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published in

*From Computational Biophysics to Systems Biology (CBSB07),
Proceedings of the NIC Workshop 2007,*
Ulrich H. E. Hansmann, Jan Meinke, Sandipan Mohanty,
Olav Zimmermann (Editors),
John von Neumann Institute for Computing, Jülich,
NIC Series, Vol. 36, ISBN 978-3-9810843-2-0, pp. 263-265, 2007.

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Receptor Specific Forcefield: Improving Classical Forcefields with Quantum Mechanical Calculations

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We report results for the in-silico screening of a database of 10000 flexible compounds against various crystal structures of the thymidine kinase receptor complexed with 10 known substrates. The ligands were docked using FlexScreen, a recently developed docking tool based on the stochastic tunneling method. We used a first-principle based scoring function. For rigid receptor conformations we find large deviations in the rank of the known inhibitors depending on the choice of receptor conformation. These data demonstrate that the failure to dock originates from the neglect of receptor degrees of freedom and is not attributable to deficiencies in the scoring function or the docking algorithm. We then performed a screen in which critical receptor sidechains were permitted to change their conformation and found improved scores for those inhibitors that did not dock well in any of the previous screens. So, the consideration of receptor sidechain flexibility in FlexScreen improves the quality of the screening approach. We also demonstrate how the inclusion of QM-calculations of receptor-ligand complexes with the Fragment Molecular Orbital Method (FMO)¹, can be used to improve a classical forcefield. In comparing this QM-forcefield for protein and ligand with a standard ab-initio forcefield (ESFF) we can demonstrate a performance gain.

1 Methods

Docking Method: Stochastic optimization with STUN²: Non-linear transformation to the potential energy surface using

$$E_{STUN}(x) = \ln \left(x + \sqrt{x^2 + 1} \right), \quad (1)$$

with $x = \gamma(E - E_0)$, $\gamma = 0.05$ Mol/kJ and E_0 is the lowest energy encountered during the simulation.

Scoring Function:

$$S = \sum_{Protein} \sum_{Lig., fl.SC.} \left(\frac{R_{ij}}{r_{ij}^{12}} - \frac{A_{ij}}{r_{ij}^6} + \frac{q_i q_j}{r_{ij}} \right) + \sum_{h-bonds} \cos \Theta_{ij} \left(\frac{\tilde{R}_{ij}}{r_{ij}^{12}} - \frac{\tilde{A}_{ij}}{r_{ij}^{10}} \right) \quad (2)$$

Partial charges q_i are usually evaluated with InsightII and ESFF forcefield, Lennard-Jones parameters R_{ij} , A_{ij} from OPLSAA or from AutoDock and Hydrogen bond parameters \tilde{R}_{ij} , \tilde{A}_{ij} from AutoDock.

2 Results

We investigate the accuracy of the predicted ligand-receptor conformation for 83 complexes of the high resolution ASTEX/CCDC dataset for which crystal structures with an experimental accuracy of better than 2 Å are available. For each receptor-ligand complex we perform 10 independent simulations. The resulting conformations are ordered by energy according to the scoring function. The median RMS deviation between the predicted and the experimental structure is 0.83 Å, only ten ligands fail to reach the binding mode within the experimental resolution.

2.1 Astex Data Set Results

With these results and the docking results³ of three other programs (Glide, Gold and FlexX) we compare: 1) RMSD as a sign of the docking accuracy, and 2) The docking reliability as the percentage of having a RMS better than 2.0 Å.

	FlexScreen	Glide	Gold	FlexX:
FlexScreen wins/total		26/56	18/25	44/56
Results < 2.0 Å in %	80	71	76	57

FlexScreen performed (almost) equally good or better in accuracy and reliability in comparison with all other automated docking methods for which data is available.

Between the remaining difficulties for our approach we find that: 1) Steric clashes in the experimental X-ray structure between ligand and the receptor, 2) Water molecules which have a direct contact to the ligand are sometimes necessary to find the experimental binding mode, 3) Deficiency of the scoring function for solvation energies, 4) Ligands binding to metal complexes: Metal complexes have their specific group geometry and should be considered in *FlexScreen*.

2.2 Docking Study to Human Estrogen α

The ER α (pdb code 1ERE) was previously characterized at the HF/STO-3G level using the fragment molecular orbital (FMO) method¹.

As QM calculations are computationally very expensive, even with the FMO-technique, the binding energies for the ligands were calculated with respect to the most important fifty amino acid residues of the receptor and is therefore also used for our docking runs.

In this study we investigated the influence on QM-based based parameters for the ligands and the receptor on the binding energy accuracy.

We distinguished three cases; 1) QM partial charges for protein and ligands, 2) ESFF partial charges for protein and ligands, 3) QM partial charges for protein and ESFF partial charges for the ligands.

With only one receptor structure *FlexScreen* could well reproduce the binding modes of the quantum mechanical calculations. This is possible, because *FlexScreen* supports side-chain flexibility: the side-chains can accommodate to different ligands.

Comparison with FMO Binding Energies: With a correlation coefficient $R = 0.94$ the correlation is highest the more parameters are from the qm calculations.

Comparison with Experimental Binding Energies: We also compare the calculated binding energies of *FlexScreen* with experimental relative binding affinities (relative to the binding affinity of 17- β -Estradiol (RBA)). Also in comparison to the experimental RBA the correlation is highest the more parameters are from the qm characterization of the protein and the ligands. Case 1 and Case 3 have a higher correlation coefficient than Case 2, for which solely the ESFF-forcefield is used. In overall we get the following correlation coefficients:

	Case 1	Case 2	Case3
QM Energies	0.94	0.71	0.79
RBA	0.68	0.37	0.52

3 Discussion

A mixed setup as in Case 3 is especially interesting for high-throughput screening, because a significant part of the improvement is retained, when only the receptor is treated with QM-based parameters, while the ligands are parameterized with a purely classical model. The protein preparation may take days of calculations, but for each ligand the calculation time is reduced to a minimum. As an additional improvement a setup as in Case 3 seems also to improve the docking accuracy for the binding mode.

Acknowledgments

We thank the Fond der Chemischen Industrie, the BMBF, the Deutsche Forschungsgemeinschaft (grant WE) and the Kurt Eberhard Bode Stiftung for financial support.

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