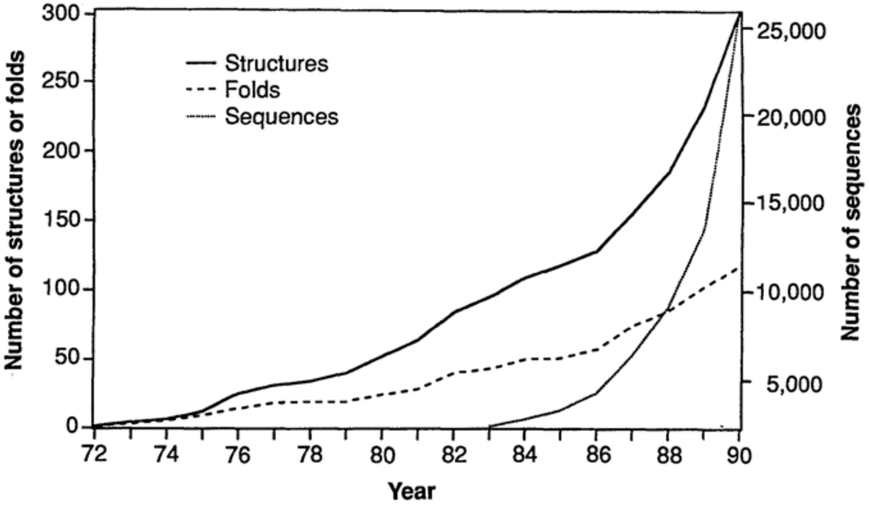
CMSC 858E Lecture 26: Protein folding – threading 12/7/06

Glossary

- Residue – any single amino-acid
- Side-chain – chemical group off the backbone
- Peptide – a short chunk of protein
- Polypeptide – protein

Threading: reverse structure prediction

- Main hypothesis: while there are many protein sequences, there are much fewer folds. I.e. nature keeps reinventing useful structures



- Given a database of structures and a query string, find which structure “fits” the string best

Initial idea: 3D-1D scores

- From a 3D structure, determine “environment” for every amino-acid
  - buried (inside the protein)
  - outside
  - inner side of helix
  - outer side of helix
  - etc...
- Annotate each position in protein with the environment information
  ACKCAHGT -> $E_1E_2E_1E_3E_4E_2E_3E_1E_4$
- Why this is reasonable? Amino-acids have “preference” for specific environments

Alignment to an environment string

- Idea: use gapped alignment algorithm to estimate how likely it is for a sequence to conform to a structure (represented as an environment string)

- $$\begin{array}{ccccccccccccc} E_1 & E_2 & - & E_1 & E_3 & - & - & E_4 & E_2 & - & E_3 & E_1 & E_4 \\ A & G & H & - & K & T & G & A & L & K & M & N & G \end{array}$$

- Question: what is the score of aligning an amino-acid to an environment?

Answer: use statistics

- For each environment – calculate likelihood (observed frequency) of all amino-acids based on known structures
- For each environment – empirical estimation of gap opening/extension penalties
- Alignment algorithm – use Gribskov's profile method: replace each environment character with the amino-acid frequency table for that environment

E_1

A 0.22 $S(E_1, G) = \sum_{AA} S(AA, G) * freq_{E1}(AA)$

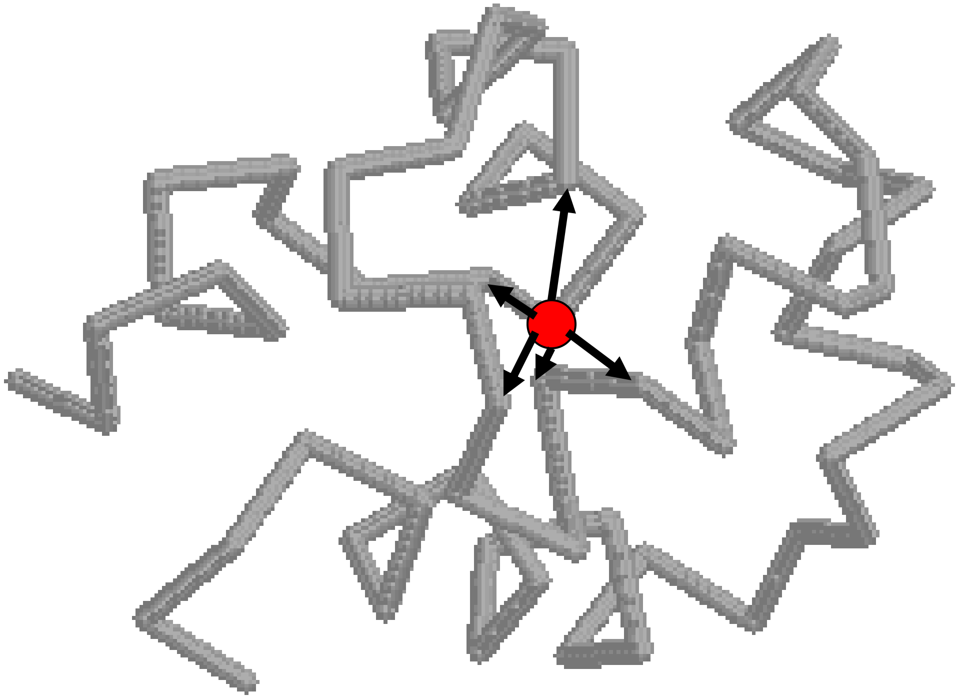
K 0.15 S(AA, G) – e.g. from BLOSUM matrix

W 0.08

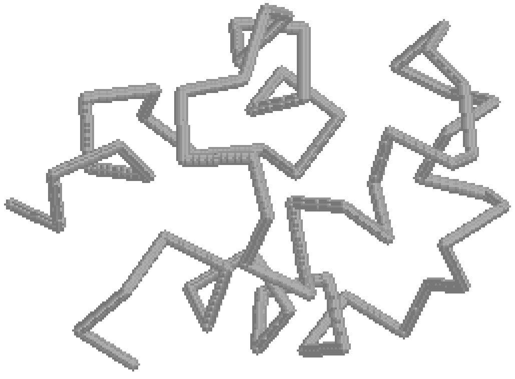
...

Environments – not good enough

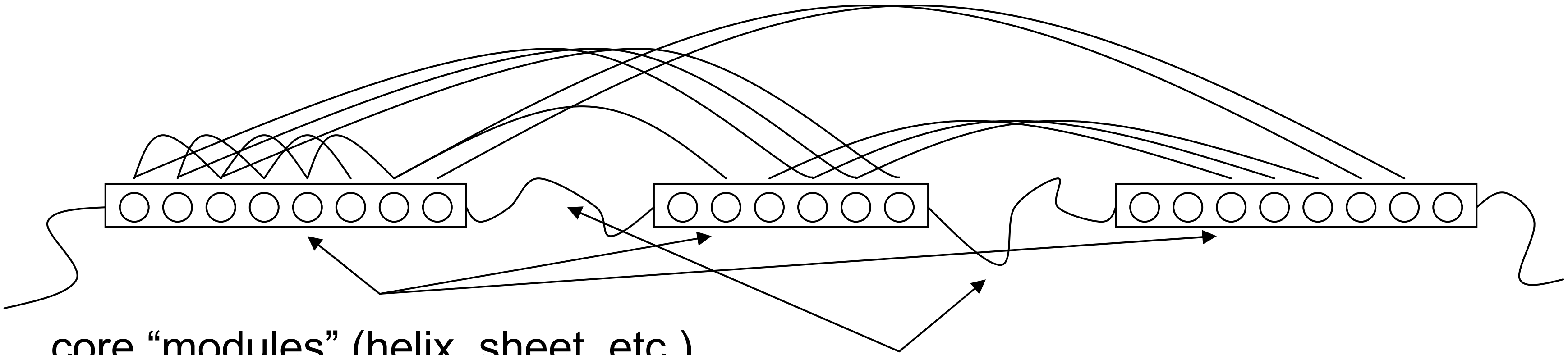
- Each amino-acid may have multiple contacts



A better model



residue interactions (and associated energy parameters)



core “modules” (helix, sheet, etc.)

variable length connections (gaps)

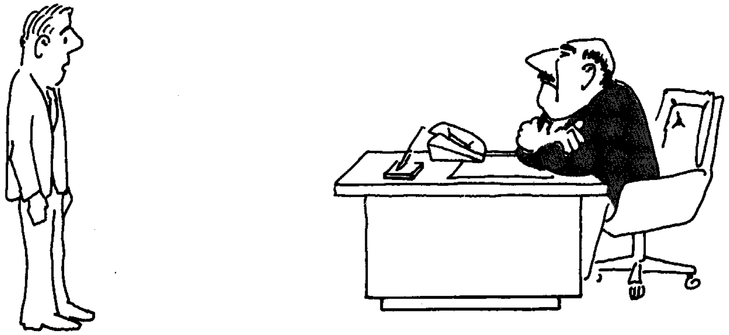
The threading problem

- Model assumptions:
  - loop AA composition and length contributes to energy score (note: can also place restrictions on minimum/maximum size in gaps)
  - interactions are pair-wise: interaction energy depends on at most two AAs
  - individual AAs in core modules also contribute to energy due to local environment
- Thread a protein sequence through a structure model s.t.
  - the place-holders are filled with amino-acids
  - a variable number of amino-acids fall in the gaps
  - overall energy is minimized
- Easy to say, hard to do: Thus defined (variable length gaps AND pair-wise interactions) the problem is NP-hard!

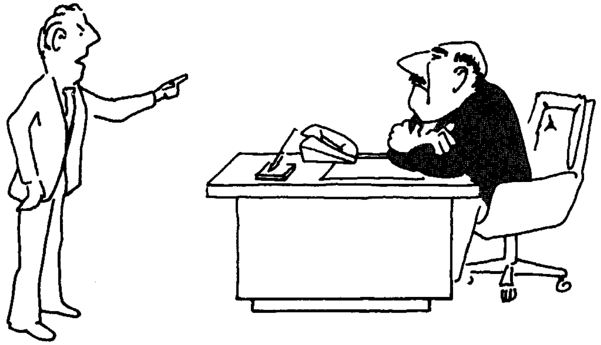
NP-hard => heuristics

- Branch and bound (Lathrop, Smith)
  - Represent all possible folds (search space) s.t. it is easy to compute a lower bound on the score
  - Note: a threading is uniquely defined by the coordinates of the core elements – a set of threadings is a hyper-rectangle in a C-dimensional space where C is the # of core elements
  - Divide search space and compute energy lower-bounds on each sub-division (choose a dimension (core) and a coordinate and split hyper-rectangle at that location)
  - Recurse on sub-division with lowest lower-bound

NP-completeness



“I can’t find an efficient algorithm, I guess I’m just too dumb.”



“I can’t find an efficient algorithm, because no such algorithm is possible!”

From: **Computers and Intractability**
M. R. Garey and D. S. Johnson
(W. H. Freeman 1979)

“I can’t find an efficient algorithm, but neither can all these famous people.”

Threading is NP-hard - proof

- Reduction from ONE-IN-THREE 3 SAT
  - n boolean variables, k boolean clauses with exactly 3 literals
  - 3 SAT – is there a setting of the variables such that all clauses are simultaneously true?
  - ONE-IN-THREE 3SAT – 3SAT but each clause made true by exactly one literal
- Proof: for any instance of 3SAT, create an instance of the protein threading problem s.t. a solution to the threading problem implies a solution to 3SAT

Proof ...cont

- Protein sequence
  - T, F – state of each boolean value
  - P,Q,R – which literal makes a clause true
  - protein: PQRPQRPQR...TFTFTF....
- Core model
  - one core element (with one AA) for each clause
  - one core element (with one AA) for each boolean
  - interactions from each clause to the booleans present in it. edge also encodes which literal (1,2,3) and whether value is negated
  - edge score = 0 if label consistent with amino-acid assignment and 1 otherwise (e.g. QF is consistent with edge 2,NOT)
  - optimal threading has score 0 and solves 3SAT

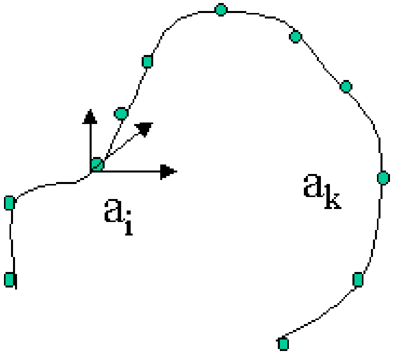
Discussion

- Both variable length gaps and pairwise interactions are essential!
- If no variable length gaps – can try all threadings in polynomial time irrespective of interactions
- If no pairwise interactions – dynamic programming can figure out the correct assignment (essentially the alignment problem)

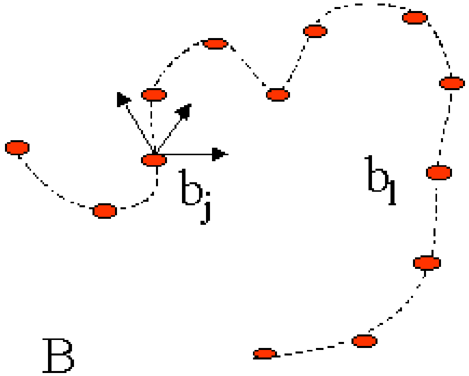
Structure to structure alignment

- Given two proteins with known structure, how do we align them to each other?
- Double Dynamic Programming
  - distance matrix depends on distance between residues
  - pick a pair of residues (i,j) and assume they are paired up
  - use dynamic programming to align the rest of the protein – score will represent score for pairing of i,j
  - use a final dynamic programming step to align the proteins based on scores determined above

Example

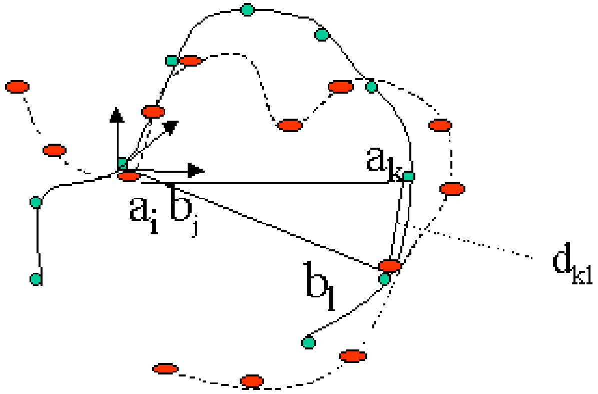


Structure A



B

Coordinate system coincidence at a_i,b_j



http://www.biotec.tu-dresden.de/schroeder/group/teaching/bioinfo3/ppt/structurealignment.ppt