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Combination of structural interaction profiles as a method for optimization of its application in docking results analysis

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Prediction of spatial orientation of a molecule in a binding pocket of a given receptor and inferring on its basis about the potential activity of a particular compound still constitutes a very challenging task for computational part of drug design campaigns [1]. There are some approaches that enable automation of the procedure of ligand-protein complexes analysis, among which there is a combination of Structural Interaction Fingerprints with machine learning algorithms [2]. However, there still remains the problem of selection of proper set of models for docking studies – should it be just one receptor providing the best discrimination between actives and inactives or maybe using ensemble approach is better, as it is in case of ALiBERO [3].

The primary objective of the study was to optimize the number of homology models used for SIFTs profiles calculations on the basis of ligand-beta2 adrenergic receptor complexes. The results obtained for homology models of the receptor constructed on 9 different templates were also compared with docking performed with the use of crystal structures of the protein. The docking outcome was represented by Structural Interaction Fingerprint (SIFt) and for each ligand such representation was averaged over various models used for particular analysis (the number of models taken into account ranged from 3 to 20). Such data was then examined with the use of the Support Vector Machine algorithm to distinguish profiles belonging to active molecules from those that were characterizing inactive compounds. The analysis enabled determination of the optimal number of models that are recommended for use in this kind of study.

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