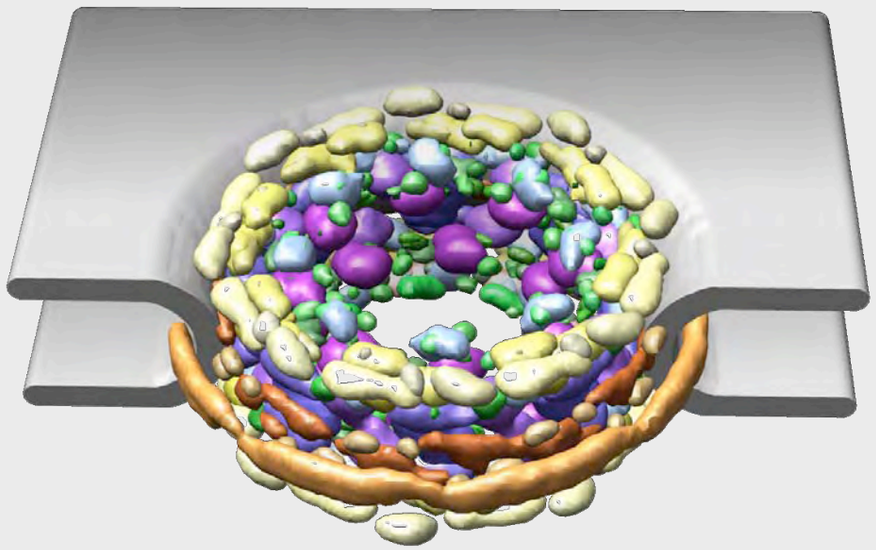
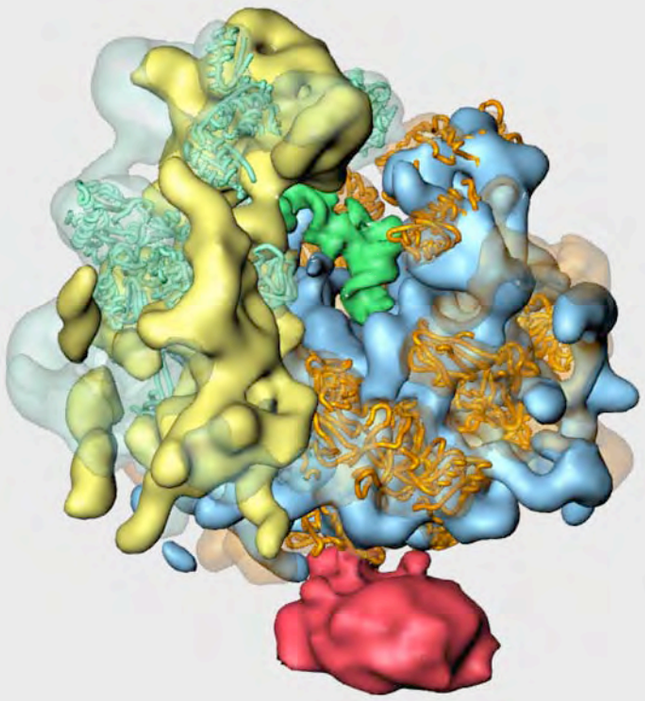
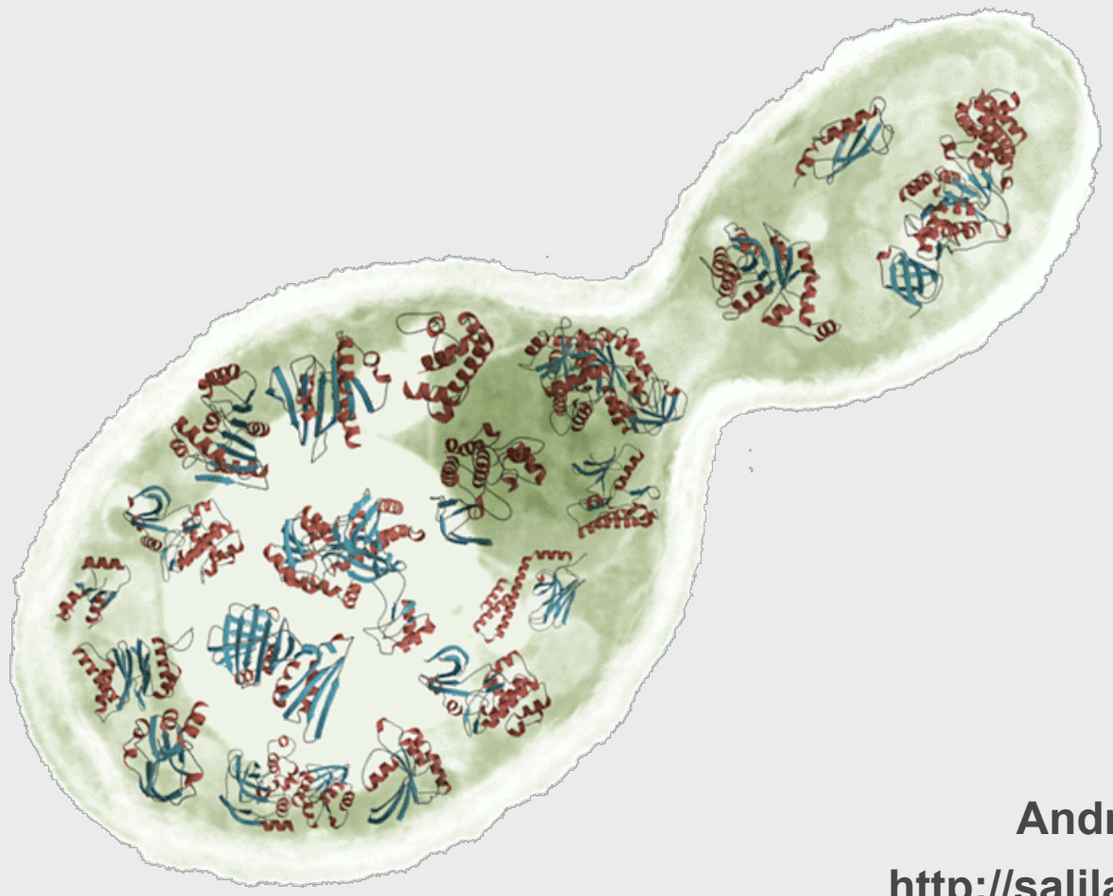
Determining the Structures of Proteins and Macromolecular Assemblies







Andrej Sali

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Topics

1. Introduction to integrative (hybrid) structure determination
2. Comparative model building
3. Predicting accuracy of atomic models
4. Iterative sequence-structure alignment and model building
5. Electron microscopy
6. Small angle x-ray scattering
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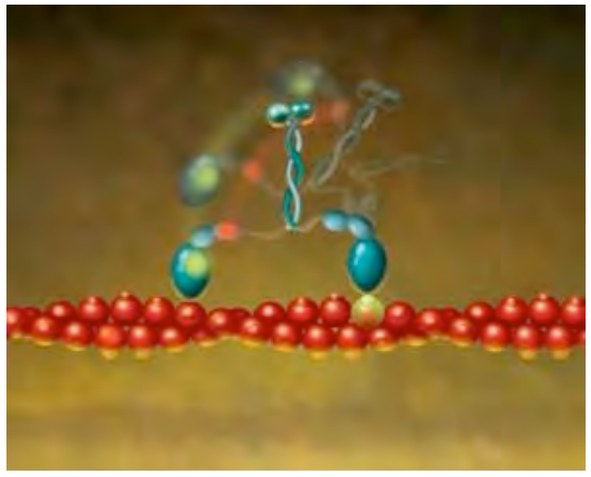
8. Concluding Remarks

Immediate Goal

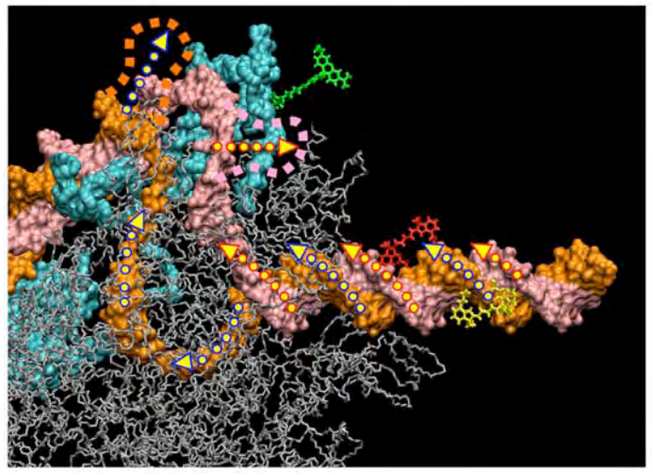
Maximize accuracy, resolution, completeness, and efficiency of the structural coverage of proteins and their assemblies (static structures).

Motivation: Structures will allow us to understand how machines work, how they evolved, how they can be controlled, modified, and perhaps even designed.



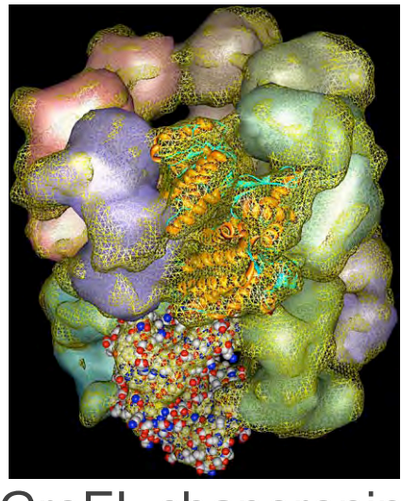
kinesin

virus

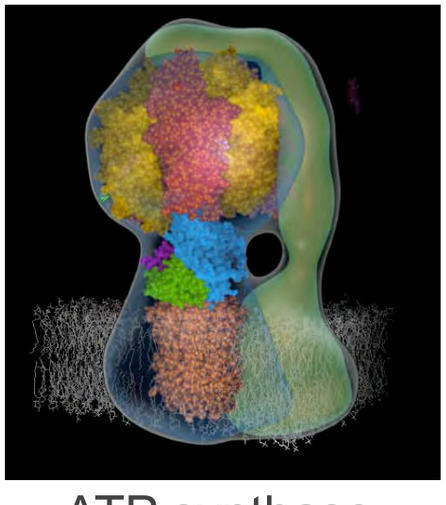


tRNA synthetase

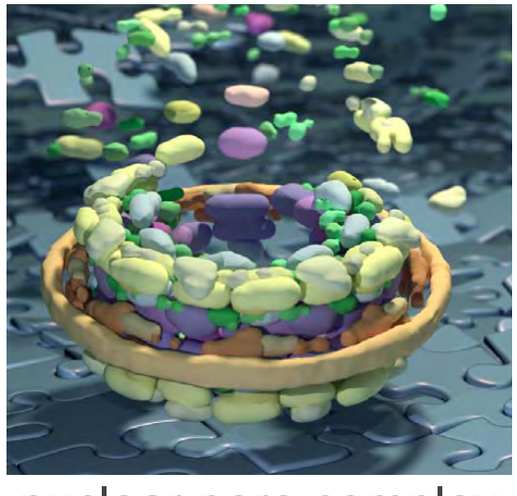
flagellar motor



GroEL chaperonin



ATP synthase



nuclear pore complex

ribosome

There are thousands of biologically relevant macromolecular complexes whose structures are yet to be characterized, involved in a few hundred core biological processes.

Mindset

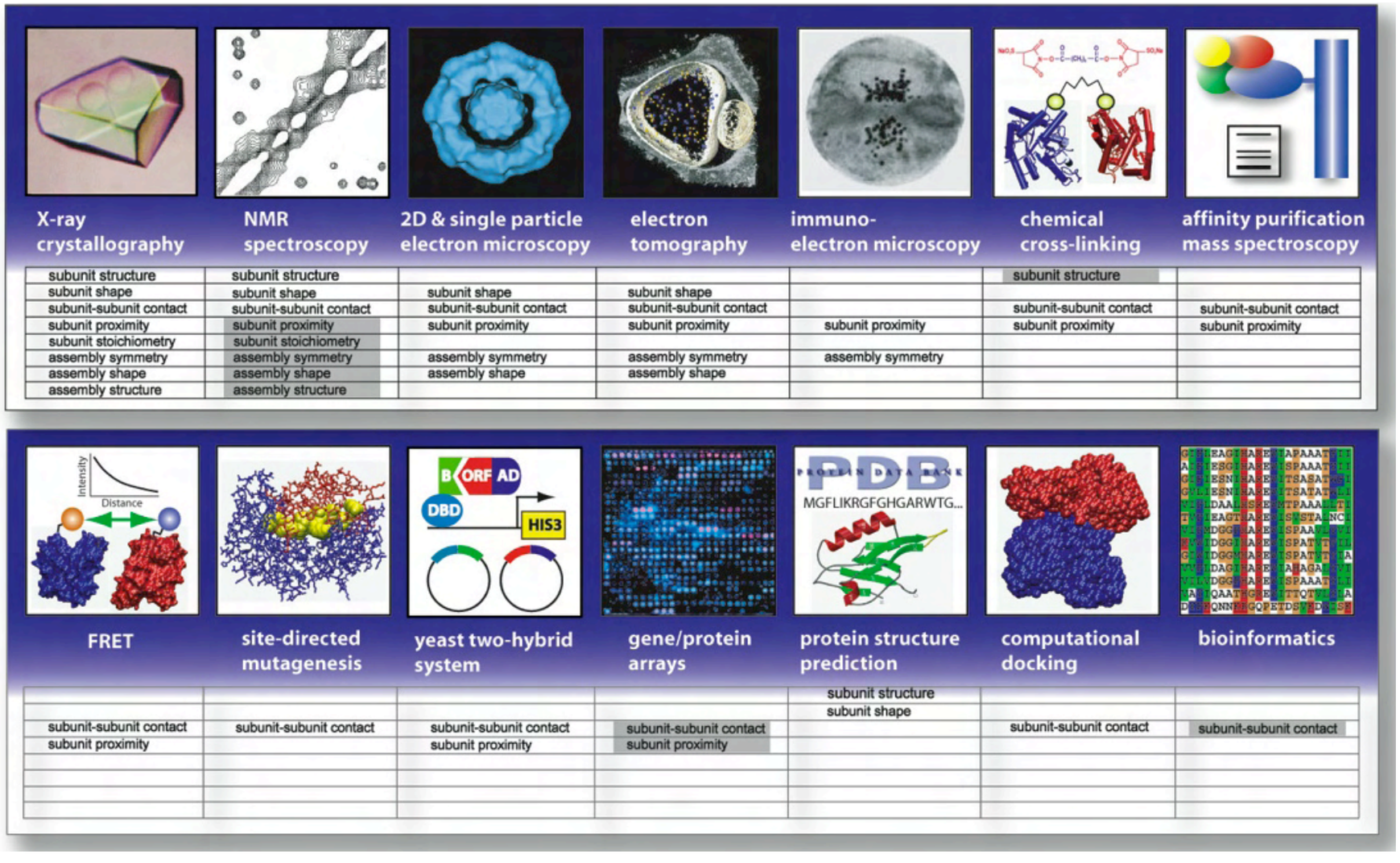
for maximizing accuracy, resolution, completeness, and efficiency of structure determination

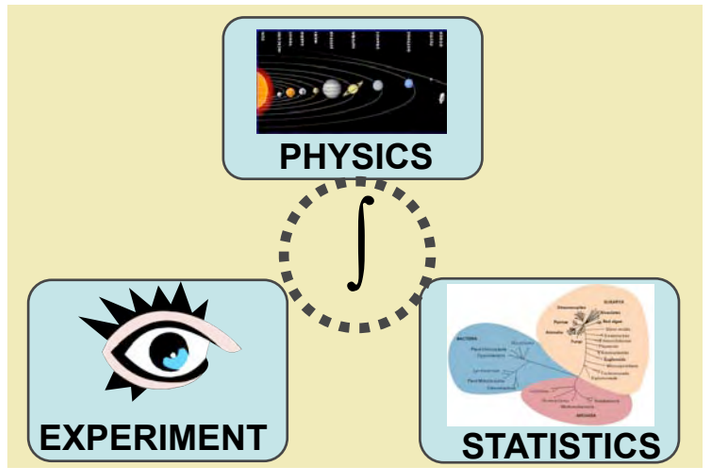
Use structural information from any

source: measurement, first principles, rules;

resolution: low or high resolution

to obtain the set of all models that are consistent with it.





Sali, Earnest, Glaeser, Baumeister. From words to literature in structural proteomics. *Nature* 422, 216-225, 2003.

Integrative (hybrid) methods for structure determination

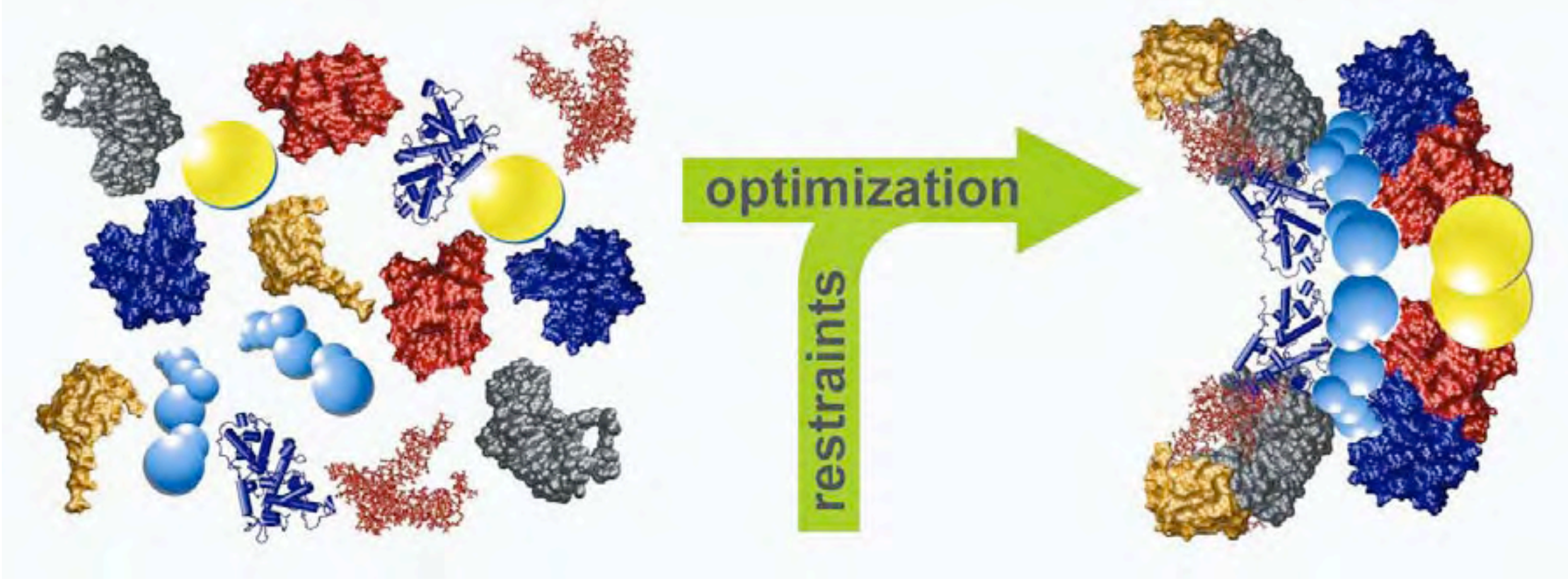
- Integrative structure determination relies on varied types of data.
- Atomic structure determination:
  - x-ray crystallography (D. Baker ...).
  - NMR spectroscopy (M. Nilges, M. Vendruscolo, A. Bax, D. Baker, G. Montelione, ...).
- Low-resolution description of macromolecular assemblies:
  - fitting of atomic models into a cryo-EM map (M. Rossman, ...).
  - integrating proteomics data (A. Sali, ...).
- Modeling can greatly leverage experimental data in order to determine the structures and dynamics of proteins and especially macromolecular assemblies.

Characterizing Structures by Satisfaction of Spatial Restraints

1. Representation of a system.
2. Scoring function (spatial restraints).
3. Optimization / sampling.

There is nothing but points and restraints on them. We seek joint pdf for **R**, given information **I**:

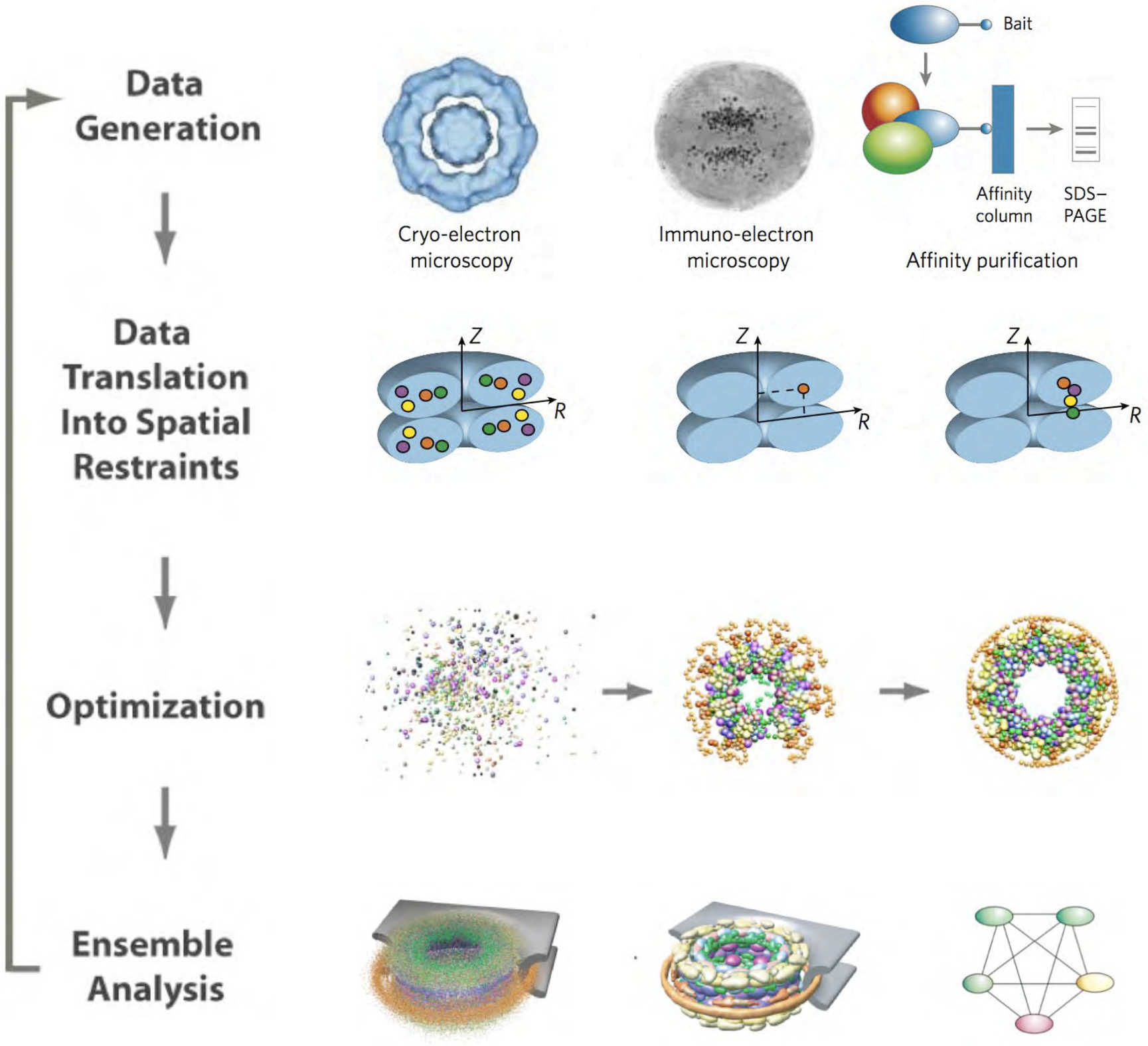
$$P(\mathbf{R} / \mathbf{I}) \approx \prod_i p_i (\mathbf{r}_i / \mathbf{I}_i)$$



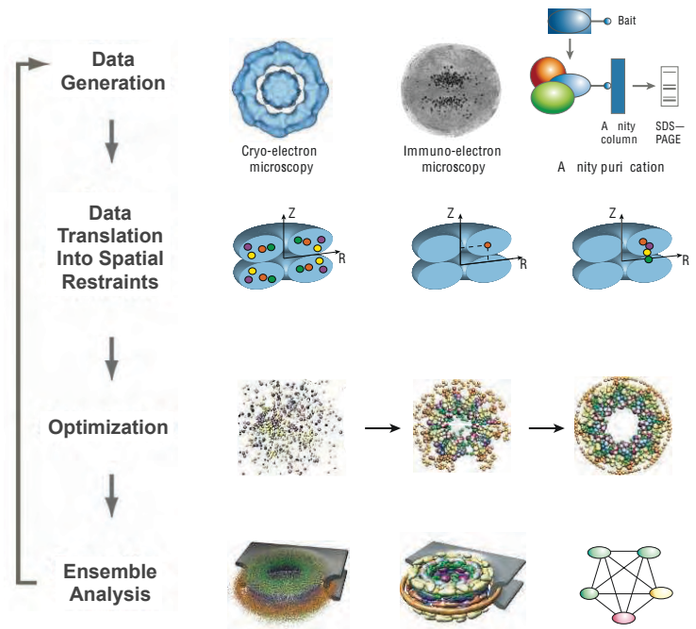
Integrative Modeling Platform (IMP): http://salilab.org/imp

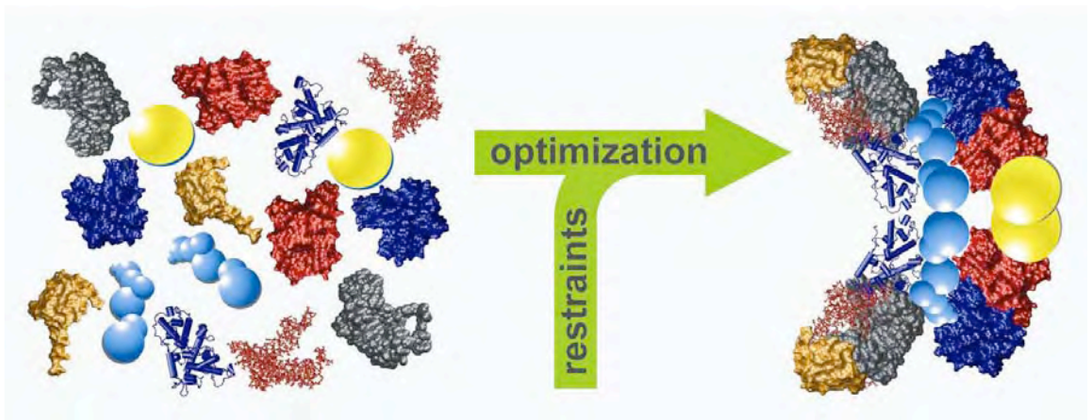
Using All Spatial Information

Alber *et al*. *Nature* 450, 683-694, 2007.
Robinson, Sali, Baumeister. *Nature* 450, 974-982, 2007.
Alber, Foerster, Korkin, Topf, Sali. *Annual Reviews in Biochemistry* 77, 11.1–11.35, 2008.



Why Integrative Modeling?





1. Benefits from the **synergy** among the input data, maximizing accuracy, resolution, completness, and efficiency of structure characterization.

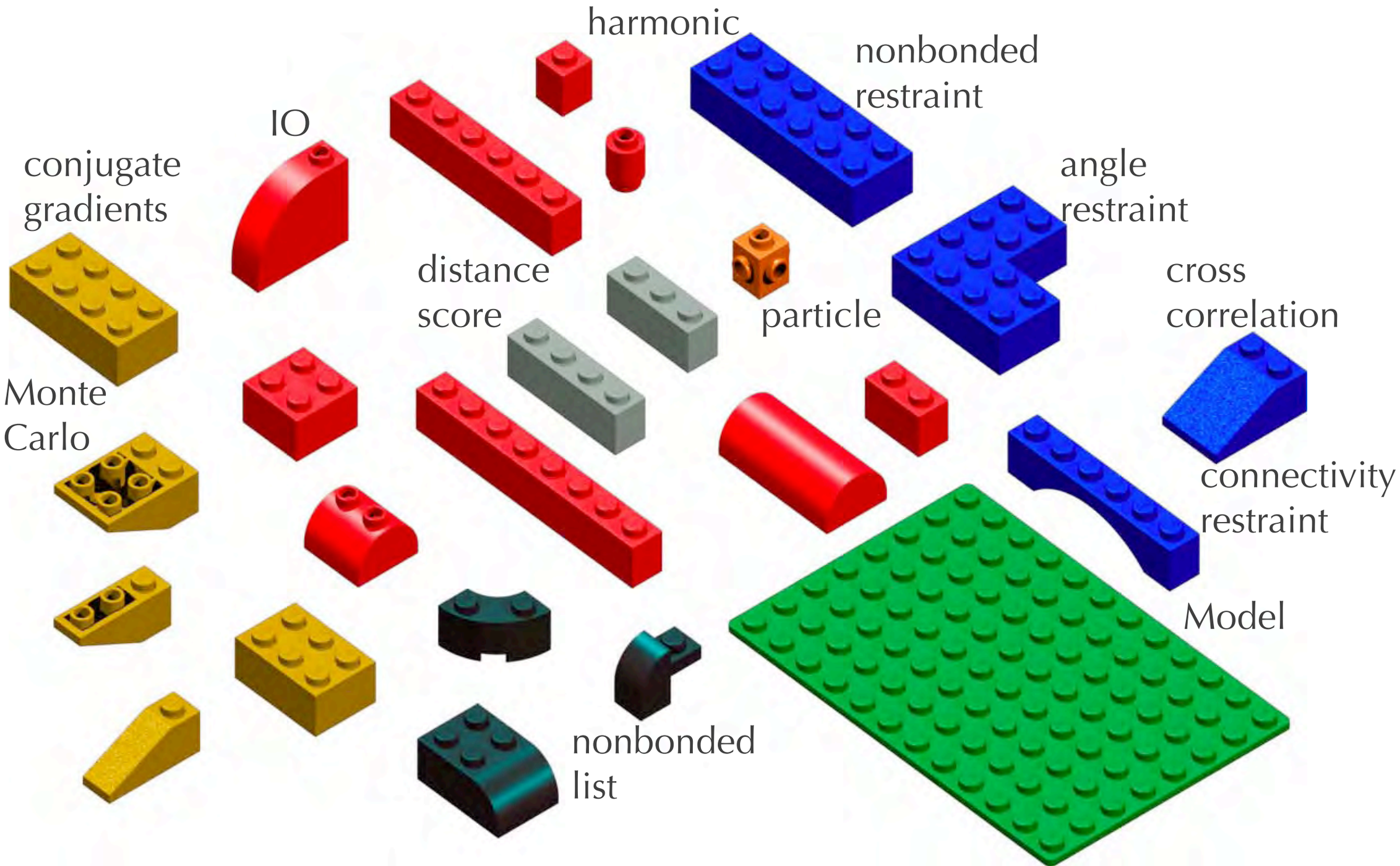
2. Finds "**all**" models consistent with the data, not just one.

3. Facilitates **assessing** the results in terms of precision and accuracy.

4. Provides feedback to **guide** future experiments (*eg*, "what if", ...).

Integrative Modeling Platform (IMP):
Building blocks for modeling

http://salilab.org/imp



D. Russel, B. Webb, K. Lasker, F. Alber, B. Peterson

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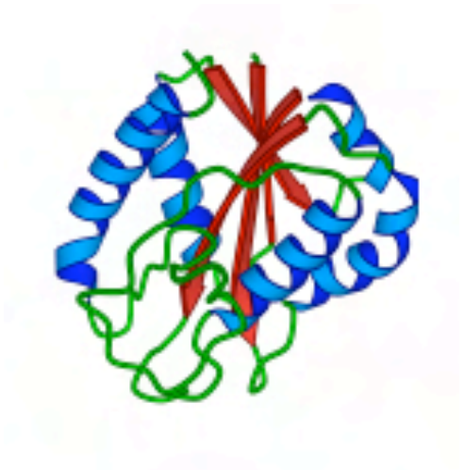
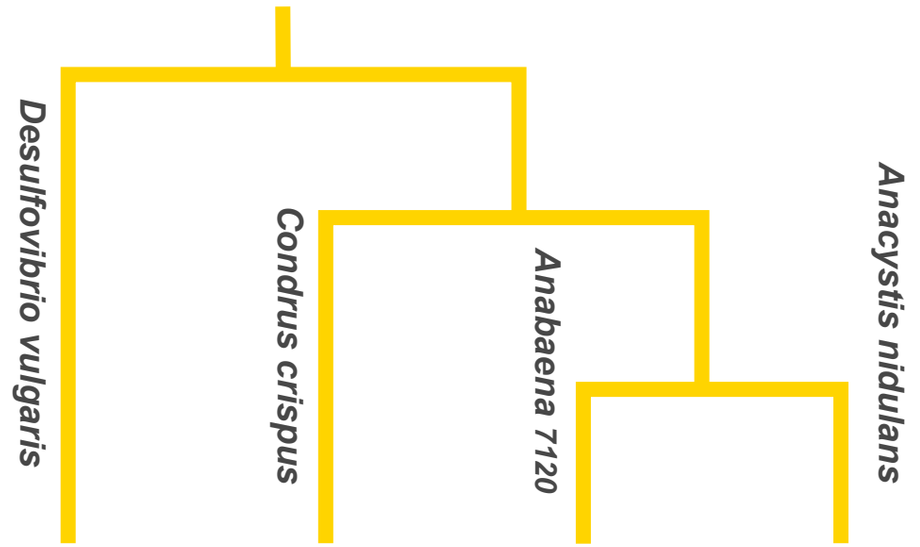
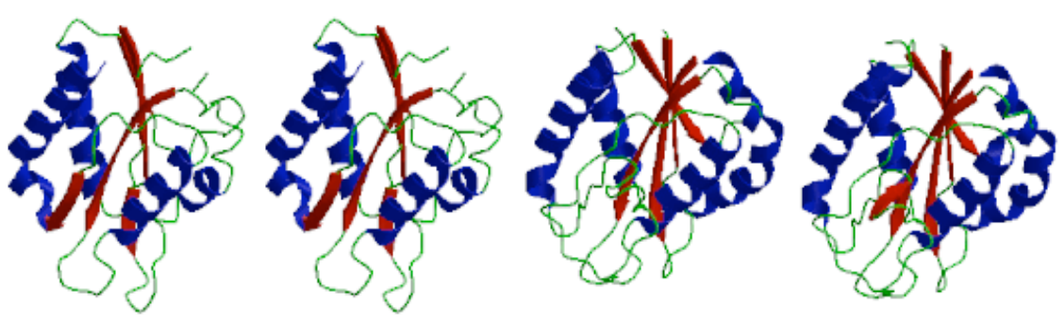
Principles of protein structure

D. Baker & A. Sali. *Science* **294,** 93-97, 2001**.**

GFCHIKAYTRLIMVG…







Folding

(physics)

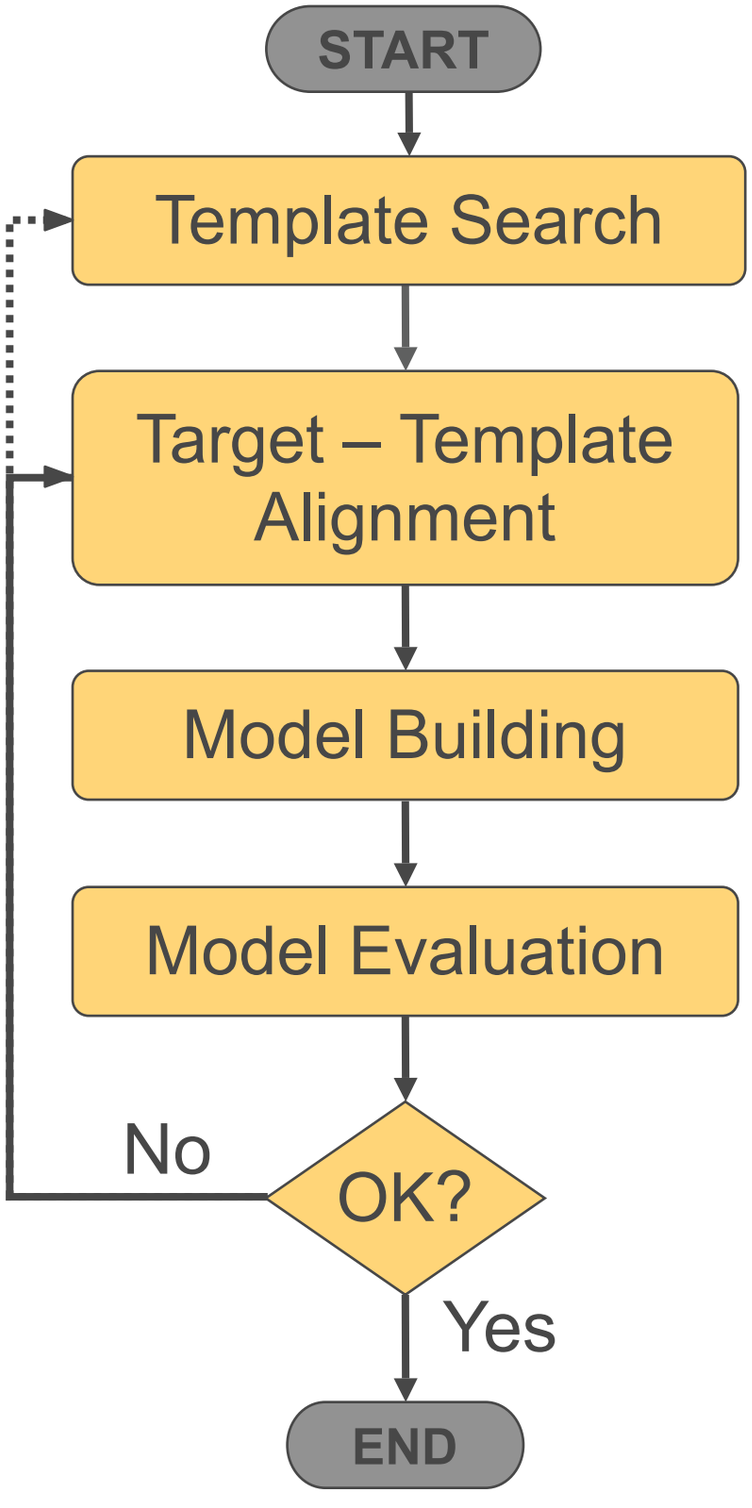
***Ab initio* prediction**

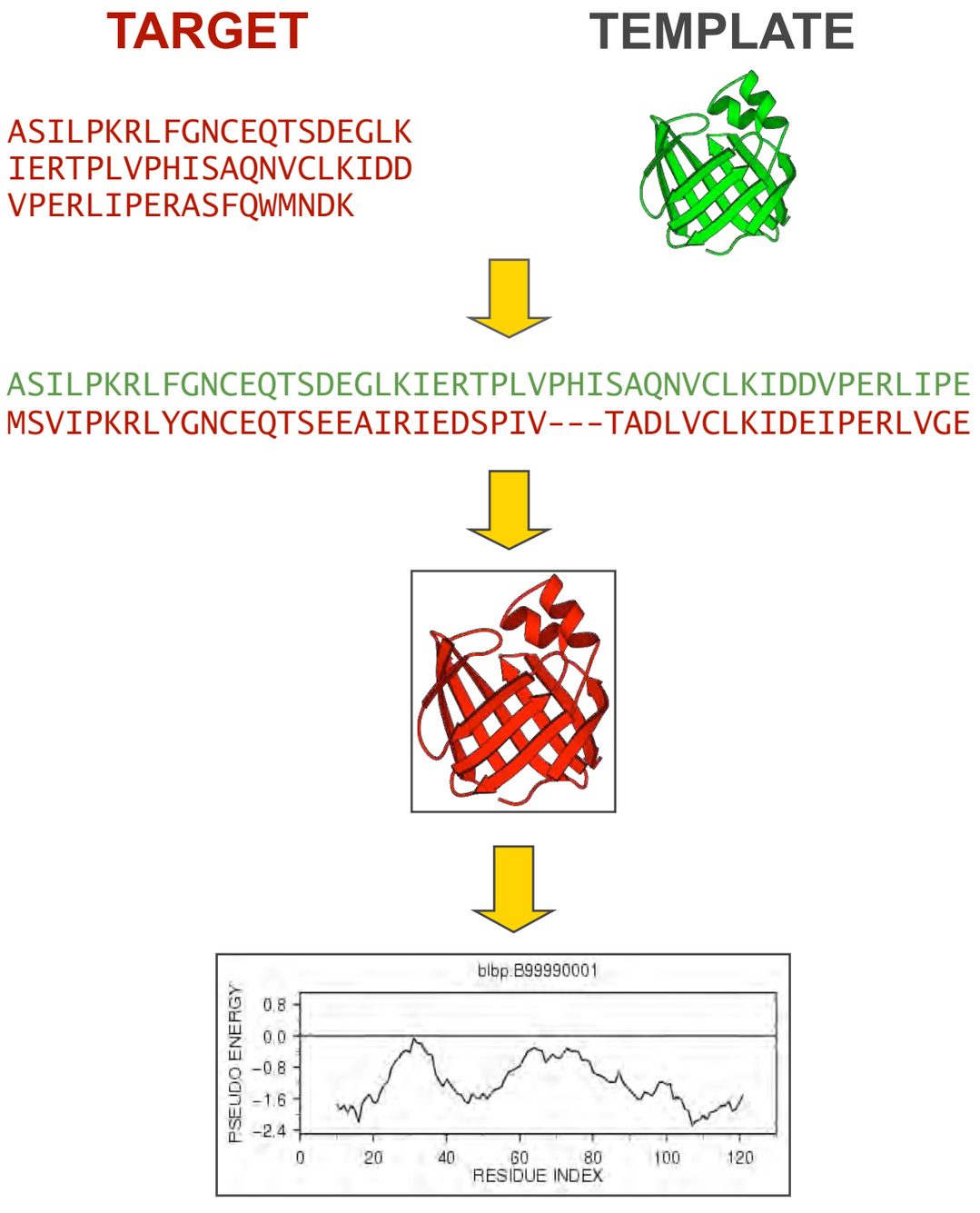
Evolution

(“statistical” rules)

Threading
Comparative Modeling

Steps in Comparative Protein Structure Modeling





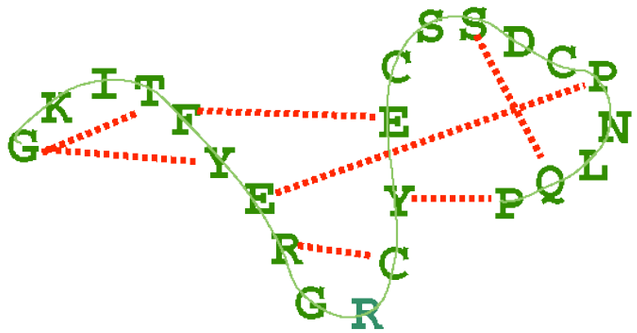
M. Marti-Renom *et al*. *Ann. Rev. Biophys. Biomolec. Struct*. **29**, 291, 2000.
http://salilab.org/

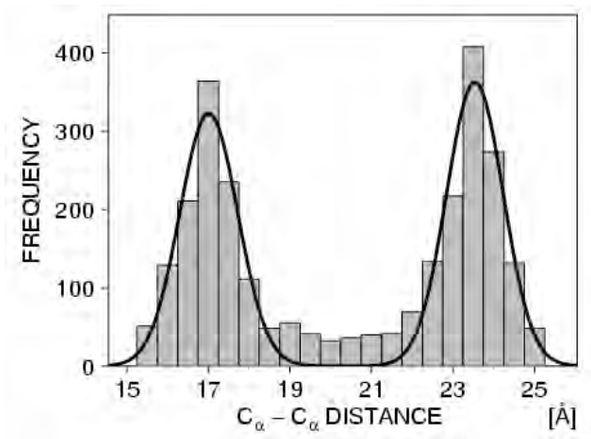
Comparative modeling by satisfaction of spatial restraints
MODELLER

3D GKITFYERGFQGHCYESDC-NLQP…

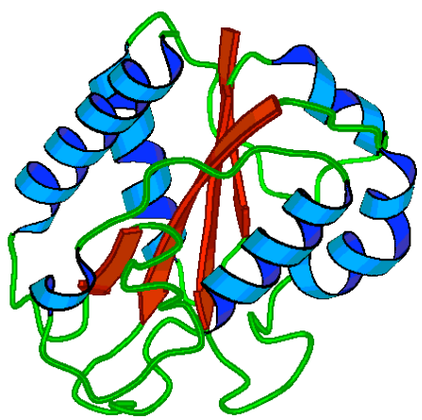
SEQ GKITFYERG---RCYESDCPNLQP…

1. Extract spatial restraints





2. Satisfy spatial restraints



$$P(\mathbf{R} \,/\, \mathbf{I}) = \prod_i p_i\,(\mathbf{r}_i \,/\, \mathbf{I}_i)$$

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.

http://salilab.org/

Typical errors in comparative models

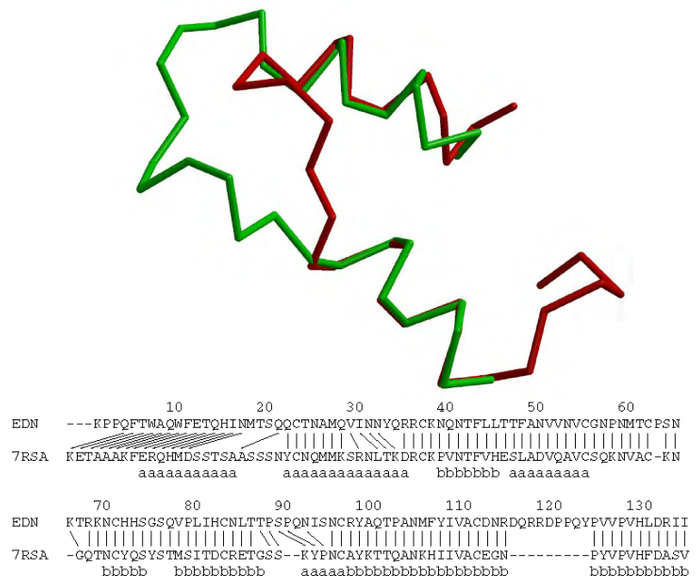
MODEL

X-RAY

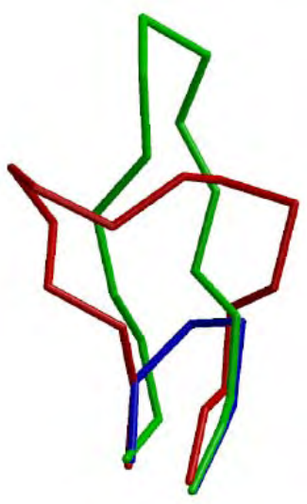
TEMPLATE

Incorrect template

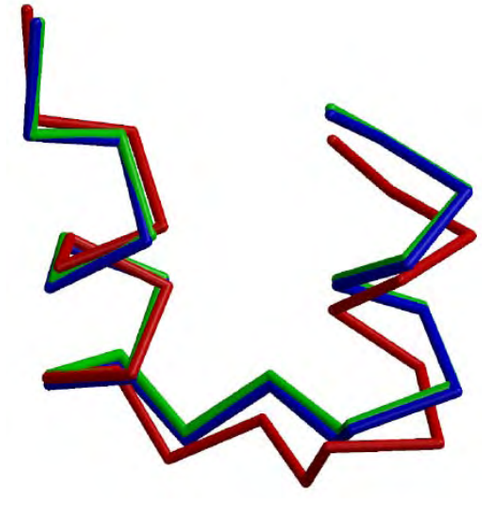
Misalignment



Region without a template



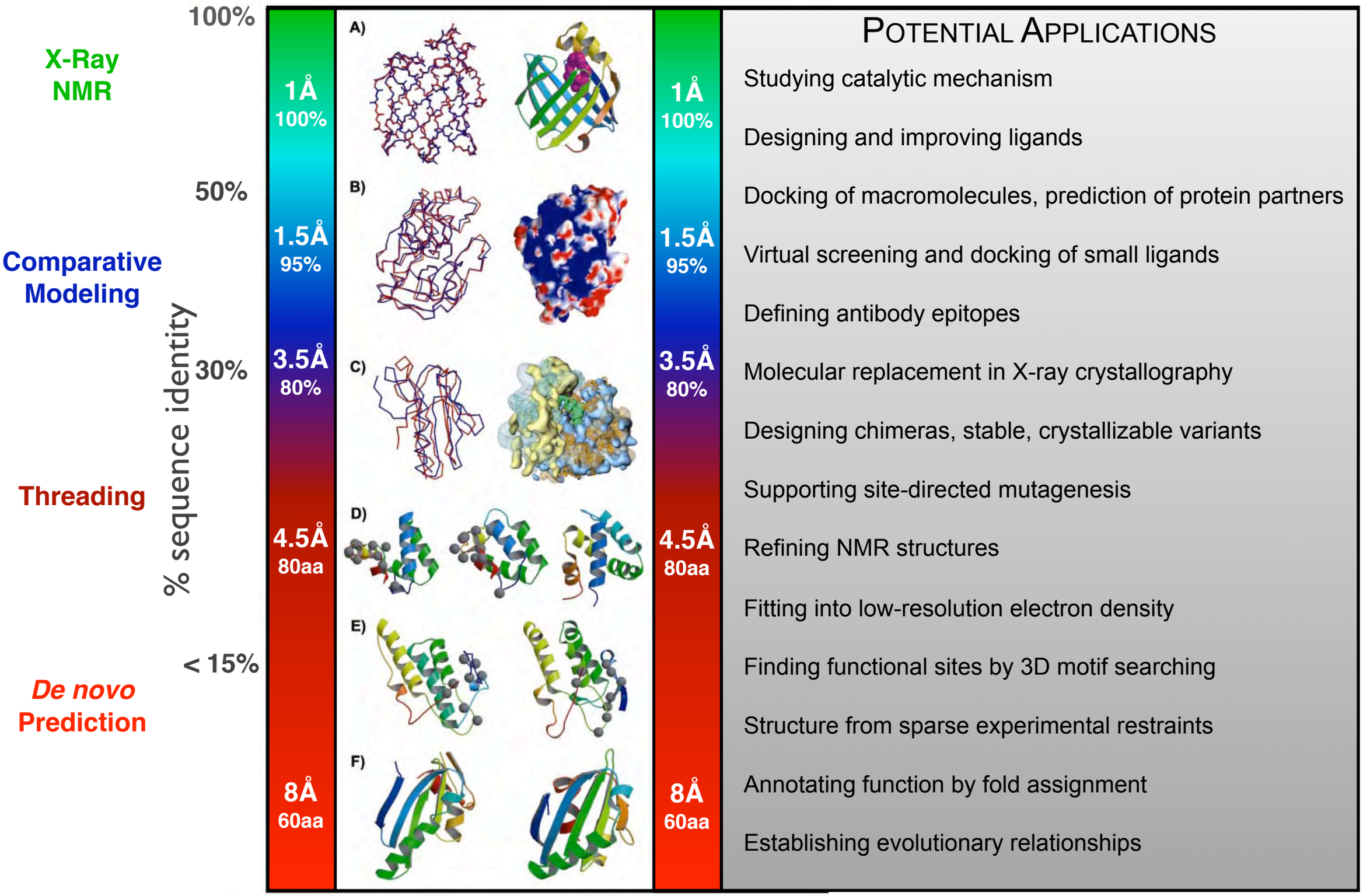
Distortion/shifts in aligned regions



Sidechain packing

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

Model accuracy determines utility



D. Baker & A. Sali. *Science* 294, 93-97, 2001.

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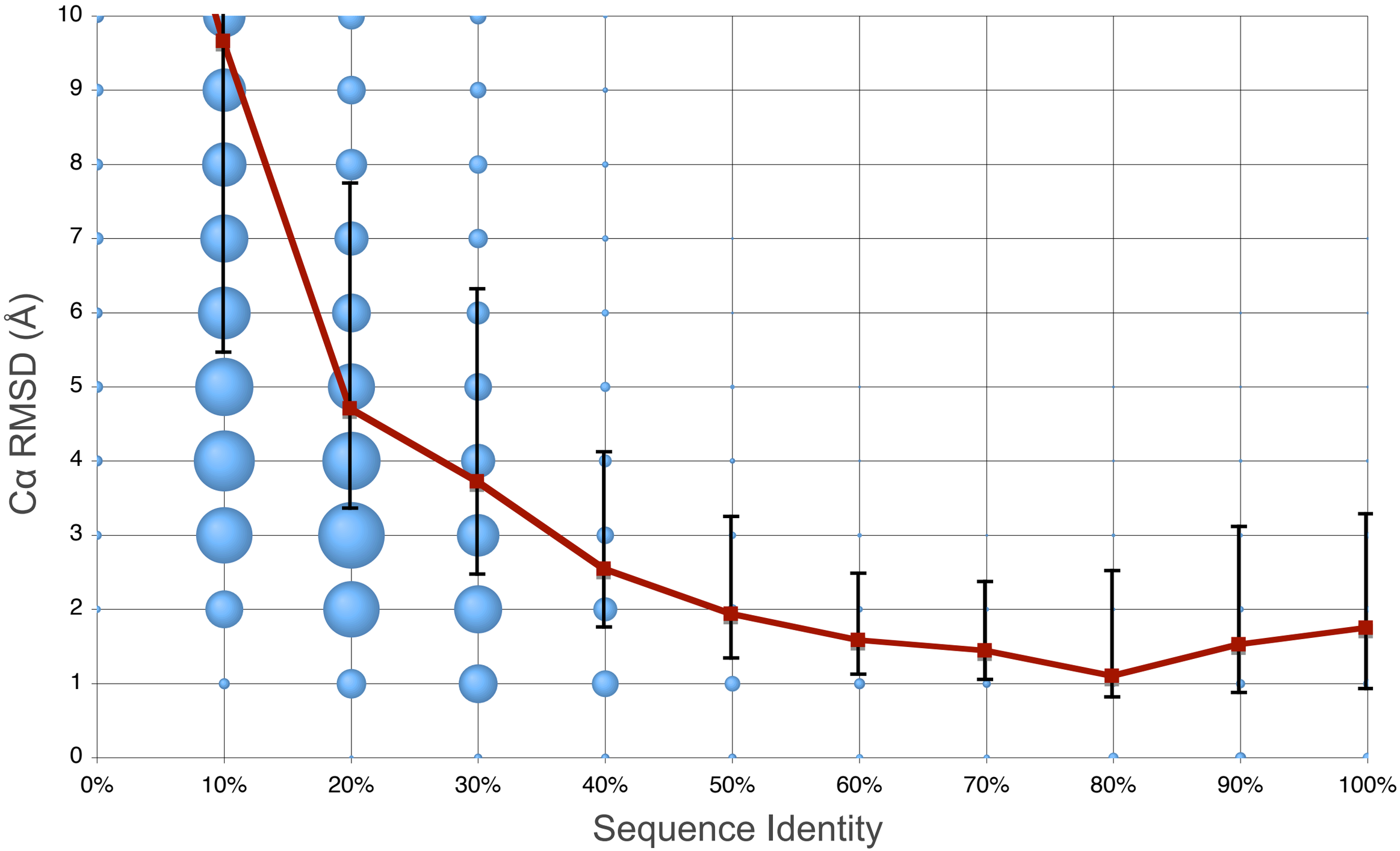
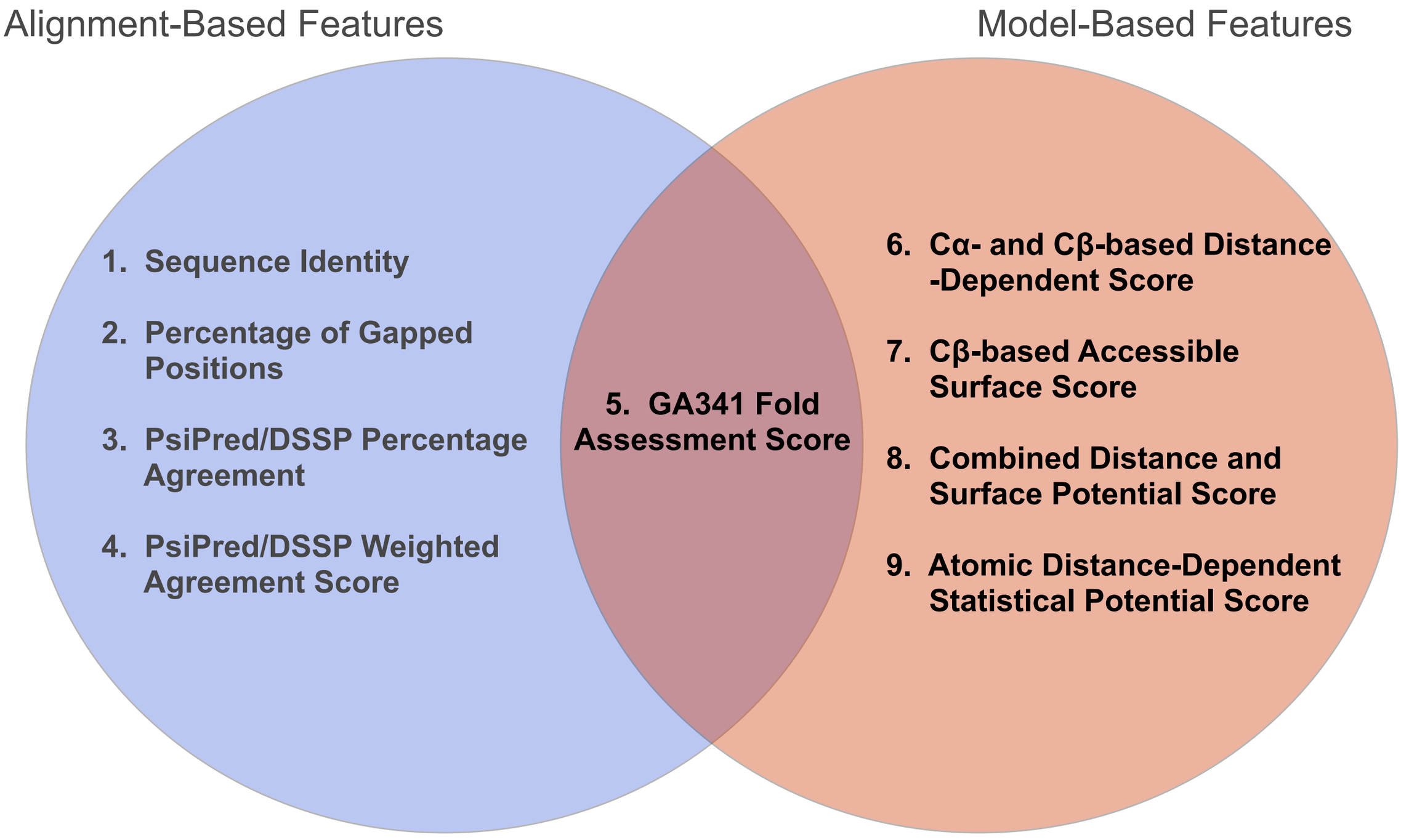
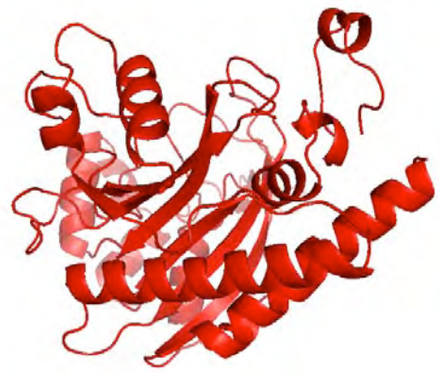
Comparative model accuracy varies widely with decreasing sequence identity



Model Assessment Scores

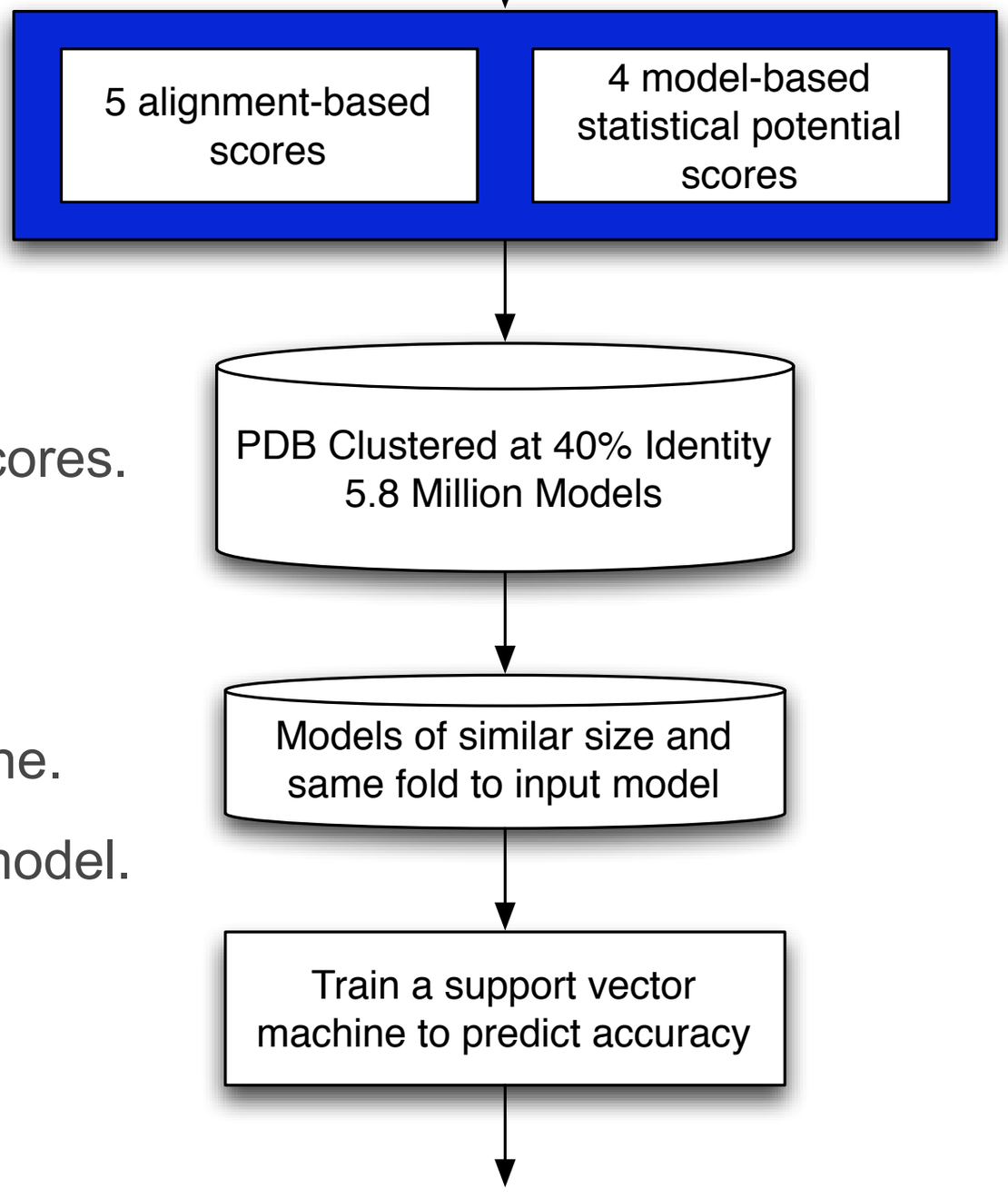


Outline of TSVMod



Input: Atomic model and optional alignment.

Output: Predicted Cα RMSD error.

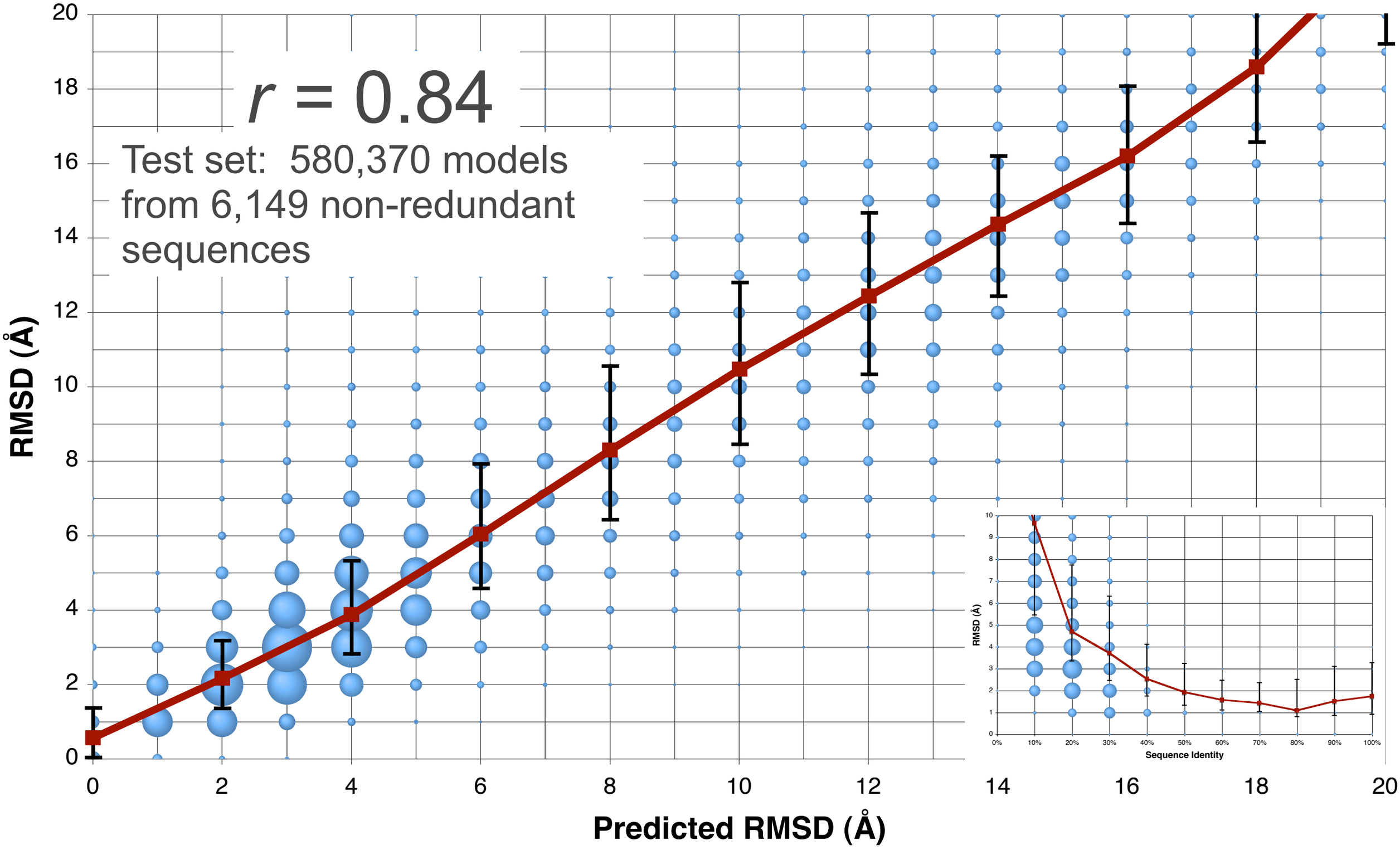


Algorithm:

1. Calculate individual model assessment scores.
2. Scan through PDB model database.
3. Construct a tailored model training set.
4. Train a specialized Support Vector Machine.
5. Run the Support Vector Machine on the model.

D. Eramian, N. Eswar, M-Y Shen, A. Sali, *Prot. Sci*, 2008.

Predicted *versus* actual Cα RMSD error

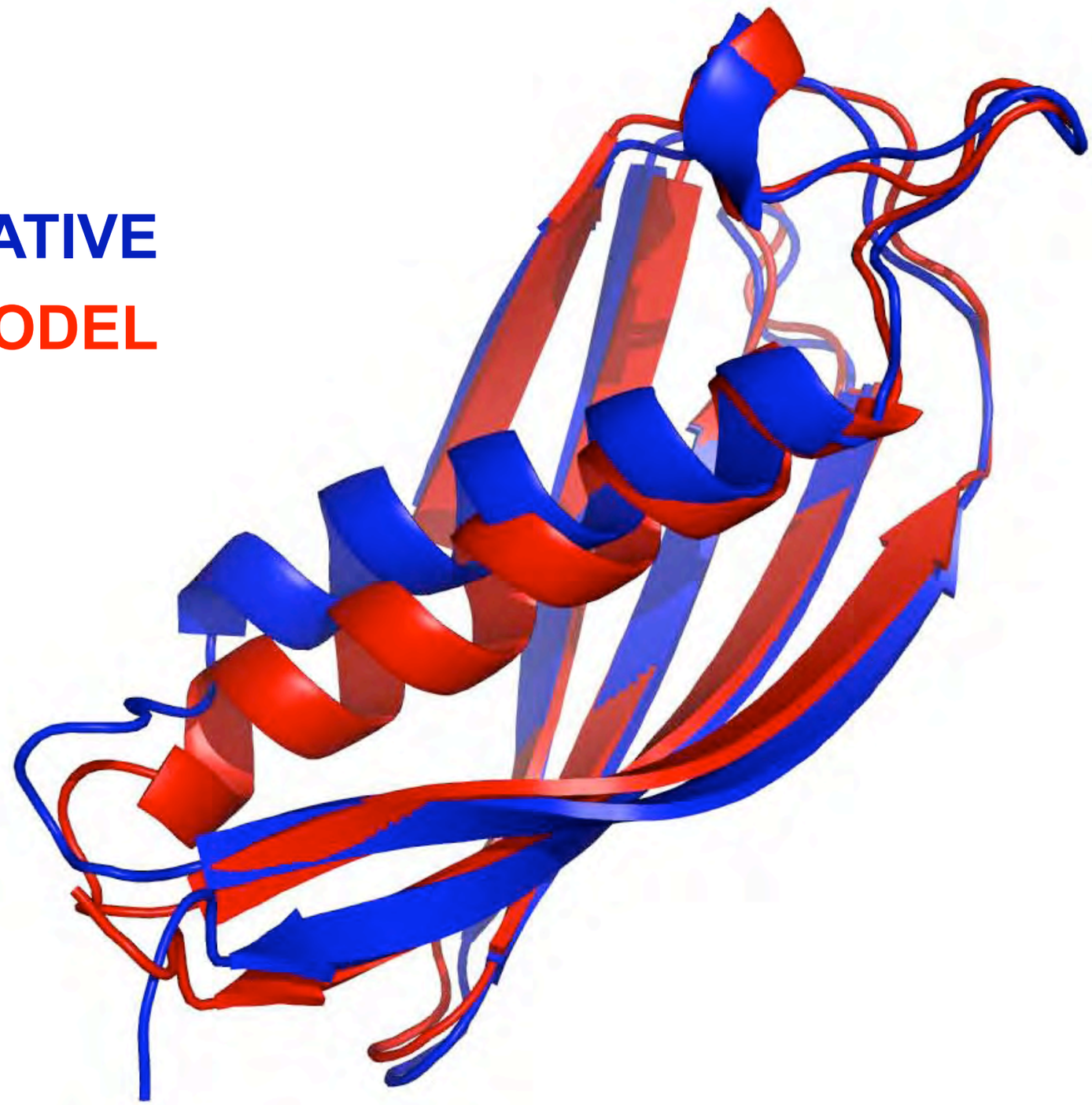


Good Model in the Midnight Zone: 12.3% Sequence Identity

Length	106
RMSD	2.0Å
Predicted RMSD	3.1Å

NATIVE

MODEL



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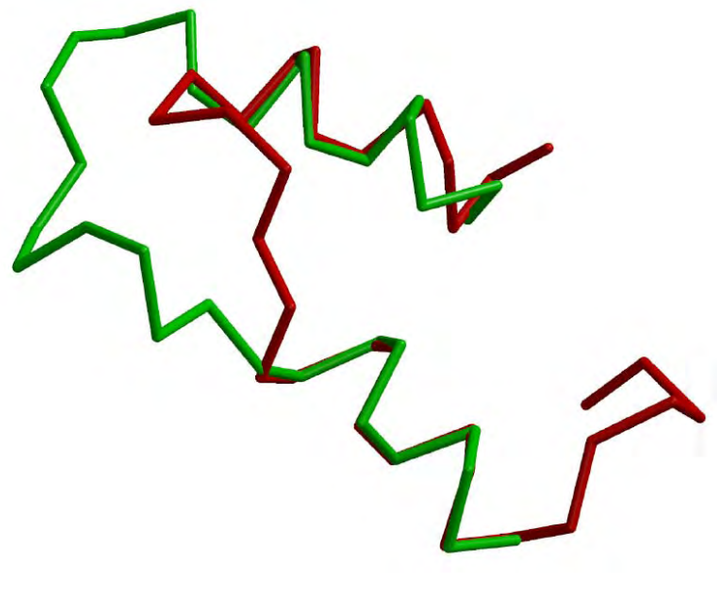
Minimizing errors in sequence-structure alignment

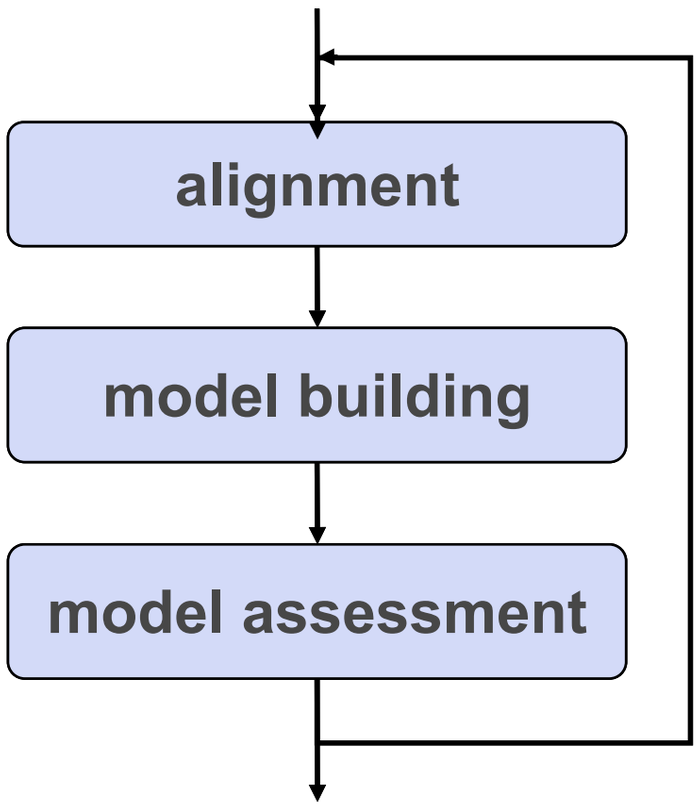
```
                10        20        30        40        50        60
EDN   ---KPPQFTWAQWFETQHINMTSQQCTNAMQVINNYQRRCKNQNTFLLTTFANVVNVCGNPNMTCPSN
                                   \\\ |||||||||||||||||||||||||||||||| ||
7RSA  KETAAAKFERQHMDSSTSAASSSNYCNQMMKSRNLTKDRCKPVNTFVHESLADVQAVCSQKNVAC-KN
          aaaaaaaaaaa     aaaaaaaaaaaaaa   bbbbbbb aaaaaaaaa

        70        80        90       100       110       120       130
EDN   KTRKNCHHSGSQVPLIHCNLTTPSPQNISNCRYAQTPANMFYIVACDNRDQRRDPPQYPVVPVHLDRII
       \ |||||||||||||||||||| \\ \\\ |||||||||||||||||||||          ||||||||||||
7RSA  -GQTNCYQSYSTMSITDCRETGSS--KYPNCAYKTTQANKHIIVACEGN---------PYVPVHFDASV
          bbbbb   bbbbbbbbbb    aaaaabbbbbbbbbbbbbbbbbb          bbbbbbbbbbb
```

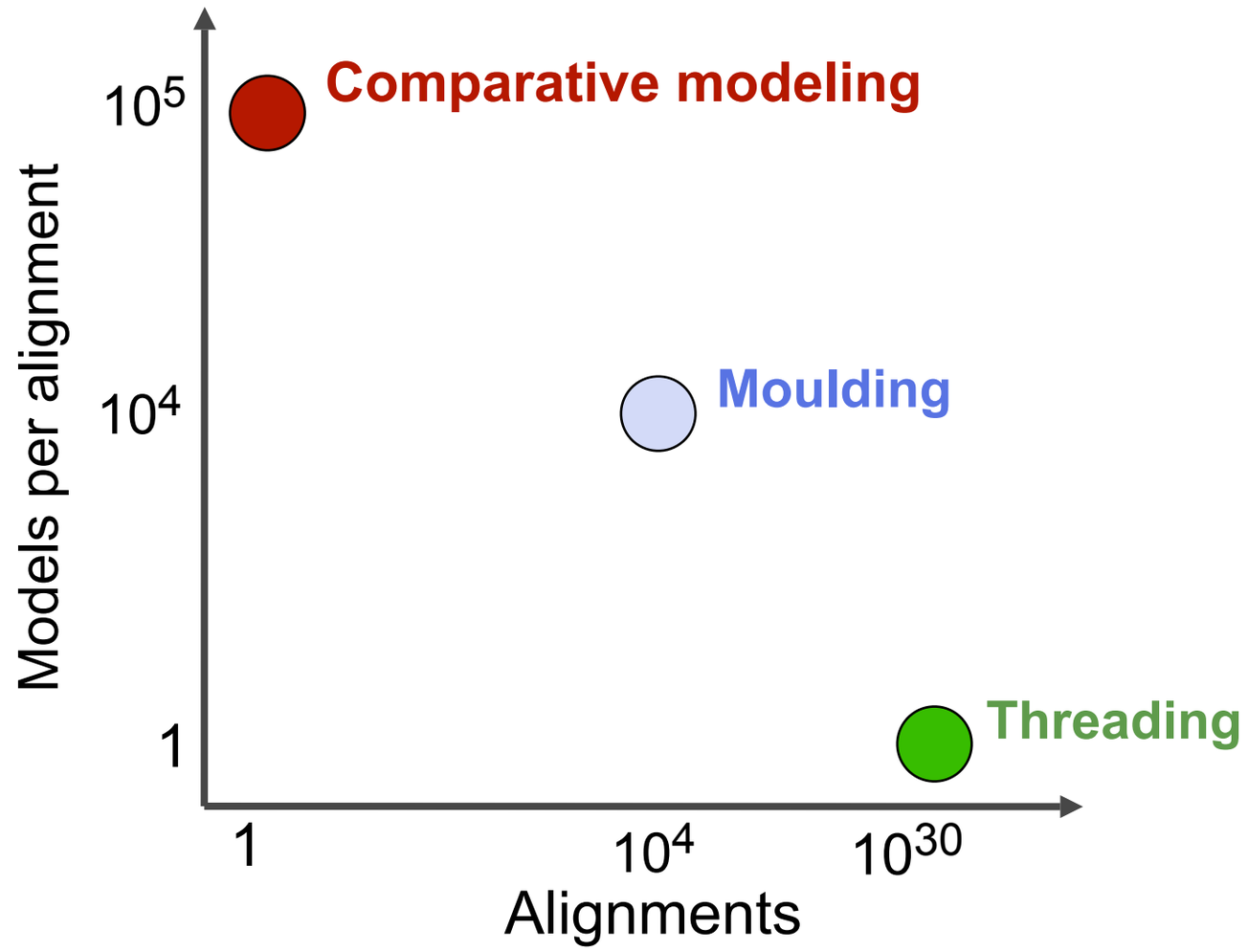


- Complex gap penalty functions.
- Multiple sequence profiles.
- Hidden Markov Models.
- Threading.

Moulding: iterative alignment, model building, model assessment

B. John, A. Sali. *Nucl. Acids Res.* **31**, 1982-1992, 2003.
D. Eramian, B. Webb.

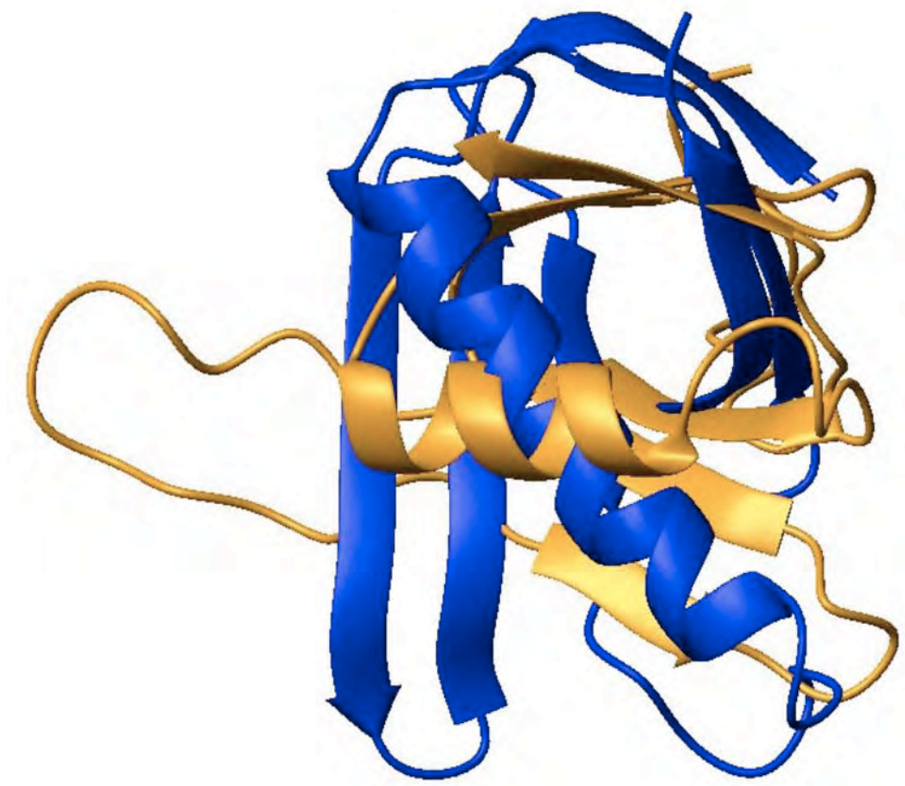




Application to a difficult modeling case

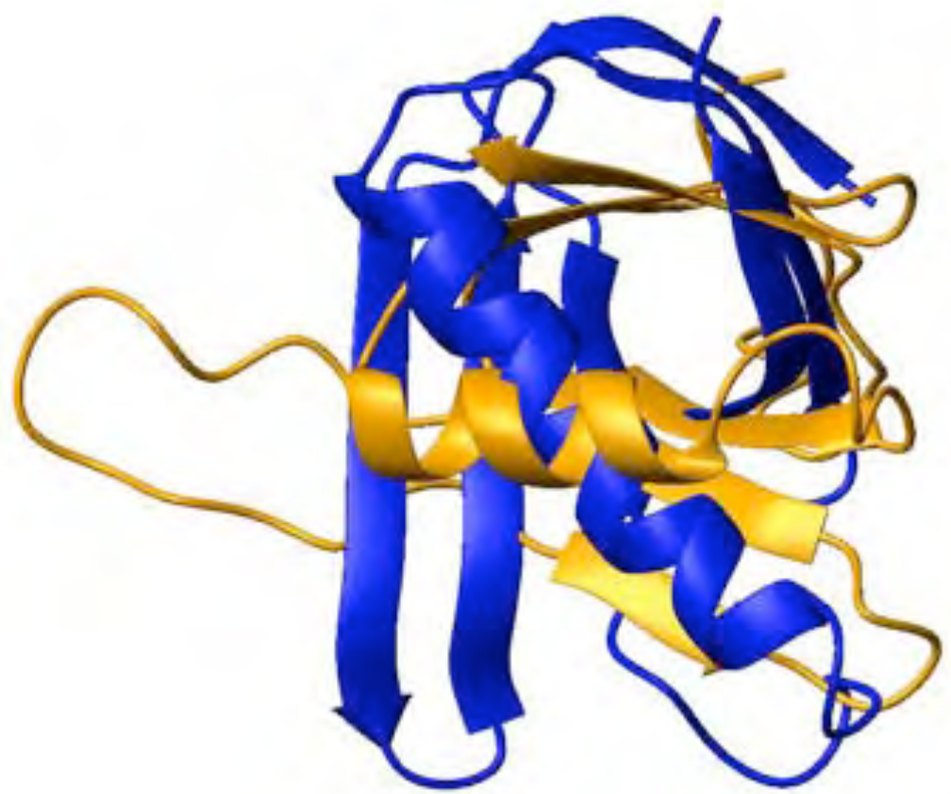
1BOV-1LTS (4.4% sequence identity)

initial



Cα RMSD 10.1 Å

final



Cα RMSD 3.6 Å

1lts structure

1lts model

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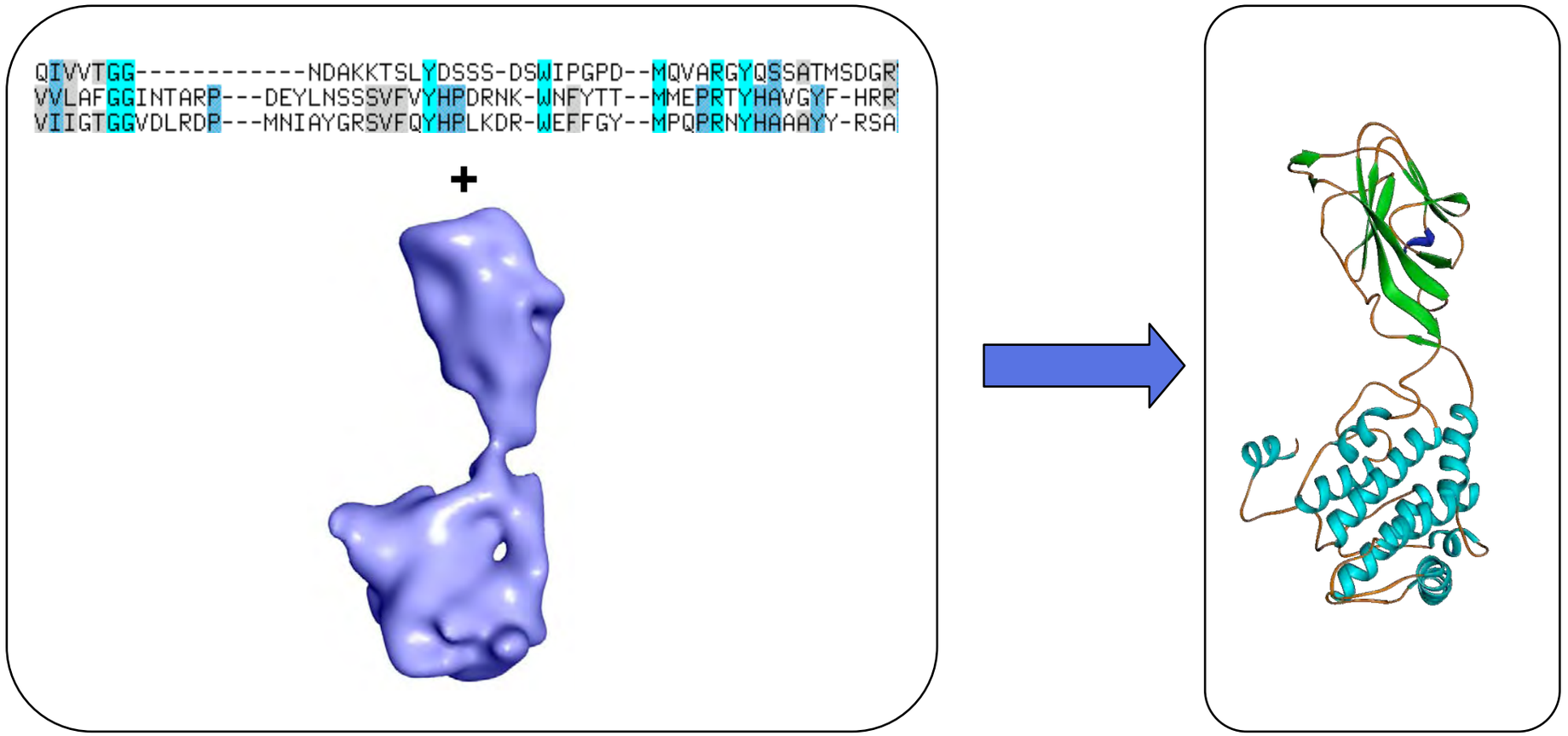
Comparative modeling and fitting into EM density

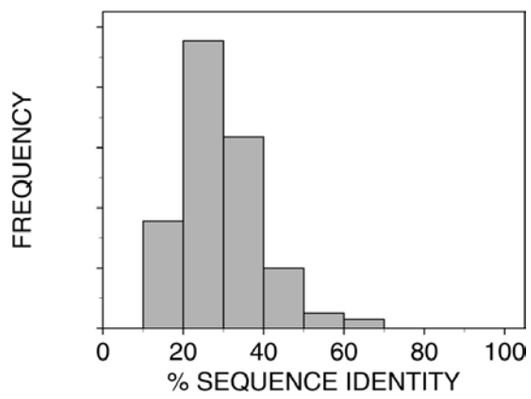
Improve comparative modeling by fitting models into the target EM density map;

Improve fitting into an EM density map by simultaneous model building.



Motivation:

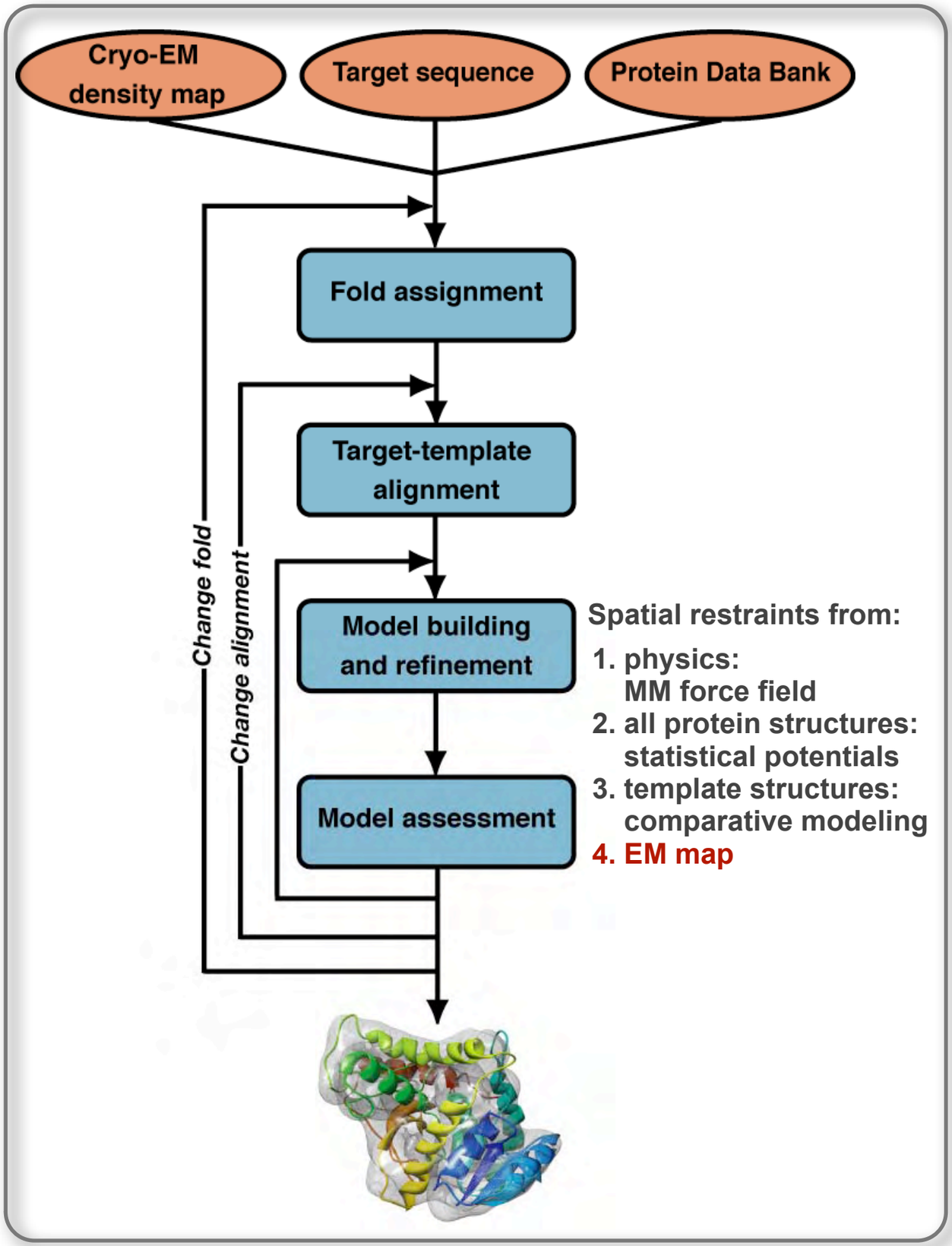
- Number of known structures in PDB: ~50,000
- Number of known sequences modeled by CM: ~1,800,000
  Pieper *et al*, Nucl. Acids Res., 2006.

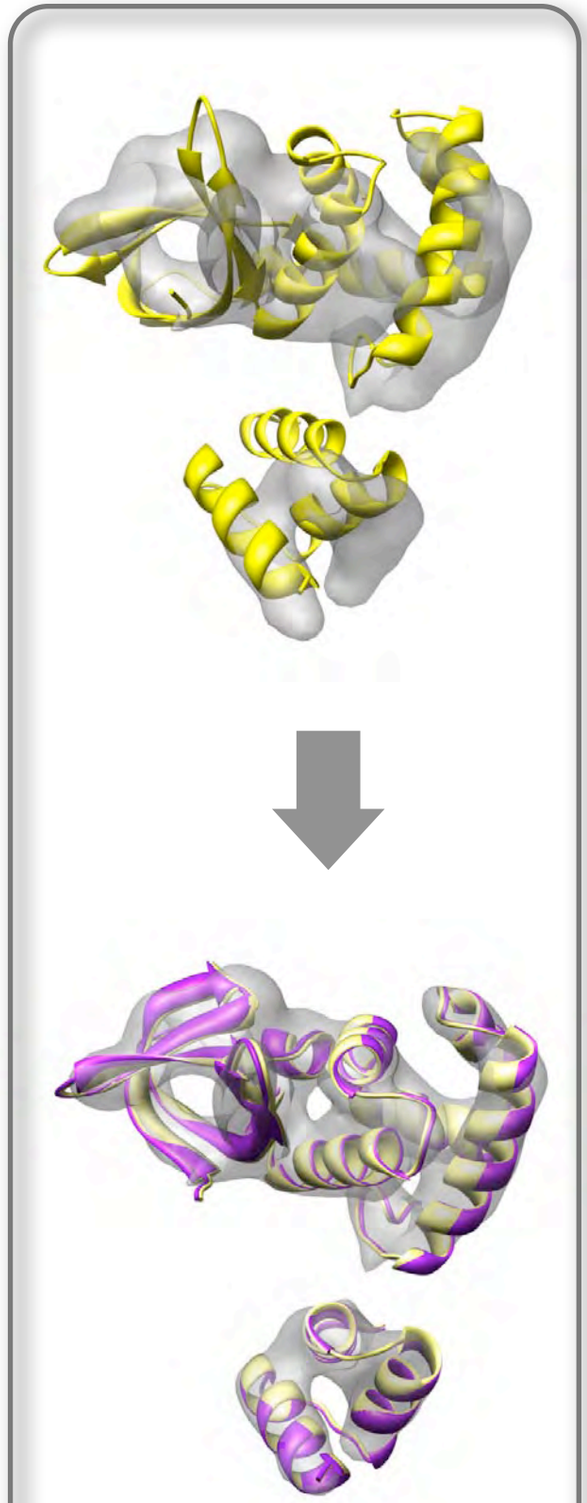


Protein structure modeling in an EM map

Topf, Baker, John, Chiu, Sali. *J. Struct. Biol*, 2004.
Topf & Sali, *Curr. Opin. Str. Biol.*, 2005.

Topf, Baker, Marti-Renom, Chiu & Sali. *J. Mol. Biol.*, 2006.
Topf, Lasker, Webb, Wolfson, Chiu & Sali. *Structure*, 2008.

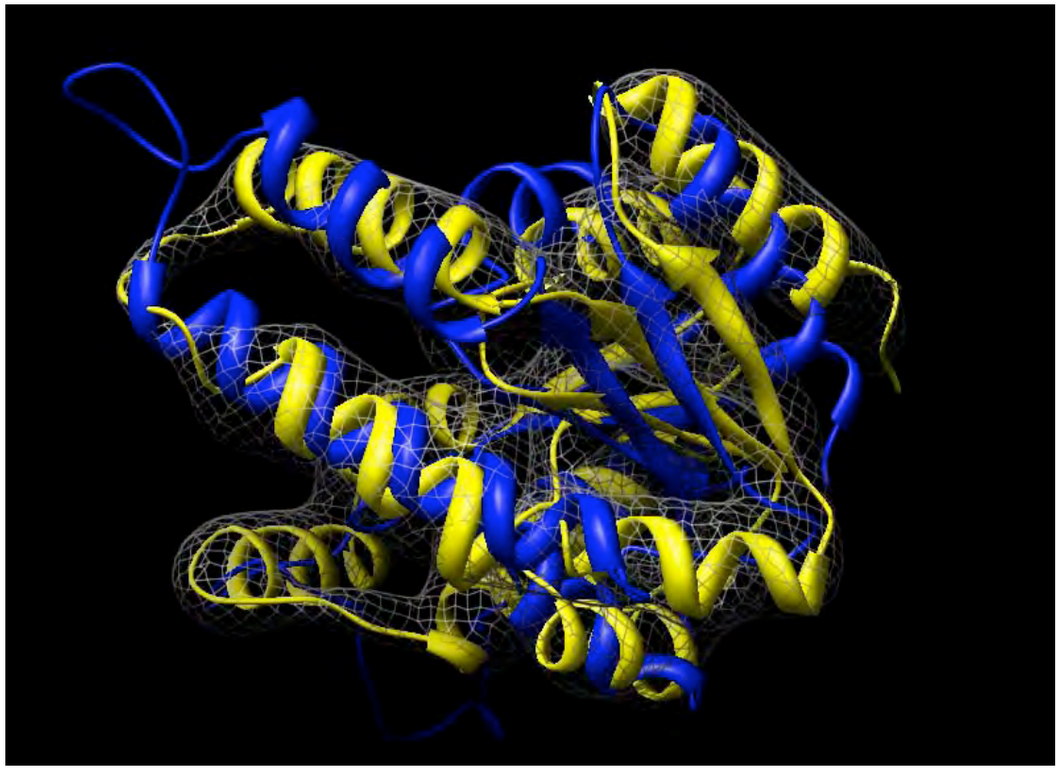


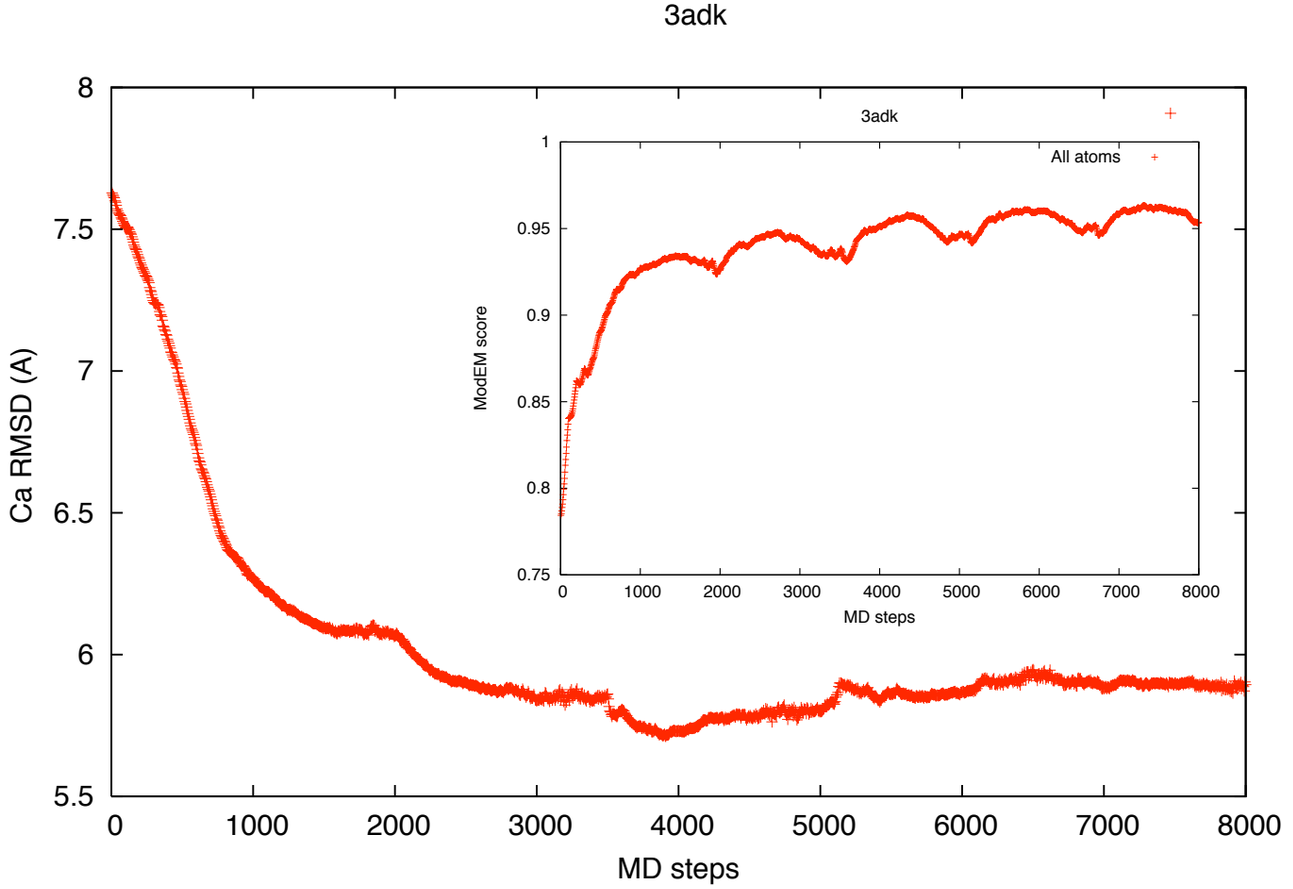


Sample refinement of 1adk

Topf, Lasker, Webb, Wolfson, Chiu & Sali. *Structure*, 2008.

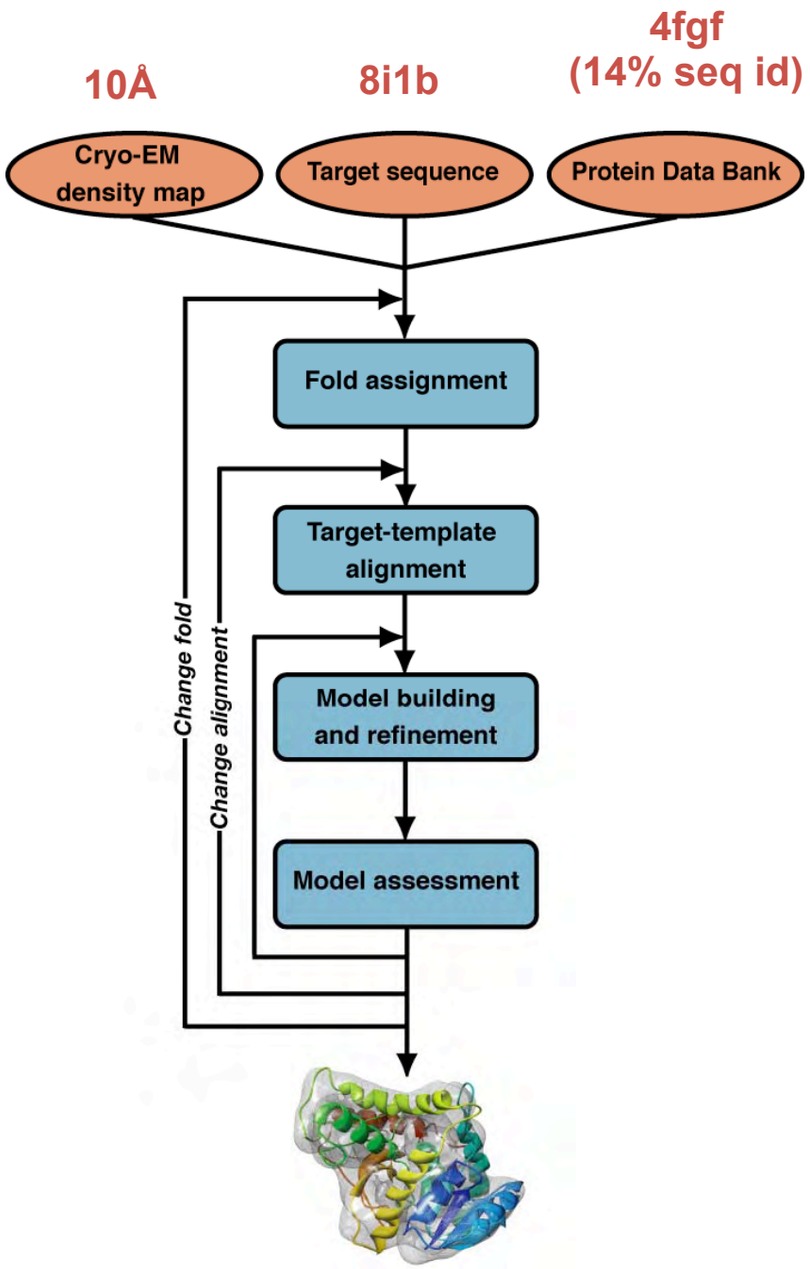
- EM map (10 Å) from native structure;
- secondary structure segments as rigid bodies, loops flexible;
- scoring function consisting only of model-map correlation coefficient, soft-sphere atom overlap, stereochemistry;
- optimization by a combination of “molecular dynamics” with simulated annealing and conjugate gradients minimization.

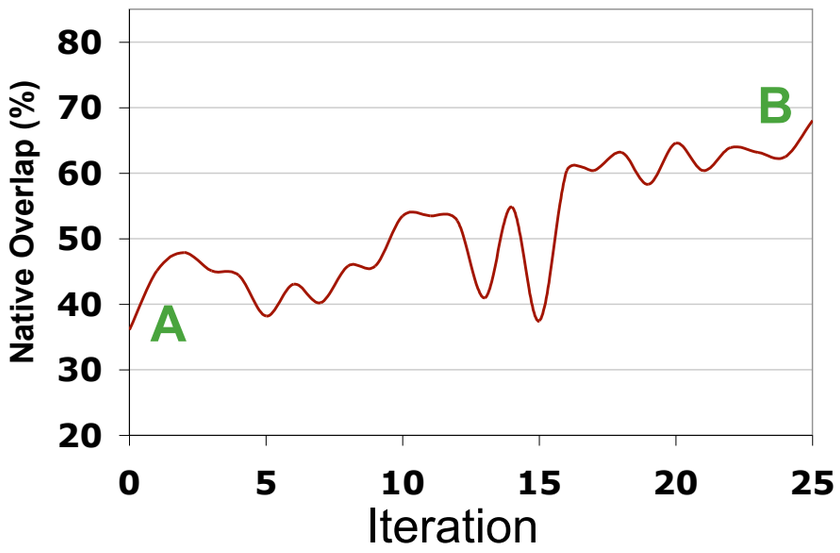




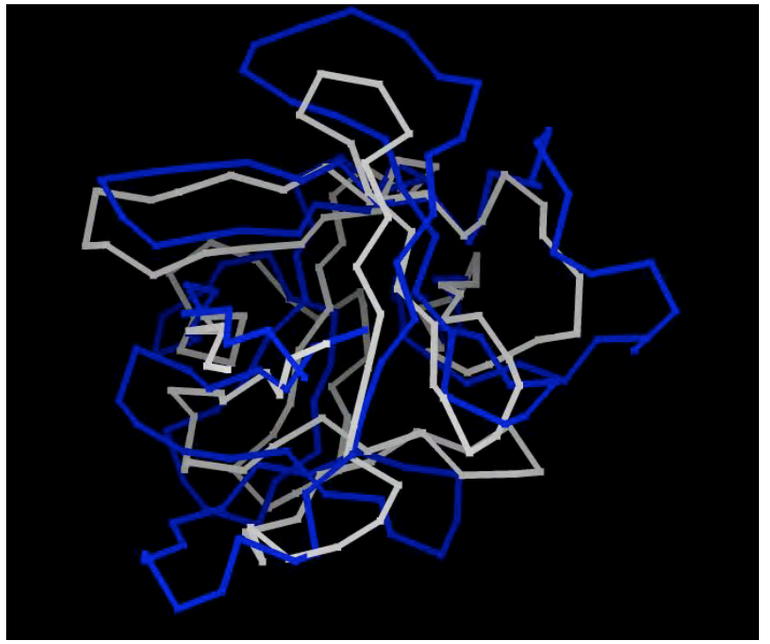
Moulding into EM maps

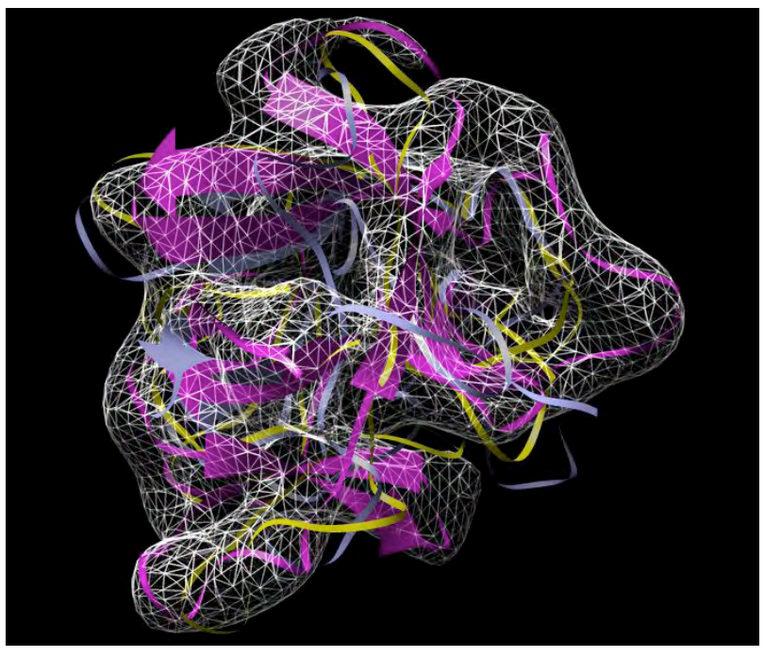
Topf, Baker, Marti-Renom, Chiu & Sali. *J. Mol. Biol.*, 2006.

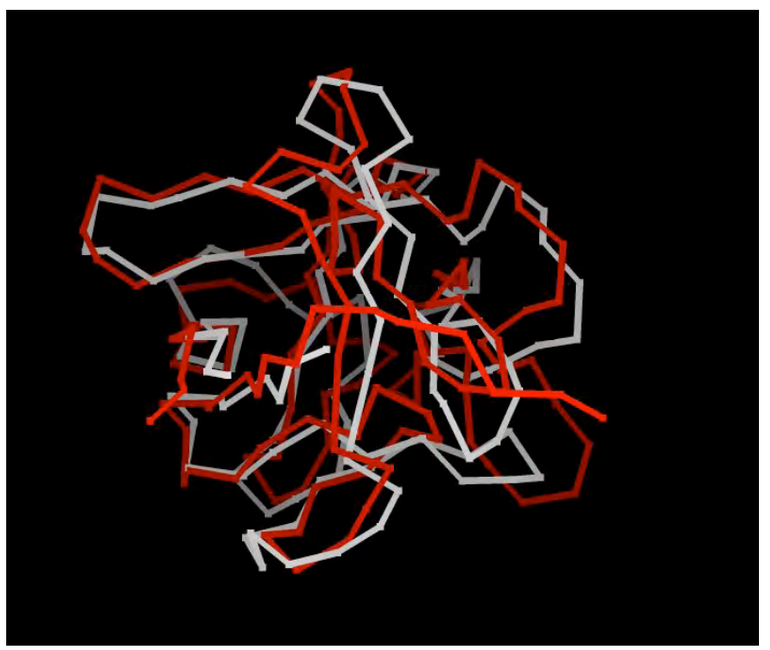




A. 37% of C_α within 5Å



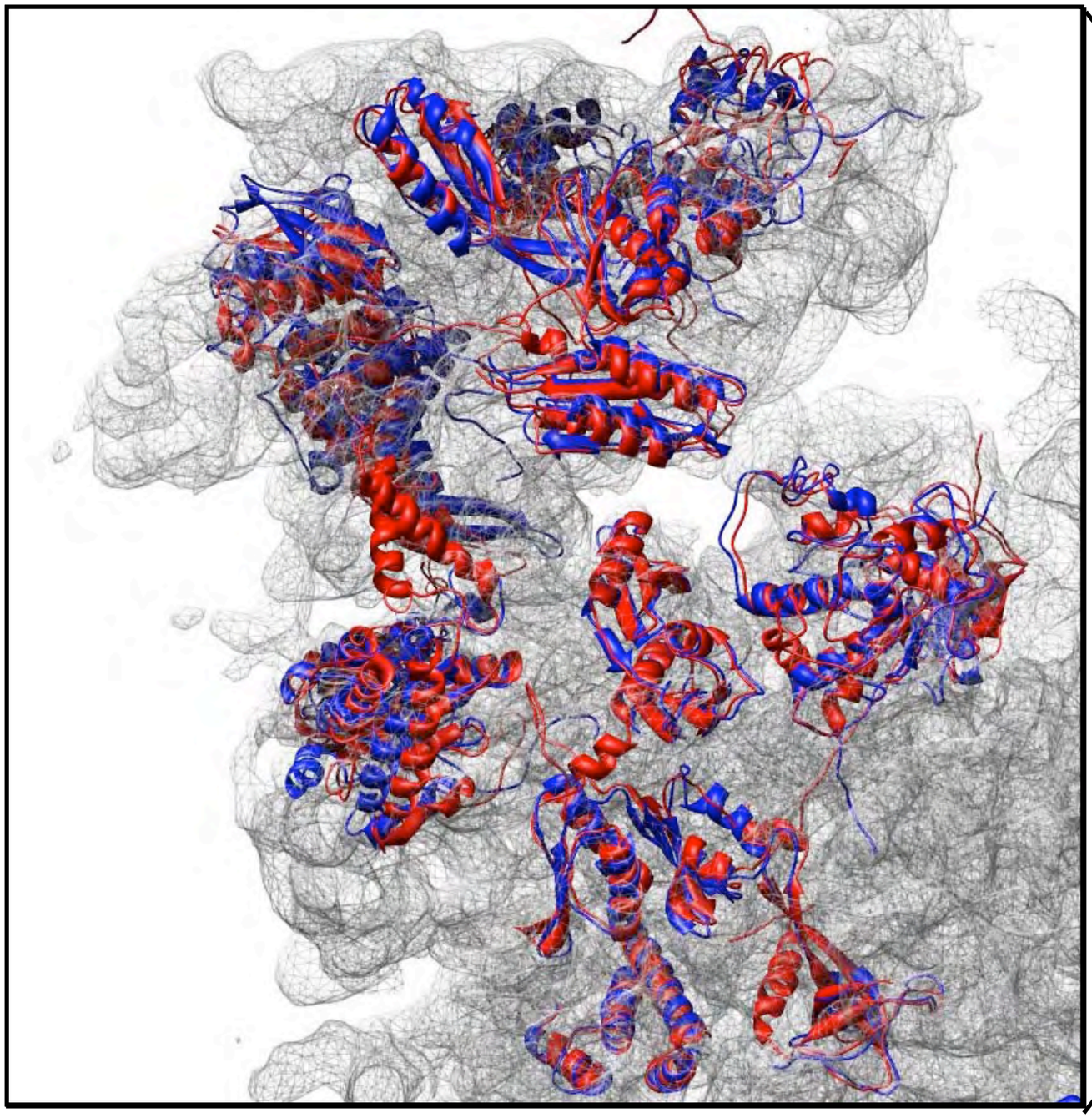


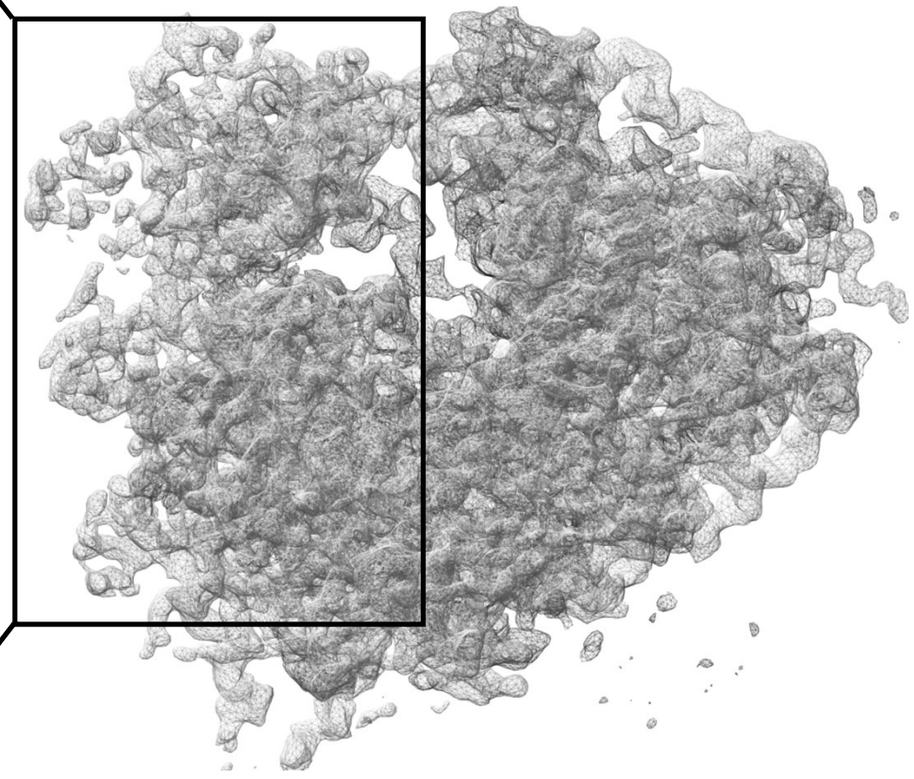


B. 69% of C_α within 5Å

Dog Ribosome at 8.7 Å

Chandramouli, Topf, Menetret, Eswar, Gutell, Sali, Akey. *Structure*, 2008.





Added value:

- **Unique insertions/deletions in proteins**
- **Unique protein-RNA contacts**
- **Mammalian-only ribosomal proteins**

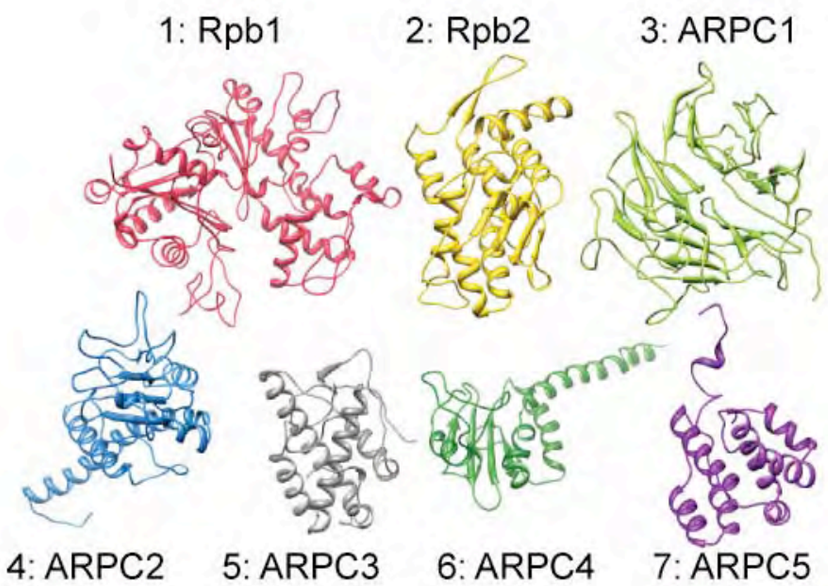
Thermus Thermophilus **30S ribosomal subunit (proteins - red; RNA - yellow)**

Homology models of the mammalian ribosomal proteins (blue)

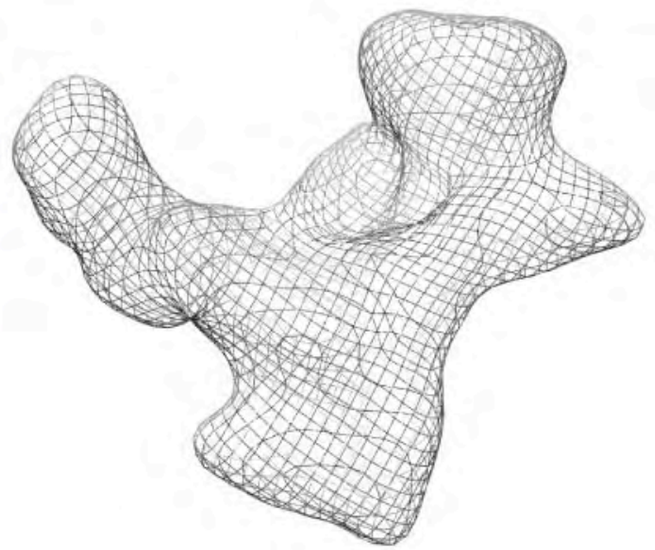
Fitting multiple components into a cryoEM map

K. Lasker, M. Topf, A. Sali, H. Wolfson

INPUT: rigid component structures

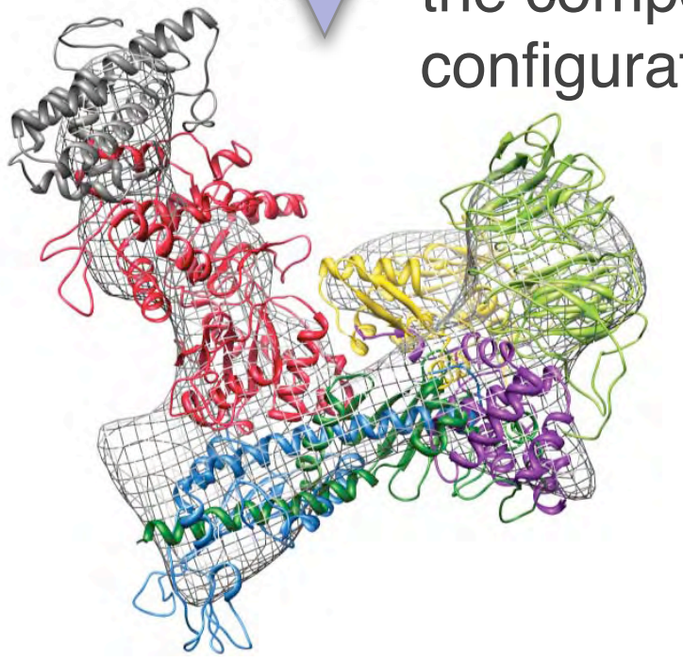


EM map



OUTPUT:

the component configuration



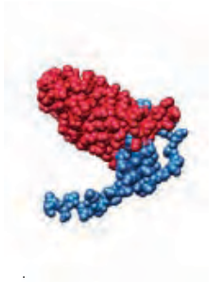
The MultiFit approach

$$S(a,b,c,d,D) = \sum_{x \in \{a,b,c,d\}} \{\varphi_1(x,D) + \varphi_2(x,D)\} + \sum_{(x,y) \in B} \varphi_3(x,y)$$

$$B = \{(a,b)(a,c),(a,d),(b,c),(b,d),(c,d)\}$$

$\varphi_1(a,D)$

$\varphi_2(d,D)$

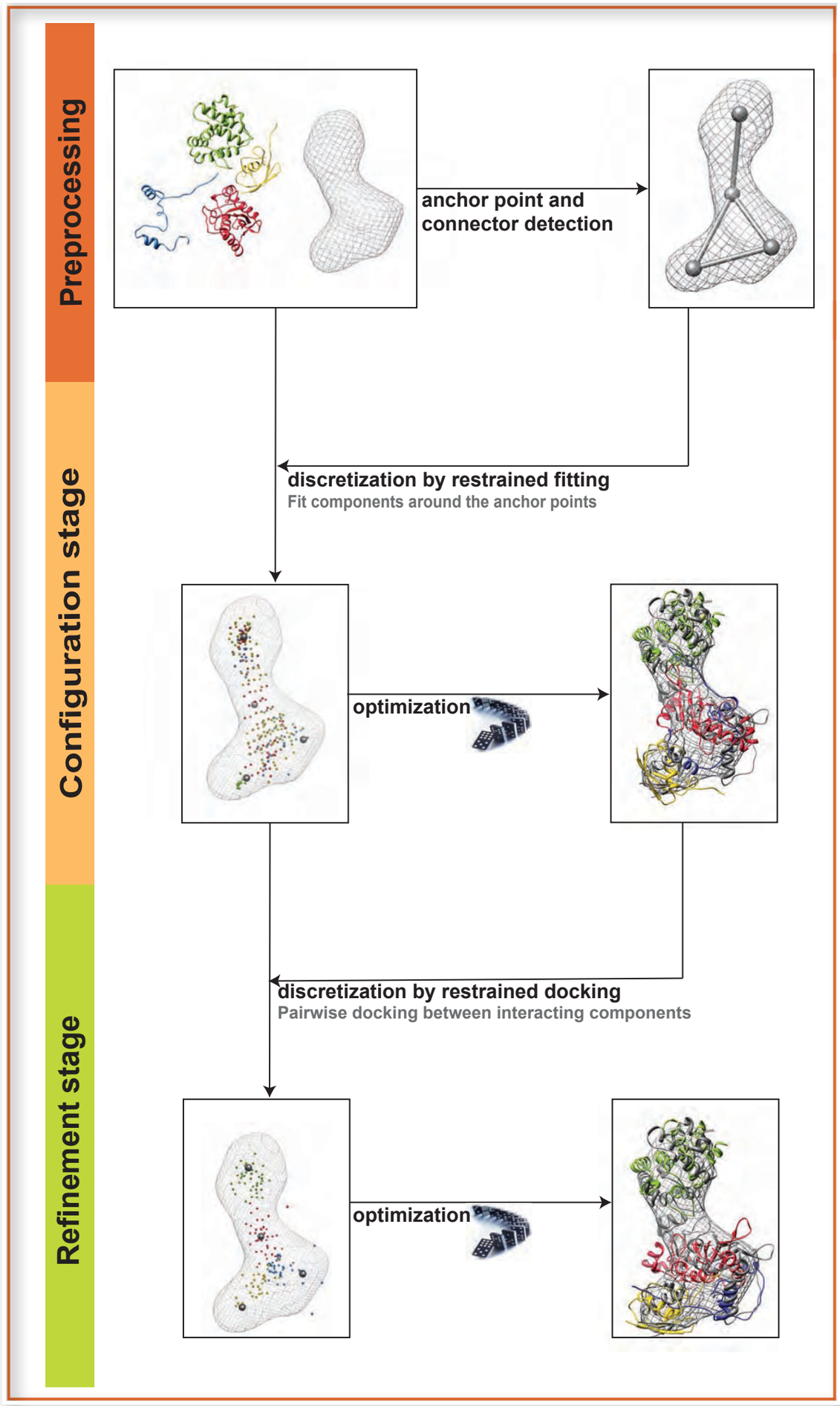


$\varphi_3(a,d)$

The scoring function includes:

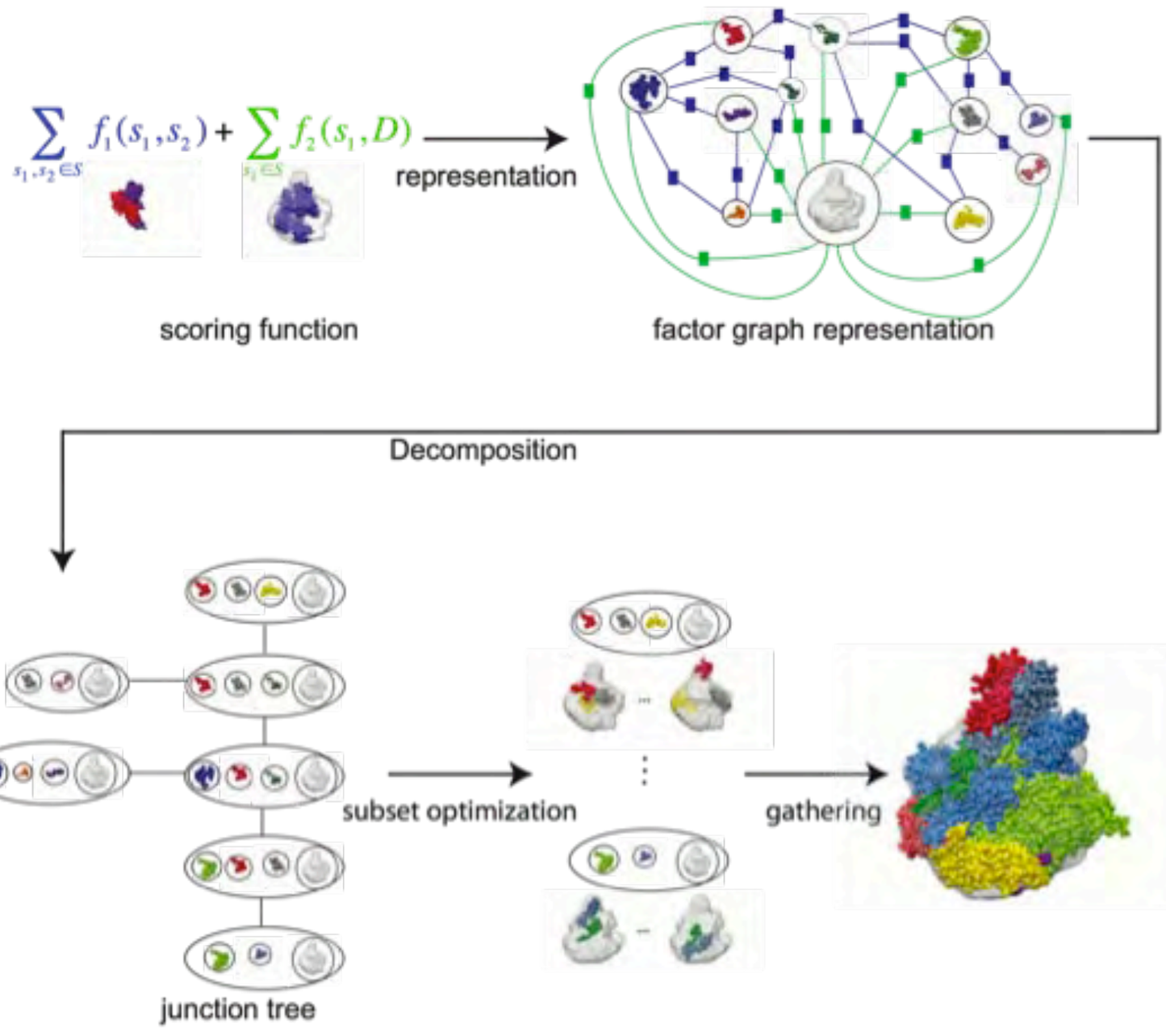
- quality-of-fit of components in the map.
- protrusion of components from the map.
- shape complementarity between pairs of components.

Lasker, Topf, Sali, Wolfson



DOMINO: Divide-and-Conquer

1. **Represent** the scoring function as a factor graph.
2. **Decompose** the set of components into relatively decoupled subsets (a junction tree algorithm from graph theory).
3. **Optimize** each subset independently by a traditional optimizer, to get the optimal and a number of suboptimal solutions (restrained fitting for configuration stage and restrained docking for refinement stage).
4. **Gather** subset solutions into the best possible global solutions (message passing algorithms from graph theory; *eg*, belief-propagation).

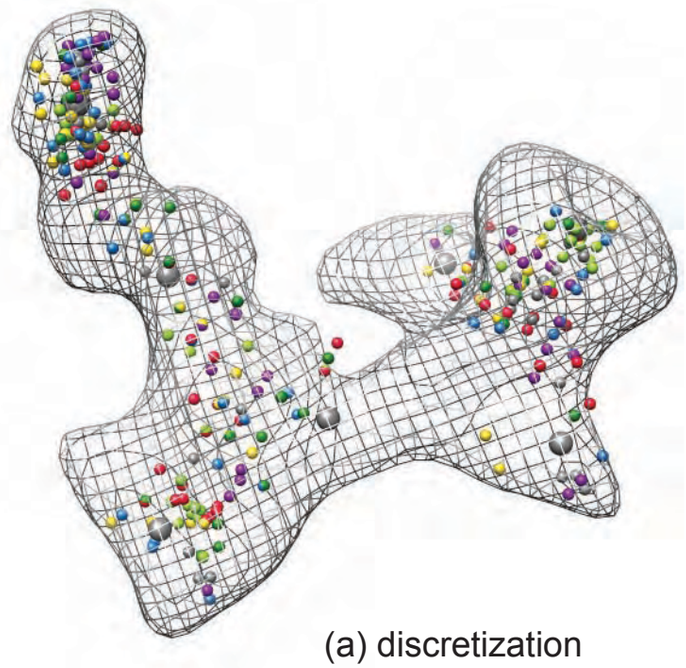


additional notes:

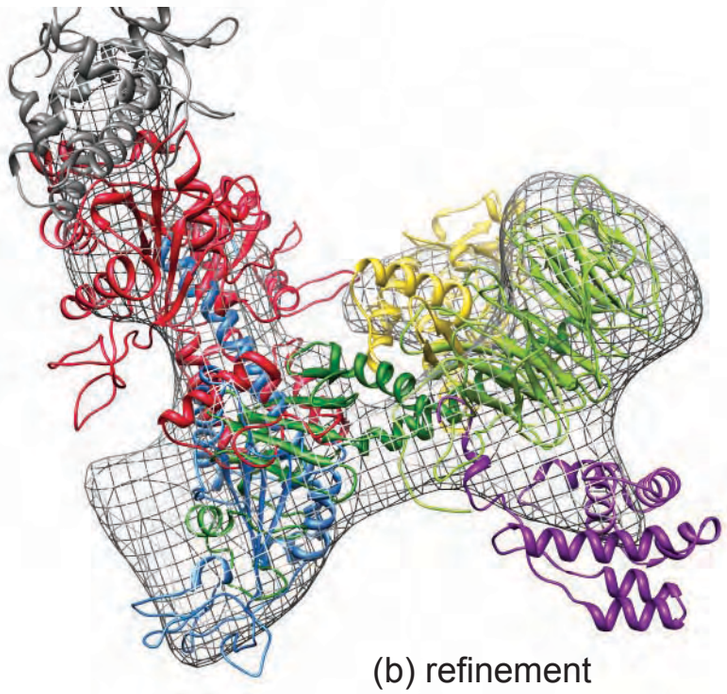
- factor graph simplification by eliminating terms for non-interacting components, given a component mapping to anchor points
- branch-and-bound for optimizing mappings, in configuration stage

Arp2/3 Example: Optimization stages

3. Configuration stage



(a) discretization

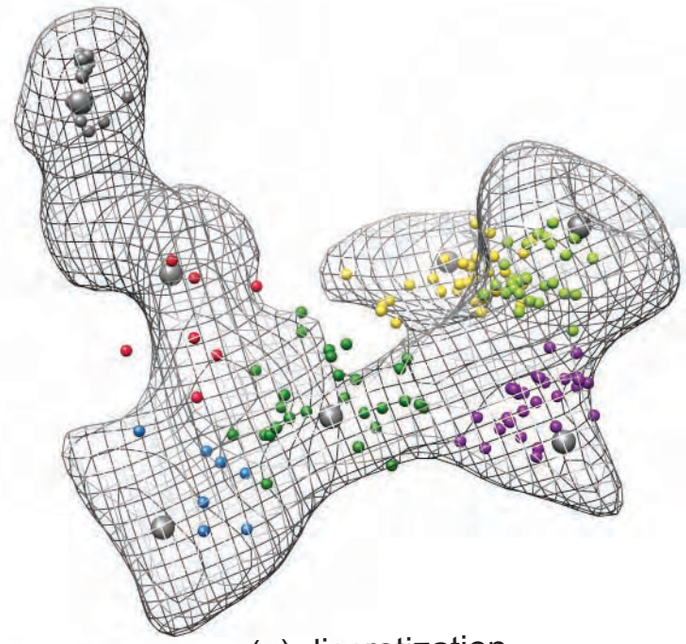


(b) refinement

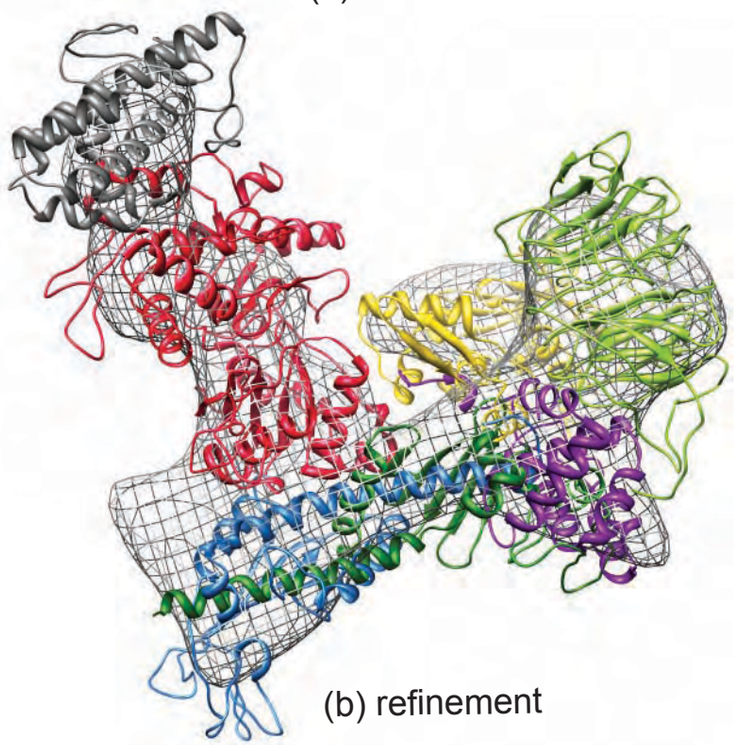
(10.8 Å, 136°)

Assembly placement score

4. Refinement stage



(a) discretization



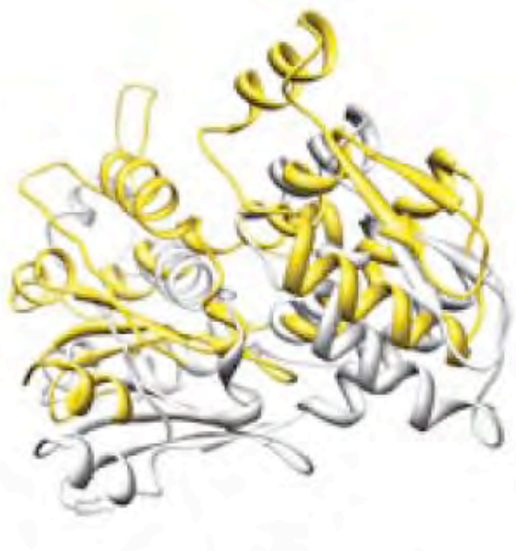
(b) refinement

(7.1 Å, 25°)

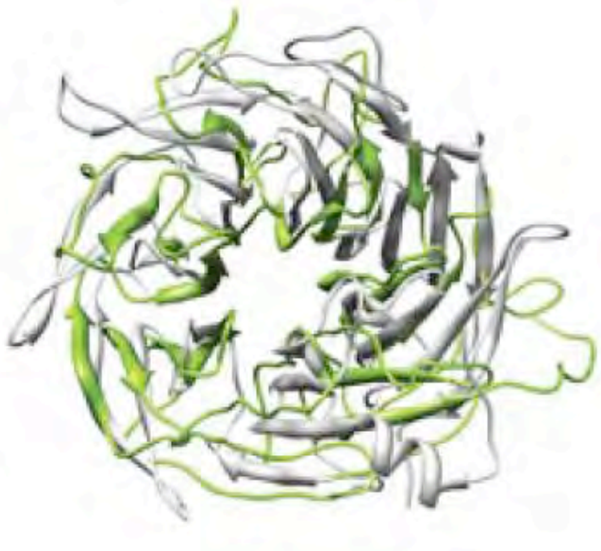
Assembly placement score

Component displacement errors

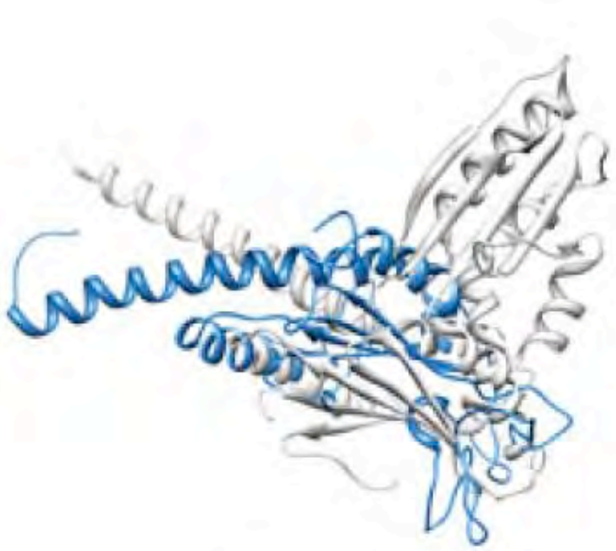
(4.4 Å, 12°)



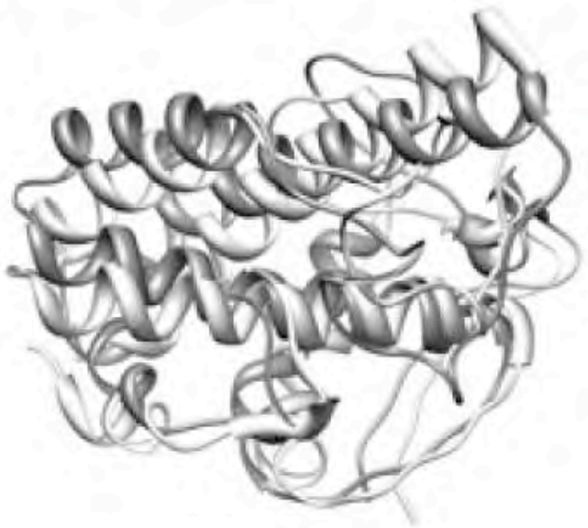
(9.2 Å, 14°)



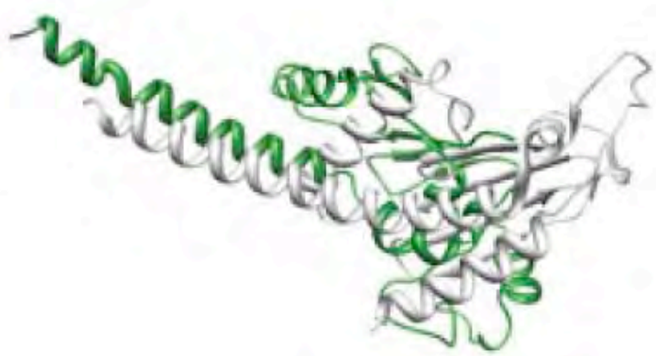
(1.4 Å, 44°)



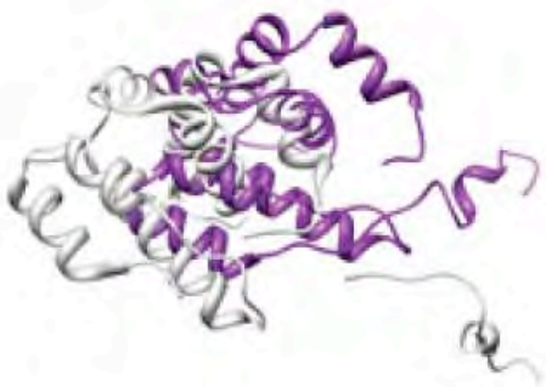
(9.1 Å, 25°)



(1.2 Å, 23°)



(11.8 Å, 46°)



(12.6 Å, 9°)

Benchmark results

Assembly name, # components	Resolution, Å	Average sequence identity (%)	Configuration Score (Å, °), **rank**
groEL, 3 domains	20	65	(2.6, 13), **1**
groEL/groES, 4 domains	experimental map 23.5	100	(9.3 Å, 74), **3**
SUMO-RanGAP1-Ubc9-Nup358 complex, 4 proteins	20	100	(5.0, 67), **1**
SUMO-RanGAP1-Ubc9-Nup358 complex, 4 proteins	20	37	(5.4, 62), **3**
Dihydropyrimidine Dehydrogenase,5 domains	20	100	(2.6, 4), **1**
Archaeon *Methanopyrus kandleri*, 6 proteins	20	61	(2.5, 8), **1**
Arp 2/3, 7 proteins	20	51	(7.1, 25),**4**

Summary

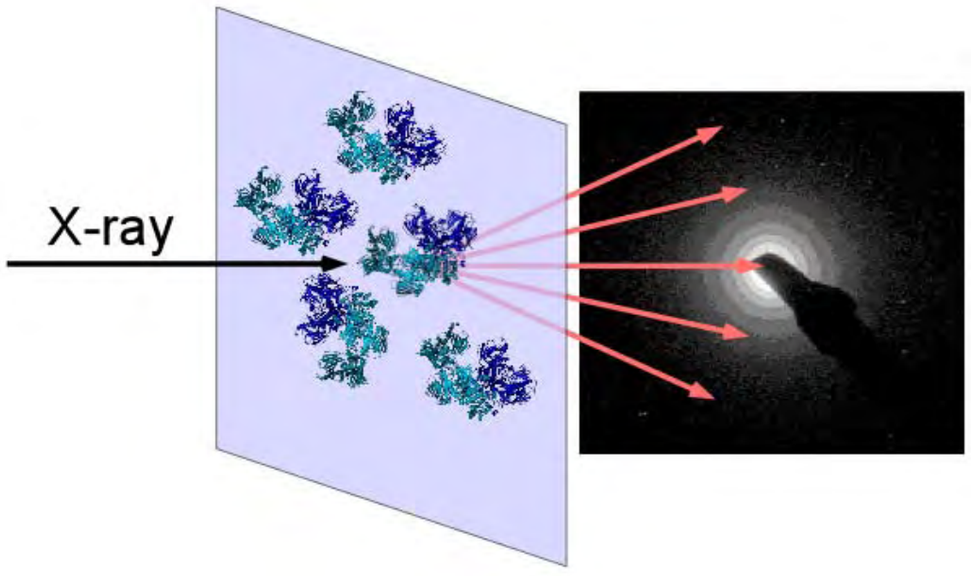
- MultiFit is method for simultaneous fitting of multiple components
- MultiFit can use near-native models of the components
- MultiFit provides a good starting model for higher resolution refinement methods

- Future work:
  - More robust discretization (anchor point computation)
  - More informative scoring function
  - Integration with flexible fitting methods

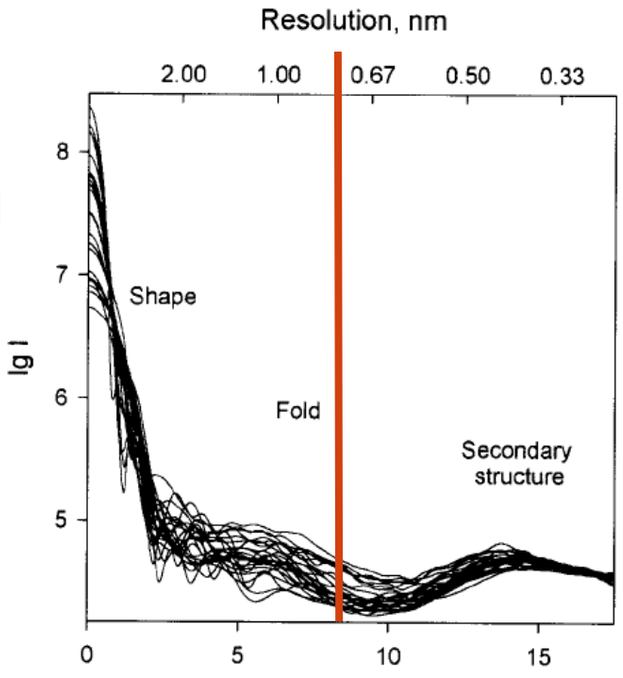
Topics

1. Introduction to integrative (hybrid) structure determination
2. Comparative model building
3. Predicting accuracy of atomic models
4. Iterative sequence-structure alignment and model building
5. Electron microscopy
6. Small angle x-ray scattering
7. Proteomics
8. Concluding Remarks

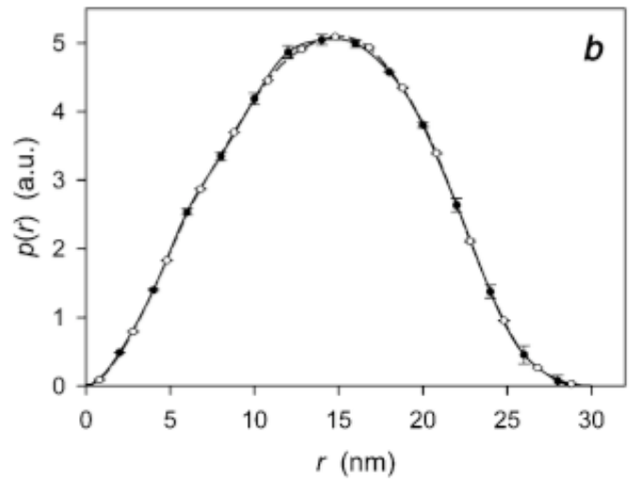
Small angle X-ray scattering (SAXS)



Rotational average



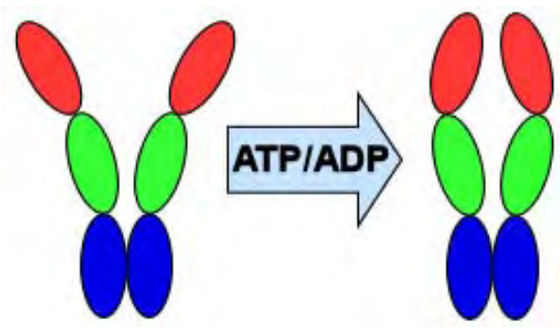
Svergun, *Biophys. J.* 2001



Fourier transform: radial distribution function $P(r)$

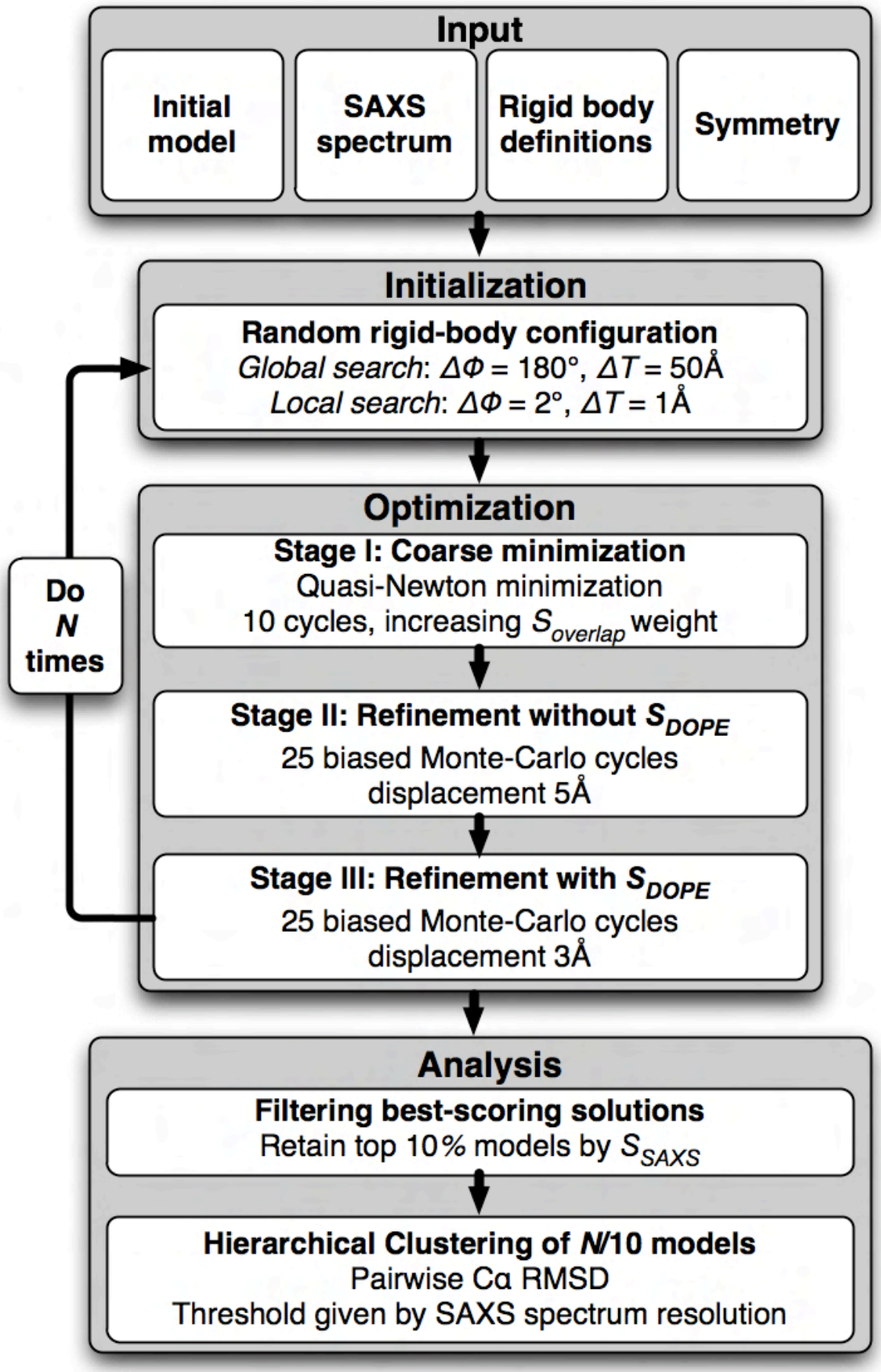
- Limited information content of a SAXS spectrum
- Integration with additional data
- Quaternary structure

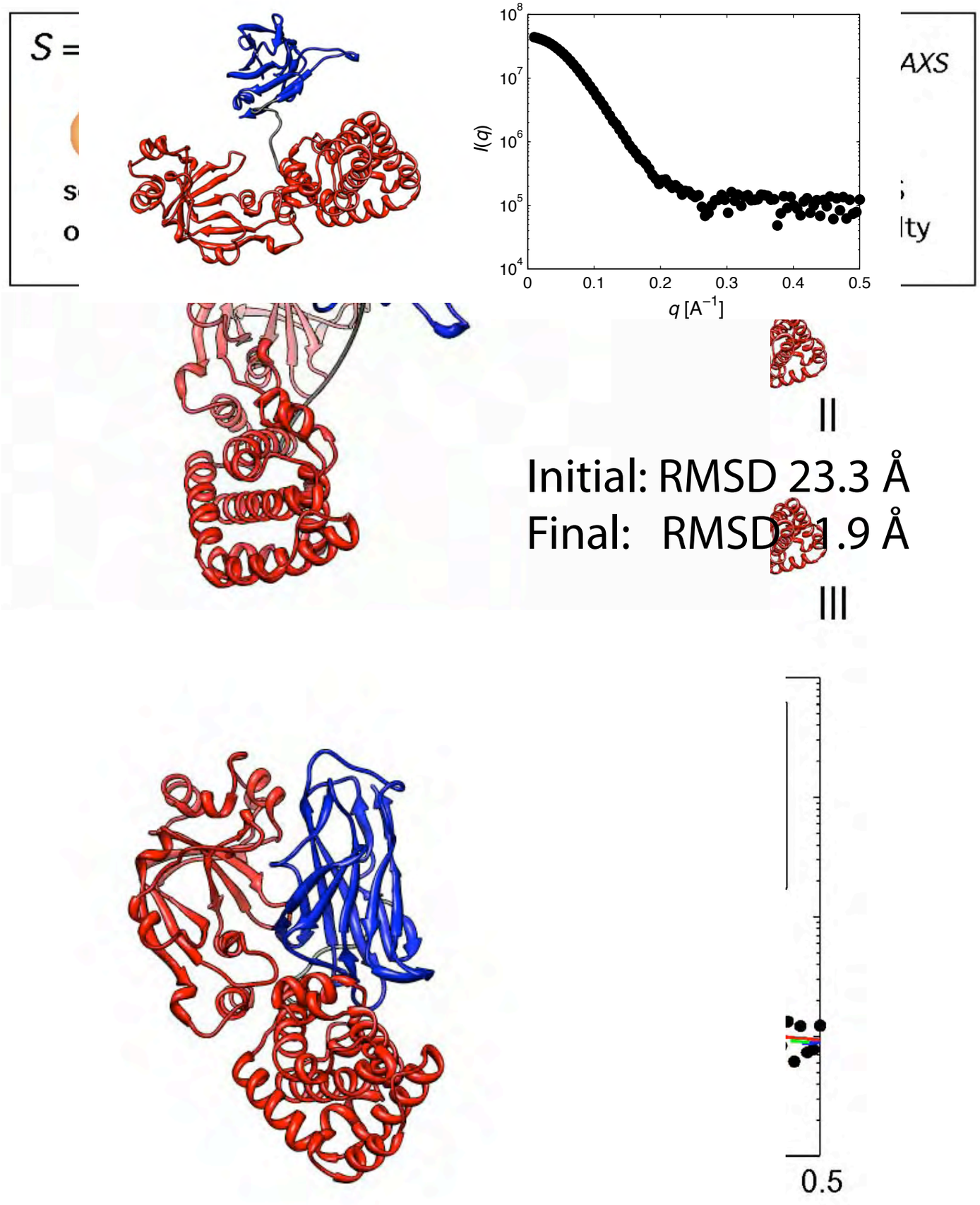
- Changes in quaternary structure



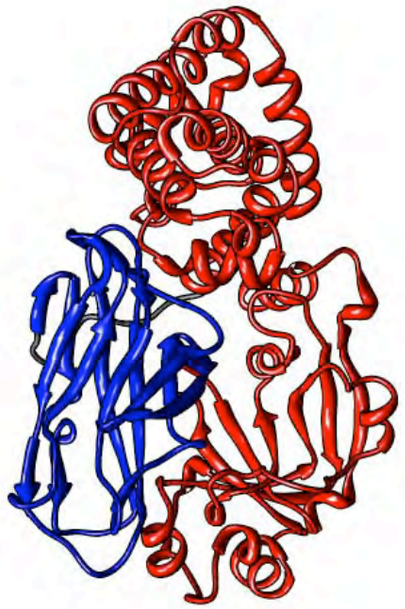
Protocol

F. Förster, B. Webb, K.A. Krukenberg, H. Tsuruta, D.A. Agard, A. Sali. *J. Mol. Biol*. 382, 1089-1106, 2008.

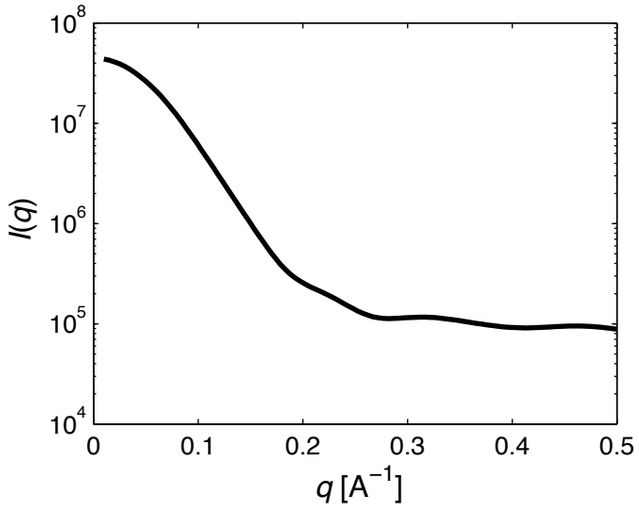




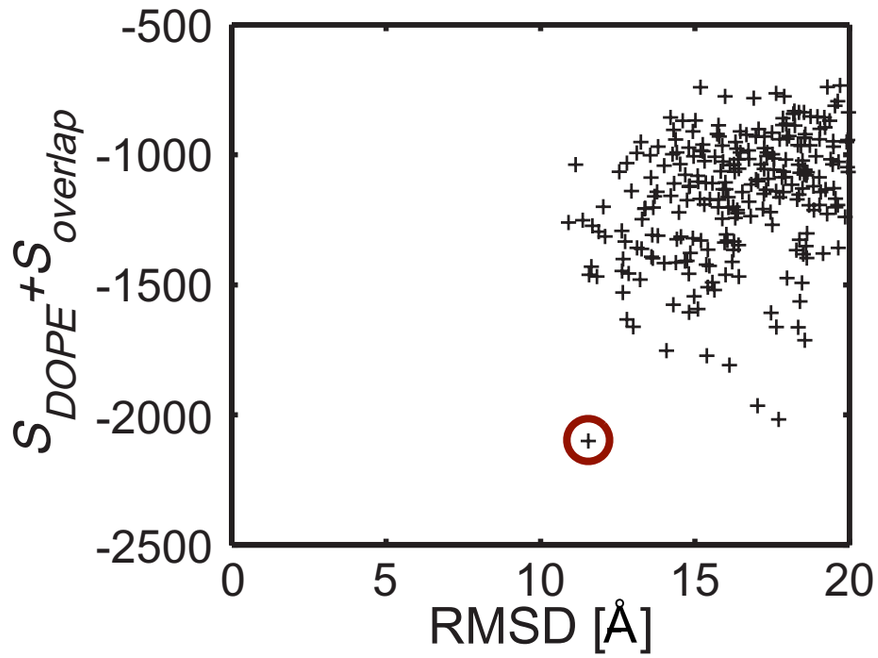
Benefit of integration of SAXS with modeling



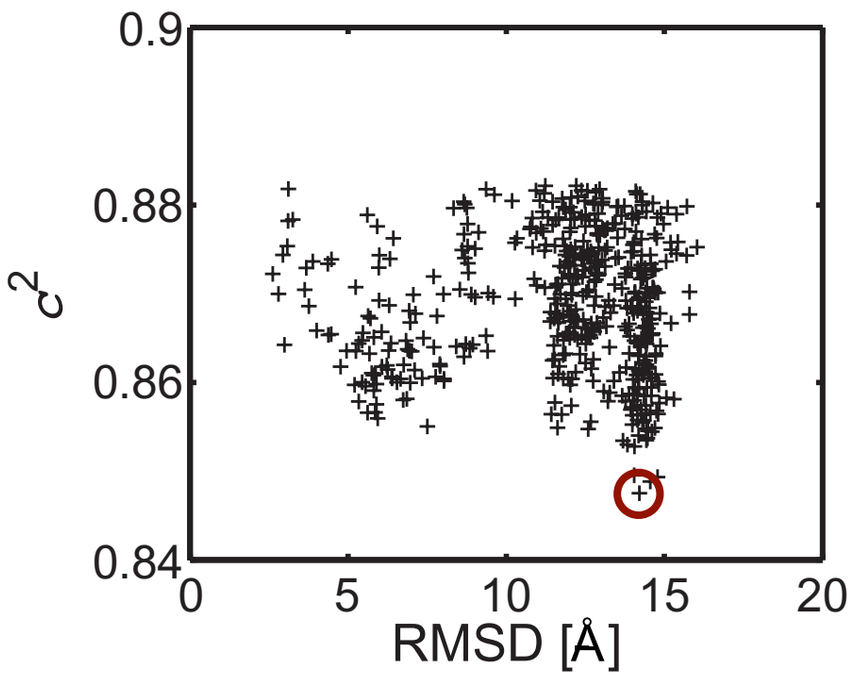
Diphteria toxin (1mdt)



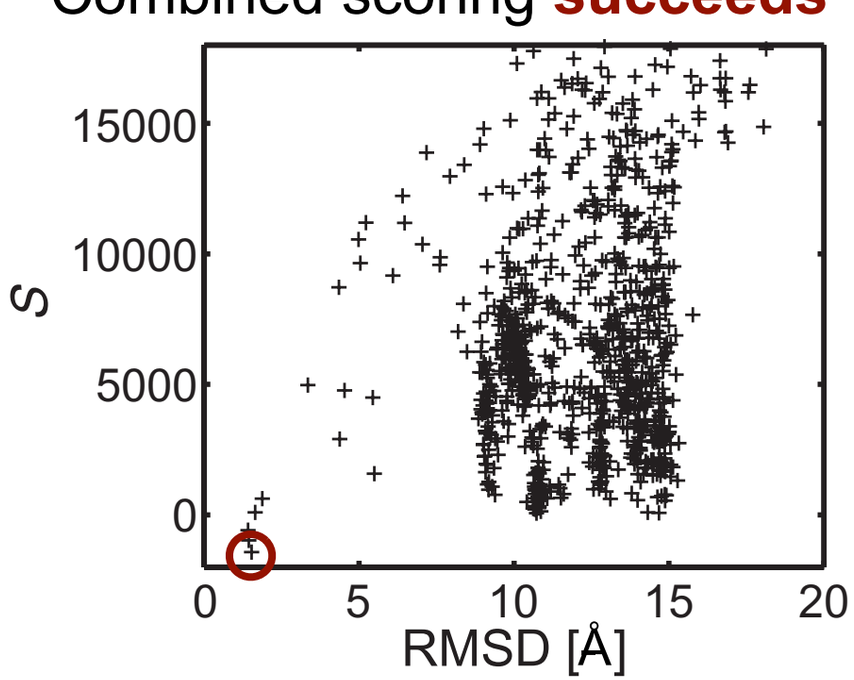
Molecular docking **fails**



SAXS on its own **fails**



Combined scoring **succeeds**



Summary of SAXS method

- Atomic models can be determined that are consistent with given SAXS data and additional restraints.
- Integration of information increases accuracy.
- Configurations can be sampled “exhaustively” for up to 4 domains.
- Configuration accuracy depends on rigid body accuracy (~3 Å Cα RMSD necessary).
- Integration of further information is possible.

SAXS maps Hsp90 states

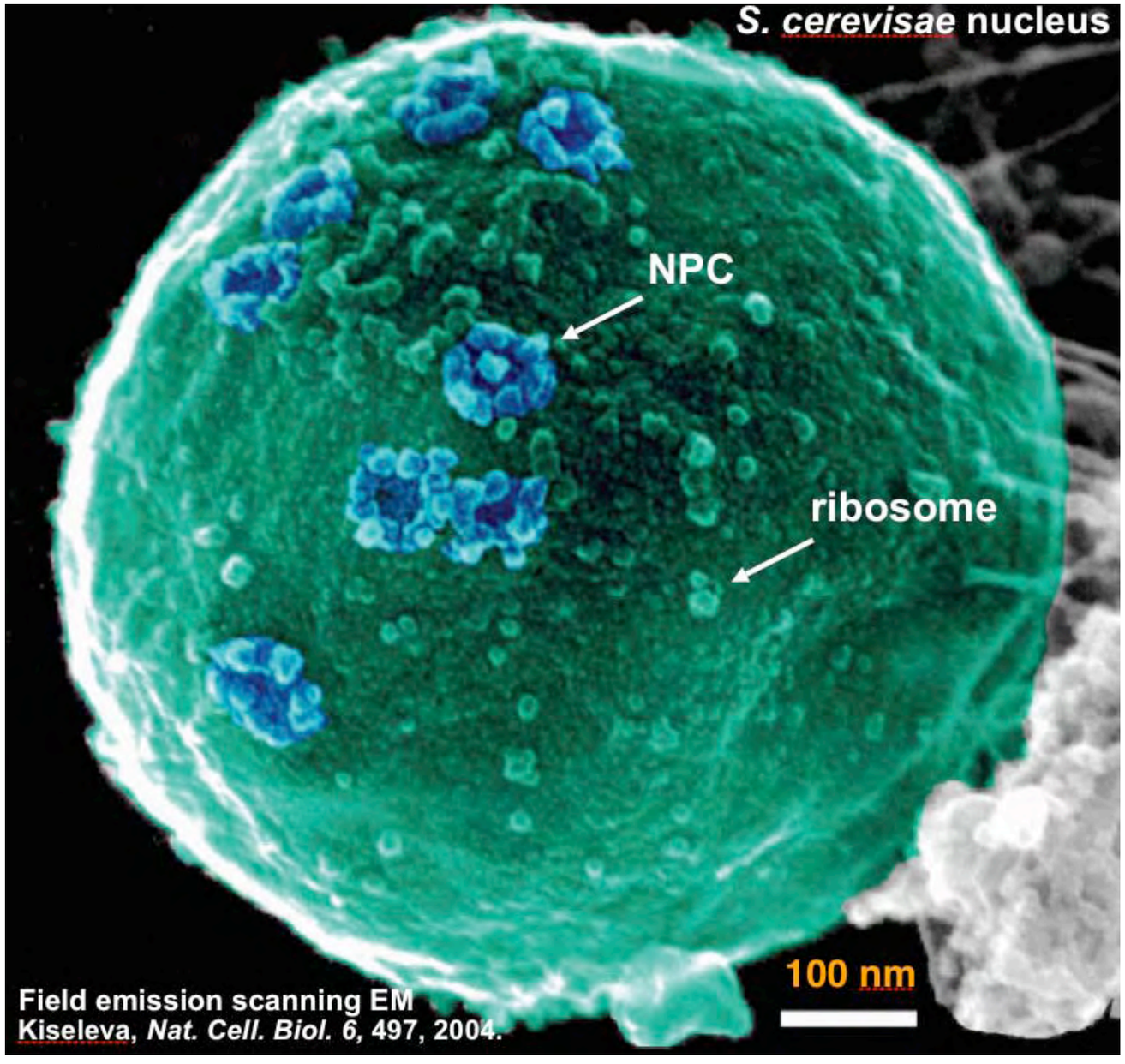
K.A. Krukenberg, F. Förster, L. Rice, A. Sali, D.A. Agard, *Structure* **16**, 755-765, 2008.

- Crystallographic structures of opened and closed states are probably inaccurate representations of solution states.
- The apo structure of *E. coli* Hsp90 is wide open.
- *E. coli* ATP-Hsp90 is in equilibrium between the wide-opened and closed states.

Topics

1. Introduction to integrative (hybrid) structure determination
2. Comparative model building
3. Predicting accuracy of atomic models
4. Iterative sequence-structure alignment and model building
5. Electron microscopy
6. Small angle x-ray scattering
7. Proteomics
8. Concluding Remarks

Nuclear Pore Complex (NPC)



Consists of broadly conserved nucleoporins (nups).

50 MDa complex: ~480 proteins of 30 different types.

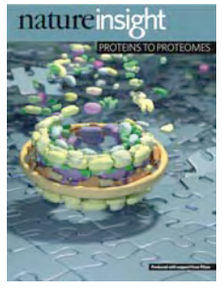
Mediates all known nuclear transport, *via* cognate transport factors.

Mike Rout
Svetlana Dokudovskaya, Liesbeth Veenhoff
Orit Karni-Schmidt, Julia Kipper, Tari Suprapto, Julia Kipper

Brian Chait
Wenzhu Zhang, Rosemary Williams

Rockefeller University

Alber *et al*. Nature 450, 683-694, 2007
Alber *et al*. Nature 450, 695-701, 2007
Devos *et al*. PNAS 14, 2172-2177, 2006
Devos *et al*. PLoS Biology 12, 1-9, 2004

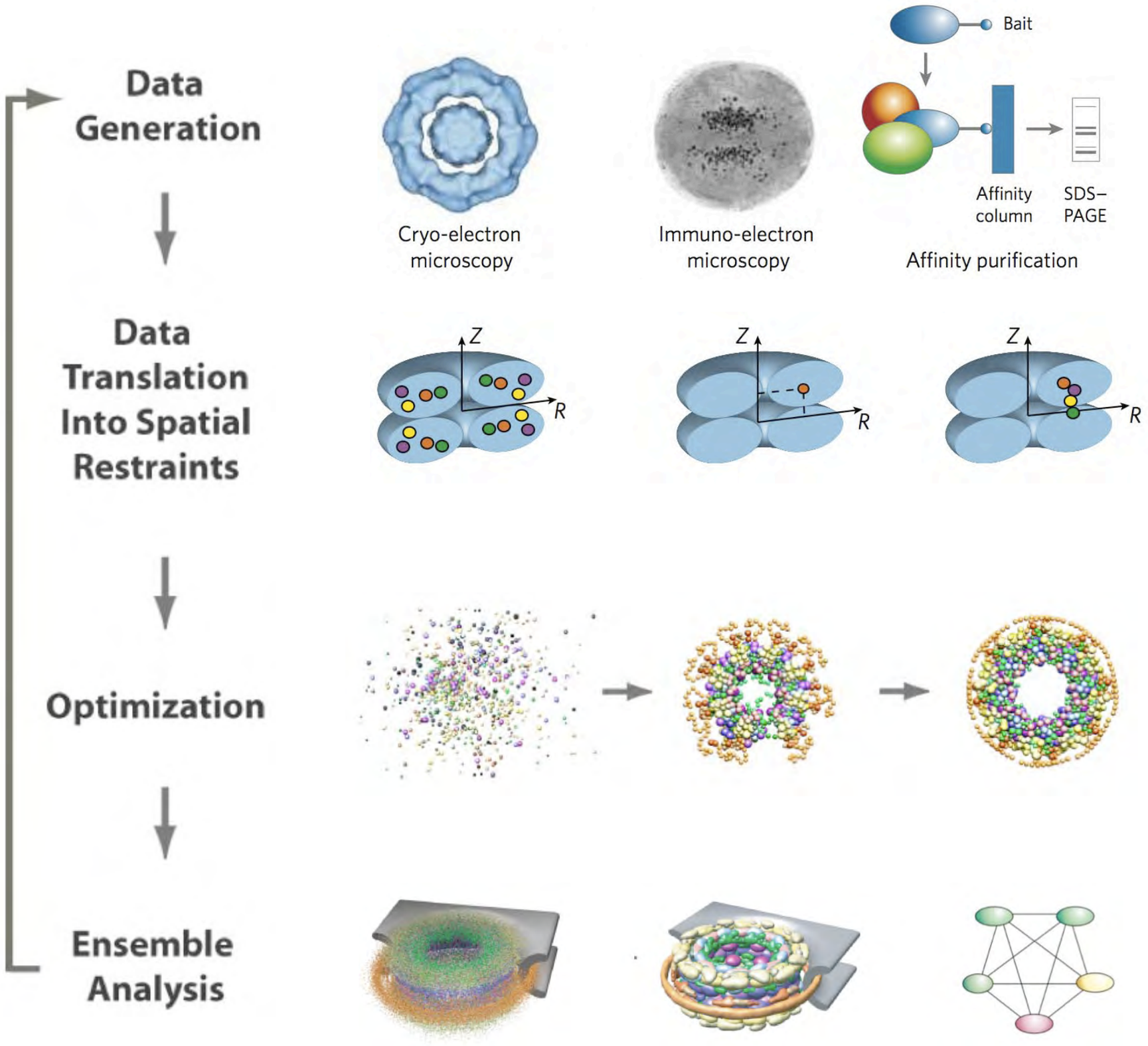


Andrej Sali
Frank Alber, Damien Devos
Narayanan Eswar, Marc Marti-Renom

UCSF

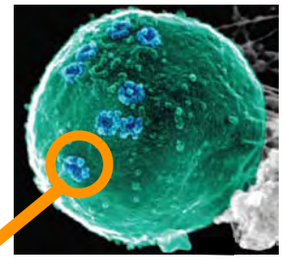
Using All Spatial Information

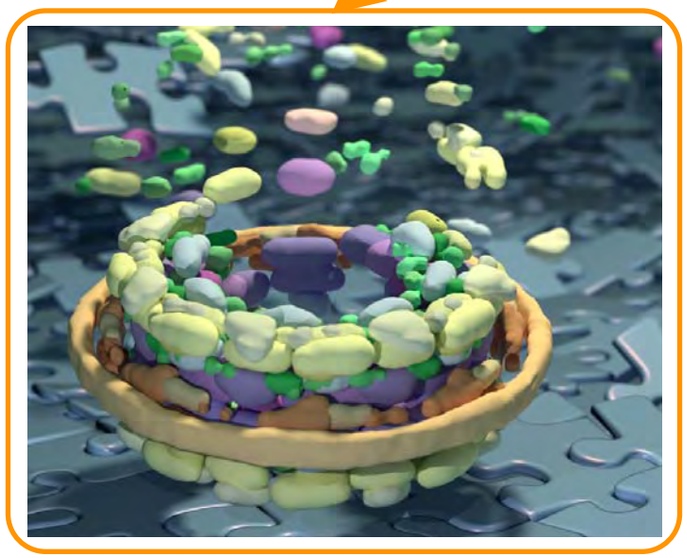
Alber *et al*. *Nature* 450, 683-694, 2007.
Robinson, Sali, Baumeister. *Nature* 450, 974-982, 2007.
Alber, Foerster, Korkin, Topf, Sali. *Annual Reviews in Biochemistry* 77, 11.1–11.35, 2008.



Configuration of proteins in NPC?

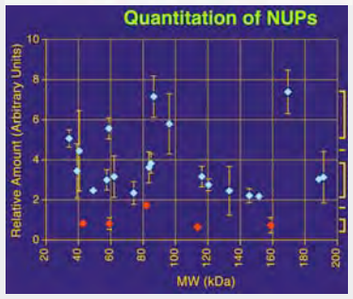
Use all information





Quantitative Immunoblotting

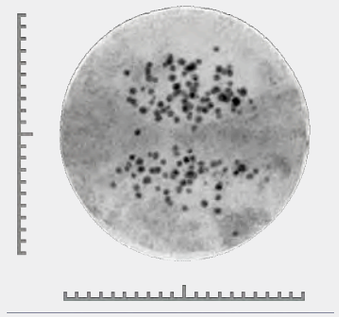
30 relative abundances



Protein Stoichiometry

Immuno-Electron Microscopy

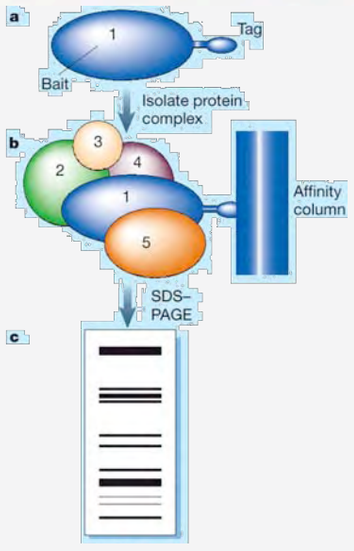
10,615 gold particles



Protein Localization

Affinity Purification **Overlay Assay**

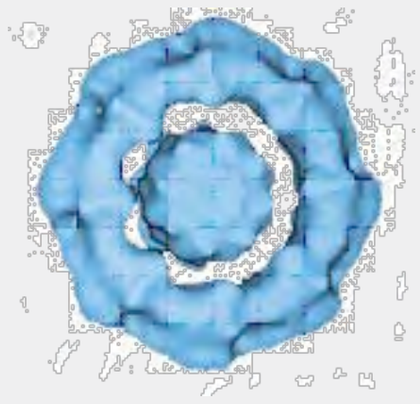
75 composites 7 contacts



Protein-protein Proximities

Electron Microscopy

electron microscopy map

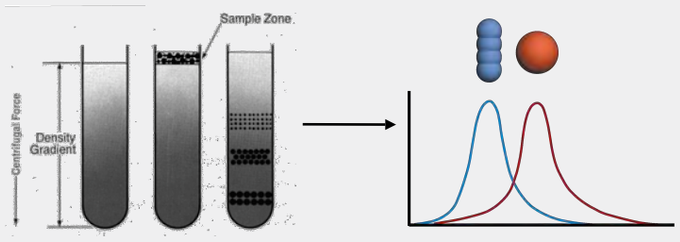


Symmetry

Protein Shape

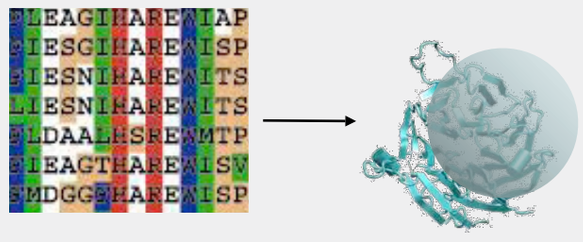
Ultracentrifugation

30 S-values 1 S-value



Bioinformatics and Membrane Fractionation

30 protein sequences



Optimization

- Start with a random configuration of protein centers.
- Minimize violations of input restraints by conjugate gradients and molecular dynamics with simulated annealing.
- Obtain an “ensemble” of many independently calculated models (~200,000).

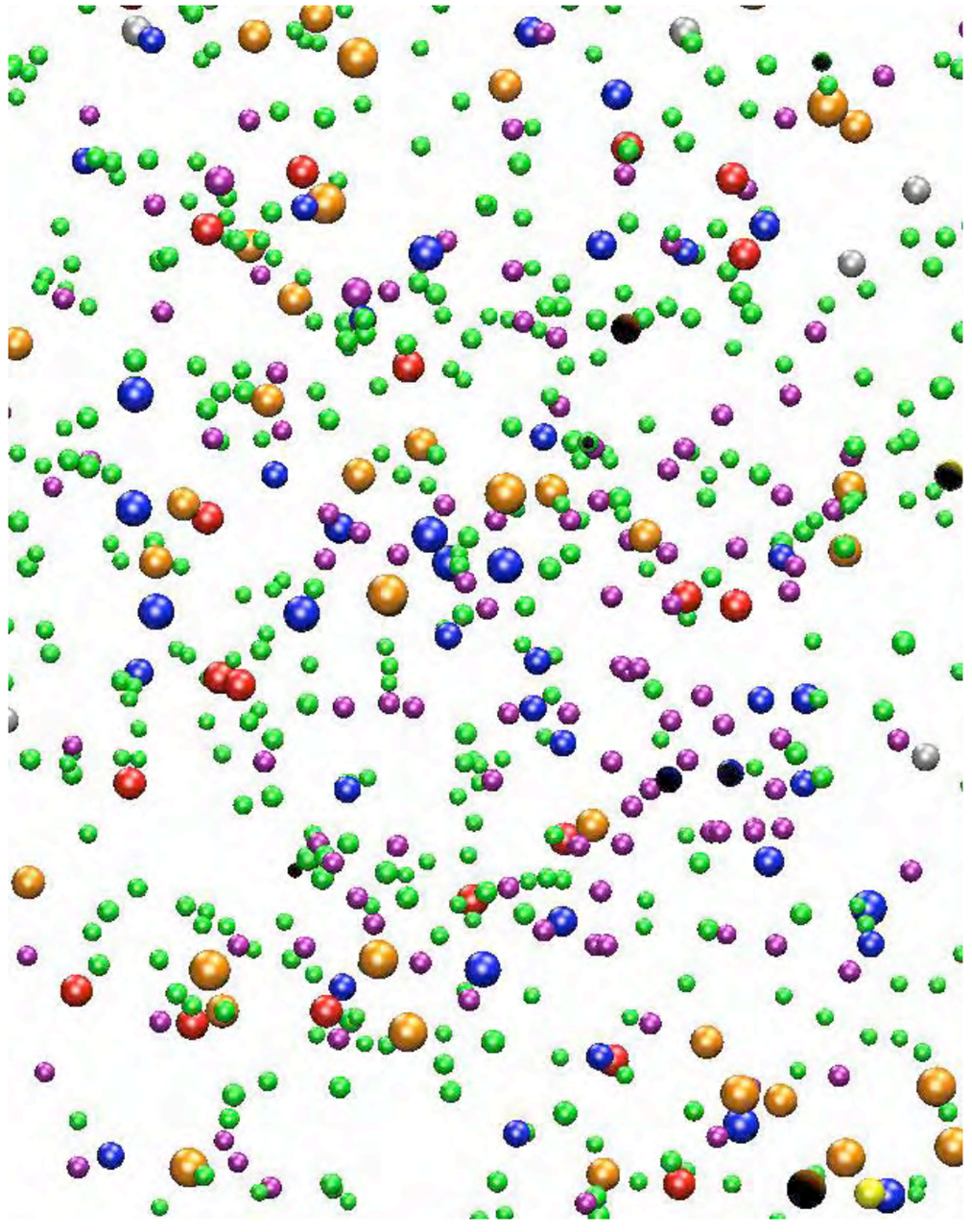
Membrane spanning proteins:
Pom152 Pom34
Ndc1

FG repeat proteins:
Nup159 Nup60
Nsp1 Nup59
Nup1 Nup57
Nup100 Nup53
Nup116 Nup49
Nup145N Nup42

Nup84 complex:
Nup84 Seh1
Nup85 Sec13
Nup120 Nup145C
Nup133

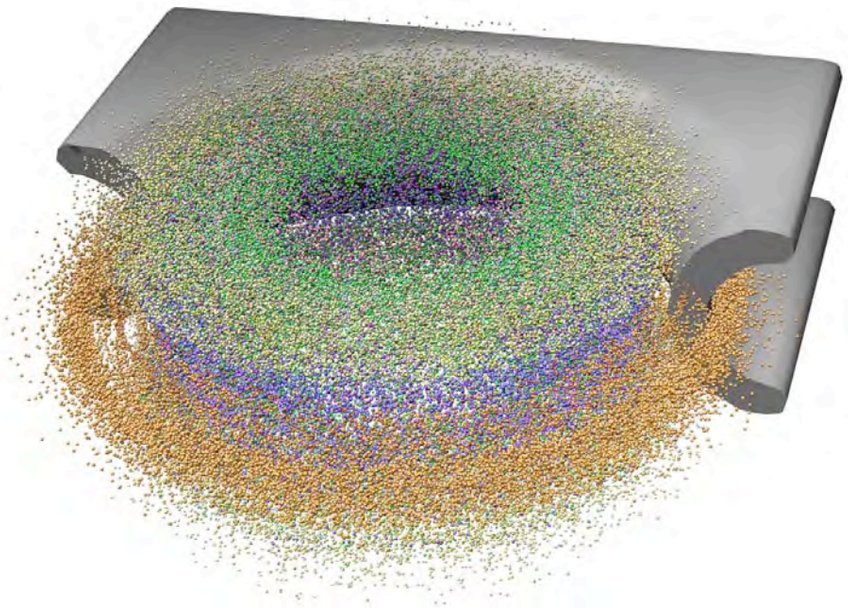
Large Core proteins:
Nup192 Nup170
Nup188 Nup157

Nup82
Nic96

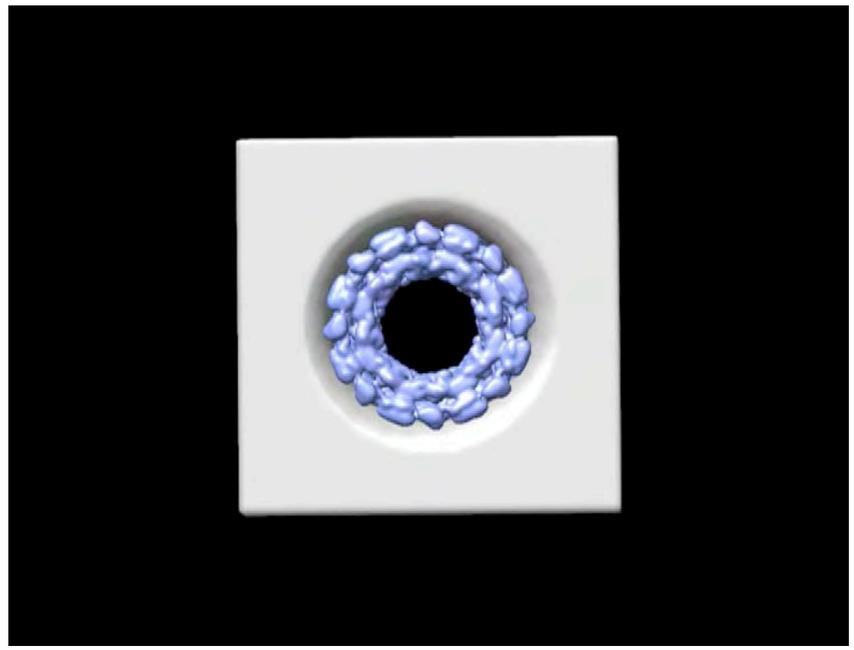


Protein Localization Probability and Volume

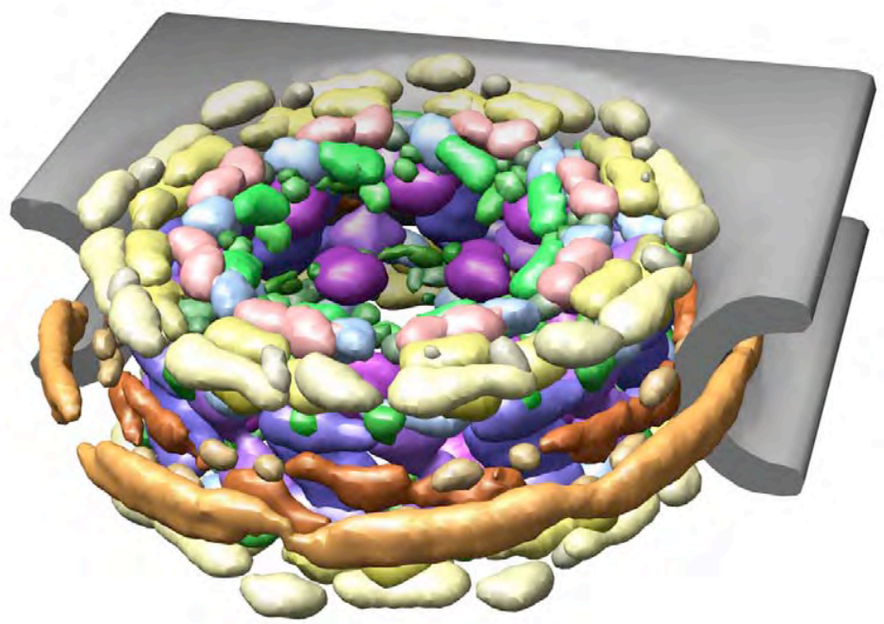
Calculated from the structural superposition of the ensemble of models that satisfy all input restraints



Ensemble of solutions



Animation



Protein localization

can see position of every NPC protein

How accurate is the structure of the NPC?
Assessing the well-scoring models

1. Self-consistency of independent experimental data.

2. Structural similarity among the configurations in the ensemble that satisfy the input restraints.

3. Simulations where a native structure is assumed, corresponding restraints simulated from it, and the resulting calculated structure compared with the assumed native structure.

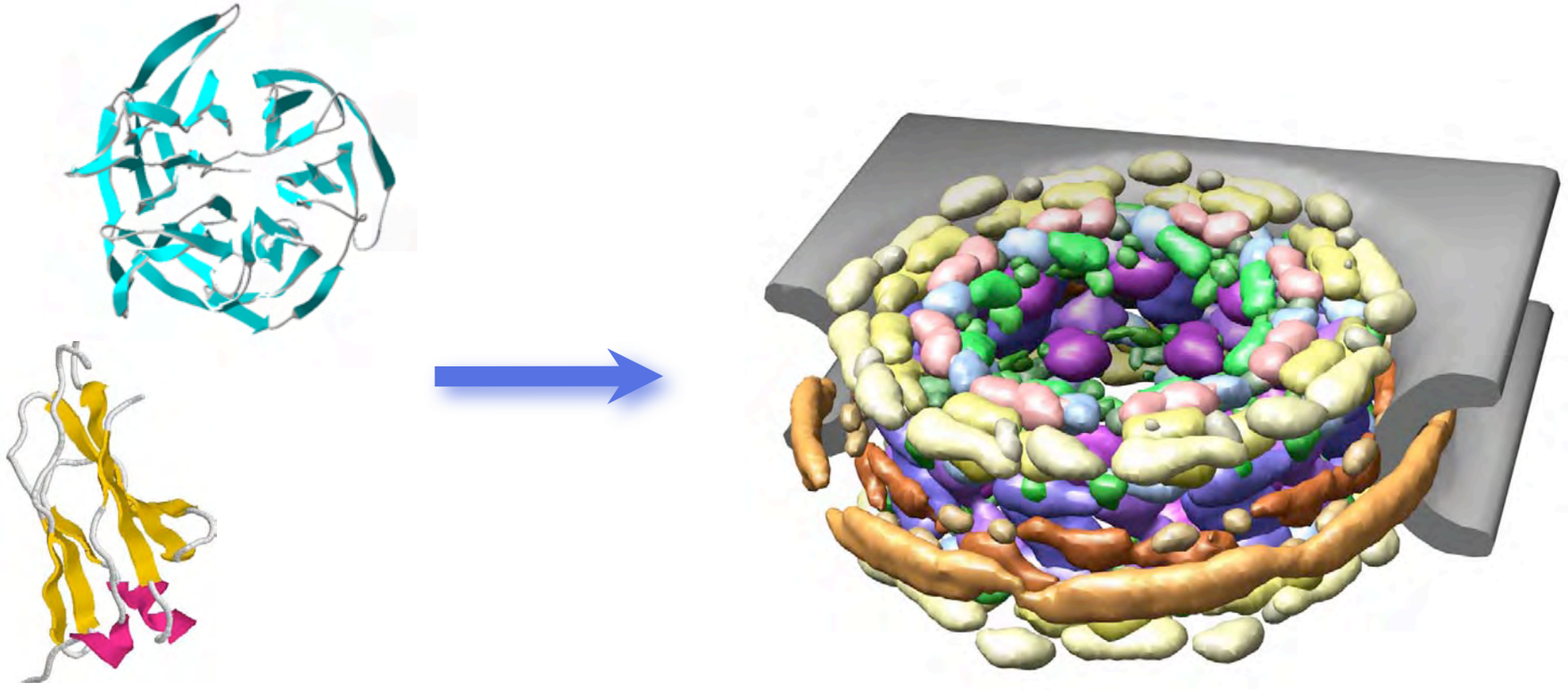
4. Patterns emerging from a mapping of independent and unused data on the structure that are unlikely to occur by chance.

5. Experimental spatial data that were not used in the calculation of the structure.

Towards a higher resolution structure of NPC?

Characterize structures of the individual subunits, then fit them into the current low-resolution structure

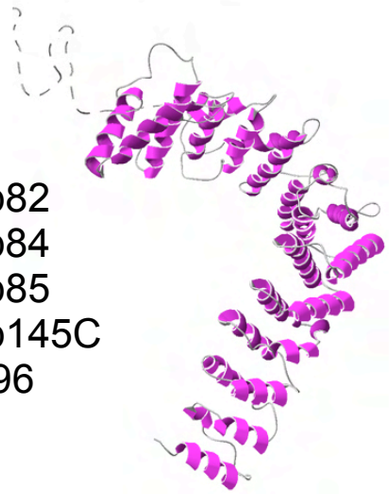
(aided by cross-linking information and cryoEM maps of subcomplexes).



Fold Prediction

Devos, Dokudavskaya, Alber, Williams, Chait, Sali, Rout. *PLoS Biology* **12**, *1,* 2004
Devos, Dokudavskaya, Williams, Alber, Eswar, Chait, Rout, Sali, *PNAS* **14**, 2172, 2006.

α-solenoid

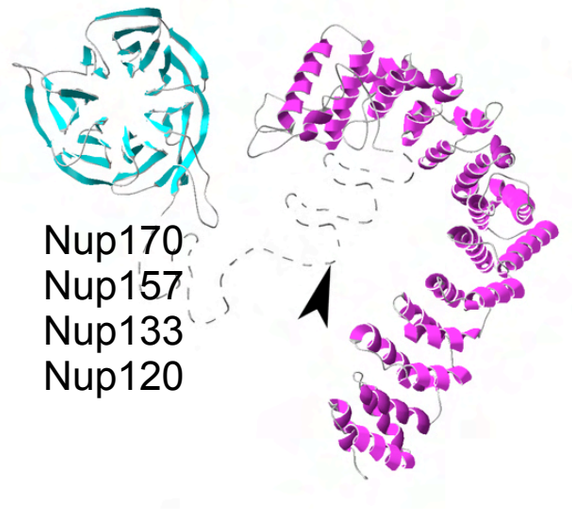


Nup82
Nup84
Nup85
Nup145C
Nic96

β-propeller

Seh1
Sec13

Clathrin-like



Nup170
Nup157
Nup133
Nup120

unstructured-FG repeat regions

Nup100 Nsp1 Nup145N
Nup1 Nup57 Nup53
Nup116 Nup60
Nup159 Nup53

Coiled-coiled

Nsp1
Nup1
Nup60
Nup159
Nup57
Nup53

IgG-fold

Pom152

Trans-membrane helices

Pom152
Ndc1
Pom34

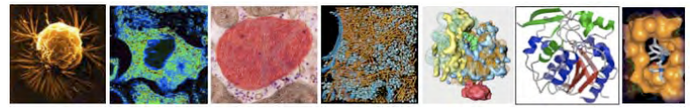
These fold assignments cover all 44 domains and 95% of the NPC residues.

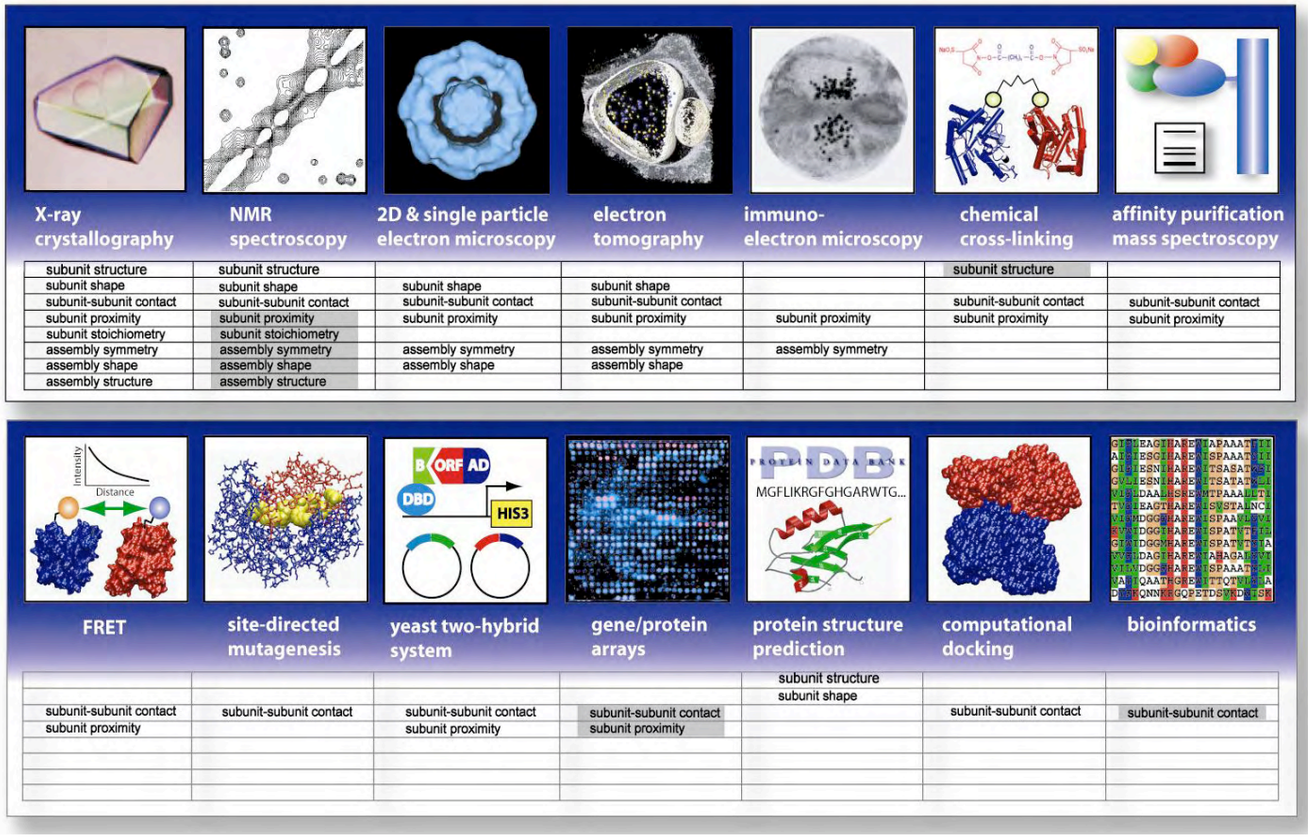
06/01/2006

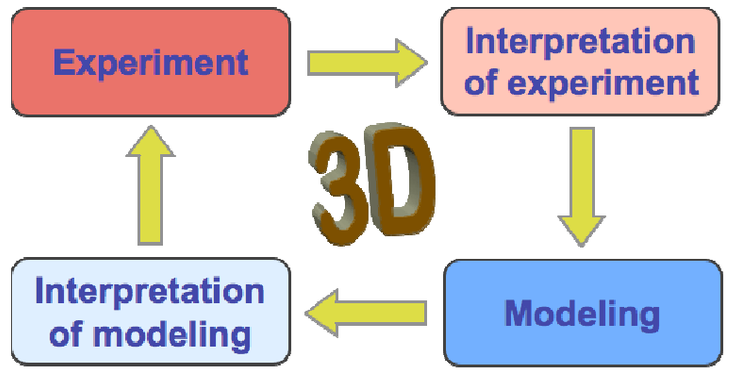
In Conclusion

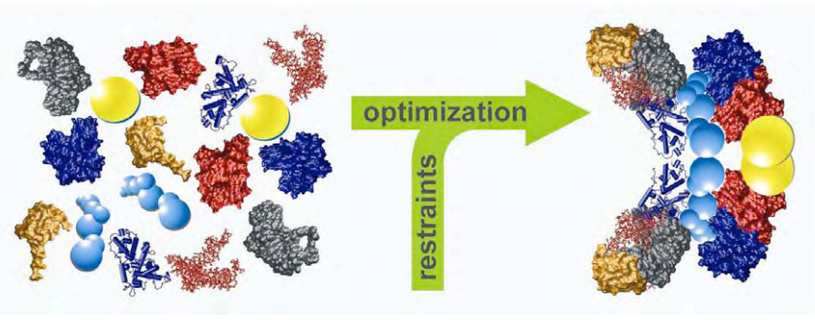
The goal is a comprehensive description of the multitude of interactions between molecular entities, which in turn is a prerequisite for the discovery of general structural principles that underlie all cellular processes.

This goal will be achieved by a ***tight*** integration of **experiment**, **physics**, and **statistical inference**, spanning all relevant size and time scales.









Sali, Earnest, Glaeser, Baumeister. From words to literature in structural proteomics. *Nature* 422, 216-225, 2003.
Robinson, Sali, Baumeister. The molecular sociology of the cell. *Nature* 450, 974-982, 2007.
Alber, Foerster, Korkin, Topf, Sali. *Annual Reviews in Biochemistry* 77, 11.1–11.35, 2008.

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