The novel approach in structure-based 3D pharmacophore model generation and its evaluation on 5-HT$_6$R homology models

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Introduction

Here, we present a novel method of receptor-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 diverse set of 128 of known 5-HT$_6$R ligands (with activity threshold K_i < 100 nM) was docked to a set of different homology models (built on A2A, Rho and β2 templates). The poses which did not interact with Asp3.32 were removed since it is the well-recognized anchoring point responsible for ligands binding. The structural interaction fingerprint (SIFt) method was used to identify amino acids that interact with the corresponding ligand [1]. 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 averaged interaction occurrence were calculated, prioritizing the most interacting amino acids.

On the docked ligand conformations a set of pharmacophore features, namely hydrogen bonding acceptor (HBA), positive ionisable group (PI), the hydrophobic region (HYD), and the aromatic ring (AR) were mapped. The same kind of pharmacophore features were then clustered and an average location was calculated. Only feature centroids complementary to the set of previously predicted interacting amino acids were kept.

The „Screen Library" Protocol from Discovery Studio 2.5 was used to generate all possible combinations of three-, four- and five-features pharmacophore models. Then, using an algorithm that maximize one of the performance parameter (e.g. MCC or Fscore), the smallest linear combination of pharmacophore models were found.

In order to evaluate the obtained linear combinations, an external test set was prepared containing 170 actives (not used in model training) and 1530 decoys (prepared followed by DUD methodology [2]). The results were compared with the performance of known ligand-based pharmacophore models [3].

Table 1. The influence of performance parameter optimization (here MCC) on the global RBPM performance.

Rec model	Recall	Precision	Specificity	EFactor	Fscore	Accuracy	MCC
Rho_205	0,97	0,11	0,40	1,54	0,20	0,44	0,20
Rho_205_MCC	0,76	0,20	0,76	2,77	0,32	0,76	0,31
A2A_127	0,95	0,11	0,41	1,54	0,20	0,45	0,19
A2A_127_MCC	0,72	0,51	0,94	6,91	0,60	0,93	0,57
β2_177	0,98	0,13	0,48	1,78	0,23	0,52	0,24
β2_177_MCC	0,78	0,60	0,96	8,08	0,68	0,94	0,65

Figure2. Comparison of different performance parameters for developed structure-based (blue bars) and reference models (yellow) [3].

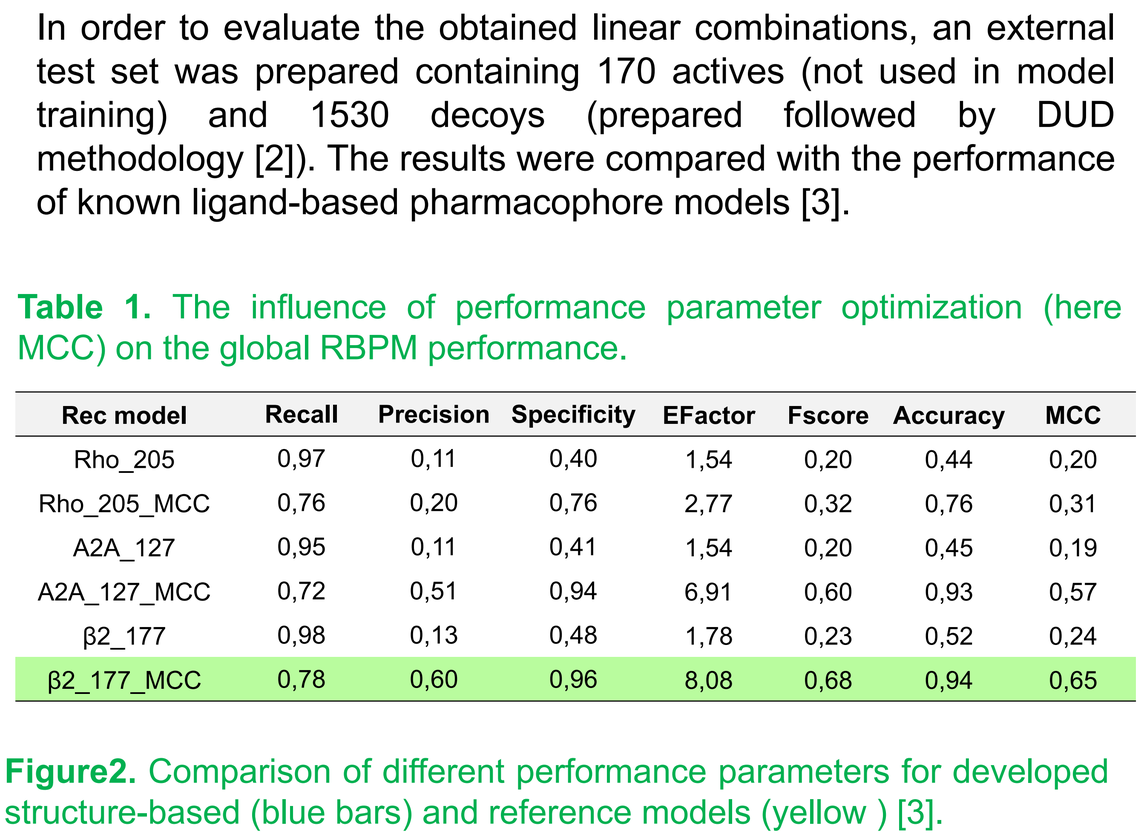
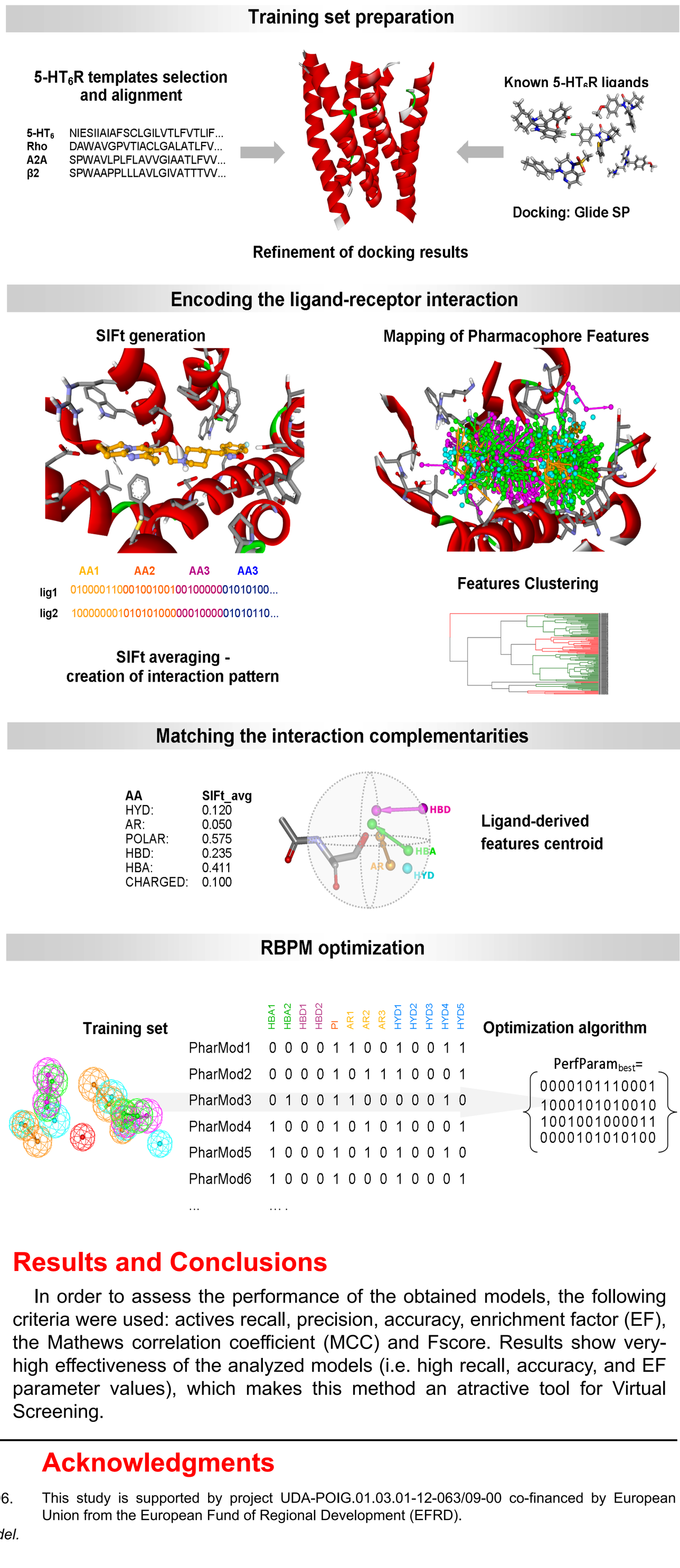


Figure 1. The schema of implemented receptor-based pharmacophore model generation.



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 Fscore. 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.

References

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