Applying a Novel Web-Tool for Performing Virtual Screening Experiments

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Abstract: The use of *in silico* methods for identifying new drugs to a target of interest is a step of a process called Rational Drug Design. The *insilico* analysis of a set of drug candidates is performed by a computational technique named as Virtual Screening (VS). In a previous work, we have developed a novel web tool for configuring different types of VS experiments using AutoDock Vina docking software. The presented tool is a framework that generates python scripts to run VS experiments in the users' computer according to the users' configuration on the framework web interface. In this paper we propose to apply the developed framework in a specific VS experiment considering one target receptor and a set of ligands. For this VS experiment the researcher informs the location of receptor and the ligands files as well as their formats. It is also possible to set receptor and ligand flexibility.　After this, the user indicates the output folder where all the results in the user's computer will be stored after the script execution. Then, the user should configure the box area that indicates where ligands will be docked in the receptor molecule. The box size and the center must be configured, the variation of box center could be configured if user wants to execute an experiment that search the binding site in the entire molecule.　In this way, this paper demonstrates the usage of the proposed framework for VS where we considered as receptor the structure of the human voltage-dependent anion channel (PDB code: 2JK4) and as ligands different types of carbon nanotubes. In the experiments performed we have defined both receptor and ligands as rigid and considered only one box for representing the receptor binding site.

1. Introduction

In Bioinformatics, one of most important research area is the Rational Drug Design (RDD) [3], a process where the costs and time involved are high. One of the RDD steps is the molecular docking, a computational technique used for the approximate determination of the interaction energy between the macromolecule receptor and a ligand candidate inhibitor [5]. One of the major challenges in RDD is related to the understanding of the behavior of biological macromolecules receptors as proteins and how they interact with a set of different small molecules or ligands, a strategy called Virtual Screening (VS) [2].

Here, in order to approximate the in-silico step of RDD process to the in vitro and in vivo tests the VS should consider that under physiological conditions, biomolecules experience various types of movement and conformational changes often crucial to their functions [7]. This flexible behavior of biological macromolecules can be simulated by molecular dynamics (MD) trajectories [2]. To incorporate flexibility in the receptors in a VS process, a possible approach is the implementation of a series of molecular docking using in each experiment a different receptor conformation generated by DM [4].

For the execution of a VS process, in addition to the target receptor (rigid or flexible), it is necessary a set of compounds which may be obtained in different public databases. These ligands should be in a specific file format and can be considered as rigid or flexible.

Another problem is when the target binding site is unknown. Thus, the entire conformational space of the target molecule should be investigated by further increasing the complexity of this kind of experiment. In a previous work we proposed a framework for virtual screening where the user can easily configure a VS experiment[7]. Different types of configurations can be set by researchers, from the generation of a simple experiment containing a receptor and a binder to a more complex experiment that will contain in its implementation, several receptors with various ligands and also the possibility of variation box (receptor molecule coordinate where the drug candidates, also called ligands, will be tested).

Therefore, this paper aims at presenting the application of the previously web framework for a VS experiment. In this experiment we consider only one rigid receptor and a group of different carbon nanotubes. This framework uses the AutoDock Vina [8] to perform the molecular docking.

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2. Results and Discussion

In this section we present the application of the proposed framework for a virtual screening experiment. The experiment performed to analyze the application of the framework consists in one target receptor, called human voltage-dependent anion channel (PDB ID: 2JK4) and a set of single walled carbon nanotubes (SWCNT-pristine amchair).

The framework's web interface consists in two parts. Part one (Figure 1) is called Input/Output Area where the configuration of the receptor(s) and ligand(s) are filled. The part two (Figure 2) is called Box Area where the box size and the center of the box (receptor molecule coordinate where the drug candidates will be tested) are filled.

Firstly, according to Figure 1, before any receptor or ligand configuration is performed the user must answer a question about the operational system (OS) where the generated

Python script is going to be performed. For this case it was selected "Linux" OS. The second question regards the amount of times that the user wants to run the same experiment. This is implemented in the framework since the AutoDock Vina starts its tests by choosing a random initial position for the ligand inside the delimited box, a parameter called seed. For this case "No" was selected.

The next area to configure is the receptor, it provides to the user the possibility of selecting a flexible receptor model or only one receptor structure. In the present case, we considered as the receptor the protein human voltage-dependent anion channel PDB ID: 2JK4 that is stored in the path "/home/script_vs/receptor/" according to figure 1. The receptor type was selected as PDBQT. The PDBQT format indicates that this receptor input file has already the charges for each atom and hydrogens were added. After this, the user needs to configure the ligand area. In this case, the ligand is one set of SWCNT (SWCNT-pristine amchair) and it is located in "/home/script_vs/ligand/". It is important to notice that the ligand type was selected as "MOL2 (file with multiple structures)" thus the the file "SWCNT.mol2" can have either one or a set of ligands. In our case study, the input ligand file is composed by many ligand files that corresponds to different types of carbon nanotubes. This functionality was implemented when user wants to perform a virtual screening considering many ligands in an experiment. In addition, the user can choose to consider the ligand(s) as rigid by selecting the checkbox *Rigid Ligand or flexible by not selecting the checkbox.*

Another parameter of a VS experiment (Figure 1) is the "Output Folder" that indicates where results should be stored on the user's computer during the execution of the Python script. If the user selects the type of receptor or ligand input file different of PDBQT format, the MGL Tools space appears in the interface called *MGL Tools path*. This path is provided by the user indicating where the MGL Tools are installed on his own computer.

The Box area (Figure 2), is the module where the user configures the simulation box that represents the binding site of receptor. During the molecular docking simulations AutoDock Vina analyses the best conformation and orientation of the ligand(s) inside the framework's interface *Box section* according to the figure 2. For the present experiment we configured the field *Box Size* with the following values: $X = 20$, $Y = 20$ and $Z = 20$. For the *Box Center* field we configured the following values: $X = 28.097$, $Y = 3.078$ and $Z = 8$. The user can also configure a variation on the box: the user fills in an initial area (X, Y and Z fields of the Box center area), a final area (X-final, Y-final and Z-final in Box center area) and a particular step (X-step, Y-step and Z-step in the Box Center area).

After the configuration of the Box Area, the user needs to answer a question in relation to the analysis module. This module allows the user to obtain a script to perform the analysis of the receptor-ligand interaction using the software LigPlot[7]. The question in the interface is "Do you want LigPlot results?". According to the figure 1, we have answered "Yes", thus a script that have to be executed after the mais script execution is generated. The user needs to inform where LigPlot is installed in his own computer in the field "LigPlot Folder" as presented in figure 2.

The LigPlot script reads all results generated by the main script creating spreadsheets to facilitate the analysis of contact between residues of receptor and ligand atoms. Finally, to

generate the main script, the user needs to click in "Generate Script" and execute it in his own computer to perform the VS experiment.

For the performed experiment we consider SWCNT-pristine amchair. The average FEB was -14.44 and the standard deviation was 2.38. It indicates that almost all tested carbon nanotubes had a good interaction with the protein human voltage-dependent anion channel.
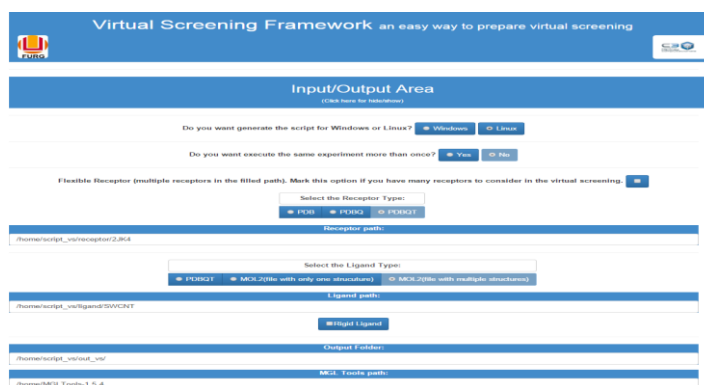
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Figure 1. Input/Output section in the Framework interface.

Figure 2. Box section in the Framework interface.

3. Materials and Methods

This section presents the materials and methods applied in the development of the proposed experiment using the VS experiment.

This is a client-server architecture implementation that works in the web environment. For performing the VS experiment the user needs to have installed Python and AutoDock Vina in his own computer.

For the development of the protein-ligand interaction module the software LigPlot was integrated to our tool. This software also needs to be installed on user's computer.

According to [9], LigPlot is a software that evaluates the intermolecular interactions that occurs in a receptor-ligand complex formation.

. The main objective of this work was to implement a tool that generates scripts enabling users to perform different types of VS experiments.

In relation to the experiment used as example, most of the results were good according to the average FEB, showing that interactions between receptor and ligands for all experiments are present.

With this tool, researchers from different fields can perform VS experiments according to their necessities. More importantly, with the use of the presented tool the VS process is automated making it easier to run complex VS experiments..

4. Conclusions

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