Fragfinder and Undertaker—new-fold methods for protein structure prediction

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Outline of Talk

- Iterative search and alignment (SAM-T2K)
- Local structure prediction (predict-2nd)
- Multi-track HMMs (SAM)
- Fold-recognition (SAM-T02)
- Fragment-packing (undertaker)
- Results

Iterative search using HMMs

SAM-T98, T99, T2K methods all use similar method for building a target HMM, given a single sequence (or a seed alignment):

loop: Construct a profile HMM with one fat state for each letter of sequence (or column of multiple alignment).

find: Find sequences in a large database of protein sequences that score well with M. This is the *training set*.

Retrain M (using forward-backward algorithm) to re-estimate all probabilites, based on the training set.

Make a multiple alignment (using Viterbi algorithm) of all sequences in the training set. The multiple alignment has one alignment column for each fat state of the HMM.

Repeat from *loop*, with thresholds in step *find* loosened.

Predicting Local Structure

- Want to predict some local property at each residue.
- Local property can be emergent property of chain (such as being buried or being in a beta sheet).
- Property should be conserved through evolution (at least as well as amino acid identity).
- Property should be somewhat predictable (we gain information by predicting it).
- Predicted property should aid in fold-recognition and alignment.
- For ease of prediction and comparison, we look only at discrete properties (alphabets of properties).

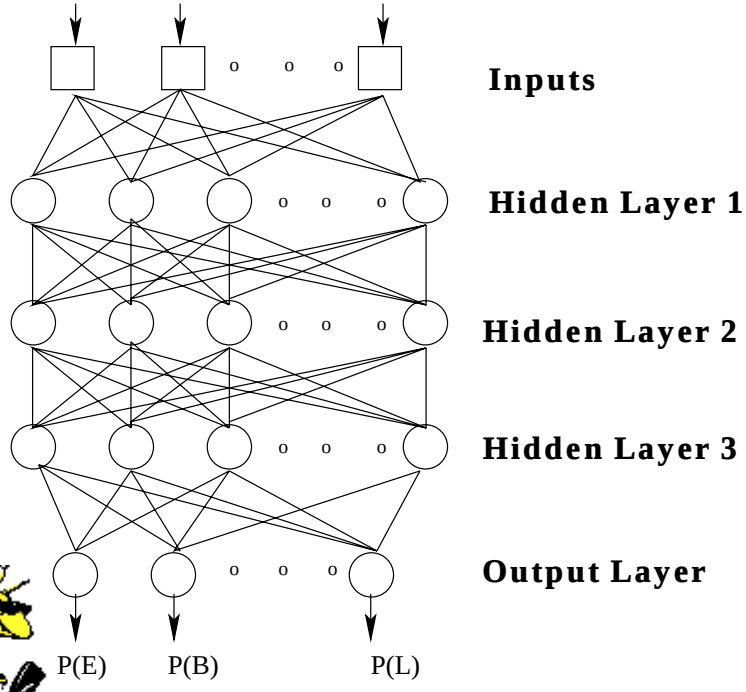
Using Neural Net

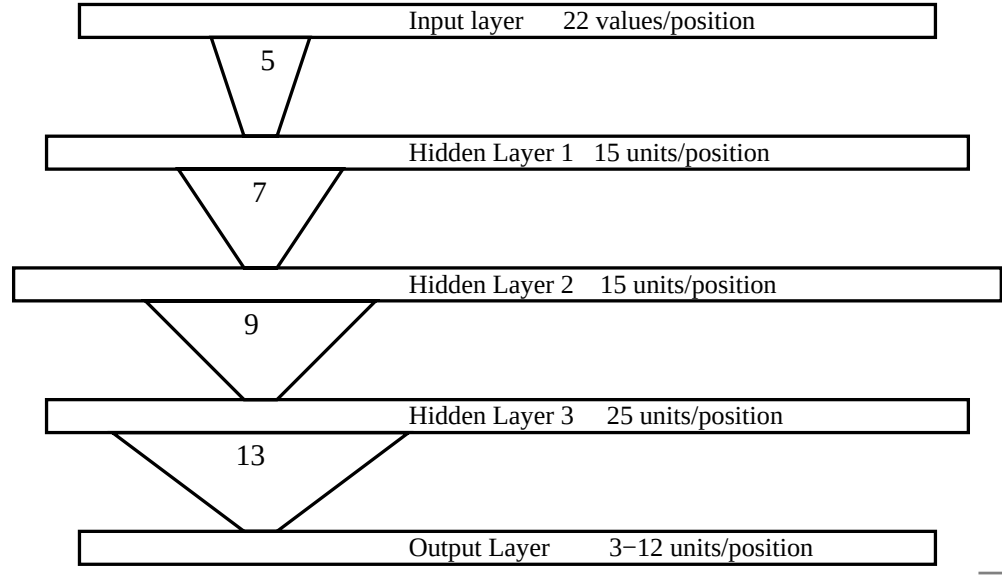
- We use neural nets to predict local properties.
- Input is profile with probabilities of amino acids at each position of target chain, plus insertion and deletion probabilities.
- Output is probability vector for local structure alphabet at each position.
- Each layer takes as input windows of the chain in the previous layer and provides a probability vector in each position for its output.

Neural Net

Typical net has 4 layers and 6471 weight parameters:

input/pos	window	output/pos	weights
22	5	15	1665
15	7	15	1590
15	9	15	2040
15	13	6	1176

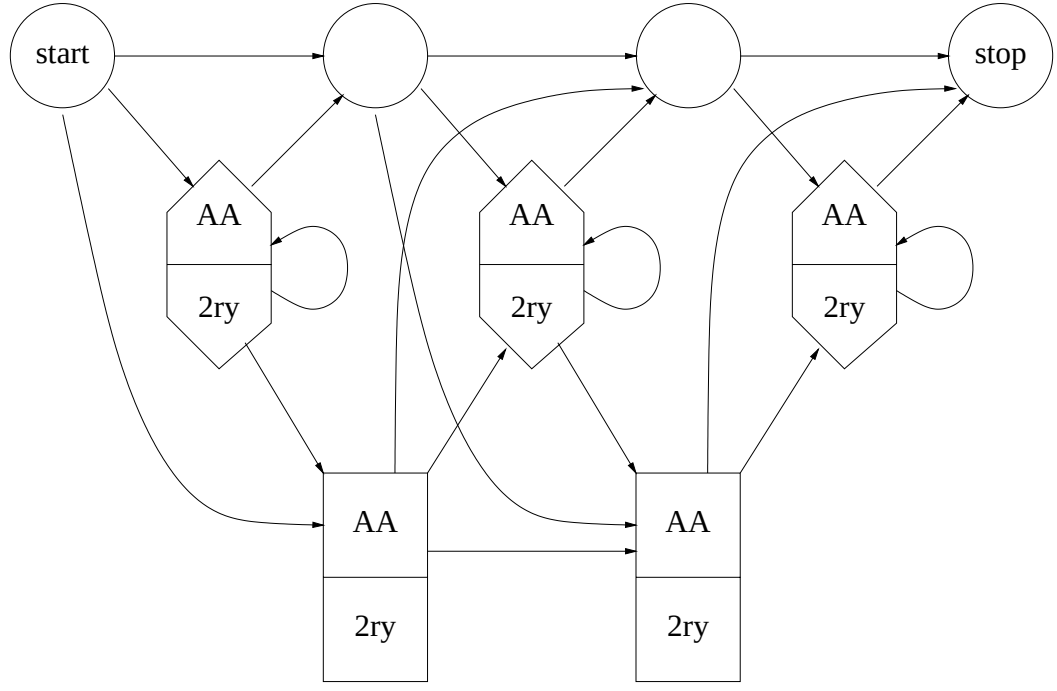




Multi-track HMMs

We can also use alignments to build a two-track target HMM:

- Amino-acid track (created from the multiple alignment).
- Local-structure track (probabilities from neural net).
- Can align template (AA+local) to target model.



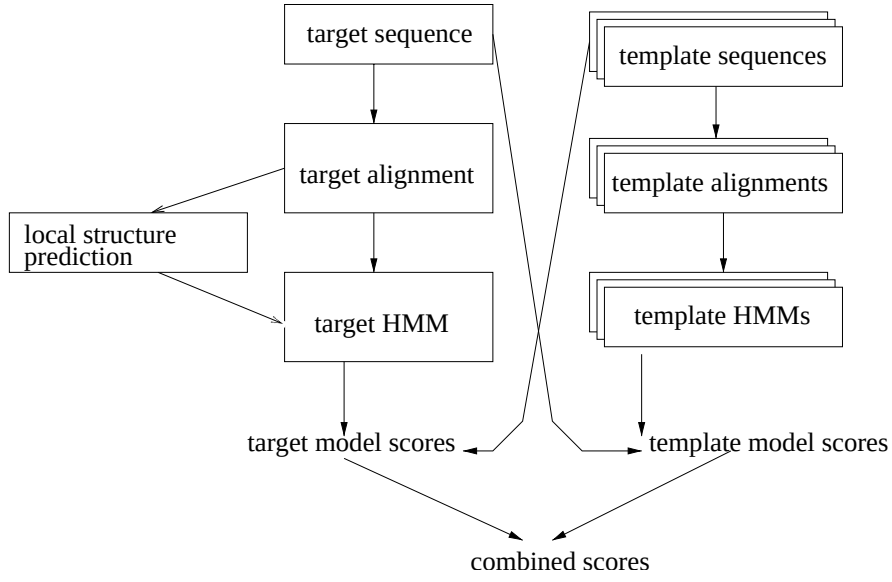
Target-model Fold Recognition

- Find probable homologs of target sequence and make multiple alignment.
- Make secondary structure probability predictions based on multiple alignment.
- Build an HMM based on the multiple alignment and predicted 2ry structure (or just on multiple alignment).
- Score sequences and secondary structure sequences for all proteins that have known structure.
- Select the best-scoring sequence(s) to use as templates.

Template-library Fold Recognition

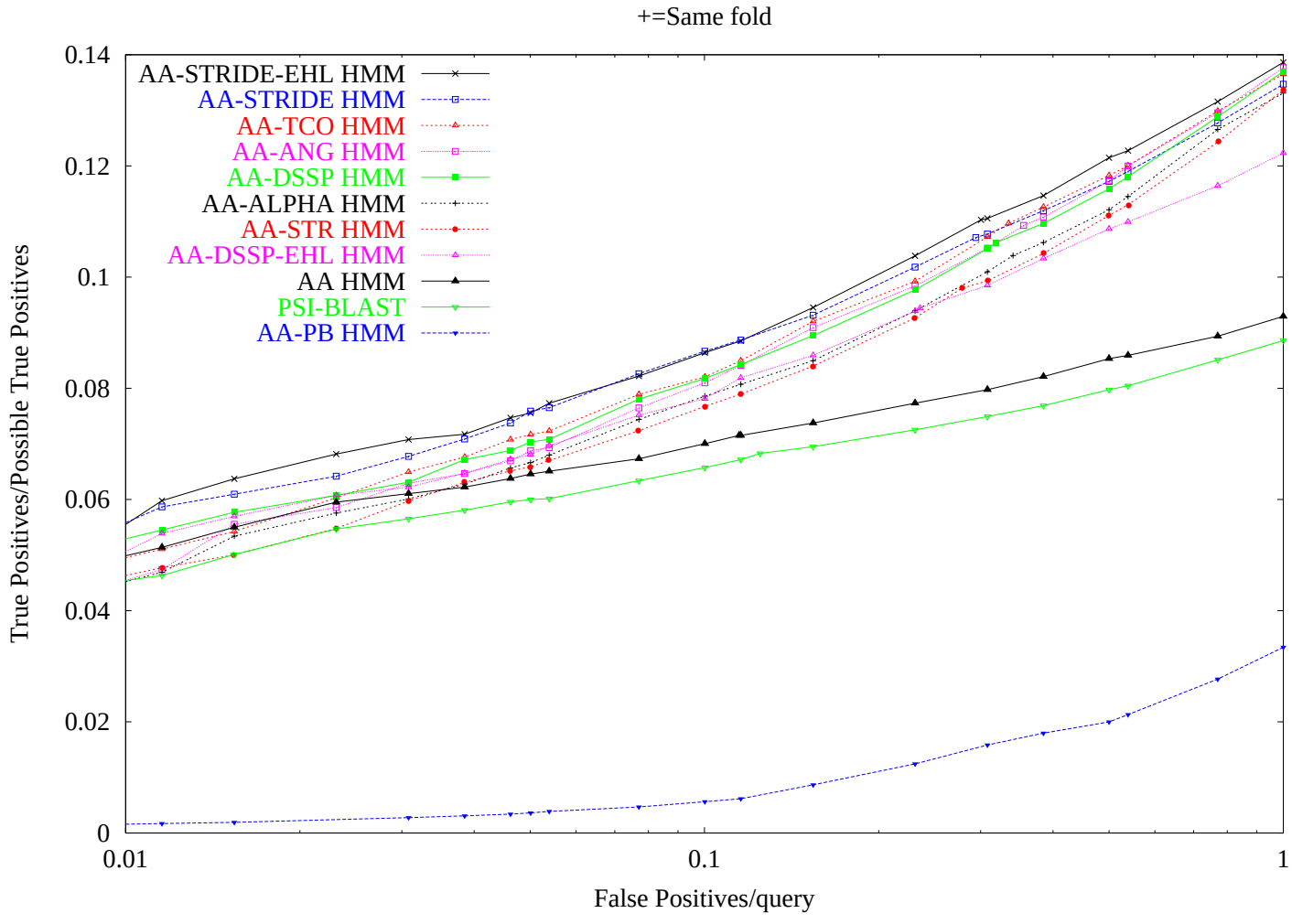
- Build an HMM for each protein in the template library, based on the template sequence (and any homologs you can find).
- The library currently has over 7000 templates from PDB.
- For the fold-recognition problem, structure information can be used in building these models (though we currently don't).
- Score target sequence with all models in the library.
- Select the best-scoring model(s) to use as templates.

Combined SAM-T02 method



- Combine the scores from the template library search and the target library searches using different local structure alphabets.
- Choose one of the many alignments of the target and template (whatever method gets best results in testing).
- `http://www.cse.ucsc.edu/research/compbio/HMM-apps/T02-query.html`

Fold recognition results



Fragment Packing

- Fragment packing was introduced by Simon and Baker's Rosetta program.
- It provides intelligent conformation generation for new folds.
- Rosetta conformation is contiguous chain.
- New conformations are created by randomly replacing fragment of backbone with different fragment (from library), keeping chain contiguous.
- Stochastic search by simulated annealing.

Undertaker

- Undertaker is UCSC's attempt at a fragment-packing program.
- Named because it optimizes burial.
- Representation is 3D coordinates of all heavy atoms.
- Can insert fragments (a la Rosetta) or full alignments—chain need not remain contiguous.
- Conformations can borrow heavily from fold-recognition alignments, without having to lock in a particular alignment.
- Use genetic algorithm with many conformation-change operators to do stochastic search.

Fragfinder

Fragments are provided to undertaker from 3 sources:

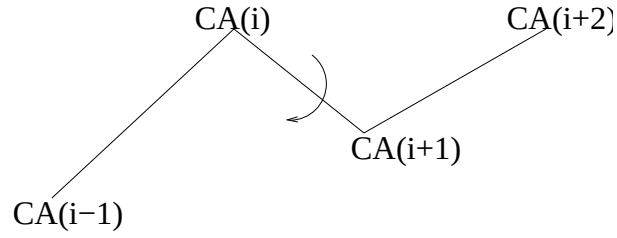
- Generic fragments (2-4 residues, exact sequence match) are obtained by reading in 500–1000 PDB files, and indexing all fragments.
- Long specific fragments (and full alignments) are obtained from the various target and template alignments generated during fold recognition.
- Medium-length fragments (9–12 residues long) for every position are generated from the HMMs with `fragfinder`, a new tool in the SAM suite.

Cost function

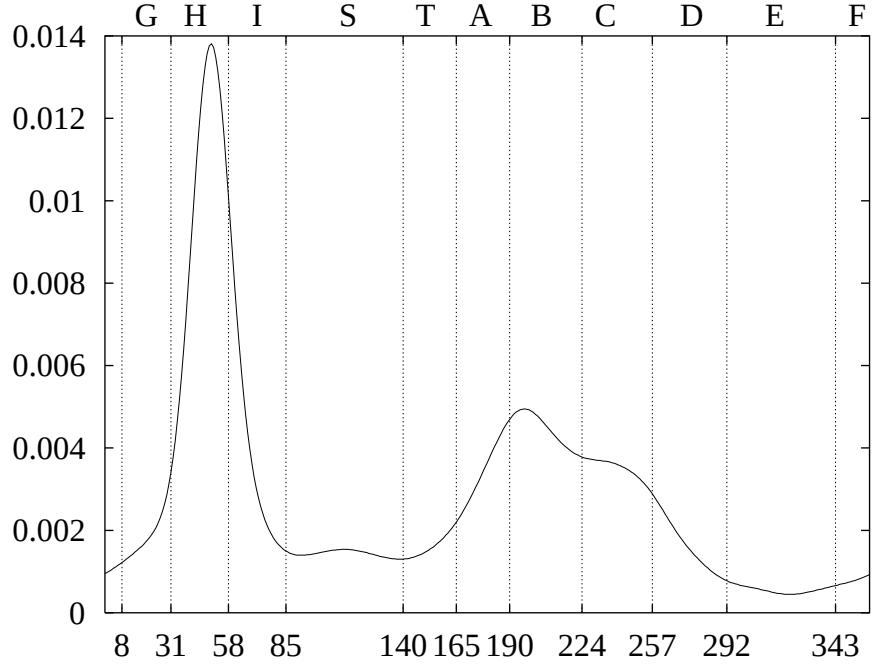
- Cost function is modularly designed—easy to add or remove terms.
- Main components are variants on burial cost:
  - *Burial* is the number of atoms whose centers are in a particular sphere.
  - We define points for each residue where burial is checked.
  - We use histograms of burial conditioned on residue type to convert burial to cost ($-\log$ Prob).
- Cost function can include predictions of local properties by neural nets.
- There are currently about 20 other cost function components (clashes, disulfides, contact order, radius of gyration, constraints, ...) that can be used.

Predicted α angle in cost

- Current cost function includes a neural-net prediction of α angle:

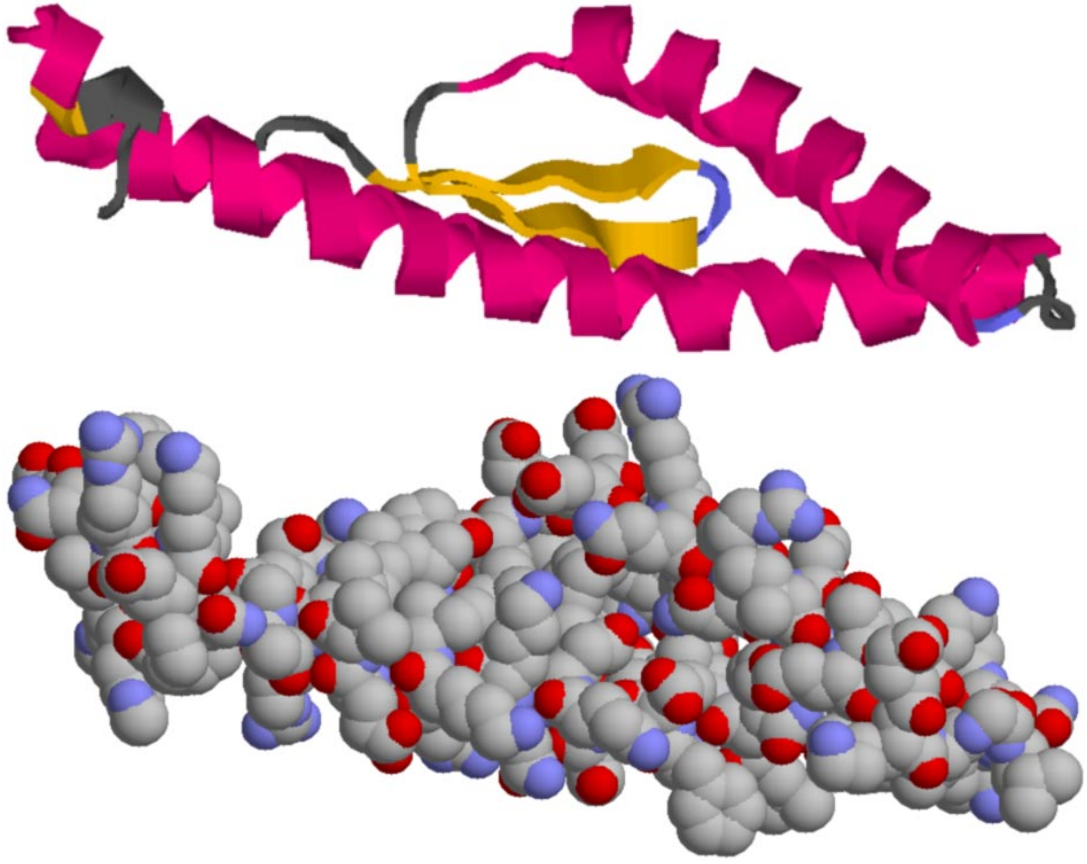


- Neural net predicts discrete alphabet:



Undertaker example: T0131

Ab-initio prediction:

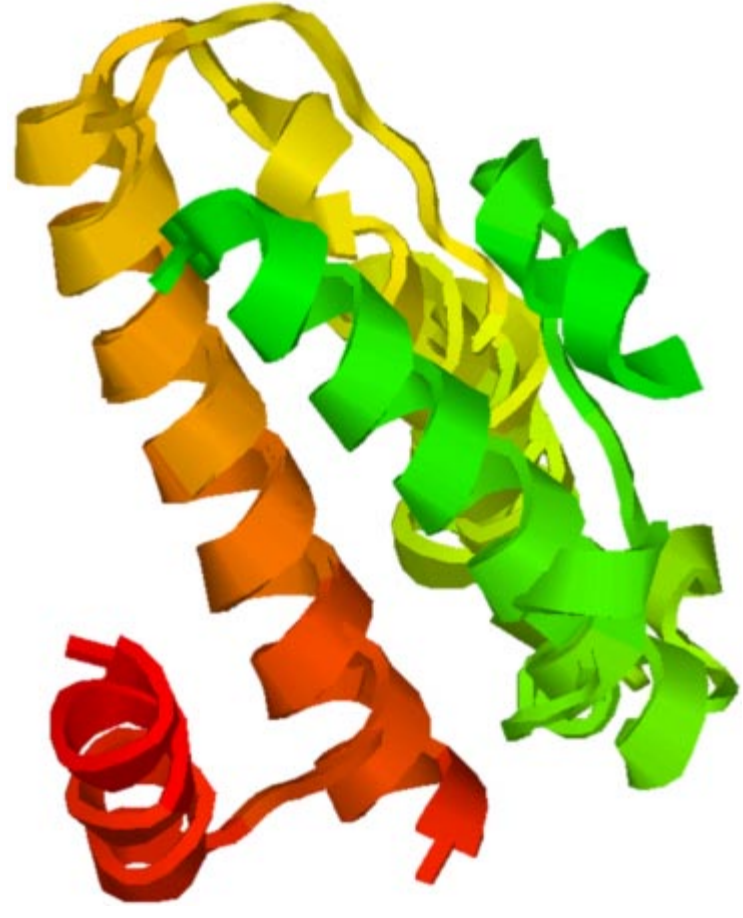


Undertaker example: T0129

New-fold prediction (model 3):

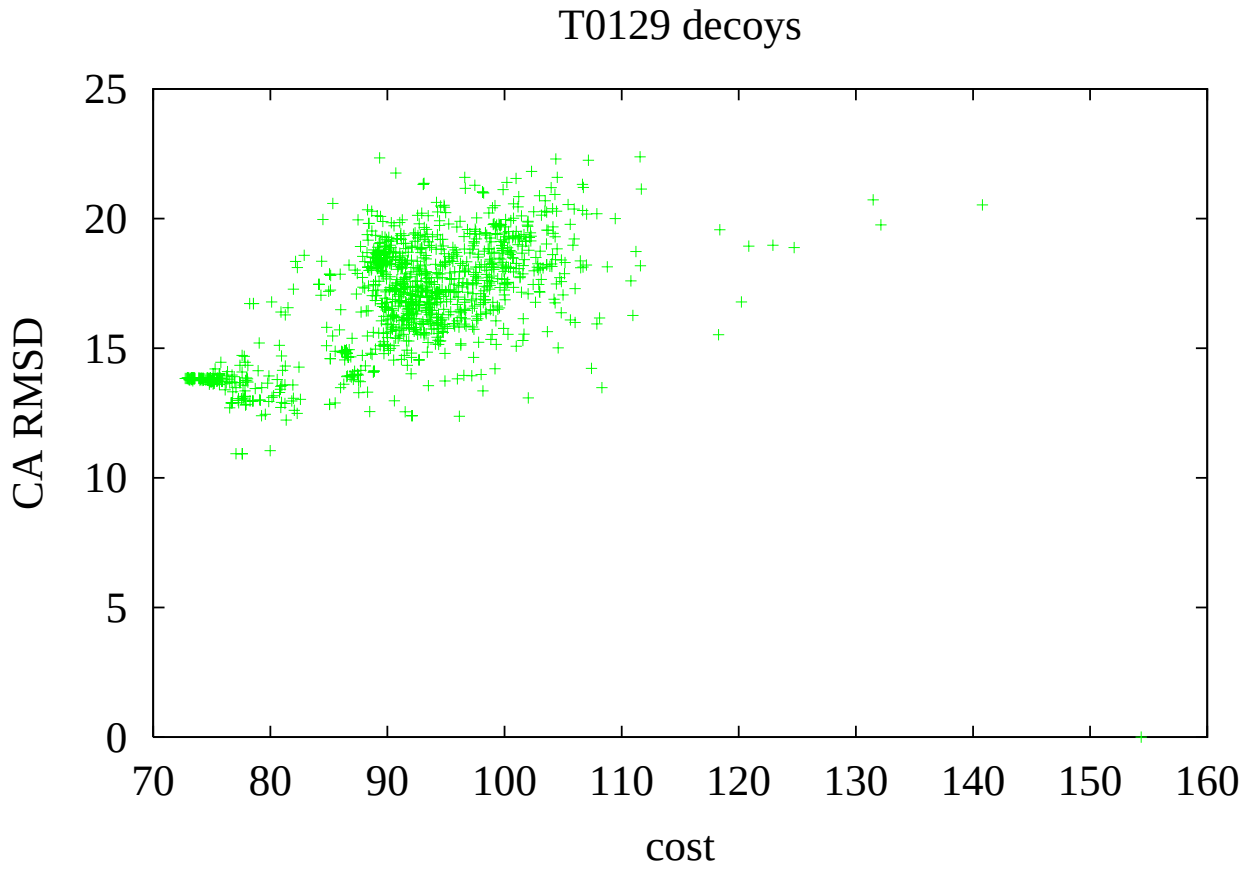
Domain 1

Domain 2



Undertaker example: T0129

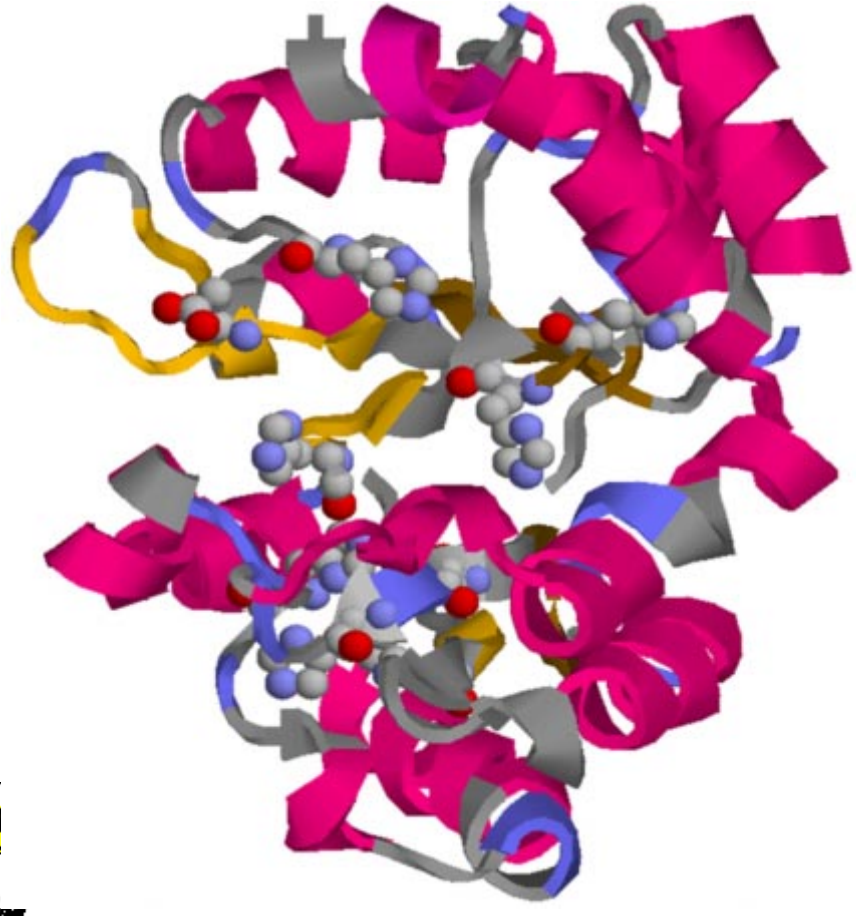
Cost correlates well with RMSD-CA—except for real structure!



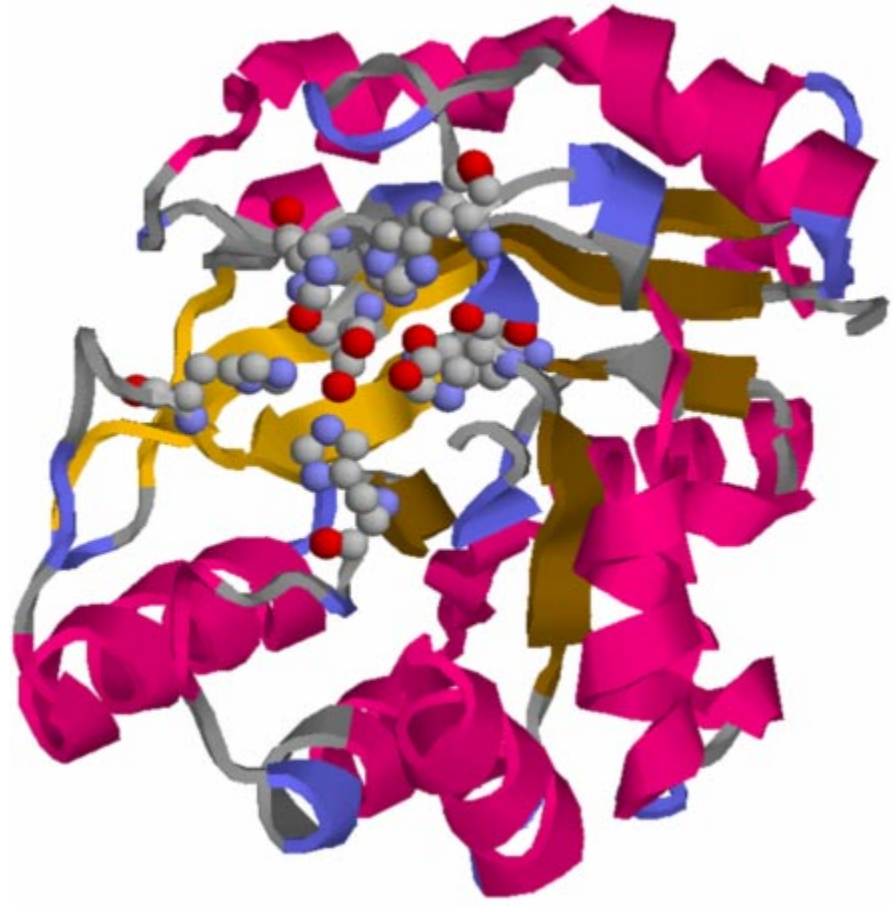
Undertaker example: T0147

Fold-recognition plus ab-initio prediction: (secondary structure prediction after 140 needs to be slid right 6-8)

Model 4



Real



Web sites

UCSC bioinformatics (research and degree programs) info:

`http://www.soe.ucsc.edu/research/compbio/`

SAM tool suite info:

`http://www.soe.ucsc.edu/research/compbio/sam.html`

HMM **servers:** `http://www.soe.ucsc.edu/research/compbio/HMM-apps/`

SAM-T02 prediction server:

`http://www.soe.ucsc.edu/research/compbio/HMM-apps/T02-query.html`

These slides:

`http://www.soe.ucsc.edu/~karplus/papers/casp5-slides.pdf`