



# High-Throughput Docking

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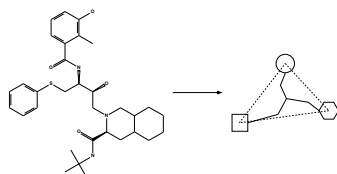


## Fragment-Based Docking

Our approach consists of four modules (I-IV), which perform different steps of the docking procedure.



**I. DAIM** preprocesses the molecules and decomposes them into chemical fragments. It also allows to filter the molecules for the occurrence of certain fragments to reduce the library size.

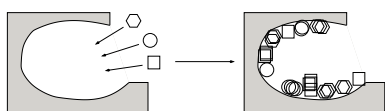


Left: The molecule (viracept). Right: The representation of this molecule with the fragments identified by DAIM.

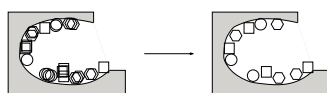


**II. SEED** [1, 2] places the rigid fragments in the binding site using an accurate energy function including electrostatic solvation based on the generalized Born approach [3]. The electrostatic component of the binding energy is approximated by the sum of the following terms:

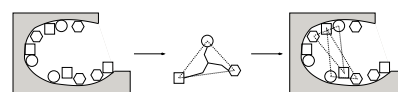
- Screened receptor-fragment interaction: intermolecular electrostatic energy between the fragment and the receptor in the solvent.
- Partial desolvation of the receptor (fragment): electrostatic energy difference caused by the displacement of high dielectric solvent by the volume of the fragment (receptor).



**III. SFI** clusters the geometrical centers found by SEED to reduce their number.



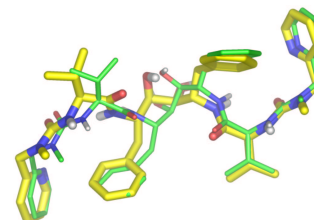
**IV. FFLD** [4] uses a Genetic Algorithm to dock the whole – fully flexible – molecules by trying to place the fragments identified by DAIM at the positions determined by SEED–SFI. The scoring function contains terms for van-der-Waals interaction, hydrogen bonds and unfavorable polar contacts.



FFLD generates a conformation and tries to put it on the corresponding SEED points.

## Validation on HIV-1 Protease

A set of 4 different HIV-1 protease–ligand complexes was used to test the docking approach. The number of ligand rotatable bonds (corresponding to the number of degrees of freedom, since the protein is kept rigid) ranged from 10 to 22. All ligands could be docked within an RMSD of 2 Å with respect to the crystallographic structure.



Structure of an HIV-1 protease inhibitor with 21 rotatable bonds docked by FFLD (thick, yellow). The X-ray structure (thin, green) is shown as a basis of comparison. RMSD (heavy atoms) 1.05 Å.

## Application on $\beta$ -Secretase (Alzheimer)

We have recently screened a library of 10'000 compounds (with 2-11 rotatable bonds) for  $\beta$ -secretase inhibitors. Experimental validation is in progress.

## References

- [1] MAJEUX, N., SCARSI, M., APOSTOLAKIS, J., EHRHARDT, C., AND CAFLISCH, A. Exhaustive docking of molecular fragments with electrostatic solvation. *Proteins* 37 (1999), 88–105
- [2] MAJEUX, N., SCARSI, M., AND CAFLISCH, A. Efficient electrostatic solvation model for protein-fragment docking. *Proteins* 42 (2001), 256–268
- [3] SCARSI, M., APOSTOLAKIS, A., AND CAFLISCH, A. Continuum Electrostatic Energies of Macromolecules in Aqueous Solutions. *J. Phys. Chem. A* 101 (1997), 8098–8106
- [4] BUDIN, N., MAJEUX, N., AND CAFLISCH, A. Fragment-based flexible ligand docking by evolutionary optimization. *Biol. Chem.* 382 (2001), 1365–1372