Molecular Docking

Introduction

In the field of molecular modelling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the preferred orientation in turn may be used to predict the **strength of association** or **binding affinity** between two molecules using various scoring functions.

Molecular docking is one of the most frequently used methods in structure-based drug design. Characterisation of the binding behaviour plays an important role in rational design of drugs as well as to explain fundamental biochemical processes.

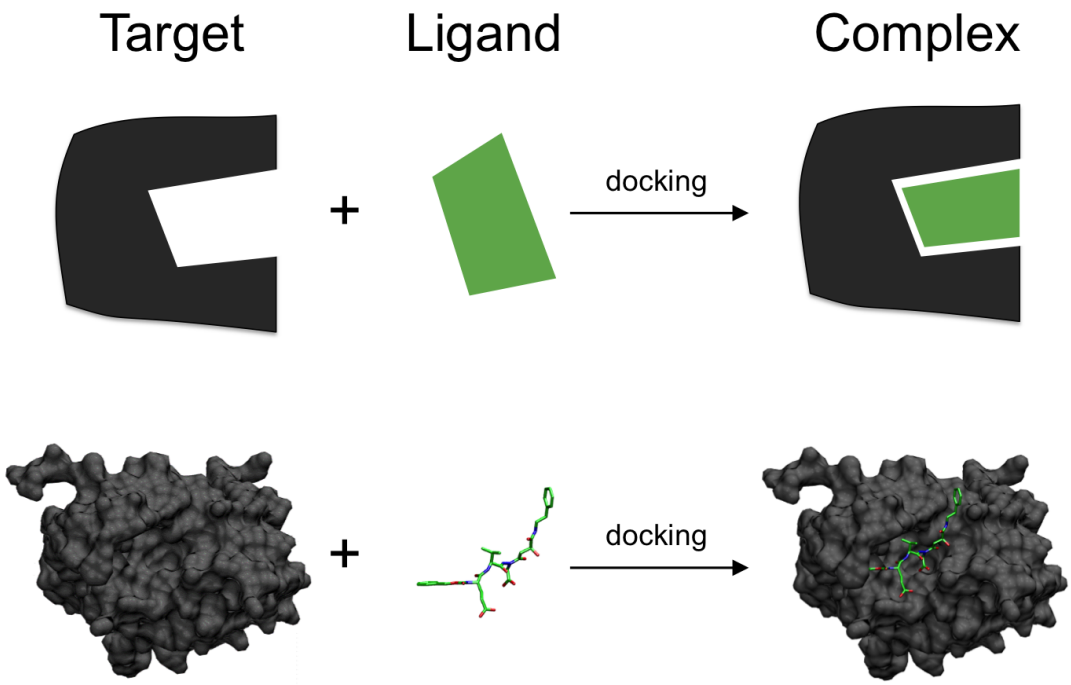

Figure 1 Schematic illustration of docking a small molecule ligand (green) to a protein target (black) producing a stable complex.

PyRx- A Molecular Modelling Simulation Software

PyRx is a Virtual Screening software for Computational Drug Discovery that can be used to screen libraries of compounds against potential drug targets. PyRx includes a docking wizard with an easy-to-use user interface which makes it a valuable tool for Computer-Aided Drug Design. PyRx also includes chemical spreadsheet-like functionality and powerful visualization engines that are essential for structure-based drug design.

Using PyRx as a tool to know the affinity of various ligands with major enzymes of SARS-CoV-2

As mentioned above, PyRx is a useful tool to assess the binding affinity of various ligands to the target enzyme (here viral RNA polymerase).

For this assessment, we require two entities- A target and a ligand

Target: This is the molecule on which we want our ligands to act. It can be an enzyme related to CoV, preferably the RNA polymerase, which helps in the replication of coronavirus, or the ACE-2 receptor, through which coronavirus internalizes and invades human cells.

Ligand: Ligand is the molecule which acts on the enzyme/target and helps to modulate their function. And yes, it is the same ligand if properly synthesized, or incorporated into a synthesizable compound, definitely has the potential to become a future drug.

STEP-1 Selection of ligands and targets.

● Selection of targets

The genome sequencing of coronavirus has allowed many potential sites where a proper small molecule can act. Some of these are the intrinsic enzymes of the virus. Many of targetable enzymes are: **3-chymotrypsin-like protease (3CLpro), Spike, RNA-dependent RNA polymerase (RdRp), and papain like protease (PLpro)**. In addition to these, the Human ACE-2 receptor can also be considered as a potential target.

Moreover, since coronavirus is a RNA virus, its major enzymes may exhibit some structural similarity with those of other RNA viruses, like the SARS, MERS, HIV, Hepatitis-C, Ebola. Hence drugs targeting enzymes of these viruses can also be used as a ligand.

● Selection of ligands

They can be pre –available molecules or newly generated molecules.

1. New small molecules can be generated from datasets like Moses, ChemBL data sets. These chemicals are in the form of SMILES. SMILES stands for **S**implified **M**olecular-**I**nput **L**ine-**E**ntry **S**ystem. It is a specification in the form of a line notation for describing the structure of chemical species using short ASCII strings. SMILES strings can be imported by most molecule editors for conversion back into two-dimensional drawings or three-dimensional models of the molecules.
2. The already available ligands for a specific enzyme can be obtained from the Protein Data Bank. The Protein Data Bank is a database for the three-dimensional structural data of large biological molecules, such as proteins and nucleic acids.
3. Ligands which are confirmed to be acting on enzymes of other RNA viruses can also be selected.

There are a number of publicly available websites where users can download target macromolecules and small molecules:

- https://www.ncbi.nlm.nih.gov/genbank/ sars-cov-2-seqs/
- https://www.gisaid.org/epiflu- applications/ next-hcov-19-app/
- http://www.rcsb.org/

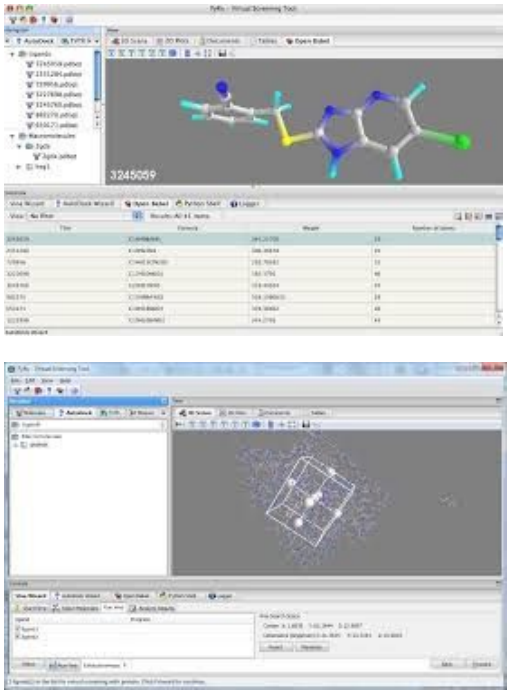

Figure 2 Showing the user interface of PyRx and 3-dimensional structure of molecules

STEP-2 Introducing targets and ligands in PyRx

- Once targets and ligands are selected their 3d structure must be downloaded from the protein data bank.
- Once downloaded, their structures must be opened in the protein data bank.
- Initially, select the downloaded macromolecule and open it in the PyRx app and then select and add ligands downloaded to the macromolecule (target).

STEP-3 Run Virtual Screening Using Vina Wizard

- Select the Vina Wizard tab under the Controls panel and click on the Start button.
- Select the desired Ligands folder
- Select your target from the Macromolecules folder and click on the Forward button on Vina Wizard.
- Click on the Maximize button under Vina Search Space and then click on Forward button. This starts AutoDock Vina and docks each ligand, one by one.
- After virtual screening is completed, PyRx automatically advances to the Analyze Results page, where you can see results of virtual screening computation.

  AutoDock Vina, by default, outputs 10 best binding modes for each docking run.On clicking Binding Affinity (kcal/mol) table header cell under Analyze Results tab to sort this table by predicted binding affinity

STEP-4 Filter out those ligands with aberrant chemical structure

- Out of the selected list of ligands having maximum negative affinity with the target, filter out those ligands with aberrant chemical, non-synthesizable chemical structure.
- The remaining molecules, if synthesizable can act as a potent source of future drug for coronavirus

References

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