CMSC423: Bioinformatic Algorithms, Databases and Tools
Lecture 22

RNA folding

Protein folding

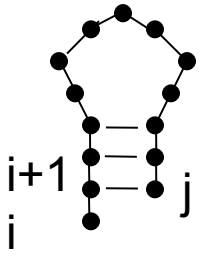
Nussinov's algorithm

- Assumes no pseudo-knots
- Dynamic programming approach – maximize # of pairings

- S – string of nucleotides representing the RNA molecule
- Sub-problem – F[i,j] – score of folding just S[i..j]
- Initial values: F[i-1,i] = F[i,i] = F[i, i+1] = 0

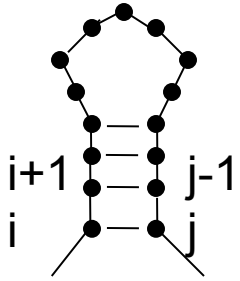
Nussinov's algorithm

F[i,j] is the maximum of:



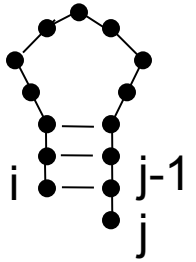
I. F[i+1,j]

S[i] unpaired



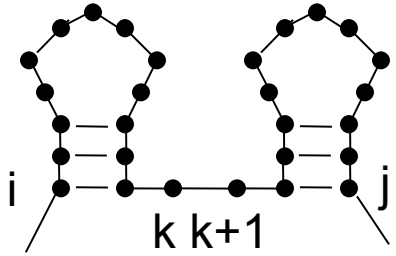
III. F[i+1,j-1] + 1
if S[i+1] complementary to S[j-1]

S[i] paired with S[j]



II. F[i,j-1]

S[j] unpaired



IV. $\max_k$ F[i,k]+F[k+1,j]

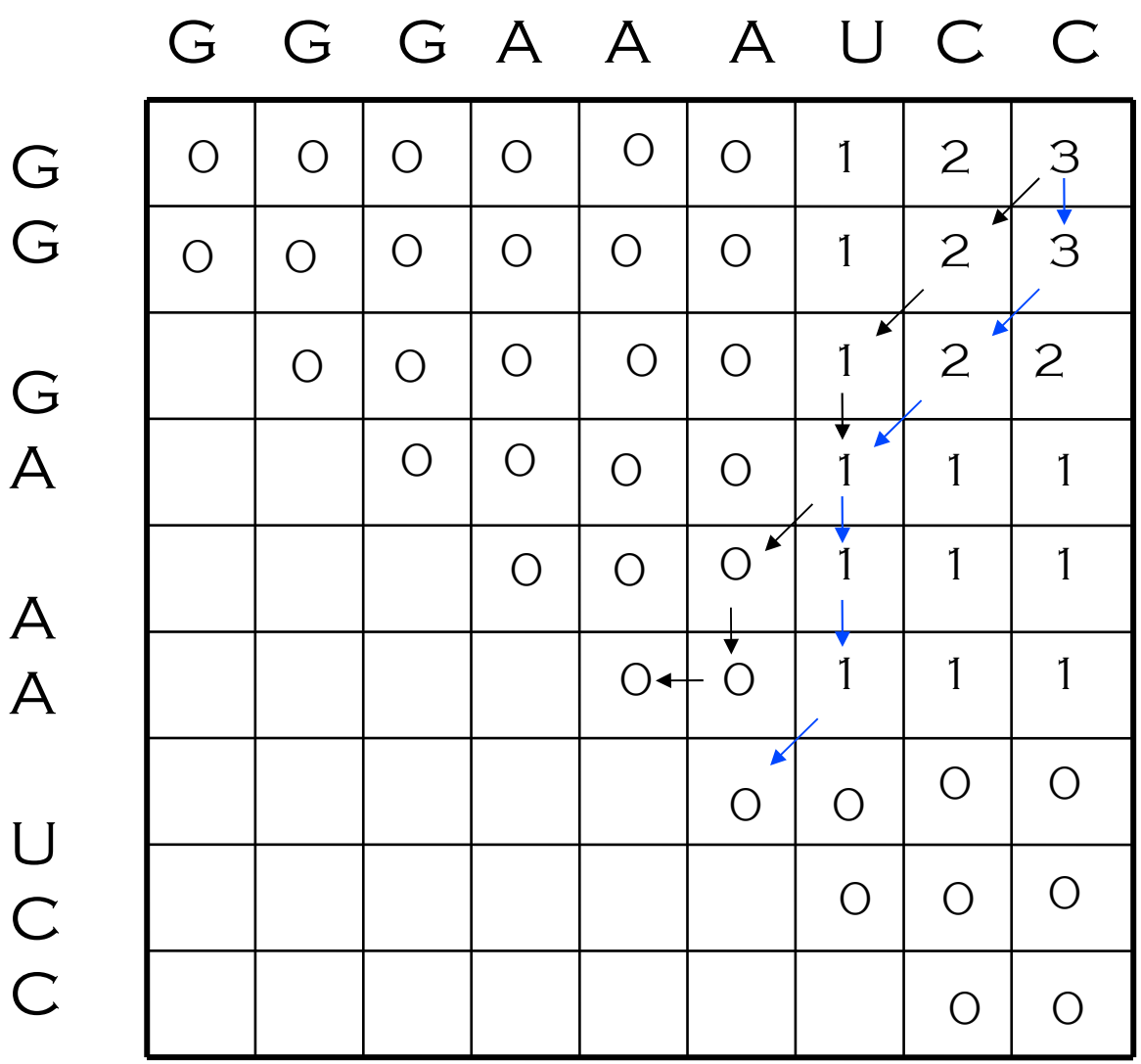
Branch

Questions

- In what order do we fill the dynamic programming table?
- How can we ensure that "loops" consist of at least k nucleotides?

	G	G	G	A	A	A	U	C	C
G									
G									
G									
A									
A									
A									
U									
C									
C									

F[i+1, j]
F[i, j - 1]
F[i+1, j-1] + 1 (if paired)
$\max_k F[i,k] + F[k+1,j]$

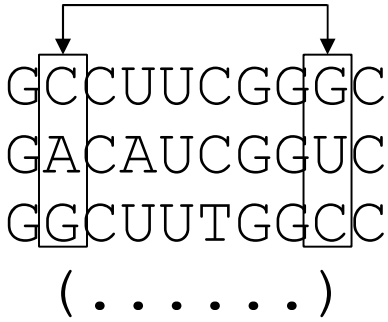

G G G A A A U C C
G
G
G
A
A
A
U
C
C
0 0 0 0 0 0 1 2 3
0 0 0 0 0 0 1 2 3
0 0 0 0 0 1 2 2
0 0 0 0 0 1 1 1
0 0 0 0 1 1 1
0 0 0 1 1 1
0 0 1 1 1
0 0 0 0
0 0 0
0 0

GGGAAAUCC

((.(..)))

.((..()))

From multiple alignment to structure



- Find columns in the alignment where mutations are correlated
- Mutual information - how correlated are the columns?

$$M_{i,j} = \sum_{x_i, x_j} f_{x_i x_j} \log\left(\frac{f_{x_i x_j}}{f_{x_i} f_{x_j}}\right)$$

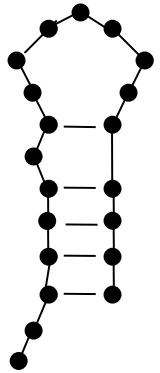
$M_{i,j}$ = mutual information between columns i and j
f_{xixj} = frequency of each of 16 pairs of nucleotides at columns i and j
f_{xi} = frequency of each of 4 nucleotides at column i
f_{xj} = frequency of each of 4 nucleotides at column j

Mutual information

- Ranges from 0 to 2 for a 4-letter alphabet
- Correlated columns - mutual information high
- Advantages:
  - Don't need to know how RNA folds - pseudo-knots should “pop” out of the alignment
- Disadvantages:
  - Need many sequences in an alignment (to compute frequencies)
  - The aligned sequences must be sufficiently divergent (conserved columns provide no information)

A better objective function

- Find the RNA fold that minimizes the Gibbs free energy
- Zucker's algorithm keeps track of:
  - Stacking energy - f(# of base-pairs in a stem)
  - Loop energy - f(length of loop)
  - Bulge energy - f(length of bulge)
  - Dangle energy - f(length of dangle)



- Computation is done with an extension of the traditional (Nussinov) dynamic programming approach
- One extension: compute sub-optimal folds
  - during backtracking, try multiple paths
- Question: how do you change Nussinov's algorithm to allow the computation of the stacking energy? Hint: think affine gap penalties.

Protein folding

- Protein shape determines protein function
- Protein sequence determines protein shape (Anfinsen's experiment)
- Levinthal's paradox – space of possible protein conformations is exponentially large, yet proteins fold fast (μsec – minutes).
- Corollary: proteins must "know" how to fold (i.e. they don't search the entire space of conformations)

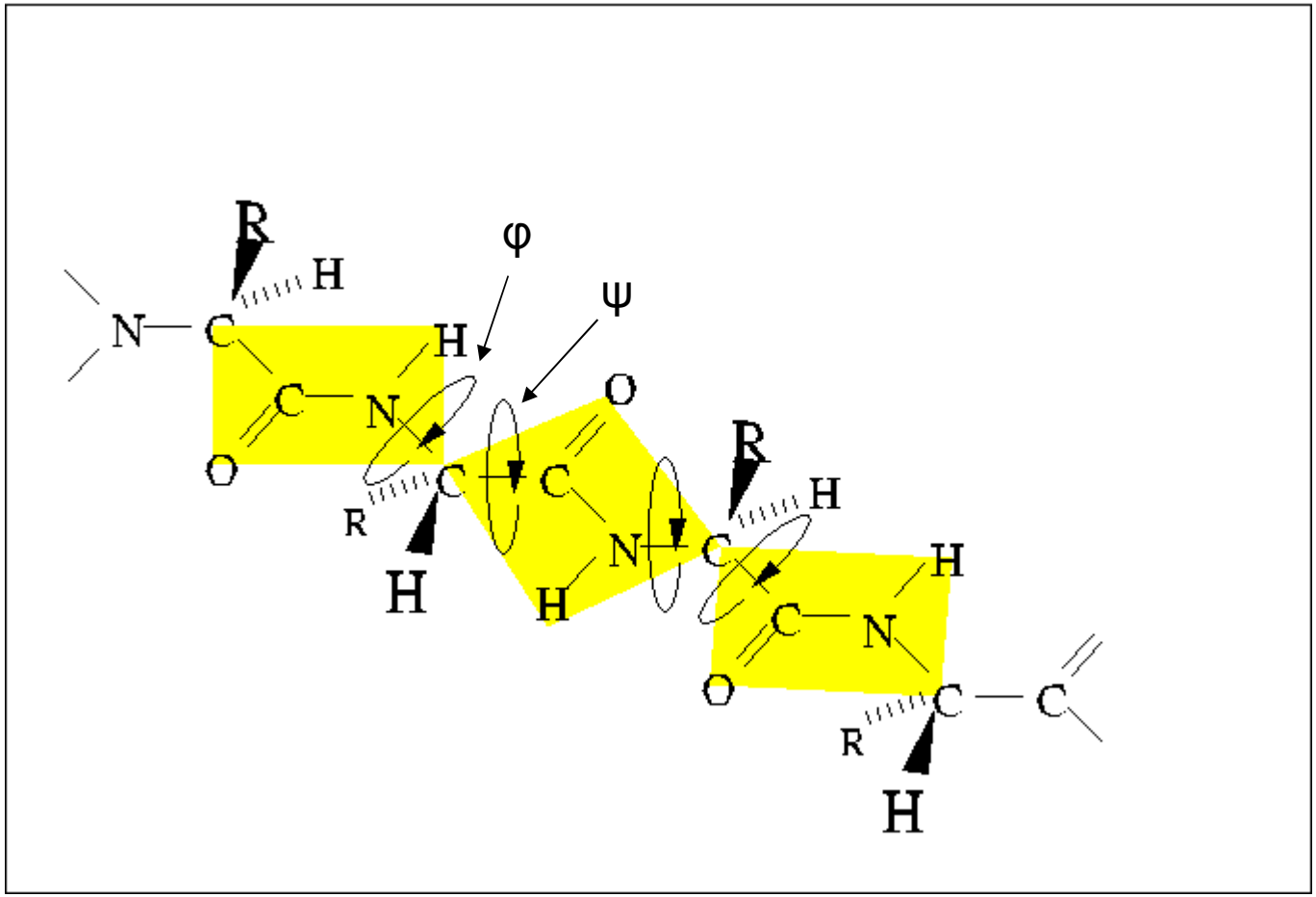
- Note: much easier to find a protein's sequence than its structure

Protein folding

- Note: mis-folded proteins may cause disease (e.g. Creutzfeld-Jakob a.k.a. mad cow)
- Drugs (e.g. antibiotics) often inhibit protein function – knowing structure can help design drugs

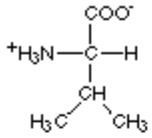
- Folding@home – lend your computer's unused cycles to help fold proteins (like SETI@home) (do you believe in evolution or aliens ?)

Protein structure
(primary structure = sequence)

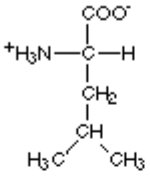


http://www.tulane.edu/~biochem/med/second.htm

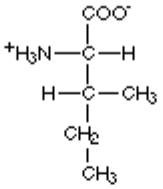
Amino acids with hydrophobic side groups



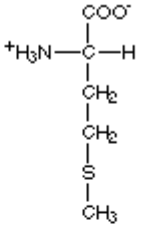
Valine
(val)



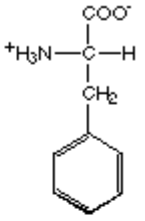
Leucine
(leu)



Isoleucine
(ile)



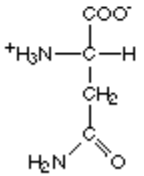
Methionine
(met)



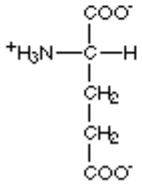
Phenylalanine
(phe)

hate water

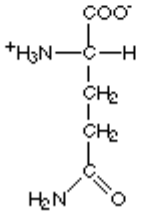
Amino acids with hydrophilic side groups



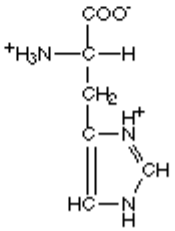
Asparagine
(asn)



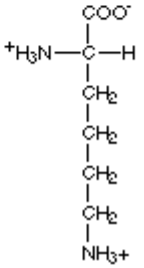
Glutamic acid
(glu)



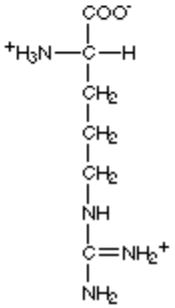
Glutamine
(gln)



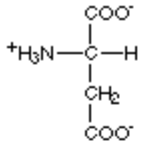
Histidine
(his)



Lysine
(lys)



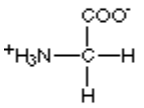
Arginine
(arg)



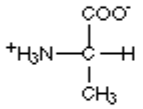
Aspartic acid
(asp)

like water

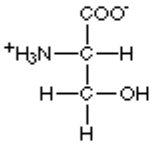
Amino acids that are in between



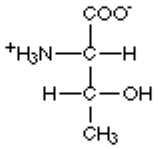
Glycine
(gly)



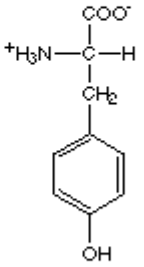
Alanine
(ala)



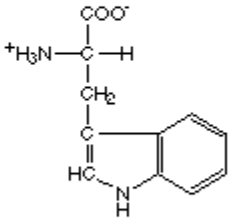
Serine
(ser)



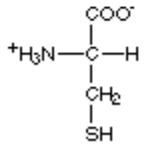
Threonine
(thr)



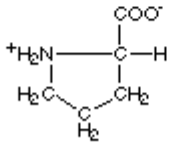
Tyrosine
(tyr)



Tryptophan
(trp)



Cysteine
(cys)

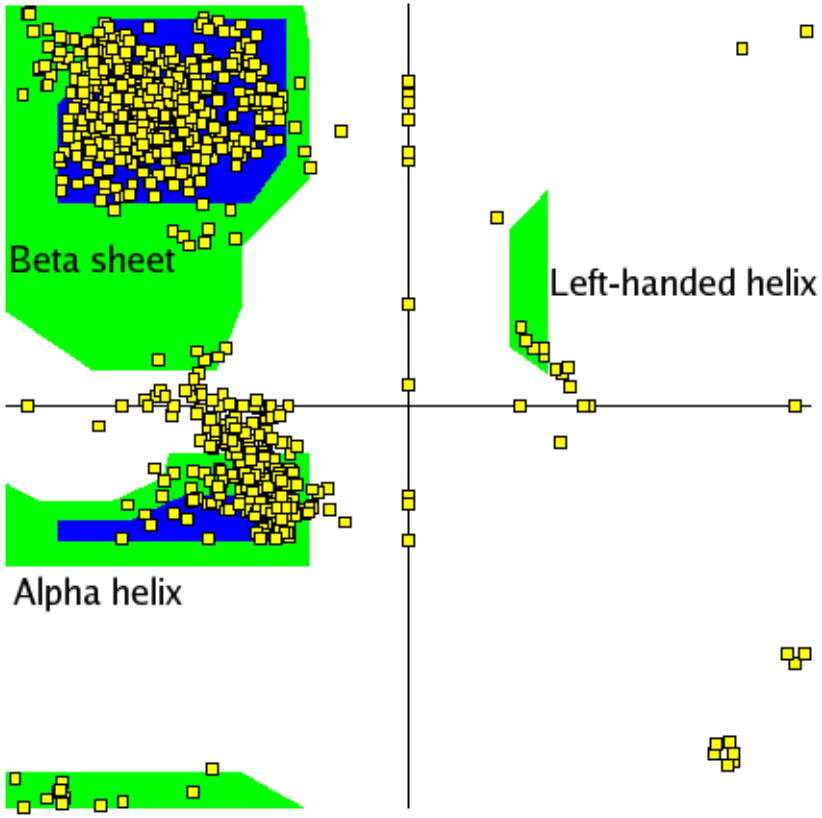


Proline
(pro)

can't decide

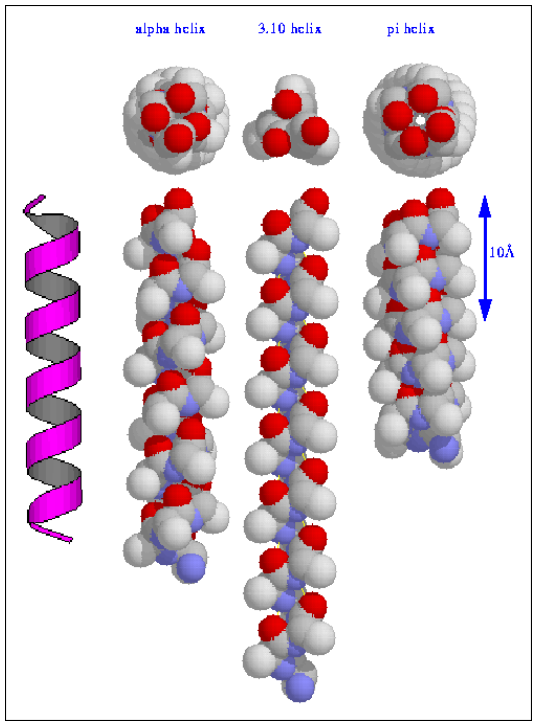
http://web.mit.edu/esgbio/www/lm/proteins/aa/aminoacids.html

Not all bends equally likely
Ramachandran plot

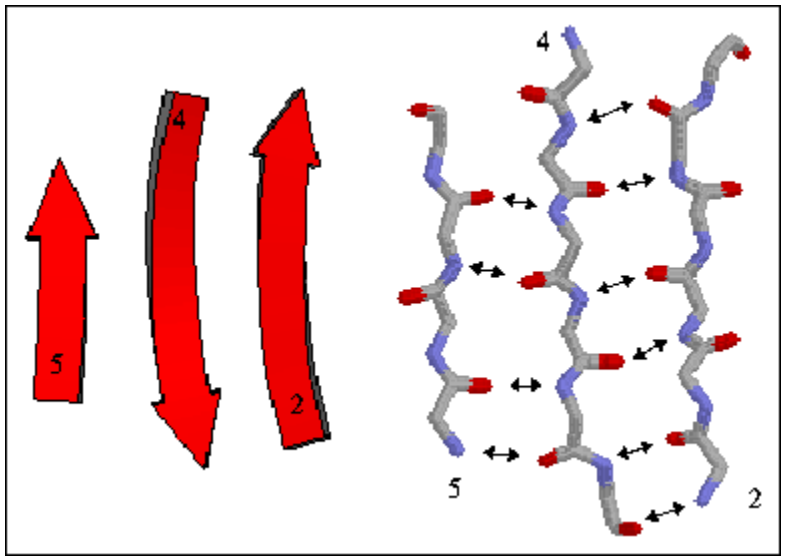


Secondary structure (motifs)

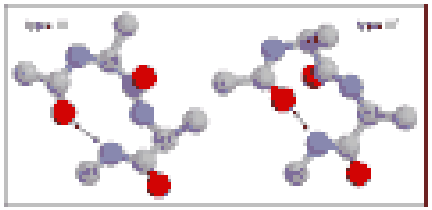
helix



sheet

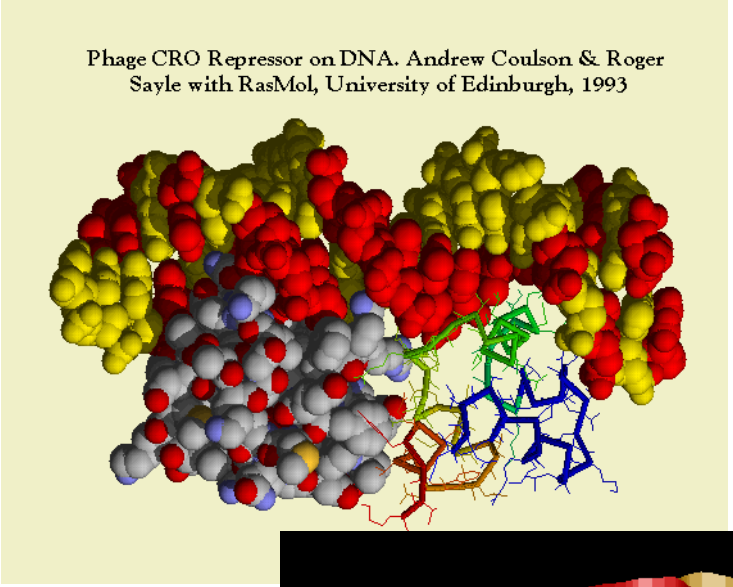


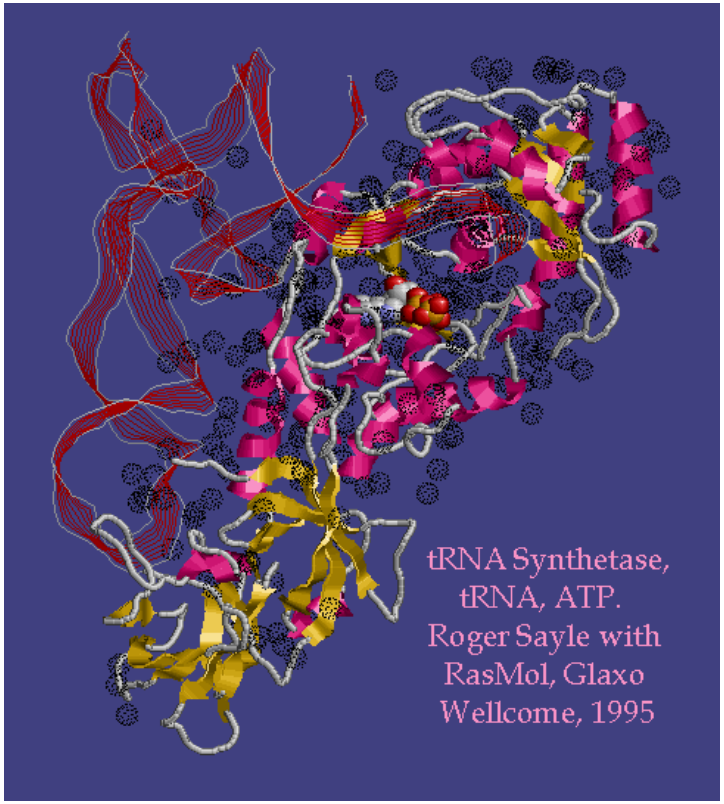
turn

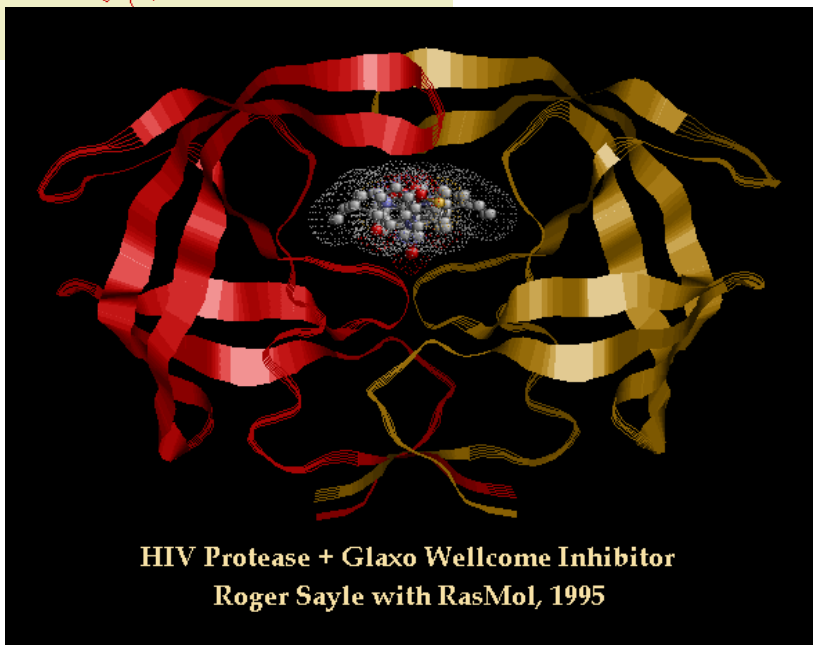


http://alpha2.bmc.uu.se/~kenth/bioinfo/structure/secondary/01.html

Tertiary structure (3D shape)







http://www.umass.edu/microbio/rasmol/sayle1.htm

Folded shape: lowest free energy

- Energy components
  - electrostatic (~$1/D^2$) (n^2 terms)
  - van der Waals (n^2 terms)
  - hydrogen bonding (n terms)
  - “bending” (n terms)
  - solvent (water/salt) (?? terms)
  - exclusion principle (no two atoms share same volume)
- Energy minimzation
  - small perturbations & computation: hill climbing, simulated annealing, etc.
- Molecular dynamics