The novel approach in structure-based 3D pharmacophore model generation. An application to searching for 5-HT$_6$R selectivity hypothesis

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Introduction

We present a new 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). Herein, it was applied to searching of selective hypothesis for 5-HT$_6$R.

Methods

The diverse set of 300 of known 5-HT$_6$R ligands (with activity threshold $K_i < 300$ nM) was docked to a set of different homology models (built on A2A, Rho and beta2 templates). 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. On the docked ligand conformations a set of pharmacophore features, namely hydrogen bonding acceptor (HBA) and donor (HBD), 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 and training set containing selective and non-selective ligands (for 5-HT$_6$/5-HT$_7$Rs and 5-HT$_6$/5-HT$_{1A}$Rs) were used to generate an initial subset of three-, four- and five-features pharmacophore models. Then, using an algorithm that maximizes the MCC parameter, the minimal linear combination of pharmacophore models was found.

In order to evaluate the obtained linear combinations, an external test set, containing selective and non-selective compounds (not used in model training) was used. The results were compared with the performance of known ligand-based pharmacophore models [3].

Figure 1. The scheme of receptor-based pharmacophore model generation.

Figure 2. Comparison of performance parameters for developed receptor-based (blue bars) and reference (yellow) models [3]. First panel corresponds to model found for 5-HT$_6$/$_7$Rs, whereas the second for 5-HT$_6$/$_{1A}$Rs.
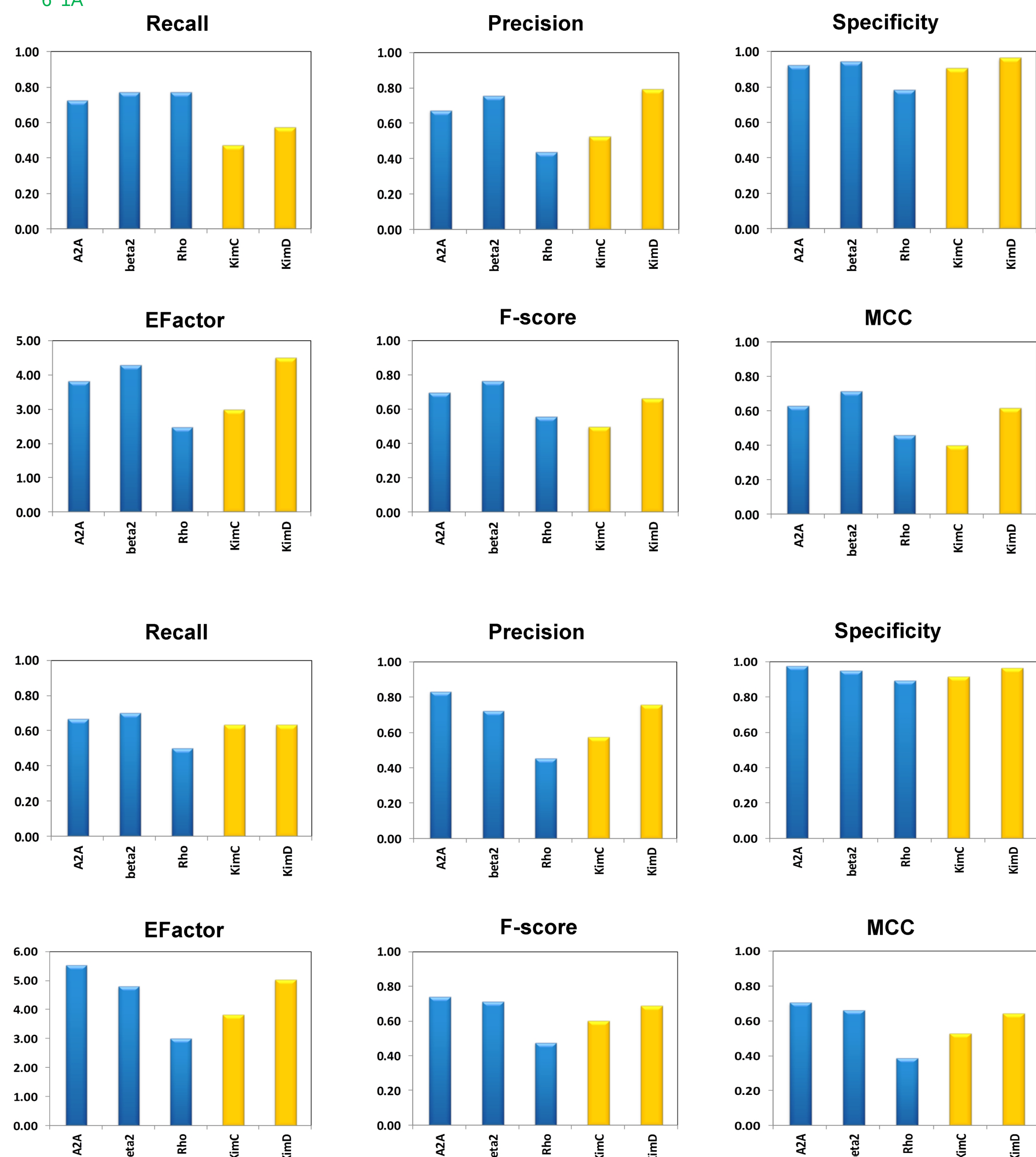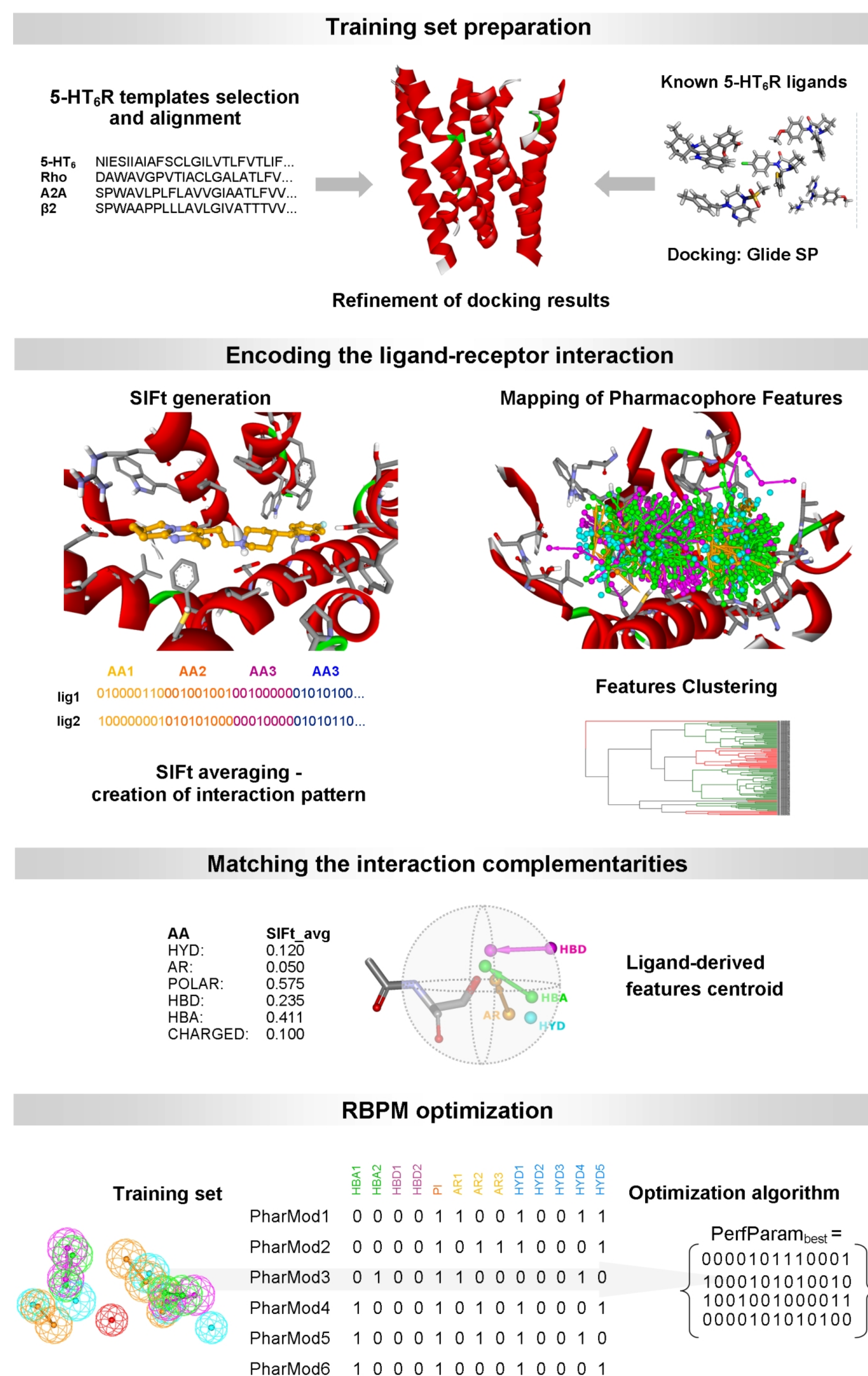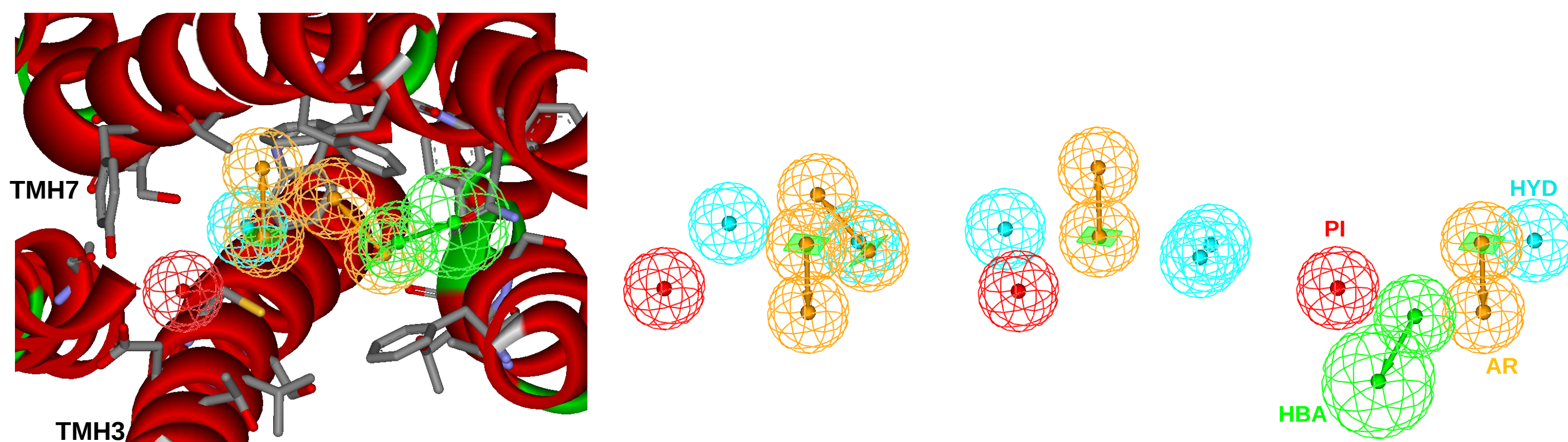

Figure 3. The best linear combination of pharmacophore models found for 5-HT$_6$/5-HT$_7$Rs selectivity on A2A template.

Results and Conclusions

The performance of the obtained pharmacophore queries were assessed by the following criteria: recall, precision, specificity, enrichment factor (EF), the Mathew's correlation coefficient (MCC) and F-score. Results showed high effectiveness of the analyzed models, which makes this method an atractive tool to search for new selective ligands. Moreover, application of linear combination of hypotheses outperformed the classic ligand-based pharmacophore approach.

Not all receptor templates could be appropriate for models creation; the most selective combination for 5-HT$_6$/$_{1A}$Rs and 5-HT$_6$/$_7$Rs was obtained on A2A and beta2 templates, respectively. In both cases, the optimized model built on the rhodopsin template showed the worst performance.

References

[1] Deng J, Leo KW, Sanchez T, Cui M, Neamati N, Briggs JM, *J. Med. Chem.* **2005**, *48*, 1496.
[2] Huang N, Shoichet BK, Irwin JJ, *J. Med. Chem.* **2006**, *49*, 6789.
[3] Kim HJ, Doddareddy MR, Choo H, Cho YS, No KT, Park WK, Pae AN, *J. Chem. Inf. Model.* **2008**, *48*, 197.

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