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The novel approach in structure-based 3D pharmacophore model generation and its potential applications in virtual screening

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The pharmacophore modelling technique is a well-know and broadly used tool in drug discovery. Up to date, various approaches to pharmacophores generation and their application in virtual screening, *de novo* design, lead optimization and multi-targeting, have been reported [1]. Construction of pharmacophore can be based solely on ligands or on information retrieved from sequence or structure of a protein. There are also hybrid approaches [2] mixing those information to get pharmacophore model recognizing broader range of ligands and trying to describe the dynamic of ligand-receptor complex.

Herein, we present the new strategy in structure-based 3D pharmacophore model generation based on docking of known ligands, and further ligand-receptor complexes analysis using structural interaction fingerprints (SIFts) [3]. In parallel, the docked ligand conformations were mapped to a set of pharmacophore features (HBA, HBD, PI, HYD and AR) creating a comprehensive map of spatial distribution of various pharmacophore points in the binding site. The pharmacophore features of the same kind were then clustered, taking distances between all pairs of centroids as a classification criterion. The final pharmacophore hypothesis were created from the averaged cluster centroid points, but only those matching crucial amino acids indicated by SIFt analysis of ligand-receptor complexes. Combinations of three-, four- and five-features pharmacophore hypotheses were next formed (Screen Library protocol from Discovery Studio 2.5) and used to search the best combination of models, optimized for a given performance parameter.

The proposed methodology, tested for 5-HT_7 and 5-HT_6 receptors, compared to some literature ligand-based pharmacophore models showed better performance in screening of databases. Additionally, it was also applied to search the best combination of models, by optimization (maximization) of selectivity coefficient between some serotonin receptor subtypes, i.e. 5-HT_6/5-HT_7 and 5-HT_6/5-HT_{1A}.

Literature:

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