Enrichment of Virtual Screening results using induced-fit techniques

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Abstract: *This project aims to improve the results of virtual screening and docking techniques used for drug design, using induced-fit techniques and a consensus scoring approach.*

Keywords: Virtual Screening; Drug design; Consensus scoring function.

I. INTRODUCTION.

The drug discovery process aims at discovering new chemical compounds (ligands) that bind to a given target (usually a protein) causing a disease. The ligand is expected to modify the target activity to cure or alleviate the effects of the disease. This process usually requires from 10 to 17 years [1] approximately, costs billions of dollars and has a low success rate.

Virtual screening (VS) procedures have been developed due to the high cost associated with experimentally testing (millions of) chemical compounds. VS is a broad term that includes all the computational methods developed to aid in the drug discovery process complementing the experimental ones. This term includes managing the compounds data, filter them according to their physic-chemical properties and the docking and hit identification processes.

The VS can be divided in two categories depending on the approach used: ligand-based VS and structure-based VS [2]. The docking methods belong to the second category and are used to screen ligands that may bind the target (binders) by ranking them with a prediction of their binding affinity. This process involves two main steps: a) identify the binding pose and b) estimate the binding affinity. In order to achieve a) in a short time they assume the protein to be rigid, which introduces error since the proteins are flexible entities. To do b) they use scoring functions, which use fast and approximate algorithms often designed to discriminate between binders and non-binders.

The overall performance of docking methods is compromised by these two aspects: lack of flexibility and accuracy of the scoring functions.

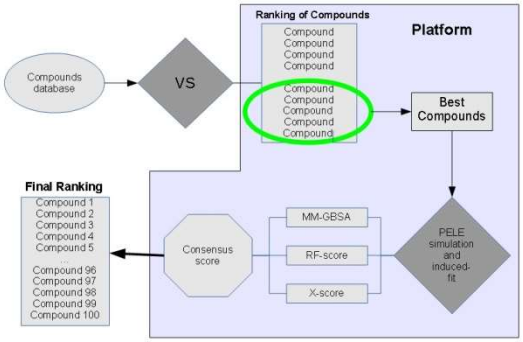

Fig. 1 Scheme of the platform workflow

II. PROJECT DESCRIPTION

This PhD project aims at developing a platform to improve the results from the current VS procedures. This platform will use the output of a VS procedure and will perform induce-fit techniques, to allow the protein to adapt its structure to the ligand, and then will compute a consensus scoring function to score the new structure, giving a better estimation of their binding affinities.

The platform will be able to do all the files conversions necessary, launch the simulations needed and compute all the scoring functions and descriptors used by the consensus scoring function. Protein preparation, for example, is a crucial step where automatic procedures have to be developed with care. The scoring function will be trained and tested on dataset of complexes formed by a protein and a ligand with known binding affinity, and the overall performance of this new platform will be tested on a common dataset for VS and a real case of VS in collaboration with AstraZeneca.

Hypothesis: By adding induced fit techniques to the best (top) thousands virtual screening results, together with the use of multiple scoring functions and machine learning techniques, we will enrich the number of true positive results (binders) in the VS process.

III. WHAT WE HAVE SO FAR.

The present work has been focused in optimizing the protocol to be applied to the top VS poses. For this, we have focused first in improving the affinity prediction by preparing a test set, selecting scoring functions, and initial steps towards adding flexibility with induced fit techniques.

A. Datasets

The training set and the test set for affinity prediction have been compiled and manually prepared using the Protein Preparation Wizard from Schrödinger [3]. The training set consists in a subset of the pdbBind refined core dataset compiled in Ref [4] and is formed by 191 structures from 64 different families. The test set is a subset of the pdbBind refined core set in Ref [5], formed by 64 structures from 64 different families. Both subsets are composed by protein-ligand complexes with known dissociation or inhibition constants (K_d and K_I, respectively)

All the structures have undergone a careful preparation process with the hydrogen added according with the protonation states at experimental pH, the missing loops and chains reconstructed using Prime [6], [7].

Furthermore both test set have been minimized using the Protein Energy Landscape Exploration (PELE) software with and without waters.

B. Scoring function selection

The criteria used to select which scoring functions to use were: their performance [4], [8], their availability (free or commercial), and the type of scoring function. The most commonly used scoring functions were selected, both commercial and free, in a way that there are at least two scoring functions for each type of scoring function according to their method to estimate the binding affinity [9].

The scoring functions being tried are MM-GBSA from Prime [6], [7], AutodockVina [10], PELE interaction Energy, Glide SP [11] and XP [12] scoring functions, XScore [13], DSX [14], RF-Score [15], NN 2.0 score [16] and Rdock [17]. They have been computed for all the structures in both the test and training sets minimized with and without water molecules. Results shown in Table 1

C. Consensus scoring function

The consensus scoring function is under development trying different machine-learning methods, such as random forest and neural networks, using 9 different scoring functions already developed and widely used.

D. Induced fit techniques

The induced-fit techniques aim to reproduce the binding pose of a ligand in a given protein taking into account the conformational changes induced in the protein by the ligand.

To obtain this kind of structure PELE simulations are being performed with some parts of the protein the backbone slightly constrained but leaving the side chains free to move, the objective is to maintain the overall structure of the protein while allowing for the small structural changes induced by the ligand when binding.

FUTURE WORK.

There is still a lot of work to do: we plan to extend the training and test set, to include in this platform a VS method able to deal with thousands of different ligands, to add this platform to the PELE GUI, etc.

TABLE 3; Pearson correlation coefficient for all the scoring functions in the training set

Scoring Function	Correlation	Scoring Function	Correlation
PELE	0.409	Xscore	0.612
MM-GBSA	0.494	DSX	0.533
Autodock Vina	0.532	RF-Score	0.677
Glide SP	0.399	NN 2.0	0.741
Glide XP	0.357	Rdock	0.214

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