

Exercise walk-through

2.1

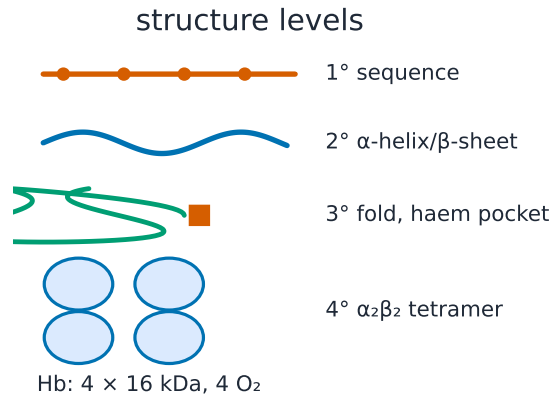
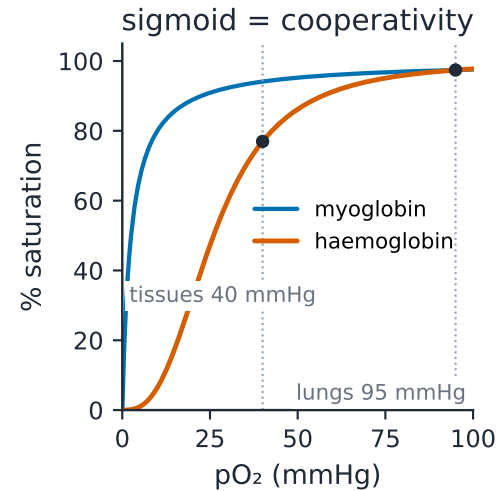
Proteins and protein structure

University Medicine

Structure levels and the sigmoid

- 1 Levels** Primary sequence $\rightarrow$ secondary helix/sheet $\rightarrow$ tertiary fold $\rightarrow$ quaternary assembly; Hb is the reference tetramer: $\alpha_2\beta_2$, 64.5 kDa, 4 O₂.
- 2 Cooperativity** Each O₂ shifts T $\rightarrow$ R so binding helps binding (Hill $n \approx 2.8$): full load in lungs, $\sim 35\%$ unloaded in tissues.
- 3 Capacity** $15 \text{ g Hb/dL} \div 64\,500 \text{ g/mol} \times 4 \text{ sites} \approx 930 \text{ } \mu\text{mol O}_2/\text{dL} \approx 20.8 \text{ mL/dL}$ ✓ - the textbook number recomputed.

From sequence to sigmoid



Hb: 4 $\times$ 16 kDa $\approx$ 64.5 kDa; sigmoid O₂ binding with Hill $n \approx 2.8$ - myoglobin hyperbolic, **haemoglobin** cooperative.

Exercises 2.1-2.3

2.1 Order the four structure levels and name the bonds/forces dominant at each. [3]

2.2 Why does myoglobin bind O₂ hyperbolically but haemoglobin sigmoidally? [3]

2.3 A mutation swaps a surface glutamate for aspartate. Predict the structural impact and justify. [3]

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2.1

- Primary: peptide bonds; secondary: backbone H-bonds; tertiary: hydrophobic effect + H-bonds + disulfides; quaternary: same forces between subunits.

2.2 Why does myoglobin bind O₂ hyperbolically but haemoglobin sigmoidally? [3]

2.2

- Myoglobin is single-site (no partners to influence); haemoglobin's four sites communicate via T $\leftrightarrow$ R subunit shifts – binding helps binding.

2.3 A mutation swaps a surface glutamate for aspartate. Predict the structural impact and justify. [3]

2.3

- Conservative surface swap (both negative, similar size): minimal impact – outside the core and the active site.

Exercise 3.1

3.1 Hb has 4 O₂ sites; p50 in tissues shifts with 2,3-BPG.

Explain the T $\leftrightarrow$ R transition and why binding is cooperative. Compute the O₂ content of blood (15 g/dL Hb) in mL/dL. State what happens to that number in anaemia (Hb 7.5 g/dL) and the compensatory mechanism. [7]

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3.1

- T is low-affinity, R high; each O₂ binding shifts equilibrium toward R, so later sites bind more easily (sigmoid, $n_H \approx 2.8$).
- $15/64 \times 500 \times 4 \times 22 \times 400 \approx 20.8 \text{ mL/dL } \checkmark$.
- Anaemia halves it to $\sim 10.4 \text{ mL/dL}$; compensation is raised cardiac output and erythropoietin-driven red-cell production.

Exercise 3.2

3.2 (Fictional) HbS: Glu6Val on the β chain.

Explain how a single primary-structure change produces sickling at the quaternary level. State the trigger state (oxy/deoxy) and why. Predict the effect on oxygen capacity per molecule and on blood viscosity. [7]

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3.2

- Val6 creates a hydrophobic patch on the β surface; in the deoxy T state it docks into a pocket on another Hb, polymerising fibres.
- Trigger: deoxy (T-state conformation exposes the patch).
- Capacity per molecule unchanged (haem intact); viscosity rises and cells deform/occlude