Comparative Analysis of Docking Programs Using Distinct Protein-Ligand Test Sets

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INTRODUCTION

Protein-ligand docking methodologies are important tools for structure-based rational drug design studies. These methods aim to predict the experimental binding mode and affinity of a small molecule within the binding site of the protein target of interest. The DockThor program, developed by the Brazilian group GMMSB/ LNCC, uses a grid based methodology and was implemented to deal with highly flexible ligands using a multiple-solution steady state genetic algorithm[1]. The scoring function is based on the MMFF94S classical force field.

In this work the Dockthor performance was evaluated through a comparative analysis of redocking experiments with three of the most used docking programs, i.e., GLIDE, GOLD and AutoDock Vina. The comparative analysis was performed using two receptor-ligand test sets: (i) the Astex Therapeutics Ltd test set[2], containing 85 diverse and curated protein-ligand complexes and (ii) the Iridium-HT[3], a high quality test set containing 120 diverse protein-ligand complexes.

METHODS

We observed that for some of the complexes of the Iridium-HT dataset the ligand and protein residues protonation and tautomeric states were not correctly taken into account. We curated this dataset using PROPKA, Epik and Protoss tools to predict the correct protonation states for both protein and ligand. For all complexes no protein-ligand pre-optimization was made (i.e., the crystallographic structures were maintained in their original conformation).

The GOLD program was evaluated using the ChemPLP scoring function. For all complexes, the docking programs were executed using their best docking protocols and using a grid of dimension of 22 Å in each dimension.

Best energy ligand pose predictions with RMSD values lower than or equals to 2.0 Å from the experimental structure were considered as a docking success.

RESULTS AND DISCUSSION

DockThor obtained very satisfactory results in the redocking experiments.

For the Astex test set, considering the top-scoring pose, Dockthor obtained a success of 77.7% and GOLD, Vina and GLIDE obtained 85,0%,77.7% and 78.8% respectively.

For the Iridium-HT test set, DockThor obtained a success rate of 78.3% when considering only the top-scoring poses and 87.5% when considering multiple solutions with similar energies with the top-scoring one.

CONCLUSIONS

In this work, we performed a comparative analysis of redocking experiments for four docking programs: Glide, GOLD, AutoDock Vina and Dockthor. The analyses show that the DockThor (http://www.dockthor.lncc.br) program has a great potential to be widely used in real receptor-ligand studies showing a comparable overall performance with the other programs evaluated.

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