Analysis of protein-ligand interactions

# System selection

For this part of the lecture we will focus on PDB 6ZUV.

Let us open PDB 6ZUV and have a look at the system.

Afbeelding met kunst

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You can clearly see the ligand (B1J) in the active site (red box), along with some other molecules used during the crystalization experiment for generating the crystal structure (sulfate, ethylene glycol).

# Ligplot

I can be a bit daunting to start analyzing the 3D structure of protein-ligand interactions. Tools have been developed to generate an initial idea of possible important interactions. Ligplot+ is one of those tools.

Open Ligplot+. LigPlot+ will ask you a couple of questions the first time that you open the program. Normally, the defaults should be appropriate but make sure that “Temporary Directory” is set to a folder that is available on the system to write to.

Afbeelding met tekst, schermopname, Lettertype, software

Door AI gegenereerde inhoud is mogelijk onjuist.Open the PDB via **File > Open > PDB** **file**. You will get a small popup window where you can choose to either open from the PDB repository by entering its PDB code and clicking “OK” or upload a local file via “Browse”

Afbeelding met tekst, schermopname, Lettertype, nummer

Door AI gegenereerde inhoud is mogelijk onjuist.Since the PDB from the repository only contains a single monomer of the protein, we can safely allow LigPlot+ to use this PDB.

LigPlot will ask us to select the correct ligand so select B1J (residue name identified through the viewer) and click “Run”.

Afbeelding met tekst, elektronica, schermopname, software

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LigPlot+ will show the following diagram (or something very similar):

Afbeelding met schermopname, tekst

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Two hydrogen bonds are identified: with Ser232 (sidechain hydroxyl) and Trp128 (backbone N). Let us have a closer look at the hydrogen bond with Trp128 according to Ligplot+.

Afbeelding met schermopname

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To help analyze the interaction, you can add a hydrogen to the specific N. The Angle formed by Trp128-N, Trp128-NH and B1J-N2 is quite sharp, namely 131°. From the diagram below, we can see that a steep rise in relative energy typically occurs at approx. 150° for this angle in a hydrogen bond which indicates that the orientation is far from ideal for a hydrogen bond in this conformation. This illustrates that although these tools are helpful, a critical review of the output is always necessary.

Afbeelding met diagram, tekst, lijn, Perceel

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(Image from Alford *et al*. doi/10.1021/acs.jctc.7b00125)

For the hydrophobic interactions, one immediately pops out: Phe268. The aromatic ring of Phe268 aligns quite nicely with the aromatic 6-membered ring of B1J. This interaction is known as π stacking. Aromatic rings are formed by delocalization of the π bonds that form the ring which basically creates a big electron cloud above and below the plane of the ring. If two aromatic rings approach each other in particular ways, an attractive force is created due to the charge distribution, see image below.

Afbeelding met tekst, schermopname, Lettertype, ontwerp

Door AI gegenereerde inhoud is mogelijk onjuist.

(image from Lewis M, Bagwill C, Hardebeck L, Wireduaah S (2016). "Modern Computational Approaches to Understanding Interactions of Aromatics". In Johnson DW, Hof F (eds.). Aromatic Interactions: Frontiers in Knowledge and Application. England: Royal Society of Chemistry. pp. 1–17)

# Molecular docking

Molecular docking is an approach in drug design that tries to predict how ligands and protein will interact. Typically, docking programs have a scoring function that is either based on empirical observations (experimental) of physics (e.g. molecular mechanics). With the current increase in interest for artificial intelligence, different AI models to predict ligand-protein interactions are also being published in large numbers.

In computer assisted drug design, docking is typically validated as a first step by verifying tha ability of the docking program to retrieve the experimental binding pose. We will now try to dock B1J with AutoDock Vina and see whether or not Autodock Vina is capable of retrieving the experimental binding pose.

The implementation of Autodock Vina in Chimera makes this a very simple process. The only requirements are two structures: a receptor structure and a ligand structure.

Afbeelding met tekst, schermopname, software, Webpagina

Door AI gegenereerde inhoud is mogelijk onjuist.We shall start to prepare the structure by copying the 6ZUV structure: Open **Model Panel**, select the 6ZUV model and click “**copy/combine**”. In the following window, change the new model’s name to “B1J” since we are only going to keep the ligand in this model.

We now have two identical copies. In model 0/6ZUV we would like to remove the ligand, whereas we would like to remove everything except the ligand in model1/B1J. The easiest way to accomplish this is through the command line: **Tools > General Controls > Command Line**. This will show an additional bar at the bottom of the Chimera screen.

* Model 0/6zuv: type the following the command line: **select #0:B1J** and press enter. You will notice the ligand has been selected. Now remove this molecule via **Actions > Atoms/Bonds > delete**. Our protein structure is now ready.
* Model 1/B1J: type in the command line : select #1&~:B1J. Now you will notice that everything except residue B1J has been selected in model 1. Delete these selected atoms again: **Actions > Atoms/Bonds > delete**. We are now ready to proceed to dock this ligand.

*A short explanation for the syntax of the used commands:*

* ***select*** *= command to be executed*
* ***#0:B1J*** *= atom specifier: residue B1J in model 0 ( # = model, : = residue, @ = atom names)*
* ***#1&~:B1J*** *= combined atom specifier: “model 1 AND NOT residue B1J” (& = AND, | = OR, ~ = not)*
* *For full syntax on atom specifiers, you are kindly referred to* [*https://www.cgl.ucsf.edu/chimera/docs/UsersGuide/midas/atom\_spec.html*](https://www.cgl.ucsf.edu/chimera/docs/UsersGuide/midas/atom_spec.html)

To open the docking window, go to: **Tools > Surface/Binding Analysis > AutoDock Vina**. The items that require modification are indicated in red boxes in the image below.

Afbeelding met tekst, schermopname

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**Output file**: browse to a specific folder on your system and give a name for the output file that Chimera will write.

**Receptor**: choose the model that contains the receptor structure that we previously prepared, i.e. model #0.

**Ligand**: choose the model that contains the receptor structure that we previously prepared, i.e. model #1.

**Receptor search volume options**: Here we define the box in which AutoDock Vina will attempt to find favorable binding poses. The box is defined by center coordinates for x, y and z coordinates along with respective size/length for each coordinate. The box “Resize search volume using [button]” is very useful. This allows to change the box size through the viewer with your mouse.

**Executable location**: Here you have to indicate the location of the AutoDock Vina executable which you should have downloaded when installing the software.

If everything is set, you can click “OK” and perform the docking. Note, in this particular case AutoDock Vina will report an issue, but this is not a critical issue and should complete the docking after a few seconds and will automatically show the results.

Afbeelding met schermopname, tekst, software, computer

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You can easily browse through the identified poses by selecting the respective one in the ViewDock window.

The docked poses generally agree with the experimental structure indicating a positive result and that subsequent dockings with similar ligands will end up with plausible results.

- Did you notice anything else changing in the structures?

Klik of tik om tekst in te voeren.

- Try changing the box dimensions, does the result change?

Klik of tik om tekst in te voeren.

# Optional: Molecular docking exercise

1) Open PubChem ID : 146425072

2) Dock this compound in the receptor structure we just prepared

3) What can you say about the predicted poses of this new compound compared to B1J?

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4) Open PDB 6ZVL and compare the experimental pose with the docked pose

Klik of tik om tekst in te voeren.

5) Try to find the experimental affinity for the ligands in 6ZUV and 6ZVL on the PDB website.

6ZUV: Klik of tik om tekst in te voeren.

6ZVL: Klik of tik om tekst in te voeren.

6) Does the difference in experimental affinity between the two ligands agree with the obtained docking scores from AutoDock Vina? Explain.

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