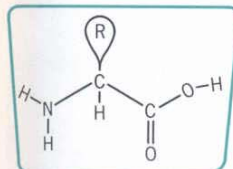


Protein Structure and Dynamics

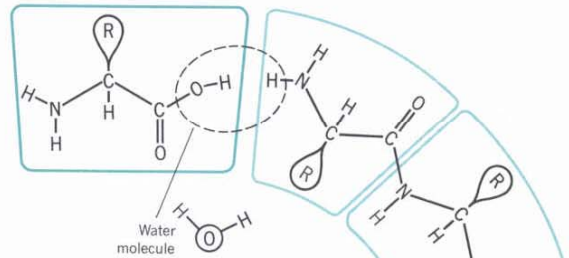
Key concepts

- Proteins have well defined 3D structure
- Structural hierarchy: from primary to tertiary
-
- Proteins are not static

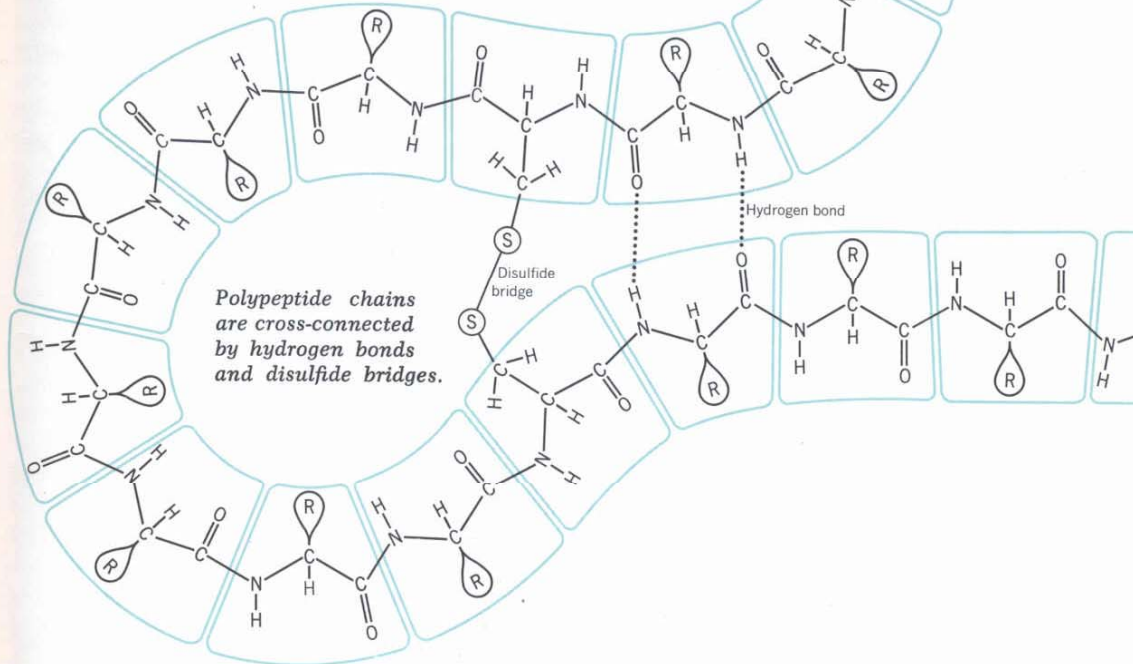
A protein consists of a sequence of amino acids bound by peptide bonds



THE AMINO ACID MONOMER



The peptide bond formed between amino acids by loss of a water molecule joins identical units to make the backbone of the polypeptide chain. The variable side chains (R) give each protein chain its distinctive character. The folding of the chain in three dimensions is considered later.



Polypeptide chains are cross-connected by hydrogen bonds and disulfide bridges.

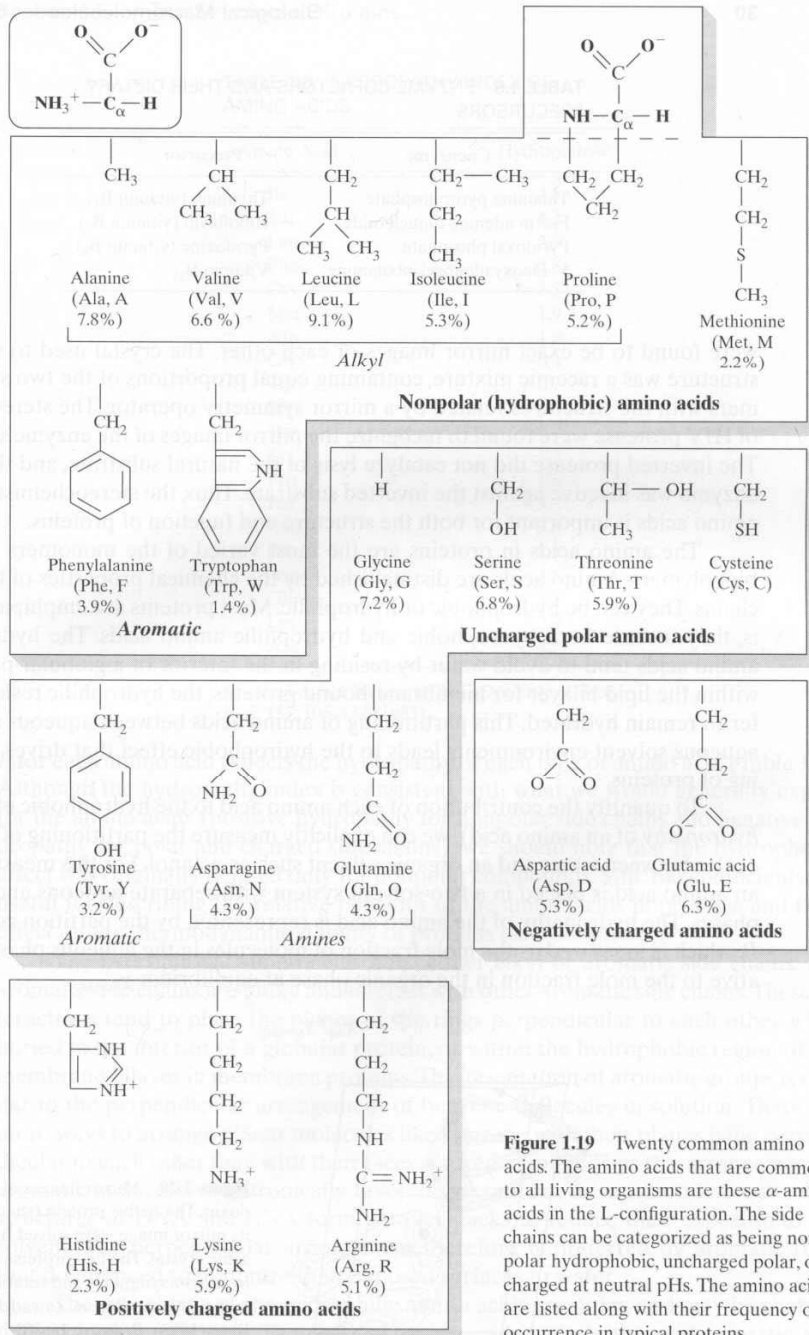


Figure 1.19 Twenty common amino acids. The amino acids that are common to all living organisms are these α -amino acids in the L-configuration. The side chains can be categorized as being nonpolar hydrophobic, uncharged polar, or charged at neutral pHs. The amino acids are listed along with their frequency of occurrence in typical proteins.

- Only 20 different types of amino acids are used by proteins
- Bonding of amino acids in different sequences makes all the protein diversity

Definition of dihedral angles

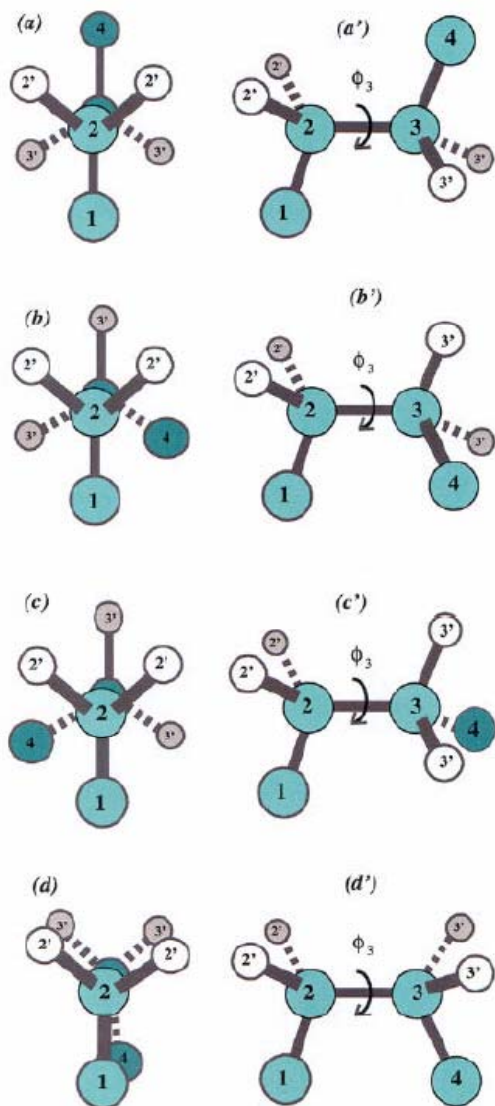
Range: -180° to 180°

$180^{\circ} = \text{trans}$

$-60^{\circ} = \text{gauche}^{+}$

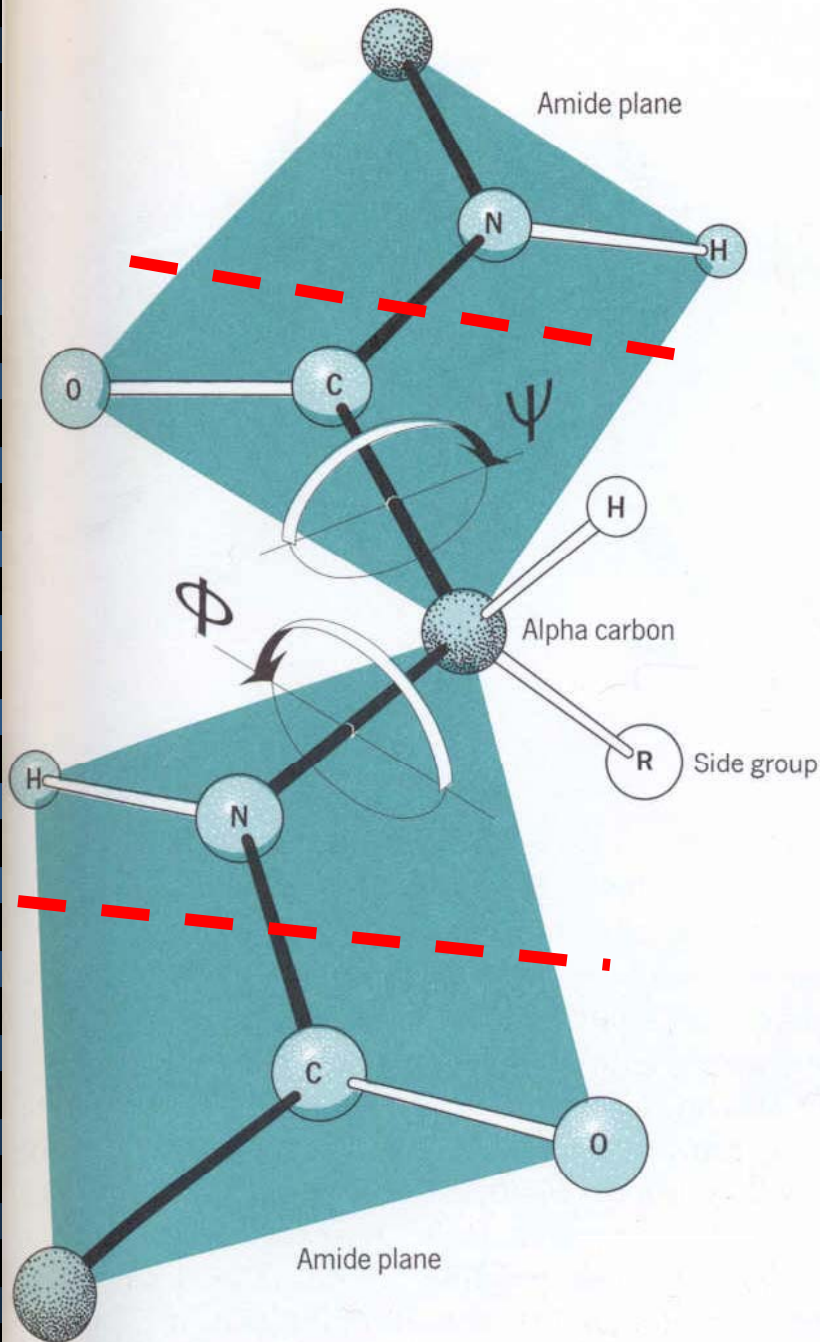
$60^{\circ} = \text{gauche}^{-}$

$0^{\circ} = \text{cis}$



Peptide chain local geometry

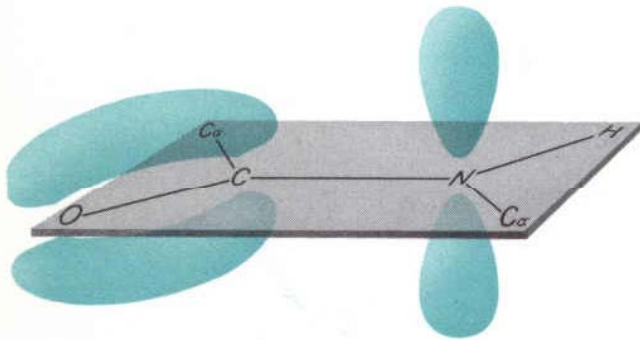
- Peptide plane is formed by C_{α} , C, O, N, H, C_{α} atoms
- ω angle is formed by Ca-C-N-Ca
- ϕ angle is formed by C-N-Ca-C
- ψ angle is formed by N-Ca-C-N
- rotations about ϕ and ψ angles are the softest



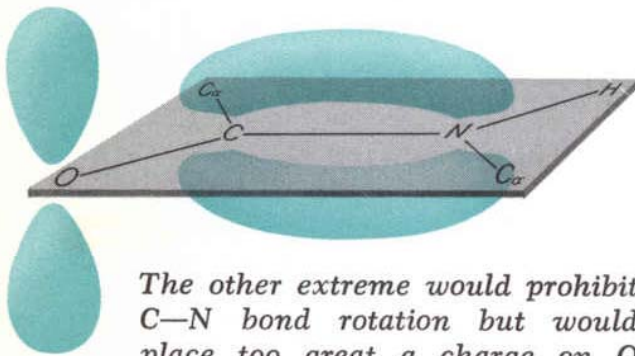
The peptide plane



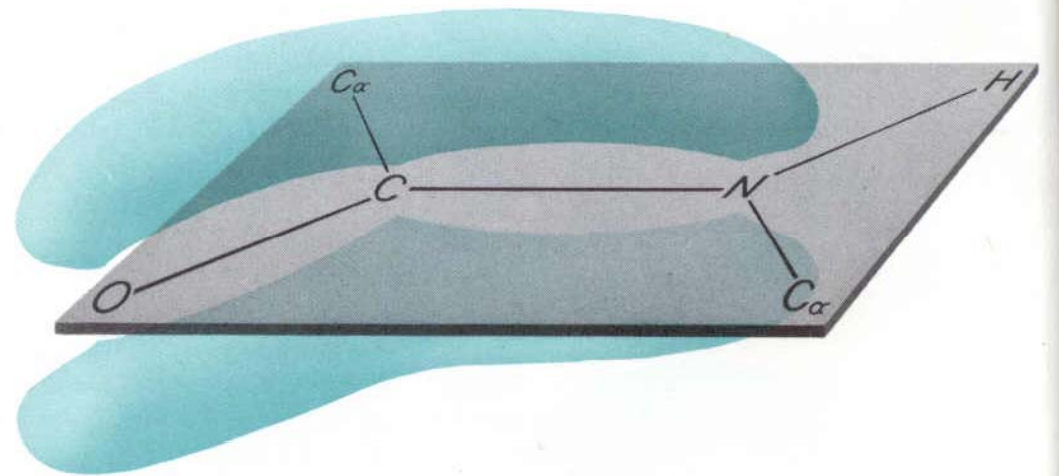
The link between carbonyl carbon and nitrogen ($-\text{CO}-\text{NH}-$) is the fundamental structural unit of the polypeptide chain.



A pure double bond between C and O would permit free rotation around the C—N bond.

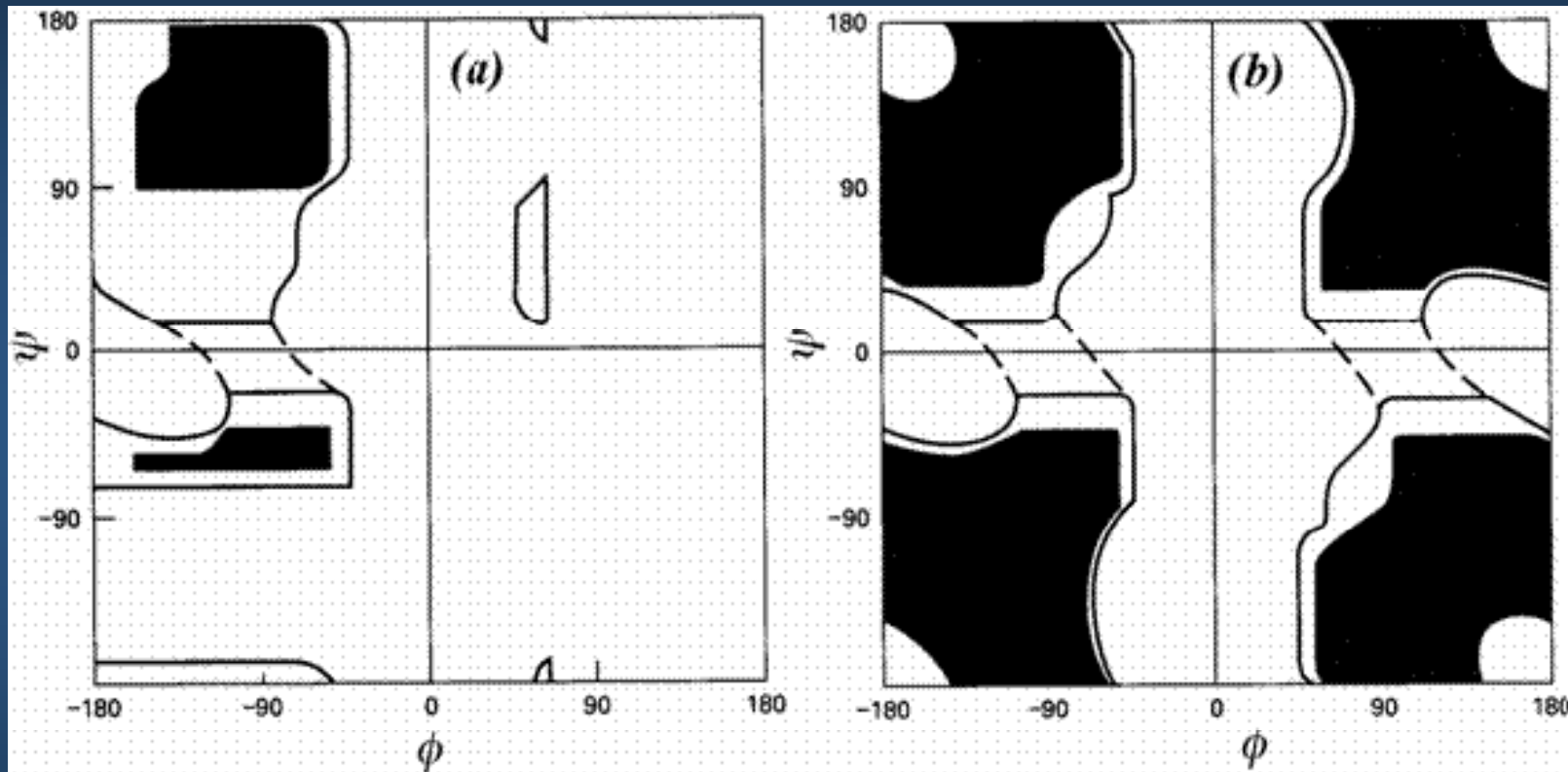


The other extreme would prohibit C—N bond rotation but would place too great a charge on O and N.



The true electron density is intermediate. The barrier to C—N bond rotation of about 21 kcal/mole is enough to keep the amide group planar.

Local restrictions on flexibility: the Ramachandran plot



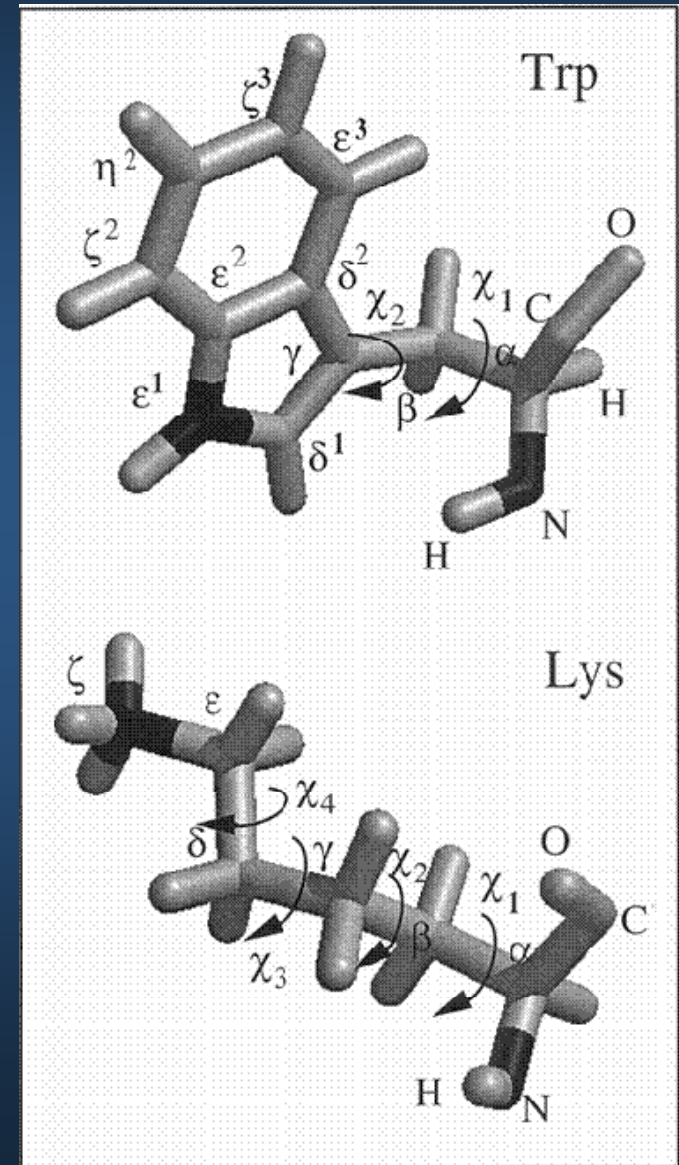
All residues

Glycine

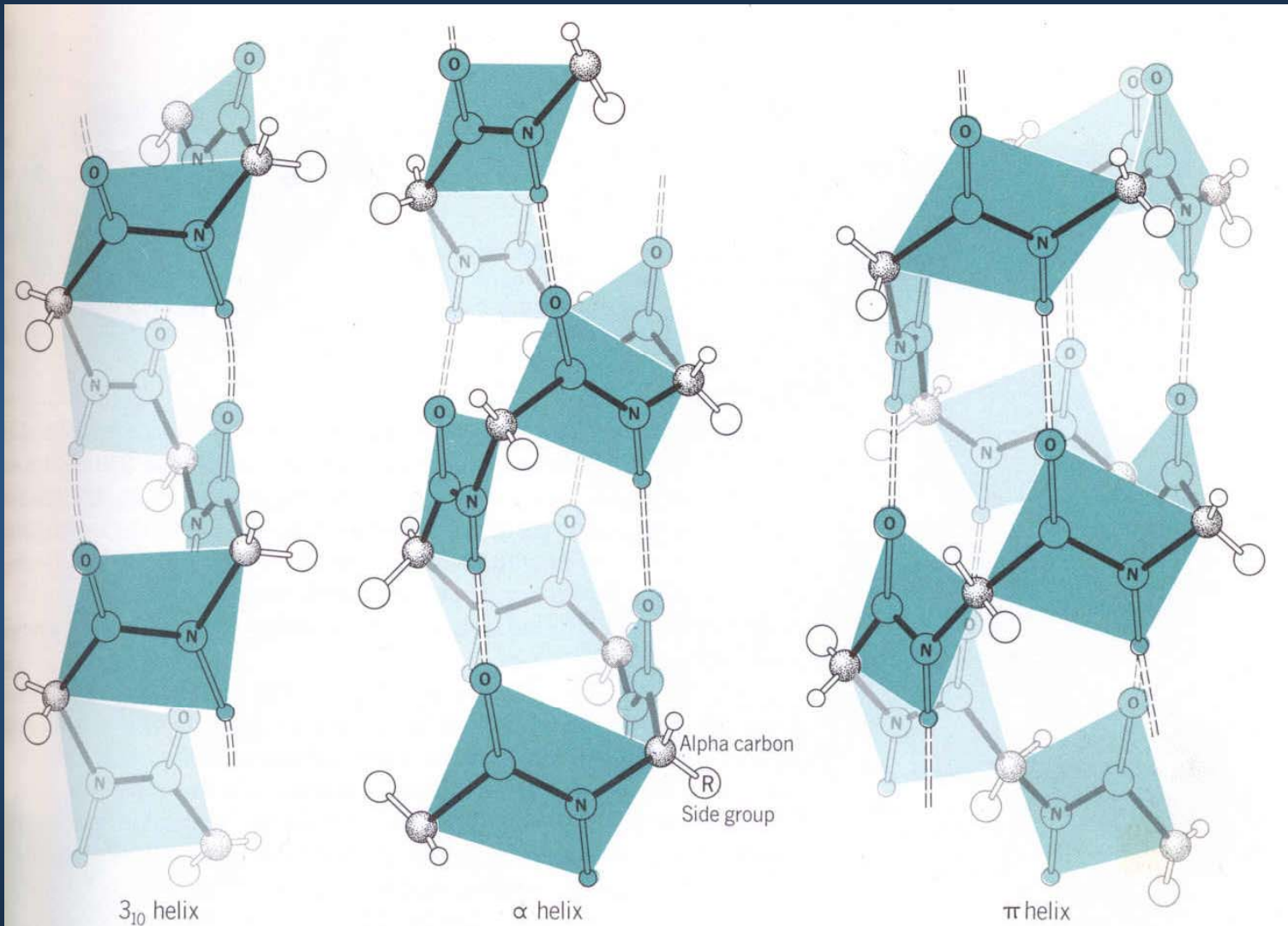
The presence of chiral C α atoms in Ala (and in all other amino acids) is responsible for the asymmetric distribution of dihedral angles in part (a), and the presence of C β excludes the portions that are accessible in Gly.

Side chains enjoy additional degrees of freedom

Side-chain angles		χ_1	χ_2	χ_3	χ_4			Atom position fixed by	
RESIDUE	ATOM	α	β	γ	δ	ϵ	ζ		η
Gly		•							Main chain
Ala		••							
Pro		•••							
Val		••	••						χ_1
Cys		••	••	S					
Ser		••	••	O					
Thr		••	••	O					
Ile		••	••	••					χ_1 and χ_2
Leu		••	••	••	••				
Asp		••	••	••	O	O			
Asn		••	••	••	O	N			
His		••	••	••	N	N			
Phe		••	••	••	••	••			
Tyr		••	••	••	••	••	O		
Trp		••	••	••	••	••	N		
Met		••	••	••	S	••			χ_1, χ_2 and χ_3
Glu		••	••	••	••	O	O		
Gln		••	••	••	••	O	N		
Lys		••	••	••	••	••	N		χ_1, χ_2, χ_3 and χ_4
Arg		••	••	••	••	N	N	N	

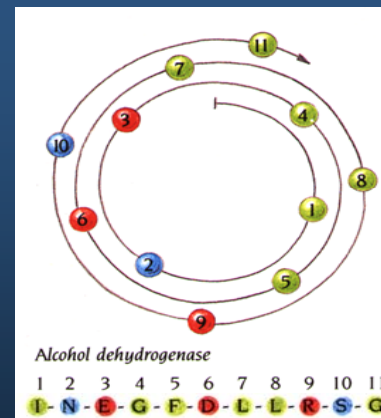
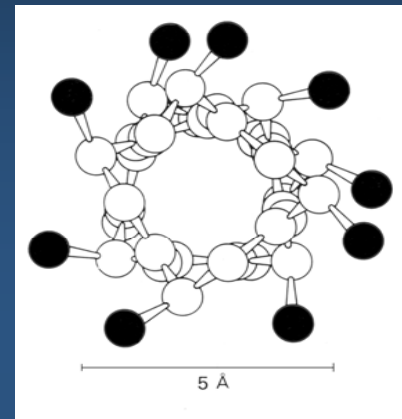
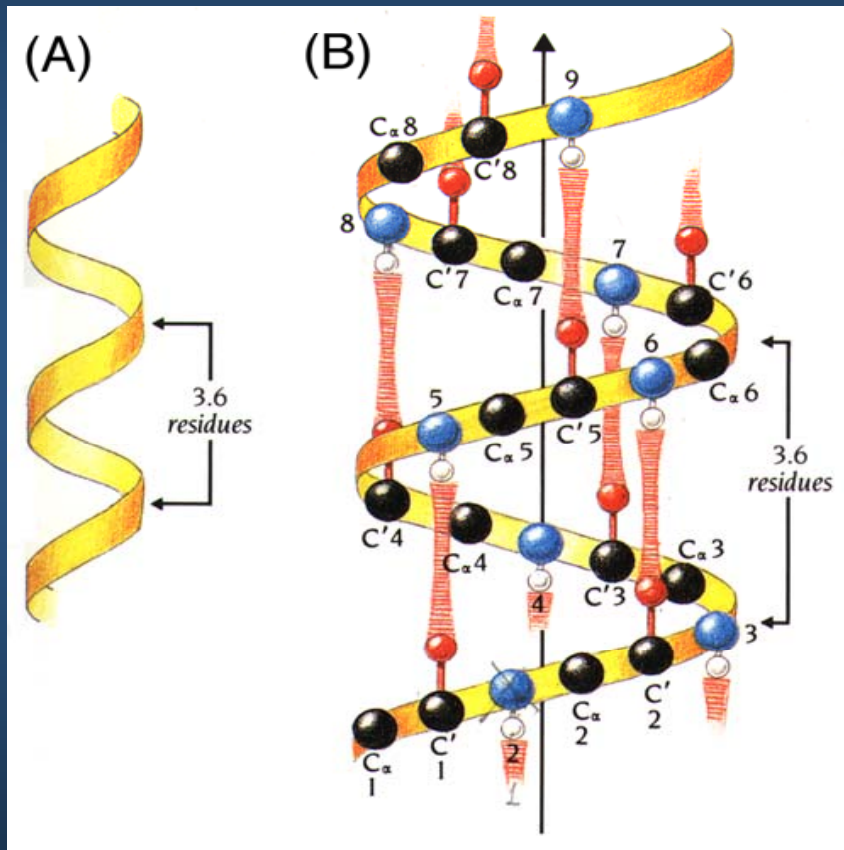


Secondary structure: helices



The 3_{10} , α , and π helices differ in their patterns of hydrogen bonding, as shown below. Hydrogen bonds in the α helix are particularly unstrained, making the α helix especially stable. The α carbons are stippled, with small attached spheres for hydrogens and larger spheres for side groups.

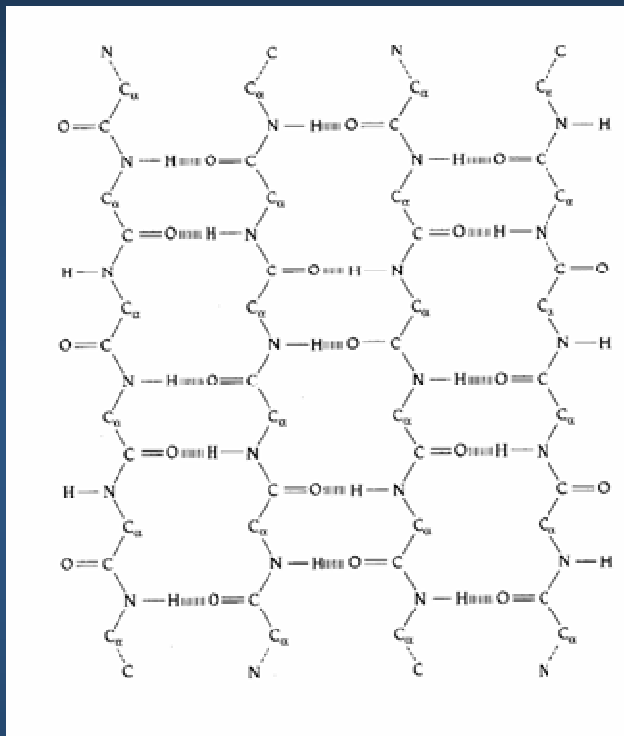
A closer look at Alpha-helix



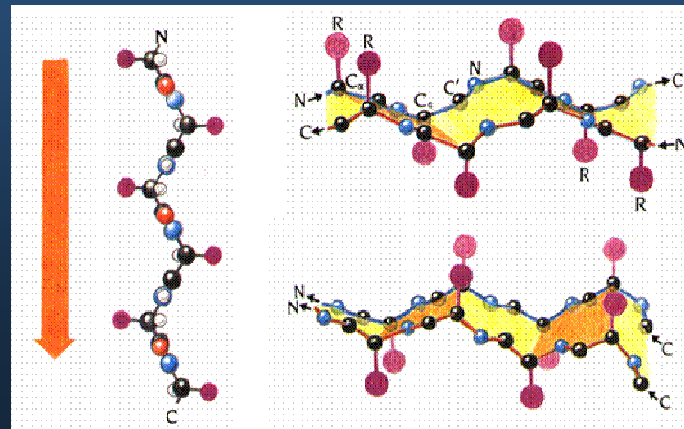
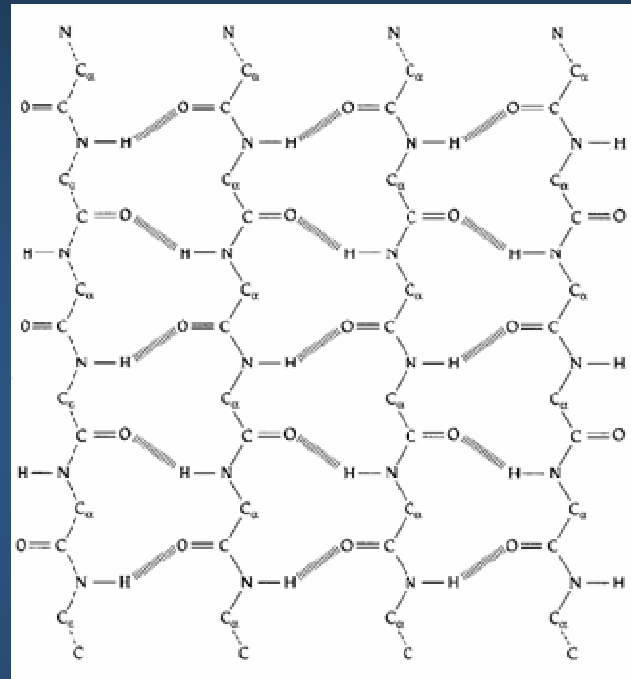
Helical wheel diagram

Secondary structure: β -sheets

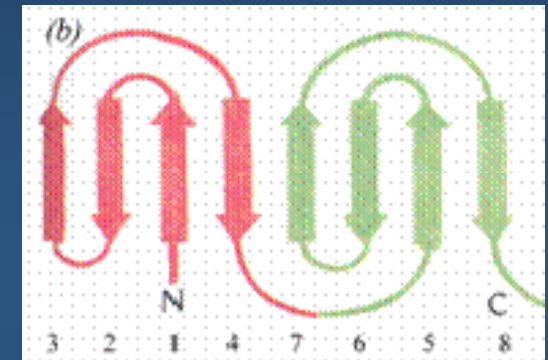
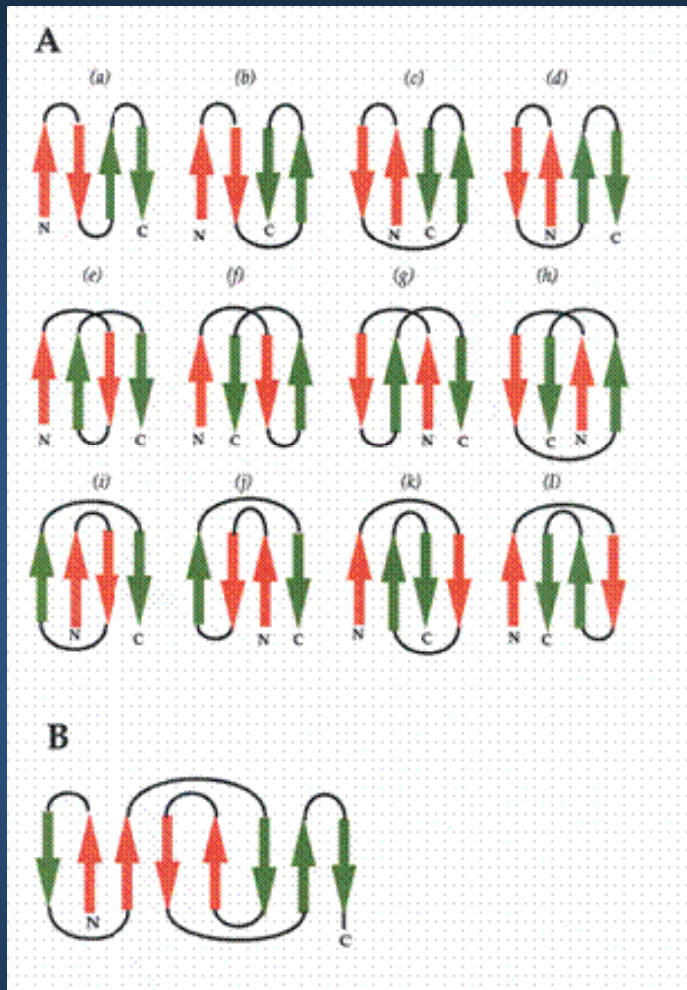
Antiparallel β -sheet



Parallel β -sheet



Supersecondary structures



Schematic view of a β -barrel fold formed by the combination of two Greek key motifs, shown in red and green, and the topology diagram of the Greek key motifs forming the fold (adapted from Branden and Tooze, 1999)

Only those topologies where sequentially adjacent b-strands are antiparallel to each other are displayed. (A) 12 different ways to form a four-stranded β -sheet from two β -hairpins (red and green), if the consecutive strands 2 and 3 are assumed to be antiparallel. Not all topologies are equally probable. (j) and (l) are the most common topologies, also known as Greek key motifs; (a) is also relatively frequent; whereas (b), (c), (e), (f), (h), (i) and (k) have not been observed in known structures (Branden and Tooze, 1999).

Tertiary Structure

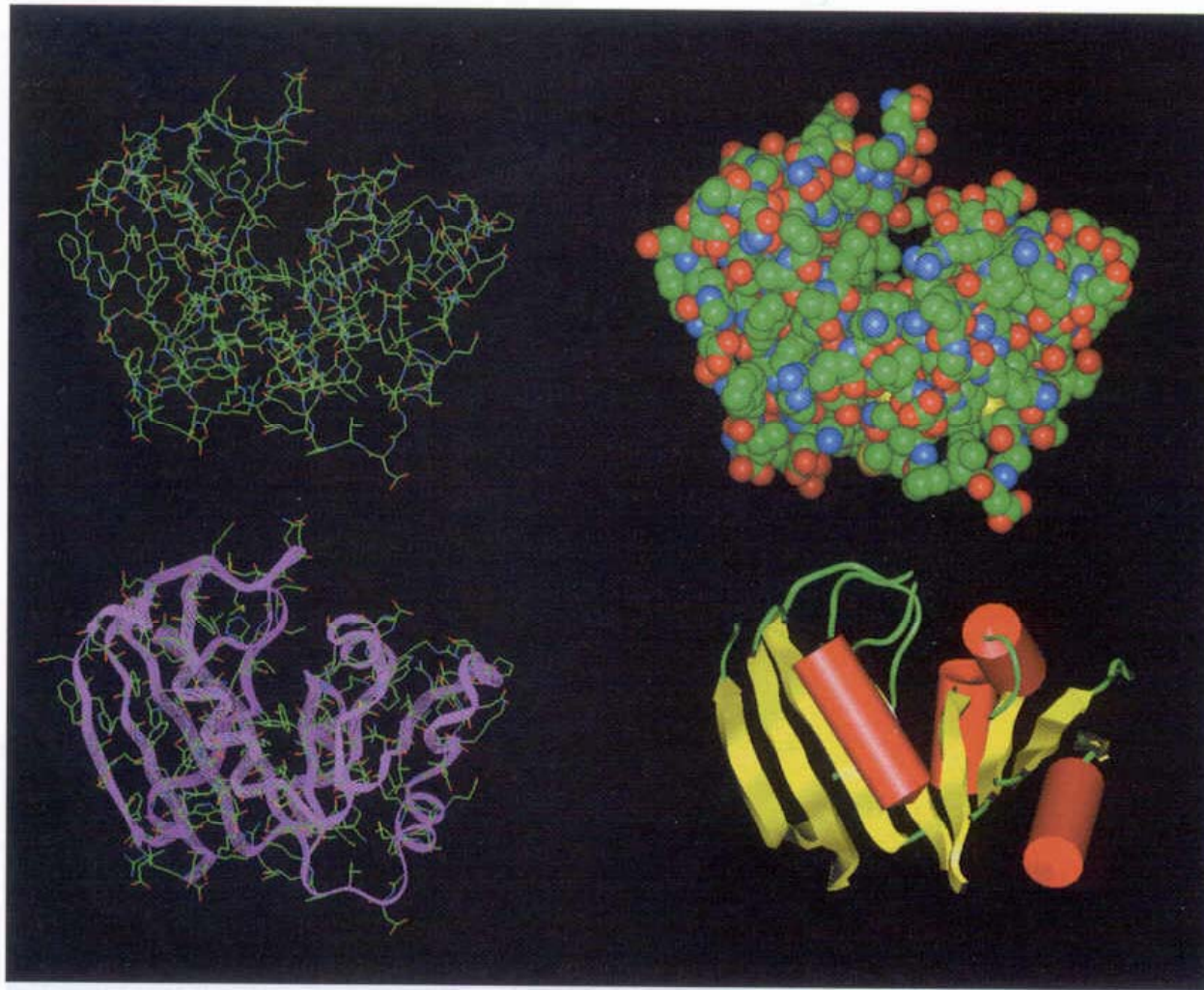
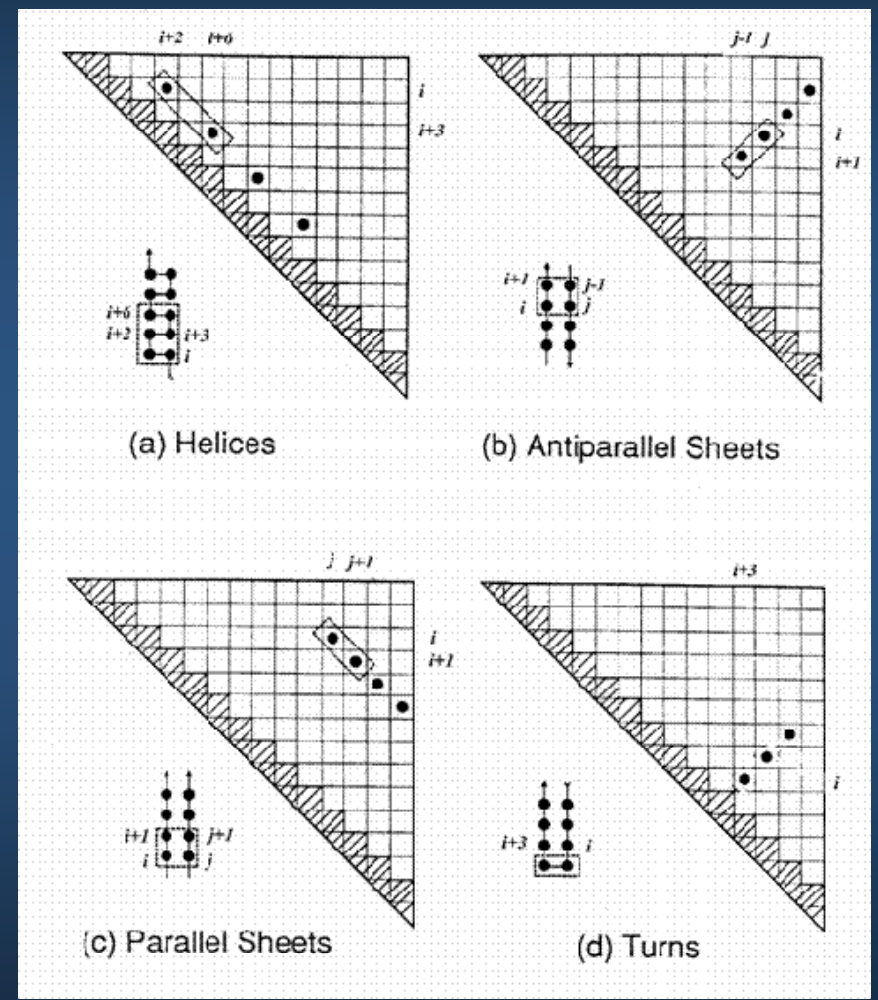
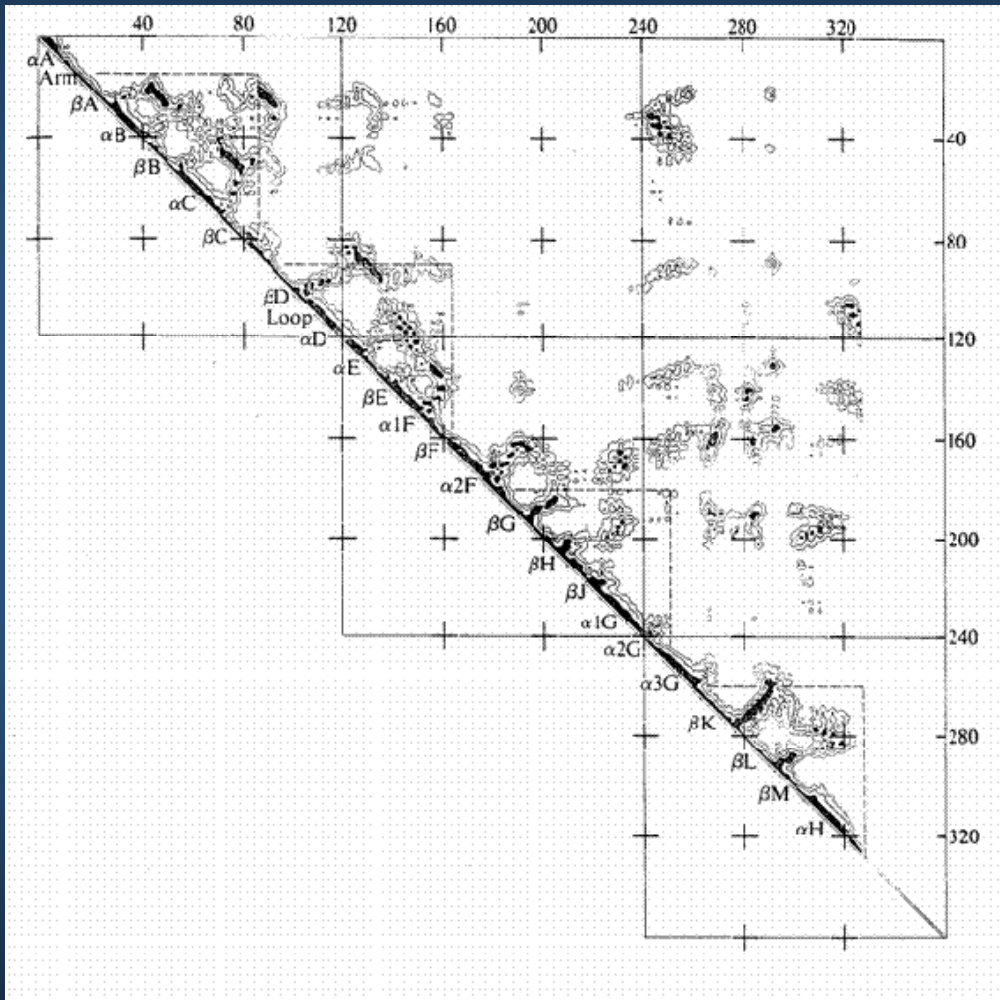


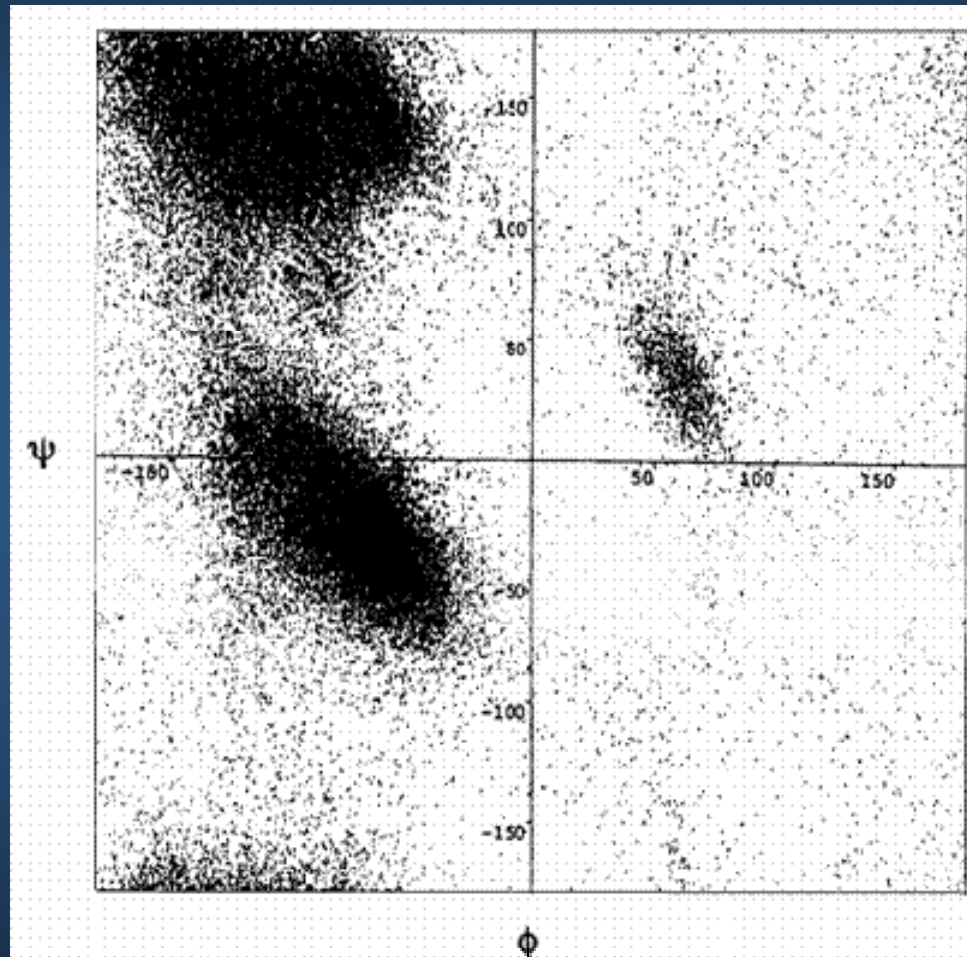
Fig. 1.5: Graphical representations of proteins illustrated using the enzyme dihydrofolate reductase [Bolin et al. 1982]. Clockwise from top left: stick, CPK, 'cartoon' and 'ribbon'.

[Leach]

Contact Maps Describe Protein Topologies



Dihedral angle distribution of database structures



Dots represent the observed (ϕ , ψ) pairs in 310 protein structures in the Brookhaven Protein Databank (adapted from (Thornton, 1992))

The Protein Data Bank (PDB)

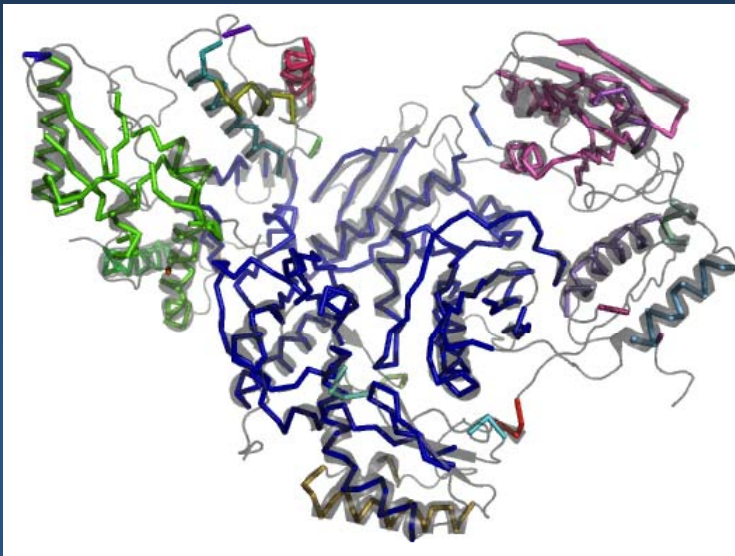
- Electronic storage, in standard format, of thousands of protein structures – including wild-type, mutants, ligand-bound, and protein-protein complexes
- Freely downloadable
- (x,y,z) coordinates of atoms given
- Data from X-ray, NMR, modelling
- <http://rutgers.rcsb.org/pdb/>

HEADER	CALCIUM-BINDING PROTEIN	29-SEP-92	1CLL	1CLL	2
COMPND	CALMODULIN (VERTEBRATE)			1CLL	3
SOURCE	HUMAN (HOMO SAPIENS) RECOMBINANT FORM			1CLL	4
AUTHOR	R.CHATTOPADHYAYA, F.A. QUIOCHO			1CLL	5
REVDAT	1 31-OCT-93 1CLL 0			1CLL	6
JRNL	AUTH R.CHATTOPADHYAYA, W.E.MEADOR, A.R.MEANS, F.A. QUIOCHO			1CLL	7
JRNL	TITL CALMODULIN STRUCTURE REFINED AT 1.7 ANGSTROMS			1CLL	8
JRNL	TITL 2 RESOLUTION			1CLL	9
JRNL	REF J.MOL.BIOL.	V. 228	1177 1992	1CLL	10

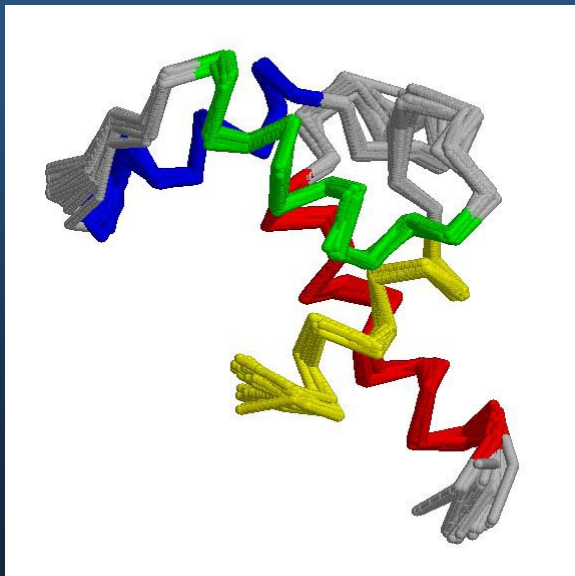
HELIX	1 I THR	5 PHE	19 1	1CLL	130
HELIX	2 II THR	29 ARG	37 1	1CLL	131
HELIX	3 III GLU	45 VAL	55 1	1CLL	132
HELIX	4 IV PHE	65 PHE	92 1 SEE REMARK 6	1CLL	133

ATOM	1 N LEU	4	-6.873	21.082	25.312	1.00	49.53	1CLL	148
ATOM	2 CA LEU	4	-6.696	22.003	26.447	1.00	48.82	1CLL	149
ATOM	3 C LEU	4	-6.318	23.391	25.929	1.00	46.50	1CLL	150
ATOM	4 O LEU	4	-5.313	23.981	26.352	1.00	45.72	1CLL	151
ATOM	5 N THR	5	-7.147	23.871	25.013	1.00	46.77	1CLL	152
ATOM	6 CA THR	5	-6.891	25.193	24.428	1.00	46.84	1CLL	153
ATOM	7 C THR	5	-6.801	26.228	25.543	1.00	45.36	1CLL	154
ATOM	8 O THR	5	-5.829	26.999	25.561	1.00	47.41	1CLL	155
ATOM	9 CB THR	5	-7.923	25.626	23.323	1.00	46.33	1CLL	156
ATOM	10 OG1 THR	5	-9.238	25.386	23.908	1.00	48.28	1CLL	157
ATOM	11 CG2 THR	5	-7.704	24.943	21.974	1.00	44.31	1CLL	158
ATOM	12 N GLU	6	-7.781	26.217	26.419	1.00	46.42	1CLL	159
ATOM	13 CA GLU	6	-7.858	27.154	27.557	1.00	45.65	1CLL	160
ATOM	14 C GLU	6	-6.502	27.343	28.224	1.00	44.22	1CLL	161
ATOM	15 O GLU	6	-6.040	28.483	28.423	1.00	42.97	1CLL	162
ATOM	16 CB GLU	6	-8.881	26.726	28.592	1.00	50.13	1CLL	163
ATOM	17 CG GLU	6	-9.358	27.699	29.657	1.00	55.79	1CLL	164
ATOM	18 CD GLU	6	-10.322	27.149	30.668	1.00	58.96	1CLL	165
ATOM	19 OE1 GLU	6	-10.775	26.034	30.334	1.00	62.89	1CLL	166
ATOM	20 OE2 GLU	6	-10.648	27.701	31.706	1.00	60.58	1CLL	167
ATOM	21 N GLU	7	-5.878	26.224	28.555	1.00	41.38	1CLL	168
ATOM	22 CA GLU	7	-4.554	26.201	29.194	1.00	39.78	1CLL	169

Protein dynamics: proteins are NOT static



- X-ray structures can be misleading:
 - appear static
 - subject to crystal-lattice artifacts



NMR PDB files often contain many structures consistent with data

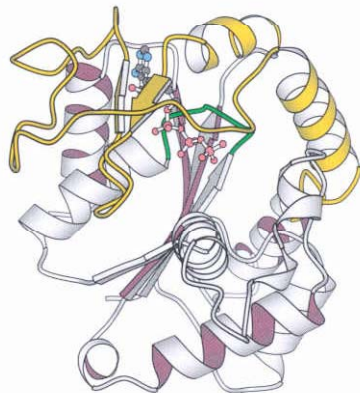
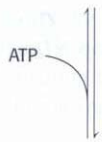
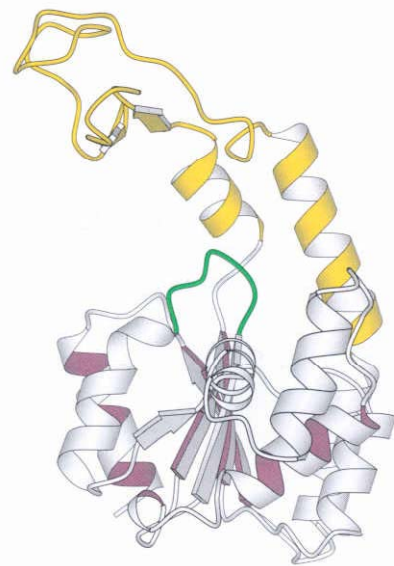
1AK8.pdb (calcium-bound calmodulin)
Note local fluctuations – e.g., helix-fraying


Large Structural Changes

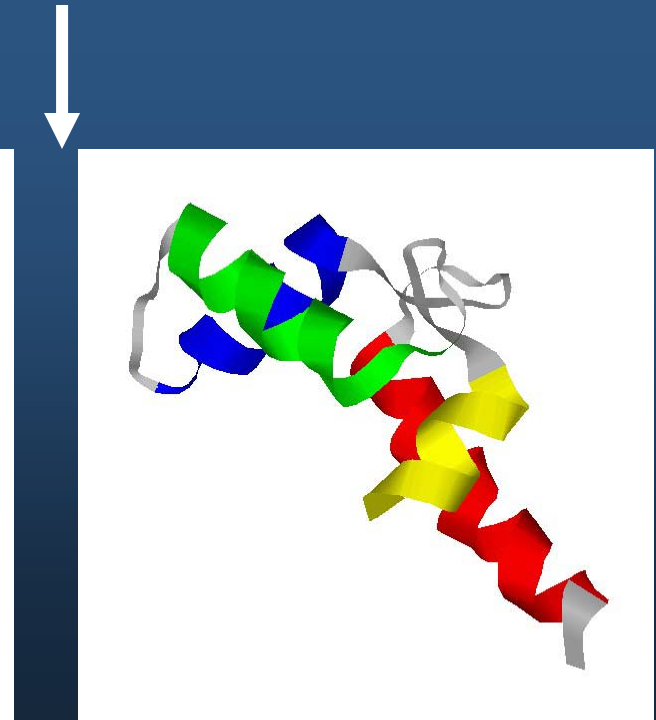
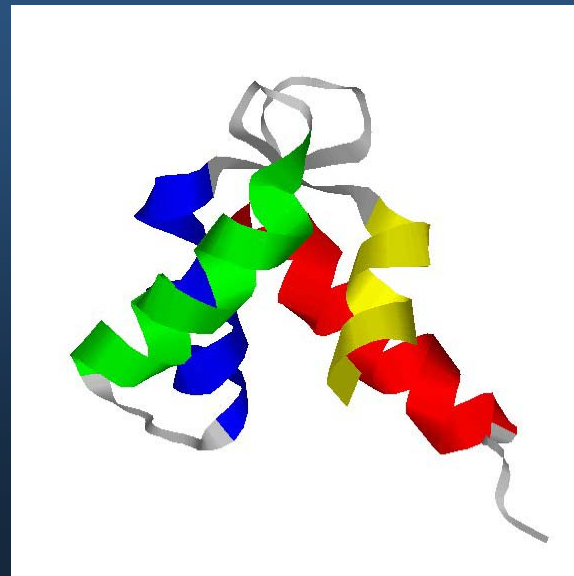
← Example: “induced fit” in adenylate kinase upon ATP binding

Example: re-arrangement of helices in calmodulin upon calcium binding

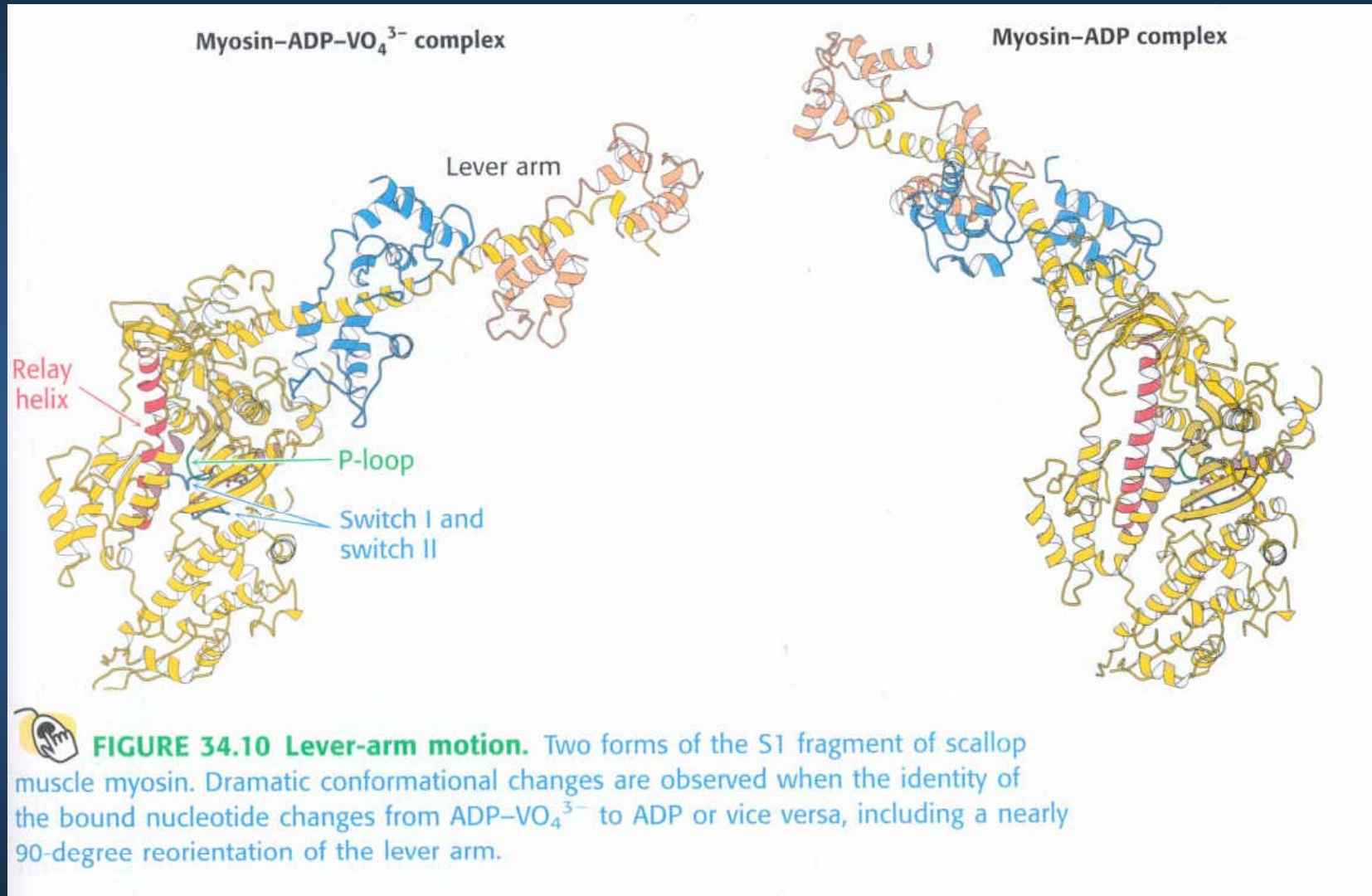
[Berg]



 **FIGURE 9.51 Conformational changes in adenylate kinase.** Large conformational changes are associated with the binding of ATP by adenylate kinase. The P-loop is shown in green in each structure. The lid domain is highlighted in yellow.

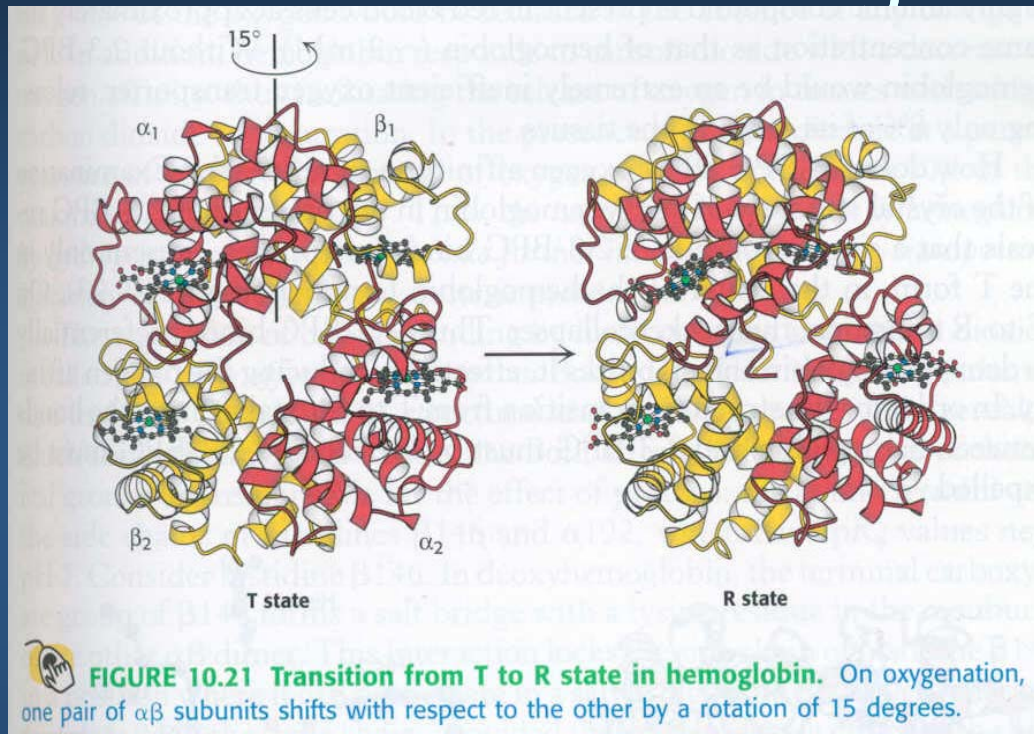


Large Structural Changes: Myosin



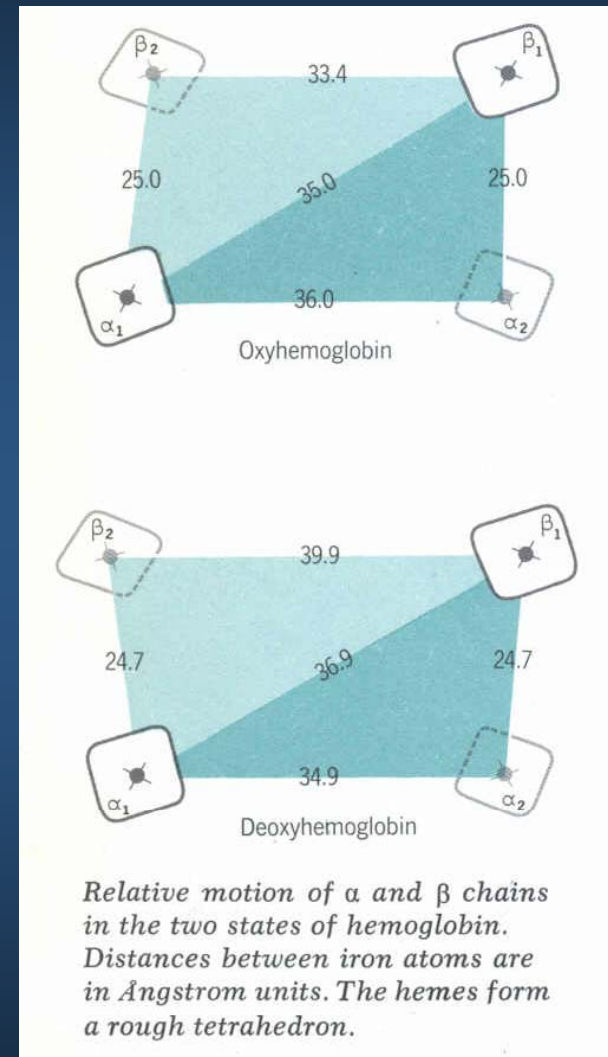
[Berg]

Large Structural Changes: Allostery in Hemoglobin



[Berg]

Allostery example: when multiple ligands bind with differing affinities due to a change in conformation after initial binding event(s).

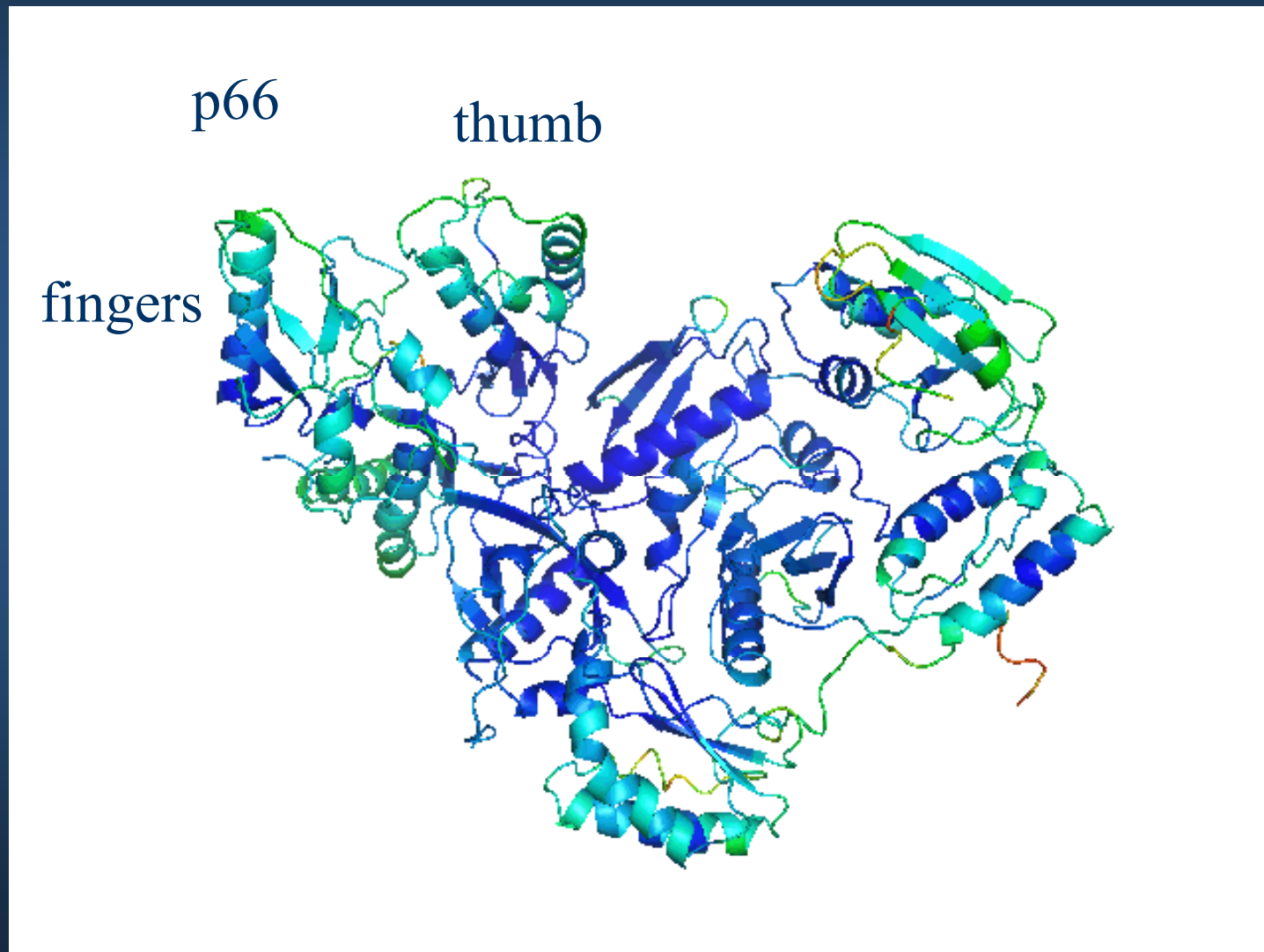


[Dickerson & Geis]

A movie of villin headpiece



Important mode in HIV-1 RT



How/why does a molecule move?

Among the $3N-6$ internal degrees of freedom, bond rotations (i.e. changes in dihedral angles) are the softest, and mainly responsible for the functional motions