The new strategy in structure-based pharmacophore model generation and its applications in virtual screening

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Introduction

The pharmacophore modelling technique is a well-established and one of the major methods used in screening of large databases during the early stages of drug development. Depending on available information about a given biological target, the pharmacophore modelling approaches could be divided in two main types: ligand-based and structure-based. Recently, hybrid methods [1,2], mixing information from both approaches to get pharmacophore model recognizing broader range of ligands and describing the dynamics of ligand-receptor complex, have been developed.

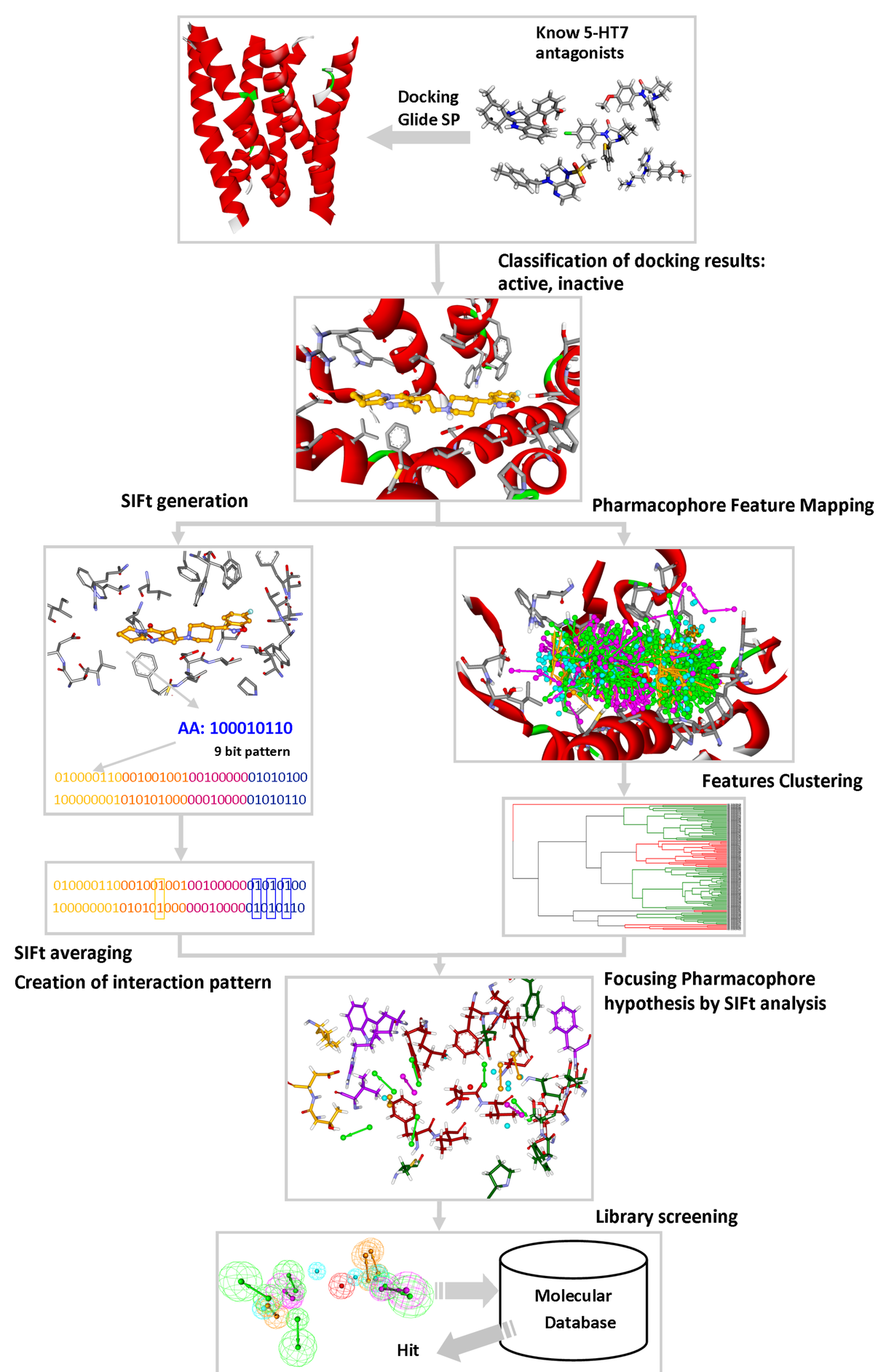
Here, we present the method of structure-based pharmacophore model generation based on docking of known ligands to a set of different receptor conformations, and further complexes analysis with structural interaction fingerprints (SIFts).

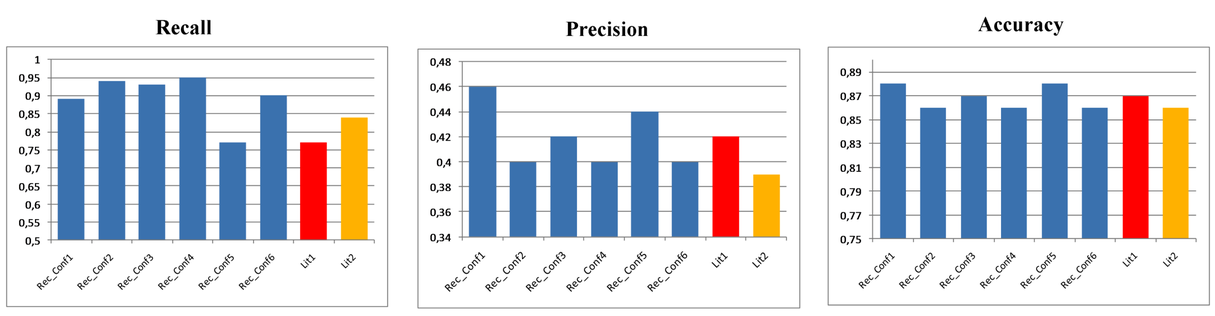
Methods

The set of over 700 known, and structurally diversified, 5-HT7R ligands was docked (Glide SP mode) to the six, previously developed [2], homology models of 5-HT7R. The poses which did not interact with Asp3.32 were removed since it is the well-recognized anchoring point responsible for ligands binding. For such focused libraries, the structural interaction fingerprint (SIFt) method was used to identify amino acids that interact with the corresponding ligand [4]. The results were stored in 1D binary string, where nine bit pattern was used to describe the interaction type: any contact, backbone, side chain, polar, aromatic, hydrophobic interaction, hydrogen bond donor/acceptor and charged. Then, for each receptor, the normalized frequencies of the given interaction occurence were calculated, prioritizing the most interacting amino acids.

The docked ligand conformations were mapped to a set of pharmacophore features, namely hydrogen bonding acceptor (HBA), positive ionisable group (PI), the hydrophobic region (HYD), and the aromatic ring (AR). The comprehensive map of the spatial distribution of various pharmacophore points in the binding site was thus obtained. The same kind of pharmacophore features were then clustered, taking into account the distances between all possible pairs of feature centroids as a classification criterion. On the basis of the obtained dendrograms, which show the clusters distribution of individual pharmacophore features, the densest clusters were selected, for which an average location was calculated. Only feature centroids complementary to the set of previously predicted interacting amino acids (interactions > 0.5) were kept.

In order to evaluate the obtained pharmacophore hypotheses in real-life experiment of Virtual Screening, an external test set was prepared. It contained 177 actives (not used in model training) and 1600 decoys. Decoys set was prepared using the same methodology as applied in DUD creation [5]. The „Screen Library" Protocol from Discovery Studio 2.5 was used to screen the test set against all possible combinations of three-, four- and five-features pharmacophore models. In the final stage, the pharmacophore models which did not contain positive ionizable group feature were removed.





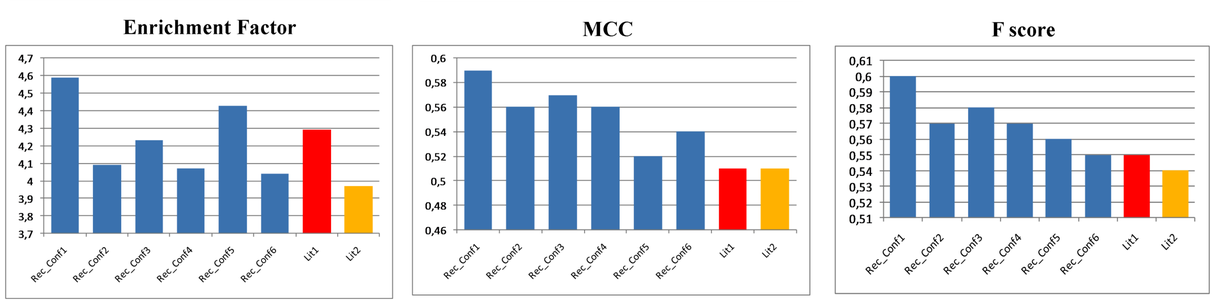


Figure 1. The schema of implemented receptor-based pharmacophore model generation.

Results and Conclusions

In order to assess the performance of the obtained models, the following criteria were used: actives recall, precision, accuracy, enrichment factor (EF), the Mathews correlation coefficient (MCC) and F-score. Results show very-high effectiveness of the analyzed models (i.e. high recall, accuracy, and EF parameter values), which makes this method an atractive tool for Virtual Screening.

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