

# A SIFt-guided approach to docking restraints assignment. An application to Virtual Screening

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## Introduction

Docking experiments play crucial role in Virtual Screening (VS) cascade designed in Dept. Of Medicinal Chemistry [1]. However unrestrained docking may lead to receiving highly scored ligand conformations within active site significantly different from biochemically confirmed binding mode.

Docking restraints allow enforcing correct ligand conformation, it is indulging the ligand positions, where predefined requirements are met. In this research we will focus on positional restraints, where specific functional groups of ligand must neighbour selected residues' sidechains. To achieve this, the previously developed tool - Structural Interaction Fingerprints (SIFt) profiles [2] will be used to quantify amino acids participating in binding the ligand and select the most frequent interactions. So selected list of important residues will be the basis for assigning complementar SMARTS patterns used for prescreening the ligands and then creating positional restraints the automatic way.

## Screening preparation

In the first step a detailed analysis of binding mode of the target protein is performed in order to setup necessary filters for screening pipeline. A set of active ligands is restrainlessly docked into target, and SIFt fingerprints are produced for resulting docking poses. In this implementation a nine-bit long bitstring describes the interactions between ligand and a single amino acid, and the following interactions are evaluated: any contact, backbone, sidechain, polar, hydrophobic, hydrogen bond acceptor and donor, aromatic and charged [2]. The individual ligand - receptor fingerprints are used to forge a SIFt profile, representing frequencies of occurrence of each interaction in the tested group of ligands (A).

The most frequently interacting residues are extracted and pharmacophore features are mapped onto them. Again, the type of most frequent interaction for each residue determines the selection of pharmacophore feature for further research (B).

## Application to the virtual screening pipeline

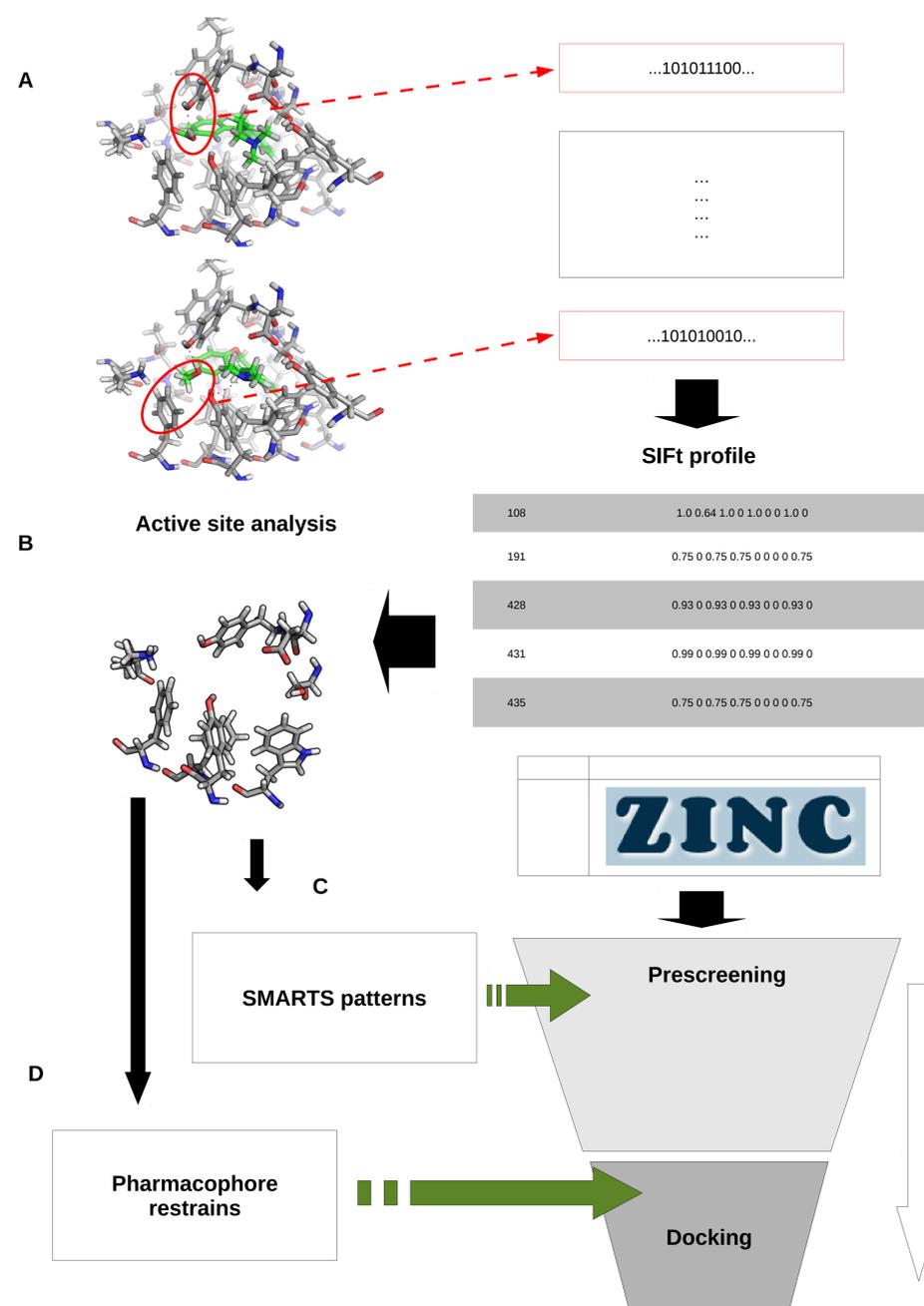
Once the crucial receptor pharmacophore points are selected, the screening itself is performed in two stages. In the first, the pharmacophore points have assigned the SMARTS patterns, that are used to prescreen the input database. In this research the ZINC dataset, containing commercially available druglike compounds, is used. The logical conjunction of SMARTS coming from different features is used to assure the quality of screening and to reduce the initial dataset for the next step.

In the last stage, the pharmacophore restraints are applied for the docking process. Similarly to the previous step, the residues and features selected as crucial are taken into account. For all types of interactions except from hydrogen bonding, the positional restraints are applied. Within 4 Å from given amino acid only ligand atoms matching the SMARTS expression are allowed to remain. Docking poses not fulfilling the restraints are being rejected. Docking is performed in HTVS (High Throughput Virtual Screening) mode, and for the set of top scored compounds the docking is rerun in XP (eXtra Precision) mode to receive the best possible accomodation of ligands within the binding site of the protein.

## Conclusions and future plans

The proposed methodology is a promising way to improve the results of developed virtual screening cascade [1]. Due to high computational cost of docking large datasets, even with the lowest possible resolution, the described workflow will be used mostly for results of pharmacophore and similarity search filtering.

We hope, that performance of the method and improvement of quality of result in comparison to unrestrained docking experiments will allow wide usage of proposed workflow in screening campaigns.



**Fig. 1**  
Stages of designed virtual screening method: Preparation of SIFt fingerprints on the basis of docking poses of known active ligands. SIFt profile constructed out of the fingerprints (A). Systematic analysis of binding site of the protein, selection of residues important for ligand accommodation, placing the pharmacophore features (B).

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## Literature

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Visualizations were prepared with PyMol