CHEM 153A Week 4

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Protein Tertiary and Quarternary Structure

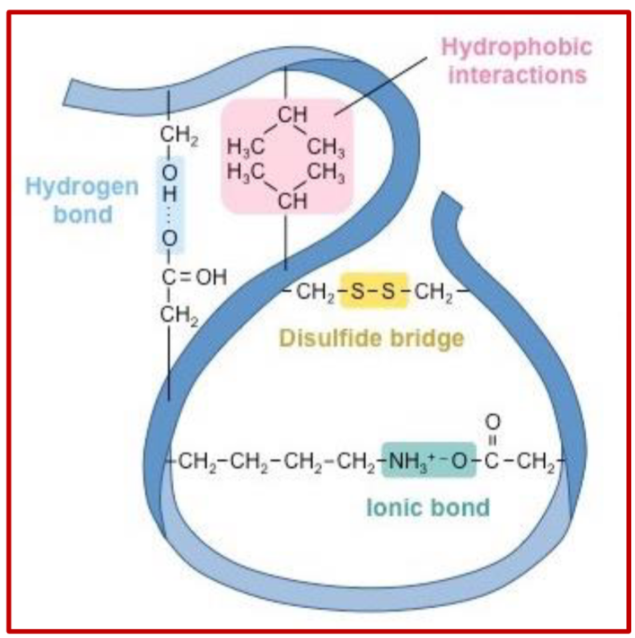
- **tertiary structure** = overall three-dimensional arrangement of all the atoms in a protein
  - weak interactions and covalent bonds hold interacting segments in position
- **quaternary structure** = arrangement of 2+ separate polypeptide chains in three-dimensional complexes

Shape → Function

Tertiary Structure - What holds it together?

- The global interactions of tertiary structure are formed through the interaction of amino acid side chains
- Electrostatic interactions forming between charged side chains
- London dispersion forces forming between nonpolar side chains
- Hydrogen bonds forming between polar/charged side chains
- Covalent bonds forming through disulfide bridges

Type of Bond	Example	Bond Strength ($kJ \cdot mol^{-1}$)
Covalent	S—S	251
Noncovalent		
Ionic interaction	$—COO^{-}\cdots{}^{+}H_3N—$	86
van der Waals forces		
Hydrogen bond	$—O—H\cdots O<$	20
Dipole–dipole interaction	$>C=O\cdots>C=O$	9.3
London dispersion forces	$—CH_2—H\cdots H—CH_2—$	0.3

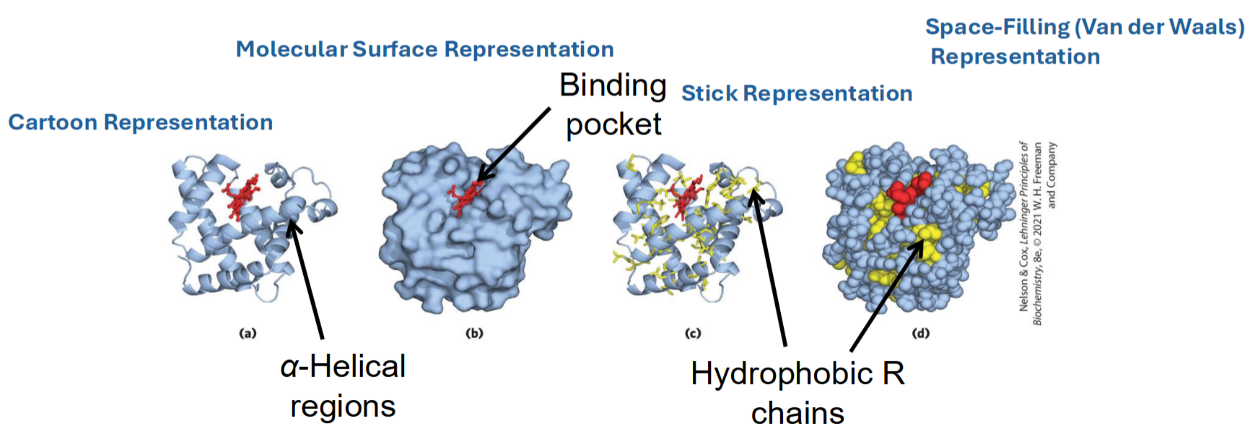


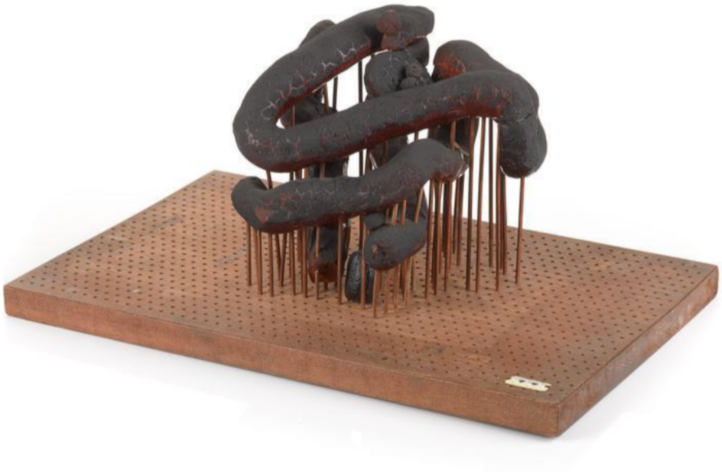
Categories of Tertiary Structure - Globular proteins

- **Globular proteins** polypeptide chains folded into a spherical or globular shape
  - fold back on each other
  - more compact than fibrous proteins
  - soluble in water
  - mixture of different secondary structures
  - quaternary structure usually held together by noncovalent forces
  - regulatory and metabolic roles (basically most proteins you can think of)
    * enzymes
    * transport proteins
    * motor proteins
    * regulatory proteins
    * immunoglobulins

Myoglobin Provided Early Clues about the Complexity of Globular Protein Structure

- several structural representations of myoglobin's tertiary structure:





Max Perutz and John Kendrew, 1962

"I always knew it would look like that—but I never expected it to be so complicated!"
John D. Bernal

The bottom picture depicts the original model of the myoglobin molecule, constructed in plasticine in 1957.

- This was the first ever model of a protein molecule. (Won a nobel prize)
- In modern day, we have so much information about protein structure that we can train AIs to simulate protein folding.

Globular Proteins Have a Variety of Tertiary Structures

Each globular protein has a distinct structure, adapted for its biological function

Approximate Proportion of α Helix and β Conformation in Some Single-Chain Proteins

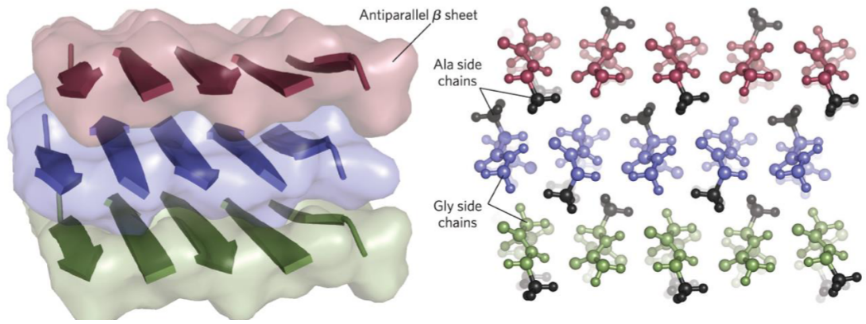
Protein (total residues)	Residues (%): α Helix	Residues (%): β Conformation
Chymotrypsin (247)	14	45
Ribonuclease (124)	26	35
Carboxypeptidase (307)	38	17
Cytochrome *c* (104)	39	0
Lysozyme (129)	40	12
Myoglobin (153)	**78**	**0**

Categories of Tertiary Structure - Fibrous proteins

- **Fibrous proteins** are long (often) rope-like proteins adapted for strength.
  - Extended structure
  - Insoluble in water
  - Simple repetitive structure (often the same secondary structure throughout)
  - Quaternary structure usually held together by disulfide bonds
  - Famously involved in a lot of extracellular structures (incl. Tendons, bones, hair, skin)

silk, a.k.a. fibroin (stacked β-sheets)

enriched with Gly and Ala (why?)



Fibrous Proteins are Adapted for a Structural Function

- give strength and/or flexibility to structures
- simple repeating element of secondary structure
- H_2O insoluble due to high concentrations of hydrophobic residues

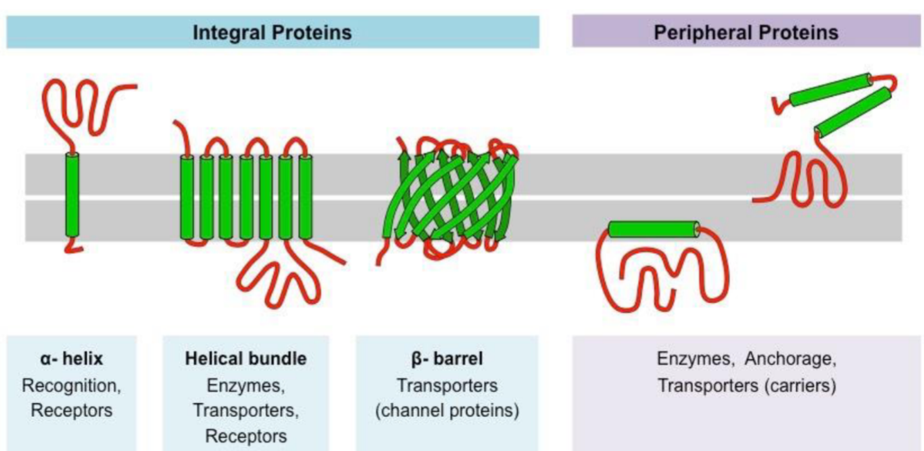
Secondary Structures and Properties of Some Fibrous Proteins		
Structure	**Characteristics**	**Examples of occurrence**
α Helix, cross-linked by disulfide bonds	Tough, insoluble protective structures of varying hardness and flexibility	*α*-Keratin of hair, feathers, nails
β Conformation	Soft, flexible filaments	Silk fibron
Collagen triple helix	High tensile strength, without stretch	Collagen of tendons, bone matrix

Membrane Proteins

Membrane proteins are proteins with polypeptide chains embedded into lipid membranes

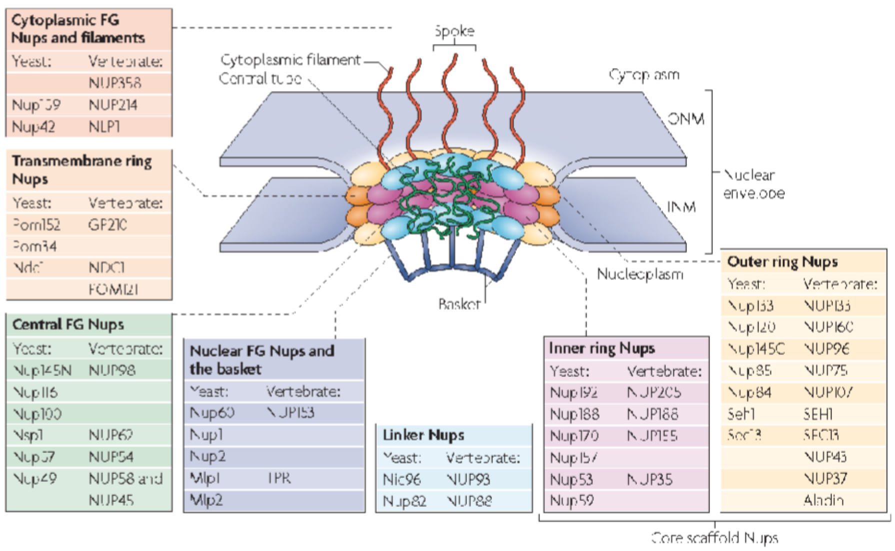
- Multiple types, commonality is that they contain hydrophobic regions so as to embed themselves
- Defined patterns of secondary structure

You don't have to know these categories or functions

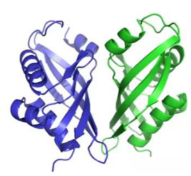


Quaternary Structure

- Folded proteins can associate forming multi-subunit complexes
  - Adds even more informational complexity to proteins as functional units
  - Variety of possibilities, anything from small oligomeric complexes to massive complexes made from many different proteins
- Subunits can be identical or different
  - Subunits are symmetrically arranged
- **oligomer** = **multimer** = multi-subunit protein

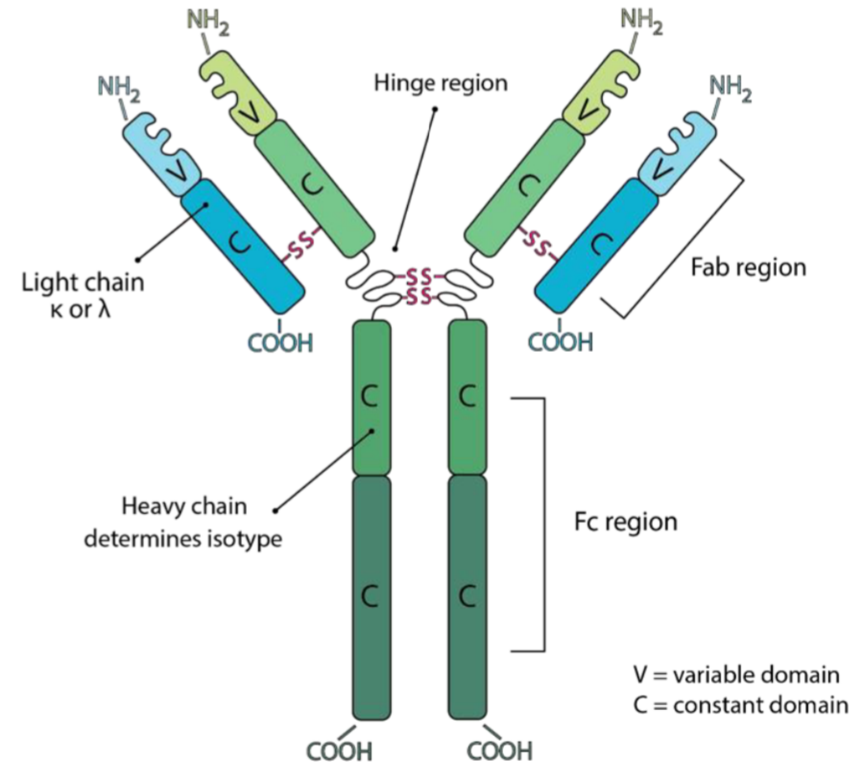


simple dimer (2 subunits)



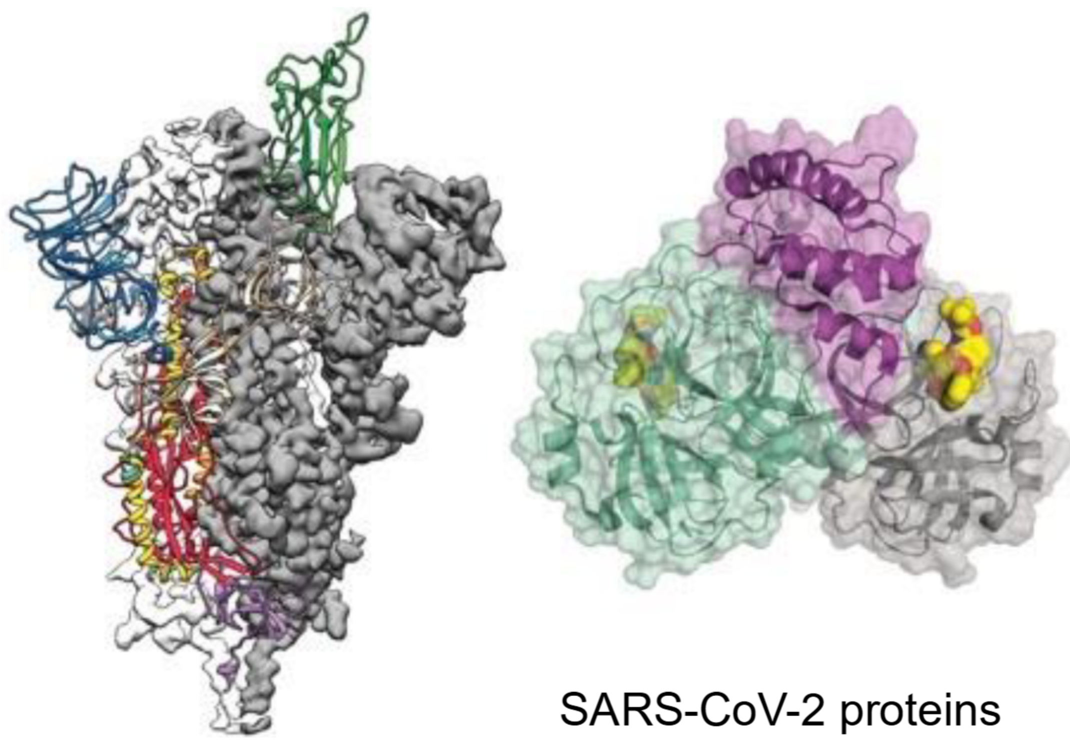
Quaternary Structure - What holds it together?

- Quaternary structure is built by interactions between protein subunits
- These take on the same characteristics as tertiary structure (this should make sense if you consider it)
- <u>Electrostatic interactions</u> forming between charged side chains (more prevalent in quaternary)
- <u>London dispersion forces</u> forming between nonpolar side chains
- <u>Hydrogen bonds</u> forming between polar/charged side chains
- <u>Covalent bonds</u> forming through disulfide bridges (less prevalent in quaternary)



Visualizing Protein Structure

Quaternary structure describes the interactions between components of a multisubunit assembly



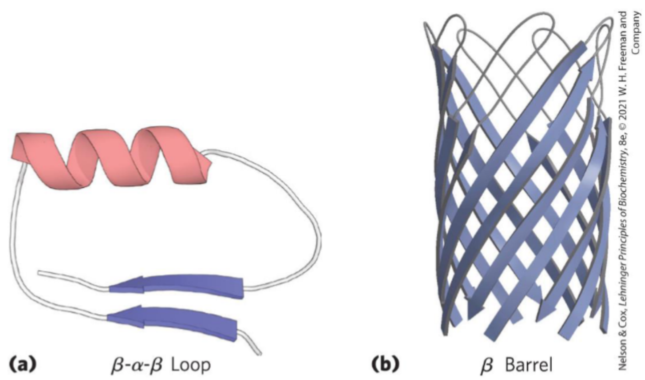
The Protein Data Bank

The **Protein Data Bank (PDB)**: www.rcsb.org

- archive of experimentally determined three-dimensional structures
- structures assigned an identifier called the PDB ID
- PDB data files describe:
  - the spatial coordinates of each atom
  - information on how the structure was determined
  - information on its accuracy (how good the model is)
  - structure visualization software can convert atomic coordinates to an image of the molecule

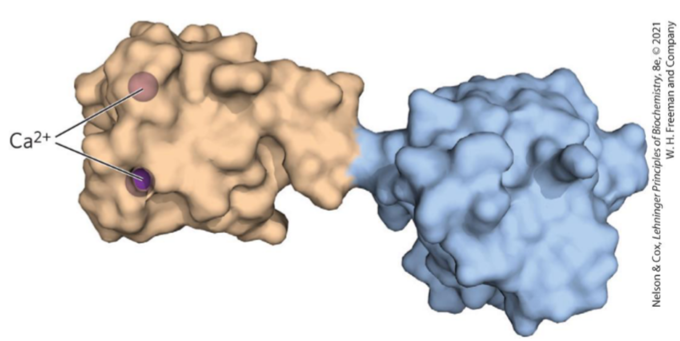
Folding Patterns of Proteins

- **motif** = **fold** = recognizable folding pattern involving 2+ elements of secondary structures and the connections(s)
  - can be simple, such as in a $\beta - \alpha - \beta$ loop
  - can be elaborate, such as in a β-barrel



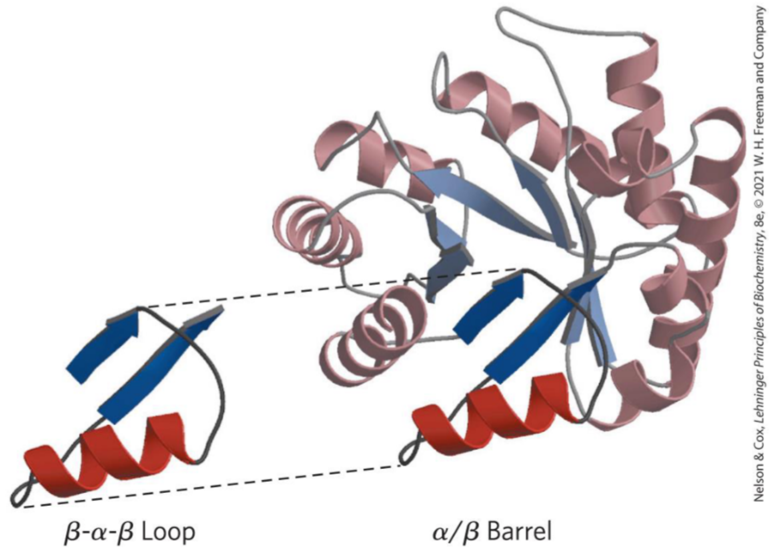
Protein Domains

- **domain** = part of a polypeptide chain that is independently stable or could undergo movements as a single entity
  - domains may appear as distinct or be difficult to discern
  - small proteins usually have only one domain



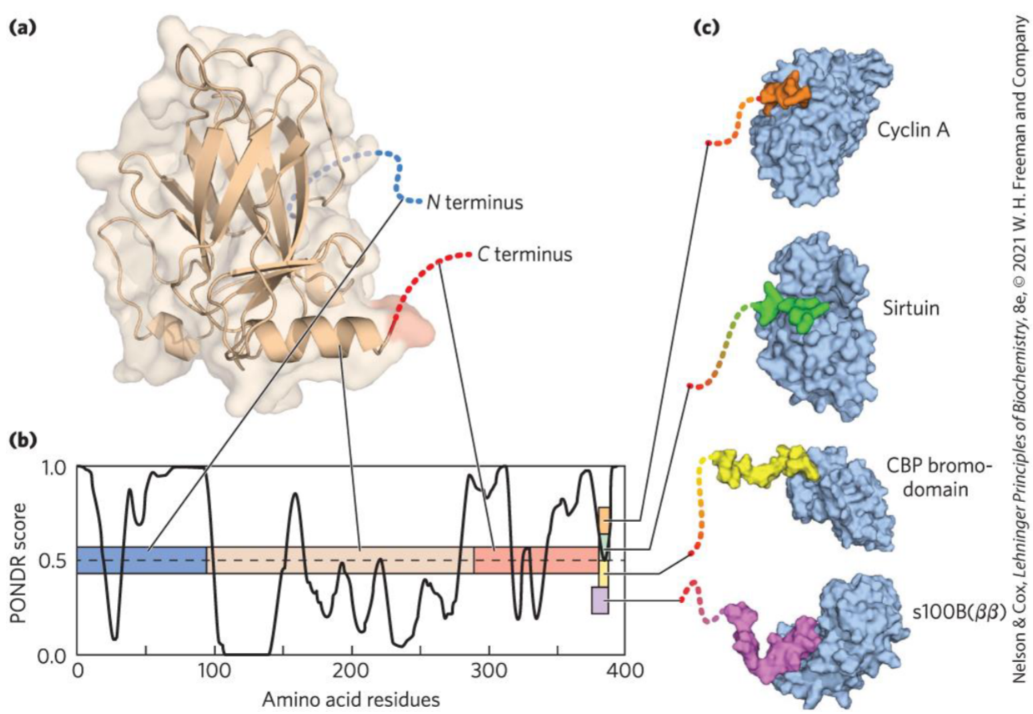
Complex Motifs are Built from Simple Motifs

α/β **barrel** = series of $\beta - \alpha - \beta$ loops arranged such that the β strands form a barrel



Intrinsically disordered proteins:

- lack definable structure
- often lack a hydrophobic core
- high densities of charged residues (Lys, Arg, Glu, and Pro)
- facilitates a protein to interact with multiple binding partners

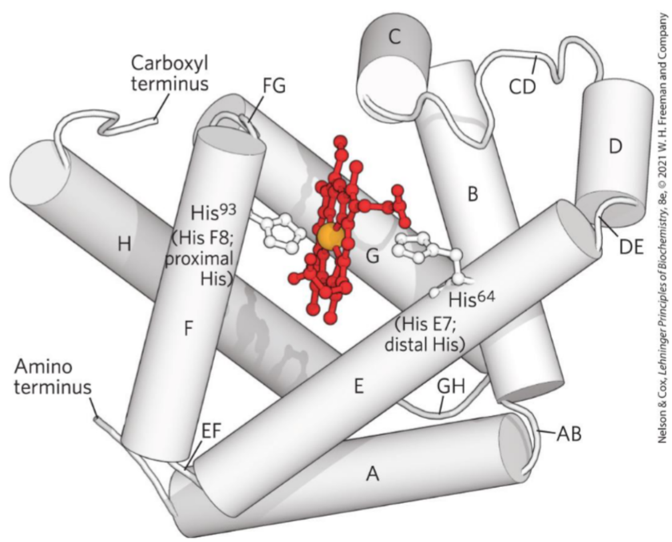


Protein Families and Superfamilies

- proteins with significant similarity in primary structure and/or tertiary structure and function are in the same **protein family**
  - ~4000 different protein families in the PDB
  - strong evolutionary relationship within a family
- **superfamilies** = 2+ families that have little sequence similarity, but the same major structural motif and have functional similarities.

Globins are a Family of Oxygen-Binding Proteins

- Globins like myoglobin and hemoglobin belong to the same protein family: **Globin Family**
- Globins are a widespread protein family:
  - highly conserved tertiary structure: eight α-helical segments connected by bends (**globin fold**)
  - most function in O_2 transport or storage



Types of Globins

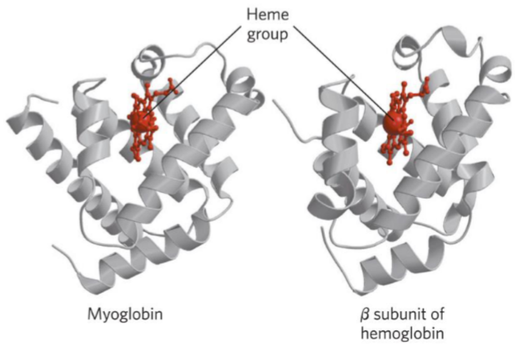
- Four types in humans and other mammals:
  - **myoglobin** = monomeric, facilitates O_2 diffusion in muscle tissue
  - **hemoglobin** = tetrameric, responsible for O_2 transport in the bloodstream
  - **neuroglobin** = monomeric, expressed largely in neurons to protect the brain from low O_2 or restricted blood supply
  - **cytoglobin** = monomeric, regulates levels of nitric oxide, a localized signal for muscle relaxation

Globins and Prosthetic Groups

- **Myoglobin** and **hemoglobin** are examples of conjugated proteins
  - Simple proteins only have a polypeptide chain
  - **Conjugated proteins** have a non-protein component called a prosthetic group

– Myoglobin and hemoglobin have a heme prosthetic group that provides them with oxygen binding functionality (amino acids can't bind oxygen well)

- The globins are examples of **hemoproteins** (proteins with heme prosthetic groups) which are subsets of metalloproteins (proteins with metal prosthetic groups)
  – This is because heme contains ferrous iron (Fe^{2+})



Oxygen-carrying proteins

- Myoglobin (Mb)
  – O_2 acts as a ligand (can bind max 1 O_2)
  – Only one subunit
  – Acts as oxygen storage and facilitates diffusion in muscular cells
  – ≈ 64 g of Mb present in an average human body
- Hemoglobin (Hb)
  – O_2 acts as a ligand (can bind up to 4 O_2)
  – Four subunits, two subunits of α-globin, and two subunits of β-globin
  – Transports O_2 from lungs to peripheral tissues (carried in erythrocytes)
  – ≈ 775 g of Hb present in an average human body
- Both rely on the heme prosthetic group