Automated docking restrains assignment based on interaction profiles

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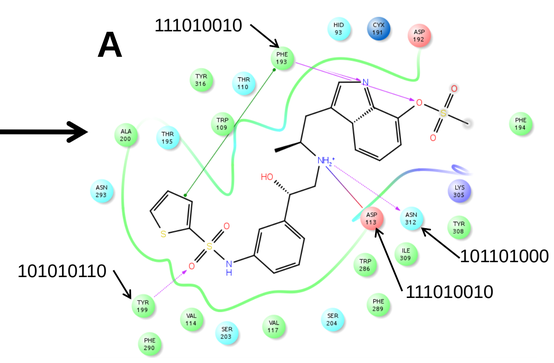
Introduction

Docking pose restrains allow enforcing desired ligand arrangement in binding site of the protein, it is indulging such ligand conformations, where predefined interactions, i.e. from biochemically confirmed binding mode, are met. Pose restricting is of great convenience for Virtual Screening protocols, where docking experiments often are used as a final step of the cascade [1], and the amount of data render the visual inspection of the results impossible. For such experiments receiving correct ligand-receptor arrangement is essential.

In this research we show a docking protocol allowing automated assignment of docking restrains based on interaction patterns – a collection of the most significantly interacting residues. The previously developed tool – **S**tructural **I**nteraction **F**ingerprin**t**s (SIFt) profiles [2] is used to quantify amino acids participating in binding the ligand and to select the most frequent contacts. So created list of important residues is the basis for assigning complementary SMARTS patterns used for prescreening the ligands and then creating positional restrains for the most important amino acids. The protocol is evaluated on targets with crystal structure available (β2AR, PDB code: 2RH1) and homology models (5-HT6R). Training and test data were acquired from ChEMBL database [3].

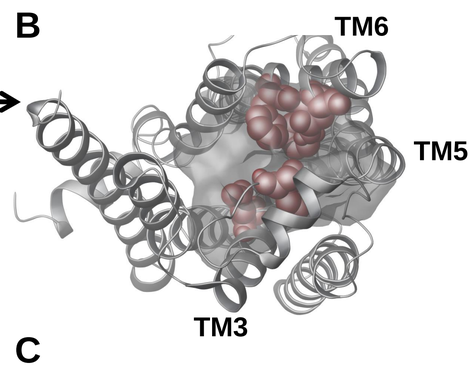
In the first step of the protocol, a set of 25 diverse ligands is docked into the target protein without restrains. Glide XP mode is used for that procedure. For each ligand- receptor complex a SIFt string is generated, describing ligand interactions with binding site residues.

Unrestrained docking



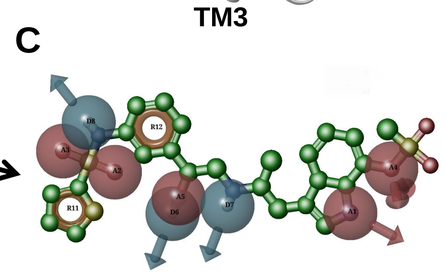
A collection of interaction fingerprints generated in step I is then used to create an interaction profile – an averaged SIFt string representing frequencies of per residue interactions. For further steps of the research only amino acids interacting with every docked ligand were taken into consideration.

Binding mode analysis



Every docking pose of the initial 25 compounds is analyzed again. Pharmacophore features are assigned to ligands, and contacts between amino acids selected in the previous step and the atoms of each ligand feature are quantified

Ligand features selection



Based on the type of selected residues as well as the interacting phamacophore features of the ligands from the training set of 25 diverse compounds, positional docking restrains are composed. Ligand features are also used to assign SMARTS patterns for the restrains. The evaluation process is conducted by screening-like docking of the test set of 200 active (Ki < 100 nM) and 314 inactive compounds (Ki > 1000 nM). The process is iterative aiming to find the best combination of number of constrains and SMARTS in terms of virtual screening performance.

Docking restrains assignment

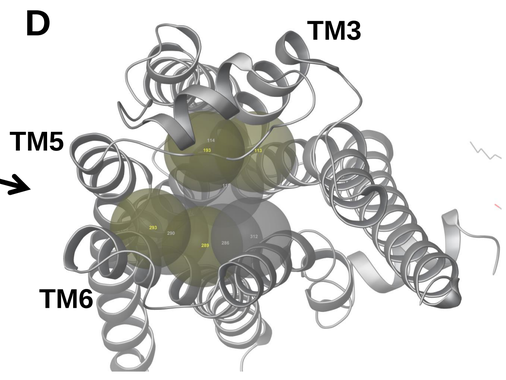


Figure 1. Visualizations of subsequent steps of the protocol. Ligand-receptor interactions as shown on the exemplary 2D diagram are converted into SIFt fingerprint **(A)**; averaging individual SIFt strings allows extraction of the most frequently interacting residues **(B)**; pharmacophore features assigned to a ligand **(C)** – analysis of the interactions between atoms forming those features and amino acids selected from SIFt profile allows formation of docking restrains **(D).**

Results

Docking with pharmacophore restrains was, as expected, more restrictive than free one. For the investigated targets it resulted in significant reduction of inactive compounds docked (35.5% for β2AR and 43% for 5-HT6R). Unfortunately, in case of serotonin receptors the applied restrains resulted also in reduction of number of active ligands docked (40%). The selection of positional restrains took 10 iterations of different settings (residues and SMARTS patterns) to reach the top efficiency in VS-like experiment. In case of β2AR the applied procedure allowed significant increase of enrichment for the screened test set (Fig. 2).

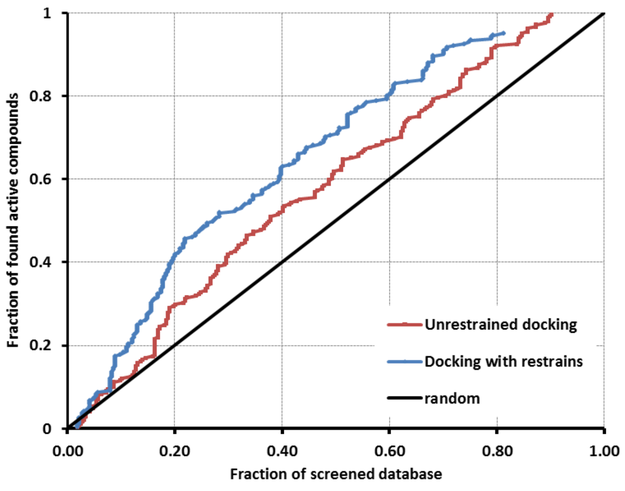


Figure 2. Enrichment improvement received for β2AR docking. Red: unrestrained, blue: docking with trained pharmacophore restrains.

Conclusions

The designed protocol of automated assignment of docking restrains indeed allows to enhance screening performance and reduces the number of docked inactive compounds. The cost of such automatic method is the computational time needed to train the best restrains.

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.

Ministry of Science and Higher Education
Republic of Poland