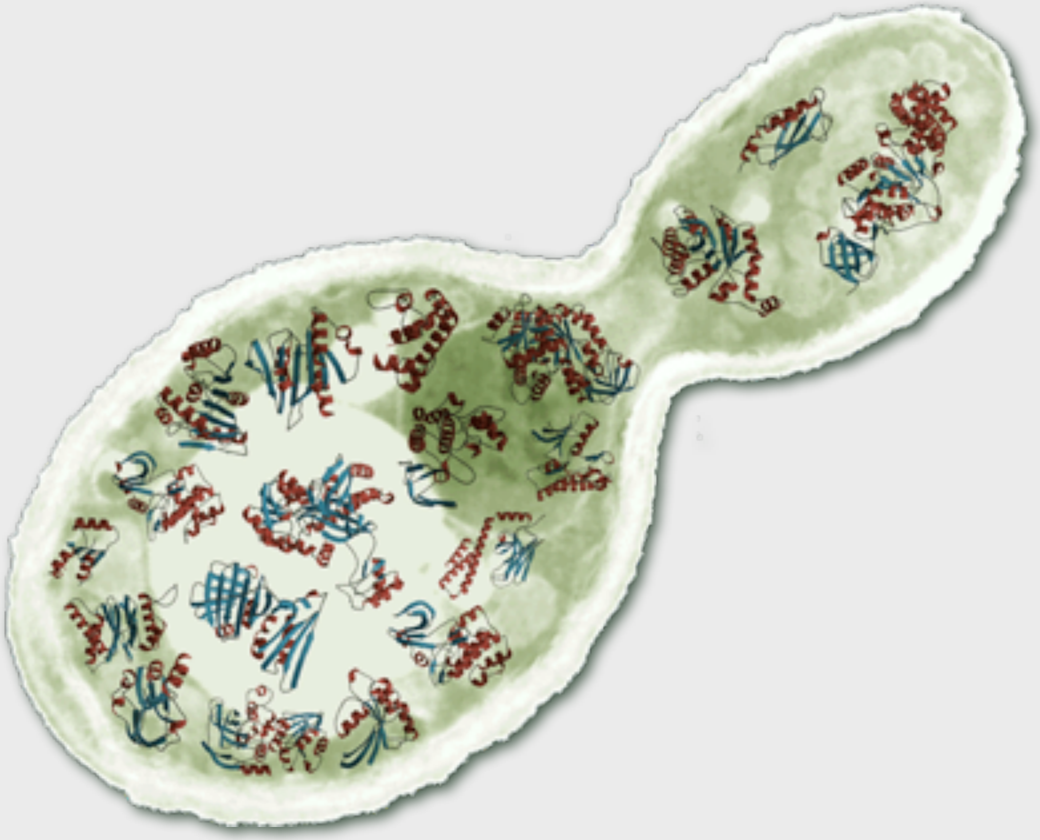
Comparative Protein Structure Prediction



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http://bioinfo.cipf.es/sgu/

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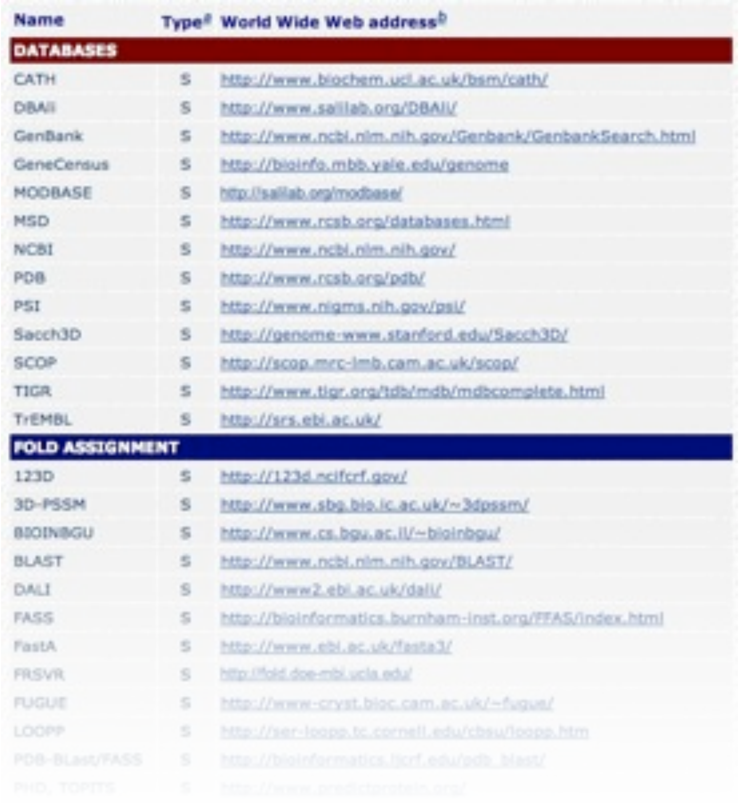
Prince Felipe Resarch Center (CIPF), Valencia, Spain

PRINCIPE FELIPE
CENTRO DE INVESTIGACION

DISCLAIMER!



Name	Type[a]	World Wide Web address[b]
DATABASES		
CATH	S	http://www.biochem.ucl.ac.uk/bsm/cath/
DBALI	S	http://www.salilab.org/DBALI/
GenBank	S	http://www.ncbi.nlm.nih.gov/Genbank/GenbankSearch.html
GeneCensus	S	http://bioinfo.mbb.yale.edu/genome
MODBASE	S	http://salilab.org/modbase/
MSD	S	http://www.rcsb.org/databases.html
NCBI	S	http://www.ncbi.nlm.nih.gov/
PDB	S	http://www.rcsb.org/pdb/
PSI	S	http://www.nigms.nih.gov/psi/
Sacch3D	S	http://genome-www.stanford.edu/Sacch3D/
SCOP	S	http://scop.mrc-lmb.cam.ac.uk/scop/
TIGR	S	http://www.tigr.org/tdb/mdb/mdbcomplete.html
TrEMBL	S	http://srs.ebi.ac.uk/
FOLD ASSIGNMENT		
123D	S	http://123d.ncifcrf.gov/
3D-PSSM	S	http://www.sbg.bio.ic.ac.uk/~3dpssm/
BIOINBGU	S	http://www.cs.bgu.ac.il/~bioinbgu/
BLAST	S	http://www.ncbi.nlm.nih.gov/BLAST/
DALI	S	http://www2.ebi.ac.uk/dali/
FASS	S	http://bioinformatics.burnham-inst.org/FFAS/index.html
FastA	S	http://www.ebi.ac.uk/fasta3/
FRSVR	S	http://fold.doe-mbi.ucla.edu/
FUGUE	S	http://www-cryst.bioc.cam.ac.uk/~fugue/
LOOPP	S	http://ser-loopp.tc.cornell.edu/cbsu/loopp.htm
PDB-BLast/FASS	S	http://bioinformatics.ljcrf.edu/pdb_blast/
PHD, TOPITS	S	http://www.predictprotein.org/

http://sgu.bioinfo.cipf.es/home/?page=resources

Summary

- INTRO
- MODELLER
- MOULDER
- MODEL(S) --> FUNCTION
- MODELLER example

Nomenclature

Homology: Sharing a common ancestor, may have similar or dissimilar functions

Similarity: Score that quantifies the degree of relationship between two sequences.

Identity: Fraction of identical aminoacids between two aligned sequences (case of similarity).

Target: Sequence corresponding to the protein to be modeled.

Template: 3D structure/s to be used during protein structure prediction.

Model: Predicted 3D structure of the target sequence.

protein prediction .vs. protein determination

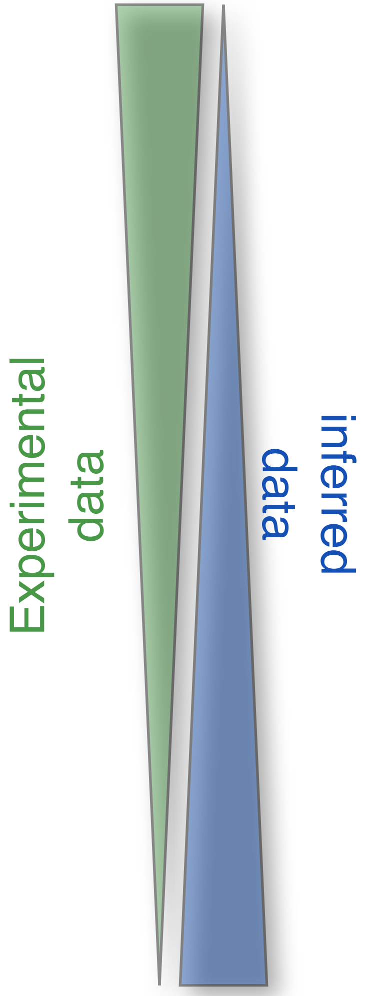
X-Ray

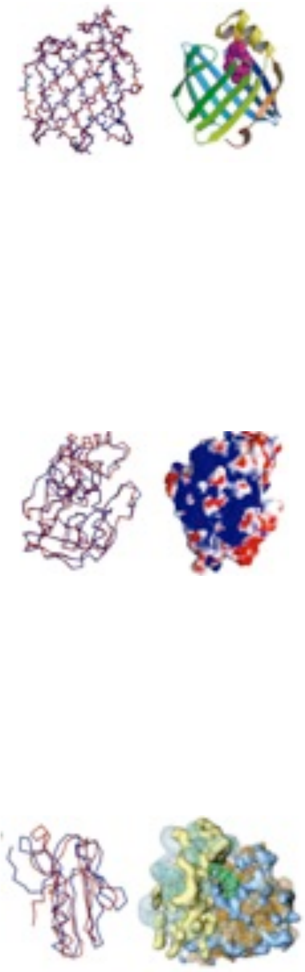
NMR

Comparative Modeling

Threading

Ab-initio



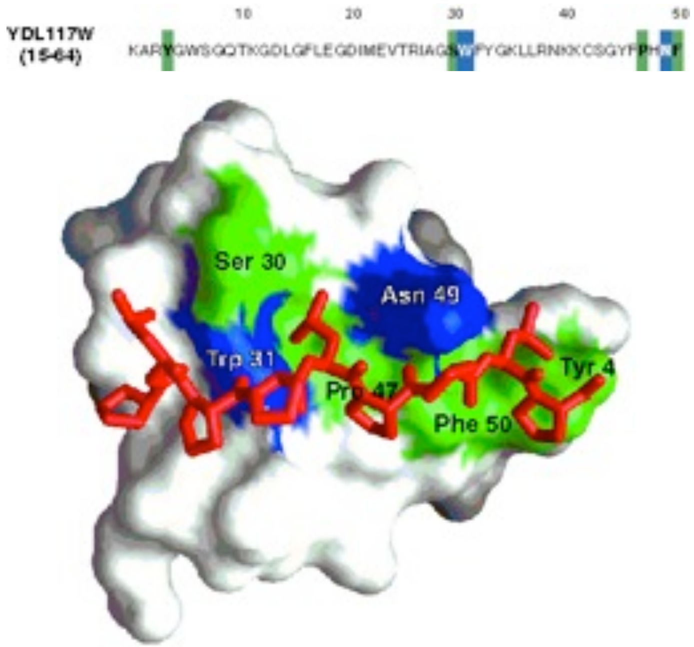


Why is it useful to know the **structure** of a protein, not only its sequence?

- The biochemical function (activity) of a protein is defined by its interactions with other molecules.

- The biological function is in large part a consequence of these interactions.

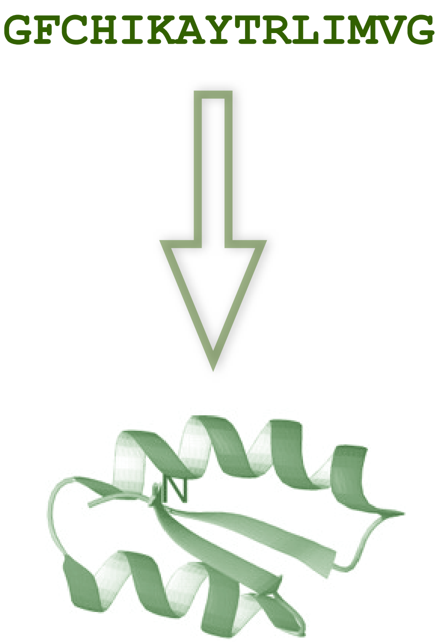
- The 3D structure is more informative than sequence because interactions are determined by residues that are close in space but are frequently distant in sequence.

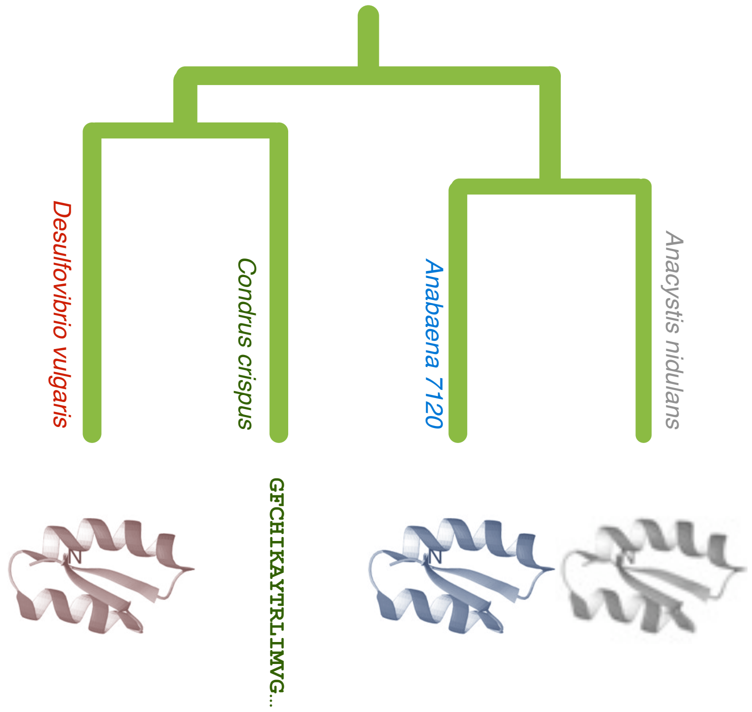


In addition, since evolution tends to conserve function and function depends more directly on structure than on sequence, **structure is more conserved in evolution than sequence**.

The net result is that **patterns in space are frequently more recognizable than patterns in sequence**.

Principles of protein structure





Folding (physics)

Ab initio prediction

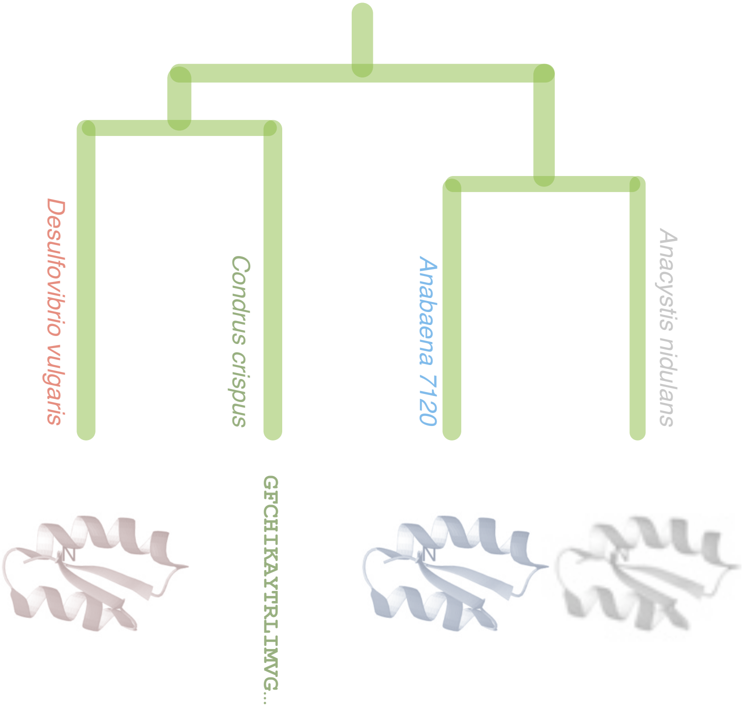
Evolution (rules)

Threading

Comparative Modeling

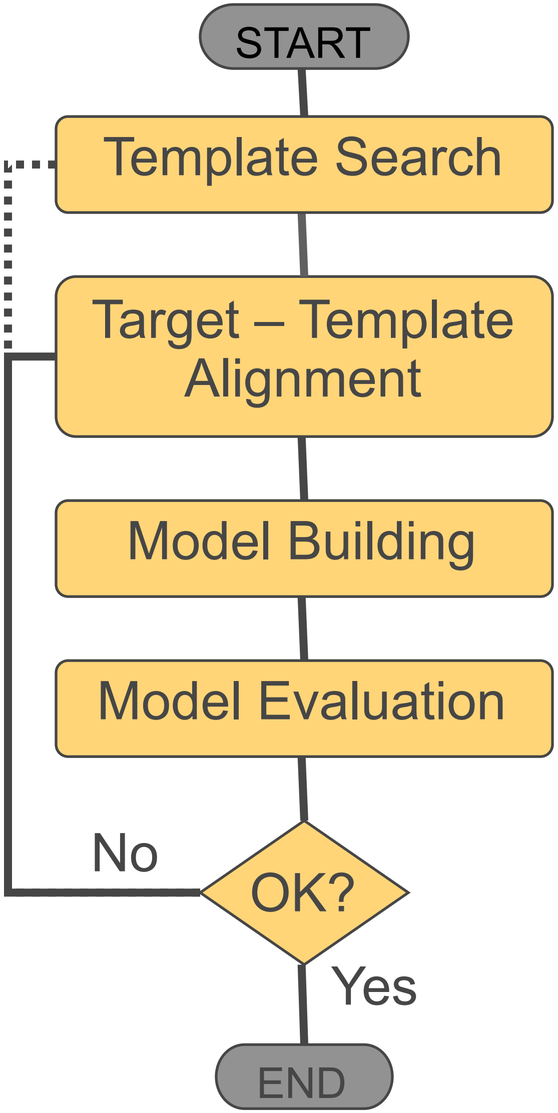
D. Baker & A. Sali. Science 294, 93, 2001.

MODELLER



1. N. Eswar, et al. *Comparative Protein Structure Modeling With MODELLER. Current Protocols in Bioinformatics, John Wiley & Sons, Inc., Supplement 15, 5.6.1-5.6.30, 2008.*
2. M.A. Marti-Renom, et al.. *Comparative protein structure modeling of genes and genomes. Annu. Rev. Biophys. Biomol. Struct. 29, 291-325, 2000.*
3. A. Sali & T.L. Blundell. *Comparative protein modelling by satisfaction of spatial restraints. J. Mol. Biol. 234, 779-815, 1993.*
4. A. Fiser, R.K. Do, & A. Sali. *Modeling of loops in protein structures, Protein Science 9. 1753-1773, 2000.*

Steps in Comparative Protein Structure Modeling



START

Template Search

Target – Template Alignment

Model Building

Model Evaluation

OK?

No

Yes

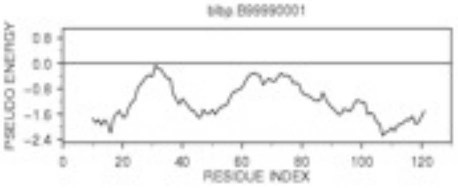
END

TARGET

TEMPLATE

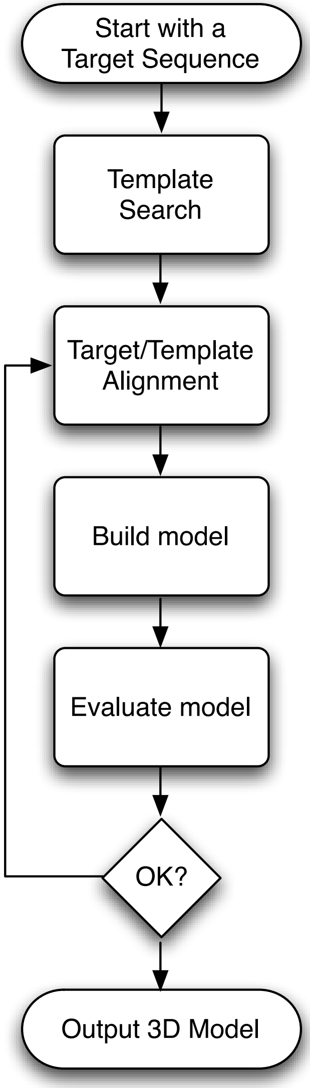
ASILPKRLFGNCEQTSDEG
LKIERTPLVPHISAQNVCLKI
DDVPERLIPERASFQWMN
DK

```
ASILPKRLFGNCEQTSDEGLKIERTPLVPHISAQNVCLKIDDVPERLIPE
MSVIPKRLYGNCEQTSEEAIRIEDSPIV---TADLVCLKIDEIPERLVGE
```



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

Comparative modeling by satisfaction of spatial restraints
MODELLER



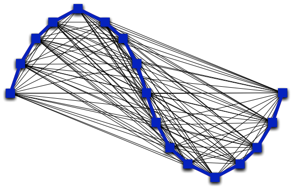
Given an alignment...

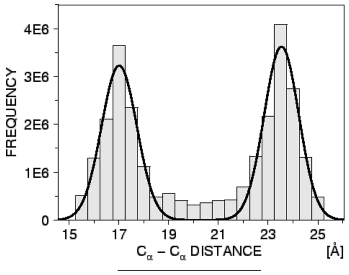
extract spatial features from the template(s) and statistics from known structures

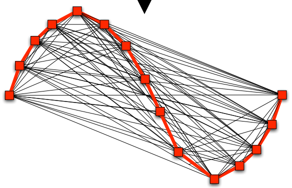
apply these features as restraints on your target sequence

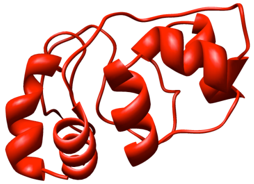
optimize to find the best solution for the restraints to produce your 3D model

```
MSVIPKR--GNCEQTSE
ASILPKRLFGNCEQTSD
```



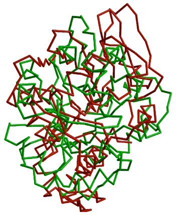




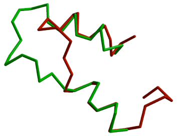


A. Šali & T. Blundell. J. Mol. Biol. 234, 779, 1993.
J.P. Overington & A. Šali. Prot. Sci. 3, 1582, 1994.
A. Fiser, R. Do & A. Šali, Prot. Sci., 9, 1753, 2000.

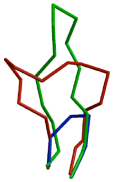
Comparative modeling by satisfaction of spatial restraints Types of errors and their impact



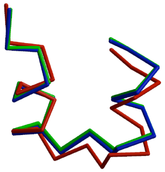
Wrong fold



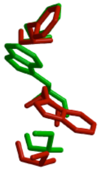
Miss alignments



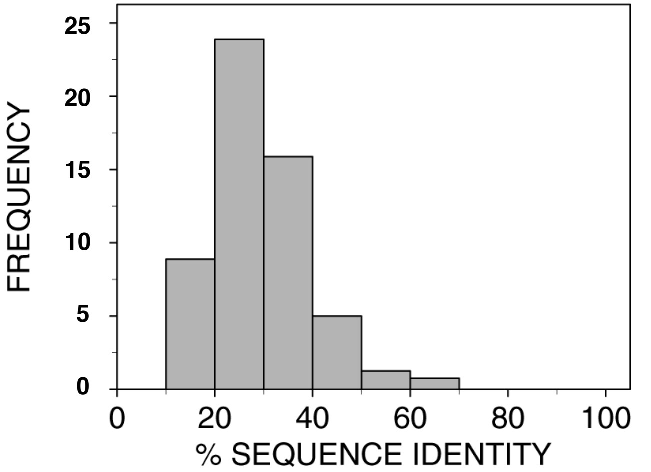
Loop regions

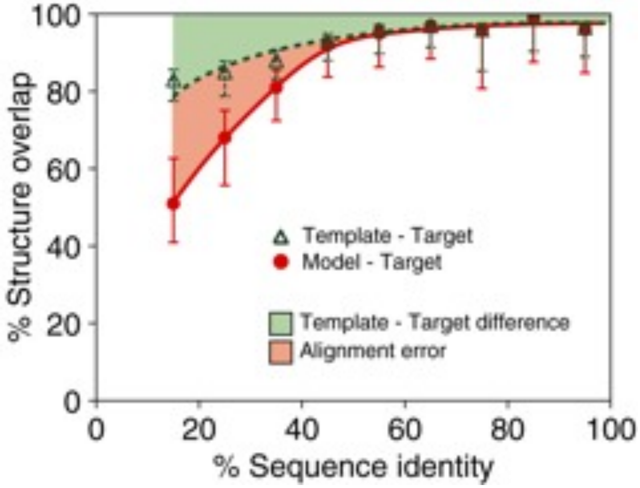


Rigid body distortions



Side-chain packing



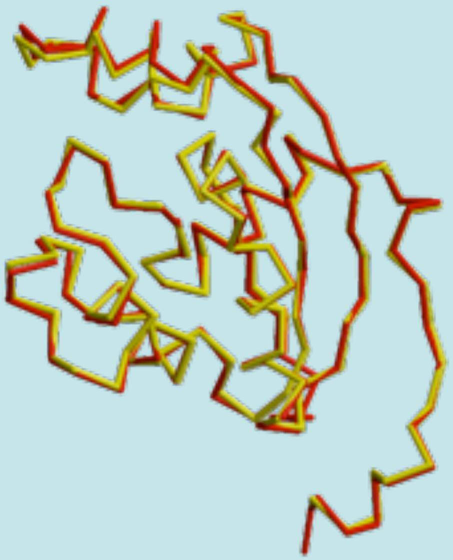


Marti-Renom etal. Ann Rev Biophys Biomol Struct (2000) 29, 291

Model Accuracy

HIGH ACCURACY

NM23
Seq id 77%
Cα equiv 147/148
RMSD 0.41Å

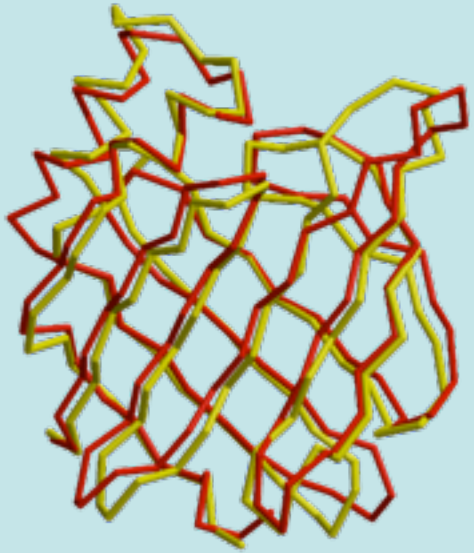


Sidechains
Core backbone
Loops

X-RAY / MODEL

MEDIUM ACCURACY

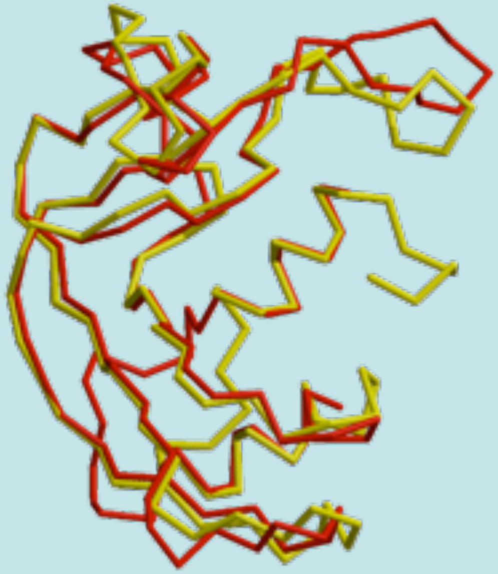
CRABP
Seq id 41%
Cα equiv 122/137
RMSD 1.34Å



Sidechains
Core backbone
Loops
Alignment

LOW ACCURACY

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



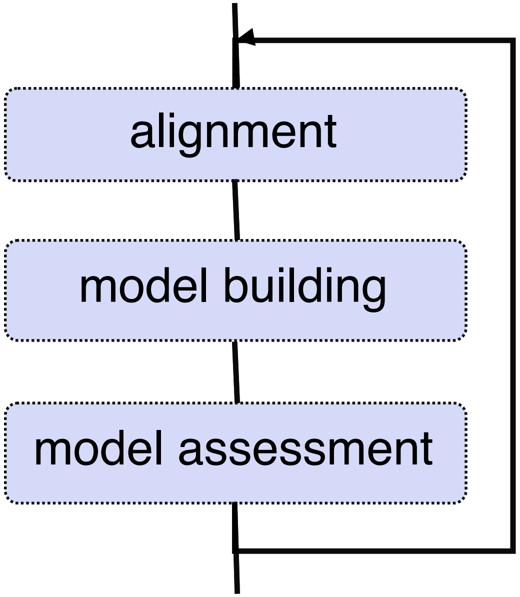
Sidechains
Core backbone
Loops
Alignment
Fold assignment

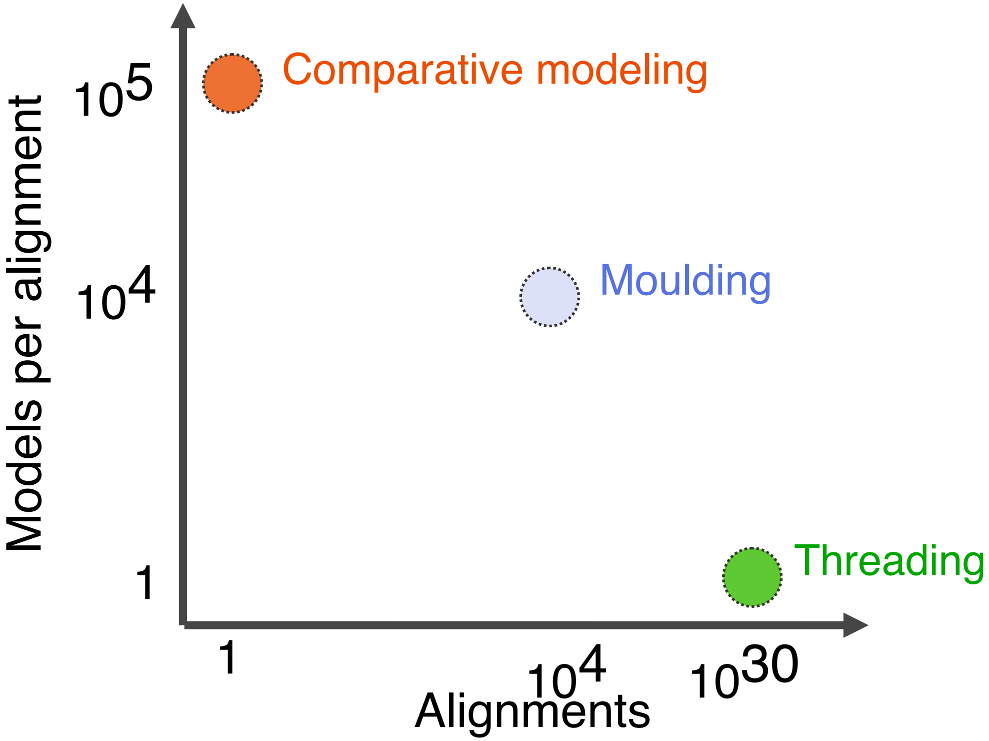
Marti-Renom et al. Annu.Rev.Biophys.Biomol.Struct. 29, 291-325, 2000.

MOULDER

John, Sali (2003). NAR pp31 3982

Moulding: iterative alignment, model building, model assessment





Genetic algorithm operators

Single point cross-over

```
...TSSQ—NMKLGVFWGY——...
...V—SSCN——GDLHMKVGV...

...TSSQNMK——LGVFWGY...
...VSSCNGDLHMKV——GV...
```

→

```
...TSSQ—NMK——LGVFWGY...
...V—SSCNGDLHMKV——GV...

...TSSQNMKLGVFWGY——...
...VSSCN——GDLHMKVGV...
```

Gap insertion

```
...TSSQNMKLGVFWGY...
...VSSCNGDLHMKVGV...
```

→

```
...TSSQN——MKLGVFWGY...
...VSSCNGDLHMKVG——V...
```

Gap shift

```
...T——SSQNMKLGVFWGY...
...VSSCNGDLHMKVGV——...
```

→

```
...—T—SSQNMKLGVFWGY...
...VSSCNGDLHMKVGV——...

...T—S—SQNMKLGVFWGY...
...VSSCNGDLHMKVGV——...

...——TSSQNMKLGVFWGY...
...VSSCNGDLHMKVGV——...

...TS——SQNMKLGVFWGY...
...VSSCNGDLHMKVGV——...
```

Also, "two point crossover" and "gap deletion".

Composite model assessment score

Weighted linear combination of several scores:

- Pair (P_p) and surface (P_S) statistical potentials;
- Structural compactness (S_C);
- Harmonic average distance score (H_a);
- Alignment score (A_S).

$$Z = 0.17\ Z(P_P) + 0.02\ Z(P_S) + 0.10\ Z(S_C) + 0.26\ Z(H_a) + 0.45\ (A_S)$$

$Z(\text{score}) = (\text{score}- \mu)/\sigma$

μ … average score of all models

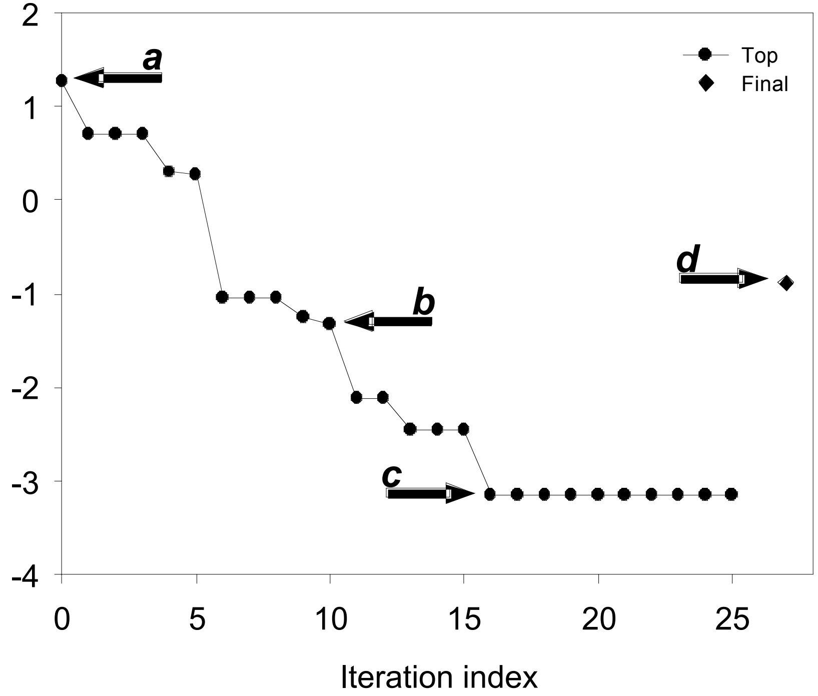
σ … standard deviation of the scores

Benchmark with the “very difficult” test set

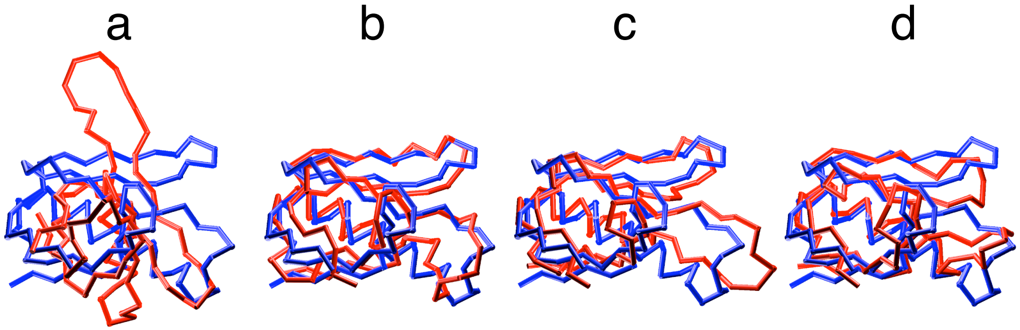
D. Fischer threading test set of 68 structural pairs (a subset of 19)

Target -template	Sequence identity [%]	Coverage [% aa]	Initial prediction		Final prediction		Best prediction	
			Cα RMSD [Å]	CE overlap [%]	Cα RMSD [Å]	CE overlap [%]	Cα RMSD [Å]	CE overlap [%]
1ATR-1ATN	13.8	94.3	19.2	20.2	18.8	20.2	17.1	24.6
1BOV-1LTS	4.4	83.5	10.1	29.4	3.6	79.4	3.1	92.6
1CAU-1CAU	18.8	96.7	11.7	15.6	10.0	27.4	7.6	47.4
1COL-1CPC	11.2	81.4	8.6	44.0	5.6	58.6	4.8	59.3
1LFB-1HOM	17.6	75.0	1.2	100.0	1.2	100.0	1.1	100.0
1NSB-2SIM	10.1	89.2	13.2	20.2	13.2	20.1	12.3	26.8
1RNH-1HRH	26.6	91.2	13.0	21.2	4.8	35.4	3.5	57.5
1YCC-2MTA	14.5	55.1	3.4	72.4	5.3	58.4	3.1	75.0
2AYH-1SAC	8.8	78.4	5.8	33.8	5.5	48.0	4.8	64.9
2CCY-1BBH	21.3	97.0	4.1	52.4	3.1	73.0	2.6	77.0
2PLV-1BBT	20.2	91.4	7.3	58.9	7.3	58.9	6.2	60.7
2POR-2OMF	13.2	97.3	18.3	11.3	11.4	14.7	10.5	25.9
2RHE-1CID	21.2	61.6	9.2	33.7	7.5	51.1	4.4	71.1
2RHE-3HLA	2.4	96.0	8.1	16.5	7.6	9.4	6.7	43.5
3ADK-1GKY	19.5	100.0	13.8	26.6	11.5	37.7	7.7	48.1
3HHR-1TEN	18.4	98.9	7.3	60.9	6.0	66.7	4.9	79.3
4FGF-81IB	14.1	98.6	11.3	24.0	9.3	30.6	5.4	41.2
6XIA-3RUB	8.7	44.1	10.5	14.5	10.1	11.0	9.0	34.3
9RNT-2SAR	13.1	88.5	5.8	41.7	5.1	51.2	4.8	69.0
AVERAGE	**14.2**	**85.2**	**9.6**	**36.7**	**7.7**	**44.8**	**6.3**	**57.8**

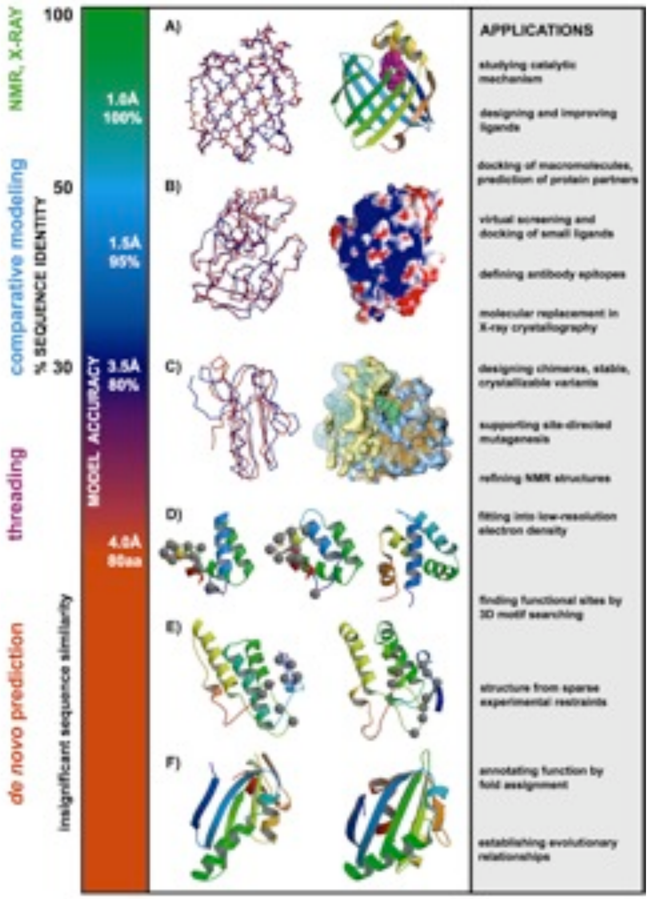
Application to a difficult modeling case
1BOV-1LTS

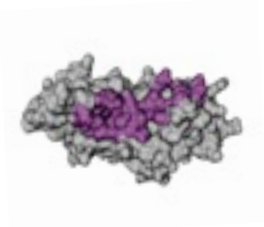


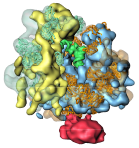
Sequence identity	4.4%
Initial model Cα RMSD	10.1Å
Final model Cα RMSD	3.6Å

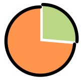


Can we use models to infer function?


NMR, X-RAY
comparative modeling
threading
de novo prediction
100
50
30
% SEQUENCE IDENTITY
insignificant sequence similarity
1.0Å
100%
1.5Å
95%
3.5Å
80%
4.0Å
80aa
MODEL ACCURACY
A)
B)
C)
D)
E)
F)
APPLICATIONS
studying catalytic mechanism
designing and improving ligands
docking of macromolecules, prediction of protein partners
virtual screening and docking of small ligands
defining antibody epitopes
molecular replacement in X-ray crystallography
designing chimeras, stable, crystallizable variants
supporting site-directed mutagenesis
refining NMR structures
fitting into low-resolution electron density
finding functional sites by 3D motif searching
structure from sparse experimental restraints
annotating function by fold assignment
establishing evolutionary relationships







T. cruzi

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

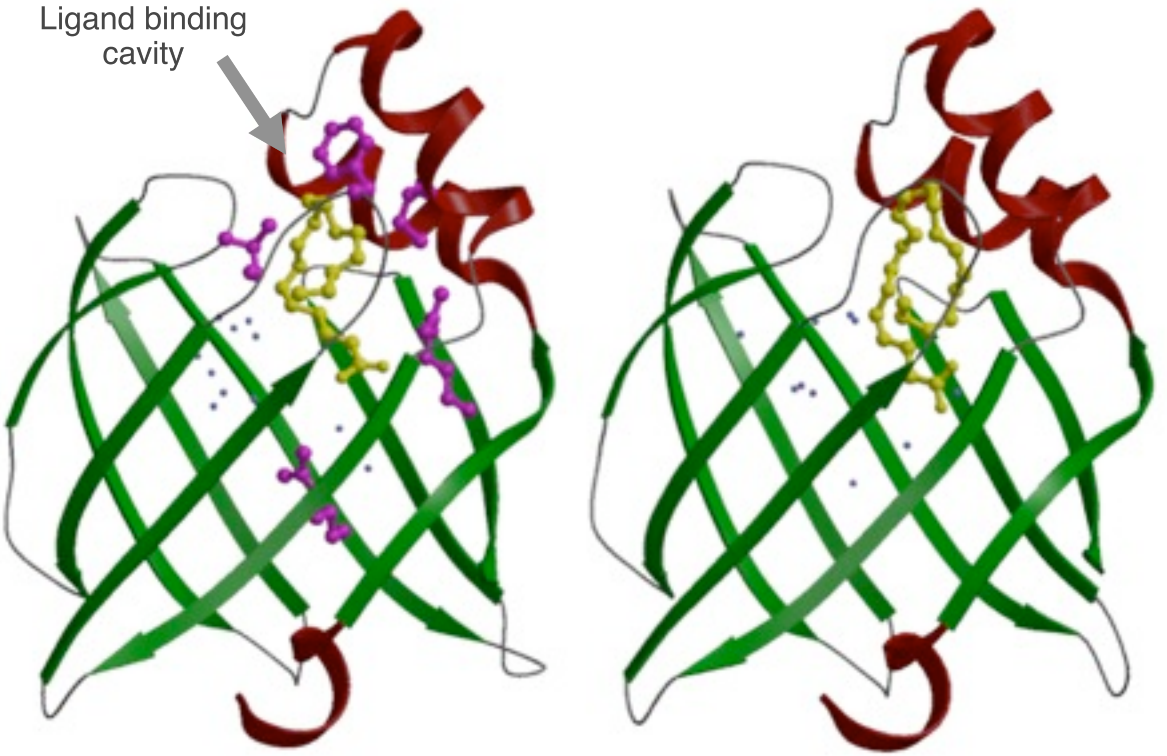
Predicting features of a model that are not present in the template

BLBP/oleic acid

Cavity is not filled

BLBP/docosahexaenoic acid

Cavity is filled



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 analysis of missense mutations in human BRCA1 BRCT domains

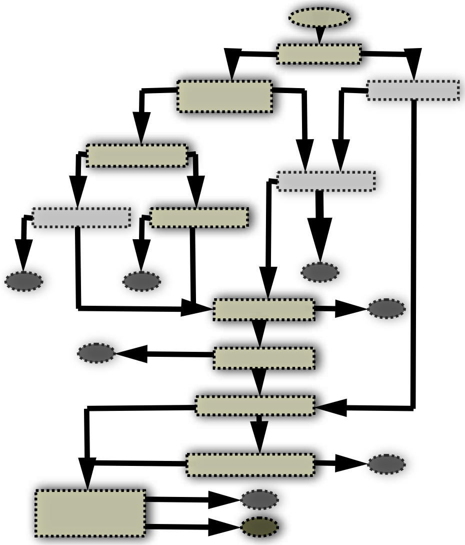
Nebojsa Mirkovic, Marc A. Marti-Renom, Barbara L. Weber,
Andrej Sali and Alvaro N.A. Monteiro

Cancer Research (June 2004). 64:3790-97

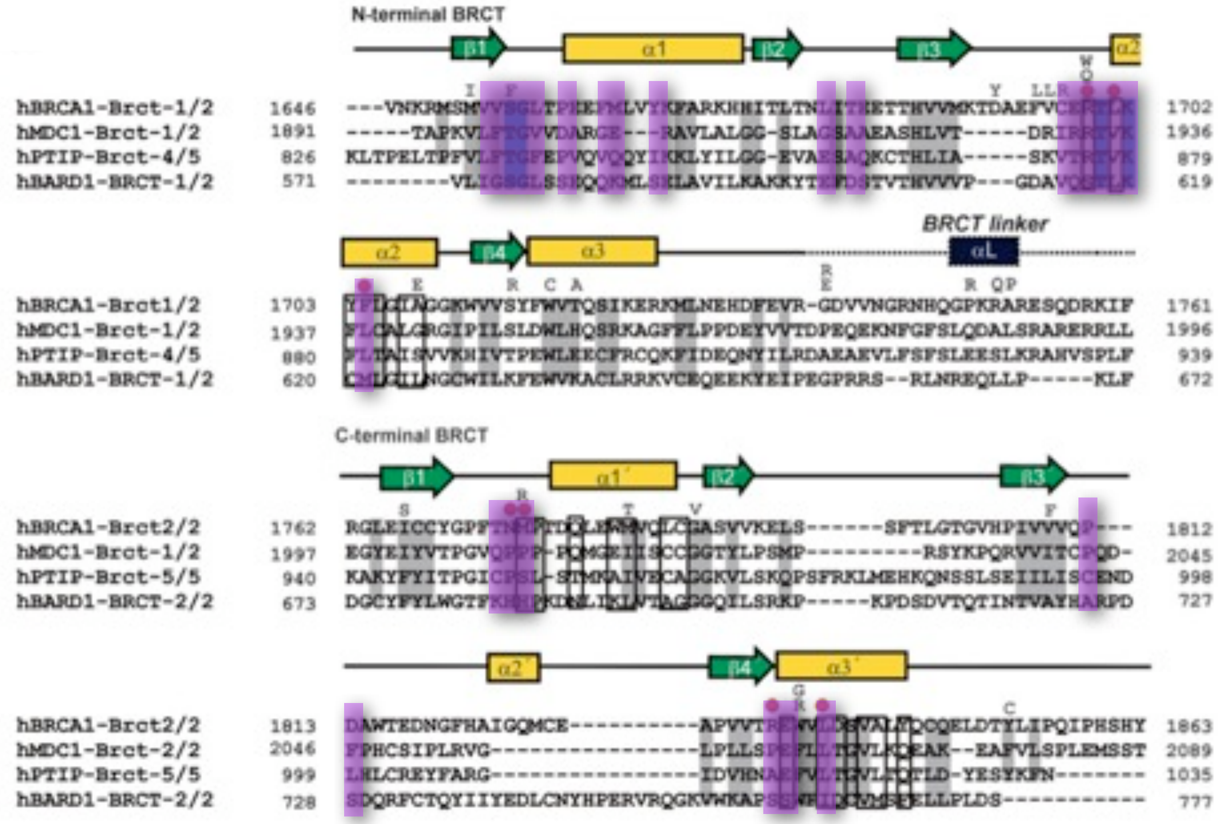
Cannot measure the functional impact of every possible SNP at all positions in each protein! Thus, prediction based on general principles of protein structure is needed.

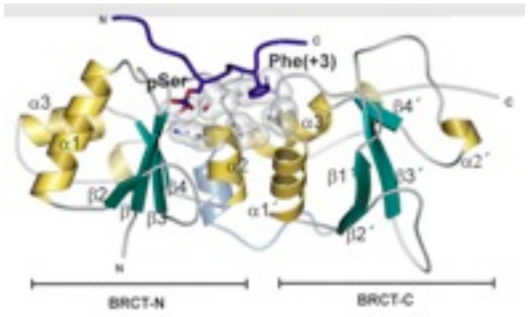
Missense mutations in BRCT domains by function

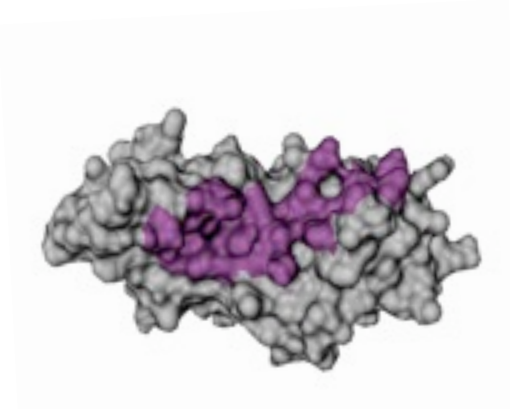
	cancer associated	not cancer associated	?
no transcription activation	C1697R R1699W A1708E S1715R P1749R M1775R		M1652K L1657P E1660G H1686Q R1699Q K1702E Y1703HF 1704S L1705PS 1715NS1 722FF17 34LG173 8EG1743 RA1752 PF1761I F1761S M1775E M1775K L1780P I1807S V1833E A1843T
transcription activation		M1652I A1669S	V1665M D1692N G1706A D1733G M1775V P1806A
?			M1652T V1653M L1664P T1685A T1685I M1689R D1692Y F1695L V1696L R1699L G1706E W1718C W1718S T1720A W1730S F1734S E1735K V1736A G1738R D1739E D1739G D1739Y V1741G H1746N R1751P R1751Q R1758G L1764P I1766S P1771L T1773S P1776S D1778N D1778G D1778H M1783T C1787S G1788D G1788V G1803A V1804D V1808A V1809A V1809F V1810G Q1811R P1812S N1819S A1823T V1833M W1837R W1837G S1841N A1843P T1852S P1856T P1859R



Putative binding site on BRCA1





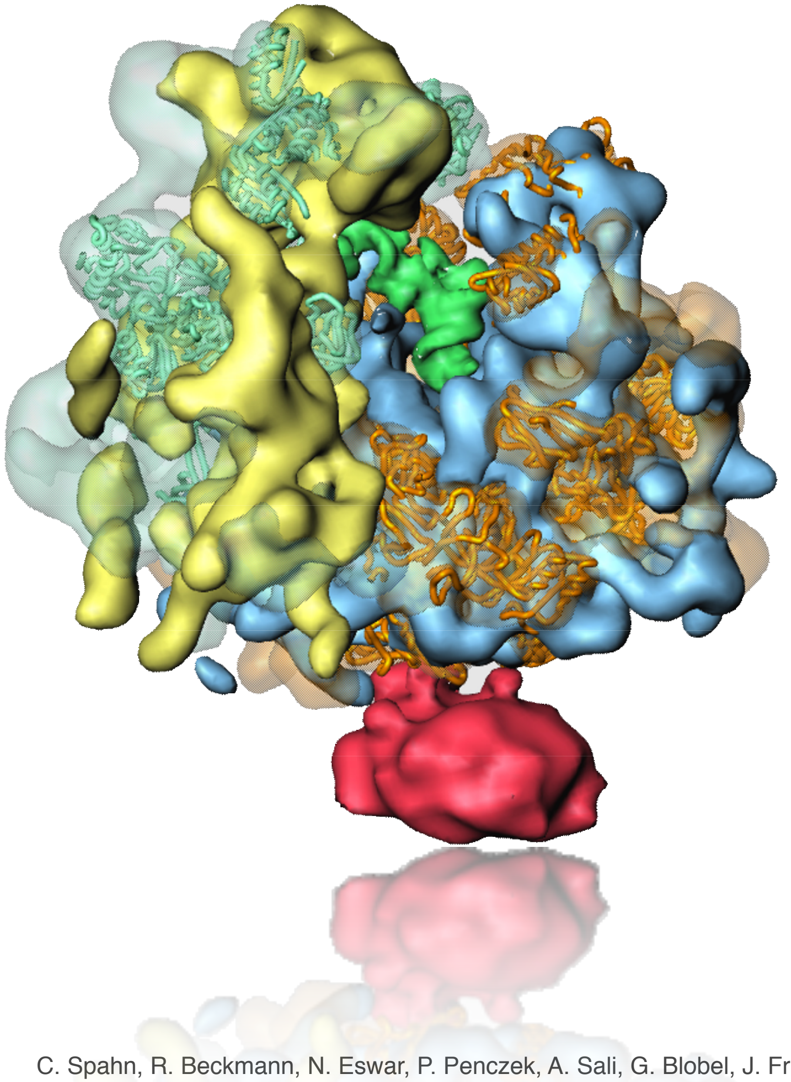


Putative binding site predicted in 2003 and accepted for publication on March 2004.

Williams *et al.* 2004 Nature Structure Biology. **June 2004 11**:519

Mirkovic *et al.* 2004 Cancer Research. **June 2004 64**:3790

S. cerevisiae ribosome



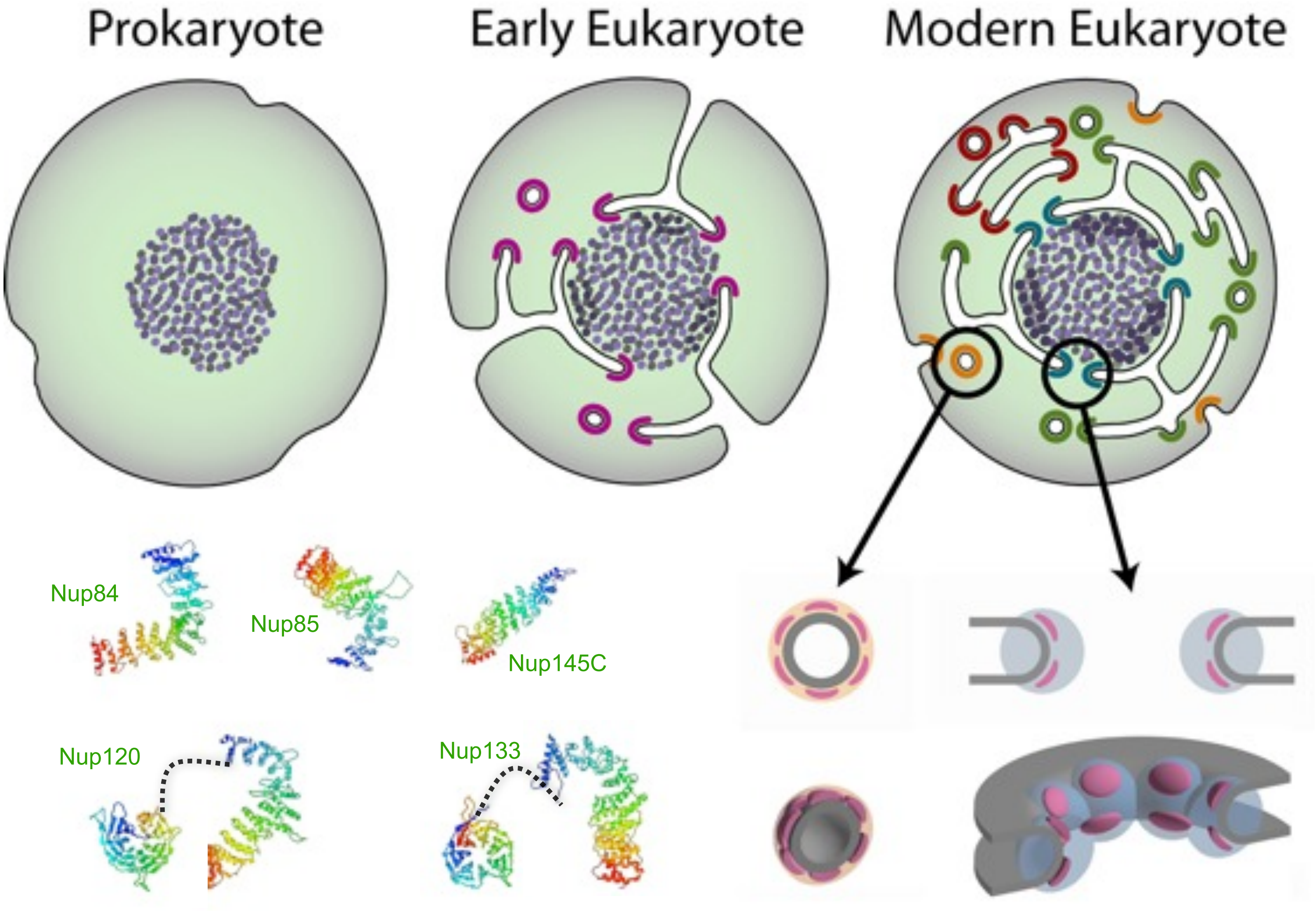
Fitting of comparative models into 15Å cryo-electron density map.

43 proteins could be modeled on 20-56% seq.id. to a known structure.

The modeled fraction of the proteins ranges from 34-99%.

C. Spahn, R. Beckmann, N. Eswar, P. Penczek, A. Sali, G. Blobel, J. Frank. Cell 107, 361-372, 2001.

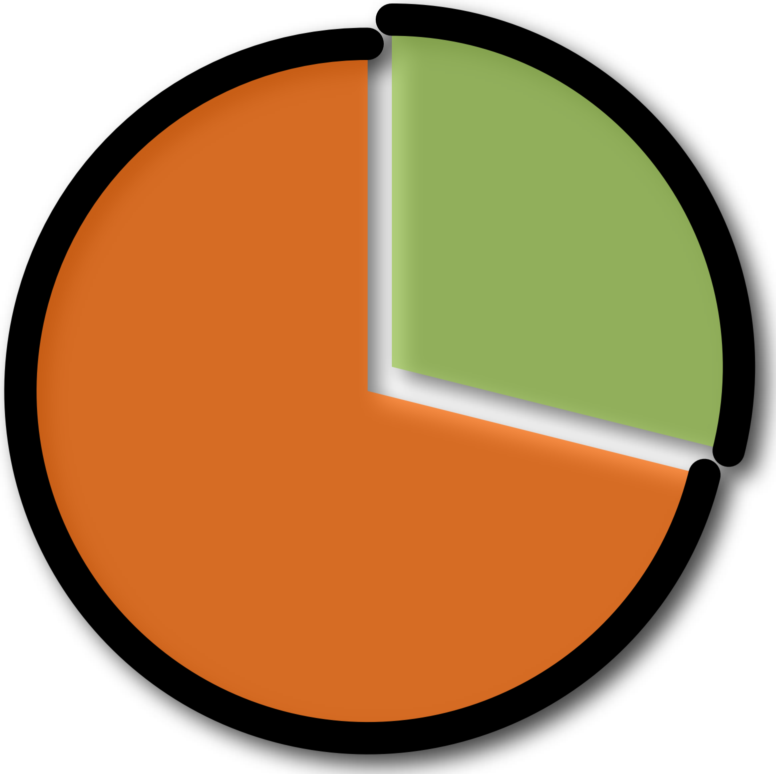
The Nucleopore complex
Cell evolution (?)



Devos et al. PLoS Biology 2, 1 (2004)

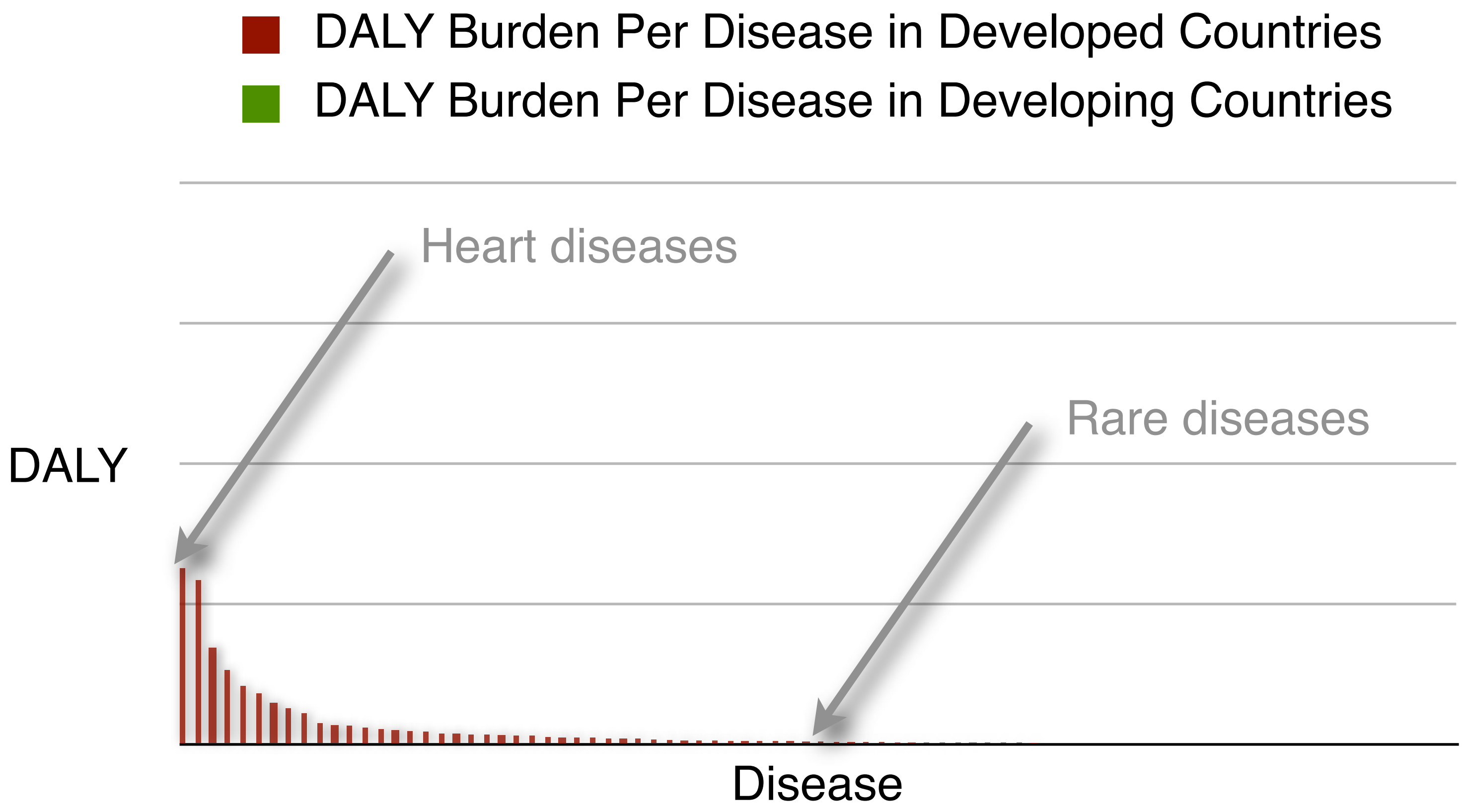
Tropical Disease Initiative (TDI)

Predicting binding sites in protein structure models.



http://www.tropicaldisease.org

Need is High in the Tail



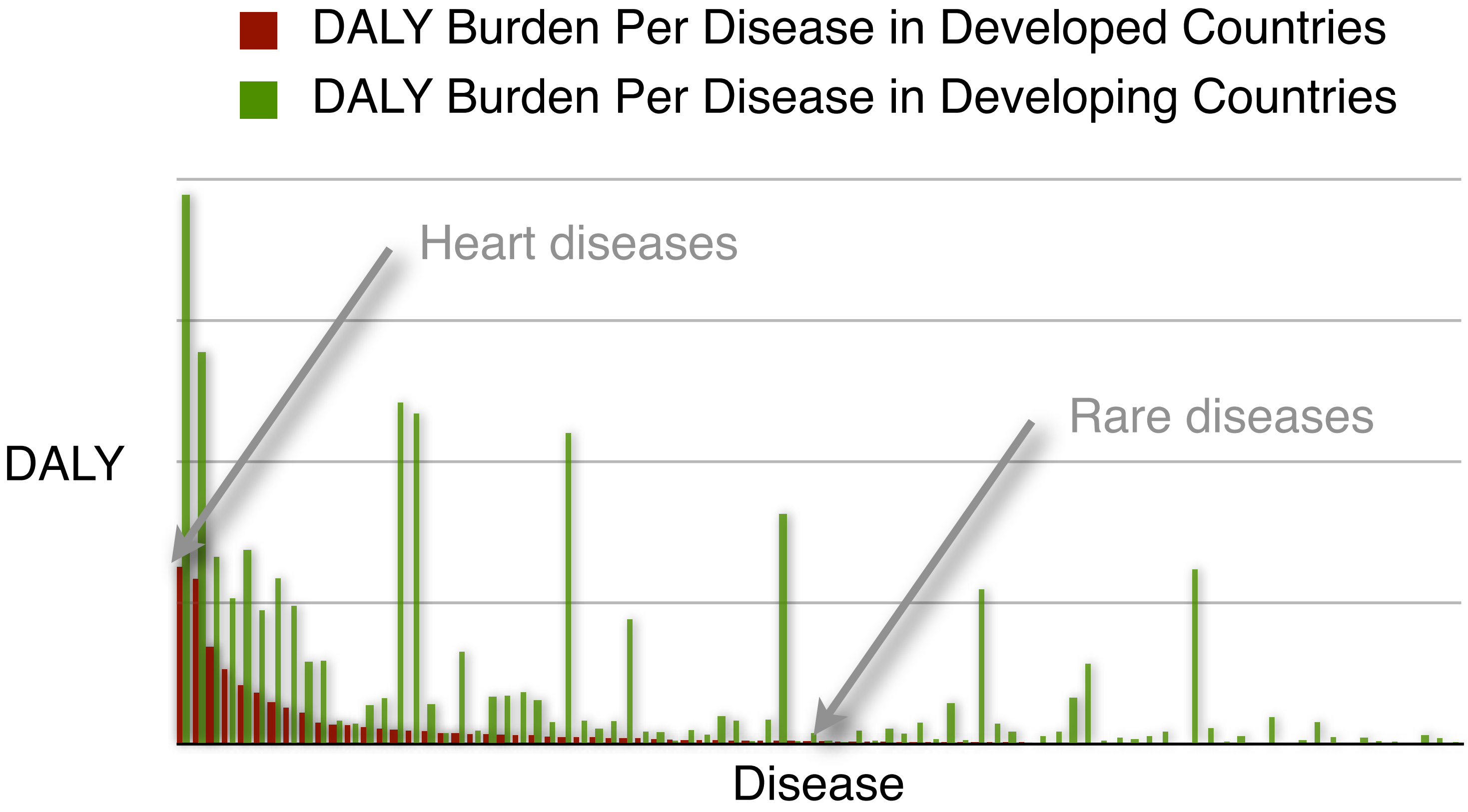
Disease data taken from WHO, *World Health Report 2004*

DALY - Disability adjusted life years

DALY is not a perfect measure of market size, but is certainly a good measure for importance.

DALYs for a disease are the sum of the years of life lost due to premature mortality (YLL) in the population and the years lost due to disability (YLD) for incident cases of the health condition. The DALY is a health gap measure that extends the concept of potential years of life lost due to premature death (PYLL) to include equivalent years of 'healthy' life lost in states of less than full health, broadly termed disability. One DALY represents the loss of one year of equivalent full health.

Need is High in the Tail



Heart diseases

Rare diseases

Disease data taken from WHO, *World Health Report 2004*
DALY - Disability adjusted life years
DALY is not a perfect measure of market size, but is certainly a good measure for importance.

DALYs for a disease are the sum of the years of life lost due to premature mortality (YLL) in the population and the years lost due to disability (YLD) for incident cases of the health condition. The DALY is a health gap measure that extends the concept of potential years of life lost due to premature death (PYLL) to include equivalent years of 'healthy' life lost in states of less than full health, broadly termed disability. One DALY represents the loss of one year of equivalent full health.

“Unprofitable” Diseases and Global DALY (in 1000’s)

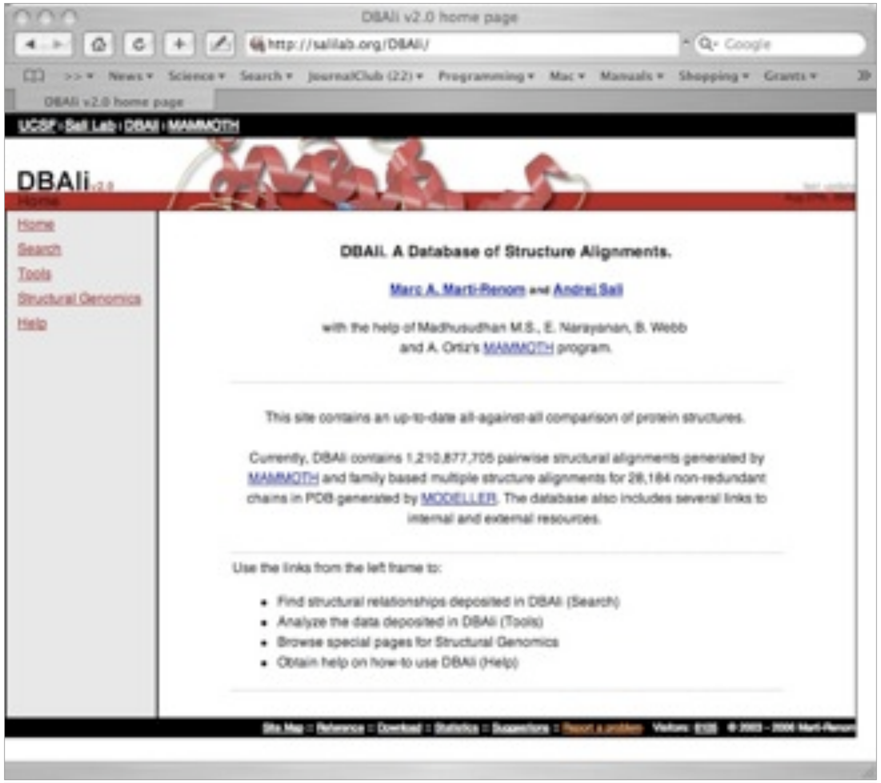
Malaria*	**46,486**
Tetanus	7,074
Lymphatic filariasis*	**5,777**
Syphilis	4,200
Trachoma	2,329
Leishmaniasis*	**2,090**
Ascariasis	1,817
Schistosomiasis*	**1,702**
Trypanosomiasis*	**1,525**

Trichuriasis	1,006
Japanese encephalitis	709
Chagas Disease*	**667**
Dengue*	**616**
Onchocerciasis*	**484**
Leprosy*	**199**
Diphtheria	185
Poliomyelitise	151
Hookworm disease	59

Disease data taken from WHO, *World Health Report 2004*
DALY - Disability adjusted life year in 1000’s.
* Officially listed in the WHO Tropical Disease Research disease portfolio.

DBAli$_{v2.0}$ database

http://www.dbali.org


DBAli v2.0 home page
http://salilab.org/DBAli/
Google
News ▾ Science ▾ Search ▾ JournalClub (22) ▾ Programming ▾ Mac ▾ Manuals ▾ Shopping ▾ Grants ▾
DBAli v2.0 home page
UCSF | Sali Lab | DBAli | MAMMOTH
DBAli$_{v2.0}$
Home
Home
Search
Tools
Structural Genomics
Help

DBAli. A Database of Structure Alignments.

Marc A. Marti-Renom and Andrej Sali

with the help of Madhusudhan M.S., E. Narayanan, B. Webb
and A. Ortiz's MAMMOTH program.

This site contains an up-to-date all-against-all comparison of protein structures.

Currently, DBAli contains 1,210,877,705 pairwise structural alignments generated by MAMMOTH and family based multiple structure alignments for 28,184 non-redundant chains in PDB generated by MODELLER. The database also includes several links to internal and external resources.

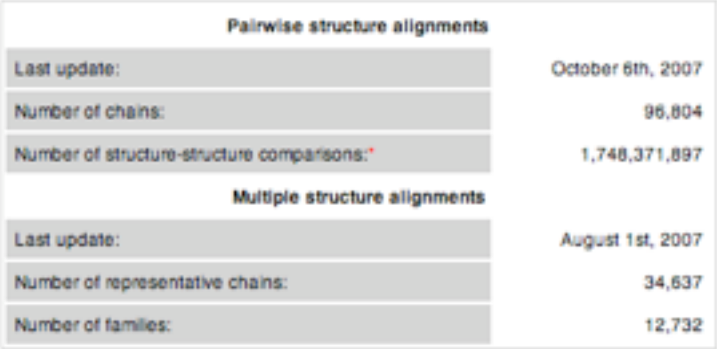
Use the links from the left frame to:

- Find structural relationships deposited in DBAli (Search)
- Analyze the data deposited in DBAli (Tools)
- Browse special pages for Structural Genomics
- Obtain help on how-to use DBAli (Help)

Site Map :: Reference :: Download :: Statistics :: Suggestions :: Report a problem Visitors: [illegible] © 2003 – 2006 Marti-Renom

- ✓ Fully-automatic
- ✓ Data is kept up-to-date with PDB releases
- ✓ Tools for “on the fly” classification of families.
- ✓ Easy to navigate
- ✓ Provides tools for structure analysis

Does not provide a stable classification similar to that of CATH or SCOP



Pairwise structure alignments	
Last update:	October 6th, 2007
Number of chains:	96,804
Number of structure-structure comparisons:*	1,748,371,897
Multiple structure alignments	
Last update:	August 1st, 2007
Number of representative chains:	34,637
Number of families:	12,732

Uses MAMMOTH for similarity detection

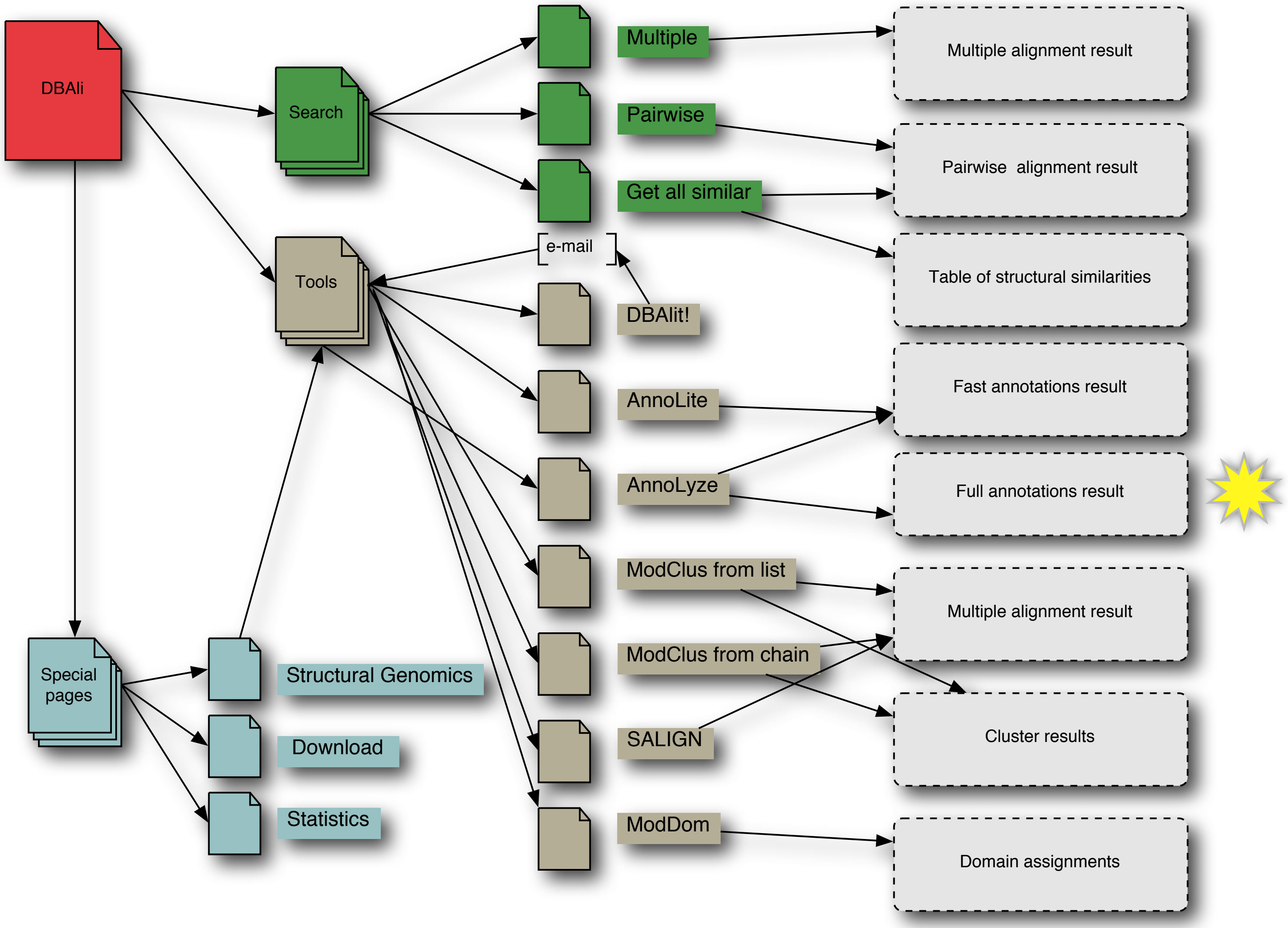
- ✓ VERY FAST!!!
- ✓ Good scoring system with significance

Ortiz AR, (2002) Protein Sci. 11 pp2606

Marti-Renom et al. 2001. Bioinformatics. 17, 746

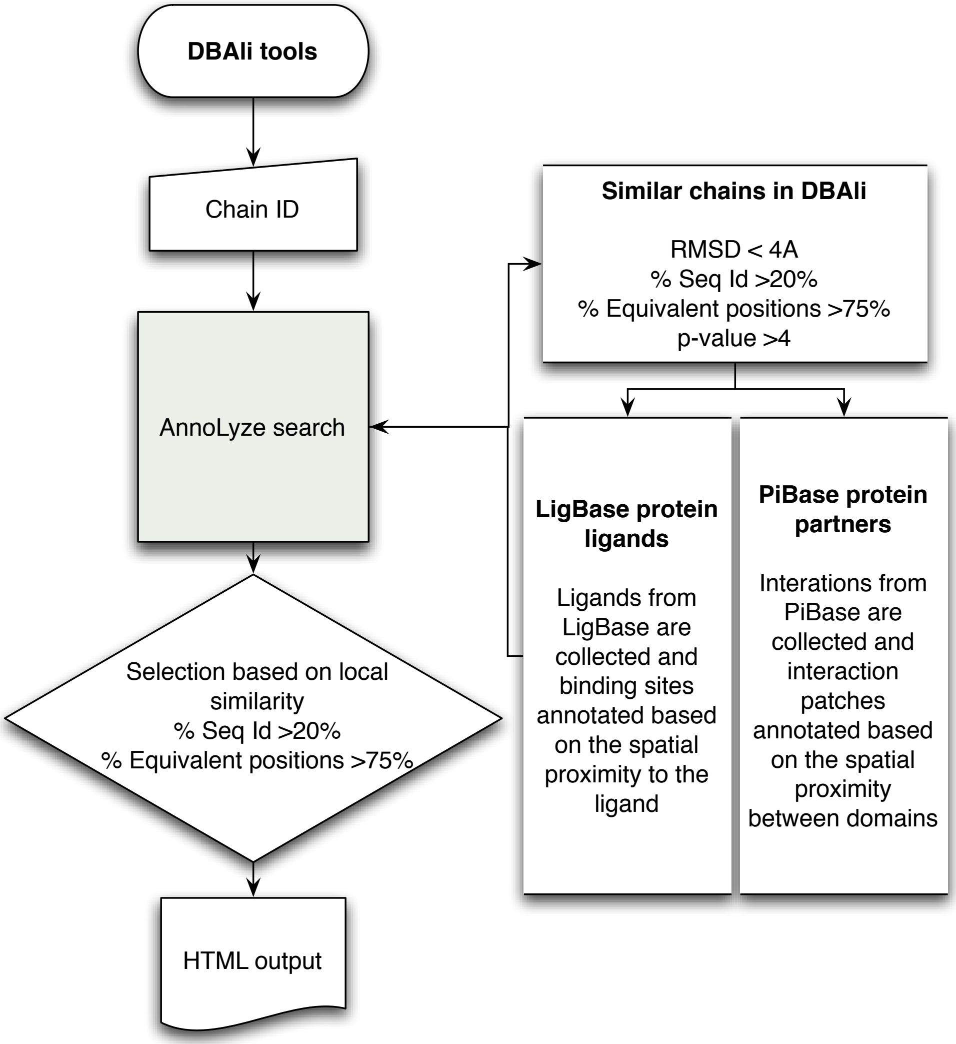
DBAli$_{v2.0}$ database

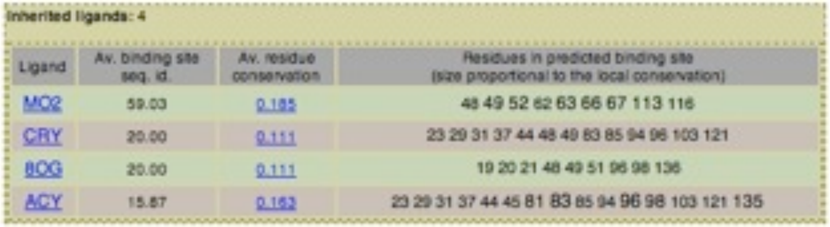
http://www.dbali.org



Marti-Renom et al. BMC Bioinformatics (2007) Volume 8. Suppl S4

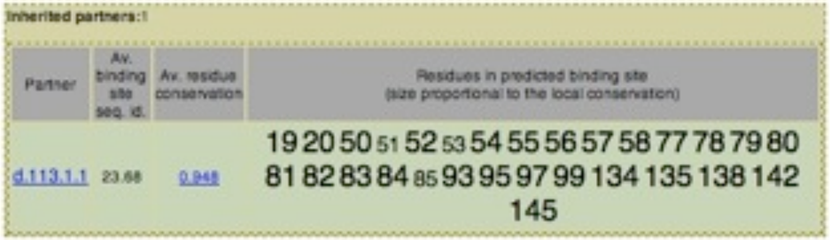
Method


DBAli tools
Chain ID
AnnoLyze search
Selection based on local similarity
% Seq Id >20%
% Equivalent positions >75%
HTML output
Similar chains in DBAli
RMSD < 4A
% Seq Id >20%
% Equivalent positions >75%
p-value >4
LigBase protein ligands
Ligands from LigBase are collected and binding sites annotated based on the spatial proximity to the ligand
PiBase protein partners
Interations from PiBase are collected and interaction patches annotated based on the spatial proximity between domains



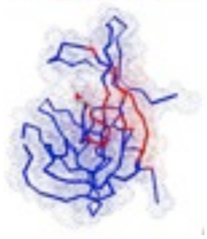
Inherited ligands: 4

Ligand	Av. binding site seq. id.	Av. residue conservation	Residues in predicted binding site (size proportional to the local conservation)
MO2	59.03	0.185	48 49 52 62 63 66 67 113 116
CRY	20.00	0.111	23 29 31 37 44 48 49 83 85 94 96 103 121
BOG	20.00	0.111	19 20 21 48 49 51 96 98 136
ACY	15.87	0.163	23 29 31 37 44 45 81 83 85 94 96 98 103 121 135



Inherited partners:1

Partner	Av. binding site seq. id.	Av. residue conservation	Residues in predicted binding site (size proportional to the local conservation)
d.113.1.1	23.68	0.948	19 20 50 51 52 53 54 55 56 57 58 77 78 79 80 81 82 83 84 85 93 95 97 99 134 135 138 142 145



Sensitivity .vs. Precision

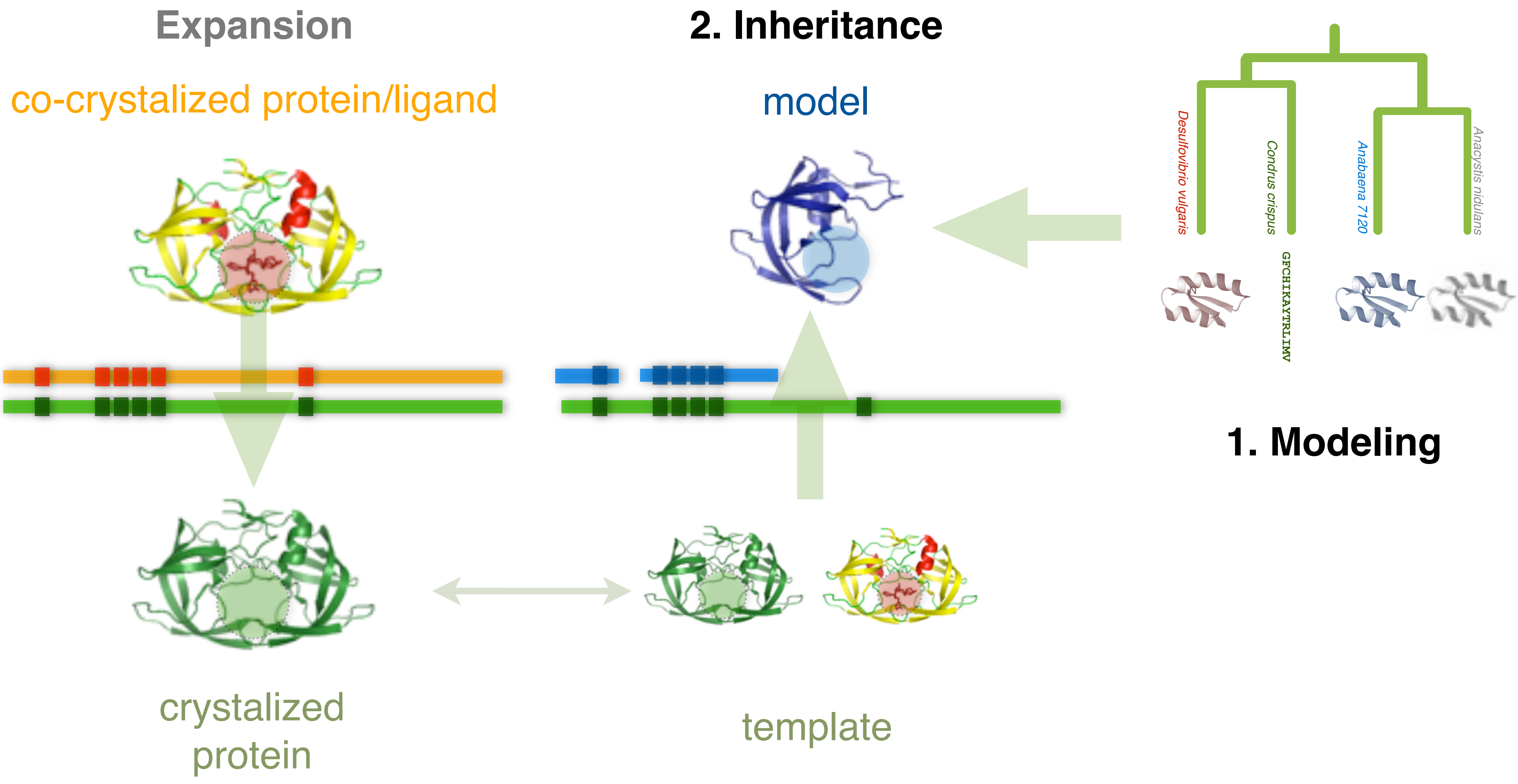
	Optimal cut-off	Sensitivity (%) Recall or TPR	Precision (%)
Ligands	30%	71.9	13.7

$$\text{Sensitivity} = \frac{TP}{TP + FN} \qquad \text{Precision} = \frac{TP}{TP + FP}$$

~90-95% of residues correctly predicted

Marti-Renom et al. BMC Bioinformatics (2007) Volume 8. Suppl S4

Comparative docking



Expansion

2. Inheritance

co-crystalized protein/ligand

model

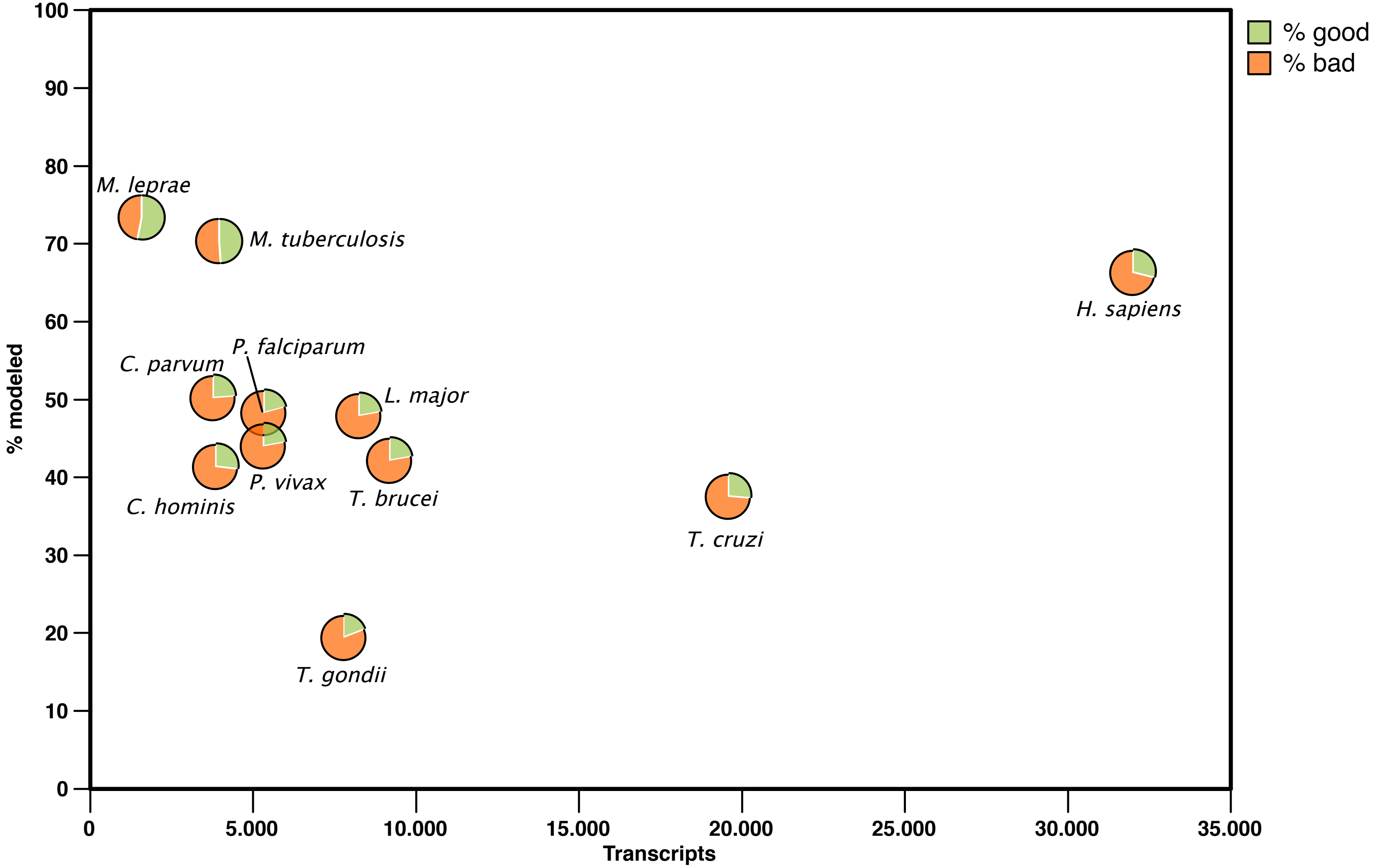
1. Modeling

crystalized protein

template

Modeling Genomes

data from models generated by ModPipe (Eswar, Pieper & Sali)



A good model has MPQS of 1.0 or higher

Summary table

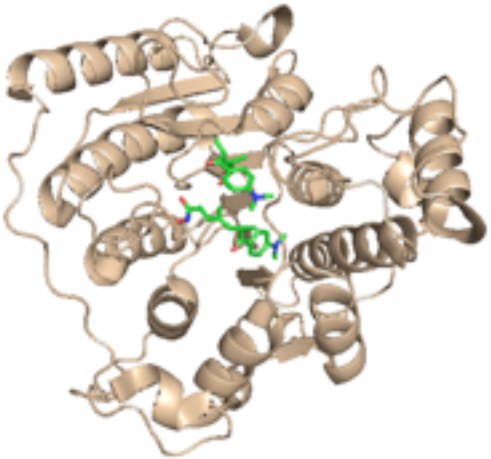
models with inherited ligands

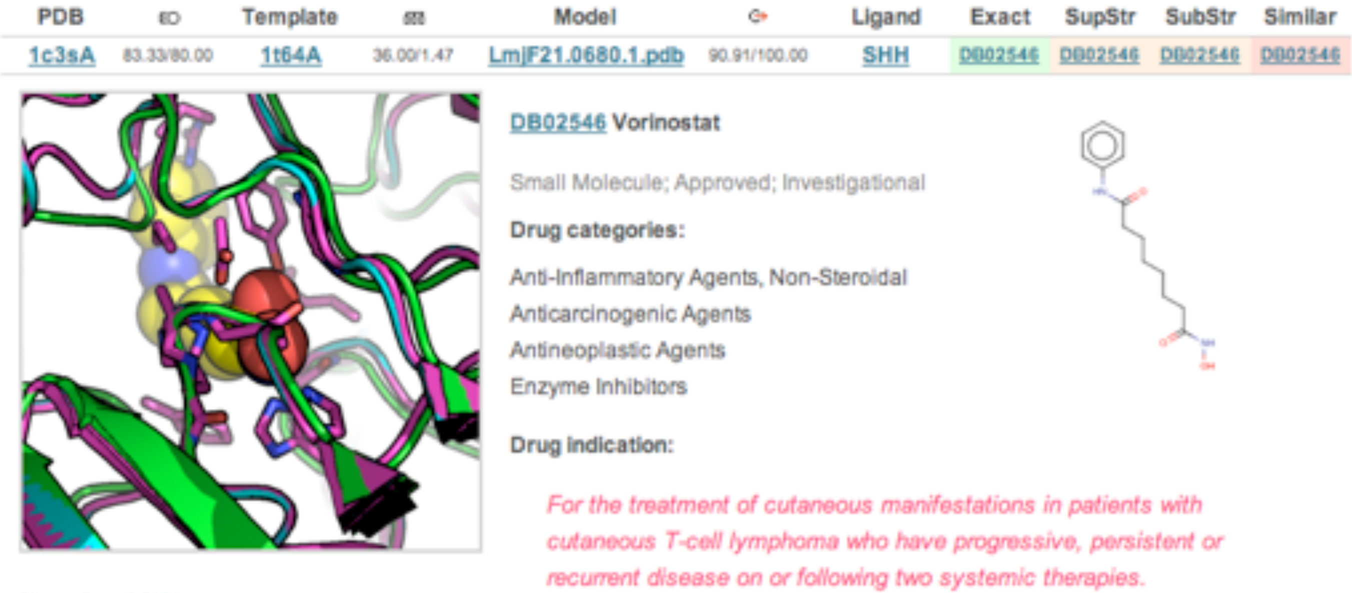
29,271 targets with good models, 297 inherited a ligand/substance similar to a known drug in DrugBank

	Transcripts	Modeled targets	Selected models	Inherited ligands	Similar to a drug	Drugs
C. hominis	3,886	1,614	666	197	20	13
C. parvum	3,806	1,918	742	232	24	13
L. major	8,274	3,975	1,409	478	43	20
M. leprae	1,605	1,178	893	310	25	6
M. tuberculosis	3,991	2,808	1,608	365	30	10
P. falciparum	5,363	2,599	818	284	28	13
P. vivax	5,342	2,359	822	268	24	13
T. brucei	7,793	1,530	300	138	13	6
T. cruzi	19,607	7,390	3,070	769	51	28
T. gondii	9,210	3,900	1,386	458	39	21
TOTAL	**68,877**	**29,271**	**11,714**	**3,499**	**297**	**143**

L. major Histone deacetylase 2 + Vorinostat

Template 1t64A a human HDAC8 protein.





PDB		Template		Model		Ligand	Exact	SupStr	SubStr	Similar
1c3sA	83.33/80.00	1t64A	36.00/1.47	LmjF21.0680.1.pdb	90.91/100.00	SHH	DB02546	DB02546	DB02546	DB02546

DB02546 Vorinostat

Small Molecule; Approved; Investigational

Drug categories:

Anti-Inflammatory Agents, Non-Steroidal

Anticarcinogenic Agents

Antineoplastic Agents

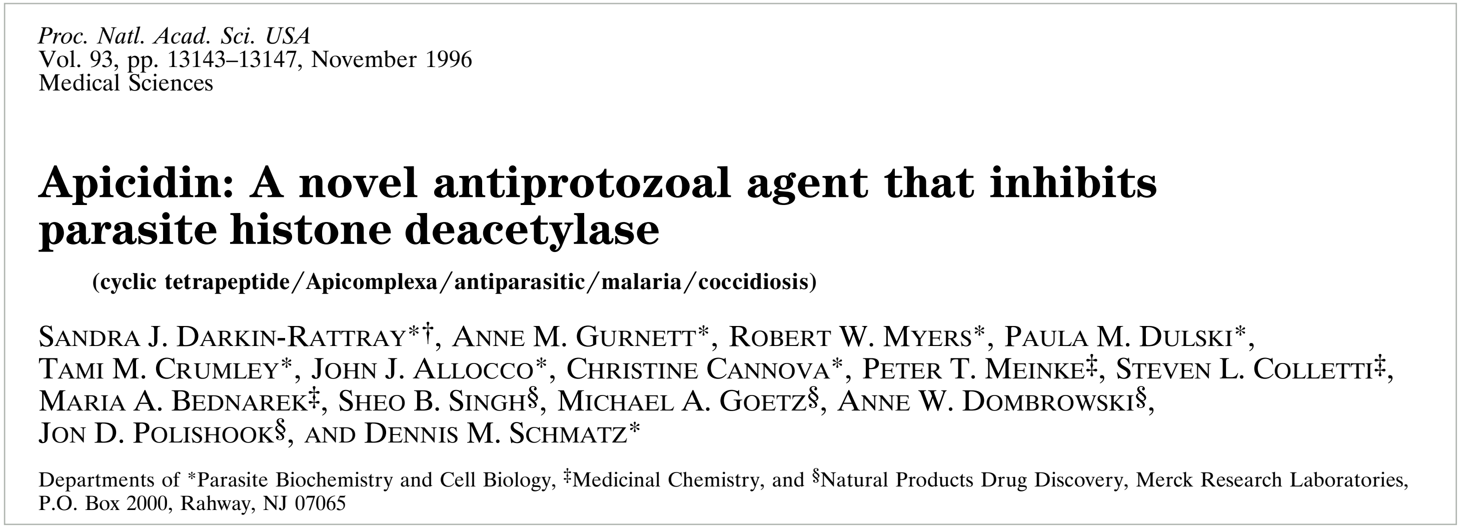
Enzyme Inhibitors

Drug indication:

For the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma who have progressive, persistent or recurrent disease on or following two systemic therapies.

L. major Histone deacetylase 2 + Vorinostat

Literature



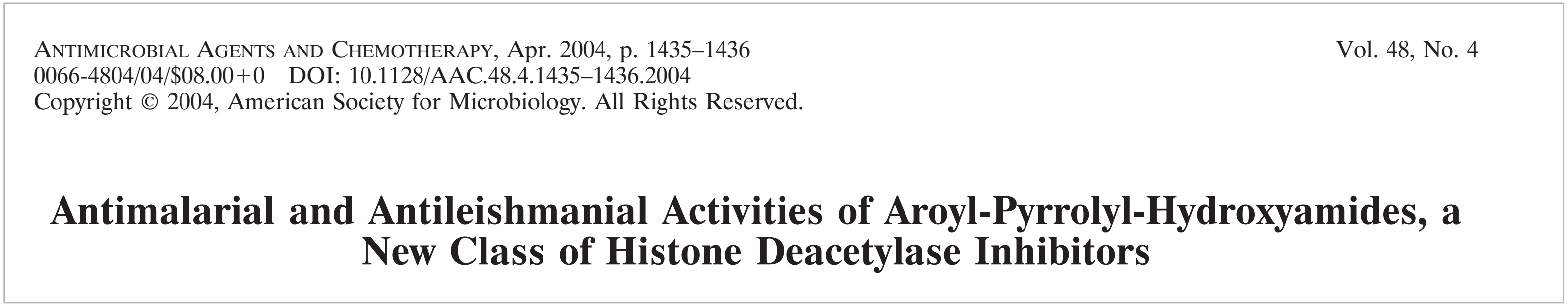
Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 13143–13147, November 1996
Medical Sciences

Apicidin: A novel antiprotozoal agent that inhibits parasite histone deacetylase

(cyclic tetrapeptide/Apicomplexa/antiparasitic/malaria/coccidiosis)

Sandra J. Darkin-Rattray[*†], Anne M. Gurnett[*], Robert W. Myers[*], Paula M. Dulski[*], Tami M. Crumley[*], John J. Allocco[*], Christine Cannova[*], Peter T. Meinke[‡], Steven L. Colletti[‡], Maria A. Bednarek[‡], Sheo B. Singh[§], Michael A. Goetz[§], Anne W. Dombrowski[§], Jon D. Polishook[§], and Dennis M. Schmatz[*]

Departments of [*]Parasite Biochemistry and Cell Biology, [‡]Medicinal Chemistry, and [§]Natural Products Drug Discovery, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065

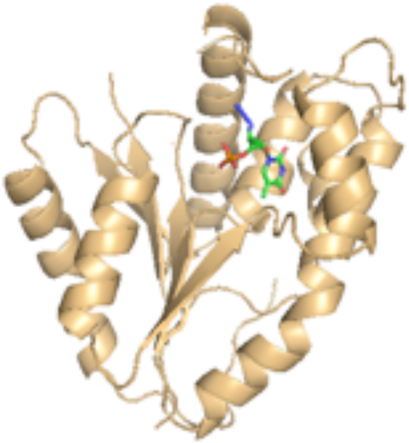


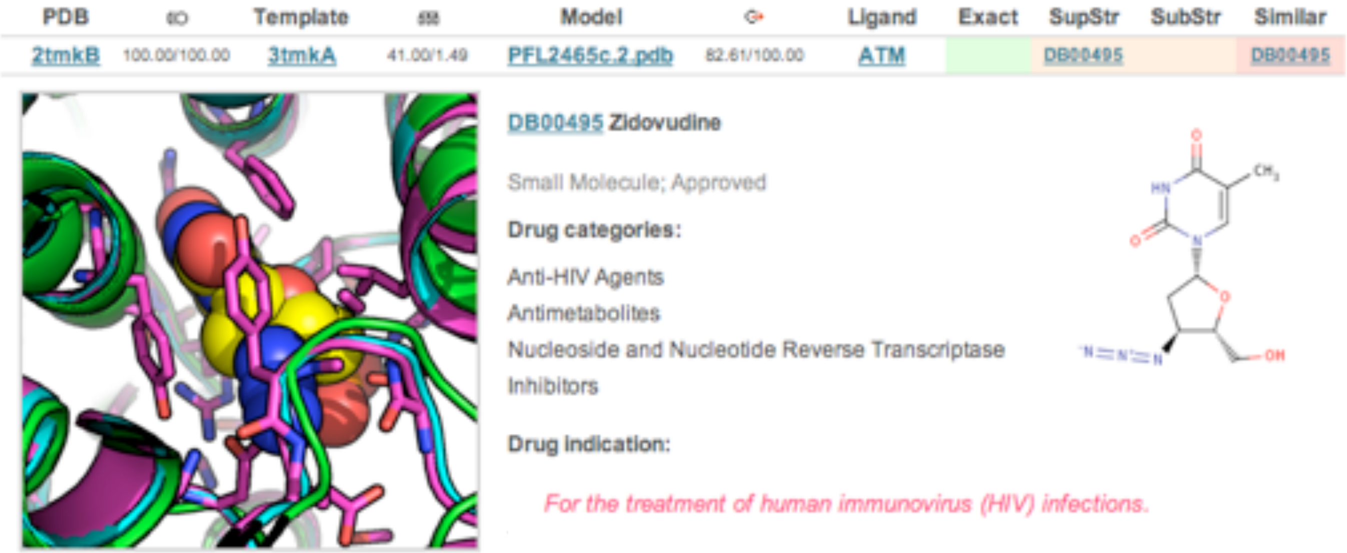
Antimicrobial Agents and Chemotherapy, Apr. 2004, p. 1435–1436 Vol. 48, No. 4
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.4.1435–1436.2004

Antimalarial and Antileishmanial Activities of Aroyl-Pyrrolyl-Hydroxyamides, a New Class of Histone Deacetylase Inhibitors

P. falciparum tymidylate kinase + zidovudine

Template 3tmkA a yeast tymidylate kinase.





PDB		Template		Model		Ligand	Exact	SupStr	SubStr	Similar
2tmkB	100.00/100.00	3tmkA	41.00/1.49	PFL2465c.2.pdb	82.61/100.00	ATM		DB00495		DB00495

DB00495 Zidovudine

Small Molecule; Approved

Drug categories:

Anti-HIV Agents

Antimetabolites

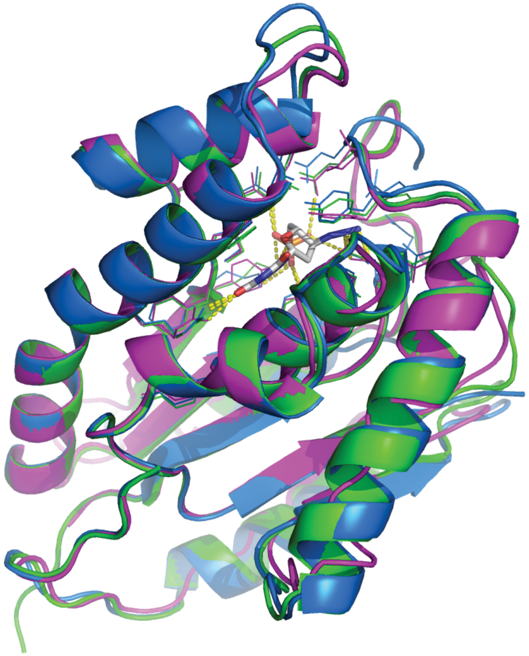
Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

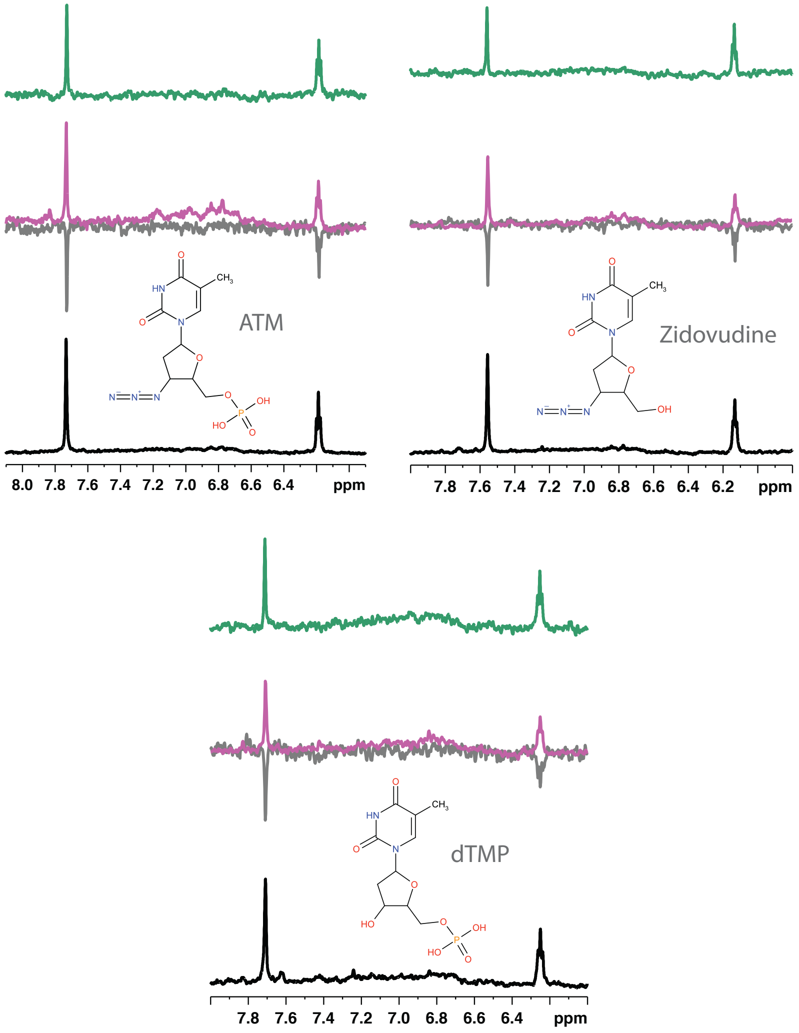
Drug Indication:

For the treatment of human immunovirus (HIV) infections.

P. falciparum thymidylate kinase + zidovudine

NMR Water-LOGSY and STD experiments



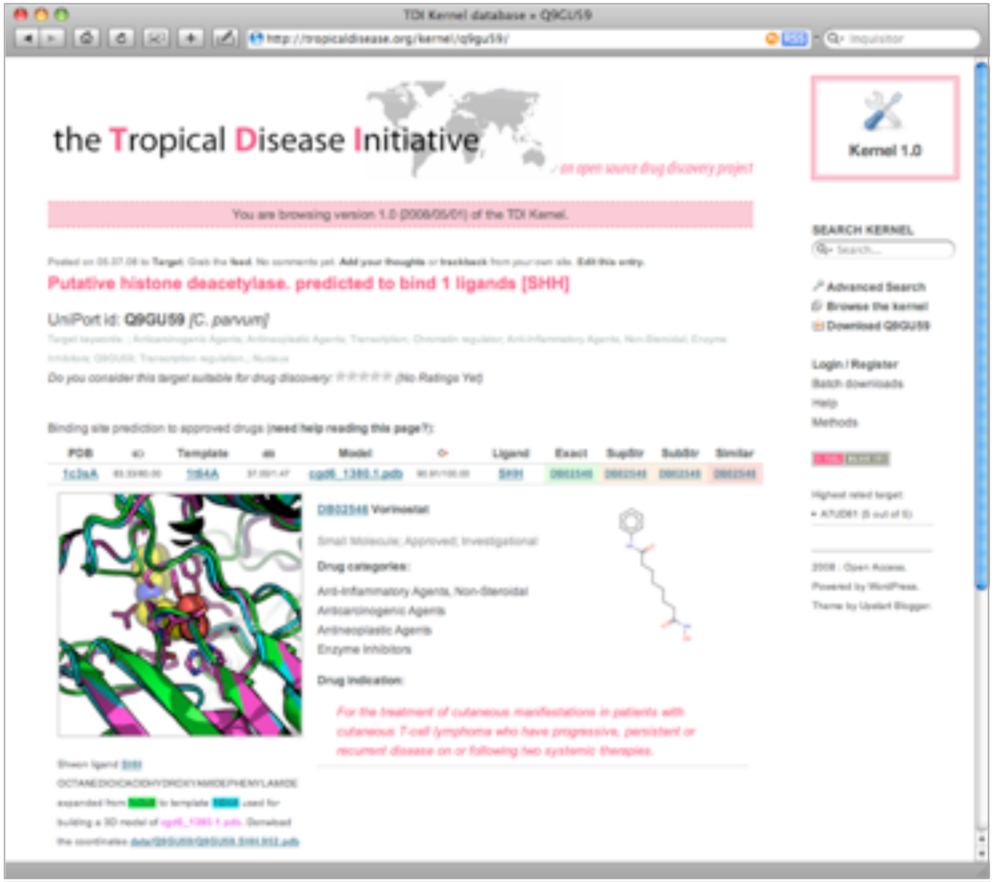

ATM
HN
O
CH3
N
O
N=N=N
O
OH
HO
P
O
8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 ppm
Zidovudine
HN
O
CH3
N
O
N=N=N
OH
7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 ppm
dTMP
HN
O
CH3
N
O
HO
O
OH
HO
P
O
7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 ppm

Leticia Ortí, Rodrigo J. Carbajo, and Antonio Pineda-Lucena

TDI’s kernel

http://tropicaldisease.org/kernel

*Ortí et al . “A kernel for open source drug discovery in tropical diseases”. PLoS Neglected Tropical Diseases. (2009) **3**:e18*
*Ortí et al . “A Kernel for the Tropical Disease Initiative”. Nature Biotechnology. (2009) **27**:320-321*



TDI Kernel database » Q9GU59

http://tropicaldisease.org/kernel/q9gu59/

the Tropical Disease Initiative

an open source drug discovery project

You are browsing version 1.0 (2008/05/01) of the TDI Kernel.

Posted on 06.07.08 to **Target**. Grab the **feed**. No comments yet. **Add your thoughts** or **trackback** from your own site. **Edit this entry.**

Putative histone deacetylase. predicted to bind 1 ligands [SHH]

UniPort id: **Q9GU59** *[C. parvum]*

Target keywords : ; Anticarcinogenic Agents; Antineoplastic Agents; Transcription; Chromatin regulator; Anti-Inflammatory Agents, Non-Steroidal; Enzyme Inhibitors; Q9GU59; Transcription regulation ; Nucleus

Do you consider this target suitable for drug discovery: ☆☆☆☆☆ *(No Ratings Yet)*

Binding site prediction to approved drugs (**need help reading this page?**):

PDB	ID	Template	sb	Model	C>	Ligand	Exact	SupStr	SubStr	Similar
1c3sA	65.33/80.00	1t64A	37.00/1.47	cgd6_1380.1.pdb	90.91/100.00	SHH	DB02546	DB02546	DB02546	DB02546

DB02546 Vorinostat

Small Molecule; Approved; Investigational

Drug categories:

Anti-Inflammatory Agents, Non-Steroidal
Anticarcinogenic Agents
Antineoplastic Agents
Enzyme Inhibitors

Drug indication:

For the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma who have progressive, persistent or recurrent disease on or following two systemic therapies.

Shown ligand SHH OCTANEDIOIC ACID HYDROXYAMIDE PHENYLAMIDE expanded from 1c3sA to template 1t64A used for building a 3D model of cgd6_1380.1.pdb. Download the coordinates data/Q9GU59/Q9GU59.SHH.922.pdb

Kernel 1.0

SEARCH KERNEL

Search...

Advanced Search
Browse the kernel
Download Q9GU59

Login / Register
Batch downloads
Help
Methods

Highest rated target:
- ATUD81 (5 out of 5)

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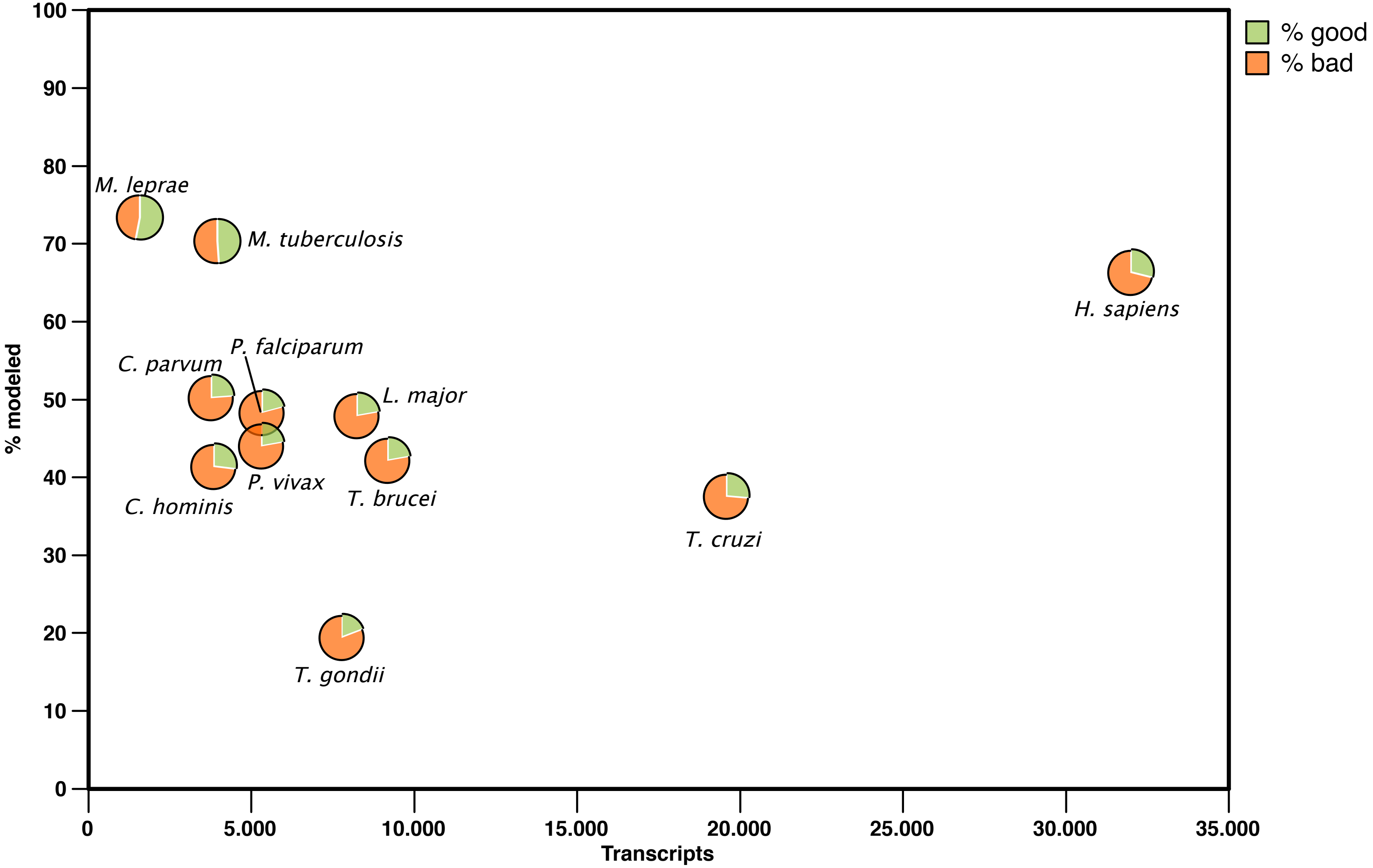
Powered by WordPress.
Theme by Upstart Blogger.

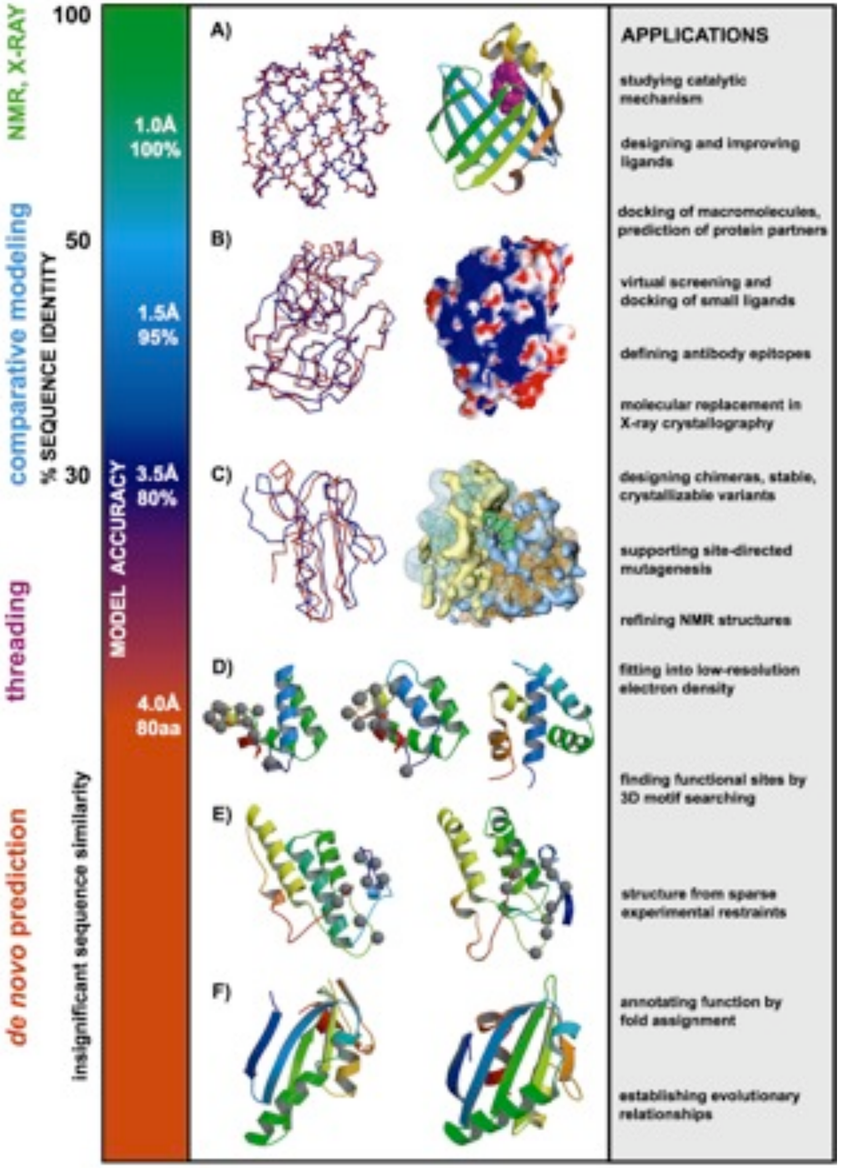
Modeling Genomes

data from models generated by ModPipe (Eswar, Pieper & Sali)



A good model has MPQS of 1.1 or higher

“take home” message


NMR, X-RAY
comparative modeling
threading
de novo prediction
% SEQUENCE IDENTITY
100
50
30
insignificant sequence similarity
MODEL ACCURACY
1.0Å
100%
1.5Å
95%
3.5Å
80%
4.0Å
80aa
A)
B)
C)
D)
E)
F)
APPLICATIONS
studying catalytic mechanism
designing and improving ligands
docking of macromolecules, prediction of protein partners
virtual screening and docking of small ligands
defining antibody epitopes
molecular replacement in X-ray crystallography
designing chimeras, stable, crystallizable variants
supporting site-directed mutagenesis
refining NMR structures
fitting into low-resolution electron density
finding functional sites by 3D motif searching
structure from sparse experimental restraints
annotating function by fold assignment
establishing evolutionary relationships

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

Comparative Protein Structure Prediction
MODELLER tutorial

```
$>mod9v6 model.py
```

Marc A. Marti-Renom

http://bioinfo.cipf.es/sgu/

Structural Genomics Unit
Bioinformatics Department
Prince Felipe Resarch Center (CIPF), Valencia, Spain

PRINCIPE FELIPE
CENTRO DE INVESTIGACION

Obtaining MODELLER and related information

- MODELLER web page
- http://www.salilab.org/modeller/
  - Download Software (Linux/Windows/Mac/Solaris)
  - HTML Manual
  - **Join Mailing List**

Using MODELLER

- No GUI! ☹
- Controlled by command file ☹☹
- Script is written in PYTHON language ☺
- You may know Python language is simple ☺☺

MODELLER 9v6

Python interface

- Modeller Python interface uses classes, e.g.:
  - ‘alignment’ *holds and manipulates aligned sequences*
  - ‘model’ *holds and manipulates protein models*
  - ‘environ’ *keeps the configuration of the environment*
  - ‘profile’ *holds and manipulates sequence profiles*
  - ‘sequence_db’ *is for sequence databases*
- These behave just like ordinary Python classes, but Modeller Fortran code is linked to them
- The Modeller data is automatically freed when the Python object is deleted (explicitly or implicitly)

Using MODELLER

- INPUT:
  - Target Sequence (FASTA/PIR format)
  - Template Structure (PDB format)
  - Python file
- OUTPUT:
  - Target-Template Alignment
  - Model in PDB format
  - Other data

Modeling of BLBP
Input

- Target: Brain lipid-binding protein (BLBP)
- BLBP sequence in PIR (MODELLER) format:

```
>P1;blbp
sequence:blbp::::::::
VDAFCATWKLTDSQNFDEYMKALGVGFATRQVGNVTKPTVIISQEGGKVVIRTQCTFKNTEINFQLGEEFEETSID
DRNCKSVVRLDGDKLIHVQKWDGKETNCTREIKDGKMVVTLTFGDIVAVRCYEKA*
```

Modeling of BLBP

STEP 1: Align blbp and 1hms sequences

Python script for target-template alignment

```
# Example for: alignment.align()

# This will read two sequences, align them, and write the alignment
# to a file:

log.verbose()
env = environ()

aln = alignment(env)
mdl = model(env, file='1hms')
aln.append_model(mdl, align_codes='1hms')
aln.append(file='blbp.seq', align_codes=('blbp'))

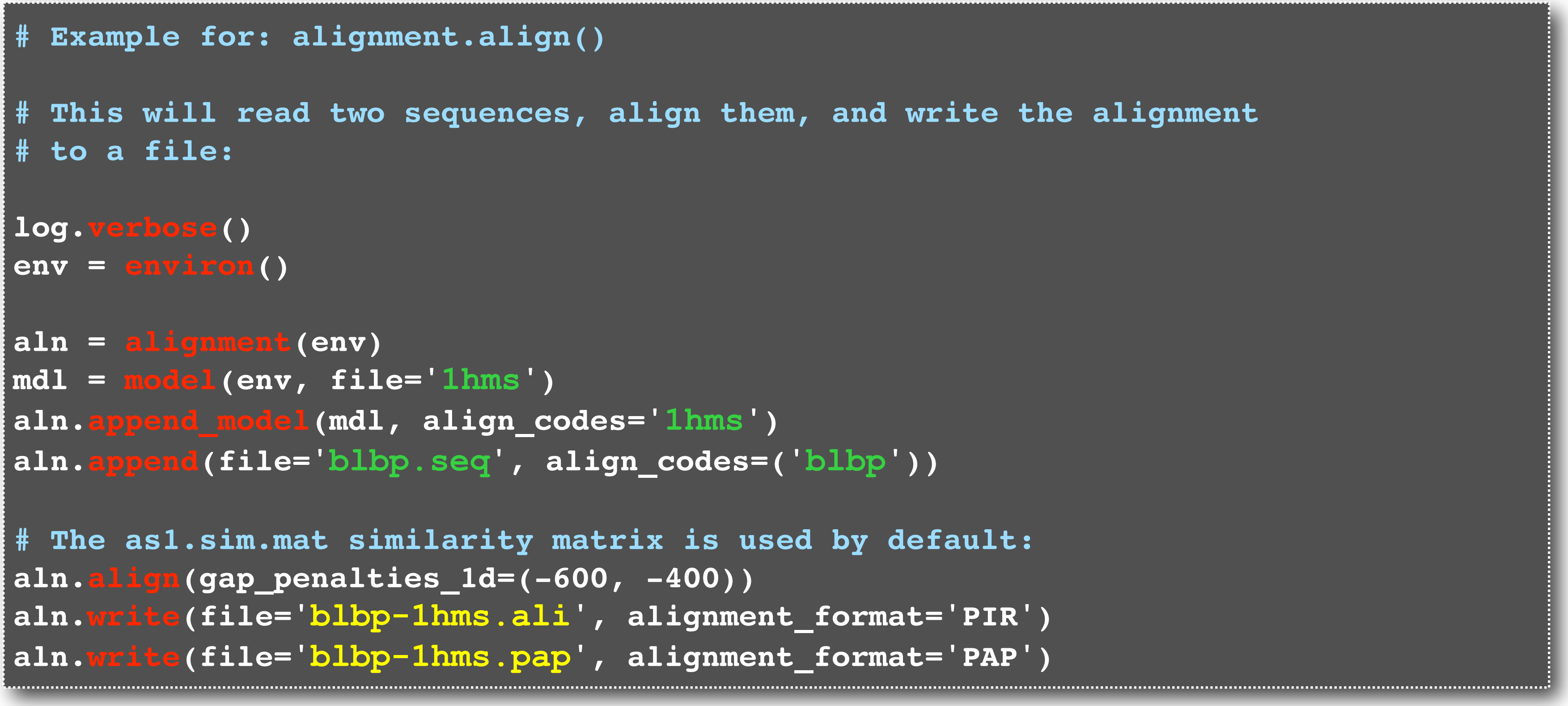
# The as1.sim.mat similarity matrix is used by default:
aln.align(gap_penalties_1d=(-600, -400))
aln.write(file='blbp-1hms.ali', alignment_format='PIR')
aln.write(file='blbp-1hms.pap', alignment_format='PAP')
```

Run by typing `mod9v6 align.py` in the directory where you have the python file.
MODELLER will produce a `align.log` file

Modeling of BLBP

STEP 1: Align blbp and 1hms sequences

Python script for target-template alignment



```
# Example for: alignment.align()

# This will read two sequences, align them, and write the alignment
# to a file:

log.verbose()
env = environ()

aln = alignment(env)
mdl = model(env, file='1hms')
aln.append_model(mdl, align_codes='1hms')
aln.append(file='blbp.seq', align_codes=('blbp'))

# The as1.sim.mat similarity matrix is used by default:
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aln.write(file='blbp-1hms.ali', alignment_format='PIR')
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```

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Modeling of BLBP
STEP 1: Align blbp and 1hms sequences
Python script for target-template alignment

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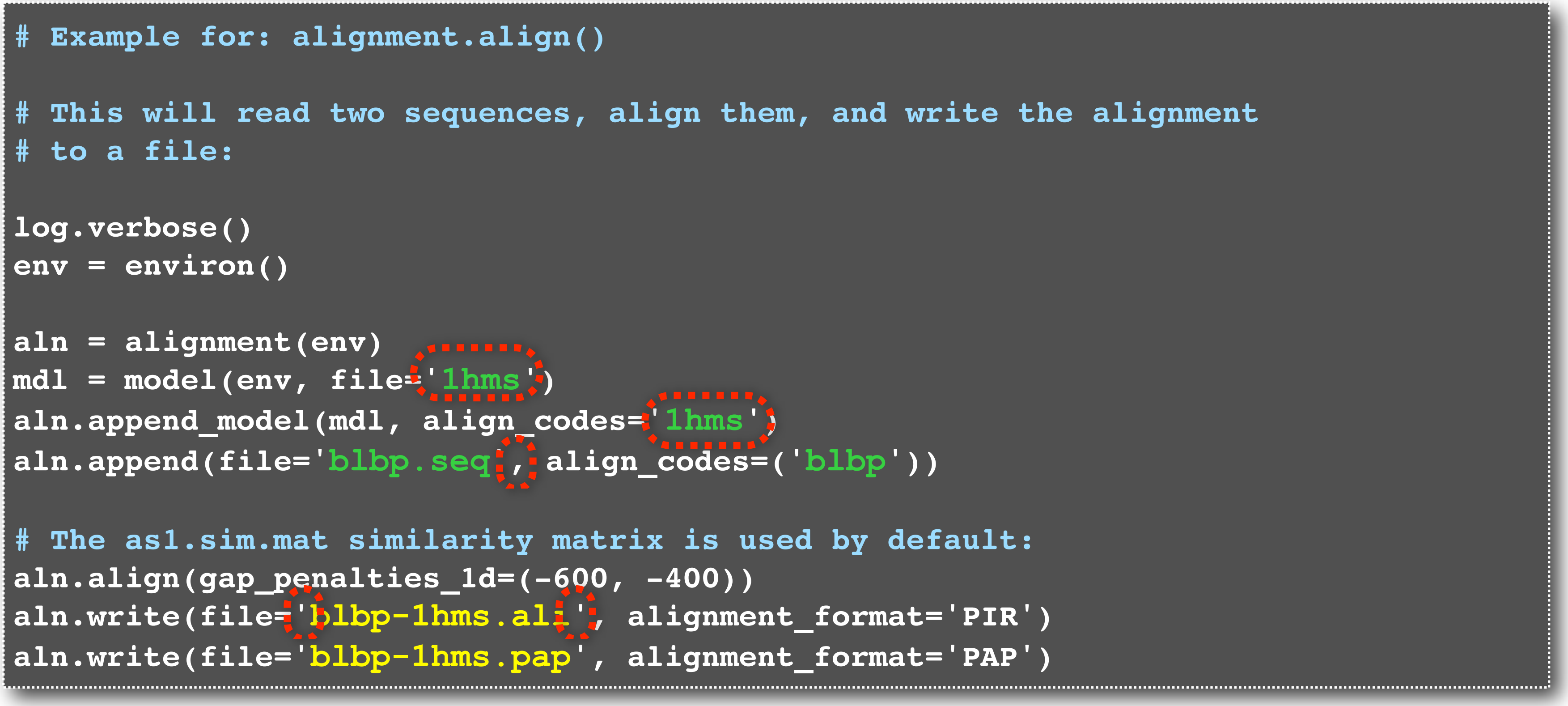
Modeling of BLBP

STEP 1: Align blbp and 1hms sequences

Python script for target-template alignment



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MODELLER will produce a `align.log` file

Modeling of BLBP

STEP 1: Align blbp and 1hms sequences

Output

```
>P1;1hms
structureX:1hms:   1 : : 131 : :undefined:undefined:-1.00:-1.00
VDAFLGTWKLVDSKNFDDYMKSLGVGFATRQVASMTKPTTIIEKNGDILTLKTHSTFKNTEISFKLGVEFDETTA
DDRKVKSIVTLDGGKLVHLQKWDGQETTLVRELIDGKLILTLTHGTAVCTRTYEKE*
>P1;blbp
sequence:blbp:     : :     : : : : 0.00: 0.00
VDAFCATWKLTDSQNFDEYMKALGVGFATRQVGNVTKPTVIISQEGGKVVIRTQCTFKNTEINFQLGEEFEETSI
DDRNCKSVVRLDGDKLIHVQKWDGKETNCTREIKDGKMVVTLTFGDIVAVRCYEKA*
```

Modeling of BLBP

STEP 1: Align blbp and 1hms sequences

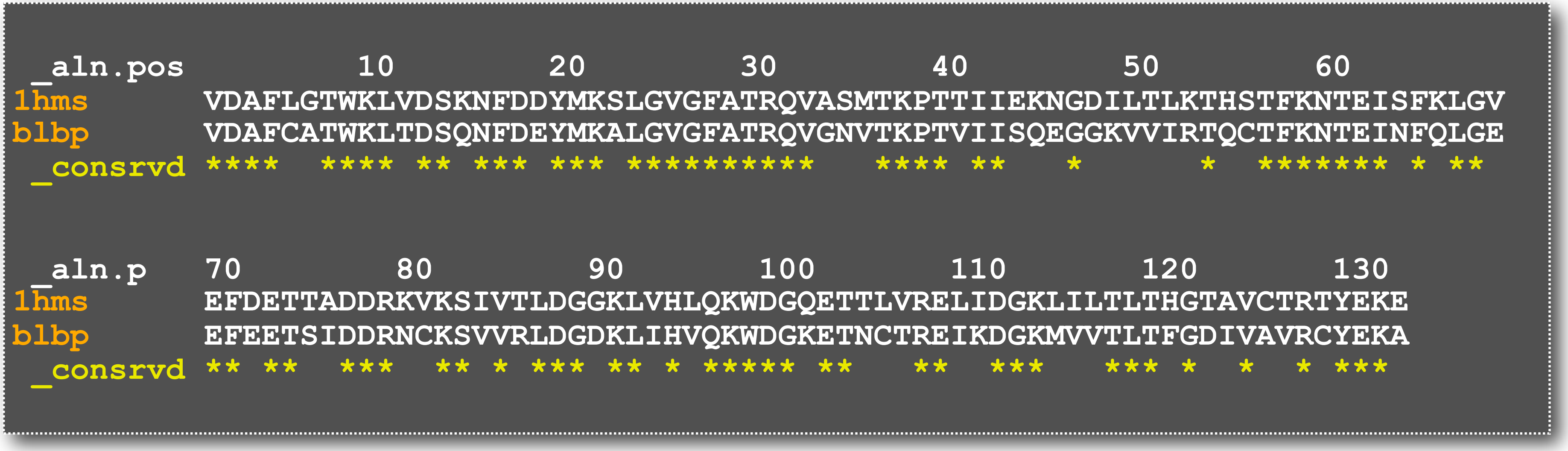
Output

```
>P1;1hms
structureX:1hms:   1 :  : 131 :  :undefined:undefined:-1.00:-1.00
VDAFLGTWKLVDSKNFDDYMKSLGVGFATRQVASMTKPTTIIEKNGDILTLKTHSTFKNTEISFKLGVEFDETTA
DDRKVKSIVTLDGGKLVHLQKWDGQETTLVRELIDGKLILTLTHGTAVCTRTYEKE*
>P1;blbp
sequence:blbp:     : :     : : : : 0.00: 0.00
VDAFCATWKLTDSQNFDEYMKALGVGFATRQVGNVTKPTVIISQEGGKVVIRTQCTFKNTEINFQLGEEFEETSI
DDRNCKSVVRLDGDKLIHVQKWDGKETNCTREIKDGKMVVTLTFGDIVAVRCYEKA*
```

Modeling of BLBP

STEP 1: Align blbp and 1hms sequences

Output



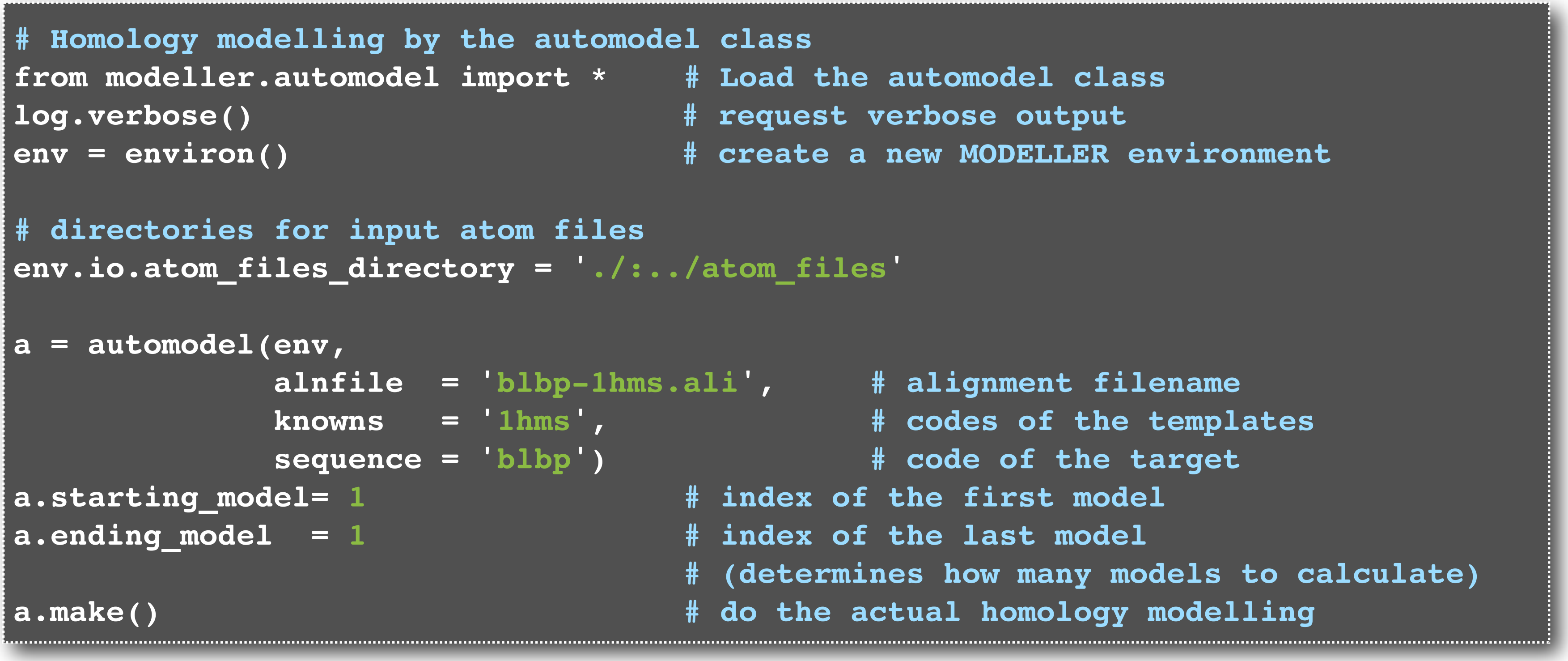
```
 _aln.pos             10        20        30        40        50        60
1hms          VDAFLGTWKLVDSKNFDDYMKSLGVGFATRQVASMTKPTTIIEKNGDILTLKTHSTFKNTEISFKLGV
blbp          VDAFCATWKLTDSQNFDEYMKALGVGFATRQVGNVTKPTVIISQEGGKVVIRTQCTFKNTEINFQLGE
 _consrvd     ****  **** ** *** *** **********   **** **   *      *  ******* * **


 _aln.p       70        80        90       100       110       120       130
1hms          EFDETTADDRKVKSIVTLDGGKLVHLQKWDGQETTLVRELIDGKLILTLTHGTAVCTRTYEKE
blbp          EFEETSIDDRNCKSVVRLDGDKLIHVQKWDGKETNCTREIKDGKMVVTLTFGDIVAVRCYEKA
 _consrvd     ** **  ***  ** * *** ** * ***** **   **  ***   *** *  *  * ***
```

Modeling of BLBP

STEP 2: Model the blbp structure using the alignment from step 1.

Python script for model building



```
# Homology modelling by the automodel class
from modeller.automodel import *    # Load the automodel class
log.verbose()                       # request verbose output
env = environ()                     # create a new MODELLER environment

# directories for input atom files
env.io.atom_files_directory = './:../atom_files'

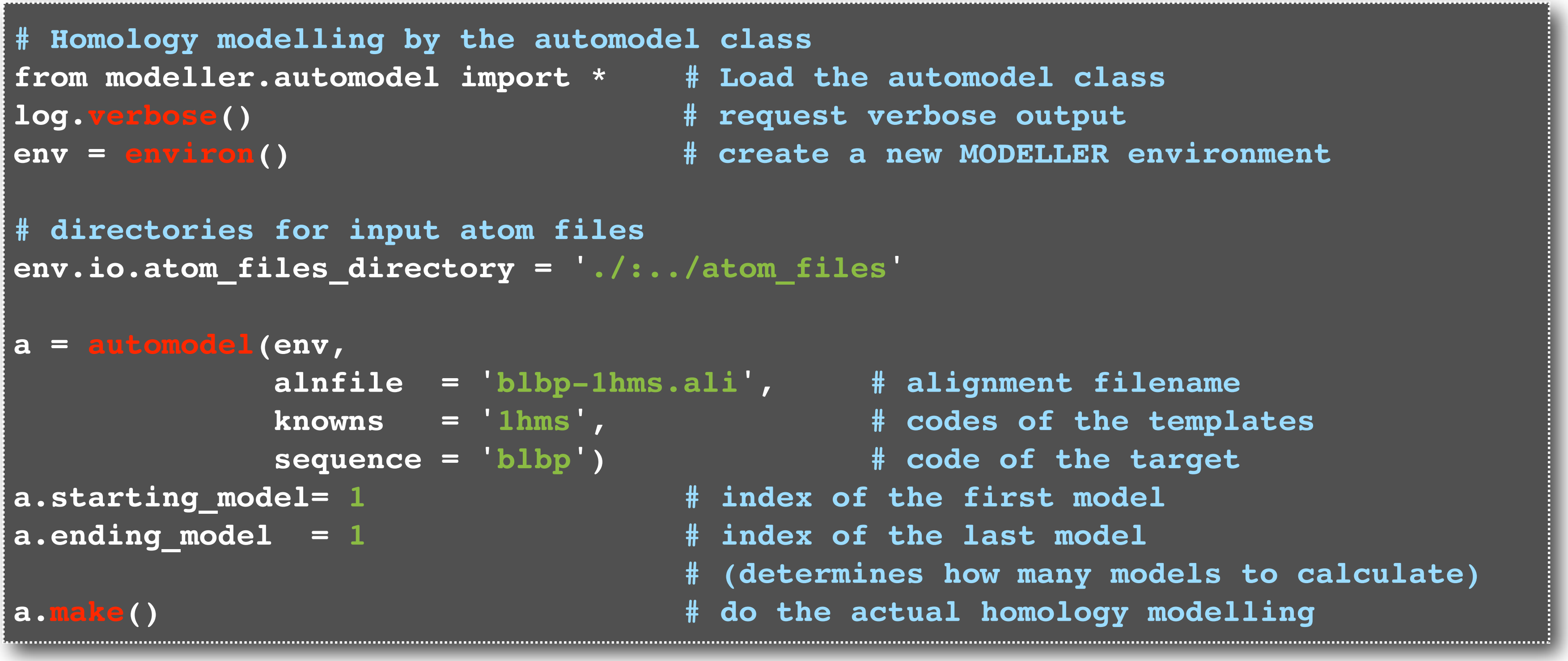
a = automodel(env,
              alnfile  = 'blbp-1hms.ali',     # alignment filename
              knowns   = '1hms',              # codes of the templates
              sequence = 'blbp')              # code of the target
a.starting_model= 1                 # index of the first model
a.ending_model  = 1                 # index of the last model
                                    # (determines how many models to calculate)
a.make()                            # do the actual homology modelling
```

Run by typing `mod9v6 model.py` in the directory where you have the python file. MODELLER will produce a `model.log` file

Modeling of BLBP

STEP 2: Model the blbp structure using the alignment from step 1.

Python script for model building



```
# Homology modelling by the automodel class
from modeller.automodel import *    # Load the automodel class
log.verbose()                       # request verbose output
env = environ()                     # create a new MODELLER environment

# directories for input atom files
env.io.atom_files_directory = './:../atom_files'

a = automodel(env,
              alnfile  = 'blbp-1hms.ali',     # alignment filename
              knowns   = '1hms',              # codes of the templates
              sequence = 'blbp')              # code of the target
a.starting_model= 1                 # index of the first model
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                                    # (determines how many models to calculate)
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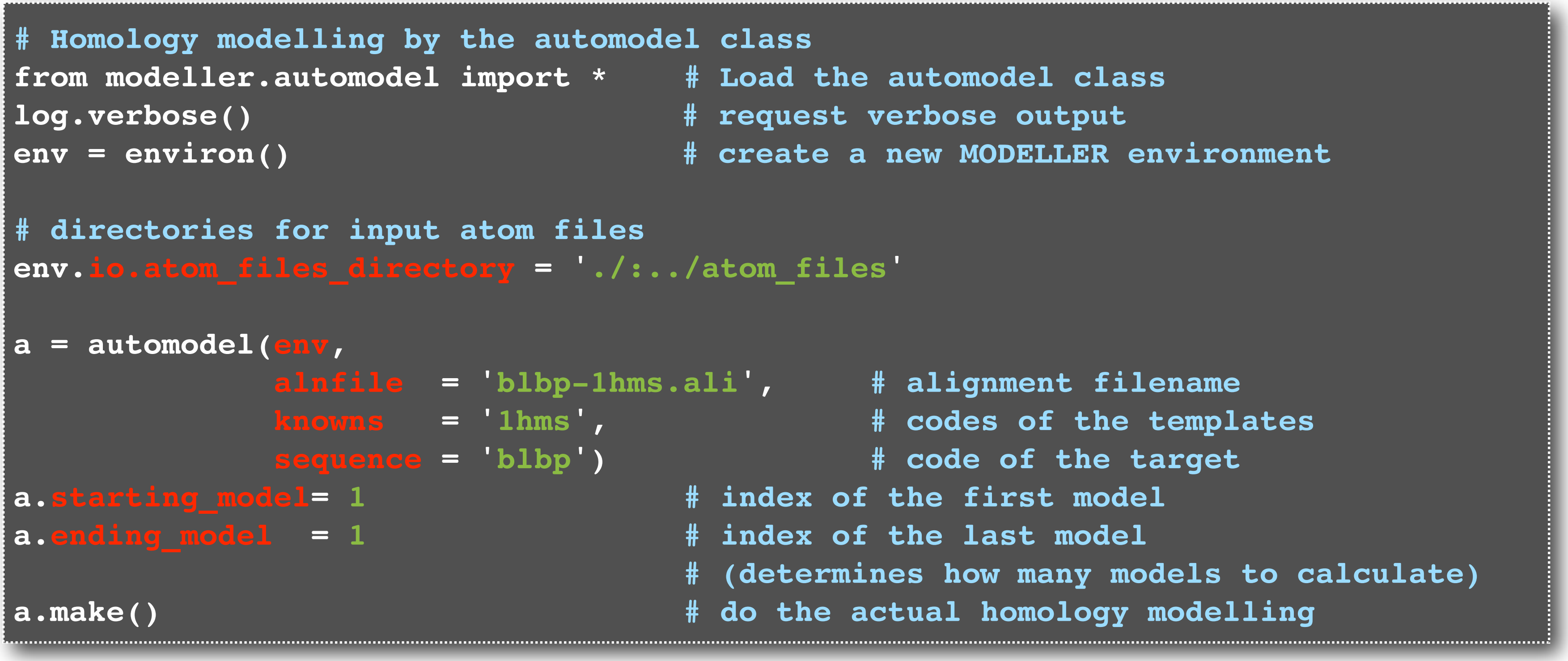
Modeling of BLBP

STEP 2: Model the blbp structure using the alignment from step 1.

Python script for model building



```
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from modeller.automodel import *     # Load the automodel class
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env = environ()                      # create a new MODELLER environment

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              alnfile  = 'blbp-1hms.ali',      # alignment filename
              knowns   = '1hms',               # codes of the templates
              sequence = 'blbp')               # code of the target
a.starting_model= 1                  # index of the first model
a.ending_model  = 1                  # index of the last model
                                     # (determines how many models to calculate)
a.make()                             # do the actual homology modelling
```

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MODELLER will produce a `model.log` file

Modeling of BLBP

STEP 2: Model the blbp structure using the alignment from step 1.

Python script for model building

PDB file

Can be viewed with Chimera

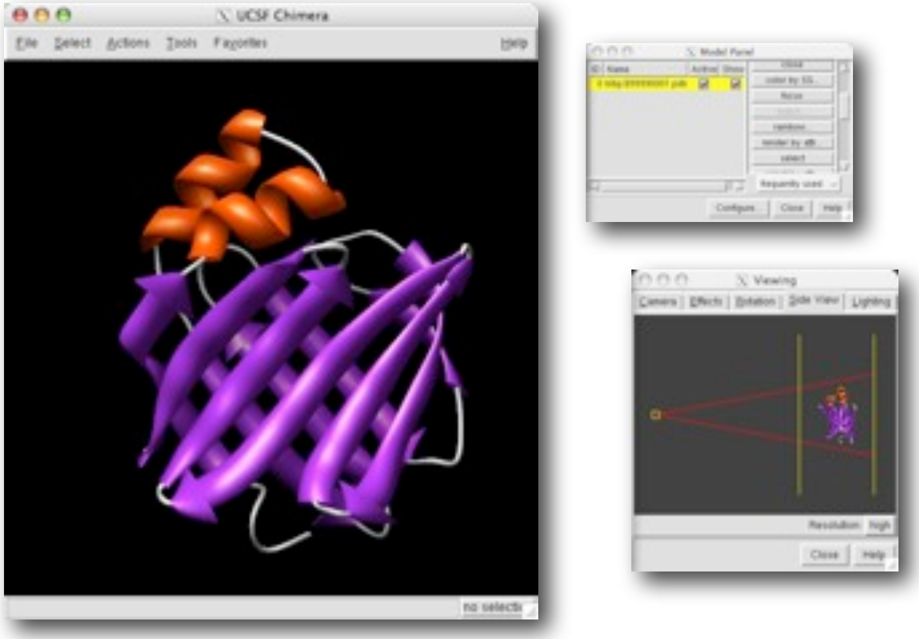
http://www.cgl.ucsf.edu/chimera/

Rasmol

http://www.openrasmol.org

PyMol

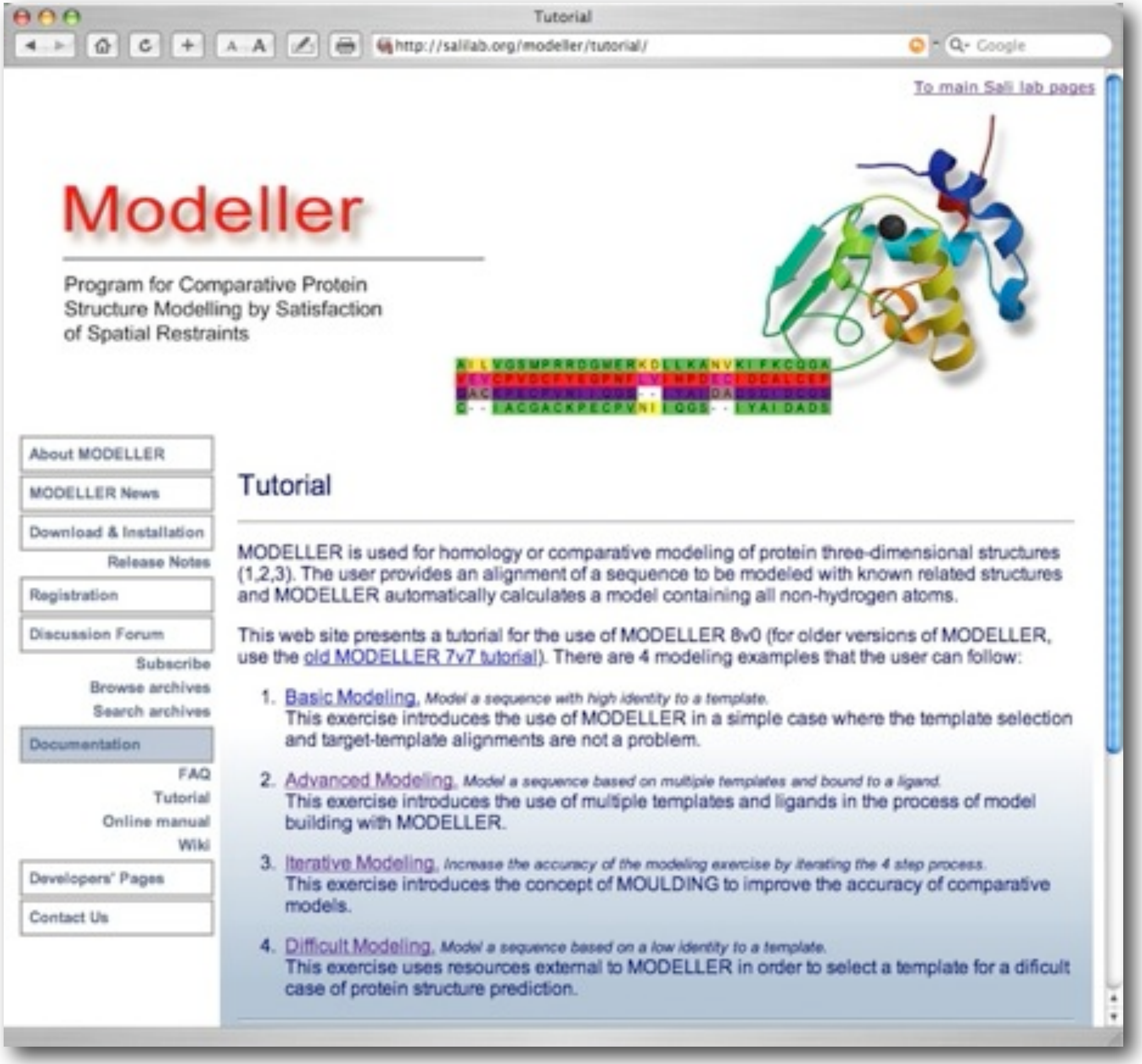
http://pymol.sourceforge.net/



Model file →

`blbp.B99990001.pdb`

http://www.salilab.org/modeller/tutorial/



To main Sali lab pages

Modeller

Program for Comparative Protein Structure Modelling by Satisfaction of Spatial Restraints

Tutorial

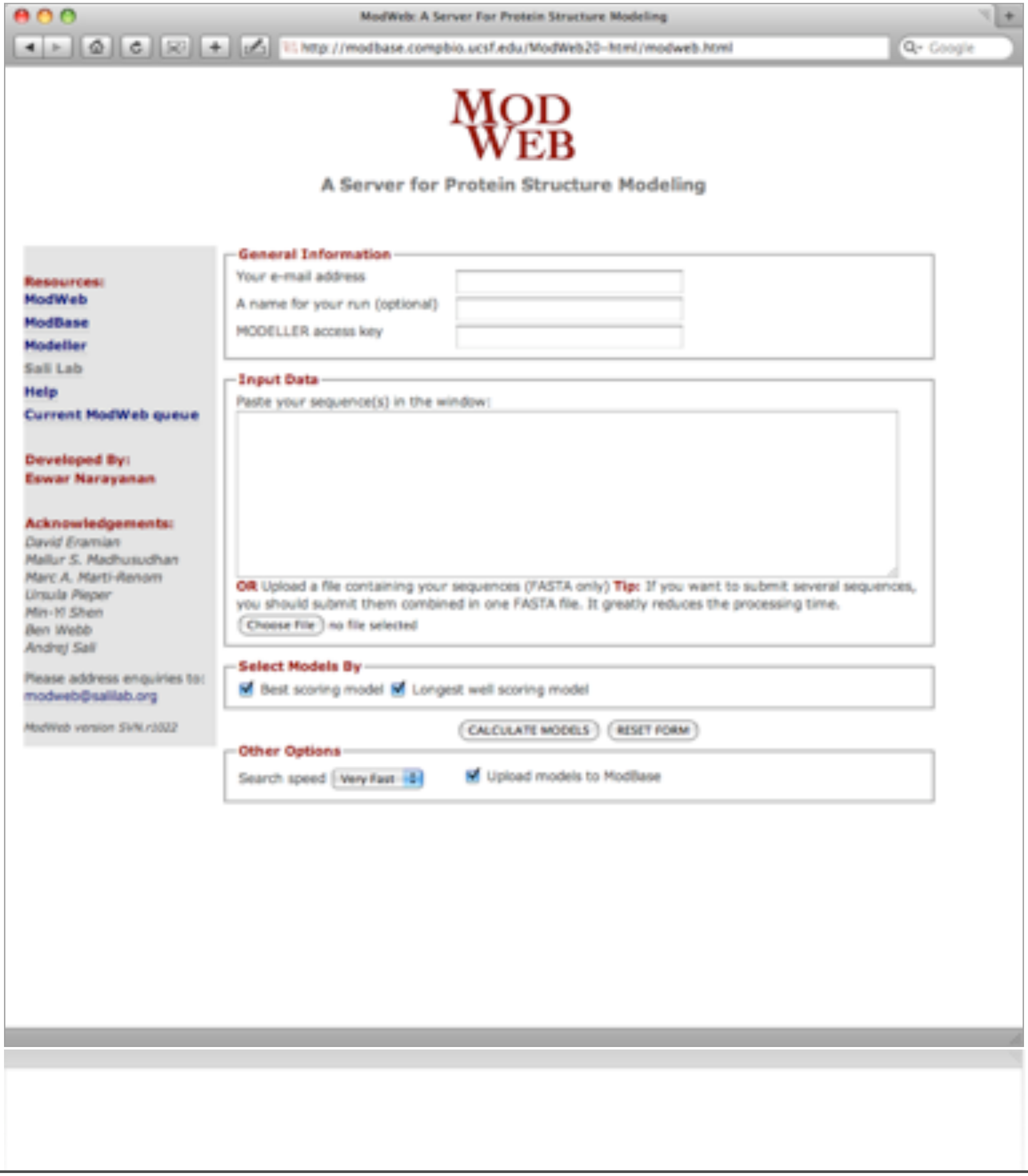
MODELLER is used for homology or comparative modeling of protein three-dimensional structures (1,2,3). The user provides an alignment of a sequence to be modeled with known related structures and MODELLER automatically calculates a model containing all non-hydrogen atoms.

This web site presents a tutorial for the use of MODELLER 8v0 (for older versions of MODELLER, use the old MODELLER 7v7 tutorial). There are 4 modeling examples that the user can follow:

1. Basic Modeling. *Model a sequence with high identity to a template.*
   This exercise introduces the use of MODELLER in a simple case where the template selection and target-template alignments are not a problem.
2. Advanced Modeling. *Model a sequence based on multiple templates and bound to a ligand.*
   This exercise introduces the use of multiple templates and ligands in the process of model building with MODELLER.
3. Iterative Modeling. *Increase the accuracy of the modeling exercise by iterating the 4 step process.*
   This exercise introduces the concept of MOULDING to improve the accuracy of comparative models.
4. Difficult Modeling. *Model a sequence based on a low identity to a template.*
   This exercise uses resources external to MODELLER in order to select a template for a dificult case of protein structure prediction.

MODWEB

http://salilab.org/modweb



ModWeb: A Server For Protein Structure Modeling
http://modbase.compbio.ucsf.edu/ModWeb20-html/modweb.html
Google
MOD WEB

A Server for Protein Structure Modeling

Resources:
ModWeb
ModBase
Modeller
Sali Lab
Help
Current ModWeb queue

Developed By:
Eswar Narayanan

Acknowledgements:
David Eramian
Mallur S. Madhusudhan
Marc A. Marti-Renom
Ursula Pieper
Min-Yi Shen
Ben Webb
Andrej Sali

Please address enquiries to:
modweb@salilab.org

ModWeb version SVN.r1022

General Information

Your e-mail address
A name for your run (optional)
MODELLER access key

Input Data

Paste your sequence(s) in the window:

OR Upload a file containing your sequences (FASTA only) **Tip:** If you want to submit several sequences, you should submit them combined in one FASTA file. It greatly reduces the processing time.

Choose File no file selected

Select Models By

☑ Best scoring model ☑ Longest well scoring model

CALCULATE MODELS RESET FORM

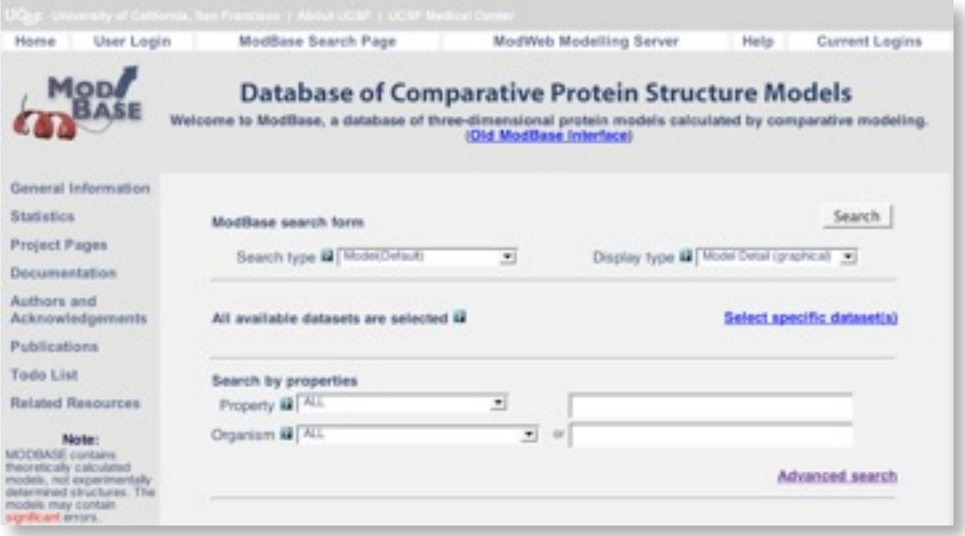
Other Options

Search speed Very Fast ☑ Upload models to ModBase

MODBASE

http://salilab.org/modbase

Search Page



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Home | User Login | ModBase Search Page | ModWeb Modelling Server | Help | Current Logins

Database of Comparative Protein Structure Models

Welcome to ModBase, a database of three-dimensional protein models calculated by comparative modeling. (Old ModBase Interface)

- General Information
- Statistics
- Project Pages
- Documentation
- Authors and Acknowledgements
- Publications
- Todo List
- Related Resources

Note: MODBASE contains theoretically calculated models, not experimentally determined structures. The models may contain significant errors.

ModBase search form [Search]

Search type: Model(Default) | Display type: Model Detail (graphical)

All available datasets are selected | Select specific dataset(s)

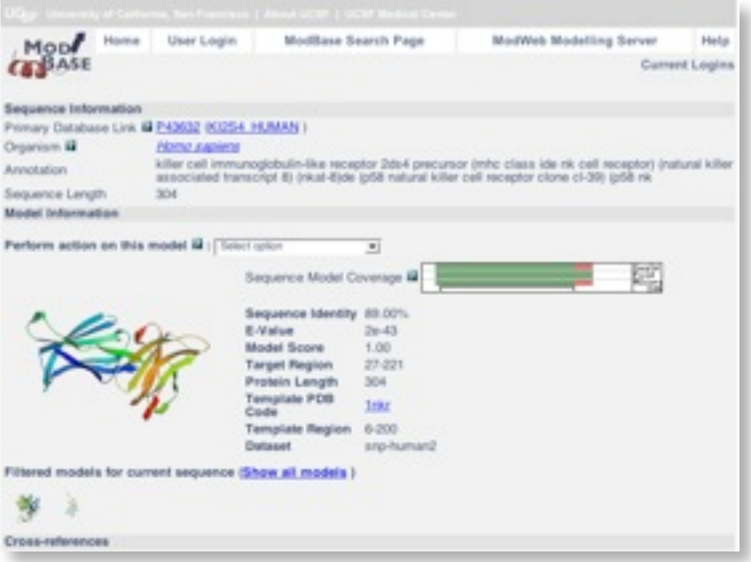
Search by properties

Property: ALL

Organism: ALL or

Advanced search

Model Details



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Home | User Login | ModBase Search Page | ModWeb Modelling Server | Help | Current Logins

Sequence Information

Primary Database Link	P43632 (KI2S4_HUMAN)
Organism	Homo sapiens
Annotation	killer cell immunoglobulin-like receptor 2ds4 precursor (mhc class ide nk cell receptor) (natural killer associated transcript 8) (nkat-8)de (p58 natural killer cell receptor clone cl-39) (p58 nk
Sequence Length	304

Model Information

Perform action on this model: Select option

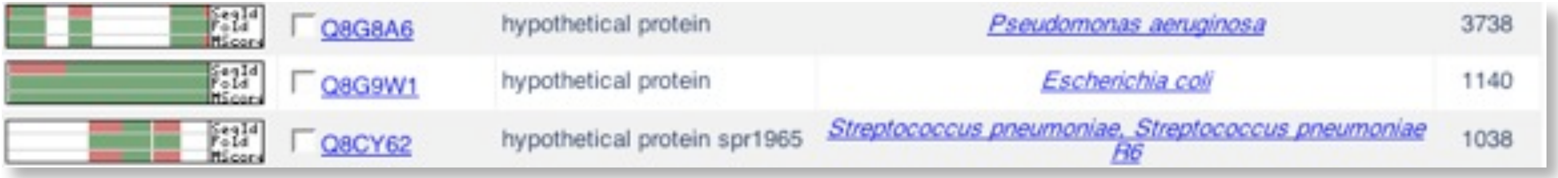
Sequence Model Coverage

Sequence Identity	89.00%
E-Value	2e-43
Model Score	1.00
Target Region	27-221
Protein Length	304
Template PDB Code	1nkr
Template Region	6-200
Dataset	snp-human2

Filtered models for current sequence (Show all models)

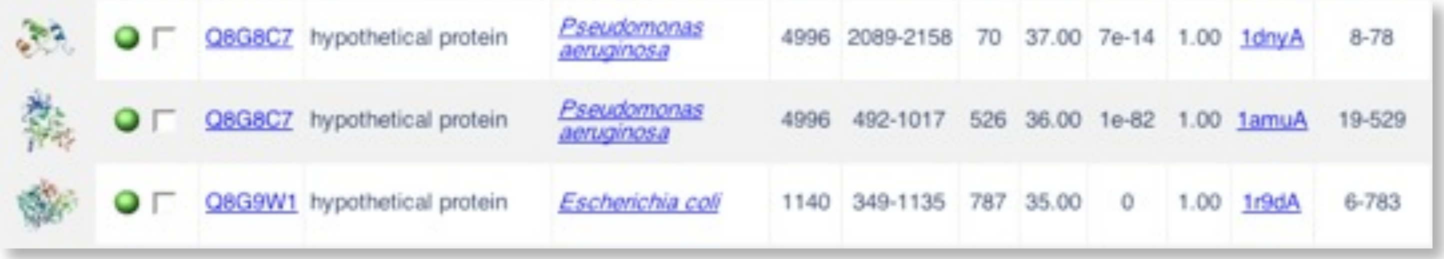
Cross-references

Sequence Overview



SeqId Fold MScore	□	Q8G8A6	hypothetical protein	*Pseudomonas aeruginosa*	3738
SeqId Fold MScore	□	Q8G9W1	hypothetical protein	*Escherichia coli*	1140
SeqId Fold MScore	□	Q8CY62	hypothetical protein spr1965	*Streptococcus pneumoniae, Streptococcus pneumoniae R6*	1038

Model Overview



	●	□	Q8G8C7	hypothetical protein	*Pseudomonas aeruginosa*	4996	2089-2158	70	37.00	7e-14	1.00	1dnyA	8-78
	●	□	Q8G8C7	hypothetical protein	*Pseudomonas aeruginosa*	4996	492-1017	526	36.00	1e-82	1.00	1amuA	19-529
	●	□	Q8G9W1	hypothetical protein	*Escherichia coli*	1140	349-1135	787	35.00	0	1.00	1r9dA	6-783

Pieper et al. (2004) Nucleic Acids Research 32, D217-D222

Acknowledgments

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