Conference abstract PO-04

Induced Fit Docking into a SERT Homology Model

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The human serotonin transporter (hSERT), embedded in the presynaptic membrane, is responsible for the reuptake of serotonin from the synaptic cleft, thus terminating neurotransmission. The structure of the SERT has not yet been resolved by experimental means. Determining hypothese for binding modes between ligands and the binding site of a protein with no available high-resolution structural data can be realized by creating a protein homology model, which further can be used as basis for ligand-protein docking experiments. Recently, an efficient docking method taking into account flexibility both of ligand and target, called Induced Fit Docking, has been introduced. Within this study we compare the results obtained with induced fit docking with those which have been obtained recently by applying a statistical approach [1].

In the case of the SERT a detailed sequence alignment with a prokaryotic leucine transporter (LeuT, PDB Code 2QB4), both belonging to the neuro-transmitter sodium symporter (NSS) or solute carrier 6 family (SLC6), is available [2]. Although the sequence identity is relatively poor, it offers a highly conserved binding site, making homology modelling possible.

The docking was performed with a library containing serotonin and a selection of drugs known to bind into the SERT using the Induced Fit application of Schrödinger, LLC, granting the binding site more flexibility than other docking programs. Surprisingly, Induced Fit docking did not necessarily lead to a significantly larger number of pose clusters than already identified by Weissensteiner et al. In addition, already published binding interactions [3] were confirmed at a good calculation time, promising reasonable propositions for substances with yet unknown interaction patterns.

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[3] Celik L, Sinning S, Severinsen K, Hansen CG, Møller MS, Bols M, Wiborg O, Schiøtt B. Binding of serotonin to the human serotonin transporter. Molecular modeling and experimental validation. J Am Chem Soc. 2008; 130: 3853–3865. doi:10.1021/ja076403h