Protein Structure Modeling for Structural Genomics

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Pels Family Center for Biochemistry and Structural Biology
The Rockefeller University

Summary

- ✓ Comparative Modeling
- ✓ Alignment problem
- ✓ Modeling genes
- ✓ Modeling genomes and structural genomics

Why protein structure prediction?

	Y 2002	Y 2005
Sequences	700,000	millions
Structures	17,000	50,000

Why protein structure prediction?

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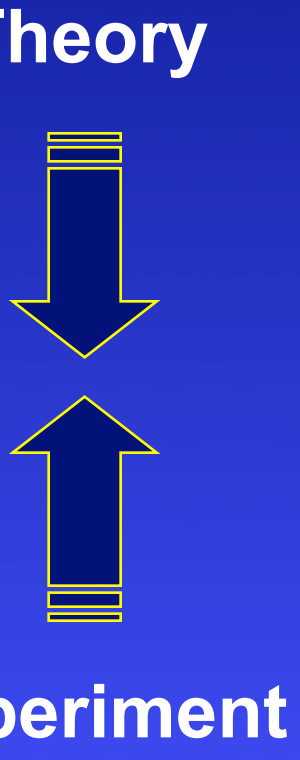

Why protein structure prediction?

	Y 2002
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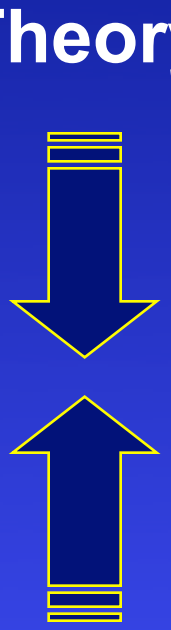
Structures	400,000



http://guitar.rockefeller.edu/modbase/

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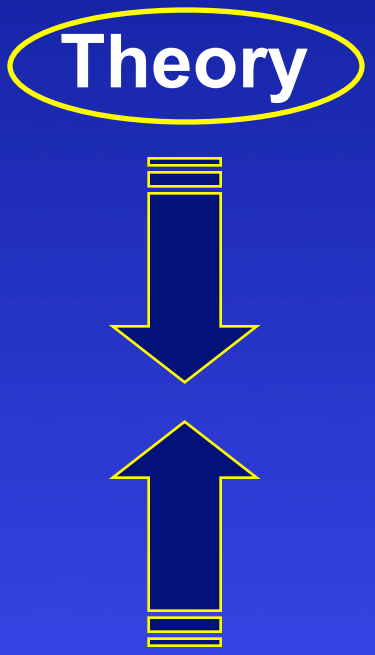
Structures	400,000



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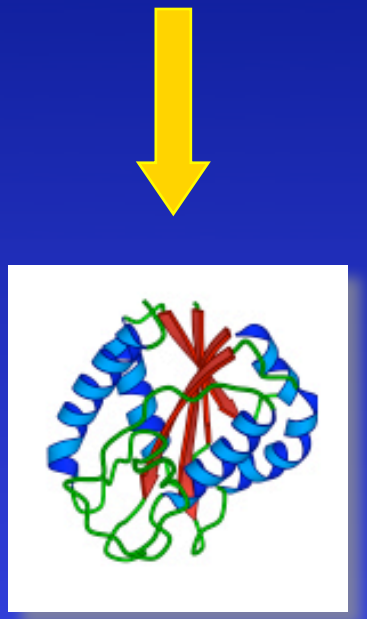
Principles of Protein Structure

Principles of Protein Structure

GFCHIKAYTRLIMVG…

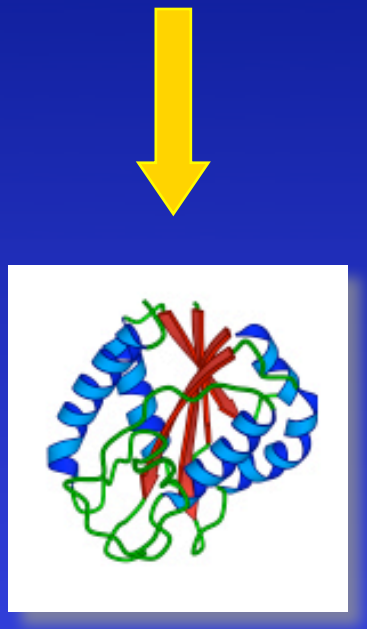


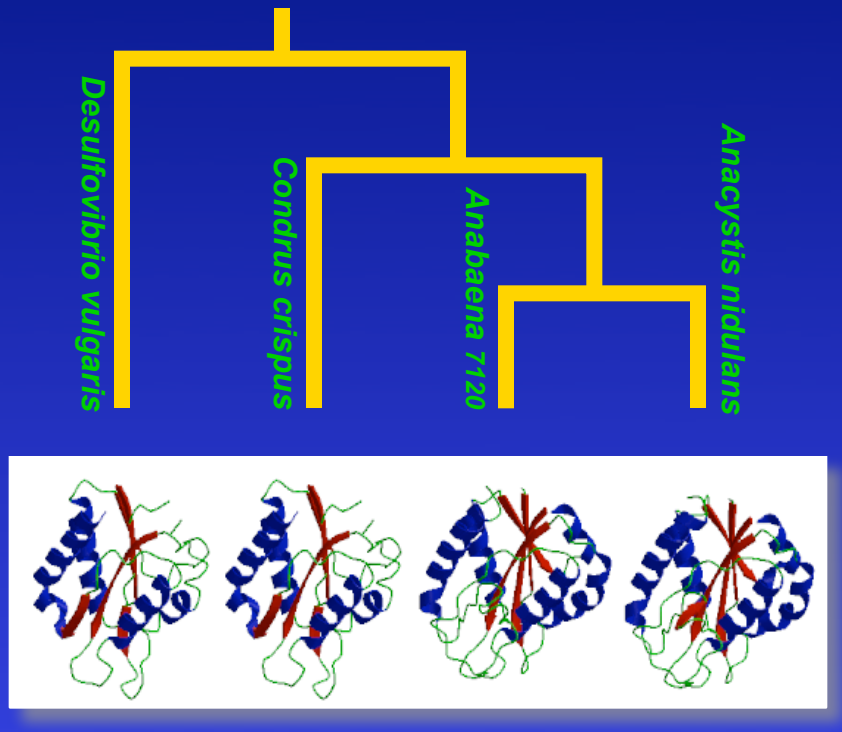
Folding

Ab initio prediction

Principles of Protein Structure

GFCHIKAYTRLIMVG…





Folding

Ab initio prediction

Evolution

Threading
Comparative Modeling

Steps in Comparative Protein Structure Modeling

START

TARGET

ASILPKRLFGNCEQTSDEGLK
IERTPLVPHISAQNVCLKIDD
VPERLIPERASFQWMNDK

A. Šali, *Curr. Opin. Biotech.* 6, 437, 1995.
R. Sánchez & A. Šali, *Curr. Opin. Str. Biol.* 7, 206, 1997.
M. A. Martí-Renom *et al. Ann. Rev. Biophys. Biomolec. Struct.*, 29, 291, 2000.

Steps in Comparative Protein Structure Modeling

START

Template Search

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ASILPKRLFGNCEQTSDEGLK
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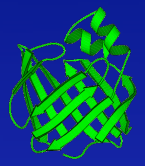
VPERLIPERASFQWMNDK

TEMPLATE



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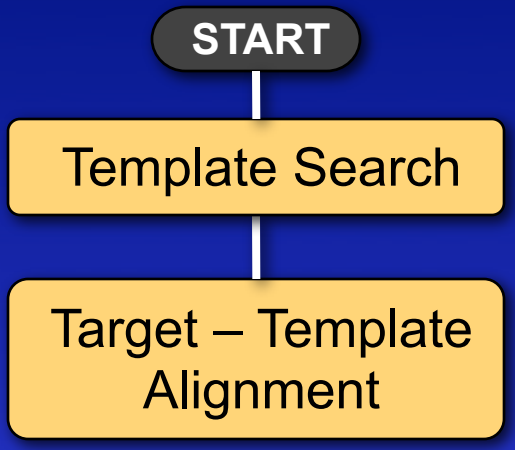

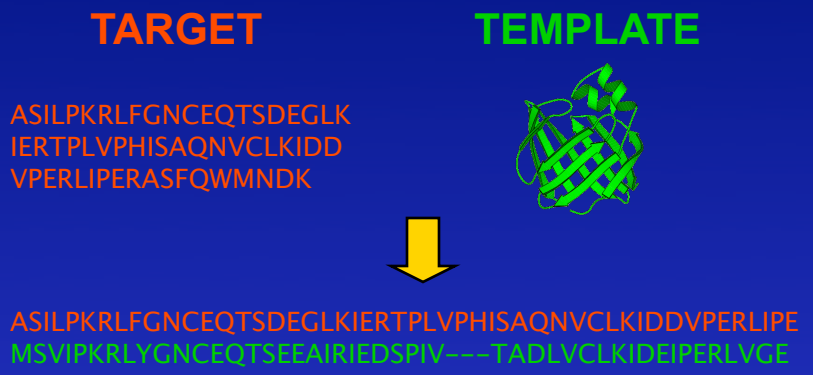

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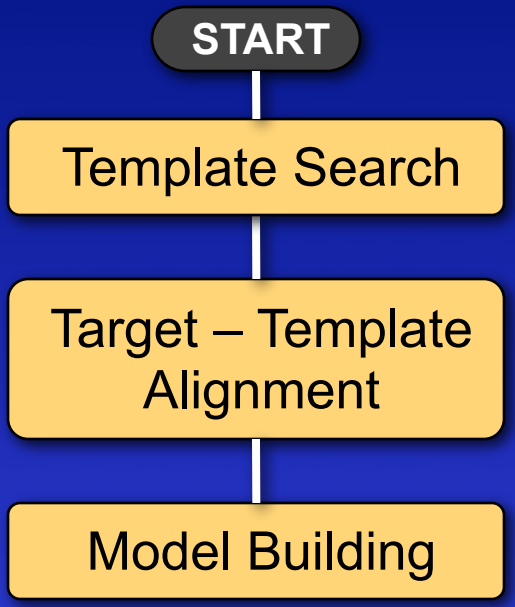

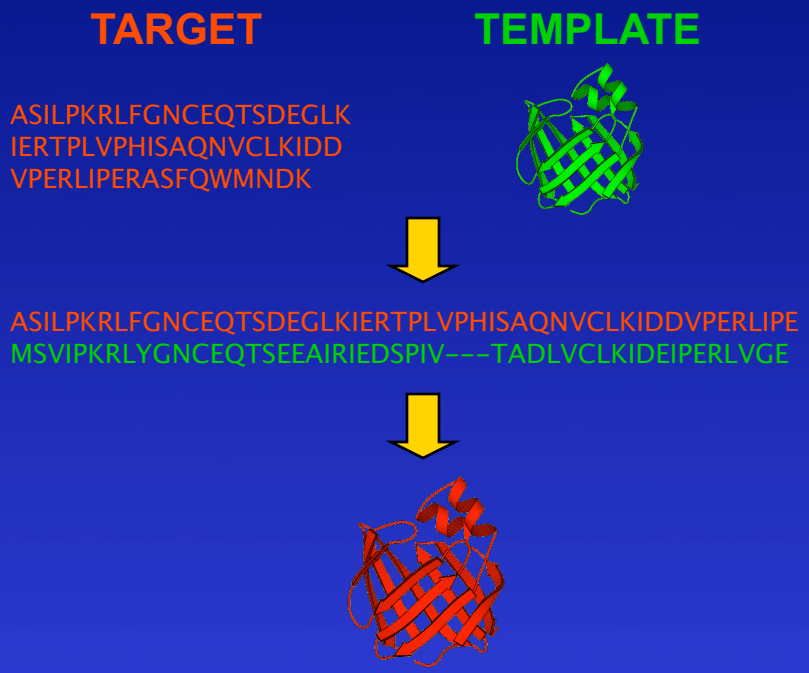

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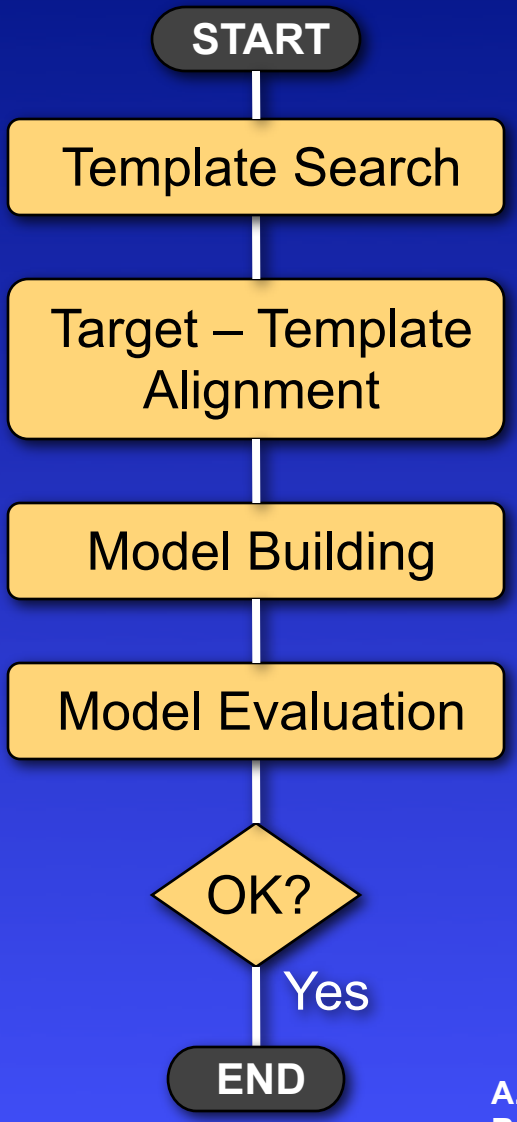

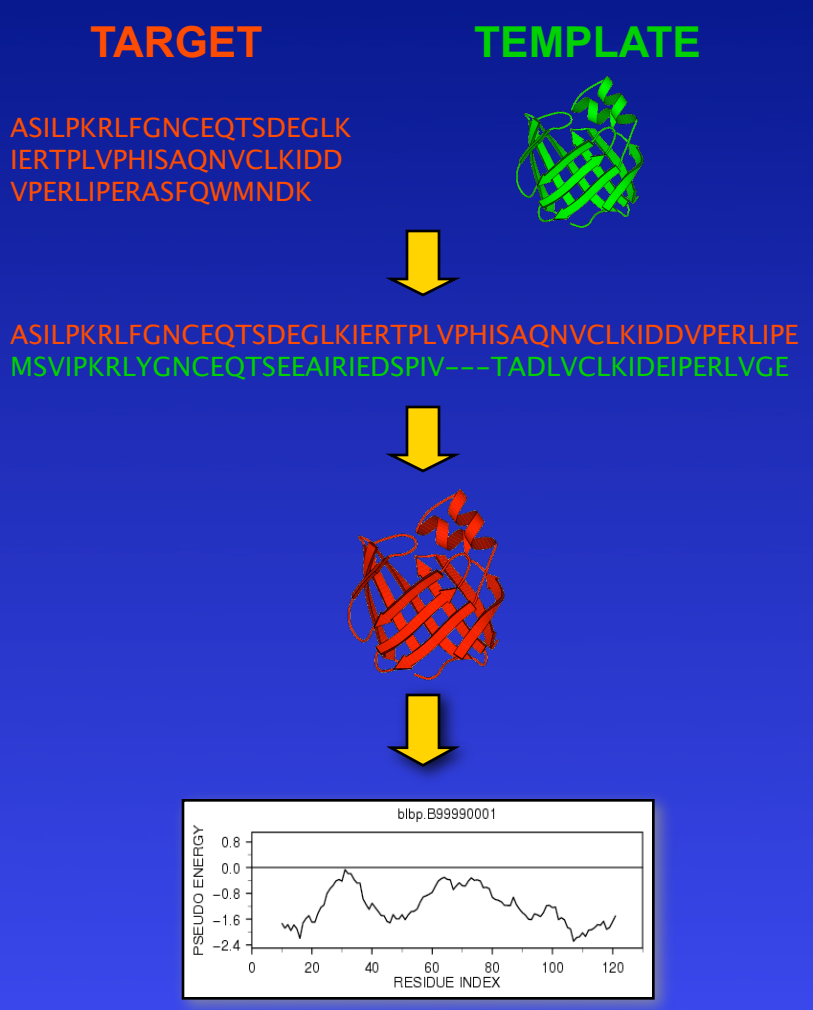

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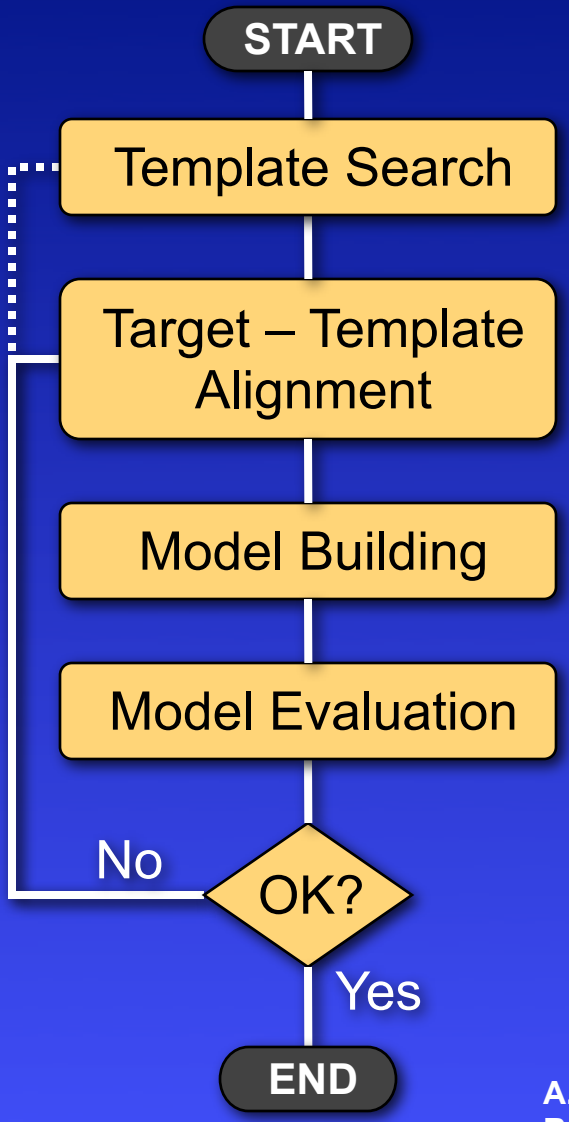

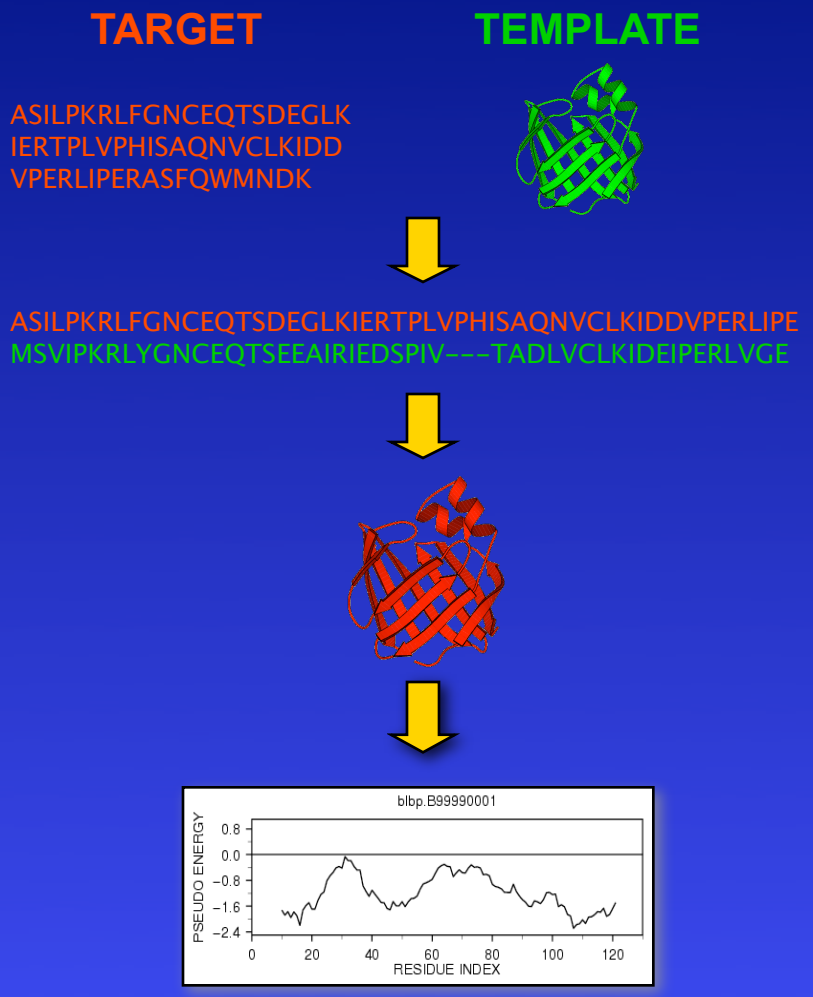

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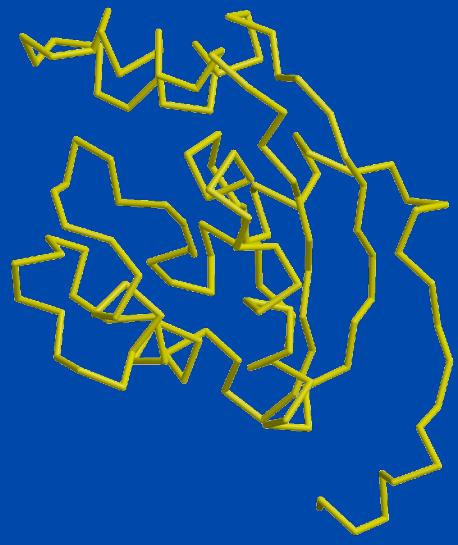
Model Accuracy

Marti-Renom *et al.* Annu.Rev.Biophys.Biomol.Struct. **29**, 291-325, 2000.

HIGH ACCURACY

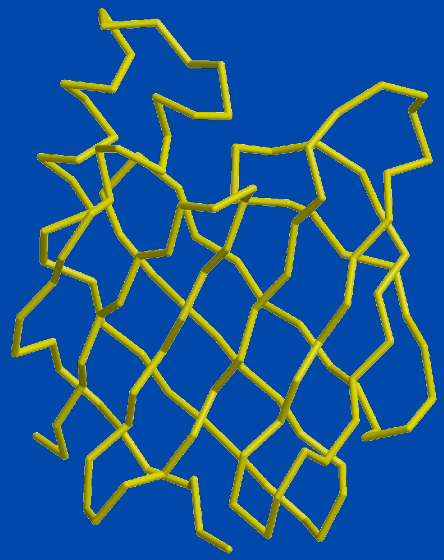
NM23
Seq id 77%



X-RAY

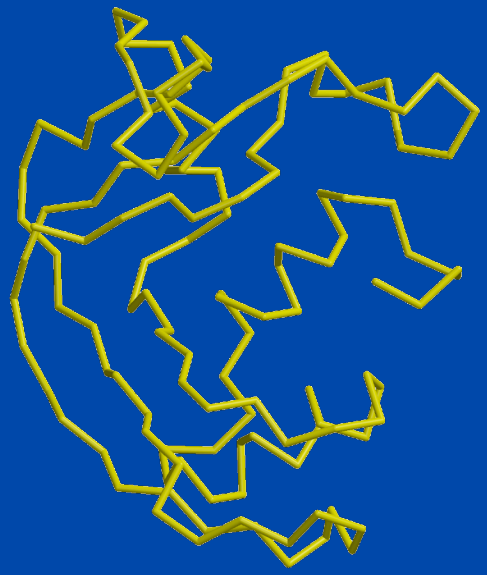
MEDIUM ACCURACY

CRABP
Seq id 41%



LOW ACCURACY

EDN
Seq id 33%



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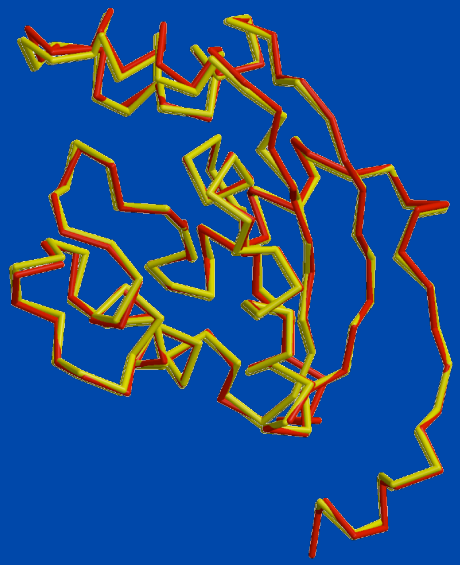
RMSD 0.41Å



Sidechains
Core backbone
Loops

X-RAY / MODEL

MEDIUM ACCURACY

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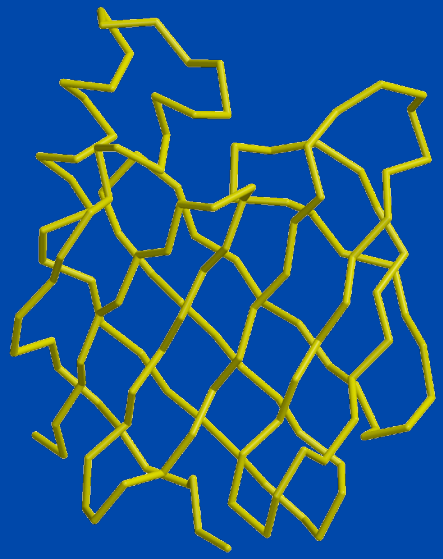

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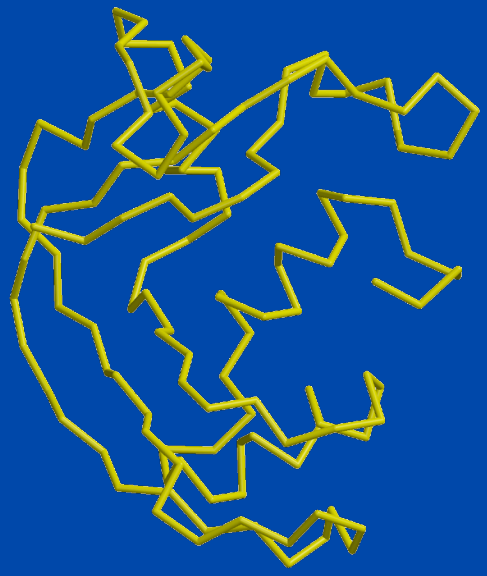

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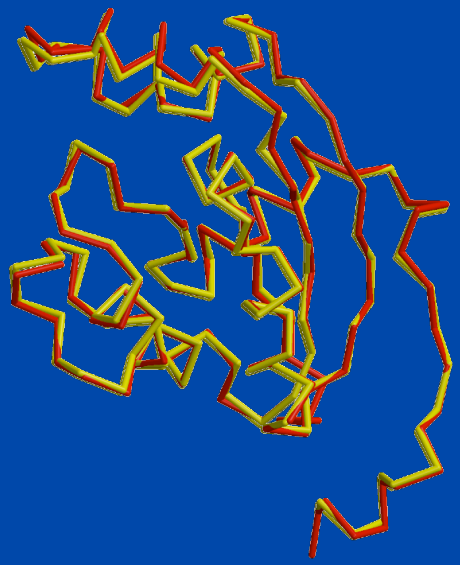

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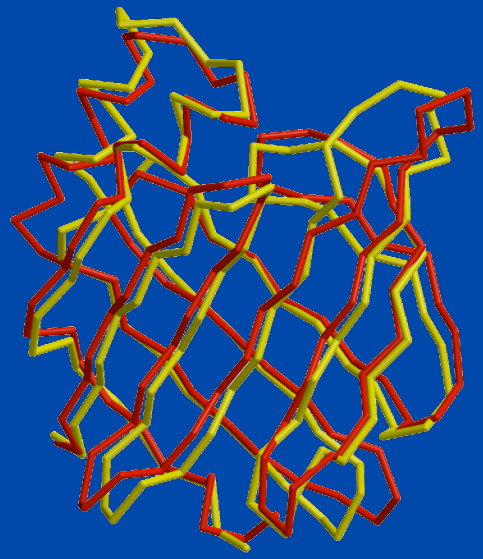
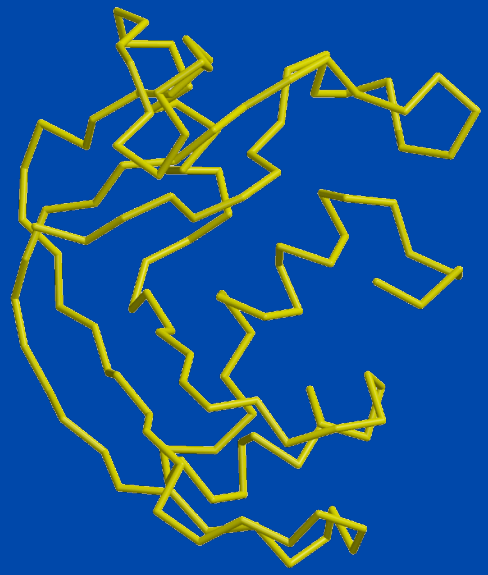


Sidechains
Core backbone
Loops
Alignment

LOW ACCURACY

EDN
Seq id 33%



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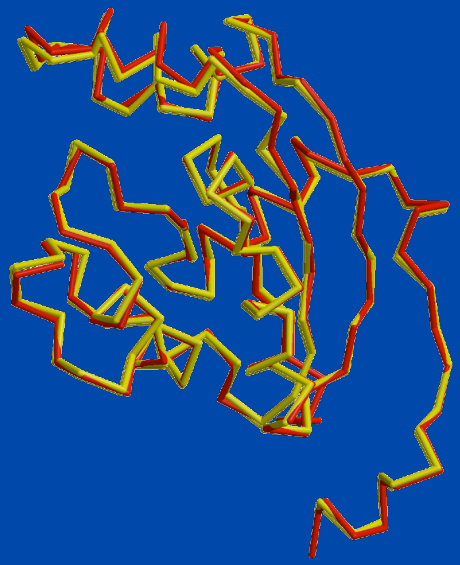

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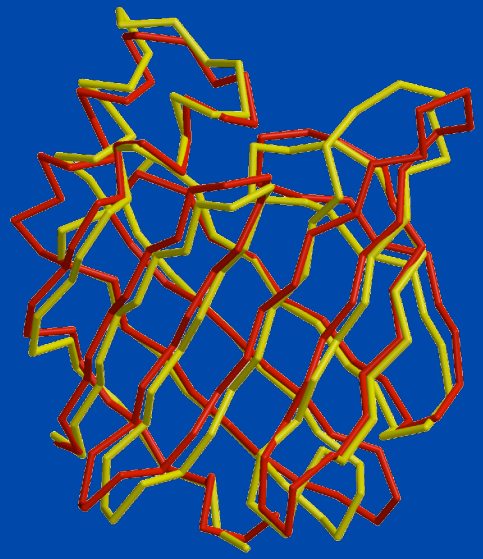
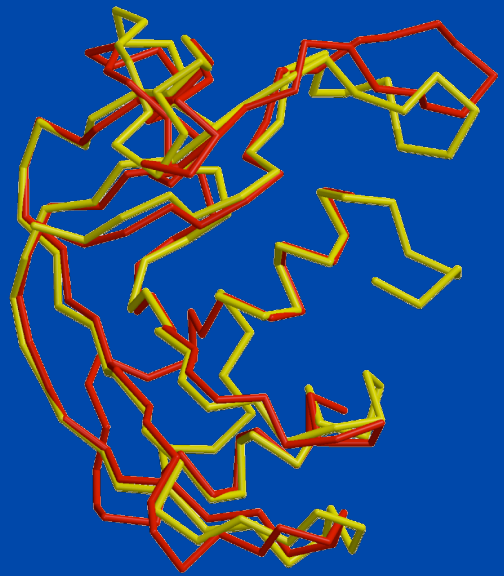


Sidechains
Core backbone
Loops
Alignment

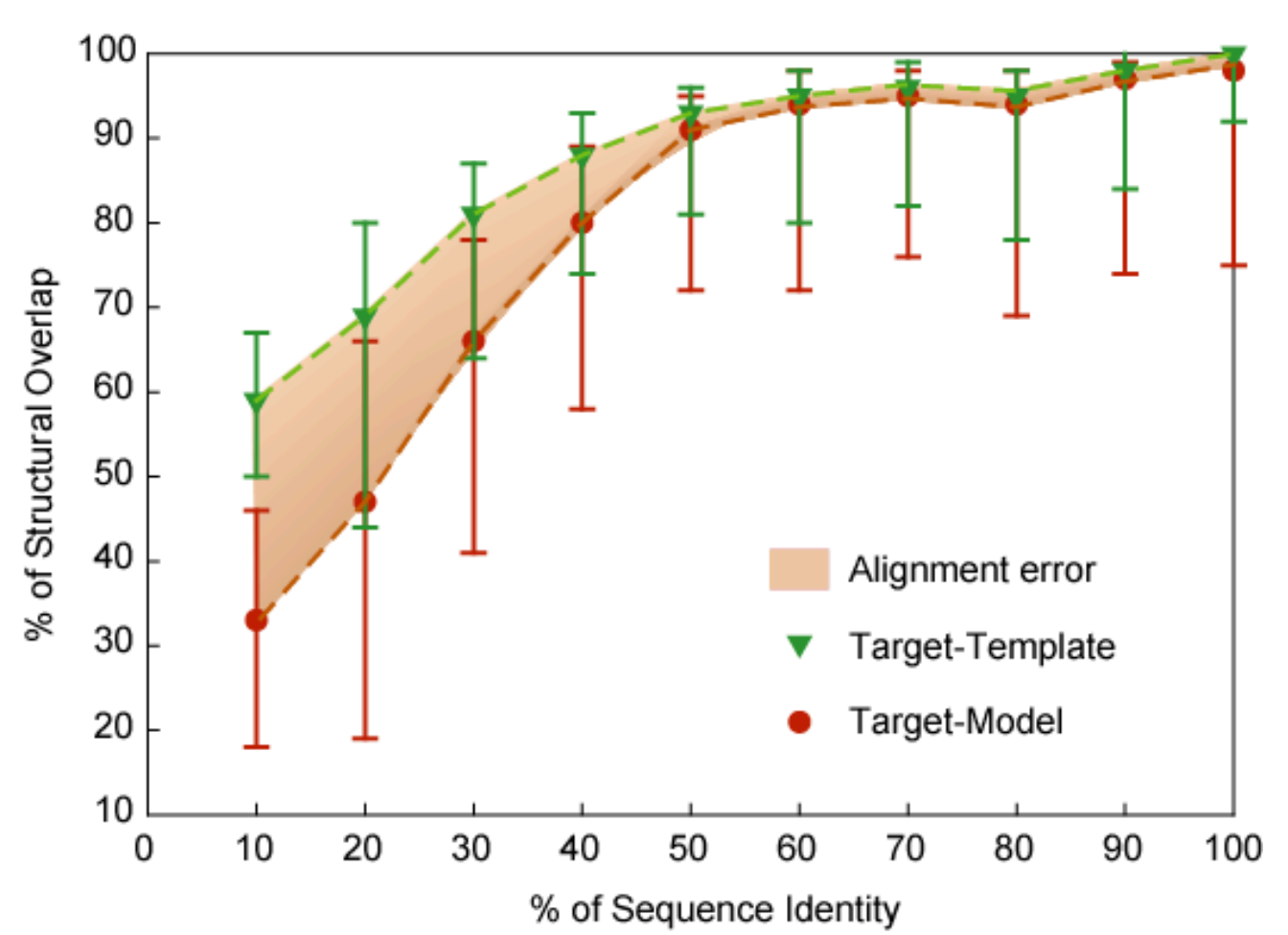
LOW ACCURACY

EDN
Seq id 33%
Cα equiv 90/134
RMSD 1.17Å



Sidechains
Core backbone
Loops
Alignment
Fold assignment

Model Accuracy as a Function of Target-Template Sequence Identity



Alignment problem: Methods

Sequence A: AGHLAHTRCELKLPTCRGNMSSRFC

Sequence B: AGHLRHTRRCLRLPTAGNARFC

Seq.-Seq.

ALIGN: DP pairwise method

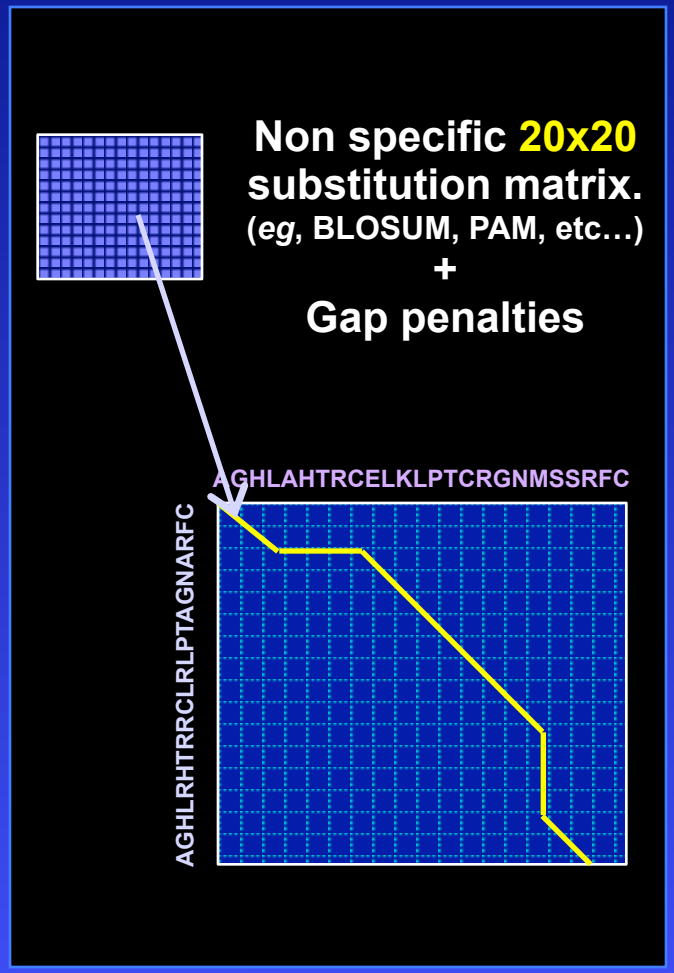
BLAST2SEQ: Local method

Prof.-Seq.

PSI-BLAST: Local search method that uses multiple sequence information for one of the sequences.

Prof.-Prof.

ALIGN4D: DP pairwise method that uses multiple sequence information for both sequences.



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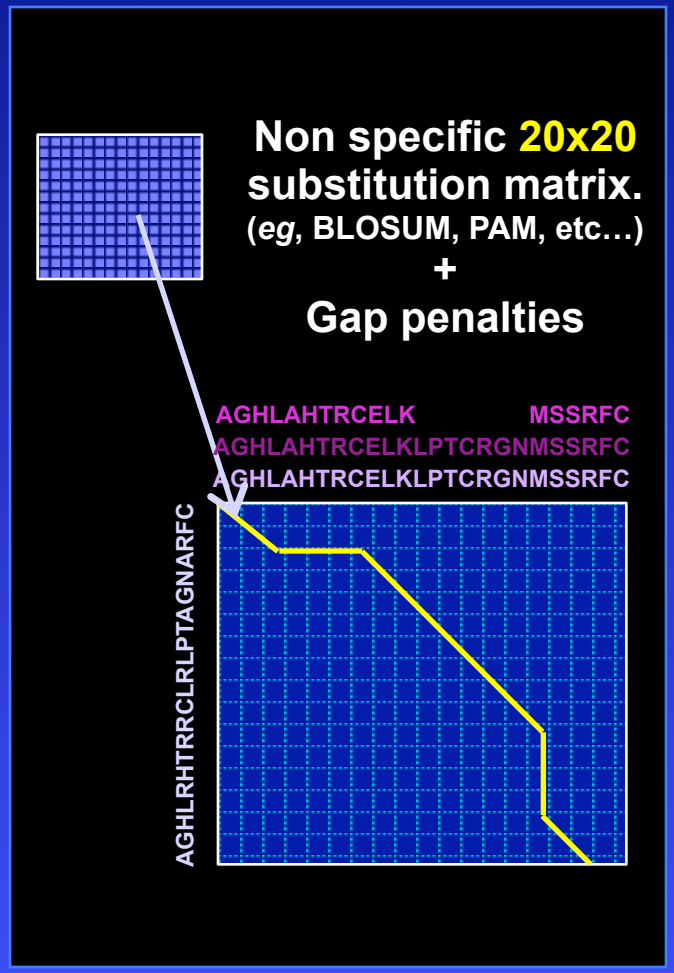

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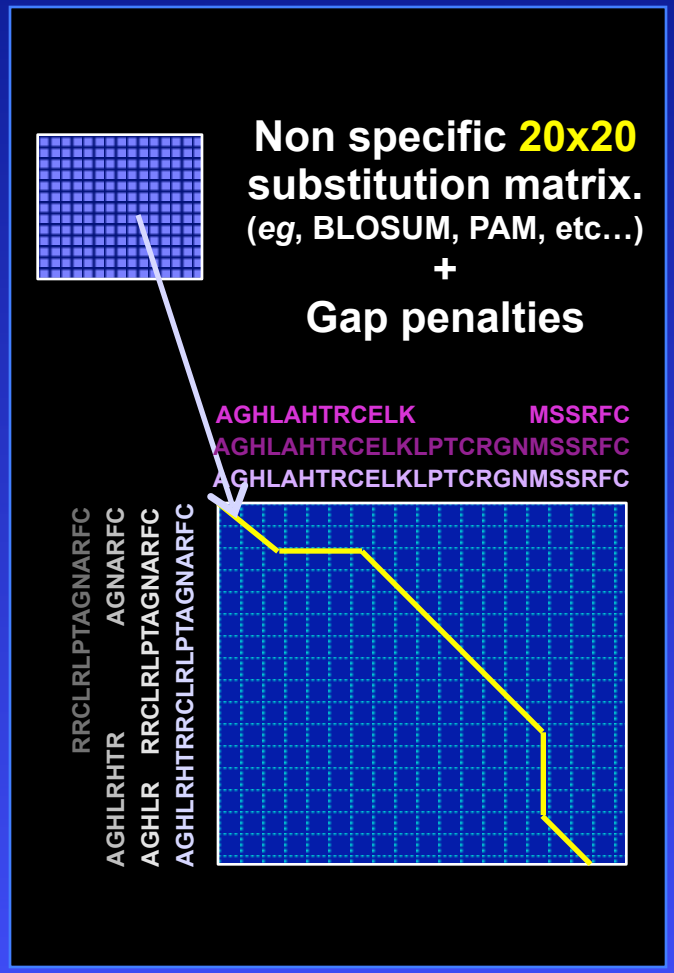


Alignment problem

Results: Comparison of alignment dependent measures

Method	% of Correct SeqA	% of Correct SeqB	Shift Score
ALIGN	41.55	41.84	0.44
BLAST2Seq	26.09	26.07	0.32
PB (e-val)	42.95	43.11	0.48
ALIGN4D	55.34	55.49	0.61

Alignment problem

Results: Comparison of success rates

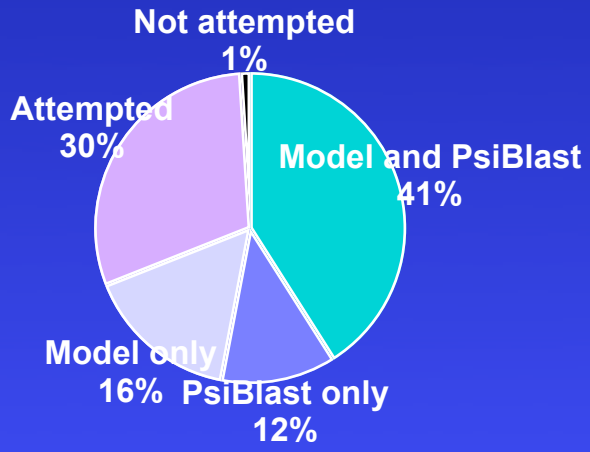
Method	% of alignments at 1Å	% of alignments at 2Å	% of alignments at 3Å	% of alignments at average
CE	20.50	82.50	100.00	82.50
ALIGN	8.50	23.00	35.00	21.00
BLAST2SEQ	8.00	21.50	30.00	20.00
PB (e-val)	8.00	31.00	45.50	29.50
ALIGN4D	11.50	37.00	55.50	35.50

Alignment problem

Results. Turn over.

Mycoplasma genitalium MODPIPE Models

Number of ORFs	479
Average ORF length	364



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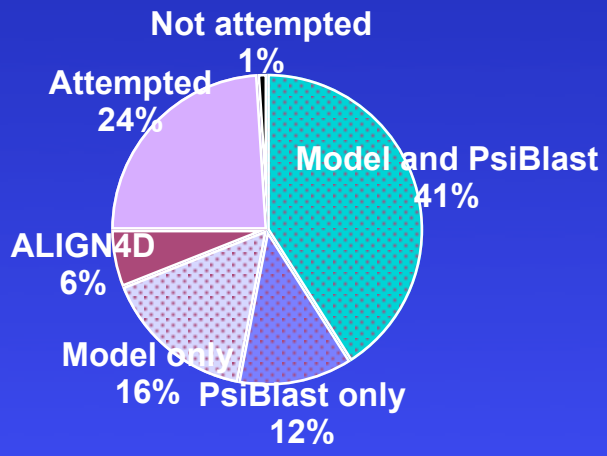

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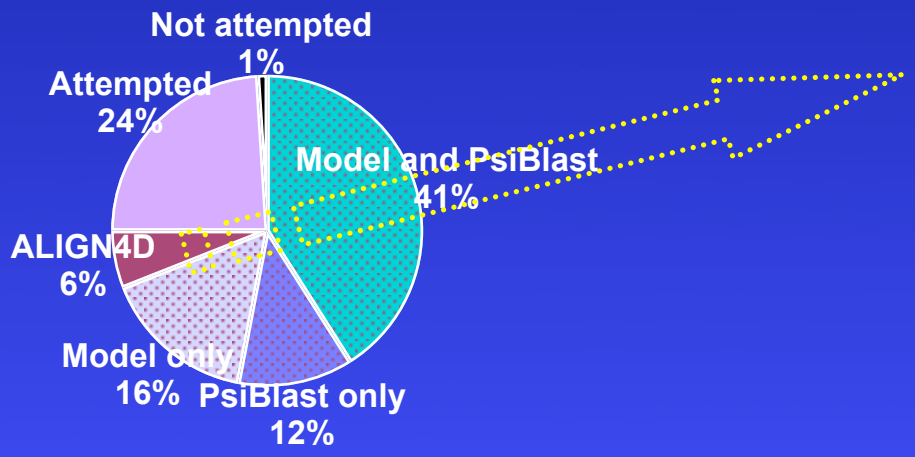
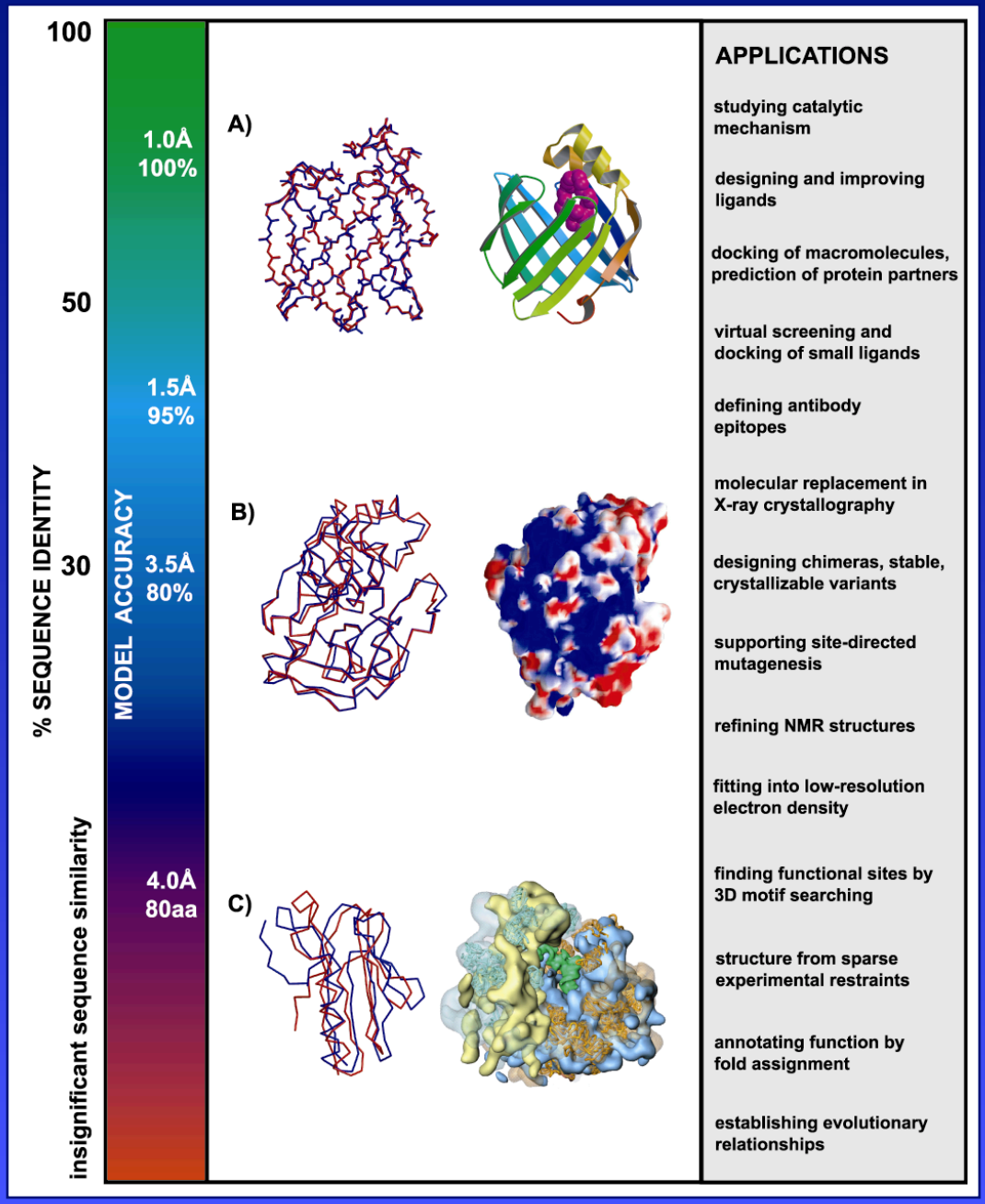


~ 30 extra accurate models for *M. g.* genome.

~ 40,000 models for TrEMBL-SP "genome".

Applications of Comparative Models



D. Baker & A. Sali.
Science **294,** 93, 2001.

A. Šali & J. Kuriyan.
TIBS **22**, M20, 1999.

Do mast cell proteases bind proteoglycans? Where? When?

Predicting features of a model that are not present in the template

1. mMCPs bind negatively charged proteoglycans through electrostatic interactions?
2. Comparative models used to find clusters of positively charged surface residues.
3. Tested by site-directed mutagenesis.

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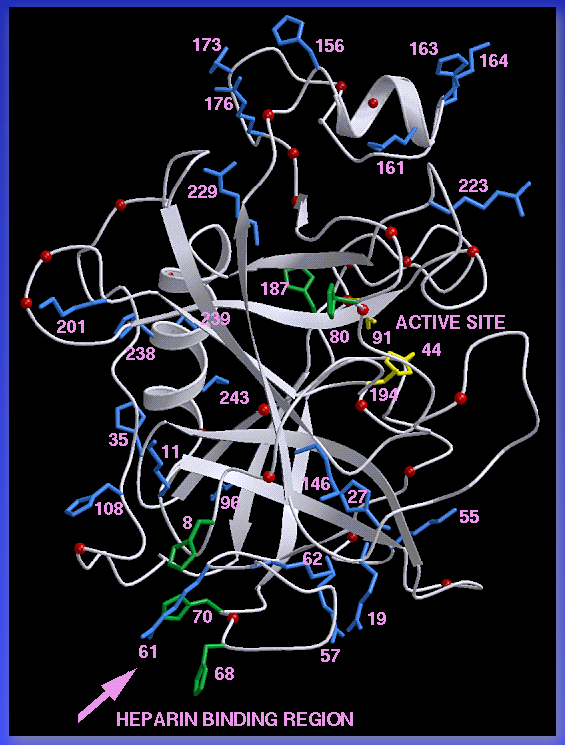

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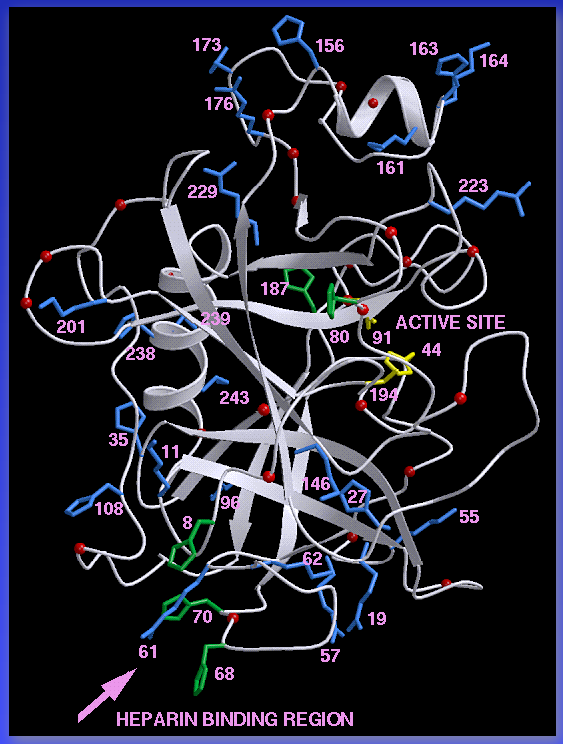
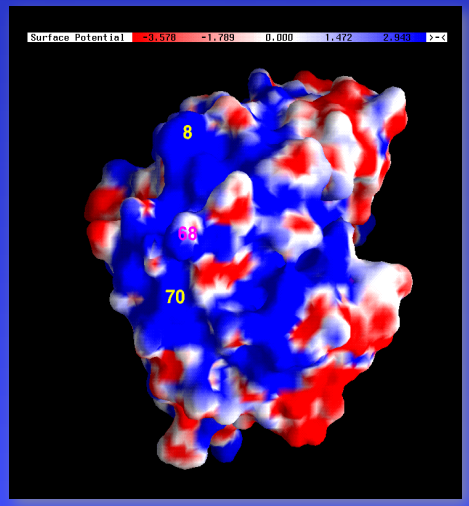
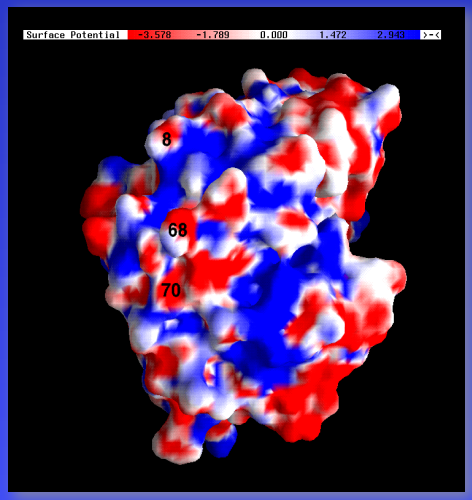




Native mMCP-7 at *p*H=5 (His^{+})



Native mMCP-7 at *p*H=7 (His^{0})

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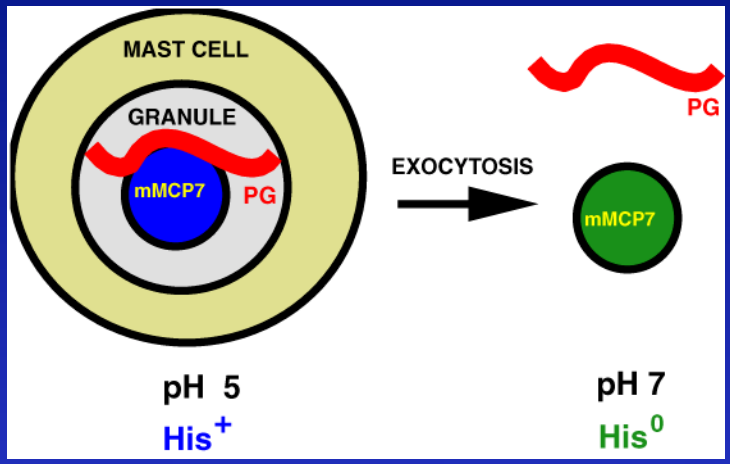
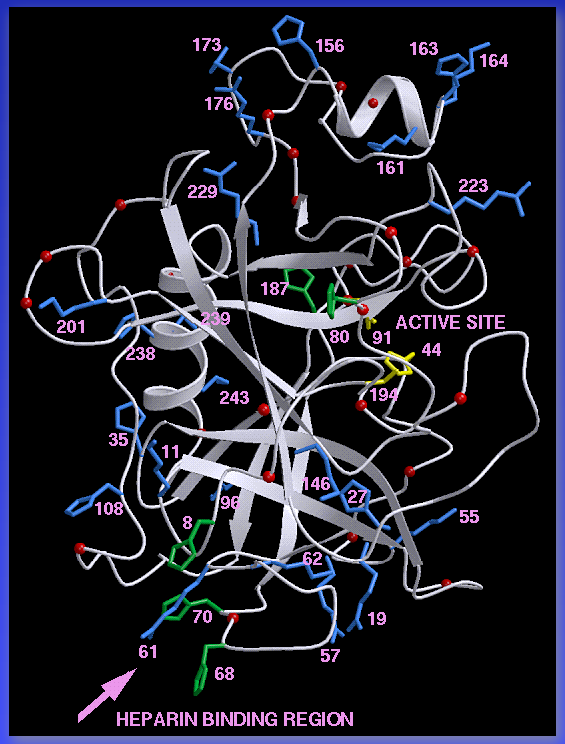
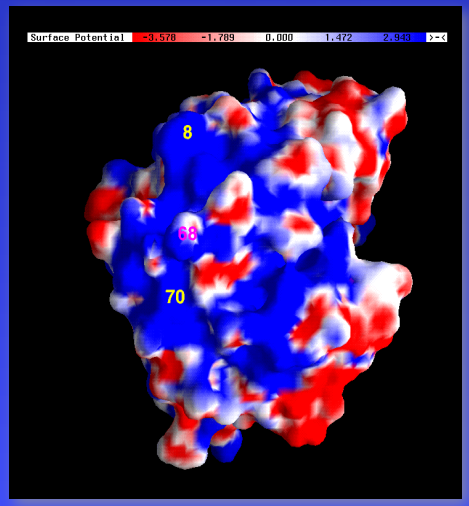
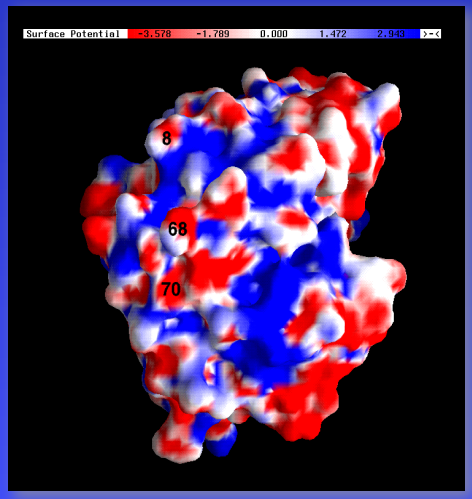


Huang *et al*. *J. Clin. Immunol*. **18**,169,1998.
Matsumoto *et al*. *J.Biol.Chem*. **270**,19524,1995.
Šali *et al*. *J. Biol. Chem*. **268**, 9023, 1993.





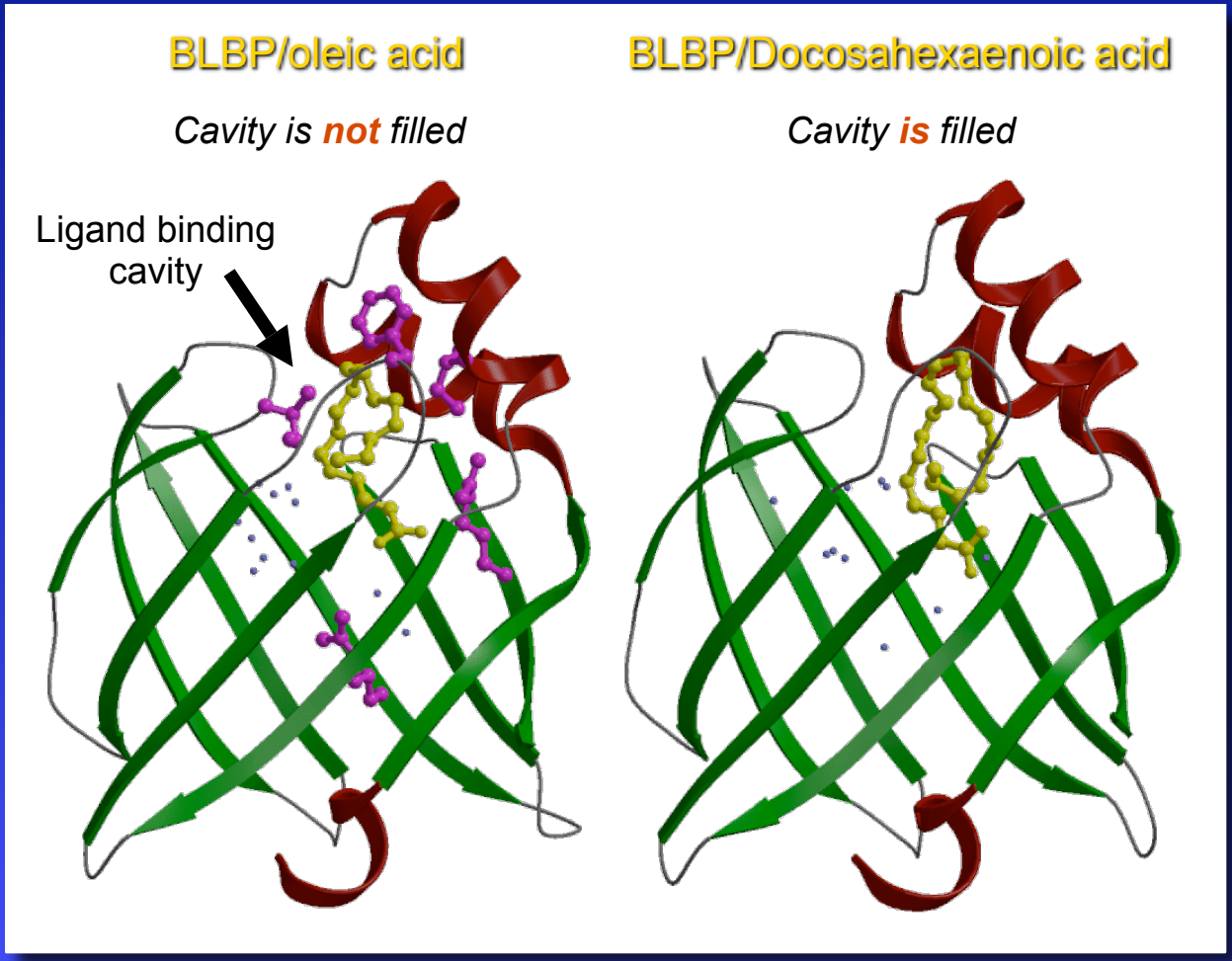
Native mMCP-7 at *p*H=5 (His^{+})



Native mMCP-7 at *p*H=7 (His^{0})

What is the physiological ligand of Brain Lipid-Binding Protein?

Predicting features of a model that are not present in the template



1. BLBP binds fatty acids.
2. Build a 3D model.
3. Find the fatty acid that fits most snuggly into the ligand binding cavity.

L. Xu, R. Sánchez, A. Šali, N. Heintz, *J. Biol. Chem.* **271**, 24711, 1996.

Structural Genomics

Sali. *Nat. Struct. Biol*. **5**, 1029, 1998.
Sali *et al. Nat. Struct. Biol*., **7**, 986, 2000.
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Characterize most protein sequences based on related known structures.

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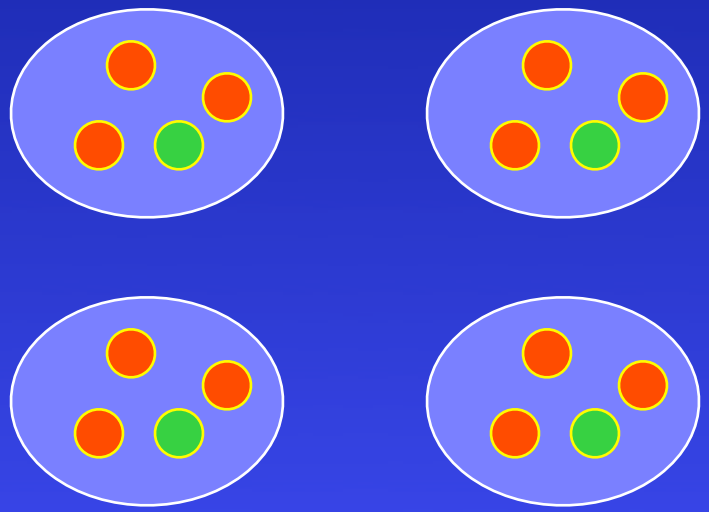

The number of “families” is much smaller than the number of proteins.

Any one of the members of a family is fine.

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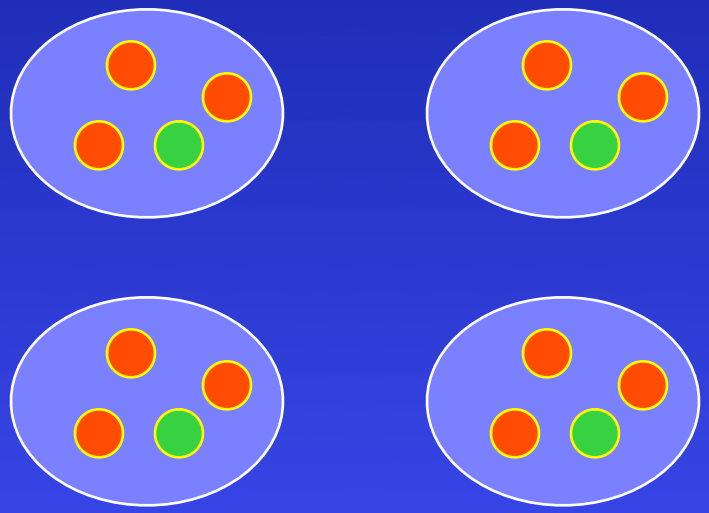

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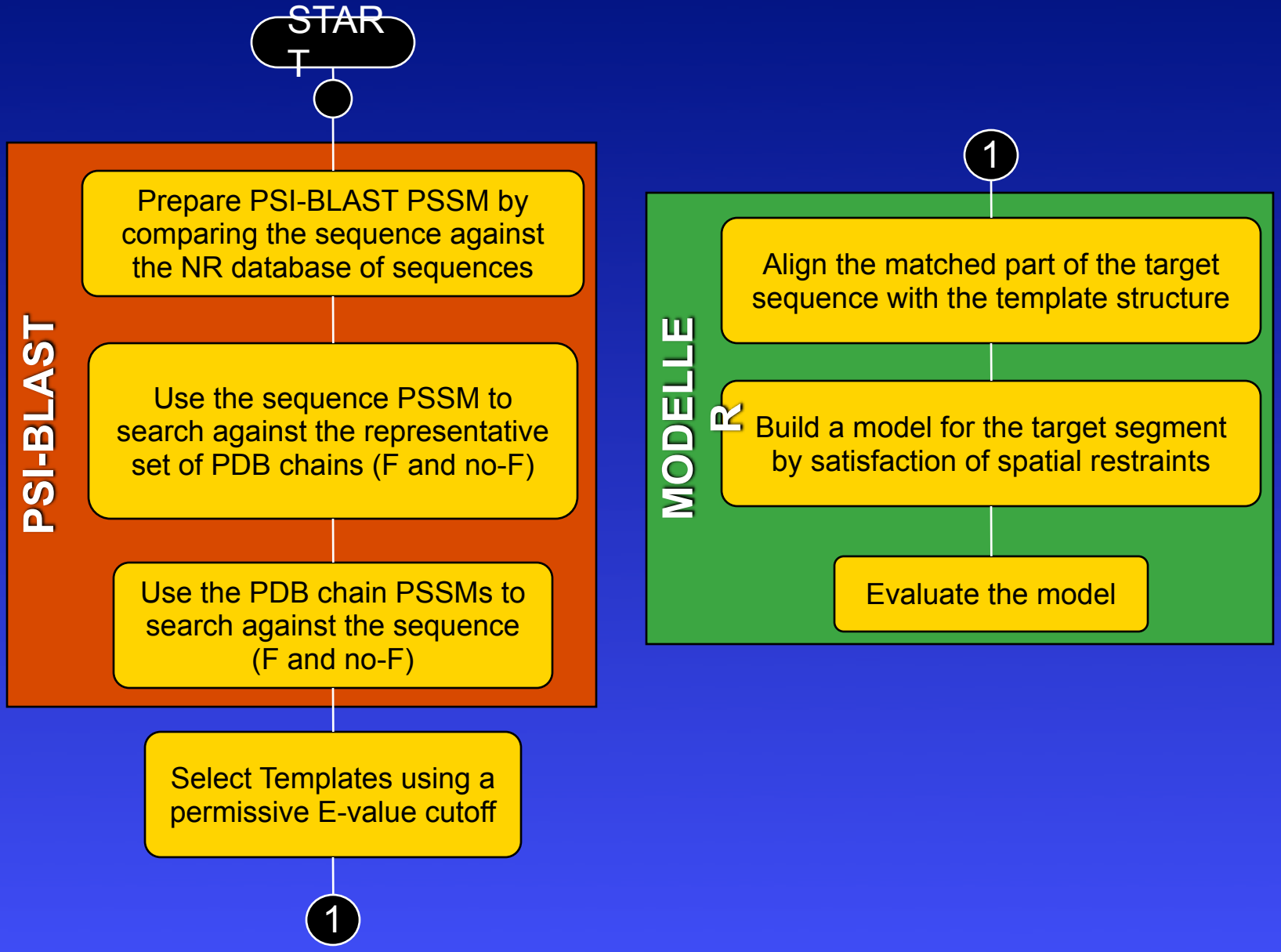
There are ~16,000 30% seq id families
(Vitkup *et al. Nat. Struct. Biol.* **8**, 559, 2001)

MODPIPE: Large-Scale Comparative Protein Structure Modeling



R. Sánchez & A. Šali, *Proc. Natl. Acad. Sci. USA* **95**, 13597, 1998
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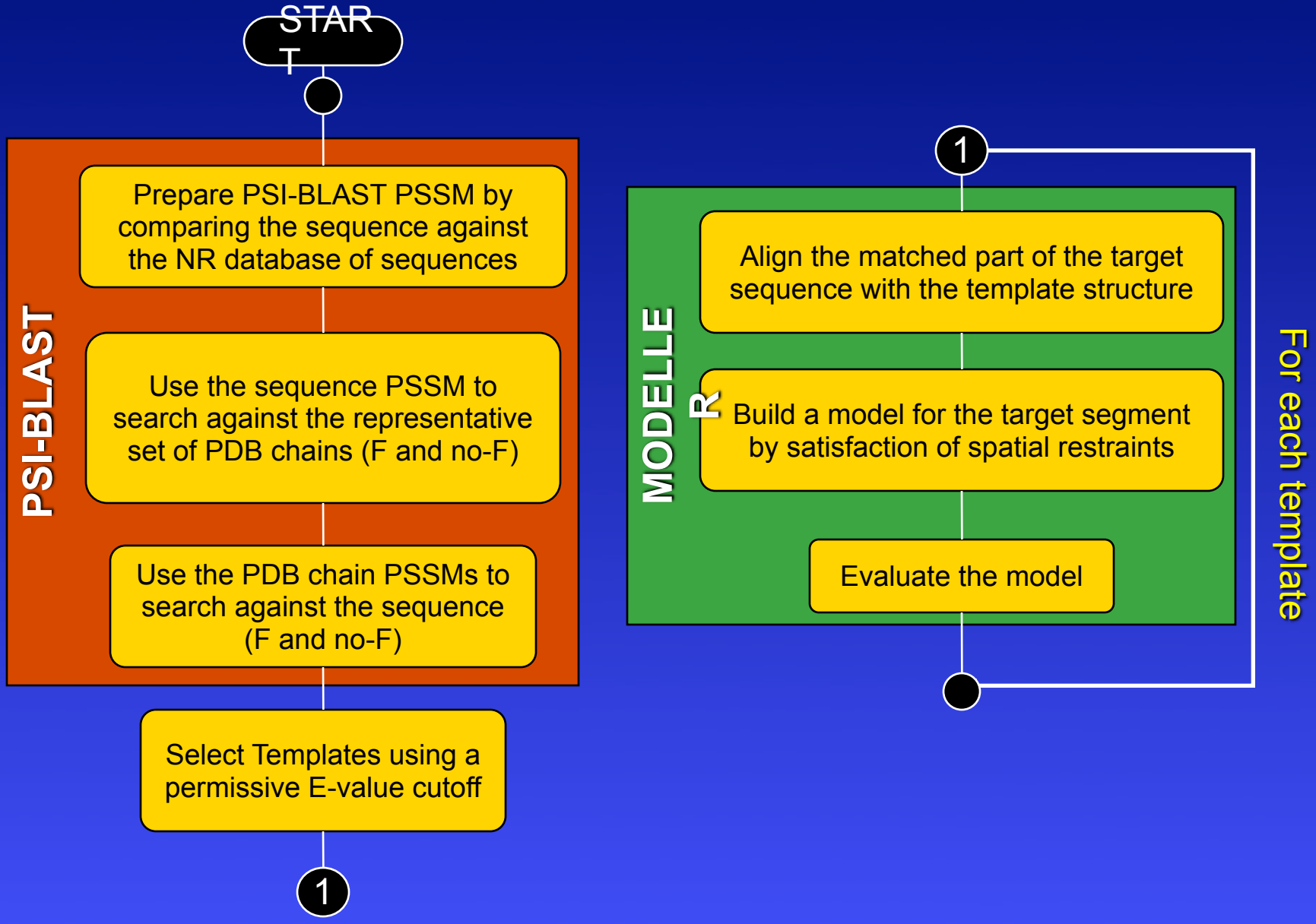

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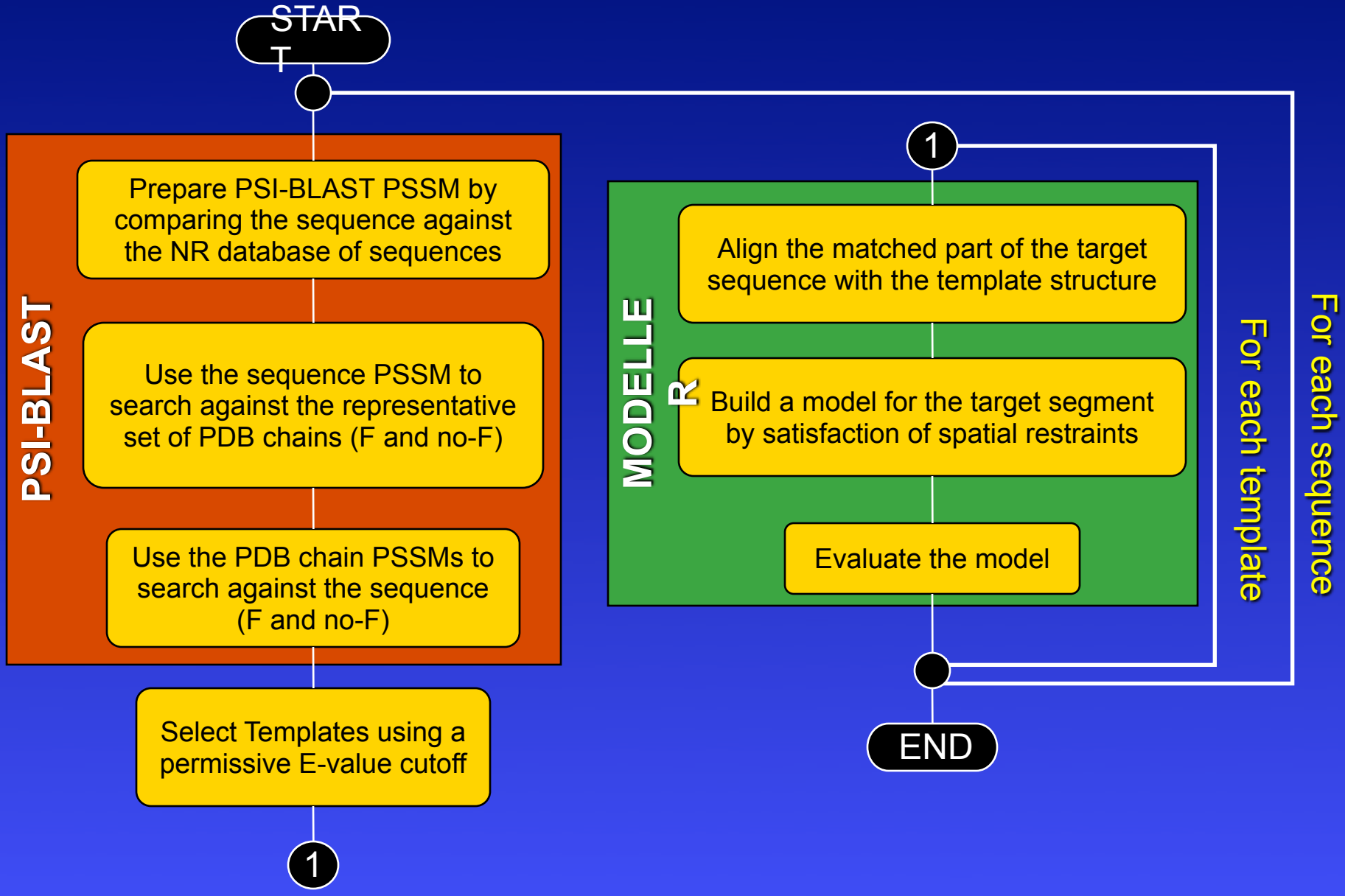

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Sequences with fold assignments or models: 415,937 (57%)

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70% of models based on <30% sequence identity to template.

On average, only a domain per protein is modeled
(an “average” protein has 2.5 domains of 175 aa).

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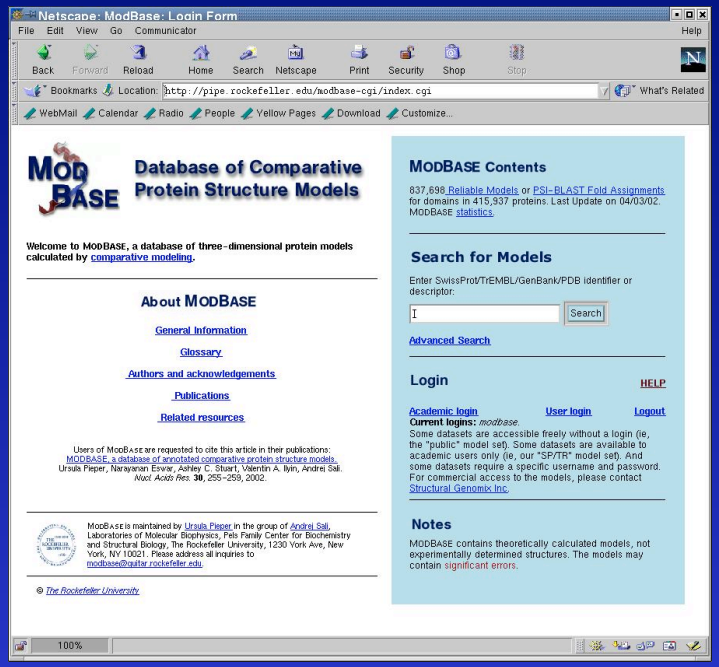
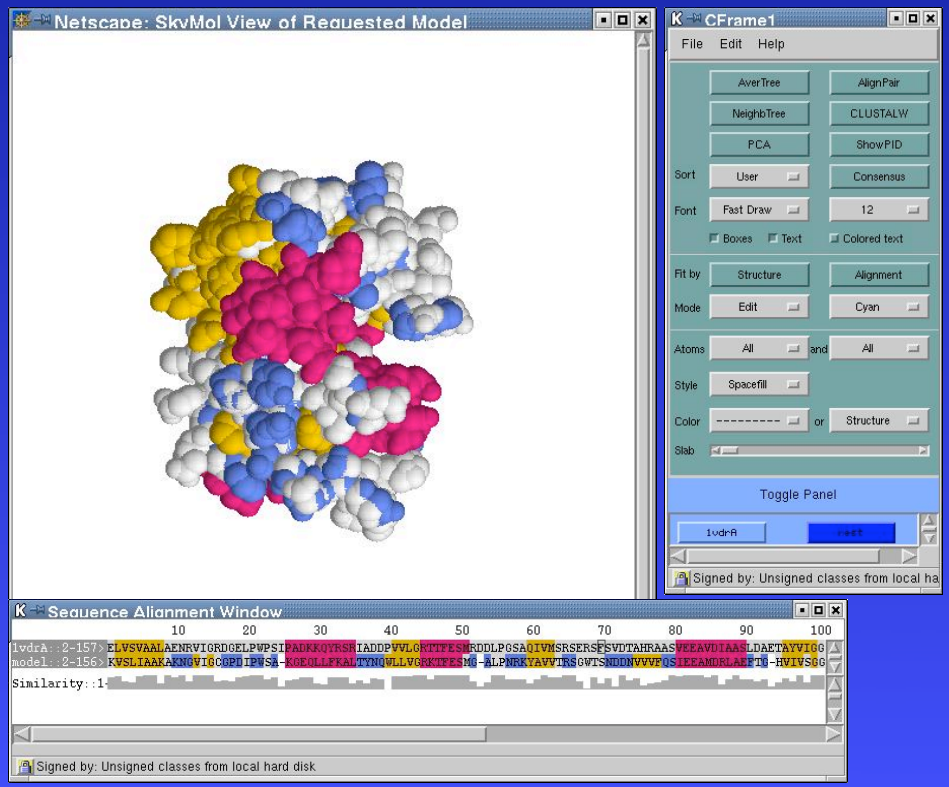


http://guitar.rockefeller.edu/modbase

Pieper *et al.*, Nucl. Acids Res. 2002.



http://guitar.rockefeller.edu/modview

Ilyin *et al.*, 2002 *(in press)*.

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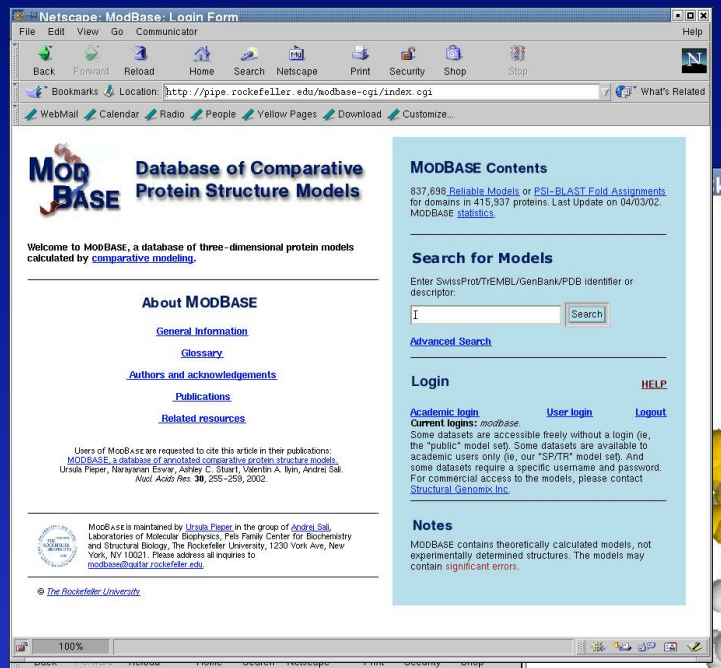

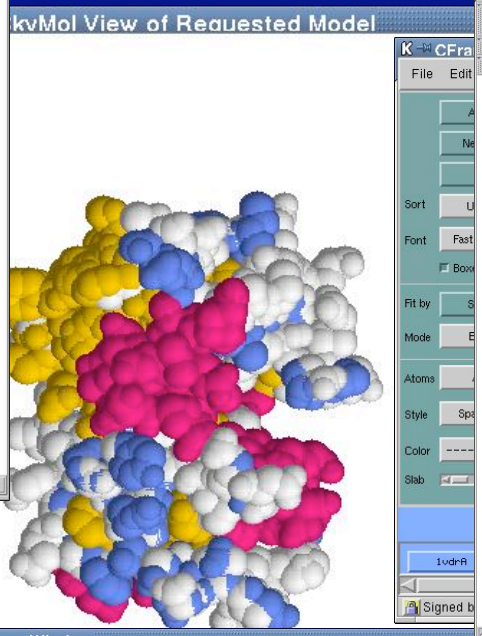

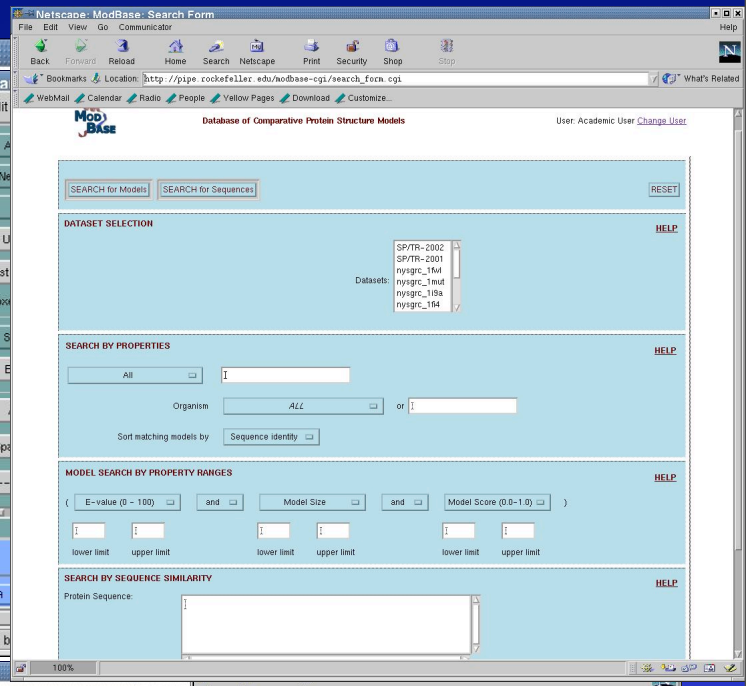

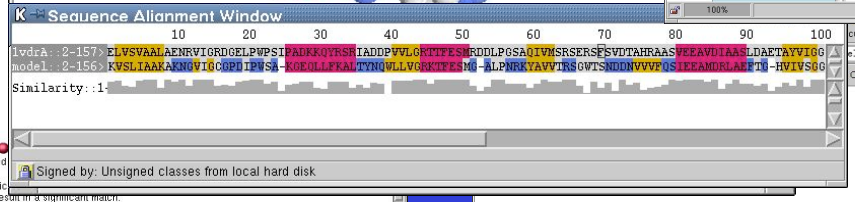

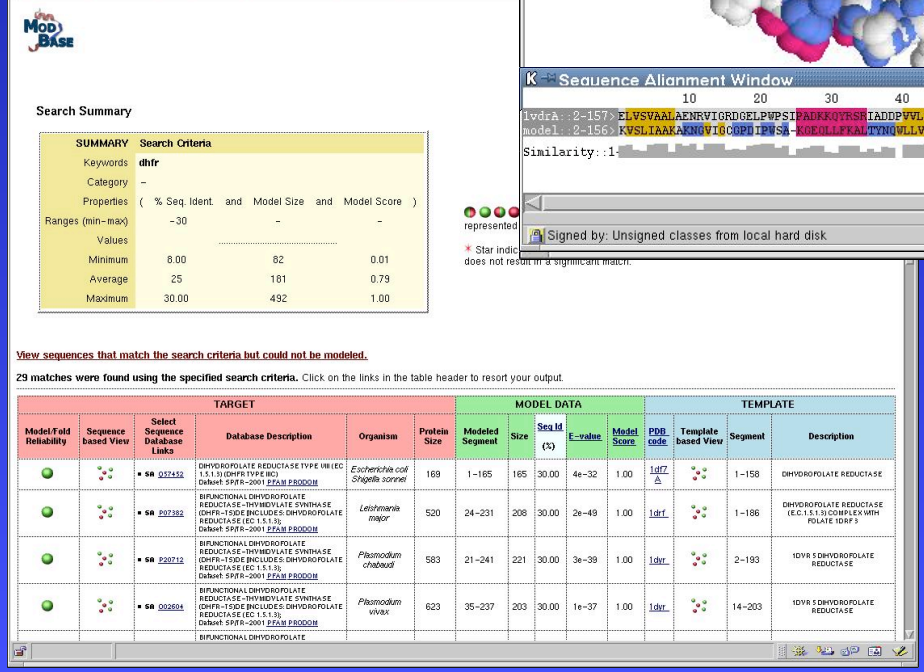

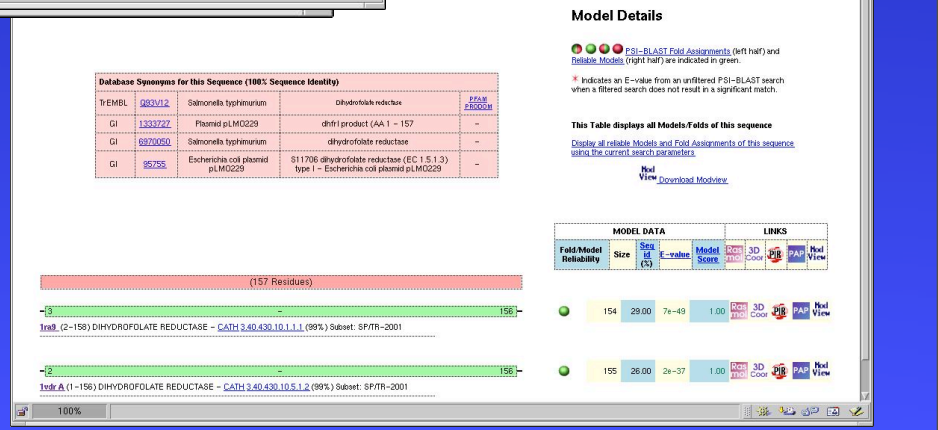

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- ✓ We will be able to calculate useful models for most globular domains in approximately 5 years, because of **structural genomics**.

Acknowledgments

Burroughs Wellcome Fund
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Ursula Pieper
Andrea Rossi
Ash Stuart

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