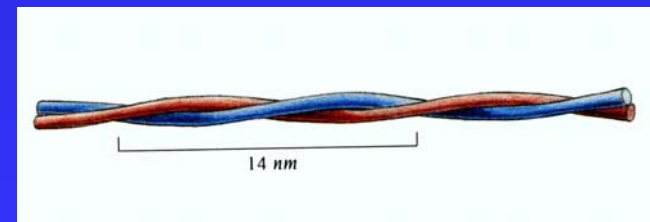
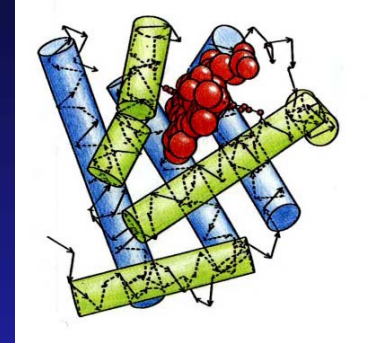
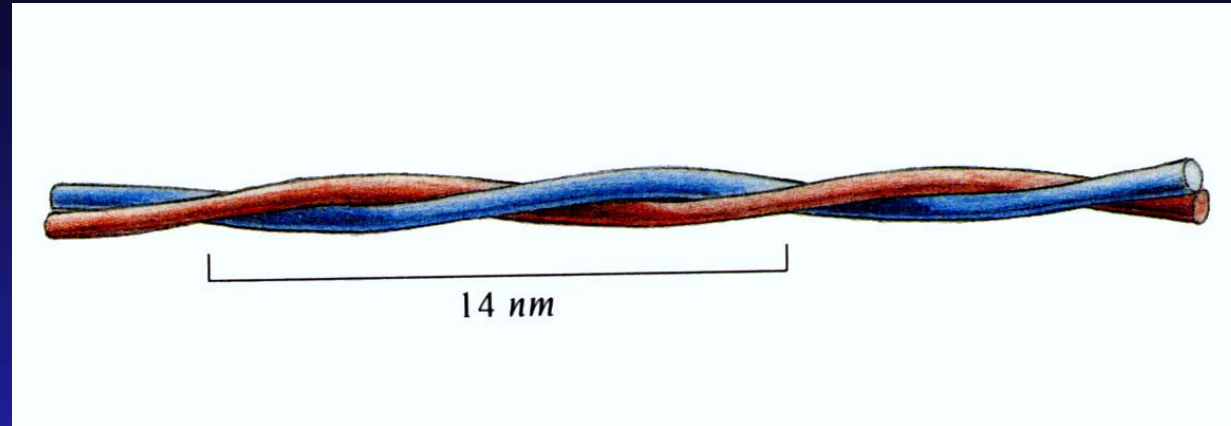


Alpha-Domain Structures

Alpha-Domain Structures

- globin fold – a representative example of one class of α domains in proteins
- membrane bound proteins – the regions inside the membranes are frequently α helices whose surfaces are covered by hydrophobic side chains suitable for the hydrophobic environment inside the membranes
- α helices are also often used to produce structural and motile proteins such as keratin, or parts of the cellular machinery such as fibrinogen or the muscle proteins myosin and dystrophin





- α helices are only marginally stable in solution; they are stabilized by being packed together through hydrophobic side chains
- the simplest way to achieve such stabilization is to pack two α helices together
- side chains interactions are maximized if the two α helices are not straight rods but are wound around each other in a supercoil, a so called coiled-coil arrangement
- this arrangement is encountered mainly in fibrous proteins
- much shorter coiled-coils are used in some transcription factors to promote or prevent formation of homo- and heterodimers

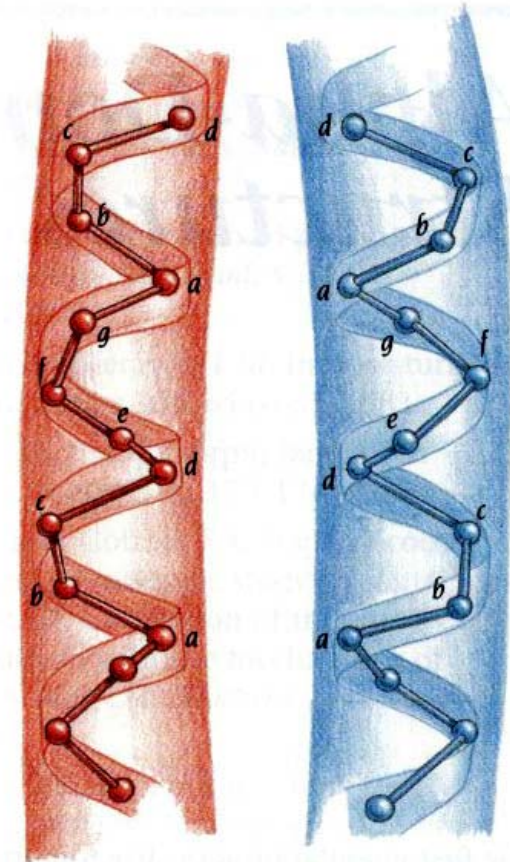
Repetitive pattern of amino acids in a coiled-coil α helix – heptad repeat

	<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>	<i>e</i>	<i>f</i>	<i>g</i>
NH ₂ -	Met	Lys	Gln	Leu	Glu	Asp	Lys
	Val	Glu	Glu	Leu	Leu	Ser	Lys
	Asn	Tyr	His	Leu	Glu	Asn	Glu
	Val	Ala	Arg	Leu	Lys	Lys	Leu - COOH

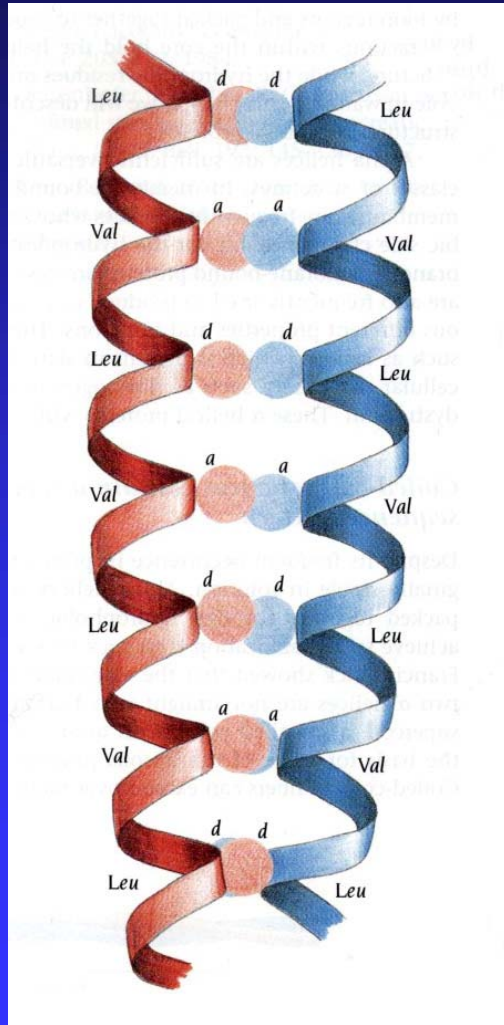
(a)

- a) the amino acid sequence of the transcription factor GCN4 showing a heptad repeat of leucine residues
- b) schematic diagram of one heptad repeat in a coiled-coil structure showing the backbone of the polypeptide chain; the alpha helices in the coiled-coil are slightly distorted so that the helical repeat is 3.5 residues rather than 3.6 as in a regular helix; there is therefore an integral repeat of seven residues along the helix

(b)

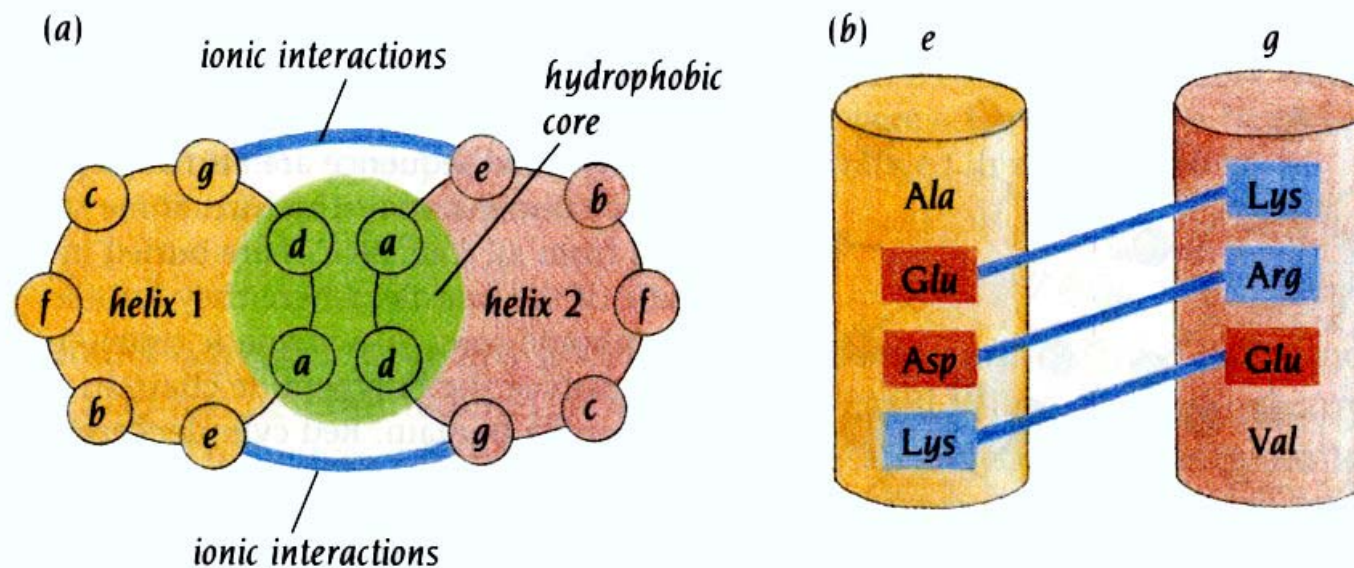


Packing of hydrophobic side chains between the two α helices in a coiled-coil structure

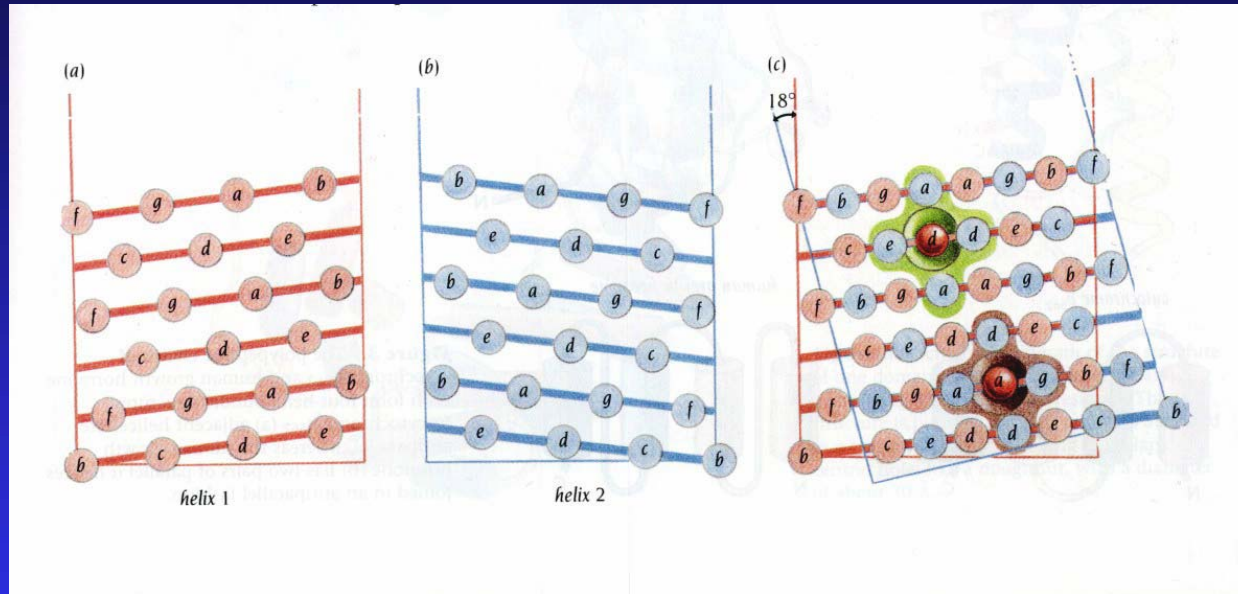


Every seventh residue in both α helices is a leucine, labeled “d”. Due to the heptad repeat, the d-residues pack against each other along the coiled-coil. Residues labeled “a” are also usually hydrophobic and participate in forming the hydrophobic core along the coiled-coil.

Salt bridges can stabilize coiled-coil structures and are sometimes important for the formation of heterodimeric coiled coil structures



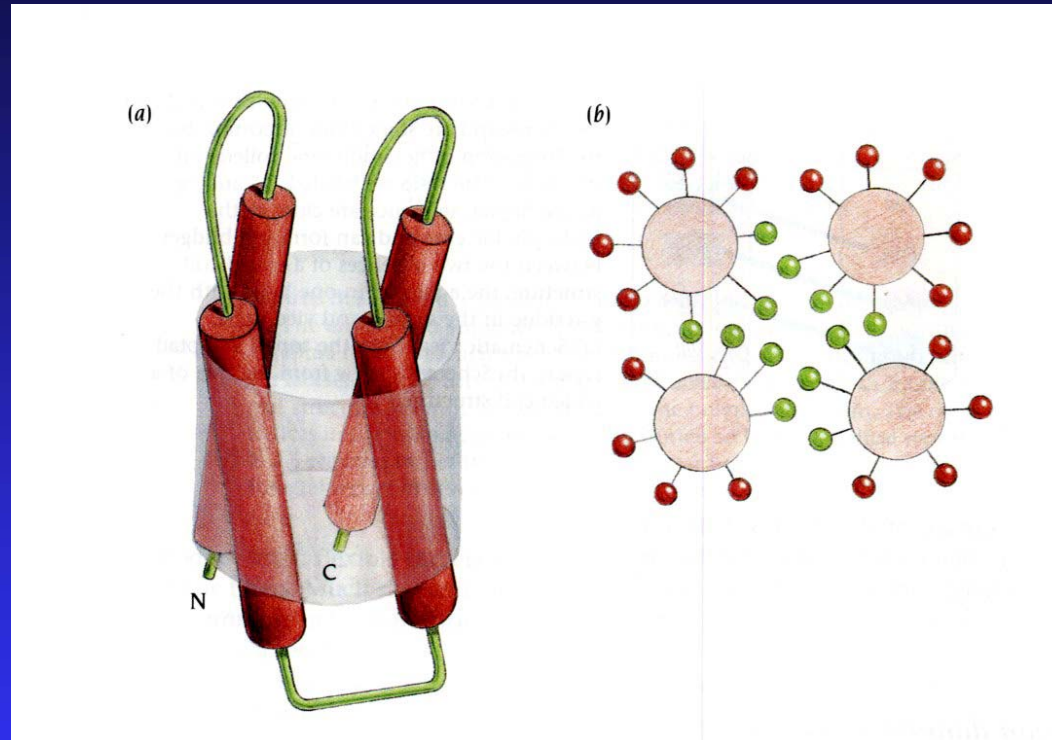
Schematic diagram of packing side chains in the hydrophobic core of coiled-coil structures according to the “knobs and holes” model



- a) projected positions of side chains in helix 1
- b) projected positions of side chains in helix 2
- c) superposition of (a) and (b) using the relative orientation of the helices in the coiled-coil structure

The green shading outlines a d-residue (leucine) from helix 1 surrounded by four side chains from helix 2, and the brown shading outlines an a-residue (usually hydrophobic) from helix 1 surrounded by four side chains from helix 2.

The four-helix bundle – a common domain structure in α proteins

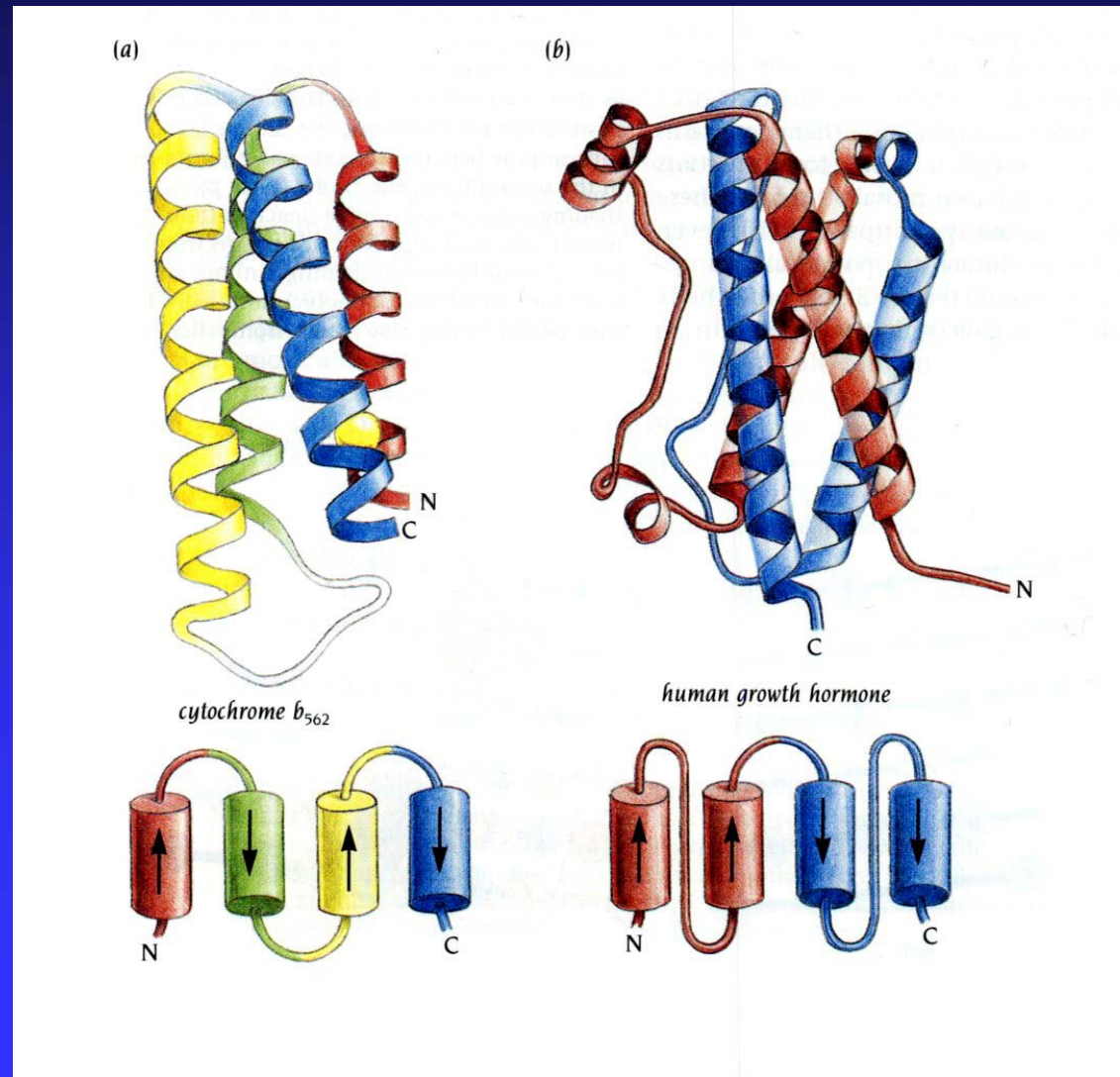


The arrangement of α helices is such that adjacent helices in the amino acid sequence are also adjacent in the three-dimensional structure.

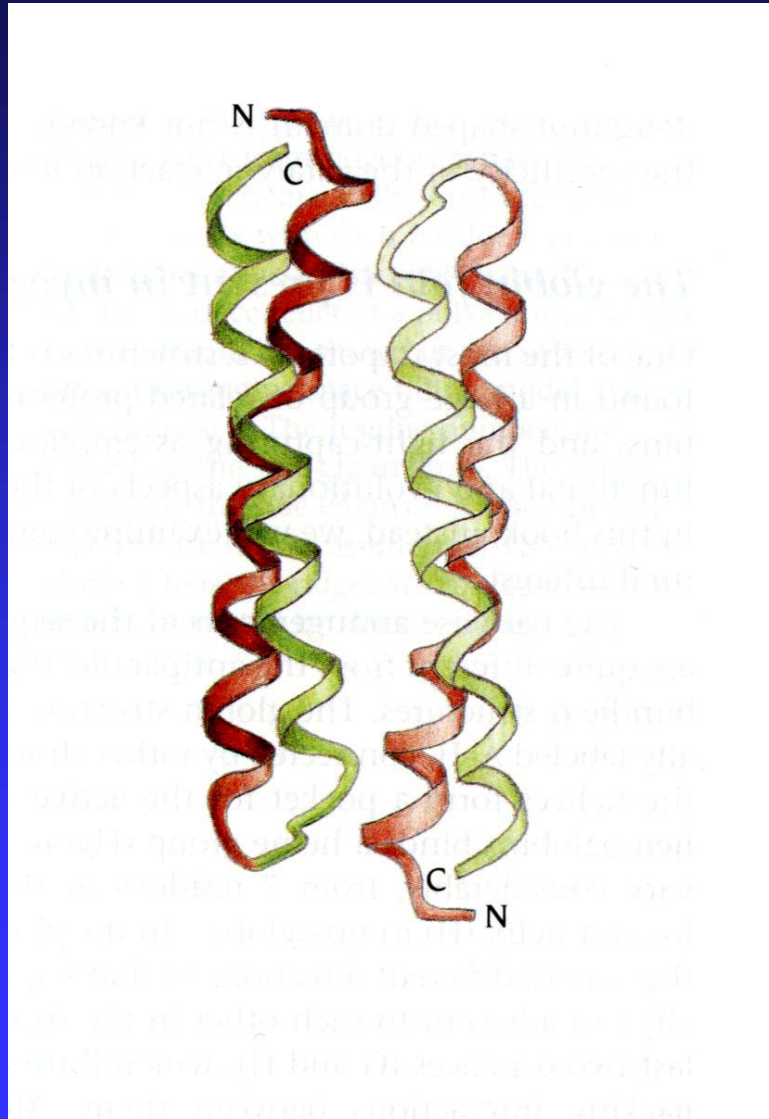
a) schematic representation of the path of the polypeptide chain in a four-helix-bundle domain

b) schematic projection down the bundle axis

The polypeptide chains of cytochrome b_{562} and human growth hormone both form four-helix-bundle structures

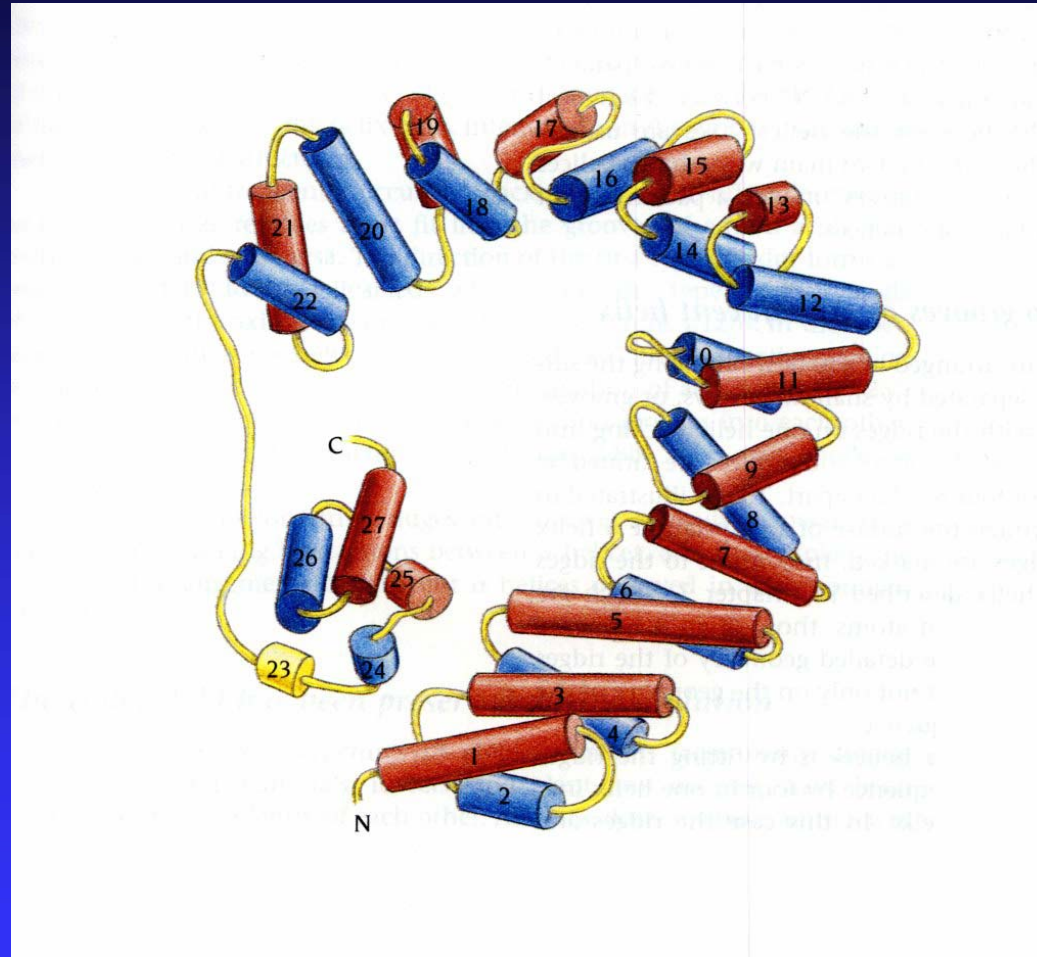


Schematic diagram of the dimeric Rop molecule



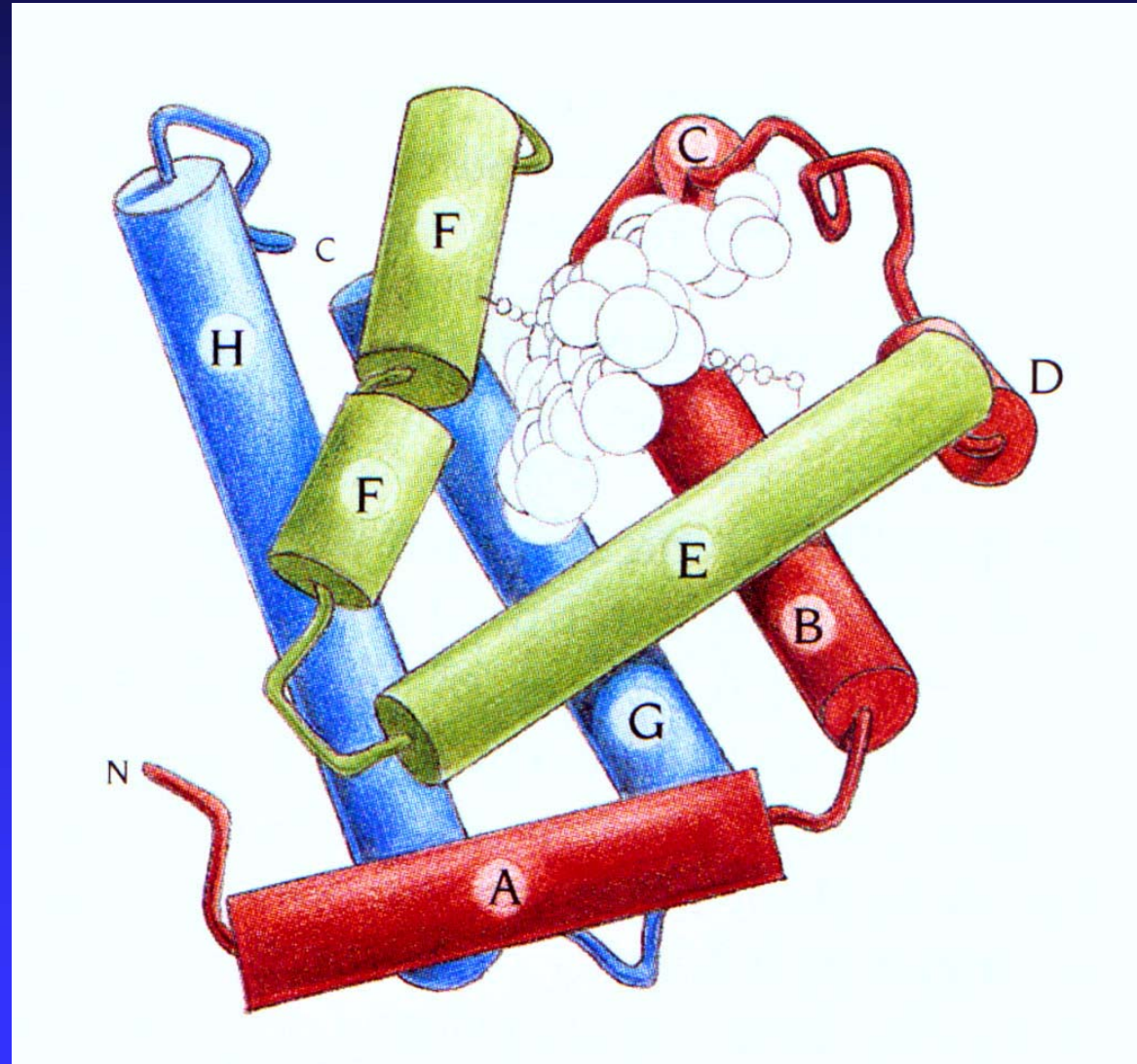
The two subunits are arranged in such a way that a bundle of four α helices is formed. The monomeric subunit of Rop is a polypeptide chain of 63 amino acids built up from two antiparallel α helices joint by a short loop of three amino acids. Rop protein is a small RNA-binding protein that is encoded by certain plasmids and is involved in plasmid replication.

Alpha-helical domains are sometimes large and complex



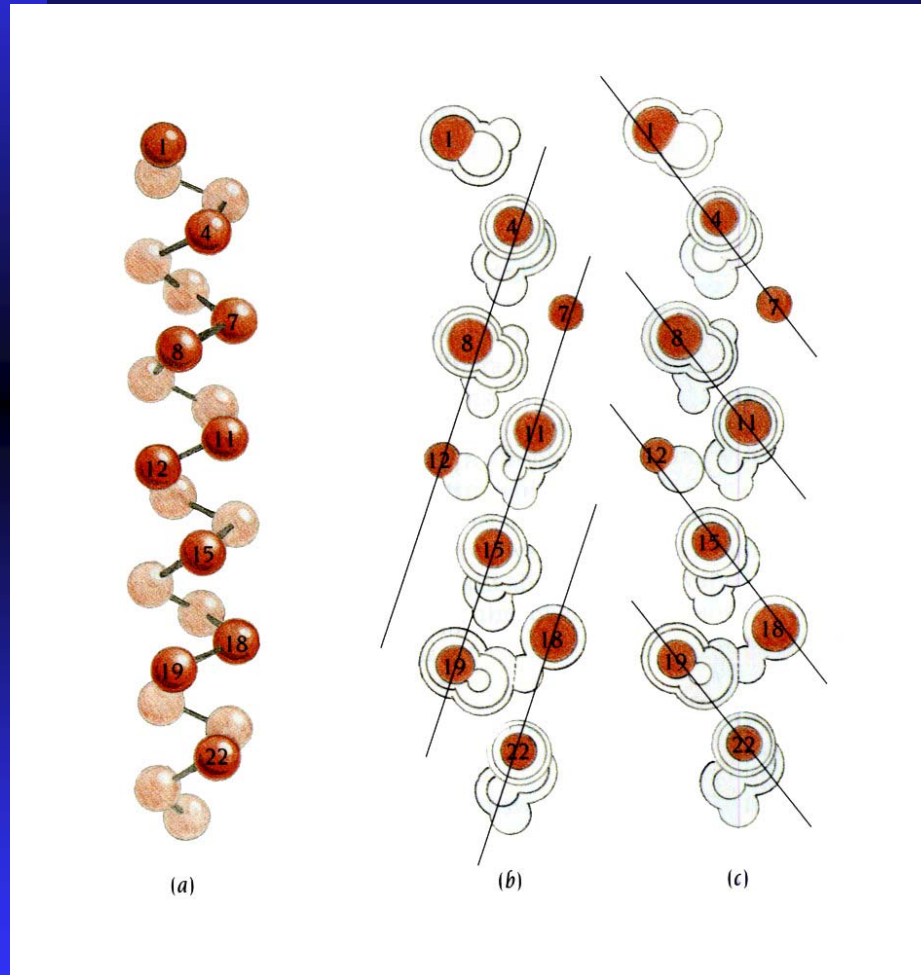
Schematic diagram of the structure of one domain of a bacterial muramidase, comprising of 450 amino acid residues. The structure is built up from 27 α helices arranged in a two-layered ring. The ring has a large central whole, like a doughnut, with a diameter of about 30 Å.

The globin fold is present in myoglobin and hemoglobin



Geometric considerations determine α -helix packing

Ridges of one α -helix fit into grooves of an adjacent helix



The side chains on the surface of an α helix form ridges separated by grooves.

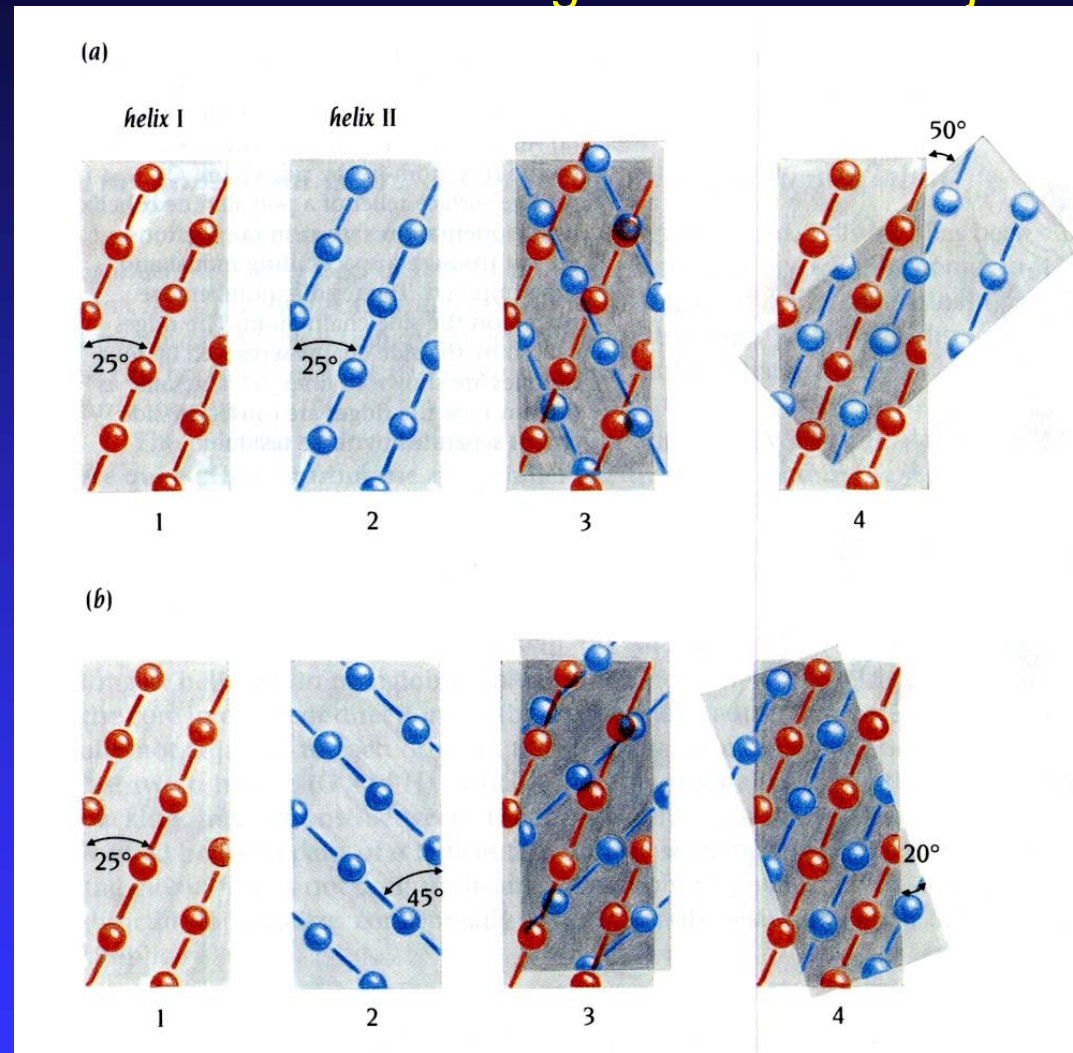
a) An α helix with each residue represented by the first atom in the side chain, $C\beta$.

b) The surface relief of a polyalanine α helix in the orientation shown in (a). Sections are cut through a space filling model and superimposed. The residue numbers are placed on the side-chain atom. The ridges caused by the side chains separated by four residues are shown as lines.

c) The same as (b), but here the ridges are caused by side chains separated by three residues.

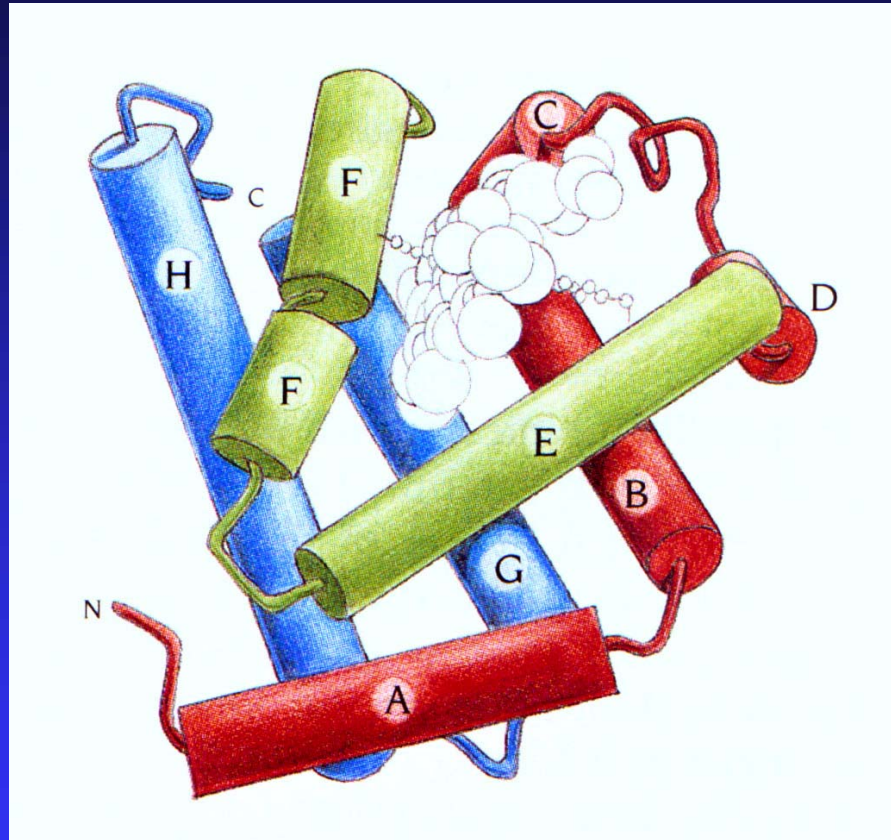
Geometric considerations determine α -helix packing

Ridges of one α -helix fit into grooves of an adjacent helix



By fitting the ridges of side chains from one helix into the grooves between side chains of the other helix and vice versa, α helices pack against each other.

The globin fold is present in myoglobin and hemoglobin



Globin domains from many diverse sources have amino acid sequence homologies that range from 99% to 16%. However, they all share the same essential features of globin fold. This family of structures is the prime example of a situation where natural selection has produced proteins whose amino acid sequences have diverged widely but whose three-dimensional structure has been essentially preserved.

The globin family is the prime example of a situation where natural selection has produced proteins whose amino acid sequences have diverged widely but whose three-dimensional structure has been essentially preserved.

How can amino acid sequences that are very different form proteins that are very similar in their three-dimensional structure?

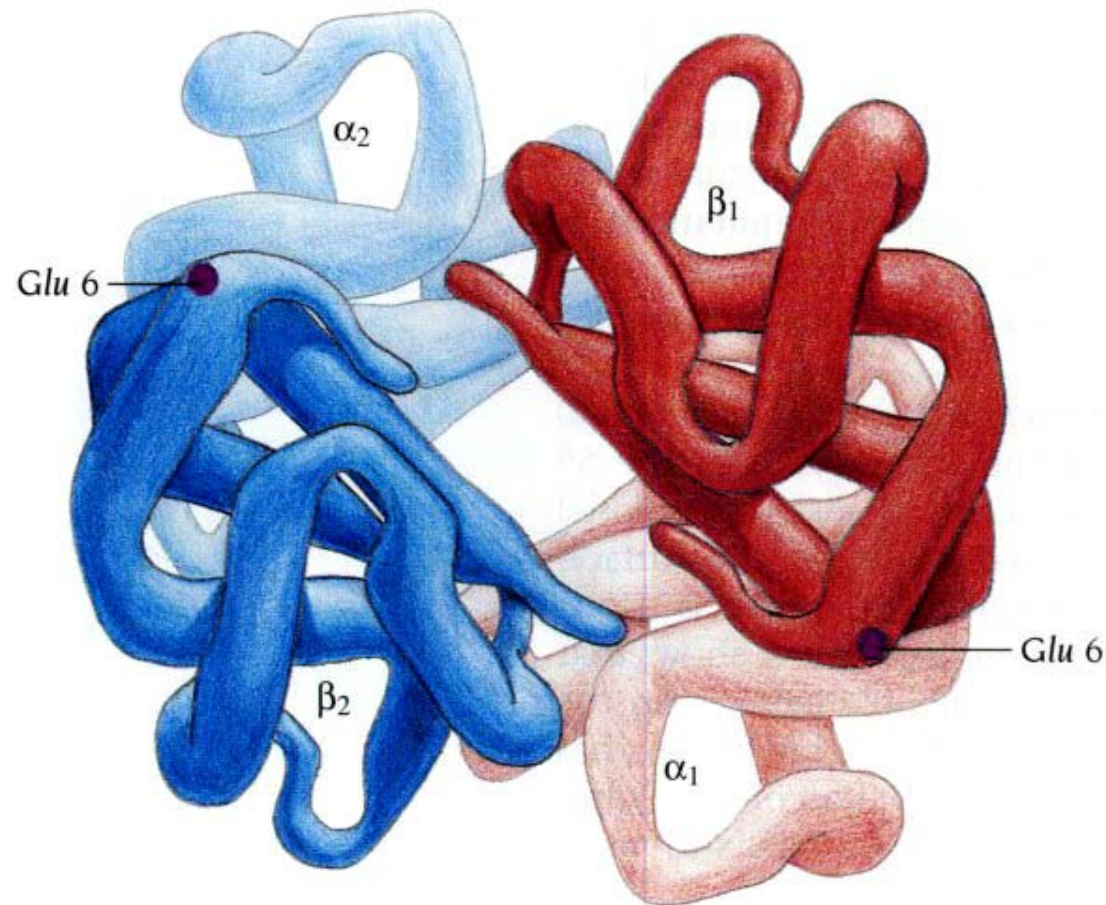
What is the mechanism by which proteins adapt to mutations in the course of their evolution?

Answers:

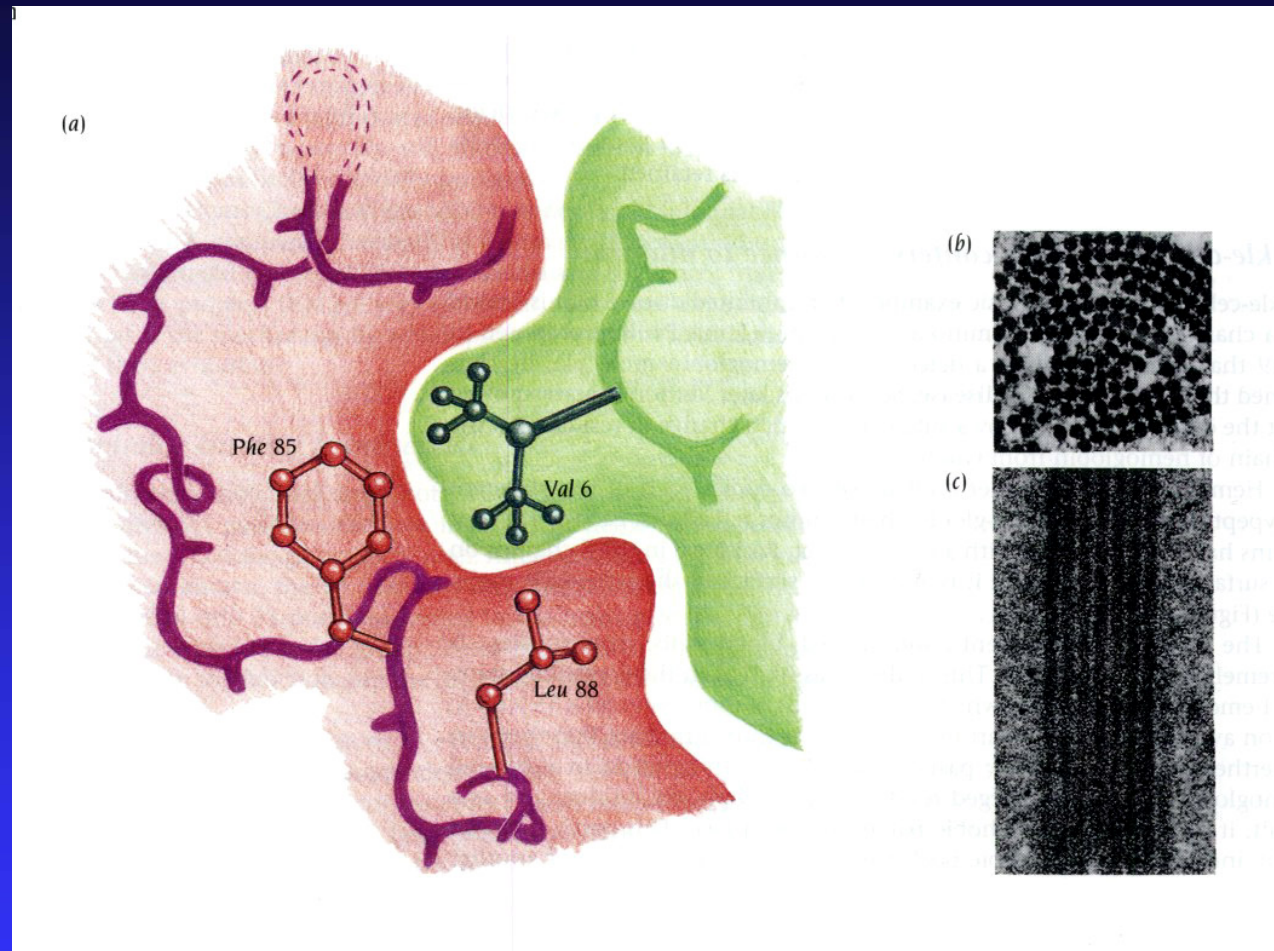
The hydrophobic interior is preserved.

Helix movements accommodate interior side-chain mutations.

The hemoglobin molecule is built up of four polypeptide chains: two α chains and two β chains
A single mutation, a change in residue 6 of the β chain of hemoglobin from Glu to Val, causes sickle-cell anemia



Sickle-cell hemoglobin confers resistance to malaria



Sickle-cell hemoglobin molecules polymerize due to the hydrophobic patch introduced by the mutation Glu 6 to Val in the β chain. The diagram (a) illustrates how this hydrophobic patch (green) interacts with a hydrophobic pocket (red) in a second hemoglobin molecule, whose hydrophobic patch interacts with the pocket in a third molecule, and so on. Electron micrographs of sickle-cell hemoglobin fibers are shown in cross-section in (b) and along the fibers in (c).

Alpha-Domain Structures - Conclusion

- Coiled-coil α -helical structures are found in both fibrous proteins and as parts of smaller domains in many globular proteins.
- Alpha-domain structures consist of a bundle of α -helices that are packed together to form a hydrophobic core. A common motif is the four-helix bundle structure, where four helices are pair-wise arranged in either a parallel or antiparallel fashion and packed against each other.
- The most intensively studied α structure is the globin fold, which has been found in a large group of related proteins, including myoglobin and hemoglobin. This structure comprises eight α helices that wrap around the core in different directions and form a pocket where the heme group is bound.

Alpha-Domain Structures - Conclusion

-Rules have been derived that explain the different geometrical arrangements of α helices observed in α -domain structures. The helix packing in coiled-coil structures is determined by fitting the knobs of side chains in the first helix into holes between side chains in the second helix. For other α -helical structures the helix packing is determined by fitting ridges of side chains along one α helix into grooves between side chains of another helix.

-The globin fold has been used to study evolutionary constraints for maintaining structure and function. Evolutionary divergence is primarily constrained by conservation of the hydrophobicity of buried residues. In contrast, neither conserved sequence nor size-compensatory mutations in the hydrophobic core are important. Proteins adapt to mutations in buried residues by small changes of overall structure that in the globins involve movements of the entire helices relative to each other.