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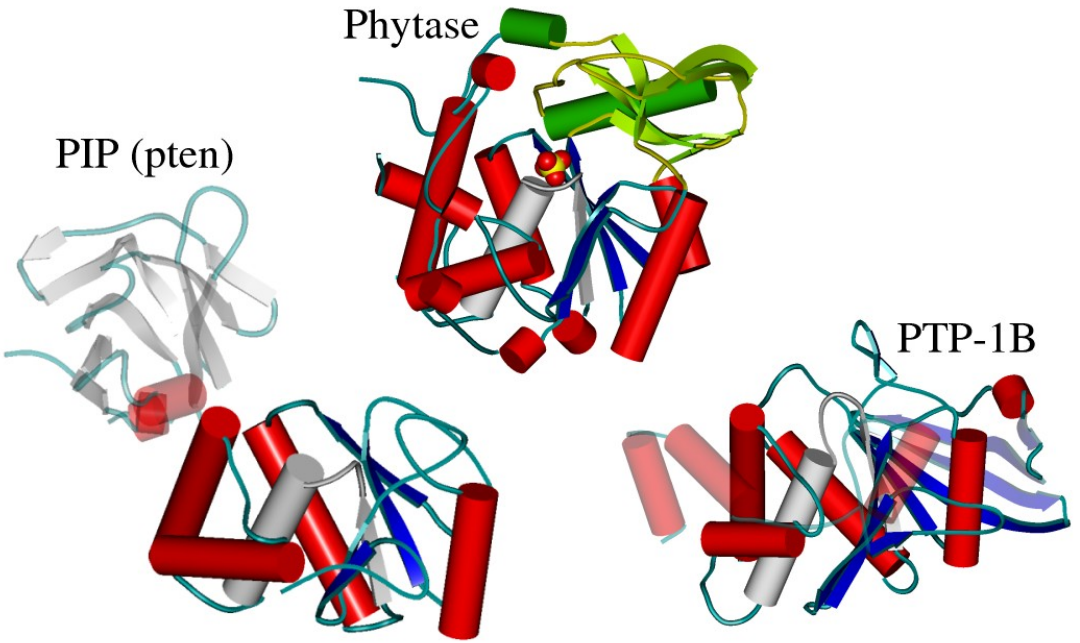
Chapter 8:
3D Structure of Proteins

Voet & Voet:
Pages 221-232, 237-271
(mostly figures)



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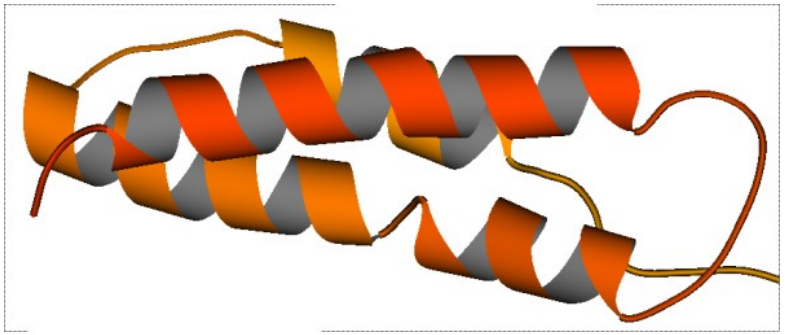
Secondary Structures

- A polymer's secondary structure is defined as *the local conformation (repeating torsion angles) of its backbone*
- For proteins, secondary structure means the *regular, repeating polypeptide backbone conformation*
  - Alternative (yet equivalent) definitions of secondary structure refer to regular, repeating patterns of backbone hydrogen bonding



A "ribbon cartoon" of a polypeptide segment containing multiple α-helical secondary structures.

- The backbone conformation of proteins is largely due to the nature of the peptide bond linking consecutive amino acid residues

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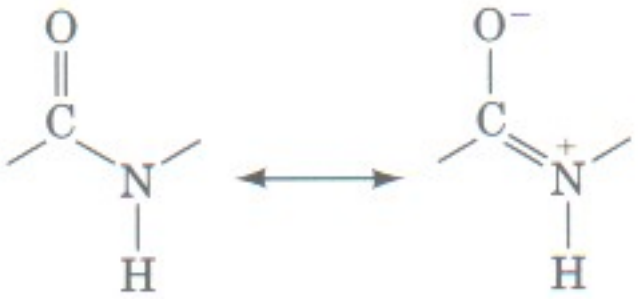
Peptide Bond

- **X-ray structures by Pauling and Corey (1930s) provided experimental evidence the peptide bond is planar and rigid**
  - **Results from resonance structures that assign the peptide bond ~40% double bond character**



  - **Supporting evidence: the C-N peptide bond is 0.13 Å shorter than a C-N single bond AND the C=O bond is 0.02 Å longer than the C=O bond of aldehydes or ketones**

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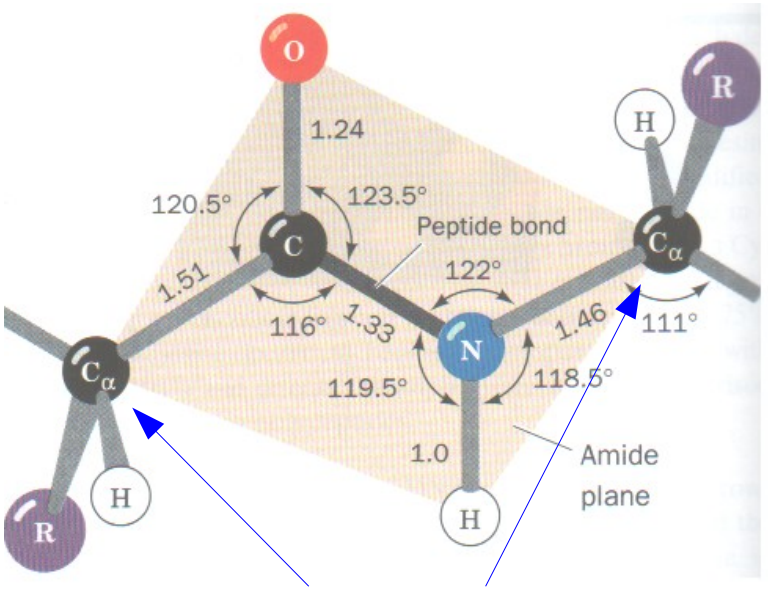
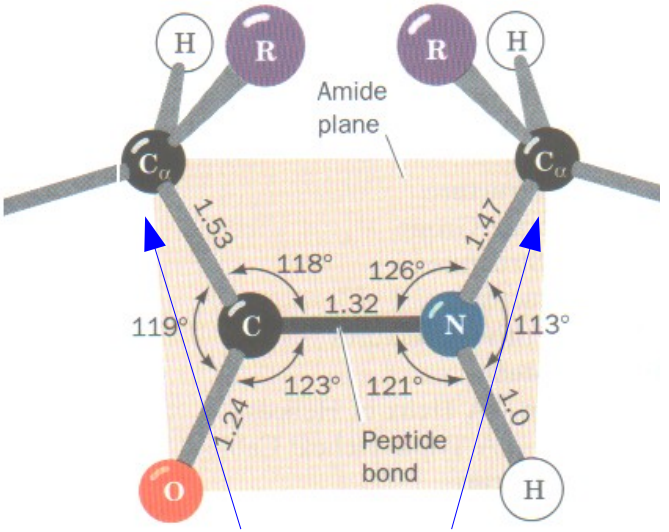
Peptide Bond Conformation

- **Peptide bonds adopt a *trans* conformation in which consecutive Cα atoms are 'above and below' the peptide bond**
  - ***trans* is favored over *cis* by ~1000 fold (reduced steric clash)**
  - **Almost all *cis* peptide bonds involve proline residues**



***trans* - Cα atoms are on opposite sides of the peptide bond**



***cis* – Cα atoms are on same sides of the peptide bond**

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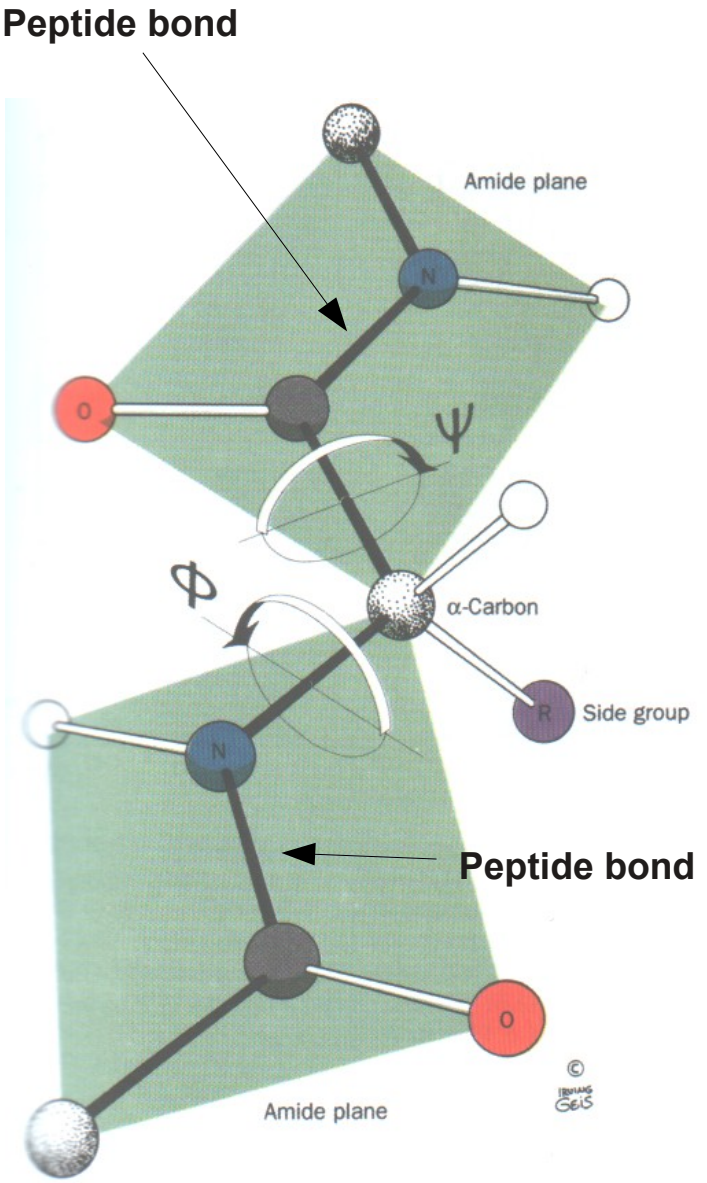
Backbone Conformation

Polypeptide backbone contains three (repeating) bonds

Bond (backbone)	Torsion Angle	Name
C – N (peptide)	Cα – C – N – Cα	Omega (ω)
N – Cα	C – N – Cα – C	Phi (ϕ)
Cα – C	N – Cα – C – N	Psi (ψ)

Given peptide bonds are almost always *trans*, the phi & psi torsion angles determine the backbone conformation

- Steric constraints limit the conformational range of backbone torsion angles
  - Larger the group attached to Cα the greater the conformational constraints



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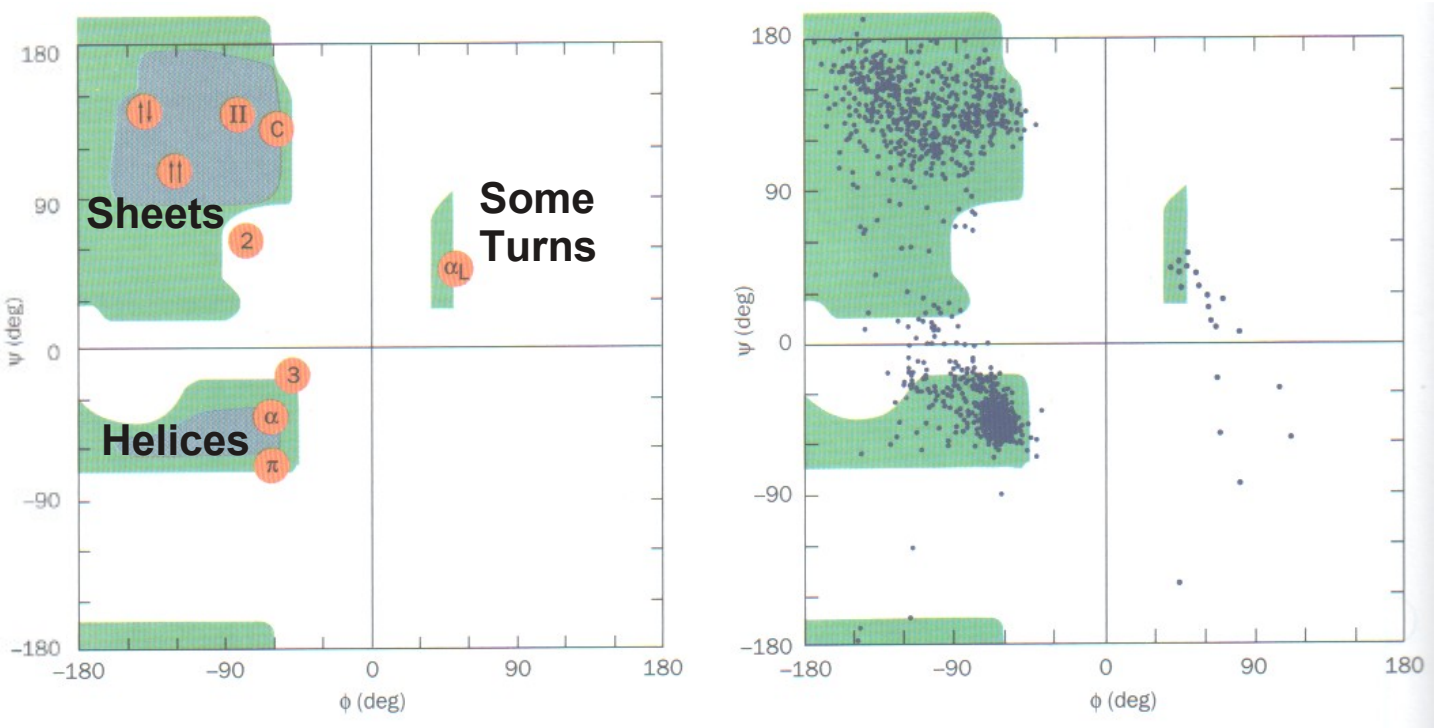
Ramachandran Plot

Sterically forbidden backbone conformations can be calculated using a tripeptide and van der Waal's radii

- **Only three small regions (~25%) of the plot are sterically allowed**



Glycine is an exception due to its small R-group

- may appear outside 'green' areas of plot

Left: Sterically allowed regions of Ramachandran plot and backbone conformation of common secondary structures

Right: Ramachandran plot for each residue of a polypeptide

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α-Helices

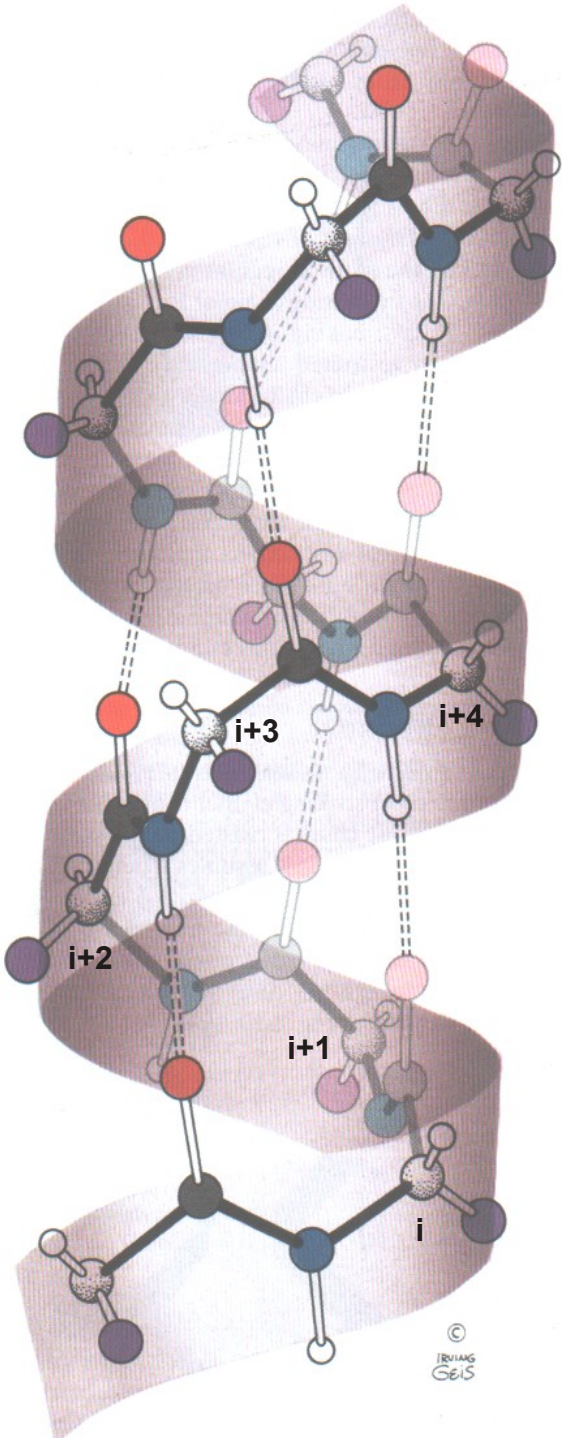
Energetically favorable conformation and hydrogen bonding interactions. Efficient packing of main-chain.

(Pauling predicted in 1951 using modeling !!!)

- **α-helices are right handed**

For left handed helices, the side chains are in steric conflict with the remainder of the helix

- **Hydrogen bonds are between residue *i* and residue *i+4***
- **n (residues/turn) = 3.6**
  pitch (distance/turn) = 5.4 Å
- **Side chains radiate out from helix and towards N-terminus (limits steric hindrance)**



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α-Helix

Helices optimize the van der Waal's packing of main-chain atoms of the helix residues

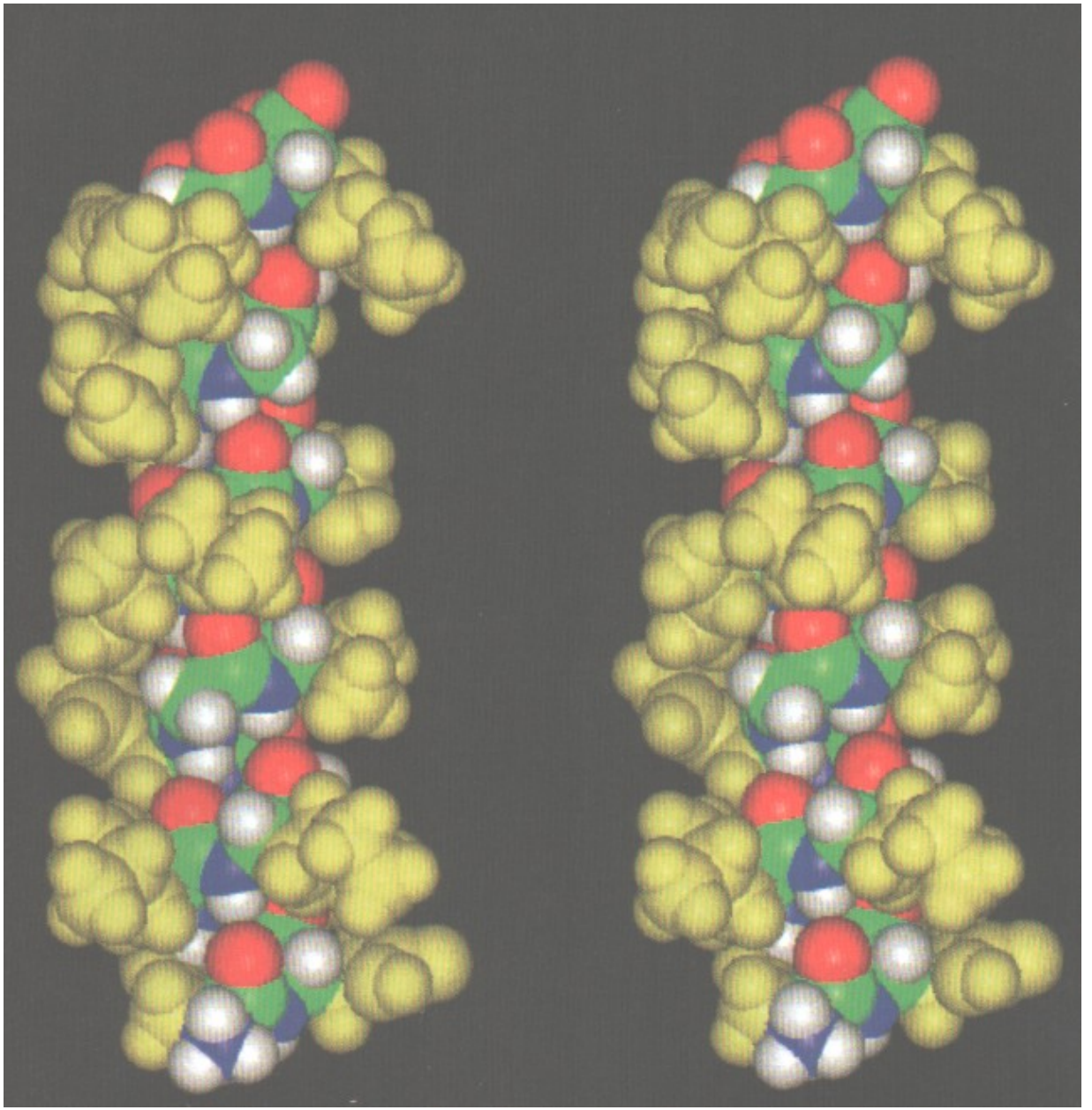

Figure: Divergent stereo diagram of an α-helix represented as a space filling model

Yellow = side chain

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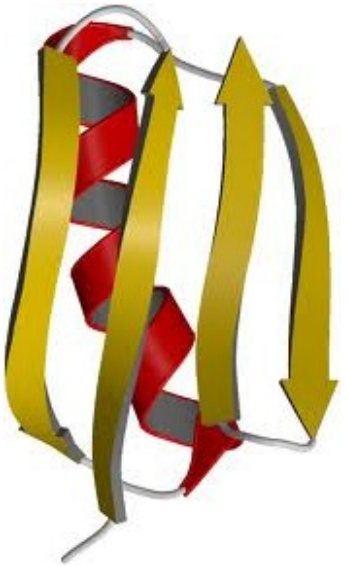
β (pleated) Sheets

- Pauling also postulated the existence of another secondary structure; the β-sheet
  - repeating ϕ and ψ torsion angles
  - utilizes full hydrogen bonding capacity of the polypeptide backbone
  - adopts an extended (linear) conformation
- Hydrogen bonding in β-sheets is between individual β-strands
- Two types of β-sheets
  - ***Antiparallel*** – individual β-strands run in opposite directions
  - ***Parallel*** – individual β-strands run in the same direction

  Note: mixtures of antiparallel and parallel β-strands also occur



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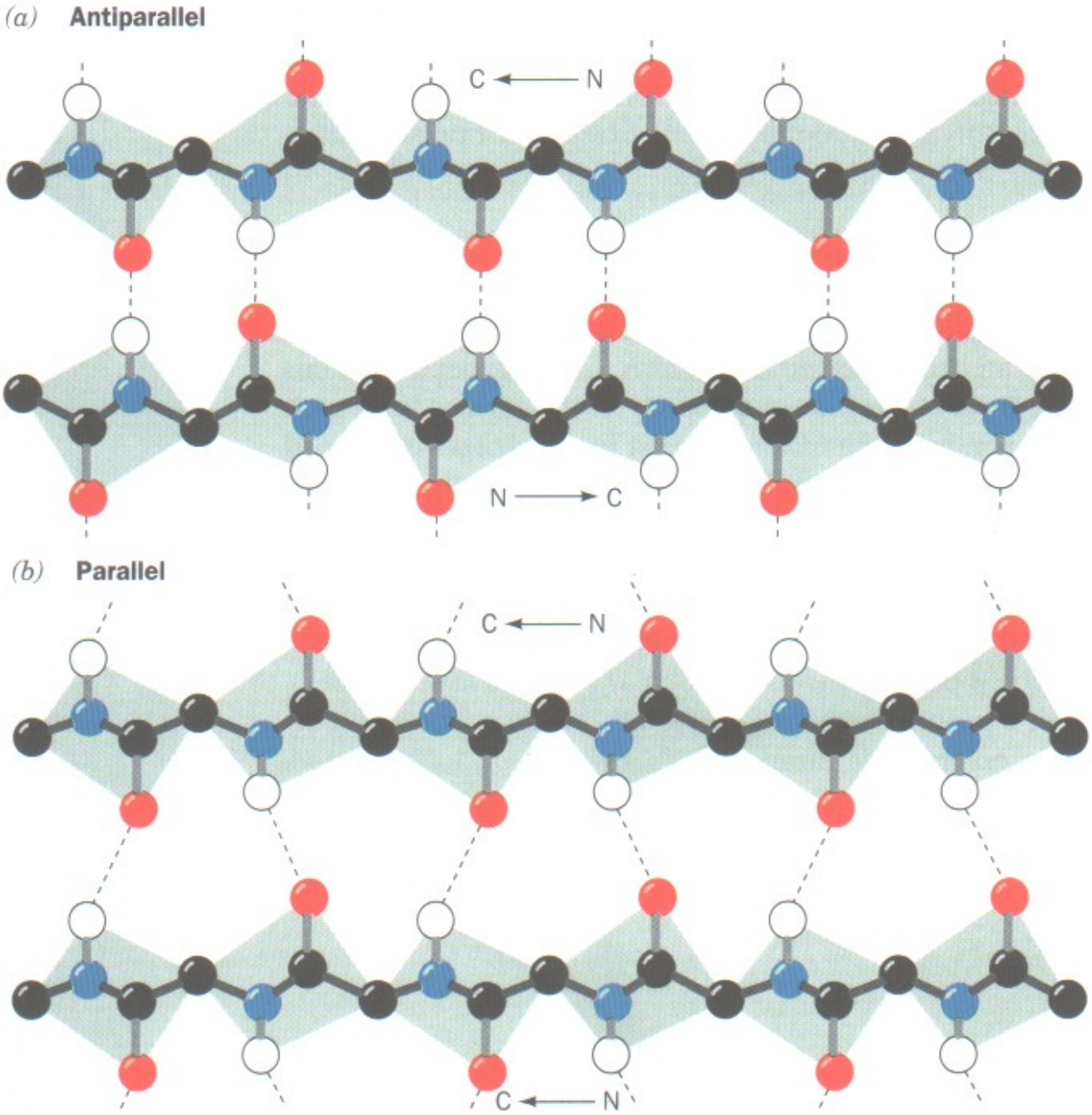
β–Sheet Structures

View perpendicular to the plane of the sheet

Antiparallel β-sheets have linear hydrogen bonds and are more stable



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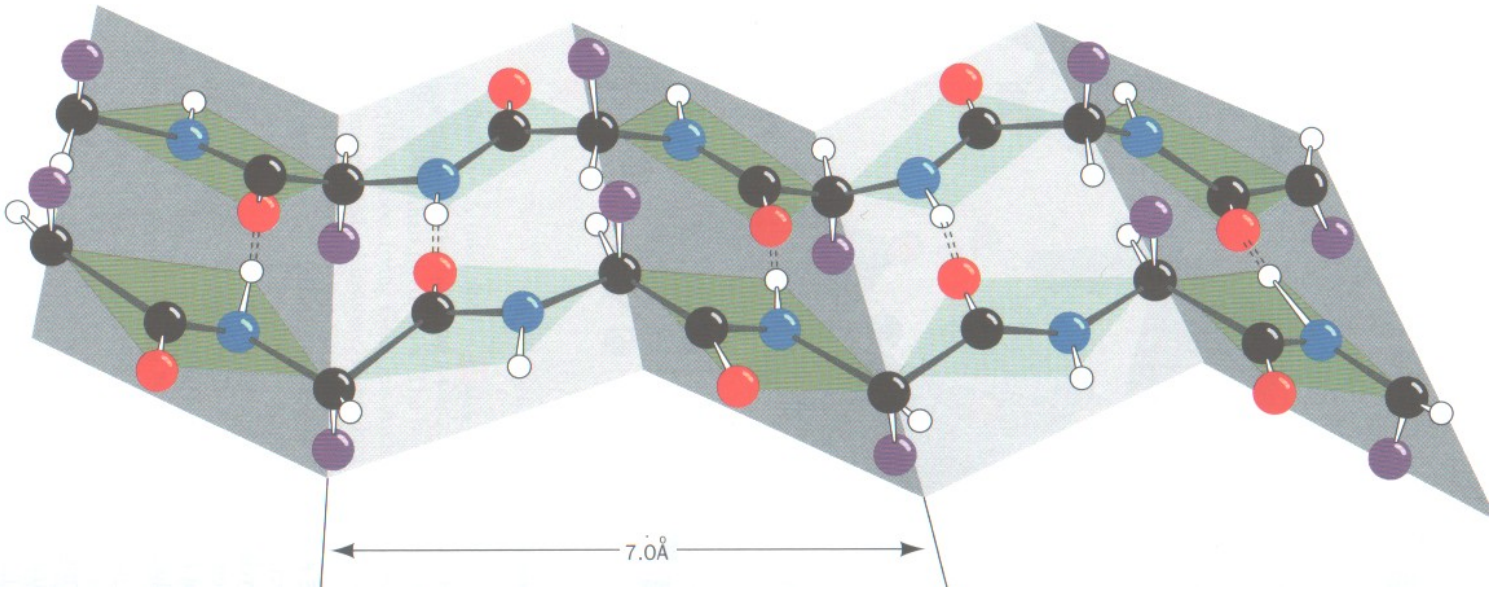
The Pleat in a β-sheet

- The ϕ and ψ torsion angles of β-sheets are not completely extended (*ie.* not 180°)
  - Results in a rippled or pleated appearance when viewed from the edge
- Allows side chains to extend orthogonal to plane of sheet and minimizes steric conflicts with the polypeptide backbone



View along plane of sheet and perpendicular to strand direction

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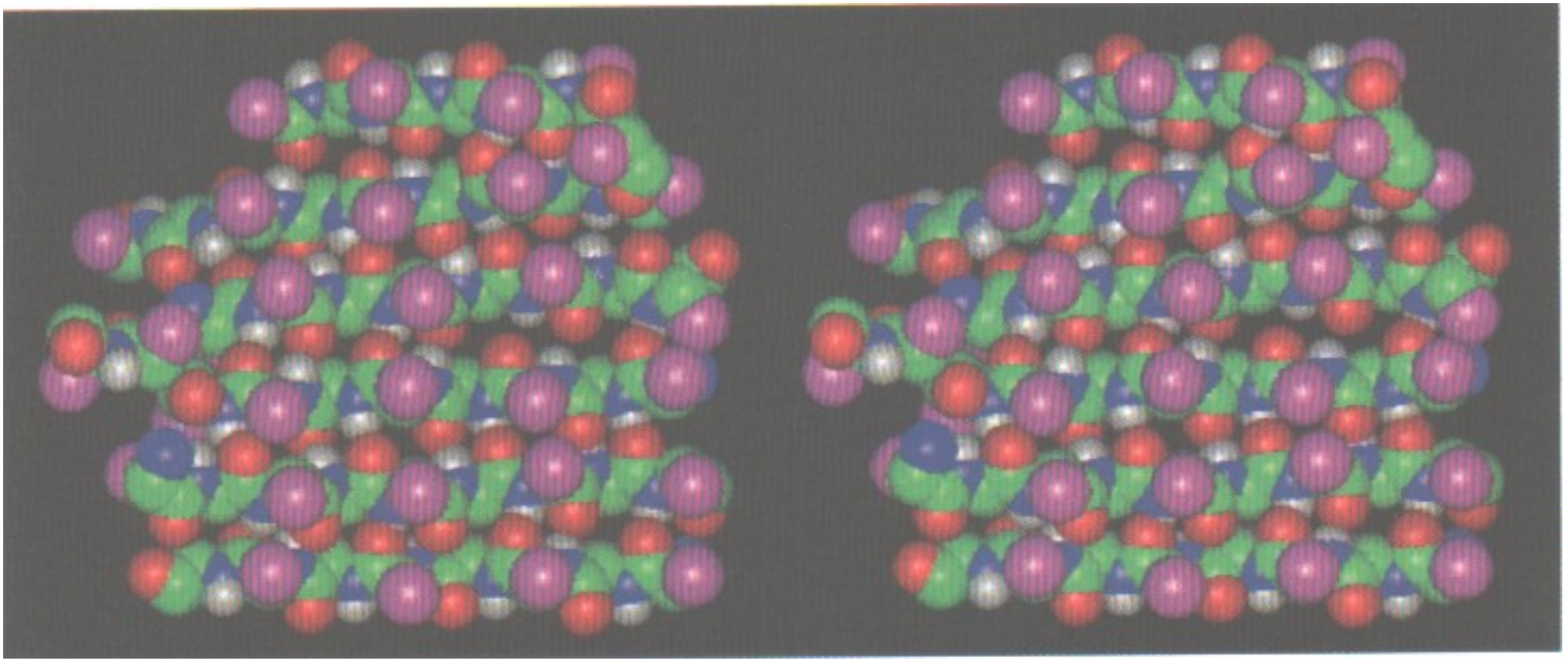
β-sheet

- The β-sheet also optimizes the van der Waal's packing of atoms of the helix residues

Figure: Divergent stereo diagram of an antiparallel β-sheet (purple side chains)



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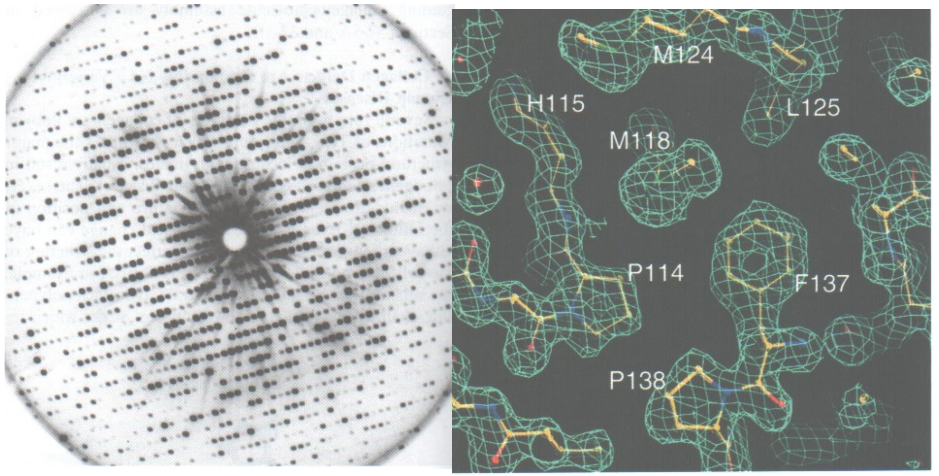
Globular Proteins

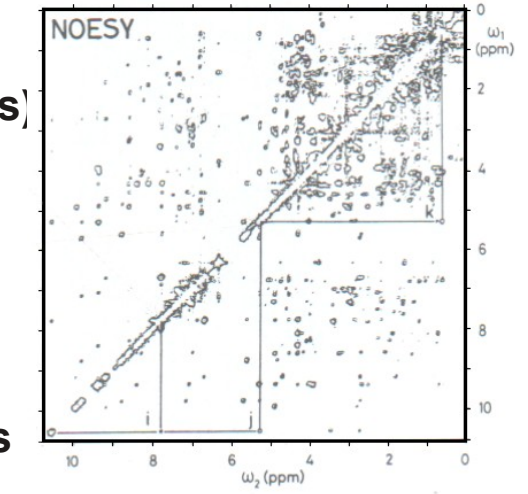
Diverse group of proteins that in their native state adopt compact spheroidal shapes

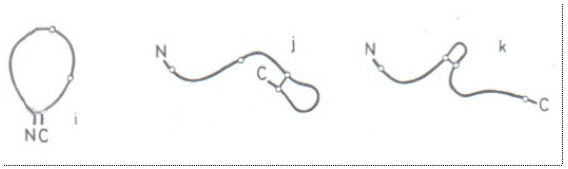
- **Includes transporters, enzymes, receptors, *etc.***
- **Knowledge of globular protein structure comes from X-ray crystallography and more recently 2D-NMR spectroscopy**
  - **Theory is complex and beyond scope of course**
  - **Not applicable to all proteins (eg. membrane proteins)**



X-ray diffraction pattern & electron density

2D-NMR spectra & NOE constraints





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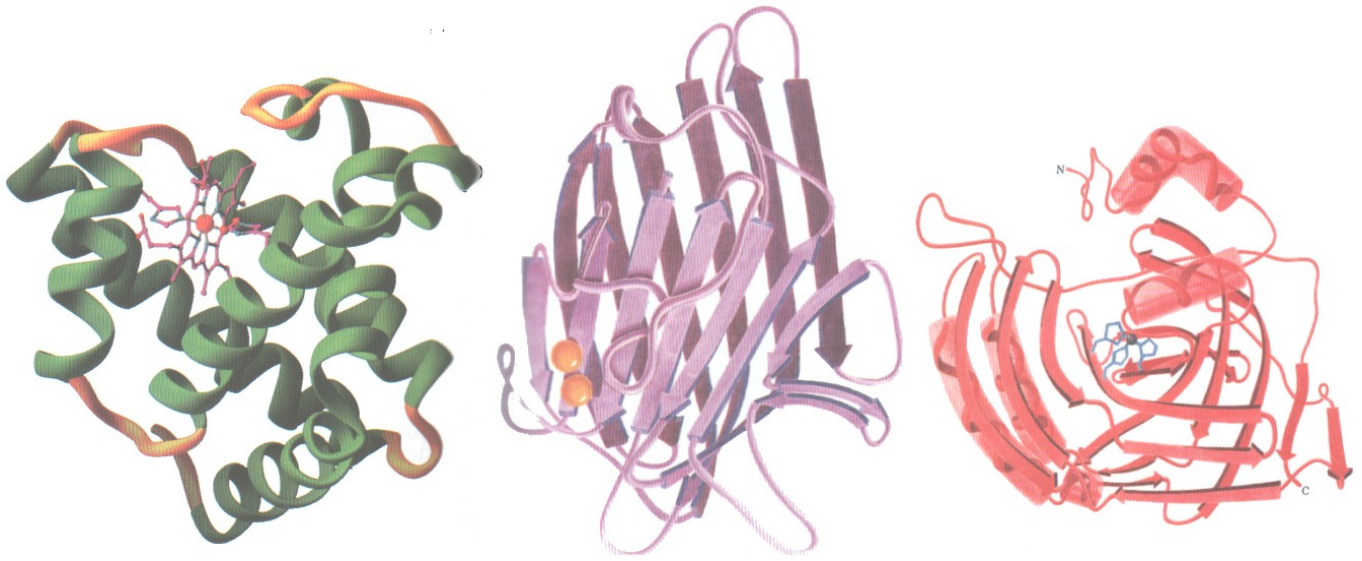
Tertiary Structure

Tertiary structure: the folding (spatial disposition) of 2° structural elements in a polypeptide and the spatial disposition of its side chains

- Each protein structure is a unique, highly complicated entity
- Protein structures share a number of common features including a significant proportion of α-helix and/or β-sheet



Examples of all helix protein(left), all sheet protein (middle) and helix and sheet protein (right)

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Side Chain Distributions
(in Tertiary Structures)

Amino acid side chains are spatially distributed according to their polarities

(1) **Nonpolar residues** largely occur in the **interior** of proteins out of contact of water – hydrophobic interaction drives this distribution and folding

(2) **Charged polar residues** largely occur on the **surface** of proteins in contact with aqueous solvent – energy of burying a charge in nonpolar environment is prohibitive

- in rare cases when charged polar residues are buried, they inevitably have a functional role such as catalysis or ion binding

(3) **Uncharged polar residues** typically occur on the surface but frequently occur within the hydrophobic core

- when uncharged polar residues occur in the hydrophobic core they form hydrogen bonds that tend to neutralize their polarity

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Side Chains Distributions: Secondary Structures

Secondary structures often have both polar & non polar surfaces (amphipathic)

- Facilitate the observed side chain distribution in tertiary structures

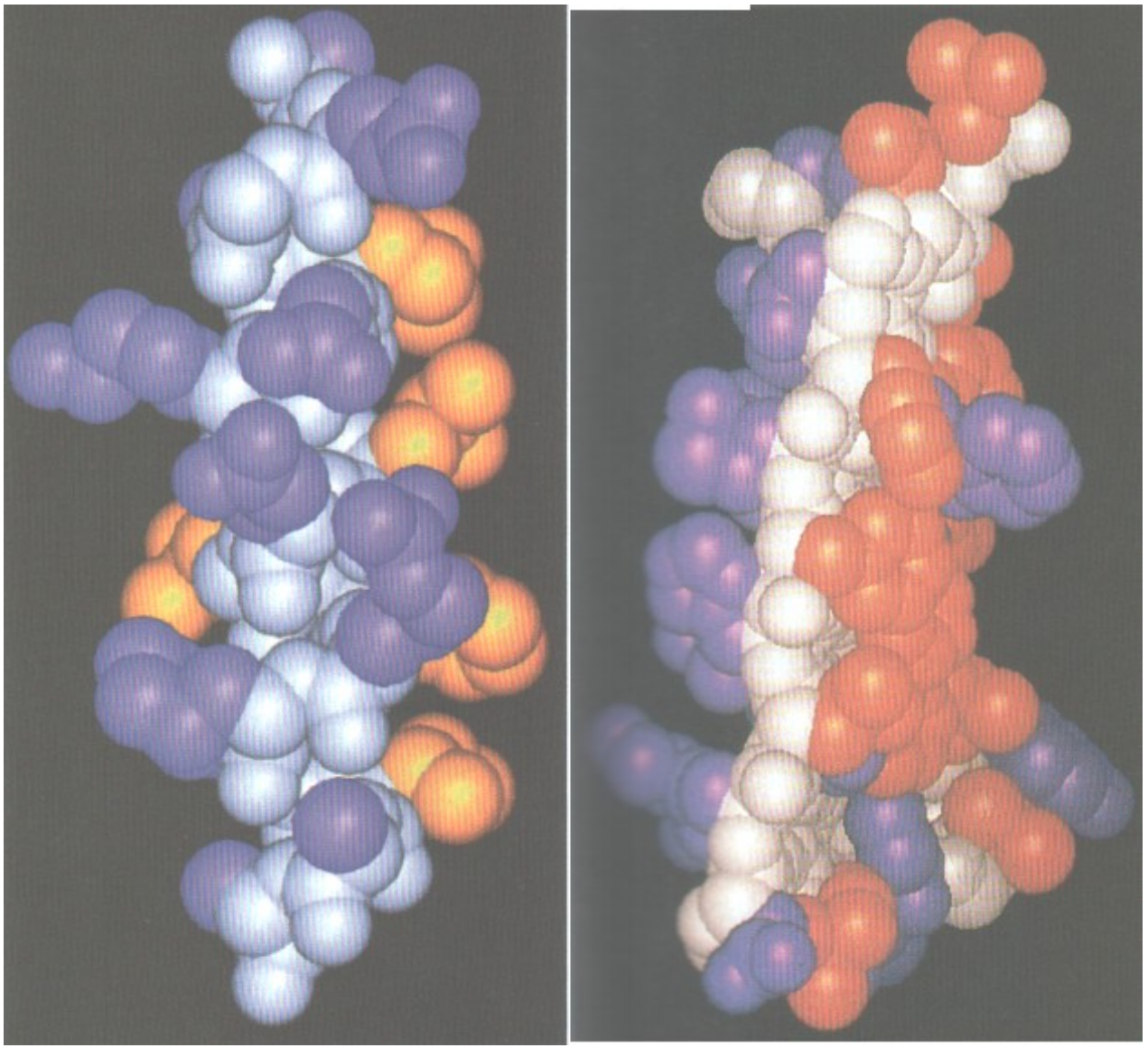

Figure: Purple is polar charged and polar uncharged side chains

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Hydrophobic Core (Interior)

- Proteins are not “oil drops with a polar coating”
  - this analogy suggests the interior of proteins is mobile or lacks organization
- **Packing density** is the ratio of the volume of atoms in a region to the total volume of the region
  - for nonpolar liquids the packing density is between 0.6-0.7
  - for globular proteins the packing density is ~0.75, which is comparable to that of molecular crystal

The interior of a protein is highly ordered and efficiently packed with side chains adopting low-energy, staggered conformations