2D-SIFt – A Matrix Describing Detailed Interactions Between Ligand And Receptor

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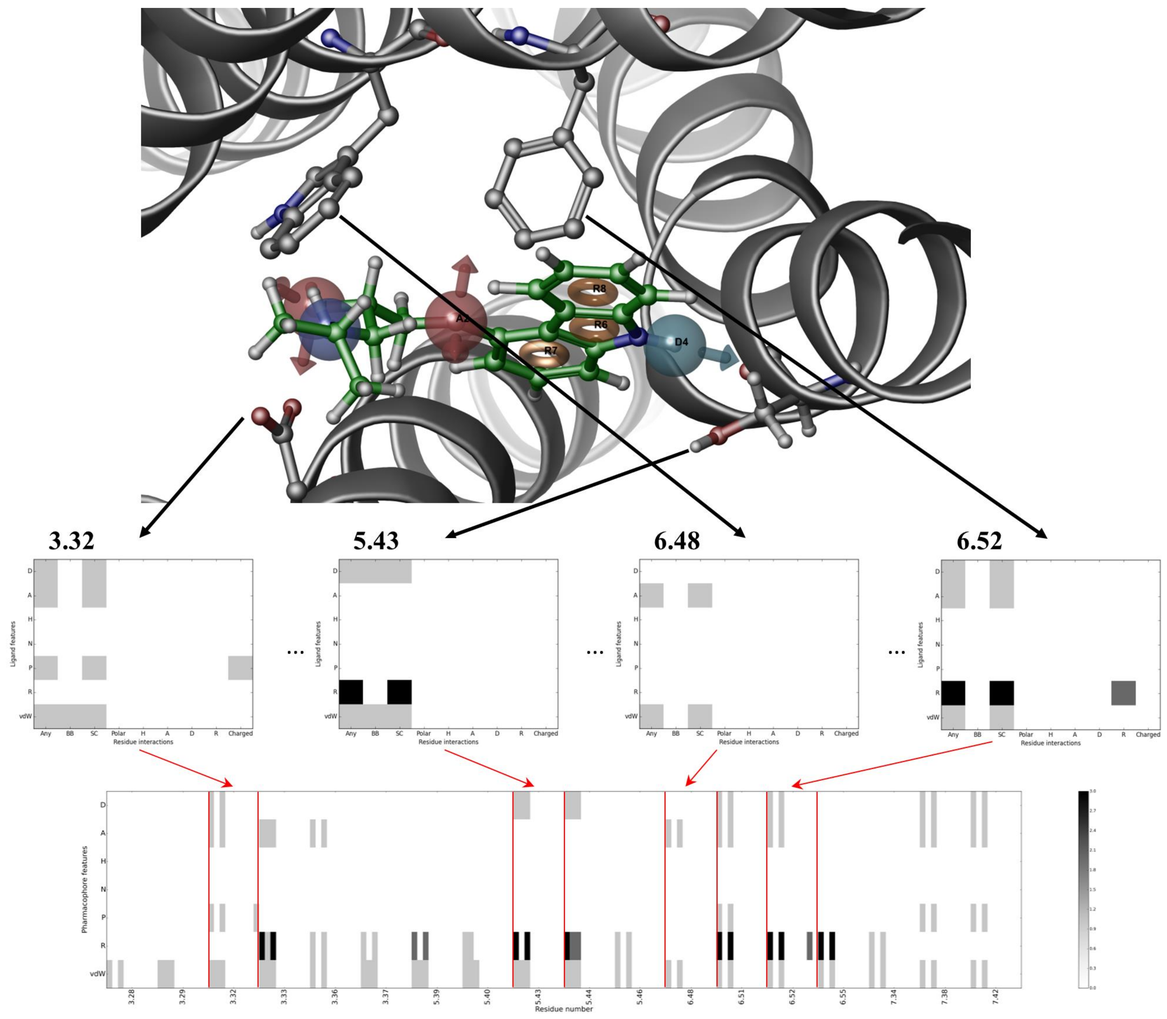

Figure 1. Workflow of constructing 2D-SIFt interaction matrix. The structure shown is the crystal structure of β2 Adrenergic receptor (PDB code 2RH1). The symbols in the tables correspond to ones of Table 1..

Table 1. Schematic representation of the 2D-SIFt chunk encoding interactions for one amino acid. The symbols in the **column** headers of the table describe types of interactions: **Any**, **BB** – with a backbone, **SC** – interaction with sidechain, **P** – polar, **H** – hydrophobic, **A** – hydrogen bond acceptor, **D** – hydrogen bond donor, **C** – charged interaction, **R** – aromatic;
rows encode standard pharmacophore features of the ligand: , **A** – hydrogen bond acceptor, **D** – hydrogen bond donor, **H** – hydrophobic, **N** – negatively charged group. **P** – positively charged group, **R** – aromatic, **vdW** – any atom

	Any	BB	SC	Polar	H	A	D	R	Charged
D	**1**	**0**	**1**	**1**	**0**	**1**	**0**	**0**	**0**
A	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
H	**2**	**1**	**1**	**0**	**2**	**0**	**0**	**2**	**0**
N	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
P	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
R	**1**	**0**	**1**	**0**	**1**	**0**	**0**	**1**	**0**
vdW	**1**	**1**	**1**	**1**	**1**	**0**	**0**	**2**	**0**

Methods

For a ligand-receptor complex, a ligand is divided into pharmacophore features using SMARTS patterns, then for every amino acid in the receptor, interactions between those features and given residue are evaluated and encrypted into the fields of interaction matrix. Six standard pharmacophore features are used in the descriptor (hydrogen bond donor, hydrogen bond acceptor, hydrophobic group, negatively charged group, positively charged group, aromatic ring). For each of the features, the occurrence of per residue interactions is evaluated and categorized according to predefined set (analogously to previously published research [2]). Default collection of residual contacts consists of nine types: any, side chain, backbone, hydrogen bond donor, hydrogen bond acceptor, charged, hydrophobic and aromatic. Concatenation of residual chunks results with a 6×(N·9) matrix of interactions, where N is a number of residues in protein. The cells in so created matrix can have value from 0 to M, M ϵ N, since there can be more than one separate pharmacophore features of one type within ligand interacting with one residue (for instance three phenyl groups surrounding a phenylalanine).

Results

The 2D-SIFt was applied to nine complexes of β_2-adrenergic receptor, four active (either crystalized with G protein or mimic; pdb: 4LDE,4LDL, 4LDO and 4QKX) and five inactive (pdb: 2RH1, 3D4S, 3NY8, 3NY9, 3NYA) with unique ligands. The comparison of average 2D-SIFt show the differences in both binding mode and pharmacophore features of the ligand types (Fig. 2).

Conclusions

The proposed descriptor allows rapid analysis of ligand-receptor complexes, allowing quick and easy identification of both protein and ligand hotspots. Such representation of the averaged complex may give hints for construction of pharmacophore models and can prove useful in virtual screening experiments (which will be tested in the future.)

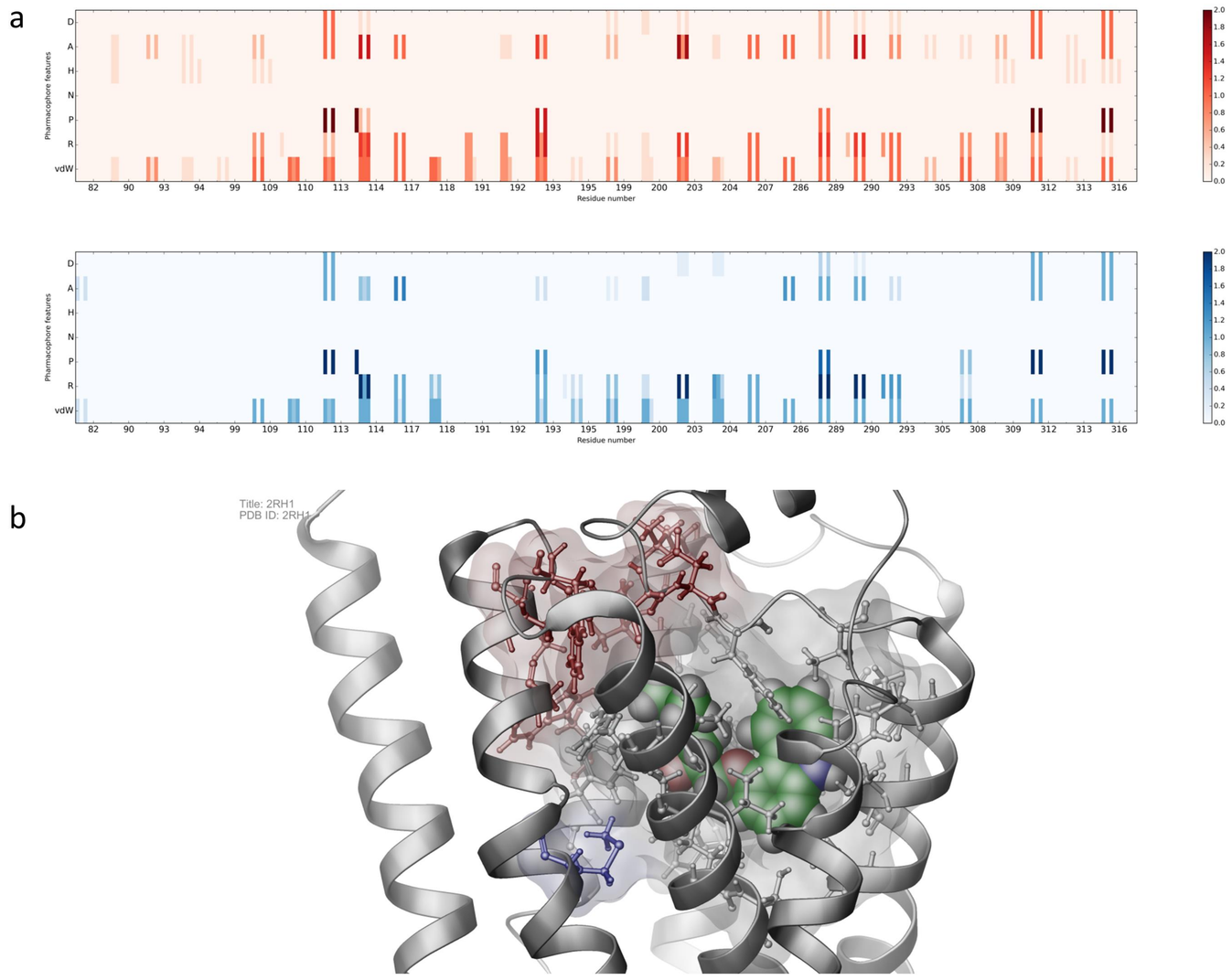

Figure 2. betweenT he agonistic and antagonistic binding site residues for β_2AR as depicted by **a)** a 2D-SIFt profile for agonists (red) and antagonists (grey), and **b)** the visualized on crystal structure 2RH1. Residues in white are common for both binding modes, blue is unique for binding antagonists and red for agonists.

References

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2. Mordalski S, Kosciolek T, Kristiansen K, Sylte I, Bojarski AJ, Protein binding site analysis by means of Structural Interaction Fingerprint patterns, Bioorg Med Chem Lett 2011 Nov 15;21(22):6816-9.

Acknowledgements

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