Protein Structure Prediction

Michael Feig

MMTSB/CTBP

2006 Summer Workshop

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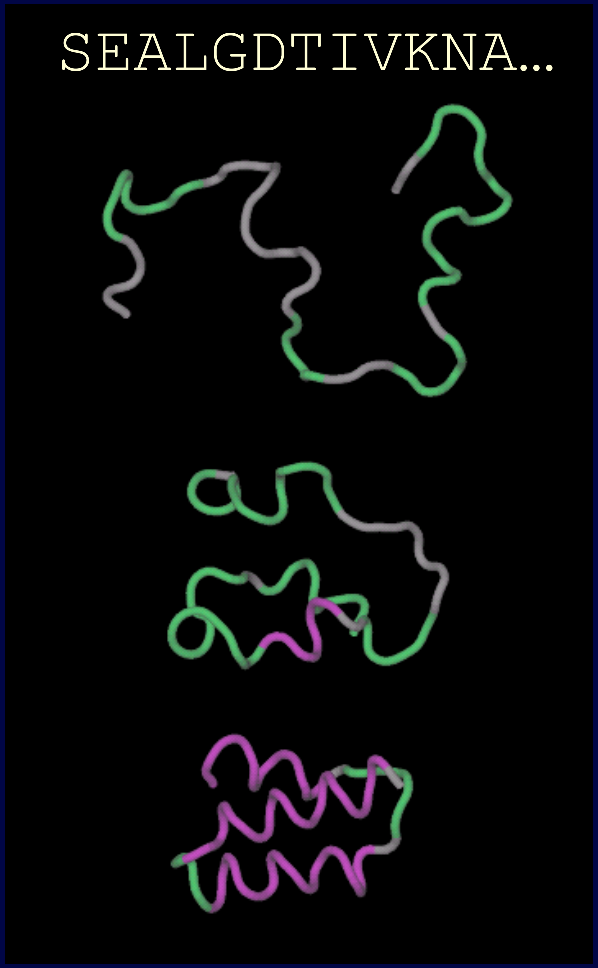
From Sequence to Structure



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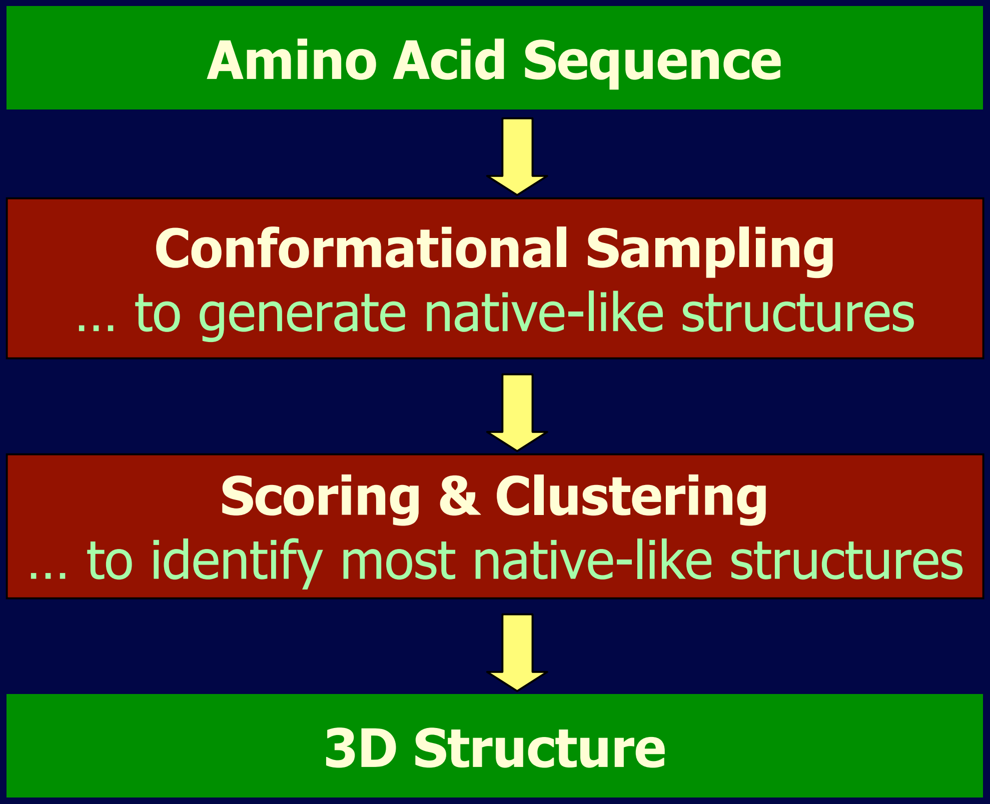
Ab initio Structure Prediction Protocol



Amino Acid Sequence

Conformational Sampling
… to generate native-like structures

Scoring & Clustering
… to identify most native-like structures

3D Structure

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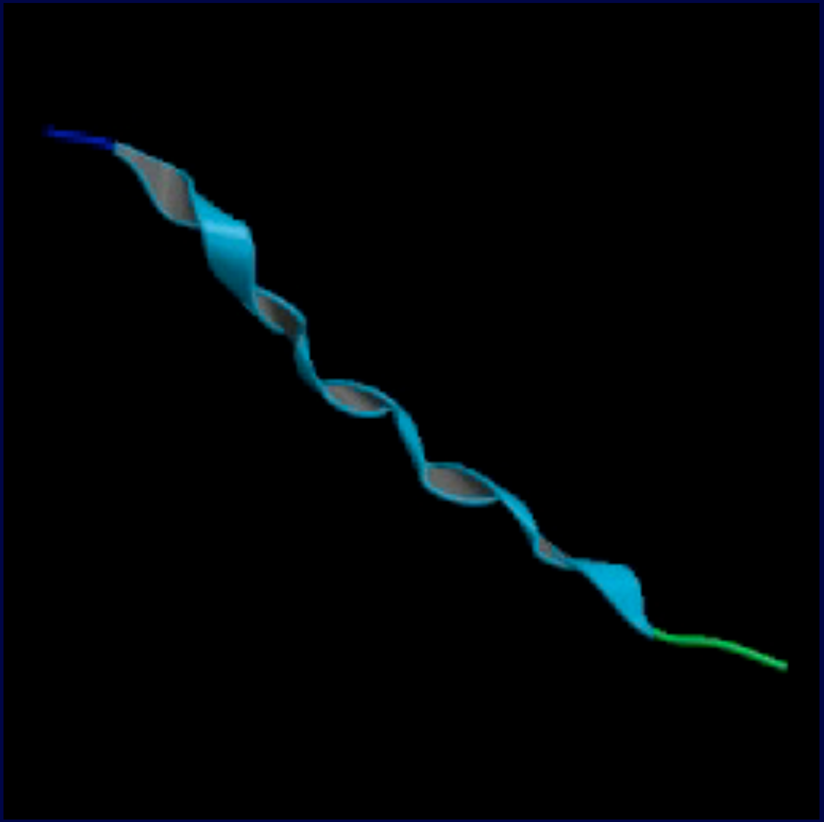
Folding with All-Atom Models

AAQAAAAQAAAAQAA



CHARMM force field
Implicit solvent replica exchange simulations
8 replicas, 10 ns/replica

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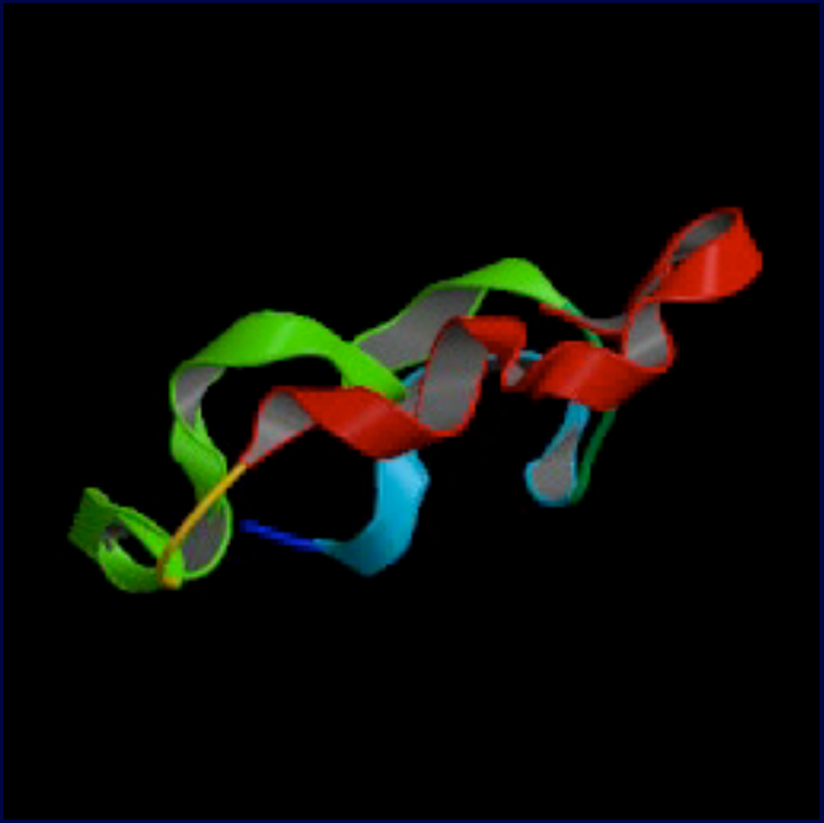
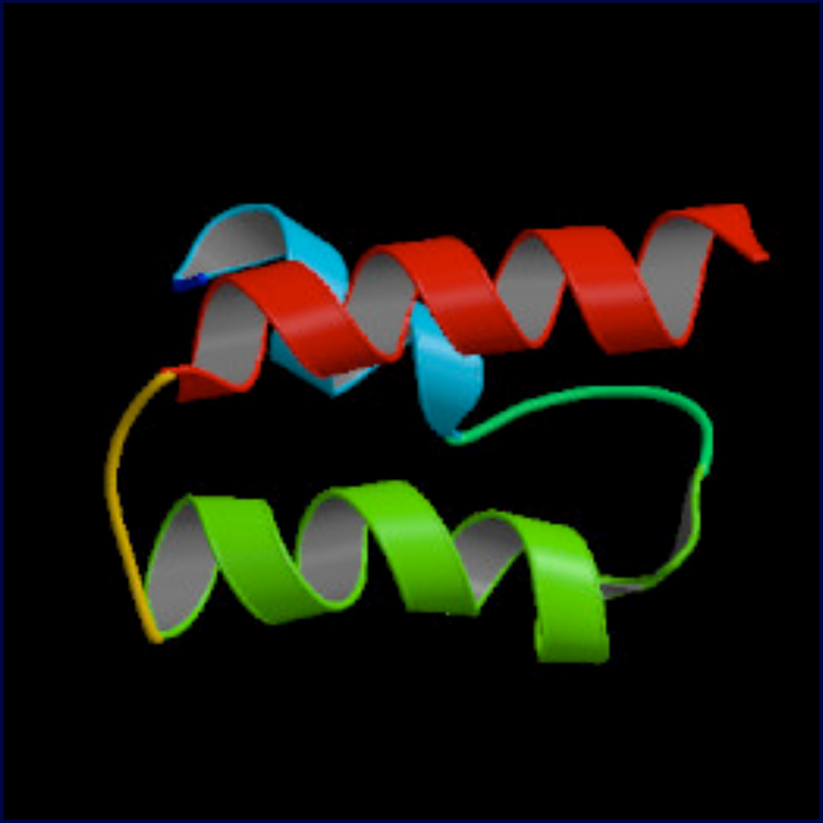
Folding with Low-Resolution Model

EQQNAFYEILHLPNLNEEQRNGFIQSLKDDPSQSANLLAEAKKLNDAQA





SICHO model, MONSSTER simulated annealing run

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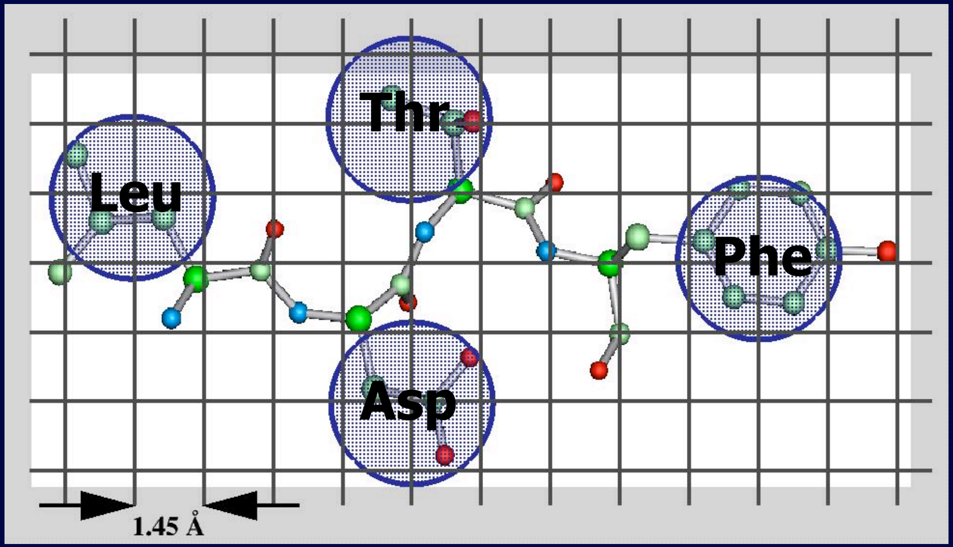
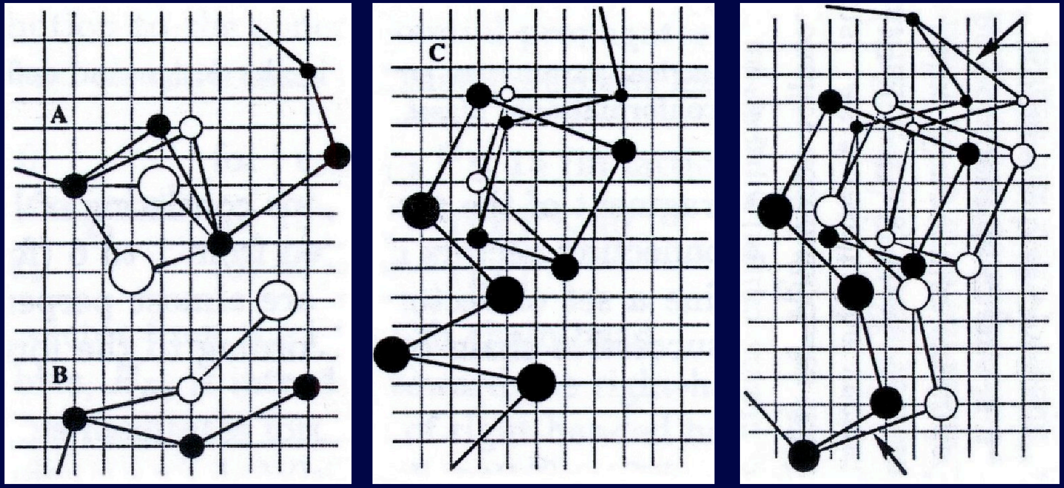
SICHO Lattice Model



Monte Carlo simulations:

- > Attempt move
- > Compute ΔE
- > Accept with probability p:

$$p = \begin{cases} 1 & \Delta E \leq 0 \\ \exp(-\Delta E / k_B T) & \Delta E > 0 \end{cases}$$



Simulated annealing

Constant Temperature

Replica Exchange Sampling

Kolinski & Skolnick: Proteins *32*, 475 (1998)

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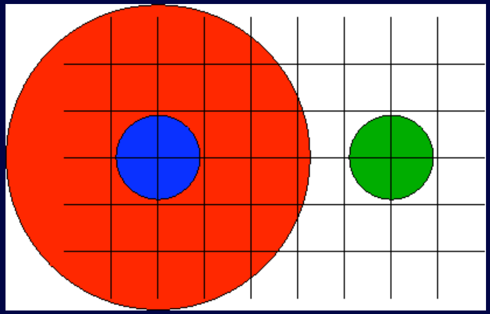
SICHO Energy Function

Knowledge-Based Terms

□ Excluded volume



□ Side chain burial propensity

follows Kyte-Doolittle scale

Ala	1.8
Arg	-4.5
Asp	-3.5
Ile	4.5

□ Centrosymmetric bias

$$r_g = 2.2\ N_{res}^{0.38}$$

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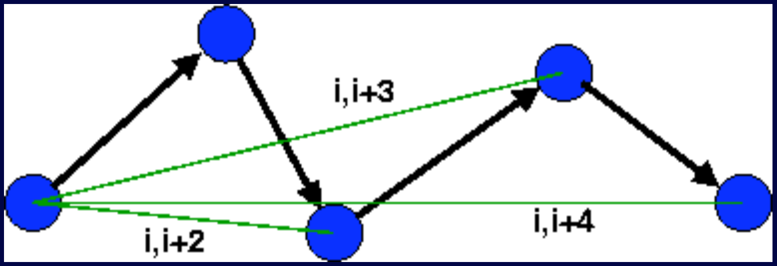
SICHO Energy Function

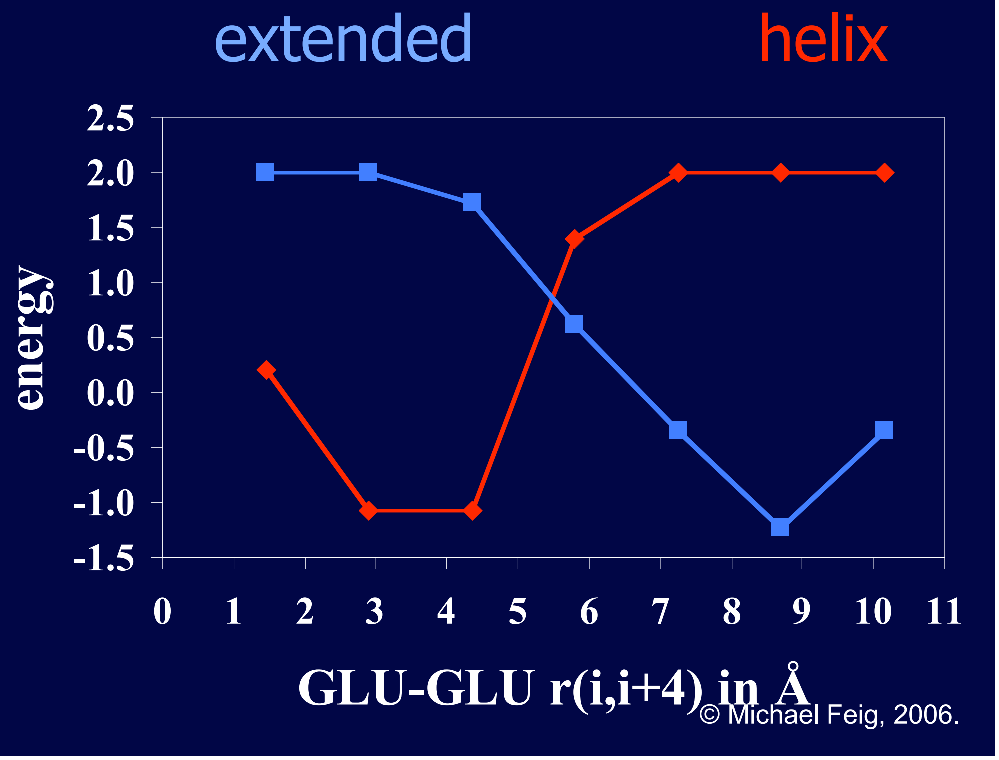
Statistical Terms

Potential of mean force (PMF):

$$\frac{p_i}{p_j} = e^{-\frac{\Delta E_{ij}}{k_B T}}$$

$$\Delta E = -kT\ln(p)$$





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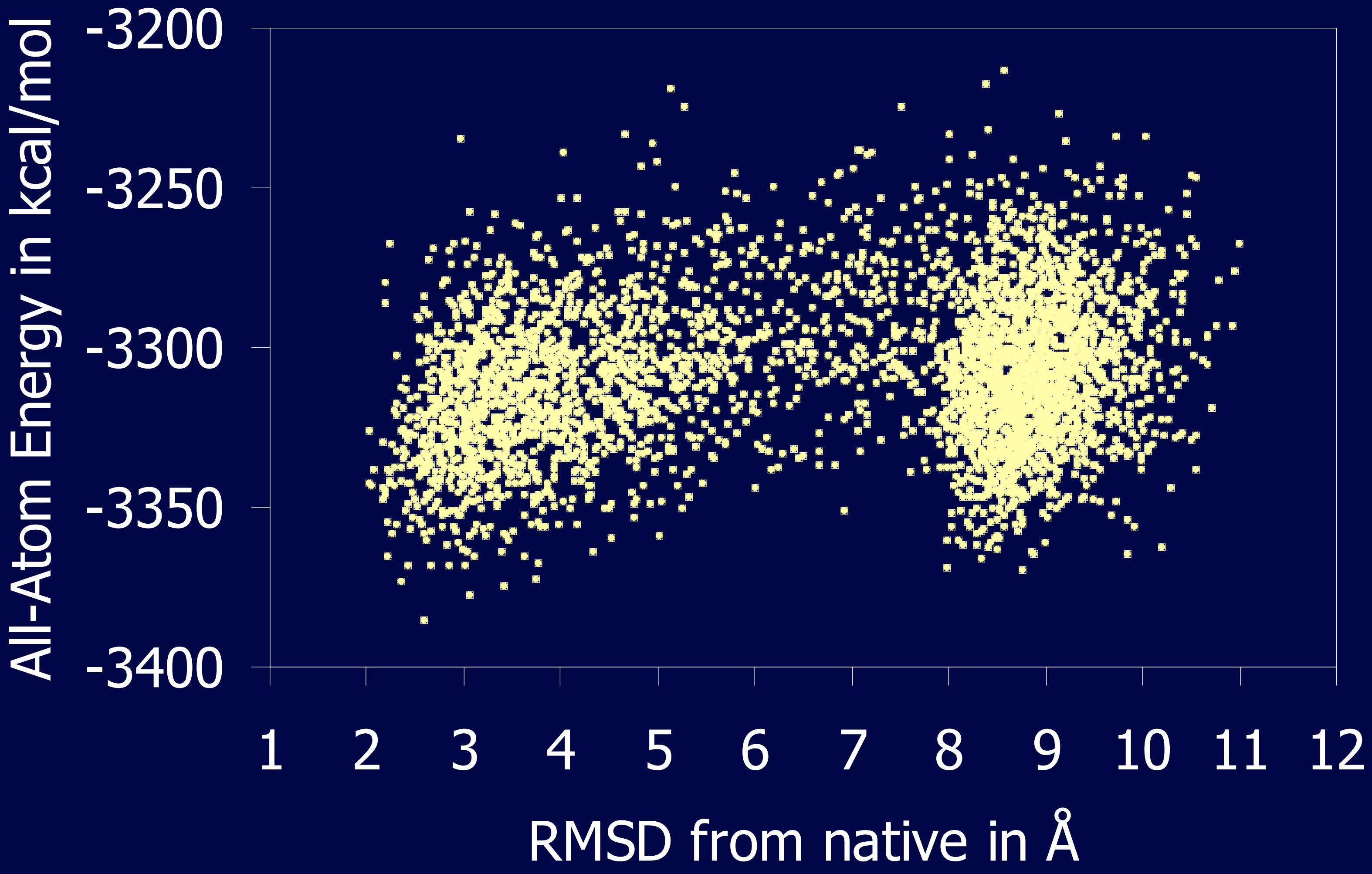
Conformational Sampling with SICHO

Protein A



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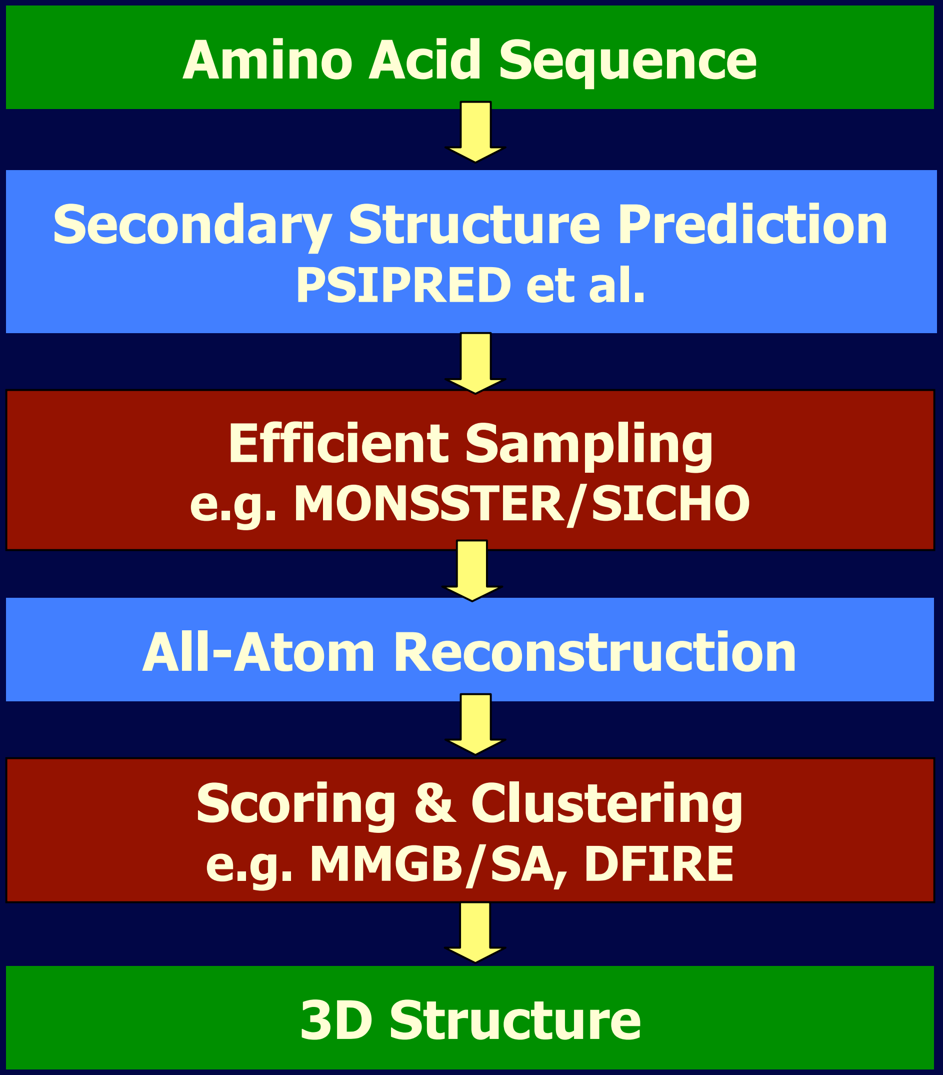
Ab initio Structure Prediction Protocol



Amino Acid Sequence

Secondary Structure Prediction
PSIPRED et al.

Efficient Sampling
e.g. MONSSTER/SICHO

All-Atom Reconstruction

Scoring & Clustering
e.g. MMGB/SA, DFIRE

3D Structure

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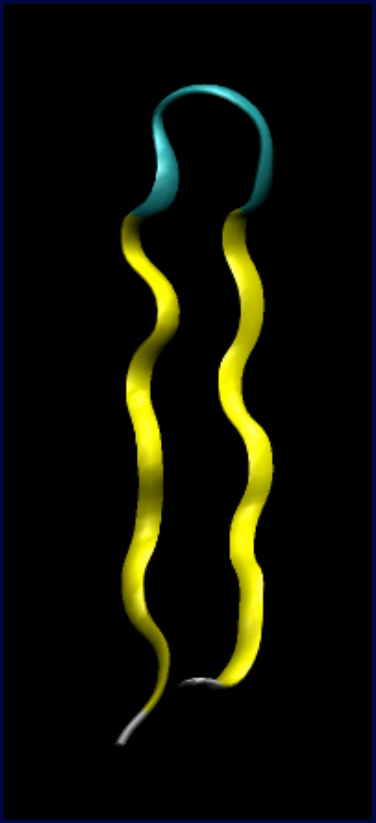
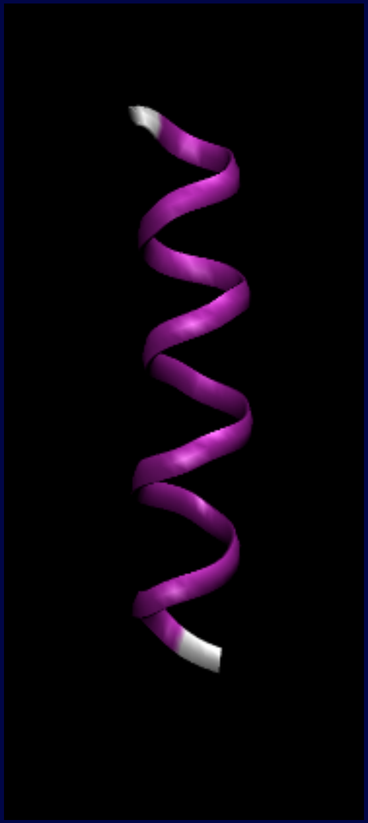
Secondary Structure Prediction

…GDPIVKNAKLDSRLANKEALRLL…



?



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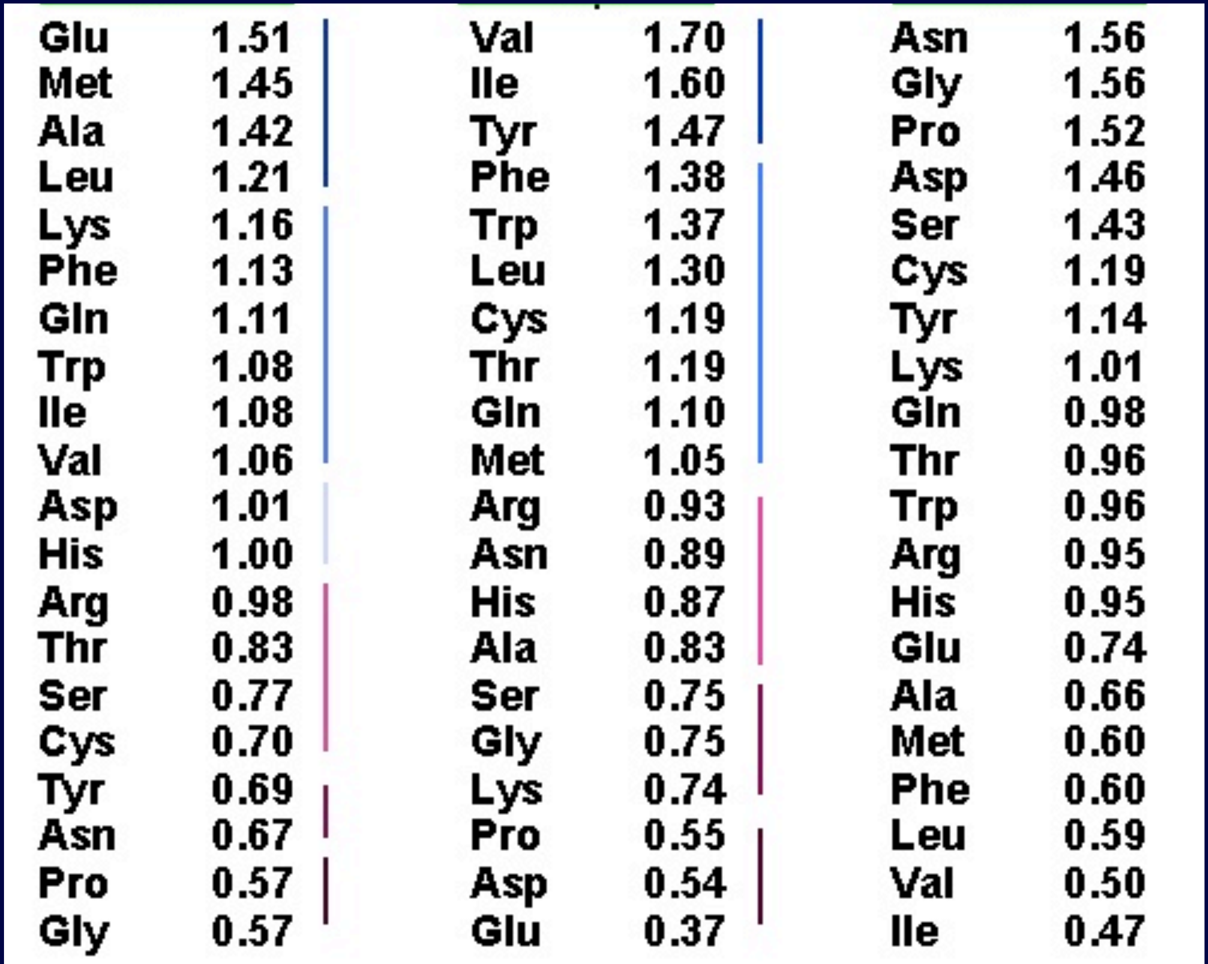
Secondary Structure Propensities



α-helix		β-sheet		turn	
Glu	1.51	Val	1.70	Asn	1.56
Met	1.45	Ile	1.60	Gly	1.56
Ala	1.42	Tyr	1.47	Pro	1.52
Leu	1.21	Phe	1.38	Asp	1.46
Lys	1.16	Trp	1.37	Ser	1.43
Phe	1.13	Leu	1.30	Cys	1.19
Gln	1.11	Cys	1.19	Tyr	1.14
Trp	1.08	Thr	1.19	Lys	1.01
Ile	1.08	Gln	1.10	Gln	0.98
Val	1.06	Met	1.05	Thr	0.96
Asp	1.01	Arg	0.93	Trp	0.96
His	1.00	Asn	0.89	Arg	0.95
Arg	0.98	His	0.87	His	0.95
Thr	0.83	Ala	0.83	Glu	0.74
Ser	0.77	Ser	0.75	Ala	0.66
Cys	0.70	Gly	0.75	Met	0.60
Tyr	0.69	Lys	0.74	Phe	0.60
Asn	0.67	Pro	0.55	Leu	0.59
Pro	0.57	Asp	0.54	Val	0.50
Gly	0.57	Glu	0.37	Ile	0.47

Chou & Fasman (1974)

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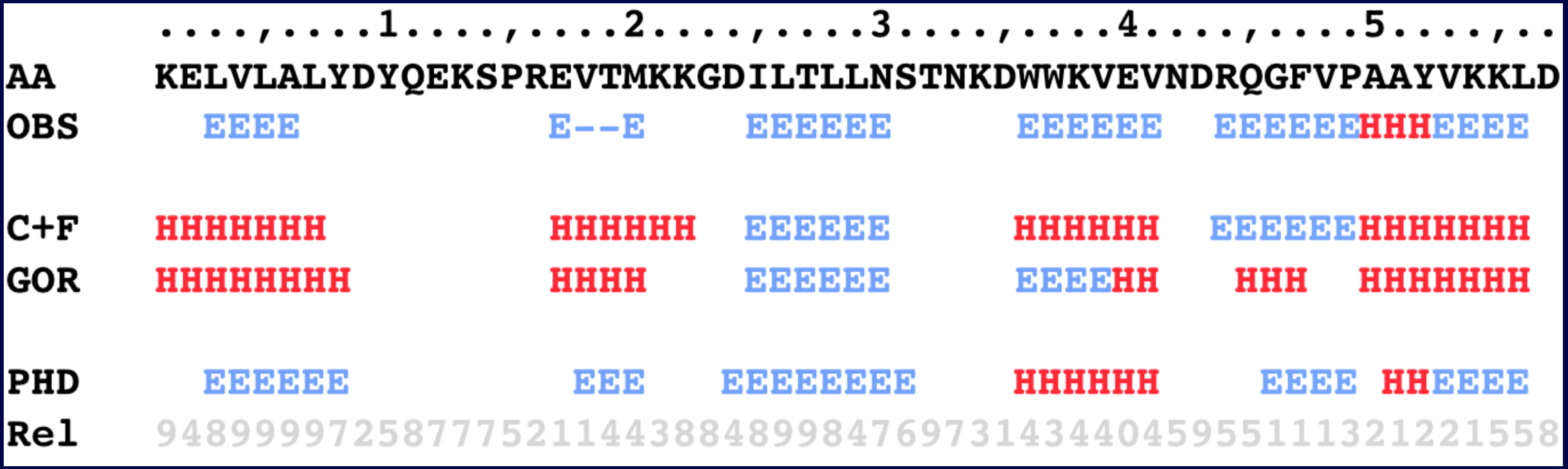
Secondary Structure Prediction Methods



```
      ....,....1....,....2....,....3....,....4....,....5....,..
AA    KELVLALYDYQEKSPREVTMKKGDILTLLNSTNKDWWKVEVNDRQGFVPAAYVKKLD
OBS     EEEE          E--E    EEEEEE     EEEEEE  EEEEEEHHHEEEE

C+F   HHHHHHH         HHHHHH  EEEEEE     HHHHHH  EEEEEEHHHHHHH
GOR   HHHHHHHH        HHHH    EEEEEE     EEEEHH   HHH  HHHHHHH

PHD     EEEEEE         EEE   EEEEEEEE    HHHHHH    EEEE HHEEEE
Rel   948999972587775211443884899847697314344045955111321221558
```

SABLE	77.6%
PSIPRED	76.2%
PSSP	75.1%
SAM-T99-sec	76.1%
PHD	72.3%
C+F	50-60%

C+F: Chou & Fasman
GOR: Garnier, Osguthorpe, Robson

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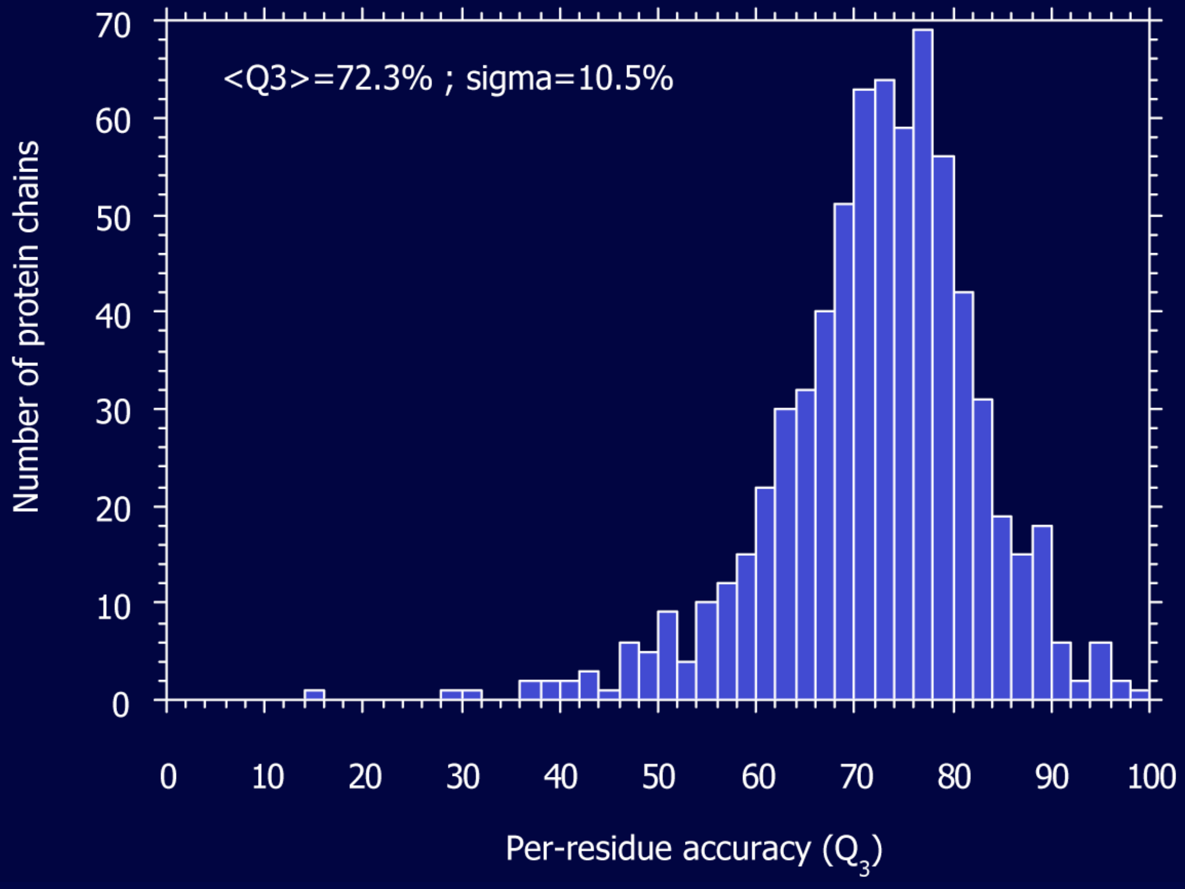
Secondary structure prediction

Per-Residue Accuracy



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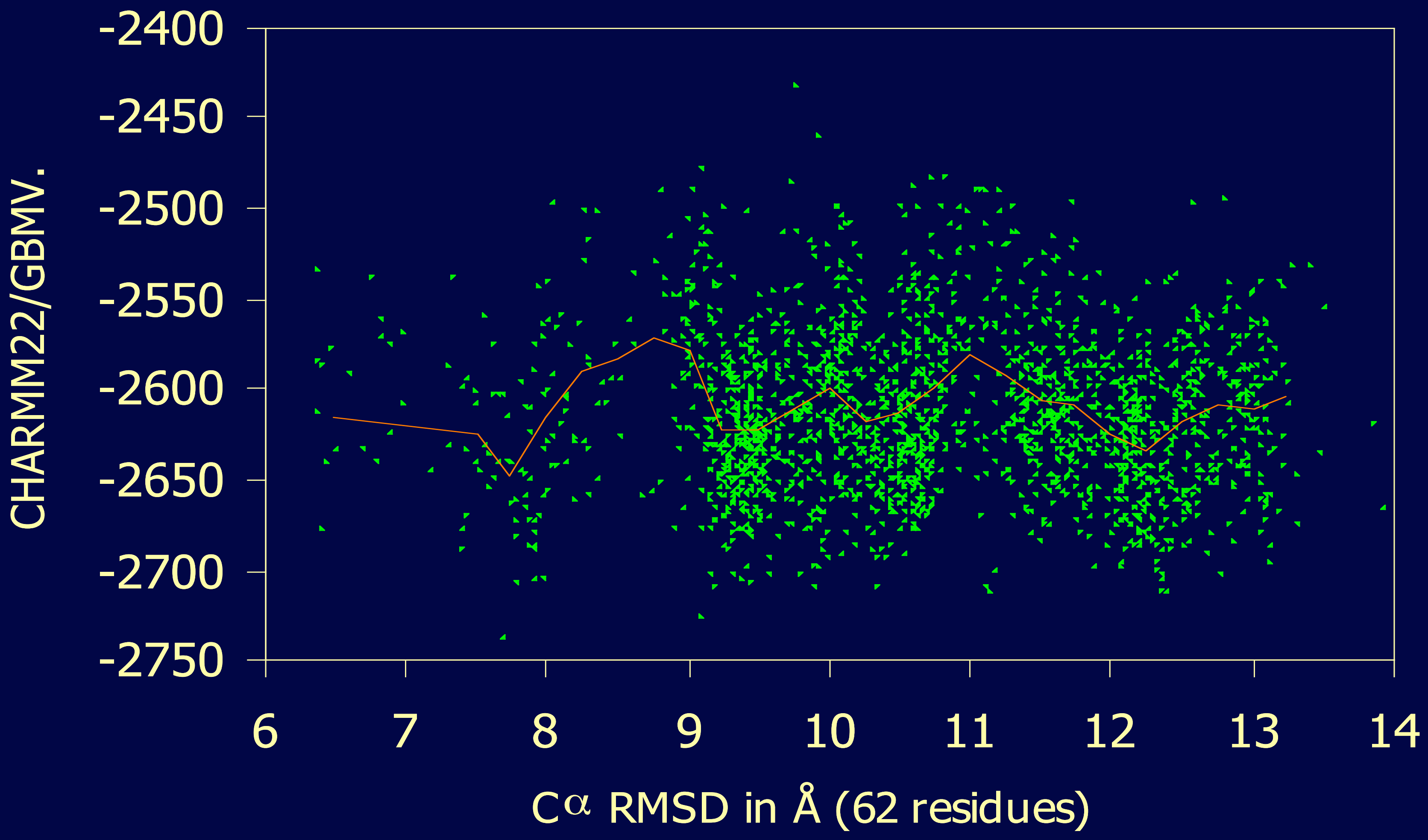
Realistic ab initio Structure Prediction



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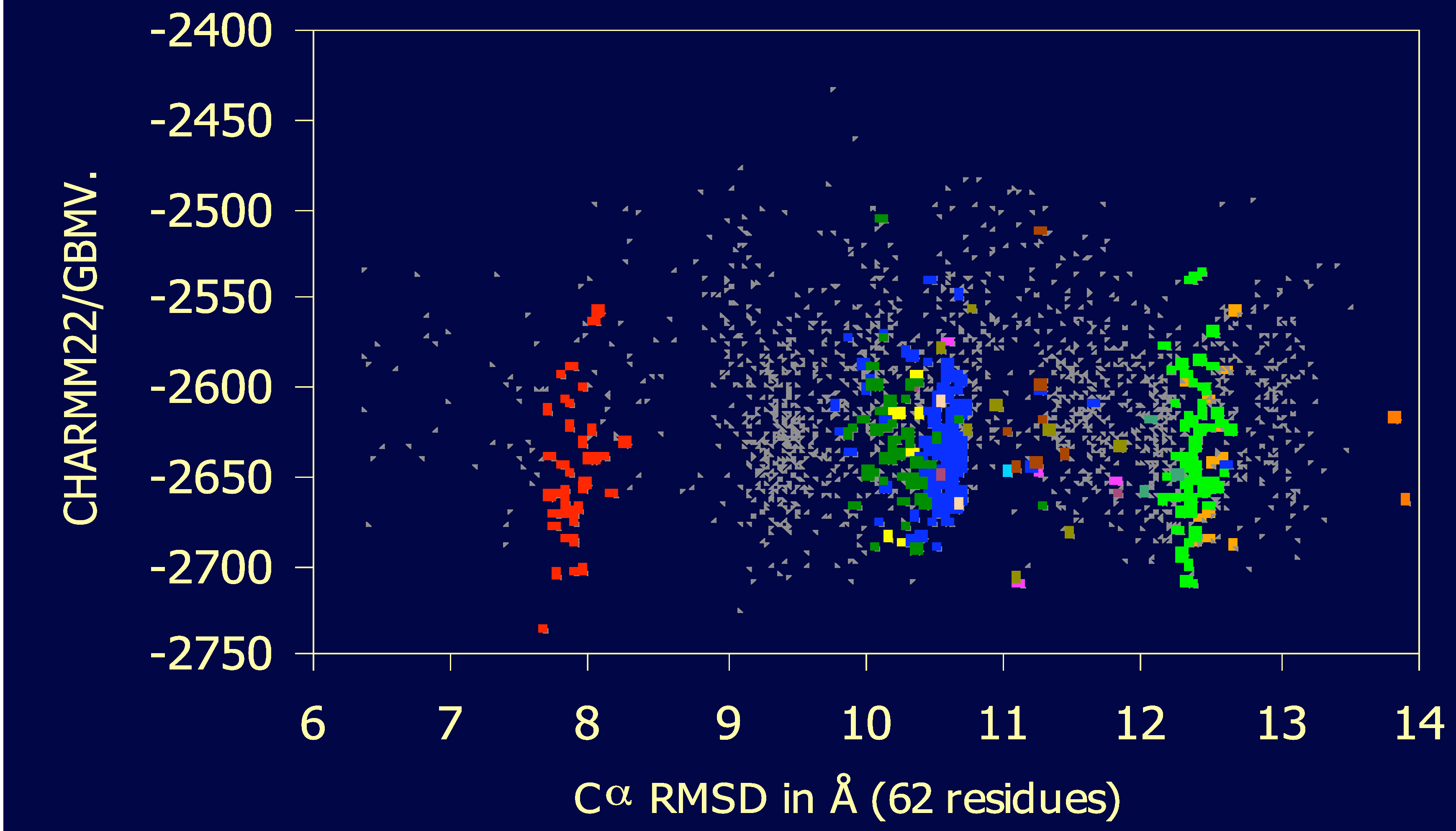
Sampling, Scoring, Clustering



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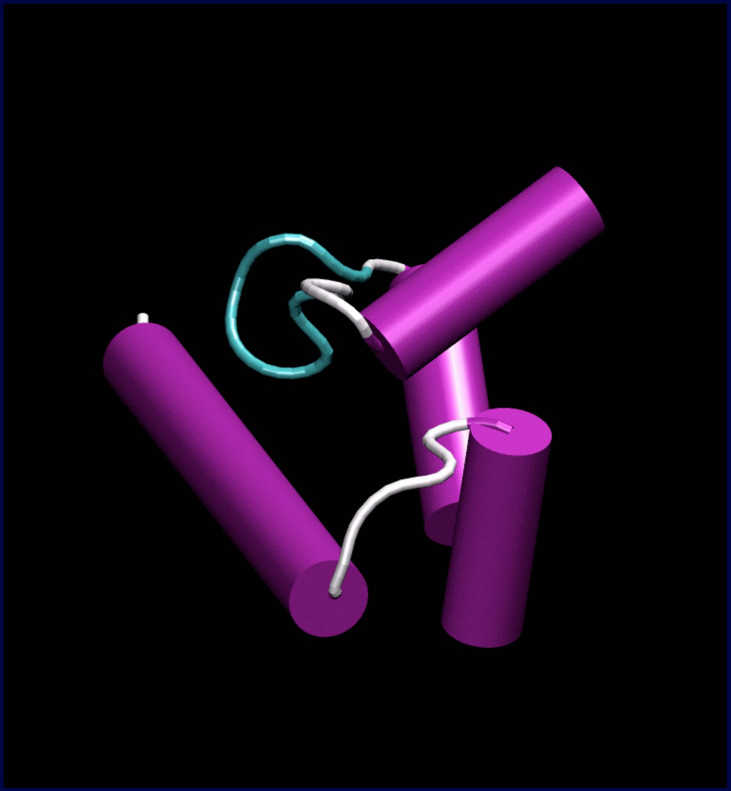
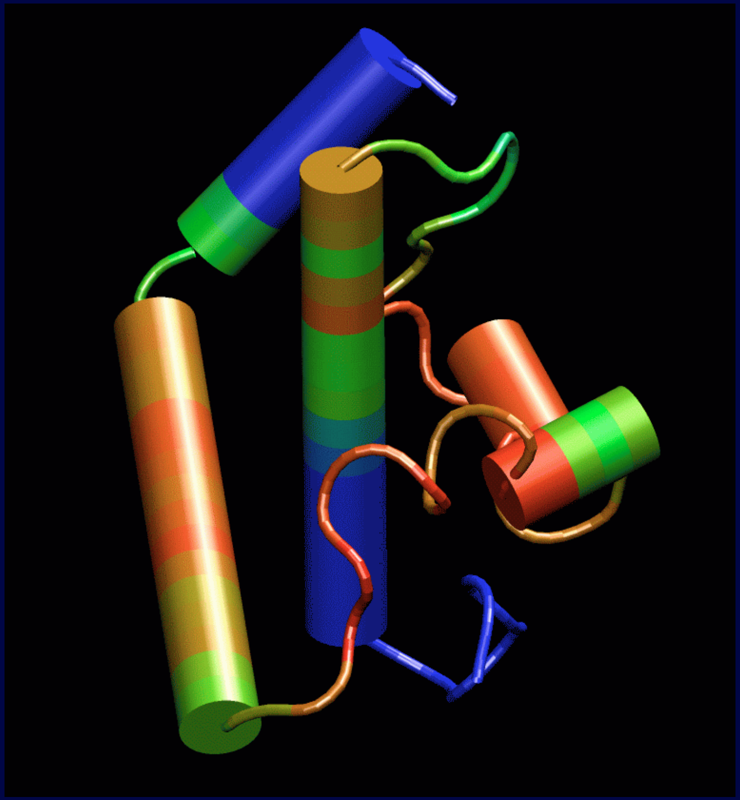
Ab initio Predictions

DNase fragmentation factor



NMR structure 1KOY



Best-scoring prediction
7.4 Å RMSD

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Scoring Functions

- □ **Knowledge-based/statistical**

  derived from known protein structures
  limited by training data
  usually fast
  e.g. DFIRE, RAPDF, prosaII

- □ **Force field based**

  model physical energy landscape
  more robust and transferable
  often expensive (require minimization)
  e.g. MMPB(GB)/SA, UNRES

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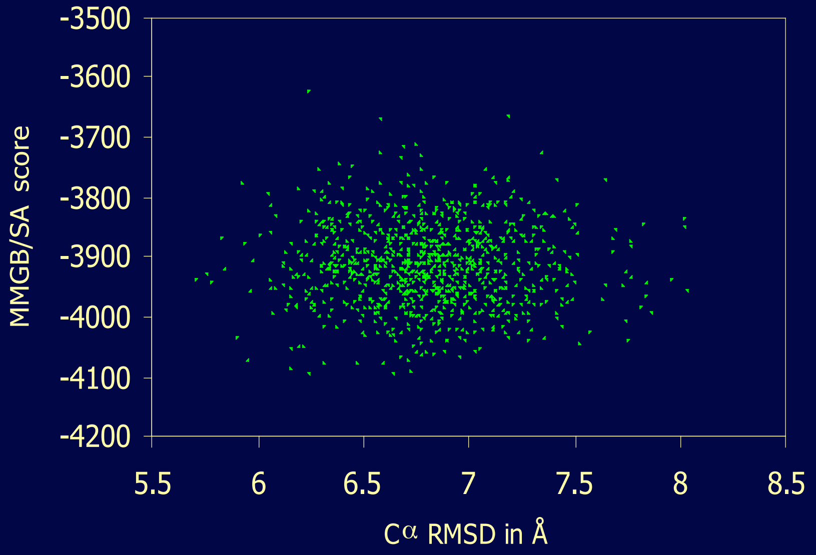
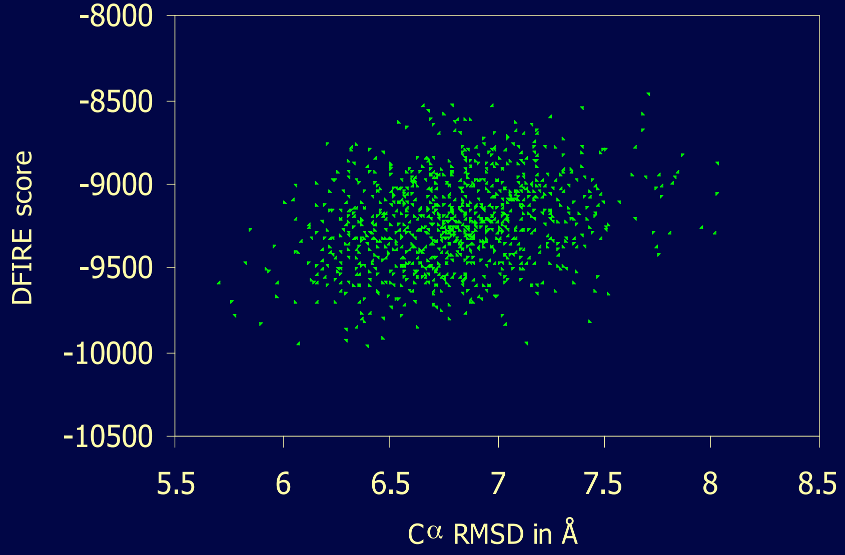
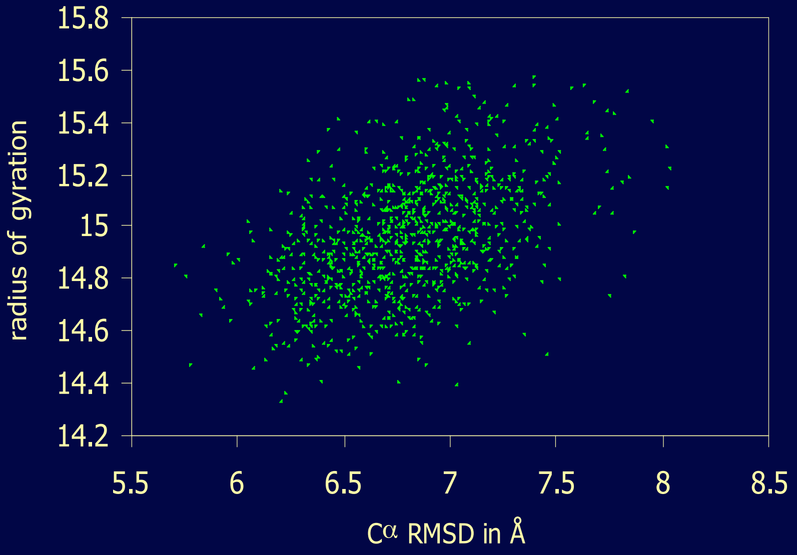
Scoring Function Comparison

MMGB/SA vs. DFIRE







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Sampling with Restraints

□ **Secondary structure bias**

- Secondary structure prediction
- NMR shift data

□ **Distance restraints**

- Experimental restraints (disulfides, NMR, EPR)
- Side chain contacts from analogous structures

□ **Shape restraints**

- cryoEM data, small-angle X-ray scattering

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… but the solution may lie elsewhere.

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Sequence Homology

Human thioredoxin (1AUC)

```
SDKIIHLTDDSFDTDVLKADGAILVDFWAEWCGPCKMIAPILDEIADEYQGKLTV
A
  : :.      ..    .:  ..::: : :::::::: :.. .....:.. . .
MVKQIESKTAFQEALDAAGDKLVVVDFSATWCGPCKMIKPFFHSLSEKYSNVIFL
-


KLNIDQNPGTAPKYGIRGIPTLLLFKNGEVAATKVGALSKGQLKEFLDAN---LA
....:.   .: .  .. .::. .::.:.    ::: .: :  :: :.:.   :.
EVDVDDCQDVASECEVKCMPTFQFFKKGQ----KVGEFS-GANKEKLEATINELV
```

E. Coli thioredoxin (1THO)

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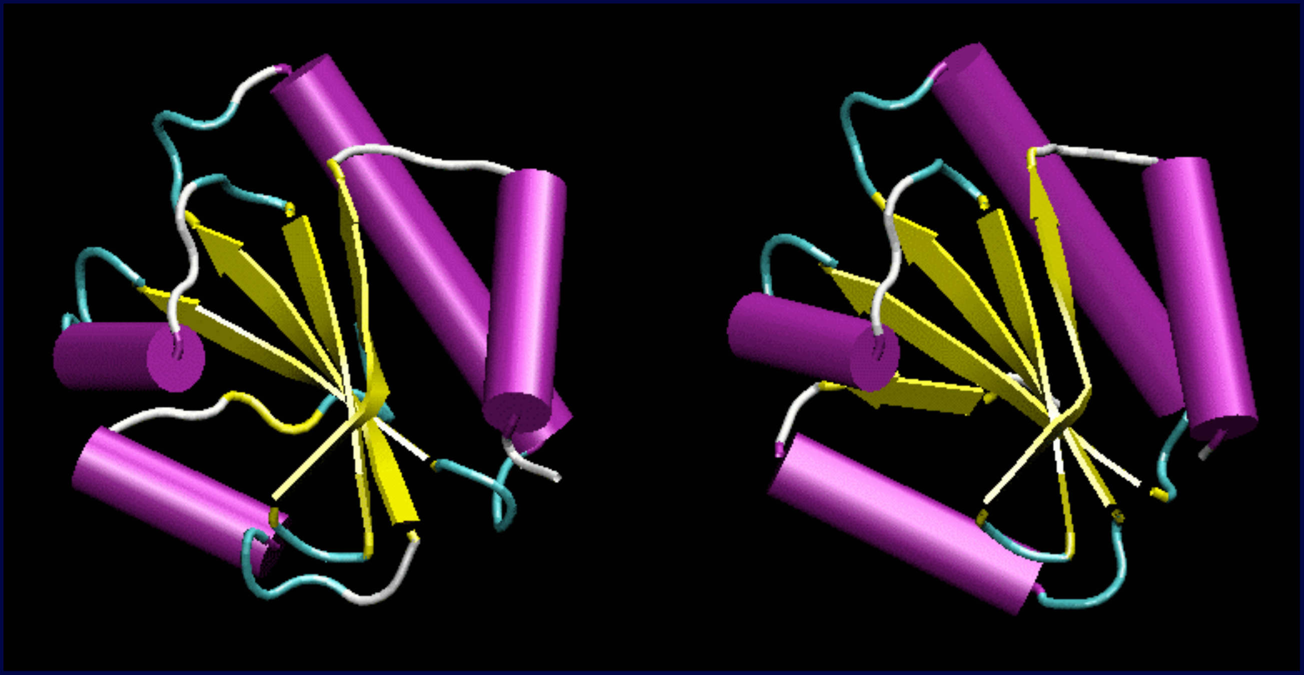
Comparative Modeling

Assumption:

Proteins with similar sequence have similar structure



Human thioredoxin
(1AUC)

E. Coli thioredoxin
(1THO)

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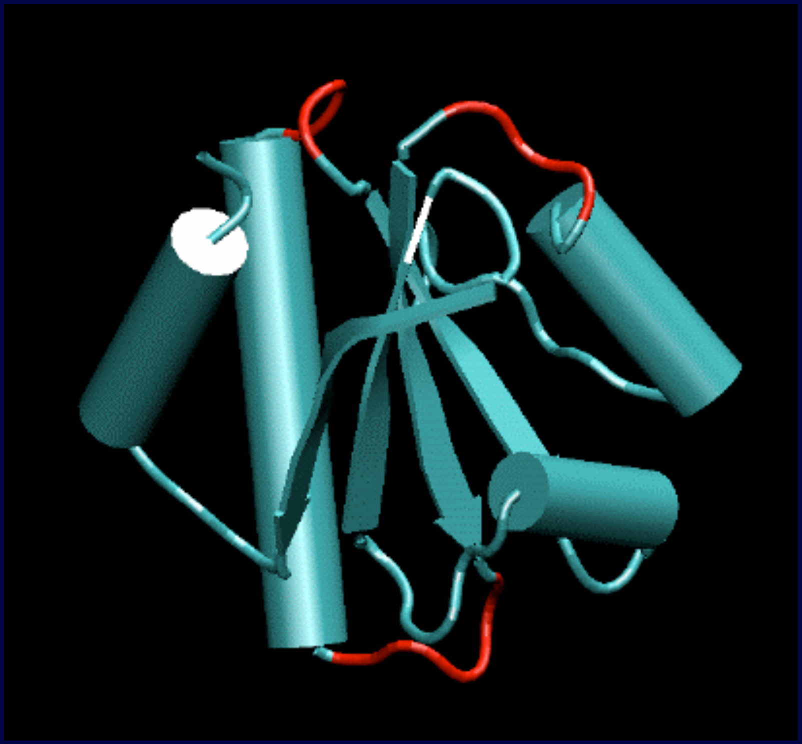
Structural Templates from Homology



Challenges:

- □ Correct alignment
- □ Loop modeling
- □ Side chain rebuilding

```
PGTAPKYGIRGIPTLLLFKNGEVAATKVGALSKGQLKEFLDAN---LA
  .: .  .. .::. .::.:.    ::: .: :  :: :.:.   :.
QDVASECEVKCMPTFQFFKKGQ----KVGEFS-GANKEKLEATINELV
```

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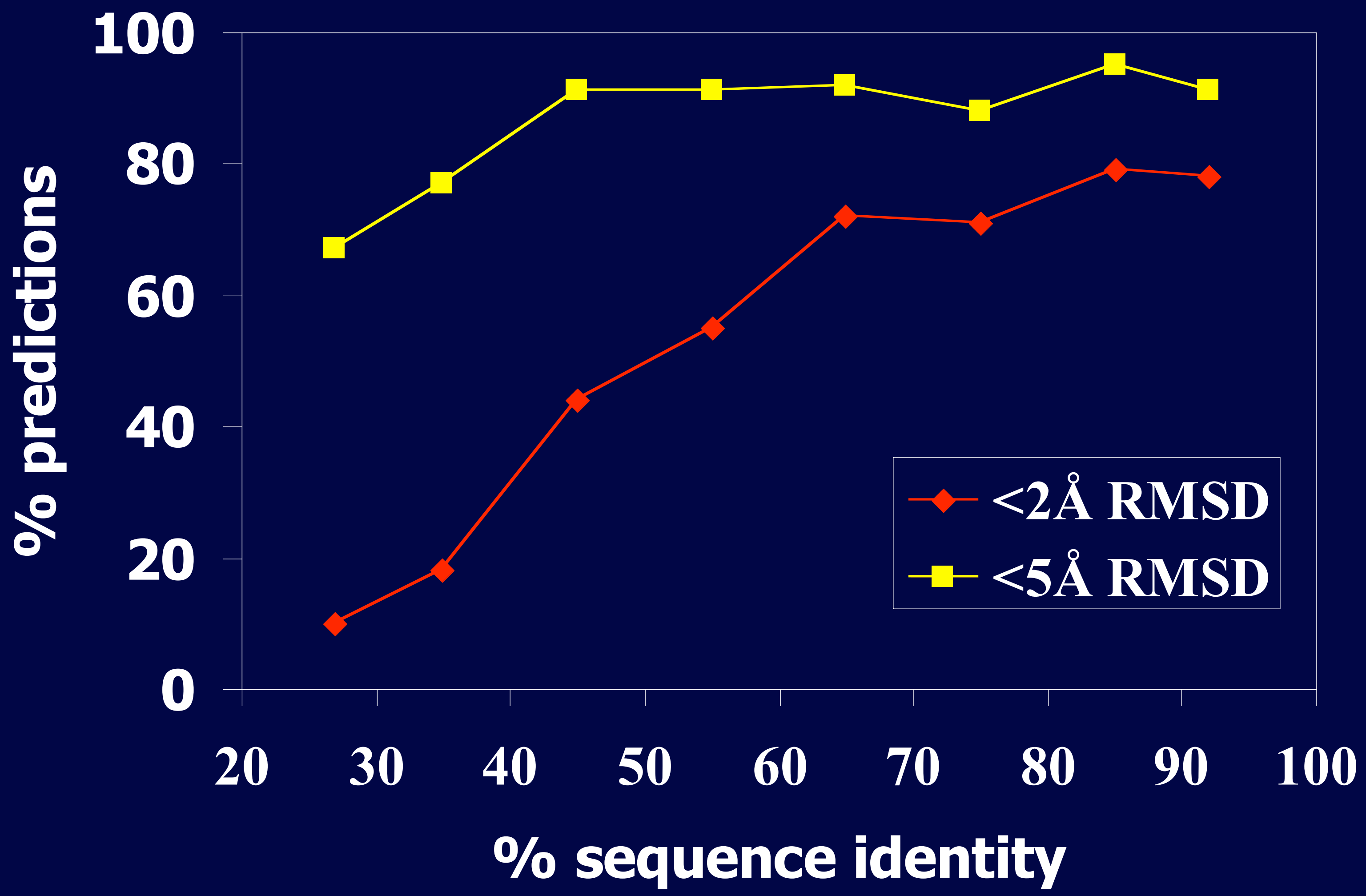
Accuracy of Predictions by Homology



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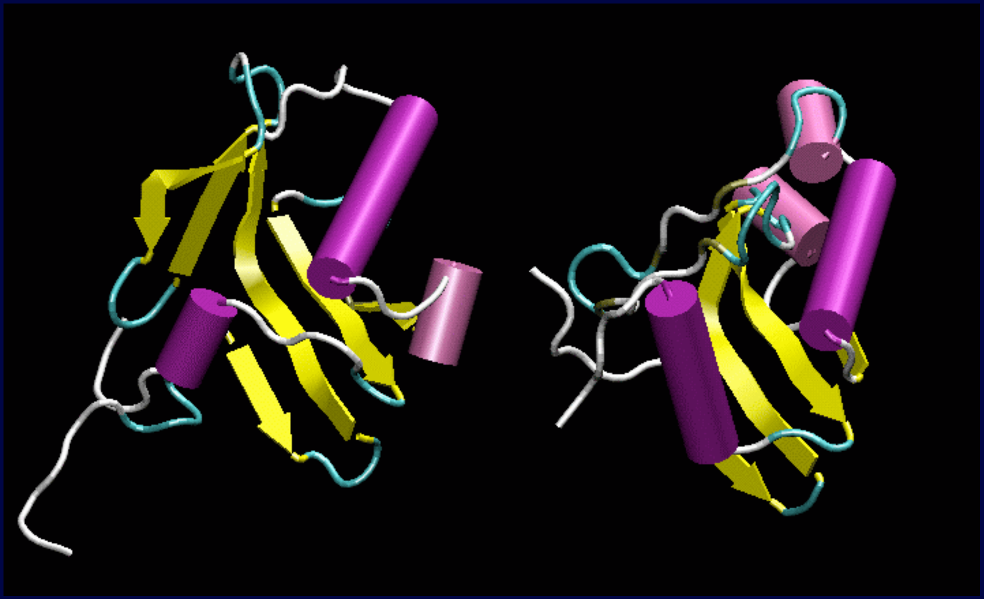
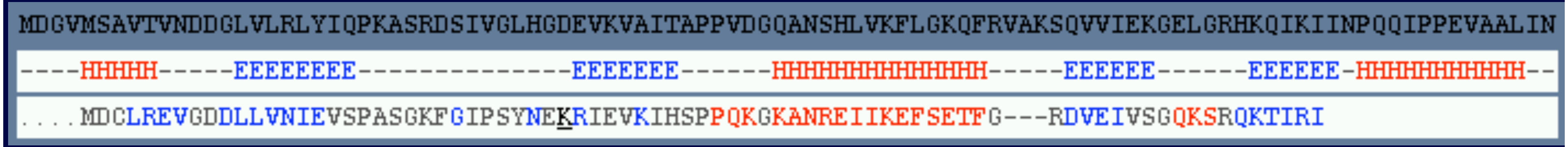
Prediction through Fold Recognition

Assumption:

Proteins with similar secondary structure share fold





```
MDGVMSAVTVNDDGLVLRLYIQPKASRDSIVGLHGDEVKVAITAPPVDGQANSHLVKFLGKQFRVAKSQVVIEKGELGRHKQIKIINPQQIPPEVAALIN
----HHHHH-----EEEEEEEE--------------EEEEEEE------HHHHHHHHHHHHHH-----EEEEEE------EEEEEE-HHHHHHHHHHH--
....MDCLREVGDDLLVNIEVSPASGKFGIPSYNEKRIEVKIHSPPQKGKANREIIKEFSETFG---RDVEIVSGQKSRQKTIRI
```

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Templates through Fold Recognition

Challenges:

- □ Wrong templates
- □ Alignment uncertain
- □ Fragment modeling
- □ Refinement needed

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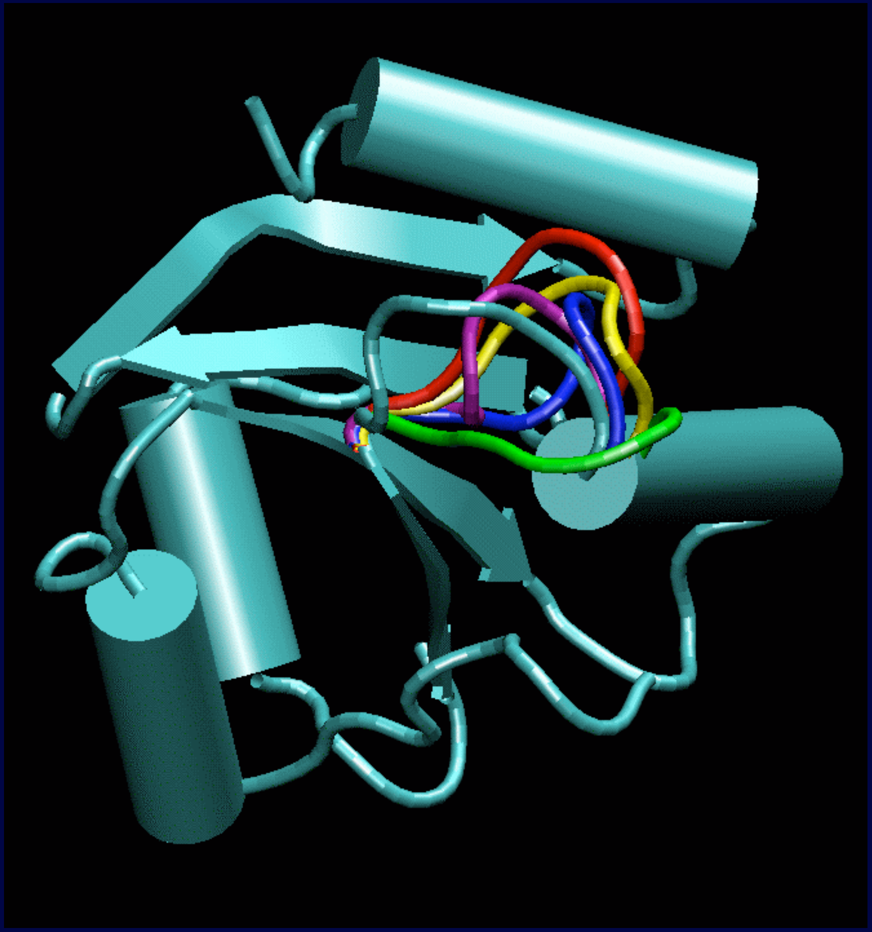
Ab initio Sampling in Template-based Structure Prediction



- □ **Template** provides known protein structure
- □ **Ab initio sampling** of unknown fragments in the context of template

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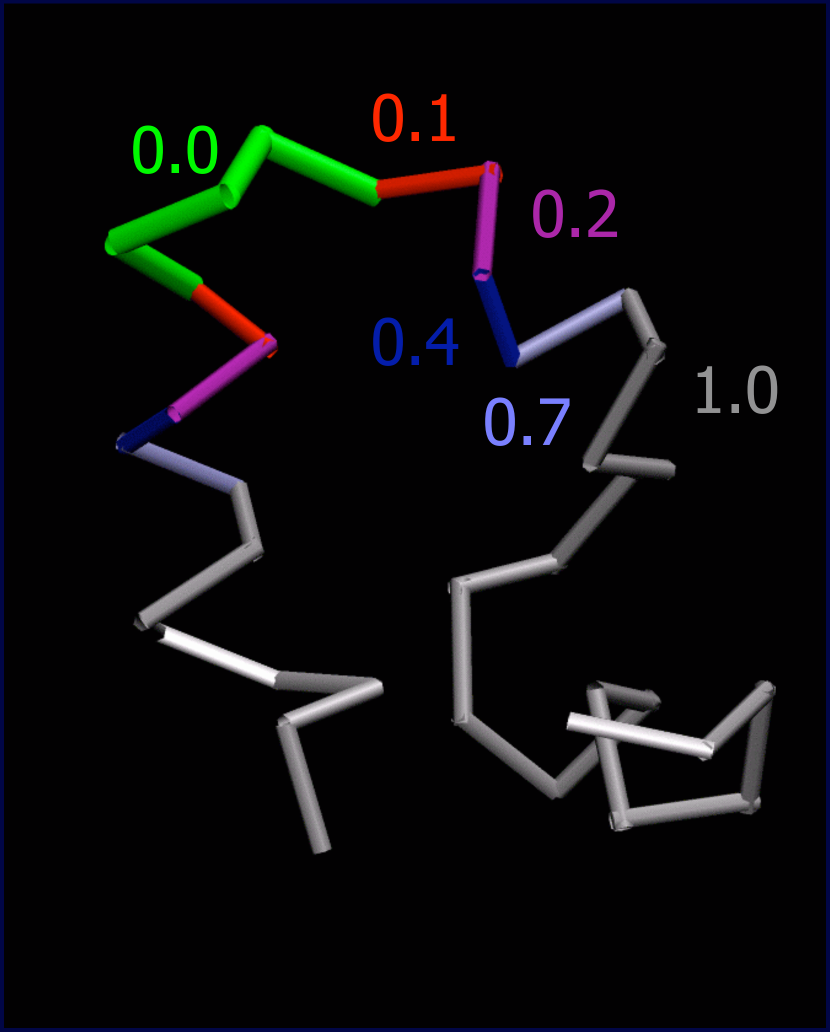
Template Restraints Near Flexible Part



Restraint potential:

$$U = f \cdot k(r - r_0)^2$$

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Loop Sampling Methods

# Residues	Sampling	Program
1-2	All-Atom Reconstruction	MMTSB Tool Set
1-3	Exhaustive Search	
2-12	Torsional Space MC/MD	Modeller (Sali)
5-30	Multi-Scale	MMTSB Tool Set
2-100	Fragment-based	Rosetta (Baker)

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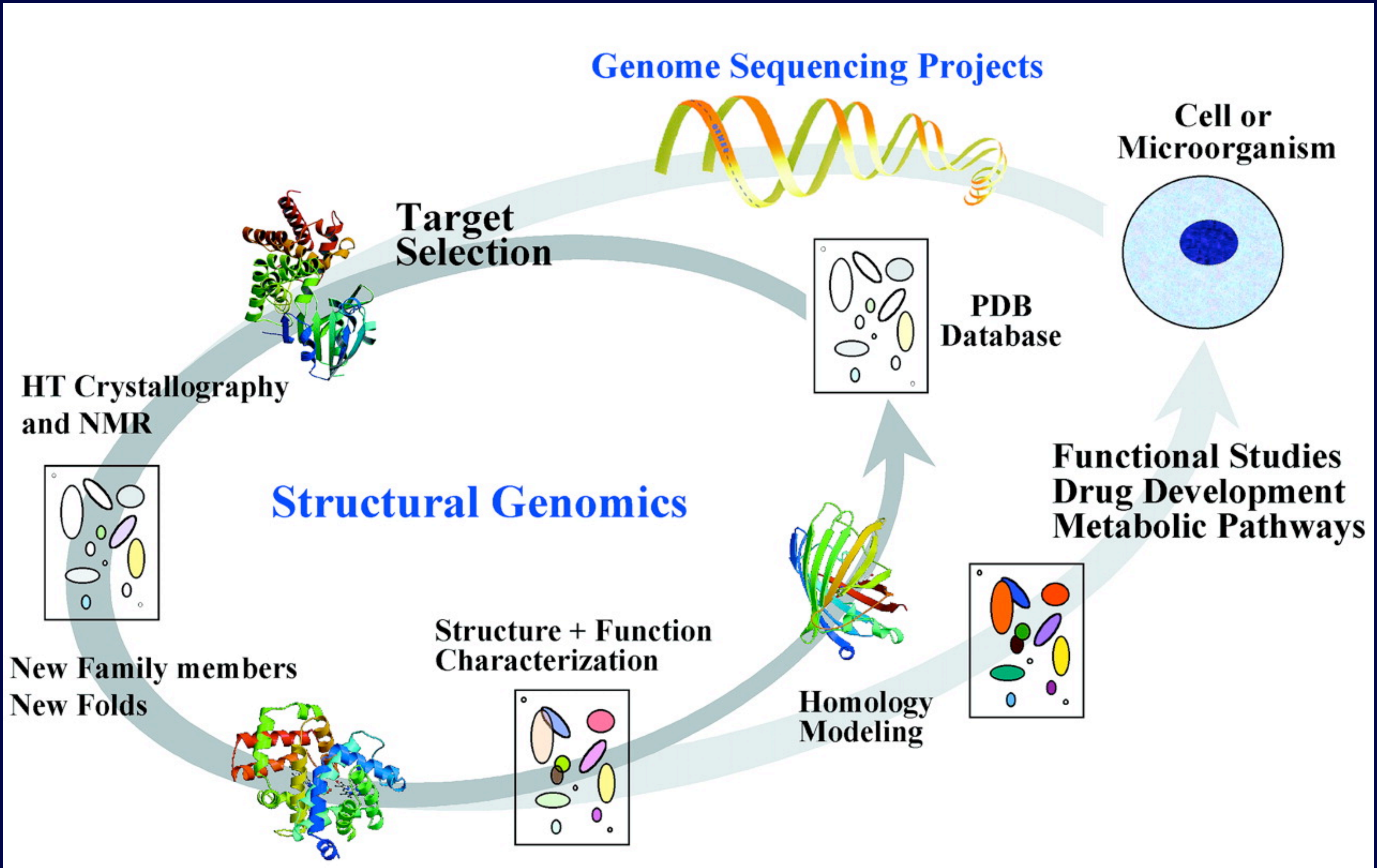
Structural Genomics Efforts



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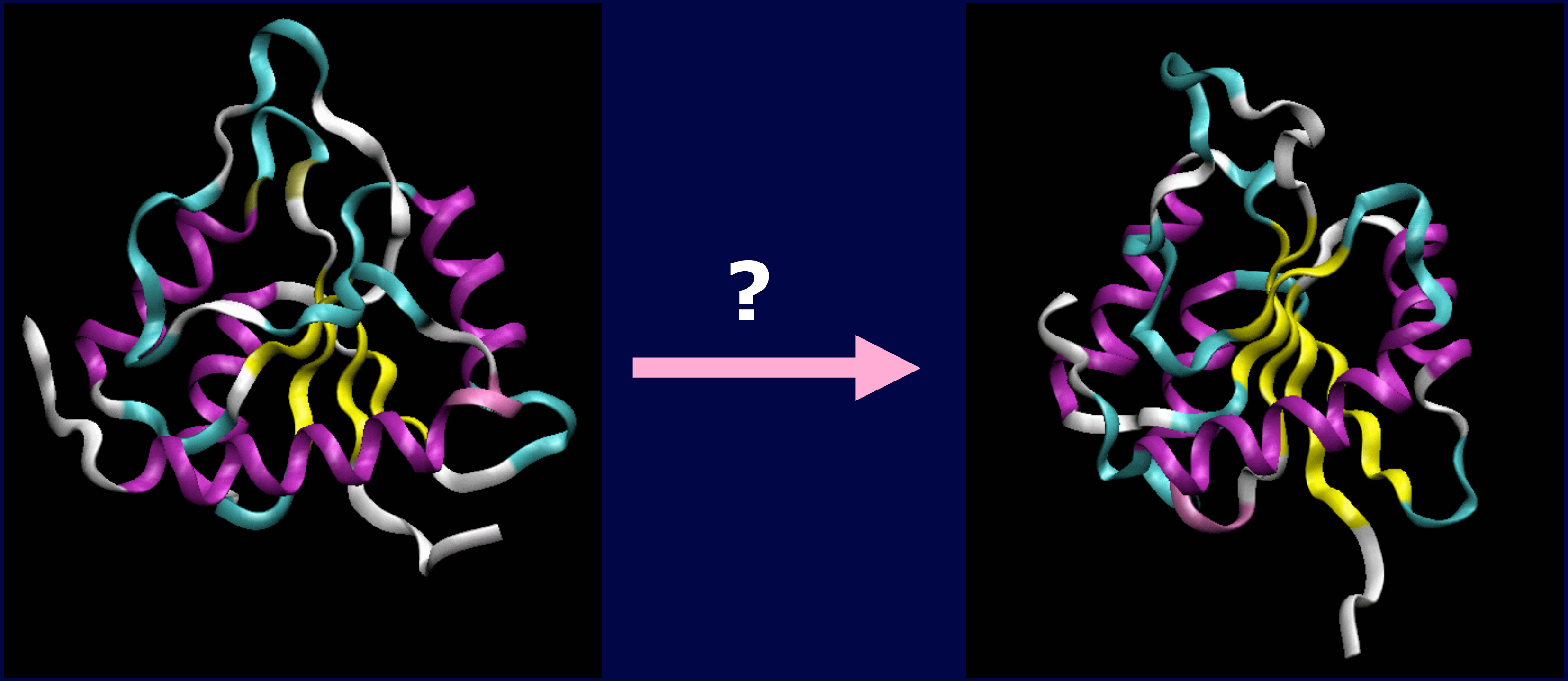
Structure Refinement



predicted

native (NMR)

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