Multiple conformational states in retrospective virtual screening – homology models vs. crystal structures. β2-adrenergic receptor case study

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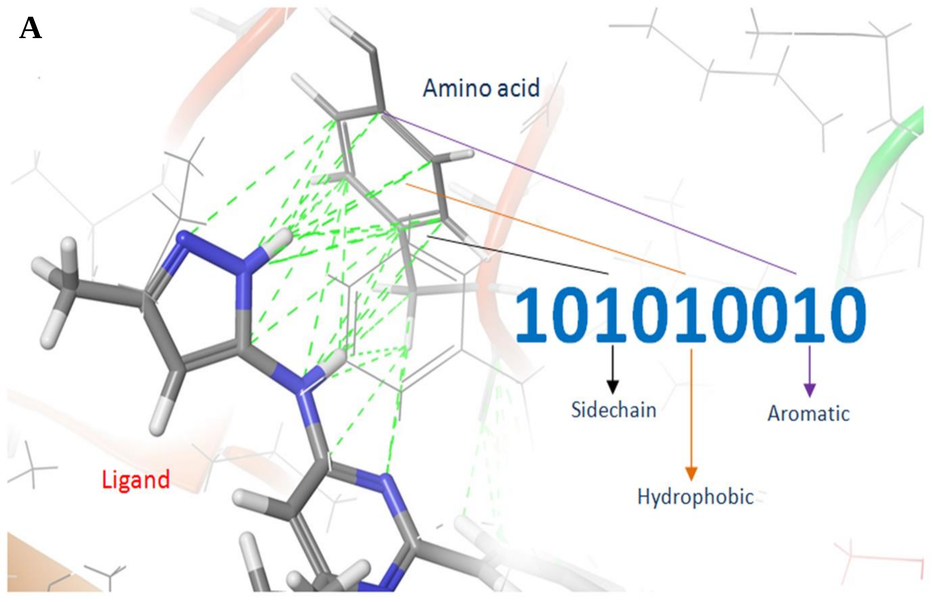
Methodology:

- Retrospective virtual screening (VS) was performed on ensembles of both homology models and crystal structures of β_2-adrenergic receptor
- 10 crystal structures of β_2-adrenergic receptor were used
- Sets of homology models based on distinct crystal templates (Table 1) – up to 20 receptor conformations were considered
- Active compounds were extracted from ChEMBL database (K_i or equivalent < 100 nM)
- Three decoy sets were used: true inactives (K_i or equivalent > 1000 nM), DUD-like decoys and random ZINC subset
- Docking poses were encoded into per-ligand SIFt profiles averaged over number of receptor conformations used for docking (Fig 1), and undergone support vector machine (SVM) classification.

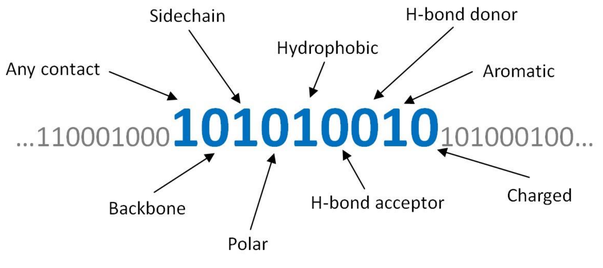
A



Template	PDB ID	Resolution [Å]
5-HT_{1B}	4IAR	2.70
5-HT_{2B}	4IB4	2.70
A_{2A}	3QAK	2.71
β_1	2Y00	2.50
CXCR4	3OE0	2.90
D_3	3PBL	2.89
H_1	3RZE	3.10
M_2	3UON	3.00
M_3	4DAJ	3.40

Table 1 Crystal structure templates used for homology modeling.

B



C

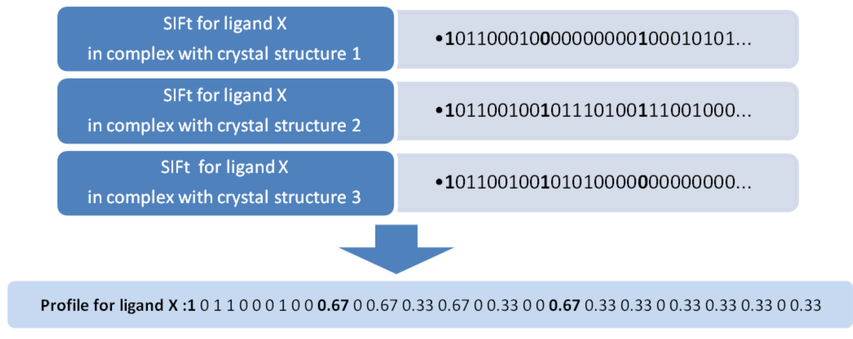


Figure 1 (right) Scheme of construction of SIFt from ligand-receptor complex **(A)**; Description of bit positions within the residue-ligand substring of SIFt **(B)**; Algorithm of assembling per-ligand SIFt profile: an example for the ensemble of three distinct complexes **(C)**.

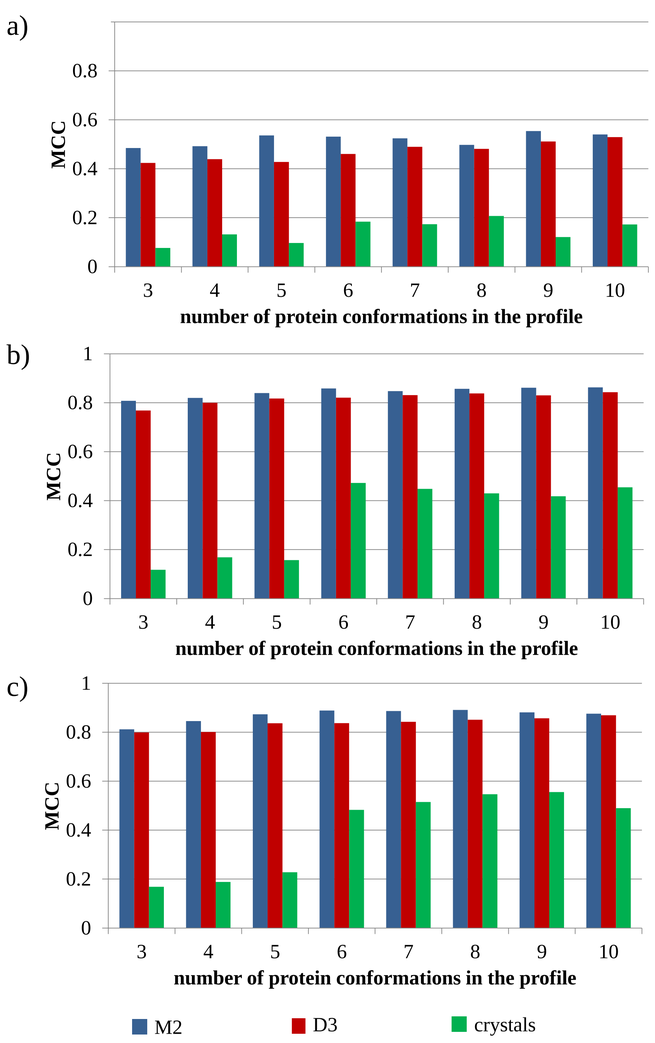


Figure 2 Comparison of MCC values obtained in the ML-based experiments of docking results to homology models built on M_2R (the best) and D_3R (the worst) template and crystal structures for discrimination between **a)** actives/true inactives, **b)** actives/DUDs, and **c)** actives/ZINC.

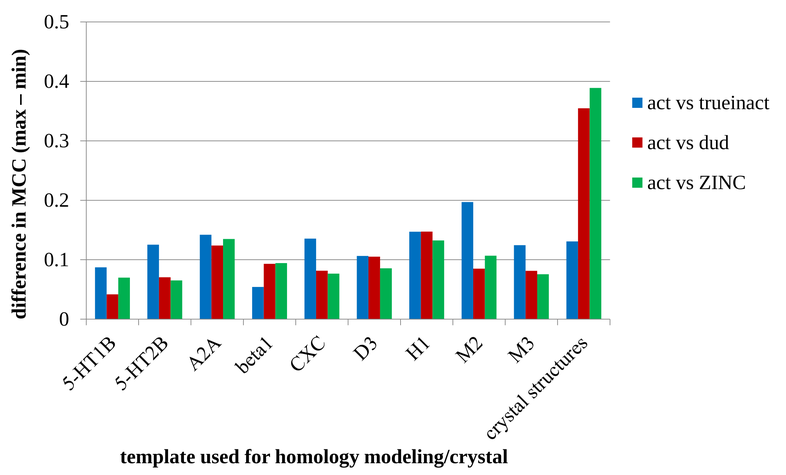


Figure 3 MCC gain being a result of using the ensemble of receptor conformations for docking experiments.

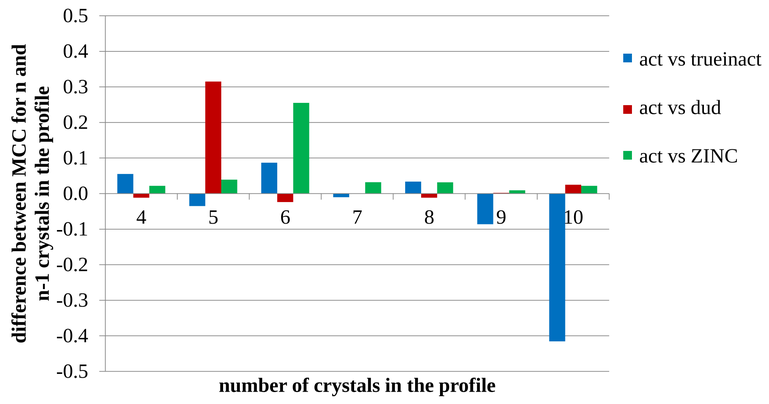


Figure 4 Changes in MCC values caused by the addition of subsequent crystals to the profile (adding one-by-one- from 3 to 10 forming at the end 10-crystals-based profile) in experiments where docking was performed to crystal structures of beta-2 adrenergic receptor.

Results:

- The use of the ensemble of homology models of the target receptor gives a significant advantage over pure crystal structures both for the best (M_2R) and the worst (D_3R) performing templates (Fig 2)
- Multiple conformations of the target increase the effectiveness of screening by great margin (by up to 0.38 MCC value, being nearly 30% improvement – Fig 3)

Conclusions:

- Homology models are more potent than the ensemble of crystal structures of the target for virtual screening purposes
- The main reason for the difference in screening performance is the limited conformational space of the crystal structures, adapting to the ligands and thus conformationaly biased

References

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3. Mordalski S., Witek J., Smusz S., Rataj K., Bojarski A.J. Multiple conformational states in retrospective virtual screening - homology models vs. crystal structures. Beta-2 adrenergic receptor case study. J. Cheminf., 2015, 7:13; 10.1186/s13321-015-0062-x

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