Instituto Politécnico Nacional

Escuela Superior de Cómputo

Bioinformatics

Practice 9 - Docking

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1 Theoretical Framework

In the field of molecular modeling, **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, for example, scoring functions [1]. Figure 1 shows a docking representation.

The associations between biologically relevant molecules such as proteins, peptides, nucleic acids, carbohydrates, and lipids play a central role in signal transduction. Furthermore, the relative orientation of the two interacting partners may affect the type of signal produced. Therefore, docking is useful for predicting both the strength and type of signal produced [1].

Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding-conformation of small molecule ligands to the appropriate target binding site. Characterisation of the binding behaviour plays an important role in rational design of drugs as well as to elucidate fundamental biochemical processes [1].

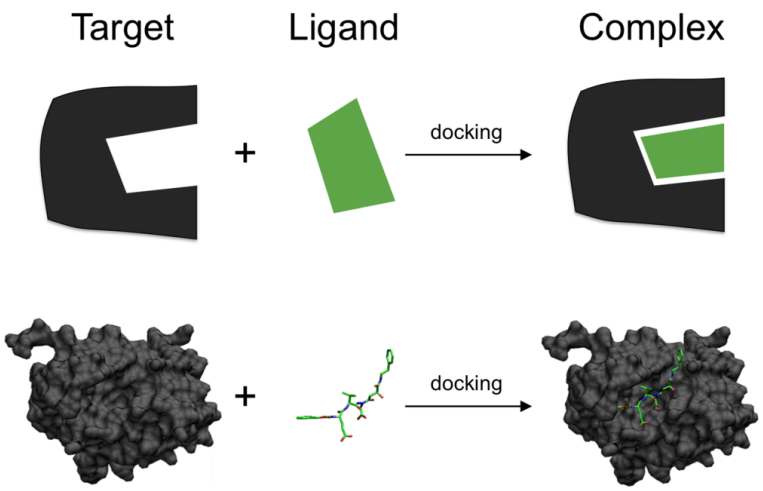


Figure 1: Schematic illustration of docking a small molecule ligand (green) to a protein target (black) producing a stable complex [1].

Molecular docking research focuses on computationally simulating the molecular recognition process. It aims to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand such that the free energy of the overall system is minimized [1].

Two approaches are particularly popular within the molecular docking community. One approach uses a matching technique that describes the protein and the ligand as complementary surfaces. The second approach simulates the actual docking process in which the ligand-protein pairwise interaction energies are calculated [1].

2 Material and Equipment

- RCSB PDB: Homepage - PDB [2].
- ZDOCK web server [3].
- ZINC15 databse [4].
- SwissDock web server [5].
- VMD Software [6].
- Crystal and Molecular Structure of Barley Alpha-Amylase model - 1AMY [7].
- Thioredoxin h2 (HvTrxh2) in a mixed disulfide complex with the target protein BASI model - 2IWT [8].
- AMY2/BASI protein-protein complex from Barley Seed model - 1AVA [9].
- Human cyclin-dependent kinase 2 in complex with roscovitine model - 2A4L [10].
- Seliciclib ligand - ZINC1649340 [11].
- Crystal structure of the truncated human cytomegalovirus pUL50-pUL53 complex model - 6T3X [12].
- Ganciclovir ligand - ZINC1505 [13].

3 Practice Development

The objective of this practice is to perform two dockings using specialized servers for this task:

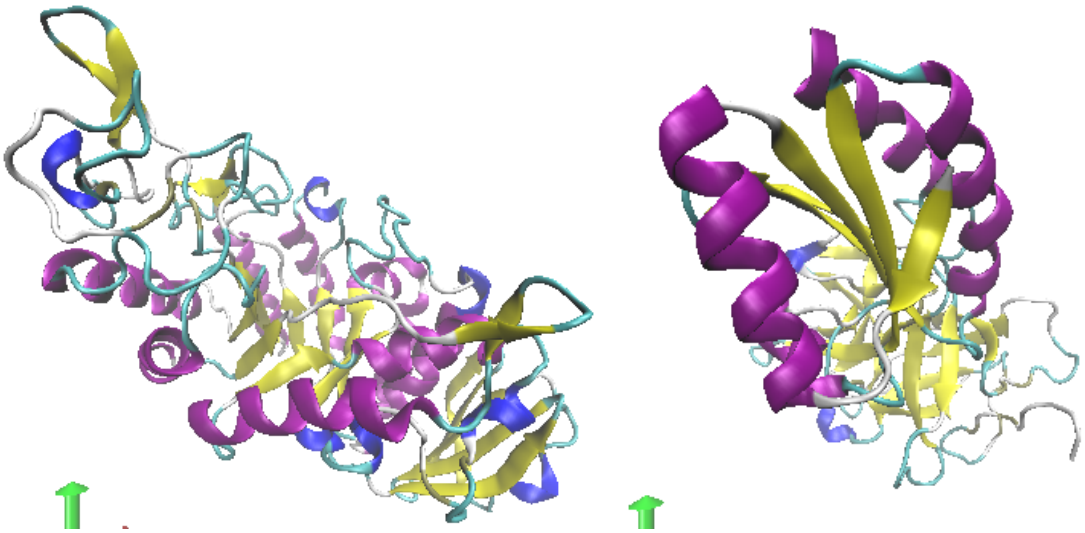
- Between two proteins: **1AMY** [7] and **2IWT** [8].
- Between a drug and a protein: **Ganciclovir** [13] and **Cytomegalovirus - 6T3X** [12].

3.1 Perform a Docking between two proteins

Go to the **PDB** web page [2], search for the two selected proteins for this docking, which its models loaded in the VMD software [6] are shown in Figure 2:

1. Crystal and Molecular Structure of Barley Alpha-Amylase Protein - **1AMY** [7].
2. Thioredoxin h2 (HvTrxh2) in a mixed disulfide complex with the target protein BASI - **2IWT** [8].

Download its .pdb files and then go to the docking server **ZDOCK** web page [3] and as shown in Figure 3, in the *Input Protein 1* field select the *PDB File* option and then upload the **1AMY .pdb file**. Do the same with the *Input Protein 2* field uploading the **2IWT .pdb file**. Enter your email and check the *Skip residue selection* option. Finally click on the *Submit* button to start the process; this could take some hours until it finishes.



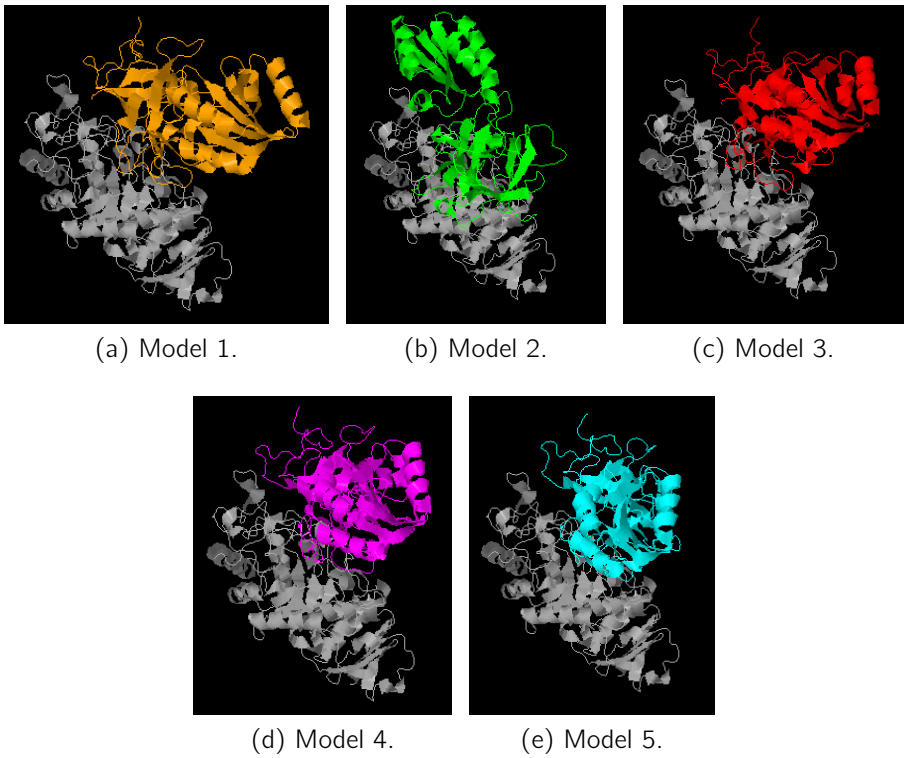
(a) **1AMY** protein model. (b) **2IWT** protein model.

Figure 2: Proteins selected for a docking between them.

Figure 3: ZDOCK server interface [3].

The top 5 predictions from this docking are shown in Figures 4 and 5, where its resulted PDB files are visualized with the same ZDOCK server [3] and with the VMD software [6] respectively.

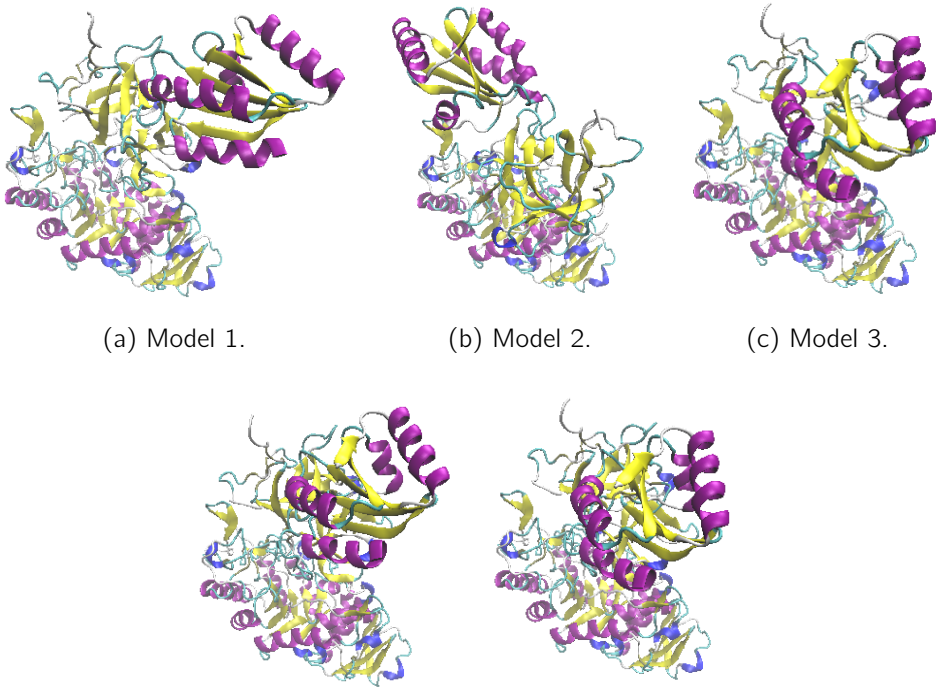
These generated models should resemble to the **AMY2/BASI protein-protein complex from Barley Seed model - 1AVA protein** [9], shown in Figure 6. The more accurate are these generated models with this protein the better is the server.



(a) Model 1. (b) Model 2. (c) Model 3.

(d) Model 4. (e) Model 5.

Figure 4: Docking results for **1AMY - 2IWT** proteins in ZDOCK [3].



(a) Model 1. (b) Model 2. (c) Model 3.

(d) Model 4. (e) Model 5.

Figure 5: Docking results for **1AMY - 2IWT** proteins in VMD [6].

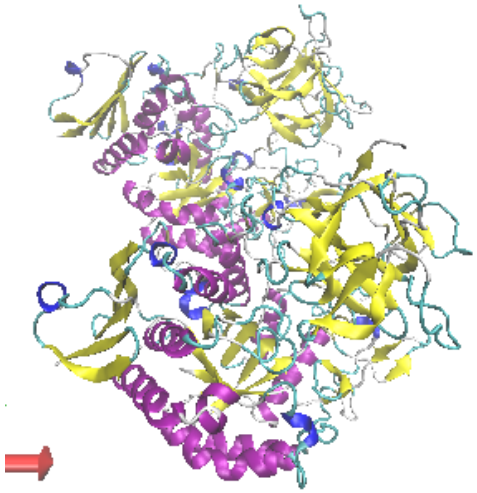
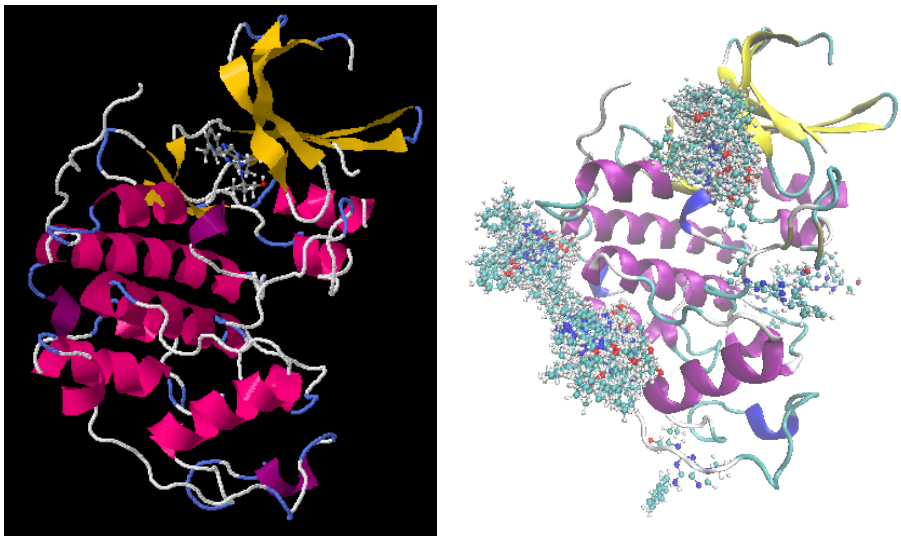


Figure 6: **1AVA** protein model [9].

3.2 Perform a Docking between a drug and a protein

In the lab session, a docking between the **Human cyclin-dependent kinase 2 in complex with roscovitine - 2A4L** protein [10] and the **Seliciclib - Riscovitine** drug [11] was performed. The results of this prediction are shown in Figure 7.



(a) Swiss Dock. (b) VMD.

Figure 7: Docking results for **Human cyclin-dependent kinase 2 in complex with roscovitine - Seliciclib**.

In this report this docking won't be reported, instead there will be used a virus protein and a potential drug that could attack it.

It is known that **Ganciclovir** has activity against the **Cytomegalovirus or CMV**, a virus that can cause blindness by affecting the retina.

For this reason, these are the selected drug and protein for this docking. Go to the **PDB** web page [2], search for the **6T3X Cytomegalovirus** protein [12] and download its .pdb file, which is loaded in the VMD Software [6] as shown in Figure 8.

After that, go to the **ZINC15** database [4], and search for the **Ganciclovir** drug [13], displayed in Figure 9. Save the ZINC code of this drug for later: **ZINC000000001505** [13].

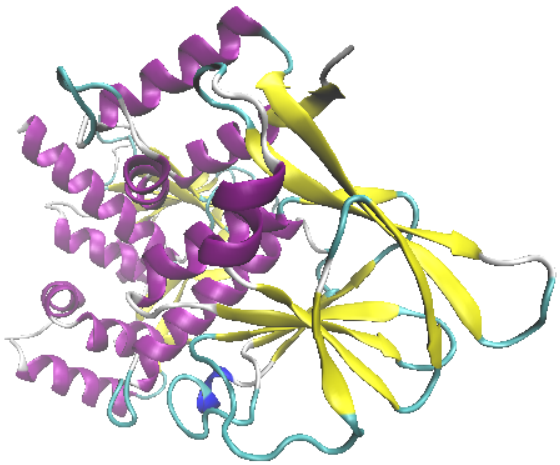


Figure 8: **6T3X** protein model [12].

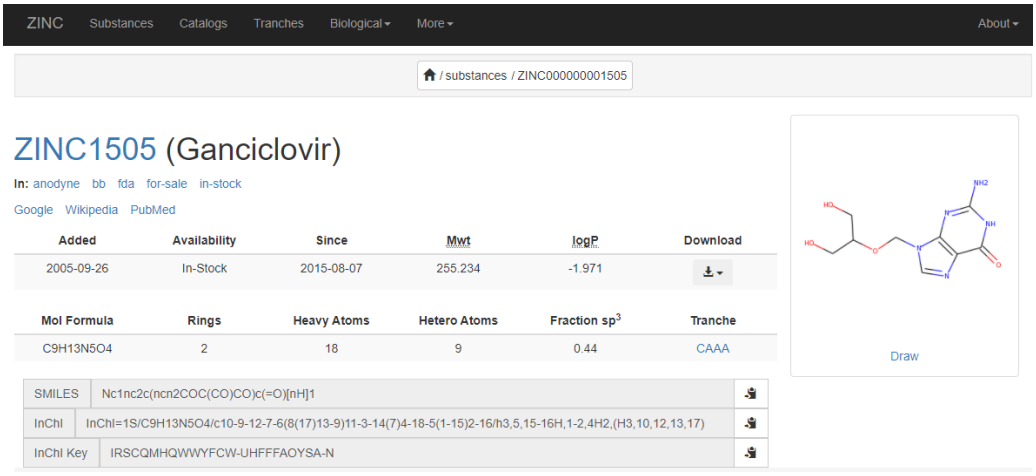


Figure 9: **Ganciclovir** entry in ZINC15 [13]

Go to the *Submit Docking* tool on the SwissDock web server [5]. In the *Target selection* section click on the **upload file (max 5MB)** link and upload the **6T3X** .pdb file. Wait until the server setups the target protein successfully.

Next, in the *Ligand selection* enter the **Ganciclovir** ZINC code **ZINC000000001505** into the *Search for ligands:* field and click on the *Search* button. A new window like the shown in Figure 10 will open, select the **1505** option and click on the *Dock 1 selected ligand* button. Wait until the server setups the ligand drug successfully.

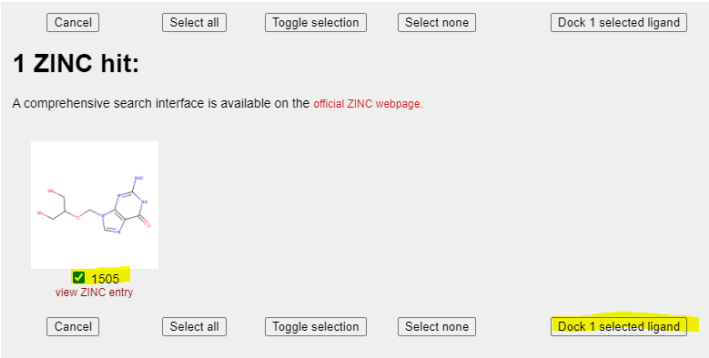


Figure 10: SwissDock interface for ligand selection [5].

Now the interface should looks like Figure 11. Click on the **Submit** button to start the docking; this could take some hours or even few days until it finishes.

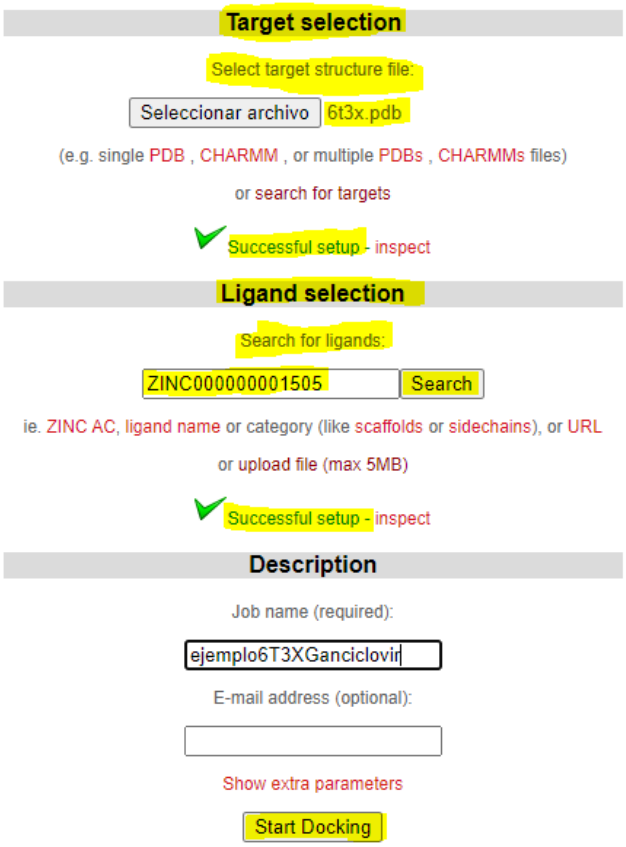


Figure 11: SwissDock interface for the Submit Docking tool with the **6T3X** protein and the **Ganciclovir** drug [5].

The top 5 clusters from this docking displayed with the same SwissDock server are shown in Figure 12, and its resulted PDB file with all the clusters predicted is visualized with the VMD software in Figure 13.

(a) Cluster 0. (b) Cluster 1. (c) Cluster 2.

(d) Cluster 3. (e) Cluster 4.

Figure 12: Docking results for **Cytomegalovirus - Ganciclovir** in SwissDock [5].

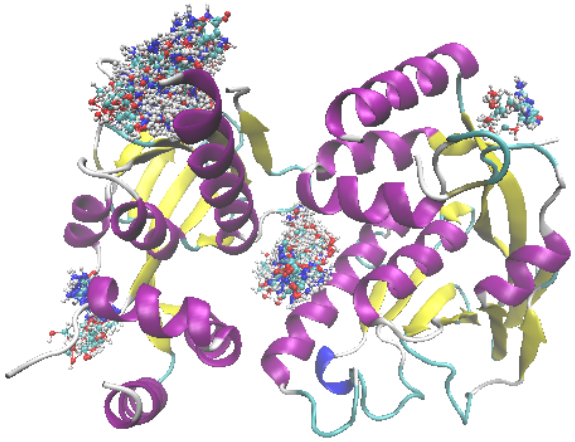


Figure 13: Docking result for **Cytomegalovirus - Ganciclovir** in VMD [6].

4 Conclusions and recommendations

The recommended actions to take in order to predict the effect of a drug on a protein, supposing that all we know about the protein is it primary structure, consists on performing a BLAST on this protein to acknowledge other similar and have a better understanding of its nature. A virtual screening is very used to reduce all the possible drugs that can have the searched effect on the protein. However, the docking results are not definitive, so there must be make tests on animals and next on humans to identify if the drug is effective or not against the protein in question.

5 References

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