

Improving binding mode predictions by docking into protein-specifically adapted potential fields

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Accurately predicting ligand binding modes by docking techniques is an essential step for the success of structure-based drug design and virtual screening. Only recently, however, general docking approaches have been improved by exploiting structural information about known ligands binding to the target protein ("similarity-driven docking") [1]. An even more convincing approach would be to include also energetic information.

Hence, in this study, structural and energetic information about known protein-ligand complexes is exploited to tailor knowledge-based potentials using a "reverse", protein-based CoMFA-type (= AFMoC) approach [2]. That way, effects due to protein flexibility and information about multiple solvation schemes can be implicitly incorporated. Interaction fields specifically adapted to one protein are developed starting from knowledge-based DrugScore potentials [3] by considering additional ligand-based information in a CoMFA-type approach. Then, the interaction fields serve as objective function in docking optimizations with AutoDock. Compared to the application of AFMoC for binding affinity predictions, a Shannon-entropy based column filtering of the descriptor matrix and the capping of adapted repulsive potentials within the binding site have turned out to be crucial for the success of this method.

The new developed approach was validated on a data set of 66 HIV-1 protease inhibitors, for which structural information was available. Convincingly, for ligands with up to 20 rotatable bonds, in more than 75 % of all cases a binding mode below 2 Å rmsd has been identified on the first scoring rank when AFMoC-based potentials were used as objective function in AutoDock. With respect to non-adapted DrugScore or AutoDock fields, the binding mode prediction accuracy was significantly improved by 14 %. Noteworthy, very similar results were obtained for training and test set compounds, demonstrating the strength and robustness of this method. We are convinced that our approach represents an important step in improving the accuracy of binding mode predictions.

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[2] H. Gohlke, G. Klebe, *J. Med. Chem.* 2002, 45, 4153.

[3] H. Gohlke, M. Hendlich, G. Klebe, *J. Mol. Biol.* 2000, 295, 337.