2D-SIFt – A Matrix Describing Ligand-Receptor Interactions

Stefan Mordalski, Andrzej J. Bojarski

Department of Medicinal Chemistry, Institute of Pharmacology Polish Academy of Sciences; Smetna 12 31-343 Krakow
e-mail: stefanm@if-pan.krakow.pl

Introduction

- New descriptor encoding ligand-receptor interactions in form of a matrix
- Basic element of 2D-SIFt represents contacts between an amino acid and each of pharmacophore features of the ligand
- Heat map produced from such descriptor allows easy identification of features of binding site and differentiation between binding modes of different ligand classes

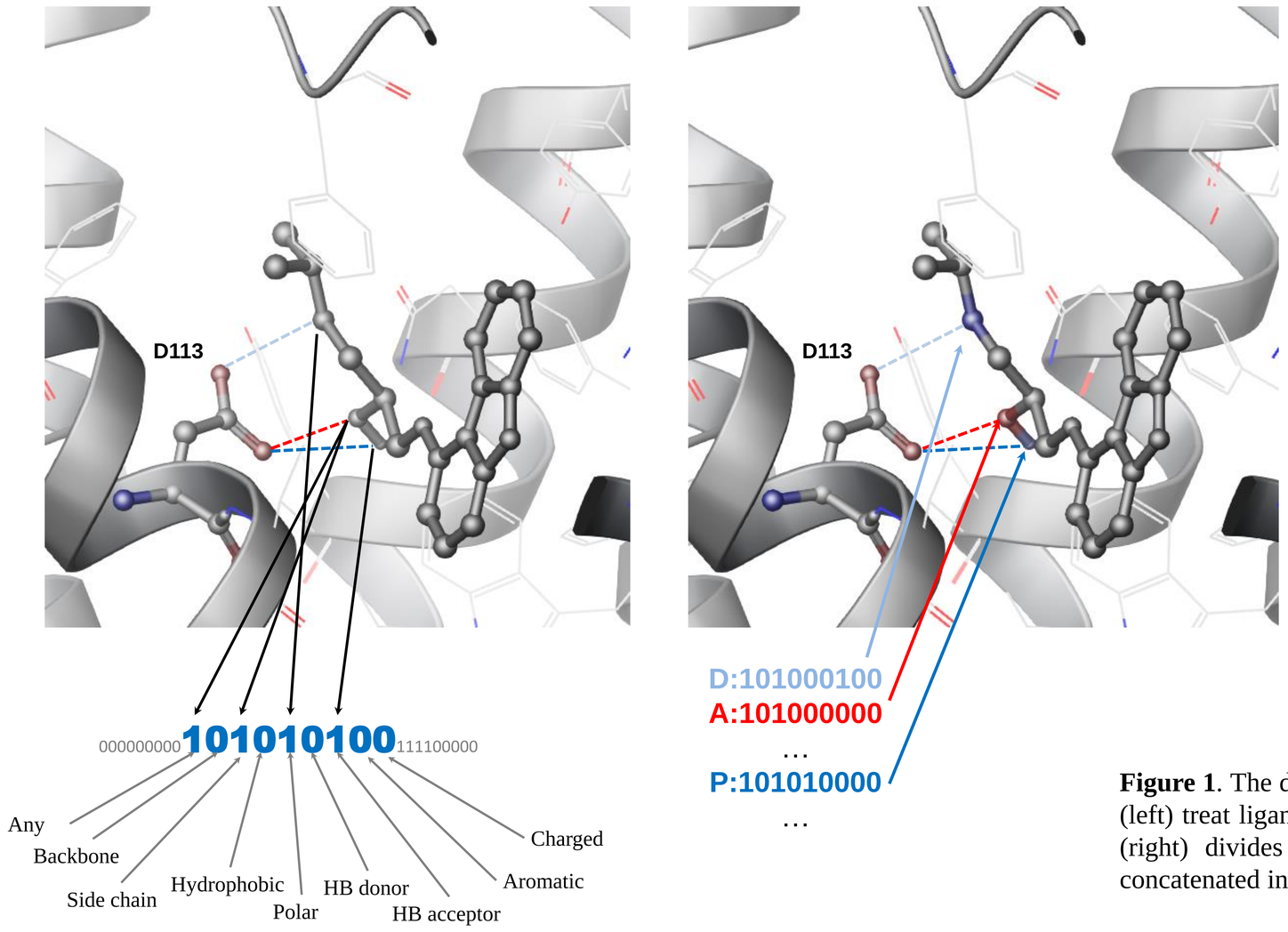

Table 1. Schematic representation of the 2D-SIFt chunk representing interactions for one amino acid. The symbols in the **column** headers of the table describe types of interactions: **Any**, **BB** – with a backbone, **SC** – interaction with sidechain, **P** – polar, **H** – hydrophobic, **A** – hydrogen 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

	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

Figure 1. The difference between construction of 1D and 2D SIFt descriptors. Linear fingerprints (left) treat ligand as one point and describes interaction from amino acid point of view, 2D-SIFt (right) divides ligand into pharmacophore features and each is described by linear SIFt, concatenated into a matrix.

Results

The descriptor was tested on crystal structures of β2 Adrenergic receptor coupled to agonist and antagonist (PDB codes 3PDS and 3P0G, respectively). A set of known ligands extracted from ChEMBL database [3] was docked into the binding site of the protein (Schrödinger GLIDE 5.0 XP) and analyzed using an in-house script generating the 2D-SIFt descriptors (Figure 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.)

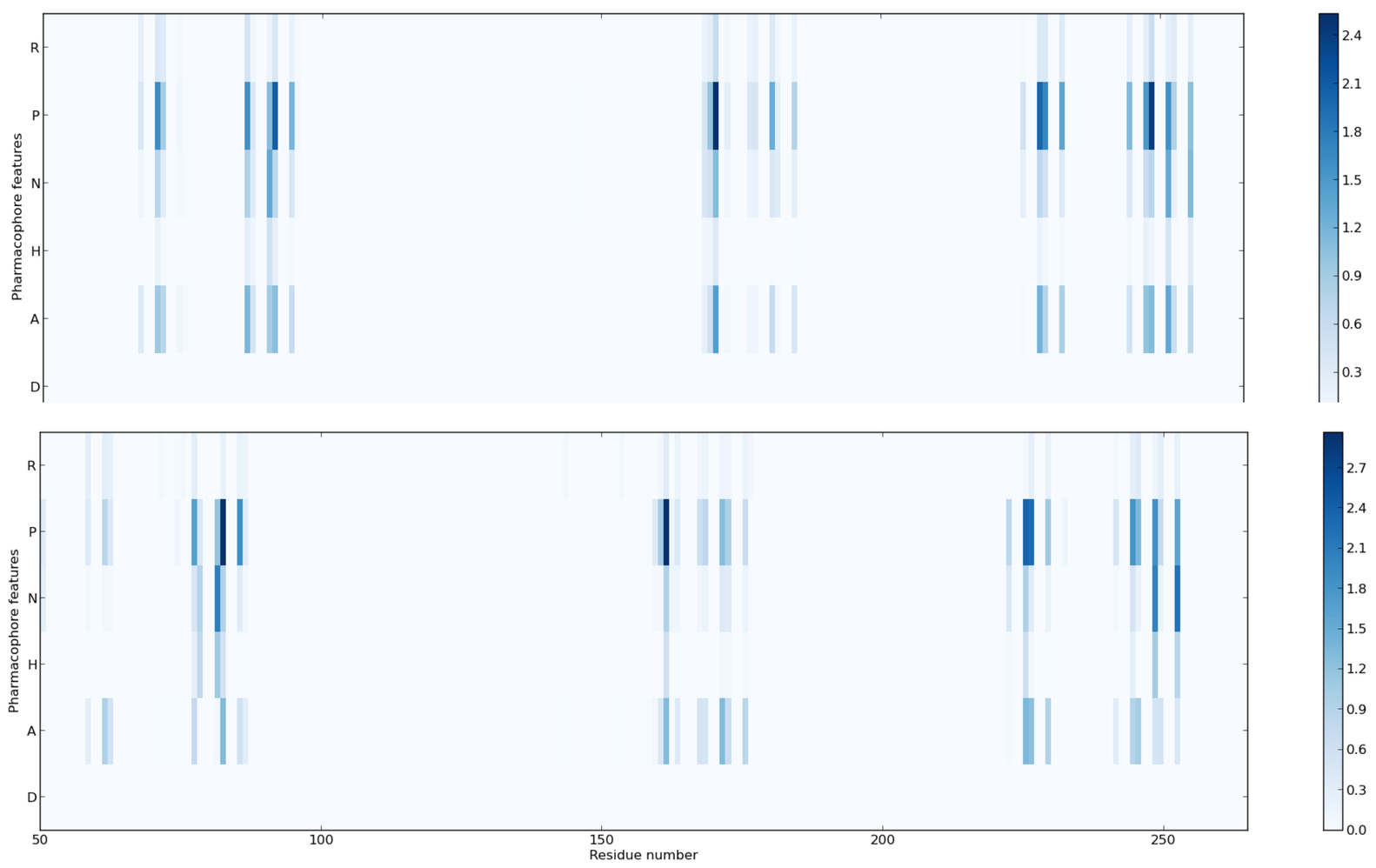

Figure 2. Results of the analysis of the binding site of the β2 Adrenergic Receptor with docked agonists (top) and antagonists (bottom). Differences in binding modes between the two classes of ligands can be easily depicted on the het map of interactions.

References

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