Karplus lab: protein structure prediction and design

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Outline of Talk

- What is Bioengineering? Biomolecular Engineering? Bioinformatics?
- What is a protein?
- The folding problem and variants on it:
  - Local structure prediction
  - Fold recognition
  - Comparative modeling
  - “Ab initio” methods
  - Contact prediction
- Protein Design

What is Bioengineering?

Three concentrations:

- Biomolecular
  - Drug design
  - Biomolecular sensors
  - Nanotechnology
  - Bioinformatics
- Rehabilitation
- Bioelectronics

What is Bioengineering?

Three concentrations:

- Biomolecular
- Rehabilitation
  - Systems to held individuals with special needs
  - Cell-phone-based systems to reach large numbers of people.
  - Novel hardware to assist the blind
  - Robotics for rehabilitation and surgery applications.
- Bioelectronics

What is Bioengineering?

Three concentrations:

- Biomolecular
- Rehabilitation
- Bioelectronics
  - Implantable devices
  - Interfacing between organisms and electronics
  - Artificial retina project

What to take early

- Mathematics
- Chemistry and then biology
- Introductory bioengineering courses:
  - BME80G, Bioethics (F)
  - BME5, Intro to Biotechnology (W, S)
  - CMPE80A: Universal Access: Disability, Technology, and Society (W, S)
- Declare your major immediately!!
  You can always change to another one latter.
  Bioengineering is one of the most course-intensive majors on campus Many courses have prerequisites.
  It's important to get advising office and faculty advise early.

What is Biomolecular Engineering?

Engineering **with**, **of**, or **for** biomolecules. For example,

with: using proteins (or DNA, RNA, . . .) as sensors or for self-assembly.

of: protein engineering—designing or artificially evolving proteins to have particular functions

for: designing high-throughput experimental methods to find out what molecules are present, how they are structured, and how they interact.

What is Bioinformatics?

Bioinformatics: using computers and statistics to make sense out of the mountains of data produced by high-throughput experiments.

- Genomics: finding important sequences in the genome and annotating them.
- Phylogenetics: “tree of life”.
- Systems biology: piecing together various control networks.
- DNA microarrays: what genes are turned on under what conditions.
- Proteomics: what proteins are present in a mixture.
- Protein structure prediction.

What is a protein?

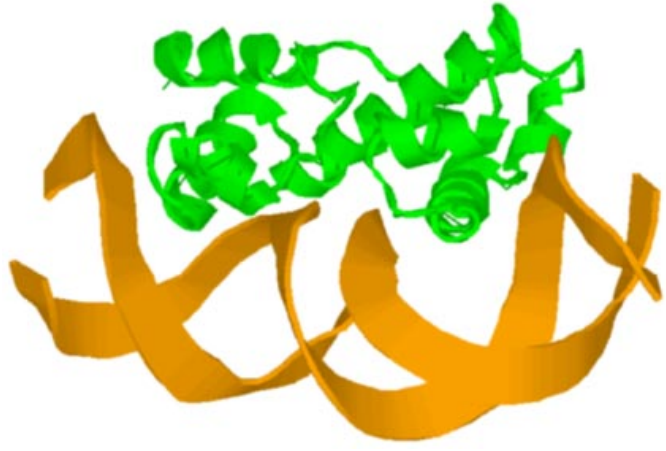
- There are many abstractions of a protein: a band on a gel, a string of letters, a mass spectrum, a set of 3D coordinates of atoms, a point in an interaction graph, ...
- For us, a protein is a long skinny molecule (like a string of letter beads) that folds up consistently into a particular intricate shape.
- The individual “beads” are amino acids, which have 6 atoms the same in each “bead” (the *backbone* atoms: N, H, CA, HA, C, O).
- The final shape is different for different proteins and is essential to the function.
- The protein shapes are important, but are expensive to determine experimentally.

Folding Problem

The *Folding Problem*:
If we are given a sequence of amino acids (the letters on a string of beads), can we predict how it folds up in 3-space?

```
MTMSRRNTDA ITIHSILDWI EDNLESPLSL EKVSERSGYS KWHLQRMFKK
ETGHSLGQYI RSRKMTEIAQ KLKESNEPIL YLAERYGFES QQTLTRTFKN
YFDVPPHKYR MTNMQGESRF LHPLNHYNS
```

↓



Too hard!

Fold-recognition problem

The *Fold-recognition Problem*:
Given a sequence of amino acids A (the *target* sequence) and a library of proteins with known 3-D structures (the *template* library),
figure out which templates A match best, and align the target to the templates.

- The backbone for the target sequence is predicted to be very similar to the backbone of the chosen template.

New-fold prediction

- What if there is *no* template we can use?
- We can try to generate many conformations of the protein backbone and try to recognize the most protein-like of them.
- Search space is huge, so we need a good conformation generator and a cheap cost function to evaluate conformations.

Secondary structure Prediction

- Instead of predicting the entire structure, we can predict local properties of the structure.
- What local properties do we choose?
- We want properties that are well-conserved through evolution, easily predicted, and useful for finding and aligning templates.
- One popular choice is a 3-valued helix/strand/other alphabet—we have investigated many others. Typically, predictors get about 80% accuracy on 3-state prediction.
- Many machine-learning methods have been applied to this problem, but the most successful is neural networks.

Contact prediction

- Use mutual information between columns.
- Thin alignments aggressively (30%, 35%, 40%, 50%, 62%).
- Compute e-value for mutual info (correcting for small-sample effects).
- Compute rank of log(e-value) within protein.
- Feed log(e-values), log rank, contact potential, joint entropy, and separation along chain for pair, and amino-acid profile, predicted burial, and predicted secondary structure for each residue of pair into a neural net.

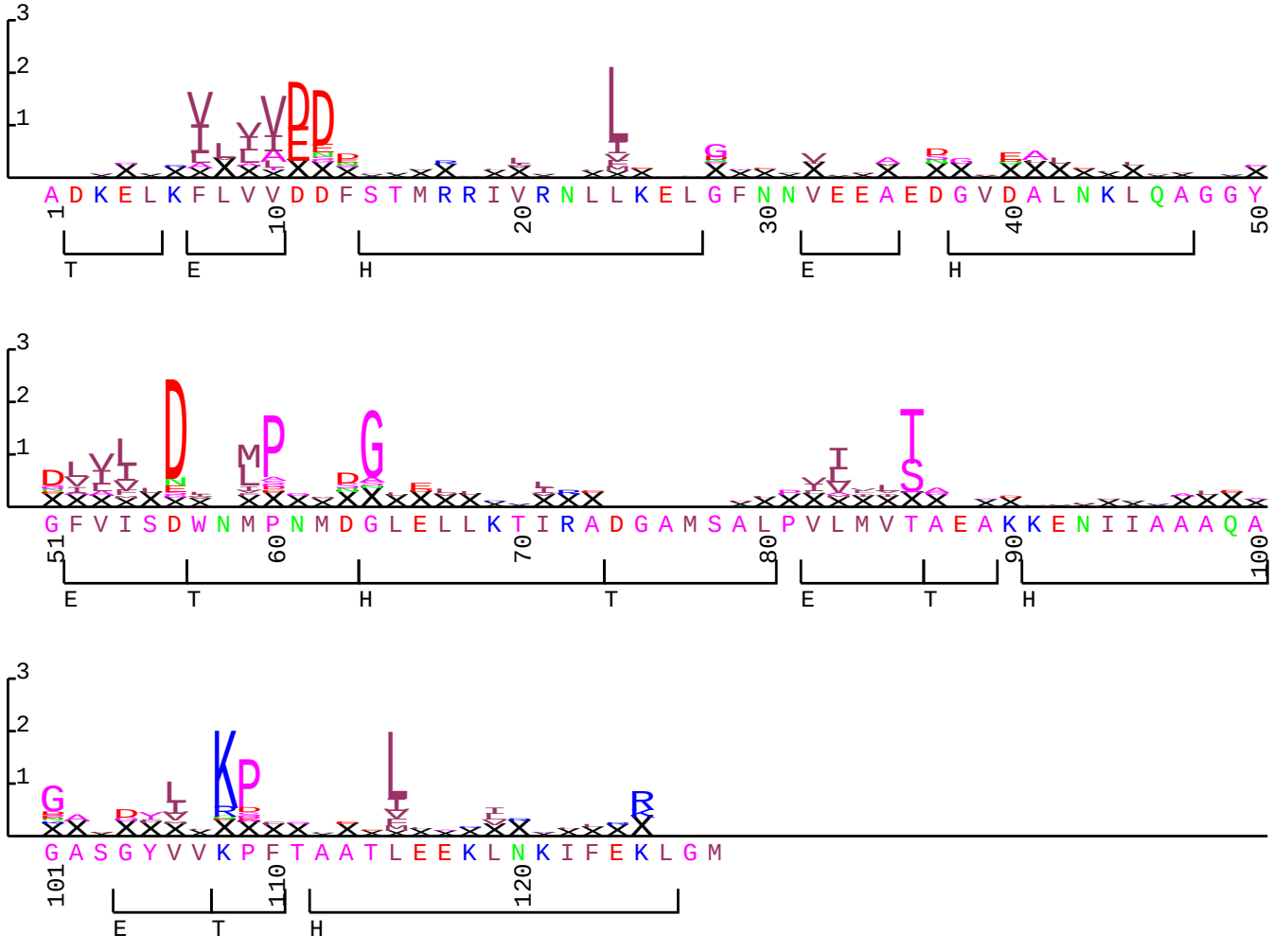
(Rational) Protein Design

- New direction for lab.
- Use local-structure neural nets in reverse (find sequences highly predicted to have right local structure).
- Use undertaker to build models.
- Use RosettaDesign to modify sequences.
- Target application: specific binding of carbon nanotubes.

Sequence logos (MSA)

Summarize multiple alignment:

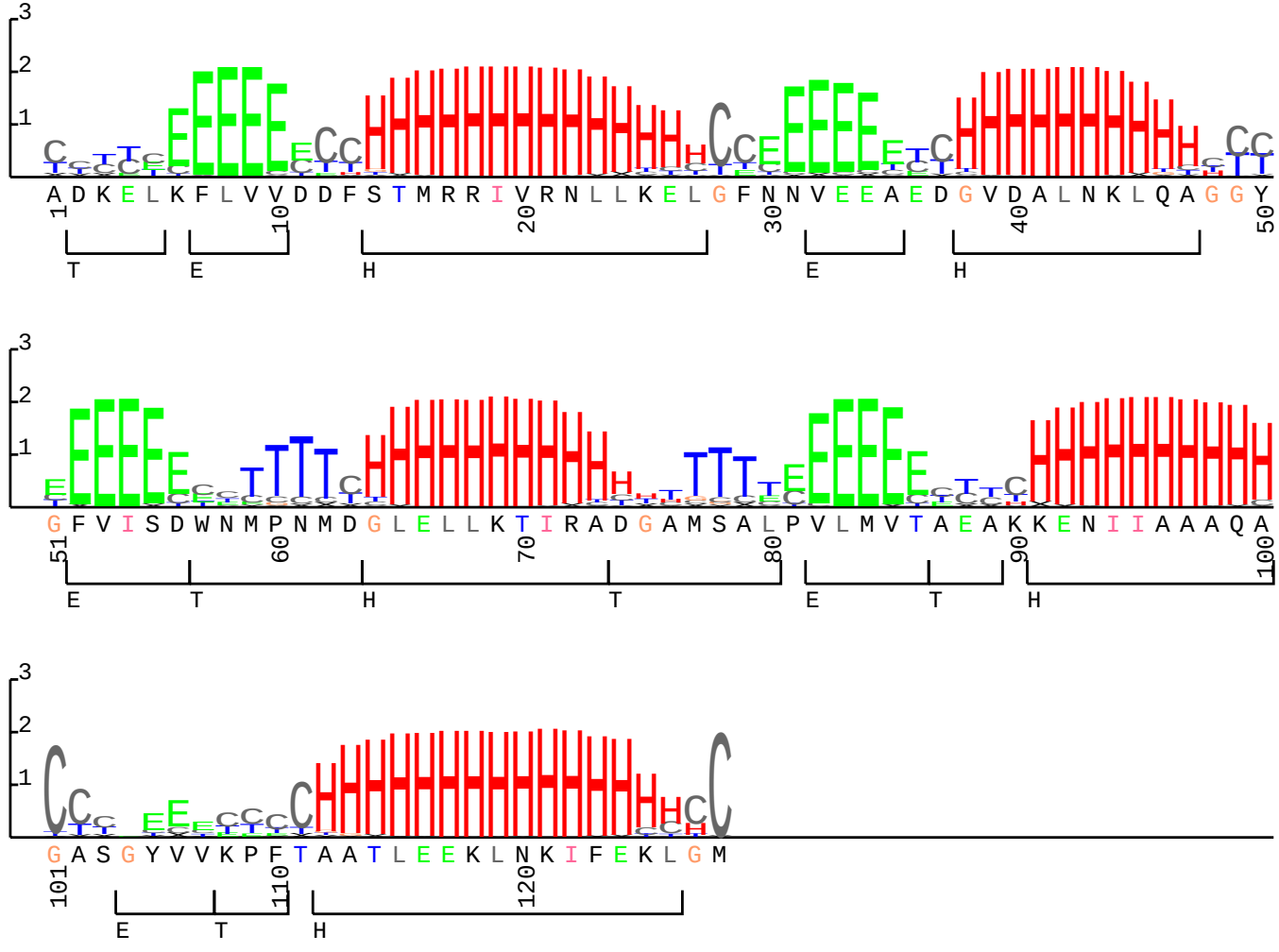
nostruct-align/3chy.t2k w0.5



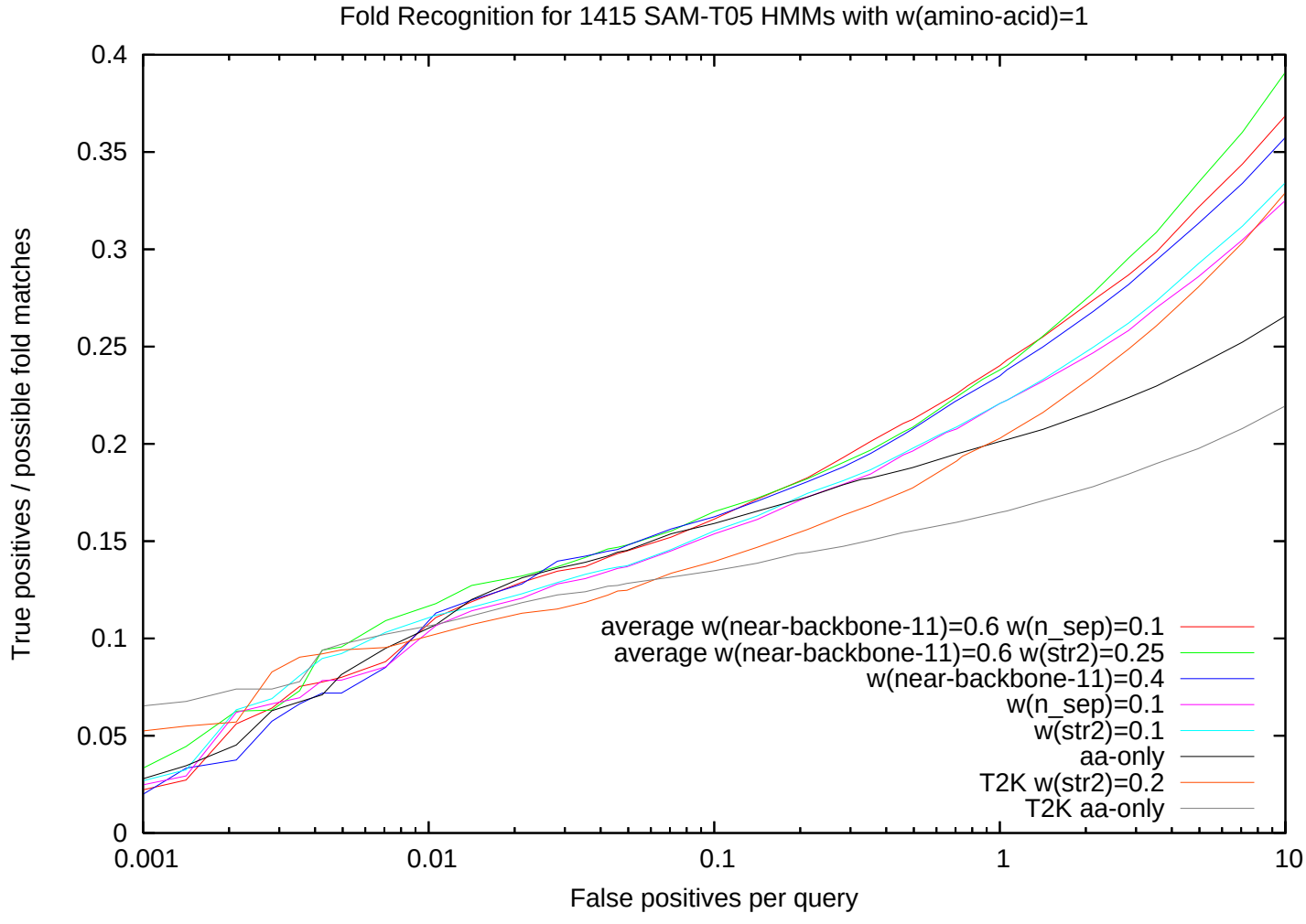
Sequence logos (NN)

Summarize local structure prediction:

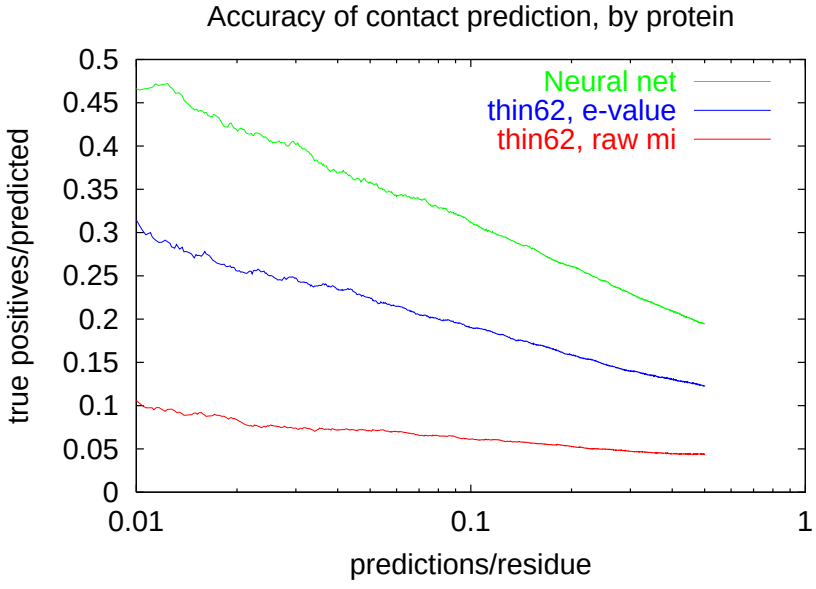
nostruct-align/3chy.t2k EBGHTL

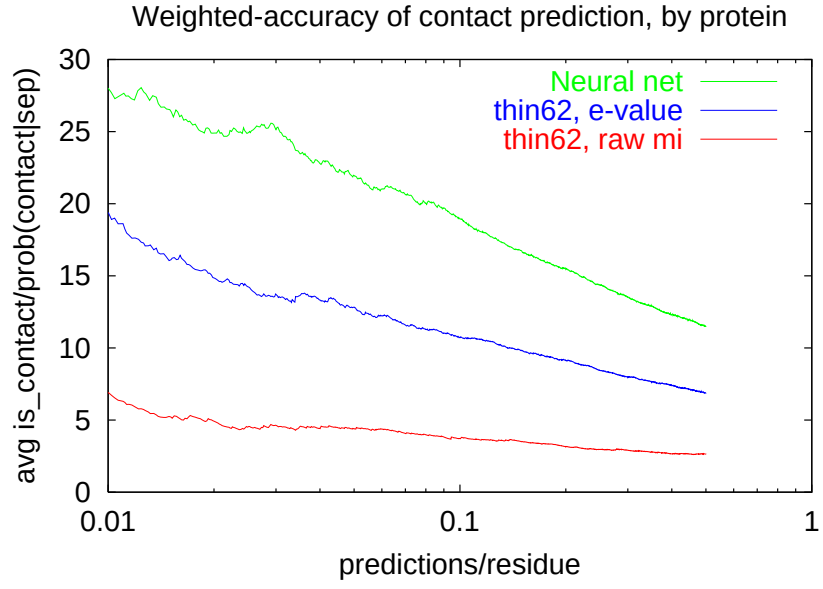


Fold recognition results



Contact prediction results



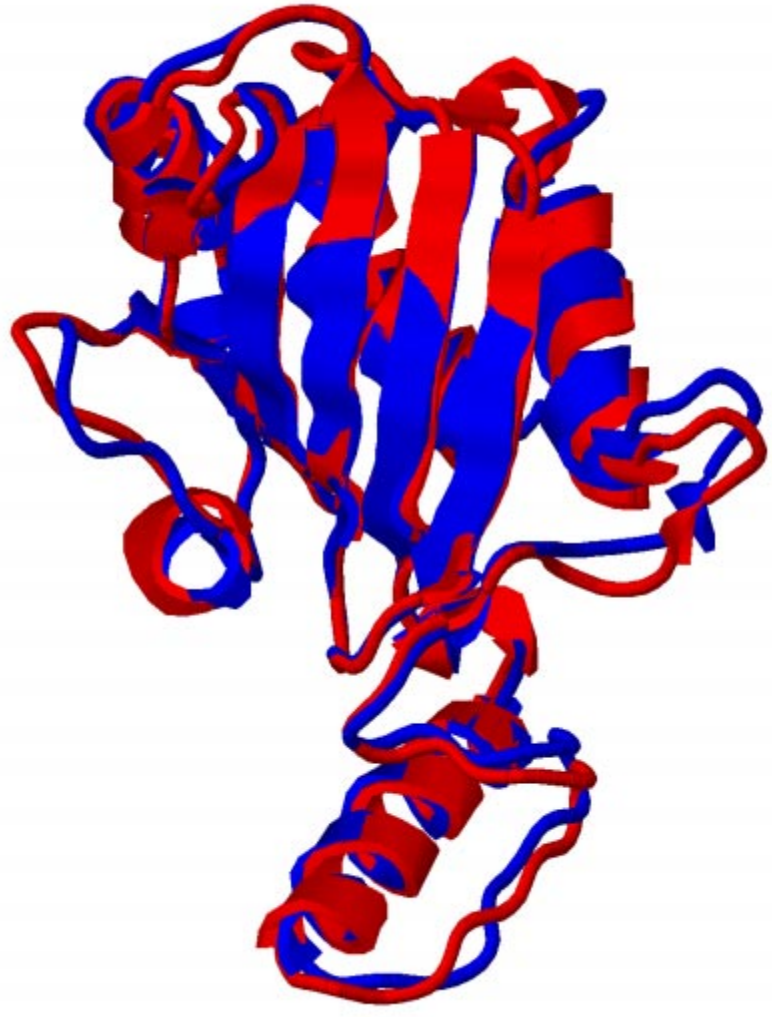


CASP ~~Competition~~ Experiment

- Everything published in literature “works”
- CASP set up as true blind test of prediction methods.
- Sequences of proteins about to be solved released to prediction community.
- Predictions registered with organizers.
- Experimental structures compared with solution by assessors.
- “Winners” get papers in *Proteins: Structure, Function, and Bioinformatics*.

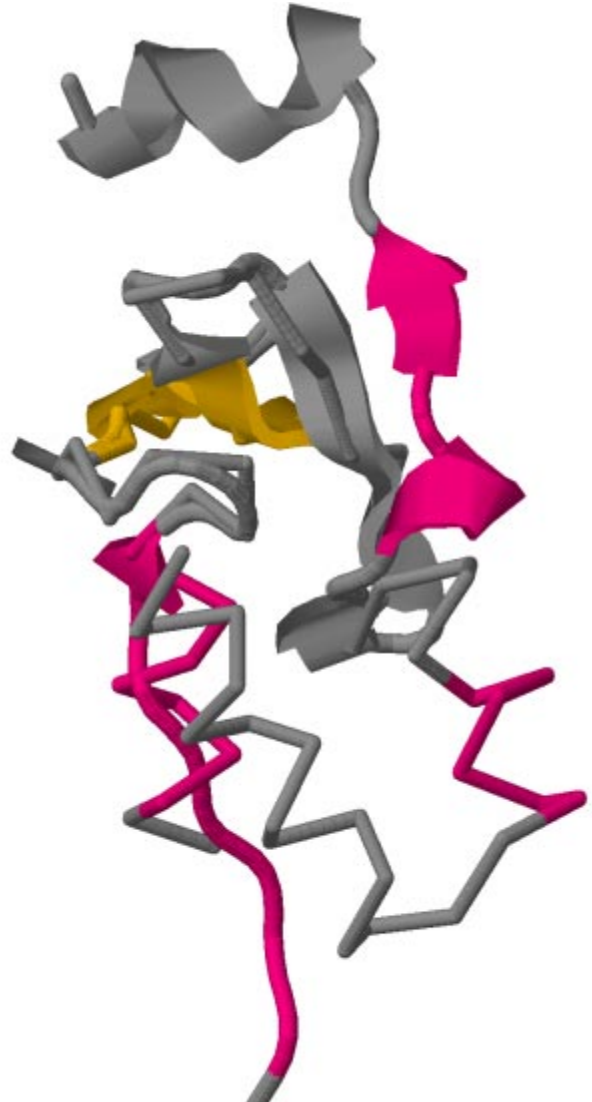
T0298 domain 2 (130–315)

RMSD= 2.468Å all-atom, 1.7567Å C_α, GDT=82.5%
best model 1 submitted to CASP7 (red=real)



Comparative modeling: T0348

RMSD= 11.8 Å C_α, GDT=58.2% (cartoon=real)
best model 1 by CASP7 GDT, Robetta1 slightly better.



Target T0201 (NF, CASP6)

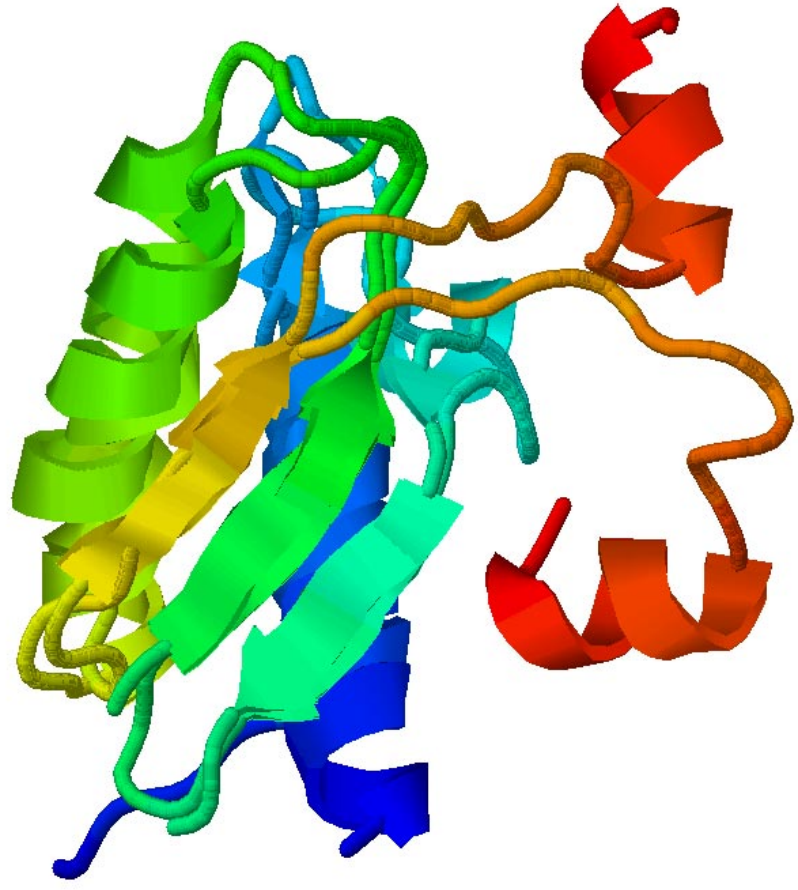
- We tried forcing various sheet topologies and selected 4 by hand.
- Model 1 has right topology (5.912Å all-atom, 5.219Å C_α).
- Unconstrained cost function not good at choosing topology (two strands curled into helices).
- Helices were too short.

Target T0201 (NF, CASP6)

Target T0230 (FR/A, CASP6)

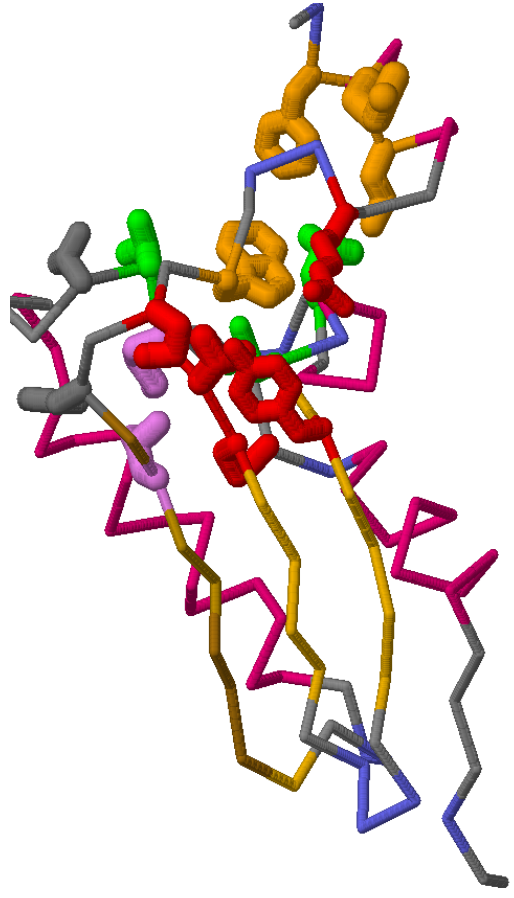
- Good except for C-terminal loop and helix flopped wrong way.
- We have secondary structure right, including phase of beta strands.
- Contact prediction helped, but we put too much weight on it—decoys fit predictions better than real structure does.

Target T0230 (FR/A, CASP6)



Target T0230 (FR/A)

Real structure with contact predictions:



Web sites

These slides:

`http://www.soe.ucsc.edu/~karplus/papers/what-lab-does-jul-2008.pdf`

CASP6 and CASP7—all our results and working notes:

`http://www.soe.ucsc.edu/~karplus/casp6/`

`http://www.soe.ucsc.edu/~karplus/casp7/`

SAM-T06 prediction server:

`http://www.soe.ucsc.edu/research/compbio/SAM_T06/T06-query.html`

Predictions for all yeast proteins:

`http://www.soe.ucsc.edu/~karplus/yeast/`

UCSC bioinformatics (research and degree programs) info:

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