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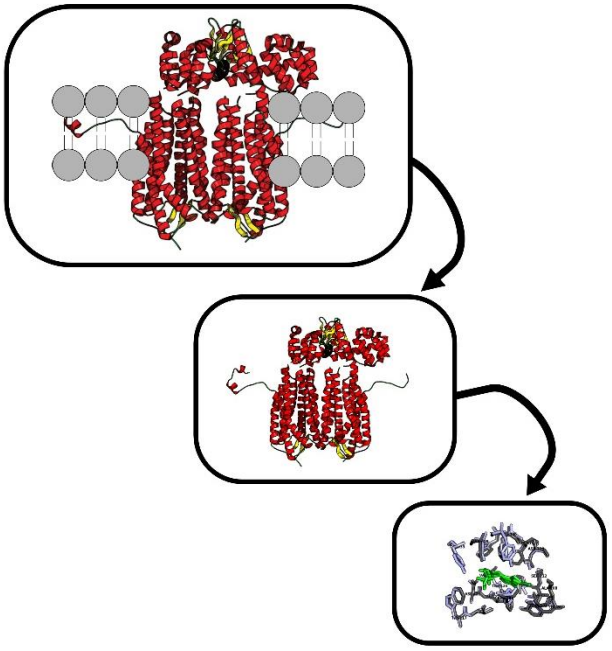
Evaluation of Different Scoring Functions for Docking and Virtual Screening against GPCR Drug Targets

Tatiana F. Vieira, Rita P. Magalhães, Nuno M. F. S. A. Cerqueira, Sérgio F. Sousa

UCIBIO/REQUIMTE, BioSIM Departamento de Biomedicina, Faculdade de Medicina, Universidade do Porto, Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal

Graphical Abstract



Abstract.

G-protein-coupled receptors (GPCRs) constitute a large family of structurally similar proteins that respond to diverse physiological and environmental stimulants and that includes many therapeutic targets. In fact, 40% of all modern medicinal drugs are thought to target G-protein-coupled receptors (GPCRs), making this large family of proteins a particular appealing target for drug discovery efforts [1, 2].

Protein-ligand docking is a computational method that tries to predict and rank the structure resulting from the association between a ligand and a target protein [3]. Virtual screening (VS) can use docking to evaluate databases with millions of compounds to identify promising new molecules that could bind to a specific target of pharmacological interest, including GPCRs [4]. This strategy if often used to limit the amount of molecules that has to be tested experimentally and to reduce the cost in the identification of new lead molecules for drug development.

This work reports a detailed comparison of the popular Autodock [5] and Vina [6] software programs in ligand/decoys discrimination against 5 GPCR proteins, (Adenosine 2a receptor, Beta-1 adrenergic receptor, Beta-2 adrenergic receptor, C-X-C chemokine receptor

	type 4 and Dopamine D3 receptor), for a total of 1480 ligands and 99763 decoys. 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.

Conclusions

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..

References

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