Feature selection for structure based pharmacophore model by means of Structural Interaction Fingerprint and 3D motif

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Introduction

Pharmacophore models are a common tool used in experiments of Virtual Screening (VS) aimed for searching active compounds. Among the various methods of developing such molds, the structure based pharmacophore model is of great importance, as it encapsulates the information about the binding site of the target protein.
In this research we present the method of selecting the pharmacophore features of the amino acids forming the binding cleft, which play an important role in accommodating the active compounds. On the basis of Structural Interaction Fingerprints (SIFts) [1], the bitstrings describing ligand – receptor contacts in a formalized manner, the frequently interacting residues are selected, and an ensemble of atoms common for a set of ligand – protein complexes named 3D motif [2] is employed to assign the appropriate pharmacophore features of the binding site.
Such a model of the binding site can be further used in the process of developing the structure based pharmacophore model, or to apply the restrains for the docking experiments.

Methods

The target for this research was a Dopamine D3 receptor, which has a crystal structure deposited in Protein DataBank (PDB code 3PBL). A collection of 76 active ligands (with activity in Ki <10 nM) were fetched from ChEMBL database v12, and docked into the binding cleft of the D3R with Glide XP.
Successfully docked compounds were a basis to generate SIFt bit strings, and then SIFt profiles [3] containing per residue ratio of interactions with ligands. Docking poses were also used to construct a 3D motif structure, accommodating frequently interacting atoms of residues along with pseudo atoms reflecting average positions of ligands.
A substructure with frequently contacted residues was then extracted and pharmacophore features were assigned using an in house script. Relevant features were then filtered using both SIFt and 3D motif based criteria.

Results

The docking experiment successfully accommodated all of the input structures within the binding site (Fig. 1A), and interaction fingerprints were generated for the docking poses. SIFt profiles were generated with a number of different cut-off settings (allowing to ignore less frequent interactions), to assure the reasonable number of residues undergoing pharmacophore features placement. The cut-off values were between 0.8 and 0.95, resulting in 15 to 4 amino acids selected respectively(Fig. 1B).
The placement of pharmacophore features on the amino acids resulted in 33 pharmacophore points, and so a number of residues had multiple features assigned. The filtering was then necessary to reach no more than one feature per residue.
Neither 3D motif nor SIFt profile based approach did allow to reduce the number of pharmacophore features to one per residue, however, the combination of the two managed to achieve that goal (Fig. 2, Table 1).

Conclusions

The proposed methodology allows semi-automatic but viable description of the binding site of the receptor in terms of pharmacophore features. Such information can be further used in the process of the structure based pharmacophore modeling or to apply pharmacophore restrains on the docking experiments.

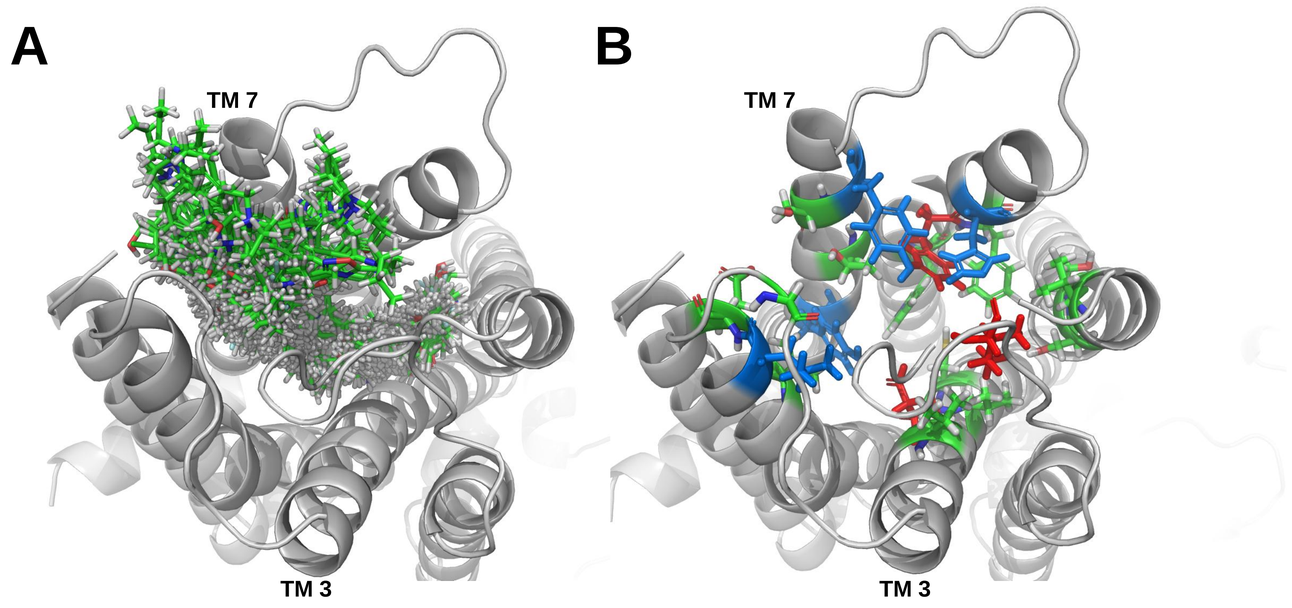

Figure 1. The docking poses of the Dopamine D3 receptor active ligands (**A**). The ensemble of ligand – receptor complexes was used to generate structural interaction fingerprints, and later on, the interaction profiles (**B**). Results for three different cut-off values are presented: 0.8 (green), 0.85 (blue) and 0.9 (red). Since the high values of cut-off narrow the residues subset to the more frequently interacting ones, the red set encloses in blue one, and blue set is a component of green one.

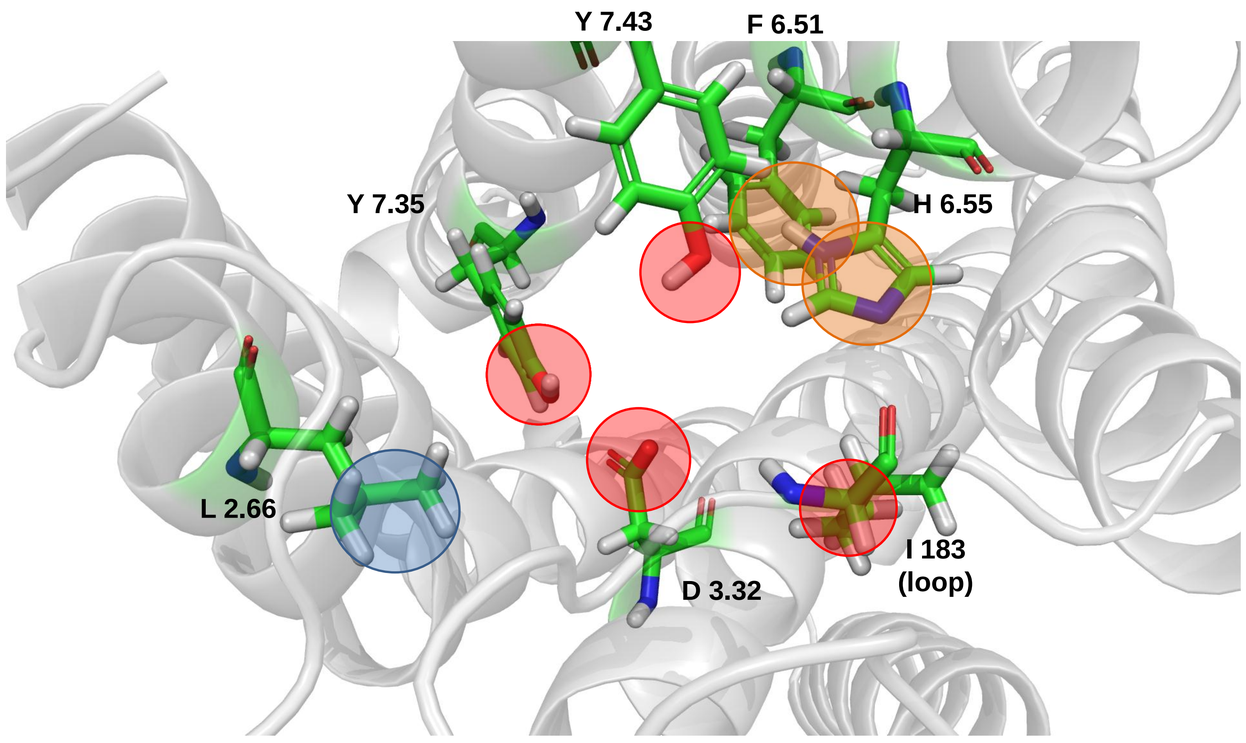

Figure 2. The results of the pharmacophore features filtering. Residues indicated in green were forming the interaction profile for cut-off value of 0.85. Color circles stand for the pharmacophore features assigned to the amino acids: blue – hydrophobic, red – hydrogen bond donor/acceptor, orange – aromatic.

Residue number	Pharmacophore features assigned	Final feature selected
L 2.66	Hb_donor, Hydrophobic	Hydrophobic
D 3.32	Hb_donor, Hb_acceptor, Charged,	Hb_acceptor
I 183 (loop)	Hb_donor, Hydrophobic	Hb_donor
F 6.51	Hb_donor, Hb_acceptor, Aromatic	Aromatic
H 6.55	Hb_donor, Hb_acceptor, Aromatic	Aromatic
Y 7.35	Hb_donor, Hb_acceptor, Aromatic	Hb_donor
Y 7.43	Hb_donor, Hb_acceptor, Aromatic	Hb_donor

Table 1. Residues selected by interaction profile with the pharmacophore features assigned by an automatic tool, and final feature filtered out by means of SIFt profiles and 3D motif.

References

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Acknowledgements

This study is supported by project “Diamentowy Grant” DI 2011 0046 41 financed by Polish Ministry of Science and Higher Education.