

Abstract

Optimization of Semiempirical Quantum Mechanical Methods for *in Silico* Drug Design

Doctoral thesis

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The subject of this thesis is the optimization of semiempirical quantum mechanical methods (SQM) for their use in *in silico* drug design. The thesis covers two topics – COSMO2 solvation model optimization part and PLF547, PLA15 dataset development part.

The first part is devoted to the optimization of COSMO solvation model by addition of a nonpolar term and reparametrization of the model for SQM methods PM6 and PM7. We have shown that the accuracy of the resulting “COSMO2“ optimized model improved on all the tested datasets and we have compared it to other selected SQM solvation models. The method has also been tested on the protein ligand complexes as a part of a scoring function, where it provides better prediction of binding affinity of drug candidates for their target protein.

The second part of the thesis describes the construction of datasets for noncovalent interactions aimed specifically to represent an environment of an enzyme active site complexed with a ligand with reliable benchmark values of interaction energies in vacuum and solvent (water). The developed PLF547 and PLA15 datasets are suitable for testing and development of methods for the use in drug design. We have assessed the accuracy of several SQM, few quantum mechanical (QM) methods and solvation models including COSMO2 on the developed datasets.