Evaluation of Different Scoring Functions for Docking and Virtual Screening against GPCR Drug Targets

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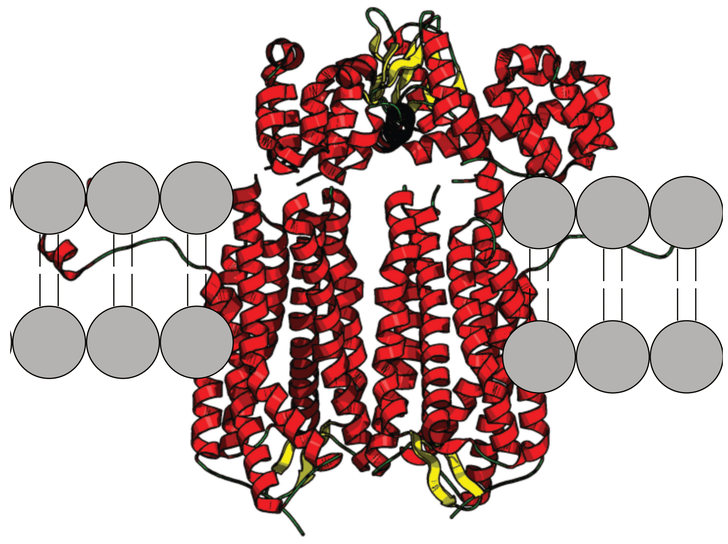
INTRODUCTION

G protein-coupled receptors (GPCRs) are the largest family of membrane-bound receptors. They mediate most of thee physiological responses to hormones, neurotransmitters and environmental stimulants. That is the reason why GPCRs have great potential as therapeutic targets. They are, however, difficult to handle experimentally. [1]

Computational methods are great allies in understanding GPCRs dynamics and lead to the discovery of new drugs. Protein- ligand docking is a computational method that tries do predict the position and interactions of a ligand when bound to a protein. It is a usefull tool in drug design and it is used with virtual screening to evaluate large databases of molecules, as an initial sitep before experimental testing. [2]

This work reports a detailed comparison of the popular Autodock[3] and Vina[4] software programs in ligand/decoys discrimination against 5 GPCR proteins for a total of 1480 ligands and 99763 decoys.



DOCKING PROTOCOL

1 Docking Software: AutoDock and Vina

2 Library of GPCRs: Active ligands; Decoys from DUD-E[5]

3 Definiton of the docking site: Optimization of residues, hidrogen positions, exclusion of water molecules, docking box size

4 Control Calculation: Active ligand must rank higher than decoys

5 Screen the library against the binding site

PDB: 3NY8 — Actives: 231 — Decoys: 14994

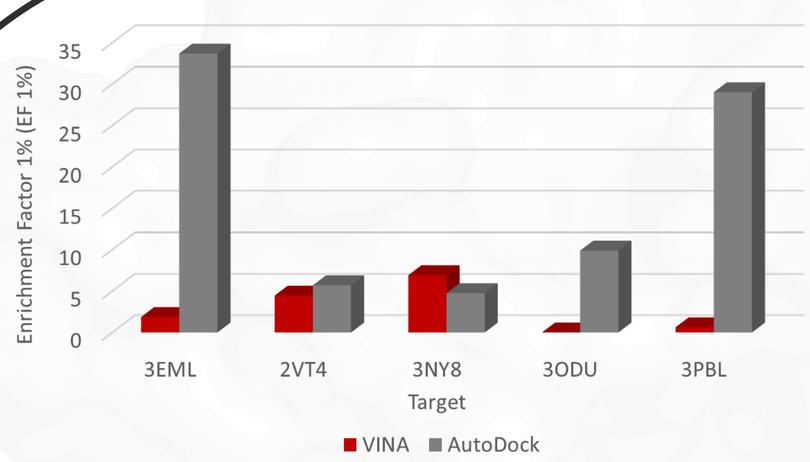
PDB: 2VT4 — Actives: 247 — Decoys: 15843

PDB: 3PBL — Actives: 480 — Decoys: 34022

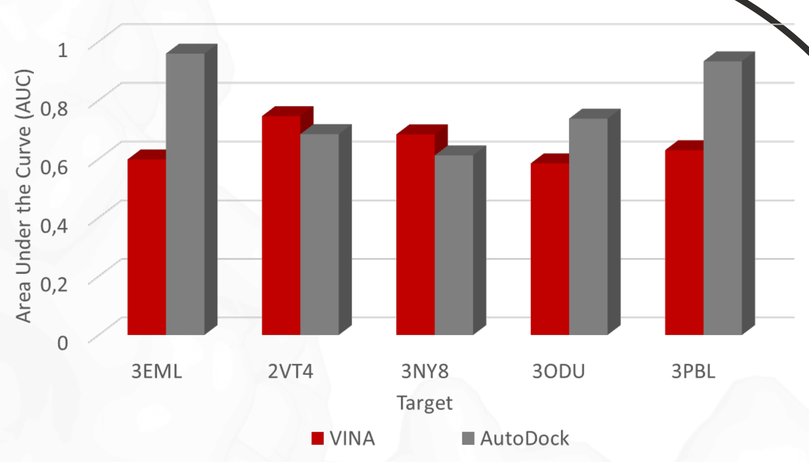
PDB: 3ODU — Actives: 40 — Decoys: 3406

PDB: 3EML — Actives: 482 — Decoys: 31498

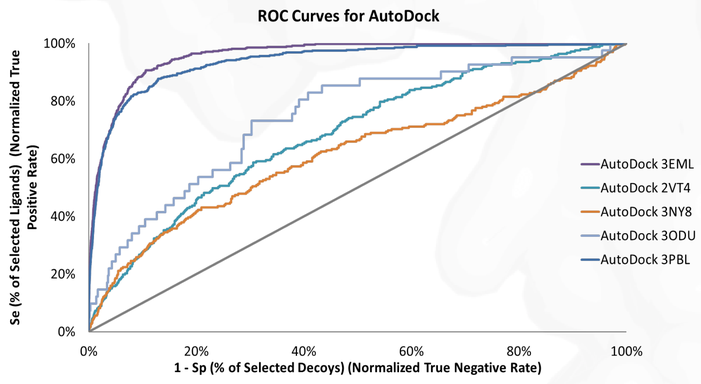
RESULTS

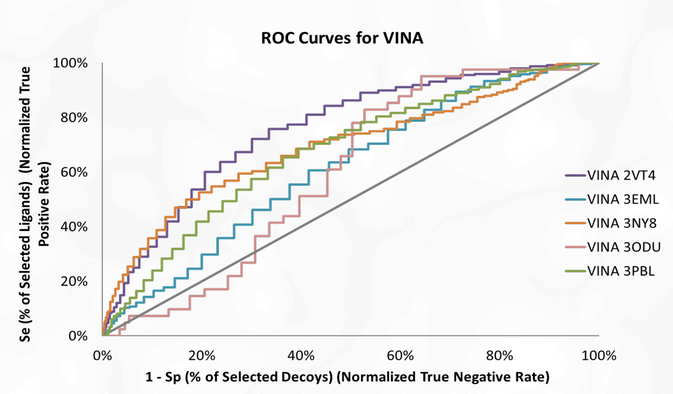


Histogram 1. Active ligands recovered at 1% of the ligand/decoy database for Vina (red) and AutoDock (grey)

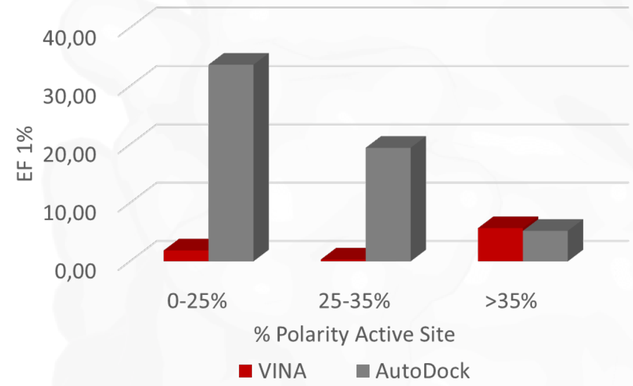


Histogram 2. Area under the curve (AUC) for the 5 GPCRs studied for AutoDock (grey) and Vina (red)





Graphic 1 and 2. Representation of the true positive rate versus the false positive rate in terms of receiver operating characteristic (ROC) plots. The higher the curve, the higher the area under the curve (AUC), the better discrimination between true positive and alse positive poses.



Histogram 3. Influnce of the polarity of the active site on the Enrichment factor 1% for AutoDock /grey) and Vina (red)

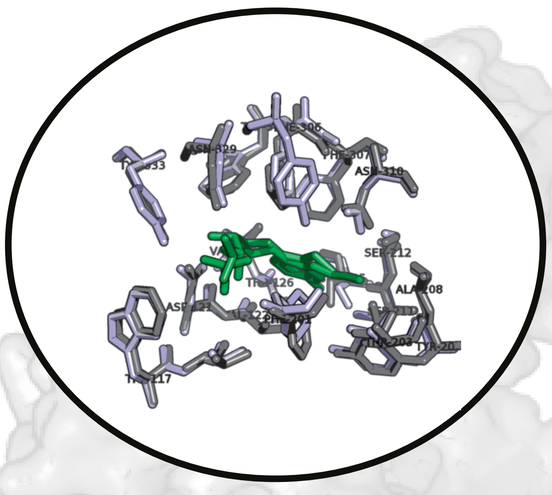


Image 1. Representation of the aminoacid residues from the active site of 2VT4 and 3NY8, aligned. Their respective ligand is represented in green. These are the proteins for which Vina exhibited better performance. These are also the proteins that have more a more polar active site.

CONCLUSION

The results show that AutoDock is more efficient in recovering real ligands among the top 1% solution than VINA, when applying virtual screening to GPCR receptors. However, the results illustrate that AutoDock and Vina have different strengths and weaknesses, with a performance that can vary significantly with the type of protein target, and with the specific characteristics of the ligands (size, flexibility, etc).

These results also highlight the need to evaluate, *a priori*, the accuracy of the docking software for the specific protein target, or family of targets, before embarking on a virtual screening study.

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