

Homology model based virtual screening for GPCR ligands using docking and target-biased scoring

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G-protein coupled receptors (GPCRs) are one of the most important drug targets for the pharmaceutical industry.^[1] For instance, metabotropic glutamate receptors (mGluRs) have attracted interest due to their role as modulators of major neurotransmitter systems in the central nervous system. Detailed structural information about GPCRs is lacking. As a consequence, computational design of modulators for GPCRs can only be accomplished by using structure-based approaches grounded on homology models, or by using ligand-based virtual screening methods.

In the present study, we investigated the combination of two recently reported techniques for the improvement of homology model based virtual screening. First, we applied ligand supported homology modeling.^[2] Clues to infer the binding modes of the ligands were provided by data from mutagenesis studies. Second, to rank order docking solutions, we developed a scoring scheme that exploits the patterns of interactions between ligands already known to bind to the target, and the binding site. As reference ligands, the compounds that have already been employed to support homology modeling were used. Patterns of interactions were modeled using binary ligand receptor fingerprints,^[3] as pioneered by Singh *et al.*^[4] The similarity of two fingerprints was evaluated using the Tanimoto coefficient.

Our methodology, subsequently referred to as interaction fingerprint based similarity (IFS), has been tested in retrospective virtual screening experiments against mGluR subtype 5. It is expected that the identification of negative allosteric modulators of mGluR5 will open up new therapeutic possibilities to treat pain, anxiety, or Parkinson's disease.^[5] To put the results into proper perspective, docking solutions were also rank ordered using conventional scoring functions (D-Score, PMF-Score, G-Score, Chemscore, and FlexX-Score). Using IFS, the enrichment rates could significantly be improved. We also show that the power of IFS to discriminate between active and inactive compounds is superior to the discriminatory power of the conventional scoring functions. Our results indicate that the presented approach might serve as a general setup for successful GPCR virtual screening.

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