

7.88 Lecture Notes - 5
7.24/7.88J/5.48J
The Protein Folding and Human Disease

Packing of Secondary Structures

- **Packing of Helices against sheets**
- **Packing of sheets against sheets**
- **Parallel**
- **Orthogonal**

Table: "Amino Acid Composition of the Ten Proteins and of the Residues at the Helix to Helix Interfaces"

Name	Total	% Total	At contacts	% at contacts
Gly	182	9	15	4
Ala	191	9	49	12
Val	151	7	46	12
Leu	148	7	48	12
Ile	114	6	36	9
Pro	67	3	41	1
Phe	68	3	25	6
Tyr	87	6	14	4
Trp	35	2	7	2
His	45	2	18	5
½Cys	21	1	3	1
Met	29	1	10	3
Ser	165	8	19	5
Thr	132	7	21	5
Asp	112	6	14	4
Asn	113	6	13	3
Glu	94	5	13	3
Gln	70	3	12	3
Lys	125	6	19	5
Arg	76	4	13	3

A. Factors Contributing to Stability of Correctly Folded Native State

1. Major source of stability = removal of hydrophobic side chains atoms from the solvent and burying in environment which excludes the solvent (Entropic contribution from water structure).

2. Formation of hydrogen bonds between buried amide and carbonyl groups is maximized
3. Retention of backbone conformations close to the minimal energies.
4. Close packing means optimal Van der Waals interactions.

You have read about alpha/beta proteins in *Brandon and Tooze*.

B. Helix to Sheet Packing

Lets examine buried contacts between the helices and the sheets.

First a quick review of beta sheet structure: Colored transparency: Theoretical model, not actual sheet.

A very general feature of beta sheets is that the strands are twisted with respect to their own elongated axis, and that sheets represented hydrogen bonded strands, are also twisted, in all cases seen so far, to the right.

This presumably represents the fact that the amino acids are all L;

This twist is expressed in the negative value of the dihedral angle omega between pairs of adjacent strands.

The packing of alpha helices against sheets examined carefully by:

Janin, and Chothia. *J. Mol. Biol.* 143: 95-128.

Chothia, Cyrus, Michael Levitt, and Douglas Richardson. "Structure of Proteins: Packing of alpha-Helices and pleated sheets." *Proc. Nat. Acad. Sci. Saa* 74 (1980): 4130-4134. [1977].

Very common to have alpha helices packed on the outsides of beta sheets.

Examined set of well determined alpha/beta structures: In the set of proteins they examine, the average strand length was 7 residues, not very much dispersion; the shorter strands represented edge strands.

Both parallel and anti-parallel sheets have a right-handed twist when viewed along axis.

C-alpha separate along strands for residues on same side is 7A, and between adjacent strand residues about 5A.

Most side chains in intimate contact with neighbors both ways.

For the docked helices in their set, helices very close to parallel to sheets; most deviate less than 20°.

For 35 pairs of adjacent beta strands (mostly parallel) in helix contacts, Omega had a mean of -19° with standard deviation of only 6.5° .

Right handed Twist very regular feature of these sheets

In the helices: Because numbers not integral, major ridges have twist, which is also right handed. . Now in an alpha helix the adjacent two rows of residues i , $i+4$ $i=8$, and $i+1$, $i+5$, $i+9$ have a surface that also represents a right handed twist. Turns out that if place helix roughly parallel to strands, helix face and sheet face form complementary surface:

Lets try to see this:

1. Where alpha helices are packed against beta sheets, there is a strong tendency for the helices to have their axes nearly parallel to the sheet strands;
2. Their sample had 39 helices packed against sheets; contact sites 4-7 residues, similar to helix-helix packing; helices:

More than 95% of the contact residues on the helical face represented adjacent i , $i+4$, $i+8$ ridges.

Sheet contact sites:

In average beta sheet; Val + Ile = 19.7%
In buried cores; Val + Ile = 21%
In helix/sheet contacts; Val + Ile about 40%!

In their sample of 8 proteins:

Leu + Val + Ile + Phe + Tyr = 65% of the sheet contact surface.

If the helix sheet axis angle omega is defined as follows, then the distribution in proteins is as follows:

when viewed in a direction parallel to the polypeptide chain. Now in an α helix the adjacent two rows of residues $i, i+4, i+8, \dots$ and $i+1, i+5, i+9, \dots$ form a surface that also has a right-handed twist (Figure 9). The essential feature of the packing model is that α helices pack onto β sheets with their axes parallel to the β -sheet strand because in this orientation these two rows

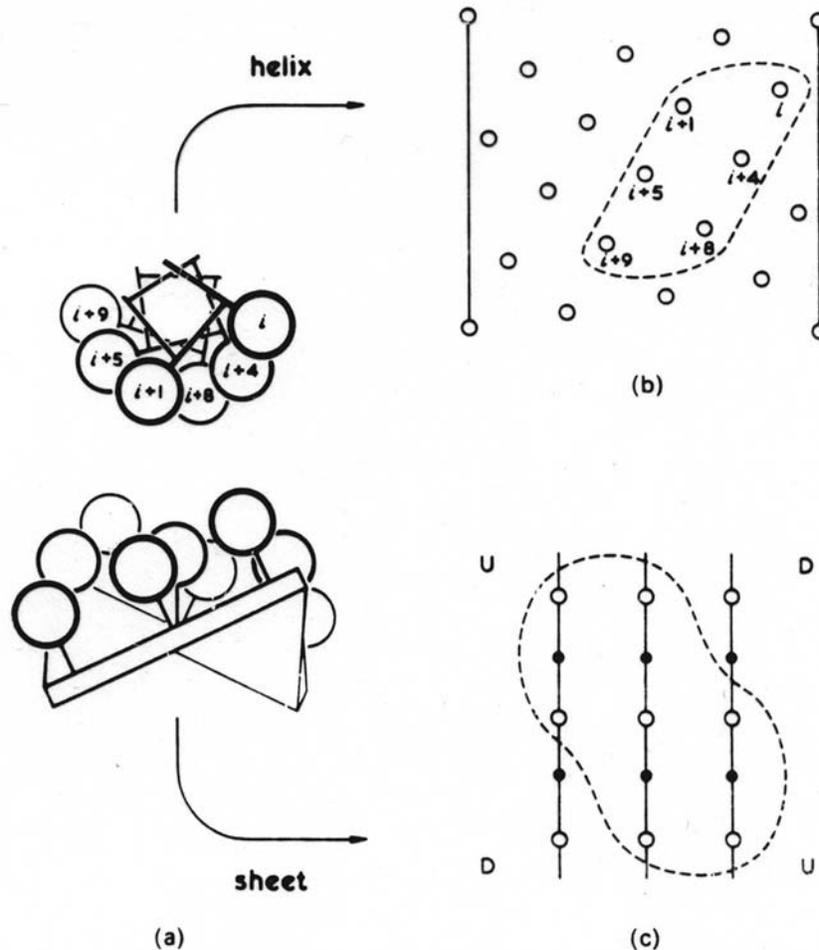


Figure 9 The complementary twist model for α -helix to β -sheet packing. Side chains on one side of an α helix and a twisted β sheet are shown as open circles (a). When the helix axis is parallel to the strand direction, the helix residues $i, i+1, i+4, i+5, i+8, i+9, \dots$ form a twisted surface that is complementary to that of the twisted β sheet. The patterns formed by the residues in contact at the interface are shown on flattened projections of the α helix (b) and β sheet (c). U and D mark the corners of the β sheet that move up and down from the plane when the β sheet is twisted. Note that the β -sheet contact residues cluster about a line joining U to U, the concave diagonal of the β sheet. [Reprinted with permission from (44).]

Figure 5.0: The Complimentary Twist Model... (from Chothia, Cyrus, and Joel Janin. "Relative Orientation of Close-Packed Beta-Pleated Sheets in Proteins." *Proc. Nat. Acad. Sci* 78 (1981): 4146-4150.)

The essential feature of the packing model is that alpha helices pack onto beta sheets with axis parallel to the beta sheet because in this orientation these two rows of residues have a complementary surface.

Note that this complementary surface is not interdigitated! Very smooth

C. Sheet/Sheet packing

Examination of beta sheets reveals that the orientation angle falls into two classes:

1. Aligned beta sheet packing = beta barrels

Mean direction of strands of one layer is at small angle, about 30, to that of other layer

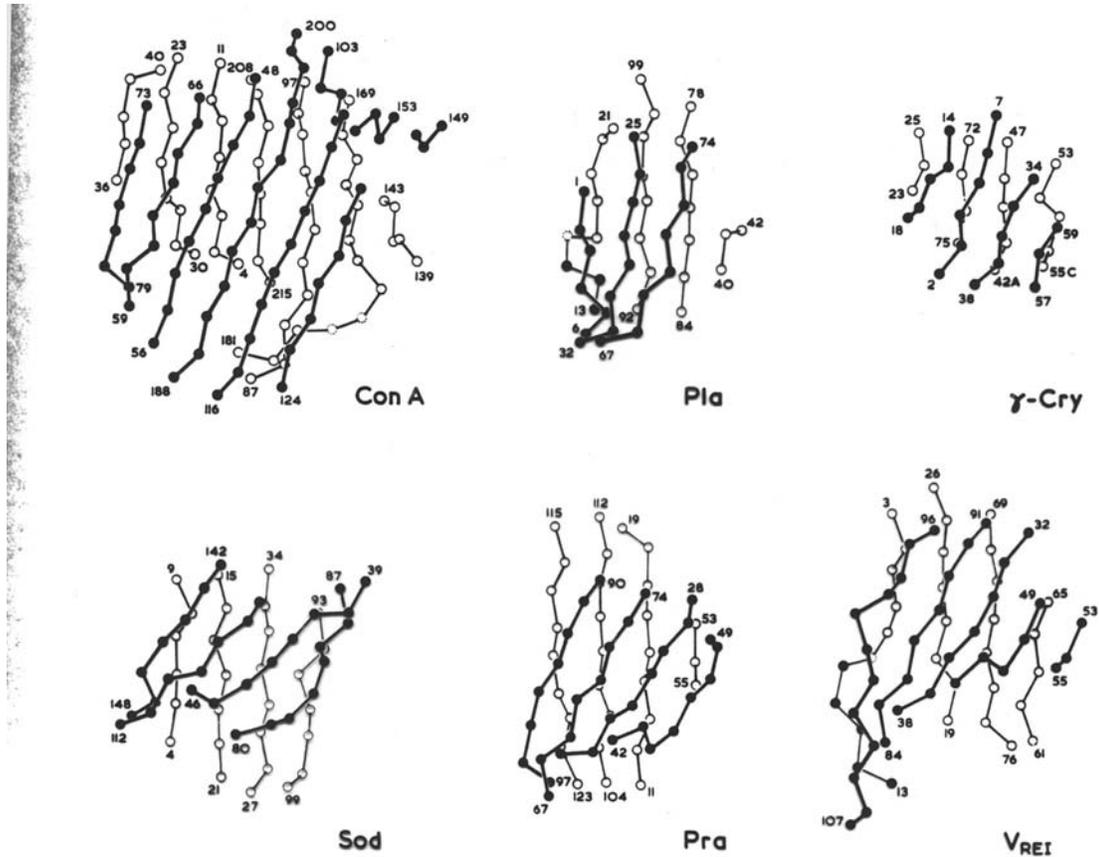


FIG. 1. The β -pleated sheets in concanavalin A (Con A), plastocyanin (Pla), γ -crystallin (γ -Cry), superoxide dismutase (Sod), prealbumin (Pra) and the immunoglobulin fragment V_{REI}. \bullet , C α atoms in the "top" β -sheet; \circ , C α atoms in the "bottom" β -sheet. Atomic coordinates are from the Cambridge Protein Data Bank (15), except for plastocyanin and γ -crystallin, gifts of J. M. Guss, H. C. Freeman, and T. Blundell (7, 8).

Figure 5.1: Series of Beta-pleated Sheets (from Chothia, Cyrus, and Joel Janin. "Relative Orientation of Close-Packed Beta-Pleated Sheets in Proteins." *Proc. Nat. Acad. Sci* 78 (1981): 4146-4150.)

Concanavalin A
 Plastocyanin
 gamma crystallin
 superoxide dismutase
 prealbumin
 immunoglobulin domains
 Tomato Bushy Stunt Virus
 Southern Bean Mosaic Virus
 Azurin

These consist of two well formed beta pleated sheets packed face to face; The azimuthal angle is about -30° of one strand relative to the other.

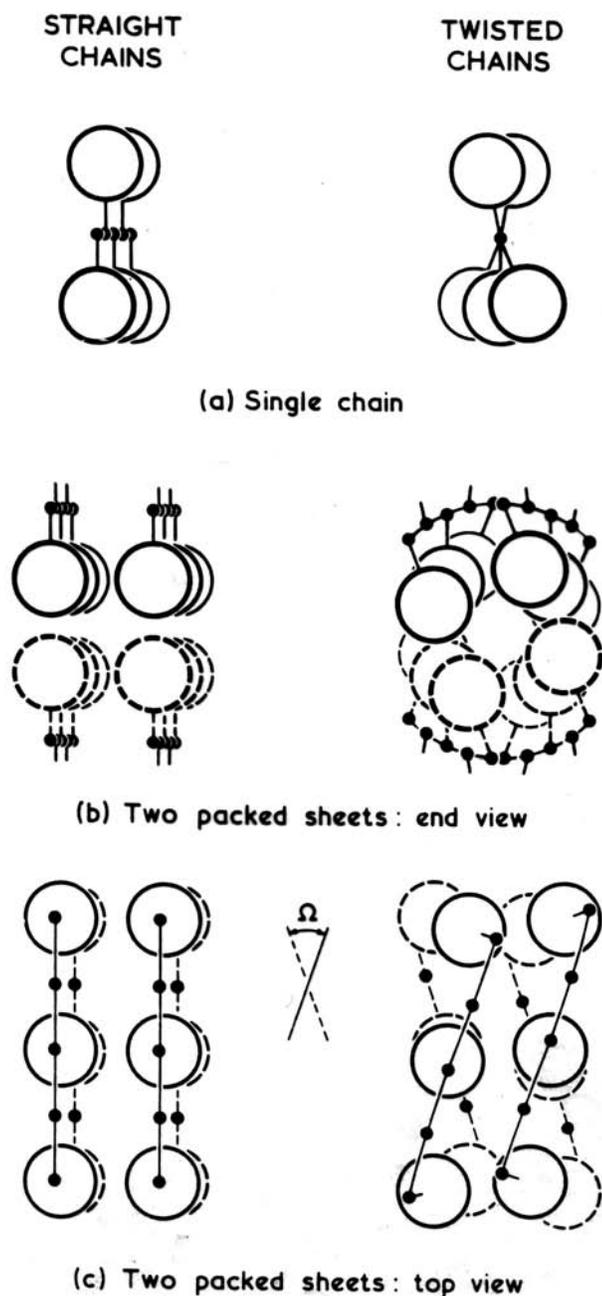


FIG. 2. A model for the packing of β -pleated sheets. The main chain is represented by one small filled circle per residue, the side chains being large open circles. In *a* we show a single strand, untwisted or twisted in the normal right-handed direction. In *b* and *c* we show views of packed β -sheets with two strands each. Only the side chains pointing into the interface are drawn.

Figure 5.2: A Model for the Packing of Beta-pleated Sheets (from Chothia, Cyrus, and Joel Janin. "Relative Orientation of Close-Packed Beta-Pleated Sheets in Proteins." *Proc. Nat. Acad. Sci* 78 (1981): 4146-4150.)

Lets go back to sheet diagrams: if look down strand an examine twist, side chains that point up curve left to right; side chain that point down curve right to left:

Now examine A sheet; We change perspective here and instead of continuing to view down axis, keep perspective constant; backbone twists to the right:

Side chains pointing up twist left to right:
So this surface tilts; Same for two strands below;

For their sample 44 pairs in twelve sheets; all but three negative, and average angle -17° ; not significantly different from twist in alpha beta proteins -19° .
Contacts between side chains are maintained if axis of backbones shifts; now side chains stay close packed;

If attempt to keep backbones parallel, side chains don't close pack very well;

In this diagram crossing angle comes to about -35 , close to observed.
Keeping axis strait

Side chains point at each, don't cross the interface much. Less than four ridges into grooves. One exception, tryp 35 in Vrei which fits into a hole in bottom sheet.

[Slow walk through of strand and packing relationships:]

Prealbumin- 12, 14, 16 from strand 11-19:
Residues 69, 71, 73 from strand 67-74 of the top sheet.

Immunoglobulin: 75, 73, 71 from the bottom sheet strand 69-76, are in contact with 86, 35, and 33 from two adjacent strands 984-91) and (32-38) in the top beta sheet

Amino acid Composition:

- Leu, Val, Ile and Phe =61% of total residues;
- 31% of average beta sheet
- 38% in average protein interior cores.

2. Orthogonal beta sheet packing

Orientation angle of one layer is close to 90 to other layer

A careful analysis of the orthogonal class was carried out by

Chothia, C., and Joel Janin. "Orthogonal Packing of B-pleated sheets in Proteins." *Biochemistry* 21 (1982): 3955 -3964.

Elastase
Penicillopepsin
Alcohol dehydrogenase
Staphylococcal nuclease
Papain

Two layers orthogonal, with two edge strands, a and d, common to both layers. Join layers covalently at both corners. These are tight corners; Other two corners are splayed out due to twist, side chains not necessarily in contact.

Packing is between side chains, but limited to diagonal band going kitty corner from close corners.

25% of residues involved in internal packing; Higher in penicillopepsin both faces of middle sheet in contact- 37%;

Total contact residues = 59.
36 (61%) = Val, Ile, Leu

For average sheet, Val, Ile, Leu = 27%;
For globular proteins - 33% of residues buried;
In aligned packing = 48%
In helix/sheet = 49%

They conclude that these are smooth hydrophobic surfaces making the contacts.

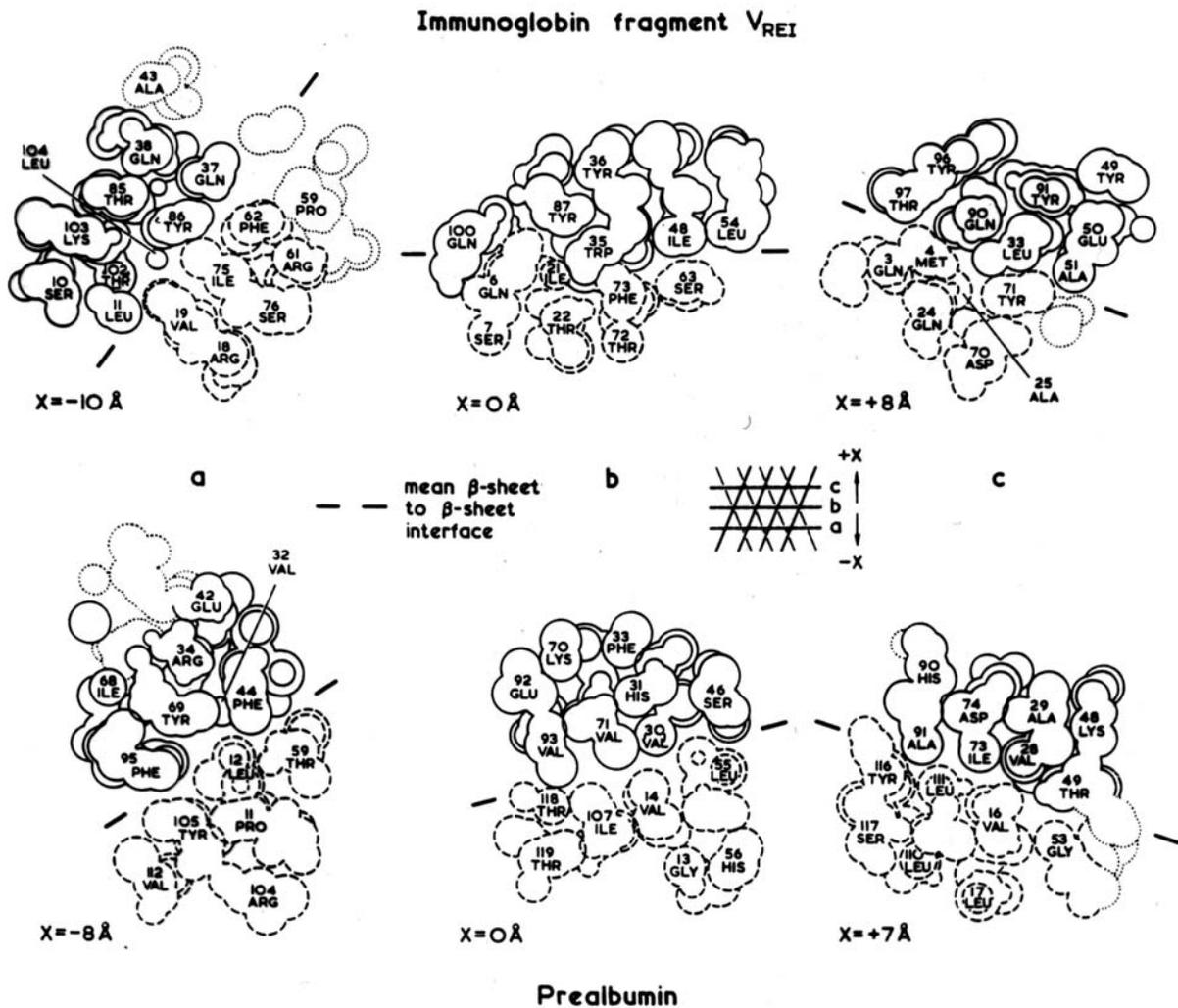


FIG. 4. The β -sheet-to- β -sheet residue packing in prealbumin and V_{REI}. Space-filling models of the proteins were generated in the computer. Sections were cut perpendicular to the mean direction of the strands in the β -sheets—see the small schematic *Inset*. Broken lines represent the edges of the van der Waals envelopes of the residues in one β -sheet and full lines the residues in the other β -sheet. Bar lines mark their mean interface. Dotted lines represent residues not in either β -sheet. Three sections separated by 1 Å are superimposed, so that each picture describes a 2-Å-thick slice. The x value gives the relative position of the middle section. The viewpoint of the proteins is the same as that in Fig. 2b and the two should be compared. The sections usually cut through two residues from each strand, one pointing into the interface and one away. Strand affiliation of the residues can be seen in Fig. 1.

Figure 5.3: Beta-sheet to Beta-sheet Residue Packing in... (from Chothia, Cyrus, and Joel Janin. "Relative Orientation of Close-Packed Beta-Pleated Sheets in Proteins." *Proc. Nat. Acad. Sci* 78 (1981): 4146-4150.)

D. Conditions Satisfied in the Formation of Globular Proteins

1. Major source of stability is removal of atoms from the solvent and burying in environment which excludes the solvent.
2. In the formation of helices, sheets and turns,
3. Formation of hydrogen bonds between buried amide and carbonyl groups is maximized
4. Retention of backbone conformations close to the minimal energies (What about side chain orientation- next week)

[Variations within these allowed conformational regions lead to variations in regular structures, included sheet twist and coil, bends and bulges, and kinks in alpha-helices].

5. No knots; links between units of secondary structure generally short (and right handed)
6. Since proteins are close packed, and since the chains are generally folded into secondary structures, secondary structures are close packed - helix to helix, helix to sheet, sheet to sheet.

Notes:

Chothia, Cyrus, and Joel Janin. "Relative Orientation of close-packed β -pleated sheets in proteins." *Proc. Nat. Acad. Sci.* 78 (1981): 4146-4150.

Concanavalin A
Plastocyanin
 γ -crystallin
superoxide dismutase
prealbumin
immunoglobulins

(also TBSV coat protein, azuirn, etc)

These proteins have two beta sheets oriented face to face one sheet -30 degrees with respect to other; - sign indicates left-handed screw rotation.

They show that this is natural consequence of the right-handed twist of normal beta-pleated sheet and allows closer packing of side chains between two beta sheets in contact.

For 44 pairs of strands in 12 proteins the mean twist was -17

Not significantly different from the mean of strands in alpha-beta proteins = -19°

If examine interfaces, residues rarely cross the line; side chain intercalation is exception rather than rule. Different from alpha helix packing.

Leu, val, Ile and Phe form 61% of residues at sheet interfaces. With respect to total beta sheet residues they represent 31%; With respect to general buried globular interiors 38%

The branched side chains of val, ile, and leu make the surface of the beta sheets approximately smooth.

Parallel beta sheets found almost exclusively in alpha/beta proteins, where alpha helices make necessary connection between strands. In these proteins described here, strands are anti-parallel:

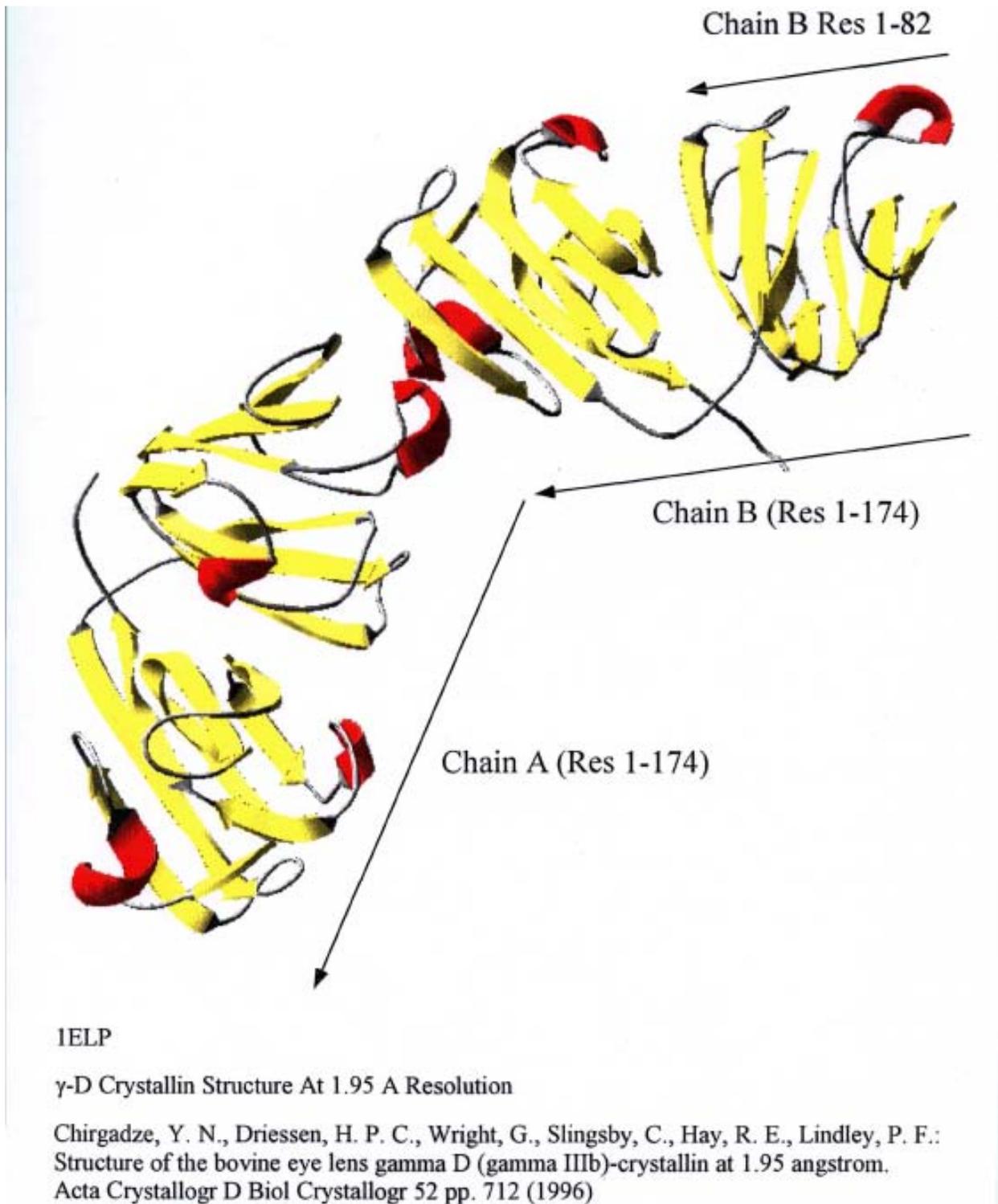
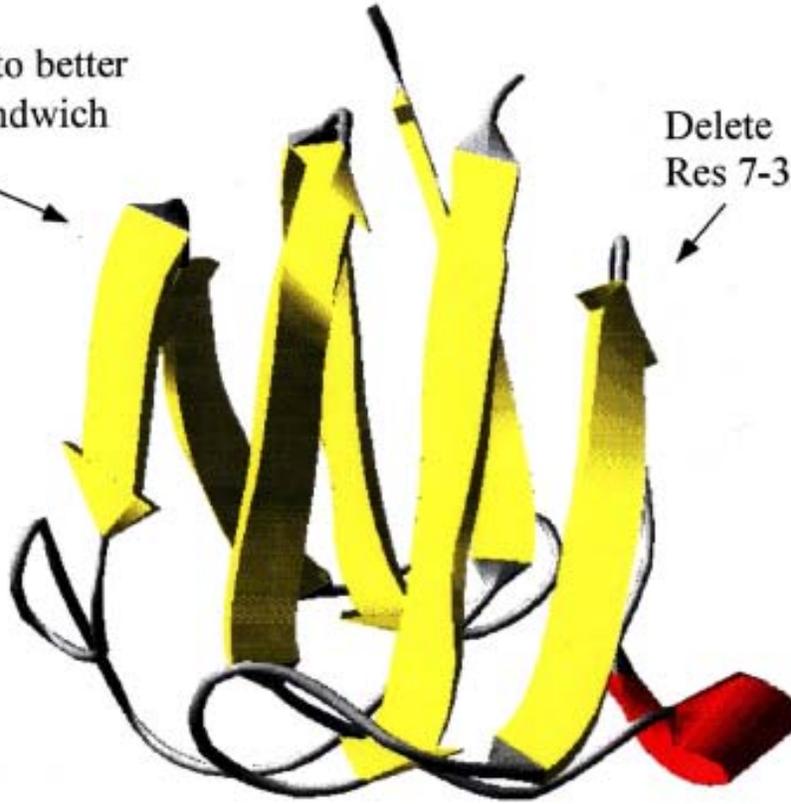


Figure 5.4

Re-orient to better
view β -sandwich

Delete
Res 7-34



"Top view"

"Side view"



Figure 5.5

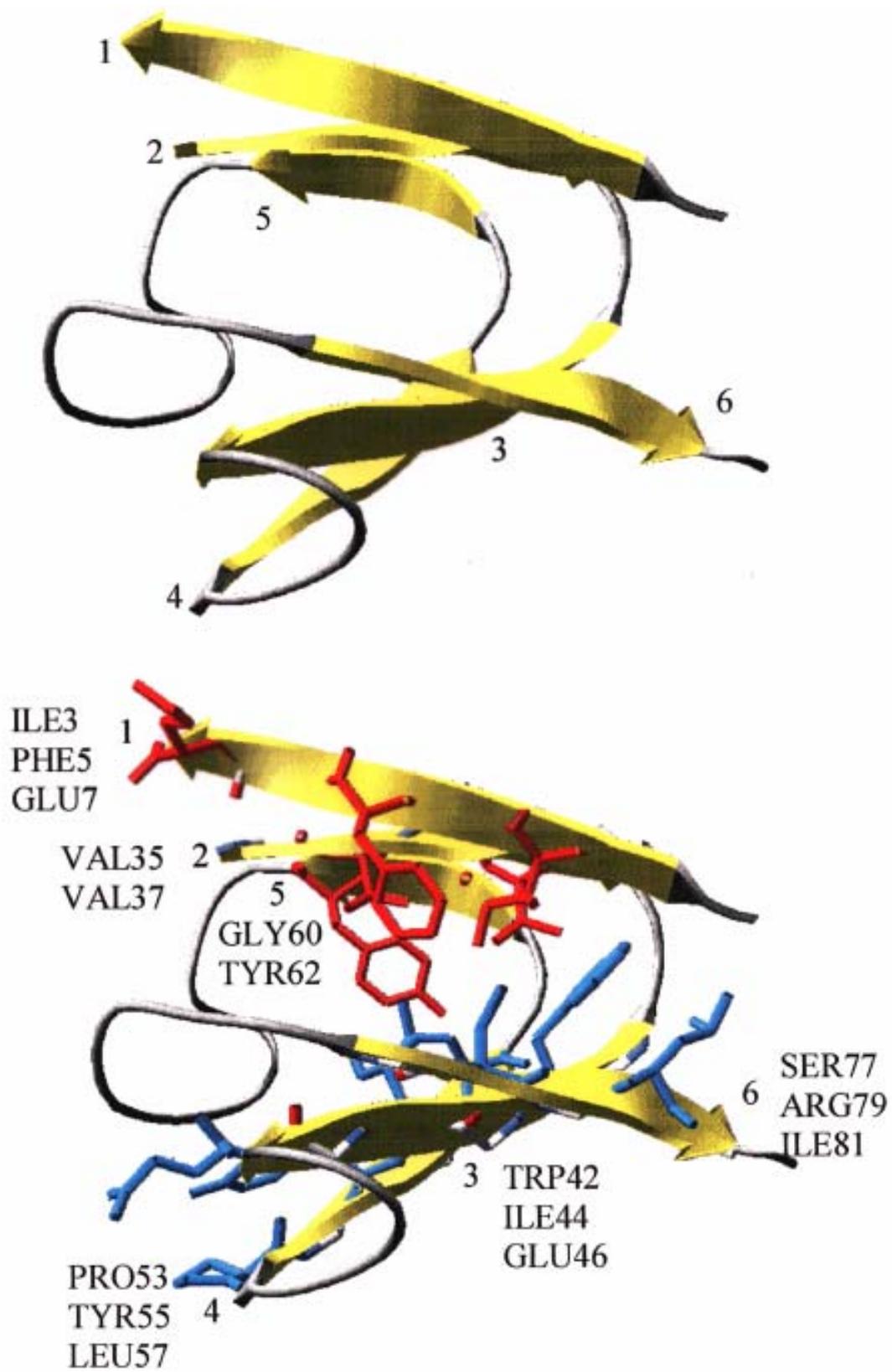


Figure 5.6

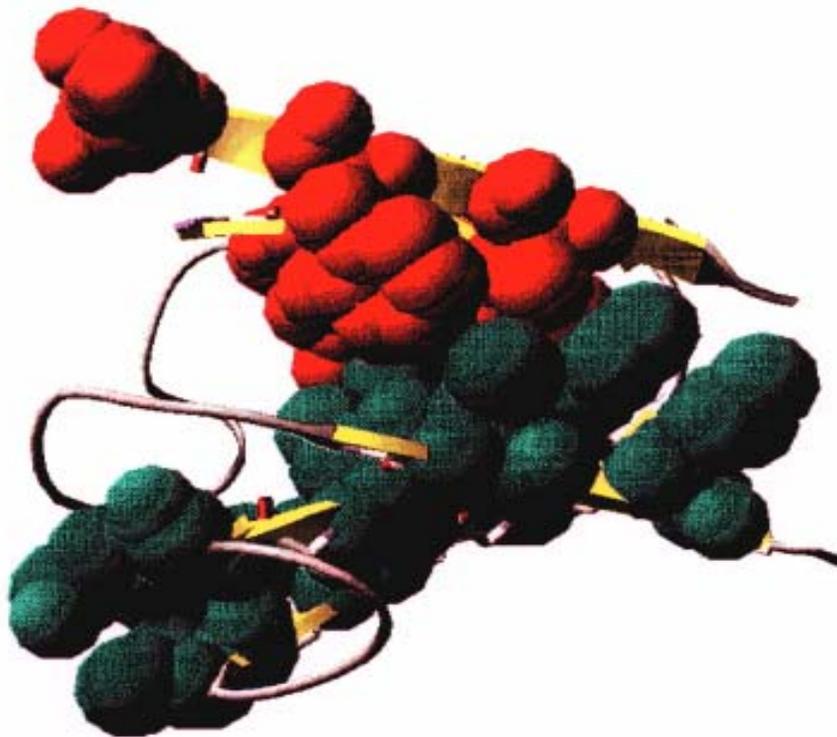


Figure 5.7

Figures 5.4 - 5.7: Series of Beta Sheet Crystallin Structures.

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