Protein-protein docking
Arrimage protéine-protéine

Dirk Stratmann
http://www.impmc.upmc.fr/ stratmann/cours/docking/index.html
dirk.stratmann@upmc.fr

Master M2 PSF, Sorbonne Université

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Outline

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   - Motivation
   - Steps of protein-protein docking
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3. Scoring
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   - Shape complementarity
4. Rigid-body docking
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5. Evaluation
   - Performance of docking programs
   - CAPRI
6. Inclusion of experimental data
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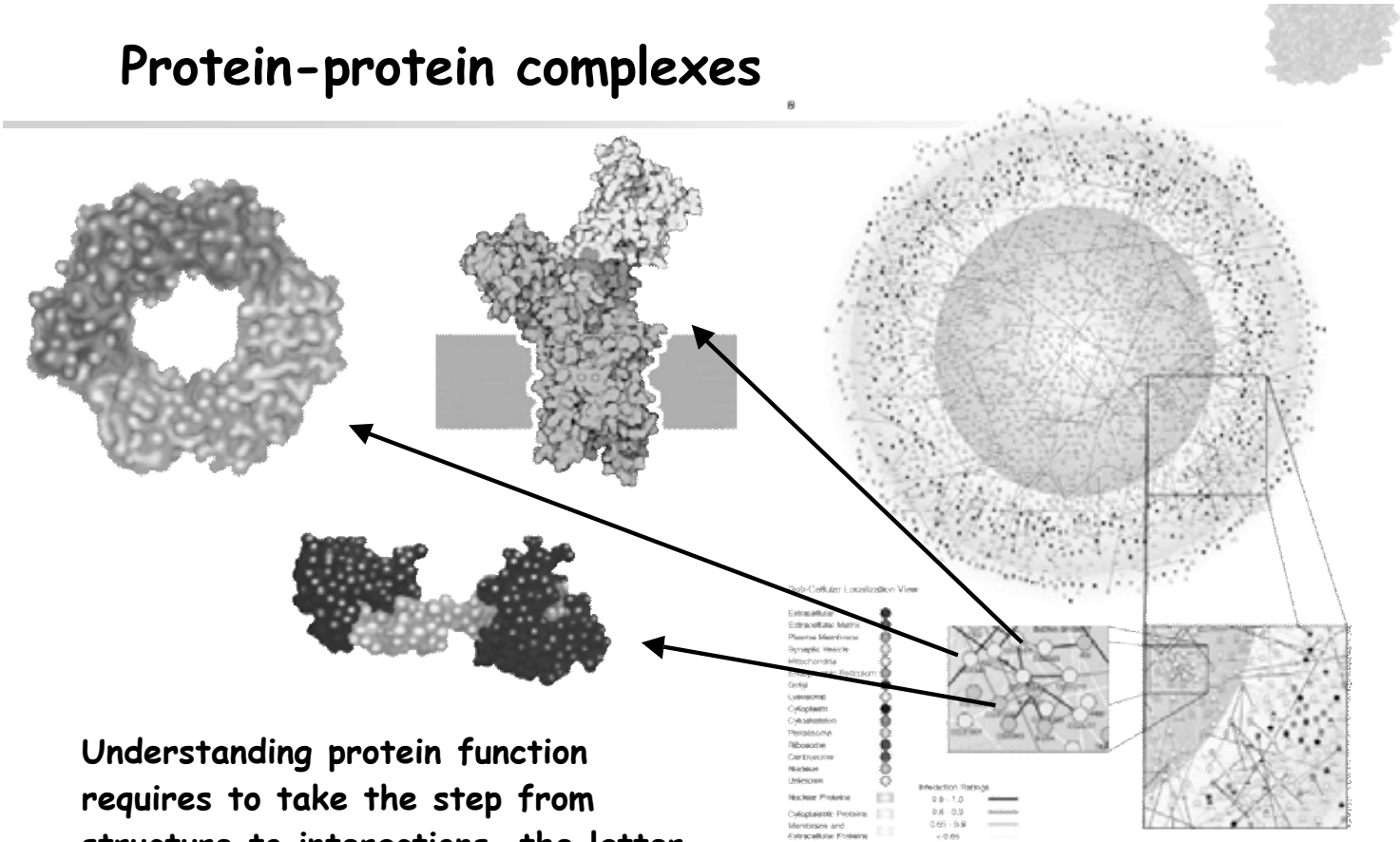
   - CS-HADDOCK
7. Bibliography

Protein function



Source: Bonvin

Free proteins - Structural genomics

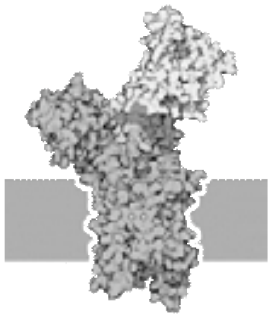
- 3D structure of a large number of unbound/free proteins solved => PDB
- Only about 1000 types of folds, almost all known.
- => Comparative modeling / Homology modeling

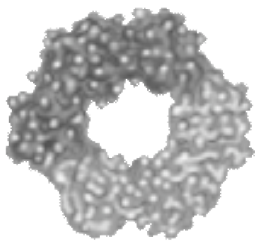
Protein-protein complexes

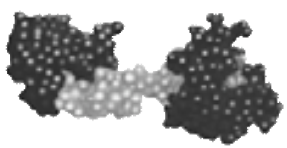
- Number of types of protein-protein interactions at least 10x times greater (> 10.000) than number of folds (1000).
- Experimental difficulties to solve protein-protein 3D structures.

Models of Protein Complexes

What can we learn from 3D structures (models) of complexes?







- **Models provide structural insight into function and mechanism of action**
- **Models can drive and guide experimental studies**
- **Models can help understand and rationalize the effect of disease-related mutations**
- **Models provide a starting point for drug design**

AB/10-07

Source: Bonvin

Protein-docking problem

M L Connolly (July 1986). In: *Biopolymers* 25.7

- Connolly has posed the protein-docking problem as: "Given the structures of any two proteins, is it possible to predict whether they associate, and if so, in what way?"
- Connolly was very optimistic at that time:
  "With a few years more development they stand a good chance of solving the protein-docking problem. If the protein-docking problem cannot be solved by a purely geometric approach, there remains the option of bringing in chemical considerations."
- The problem of docking molecules of any complexity based on the complementarity of their features has been shown to be NP-complete (Kuhl et al., 1984).

Representation, Sampling and Scoring

Three key ingredients:

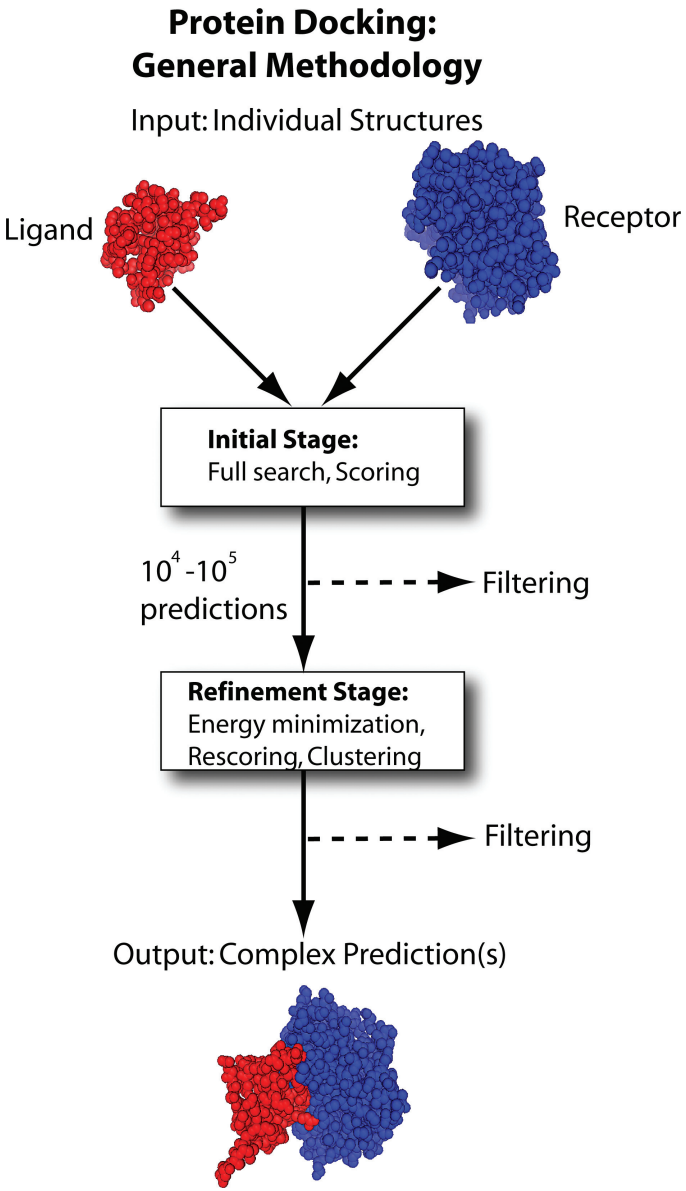
- *Representation of the system*
- *Global conformational space search*
- *Reranking of top solutions based on scoring function*

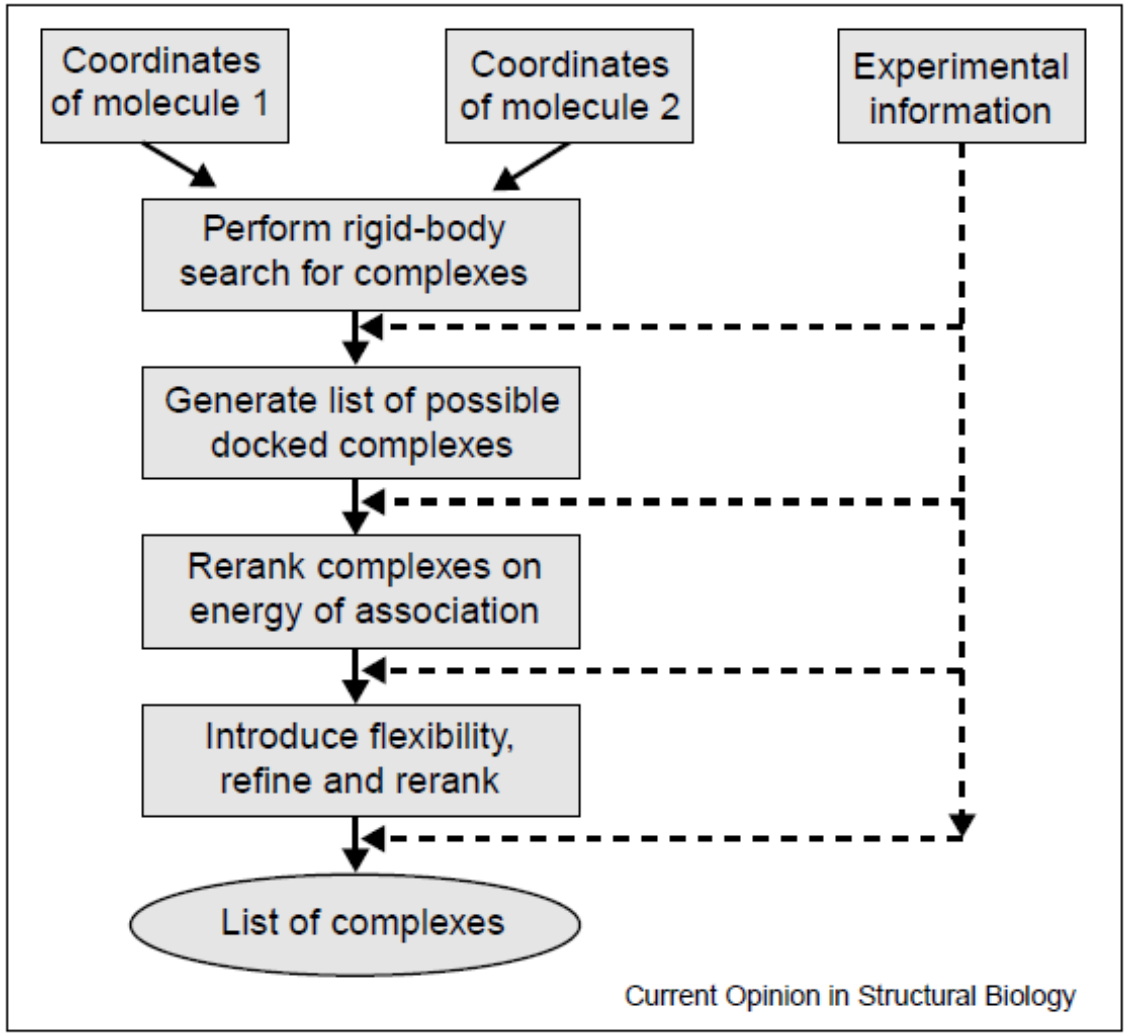
Similar steps as for protein folding

Reviews:

Graham R Smith and Michael J E Sternberg (Feb. 2002). In: *Curr. Opin. Struct. Biol.* 12.1

Inbal Halperin et al. (June 2002). In: *Proteins* 47.4



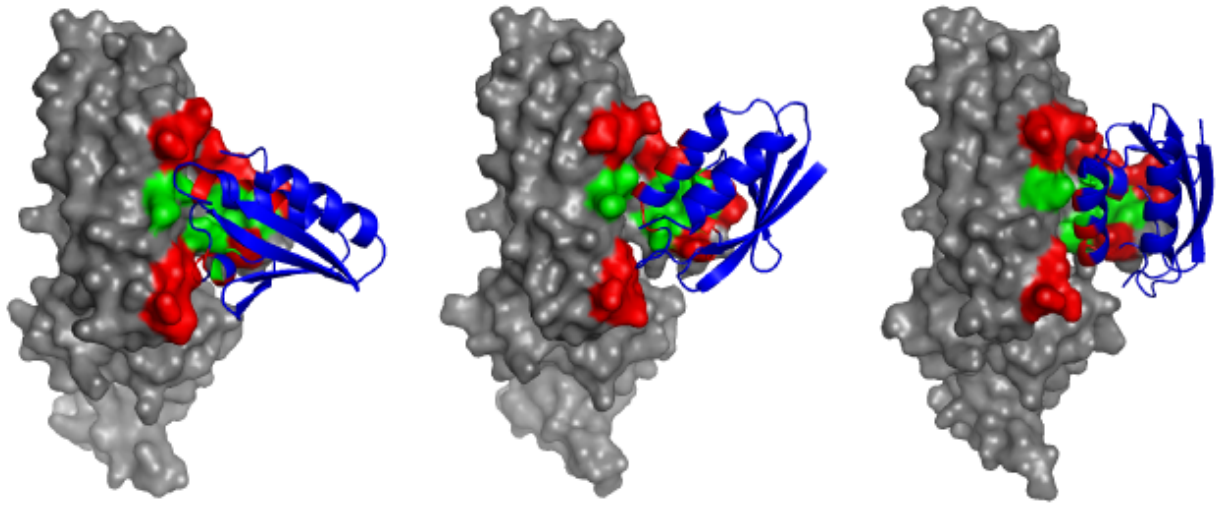


Graham R Smith and Michael J E Sternberg (Feb. 2002). In: *Curr. Opin. Struct. Biol.*

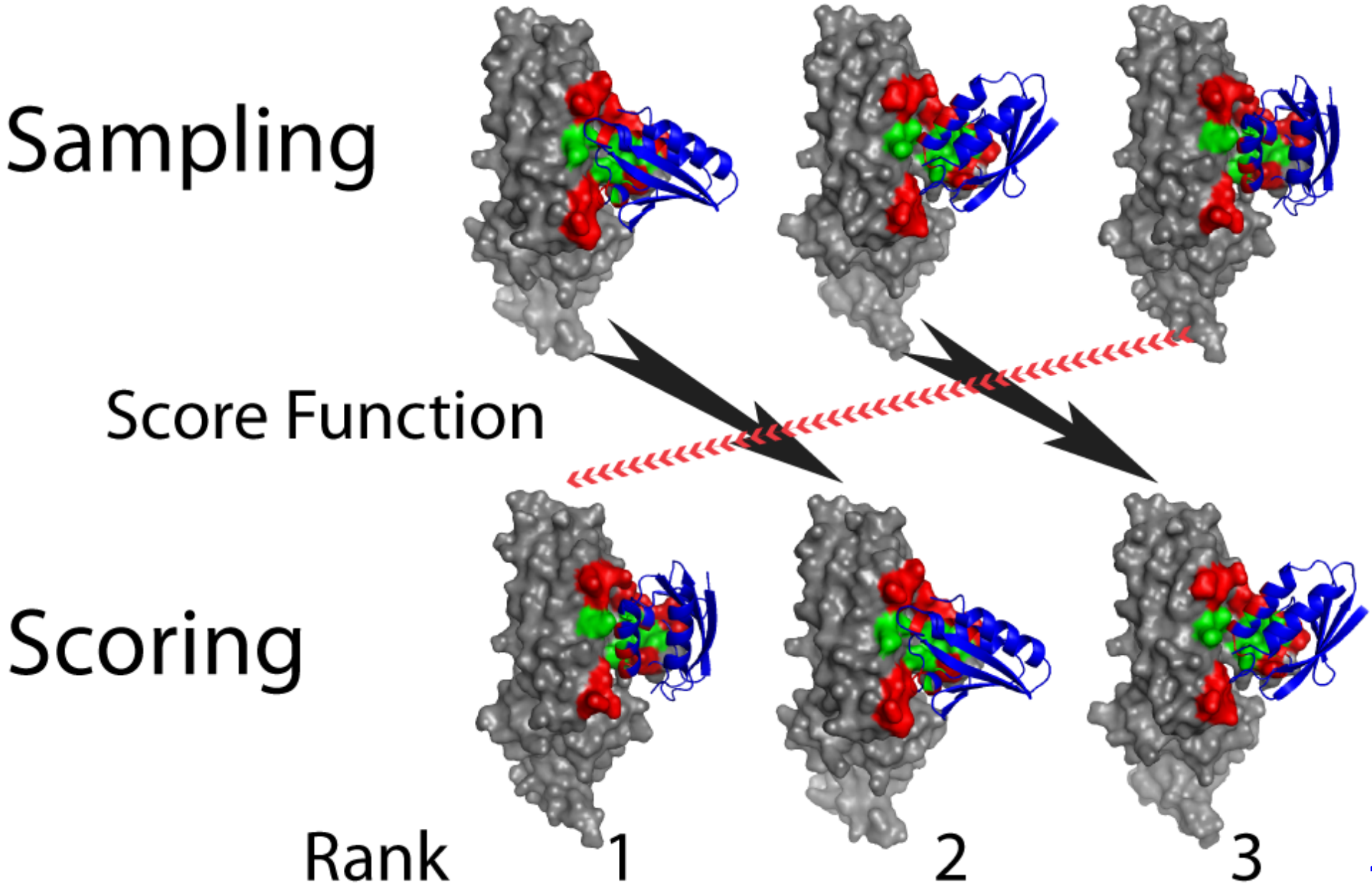
12.1

Sampling and Scoring

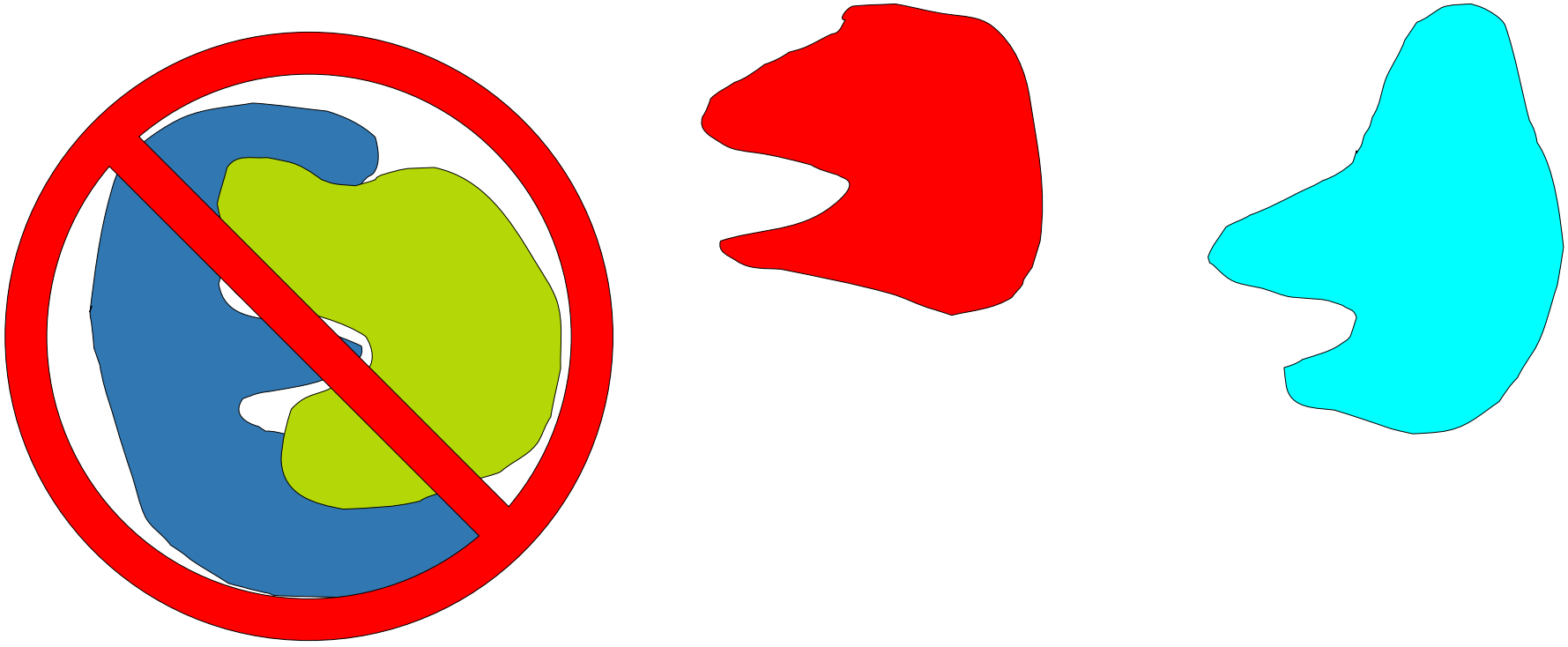
Sampling



Sampling and Scoring



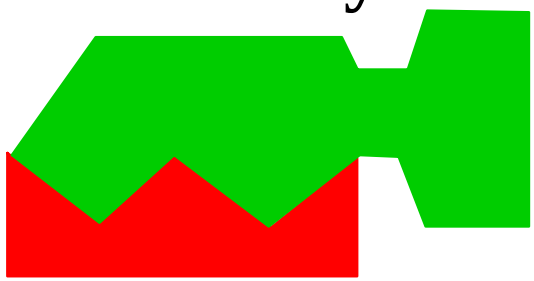
Lock and Key



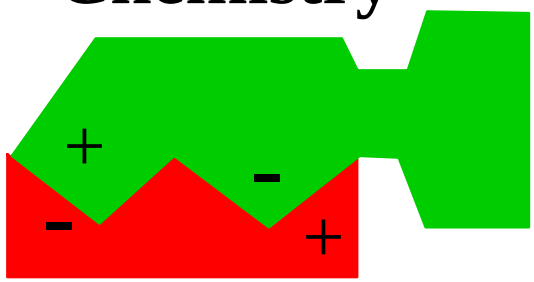
Source: Kohlbacher and Lenhof

Lock and Key

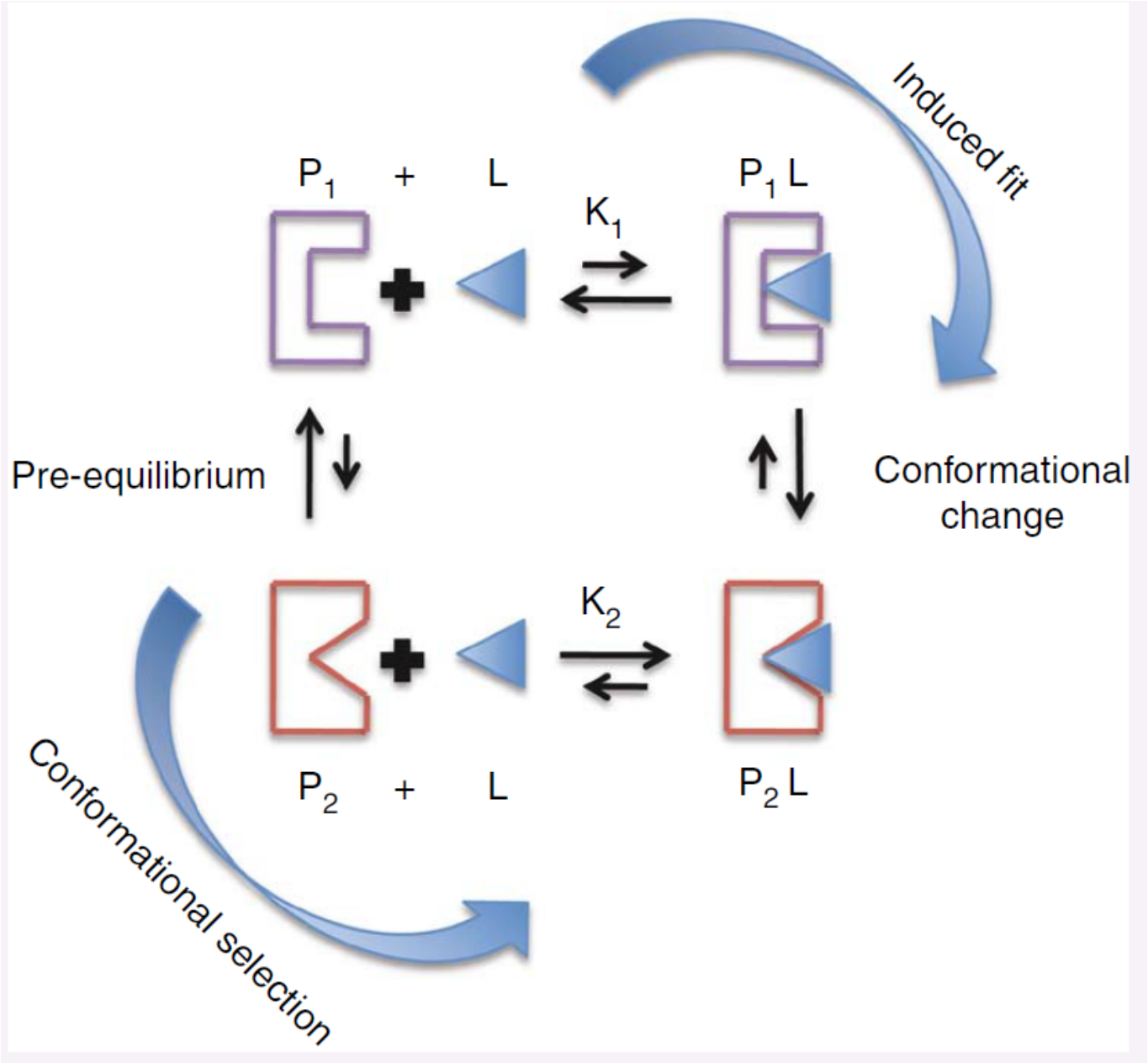
Geometry



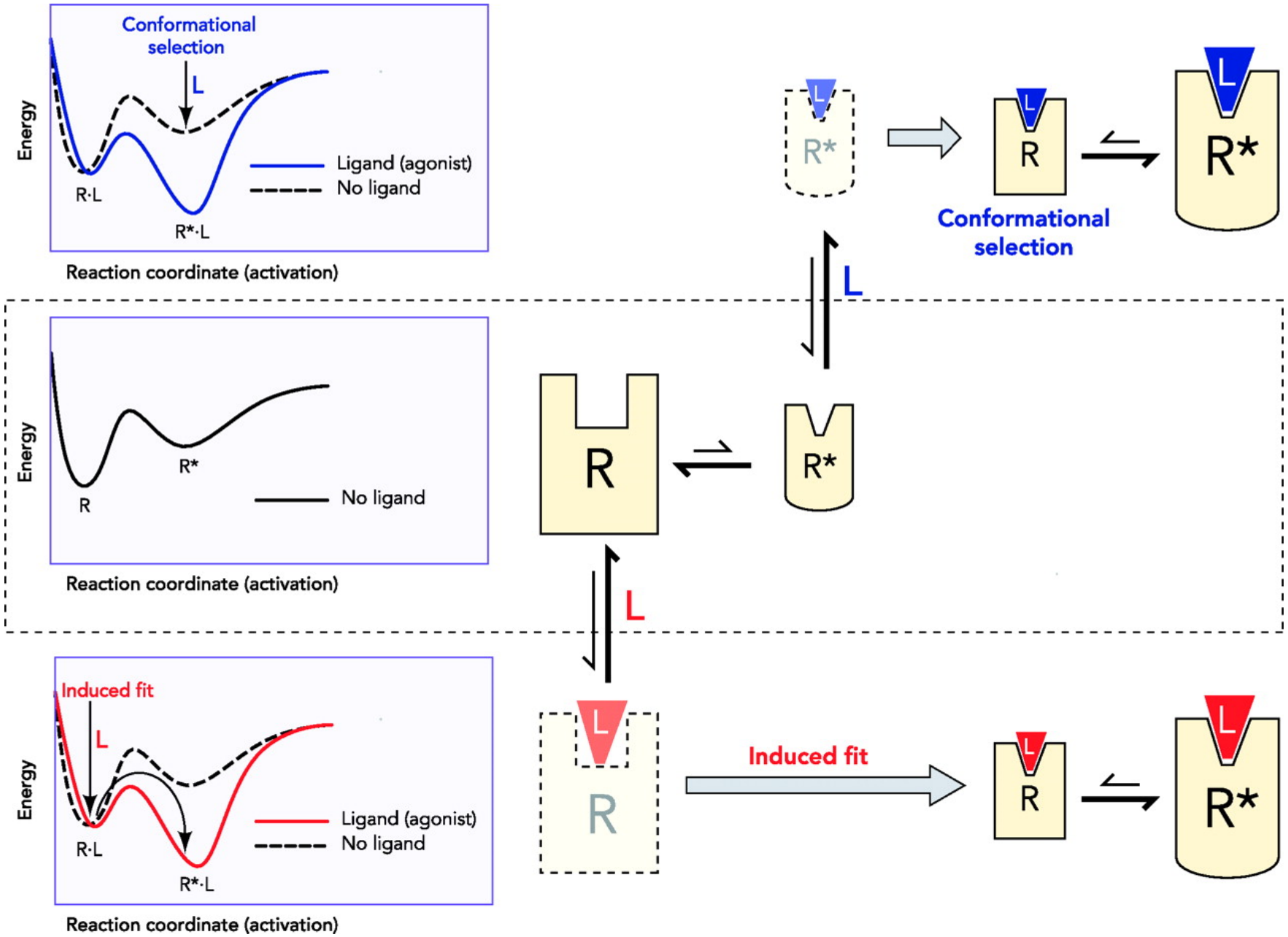
Chemistry



Source: Kohlbacher and Lenhof



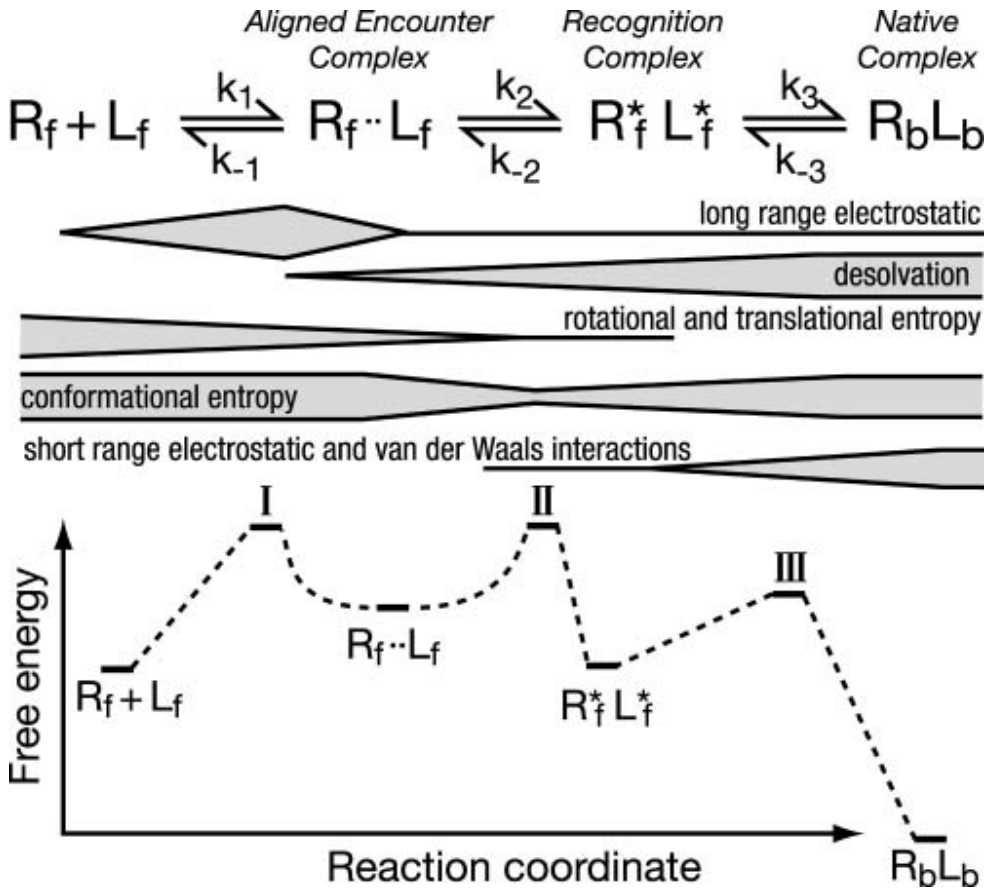
David D Boehr, Ruth Nussinov, and Peter E Wright (Nov. 2009). In: *Nat. Chem. Biol.*



Xavier Deupi and Brian K. Kobilka (Jan. 2010). en. In: *Physiology* 25.5

Flexible Protein Recognition

3-step mechanism of diffusion, free conformer selection, and refolding:



Raik Grünberg, Johan Leckner, and Michael Nilges (Dec. 2004). In: *Structure* 12.12

Enzyme / Inhibitor

Enzymes and their inhibitors have co-evolved to form an interface with a high degree of surface complementarity

Antibody / Antigen

The immune system produces many different antibodies in response to an antigen, some of which bind their respective epitopes quite well while others bind quite poorly.
Antibody => always the same binding site location
Antigen => Highly variable binding site locations

Protein-Protein Docking Benchmark 4.0

http://zlab.umassmed.edu/benchmark/
PDB => 1667 complex structures with unbound structures
=> 109 non-redundant complexes (according to SCOP families)
=> 176 unbound-unbound cases with reference complex structure

Table II
Statistics of the Three Classes of Difficulty in the Entire Benchmark 4.0 and the New Cases (in Parentheses)

	I-RMSD	f_{nat}	$f_{non\text{-}nat}$	Number
Rigid body	0.90 (1.12)	0.79 (0.80)	0.21 (0.19)	121 (33)
Medium	1.76 (1.86)	0.63 (0.66)	0.35 (0.27)	30 (11)
Difficult	3.76 (3.45)	0.51 (0.60)	0.51 (0.41)	25 (8)

52 enzyme-inhibitor, 25 antibody-antigen, 99 other functions
[Hwang et al., Proteins 2010]

Introduction

- What distinguishes the true complex structure from "false positives"?
- *Physical chemistry:* Complex structure with the lowest binding free energy is the one observed in nature.
- *Caveat:* relies on sufficiently complete sampling of conformation space

Prediction of Binding Free Energy

- Currently very difficult
- Would need to include entropic contributions and solvent effects
- Free energy prediction is also very difficult in:
  - Protein-ligand docking
  - Protein structure prediction

Prediction of Binding Free Energy

$$\Delta G_{binding} = \Delta G_{elec} + \Delta E_{vdW} + \Delta G_{des} + \Delta E_{int} - T\Delta S_{sc} - T\Delta S_{bb} \quad (1)$$

ΔG_{elec} electrostatic, ΔE_{vdW} van der Waals, ΔG_{des} desolvation, ΔE_{int} conformational changes upon binding
$-T\Delta S_{sc}$ and $-T\Delta S_{bb}$ entropy changes from side chain and backbone, respectively.

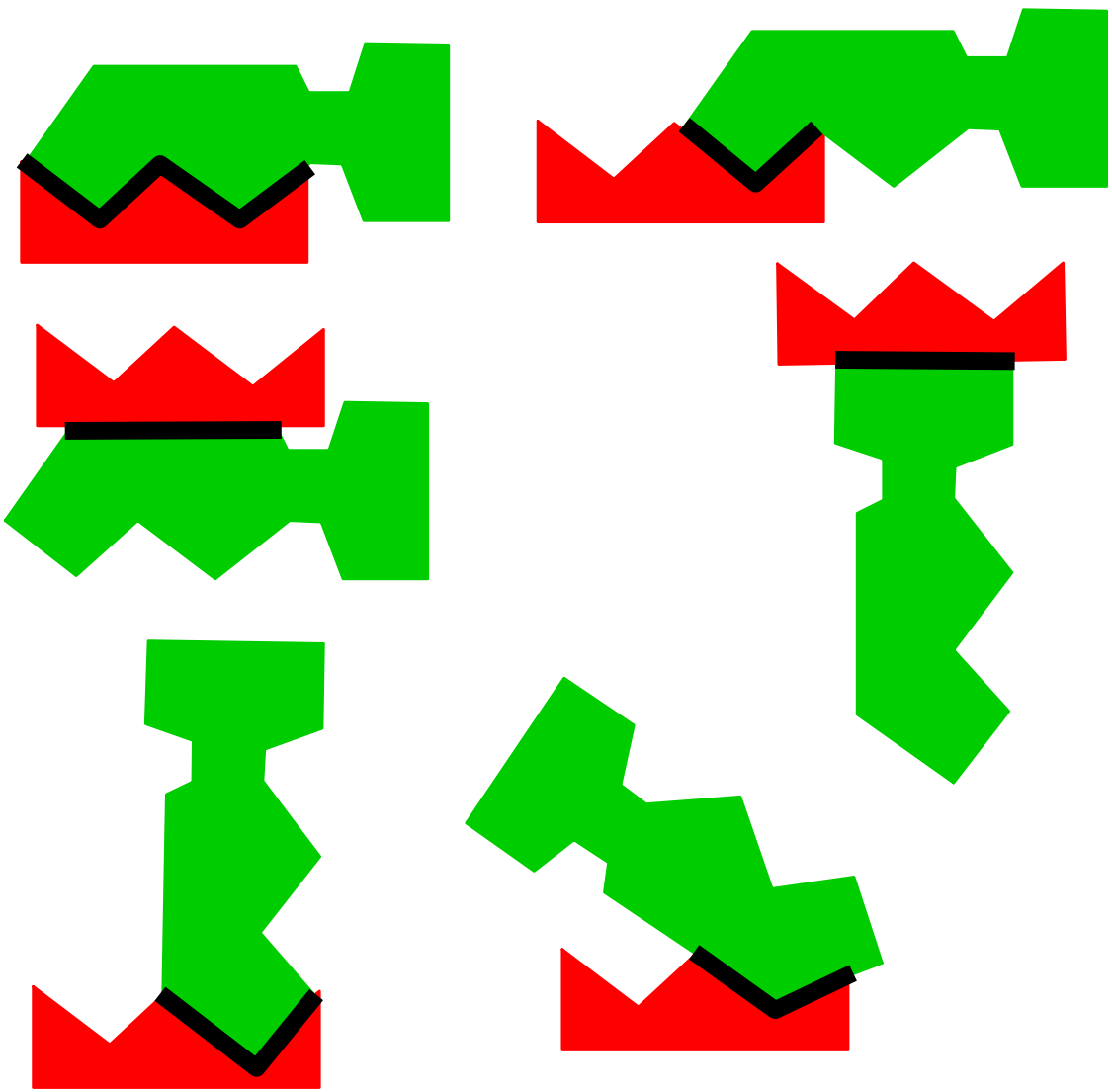
Brian Pierce and Zhiping Weng (Jan. 2007). en. In: *Computational Methods for Protein Structure Prediction and Modeling*. Biological and Medical Physics, Biomedical Engineering

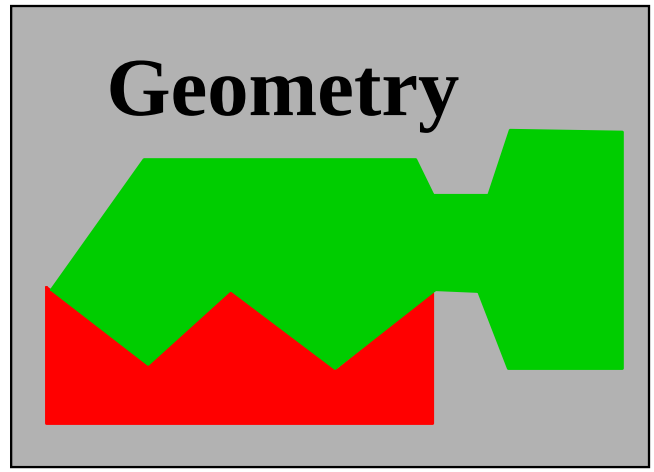
Alternative: Scoring Functions

- Geometry:
  - Lock and key principle
  - Large contact areas are favorable
  - Steric clashes / overlaps should be avoided
- Chemistry:
  - Models based on physicochemistry
  - Compromise between speed and accuracy

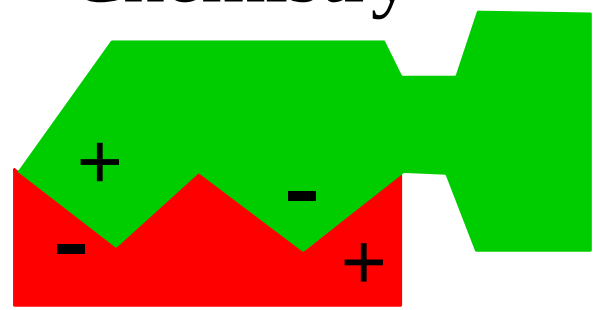
Scoring functions must be accurate and fast at the same time to evaluate serval billions of docking poses.
Scoring functions based only on geometry or only on chemistry are not successful in general.

Geometry and Chemistry



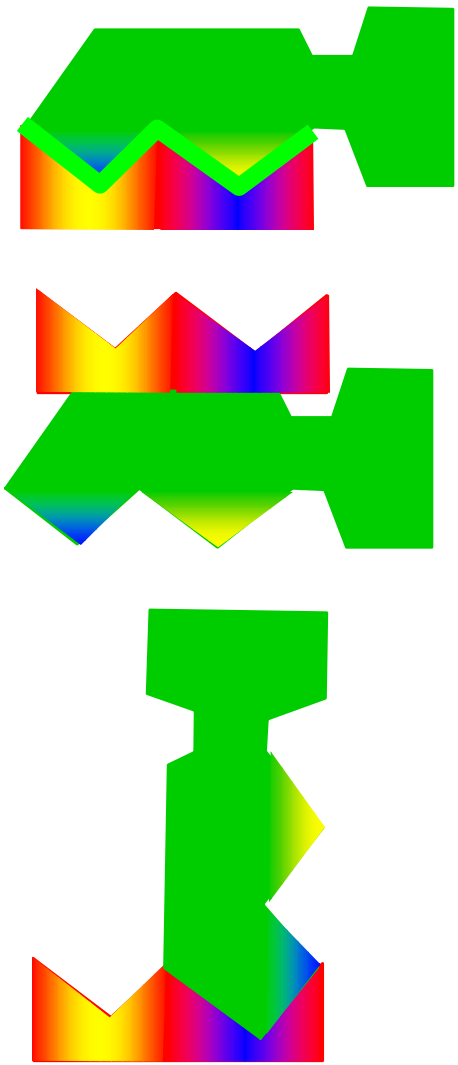


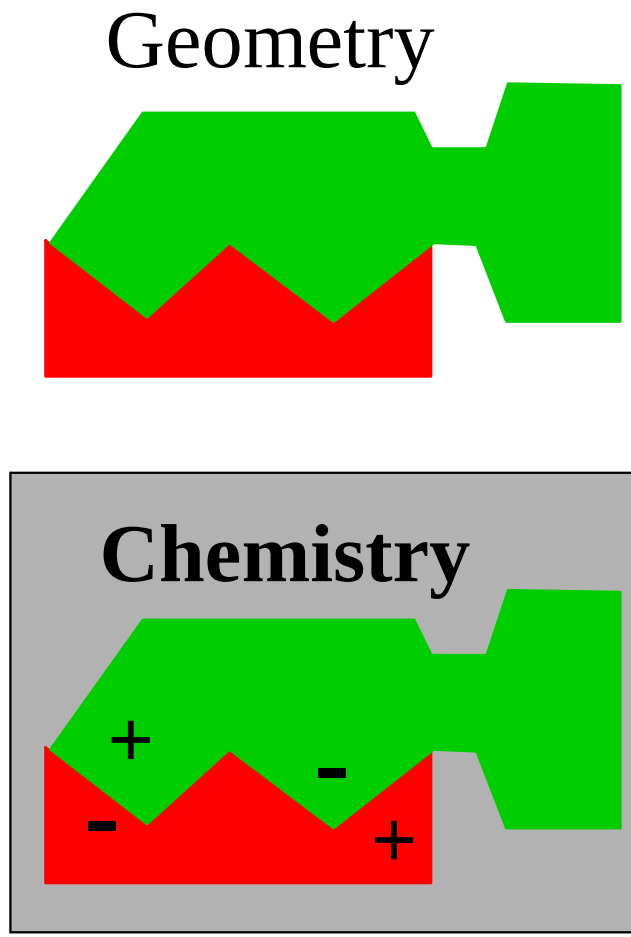
Chemistry



Source: Kohlbacher and Lenhof

Geometry and Chemistry





Source: Kohlbacher and Lenhof

Geometry

1. Steric complementarity of shapes
2. Buried surface area (BSA) = $SAS_A + SAS_B - SAS_{AB}$, typical values for complexes: 1200-2200 Å^2

Chemistry

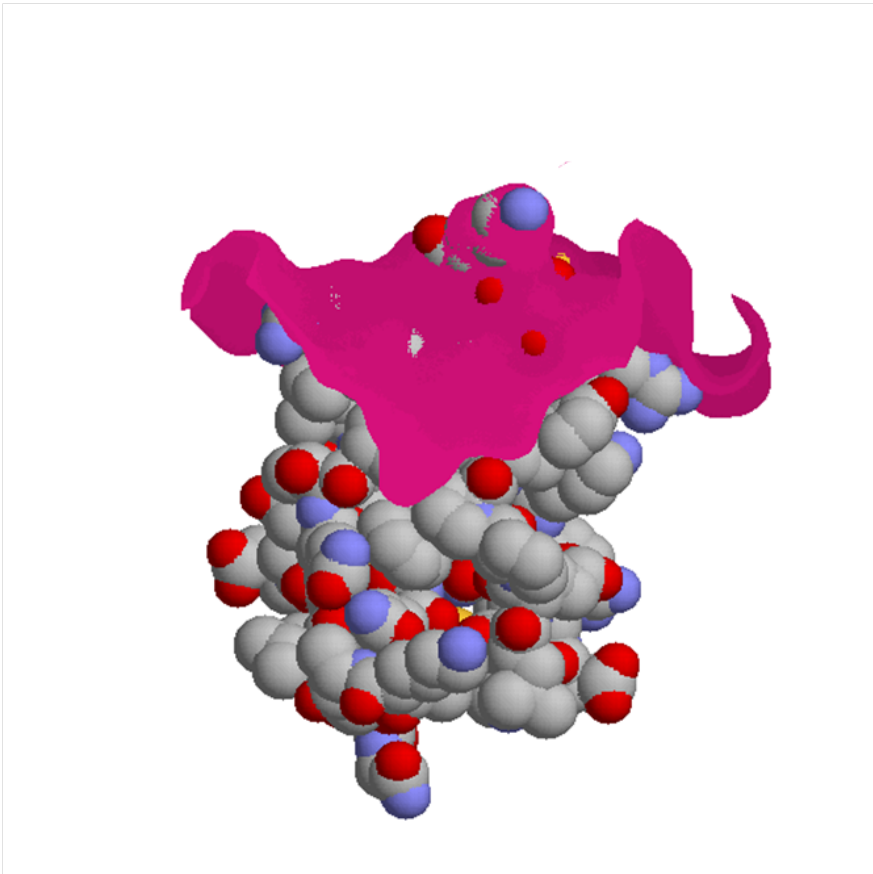
- Electrostatic interactions
- Hydrogen bonding
- *Desolvation*: Exclusion of the solvent from the interface => solvent entropy change

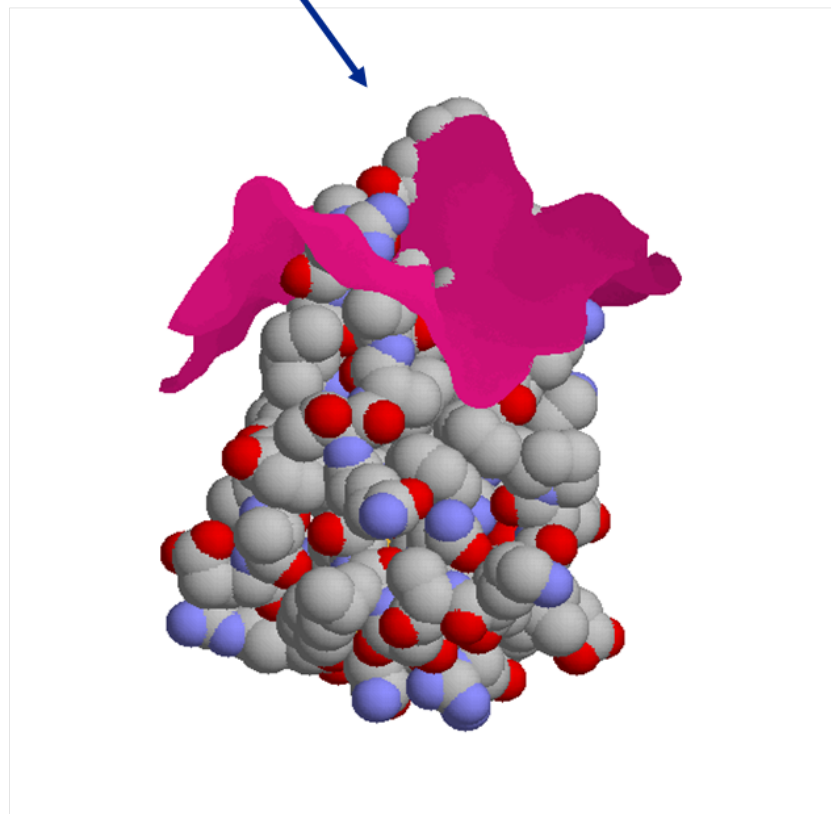
Categories of scoring functions

- *Knowledge-based*
- *Empirical*
- *Forcefield-based*

Irina S Moreira, Pedro A Fernandes, and Maria J Ramos (Jan. 2010). In: *J Comput Chem* 31.2

Bound VS unbound

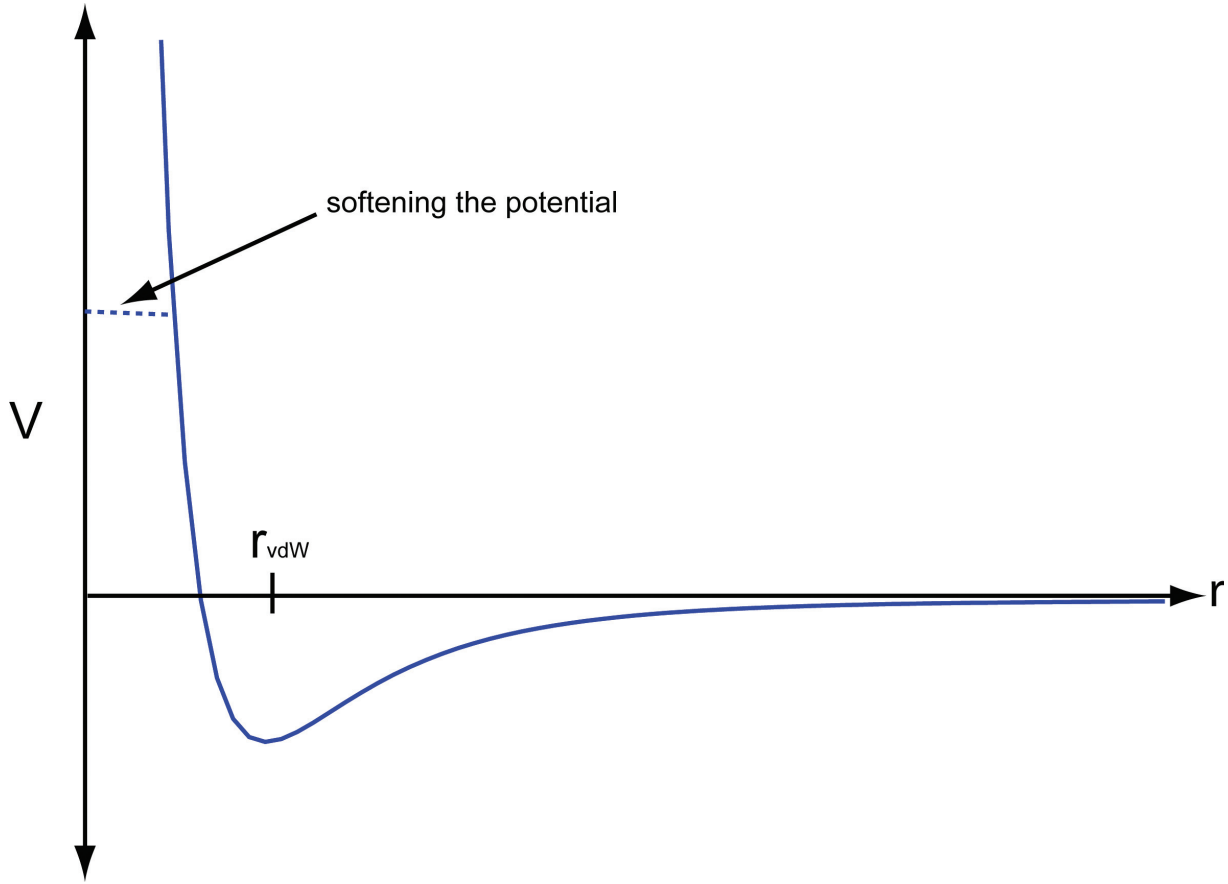




Kallikrein A/trypsin inhibitor complex (PDB codes 2KAI,6PTI)

Soft van der Waals

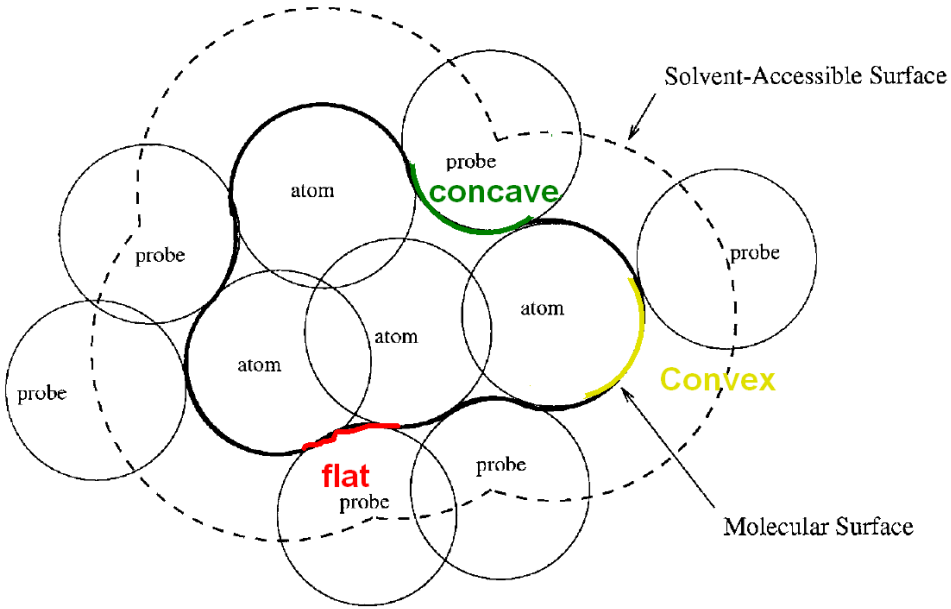
$$V_{L-J} = A/r^{12} - B/r^{6} \tag{2}$$

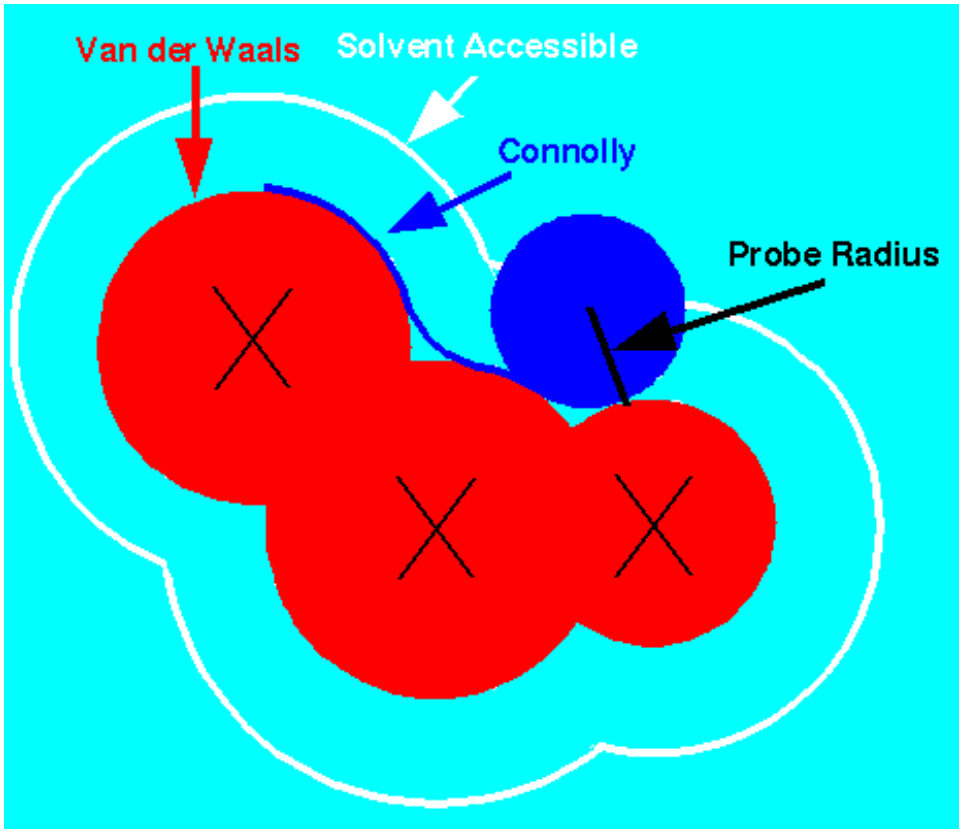


Brian Pierce and Zhiping Weng (Jan. 2007). en. In: *Computational Methods for Protein Structure Prediction and Modeling*. Biological and Medical Physics, Biomedical Engineering

Solvent accessible surface - SAS

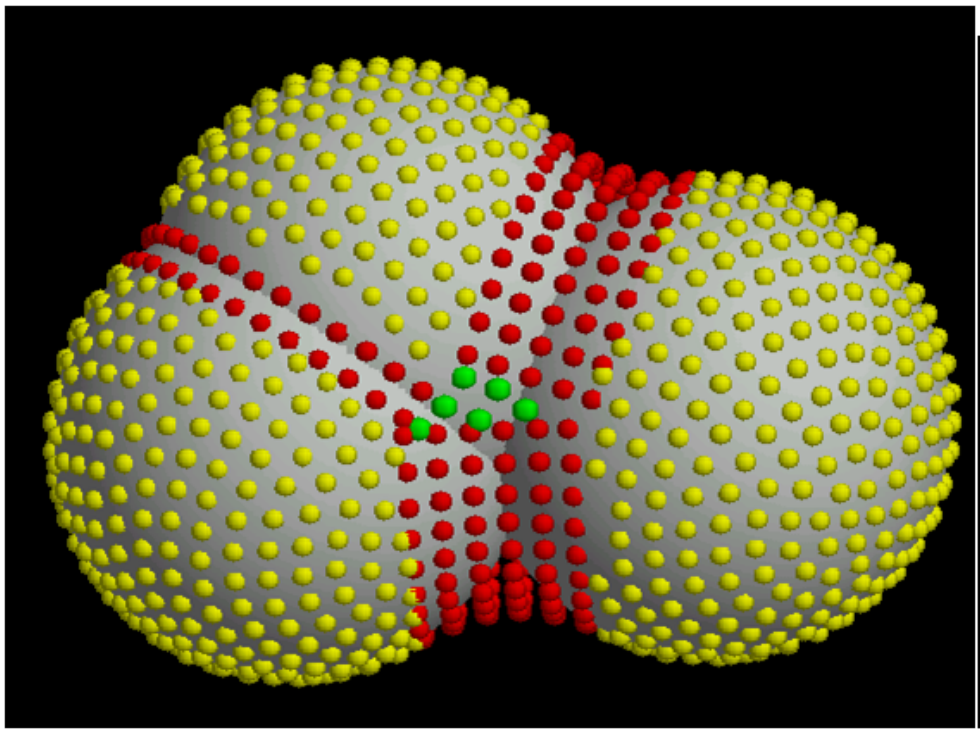
Connolly's MS (molecular surface) algorithm



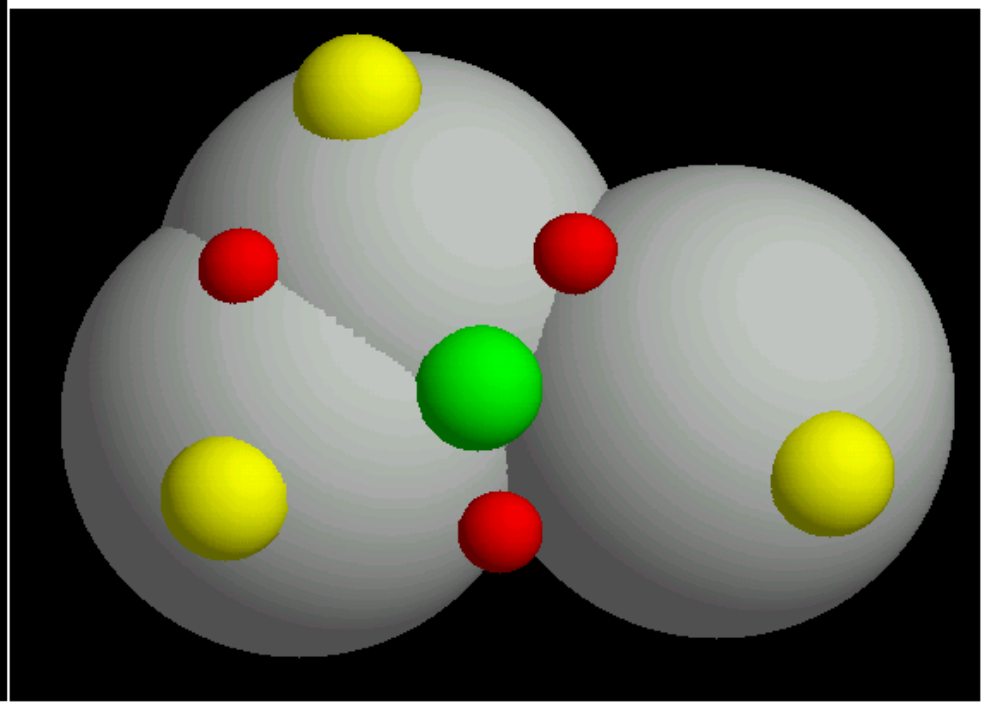


Cai 1998 / http://www.simbiosys.ca/sprout/eccc/cangaroo.html

Dot surface VS critical points



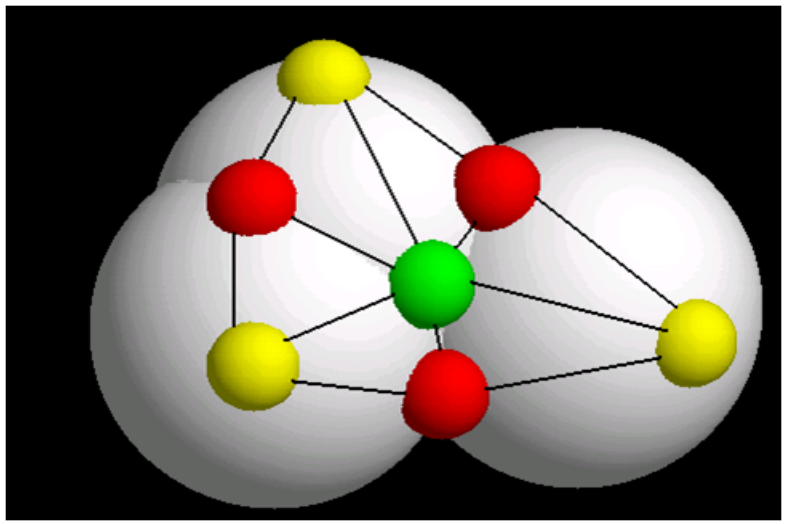
(a) dense, Connolly

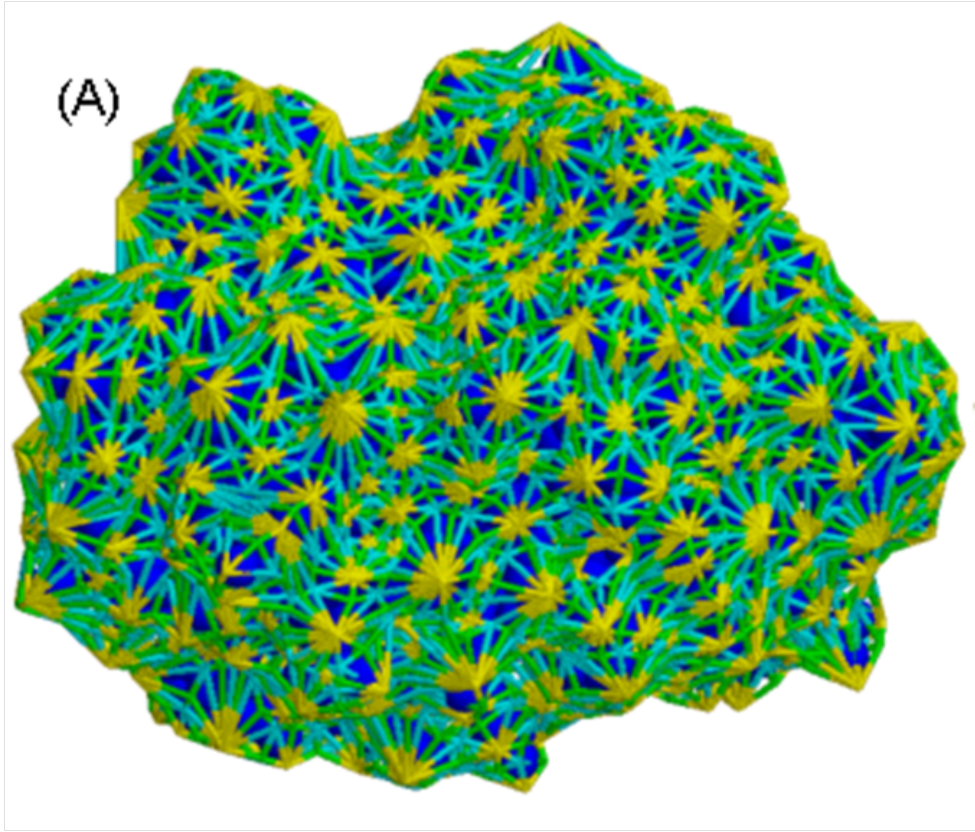


(b) sparse, Lin et al. 1994

green = concave, yellow = convex, red = flat

Topological graph G_{top}





Color code of the right figure: yellow = knob, cyan = hole, green = flat, dark blue = protein surface
http://bioinfo3d.cs.tau.ac.il/Education/Workshop02a/

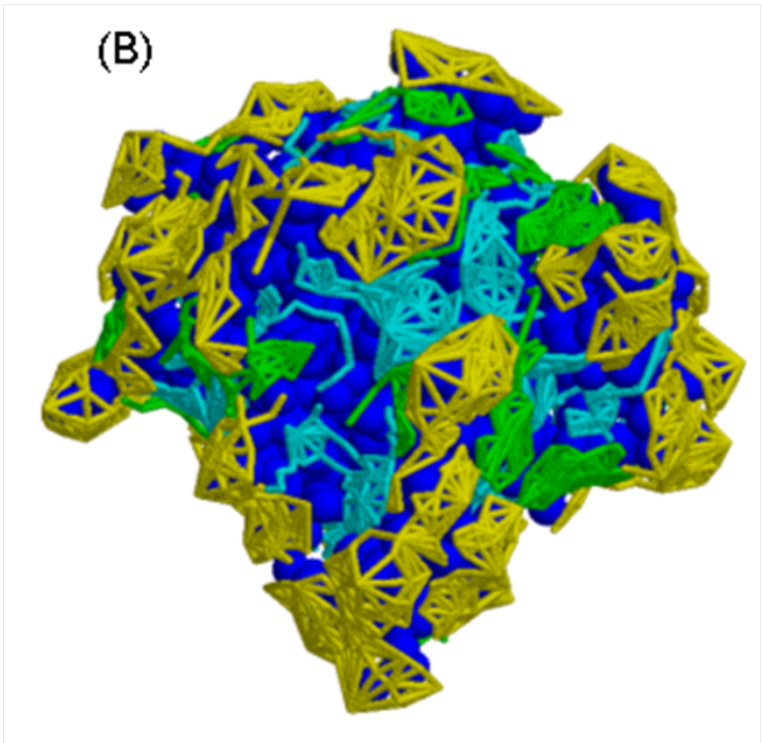
Group critical points as patches

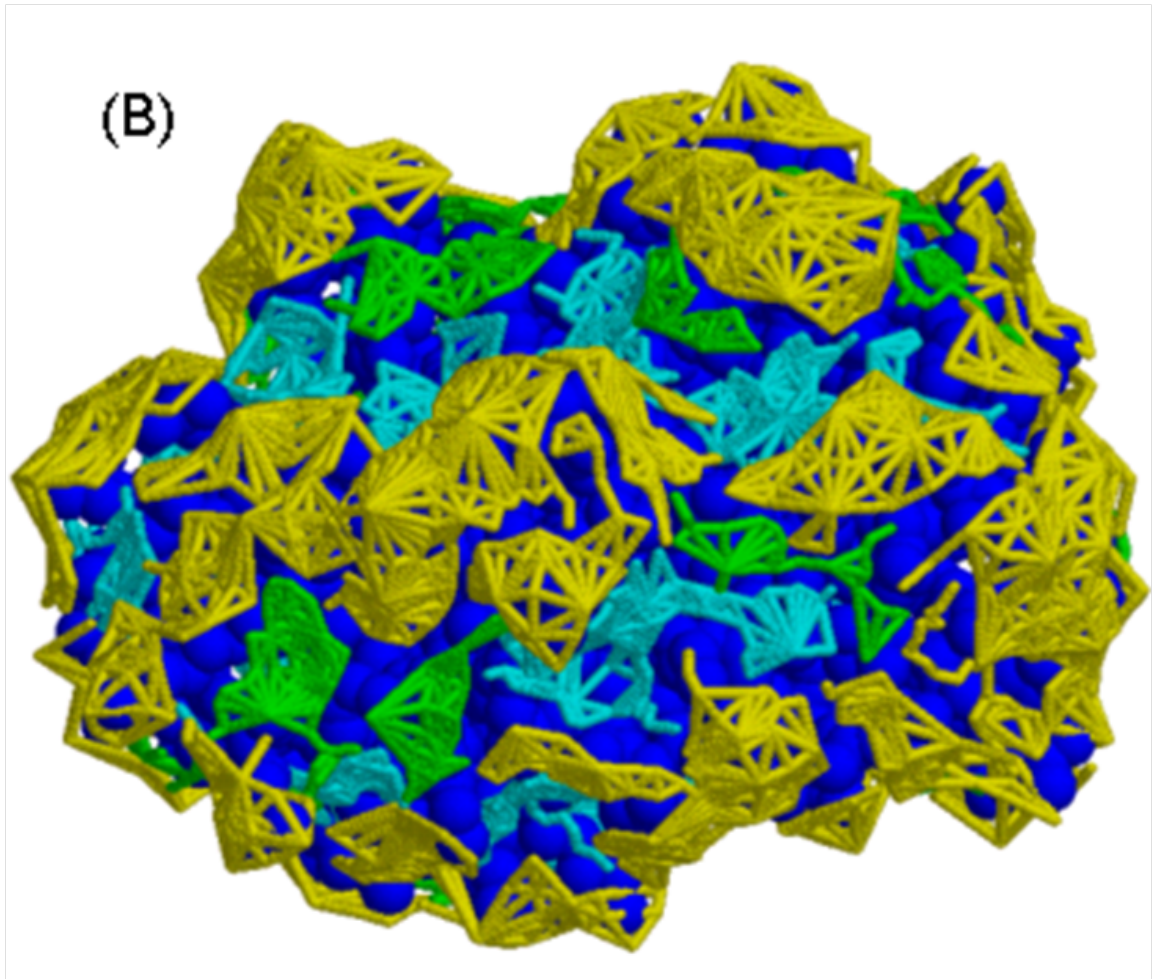
Goal: divide the surface into connected, non-intersecting, equal sized patches of critical points with similar curvature.

- *connected* the points of the patch correspond to a connected sub-graph of G_{top}.
- *similar curvature* all the points of the patch correspond to only one type: knobs, flats or holes.
- *equal sized* to assure better matching we want shape features of almost the same size.

http://bioinfo3d.cs.tau.ac.il/Education/Workshop02a/

Group critical points as patches





yellow = knob, cyan = hole, green = flat, dark blue = protein surface
http://bioinfo3d.cs.tau.ac.il/Education/Workshop02a/

Surface Patch Matching

Knob <-> hole patches and flat patches <-> any patch

1. *Single Patch Matching*: One patch of the receptor with one patch of the ligand, for small ligands
2. *Patch-Pair Matching*: Two patches of the receptor with two patches of the ligand, for protein-protein complexes

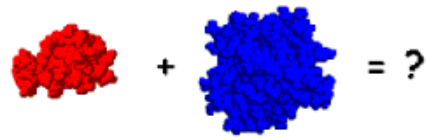
Match critical points within patches by computer vision techniques:

- Geometric Hashing
- Pose Clustering

Dina Duhovny, Ruth Nussinov, and Haim J. Wolfson (2002). In: *In WABI '02: Proceedings of the Second International Workshop on Algorithms in Bioinformatics*

Surface Patch Matching

PATCHDOCK



Molecular Docking Algorithm Based on Shape Complementarity Principles

[About PatchDock] [Web Server] [Download] [Help] [FAQ] [References]

Type PDB codes of receptor and ligand molecules or upload files in PDB format

Receptor Molecule:		(PDB:chainId e.g. 2kai:AB) **or** upload file:	Parcourir...
Ligand Molecule:		(PDB:chainId e.g. 2kai:I) **or** upload file:	Parcourir...
e-mail address:		(the results are sent to this address)	
Clustering RMSD:	4.0		
Complex Type:	Default	Be sure to give receptor and ligand in the corresponding order!	

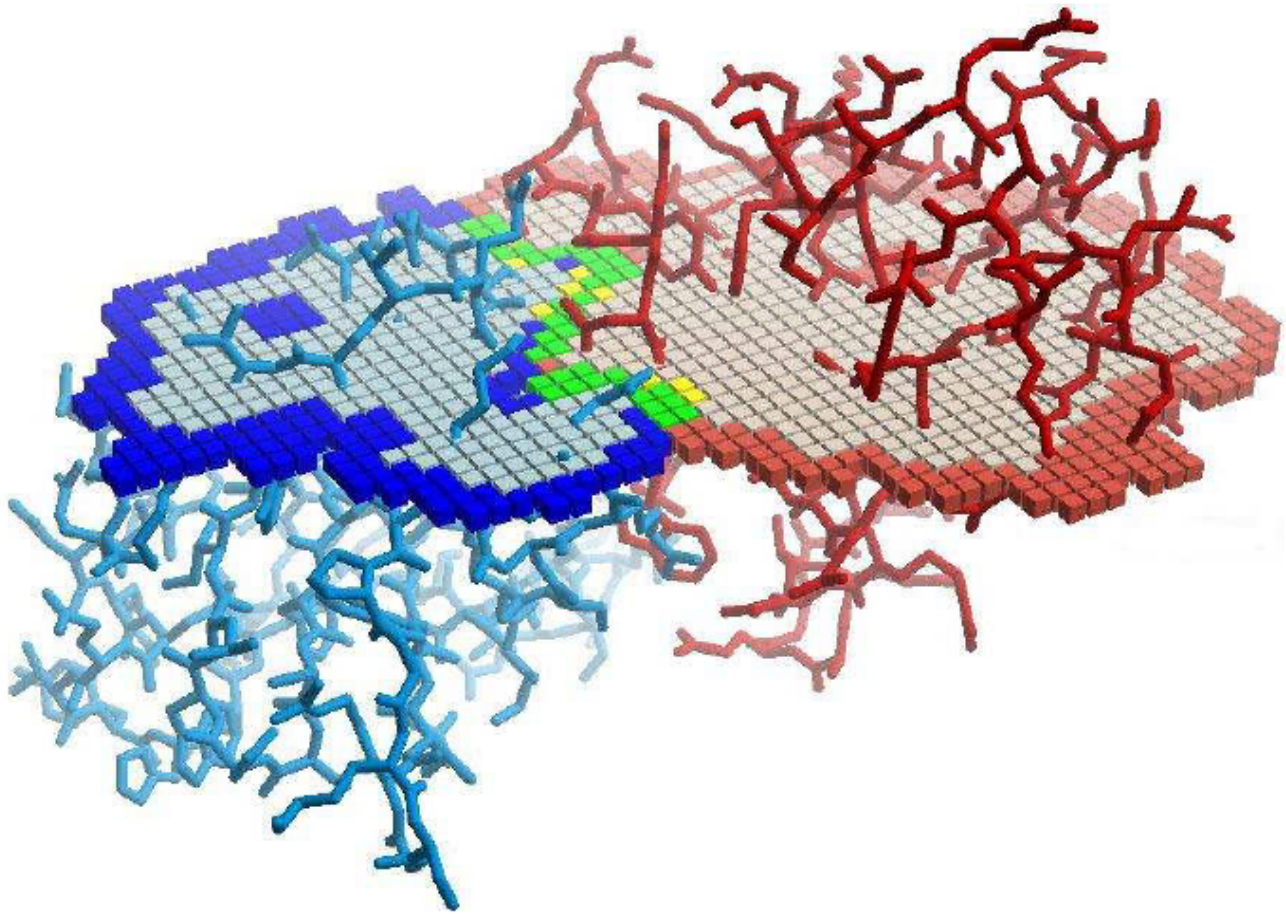
Submit Form Clear

Advanced Options:
[Show][Hide]

FireDock - Fast Interaction Refinement in Molecular Docking
SymmDock - An Algorithm for Prediction of Complexes with C_n Symmetry

Beta 1.3 Version, Contact: duhovka@gmail.com

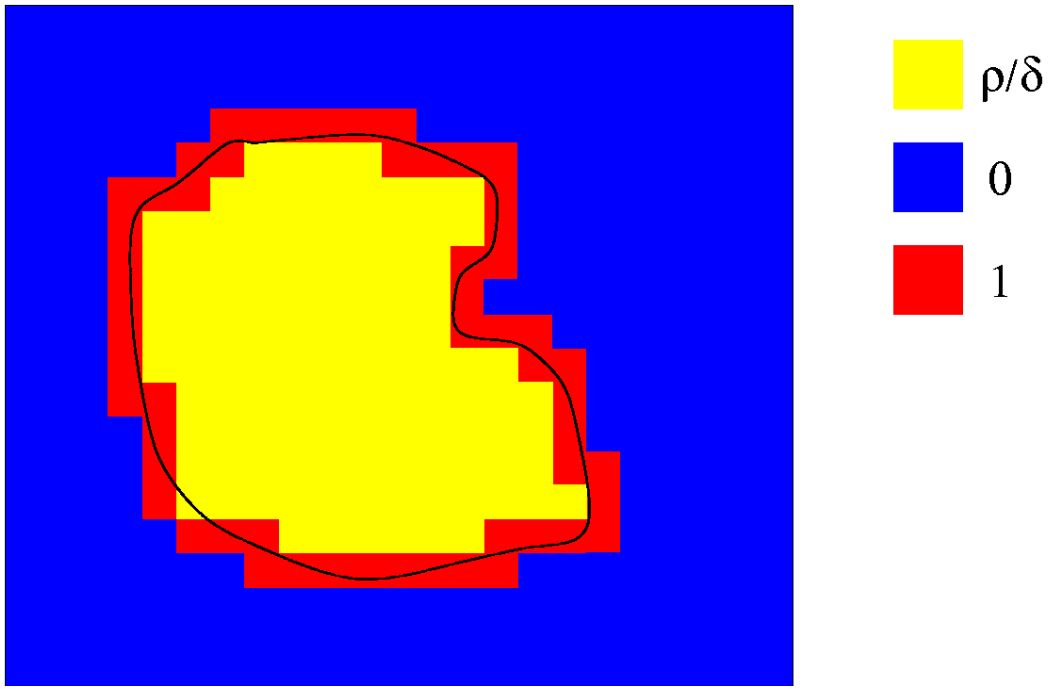
3D grid



Ludwig Krippahl, José J Moura, and P N Palma et al. (June 2000). In: *Proteins* 39.4 P Nuno Palma (July 2003). In: *Proteins* 52.1

Katchalski-Katzir et al., PNAS 1992

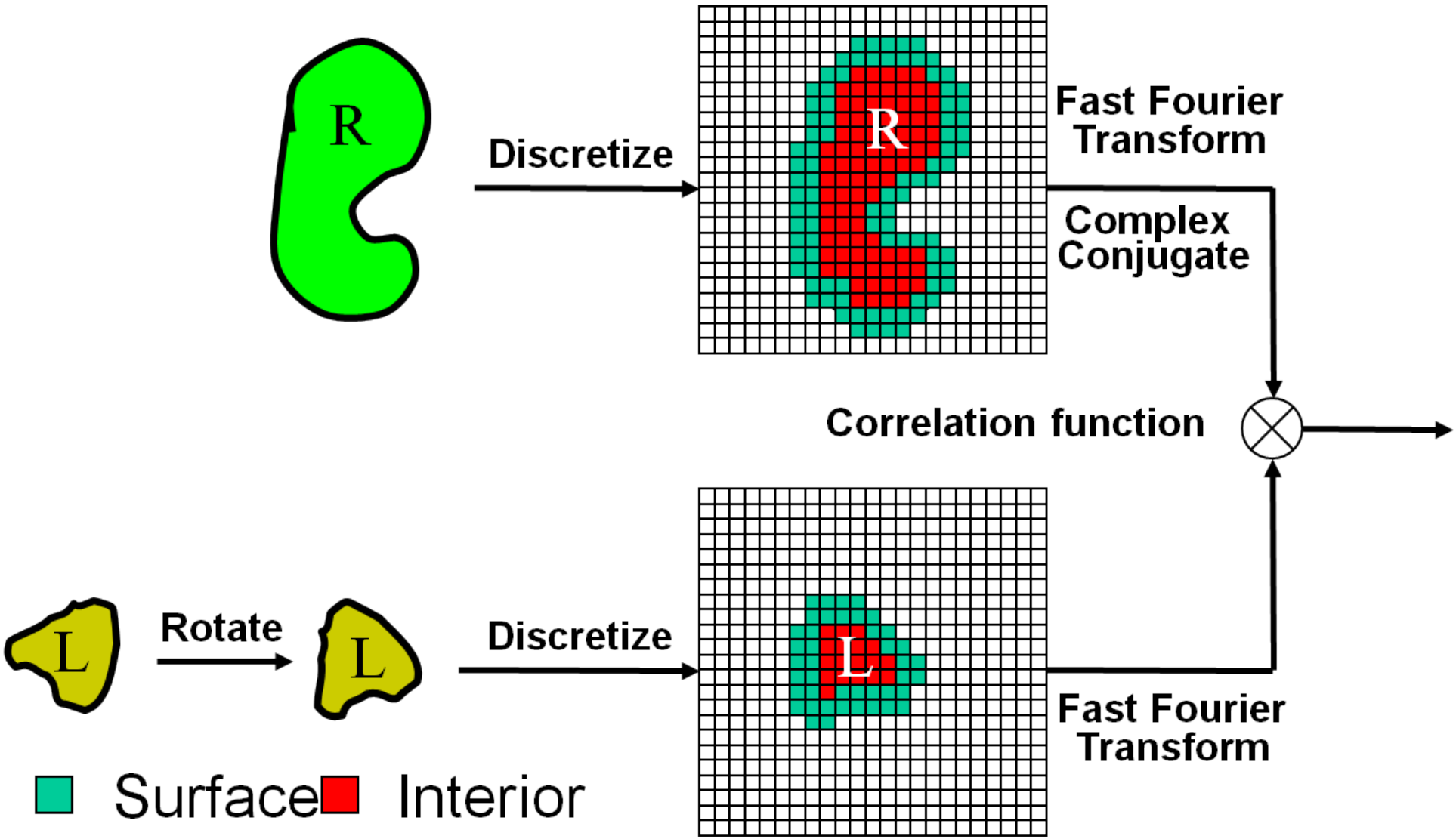
- Protein on grid
- Assign values
  - $a_{i,j,k}$ =
    - 1 at the surface of A
    - $\rho << 0$ inside A
    - 0 outside
  - $b_{i,j,k}$ =
    - 1 at the surface of B
    - $\delta > 0$ inside B
    - 0 outside B



A \ B	inside	surface	outside
inside	$\rho^* \delta < 0$	$\rho < 0$	0
surface	$\delta > 0$	1	0
outside	0	0	0

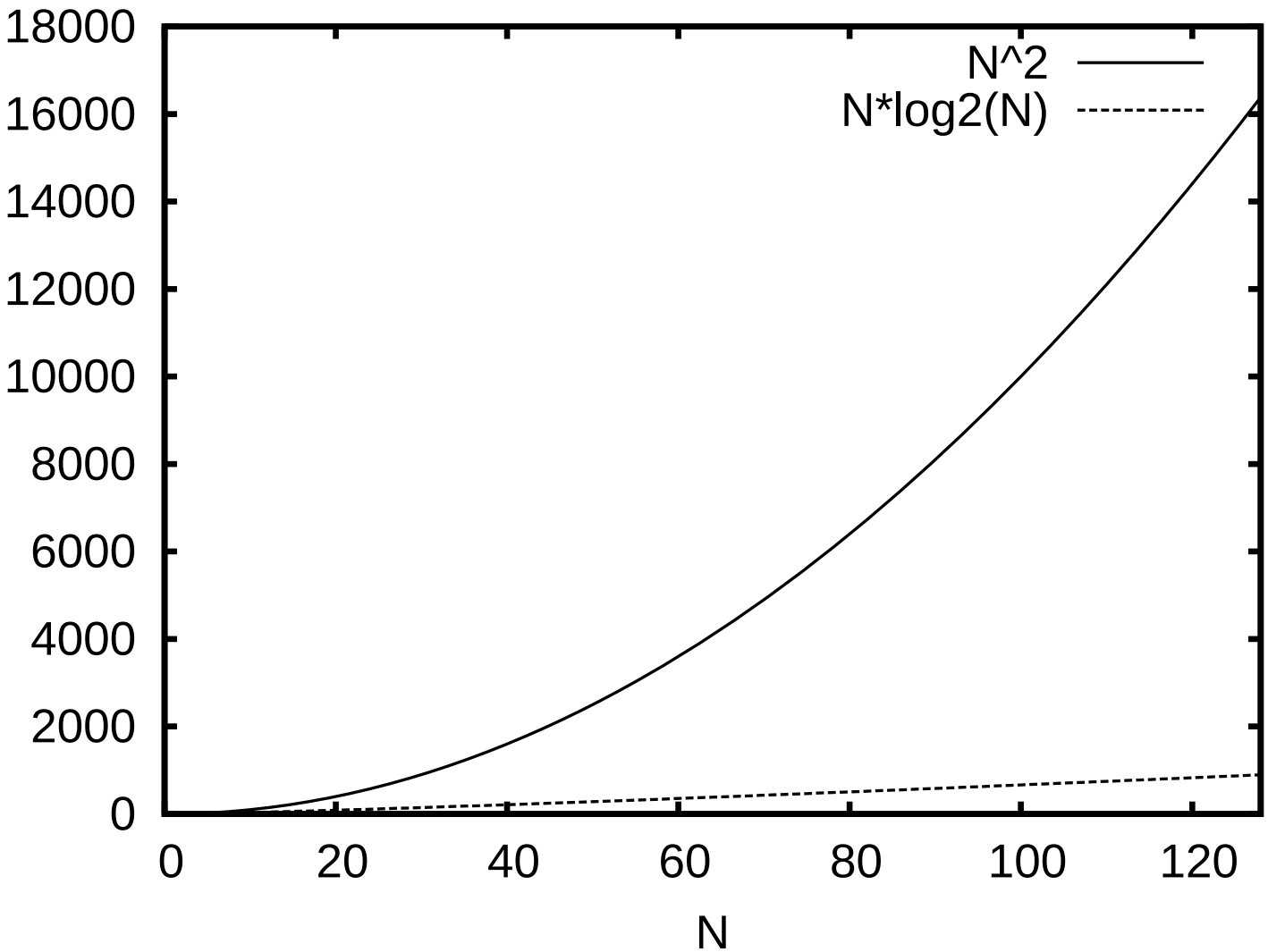
Source: Kohlbacher and Lenhof

Discrete Fast Fourier Transform

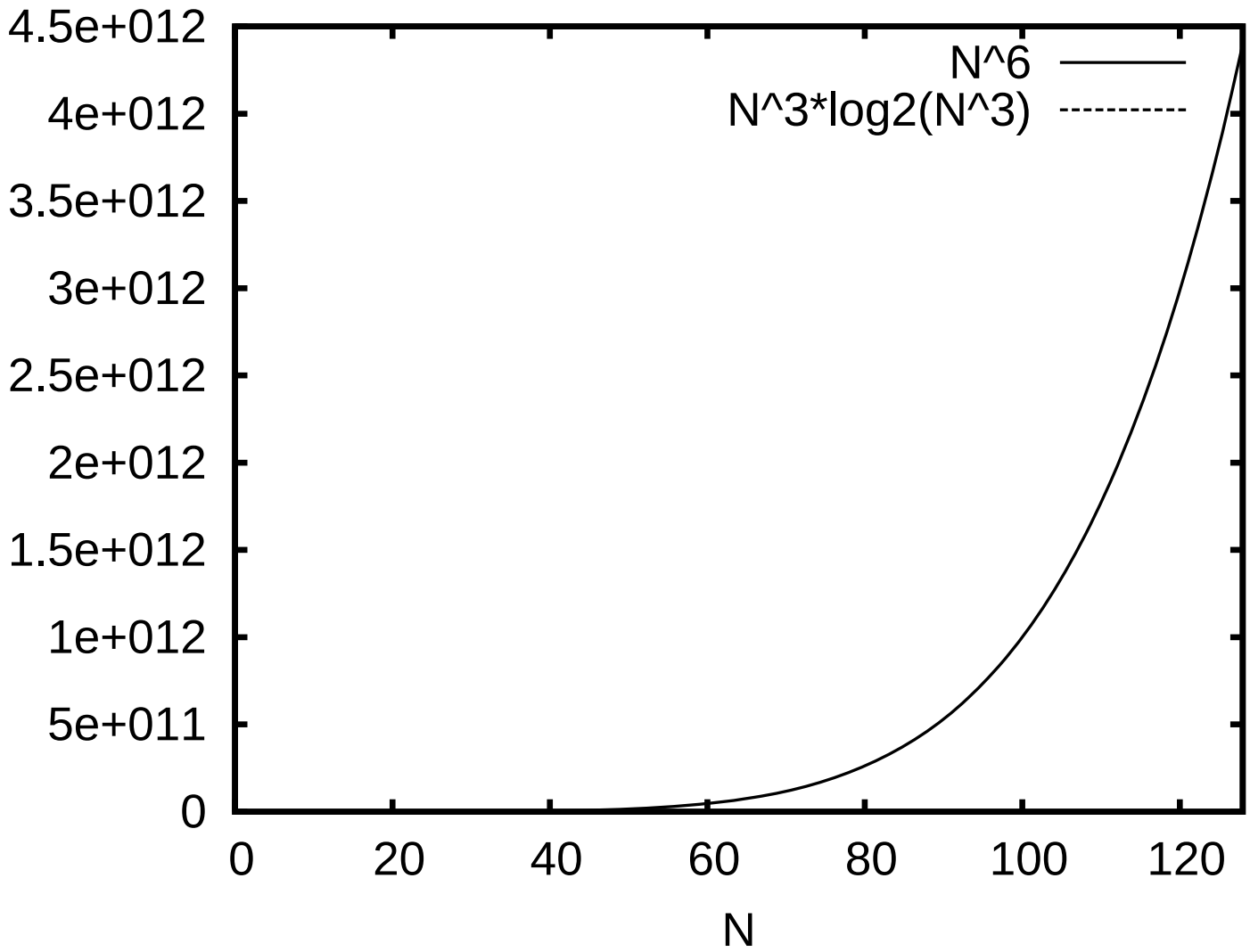


Source: Rong Chen

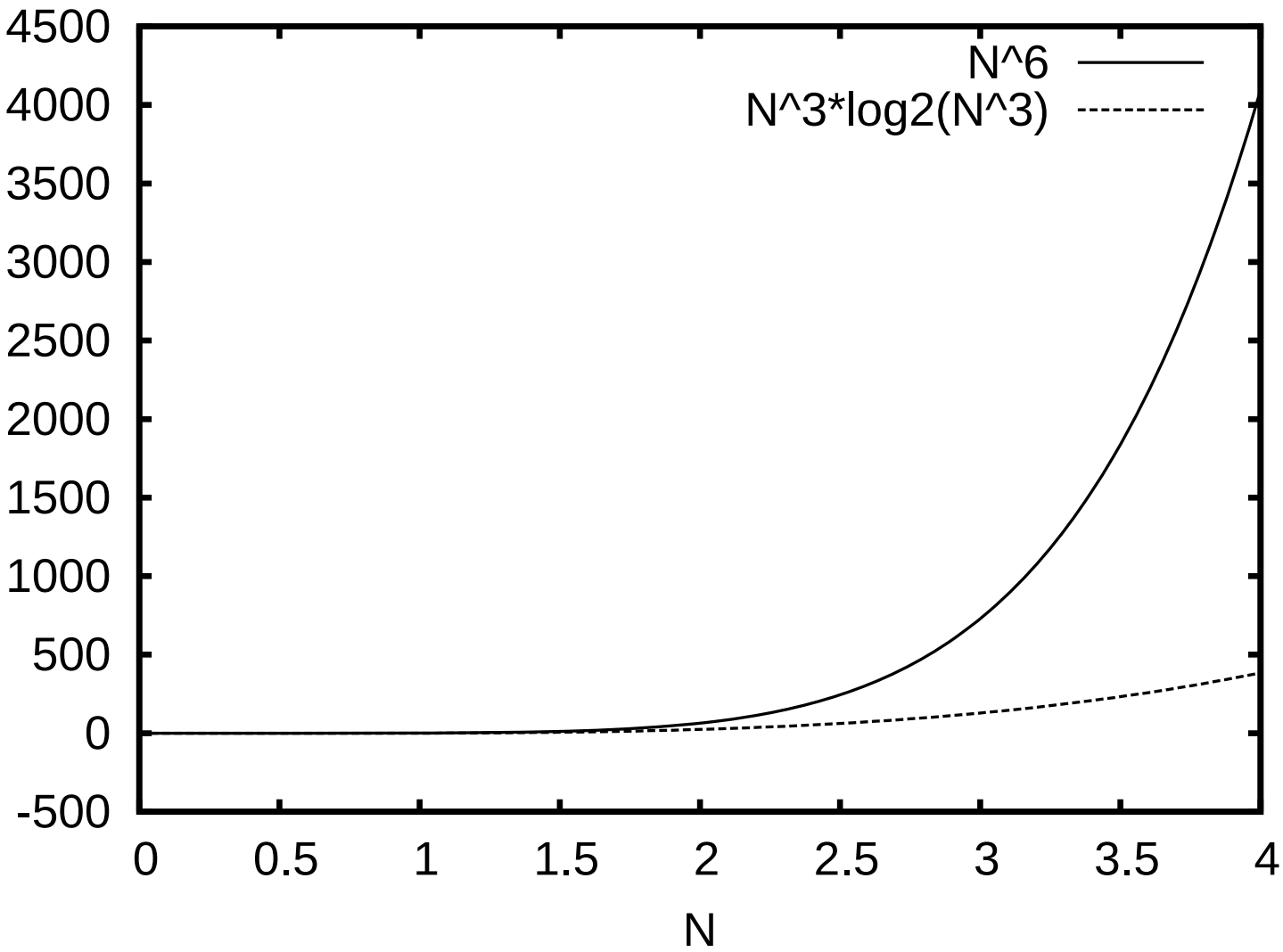
FFT speedup - 1D



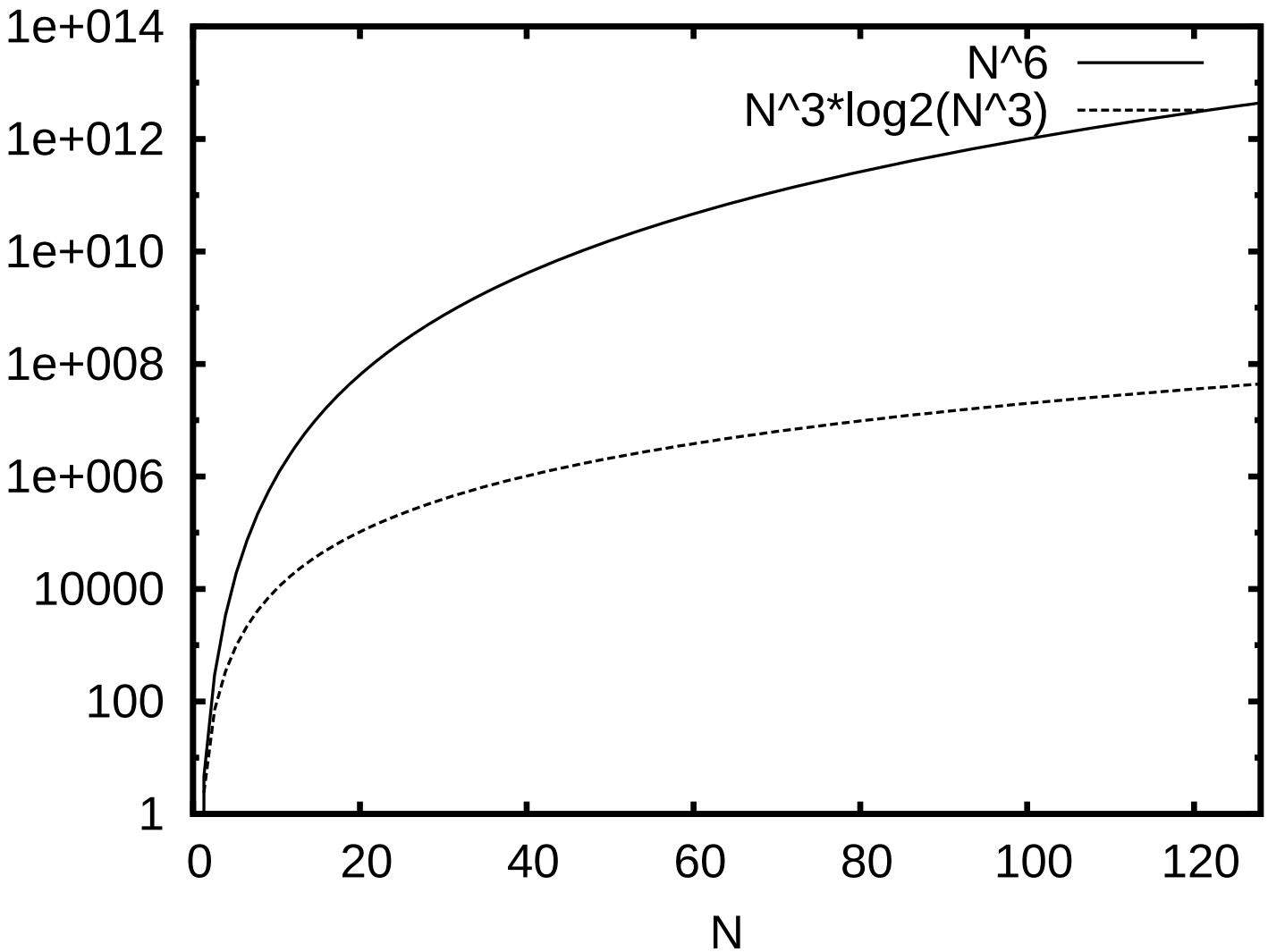
FFT speedup - 3D



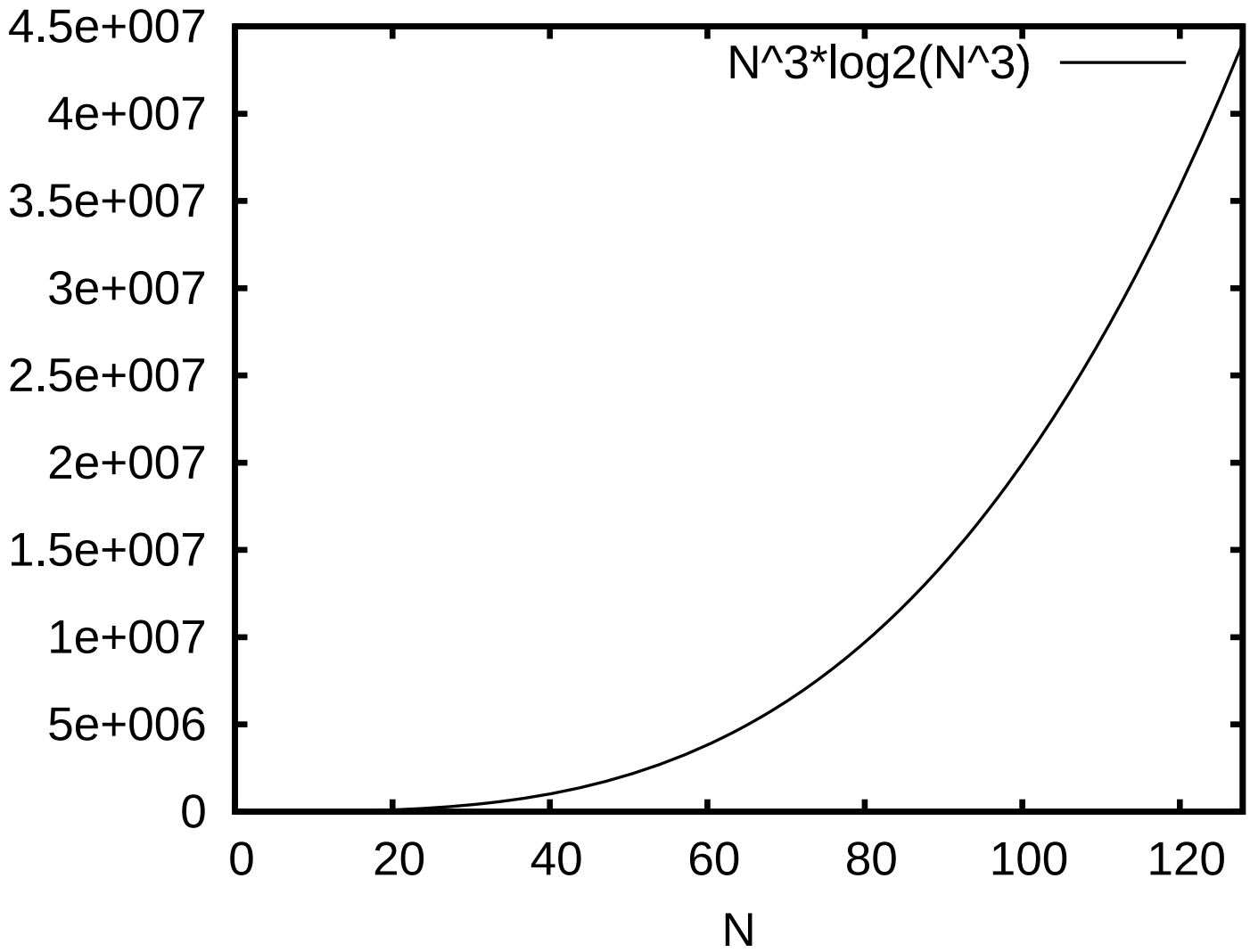
FFT speedup - 3D



FFT speedup - 3D



FFT speedup - 3D



ZDOCK: a FFT docking program

- Grid spacing: 1.2 Å
- Grid points N = 128 for the largest protein (about 150 Å cube side length), otherwise N = 100
- 128^3 = 2 million grid points => 2 million different translation vectors (α, β, γ)
- Without FFT => $128^6 = 4.4 \cdot 10^{12}$ = 4400 billion elementary operations (addition or multiplication)
- With FFT => $128^3 \cdot log_2(128^3) = 2.1 \cdot 10^6 \cdot 21$ = 44 million elementary operations

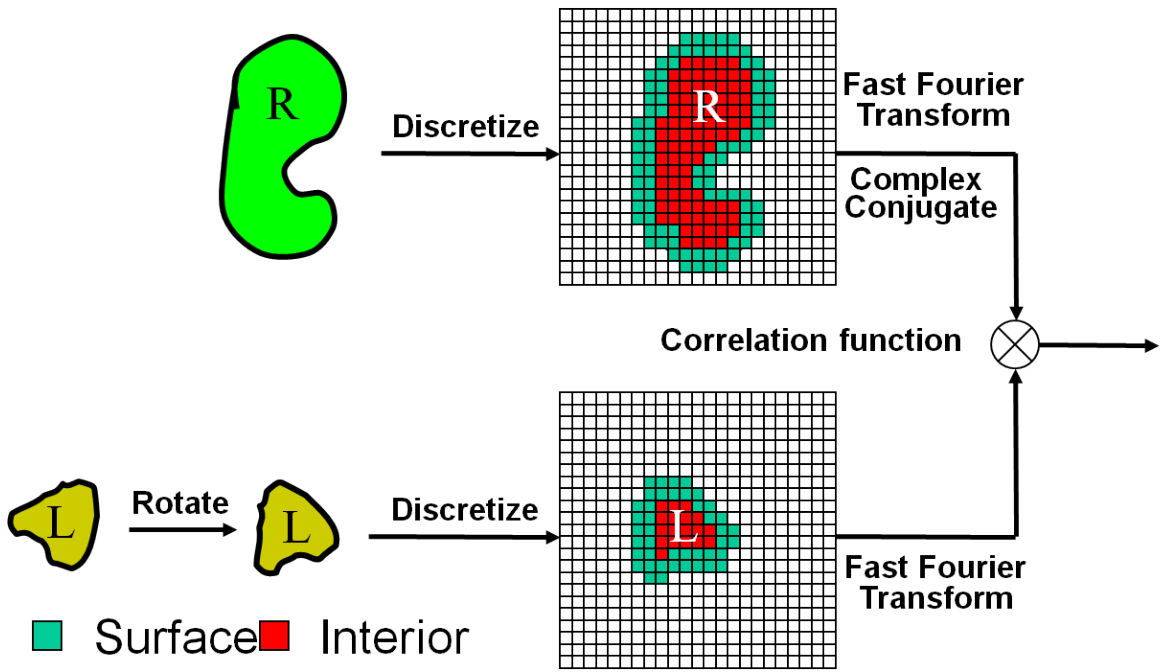
=> 10^5 times faster with FFT !

Rong Chen and Zhiping Weng (May 2002). In: *Proteins* 47.3

Ligand rotations

ZDOCK 2.3-3.x => two rotational sampling options (non-redundant rotations, uniform sampling of the sphere):

1. $\Delta = 15 degrees$ => $M_{rot} = 3600$
   => $M_{rot} \cdot N^3$ = 7.5 billion docking poses
2. $\Delta = 6 degrees$ => $M_{rot} = 54000$
   => $M_{rot} \cdot N^3$ = 113 billion docking poses



Total number of operations

$$M_{trans+corr} = N^3 \cdot log_2(N^3) \tag{3}$$

$$M_{total} = M_{rot} \cdot M_{trans+corr} = M_{rot} \cdot N^3 \cdot log_2(N^3) \tag{4}$$

ZDOCK 2.3-3.x =>

M_{total} = 160 billion operations with M_{rot} = 3600 => average runtime (2.3: 1h, 3.0: 3h)

M_{total} = 2300 billion operations with M_{rot} = 54000 => average runtime (2.3: 15h, 3.0: 45h)

Brian G Pierce, Yuichiro Hourai, and Zhiping Weng (2011). In: *PLoS ONE* 6.9

Assessing structural predictions in community-wide experiments:
CAPRI and CASP

- **CASP (Critical Assessment of methods of Structure Prediction)**:
  - predict the mode of **folding** of a protein based on the amino acid sequence
  - compare to an unpublished X-ray or NMR structure.
  - J. Moult (CARB, Rockville MD) launched CASP in 1994
  - round of predictions once every two years (CASP8 in 2008) with 50-100 targets
- **CAPRI (Critical Assessment of PRedicted Interactions)**:
  - predict the **mode of recognition** of two proteins by docking their 3D structures
  - compare to unpublished X-ray structures of **protein-protein complexes**.
  - CAPRI started in 2001
  - a round of prediction begins **any time a target is made available**

http://capri.ebi.ac.uk/

CAPRI star evaluation

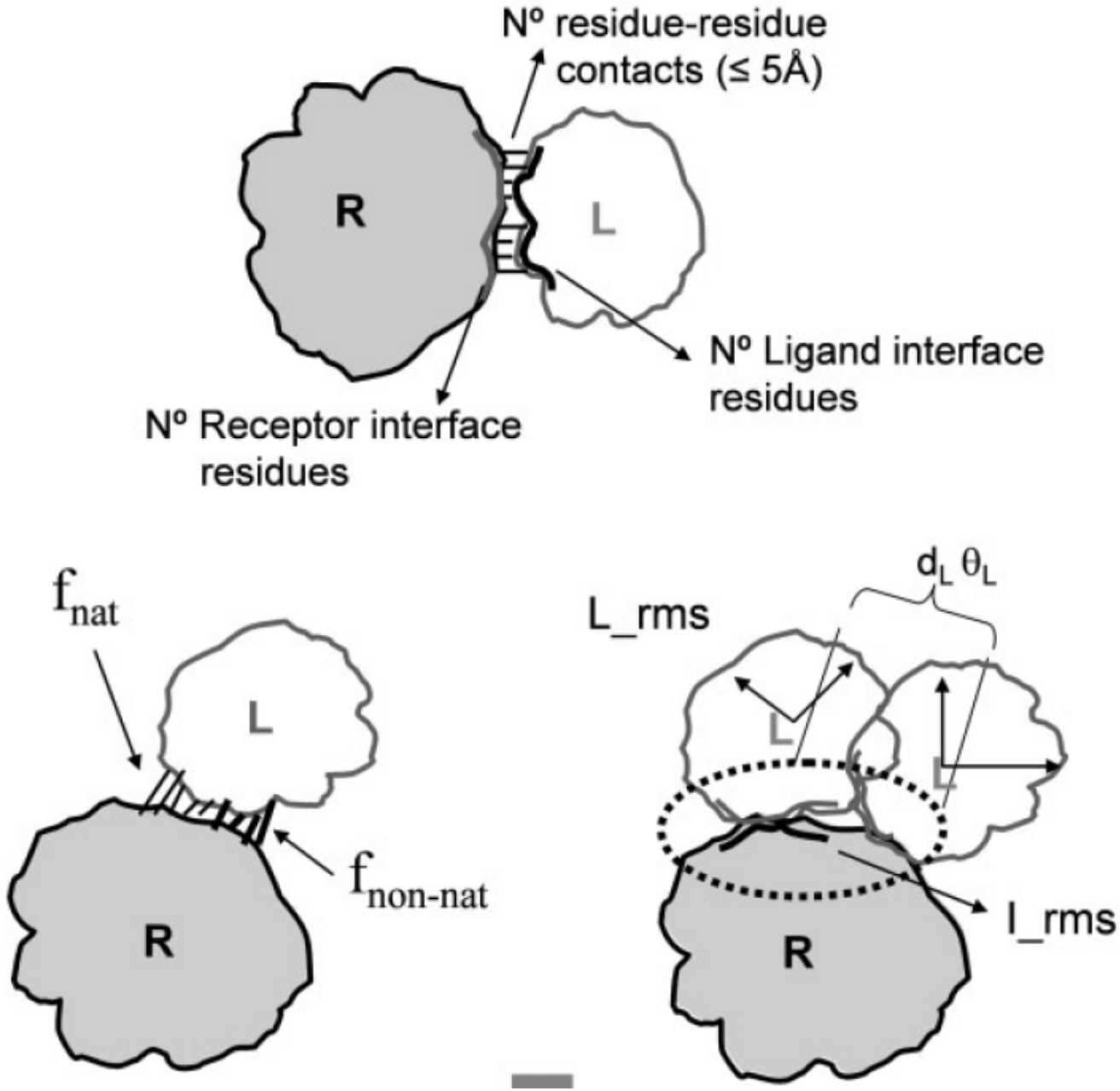
The CAPRI star system

Mendez, Leplae, Wodak 2003

Lensink et al. 2005, 2007, 2010

Model quality		% native contacts (correctly predicted residue pairs) f_{nc}	main chain RMSD (Å) Ligand L_{rms}		Interface I_{rms}
High	**(three-star)**	**> 50%**	< 1 Å	or	**< 1Å**
Good	**(two-star)**	**>** 30%	< 5	or	< 2
Acceptable	(one-star)	> 10%	< 10	or	< 4
Incorrect		< 10%	>10	and	> 4

Source: Janin, LIX 2010



Raúl Méndez et al. (Aug. 2005). In: *Proteins* 60.2

CAPRI rules

1. Each group gets the input structures (bound, unbound or sequence only).
2. Some weeks later they have to submit 10 models for the complex.
3. Exception: web-servers have to submit within 24h to prevent "human scoring".
4. The best model out of the 10 models is used to evaluate the performance of one group or web-server.
5. Group $\neq$ Program: each group can use the programs they like, but usually they are using their own programs.

Table III

Summary of Target Prediction Performance in CAPRI Rounds 13–19

			***			**			*		
	L-rms (Å)	R-rms (Å)	P	U	S	P	U	S	P	U	S
T29	1.7	**B**	0	2	1	9	78	13	8	87	13
T30	1.7	2.3	0	0	0	0	0	0	2	2	0
T32	0.3	2.1	15	0	0	13	3	0	6	12	2
T33	2.0	2.6	0	0	0	0	0	0	0	0	0
T34	2.0	**B**	0	0	0	25	13	4	40	165	26
T35	2.9	2.9	0	0	0	0	0	0	1	2	1
T36	2.9	**B**	0	0	0	0	0	0	1	0	0
T37	0.6	0.4	1	8	5	7	34	13	13	34	11
T38	3.2	1.9	0	0	0	0	0	0	0	0	0
T39	3.2	**B**	1	0	0	2	3	0	0	1	0
T40	**B**	0.4	79	176	39	54	163	40	31	149	13
T41	2.0	1.5	24	2	2	58	99	16	67	198	51
T42	1.5	1.5	9			5			6		

Web-server

Table V

Prediction Performance of Web-Servers

Target	29	30	32	33	34	35	36	37	38	39	40	41	42
ClusPro	0	0	0	0	1*	0	0	0	0	1**	2/1**	1**	1***
FiberDock												10/1***	0
FireDock			0	0	0	0	0	0	0	0	2/1***		
GRAMM-X	0	0	0	0	0	0	0	0	0	0	2***	1***	0
HADDOCK			0	0	7*	0	0	0	0	0	1***	4/1**	1*
SKE-DOCK	0	0	0	0	0	0	0	2*	0	0	2/1***	0	0
Top down								0	0		2/1**	0	0

Marc F Lensink and Shoshana J Wodak (Nov. 2010). In: *Proteins* 78.15

Conclusion

Is the protein-protein docking problem solved ?
Not really:

- Final goal: best structure at first rank
- CAPRI results:
  - Best structure at top 10 => still up to 90% (worst case) false positives
  - No program works for all complexes
  - Bad performance of non-human scores, i.e. web-servers
  - Scores are only a first help for "human scorers"

Conclusion

Is the protein-protein docking problem solved ?
Challenges:

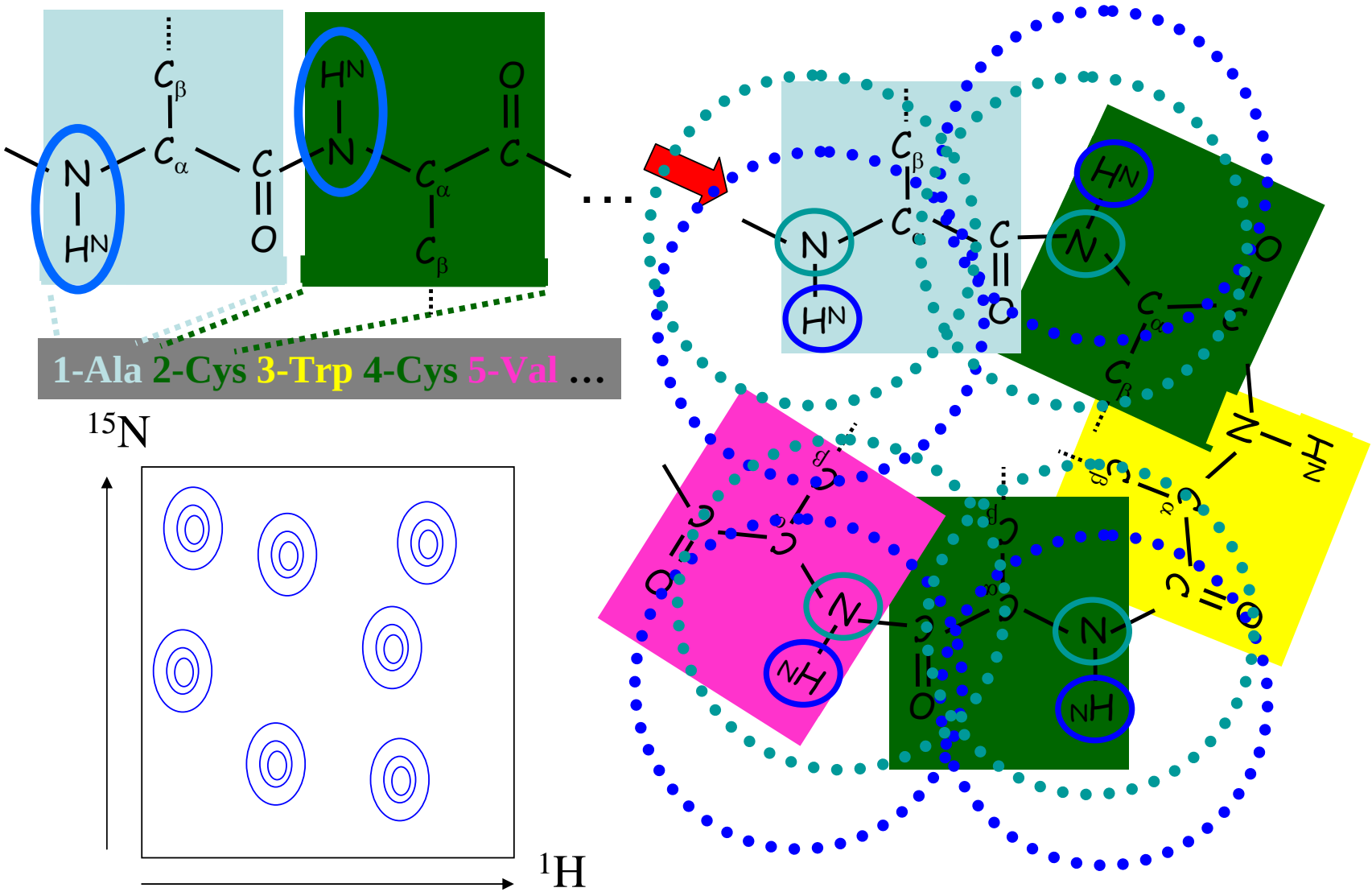
- Better sampling and scoring
- Conformational changes upon binding
- Predicting domain motions
- Folding upon binding
- Large scale docking => Interactome, Large molecular assemblies
- Predicting which proteins interact => Predicting binding affinities

Conclusion

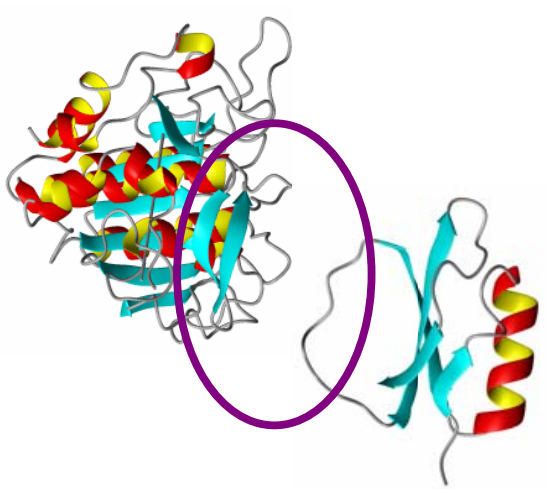
Is the protein-protein docking problem solved ?
Not really and a there are still a lot of challenges.
One possible solution:

- Combine docking with experimental data (NMR, mutagenesis, cryo-EM, SAXS, ...)

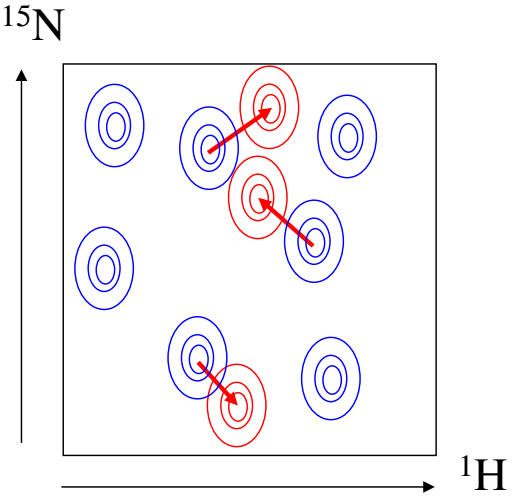
Chemical shift

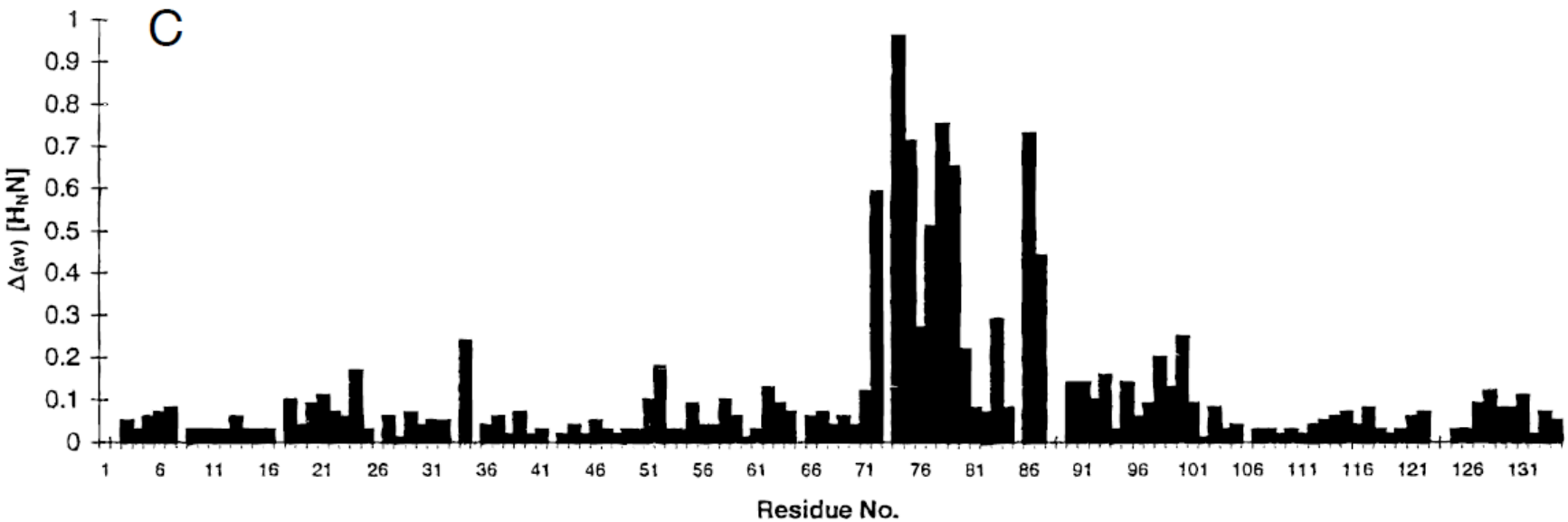


Chemical Shift Perturbation (CSP)

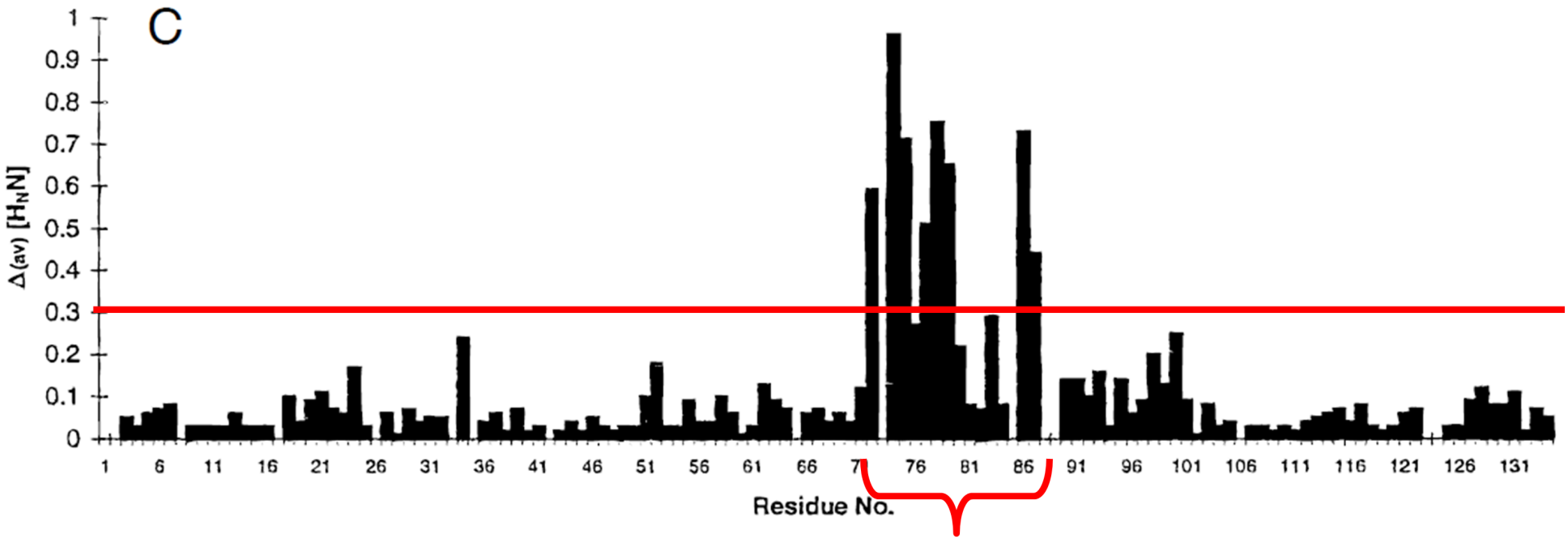


1-Ala 2-Cys 3-Trp 4-Cys 5-Val …

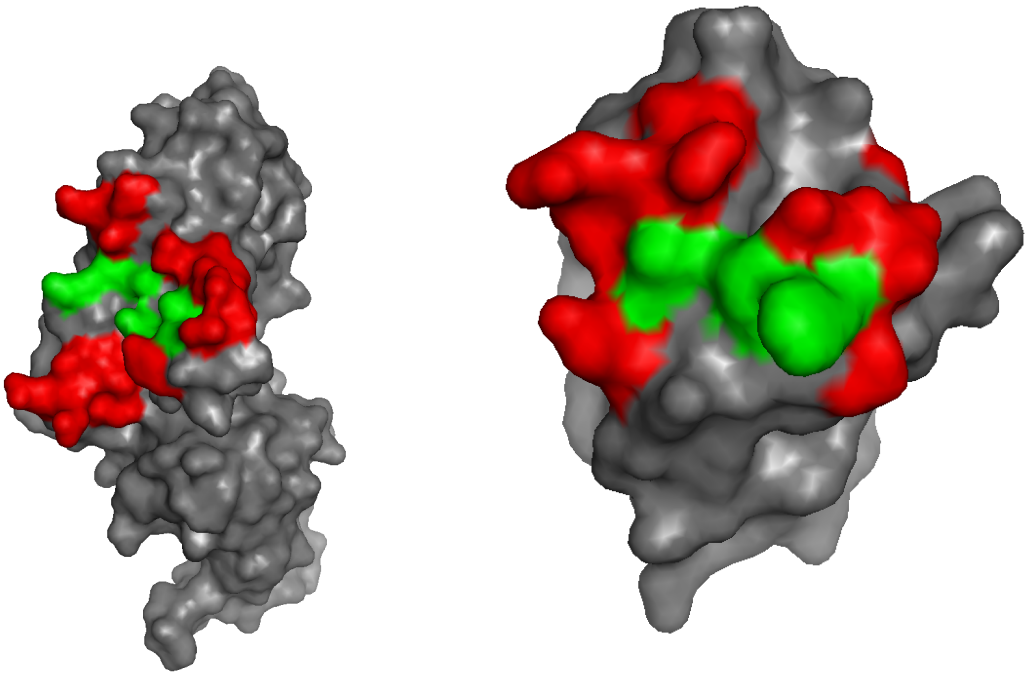




Chemical Shift Perturbation (CSP)



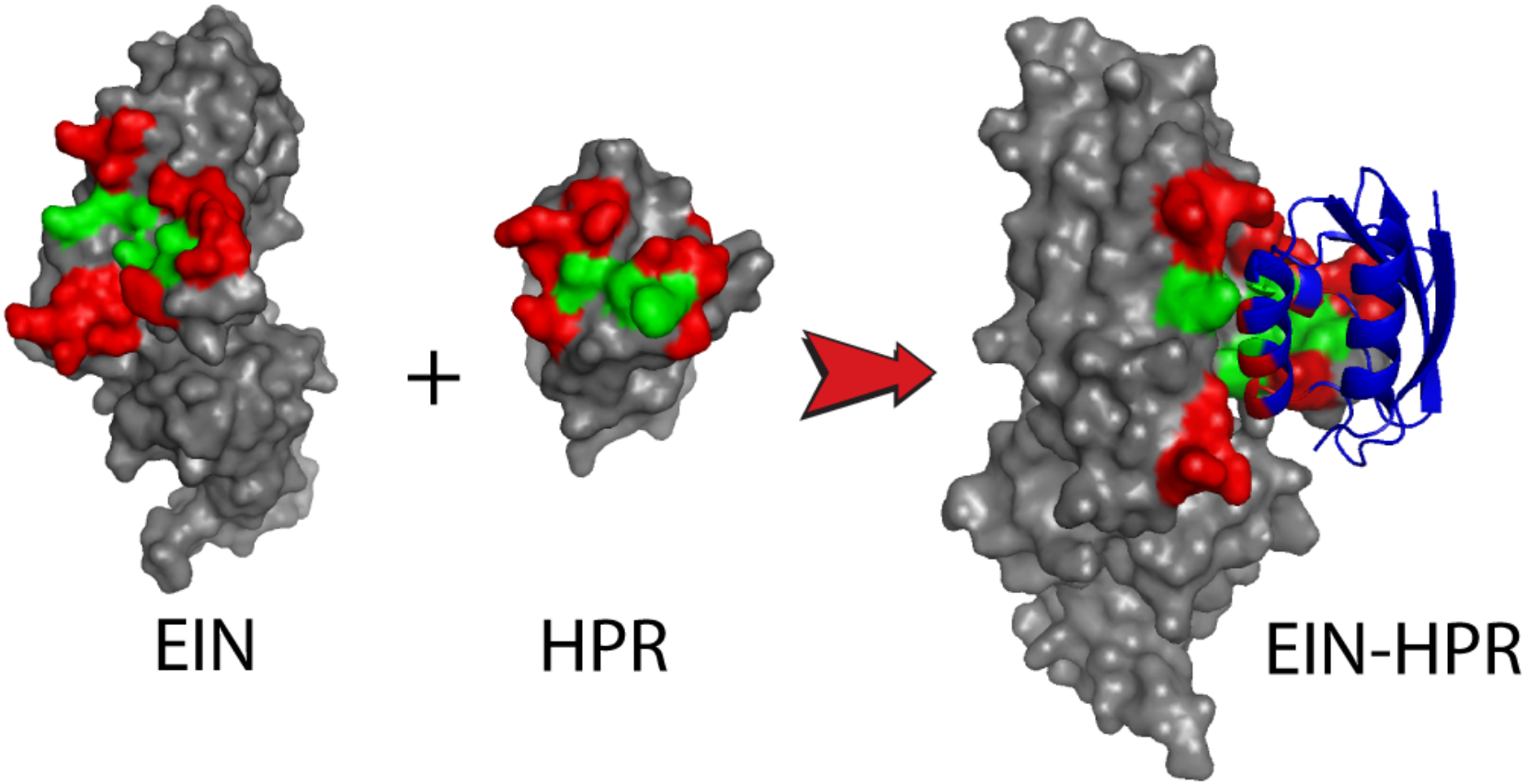
Interface localization on 3D structures



EIN HPR

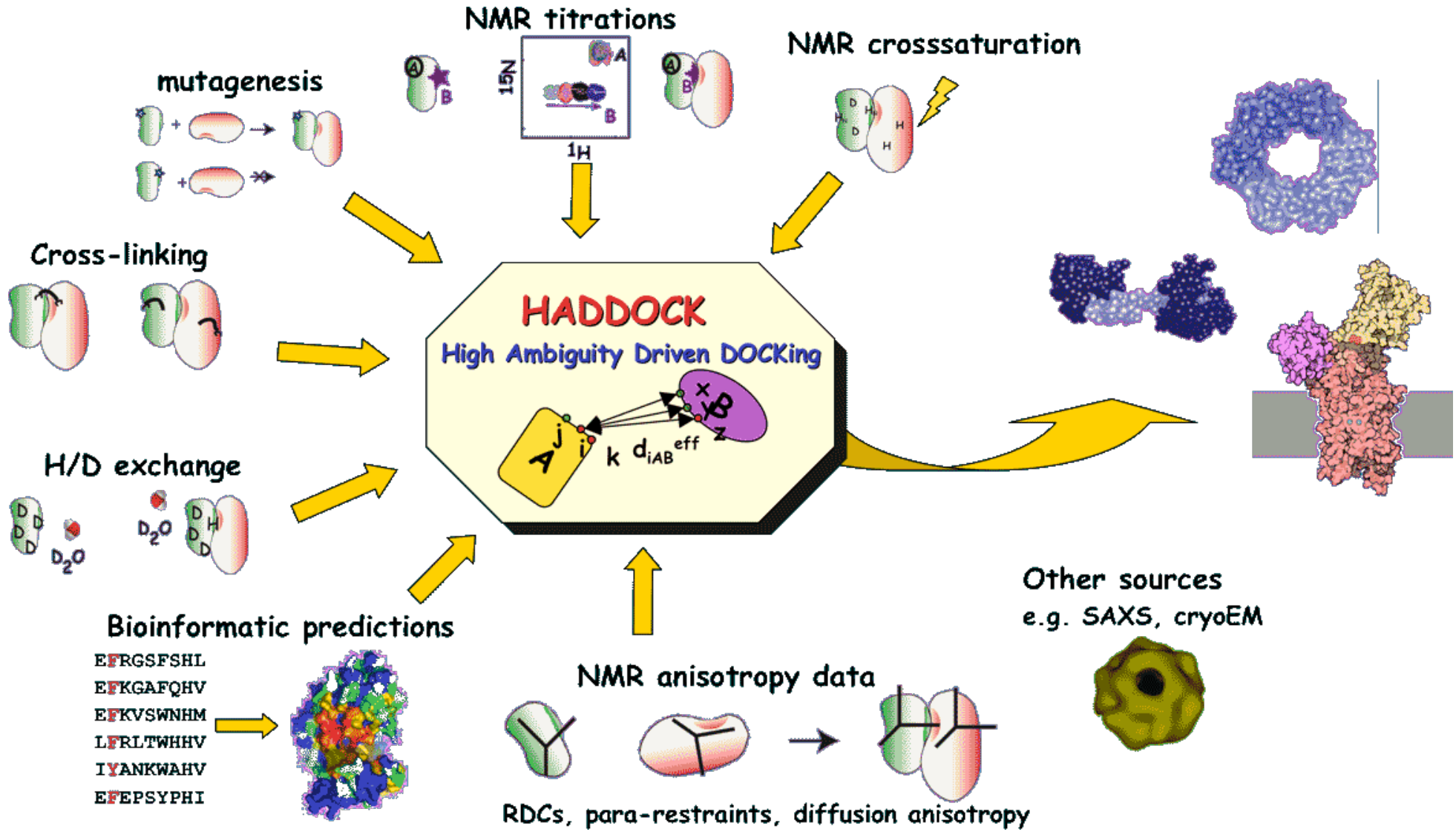
red = active residues derived from CSP data and surface accessibility
green = passive residues, i.e. the surface neighbors of the active residues

Docking

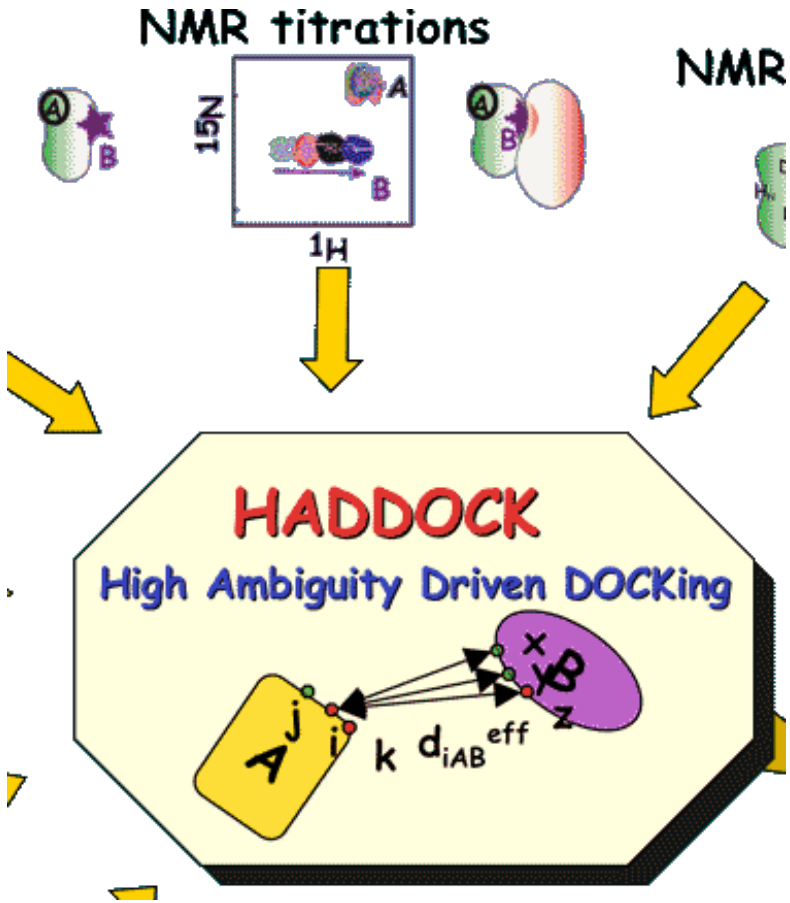


red = active residues derived from CSP data and surface accessibility
green = passive residues, i.e. the surface neighbors of the active residues

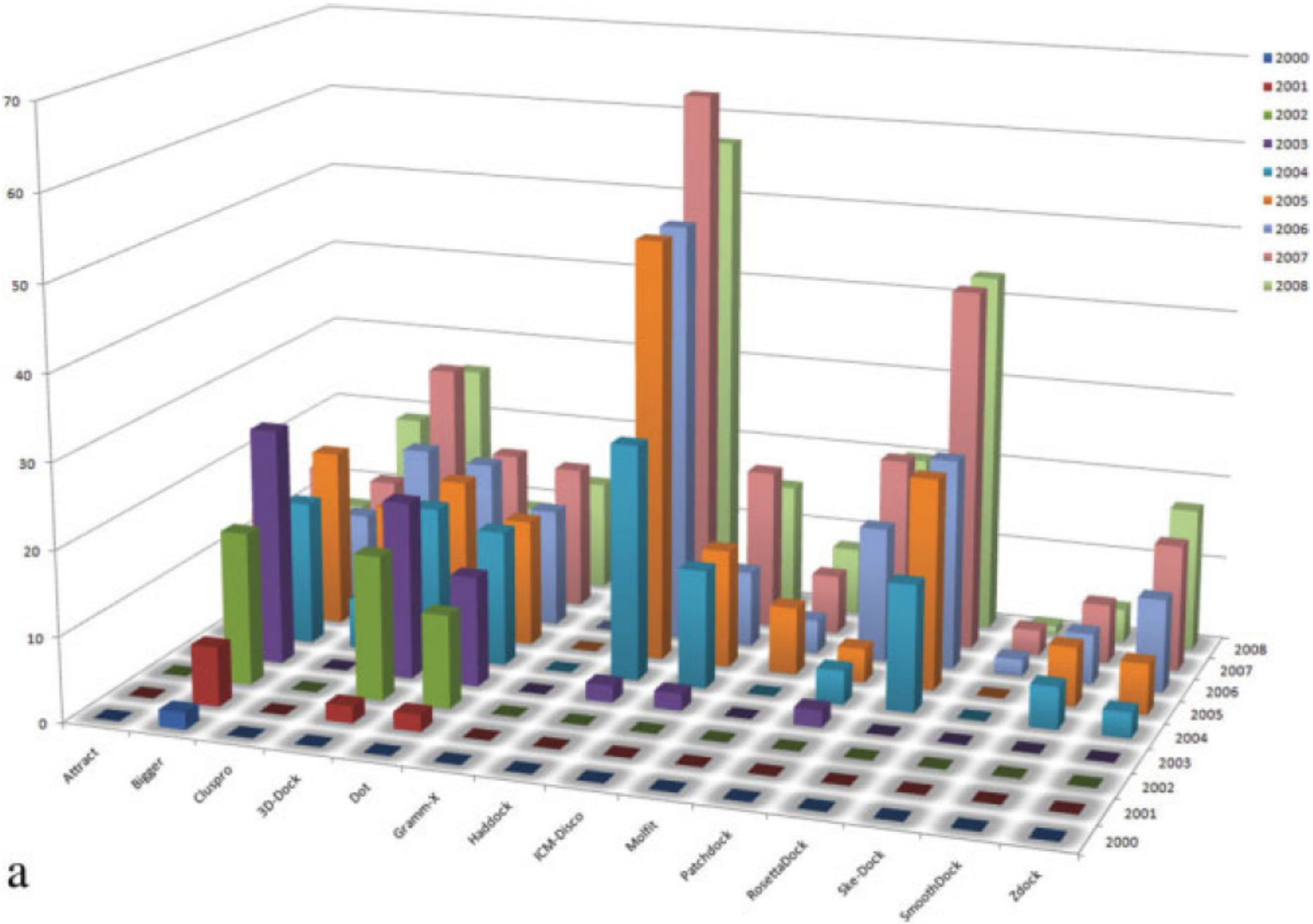
Haddock - http://haddock.chem.uu.nl



Haddock - http://haddock.chem.uu.nl



$$E_{Haddock} = E_{vdW} + E_{elec} + E_{AIR} + E_{desolv}$$


70
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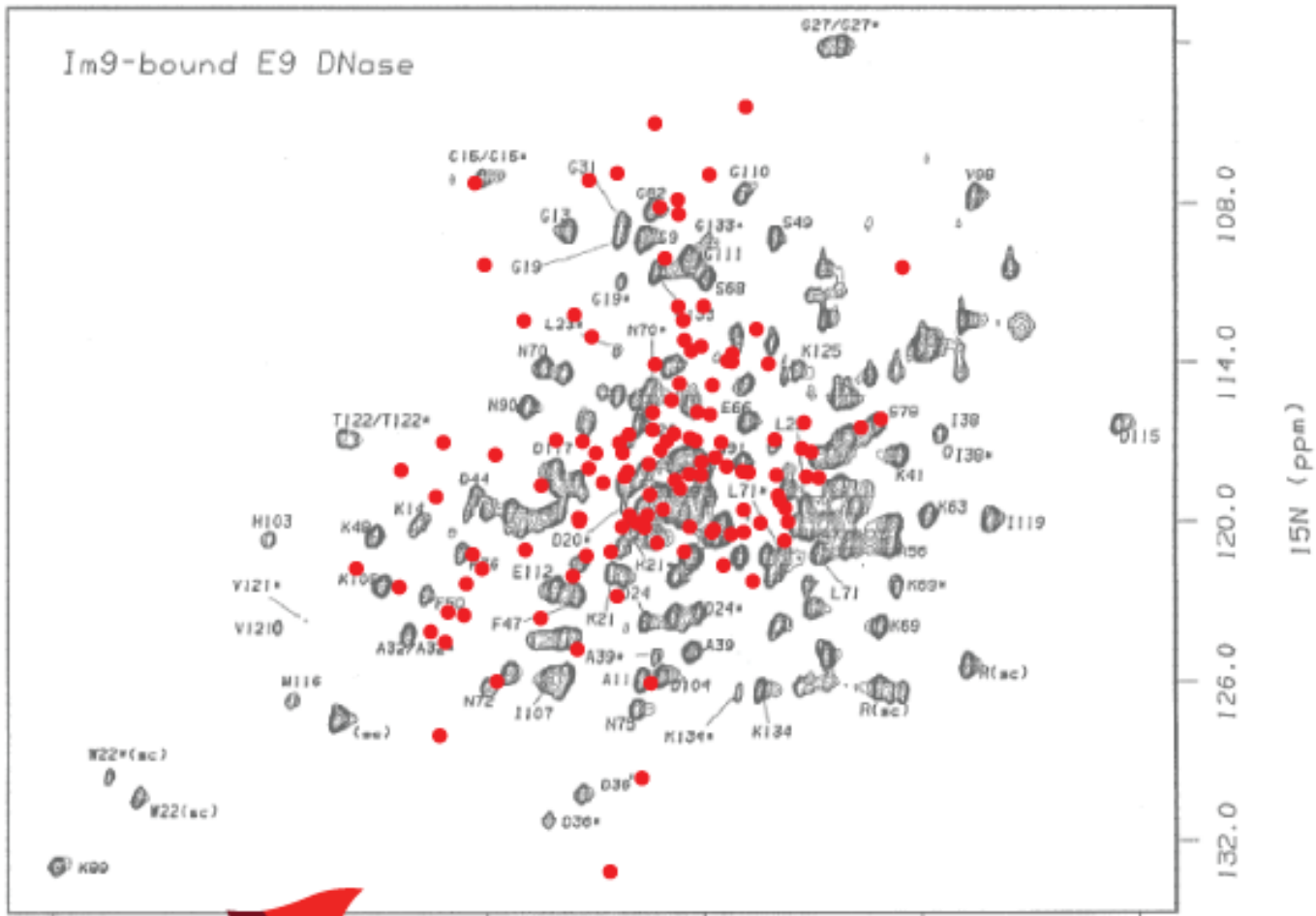
Attract
Bigger
Cluspro
3D-Dock
Dot
Gramm-X
Haddock
ICM-Disco
Molfit
Patchdock
RosettaDock
Ske-Dock
SmoothDock
Zdock

a

3D to CS



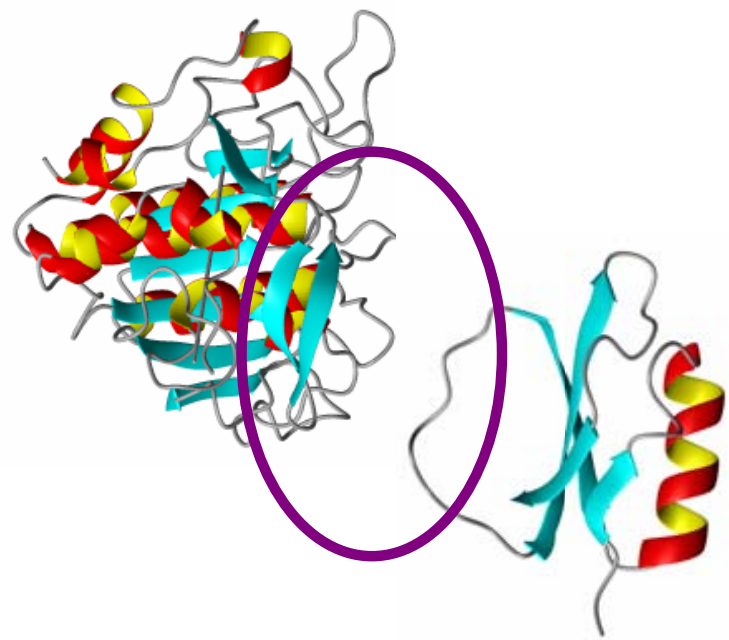
CS-predictor

3D to CS with ShiftX

Contributions to calculated CS δ_{calc}:

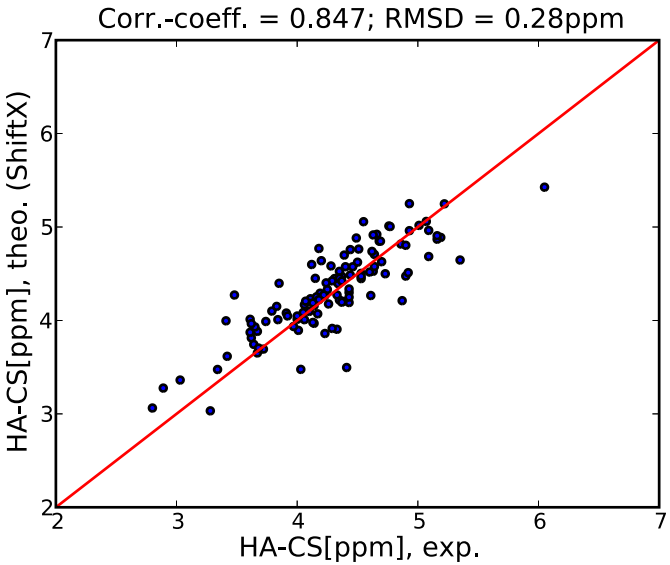
$$\delta_{calc} = \delta_{coil} + \delta_{RC} + \delta_{EF} + \delta_{HB} + \delta_{HS}$$

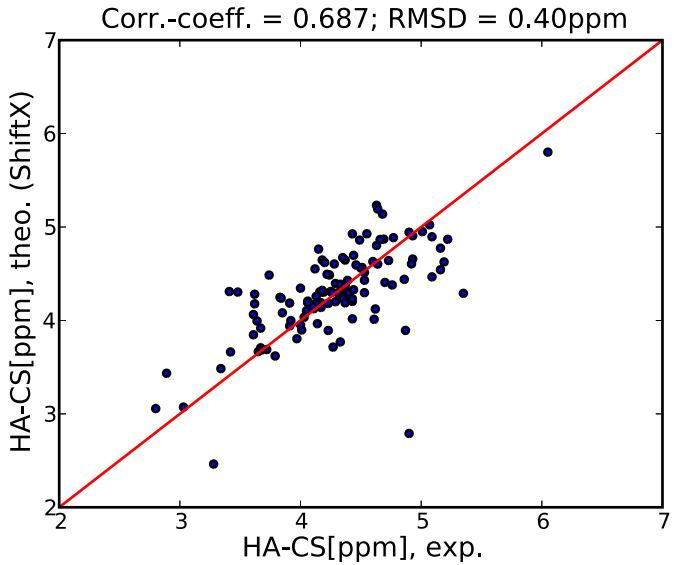
- δ_{coil} - random coil (amino acid type)
- δ_{RC} - ring current
- δ_{EF} - electric field
- δ_{HB} - hydrogen bonding
- δ_{HS} - empirical hypersurfaces (backbone dihedral angles)

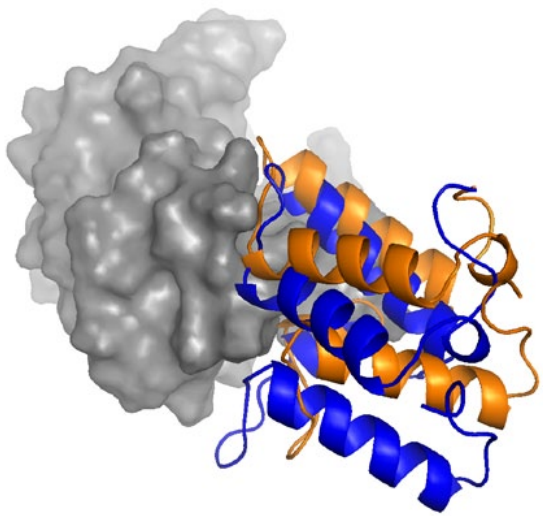


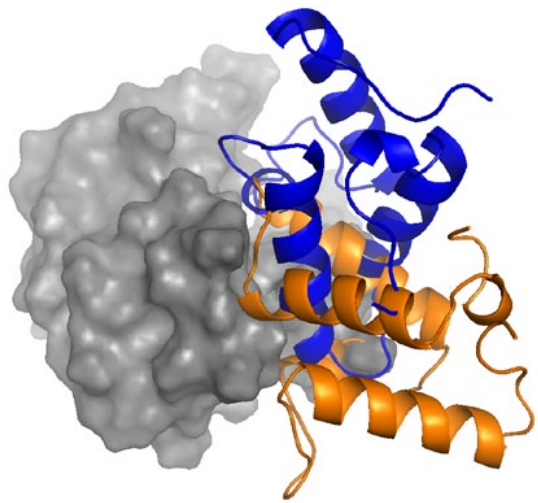
Neal et al., *J. Biomol. NMR* 26: 215-240, 2003

RMSD between δ_{calc} and δ_{exp} for $^{1}H^{\alpha}$-CS

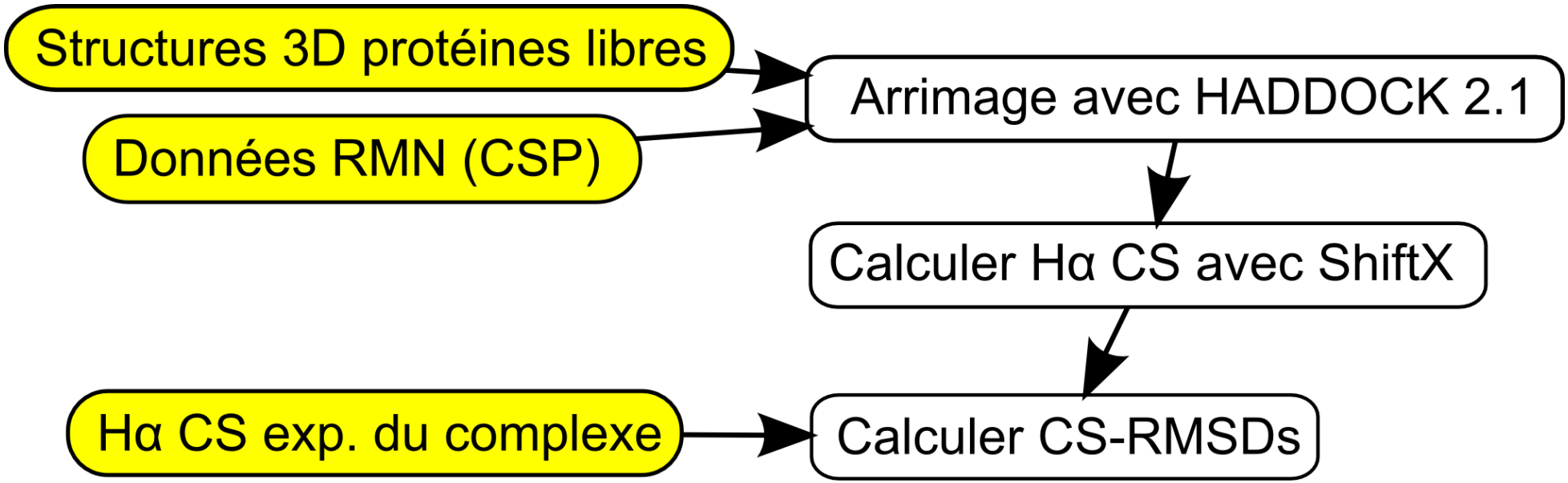








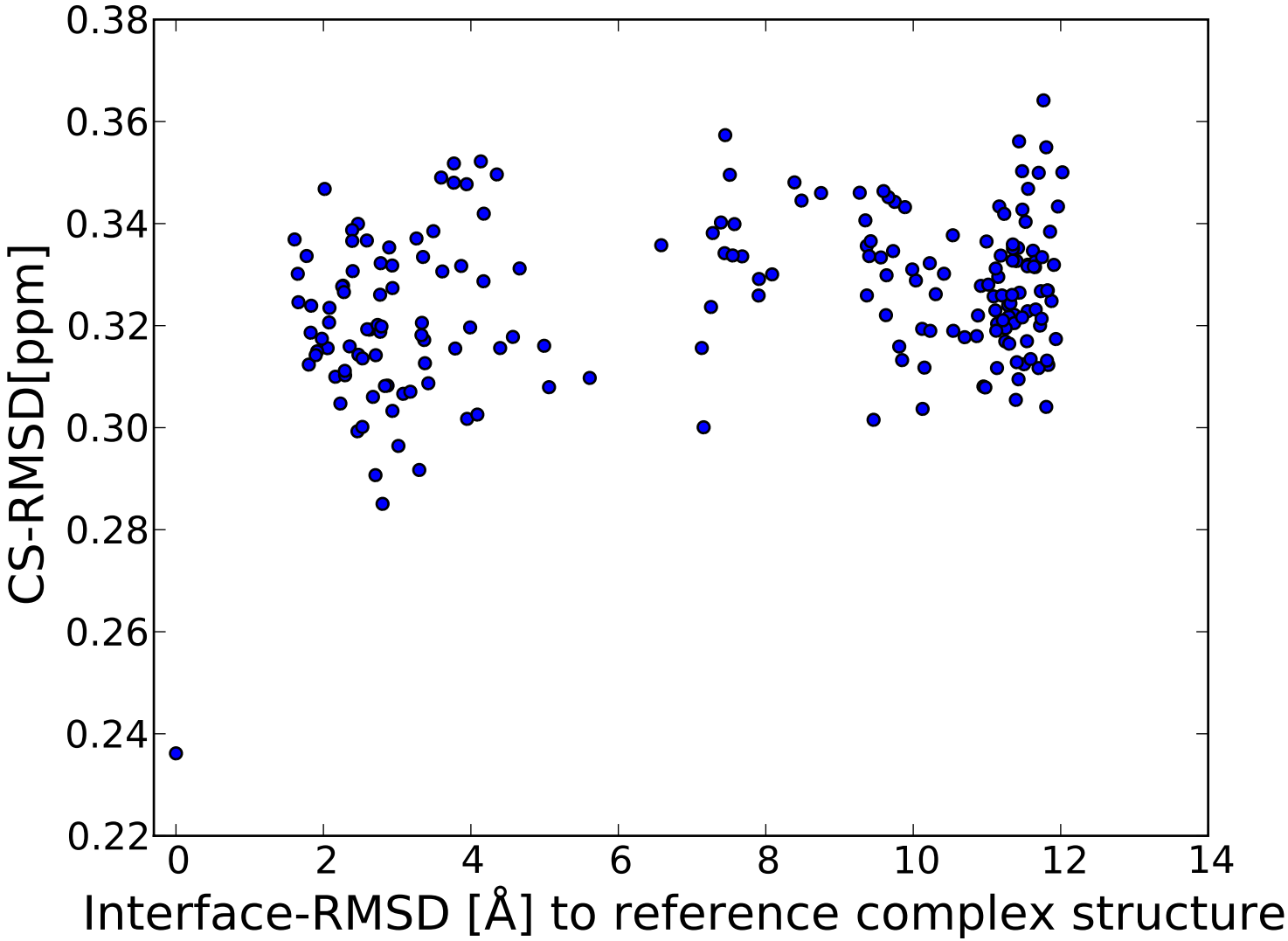
Protocole d'arrimage CS-HADDOCK



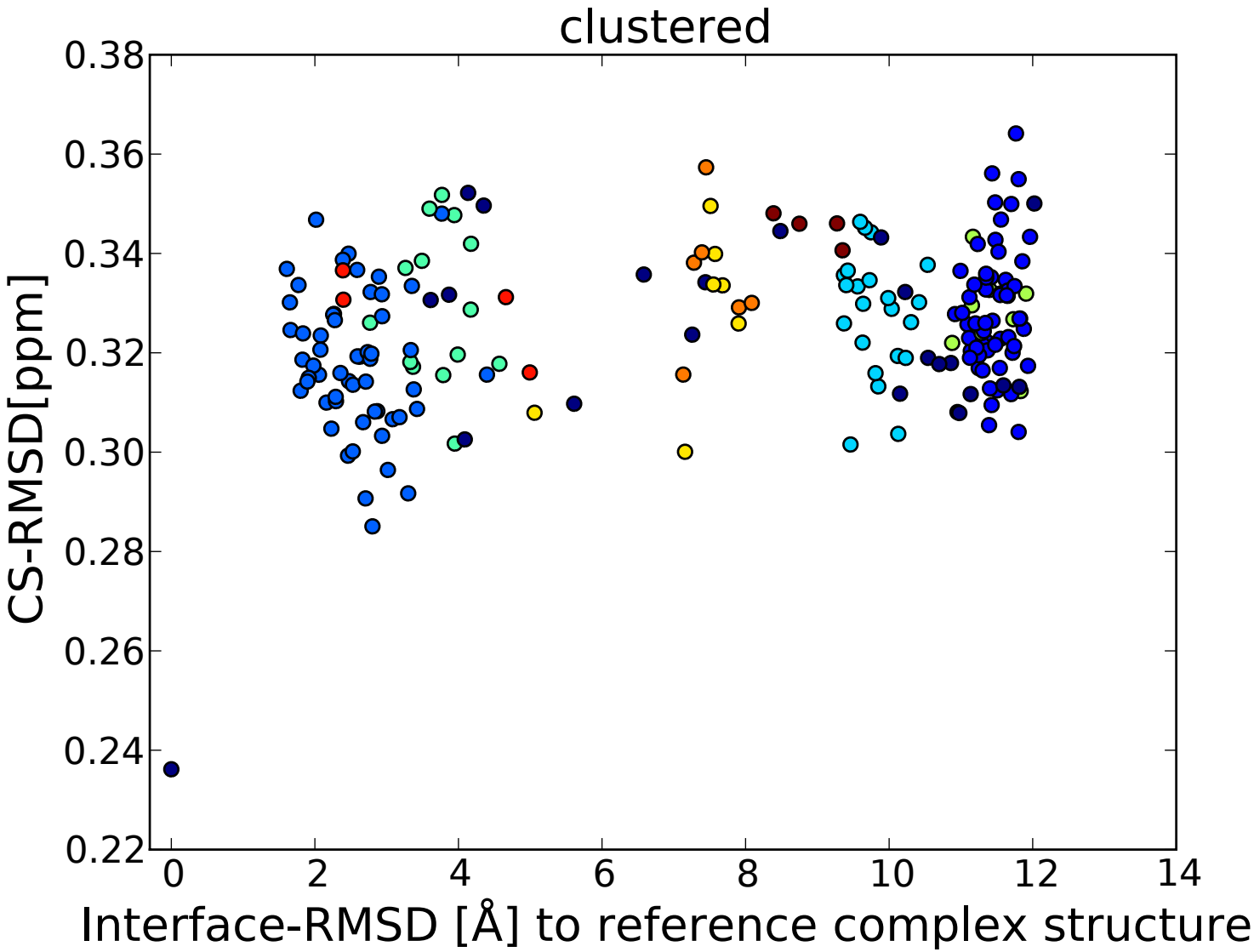
$$\text{CS-RMSD} = \frac{\sqrt{\frac{\sum_{i=1}^{n_A}(\delta_i^{exp}-\delta_i^{theo})^2}{n_A}} + \sqrt{\frac{\sum_{i=1}^{n_B}(\delta_i^{exp}-\delta_i^{theo})^2}{n_B}}}{2}$$

Dirk Stratmann, Rolf Boelens, and Alexandre M J J Bonvin (Sept. 2011). In: *Proteins*

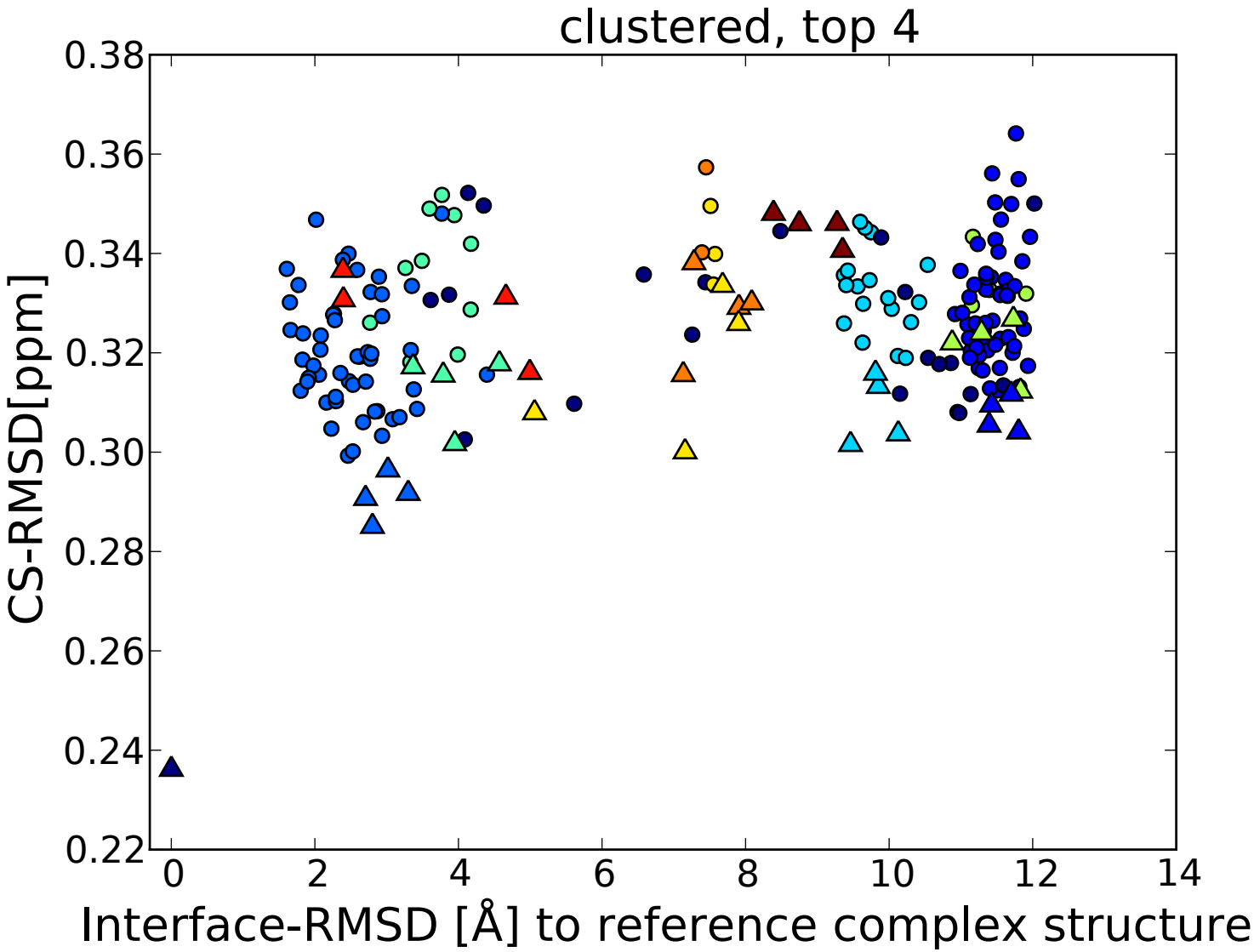
CS-RMSD scoring on all generated structures



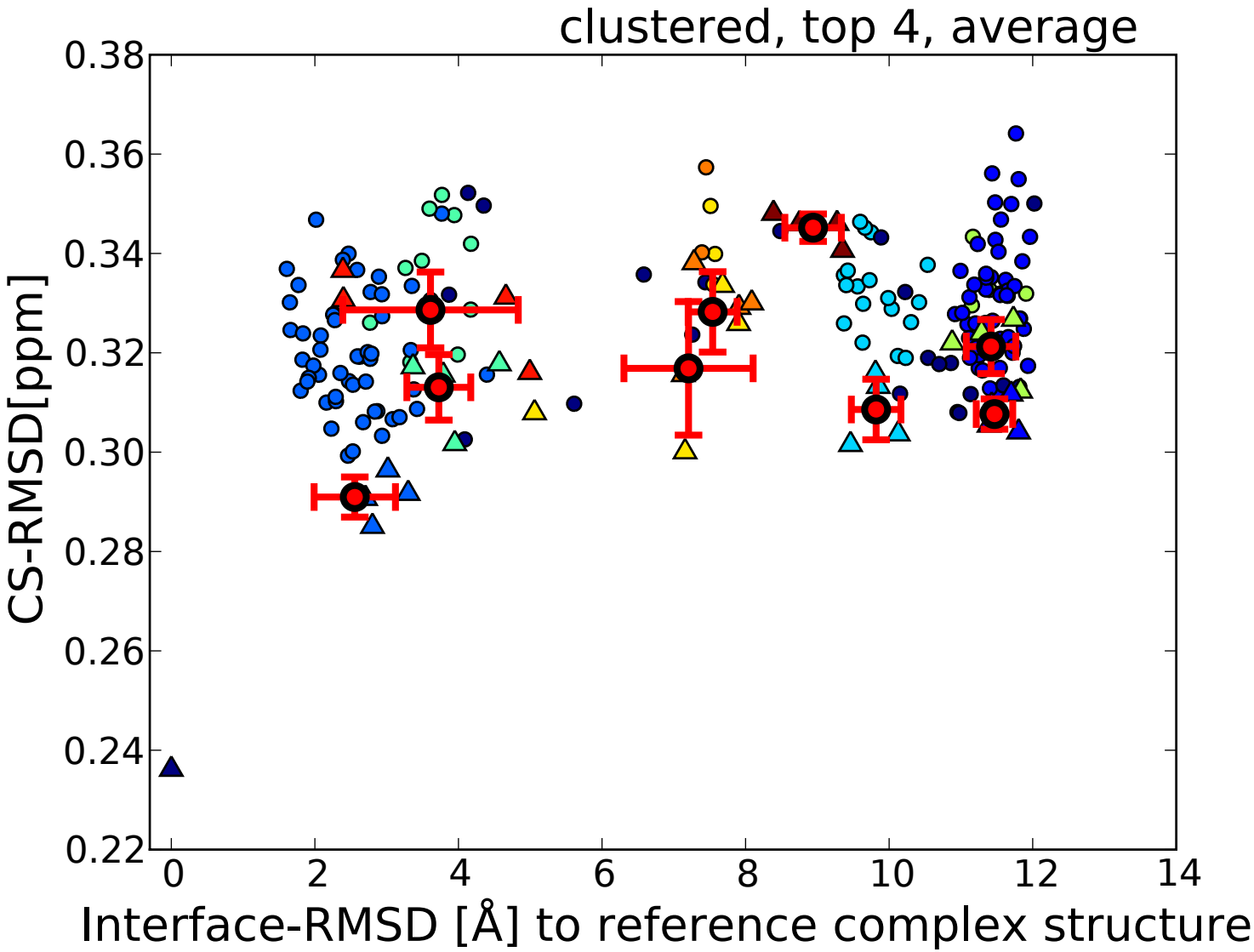
CS-RMSD scoring on all generated structures



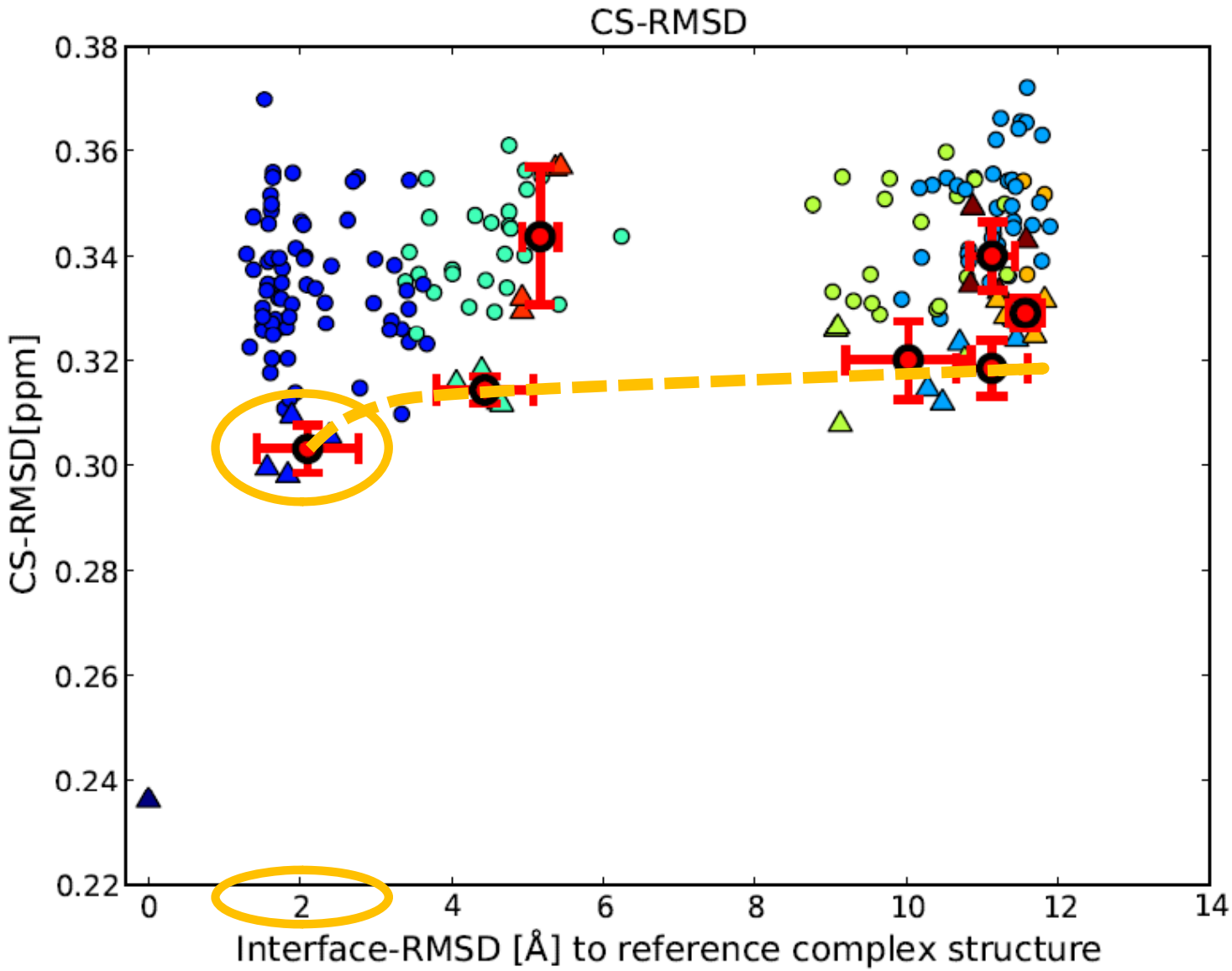
CS-RMSD scoring on all generated structures



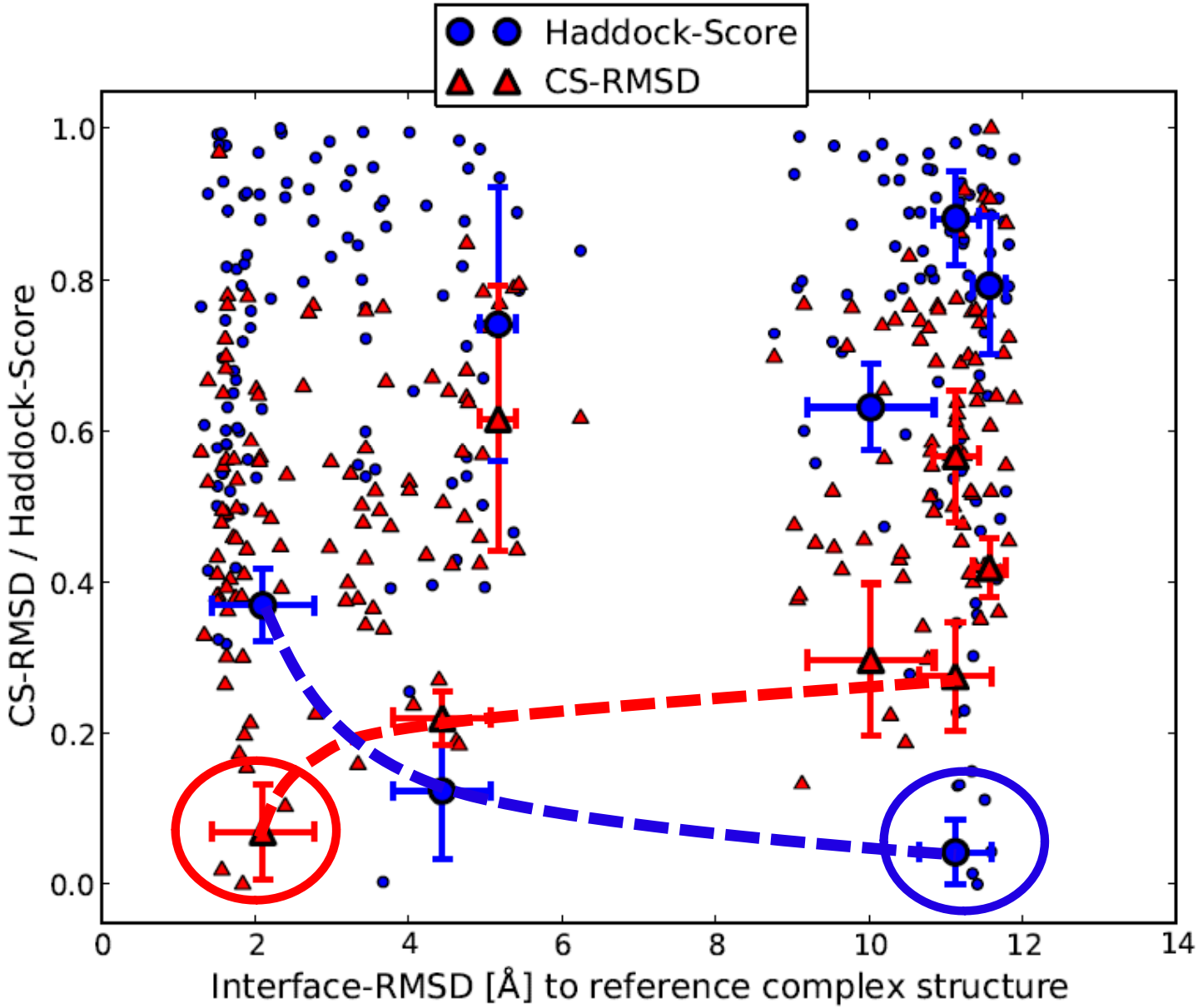
CS-RMSD scoring on all generated structures



Classement des clusters de structures par CS-RMSD

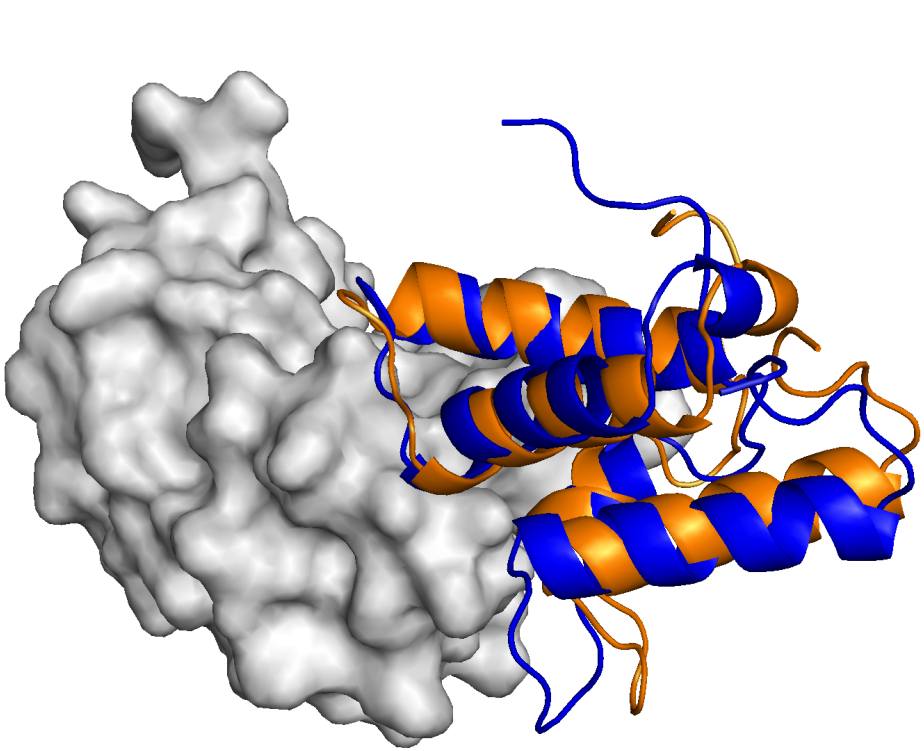


CS-HADDOCK vs HADDOCK

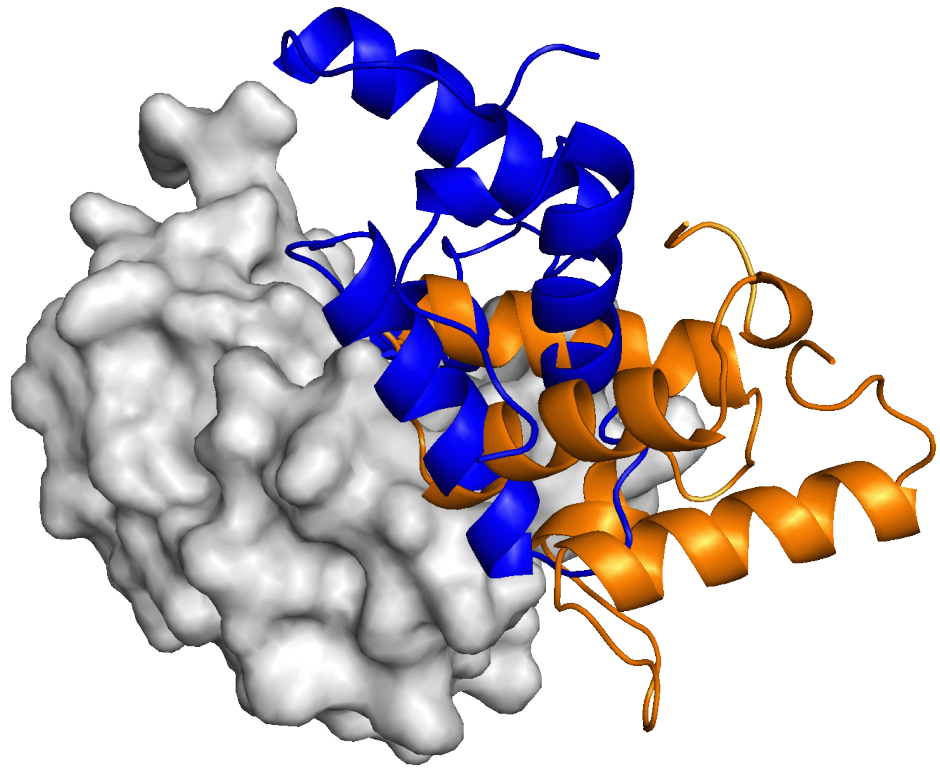


CS-HADDOCK vs HADDOCK

Meilleure structure (en bleu) par rapport à la référence (en orange):



(c) CS-RMSD score



(d) HADDOCK score

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