

(Aspekte der Thermodynamik in der Strukturbiologie)

# **Einführung in die Bioinformatik**

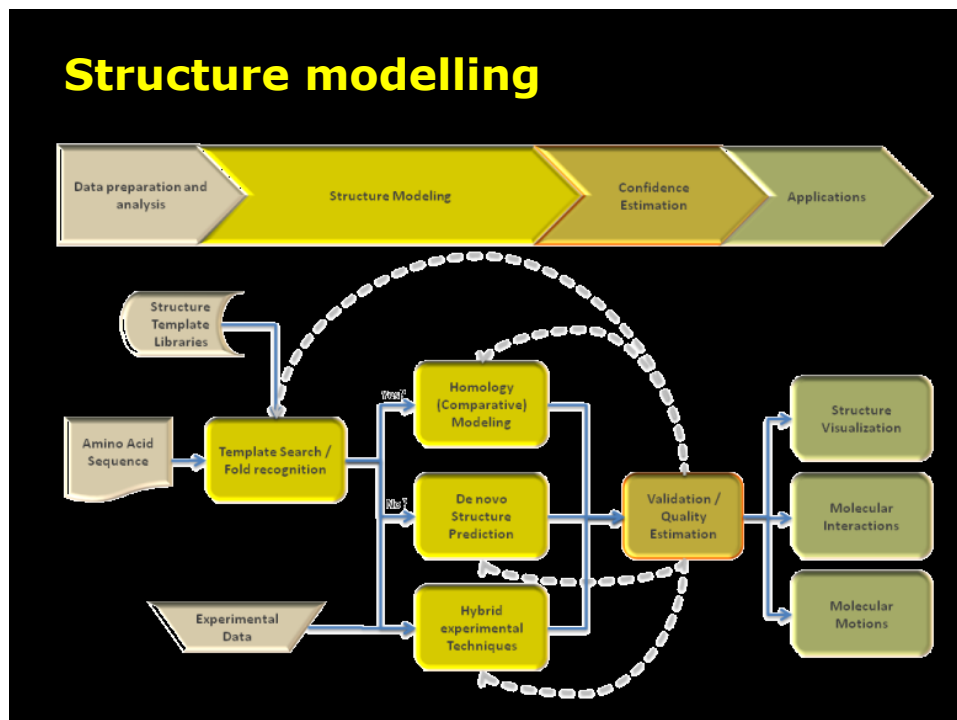
Wintersemester 2012/13

Peter Güntert

## **Structure modelling**

## Outline

- Structure modeling:
  - Homology modeling
  - Fold recognition
  - ab initio modeling



## Sequence identity → Structural similarity

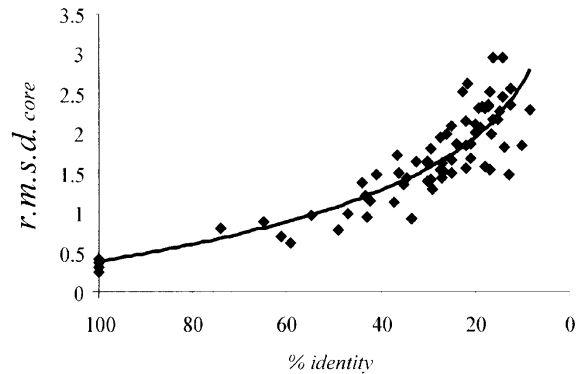


Figure 1.25 Relationships between sequence identity and structural similarity.

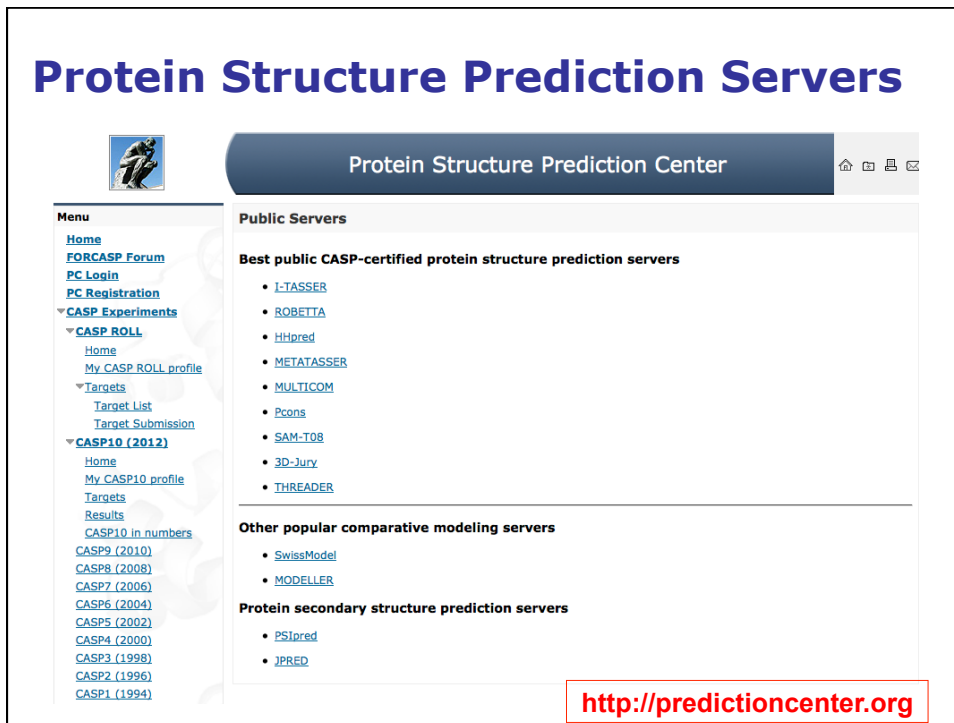
**BUT:**  
**Structural similarity ✗ Sequence identity**

## Methods for protein structure prediction

Methods are distinguished according to the relationship between the target protein and proteins of known structure:

- **Comparative modelling:** A clear evolutionary relationship between the target and a protein of known structure can be easily detected from the sequence.
- **Fold recognition:** The structure of the target turns out to be related to that of a protein of known structure although the relationship is difficult, or impossible, to detect from the sequences.
- **New fold prediction:** Neither the sequence nor the structure of the target protein are similar to that of a known protein.

# Protein Structure Prediction Servers



The screenshot shows the Protein Structure Prediction Center website. The main heading is "Protein Structure Prediction Center". Below the heading, there is a navigation menu on the left and a main content area on the right. The main content area is titled "Public Servers" and lists "Best public CASP-certified protein structure prediction servers" and "Other popular comparative modeling servers".

**Menu**

- Home
- FORCASP Forum
- PC Login
- PC Registration
- CASP Experiments
  - CASP ROLL
    - Home
    - My CASP ROLL profile
  - Targets
    - Target List
    - Target Submission
- CASP10 (2012)
  - Home
  - My CASP10 profile
  - Targets
    - Results
    - CASP10 in numbers
  - CASP9 (2010)
  - CASP8 (2008)
  - CASP7 (2006)
  - CASP6 (2004)
  - CASP5 (2002)
  - CASP4 (2000)
  - CASP3 (1998)
  - CASP2 (1996)
  - CASP1 (1994)

**Public Servers**

**Best public CASP-certified protein structure prediction servers**

- I-TASSER
- ROBETTA
- HiPred
- METATASSER
- MULTICOM
- Pcons
- SAM-T08
- 3D-Jury
- THREADER

**Other popular comparative modeling servers**

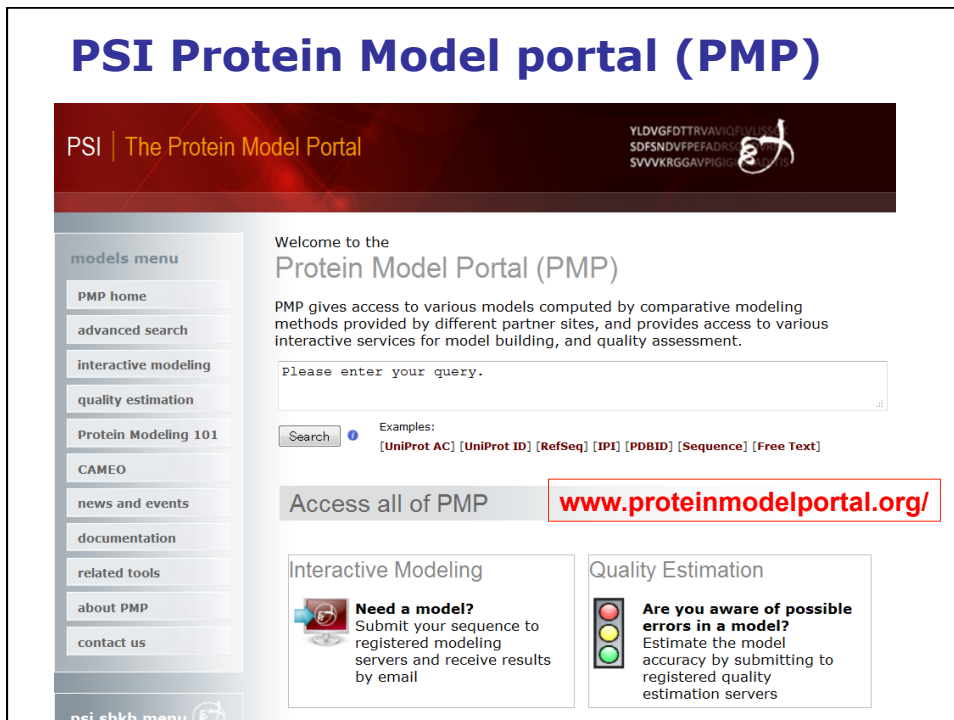
- SwissModel
- MODELLER

**Protein secondary structure prediction servers**

- PSIpred
- JPRED

<http://predictioncenter.org>

# PSI Protein Model portal (PMP)



The screenshot shows the PSI Protein Model Portal (PMP) website. The main heading is "PSI | The Protein Model Portal". Below the heading, there is a navigation menu on the left and a main content area on the right. The main content area is titled "Welcome to the Protein Model Portal (PMP)" and provides information about the portal's services. There is a search bar and a list of examples for the search query. Below the search bar, there are two main sections: "Interactive Modeling" and "Quality Estimation".

**PSI | The Protein Model Portal**

YLDVGFDTTRVAVIQFVLSG  
SDFSNDVFPFADRSQ  
SVVVKRGGAVPIGK

**models menu**

- PMP home
- advanced search
- interactive modeling
- quality estimation
- Protein Modeling 101
- CAMEO
- news and events
- documentation
- related tools
- about PMP
- contact us

Welcome to the  
**Protein Model Portal (PMP)**

PMP gives access to various models computed by comparative modeling methods provided by different partner sites, and provides access to various interactive services for model building, and quality assessment.

Please enter your query.

Search

Examples:  
[UniProt AC] [UniProt ID] [RefSeq] [IP1] [PDBID] [Sequence] [Free Text]

**Access all of PMP** [www.proteinmodelportal.org/](http://www.proteinmodelportal.org/)

**Interactive Modeling**

**Need a model?**  
Submit your sequence to registered modeling servers and receive results by email

**Quality Estimation**

**Are you aware of possible errors in a model?**  
Estimate the model accuracy by submitting to registered quality estimation servers



# PSI Protein Model portal (PMP)

PSI | The Protein Model Portal

YLDVGFDTTRVAVIQEFLK  
SDFSNDVFPFADRS  
SVVVKRGGAVPIGIG

## models menu

- PMP home
- advanced search
- interactive modeling
- quality estimation

## PMP | Interactive Modeling

Name:

Request Title:

Email:

Amino Acid Sequence:

### ModWeb

Server Policy:  By checking this box, I assert that I am part of an academic institution (not a government research lab such as the NIH, or a commercial entity) and agree to the terms of the **Modeller license**.

I have a MODELLER access key:

### M4T

Server Policy:  I am a non-profit/academic user and this server will be used solely for educational purposes or for basic research intended to advance scientific knowledge.

### SWISS-MODEL

Server Policy: Usage of SWISS-MODEL Server and Workspace are free of charge.

### I-TASSER

Server Policy: Usage of I-TASSER is free of charge. However, there is a limitation of one job per email address and only academic email addresses are allowed.

### HHpred

Server Policy: Usage of HHpred is free of charge for academic use.

[www.proteinmodelportal.org/](http://www.proteinmodelportal.org/)

# CASP: Critical Assessment of Structure Prediction



Protein Structure Prediction Center

**Retrospective and prospective views of the field from**

- Celebrating 10 CASP experiments
- Tracking nearly 20 years of progress in protein structure modeling
- The latest assessment of the state of the art

David Jones  
Gaeta, Italy  
December 9-12, 2012

- Menu**
- Home
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      - CASPs (2004)
      - CASPs (2002)
      - CASP4 (2000)
      - CASP4 (1998)
      - CASP2 (1996)
      - CASP1 (1994)
  - Initiatives
    - Data Archive
    - Local Services
    - Proceedings
    - Feedback
    - Assessors
    - People
    - Community Resources

## Welcome to the Protein Structure Prediction Center!

Our goal is to help advance the methods of identifying protein structure from sequence. The Center has been organized to provide the means of objective testing of these methods via the process of blind prediction. The Critical Assessment of protein Structure Prediction (CASP) experiments aim at establishing the current state of the art in protein structure prediction, identifying what progress has been made, and highlighting where future effort may be most productively focused.

There have been nine previous CASP experiments. The tenth experiment is planned to start in April 2012. Description of these experiments and the full data (targets, predictions, interactive tables with numerical evaluation results, dynamic graphs and prediction visualization tools) can be accessed following the links:

[CASP1 \(1994\)](#) | [CASP2 \(1996\)](#) | [CASP3 \(1998\)](#) | [CASP4 \(2000\)](#) | [CASPs \(2002\)](#) | [CASP6 \(2004\)](#) | [CASP7 \(2006\)](#) | [CASP8 \(2008\)](#) | [CASP9 \(2010\)](#) | [CASP10 \(2012\)](#)

Raw data for the experiments held so far are archived and stored at our [data archive](#).

Starting November 2011, we are opening a new rolling CASP experiment for all-year-round testing of ab initio modeling methods:

### CASP ROLL

Details of the experiments have been published in a scientific journal *Proteins: Structure, Function and Bioinformatics*. [CASP proceedings](#) include papers describing the structure and conduct of the experiments, the numerical evaluation measures, reports from the assessment teams highlighting state of the art in different prediction categories, methods from some of the most successful prediction teams, and progress in various aspects of the modeling.

Prediction methods are assessed on the basis of the analysis of a large number of blind predictions of protein structure. Summary of numerical evaluation of the methods tested in the latest CASP experiment can be found [on this web page](#). The main numerical measures used in evaluations are described in the papers [1], [2]. The latter paper also contains explanations of data handling procedures and guidelines for navigating the data presented on this website.

Some of the best performing methods are implemented as [fully automated servers](#) and therefore can be used by public for protein structure modeling.

To proceed to the pages related to the latest CASP experiments click on the logo below:



**FORCASP**  
"no more dead trees"

Discussion Forum  
Old Discussion Forum

<http://predictioncenter.org>

## Message Board

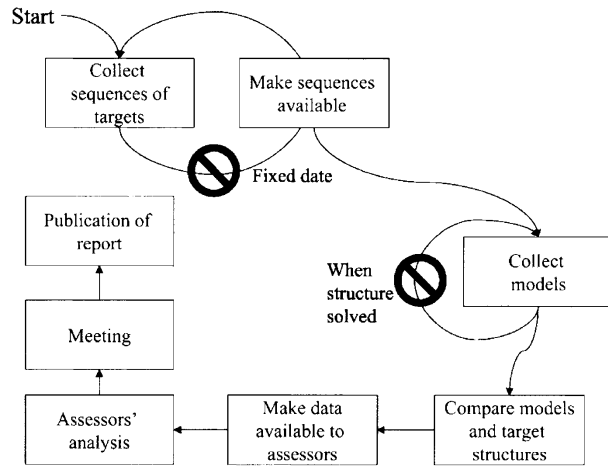
**Extra CASP experiments**  
At the most recent CASP meeting, members of the modeling community suggested launching several additional experiments that would benefit developers of predictive methods. We have successfully started...

**CASP ROLL targets**  
The second CASP ROLL target will be released next Monday, December 5, 2011...

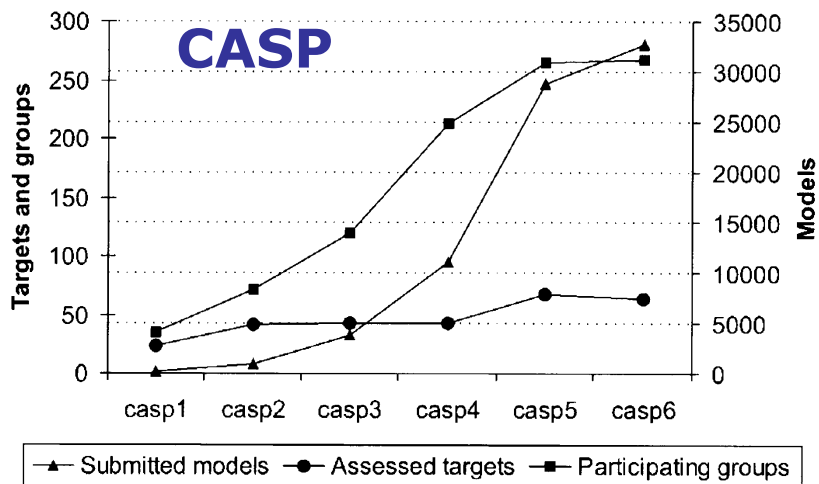
### Rolling CASP experiment - Start

Dear Caspers... This is the last call to register for the CASP ROLL experiment in time for the first target release. We are pleased to announce that 40+ groups, including 20 servers, have already reg...

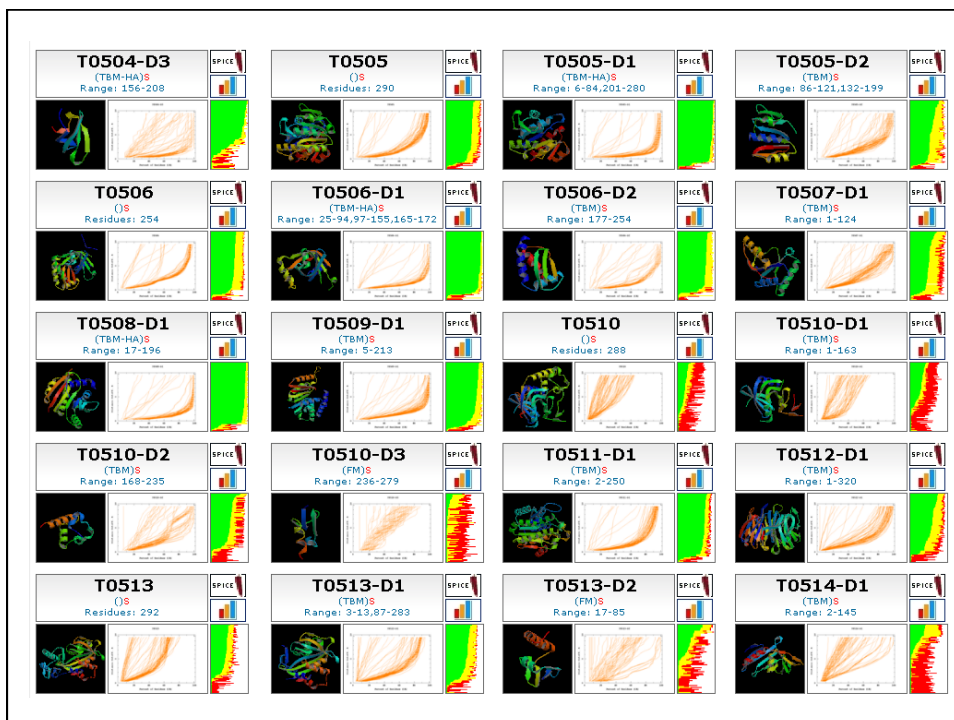
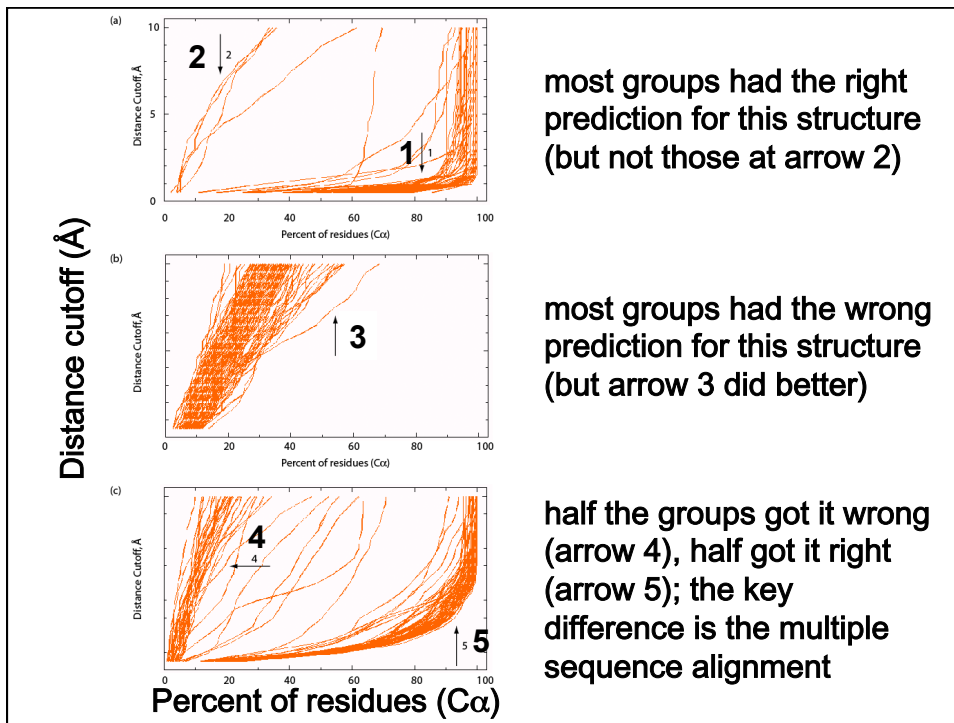
# CASP: Critical Assessment of Structure Prediction



**Figure 2.9** The CASP experiment runs every two years. In the spring, approximately, targets are collected from experimenters working on the resolution of their structure. The sequences are made available to predictors who can submit predictions until the structure is solved. Numerical comparison of models and targets is performed by a group of scientists led by John Moult and Krzysztof Fidelis. The data are then passed to the assessors, chosen by the community on the basis of their expertise, who analyze the data and try to derive general conclusions about the state of the art in the prediction field. In approximately December of the same year, predictors, assessors, and organizers convene in a meeting to discuss the results and, later, publish the final reports in the scientific journal *Proteins: Structure, Function and Bioinformatics*.

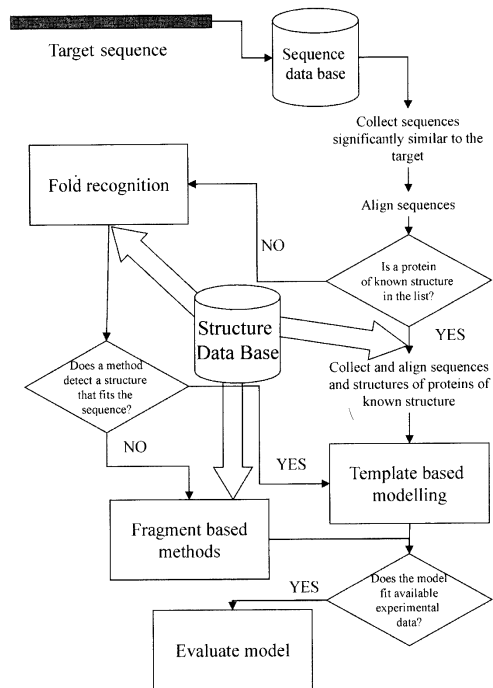


**Figure 2.10** The plot shows the numbers of targets, participating groups, and models submitted to each of the editions of CASP from 1994 (CASP1) to 2004 (CASP6). All the thousands of models are publicly available on the CASP web site.



## Scheme of protein structure prediction

**Figure 4.1** A guide to protein-structure prediction. The first step is always a search in the protein sequence database. Comparative modeling should be used when a protein of known structure sharing sequence similarity with the protein under examination is present in the database. If this is not so, fold-recognition methods should be applied and, should they fail, the user should resort to new fold or fragment-based methods. Note the central role played by the structure database in all these heuristic methods.



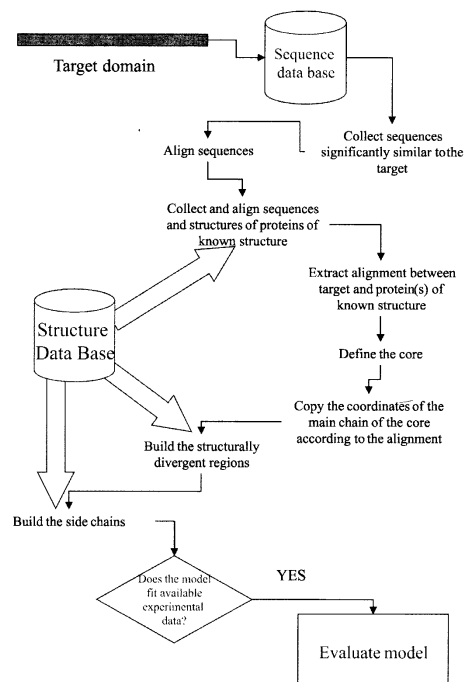
## Comparative protein structure modelling

## Classical procedure for construction of a homology model

1. Given a protein of unknown structure, identify proteins of known structure that are evolutionarily related to it.
2. If they exist, construct a reliable alignment, i.e. deduce the correspondence between related amino acids in the core, i.e. in regions other than those affected by insertions, deletions, and local refolding.
3. Assign the coordinates of the backbone atoms of the corresponding amino acids of the target protein according to the sequence alignment.
4. Model the regions outside the conserved core.
5. Model the positions of the side-chains of the target.
6. Optimize the final three-dimensional structure.

## Scheme of comparative modelling

**Figure 4.2** Schematic diagram of a typical comparative modeling procedure. The protein of interest should first be split into its domains. For each domain, sequences similar to the target sequences should be collected using a database search tool such as FASTA, BLAST, or PSI-BLAST. The sequences retrieved should be realigned using a multiple sequence alignment program (for example CLUSTAL or T-COFFEE). The implied alignment between the target protein and the protein(s) of known structure will form the basis of construction of the model. This can proceed by first building the main chain of the core regions, then the main chain of the structurally divergent regions, and, finally, the side-chains. The final evaluation of the model should take into account any available information on the protein of interest.



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## Building structurally divergent regions

- Reinspect alignment, e.g. shift gaps/insertions outside regular secondary structure elements
- Short canonical loops (type I, type II etc.)
- Rely on sequence pattern
- Loops that form compact substructures: internal H-bonds
- Packing inward pointing side-chain between secondary structure elements connected by the loop

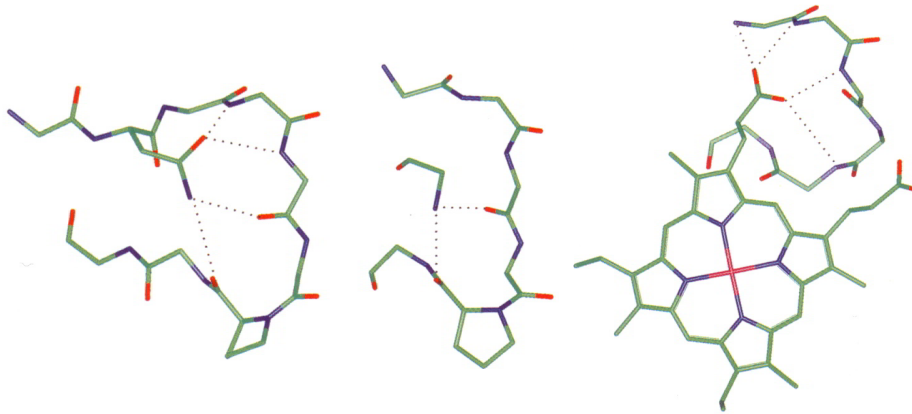
## Loops with similar conformation



**Figure 4.16** The figure shows two loops with similar conformations stabilized by the packing of a central hydrophobic amino acid. Note that one of the loops connects two alpha helices and the other two beta strands.



## Similar loops, different environment



**Figure 4.17** The three loops shown in the figure are very similar and stabilized by hydrogen-bonds, however the partners of these interactions are different in the three different proteins (an immunoglobulin, a viral protein, and a cytochrome).

## Classical procedure for construction of a homology model

- Given a protein of unknown structure, identify proteins of known structure that are evolutionarily related to it.
- If they exist, construct a reliable alignment, i.e. deduce the correspondence between related amino acids in the core, i.e. in regions other than those affected by insertions, deletions, and local refolding.
- Assign the coordinates of the backbone atoms of the corresponding amino acids of the target protein according to the sequence alignment.
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- **Model the positions of the side-chains of the target.**
- Optimize the final three-dimensional structure.

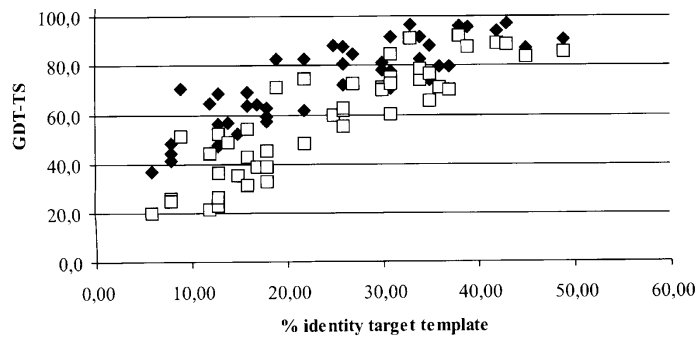
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- Assign the coordinates of the backbone atoms of the corresponding amino acids of the target protein according to the sequence alignment.
- Model the regions outside the conserved core.
- Model the positions of the side-chains of the target.
- **Optimize the final three-dimensional structure.**

## Difficulties of comparative modelling

- Identification of domain boundaries
- Identify correct template
- Find correct alignment between target and template sequence
- Prediction of loop structures
- Side-chain conformation prediction
- Energy refinement is not effective in finding a better model.
- Multi-domain proteins when using different templates for individual domains
- Active sites are better modeled than regions with less evolutionary constraints

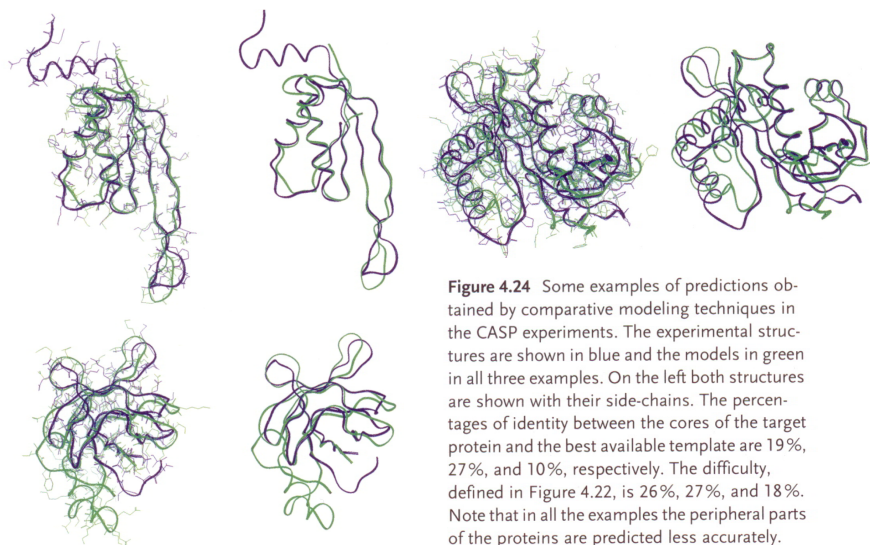
## Prediction accuracy



**Figure 4.21** The relationship between the GDT-TS of the best (filled symbols) and average (open symbols) models and the sequence identity between the target protein sequence and the sequence of the best structural template. The data are taken from the CASP5 results and indicate that, above

40% sequence identity between target and template sequence, most methods can produce very respectable models. In more difficult examples the best methods can still produce useful results, but the gap between the quality of their results and those that can be obtained on average increases.

## Comparative modelling examples



**Figure 4.24** Some examples of predictions obtained by comparative modeling techniques in the CASP experiments. The experimental structures are shown in blue and the models in green in all three examples. On the left both structures are shown with their side-chains. The percentages of identity between the cores of the target protein and the best available template are 19%, 27%, and 10%, respectively. The difficulty, defined in Figure 4.22, is 26%, 27%, and 18%. Note that in all the examples the peripheral parts of the proteins are predicted less accurately.

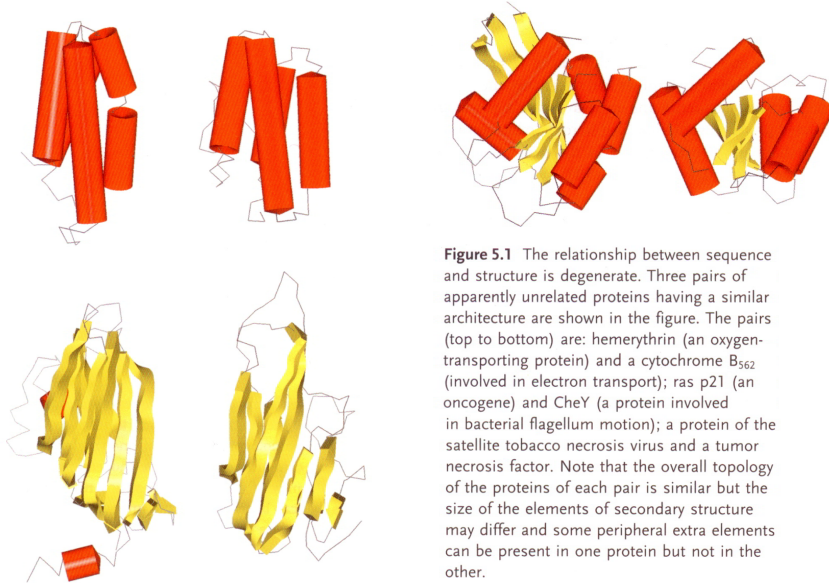
# Fold recognition

## Methods for protein structure prediction

Methods are distinguished according to the relationship between the target protein and proteins of known structure:

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- **New fold prediction:** Neither the sequence nor the structure of the target protein are similar to that of a known protein.

## Structural similarity $\nrightarrow$ Sequence identity



## Non-uniform distribution of folds

- Few (~10) folds are shared by a large number (~30%) of known proteins
- Large diversity in sequences and functions among members of these “superfolds”

### Examples:

- Immunoglobulin fold
- Rossmann fold
- TIM barrel fold
- Globin fold

## **Inverse protein folding problem**

Which amino acid sequences fold into a known three-dimensional structure?

## **Protein folding problem**

Which three-dimensional structure is adopted by a given amino acid sequence?

## **Fold recognition methods**

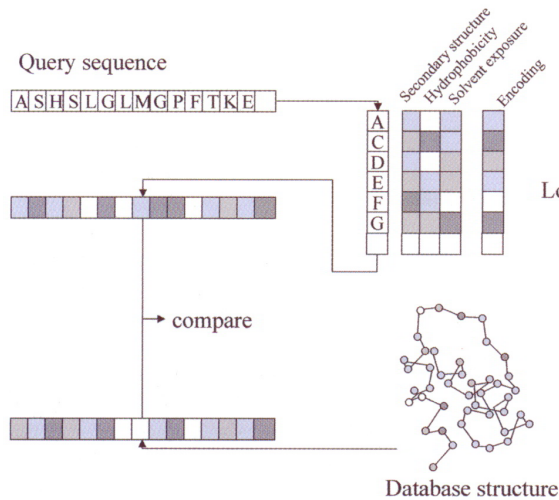
- **3D profile methods**

Physico-chemical properties of the amino acids of the target protein must “fit” with the environment in which they are placed in the modeled structure.

- **Threading**

Sequences are fitted directly onto the backbone coordinates of known protein structures.

## Profile method for fold recognition



**Figure 5.2** Schematic diagram of a possible profile-based method for fold recognition. The amino acids of the query sequence are replaced by a code that summarizes their hydrophobicity and their propensity for secondary structure type and solvent exposure. Each structure in the database is also encoded as a string by assigning a code to each of its amino acid positions. The code reflects their structural environment (secondary structure, solvent accessibility, and hydrophobicity of their environment). This does not depend on the actual amino acid present in the position analyzed. The string encoding the query sequence and each of the strings encoding the database structures are aligned and compared.

Bowie, Lüthy & Eisenberg. *Science* 253, 164-170 (1991)

## Threading

### A new approach to protein fold recognition

D. T. Jones<sup>\*†</sup>, W. R. Taylor<sup>†</sup> & J. M. Thornton<sup>\*</sup>

<sup>\*</sup> Biomolecular Structure and Modelling Unit,  
Department of Biochemistry and Molecular Biology,  
University College, Gower Street,  
London WC1E 6BT, UK

<sup>†</sup> Laboratory of Mathematical Biology, National Institute for Medical Research,  
The Ridgeway, Mill Hill, London, NW7 1AA, UK

- Sequences are fitted directly onto the backbone coordinates of known protein structures.
- Matching of sequences to backbone coordinates is performed in 3D space, incorporating specific pair interactions explicitly.

THE prediction of protein tertiary structure from sequence using molecular energy calculations has not yet been successful; an alternative strategy of recognizing known motifs<sup>1</sup> or folds<sup>2-4</sup> in sequences looks more promising. We present here a new approach to fold recognition, whereby sequences are fitted directly onto the backbone coordinates of known protein structures. Our method for protein fold recognition involves automatic modelling of protein structures using a given sequence, and is based on the frameworks of known protein folds. The plausibility of each model, and hence the degree of compatibility between the sequence and the proposed structure, is evaluated by means of a set of empirical potentials derived from proteins of known structure. The novel aspect of our approach is that the matching of sequences to backbone coordinates is performed in full three-dimensional space, incorporating specific pair interactions explicitly.

*Nature* 358, 86-89 (1992)

## Threading

- A library of different protein folds is derived from the database of protein structures.
- Each fold is considered as a chain tracing through space; the original sequence being ignored completely.
- The test sequence is then optimally fitted to each library fold, allowing for relative insertions and deletions in loop regions.
- The 'energy' of each possible fit (or threading) is calculated by summing the proposed pairwise interactions and the solvation energy.
- The library of folds is then ranked in ascending order of total energy, with the lowest energy fold being taken as the most probable match.

## Knowledge-based (pair) potentials

$$E(r) = -k_B T \ln[f(r)]$$

- $r$  distance between two atoms  
(or some other parameter, like dihedral angles or solvent accessible surface)
- $E(r)$  is the energy at  $r$
- $f(r)$  is the probability density at  $r$
- $k_B$  is the Boltzmann constant
- $T$  is the absolute temperature



## Statistically derived potentials

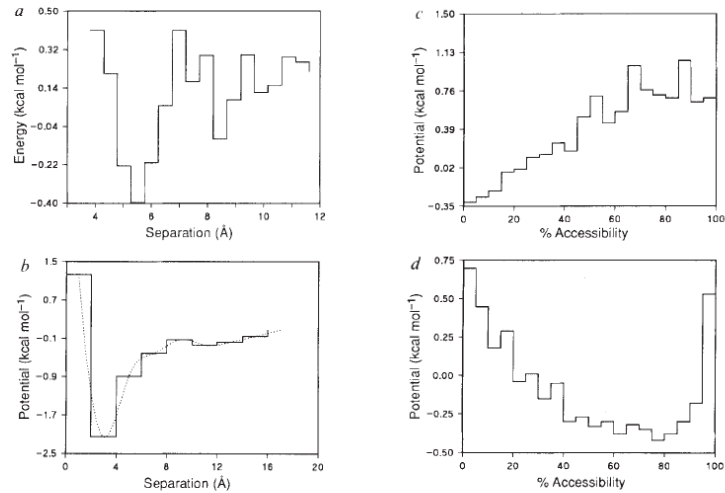
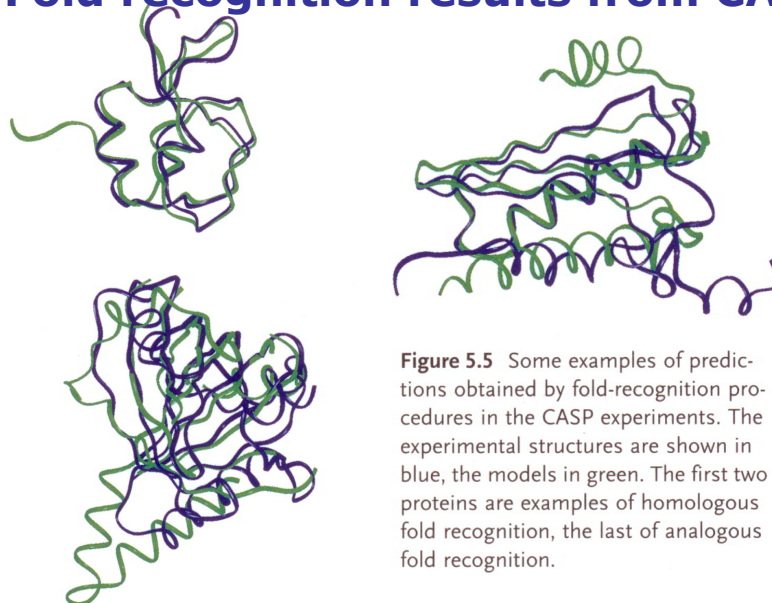


FIG. 1 Samples of the statistically derived potentials are shown. *a* Short-range ( $k=3$ ) Ala-Ala C $\beta$  → C $\beta$  interaction. Low-energy states are observed for distances around 6 Å, corresponding mainly to  $\alpha$ -structure, and 9 Å, corresponding mainly to  $\beta$ -structure. *b* Long-range ( $k > 30$ ) Cys-Cys C $\beta$  → C $\beta$  interaction. The most significant energy minimum around 4 Å corresponds to disulphide bridge formation. *c*, Solvation potential for leucine, and *d*, solvation potential for glutamic acid.

## Fold recognition results from CASP



**Figure 5.5** Some examples of predictions obtained by fold-recognition procedures in the CASP experiments. The experimental structures are shown in blue, the models in green. The first two proteins are examples of homologous fold recognition, the last of analogous fold recognition.

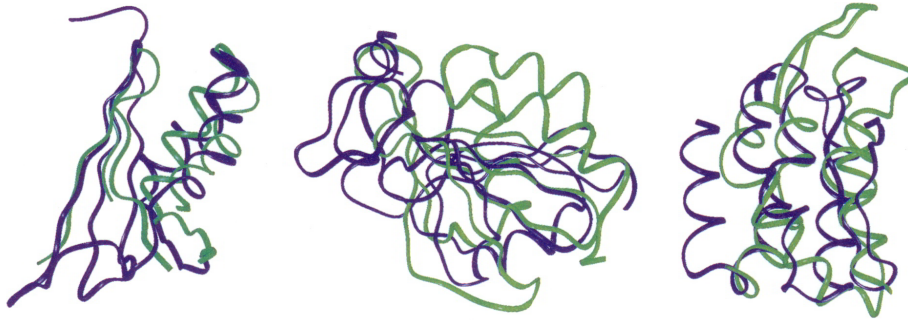
# New fold prediction

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## CASP: Fragment-based predictions



**Figure 6.2** Some examples of fragment-based predictions submitted to CASP experiments.

## Fragment-based approaches

- **Rosetta (David Baker)**
- **Fragfold (David Jones)**

# Toward High-Resolution de Novo Structure Prediction for Small Proteins

Philip Bradley, Kira M. S. Misura, David Baker\*

The prediction of protein structure from amino acid sequence is a grand challenge of computational molecular biology. By using a combination of improved low- and high-resolution conformational sampling methods, improved atomically detailed potential functions that capture the jigsaw puzzle-like packing of protein cores, and high-performance computing, high-resolution structure prediction (<1.5 angstroms) can be achieved for small protein domains (<85 residues). The primary bottleneck to consistent high-resolution prediction appears to be conformational sampling.

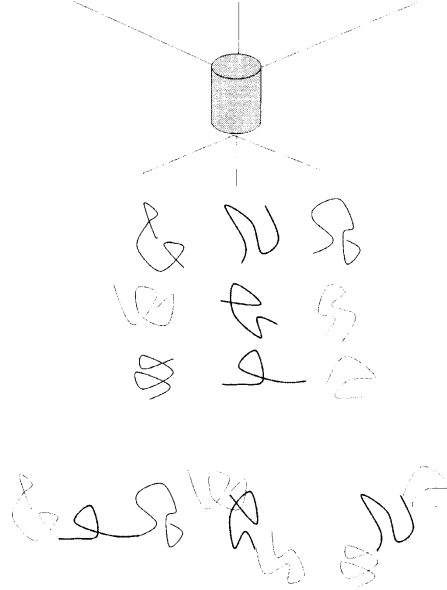
*Science* 309, 1868–1871 (2005)

## Steps of fragment-based structure prediction

- Split sequence into fragments
- For each fragment, search the database of known structures for regions with a similar sequence (“neighbors”)
- Use an optimization technique to find the best combination of fragments

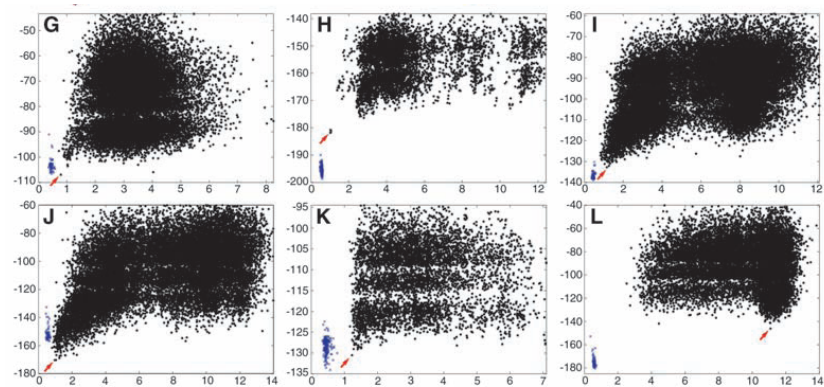
## Fragment search

Sequence: ATRFGCTGFKLMTYPFDGEWRTRSDEF...



**Figure 6.3** Schematic explanation of the first steps of the Rosetta method. The query sequence is split in fragments nine amino acids long. Each fragment sequence is used to search for similar fragments among the sequences of proteins of known structure. Next, the fragments are joined.

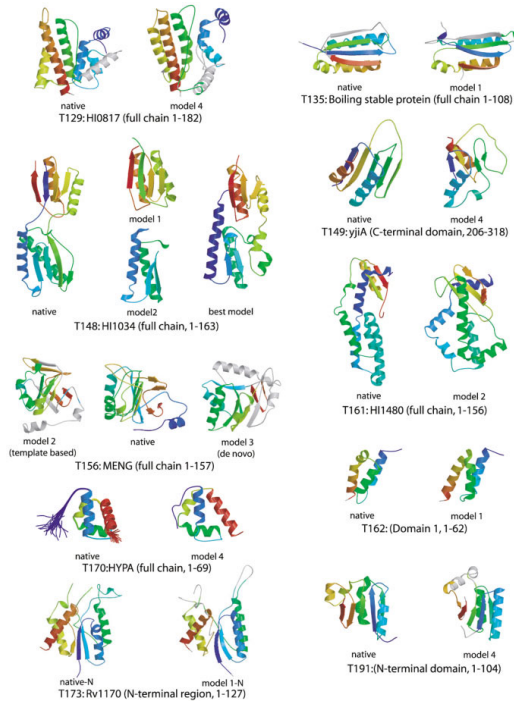
## Energy vs. accuracy



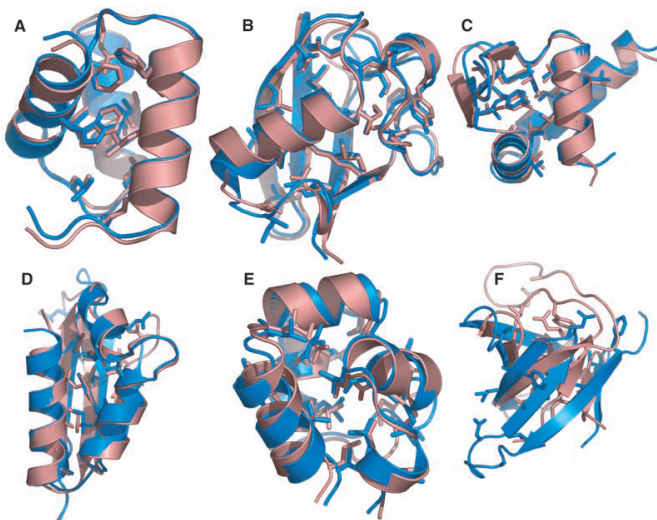
Plots of C $\alpha$ -RMSD (x axis) against all atom energy (y axis) for refined natives (blue points) and the de novo models (black points). Red arrows indicate the lowest energy de novo models.

## ROSETTA results in CASP5

Ribbon diagrams of predictions made by using the fragment insertion approach. The native structure and best submitted model are shown colored from the N-terminus (blue) to C-terminus (red). For T148, the best generated model is also shown, and for T156, both template-based and fragment insertion based models are shown. For targets T173, T135, T156, and T191, colored regions deviate from the native structure by  $<4 \text{ \AA}$ , and gray regions deviate by  $>4 \text{ \AA}$ . For targets T129 and T156, colored regions deviate from the native structure by  $<6 \text{ \AA}$  C $\alpha$  RMSD, whereas the gray regions deviate by  $>6 \text{ \AA}$ .



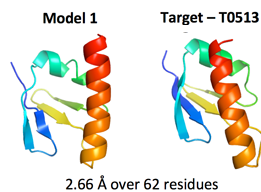
## High-resolution de novo structure predictions



Superposition of low-energy models (blue) with experimental structures (red) showing core side chains.

A: Hox-B1  
 B: Ubiquitin  
 C: RecA  
 D: KH domain of Nova-2  
 E: 434 repressor  
 F: Fyn tyrosine kinase

# Robetta protein structure prediction server



*de novo* prediction by Robetta in CASP-8

<http://robetta.bakerlab.org>

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<http://www.bpc.uni-frankfurt.de/guentert/wiki/index.php/Teaching>