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

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## Introduction

Structural Interaction Fingerprints (SIFts), as defined by Deng et al. [1], encode a ligand-receptor complex in form of a bit string with detailed description of the ligand-receptor interactions but ignoring the pharmacophore features of ligand. In this work, we show a modification of original SIFt methodology, encapsulating interactions between the features of ligand and receptor in form of 6x9xN matrix (6 standard pharmacophore features, 9 types of interactions with amino acid [2], N – number of residues in described receptor). Matrix fields can take values greater than 1, as there can be more pharmacophore features of one type interacting with one residue (for instance three phenyl groups surrounding a phenylalanine).
Analogously to the previously demonstrated methodology, such matrices can be averaged to create profiles showing the most important interactions, thus being a hybrid between structure-based pharmacophore model and classical interaction fingerprint.

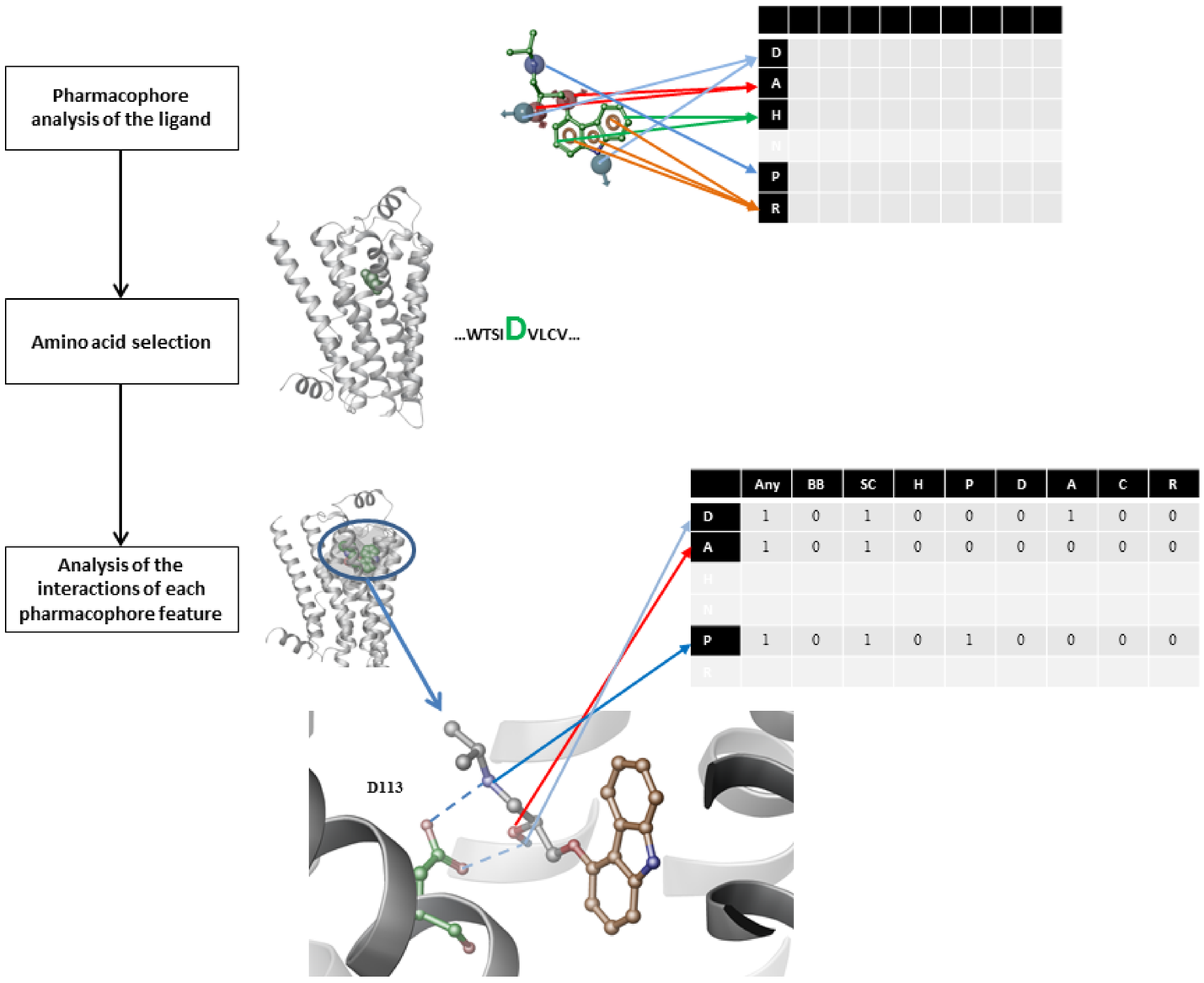


**Figure 1**. Workflow of constructing 2D-SIFt interaction matrix. The structure shown is the crystal structure of β2 Adrenergic receptor complexed with inverse agonist (S)-Carazolol (PDB code 2RH1). The symbols in the tables corespond to those of Table 1. Grayed out rows indicate lack of interaction between a given pharmacophore feature and a residue.

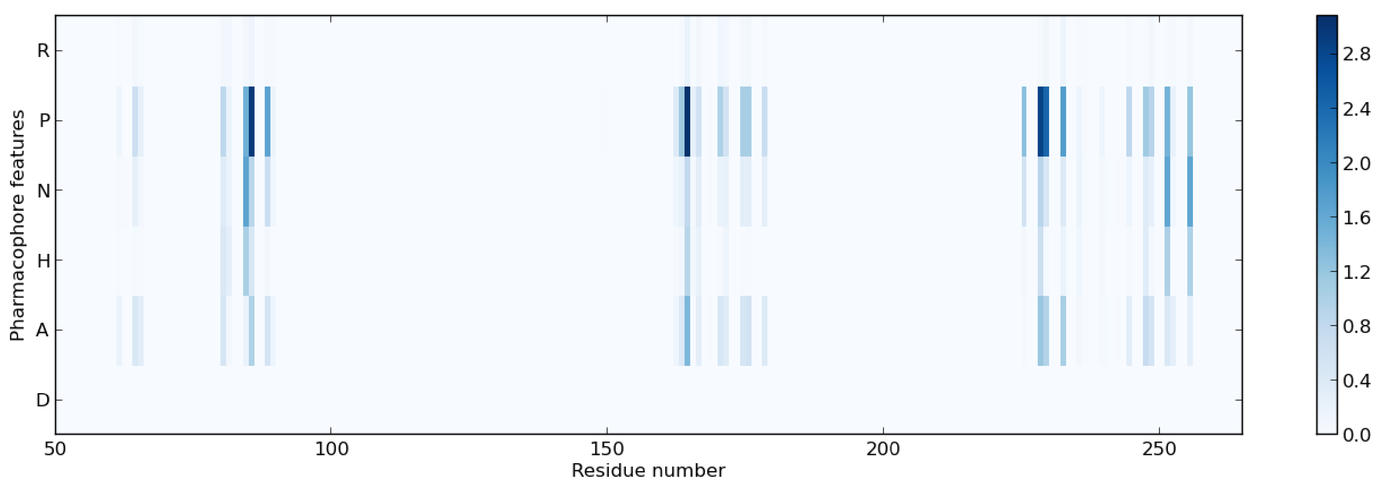


**Figure 2.** Results of the analysis of the binding site of the β2 Adrenergic Receptor. For clarity, the 2D-SIFt profile is represented by heat map of occurence of certain interactions.

**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** |

## Methods

The algorithm takes ligand-receptor complex as an input (the complex may be a crystal structure or a docking pose). In the first step, a ligand is simplified into pharmacophore features using appropriate SMARTS patterns. Then for every amino acid in the analyzed complex, interaction 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 a 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 descriptor was tested on crystal structure of β2 Adrenergic receptor complexed with inverse agonist (S)-Carazolol (PDB code 2RH1). A set of 271 known ligands (measured $K_i$ value of 100 nM or less) extracted from ChEMBL database [3] was docked into the binding site of the receptor (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.)

## References

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3. Gaulton A, Bellis LJ, Bento AP, Chambers J, Davies M, Hersey A, Light Y, McGlinchey S, Michalovich D, Al-Lazikani B, Overington JP. ChEMBL: a large-scale bioactivity database for drug discovery Nucleic Acids Research. Volume 40. Issue D1. Pages D1100-D1107. 2011.

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