CMPS 6630: Introduction to Computational Biology and Bioinformatics

Secondary Structure Prediction

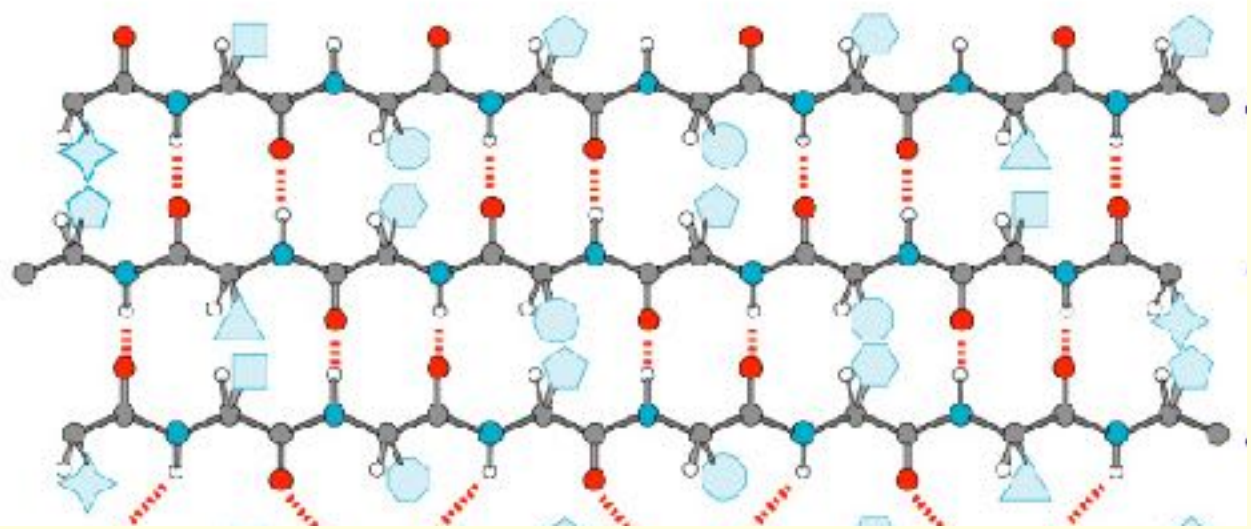
Secondary Structure Annotation

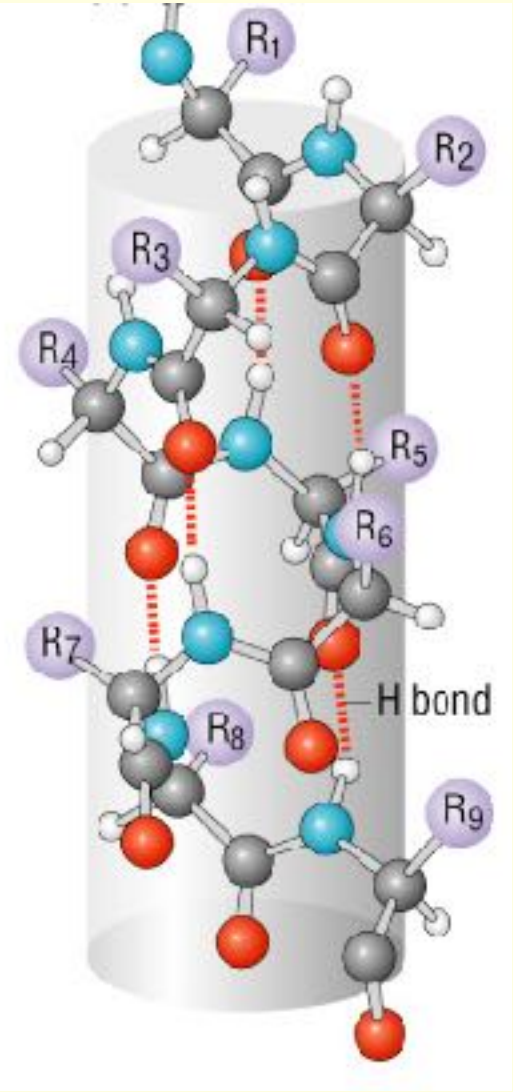
- Given a macromolecular structure
- Identify the regions of secondary structure

Assumptions:

High resolution structure

There is a reasonable and consistent way to define Secondary Structure





Petsko, Ringe, Prot Struct and Function, 2004

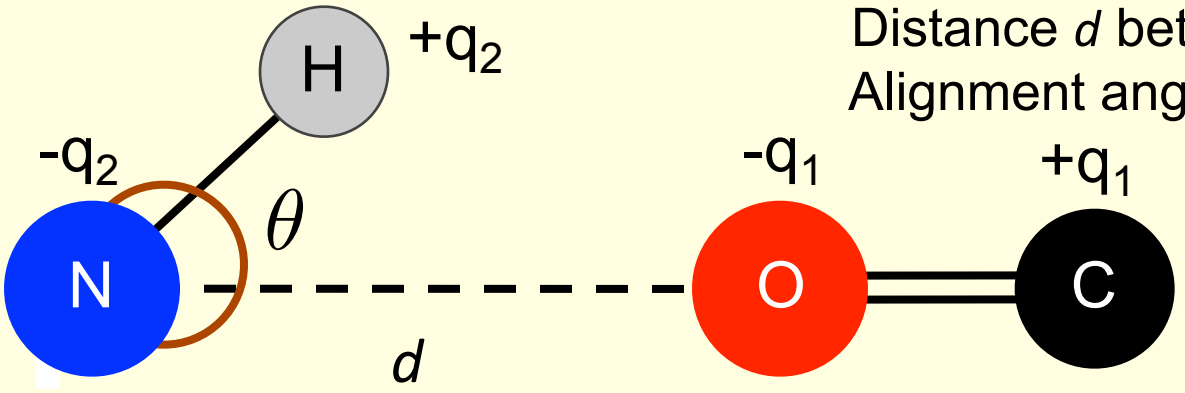
DSSP (Defined Secondary Structure of Proteins)

- A gold standard for secondary structure identification (NOT prediction)
- Used by the PDB database for secondary structure annotation
- Based on **Hydrogen-Bonding Patterns**

Quality of H-bond is function of:

Distance *d* between donor and acceptor

Alignment angle θ



$$E = f\frac{q_x q_y}{r_x y}$$

$$E = q_1 q_2 \left(\frac{1}{r_{\mathrm{ON}}} + \frac{1}{r_{\mathrm{CH}}} - \frac{1}{r_{\mathrm{OH}}} - \frac{1}{r_{\mathrm{CN}}} \right) f$$

DSSP

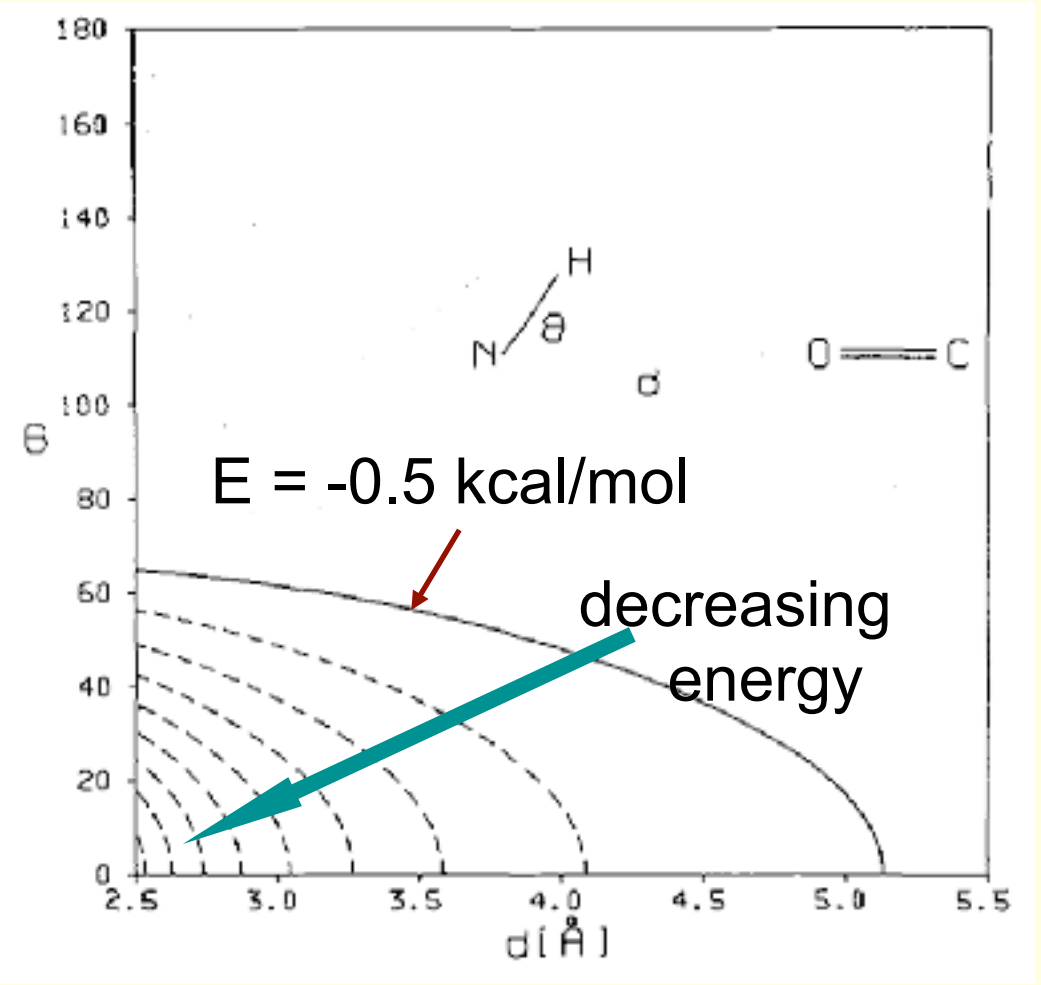
Defines a **Polar Interaction** as a H-bond with computed energy < -0.5 kcal/mol

An ideal H-bond has

d = 2.9 Å

θ = 0

E = -3.0 kcal/mol



DSSP

n-Turn

An *n*-turn is present at residue *i* if there is an H-bond from CO(*i*) to NH(*i*+*n*). Two or more form a helix.

***alpha*-turn**(*i*) = Hbond(*i*,*i*+*4*) (most common)

***3*-turn**(*i*) = Hbond(*i*,*i*+*3*) (3_{10} -helix)

***pi*-turn**(*i*) = Hbond(*i*,*i*+*5*) (very rare)

Bridge

A bridge is formed from two non-overlapping stretches of 3 residues if one of the following H-bond patterns is seen:

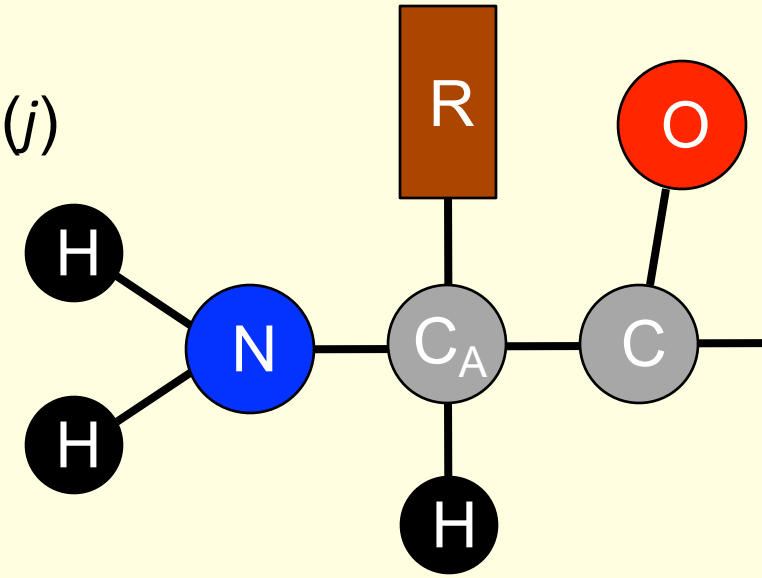
Parallel Bridge (*i*, *j*) = [Hbond(*i*-1,*j*) and Hbond(j,*i*+1)] OR
[Hbond(*j*-1,*i*) and Hbond(*i*,*j*+1)]

AntiParallel Bridge (*i*, *j*) = [Hbond(*i*,*j*) and Hbond(j,*i*)] OR
[Hbond(*i*-1,*j*+1) and Hbond(*j*-1,*i*+1)]

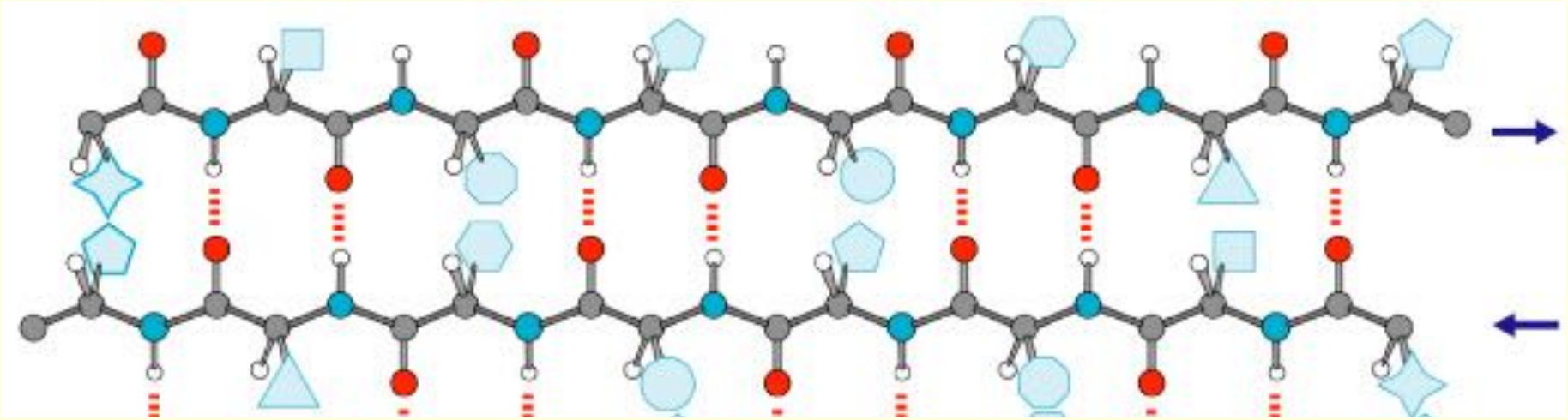
Directionality

Hbond(*i*,*j*) = H-bond from CO(*i*) to NH(*j*)

Proteins written from
N-terminus to C-terminus



i

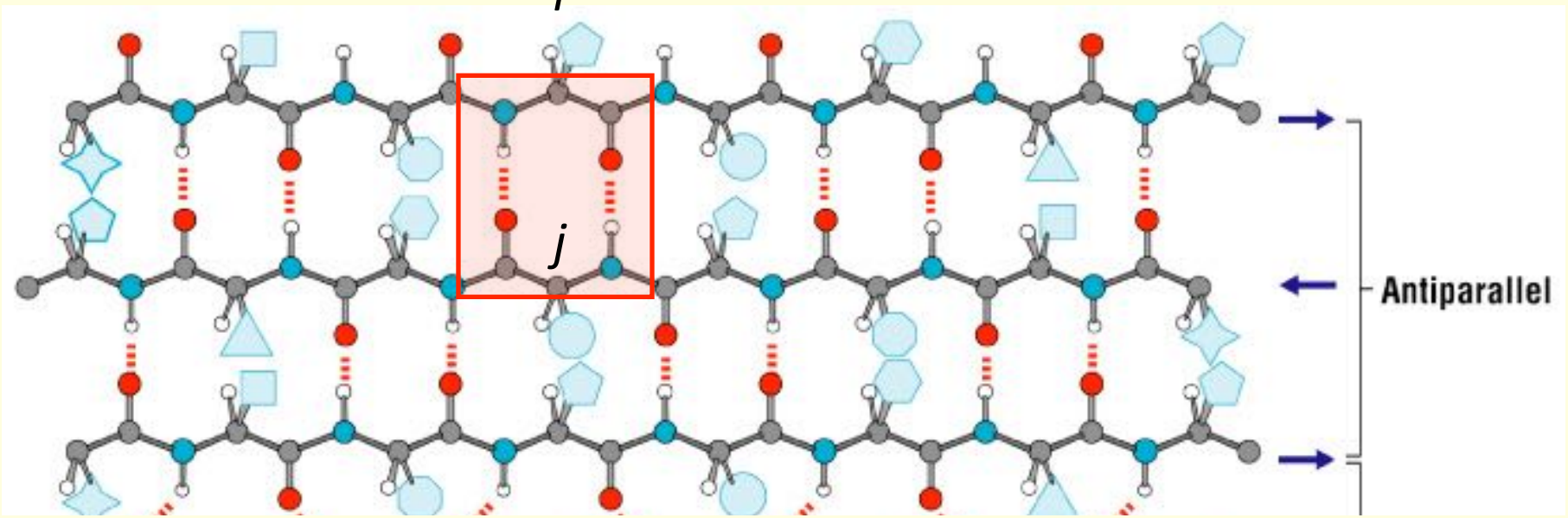


j

DSSP

AntiParallel Bridge (i, j) = [Hbond(i,j) and Hbond(j,i)] OR
[Hbond(i-1,j+1) and Hbond(j-1,i+1)]

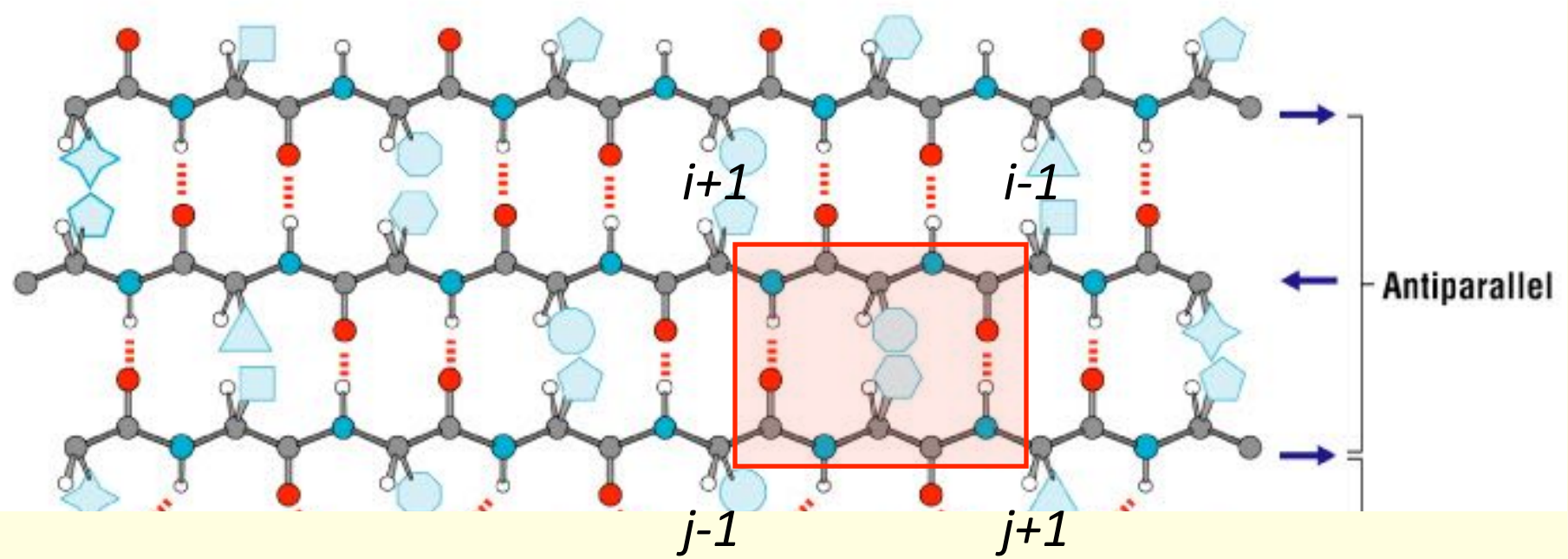
Hbonds $i \rightarrow j$, $j \rightarrow i$



DSSP

AntiParallel Bridge (*i*, *j*) = [Hbond(*i*,*j*) and Hbond(j,*i*)] OR
[Hbond(*i*-1,*j*+1) and Hbond(*j*-1,*i*+1)]

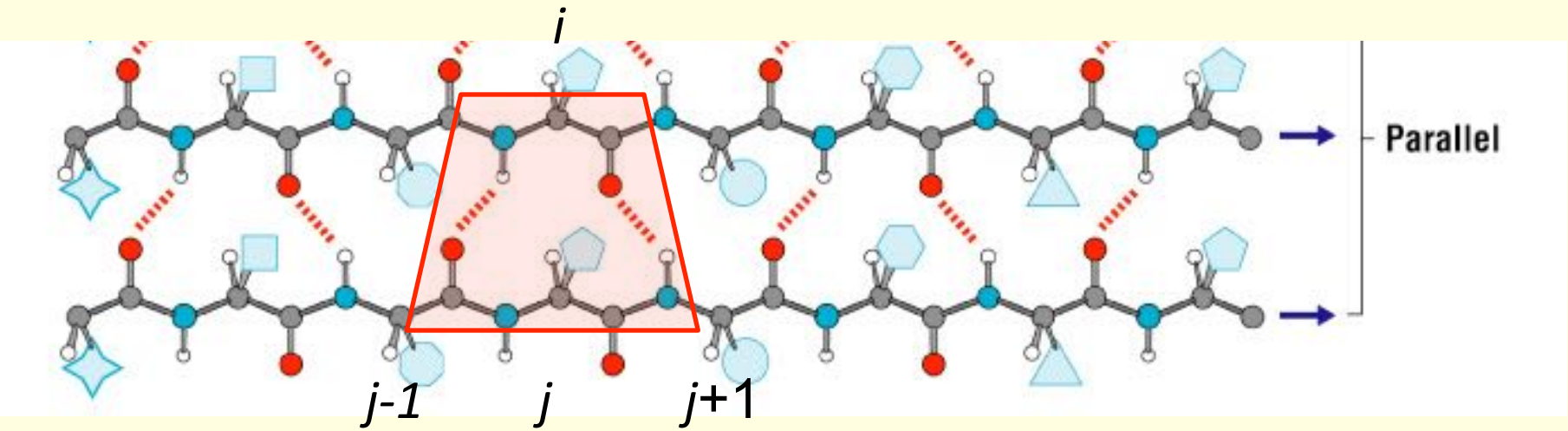
Hbonds *i-1*➡*j+1*, *j-1*➡*i+1*



DSSP

Parallel Bridge (i, j) = [Hbond(i-1,j) and Hbond(j,i+1)] OR
[Hbond(j-1,i) and Hbond(i,j+1)]

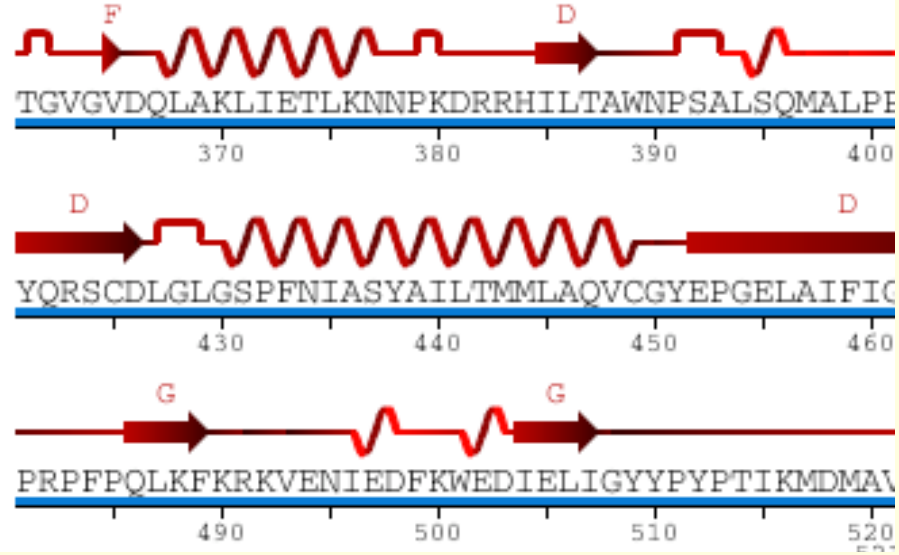
Hbonds *j-1*➡*i*, *i*➡*j*+1



Secondary Structure Prediction

Input: Primary Sequence only

Output: Annotation of alpha-helices, beta-strands, loops



Amino acid	Preference α-helix	β-strand	Reverse turn
Glu	**1.59**	0.52	1.01
Ala	**1.41**	0.72	0.82
Leu	**1.34**	1.22	0.57
Met	**1.30**	1.14	0.52
Gln	**1.27**	0.98	0.84
Lys	**1.23**	0.69	1.07
Arg	**1.21**	0.84	0.90
His	**1.05**	0.80	0.81
Val	0.90	**1.87**	0.41
Ile	1.09	**1.67**	0.47
Tyr	0.74	**1.45**	0.76
Cys	0.66	**1.40**	0.54
Trp	1.02	**1.35**	0.65
Phe	1.16	**1.33**	0.59
Thr	0.76	**1.17**	0.90
Gly	0.43	0.58	**1.77**
Asn	0.76	0.48	**1.34**
Pro	0.34	0.31	**1.32**
Ser	0.57	0.96	**1.22**
Asp	0.99	0.39	**1.24**

Petsko, Ringe, Prot Struct and Function, 2004

Chou-Fasman (First-Generation)

Compute propensities for each amino acid, a_i in structural conformation $s_j \in \{\alpha, \beta, \rho\}$

$$\frac{\Pr[A = a_i \mid S = s_j]}{\Pr[A = a_i]}$$

Categorize each AA as *helix-former*, *helix-breaker*, *helix-indifferent* and *sheet-former*, *sheet-breaker*, *sheet-indifferent*.

Keep chaining residues to SS element while average propensity is above some threshold.

Accuracy?

3-State Accuracy: Percent of residues for which a method's predicted secondary structure (Helix (α), Strand (β), Neither (ρ)) is correct.

Chou-Fasman: 50-60% 3-State Accuracy

Priors:

30% Helices
20% Strands
50% Neither

If you always predicted 'Neither' you would have 50% 3-State Accuracy

Need to incorporate additional information!

GOR Method

What if we look at “blocks” of sequence to determine secondary structure? (Garnier-Osguthorpe-Robson, late 70s)

$$s_j = f(r_{j-k}, \ldots, r_{j+k})$$

GAVLIFYWMVLLAGIFFST

GOR Method

Main Idea: Look at the mutual information between nearby amino acids to assess whether they influence secondary structure at a particular position.

$$
\begin{aligned}
I(x;y) &= \sum_x \sum_y \Pr[x,y] \log \frac{\Pr[x,y]}{\Pr[x]\Pr[y]} \\
&= \sum_x \sum_y \Pr[x,y] \log \frac{\Pr[x \mid y]\Pr[y]}{\Pr[x]\Pr[y]} \\
&= \sum_x \sum_y \Pr[x,y] \log \frac{\Pr[x \mid y]}{\Pr[x]}
\end{aligned}
$$

GOR Method

Consider mutual information between structural class and sequence:

$$I(s_j; r_{j-8}, \ldots, r_{j+8}) = \sum_{s_j} \sum_{\langle r_{j-8}, \ldots, r_{j+8} \rangle} \Pr[s_j, r_{j-8}, \ldots, r_{j+8}] \log \frac{\Pr[s_j \mid r_{j-8}, \ldots, r_{j+8}]}{\Pr[s_j]}$$

Select the structural class which maximizes:

$$I(s_j = x; r_{j-8}, \ldots, r_{j+8}) - I(s_j \neq x; r_{j-8}, \ldots, r_{j+8})$$

Problem: Each conditional probability needs to be computed.

$\Pr[s_j \mid r_{j-8}, \ldots, r_{j+8}]$ table size: 3×20^{17}

Assume 'independence':

$$I(s_j; r_{j-8}, \ldots, r_{j+8}) = \sum_{k=-8}^{8} I(s_j = x; r_{j+k})$$

GOR Method Extension

Larger training set (513 vs 267 sequences)
Because 'Neither' regions were over predicted, they added a margin by which Neither must be preferred over Helix or Coil
Use of doublet and triplet statistics
Optimized window length - 13 better than 17...

Previously:

$$I(s_j; r_{j-8}, \ldots, r_{j+8}) = \sum_{k=-8}^{8} I(s_j = x; r_{j+k})$$

Incorporating conditional information on residue r_j :

$$I(s_j; r_{j-8}, \ldots, r_{j+8}) = I(s_j = x; r_j) + \sum_{k=-8, k\neq 0}^{8} I(s_j = x; r_{j+k} \mid r_j)$$

Other “Learning” Methods

Neural Networks

17 Residue Window

Each Residue represented with 21-bits

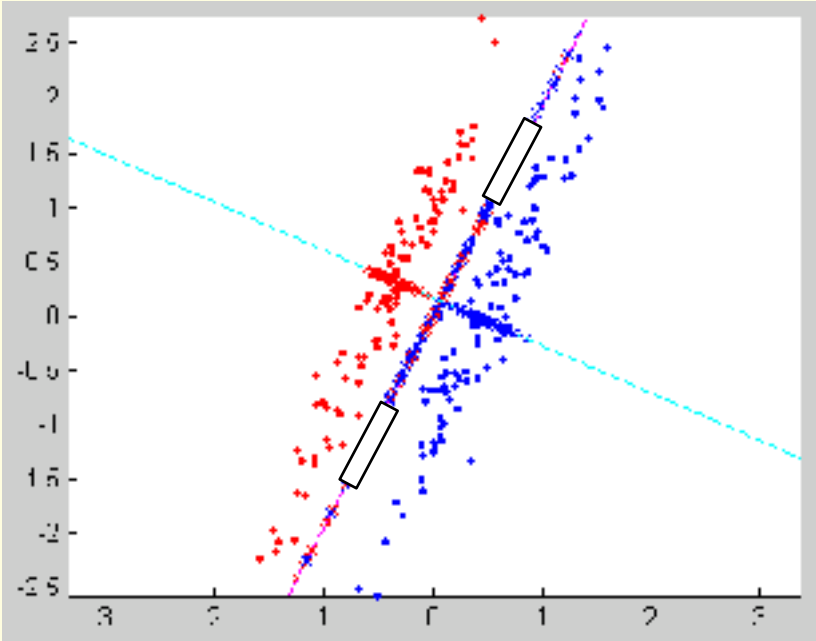
One for each AA, one for beginning/end of sequence

Each sample has 17x21 bit feature vector with 17 non-zero entries

Support Vector Machines (SVM)

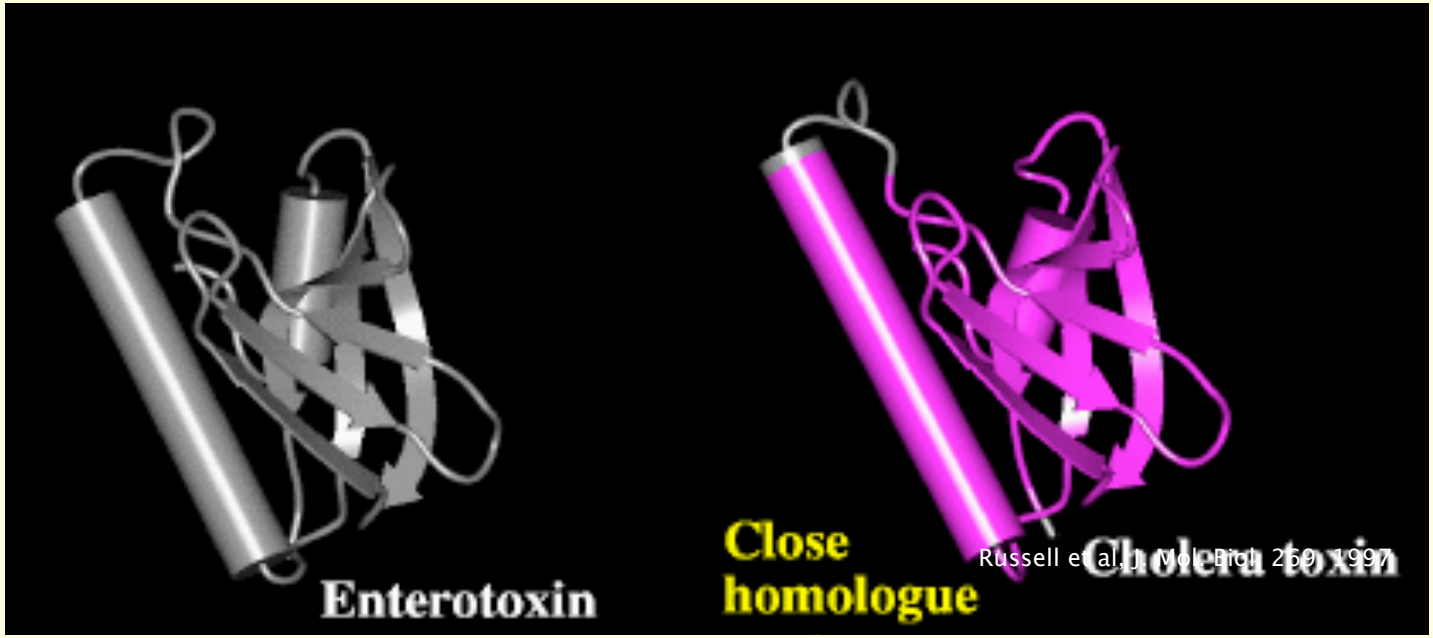
Linear Discriminant Analysis (LDA)

- Returns H, E, or C with confidence or probability.
- Requires k sequential residues with confidence above some threshold.



Third-Generation

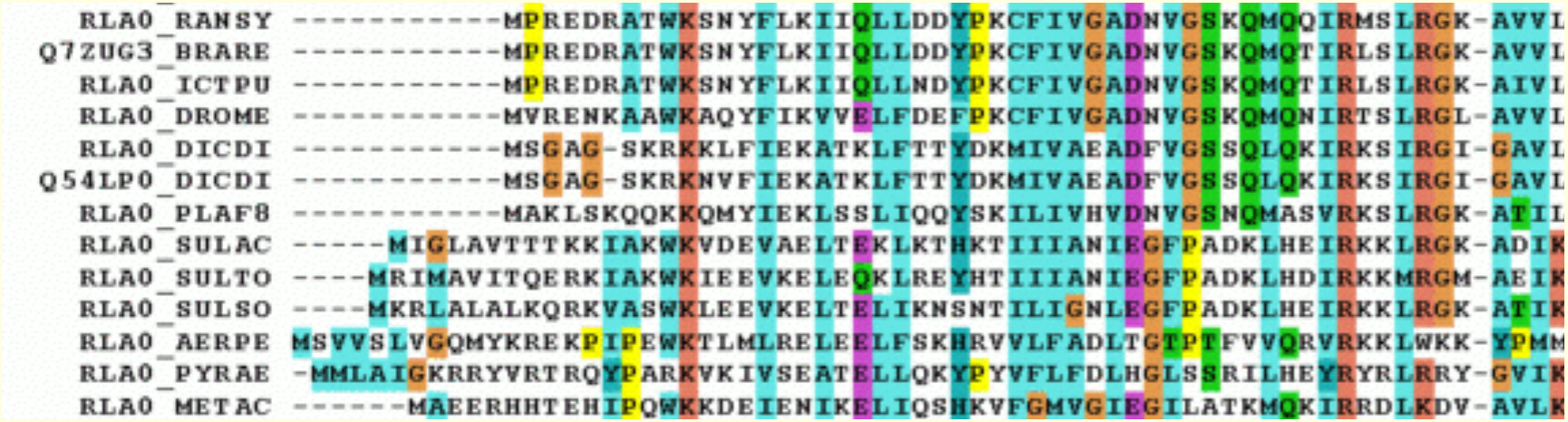
Observation: Protein structure is more conserved than protein sequence.



Two proteins with >30% sequence identity are likely to have similar structures.

Multiple Sequence Alignment

We saw that multiple primary sequences of DNA, RNA, or protein identify similarity that may be a consequence of functional, structural, or evolutionary relationships.



Idea:

Predict secondary structure type by using information from homologs, then combine predictions.

Multiple Sequence Alignment

Have:

List of similar (but different) sequences

Assumption:

These aligned sequences fold into the same structure

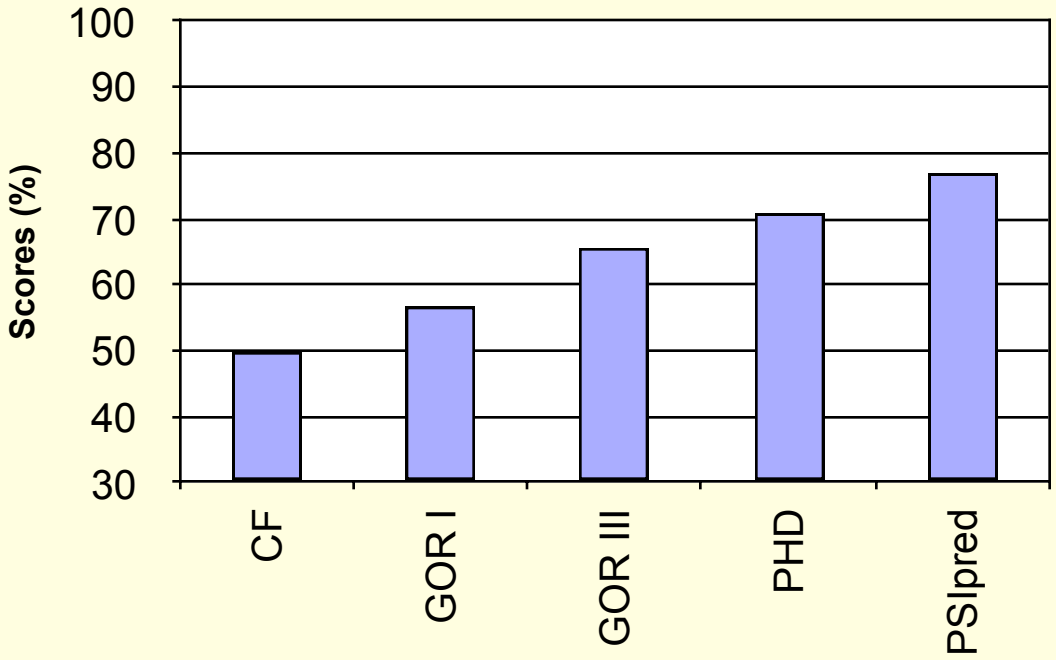
Consider the probability distribution over all amino acids at residue i, a 20-dimensional vector

Examine 13-residue window

Each residue represented by the 20-dimensional probability vector

Use favorite classification technique (NN, LDA, SVM)

Accuracy Limits



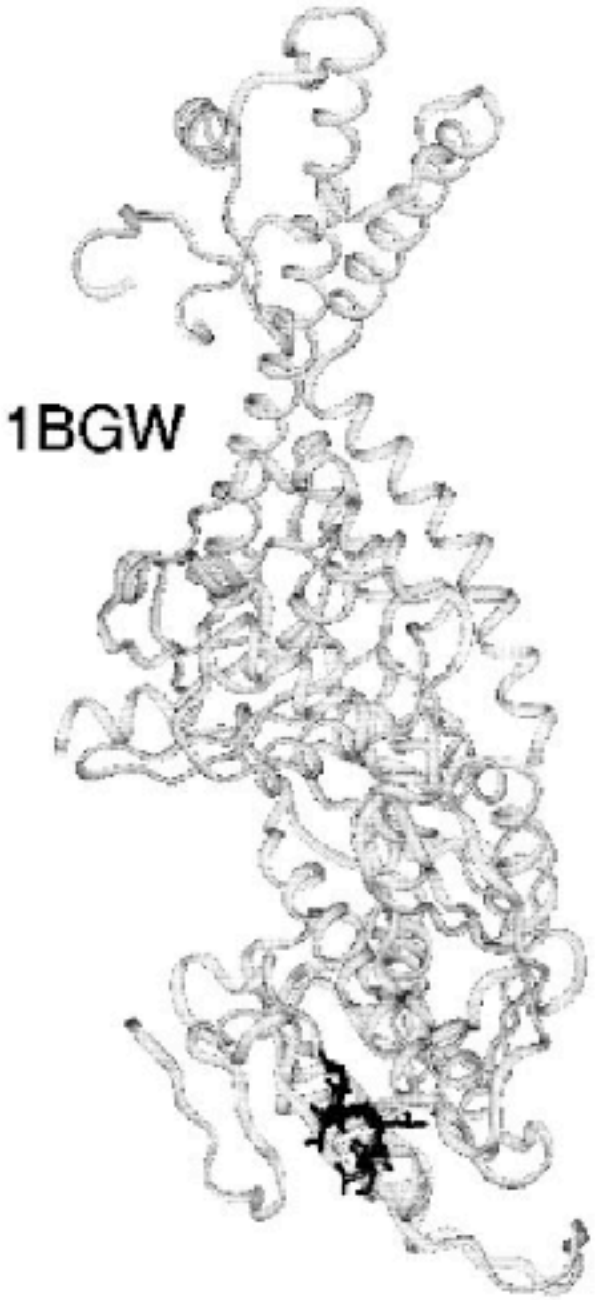
What is the ***gold standard***? (~12% variability)

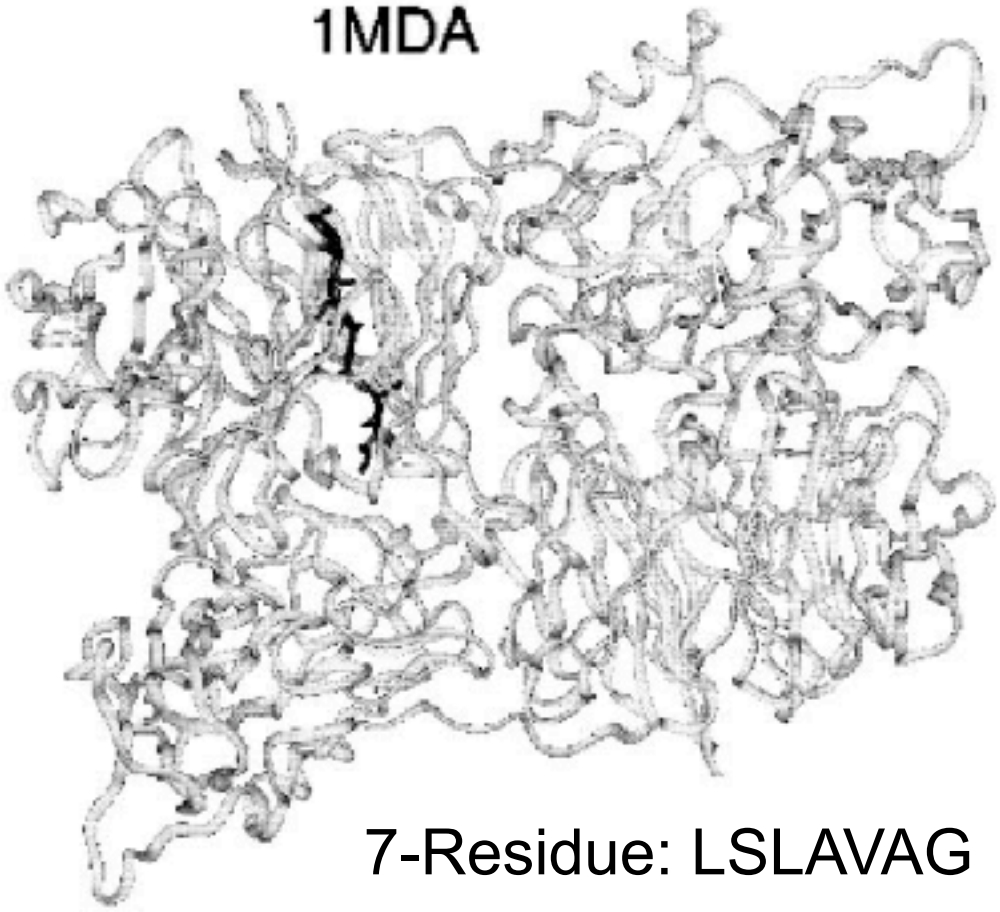
Puts upper bound at 88% accuracy

Sequence ➡ Structure Degeneracy

Some 11-long AA sequences can fold into both an alpha-helix and a beta-strand

Chameleon Sequences



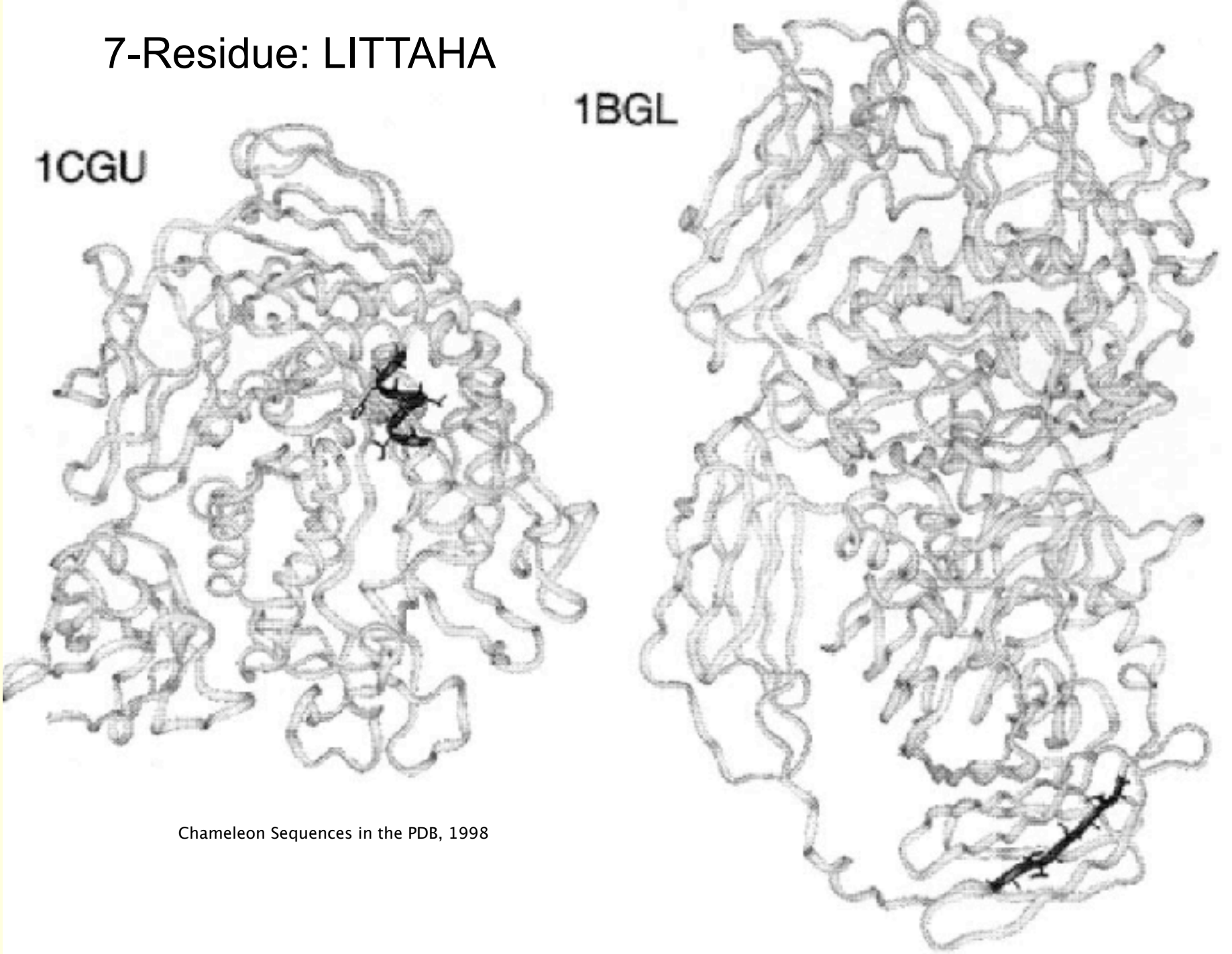


7-Residue: LSLAVAG

Many 5-residue chameleons
Fewer 6-residue chameleons
Few 7-residue chameleons

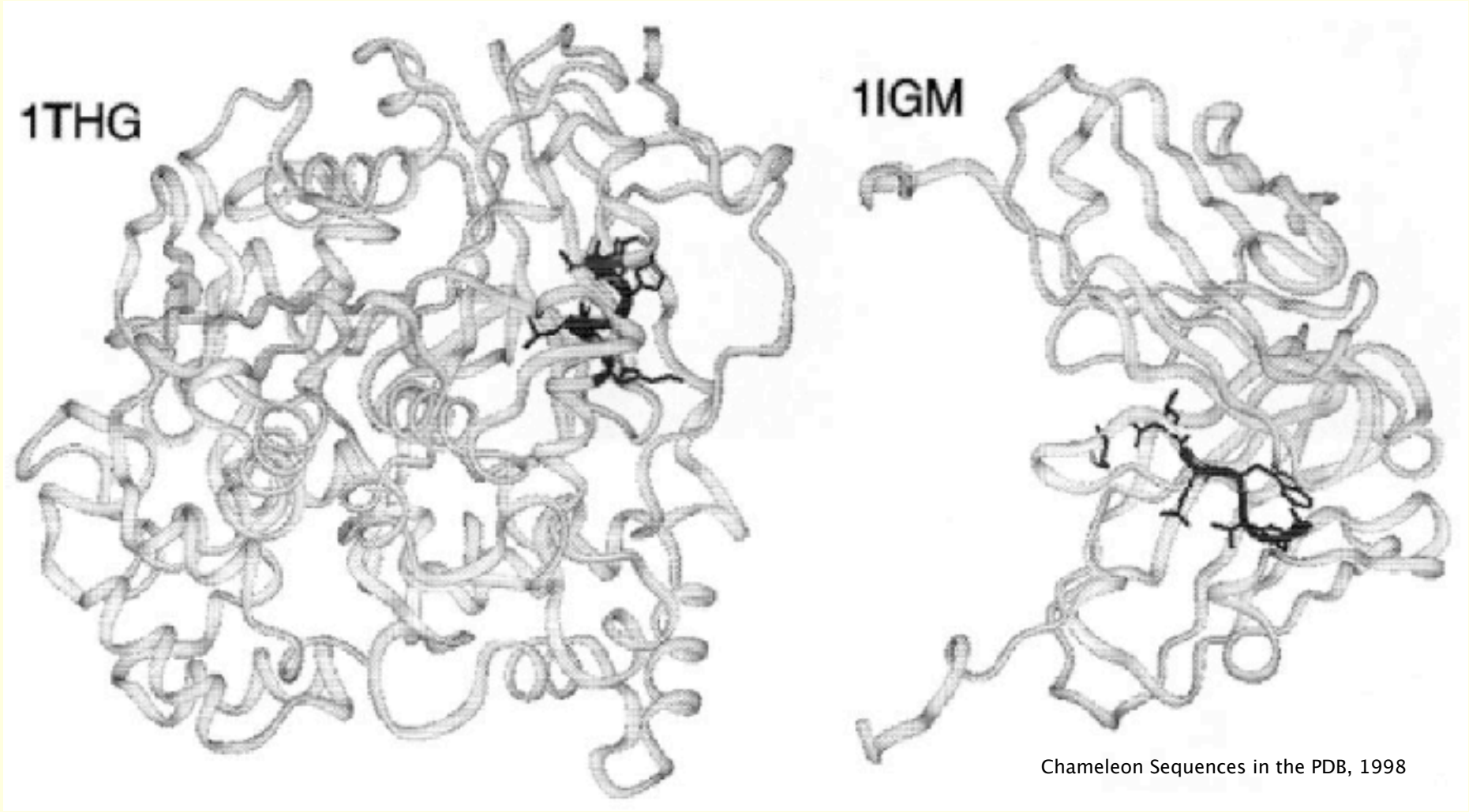
Chameleon Sequences in the PDB, 1998

7-Residue: LITTAHA



Chameleon Sequences in the PDB, 1998

7-Residue: KGLEWVS



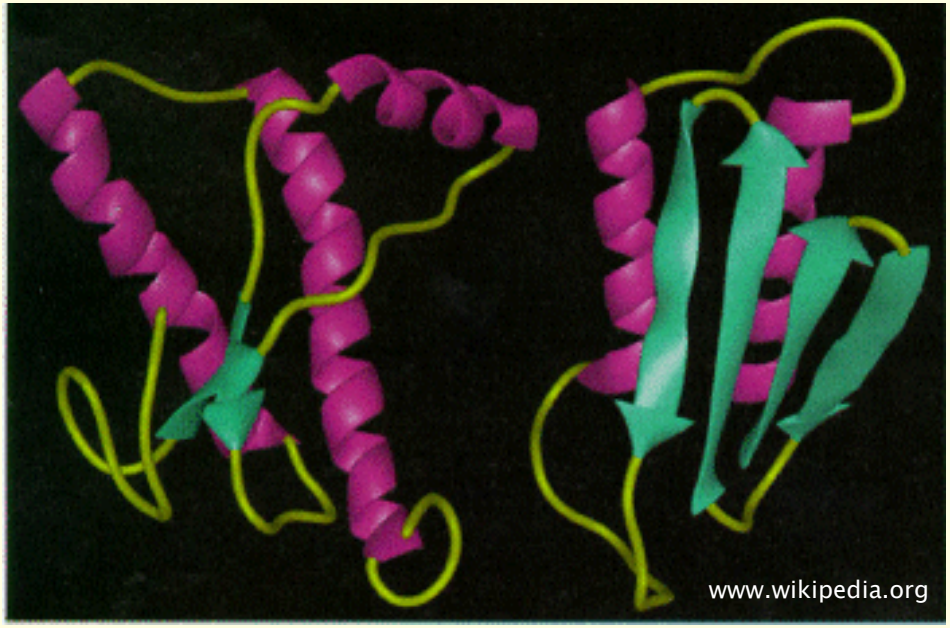
Chameleon Sequences in the PDB, 1998

Prions

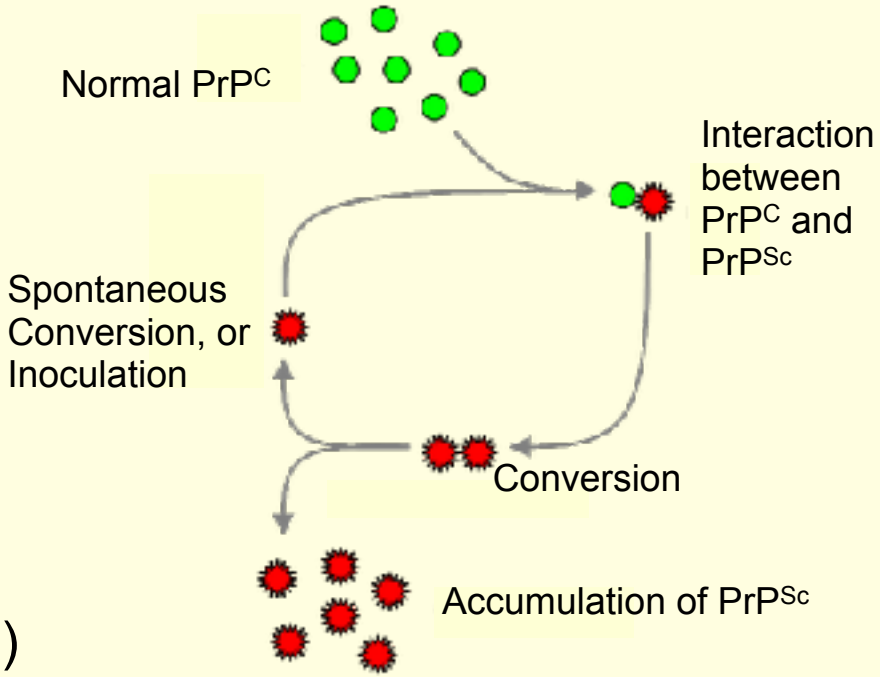
Prion: from “proteinaceous infectious”
The prion protein is naturally found in the body.
The infectious agent is the same protein but with a different fold.

Disease fold induces normal copies of the protein to fold into disease form.

Accumulation of disease folds forms cytotoxic aggregates.



PrP^{C} (NMR) PrP^{Sc} (Proposed)



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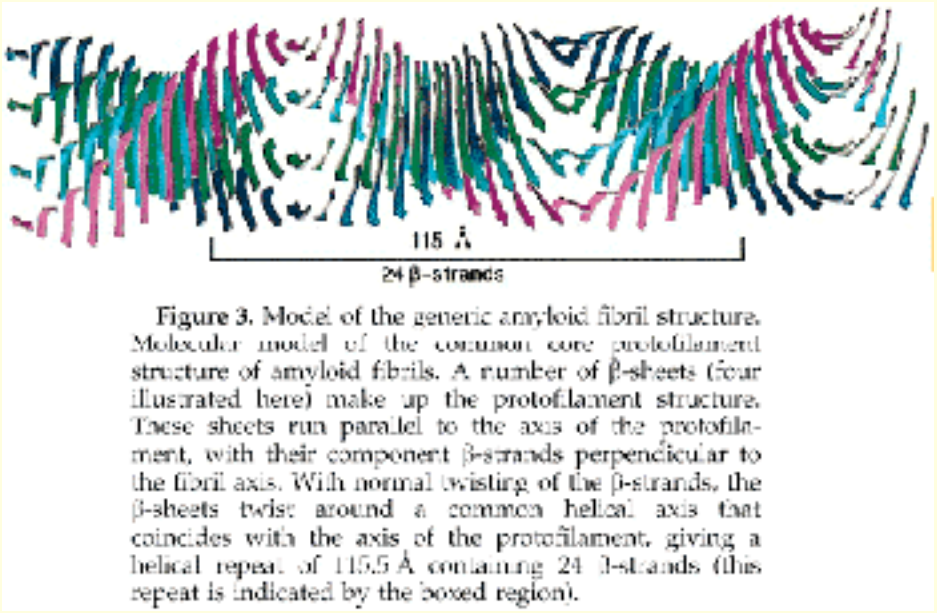
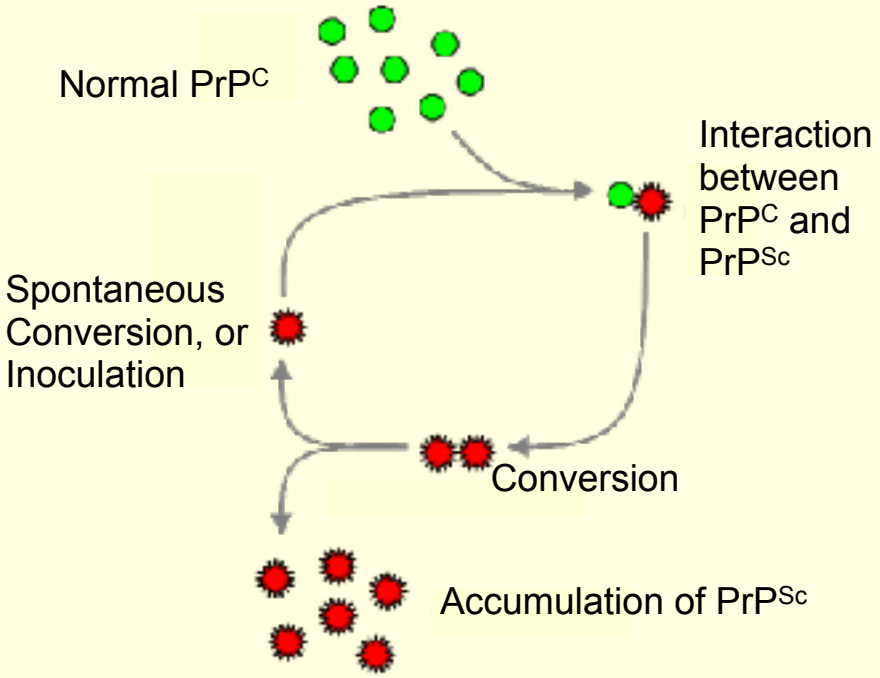


Figure 3. Model of the generic amyloid fibril structure. Molecular model of the common core protofilament structure of amyloid fibrils. A number of β-sheets (four illustrated here) make up the protofilament structure. These sheets run parallel to the axis of the protofilament, with their component β-strands perpendicular to the fibril axis. With normal twisting of the β-strands, the β-sheets twist around a common helical axis that coincides with the axis of the protofilament, giving a helical repeat of 115.5 Å containing 24 β-strands (this repeat is indicated by the boxed region).

Sunde et al, J Mol Biol, 273(3), 1997.



“Amyloidosis” leads to tissue damage.