CMSC 858E
Lecture 25: RNA folding cont’d; Protein folding
12/5/2006

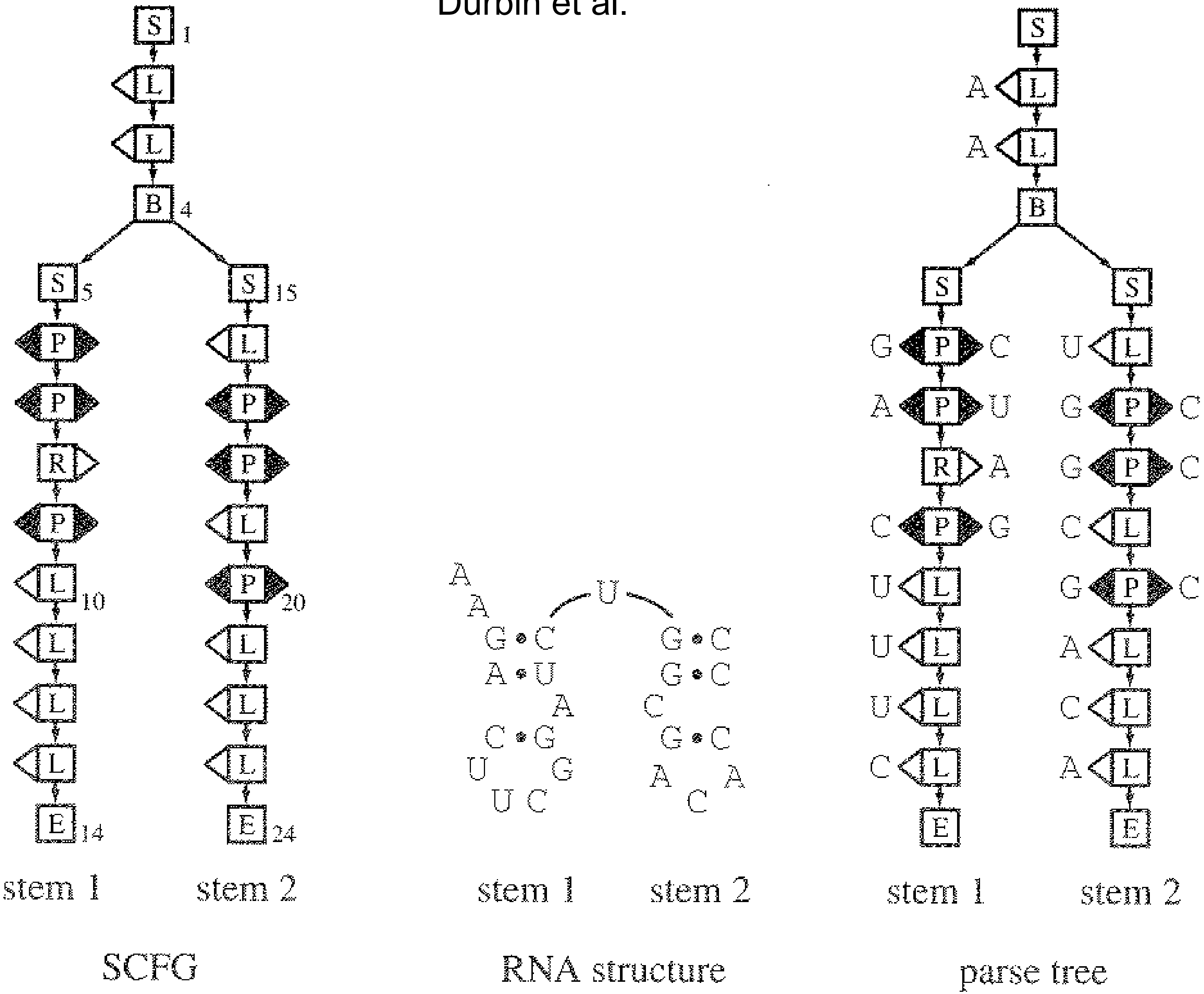
RNA Folding – covariance models

- Based on stochastic context free grammars (SCFGs)

W – (P|L|R|B|S|E)	
P -> aWb	*pair (a is paired with b)*
L -> aL	*left (a unpaired on the left)*
R -> Lb	*right (b unpaired on the right)*
B -> SS	*bifurcation*
S -> W	*start*
E -> ε	*end*

- State transitions associated with transition probabilities

Durbin et al.



SCFG

RNA structure

parse tree

Parsing problem

- How likely is it that the RNA sequence observed was generated by the covariance model (CM)?
- Scoring (calculating this probability) can be done with dynamic programming (inside/outside/CYK/forward/backward, etc.)
- High-scoring regions of the genome are likely to be RNAs with the structure encoded in the CM.
- tRNAscan-SE – finds transfer RNAs
- More on machine learning techniques in CMSC 828N Spring 2007

Protein folding

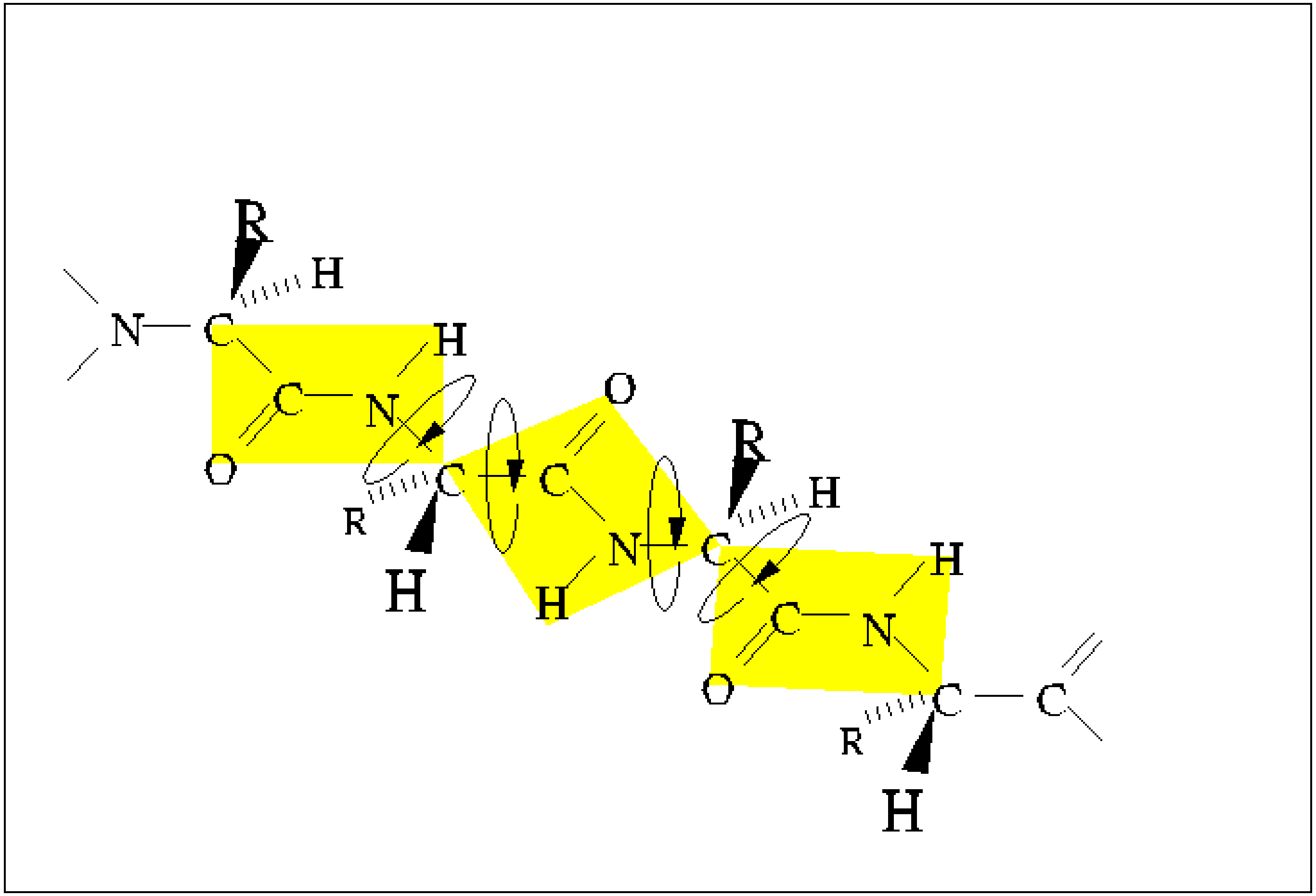
- Protein shape determines protein function
- Protein sequence determines protein shape (Anfinsen’s experiment)
- Levinthal’s paradox – space of possible protein conformations is exponentially large, yet proteins fold fast (usec – minutes).
- Corollary: proteins must “know” how to fold (i.e. they don’t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

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

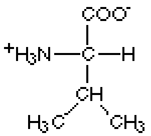
- Folding@home – lend your computer’s unused cycles to help fold proteins (like SETI@home) (do you believe in evolution or aliens ?)

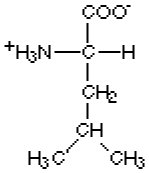
Protein structure
(primary structure = sequence)

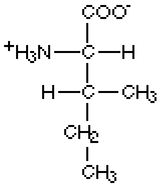


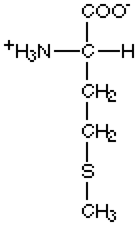
http://www.tulane.edu/~biochem/med/second.htm

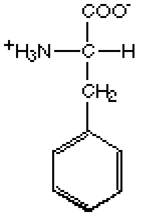
Amino acids with hydrophobic side groups


Valine
(val)


Leucine
(leu)

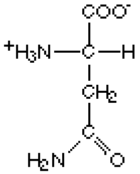

Isoleucine
(ile)

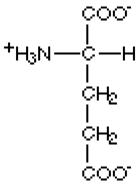

Methionine
(met)

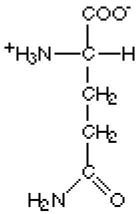

Phenylalanine
(phe)

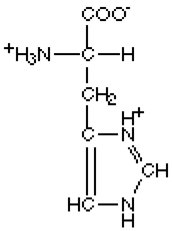
hate water

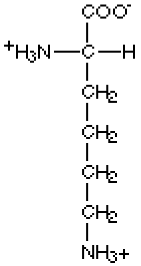
Amino acids with hydrophilic side groups

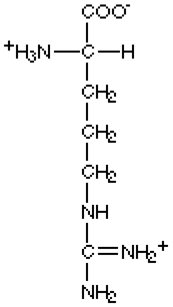

Asparagine
(asn)

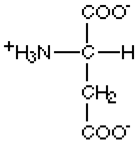

Glutamic acid
(glu)


Glutamine
(gln)


Histidine
(his)

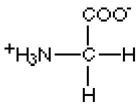

Lysine
(lys)

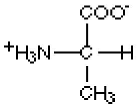

Arginine
(arg)

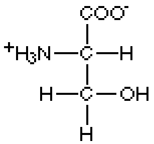

Aspartic acid
(asp)

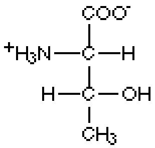
like water

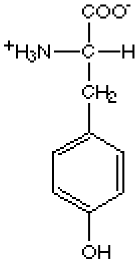
Amino acids that are in between

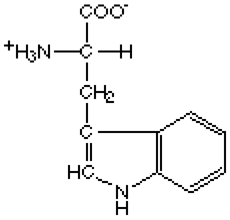

Glycine
(gly)

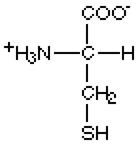

Alanine
(ala)

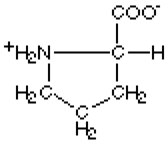

Serine
(ser)


Threonine
(thr)


Tyrosine
(tyr)


Tryptophan
(trp)

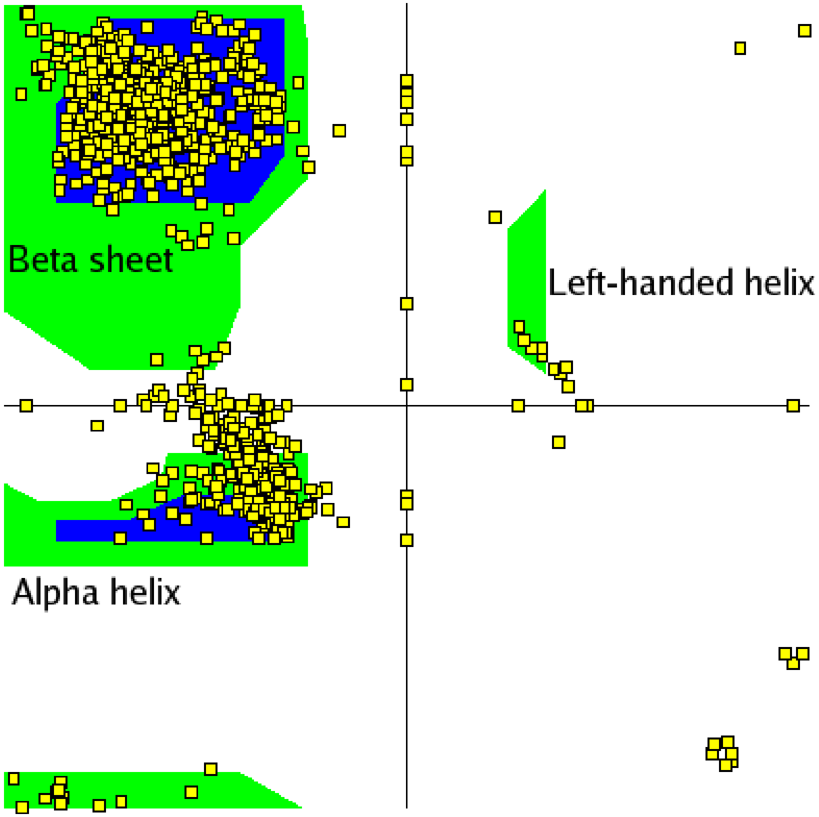

Cysteine
(cys)


Proline
(pro)

can't decide

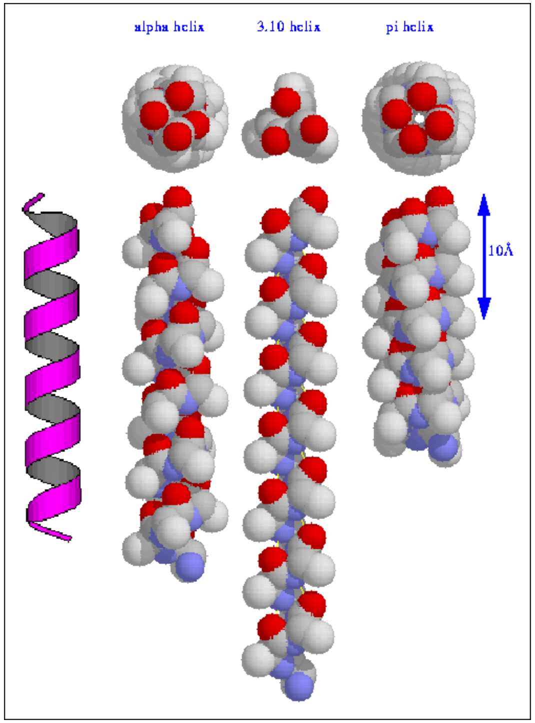
http://web.mit.edu/esgbio/www/lm/proteins/aa/aminoacids.html

Not all bends equally likely
Ramachandran plot

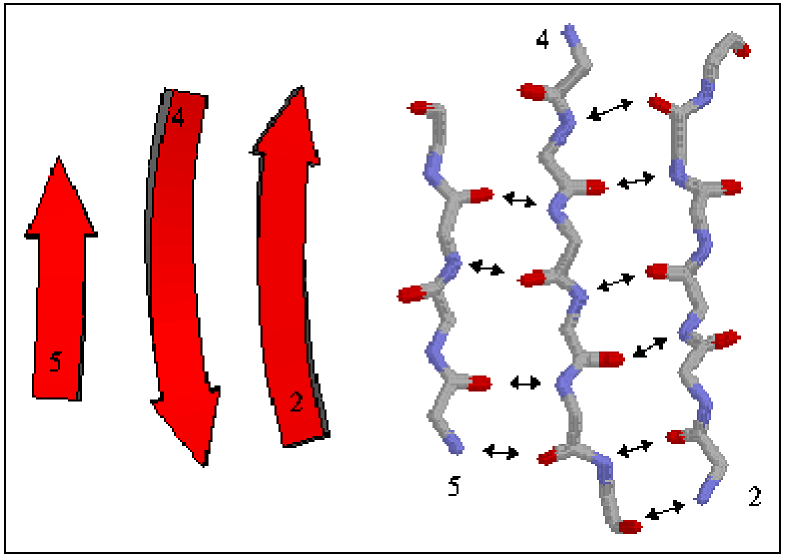


Secondary structure (motifs)

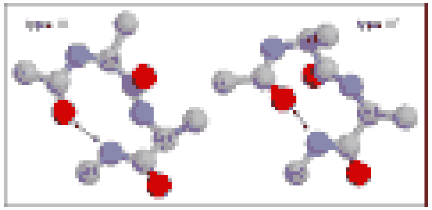
helix



sheet

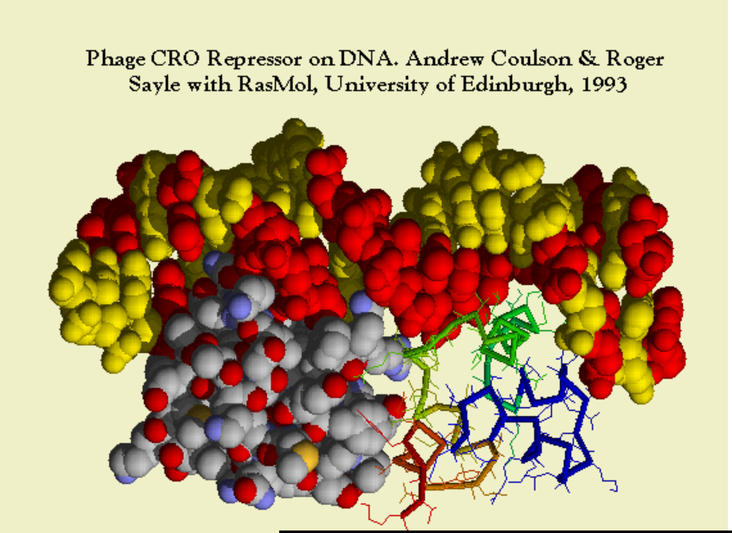


turn

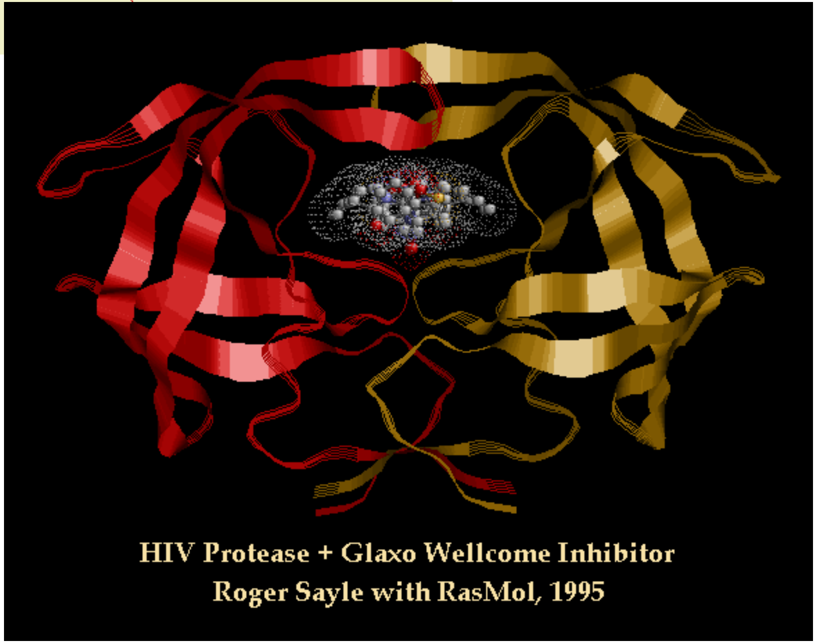


http://alpha2.bmc.uu.se/~kenth/bioinfo/structure/secondary/01.html

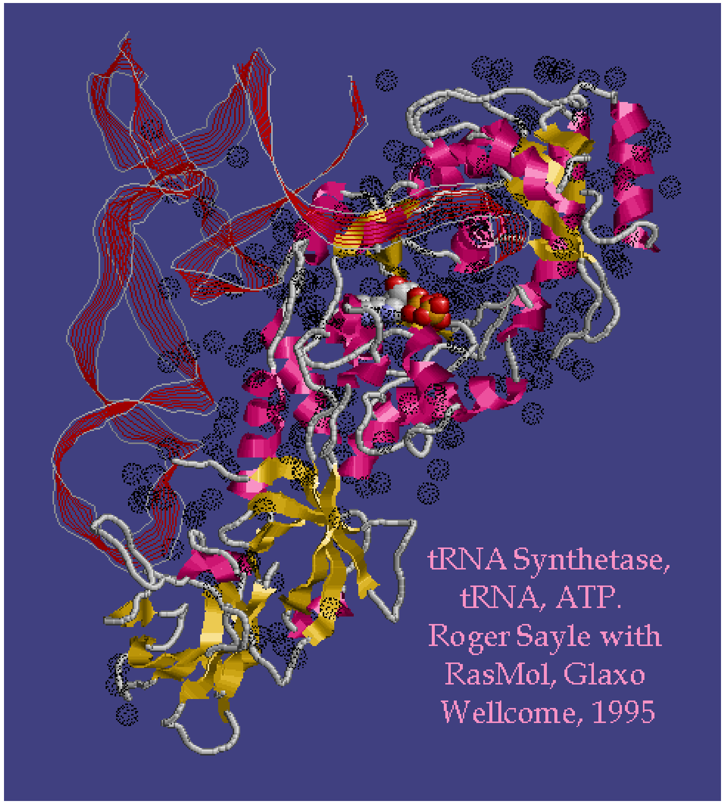
Tertiary structure (3D shape)



Phage CRO Repressor on DNA. Andrew Coulson & Roger Sayle with RasMol, University of Edinburgh, 1993



HIV Protease + Glaxo Wellcome Inhibitor
Roger Sayle with RasMol, 1995



tRNA Synthetase, tRNA, ATP. Roger Sayle with RasMol, Glaxo Wellcome, 1995

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

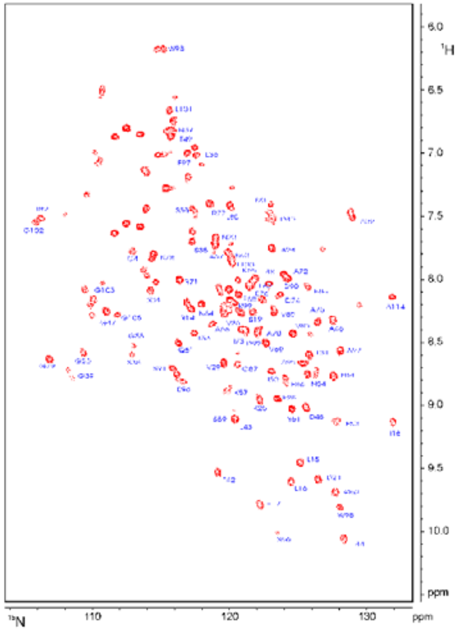
Folded shape: lowest free energy

- 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

How do we know the truth?

- X-ray crystallography
  - crystallize protein
  - shine X-rays
  - examine diffraction patterns

http://www.cryst.bbk.ac.uk/BBS/whatis/cryst_an.html



- Nuclear Magnetic Resonance (NMR)
  - no crystallization necessary
  - magnetic field “vibrates” hydrogen atoms
  - Nobel prize: Kurt Wuethrich

http://www.cryst.bbk.ac.uk/PPS2/projects/schirra/html/2dnmr.htm

Simpler problems

- Secondary structure prediction
- Side-chain conformation (assuming fixed backbone)
- Protein docking (how do proteins interact)
- Database searches (protein threading)

- Simpler energy functions
- Folding on a lattice (theoretical approximation)

- Critical Assessment of Fully Automated Structure Prediction – competition on proteins with unpublished 3D structure

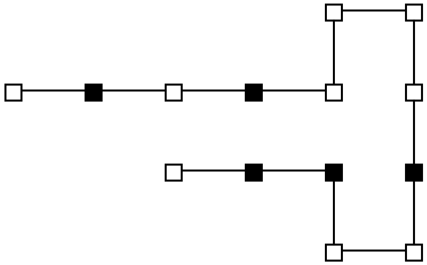
Secondary structure prediction

Chou-Fasman algorithm

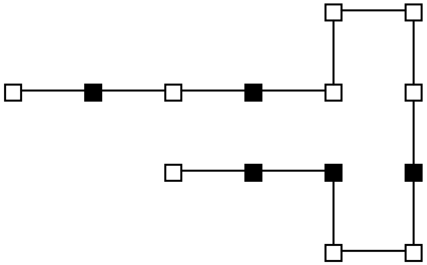
- Estimate amino-acid propensities for helix/sheet structures (from known structures)
  - mostly found in helix/often found in helix
  - mostly found in sheet/often found in sheet
  - ambiguous
- Find helix/sheet “seeds” - regions with many “mostly” AAs
- Extend seeds while overall propensity/likelihood of structure is good
- Clean up prediction (e.g. overlapping modules)

Folding on a lattice

- Protein – colored beads on a string
- Lattice – beads can occupy nodes in a 2D/3D lattice (not necessarily square lattice)
- Hydrophobic (black or 1) / hydrophilic (white or 0) model
- Objective: maximize # of contacts between hydrophobic beads
- NP-hard, constant approximation computable in linear time



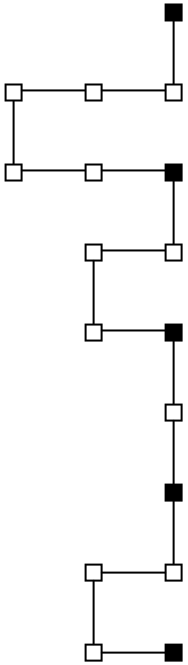
Folding on a lattice



- Note: sheets are reason why RNA folding dynamic programming algorithm doesn't work (lots of pseudo-knots in proteins)
- Residues i and j are adjacent iff |j – i| is odd
- Block decomposition:
  - b = 1 or $1Z_1 1Z_2 1Z_3 ... 1Z_k 1$ Z_i – odd # of 0s
  - blocks separated by even # of 0s
- Properties:
  - 1s from a same block cannot be paired
  - 1s from even blocks can only be paired with 1s from odd blocks

Block decomposition

- Odd blocks – X blocks, even blocks – Y blocks (1s from X blocks can only line up to 1s from Y blocks)
- Normal form – 1s in a line separated by single 0s. Block separators fall to the side (the “face”)
- X – super-block structure – treat Y blocks like 0s
- Y – super-block structure – treat X blocks like 0s



Approximation algorithm

- Decompose protein into blocks
- Find the optimal “folding” place
- Build “super-block” structure for each half (one half as an X super-block, the other as a Y super-block)
- Fold the halves onto each other

- Claim: 1/4 approximation in 2D, 1/8 in 3D. iterative algorithm leads to 3/8 approximation. All algorithms run in linear time!!
- Proof: read the paper (careful counting of contacts)