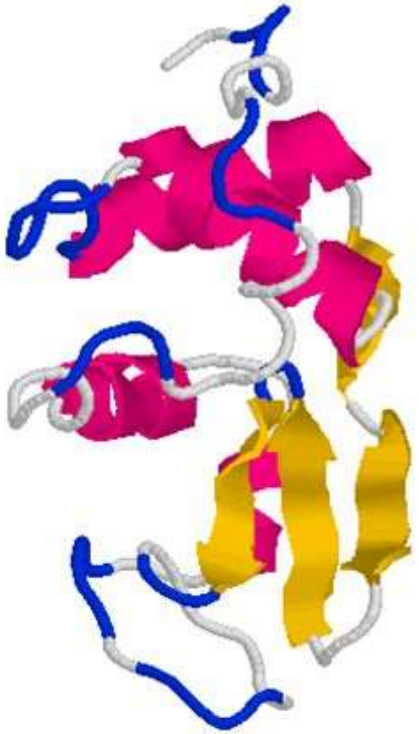
Protein Folding Problem

A protein folds into a unique 3D structure under physiological conditions

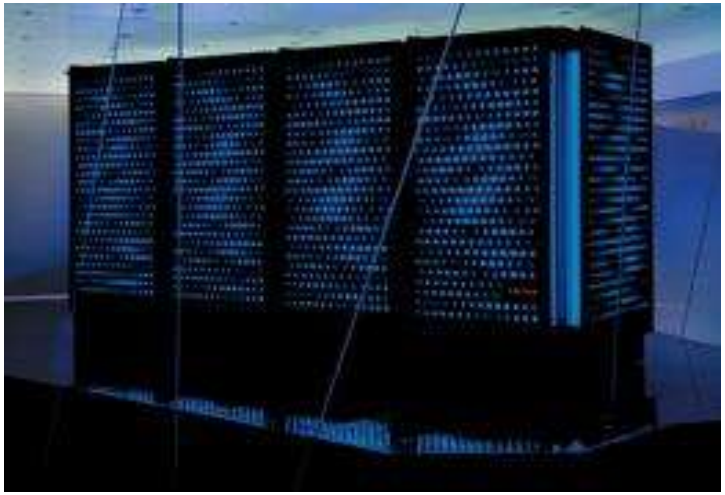
Lysozyme sequence:

KVFGRCELAA AMKRHGLDNY
RGYSLGNWVC AAKFESNFNT
QATNRNTDGS TDYGILQINS
RWWCNDGRTP GSRNLCNIPC
SALLSSDITA SVNCAKKIVS
DGNGMNAWVA WRNRCKGTDV
QAWIRGCRL



Anfinsen, 1960: denatured proteins can refold to active enzymes

Protein folding problem - the Holy Grail of the structural biology

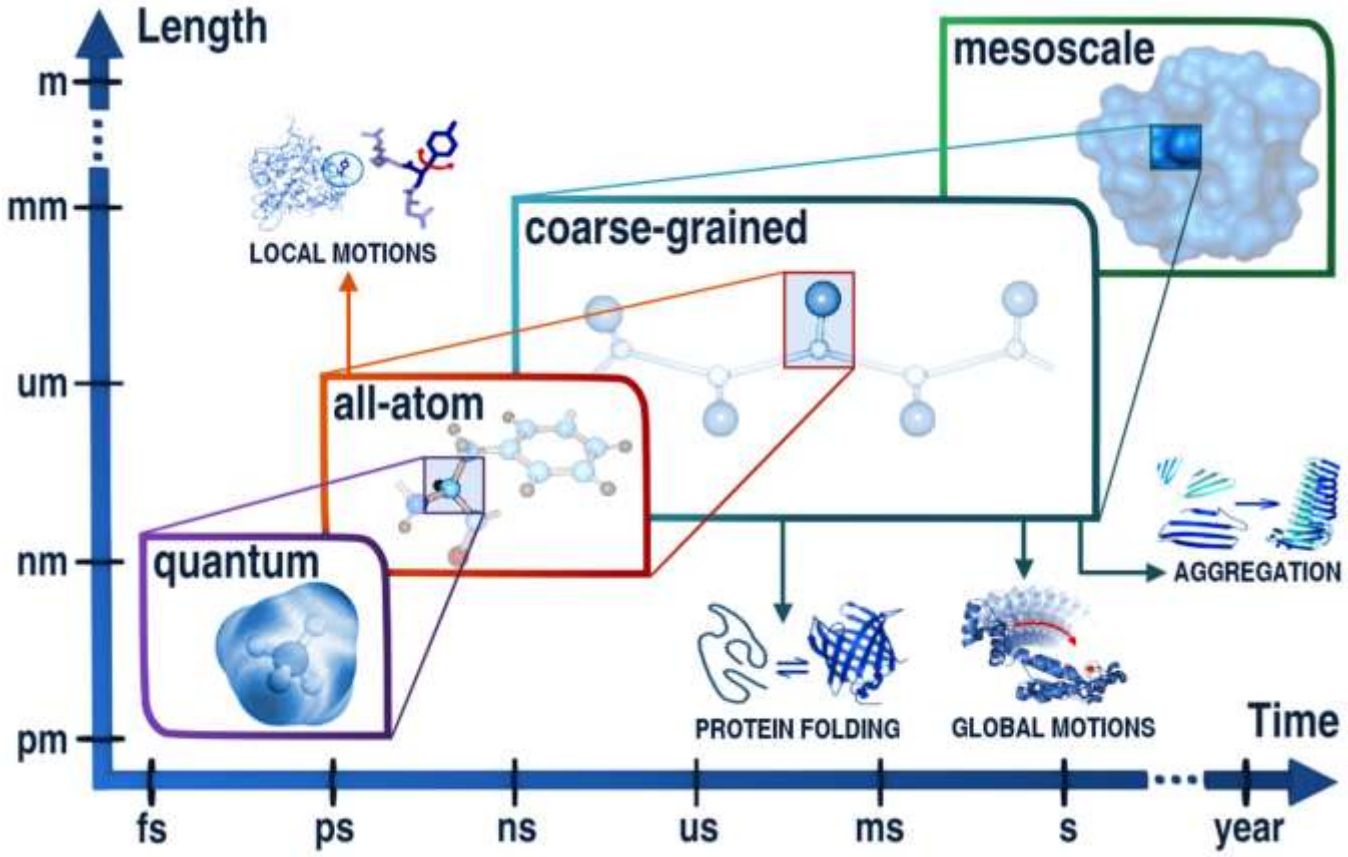


Anton
David E. Shaw Research

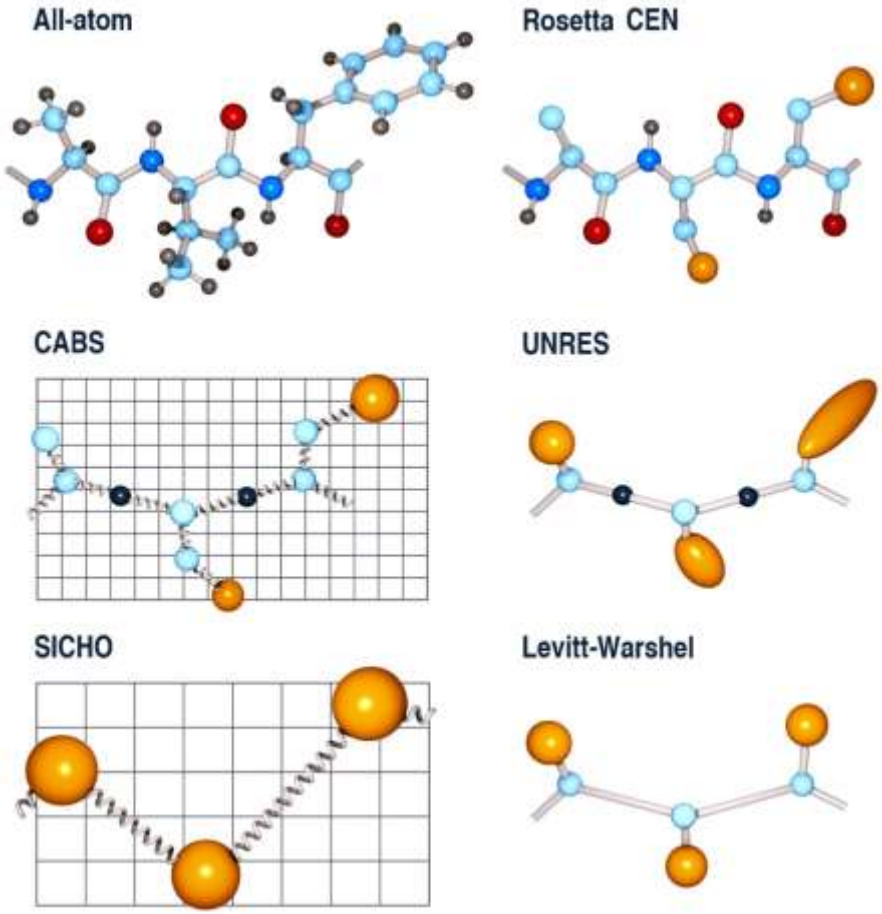
All-atom MD with explicit water
- milliseconds of folding process of a small protein.

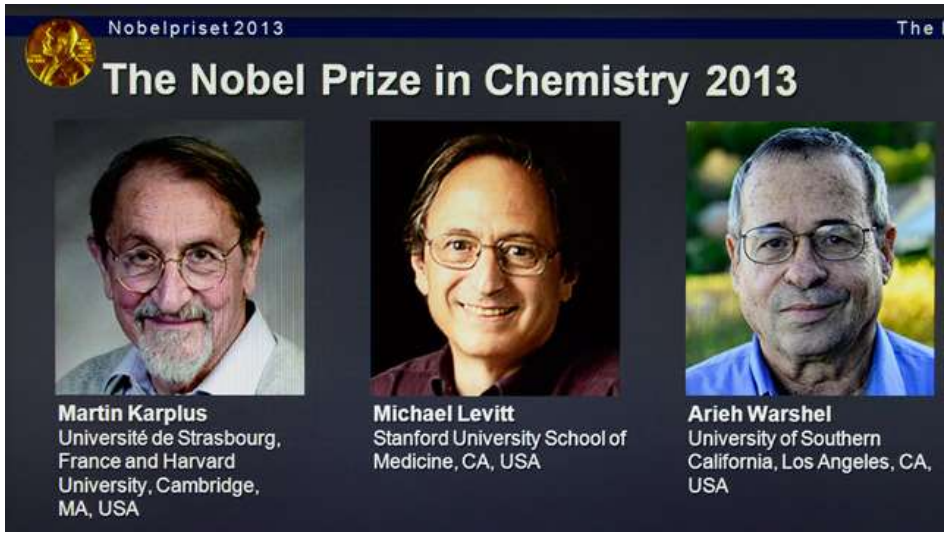
For realistic modeling of larger biomolecular systems, including flexible protein-protein docking, we need much faster simulations.

How to solve the Holy Grail problem



How to solve the Holy Grail problem – Multiscale Modeling





for *"the development of multiscale models for complex chemical systems"*

„Coarse-grained protein models and their applications"

Chem. Rev. **2016**, *116* (14), 7898–936

CABS model

Cα-Cβ-Side chain

High-coordination lattice

Statistical force-field

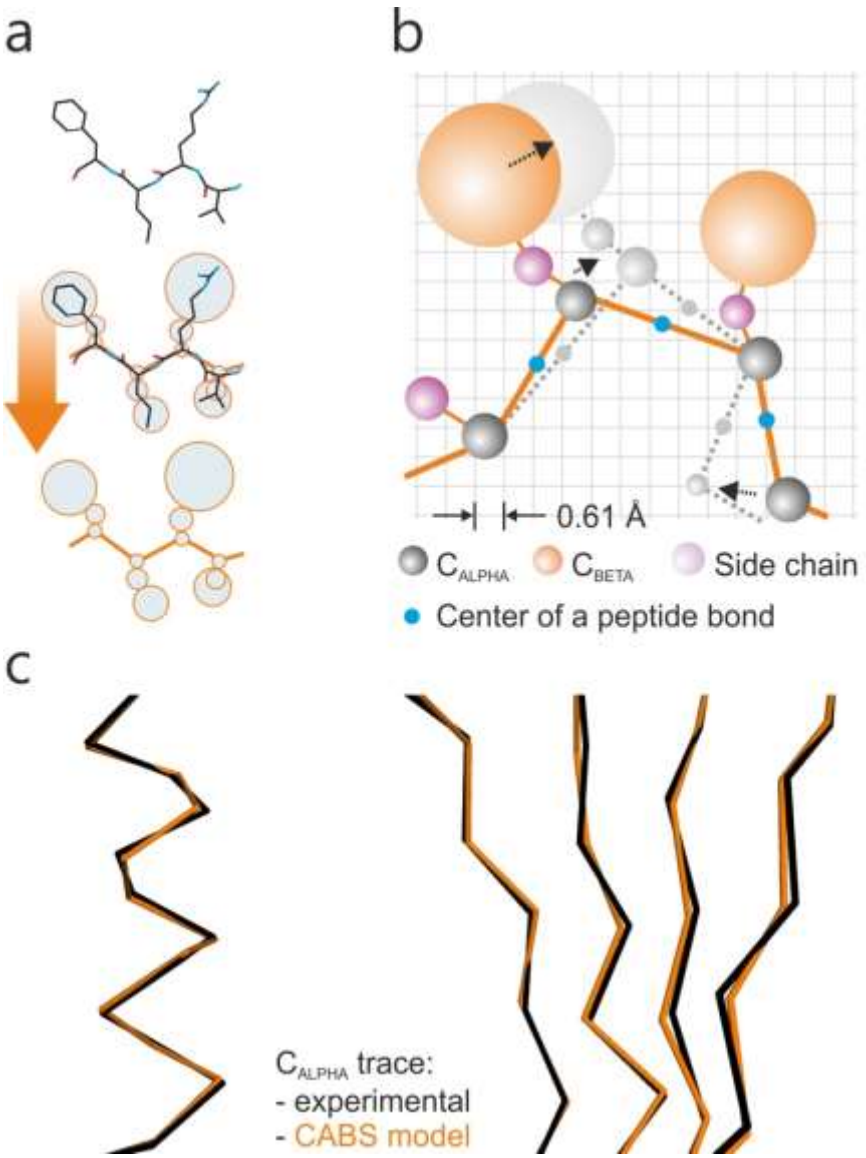
Monte Carlo dynamics

Figures:

a) Building reduced model

b) MC moves on the high-coordination lattice

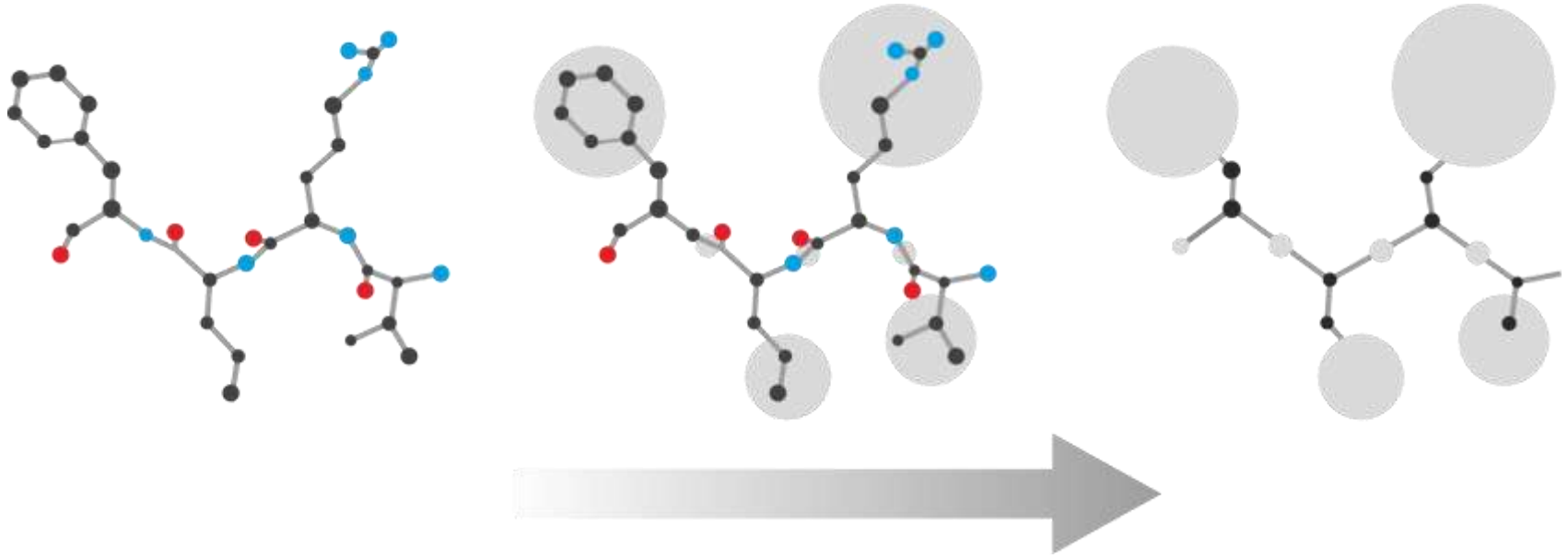
c) Accuracy (Cα-traces)



Time scales MD vs. CABS

All-atom molecular dynamics (MD)

CABS Monte Carlo dynamics



Max ~ 1 millisecond

~ 10^3 / 10^4 faster

Multiscale

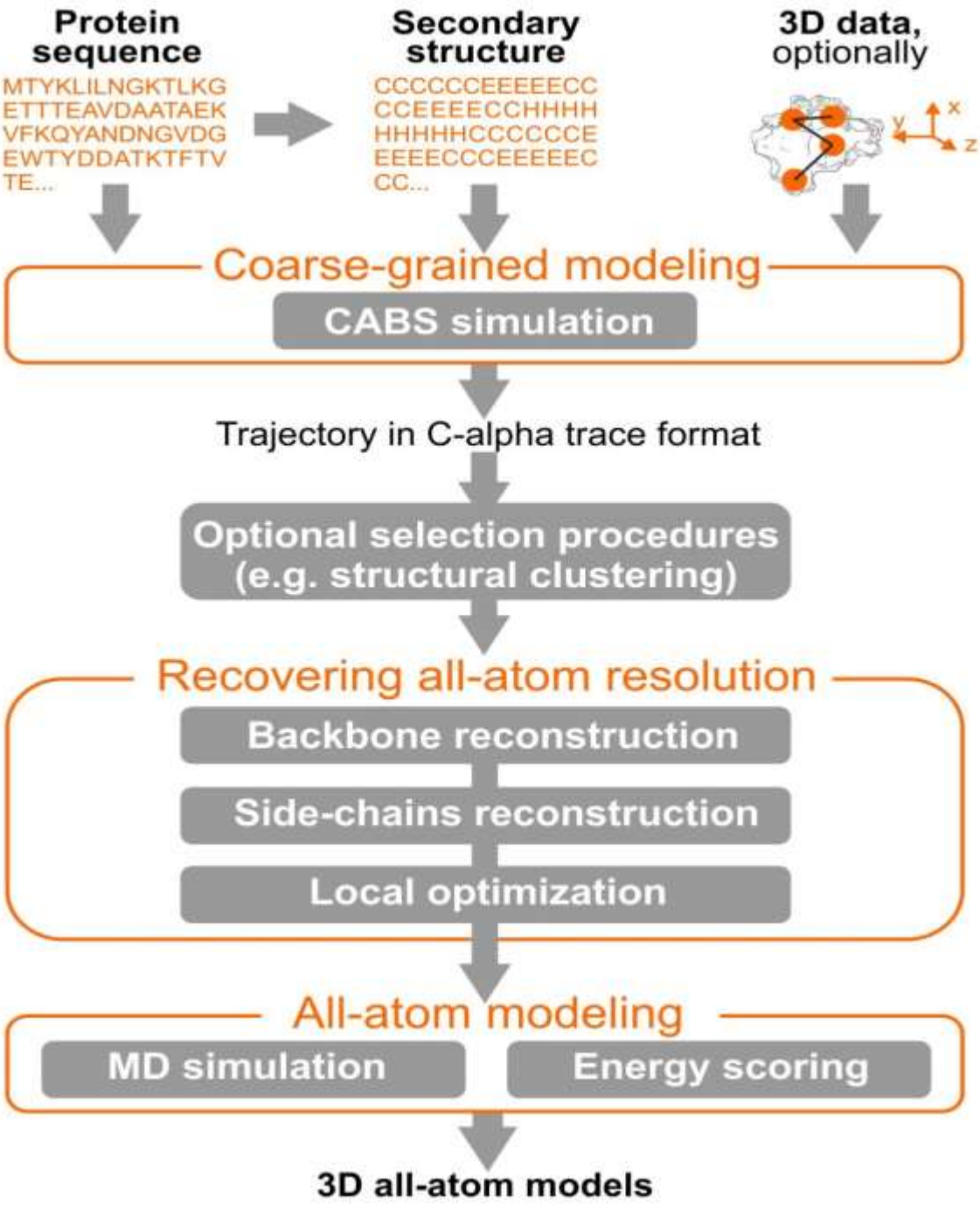
modeling with CABS

APPLICATINS

Structure prediction

Protein dynamics

Protein docking



CASP and CAPRI

CASP Competition

- CASP competition (Critical Assessment of Techniques for Protein Structure Prediction) http://predictioncenter.llnl.gov/
- Their goal is to help advance the methods of identifying protein structure from sequence.

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CASP Experiment

- Experimentalists are solicited to provide information about structures expected to be soon solved
- Predictors retrieve the sequence from prediction center (predictioncenter.llnl.gov)
- Deposit predictions throughout the season
- Meeting held to assess results

Polish scientists in CASP: Ginalski, Rychlewski, Bujnicki, Kolinski, Liwo, and others

CASP –every 2 years since 1994

Leading trends:

- Art of modeling (knowledge-based homology modeling) by Alexey Murzin
- Careful alignment + Modeller by Krzysztof Ginalski
- Rosetta fragment assembly (copmpartive and de novo) by David Baker and co-workers
- Refined allignments and Coarse-Grained modeling using CABS tools by Janusz Bujnicki and Andrzej Kolinski
- Sofisticated ranking of allignments and fragment modeling using CAS (a version of CABS) by Yang Zhang
- Computer deep-learning and fragment assembly (Rosetta) Lee Sedol

CASP6: Average scoring, all categories

(New Folds, Fold Recognition, Comparative Modeling)

1 Ginalski (ICM, POLAND)
2 Kolinski & Bujnicki (UW-IIMCB, POLAND)
3 Baker (USA)
4 Skolnick_Zhang (USA)
5 GeneSilico (IIMCB, POLAND)

A. Kolinski and J. M. Bujnicki,"Generalized protein structure prediction based on combination of fold-recognition with de novo folding and evaluation of models", *Proteins* **61**(S7):84-90 (2005)

Multiscale

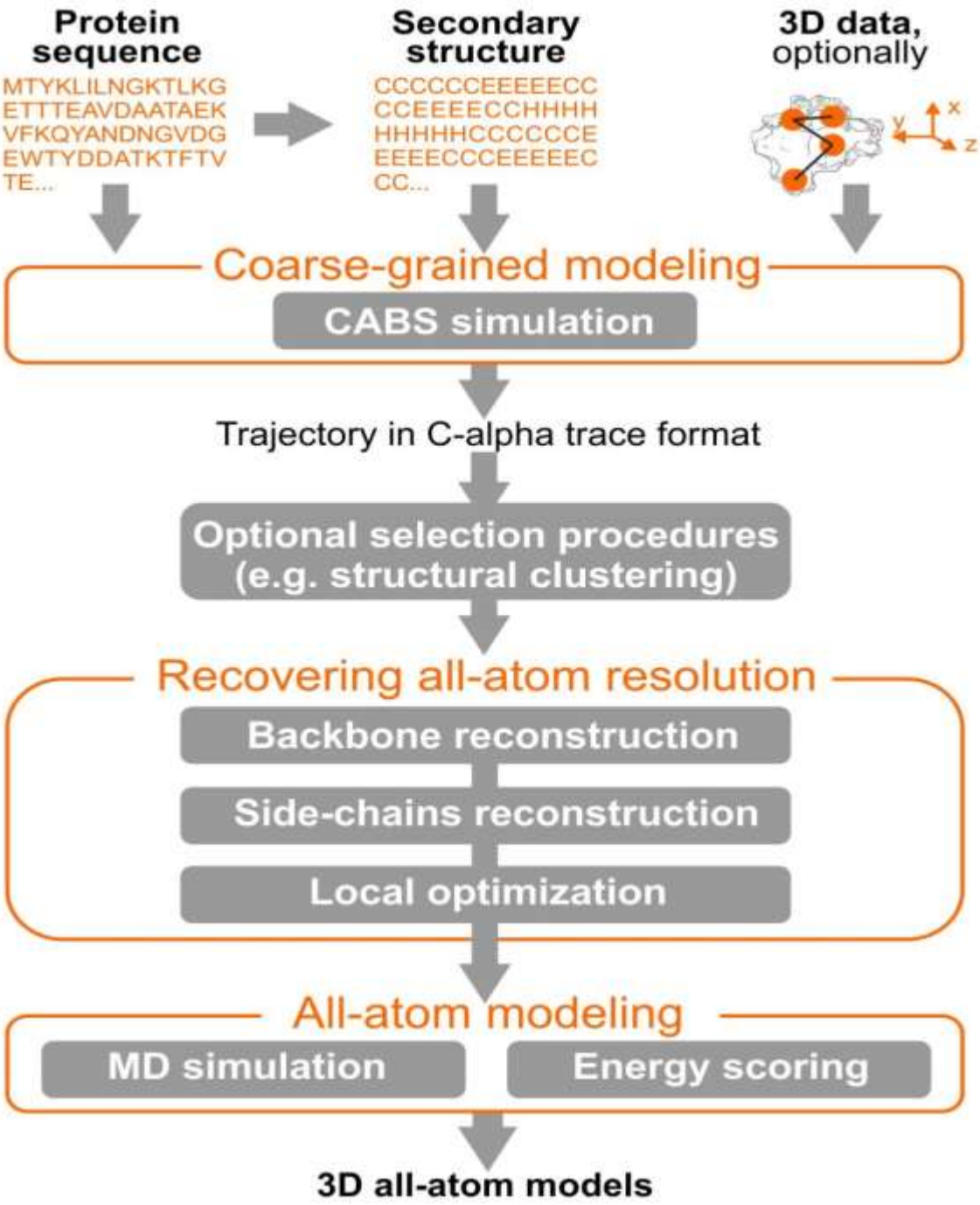
modeling with CABS

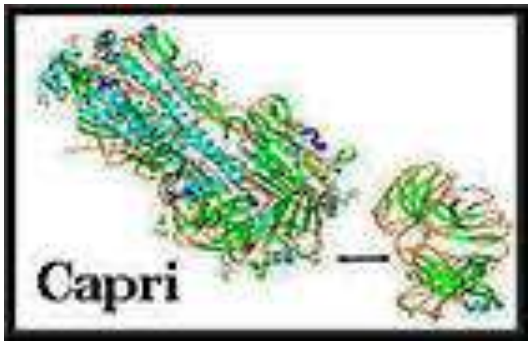
APPLICATINS

Structure prediction

Protein dynamics

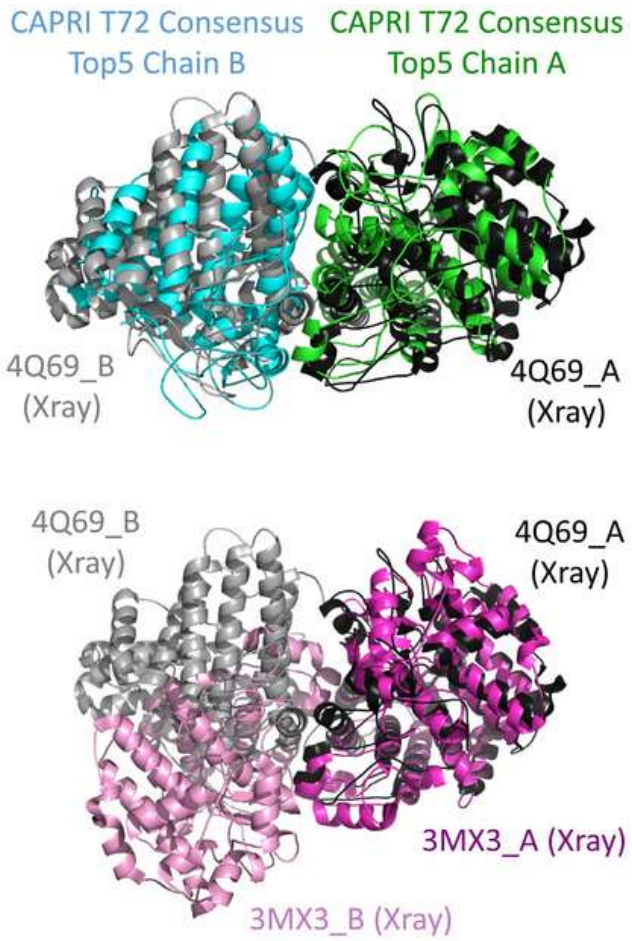
Protein docking



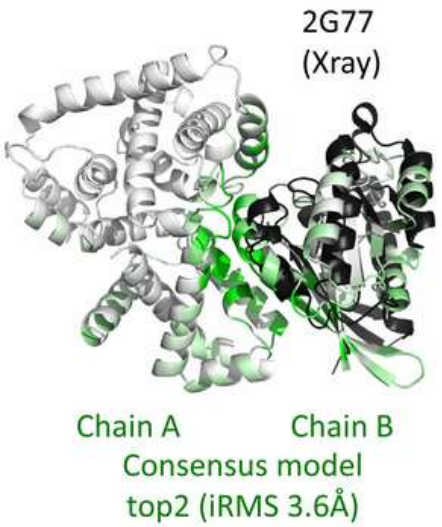


CAPRI: Critical Assessment of PRediction of Interactions

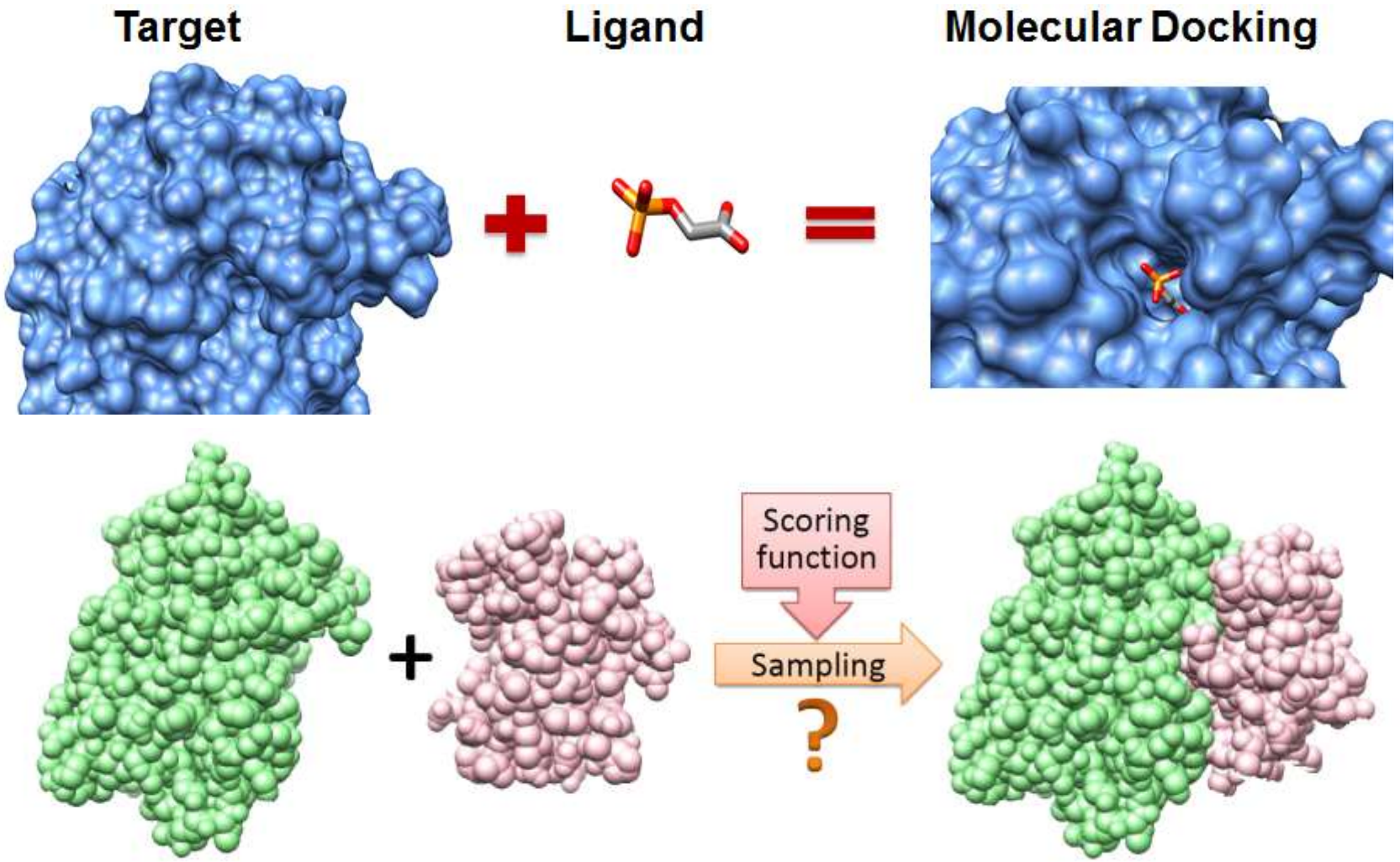
A

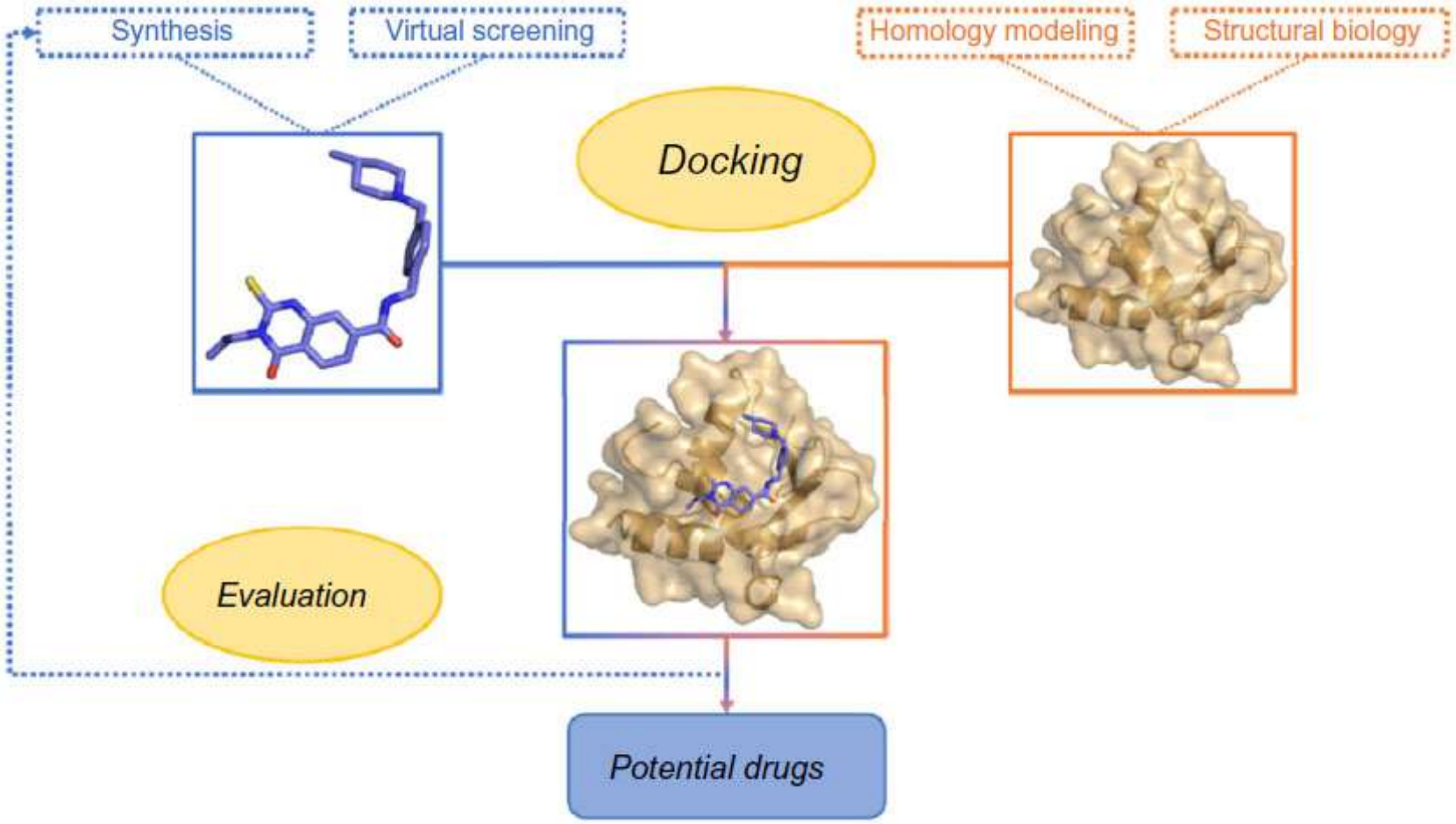


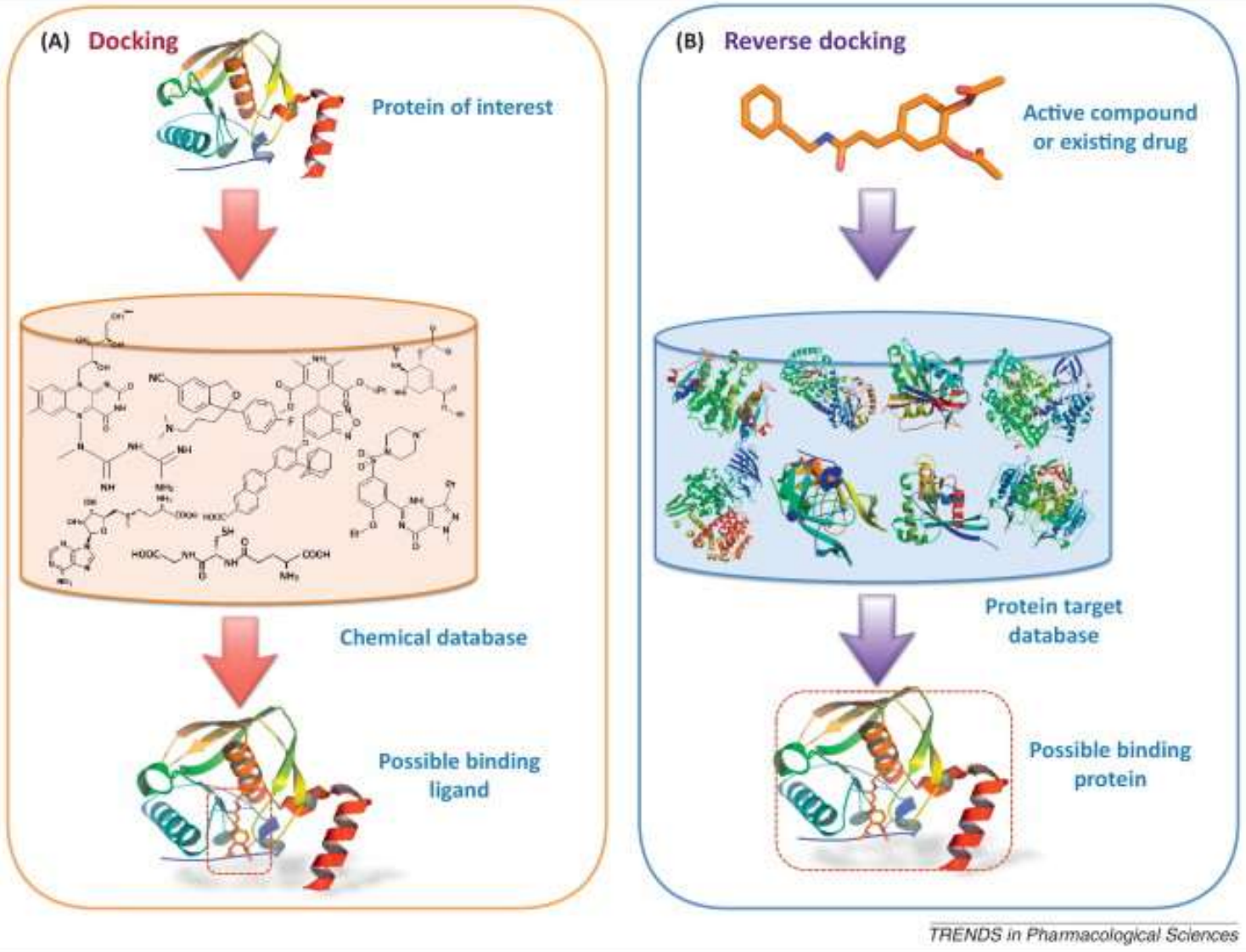
B



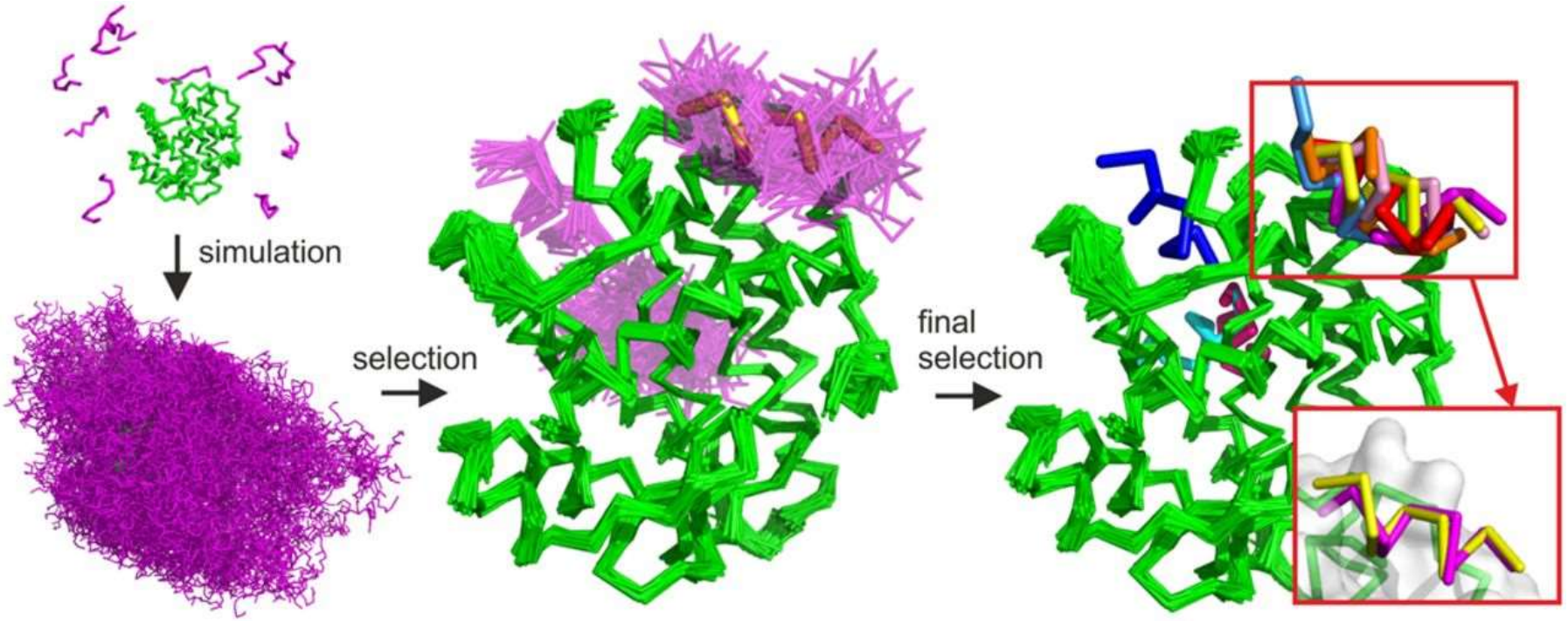
Molecular docking




Synthesis
Virtual screening
Homology modeling
Structural biology
Docking
Evaluation
Potential drugs


(A) Docking
Protein of interest
Chemical database
Possible binding ligand
(B) Reverse docking
Active compound or existing drug
Protein target database
Possible binding protein
TRENDS in Pharmacological Sciences

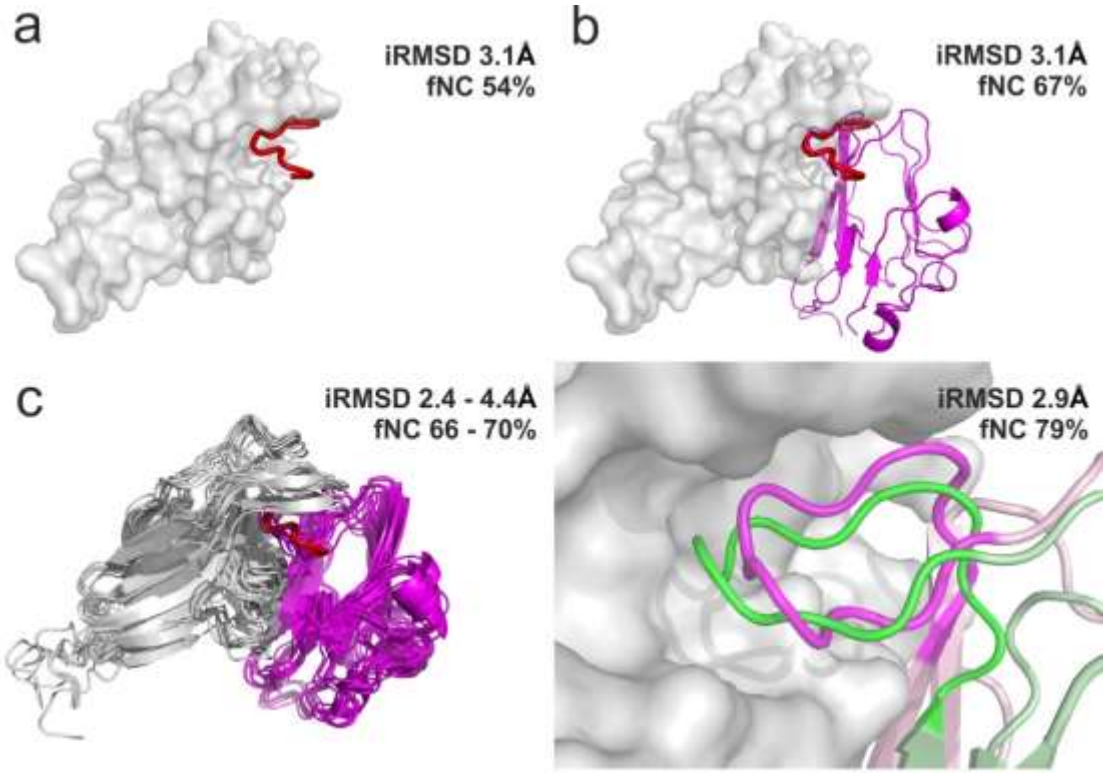
Peptide docking with CABS model



M. Kurcinski, M. Jamroz, M. Blaszczyk, A. Kolinski & S. Kmiecik, “CABS-dock web server for the flexible docking of peptides to proteins without prior knowledge of the binding site”, *Nucleic Acids Research*, 2015

Using CABS-dock peptide docking in protein-protein docking

„Modeling EphB4-EphrinB2 protein-protein interaction using flexible docking of a short linear motif”



BioMedical Engineering OnLine **16(Suppl 1)**:71 (2017)

Check our tools at:

http://biocomp.chem.uw.edu.pl/tools

LABORATORY of THEORY of BIOPOLYMERS

TOOLS

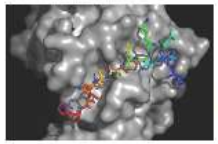
- CABS-DOCK
- CABS-FLEX
- CABS-FOLD
- AGGRESCAN3D
- CABS
- SURPASS
- CABS-NMR
- PYCABS
- CLUSCO
- BBQ
- BIOSHELL
- CCOMP
- MSITE
- BIODESIGNER
- IMOL

METHODS: The used methodologies were reviewed in our Tutorial review paper on Coarse-Grained Protein Models and Their Applications [pdf] in Chemical Reviews journal.

FUNDING: CABS-dock, CABS-flex, CABS-fold and Aggrescan3D tools were funded by the Foundation for Polish Science TEAM project (TEAM/2011-7/6) co-financed by the European Regional Development Fund operated within the Innovative Economy Operational Program.

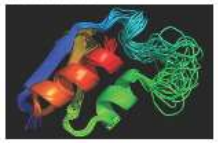
CABS-dock

server for protein-peptide docking and prediction of binding sites



CABS-flex

server for fast simulations of flexibility of protein structures

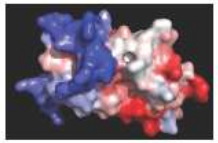


CABS-fold

server for de novo and consensus-based prediction of protein structure

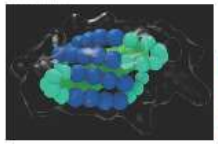
AGGRESCAN3D

server for prediction of aggregation properties of protein structures



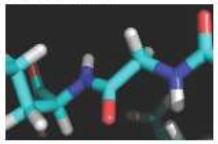
SURPASS

SURPASS coarse-grained protein model of low-resolution



BBQ

program for protein backbone reconstruction from C-alpha coordinates



pyCABS

package for simulations of long-time protein dynamics using CABS reduced model

ClusCo

a software for GPU/CPU clustering and comparison of protein models