

# Lead Optimisation Problems to Solve

**'EXPLAIN DIFFICULT SAR in TRADITIONAL DOCKING STUDY'**

Prioritise compounds for purchase/testing from existing compound database. Rank ordering ...?

Understanding Docking, Inspecting poses and breaking down the Scoring Function

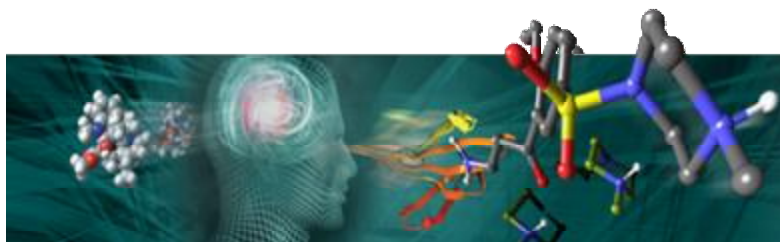
**'MY DOCKING RESULTS DO NOT MATCH THE EXPERIMENTAL ACTIVITY PREDICTIONS'**

Treating the active binding site as a flexible entity may emulate the true nature of docking better...?

Understanding Induced Fit Docking Examples

# Induced-Fit Docking (IFD)

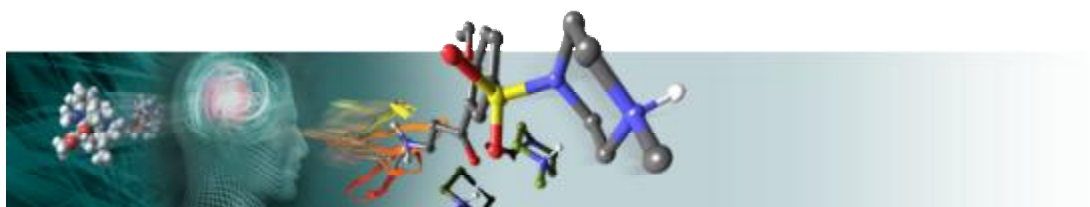
Accounting for Ligand-Induced Receptor Flexibility with Glide & Prime



SCHRÖDINGER.

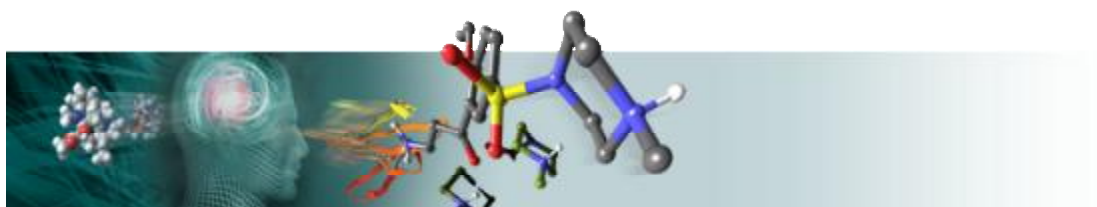
# Protein Flexibility

- PDB structures provide a single snapshot of a protein
  - The exact conformation of the protein depends on the crystallisation conditions
  - And also what was bound to the protein
- Proteins are much more dynamic than these static pictures suggest
  - Exploiting these dynamics can yield new methods of tackling difficult drug-design problems

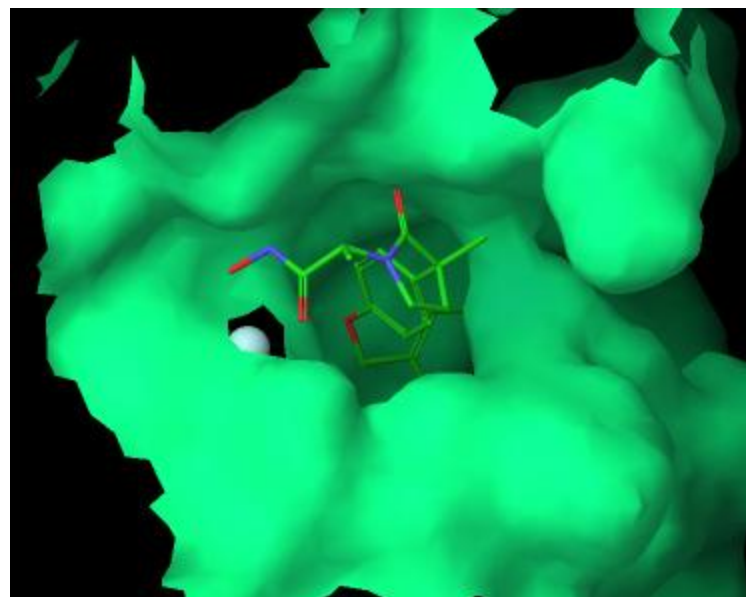
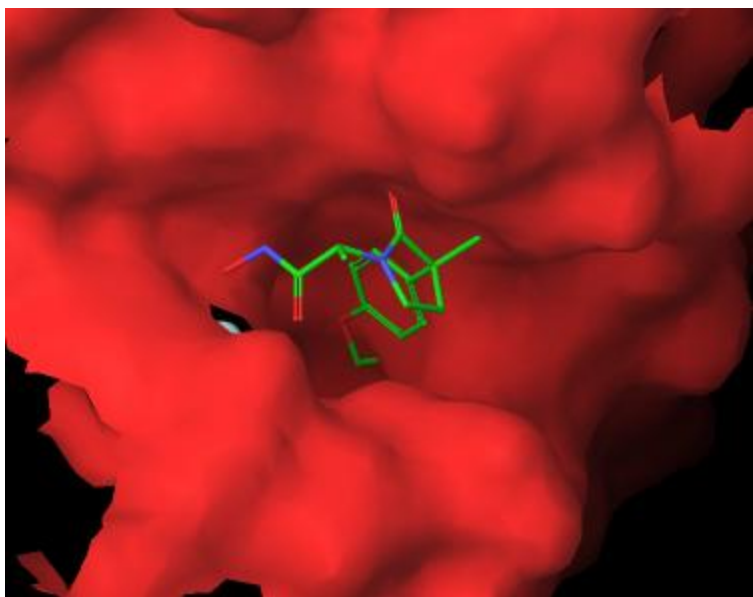


## Prime Loop Refinement: Exploring Loop Conformations

- Prime loop refinement can be used to explore the different conformations accessible to a protein loop
  - This may show areas where there is additional space within one protein over another
    - Such additional space is key to gaining selectivity between proteins



# MMP and TACE: Case Study

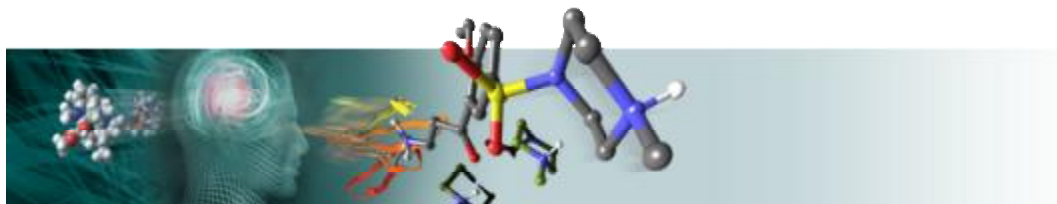


## A side-by-side comparison of the **MMP-8** and **TACE** active sites.

Binding to the  $\text{Zn}^{2+}$  gives compounds a massive amount of potency, so virtually all MMP and TACE inhibitors make this interaction, frequently via a powerful  $\text{Zn}^{2+}$  binder such as the hydroxamic acid shown here.

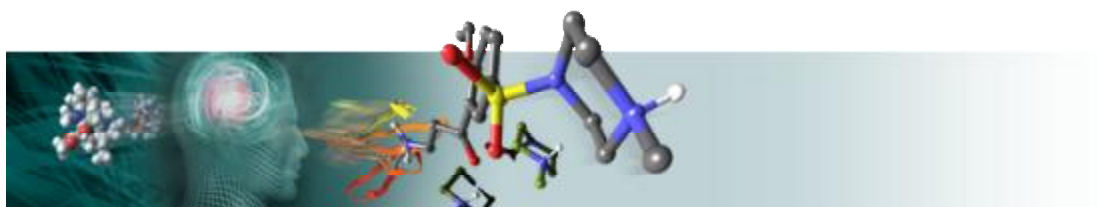
Substrate recognition by MMPs and TACE is largely dominated by the deep  $\text{P}_1'$  pocket, which accepts a large hydrophobic residue. This is an obvious place for MMP-inhibitors and TACE inhibitors to gain further activity. Consequently after making the  $\text{Zn}^{2+}$  interaction a large number of MMP and TACE inhibitors position a large hydrophobe into the  $\text{P}_1'$  site. At first sight the  $\text{P}_1'$  pocket of TACE and the MMPs are similar.

**However an analysis of the dynamics tells a different story...**



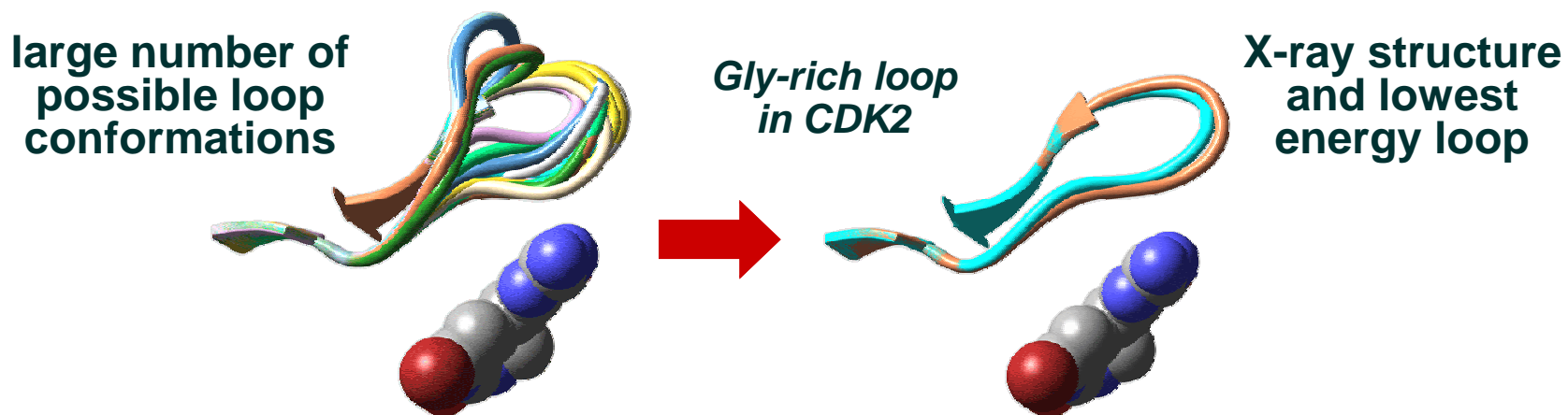
SCHRÖDINGER.

## Live Demo of Interface & Project...



SCHRÖDINGER.

# Comparative Modeling - Accuracy of Loop Prediction

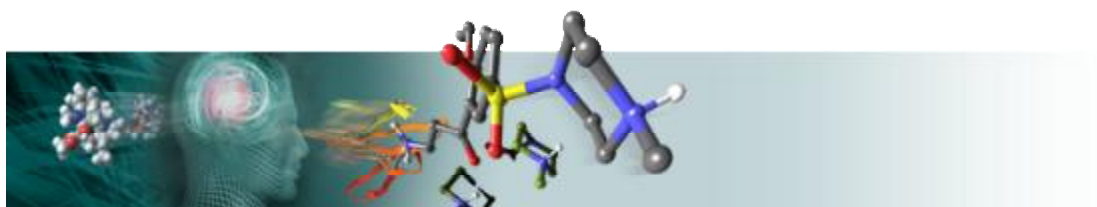


Loop Length	# of Loops	Avg. Backbone RMSD (Å)	Median Backbone RMSD (Å)	Sali	Honig
5	134	0.47	0.28	1.2	0.85
6	110	0.54	0.28	1.9	0.92
7	88	0.65	0.28	2.2	1.23
8	74	0.81	0.42	2.6	1.45
9	63	1.23	0.40	3.7	2.68
10	43	1.27	0.68	3.8	2.21
11	21	1.63	1.24	—	3.52
12	11	2.28	2.06	—	3.42

# Comparative Modeling - Accuracy of Loop Prediction

- New sampling algorithm to improve prediction of longer loops
  - Major sampling errors have been completely eliminated
  - Statistical data (~40 loop filtered test set)

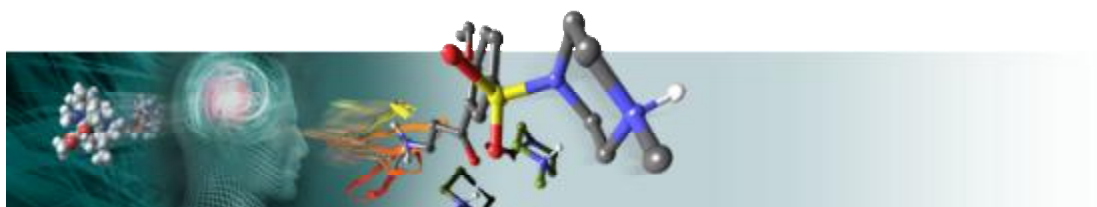
Loop Length	RMSD (Old)		RMSD (New)	
	Avg.	Median	Avg.	Median
11	1.56	1.13	0.84	0.48
12	2.43	1.95	1.87	0.87





# From Loop Refinement To Flexible Docking

- As we have stated, proteins move in response to the ligand which is bound
  - Therefore it makes sense to consider this when searching for ligands which will fit a given protein
- Induced Fit Docking, provides a work-flow which links protein conformation exploration with docking



# Default BASIC IFD Protocol

**Receptor** + **Ligand**

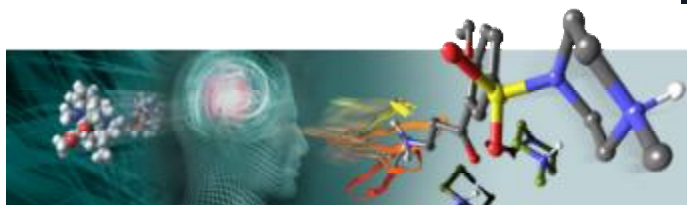
**Glide Docking**  
(reduced vdW scaling and/or  
mutation of active site residues to Ala)

**Receptor/Ligand Complexes**

**Prime Refinement/Scoring**  
(side chains and minimization)

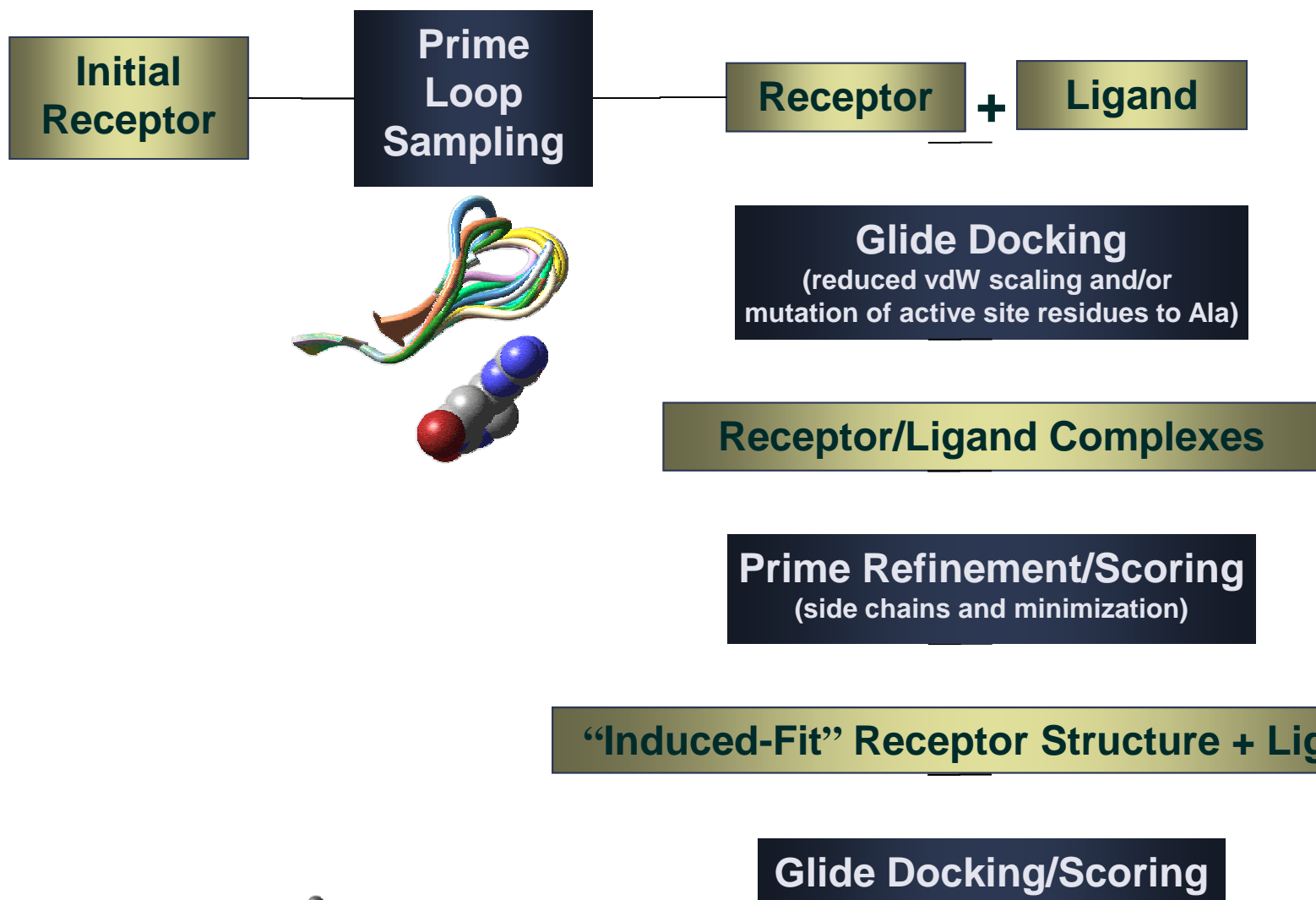
**“Induced-Fit” Receptor Structure + Ligand**

**Glide Docking/Scoring**



**SCHRÖDINGER.**

# IFD ADVANCED Protocol with Initial Loop Sampling



W Sherman, HS Beard, R Farid, "Use of an Induced Fit Receptor Structure in Virtual Screening" *Comp. Bio. Drug. Des.* **67** (2006) 83-85.

SCHRÖDINGER.

# IFD Results for 21 Cases

<sup>1</sup>RMSD of 2nd ranked IFD structure that has nearly identical composite score as top ranked structure

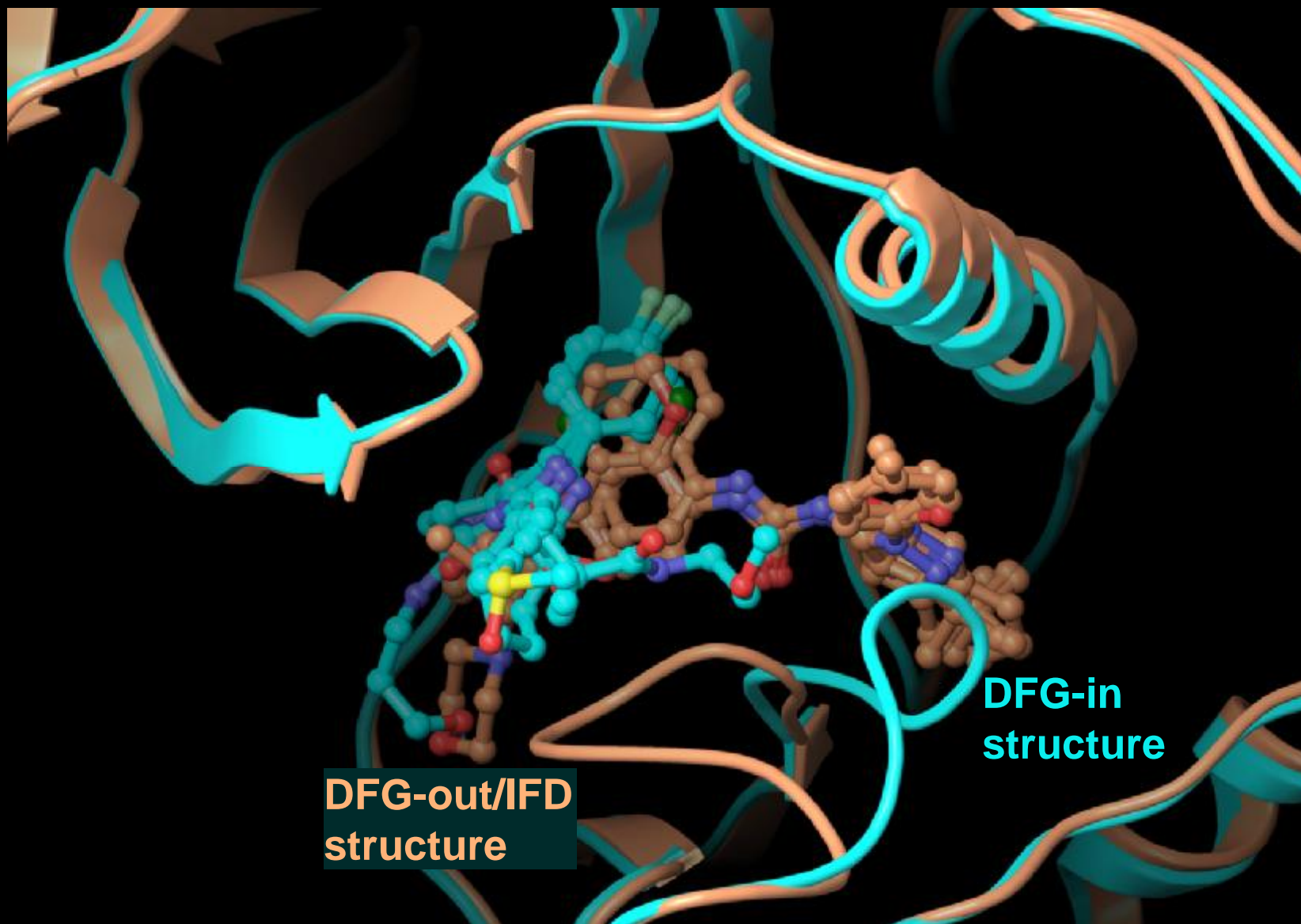
<sup>2</sup>RMSD excluding 13 atoms in the partially solvent exposed methylphenyloxazole tail of the ligand

<sup>3</sup>RMSD excluding 10 atoms in partially solvent exposed methyl-2-pyridinylamino tail of ligand that has very high B-factors ( $>60 \text{ \AA}^2$ )

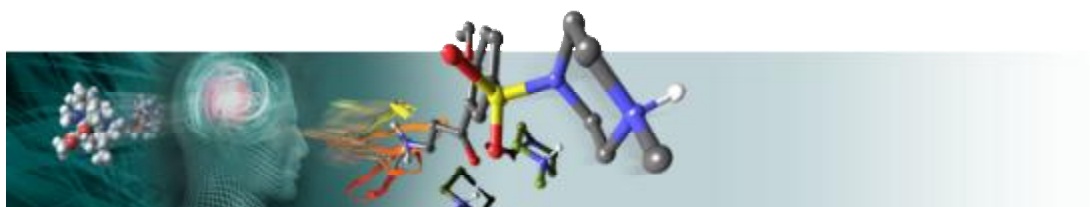
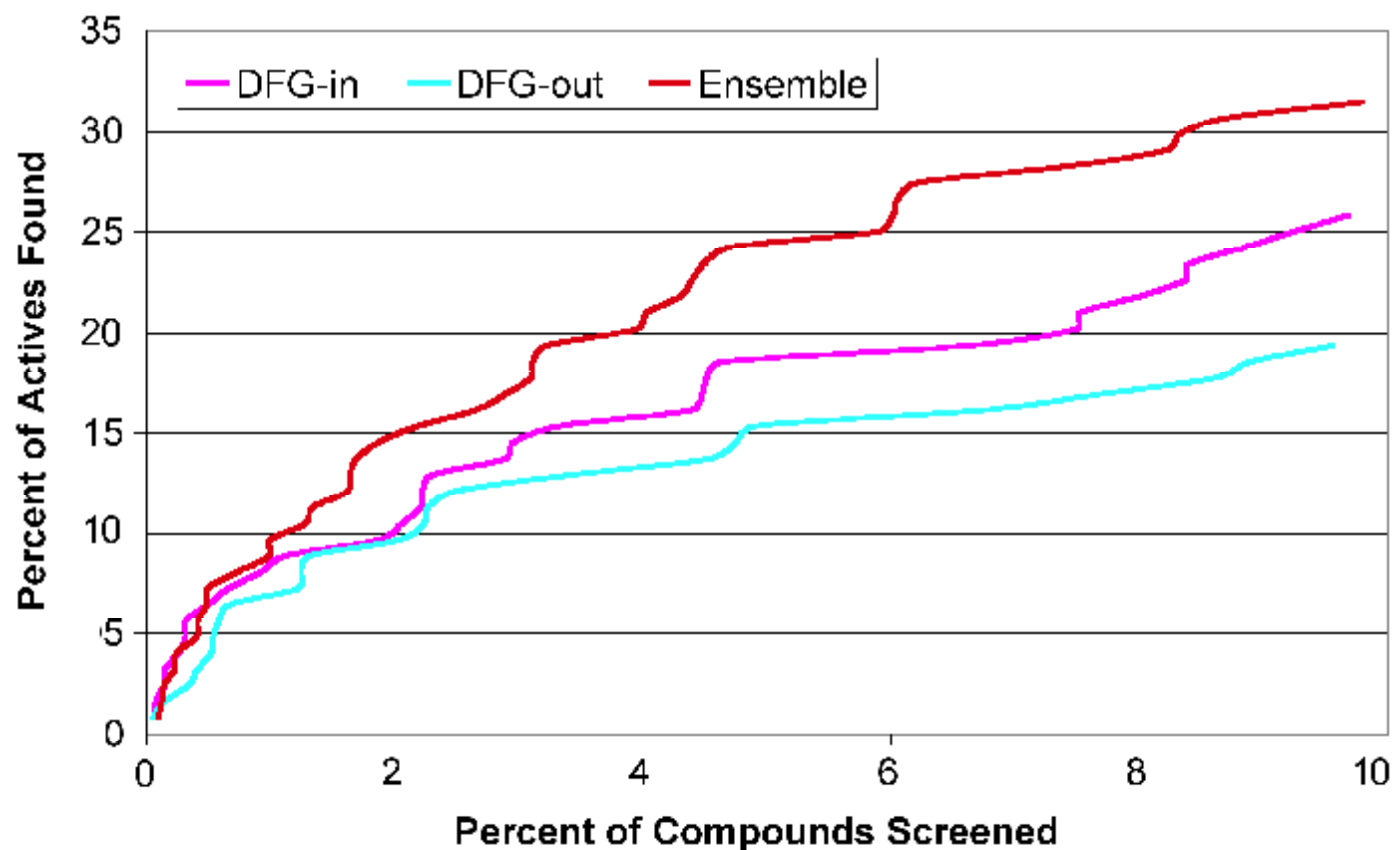
<sup>4</sup>RMSD excluding 6 atoms in the quasi-symmetric di-carboxylate that are flipped  $180^\circ$  in the IFD structure

Sherman, W.; Day, T.; Jacobson, M. P.; Friesner, R. A.; Farid, R., "Novel Procedure for Modeling Ligand/Receptor Induced Fit Effects", *J. Med. Chem.* **49** (2006) 534 -553.

**Screening of DFG-out/IFD structure finds actives that otherwise would not be identified**



## Virtual Screening (100K compounds, 124 actives): 1a9u DFG-in X-ray and 1kv2 DFG-out from IFD:



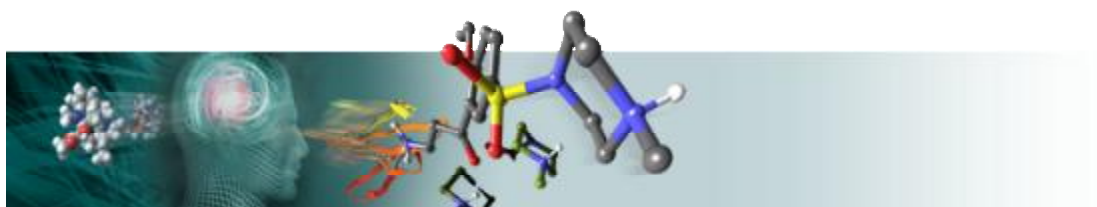
SCHRÖDINGER.

# Prime-Related Publications

- X. Li, M. P. Jacobson, and R. A. Friesner. "High Resolution Prediction of Protein Helix Positions and Orientations" *Proteins*, 55 (2004) 368-382.
- M. P. Jacobson, D. L. Pincus, C. S. Rapp, T. J. F. Day, B. Honig, D. E. Shaw, and R. A. Friesner. "A Hierarchical Approach to All-Atom Loop Prediction" *Proteins*, 55 (2004) 351-367.
- V. Guallar, M. P. Jacobson, A. McDermott, and R. A. Friesner. "Computational Modeling of the Catalytic Reaction in Triose Phosphate Isomerase" *J. Mol. Biol.*, 337 (2004) 227-239.
- E. A. Coutsiias, C. L. Seok, M. P. Jacobson, and K. A. Dill. "A Kinematic View of Loop Closure" *J. Comp. Chem.*, 25 (2004) 510-528.
- M. P. Jacobson, R. A. Friesner, Z. Xiang, and B. Honig. "On the Role of Crystal Packing Forces in Determining Protein Sidechain Conformations", *J. Mol. Biol.*, 320 (2002) 597-608.
- M. P. Jacobson, G. A. Kaminski, R. A. Friesner, and C. S. Rapp. "Force Field Validation Using Protein Sidechain Prediction" *J. Phys. Chem. B*, 106 (2002) 11673-11680.
- M. Andrec, Y. Harano, M. P. Jacobson, R. A. Friesner, and R. M. Levy. "Complete Protein Structure Determination Using Backbone Residual Dipolar Couplings and Sidechain Rotamer Prediction" *J. Struct. Funct. Genomics*, 2 (2002) 103-111.
- Z. Yu, M. P. Jacobson, C. S. Rapp, and R. A. Friesner. "First-Shell Solvation of Ion Pairs: Correction of Systematic Errors in Implicit Solvent Models" *J. Phys. Chem. B*, 108 (2004) 6643-6654.

# IFD Publications

- [Recent lists](#)
- <http://www.schrodinger.com/Publications.php?mID=15&sID=18&cID=45>



SCHRÖDINGER.