Lecture 4   Tertiary structural motifs

James Chou

BCMP201   Spring 2008
Understanding helix-helix packing from the coiled-coil structure

parallel supercoil

anti-parallel supercoil
Examples of proteins involving coiled-coil dimer

DNA-binding domain of GCN4, a coiled-coil dimer which interacts with DNA

C-Terminal fragment of rabbit skeletal tropomyosin
Coiled-coil proteins have a unique heptad periodicity

Example:

```
a     b     c     d     e     f     g
NH2 - 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
```
Francis Crick derived the model of a super-coiled helix to explain the x-ray diffraction of alpha keratin

\[ x(t) = r_0 \cos \omega_0 t + r_1 \cos \omega_0 t \cos \omega_1 t - r_1 \cos \alpha \sin \omega_0 t \sin \omega_1 t \]
\[ y(t) = r_0 \sin \omega_0 t + r_1 \sin \omega_0 t \cos \omega_1 t + r_1 \cos \alpha \cos \omega_0 t \sin \omega_1 t \]
\[ z(t) = p_0(\omega_0 t) - r_1 \sin \alpha \sin \omega_1 t \]

Packing of two right-handed a helices into a left-handed supercoil distort the helices such that number of residues per turn decreases slight from 3.6 to 3.5.

This is the explanation for the heptad repeats (2 x 3.5) of a coiled-coil.
Physical properties of the coiled-coil sequence

Heptad repeat $- [a \ b \ c \ d \ e \ f \ g ]_n$

a and d are mostly hydrophobic

e and g are mostly charged

b, c and f are usually hydrophilic

Diagram showing polar and non-polar regions with arrows indicating interactions.
Significance of heptad repeat in helix-helix packing

Ion pair

Hydrophobic core
Helical wheel representation of the GCN4 coiled-coil dimer

O’Shea et al., Science 1991
Prediction of coiled-coil based on sequences


http://www.ch.embnet.org/software/COILS_form.html

Structure of a parallel coiled-coil dimer - helices are packed in the “Knob in Holes” fashion

The coiled-coil domain of the transcription factor GCN4
Peripheral ion pairs further stabilize the packing

Glu6, Lys8

Lys15, Glu20

Glu22, Lys27

<table>
<thead>
<tr>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
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Why are helices packed at a crossing angle?

“Knob in Holes” packing

3D viewing of the GCN4 Leucine Zipper (2ZTA)
How about coiled-coil trimer?
An example of coiled-coil trimer

Hemagglutinin fusion protein of influenza A
How about parallel coiled-coil tetramer?
Examples of coiled-coil tetramer

Phosphoprotein coiled-coil domain of Sendai virus (Tarbouriech et al., 2000 Nature).

A coiled-coil tetramer is involved in the proper assembly of the Kv7.x voltage-gated K+ channel (Howard et al., Neuron 2007).
How to convert the GCN4 dimer into a tetramer?

Hint: the volume of the hydrophobic core is larger in the tetramer.
Mutate the core residues to bulkier amino acids so that the dimer interface can no longer accommodate

**GCN4 dimer**

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<td>Val23</td>
<td>Leu19</td>
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Parallel coiled-coil tetramer!

Harbury et al., *Science* 1993; 262:1401-7
The mutagenized GCN4 is a parallel coiled-coil tetramer

3D viewing of the GCN4 tetramer (PDB code: 1GCL)
Regular helix-helix packing

Packing of regular helices is almost the same as coiled-coil except there are no heptad periodicity in the packing interface.

The classic four-helix bundle
Surface ridges of $\alpha$ helix
Left-handed and right-handed helix-helix packing

left-handed packing

right-handed packing
left-handed vs right-handed packing

Call & Schnell et al., Cell 2006

Mckenzie et al., Science 1997
Examples of helical proteins

cytochrome b₅₆₂
human growth hormone
$\beta$ structures

$\phi = -140^0$, $\psi = 135^0$
right-handed twist

pleat

ψ

Φ

twisted sheet

pleated sheet
Definition of beta twist

right-handed twist

left-handed twist

inter-chain

along the chain
Variations of beta sheets

regular planar

Bacteriochlorophyll A Protein
(electron transport) (PDB code: 4BCL)

right-handed twist

Thioredoxin (oxidized)
(PDB code: 1XW9)
Beta sheets can also be curled along the strand direction or arched perpendicular to it

Arching - nonlinear H-bonds, no change in strand $\phi$, $\psi$

Curling - no change in H-bonds, but alternating perturbation of $\phi$, $\psi$

Retinal Binding Protein  
(PDB code: 1RLB)

Lactate dehydrogenase
3D viewing of the retinol-binding protein (PDB code: 1RLB)
Tertiary folds stabilized by metal coordination

Transcription factors containing zinc fingers rapping around DNA (PDB code: 1AAY)

Elrod-Erickson et al., Structure 1996
Zn$^{2+}$ is coordinated by the electronegative N of the imidazole rings of His and the highly reactive SH groups of Cys.
The EF hand motif for calcium binding

The linker is flexible in solution.

$\text{Ca}^{2+}$-Calmodulin (ref)

The EF hand
Wilson & Brunger *JMB* 2000

Ikura et al. *Science* 1992
Ca$^{2+}$ can have a max of 18 e’s in the outer shell, or 9 bonds total

Metal coordination by the compound EDTA
Ca$^{2+}$ coordination significantly alters the EF-hand conformation

PDB code 1F70, 1J70
Proteins secreted to outside of cells are usually stabilized or folded by disulfide bonds.
Disulfide formation is usually a catalyzed event.