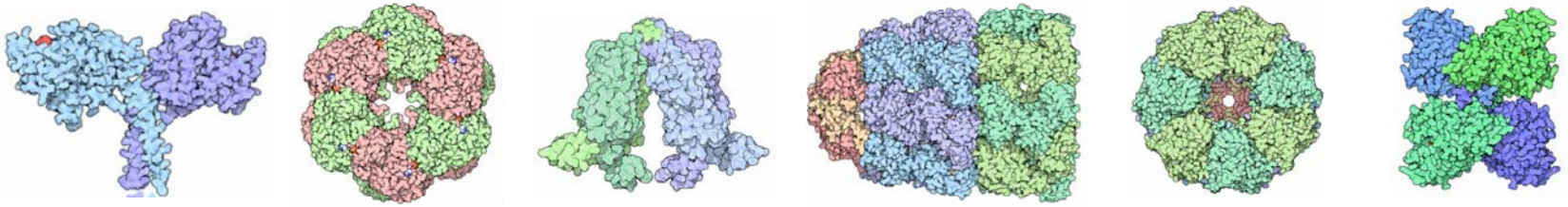
Refinement of reduced protein models with all-atom force fields



Liliana Wróblewska

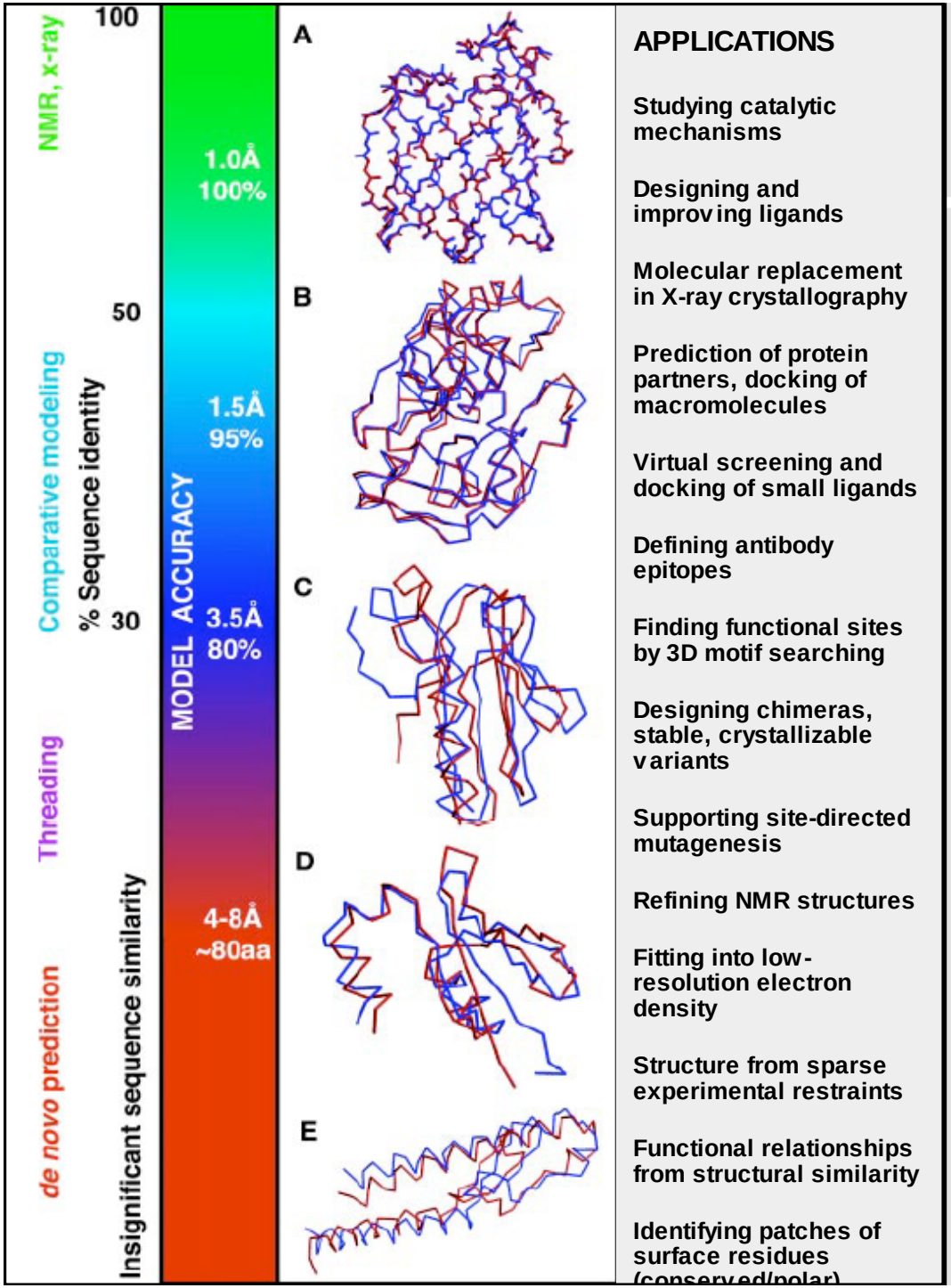
Jeffrey Skolnick's lab

School of Biology

Ph.D. defense 10/30/07

Outline

- General and Specific Aims
- Background and Significance
- Results
- Summary
- Future Work



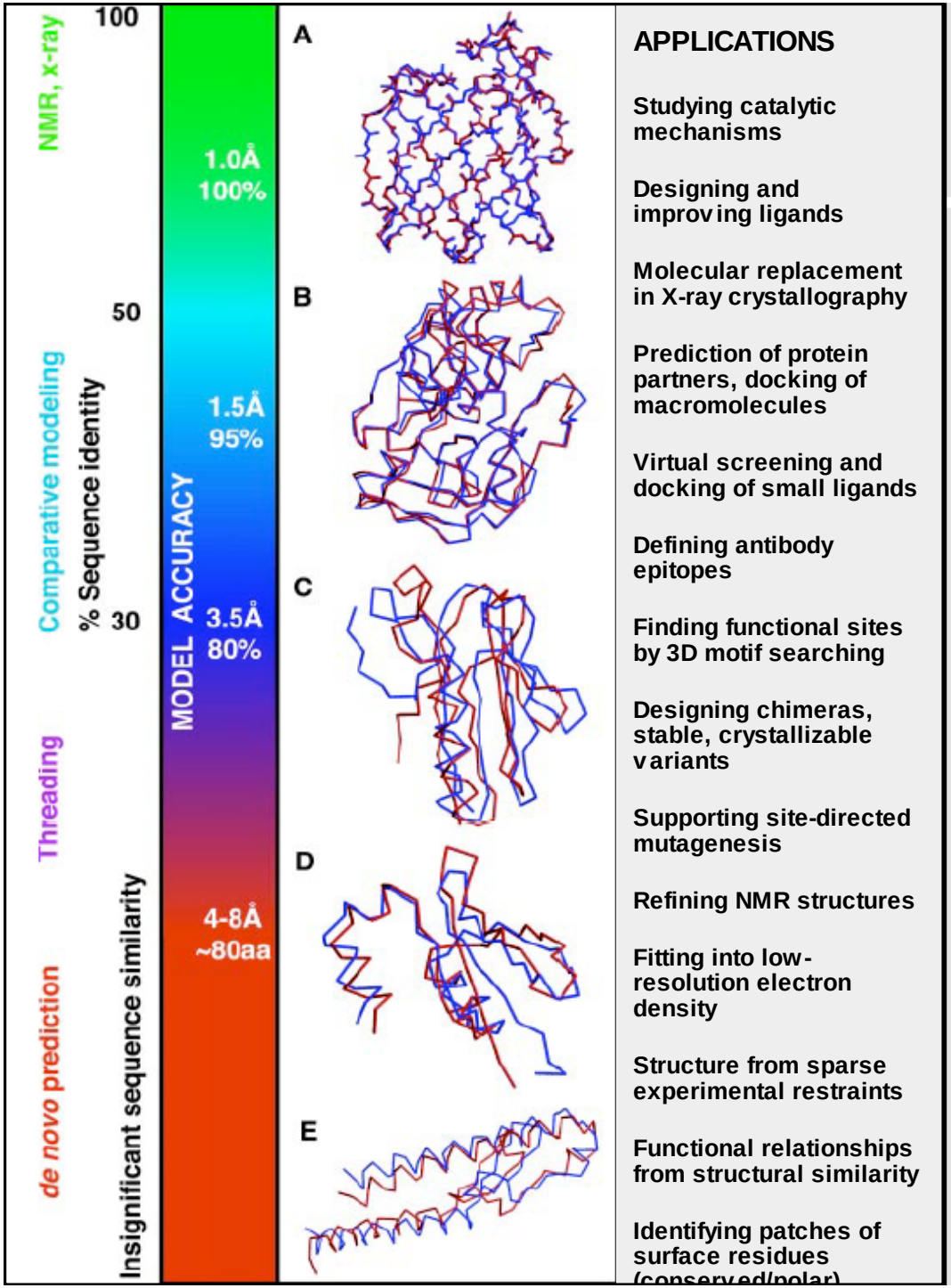
General Aim

refinement of protein models to higher resolution (from ~2-6.5Å backbone RMSD to less than 2 Å)

→

development of a systematic approach

D.Baker, A.Sali, Science, 2001, 294: 93-6



General Aim

refinement of low resolution predicted protein models to higher resolution (from ~2-6.5Å backbone RMSD to less then 2 Å)

→

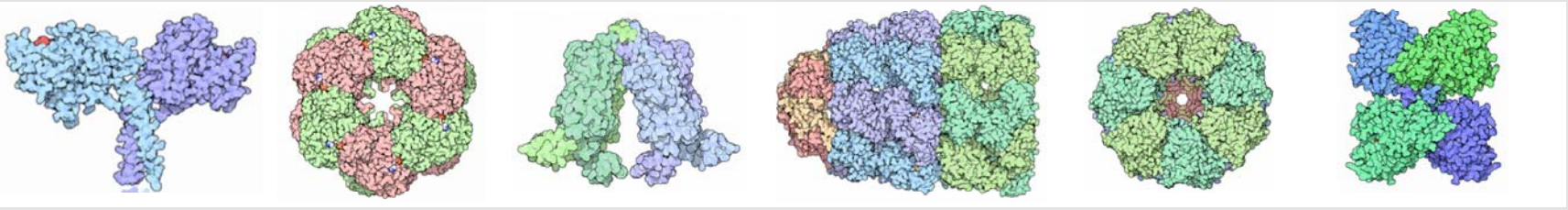
development of a systematic approach

D.Baker, A.Sali, Science, 2001, 294: 93-6

Specific Aims

- An assessment of ability of the existing all-atom force fields to refine protein models
- Identification of the key problems in the all-atom force fields
- Optimization of the all-atom force field components
- Modification of the energy function
- Refinement using optimized force field

Background and Significance



Protein structure prediction – the rationale

"The amino acid sequences of polypeptide chains (…) only make functional sense when they are in the three dimensional arrangement that characterizes them in the native protein structure"

- C.B.Anfinsen, 1972, Nobel Lecture

Protein structure prediction – the foundation

THERMODYNAMIC HYPOTHESIS:

"The three-dimensional structure of a native protein in its normal physiological milieu (…) is the one in which the Gibbs free energy of the whole system is lowest"

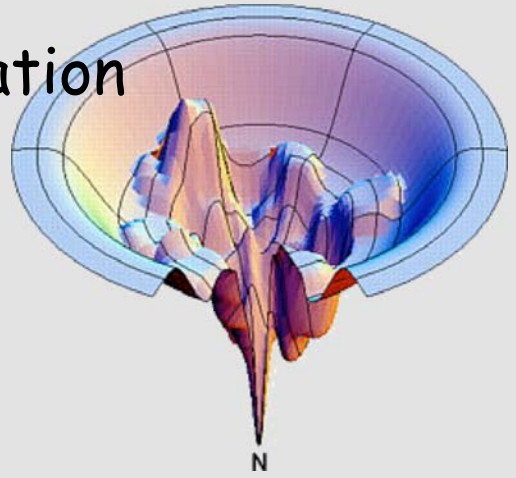
- C.B.Anfinsen, 1972, Nobel Lecture

Protein structure prediction

Ideal protocol:

- Generate all possible conformations of a polypeptide chain
- Calculate the free energy for each model
- Choose the lowest energy conformation

→ native structure (N)



Ken A. Dill and Hue Sun Chan, *Nature Structural Biology*, January 1997 4(1)

Protein structure prediction

Ideal protocol:

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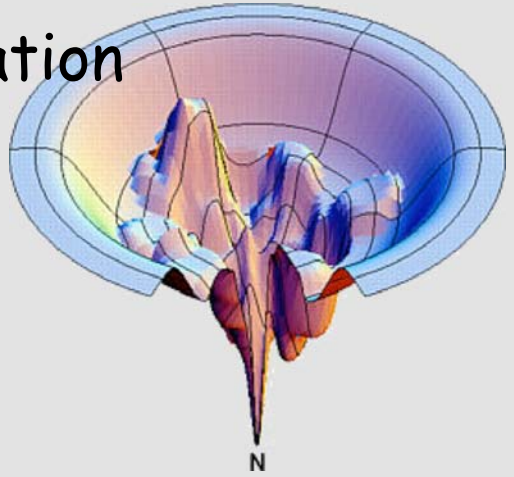
IMPOSSIBLE



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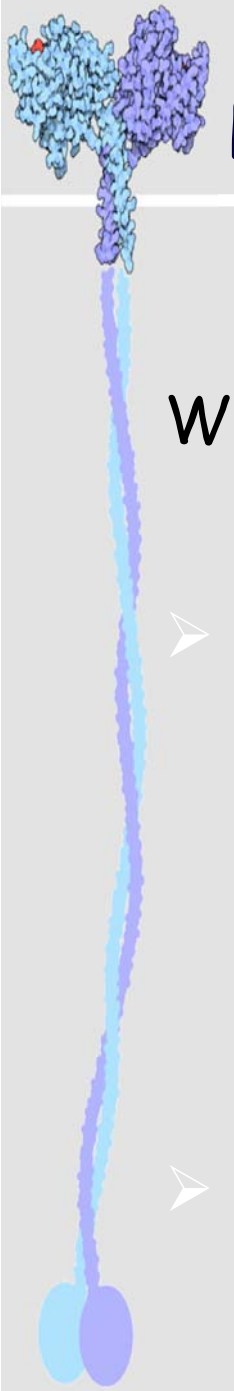
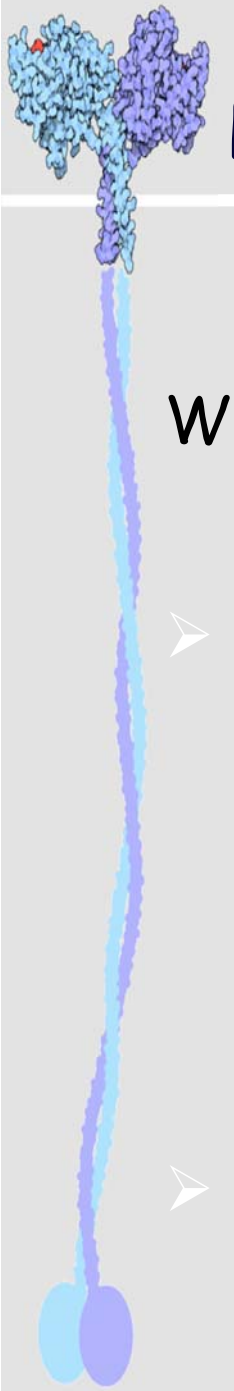


Protein structure prediction

Why impossible?

- Generation of all possible conformations of a polypeptide chain
  - 100 amino acid protein, 2 configurations per amino acid:
  - 2^{100} (~ 10^{30}) conformations
  - 1000 conformations/1s ~ 10^{20} years
- Calculation of the free energy for each model
  - high accuracy quantum methods can handle on the order of tens of atoms

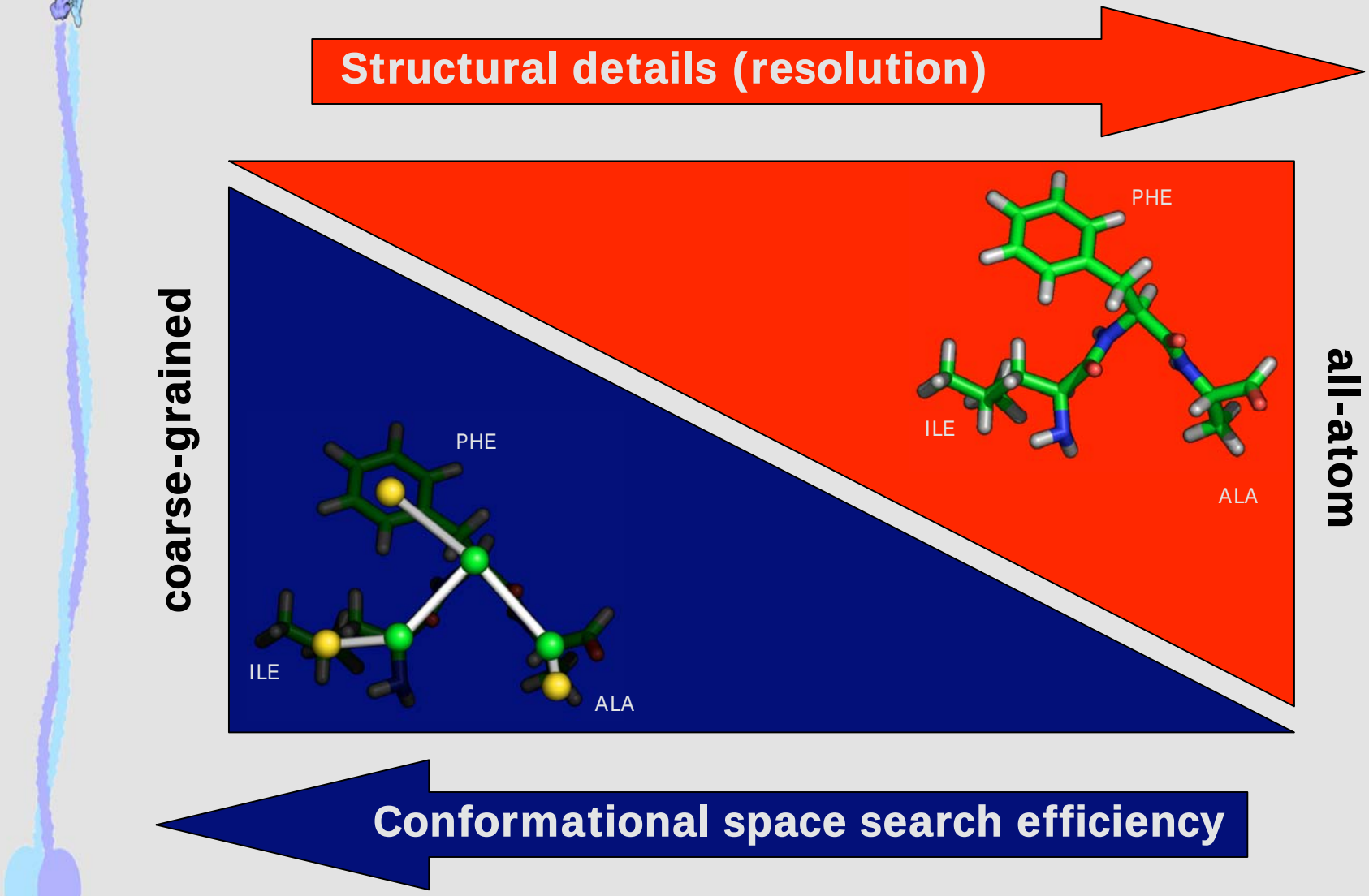


Protein structure prediction

Why impossible?

- Generation of all possible conformations of a polypeptide chain
  - 100 amino acid protein, 2 configurations per amino acid:
  - 2^{100} (~ 10^{30}) conformations
  - 1000 conformations/1s ~ 10^{20} years
    - SAMPLING PROBLEM
- Calculation of the free energy for each model
  - high accuracy quantum methods can handle on the order of tens of atoms

The trade-off



Hierarchical approach

Conformational space search efficiency

- Reduction of the number of interaction centers (coarse-grained models) for GLOBAL SEARCH

Structural details (resolution)

- Reconstruction of the atomic details for REFINEMENT

Hierarchical approach

- Reduction of the number of interaction centers (coarse-grained models) for GLOBAL SEARCH

• Explored extensively - the performance of current state-of-the-art methods for structure prediction: 70% of sequences <200aa have structures predicted with accuracy of < 6.5 Å (TASSER)

- Reconstruction of the atomic details for REFINEMENT

TASSER: Y.Zhang, J.Skolnick, PNAS, 2004, 101: 7594-7599

Hierarchical approach

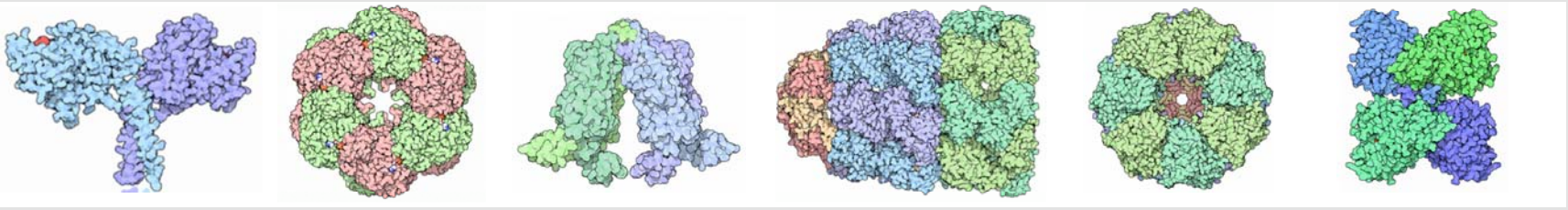
- Reduction of the number of interaction centers (coarse-grained models) for GLOBAL SEARCH

• Explored extensively - the performance of current state-of-the-art methods for structure prediction: 70% of sequences <200aa have structures predicted with accuracy of < 6.5 Å (TASSER)

- Reconstruction of the atomic details for REFINEMENT

• There is no method for systematic all-atom refinement of protein models

Results



Part I

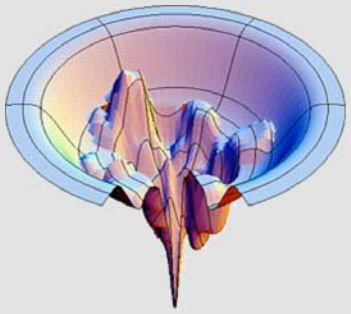
Can contemporary all-atom potentials refine protein models?

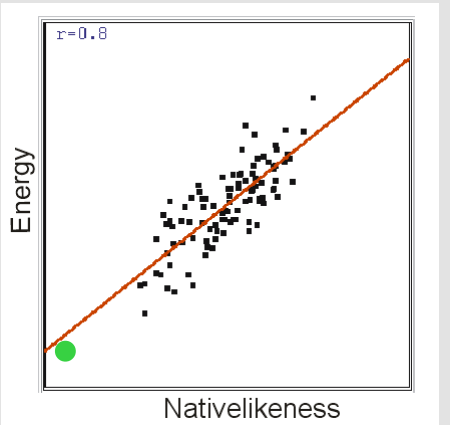
L. Wróblewska and J. Skolnick, J. Comput. Chem. (2007) 28:2059-2066

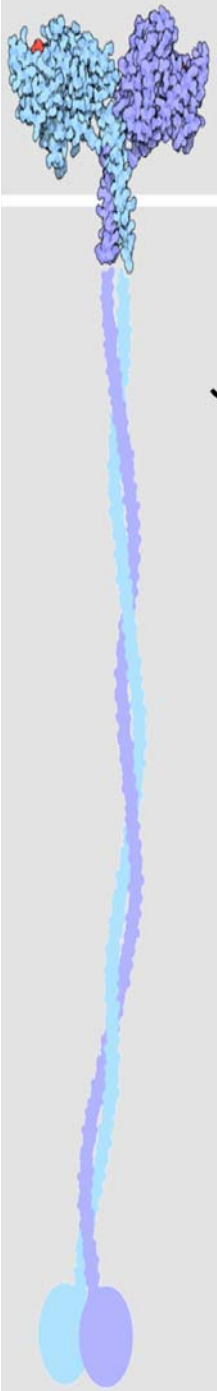
I. Desired characteristics of a force field

1. Native structure is the lowest energy conformation of a given protein sequence

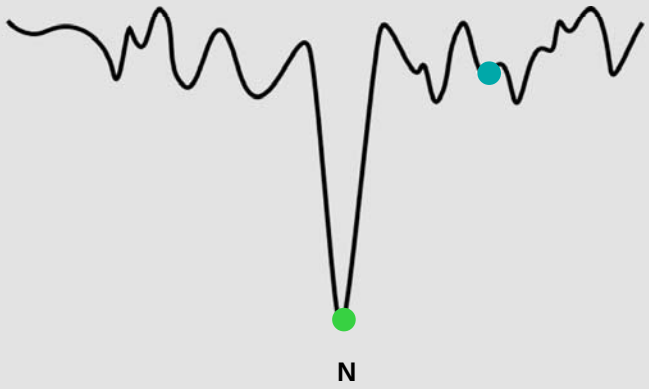
2. Energy correlates with native-similarity (the lower the energy, the closer a particular conformation is to the native structure)

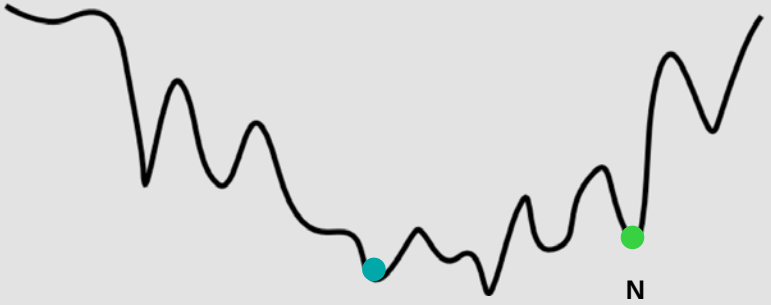


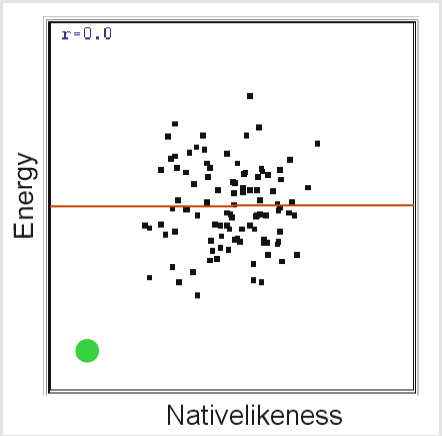


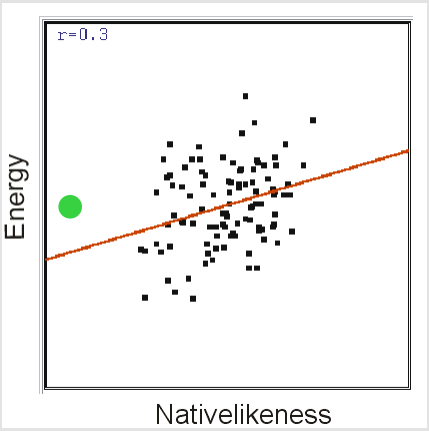


I. Typical energy landscapes

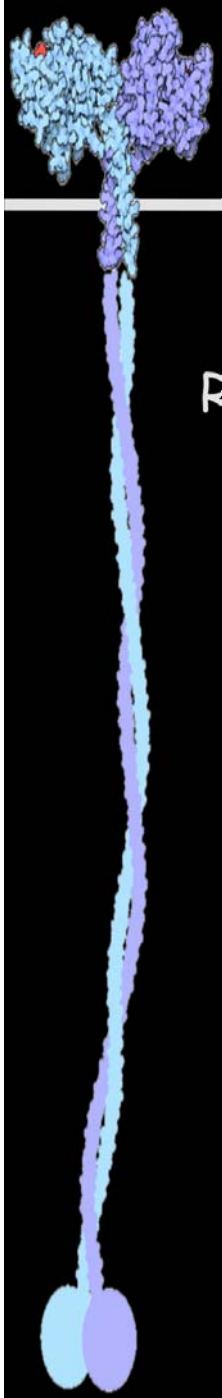






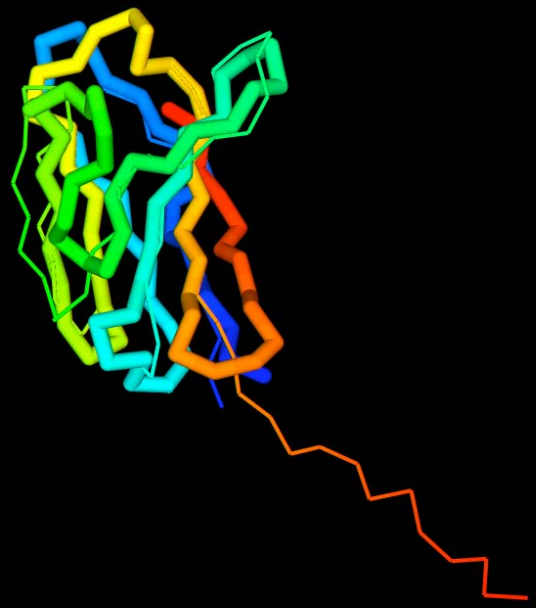


BAD SHAPE



I. Structure similarity metrics

	RMSD	TM-score
Range:	0-up	1-0
	chain length dependent	chain length independent



Thick tube: native
Thin tube: decoy
RMSD: 10.91 Å, TM-score: 0.72

Thick tube: native
Thin tube: decoy
RMSD: 10.30 Å, TM-score: 0.31

I. AMBER force field

E = E (bond) +	harmonic bond stretching
E (angle) +	harmonic angle bending
E (dihedral) +	cosine-like dihedral angle term
E (van der Waals) +	6-12 Lennard Jones potential
E (electrostatics) +	coulombic potential
E (solvation)	free energy of solvation consisting of polar contribution modeled by Generalized Born approximation and non-polar surface area dependent component (SA)

(GB)

AMBER: D.A.Case *et.al.*, J. Computat. Chem. 2005, **26:** 1668-1688.

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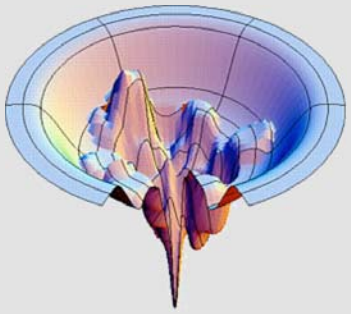

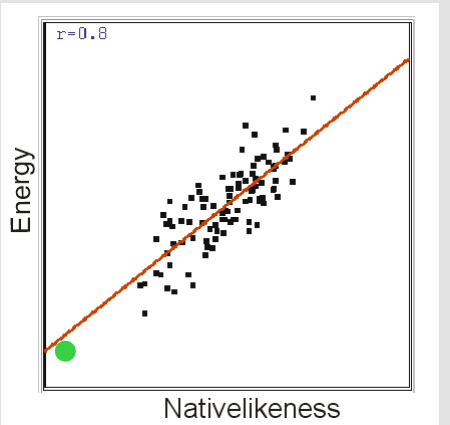

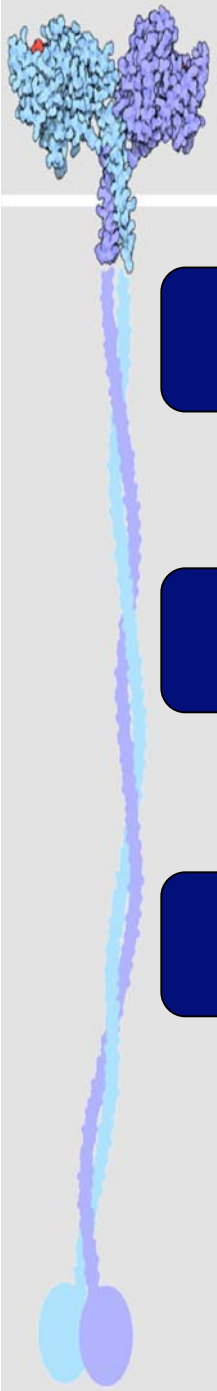

I. Assessment of AMBER force field

TASSER decoys
in reduced representation

↓

All-atom reconstruction

↓

Energy minimization
with AMBER

- 100 nonhomologous proteins
- 50-200 amino acids
- 1000 decoys per protein

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TASSER decoys
in reduced representation

All-atom reconstruction

Energy minimization
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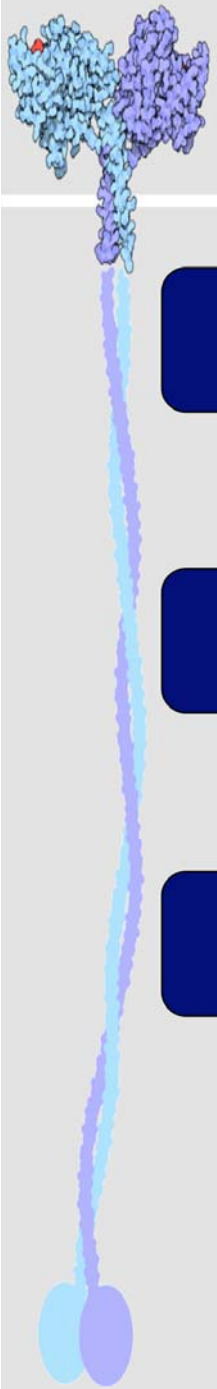

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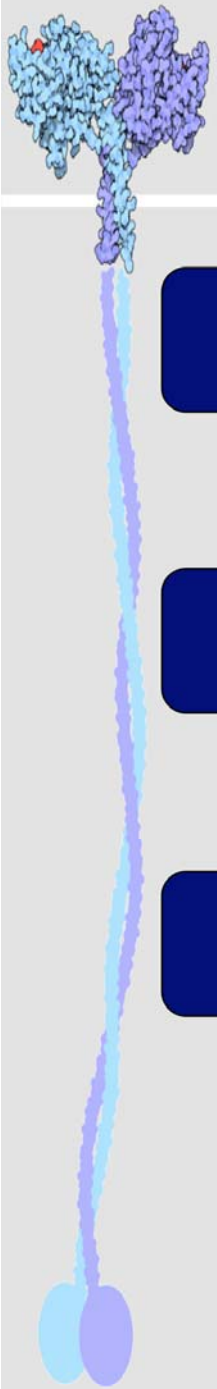

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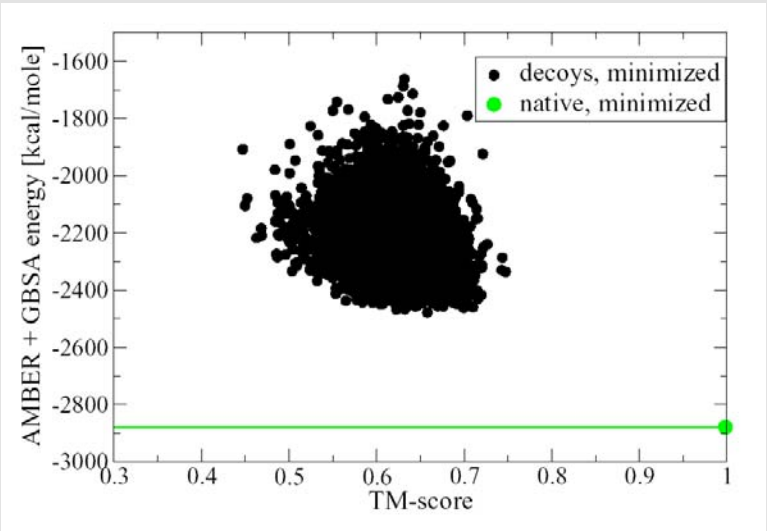

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Energy minimization
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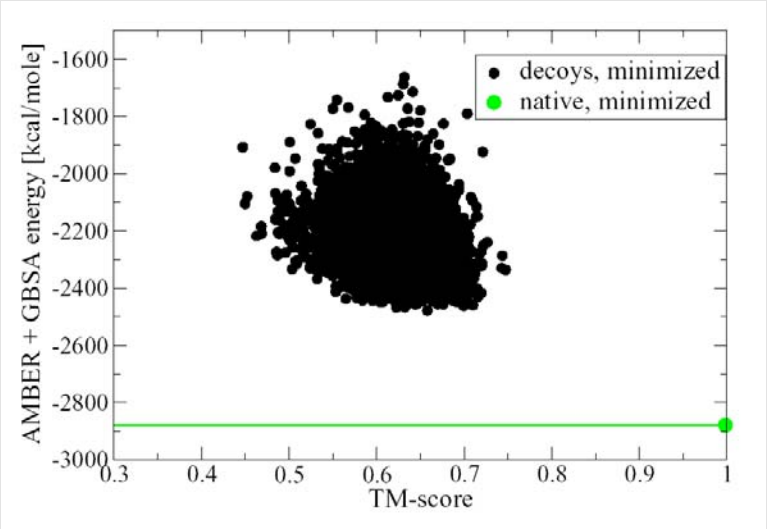
AMBER conformational search
1000 decoys per protein



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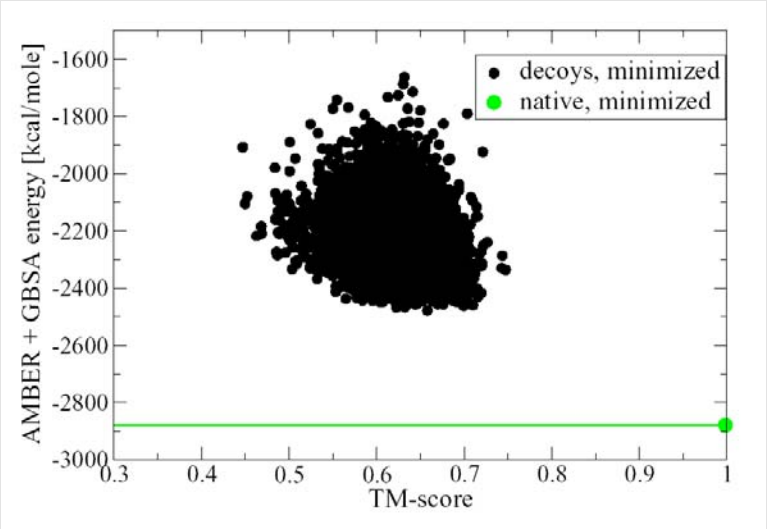

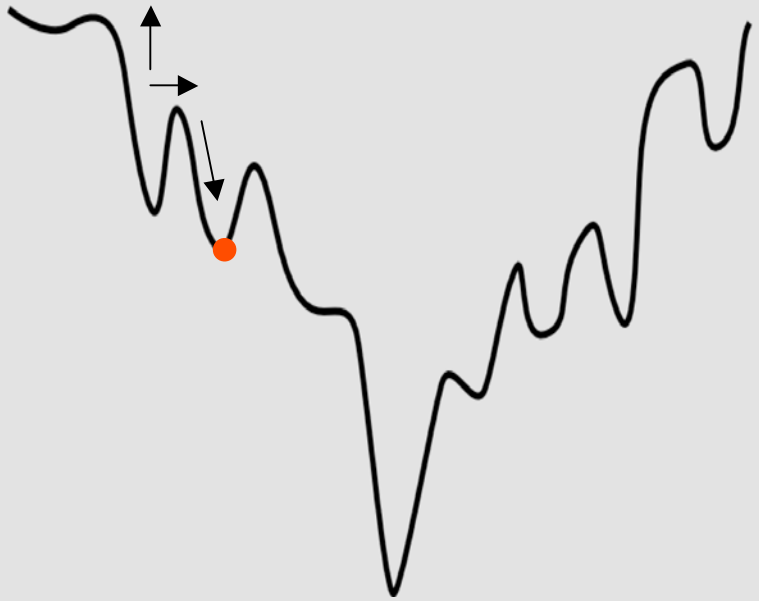

I. Assessment of AMBER force field

TASSER decoys
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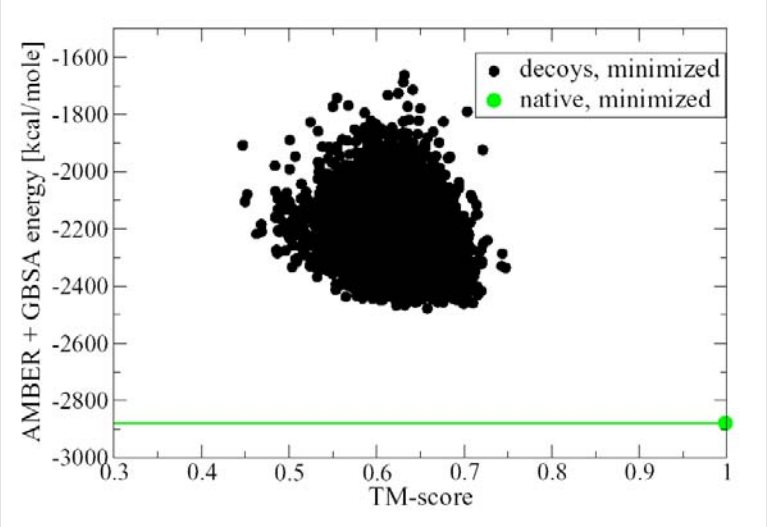
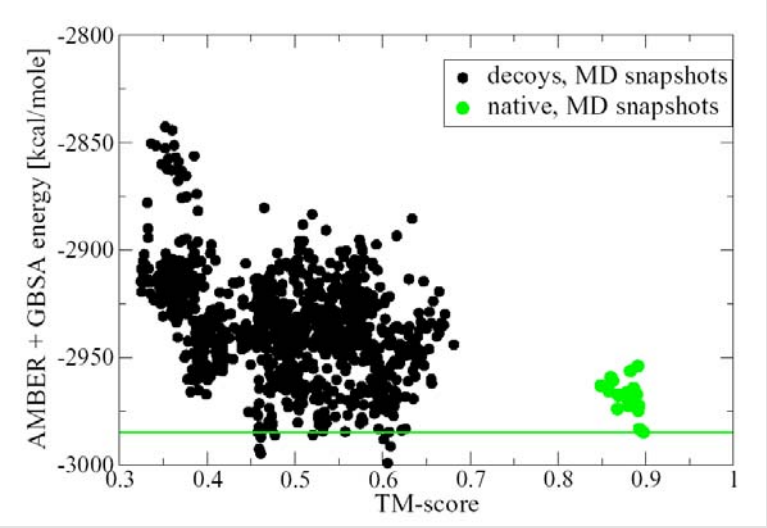
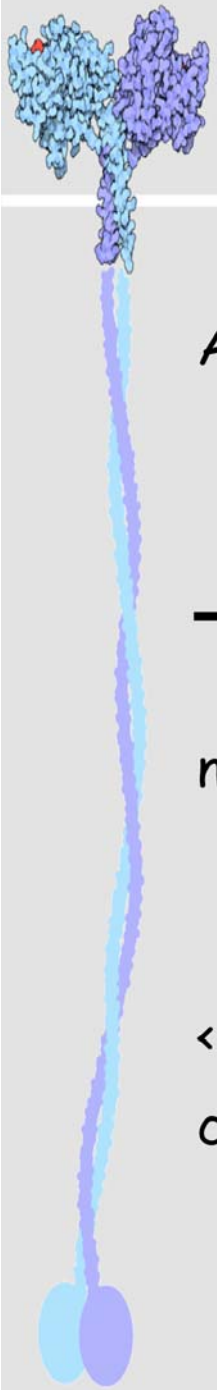






I. Assessment of AMBER force field

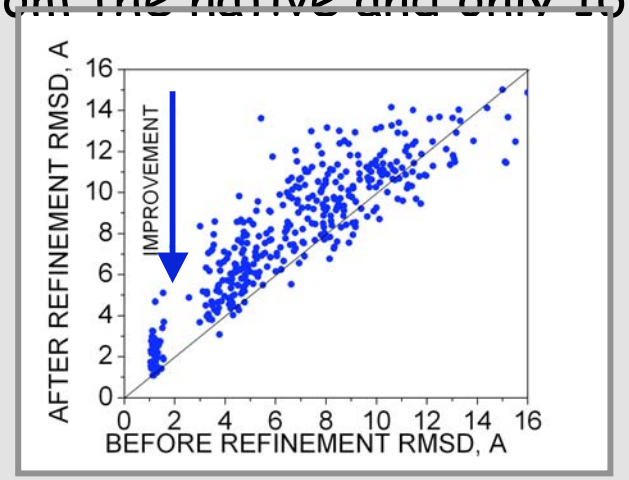
Average results:

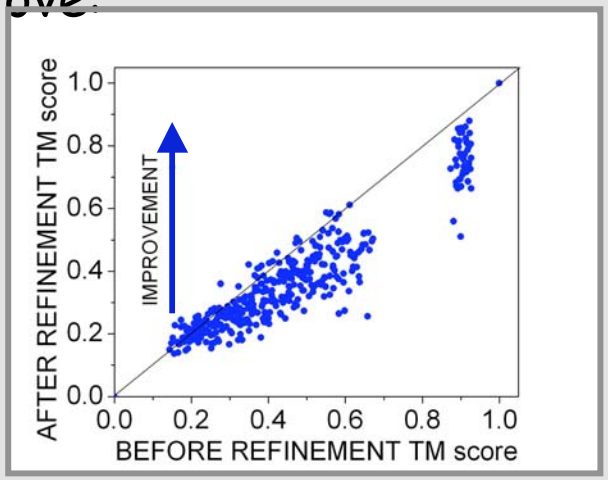
	FF99	FF03
native ranking #1	20%	48%
<energy – TM-score correlation coeff.>	0.1	0.25

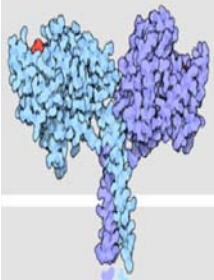
I. Assessment of AMBER force field

- AMBER ff03 performs better than ff99
- Neither version is capable of model refinement

during search models 84% of decoys drift farther away from the native and only 16% improve:







I. Identification of the key problems

- The energy components that mostly disfavor native-like structures:
  - dihedral angle energy
  - electrostatics of bonded atoms (1-4)

- The energy components that display no native-likeness specificity:
  - electrostatics
  - generalized Born solvation

} large contributions

- Hydrogen bond energy seems to be underestimated

(numerous hydrogen bonds are distorted during simulations)

I. Conclusions

- The original AMBER potential is not capable of protein model refinement (flat energy landscape)

Part II

Development of a physics-based force field for the scoring and refinement of protein models

L. Wróblewska A. Jagielska and J. Skolnick, Biophys. J. (submitted)

II. Optimization of AMBER energy components

- Data set: 58 proteins, diverse set of ~20,000 decoys per protein generated by AMBER molecular dynamics and atomic-TASSER Monte Carlo search

- Methodology: optimizing w_i in: $E = \sum w_i e_i$ to:
  - maximize energy - TMscore correlation coefficient
  - maximize native - decoy energy gap (Z-score)

II. Optimization of AMBER energy components

	FF03	FF03 OPT	
		training set	testing set
<energy – TM-score CC>	0.25	0.63	0.61
CC > 0.60	12%	47%	49%
TM-score > 0.90	22%	93%	84%
RMSD < 2.0 A	48%	93%	88%
<Z-SCORE>	0.16	2.65	2.18

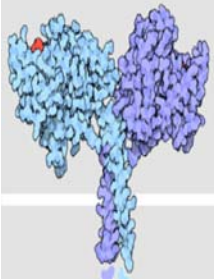
II. Modification of the energy components

- New component for hydrogen bond energy added

$$E_{HB} = q_1 q_2 (1/r_{NO} + 1/r_{CH} - 1/r_{OH} - 1/r_{CN}) \cdot f \qquad \text{(DSSP)}$$

	FF03	FF03 OPT	FF03/HB OPT
<energy – TM-score CC>	0.28	0.62	0.65
CC > 0.60	12%	48%	64%
TM-score > 0.90	22%	86%	90%
RMSD < 2.0 A	48%	89%	91%
<Z-SCORE>	0.16	2.30	2.29

DSSP: W. Kabsch, C. Sander, Biopolymers, 1983, 22: 2577-2637.



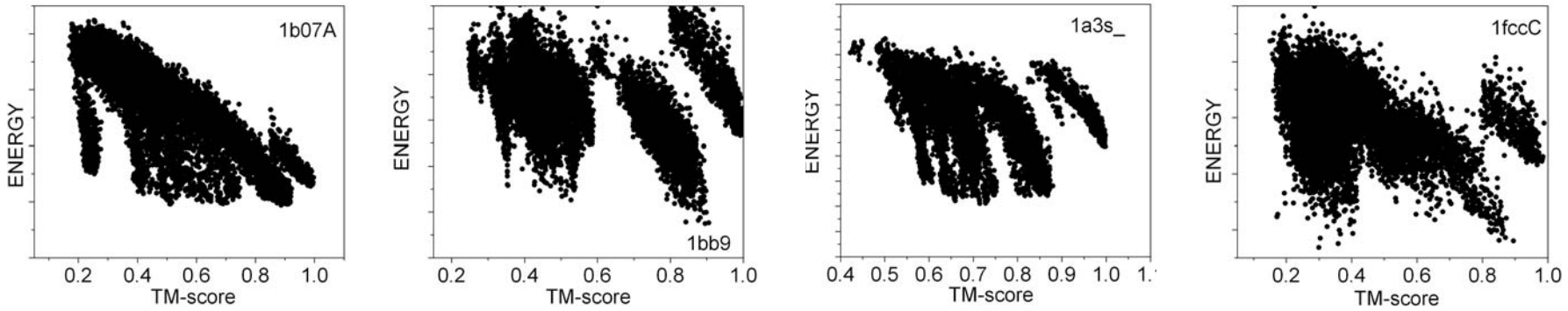
II. Modification of the energy components

- Electrostatics and Generalized Born solvation parts omitted

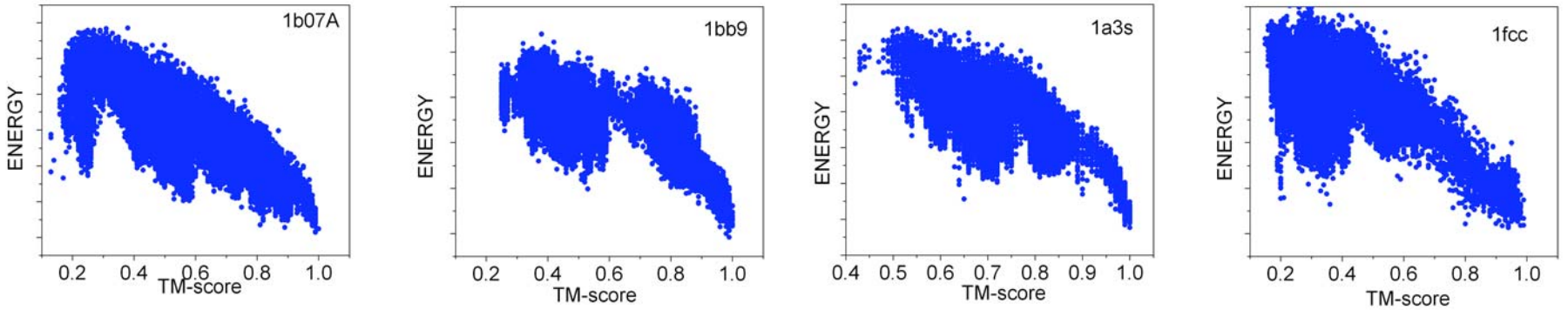
	FF03	FF03 OPT	FF03/HB OPT	FF03/HB Reduced/OPT
<energy – TM-score CC>	0.28	0.62	0.65	0.58
CC > 0.60	12%	48%	64%	43%
TM-score > 0.90	22%	86%	90%	71%
RMSD < 2.0 A	48%	89%	91%	84%
<Z-SCORE>	0.16	2.30	2.29	1.56

II. The optimized force field

Before optimization



After optimization (FF03/HB)



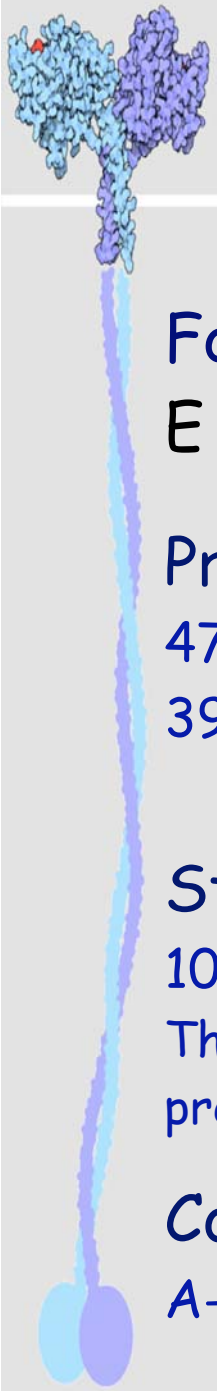
II. Conclusions

- Optimization of weights of AMBER FF03 energy significantly improved
  - native scoring
  - energy – native-similarity correlation coefficient
- Explicit hydrogen bond potential further improved the optimized force field
- Reduced optimized potential, without time consuming electrostatics and GB solvation is still much better than the original FF03 force field

Part III

Systematic refinement of reduced protein models with all-atom force field

A. Jagielska, L. Wróblewska and J. Skolnick (in prep.)



III. Refinement protocol

Force field:

$$E = w_1 E_{dihedral} + w_2 E_{VdWaals} + w_3 E_{SA} + w_4 E_{HB}$$

Protein set

47 proteins 54-123 amino acids (a, b, a/b)

39 proteins were not used in the optimization of the potential

Starting decoys

100 decoys per protein, that span 0-8 Å RMSD to the native

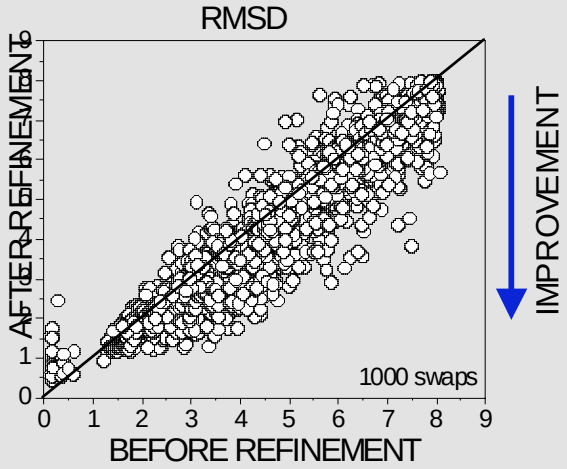
The decoys were randomly chosen from the decoy clouds obtained previously using TASSER/ff03-MD/ff03-ATASSER

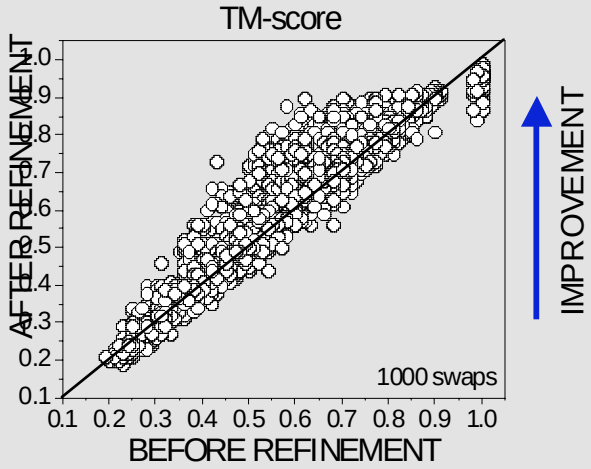
Conformational Search

A-TASSER Monte Carlo Replica Exchange

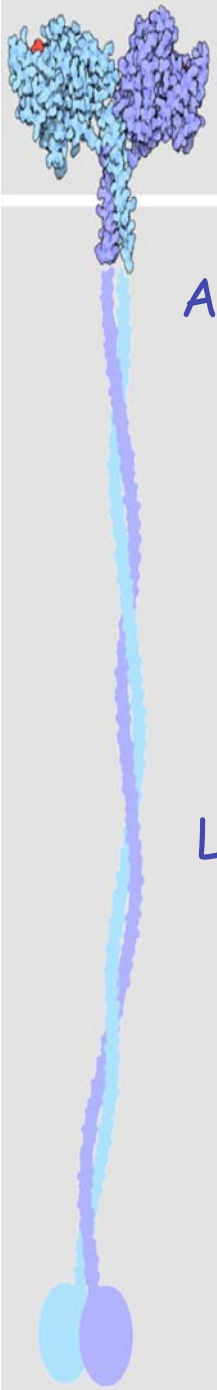
III. Refinement

refined model = lowest energy model from the refinement run



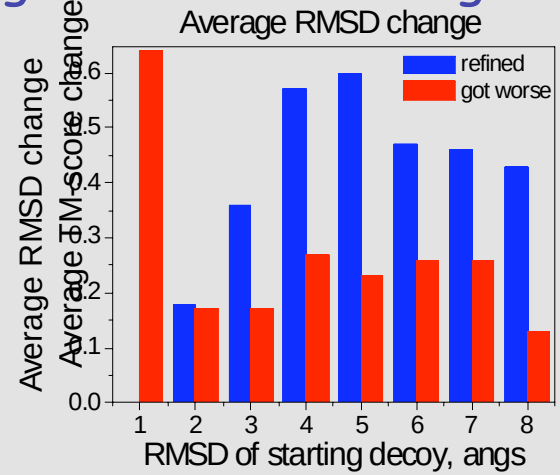


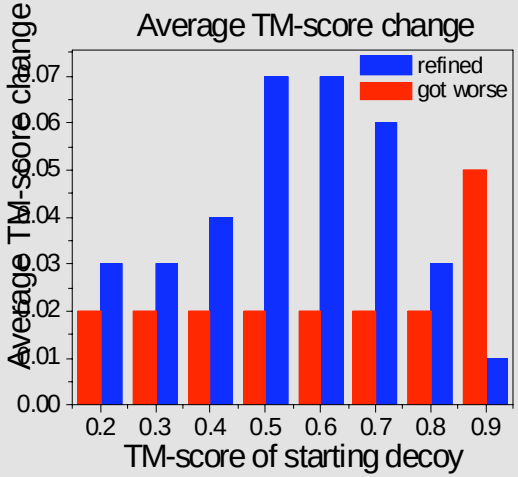
	RMSD	TM-score
Improvement	70%	70%
Deterioration	28%	18%
no change	2%	12%



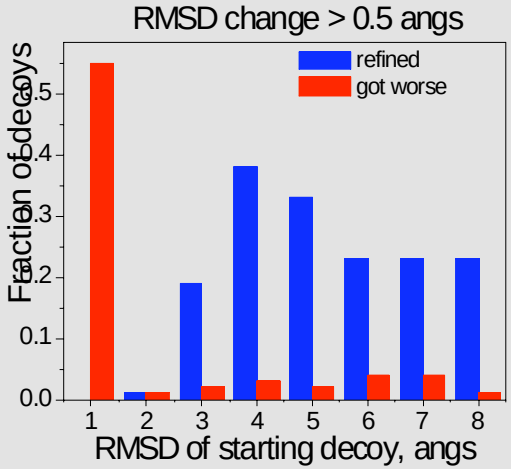
III. Refinement

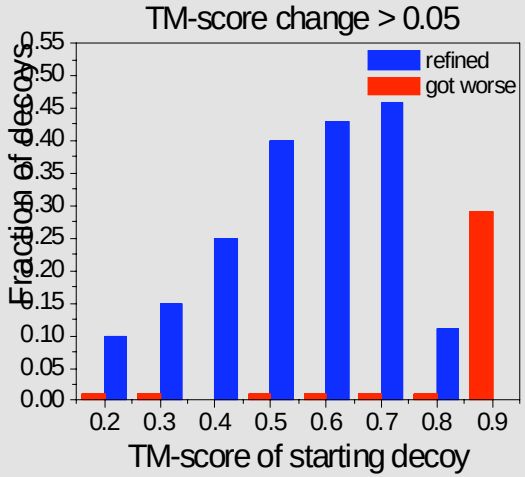
Average structural changes



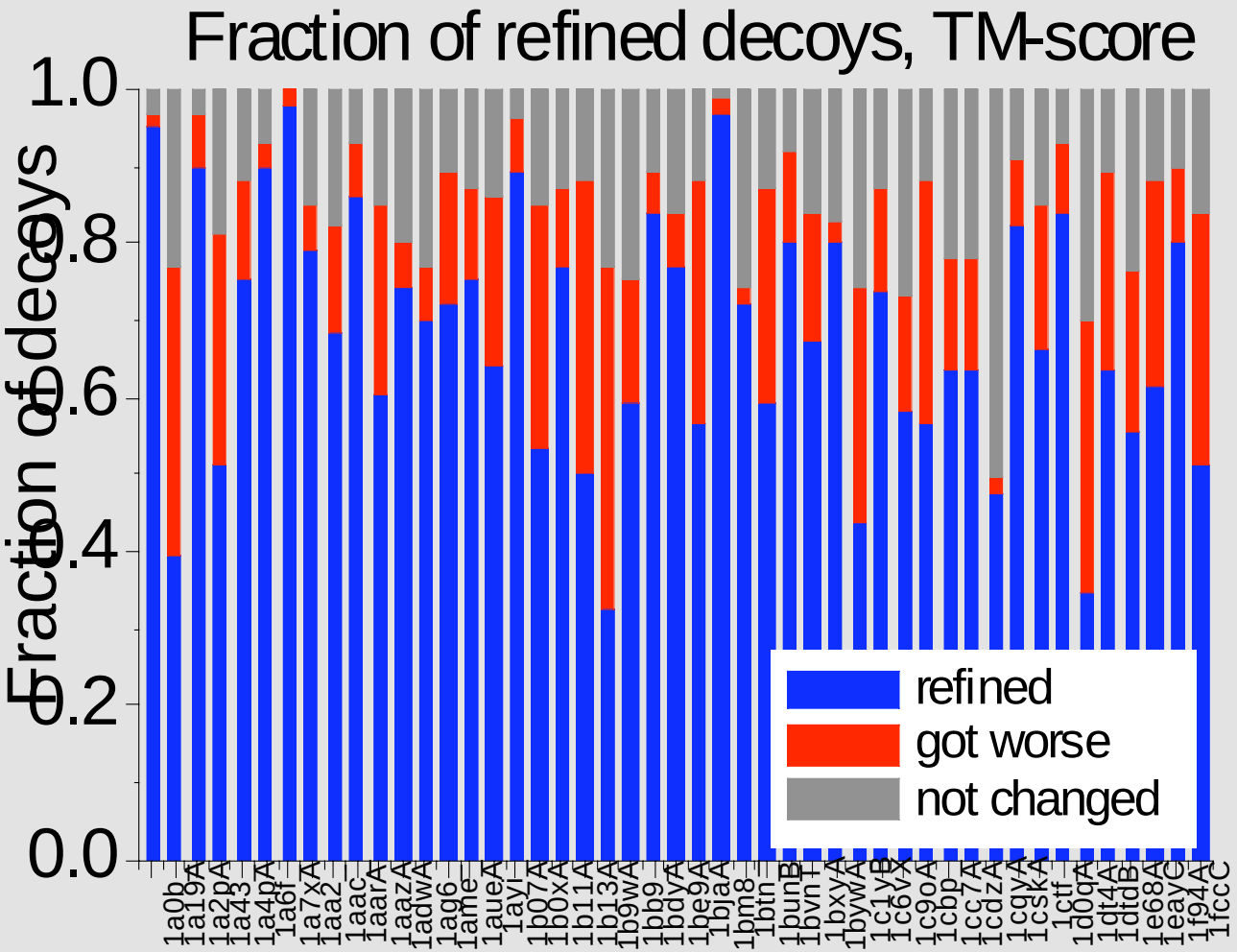


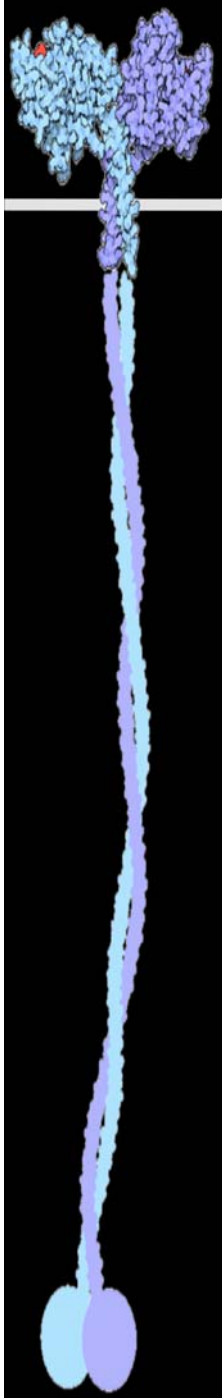
Large structural changes



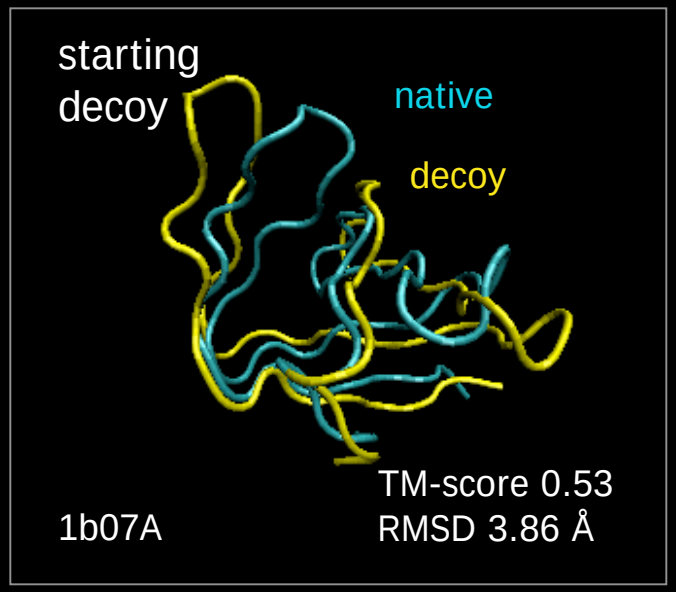


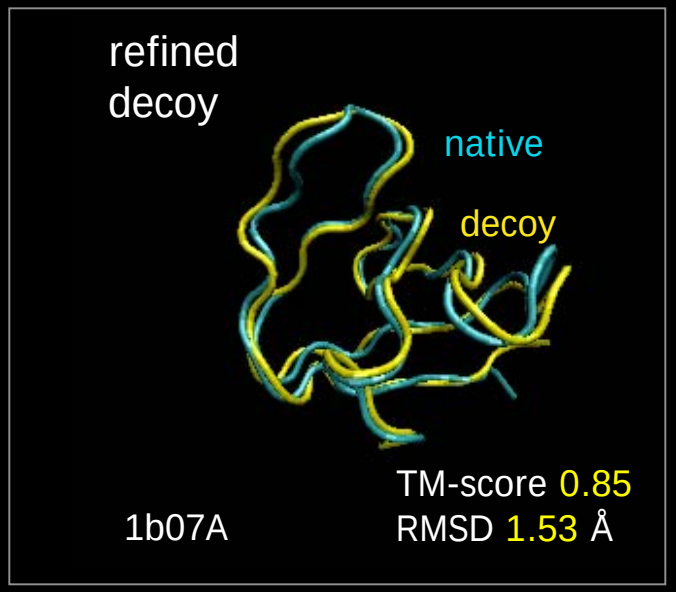
III. Refinement



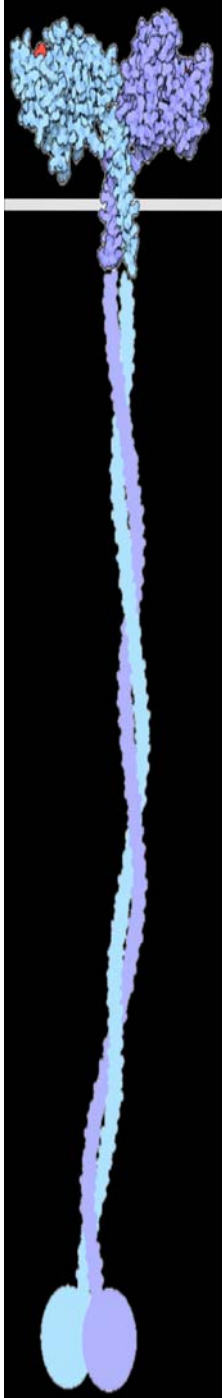


III. Refinement

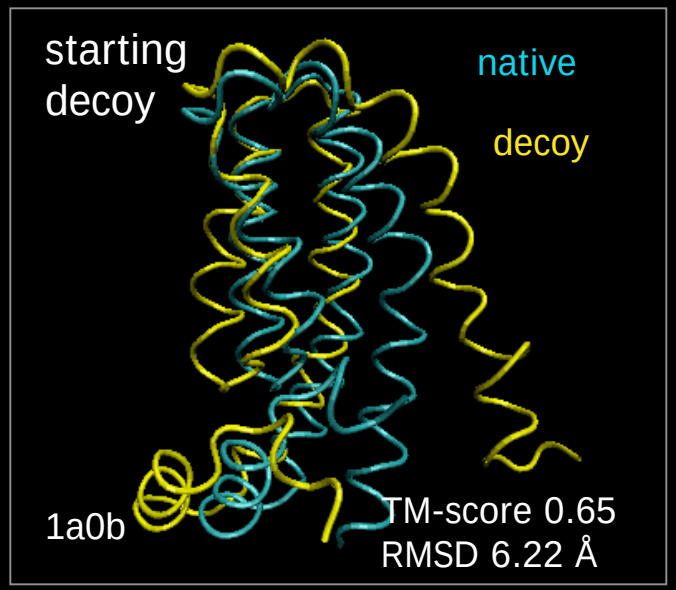


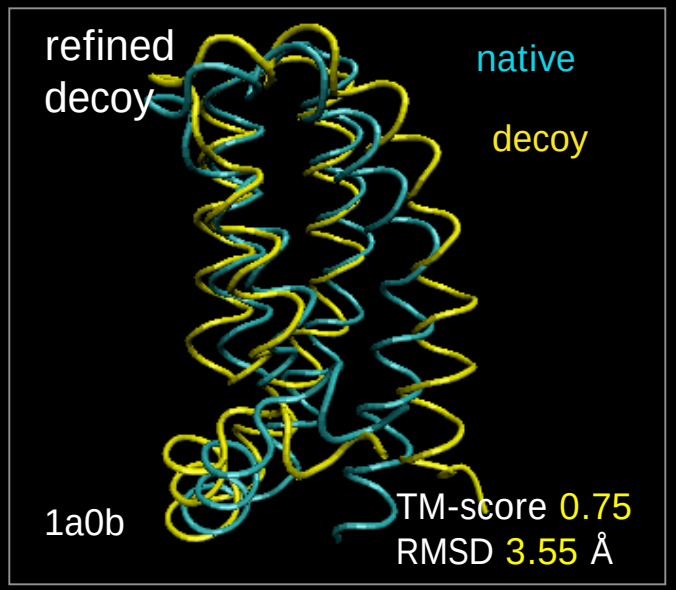


the lowest energy structure is shown



III. Refinement

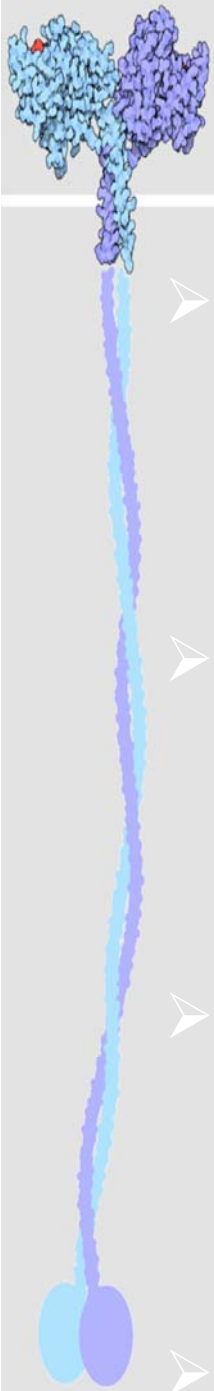




the lowest energy structure is shown

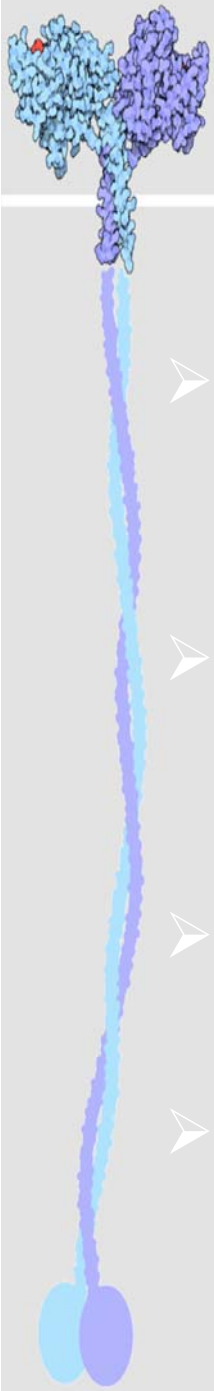
III. Conclusions

- The optimized force field allows for a systematic refinement of protein models
- For the first time such unrestrained, systematic all-atom refinement has been achieved



Summary

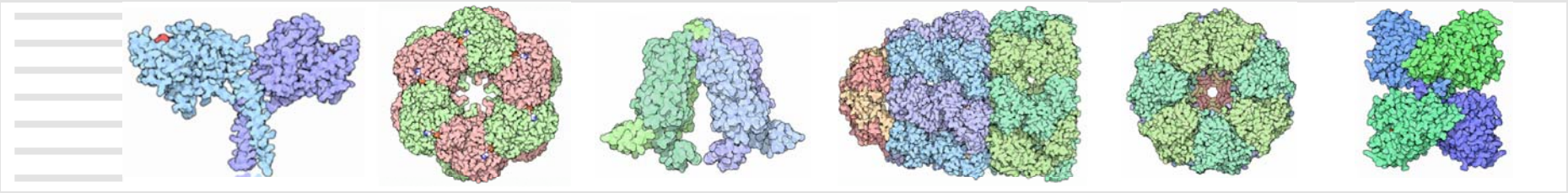
- Extensive testing of AMBER potential allowed for identification of the key problems in terms of refinement purposes
- Optimization of the AMBER energy contributions improved both: correlation between energy and TM-score, and scoring of native structures
- With the addition of the hydrogen bond energy and further optimization the improvement was much more pronounced
- In our set of representative decoy structures, the



Future Work

- Incorporation of the refinement procedure in the automated protein structure prediction pipeline
- Development of a confidence score for model selection
- Improvement of the dihedral angle energy term
- Reiteration of the optimization procedure with the new decoy structures obtained during refinement

Acknowledgements



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Thank You!