7.88 Lecture Notes - 4
7.24/7.88J/5.48J
The Protein Folding Problem

- Professor Gossard – “Retrieving, Viewing Protein Structures from the Protein Data Base”
- Helix helix packing

Packing of Secondary Structures

One of the determinants of the shapes of proteins and the folds is the packing of the units of secondary structure against each other.

In trying to interpret fibrous diffraction patterns from muscle, Frances Crick Model: surface of helices composed of knobs and holes. Orientation angles of +20 and -70 yield good contact.

With the accumulation of solved protein structures - However these helices very long, not interrupted by turns, loops or beta strands:

What is distribution and organization of helices in globular proteins:

Helical Protein Subset; T With the accumulation of solved protein structures

"Helix to Helix Packing in Proteins" Cyrus Chothia, Michael Leavitt and Doug Richardson (1981) J. Mol. Biol 145, 215- 250.

Analyzed the actual packing of helices against each other in a set of globular proteins.

Analyzed 50 contacts, 100 surfaces.

Helices ranged from 6 to 23 residues long, mean of 15.

The intersections of the helix surfaces – interfaces had between 3 and 7 residues in van der waal’s contact, mean 4.7.

How many contacts in coiled coil stretch of 10 amino acids? Depends on helix length; from packed helices independent of helix length!

If one plots the angle, defined thusly…

[Note: Relevant figure may be found in "Helix to Helix Packing in Proteins" Cyrus Chothia, Michael Leavitt and Doug Richardson (1981) J. Mol. Biol 145, 215- 250.]

between close packed helices in globular proteins, they cover a relatively broad range, but with a distinctive peak at about-50o and a shoulder at +20 with

[Note: Relevant figure may be found in the "Ridges into Grooves" model articulated by Cyrus Chothia, Michael Leavitt and Doug Richardson (1981) J. Mol. Biol 145, 215- 250.]

This kind of packing was explained by:

"Ridges into Grooves" model articulated by Cyrus Chothia, Michael Levitt, and David Richardson (1981) J. Mol. Biol., 145, 215-250.

If you examine the surface of an alpha helix you see that residues on the surface from ridges made of residues 4 apart in sequence, 3 apart, and one apart.

The +/- 4n rows form most prominent feature.

- Adjacent - Cβ atoms 6.4A apart and as proceed along row
- rotated 40^{o}C.

If side chains bigger than alanine, likely be in contact.
In the +/-3n row atoms are a little closer, 5.6 A, but rotated 60^{o}C, so ridge less prominent.

Even side chains still separated because of rotation angle. Bigger angle separated by grooves. In the ridges into grooves model, helices pack together by the ridges of one helix packing into the grooves of the other and vice versa. The ridges on the helix surface are usually formed by the side chains of residues four separate in the sequence, i i+4, I + 8, ...i+1, i+5, i+9, etc. (the +-4n ridges). Occasionally can be formed by residues separated by three residues

If both helices intercalate through their 4n ridges and grooves, omega is close to 50^{o}.

If one helix uses the 4n groove and the other the 3n groove, the resulting angle is close to 20^{o}.

The use of particular ridges depends upon the size and conformation of the side chains, and upon the surface of the other helix.

This can be violated if have a very small residue, for example glycine or serine forming a gap in the ridge, in which case a ridge can cross a ridge!?.

This packing angle encoded in amino acid sequence in comprehensible manner!

In helix packings, the axis to axis distance varies between 6.8 Angstrom and 12.0 Angstra. This variation is principally a function of the size of the side chains at the center of the interface.

Mean interaxial distances for packed helices is 9.4 A.

The mean interpenetration of atoms at the interface is 2.3A?! Thus the contacts between packed helices mainly involved the ends of the side chains.

In particular backbone atoms not involved in helix packing
Now we have enough information to begin formulating formal models;

Chain appears sequentially, we will assume initiation of a helix, propagation, termination
Soluble, unstructured
initiate helix
propagate, terminate
Diffuse and collide and
Dock.

This is reasonable Newtonian model; Alternate formulations; helix might nucleate in model and propagate bidirectionality.

One problem; if these are going to form buried hydrophobic patches expect to be hydrophobic patches. This should be very unstable conformation as free helix. So perhaps they are not; perhaps at these spots ion pairs concentrated or h-bonded across gap

Table 4: "Amino Acid Composition of the Ten Proteins and of the Residues at the Helix to Helix Interfaces"
Total Residues: Contact Residues:

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

Of the interface residues,

- 50% are Ala, Val, Leu, Ile and Phe
- 25% = Asp, Asn, Glu, Gln, Lys and Arg.

Latter group tends to be at edge with non polar group involved in packing and polar group accessible to the solvent.

Below: Major contact subset pulled out from Table 4 above:

Name	Total	% Total	At contacts	% at contacts
Ala	191	9	49	12
Val	151	7	46	12
Leu	148	7	48	12
Ile	114	6	36	9
Phe	68	3	25	6

32% of total 51% of contact

Other interesting numbers:

- of 50 interfaces, 17 had either H-bonds or salt bridges across the interface
- Twelve had one H-bond or salt bridge;
- four have two,
- one has three.
- Nineteen of these between two side chains;
- four are between a side chain and a main chain atom.

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.