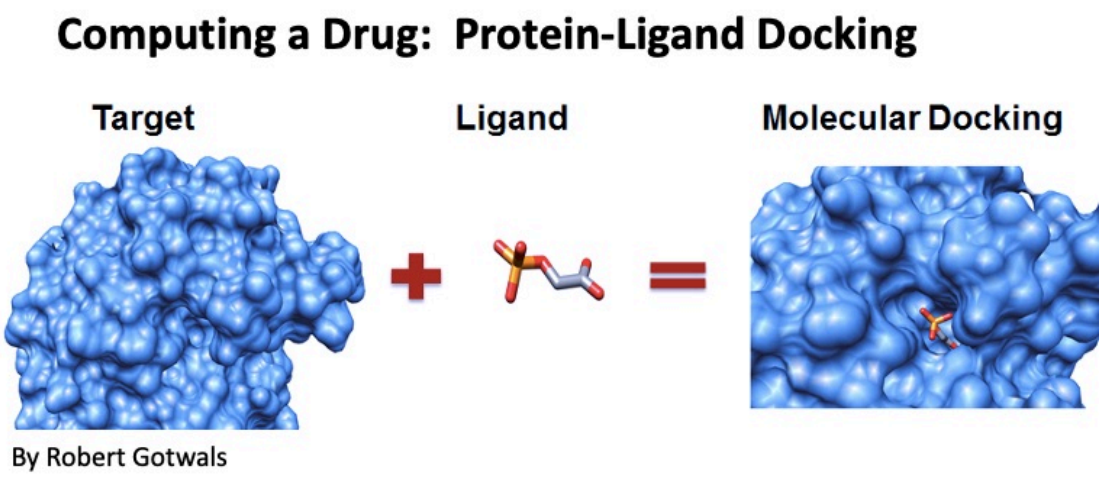


Computing CoVID-19: Summer 2020

# Protein-Ligand Docking

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# 1

# Introduction

Protein-ligand binding is one of the most important components of the drug discovery process. In protein-ligand docking, a drug – the ligand – is "docked", or inserted, into an *active site* in a target protein. The docking program determines *binding affinities*, which is measured as a $K_i$, or, more commonly, as a $pK_i$, where K is an equilibrium constant like you have seen in general chemistry, and the "i" stands for inhibition.

When a ligand docks with a protein, the structure of the protein changes. That structural change results in the protein either being enabled or disabled. For example, Figure 1 shows the protein protease PDB ID:1HVR, the protein that controls the replication of the HIV virus. This protease helps to replicate the HIV virus in cells. By inserting a drug into the active space, we can prevent the protease from replicating the virus.

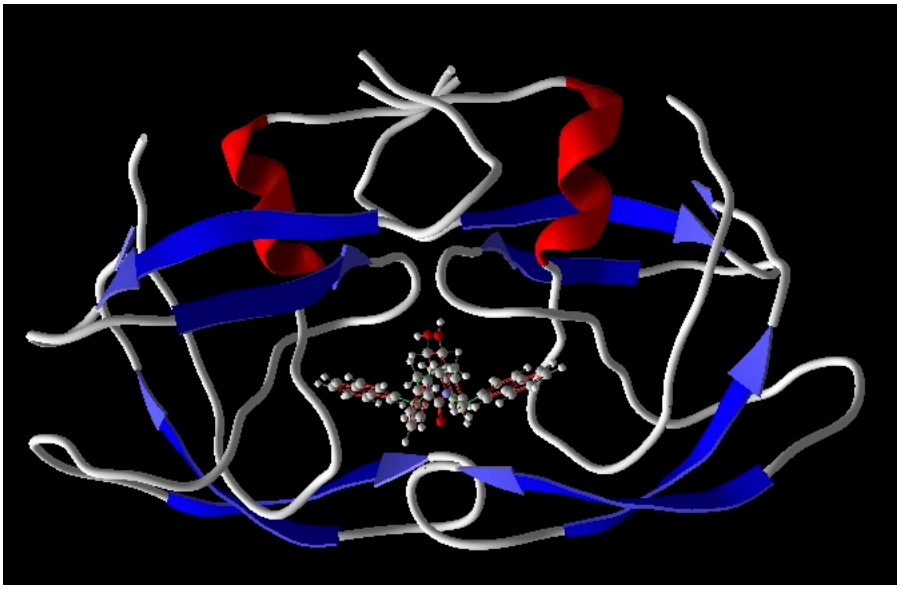

Figure 1: PDB ID: 1HVR HIV-protease with inhibitor

A docking produces a docking score. During the process, a drug undergoes a number of *conformationals*, in which the shape of the molecule changes. These conformers are typically

known as *poses*. The goal for a specific ligand is to find the pose that best binds to the protein. This is typically indicated by the docking score, a relative number. The lower the docking score, the better the "fit" in the pocket.

Figure 2 shows the drug dexamethasone, recently identified as a possible therapeutic for CoVID-19 patients who have been on oxygen and/or a ventilator for long periods of time. The graphic shows two poses for the drug, superimposed on top of each other. Notice that the shapes of the two poses are slightly different. This allows for the drug to "wiggle around" and find a nice cozy fit in some binding pocket of the protein.

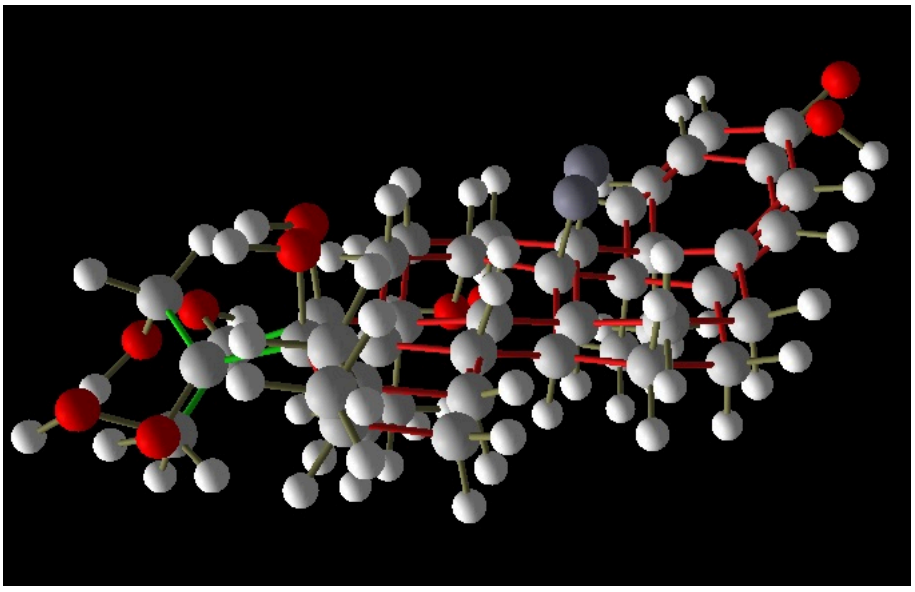

Figure 2: Two poses for the steroid dexamethasone

One of the most important steps in the docking process is finding the *active site* in the protein. Typically there are more than one! This is the location in the protein where the ligand is most likely to bind. This site is also known as a binding site, a pocket, or a cavity. Figure 3 shows the protein glucocorticoid, the receptor for the drug dexamethasone.

Figure 3: Binding pocket for the steroid dexamethasone

The overall goal of protein-ligand docking is to find the best fit of the ligand in this pocket. Figure 4 shows dexamethasone after it has been docked into one of the binding sites, or cavities, of the target protein receptor glucocorticoid.

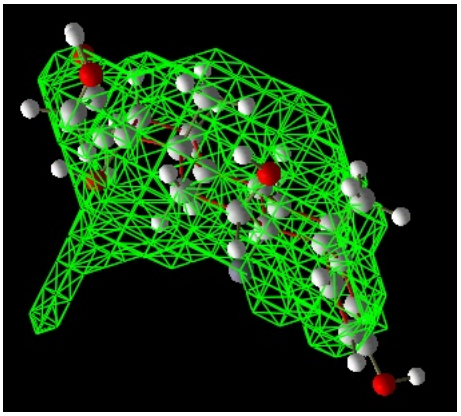

Figure 4: Dexamethasone docked into a cavity

There are a number of docking tools available. Typically, we would use Molegro, but the current version no longer runs on newer Macs (Catalina), and we are awaiting an updated version! Other programs include AutoDock, Glide, and Vina. The free tool pyrx (https://pyrx.sourceforge.io/) is also useful, but as with Molegro, it does not run on newer Macs. For our docking studies, we will use the SeeSAR module in StarDrop. This module is developed by BioSolveIT (https://www.biosolveit.de/). SeeSAR produces two scores: a Flex X score, which is a relative docking score. As above, the lower the docking score, the better. It also produces a HYDE score, which stands for HYdrogen bond/DEhydration energies ([1]).

In evaluating the HYDE scores, we can look at atoms that contribute to the binding, and those that weaken the binding. Figure 5 shows that green atoms contribute to the binding, while the red atoms detract from the binding. We represent this with HYDE "coronas", which will be demonstrated in the webinar!

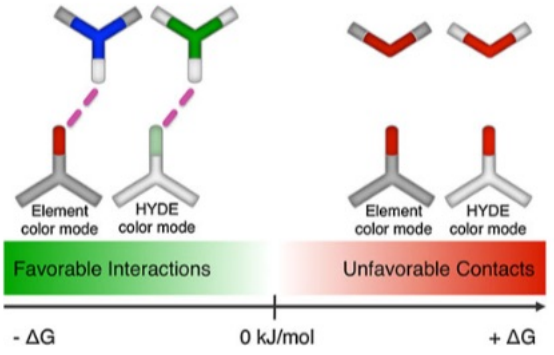


**Fig. 4** Hyde coloring scheme: *Green atoms* contribute favorably to $\Delta G_{HYDE}$. *Red atoms* contribute unfavorably to $\Delta G_{HYDE}$. *White atoms* are energetically negligible. On the *left*, a hydrogen bond with ideal geometry is depicted; both atoms—donor and acceptor—are *colored green*. On the right, two hydrogen bond acceptor atoms (ether and carbonyl) making an unfavorable contact are both *colored red*

Figure 5: HYDE scoring profile

# 2

# Student Activity

**NOTE! The majority of the steps for the activity will be demonstrated in the webinar. These instructions are meant only as short reminders of the steps you need to take to effectively modify the lead drug and test the new compounds!**

## 2.1 Part 1 – Comparing Docking Scores

Using the file "CoVIDAntivirals7.csv", find the 2C9 pKi values for the seven drugs. Then, using the spreadsheet (as demonstrated in the webinar), determine the docking score for the unknown anti-viral that has a 2C9 score of 5.58.

## 2.2 Part 2 – Docking of Seven Anti-Virals to 6M2N

Your goal is to dock seven anti-viral ligands to the protein receptor PDB ID:6M2N. Your target/reference ligand is 3WL-401-A, a novel inhibitor located in Chain A of the protein. By now you should have some familiarity with this protein! Figure 6 shows a screenshot from the Protein Data Bank:

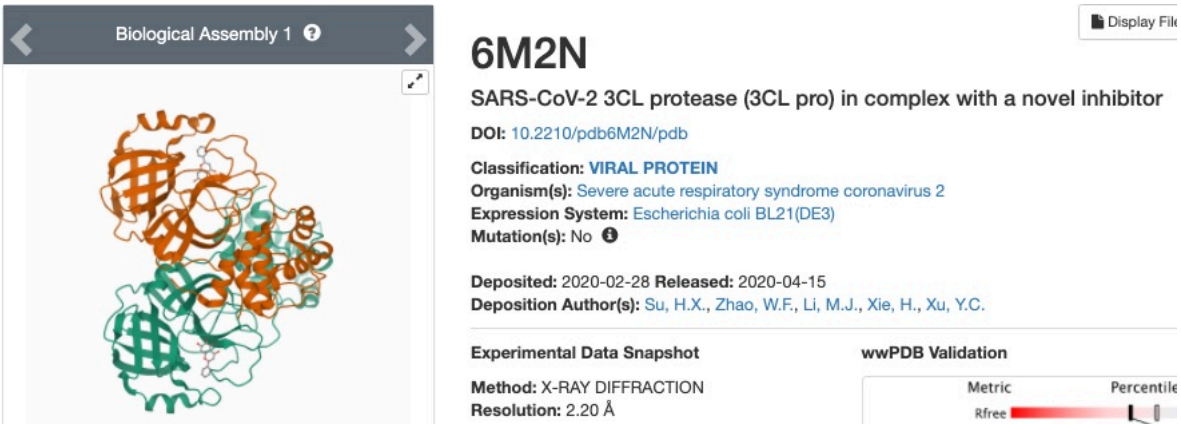


Figure 6: Screenshot of PDB ID:6M2N ([2])

The drugs to be docked can be found on Canvas, a CSV-file named "CoVID Docking Drugs". Using SeeSAR, dock the seven drugs and respond to the questions on the lab activity "Day 10 Lab 1: Protein-Ligand Docking"

# References

[1] Schneider, Nadine, et al. "A consistent description of HYdrogen bond and DEhydration energies in protein–ligand complexes: methods behind the HYDE scoring function." Journal of computer-aided molecular design 27.1 (2013): 15-29.

[2] https://www.rcsb.org/structure/6M2N, accessed July 11, 2020.