Drug screening with the Autodock Vina on a set of kinases without experimentally established structures

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***Abstract* - Virtual drug screening is one of the most widely used approaches for finding new drugs candidates. The process consists in selecting one or more chemical compounds with the highest binding free energy to target proteins. Given that the empirical space of chemical compounds is extremely large and estimated to has over 50 millions of them, finding the most effective drug is computationally challenging. Furthermore, the vast majority of proteins still lack the experimentally obtained 3D structures, making it hard to accurately calculate their binding free energies with chemical compounds. With this in mind, the aim of our study was to investigate the accuracy of the Autodock Vina program in a virtual drug screening on a set of proteins that do not have experimentally determined structures. To do this, we performed a virtual drug screening with the Autodock Vina on a large set of drug-kinase pairs taken from the IDG-Dream Drug-Kinase Binding Prediction Challenge. The results obtained show that the Autodock Vina can be used effectively in such unstructured environments.**

Keywords - Autodock Vina; virtual drug screening; drug discovery; binding free energy; unstructured proteins, kinase inhibitors

I. INTRODUCTION

Virtual drug screening is a computer technique often used in finding new drugs [1]. Virtual drug screening approaches, including ligand based ones, have been used in the discovery of Janus kinase 2 (JAK2) inhibitors. Developing JAK2 inhibitors has become a significant focus for small molecule drug discovery programs in recent years because the inhibition of JAK2 may be an effective approach for the treatment of polycythemia vera, primary myelofibrosis and essential thrombocythemia. Yang and colleagues reported a strategy using virtual screening approaches that can be a starting point for development of novel JAK2 inhibitors with high potency and selectivity [2]. A promising results were reported by Viegas and associates, emphasizing importance of virtual drug screening as a useful strategy to prospect active compounds, showing satisfactory pharmacokinetic and toxicological profiles They have presented novel anti Herpes simplex virus 1 (HSV-1) compounds which can be used for development of new drugs for the treatment of HSV-1 infections with different modes of action than acyclovir [3]. Results from a study by Lim et al. showed also encouraging results in the field of Hepatitis C virus (HCV) helicase inhibitors, revealing 10 potential drugs discovered via new docking optimization protocol with better docking accuracy [4]. Their findings could contribute to the discovery of novel HCV antivirals, serving as an alternative approach of in silico rational drug discovery.

In doing so, libraries [5] containing the structures of small-molecules with molecular weights less than 900 Daltons (in further text referred as compounds), are searched in order to identify those compounds that have the highest free energy of binding with target molecules. These target molecules are most commonly proteins and enzymes. While some compound libraries like PubChem already contain molecular structures [6], others are based on make-on-demand creation of compound structures, e.g. from 130 well-characterized chemical reactions [7]. However, in both cases, a fast and effective search and processing of libraries consisting of thousands and even tens of millions of compounds is required. This poses a significant challenge, both in terms of the required computing resources and the accuracy of the results obtained [8]. Although artificial neural networks coupled with deep-learning techniques promote the dramatic reduction of computing resources required for virtual drug screening [9], there is still a work to match their accuracy with a structure-based tools. The computation of the free binding energy between protein and compound is usually performed in three steps. In the first step protein and compound structures are prepared for docking and docking site on the protein surface is identified. As the next, docking between protein and compound is performed. Final step is scoring, where binding free energy between protein and compound is calculated [10]. There are several dozens of docking tools available, with various implementations of their scoring function [11]. The accuracy of docking and scoring varies from tool to tool, and is also conditioned by the structure of the protein and compound [12]. Higher accuracy in the computation of binding free energy can be achieved through the use of molecular dynamics (MD) computer programs [13]. However, due to the high demand on computational resources, their use in virtual drug screening on a large data sets is still prohibitive [14]. Another problem with structure-based virtual drug screening is that docking tools demand the existence of

well-defined 3D protein structures (in the further text referenced as structured proteins). RCSB portal [15] is usually searched for these structures. But, there are much more proteins without experimentally determined 3D structure (in the further text referenced as unstructured proteins), then structured proteins. During the preparation of this paper, and according to the statistics on RCSB portal, there was near 150.00 protein structures available. However, many of them are redundant, as they describe the same protein in complex with different compounds. Because of that, the total number of structured proteins is smaller and is currently near 10.000. This is by far less than the estimated number of different proteins in the human genome, which according to some sources equals to about 80.000 [16]. In order to perform virtual drug screening on unstructured proteins, one needs to predict their structures from their respective amino acid sequences [17]. Furthermore, some protein structures are complete as they have spatial coordinates defined for every atom in the protein, while others have coordinates for only a fraction of them. This is called the completeness. In addition, different structures for the same protein may have different resolution levels dependent on which method for obtaining the structure was applied (NRM spectroscopy, X-ray crystallography, X-ray free electron lasers, 3D electron microscopy). Besides, the number of structures describing proteins without compounds is relatively small compared to the number of structures describing proteins in complex with one or more compounds. And because compounds cause a deformations on protein surface, it is of the advantage to take structures without compounds. Therefore, for the best possible accuracy of virtual drug screening, one needs to take protein structures with highest completeness and resolution, and with the lowest number of compounds. Afterall, if compounds are present in the structure, one needs to remove them. The next step is to prepare the protein and compound structures. The most crystal structures on RCSB portal are missing residues [18], so they need to be added before docking and scoring. Furthermore, hydrogen atoms in protein and compound structures must be added, partial charges assigned, missing loops filled, and the protein structures minimized to relieve steric clashes [19] [20]. On the other hand, if we have unstructured proteins, it is advisable to predict their structures as accurately as possible. And once a virtual drug screening is launched, it should be performed without interruption and human intervention, until the very end. All relevant information should be recorded for the later analysis and possible corrections. A good example of how a virtual drug screening process should be conducted is found in [21].

II. MATERIALS AND MEHODS

We used the Vini in silico model of cancer [22] for testing the accuracy of Autodock Vina performing docking on large datasets with unstructured proteins. The main reason for this choice is the fact that the Vini model has already implemented virtual drug screening workflow, and the software necessarry for selecting the best protein structures, preparing them, and predicting the high-quality structures for unstructured proteins. The VINI model uses UCSF Chimera [23], MGLTools [24], Autodock Vina [25], and Open Babel [26] for virtual drug screening. In addition, it has its own modules to support virtual drug screening workflow. These are create_completeness_list module for selecting and retrieving the best RCSB protein structures, prepare_protein module for preparing protein structures for docking, and predict_protein_structure module for selecting and retrieving predicted protein structures from the SWISS-MODEL repository[27]. For the testing purposes, we used part of the experimentally obtained data from the IDG-Dream Drug-Kinase Binding Prediction Challenge [28], aimed at accurately predicting the binding intensity between protein kinase inhibitors [29] and target proteins. We obtained this information in the form of a list of 5329 pairs of protein kinase inhibitors and target proteins, with experimentally measured values of binding free energy expressed with pkd values, where pkd is defined as:

$$pkd = -1000log(Kd) \quad (1)$$

Kd in (1) is the dissociation constant, measuring the propensity of a larger object to separate (dissociate) reversibly into smaller components. The relation between the binding free energy ΔG and the dissociation constant is defined as [30]:

$$\Delta G = RTlog(Kd) \quad (2)$$

where R is gass constant and has a value 8.3145 J/mol·K, while T is the temperature at which the experiments were performed and is 293 Kelvin. By including Kd from (1) into (2), it follows:

$$\Delta G = - (pkd\ R\ T) / 1000 \quad (3)$$

Further on, we decided to use mean absolute error (MAE) instead of root mean square error (RMSE) in our analysis. MAE provides us with physically more understandible interpretation of data then it RMSE does. The advantage of using MAE over RMSE in evaluating the mean performance of the model is given in [31]. For the total of M pairs with structured proteins and N pairs with unstructured proteins, MAE can be expressed as

$$MAEe = \frac{1}{M}\sum_{m=1}^{M}|\Delta Ge(m) - \Delta Gc(m)| \quad (4)$$

for the experimentally obtained protein structures, and

$$MAEp = \frac{1}{N}\sum_{n=1}^{N}|\Delta Ge(n) - \Delta Gc(n)| \quad (5)$$

for the predicted protein structures, where ΔGe(m) and ΔGc(m) are measured and computed binding free energy values for pairs with structured proteins, and ΔGe(n) and

ΔGc(n) are measured and computed binding free energy for pairs with unstructured proteins. In the case of accurate prediction of all protein structures, MAEe equals MAEp, but due to the limited prediction accuracy of SWISS-MODEL, the following inequality applies:

$$MAEe < MAEp \quad (6)$$

From eqs. (4) and (5), and considering eq. (6), one can define the average quality of the N predicted structures as:

$$q(N) = 100\,\frac{MAEe}{MAEp}\ ;\ \text{subject to MAEe} < \text{MAEp} \quad (7)$$

Defined in such a way, *q(N)* will have a value of 100 if all (N) protein structures are predicted accurately (MAEp = MAEe). Also, it will decrease with lower prediction accuracy (MAEp > MAEe), and has a value near zero if the prediction is bad (MAEp >> MAEe). Equation (7) was used to evaluate the accuracy of binding free energy calculations using predicted protein structures *versus* binding free energy calculations using experimentally established protein structures. The Vini model carried out virtual drug screening without human intervention from start to end, in three separate stages. First, protein and compound structures were prepared, then binding and binding free energy calculation for each pair was performed. Finally, MAEe and MAEp were computed. In addition to calculating the free binding energy for protein-compound pairs given by the IDG-Dream Drug-Kinase Binding Prediction Challenge, the Vini model also calculated the free binding energy for all other possible protein-compound pairs. In total, the Vini model calculated the binding energy for 34,748 protein-compound pairs using 96 processor cores over a 27-hour period.

The virtual drug screening process for each protein-compound pair is shown schematically in Figure 1.

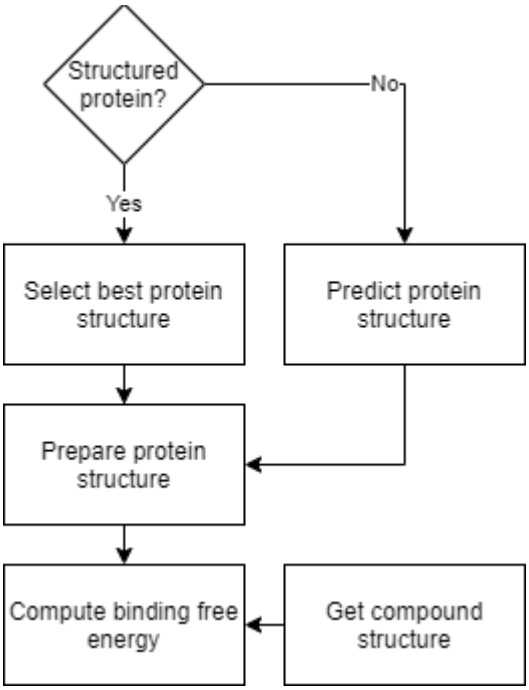

Figure 1. Overview of a virtual drug screening procedure for a particular protein-compound pair.

The Vini model repeated this procedure for each protein-compound pair, in two stages. In the first stage, it selected and prepared the experimentally determined protein structures. In case the protein structure did not exist, the model performed the structure prediction by using the SWISS-MODEL [27]. In the next stage, the Vini model performed binding between proteins and compounds, and the binding free energy calculations.

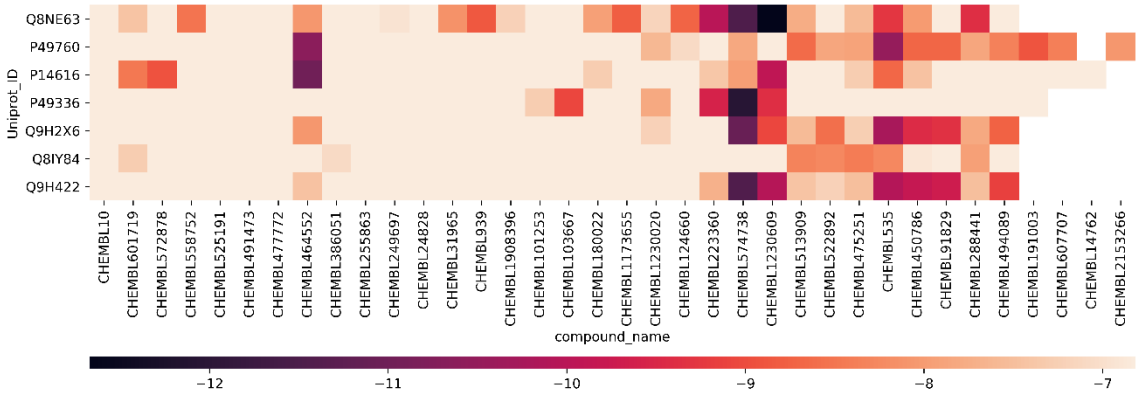

Figure 2. Heatmap of experimental value for failed protein-compound pairs

a) Preparation of protein structures

In this initial stage of virtual screening, the Vini model tried to select and prepare protein structures, and also 238 compound structures from the CHEMBL base [32] were prepared by converting their smiles to pdb format, and by adding hydrogen atoms to them. The Vini model identified 151 proteins from the Uniprot base [33] among 5329 protein-compound pairs. Among them, 136 were

structured, and 25 unstructured proteins. For unstructured proteins, the Vini model attempted to find and retrieve predicted structures in the SWISS-MODEL repository with the highest estimated quality using the QMEAN rating [34]. For five unstructured proteins, the Vini model could not find predicted structures, and they omitted from further analysis. In case of a structured proteins, the Vini model attempted to select and obtain from the RCSB database for each protein its 3D structure with the highest completeness. The next step was to remove water molecules and ligands from that structure, and then to add partial charges [35], hydrogen atoms to polar bonds [36], and missing residues. In doing so, the Vini model used the Dock Prep module of the UCSF Chimera software, the prepare_receptor4 module of the MGLTools software package, and the Open Babel software. If an error occurred during the preparation of the protein structure, the Vini model attempted to prepare the next structure with the next lower QMEAN. The process was repeated until some structure was sucesfully prepared for docking, or until the preparation of all available structures failed. If no structure could be prepared for docking, the Vini model additionally tried to prepare the predicted structure for docking. If this also failed, the VINI model dropped from further analysis all the protein-compound pairs containing that protein. For 231 from a total of 5329 protein-ligand docking pairs, the simulation could not be performed due to the limitation of used tools for seven protein structures with Uniprot_ID's P49760 (35), P14616 (35), P49336 (33), Q8NE63 (32), Q9H2X6 (32), Q9H422 (32) and Q8IY84 (32). Experimental values for failed pairs are presented in Figure 2. The average experimental (affinity) value for the 'failed' docking pairs is -7.439 kcal/mol with a standard deviation of 1.127, while the median is -6.817 with 148 pairs having the same experimental value.

b) Binding and binding free energy calculations

At this stage, the Vini model performed docking between proteins and compounds, and calculated free binding energies betwen them. The size of the simulation box was set to 40 Angstroms for all pairs. The spatial coordinates of the docking positions were calculated using the AutoGrid4 module from MGL Tools. Docking simulations and binding free energy calculations were performed with the Autodock Vina. In case the docking between protein and compound failed, the Vini model dropped that pair from further analysis.

Finally, the Vini model calculated the MAEe value of binding free energy for pairs with structured proteins by using eq. (4), and the MAEp value of free binding energies for pairs with unstructured proteins by using eq. (5).

III. RESULTS AND DISCUSSION

In total, 5329 protein-compound pairs from the Grand Challenge data set were analyzed. Binding free energy was calculated for 3979 pairs with structured proteins, for 1119 pairs with unstructured proteins, while the binding free energy of 231 pairs was not calculated, either as they contained proteins whose predicted structure was not found in the SWISS-MODEL repository, or the binding simulation failed. For pairs with structured proteins, the mean experimentally determined binding free energy was -7.612 kcal/mol and the mean calculated binding free energy was –7.210 kcal/mol. The MAEe value of 0.401 kcal/mol was calculated. For pairs with unstructured proteins, the mean of experimentally determined binding free energies was -7.580 kcal/mol and the mean of computed binding free energies was -6.990 kcal/ mol. MAEp of 0.590 kcal/mol was calculated. In Figure 3, we show for each protein-compund pair its corresponding MAE. In addition, in Figure 4 we show distributions of corresponding MAE for experimentally determined (E) and predicted protein structures (P) with median values of 0.897 and 0.931, respectively. The mean quality factor q(N) of 25 predicted protein structures calculated by eq. (7) was 67.9. This value is in a good agreement with the average IDDT test result [37] on the CAMEO portal [38] of 65.5 for 65 protein structures predicted by SWISS-MODEL.

Significant deviation of the computed binding free energy relative to the experimentally determined value has been obtained for multiple pairs, and the largest absolute error (8.70 kcal/mol) was identified for the pair between the Q15349 protein and the CHEMBL191003 compound,.

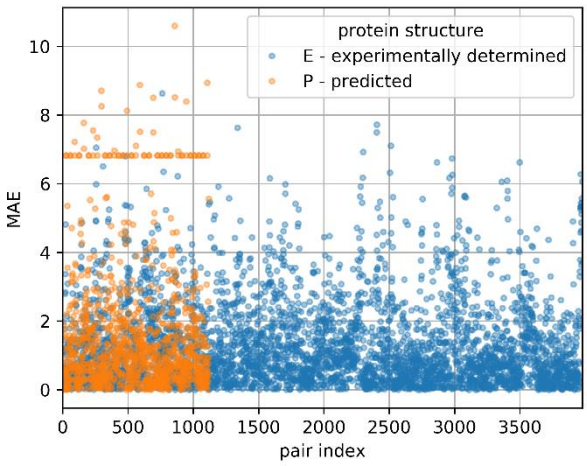

Figure 3. Mean absolute error distribution for pairs with experimentally determined (E) and predicted (P) protein structure

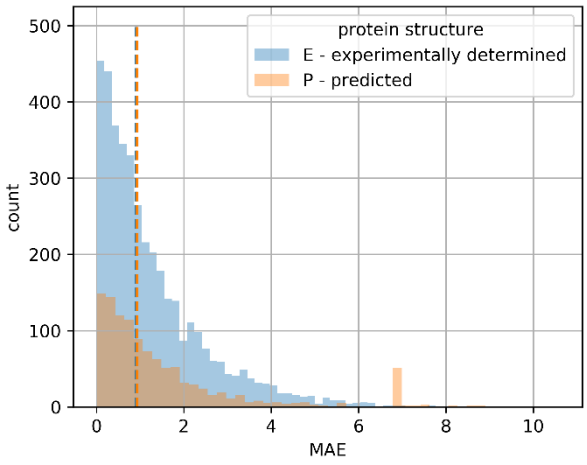

Figure 4 Distributions of mean absolute error for pairs with experimentally determined (E) and predicted (P) protein structure

Besides the virtual drug screening of 5329 pairs, we let the Vini model to perform simulation run on first 1000 pairs, and perform it 10 times. The rationale behind was to find out how well the results for the same pairs dissipate around a certain mean value. The results of this runs are shown in Figure 5.

The relatively small MAE was found both for pairs with structured and unstructured proteins, thus indicating that the Autodock Vina is a good tool for initial virtual drug screening on a large data sets. On the other hand, large and relatively frequent absolute errors indicate that Autodock Vina gives (in some cases) a false estimate of the binding free energy. For this, it is advisable to re-check all drug candidates resulting from initial virtual drug screening on a large datasets with more accurate molecular MD tools. However, it should be kept in mind that MD tools put high demand on computer resources. Therefore, in the final screening, the number of drug candidates must be appropriate to the available computer resources. The q(N) value of 67.9 obtained in this experiment overhelmes the accuracy of the ten docking programs, including the Autodock Vina [39]. Therefore, it seems appropriate to use the predicted protein structures in the virtual drug screening process. On the other hand, their use by much more accurate MD tools seems still to be prohibitive and deserves the future research.

Regarding some very high absolute errors found in this experiment, one possible cause may be that many of the compounds in the experimental dataset were large molecules with a molecular mass having > 900 Daltons, and Autodock Vina is not built and optimized to work with a large ligands. Another possible cause of such major errors is that many compounds in the test datasheet are biotech drugs, and Autodock Vina was not trained on them. Notwithstanding the relatively large individual errors in the calculation of free binding energies, the test results show that the predicted structures contribute very little to reducing the accuracy of the results. Furthermore, the results obtained show that SWISS-MODEL predicts protein structures that may be used in docking programs.

The possible cause of relatively high absolute errors between experimental and computed values may also rest in 3D structures of compounds of the experimental dataset. Concretely, the IDG-Dream Drug-Kinase Binding Prediction Challenge delivered the description of the compounds in SMILES [40] data format. SMILES were converted to 3D structures with Open Babel and delivered to us. Based on our previous research and the experience, conversion from SMILES format to 3D structures by Open Babel is not the best solution and may introduce a certain amount of errors in obtained structures. However, this part is beyond the research scope of this paper. Based on the results obtained, our conclusion is that it is justified to use the predicted 3D protein structures in virtual drug screening of a large datasets containing unstructured proteins. We expect that with a more accurate 3D structures of compounds, the absolute error values will be considerably lower. This will be a part of our future research.

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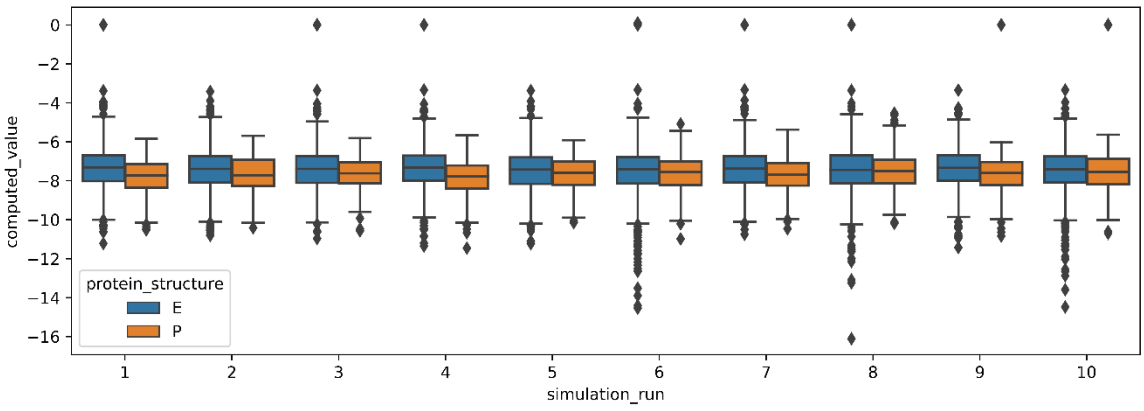

Figure 5. Box plot of computed affinity values for first 1000 protein-compound pairs across 10 simulation runs

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