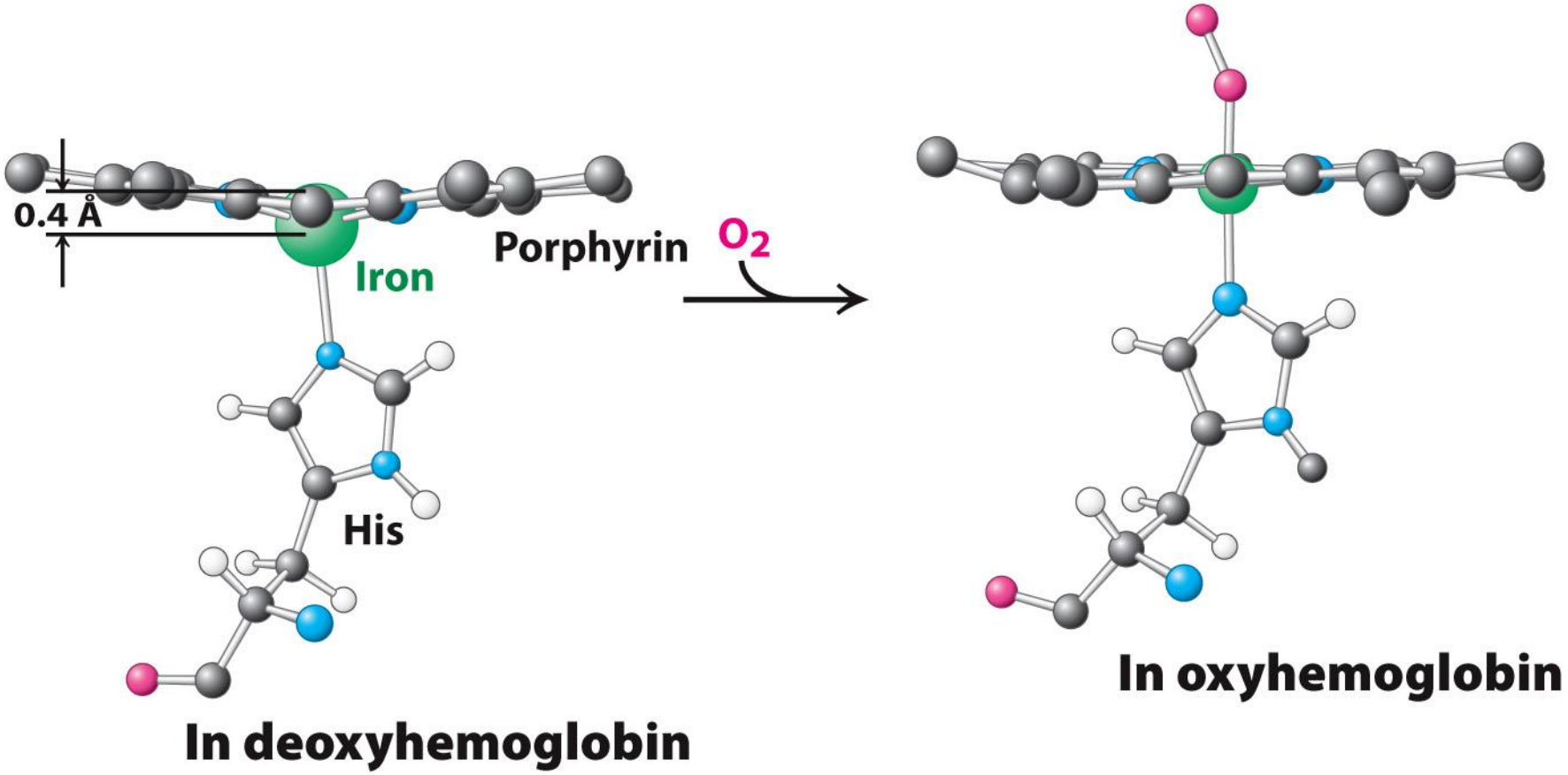

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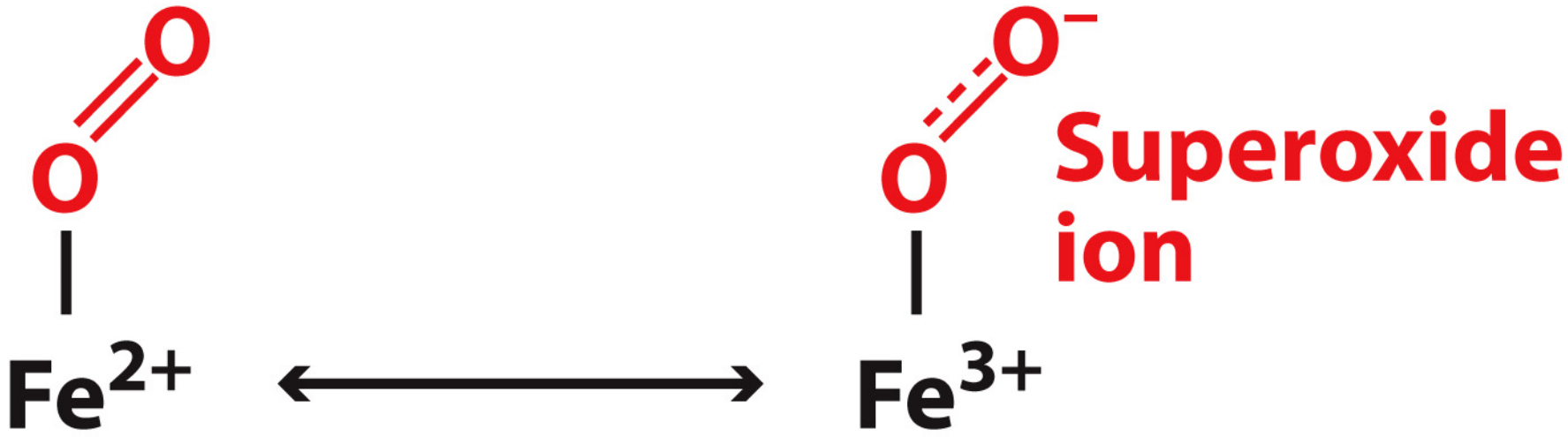
The interaction between iron and oxygen exists as resonance structures, one with Fe2+ and O2 and another with Fe3+ and superoxide ion (O2-).

Superoxide is very reactive, and should it leave the heme, ferric iron (Fe3+) would result. Heme with Fe3+ does not bind oxygen.

Myoglobin with iron in the Fe3+ state is called metmyoglobin.

The distal histidine of myoglobin prevents the release of superoxide ion.



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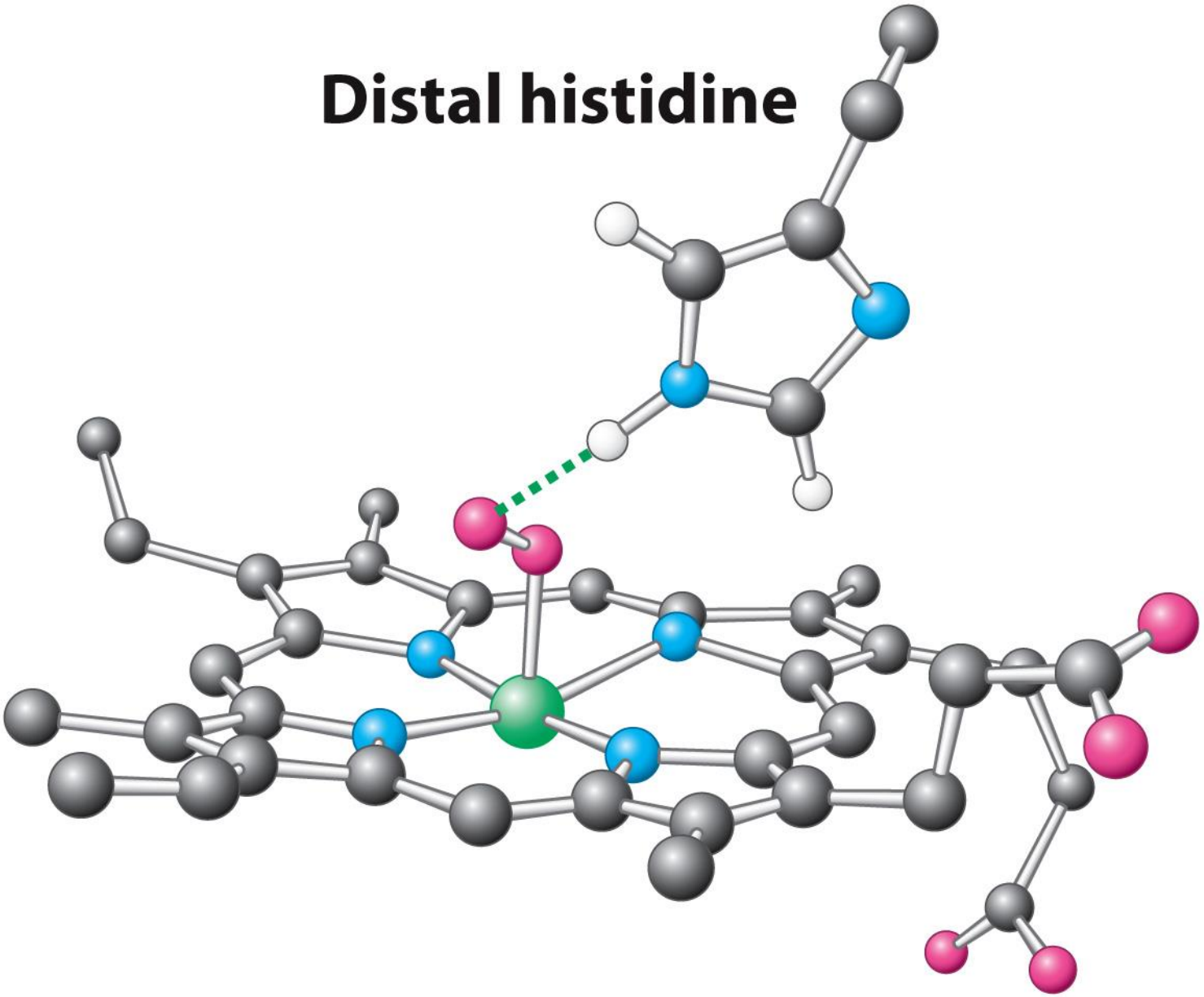

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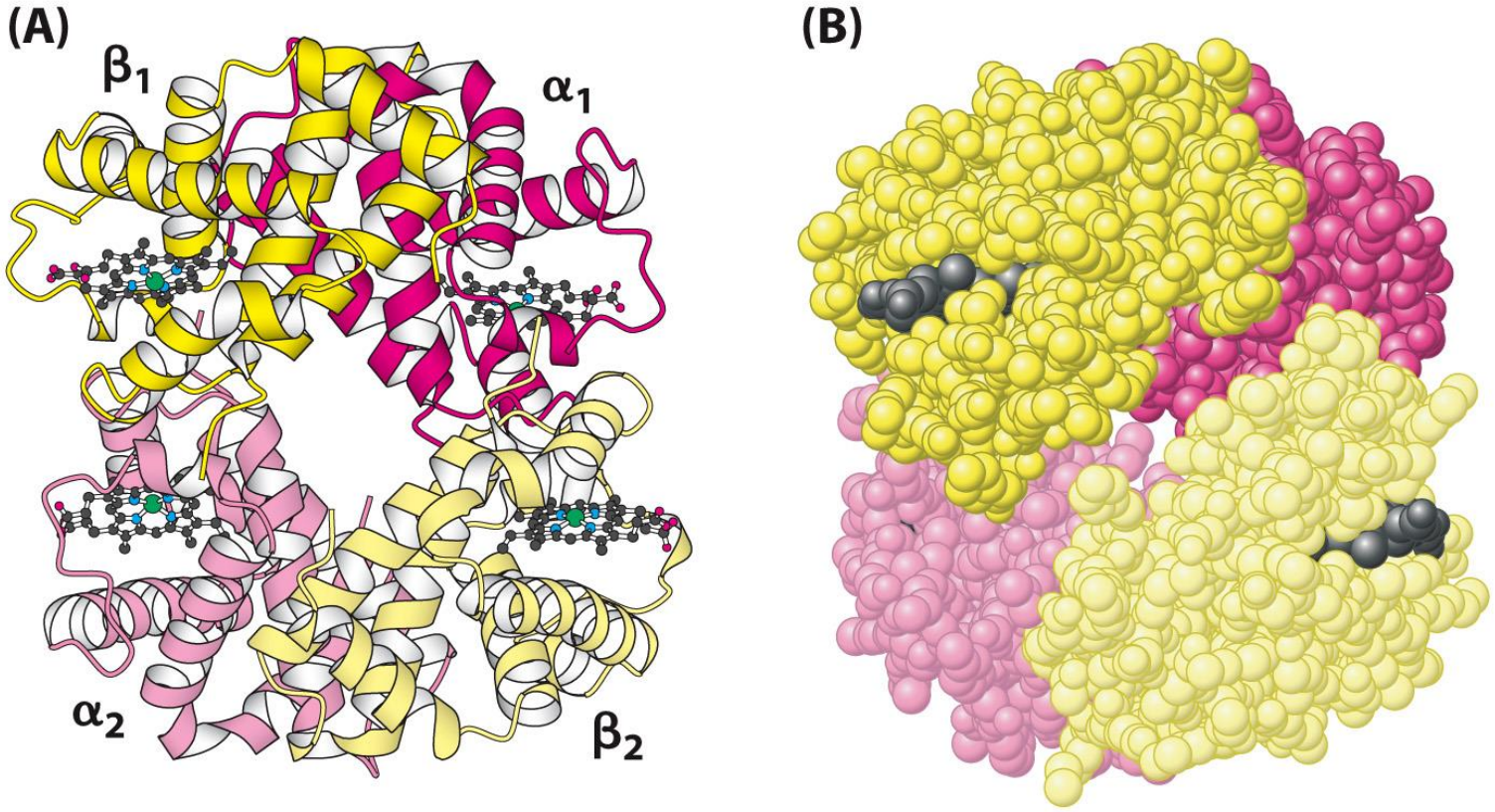
Hemoglobin consists of four chains, 2 identical α chains and 2 identical β chains.

Many of the helices in each subunit are arranged in a pattern also found in myoglobin, a structure called the globin fold.



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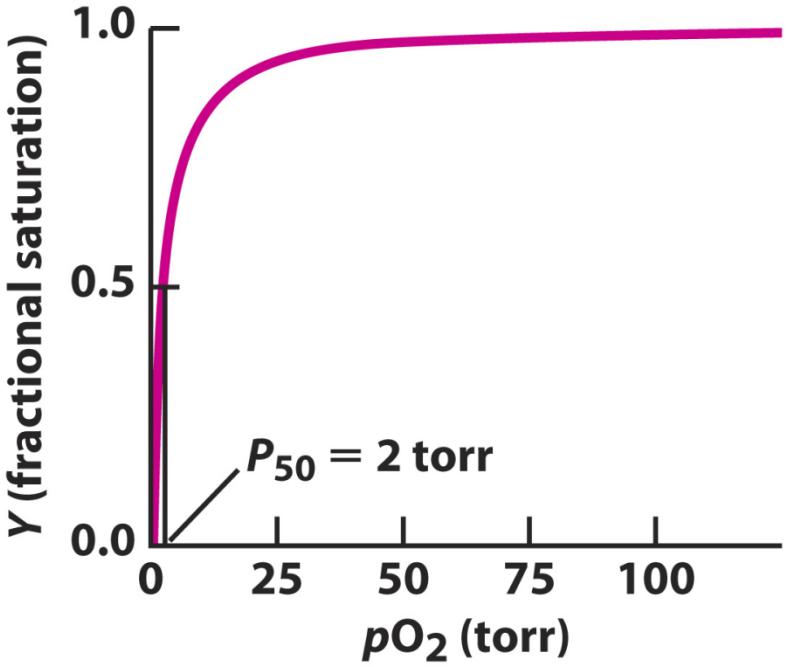
An oxygen binding curve is a plot of the fractional saturation versus the oxygen concentration, which is shown as partial pressure with the unit of torr.

Myoglobin displays a hyperbolic oxygen binding curve, while hemoglobin exhibits a sigmoid curve, indicating that O_2 binding and release is cooperative.

The cooperativity allows hemoglobin to bind oxygen in the lungs, where it is plentiful, and release oxygen at the tissues.



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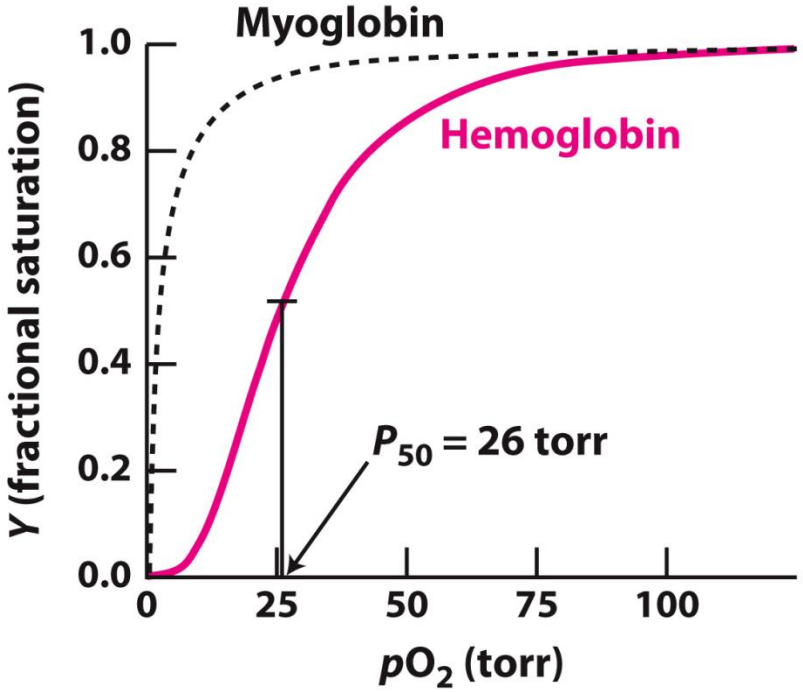

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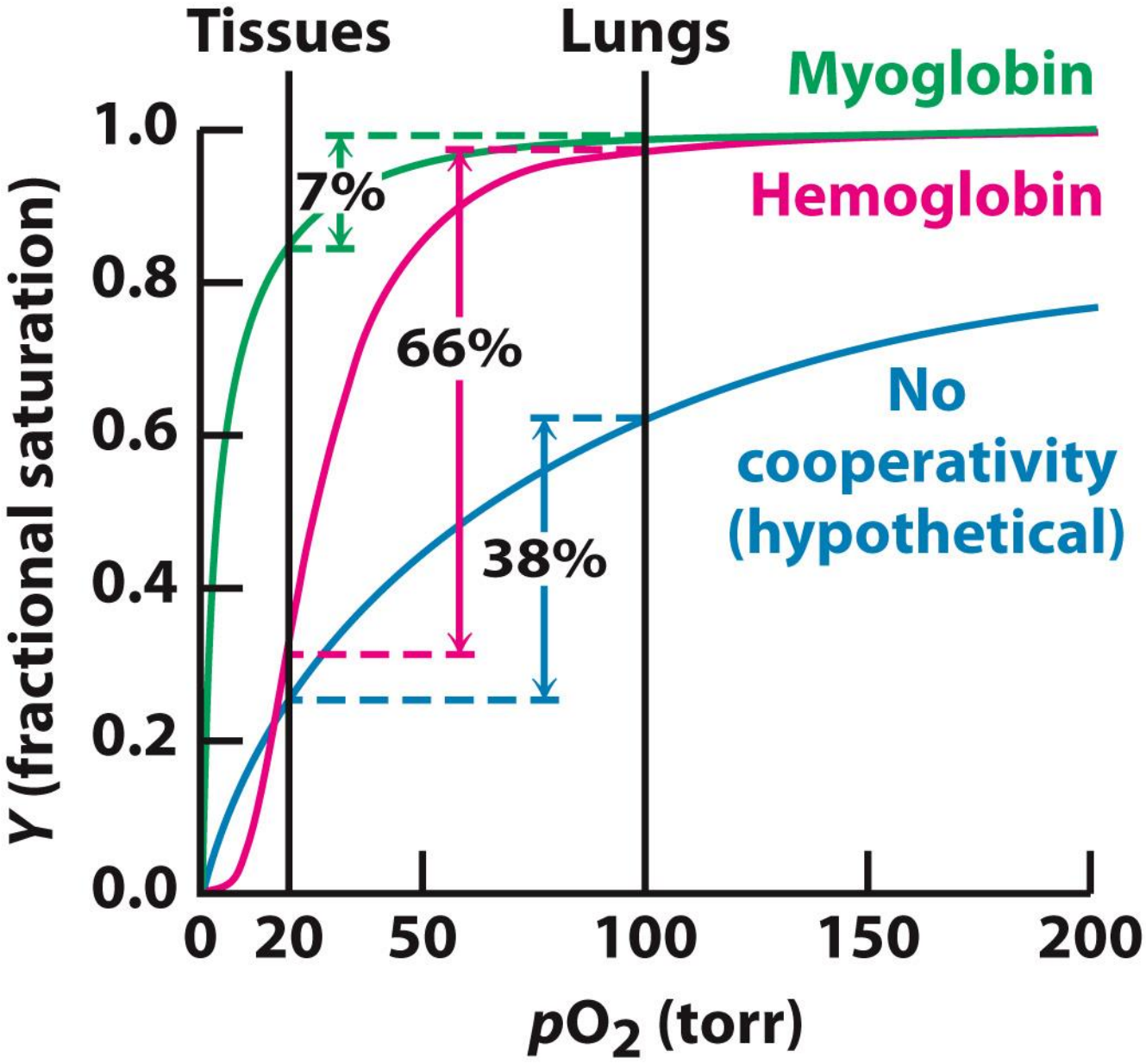

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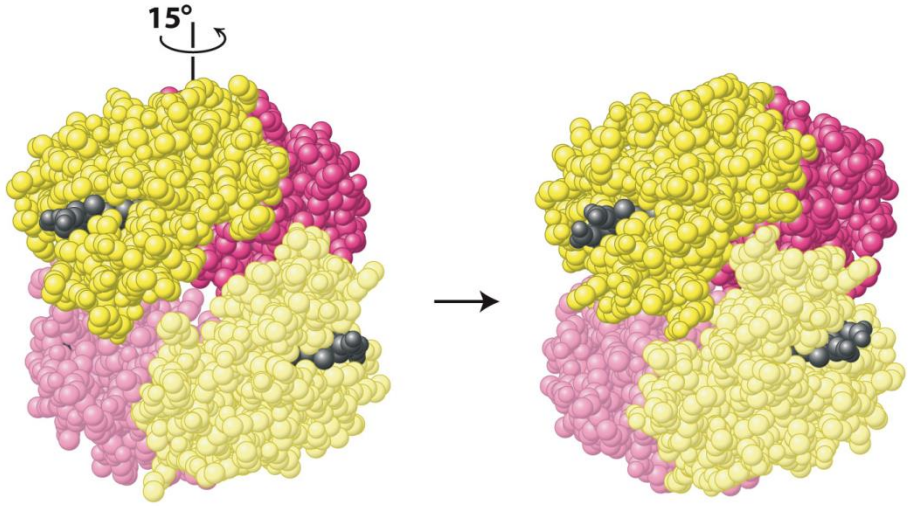
Cooperativity of oxygen binding

The quaternary structure of deoxyhemoglobin is referred to as the T state, while that of oxyhemoglobin is the R state.

The hemoglobin tetramer can be thought of as two αβ dimers. The α1β1 dimer rotates 15o relative to the α2β2 dimer on oxygen binding.

This structure alteration, conversion from the T state to the R state, facilitates oxygen binding.



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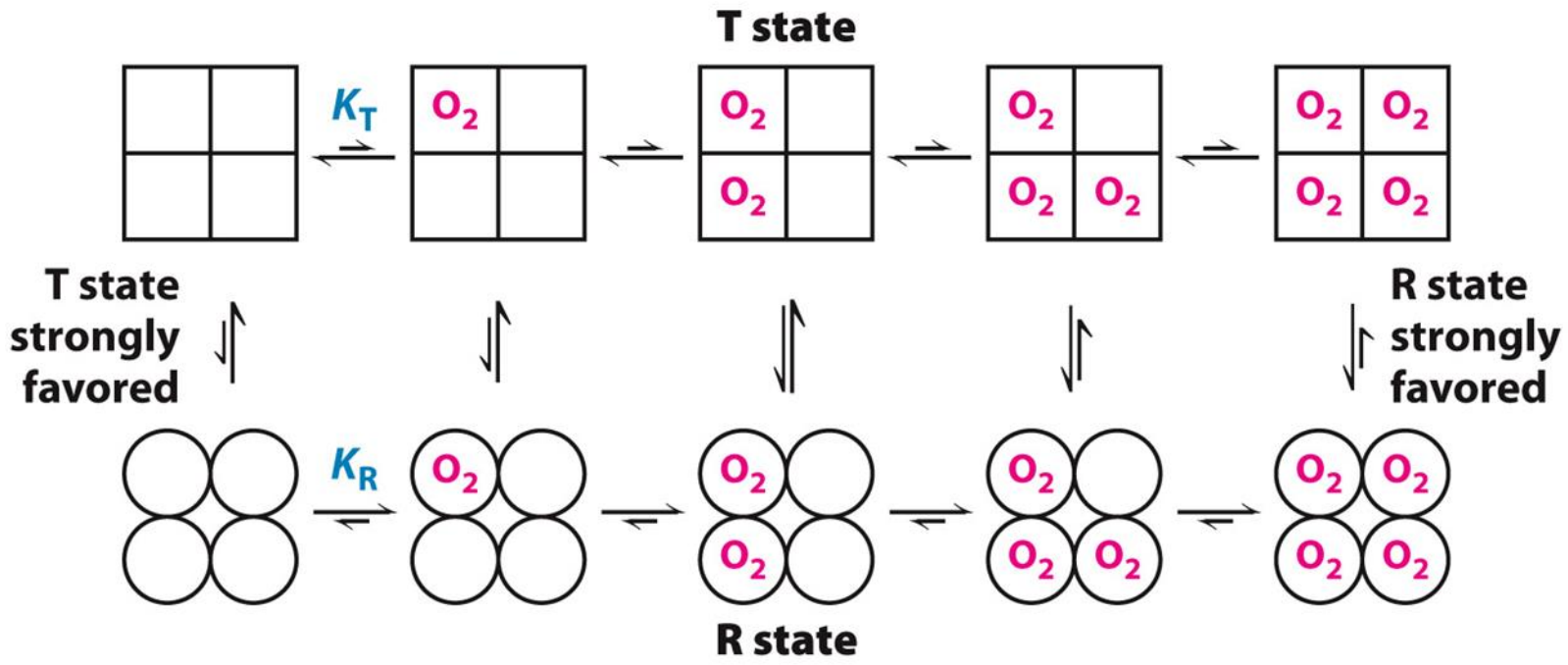
Models of cooperativity of oxygen binding to hemoglobin

Hemoglobin cooperativity incorporates aspects of both the concerted and sequential models of allostery.

It is sequential in that in hemoglobin with one O_2 bound, the remaining subunits are in the T state.

It is concerted in that in hemoglobin with three O_2 bound, the remaining subunit is in the R state.

Concerted model



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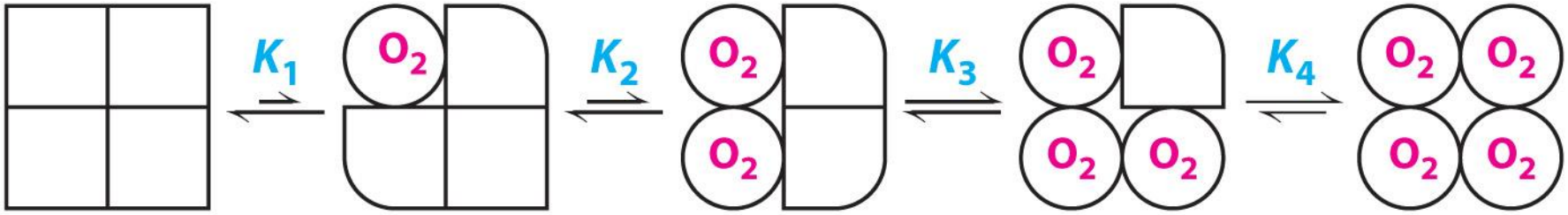
Sequential model



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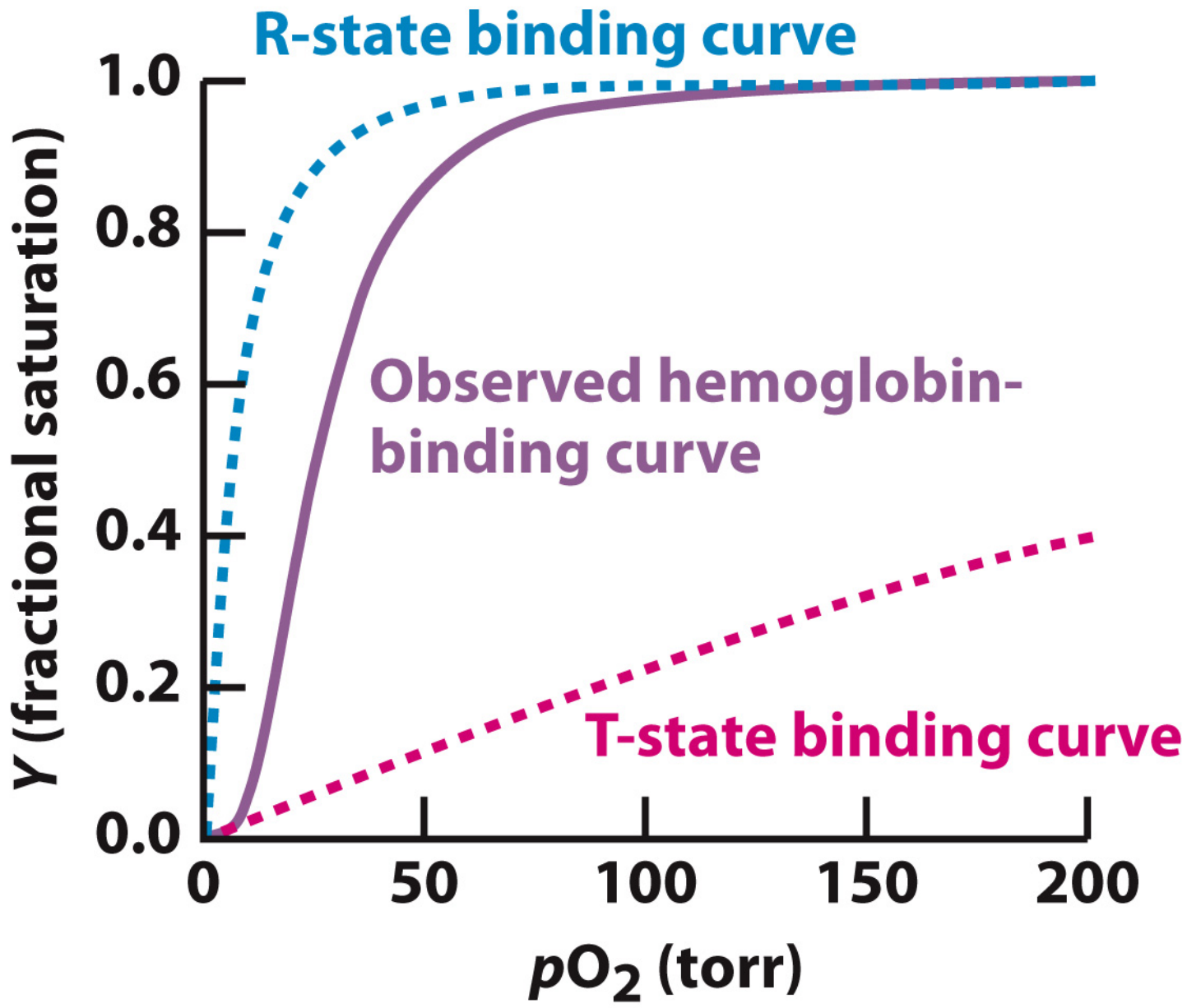
The binding of a ligand changes the conformation of the subunit to which it binds. This conformational change induces changes in neighboring subunits that increase their affinity for the ligand



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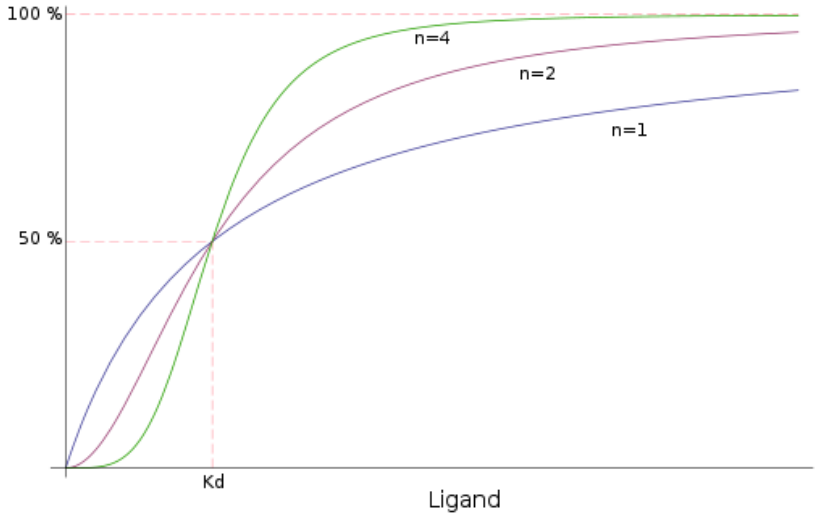
Hill equation

$$\theta = \frac{[\mathrm{L}]^n}{K_d + [\mathrm{L}]^n} = \frac{[\mathrm{L}]^n}{(K_A)^n + [\mathrm{L}]^n} = \frac{1}{\left(\frac{K_A}{[\mathrm{L}]}\right)^n + 1}$$



Allosteric constant

L = [To]/[Ro]

How more strongly R state binds oxygen than T state

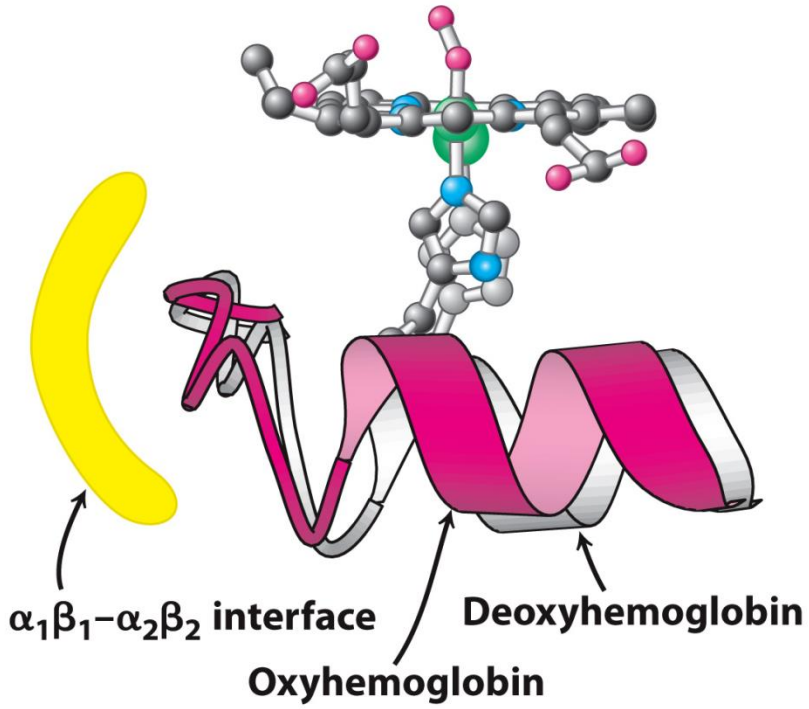
C = K_R/K_T wth c< 1 since K are dissociation constants

Structural bases for the cooperativity

The transition from deoxyhemoglobin (T state) to oxyhemoglobin (R state) occurs upon oxygen binding.

The iron ion moves into the plane of the heme when oxygen binds. The proximal histidine, which is a member of an α-helix, moves with the iron.

The resulting structural change is communicated to the other subunits so that the two αβ dimers rotate with respect to one another, resulting in the formation of the R state.
The carboxy end of the F-helix lies in the interface between the two dimers and the change in its position facilitate T to R transition



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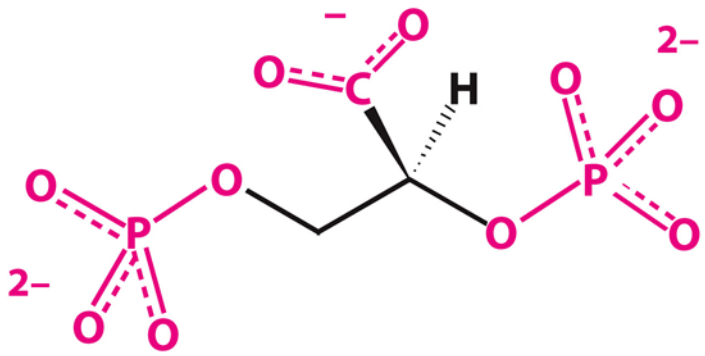
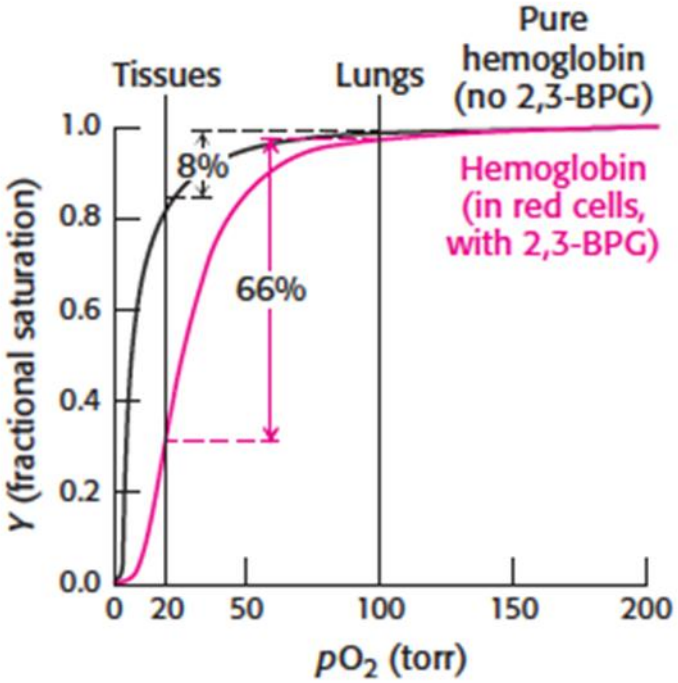
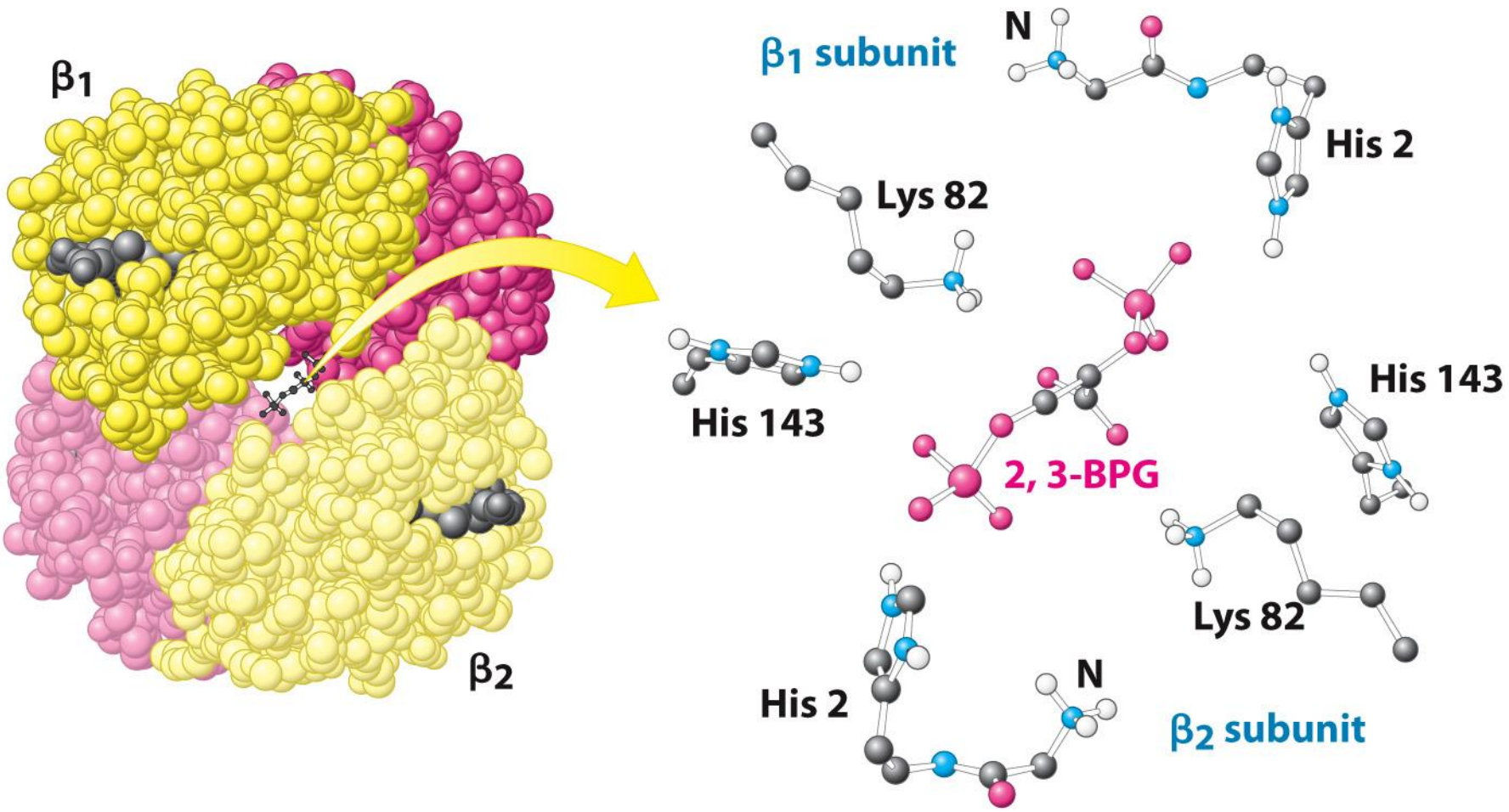
Allosteric effectors

2, 3-Bisphosphoglycerate (2,3-BPG) stabilizes the T state of hemoglobin and thus facilitates the release of oxygen.

2, 3-BPG binds to a pocket in the hemoglobin tetramer that exists only when hemoglobin is in the T state







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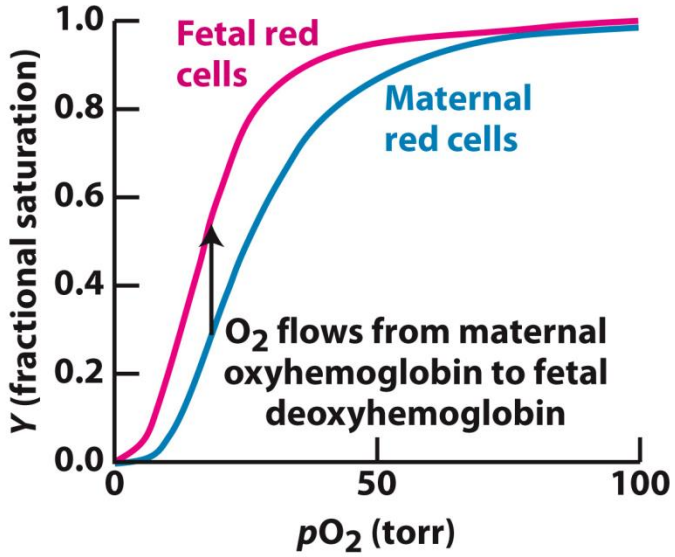
Fetal hemoglobin

Fetal hemoglobin must bind oxygen at the pO_2 that mother's hemoglobin is releasing oxygen.

In fetal hemoglobin, the β chain is replaced with a γ chain.

The fetal $\alpha_2\gamma_2$ hemoglobin does not bind 2, 3-BPG as well as adult hemoglobin does. The reduced affinity for 2, 3-BPG results in fetal hemoglobin having a higher affinity for oxygen, binding oxygen when the mother's hemoglobin is releasing oxygen.



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CO poisoning

Carbon monoxide binds so tightly to iron of hemoglobin that it stabilizes the R state to such a degree that the R to T transition does not occur.

Peripheral tissues are thus deprived of oxygen.

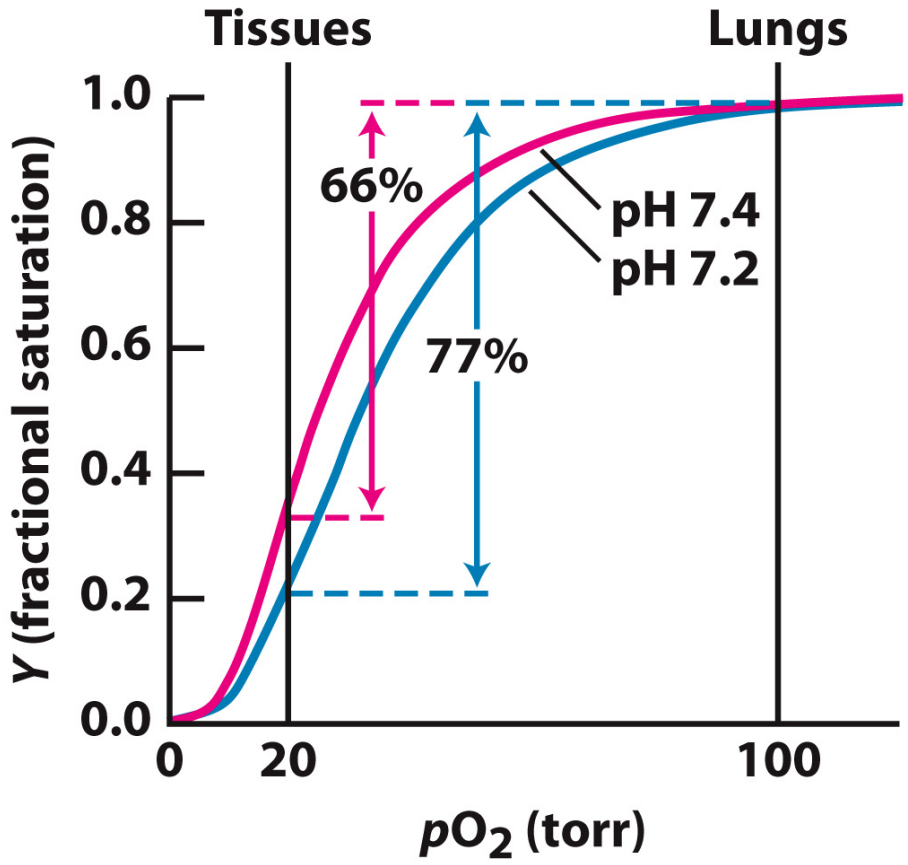
Bohr's effect

Carbon dioxide and H+, produced by actively respiring tissues, enhance oxygen release by hemoglobin. Carbon dioxide and H+ are thus allosteric effectors of hemoglobin.

At lower pH, salt bridges (ionic bonds) form that stabilize the T state. the N-terminal amino groups of the α-subunits and the C-terminal histidine of the β-subunits are protonated in the T state.

The stimulation of oxygen release by carbon dioxide and H+ is called the Bohr effect.

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$



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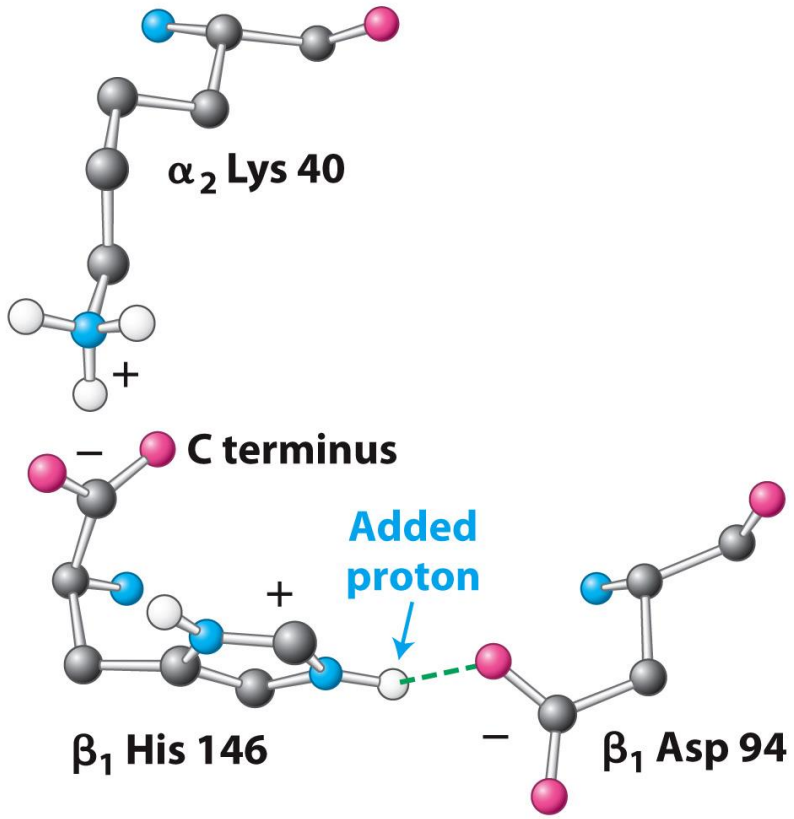

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Mutations in the genes coding for Hb

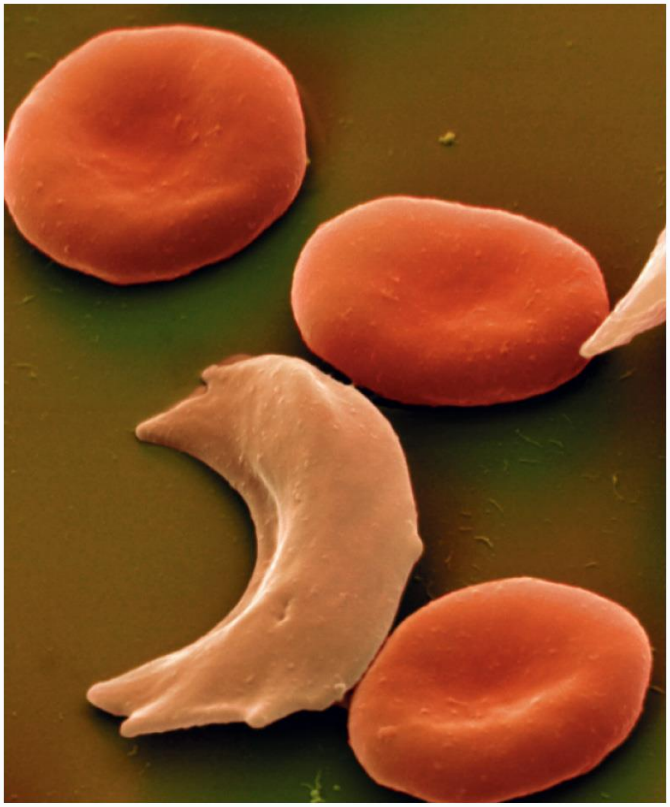
Sickle-cell anemia is a genetic disease caused by a mutation resulting in the substitution of valine for glutamate at position 6 of the β chains.

Sickle-cell anemia can be fatal when both alleles of the β chain are mutated.

In sickle-cell trait, one allele is mutated and one is normal. Such individuals are asymptomatic.

Sickle cell hemoglobin is called hemoglobin S (HbS). The substituted valine is exposed in deoxyhemoglobin and can interact with other deoxy HbS to form aggregates that deform the red blood cells.

The sickled cells clog blood flow through the capillaries, leading to tissue damage.



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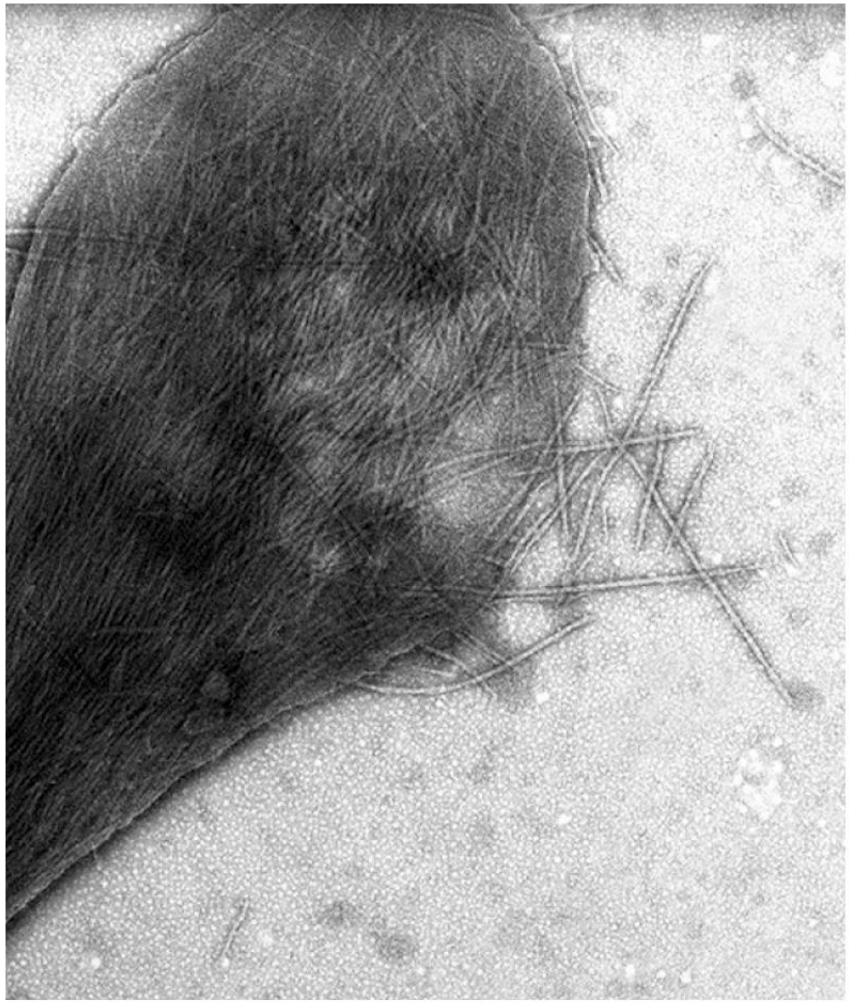

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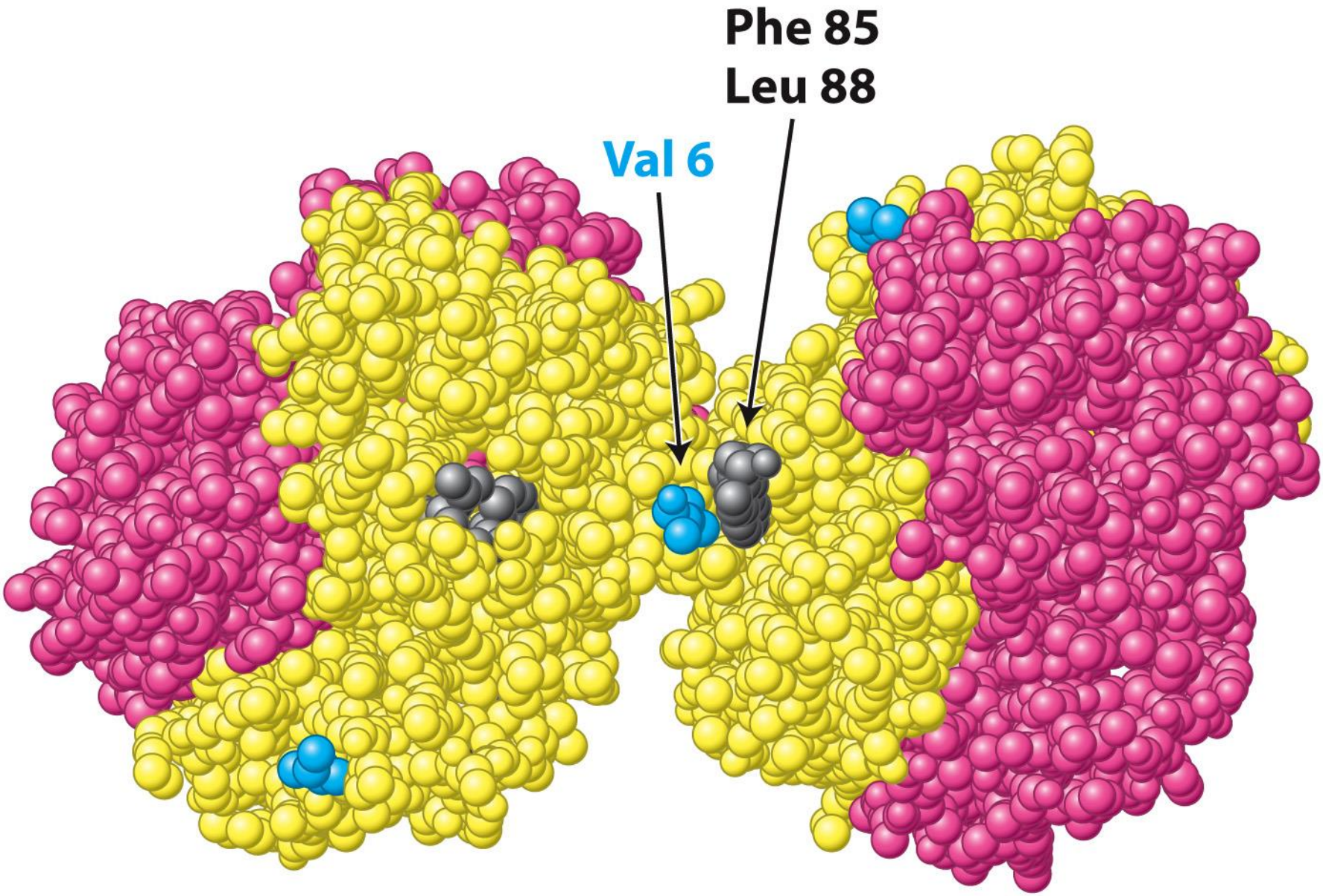

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