Comparative Protein Structure Prediction

Marc A. Marti-Renom
http://bioinfo.cipf.es/sgu/

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

Summary

- INTRO
- MOULDER
- Function from models
- Examples

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

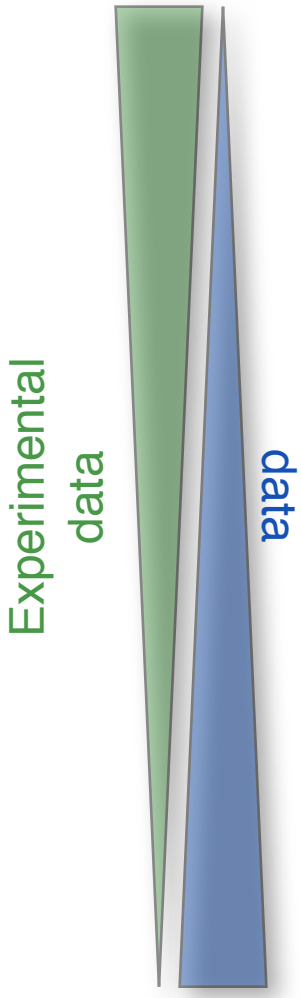
X-Ray

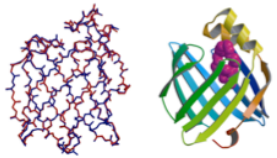
NMR

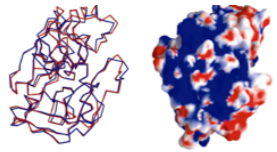
Comparative Modeling

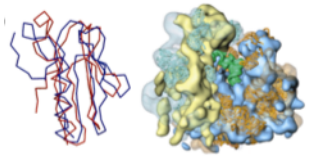
Threading

Ab-initio



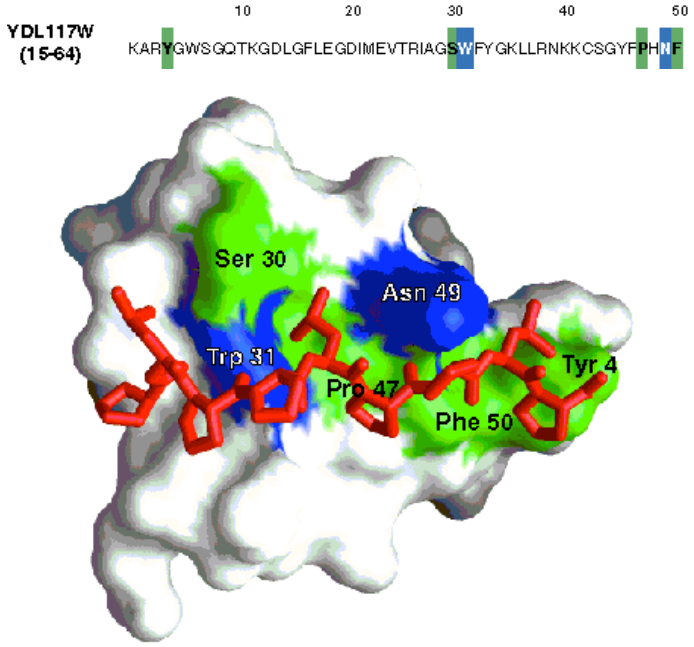






Why is it useful to know the structure of a protein, not only its sequence?

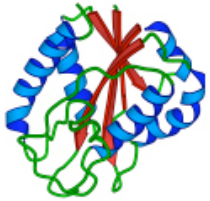
- The biochemical function (activity) of a protein is defined by its interactions with other molecules.
- The biological function is in large part a consequence of these interactions.
- The 3D structure is more informative than sequence because interactions are determined by residues that are close in space but are frequently distant in sequence.



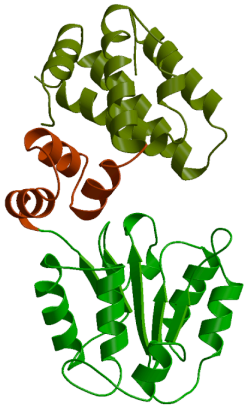
In addition, since evolution tends to conserve function and function depends more directly on structure than on sequence, **structure is more conserved in evolution than sequence**.

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

From domains to assemblies

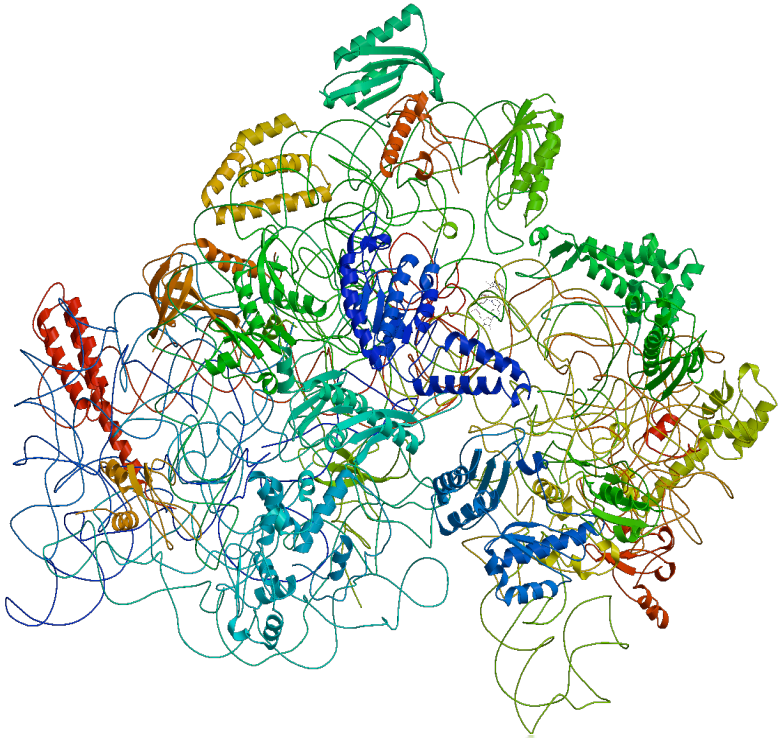


domains



proteins

assemblies

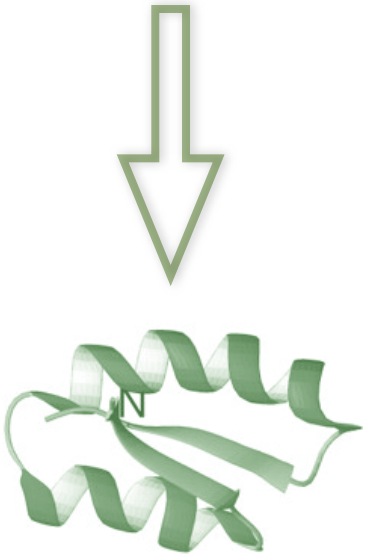


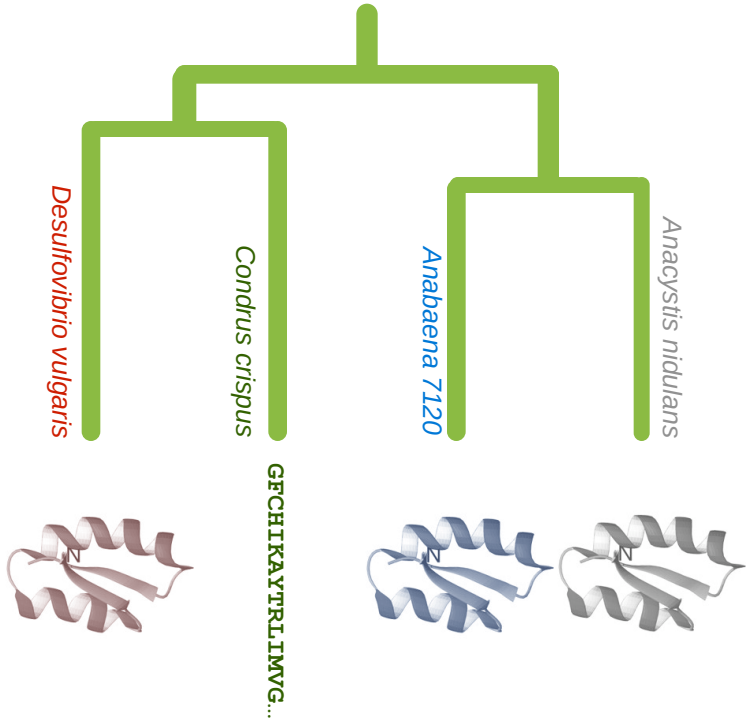
~2.5 domains in a protein
a few domain partners per domain

Russell etal. Curr Opin Struct Biol 14, 313, 2004.

Principles of protein structure

GFCHIKAYTRLIMVG...





Folding (physics)

Ab initio prediction

Evolution (rules)

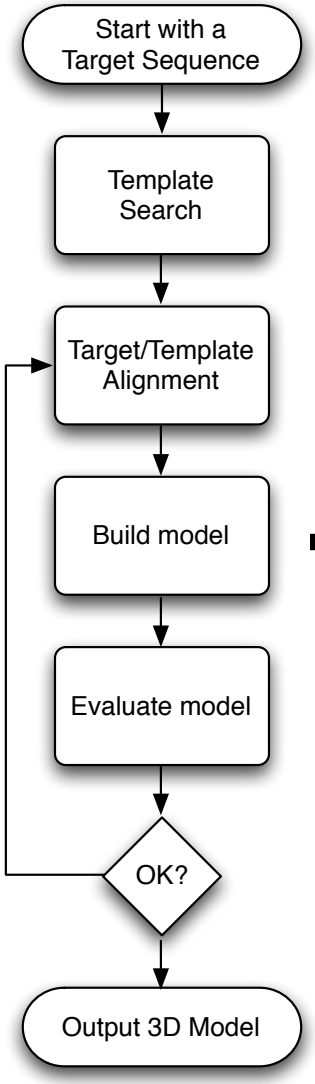
Threading

Comparative Modeling

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

Comparative modeling by satisfaction of spatial restraints

MODELLER

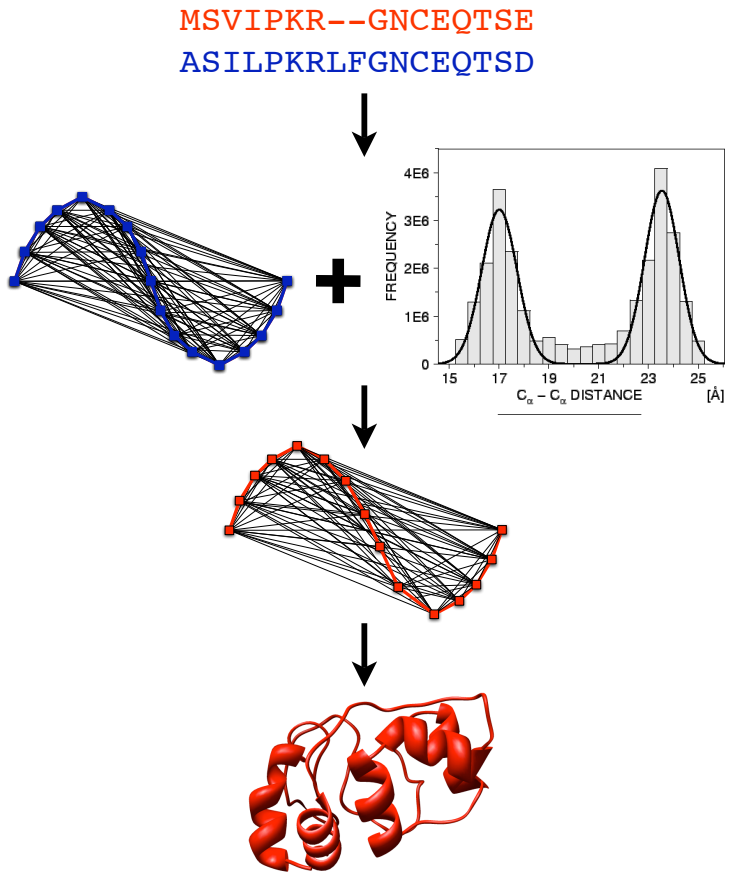


Given an alignment...

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

apply these features as restraints on your target sequence

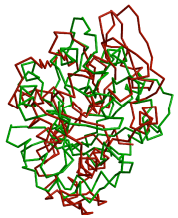
optimize to find the best solution for the restraints to produce your 3D model



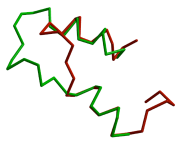
A. Šali & T. Blundell. J. Mol. Biol. 234, 779, 1993.
J.P. Overington & A. Šali. Prot. Sci. 3, 1582, 1994.
A. Fiser, R. Do & A. Šali, Prot. Sci., 9, 1753, 2000.

Comparative modeling by satisfaction of spatial restraints

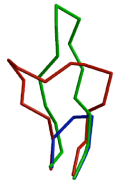
Types of errors and their impact



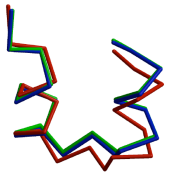
Wrong fold



Miss alignments

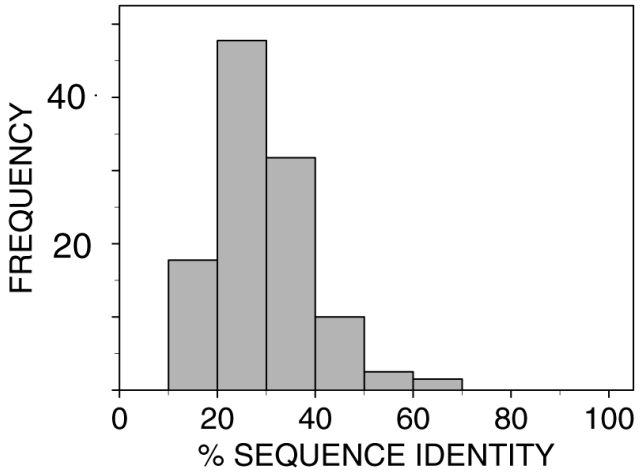


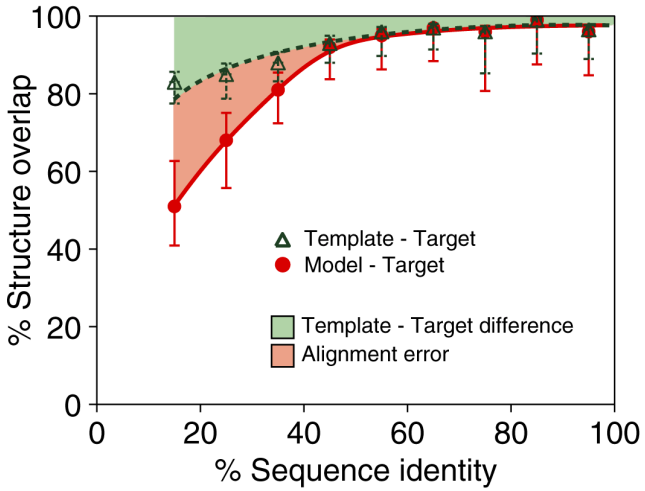
Loop regions



Rigid body distortions

Side-chain packing





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

Model Accuracy

HIGH ACCURACY

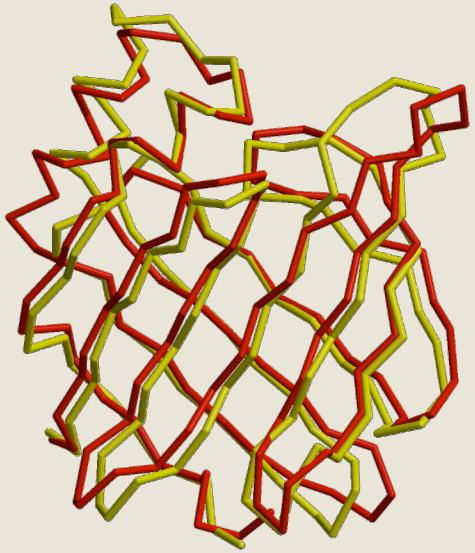
NM23
Seq id 77%
Cα equiv 147/148
RMSD 0.41Å

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

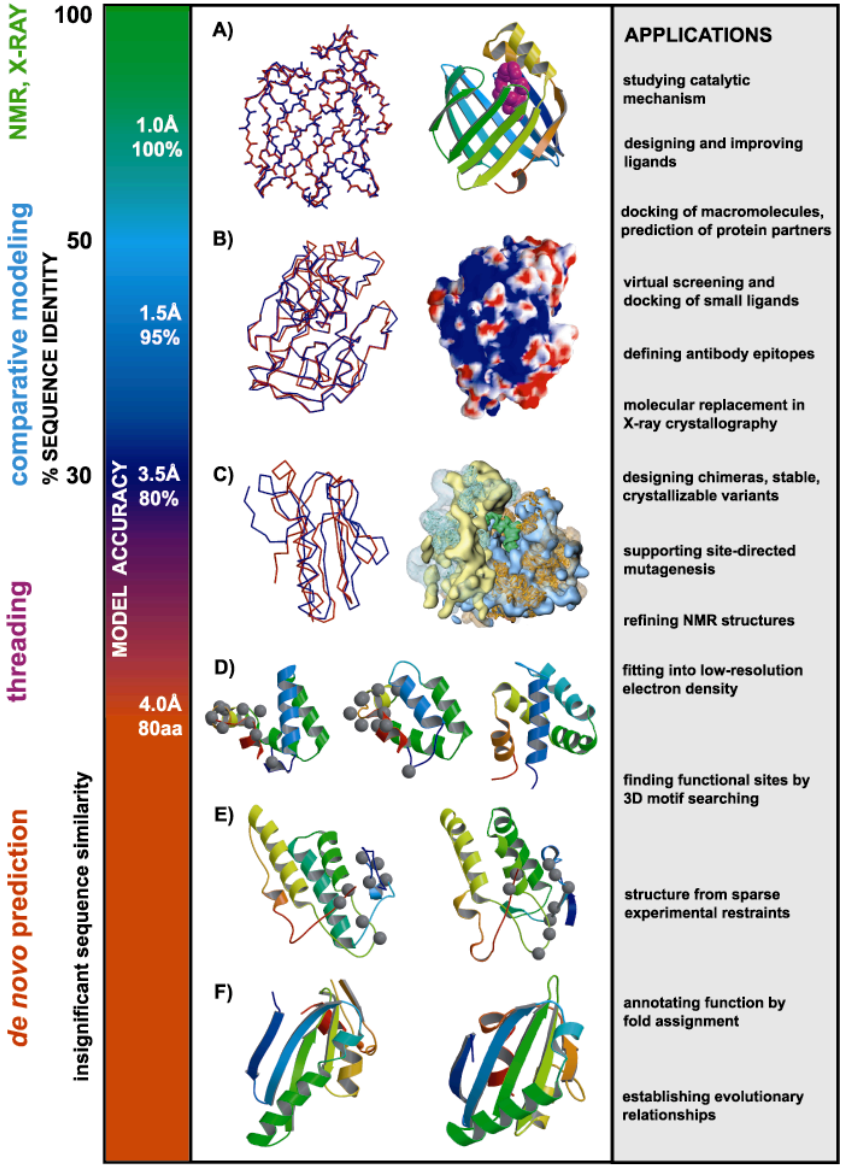
LOW ACCURACY

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

Sidechains
Core backbone
Loops
Alignment
Fold assignment

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

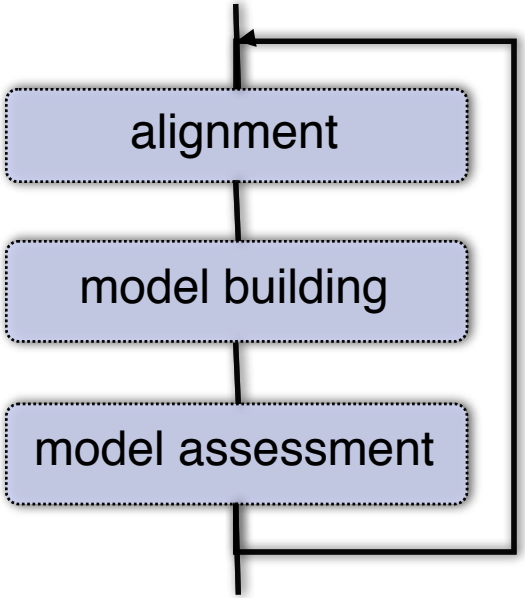
Utility of protein structure models, despite errors

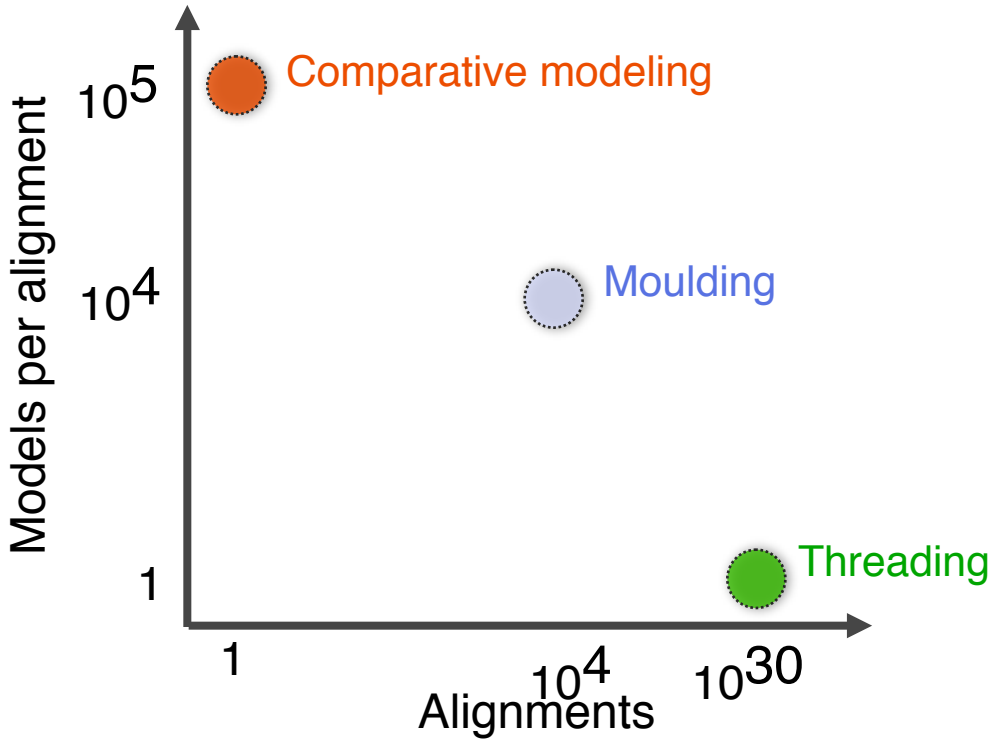


D. Baker & A. Sali. Science 294, 93, 2001.

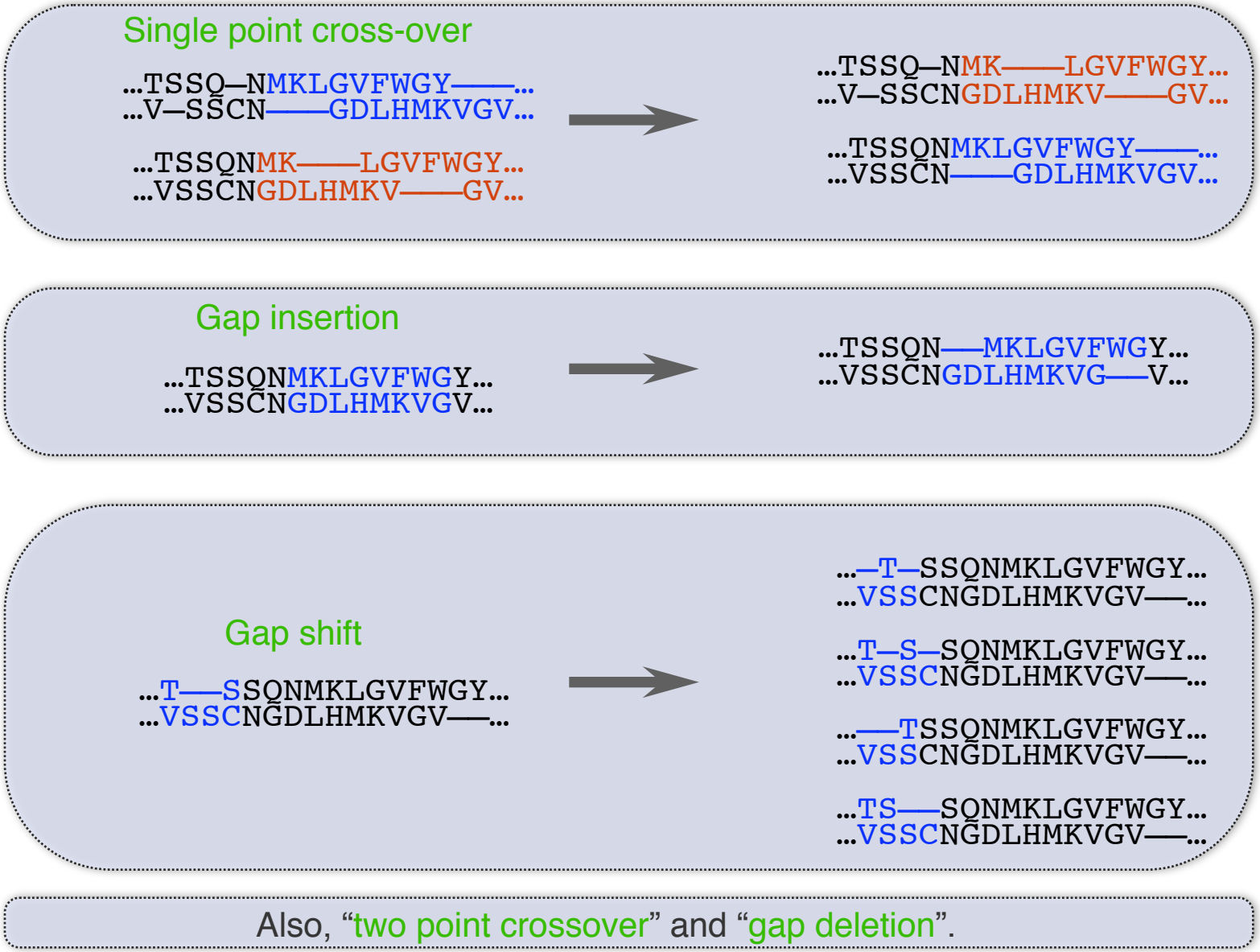
John, Sali (2003). NAR pp31 3982

Moulding: iterative alignment, model building, model assessment





Genetic algorithm operators



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).

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

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

μ … average score of all models

σ … standard deviation of the scores

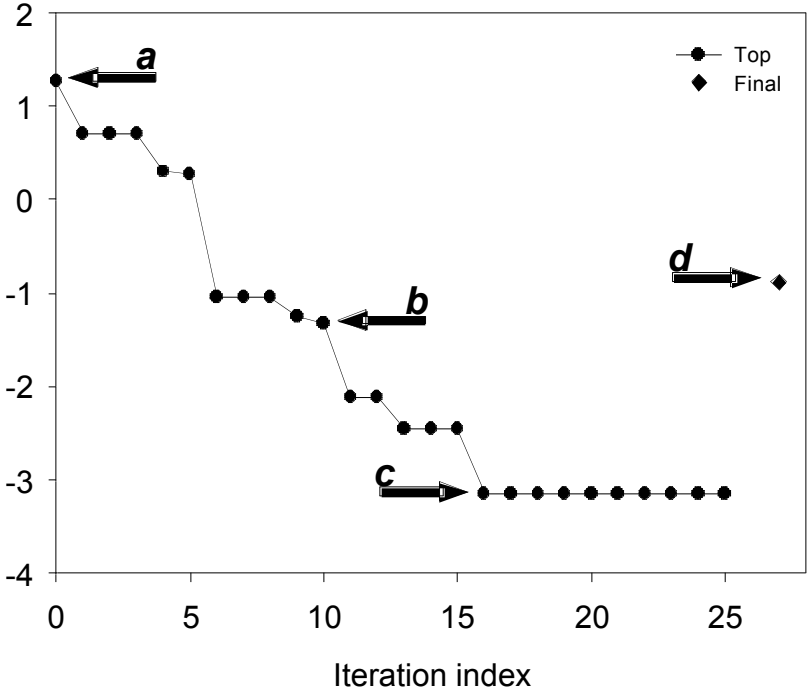
Benchmark with the “very difficult” test set

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

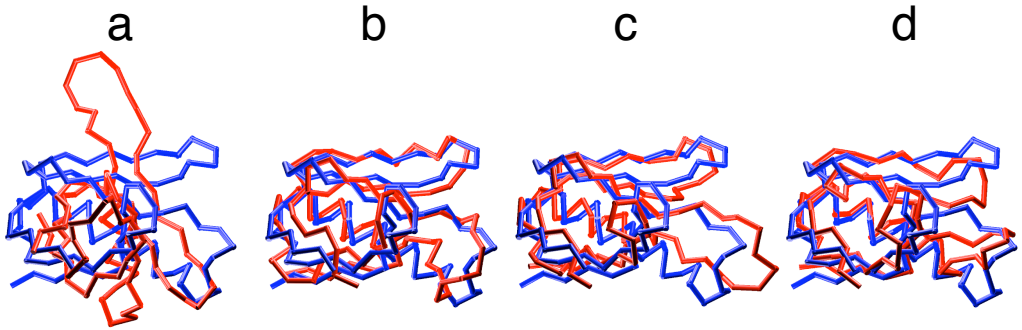
1BOV-1LTS

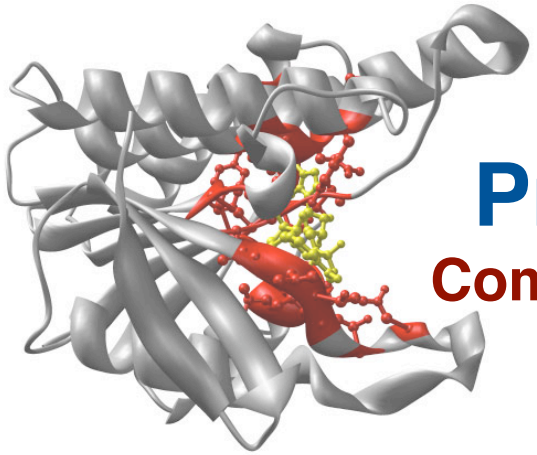


Sequence identity 4.4%

Initial model Cα RMSD 10.1Å

Final model Cα RMSD 3.6Å



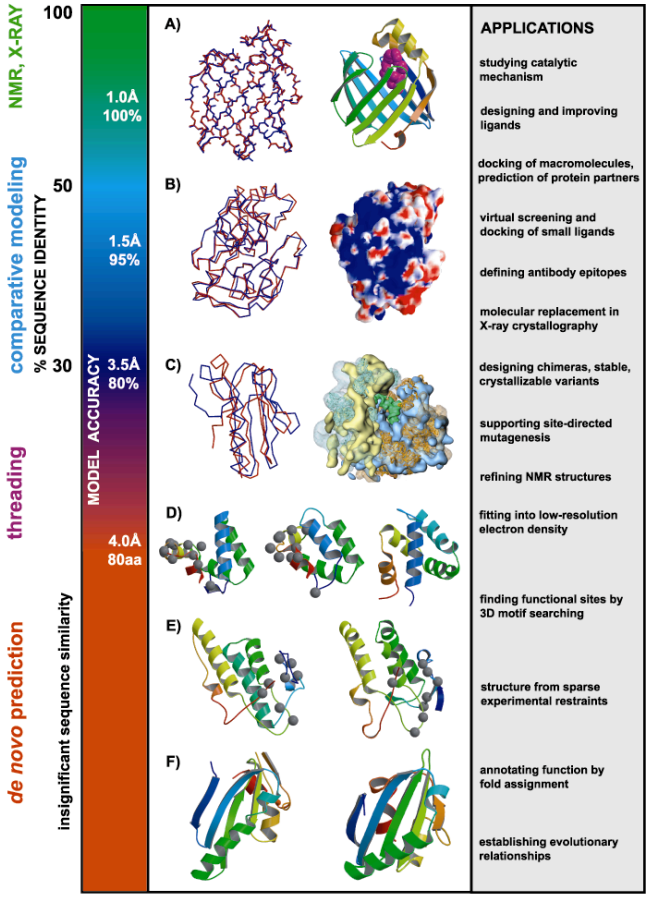


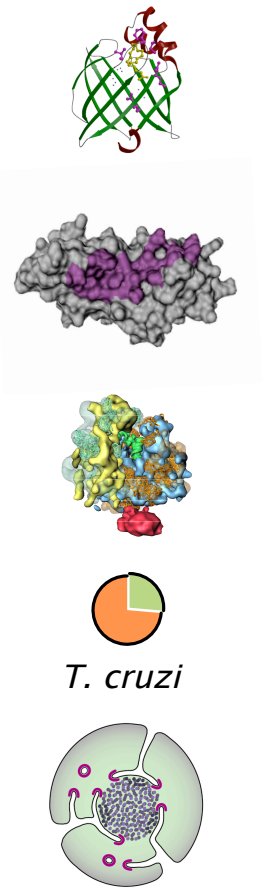
Protein function from structure

Comparative annotation. AnnoLite and AnnoLyze.

Marti-Renom et al. BMC Bioinformatics (2007) in press

Can we use models to infer function?





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

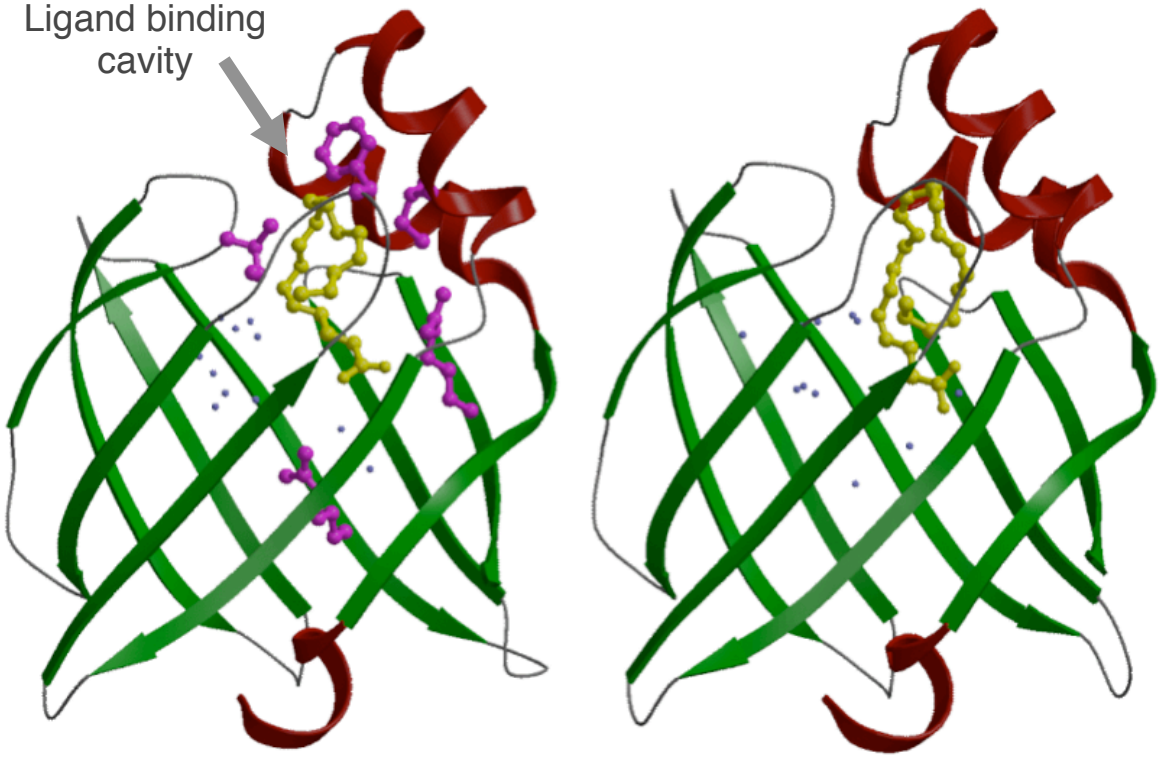
Predicting features of a model that are not present in the template

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

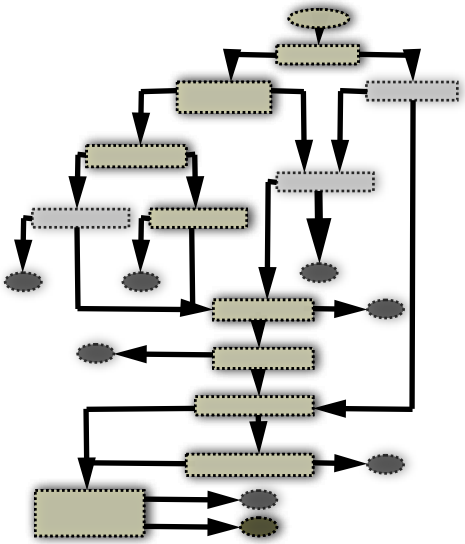
Nebojsa Mirkovic, Marc A. Marti-Renom, Barbara L. Weber, Andrej Sali and Alvaro N.A. Monteiro

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

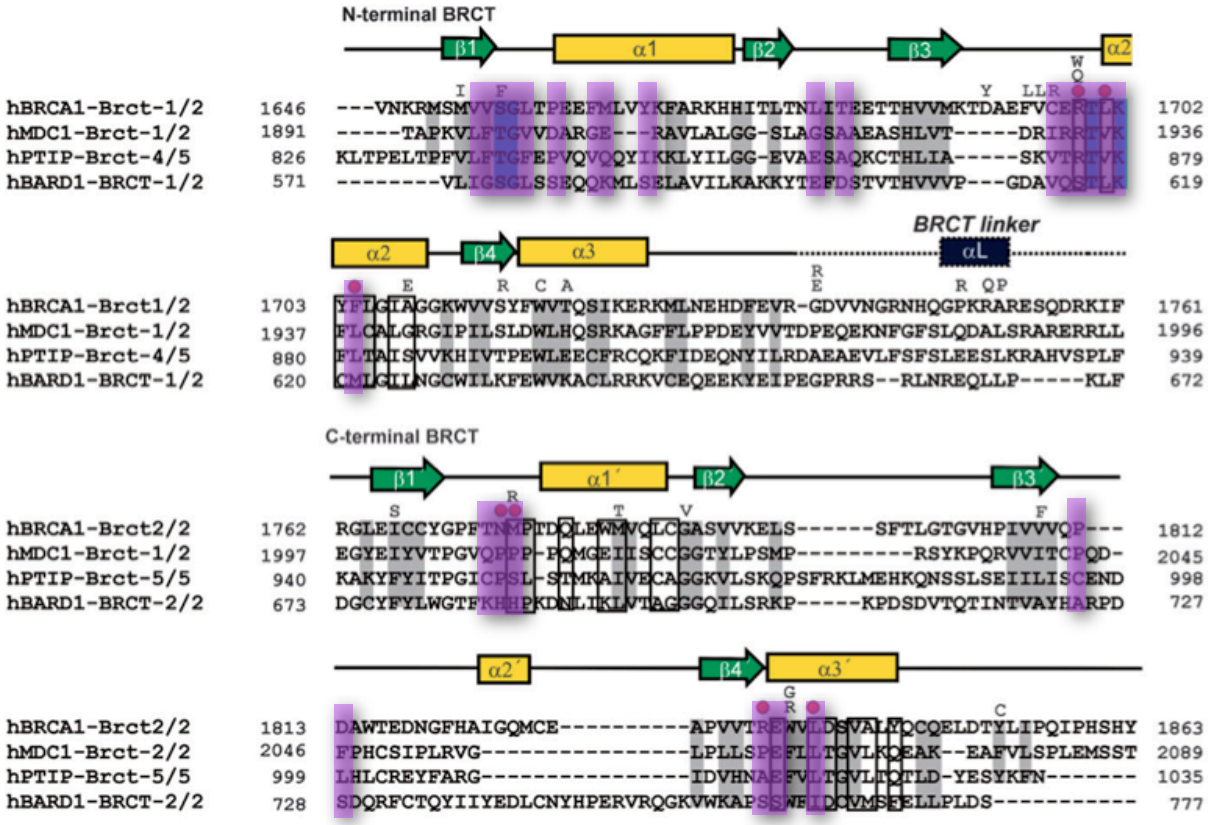
Cannot measure the functional impact of every possible SNP at all positions in each protein! Thus, prediction based on general principles of protein structure is needed.

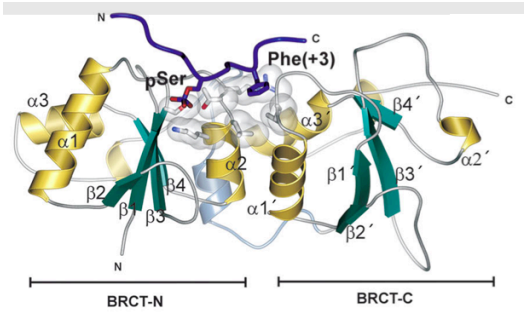
Missense mutations in BRCT domains by function

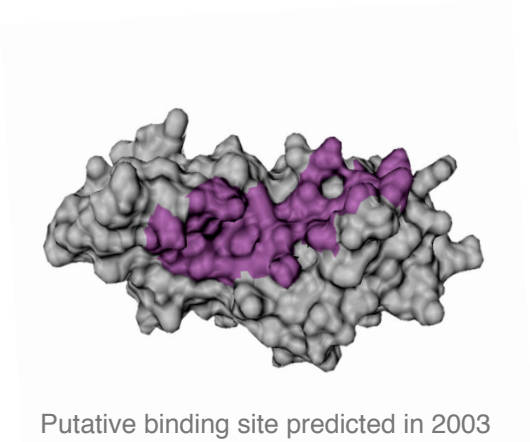
	cancer associate	not cancer associated	?
no transcription activation	C1697R R1699W A1708E S1715R P1749R M1775R		M1652K L1657P E1660G H1686Q R1699Q K1702E Y1703HF 1704S L1705PS 1715NS1 722FF17 34LG173 8EG1743 RA1752 PF1761I F1761S M1775E M1775K L1780P I1807S V1833E A1843T
transcription activation		M1652I 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





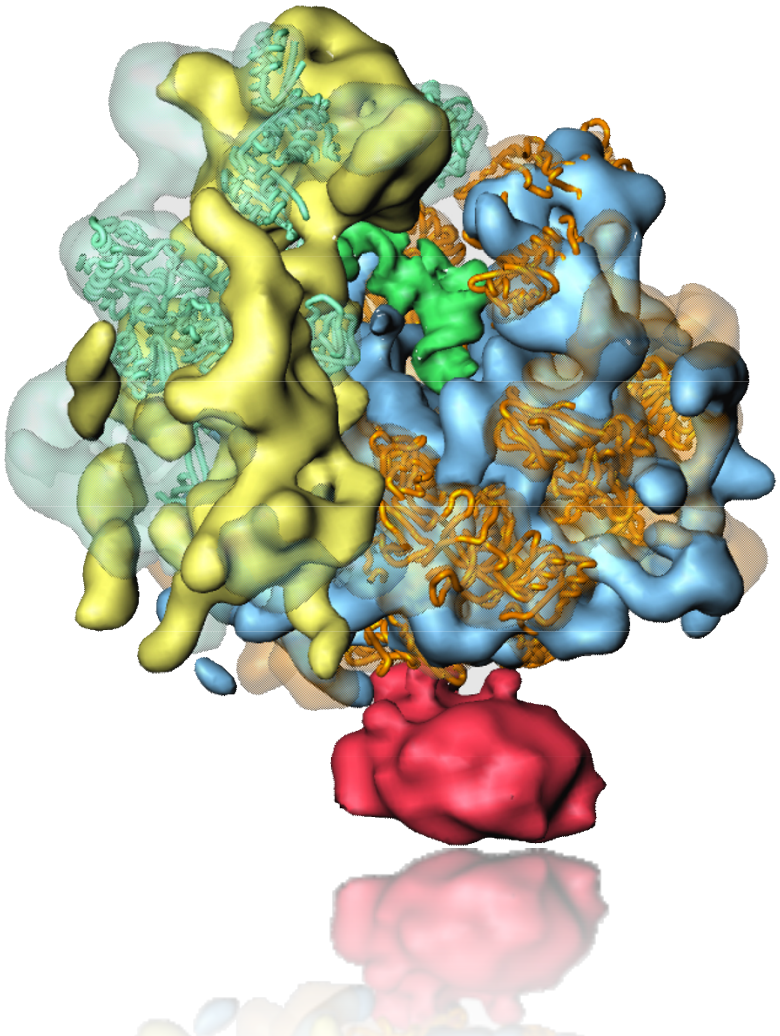


Putative binding site predicted in 2003 and accepted for publication on March 2004.

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

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

S. cerevisiae ribosome



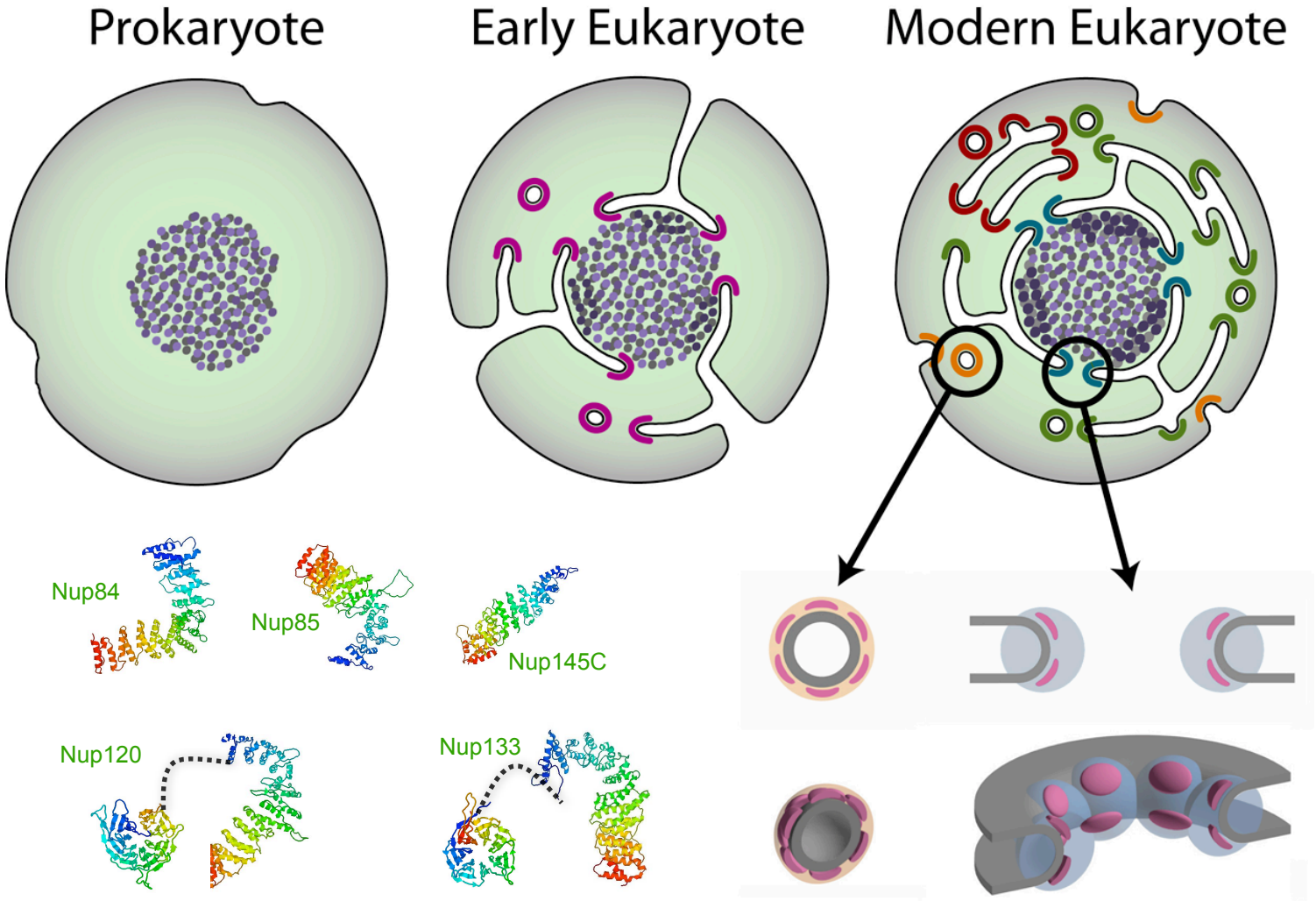
Fitting of comparative models into 15Å cryo-electron density map.

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.

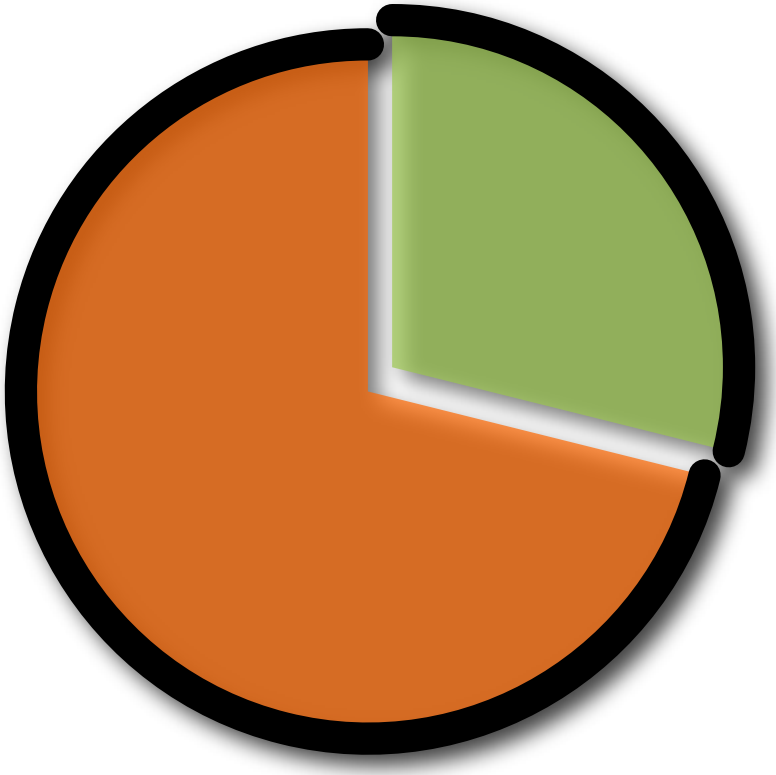
The Nucleopore complex
Cell evolution (?)



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

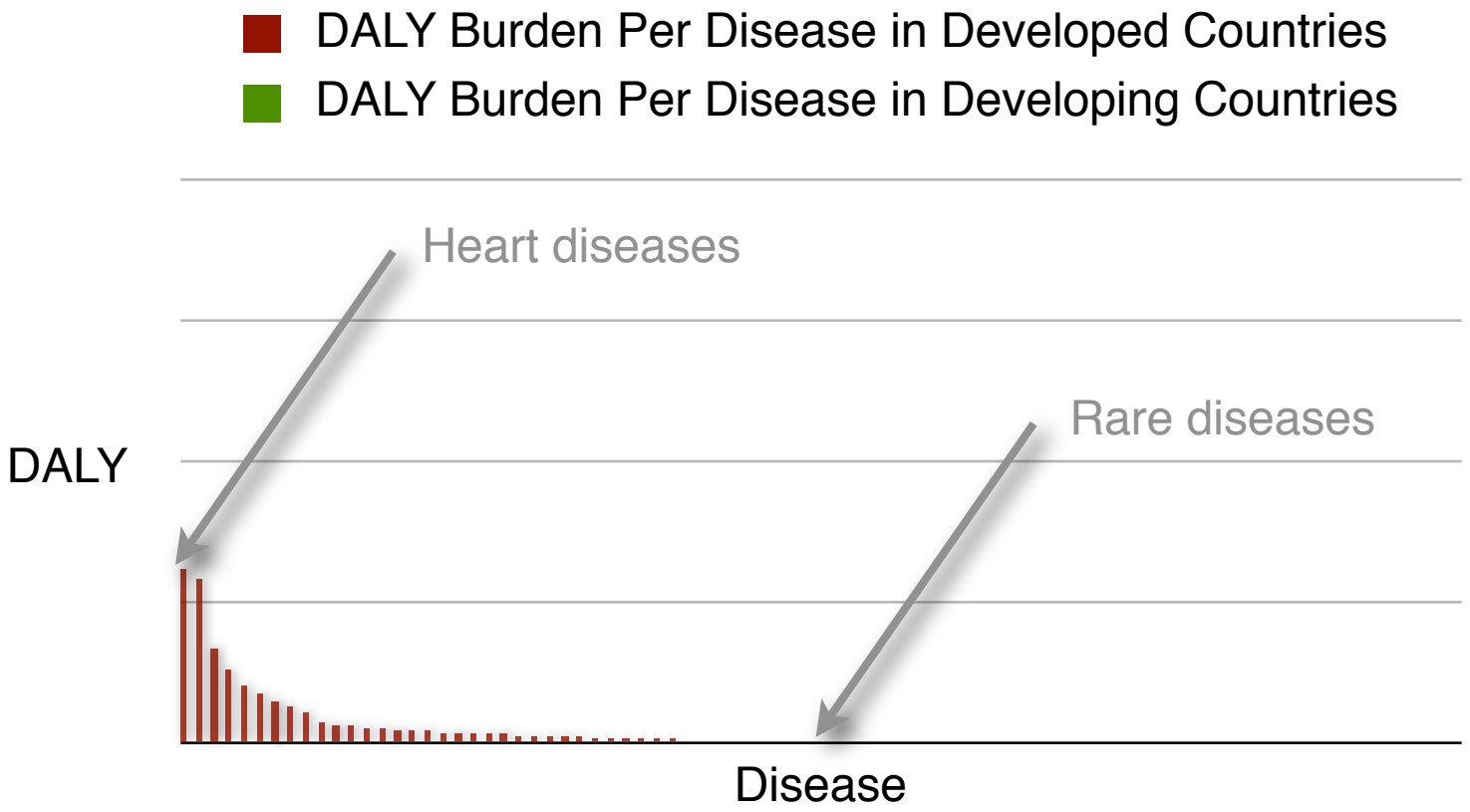
Tropical Disease Initiative (TDI)

Predicting binding sites in protein structure models.



http://www.tropicaldisease.org

Need is High in the Tail



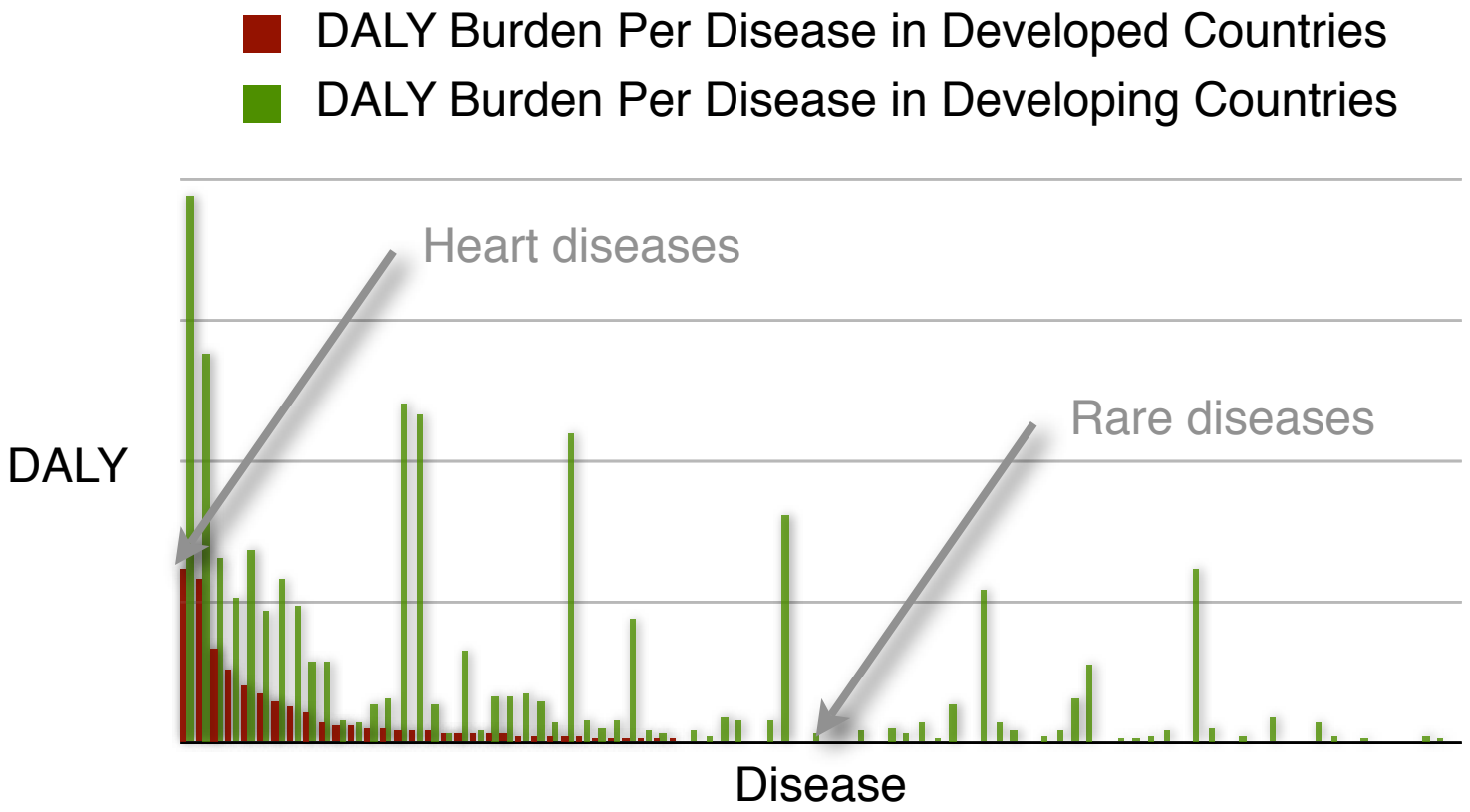
Disease data taken from WHO, *World Health Report 2004*

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



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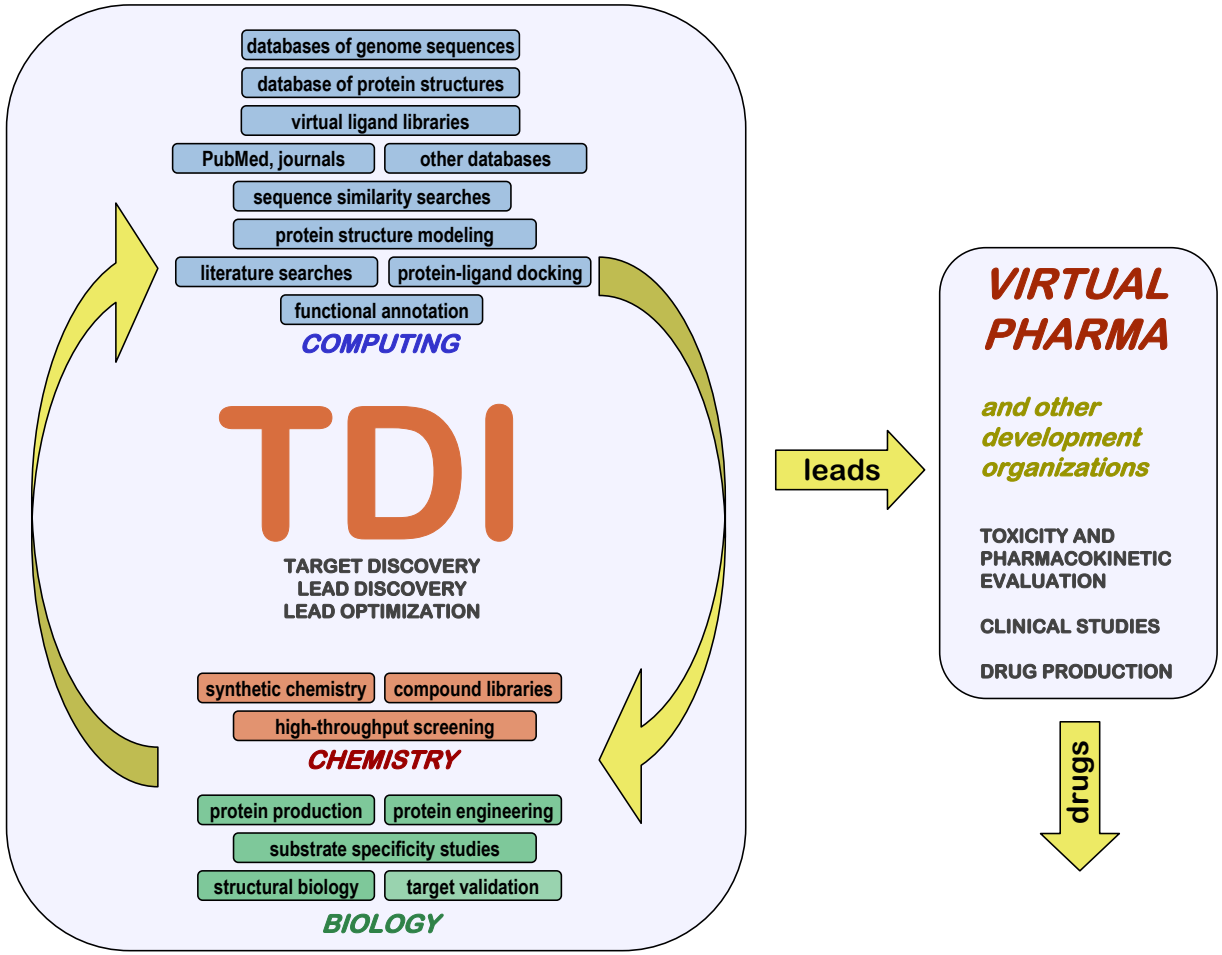
"Unprofitable" Diseases and Global DALY (in 1000's)

Malaria*	**46,486**	Trichuriasis	1,006
Tetanus	7,074	Japanese encephalitis	709
Lymphatic filariasis*	**5,777**	**Chagas Disease***	**667**
Syphilis	4,200	**Dengue***	**616**
Trachoma	2,329	**Onchocerciasis***	**484**
Leishmaniasis*	**2,090**	**Leprosy***	**199**
Ascariasis	1,817	Diphtheria	185
Schistosomiasis*	**1,702**	Poliomyelitise	151
Trypanosomiasis*	**1,525**	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.

TDI flowchart

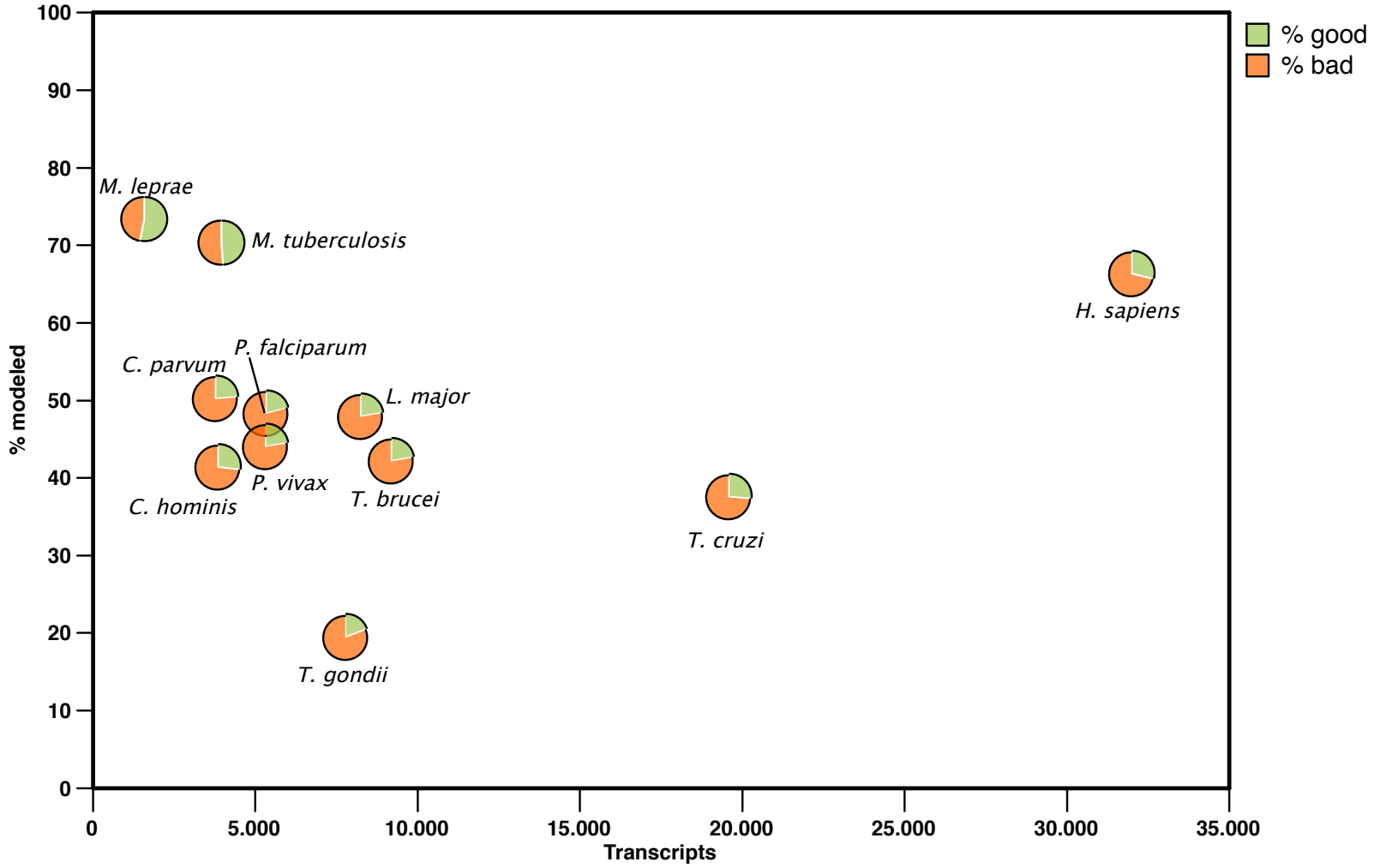
http://www.tropicaldisease.org



Sali, Rai, Maurer. PLoS Medicine (2004)
Kepler, et al. Australian Journal of Chemistry (2006)

Modeling Genomes

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

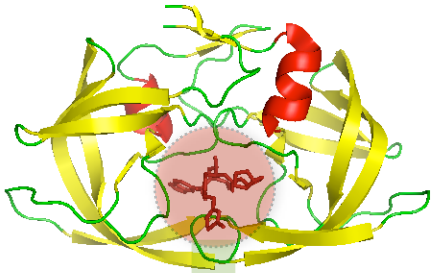


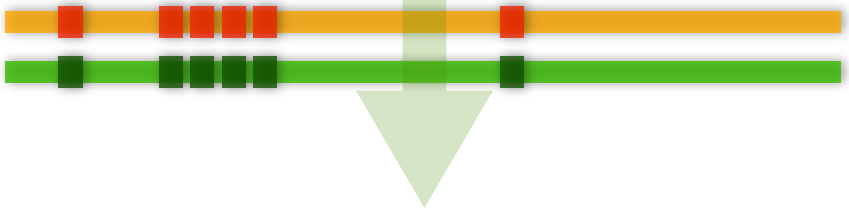
A good model has MPQS of 1.1 or higher

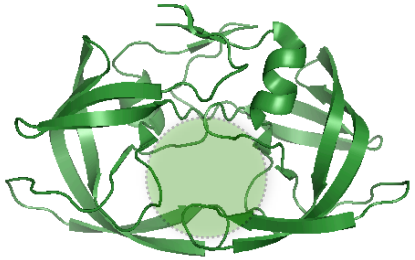
Comparative docking

1. Expansion

co-crystalized protein/ligand



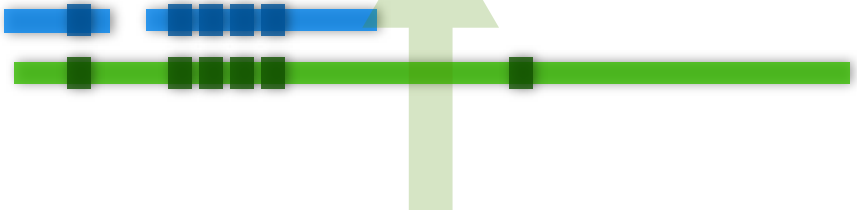




crystalized protein

2. Inheritance

model



template

Ligand “expanded” space

from 6,859 templates used in “good” models

Expansion cut-off	Templates	Expanded	Unique
30%	4,639	64,800	3,178
50%	4,242	37,945	3,030
70%	3,323	20,603	2,786

Ligand “inherited” space

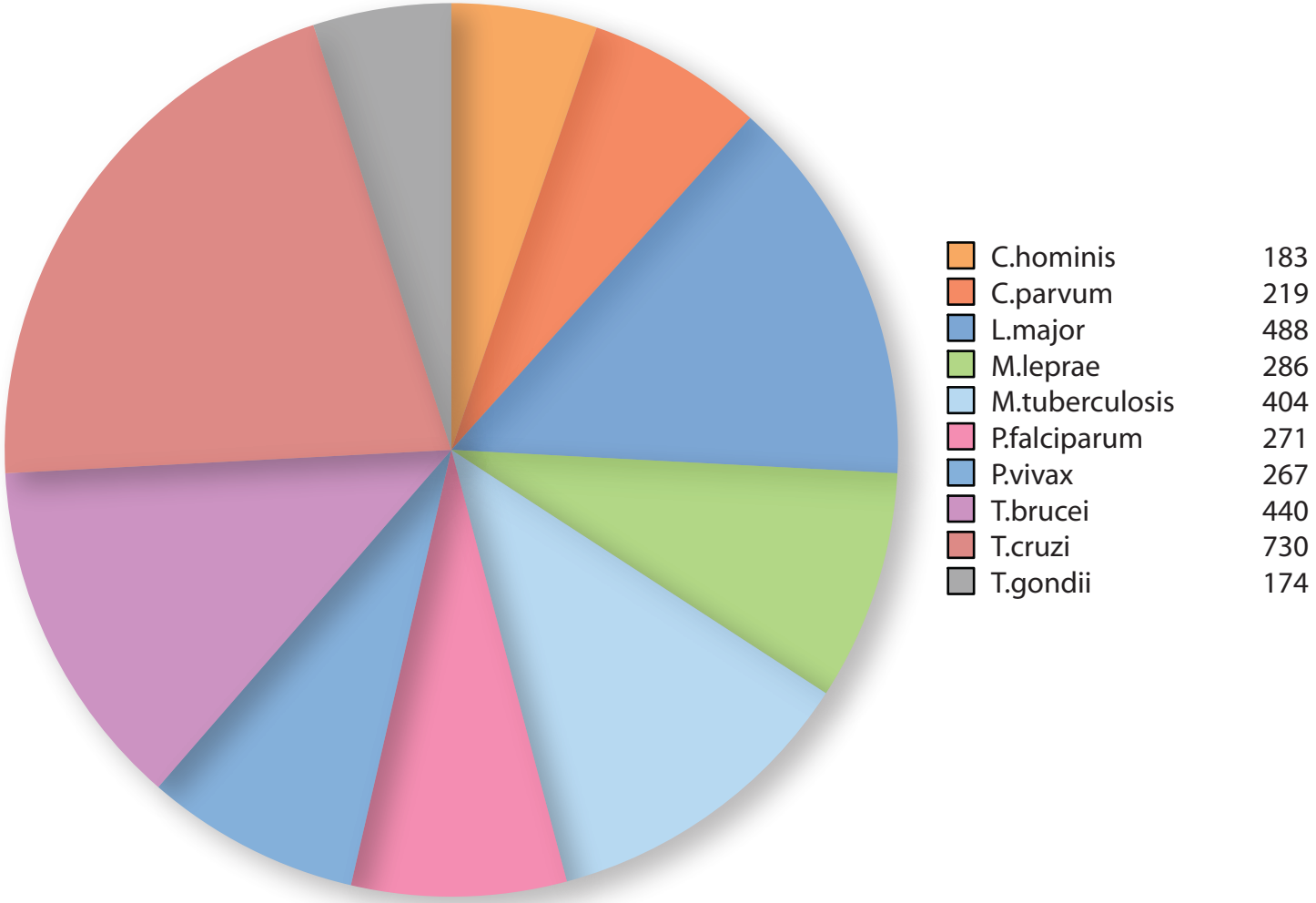
second cut-offs

Using a 70% “expansion” cut-off

Inheritance cut-offs	Models	Inherited	Unique
90% / 70%	5,181	23,286	1,137
90% / 80%	4,383	17,842	1,027
90% / 90%	3,462	11,803	827

Distribution of models with inherited ligands

from 3,882 “good” models
using a 90% / 90% “inherited” cut-offs



Summary table

models with inherited ligands

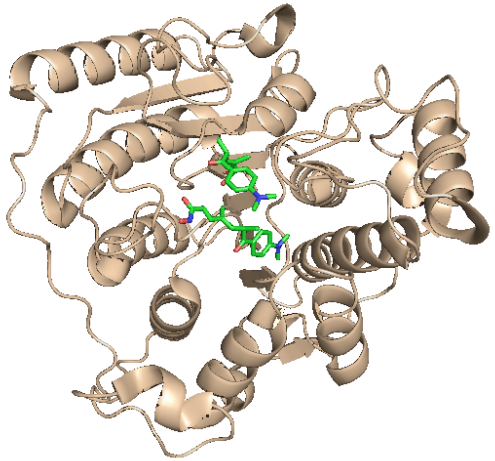
from 16,284 good models, 295 inherited a ligand/substance with at least one compound already approved by FDA and ready to be used from ZINC

	Transcripts	Good	Ligands	Lipinski	Lipinski+ZINC	FDA+ZINC
C. hominis	3,886	886	183	131	28	12 (10)
C. parvum	3,806	949	219	145	30	12 (10)
L. major	8,274	1,845	488	334	84	44 (34)
M. leprae	1,605	1,321	286	189	39	29 (25)
M. tuberculosis	3,991	2,887	404	285	71	44 (37)
P. falciparum	5,363	1,057	271	191	48	20 (16)
P. vivax	5,342	1,042	267	177	37	18 (15)
T. brucei	921	1,795	440	309	94	46 (36)
T. cruzi	19,607	3,915	730	493	127	62 (52)
T. gondii	7,793	587	174	124	28	8 (7)
TOTAL	**60,588**	**16,284**	**3,462**	**2,378**	**586**	**295 (242)**

Example of inheritance (expansion)

LmjF21.0680 from L. major *"Histone deacetylase 2" (model 1)*

Template 1t64A a human HDAC8 protein.



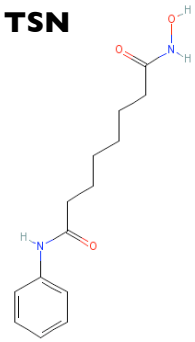
	Origen	Formula	Name	Cov.	Seq, Id. (%)
ZN	X-ray	Zn^{2+}	Zinc ion	--	--
NA	X-ray	Na^{+}	Sodium ion	--	--
CA	X-ray	Ca^{2+}	Calcium ion	--	--
TSN	X-ray	$C_{17}H_{22}N_2O_3$	Trichostatin A	--	--
SHH	Expanded	$C_{14}H_{20}N_2O_3$	Octadenioic acid hudroxyamide phenylamide	100.00	83.8

Example of inheritance (inheritance)

LmjF21.0680 from L. major *"Histone deacetylase 2" (model 1)*

	Formula	Name	Cov.	Seq, Id. (%)	Residues
TSN	$C_{17}H_{22}N_2O_3$	Trichostatin A	100.00	90.9	90 131 132 140 141 167 169 256 263 293 295
SHH	$C_{14}H_{20}N_2O_3$	Octadenioic acid hudroxyamide phenylamide	100.00	90.9	

TSN



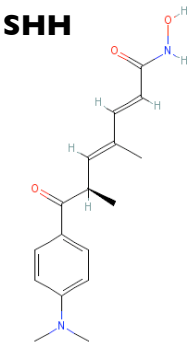
suberoylanilide hydroxamic acid

Pharmacological Action:

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

Inhibits histone deacetylase I and 3

SHH



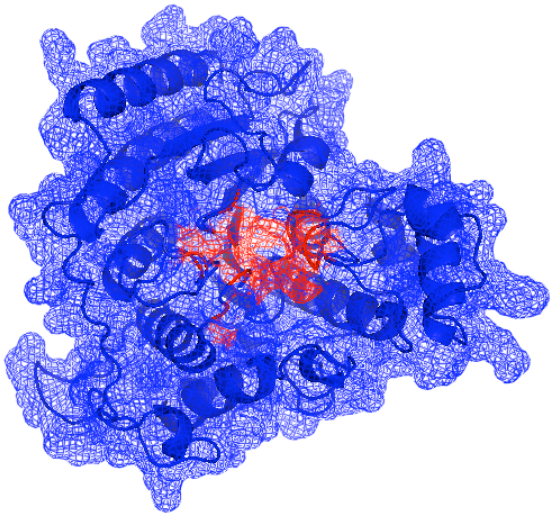
trichostatin A

Pharmacological Action:

Antibiotics, Antifungal
Enzyme Inhibitors
Protein Synthesis Inhibitors

chelates zinc ion in the active site of histone deacetylases, resulting in preventing histone unpacking so DNA is less available for transcription

	LmjF21.0680.1.pdb
Template	1t64A
Seq. Id (%)	**38.00**
MPQS	1.47



Example of inheritance (CDD-Roos-literature)

LmjF21.0680 from L. major *"Histone deacetylase 2" (model 1)*

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*

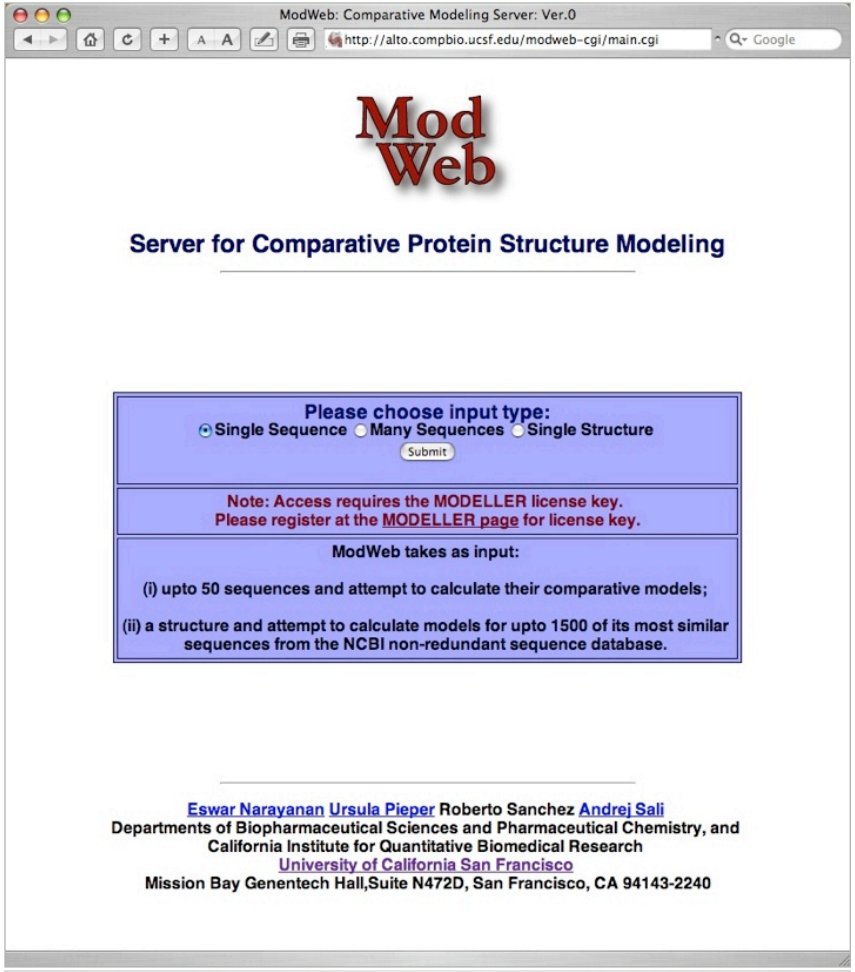
Departments of *Parasite Biochemistry and Cell Biology, ‡Medicinal Chemistry, and §Natural Products Drug Discovery, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065

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

MODWEB

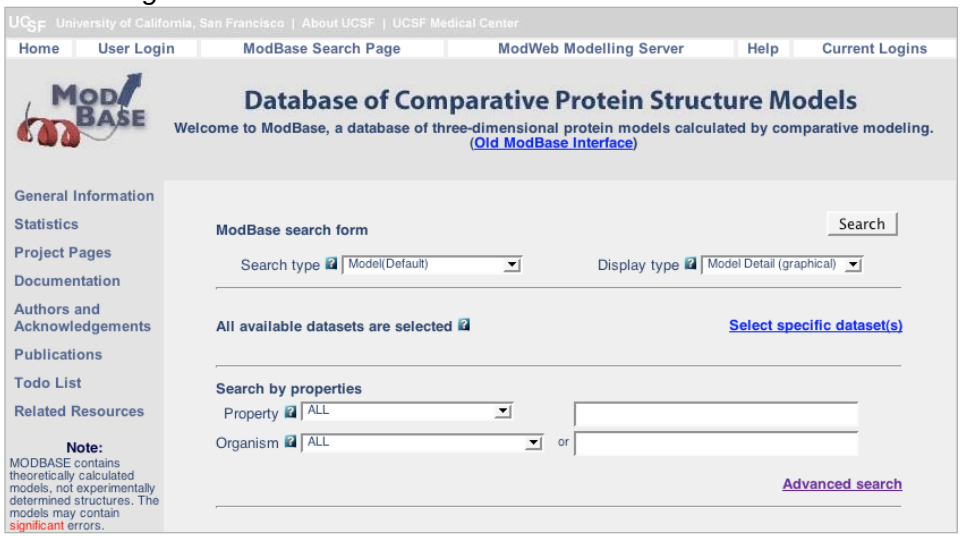
http://salilab.org/modweb



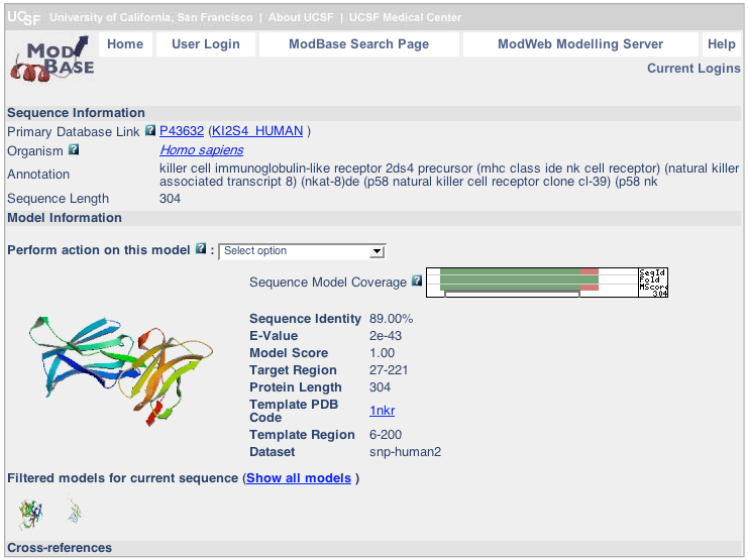
MODBASE

http://salilab.org/modbase

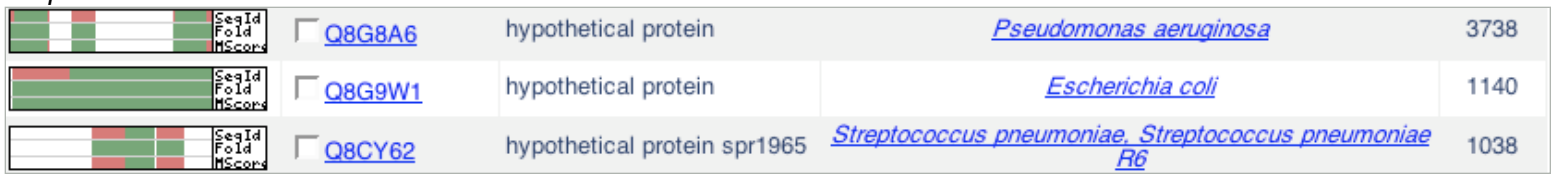
Search Page



Model Details



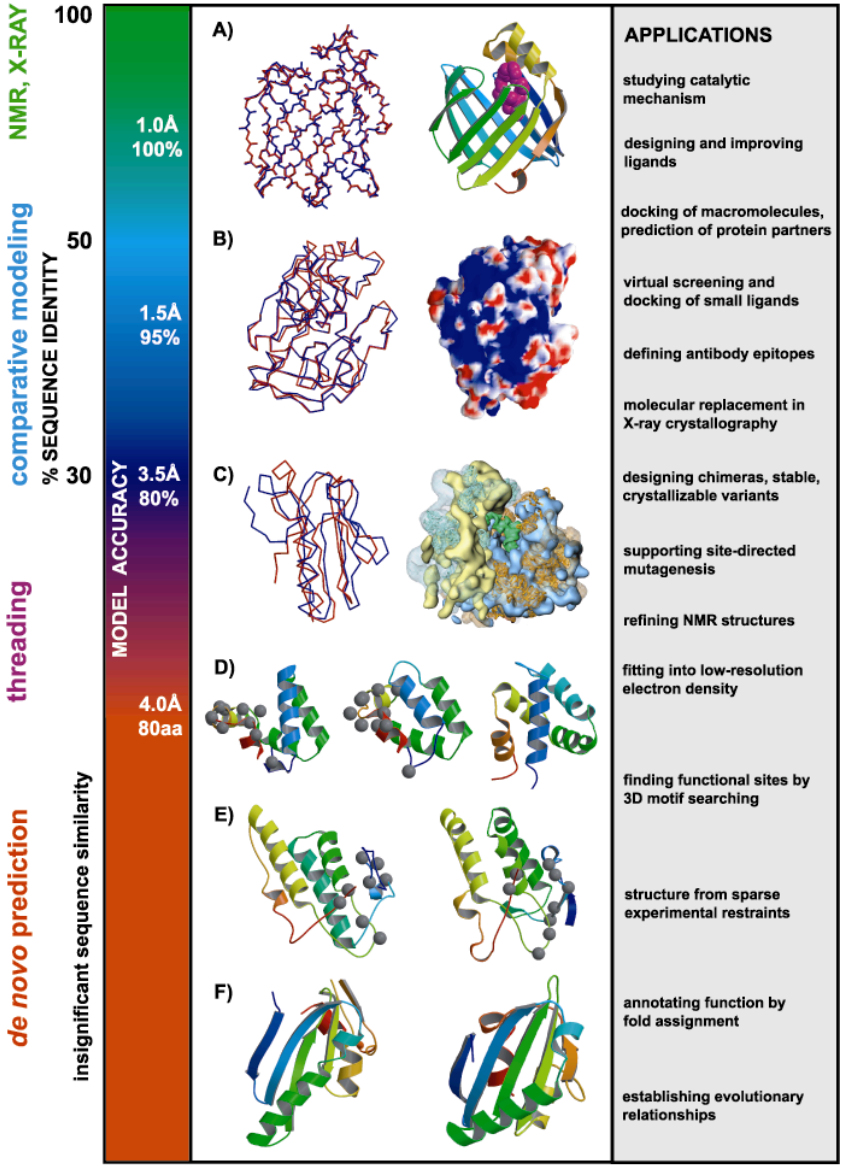
Sequence Overview



Model Overview

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

“take home” message



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

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Andrej Sali
M. S. Madhusudhan
Narayanan Eswar
Min-Yi Shen
Ursula Pieper
Bino John
Maya Topf

MODEL ASSESSMENT
David Eramian
Min-Yi Shen
Damien Devos

FUNCTIONAL ANNOTATION
Andrea Rossi
Fred Davis

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MODEL ASSESSMENT
Francisco Melo (CU)
Alejandro Panjkovich (CU)

STRUCTURAL GENOMICS
Stephen Burley (SGX)
John Kuriyan (UCB)
NY-SGXRC

MAMMOTH
Angel R. Ortiz

FUNCTIONAL ANNOTATION
Fatima Al-Shahrour
Joaquin Dopazo

BIOLOGY
Jeff Friedman (RU)
James Hudsped (RU)
Partho Ghosh (UCSD)
Alvaro Monteiro (Cornell U)
Stephen Krilis (St.George H)

Tropical Disease Initiative
Stephen Maurer (UC Berkeley)
Arti Rai (Duke U)
Andrej Sali (UCSF)
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CCPR Functional Proteomics
Patsy Babbitt (UCSF)
Fred Cohen (UCSF)
Ken Dill (UCSF)
Tom Ferrin (UCSF)
John Irwin (UCSF)
Matt Jacobson (UCSF)
Tack Kuntz (UCSF)
Andrej Sali (UCSF)
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