Problem Set and Term Project

You are expected to choose a group (A or B), and complete the **Problem Set questions** of that group as well as the **Term project** of that group. For example, if you choose group A, you will complete Problem Set for Group A and Term Project for Group A.

For the Problem Set, you will conduct your own literature search to answer the questions. You do not need to use Schrodinger for the Problem Set. For the term project, you will follow the tutorial (https://learn.schrodinger.com/public/TwS/gb-docking-ls.pdf), which requires you to use Schrodinger, and then answer the questions. The poses you need to assess (as part of the Term project questions) come from going through the docking procedure in the tutorial.

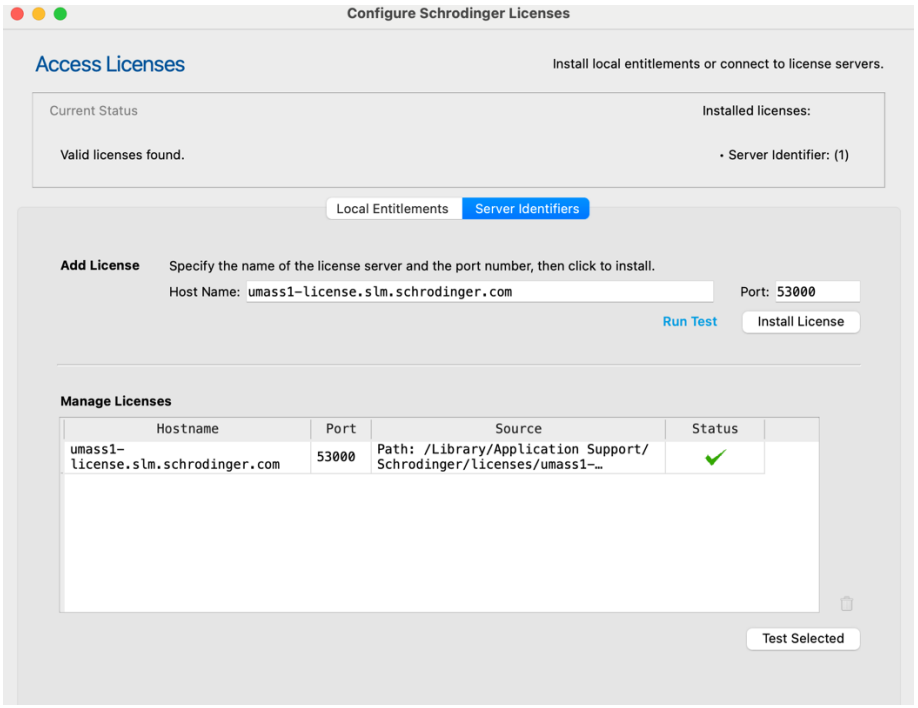
Schrödinger Docking Tutorial – Installation and Instructions

Installing Schrödinger Software

For the hands-on docking tutorial, we will use Schrödinger Maestro. The University of Massachusetts Lowell (UML) has a site license that covers student use at no cost. You are expected to either: 1) install the software and complete the tutorial, as the results are required for the problem set, or 2) use one the lab computers (Linux) to access Schrodinger.

Steps to Access and Install Schrödinger, should you choose to install on your own device:

1. **Create an Account:**
   - Go to the Schrödinger website and create an account using your **UML email**.
2. **Request Download Access:**
   - Navigate to the **Download** section and request access to the software.
   - Schrödinger will process your request. You will receive an email indicating that you are **eligible for download**. Note: this may take several business days.
3. **Download and Install:**
   - Once your account is approved, log in to Schrödinger and go to the download page.
   - Download the version compatible with your operating system.
   - Follow the **installation guide** provided by Schrödinger to complete the installation.
4. University of Massachusetts has access to a hosted license server:
   Hostname: umass1-license.slm.schrodinger.com
   Port: 53000
   If you install Schrodinger on your device, you may need to be on campus (using campus network). Alternatively, you can use vpn to connect to campus network to use Schrodinger.



Tip: Start this process early to allow for account verification and download approval.

Tutorial Expectations

- Follow the tutorial here: https://learn.schrodinger.com/public/TwS/gb-docking-ls.pdf
- Although the tutorial is written for release 2021-3, it is applicable to any versions beyond 2021-3 (i.e. until 2025-3)
- The tutorial is designed to be completed independently.
- You are responsible for working through all steps on your own, including generating docking poses, examining ligand interactions, and exporting results.

Problem Set for Group A (You do not need to use Schrodinger for this. You will conduct literature search and answer these questions)

1. Pick a published docking study.
2. Write a ≤300-word response addressing:
    - What was the biological question?
    - What assumptions did the docking rely on (rigid receptor, scoring approximations, protonation states, etc.)?
    - What challenges were discussed (flexibility, selectivity, water molecules, cofactor effects, unusual binding modes)?
    - How did the authors validate docking results? (e.g., crystal structures, mutagenesis, SAR)
3. Include one figure from the paper or PDB showing ligand–protein interactions.
4. Evaluate whether the docking results could have been misleading due to scoring limitations, neglected receptor flexibility, or other factors. Explain briefly.

Molecular Docking Module Problem Set

Deliverable: a 300-word max reflection that answer questions #1-4.

Problem Set for Group B (You do not need to use Schrodinger for this. You will conduct literature search and answer these questions)

1. Select two PDB structures of the same protein (different resolutions or conformations).
2. Compare:
    - Resolution and completeness (missing residues, loops).
    - Ligands or cofactors present.
    - Crystallographic differences that may affect docking (water molecules, alternative conformations).
3. Decide which structure is preferable for docking and justify your choice.
4. Write a ≤300-word response and include screenshots or figures highlighting key structural differences.
5. Suggest how you would address missing residues or flexible loops for docking (e.g., modeling loops, induced fit considerations).

Deliverable: a 300-word max reflection that answer questions #1-5.

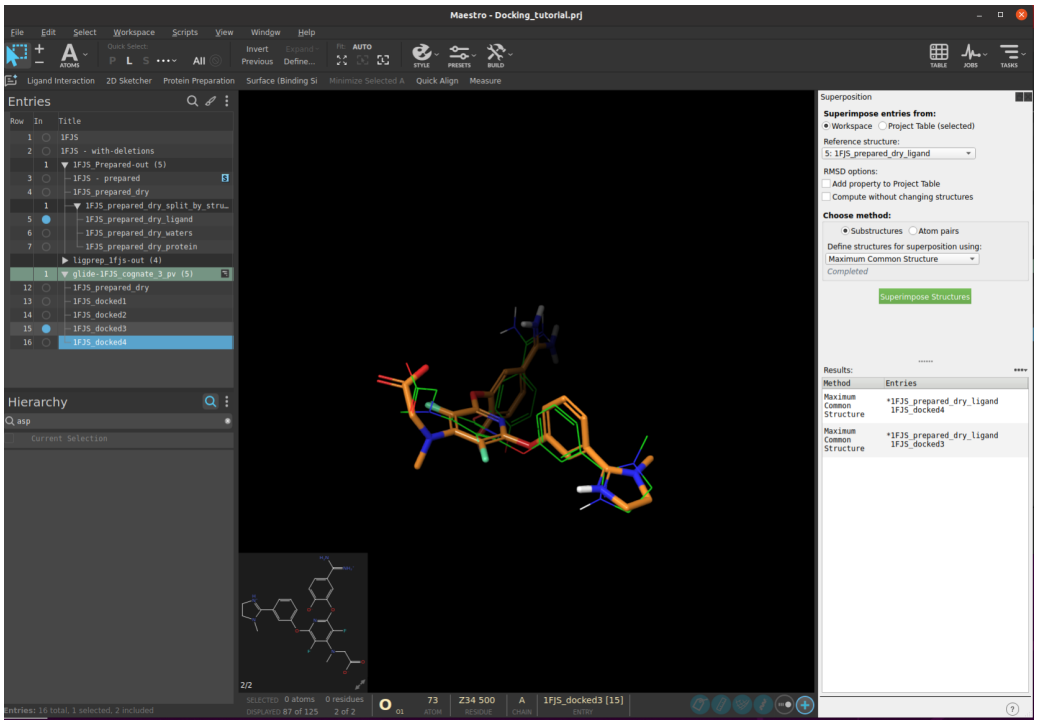
Term Project for Group A (You will go through the tutorial, which uses Schrodinger and goes through docking, and answer these questions)

After going through the tutorial (https://learn.schrodinger.com/public/TwS/gb-docking-ls.pdf):

1. Record GlideScore and Emodel for 4 poses.
2. Plot GlideScore vs Emodel.
3. Analyze which score favors geometrically reasonable poses.
4. Compare the best-scoring pose to the crystal pose; discuss why it may or may not match.
5. Identify at least one pose with a poor score that is chemically reasonable (good hydrogen bonds, hydrophobic contacts) and explain why it may have scored worse.

    Hint: You can calculate the RMSD between the ligand in your crystal structure and the ligand in your docked pose to help explain your observations. To do this, go to **Tasks** and search for **Superposition**. Select **Superimpose Entries**, choose your crystal structure (e.g., *1FJS_prepared_dry_ligand*), and click **Superimpose Structures**. The RMSD value will then be displayed in the results panel. Below is a snapshot of the superposition panel and of calculating the RMS between 2 ligand poses.

Molecular Docking Module Problem Set



Deliverable: 500 words max reflection that includes the plot from #2, written answer to #3, #4, and #5. And then conclude with "How does this illustrate scores ≠ binding affinity? Include reasoning about geometry vs scoring and any observed discrepancies.

Term Project for Group B (You will go through the tutorial, which uses Schrodinger and goes through docking, and answer these questions)

After going through the tutorial (https://learn.schrodinger.com/public/TwS/gb-docking-ls.pdf):

1. Select the top 3 docked poses.
2. Align them with the crystal pose in Maestro.
3. Generate Ligand Interaction Diagrams for each docked pose and the crystal pose.
4. Compare conserved interactions, lost/distorted interactions in the "best-scoring" pose, and identify dominant binding interactions.

Deliverable: 500 words max reflection that includes the diagram for #3, written answer to #3, #4. And discuss why visual inspection is important.

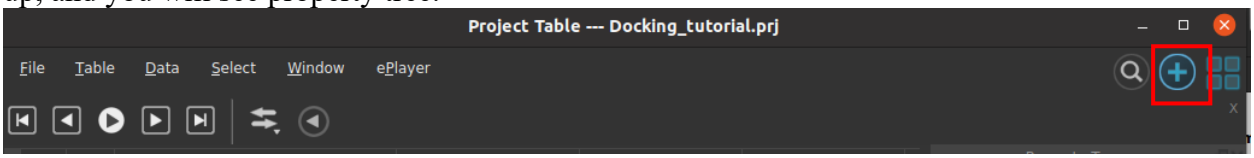
Notes on Schrodinger Docking Tutorial PDF

Below are additional notes to clarify some steps in the Schrodinger Protein Ligand Docking manual (https://learn.schrodinger.com/public/TwS/gb-docking-ls.pdf)

1 What you will need for this lesson
Omit step 1 "Go to the Data folder and open your class folder …." And step 2 "right-click on the folder called Protein_ligand_docking …" Instead, you will create a folder called "Protein_ligand_docking" on your desktop or any location of your choice. Then, proceed directly to step 3 "Open Maestro …"

3.1 Prepare the protein using the protein preparation workflow
Step 17. Instead of "clean up," this may show up as "minimize the delete waters" depending on your version. Confirm that it is toggled on.

4.2 Run LigPrep
Step 7. You may need to go to the right button that looks like "+" sign, and a subpanel will pop up, and you will see property tree.



5.1 Identify the binding site
Step 1. This step means select the entry "1JFS_prepared_dry."
Step 3. If you cannot find it in your browse list, just type in the search bar "receptor grid generation," and it will show up.

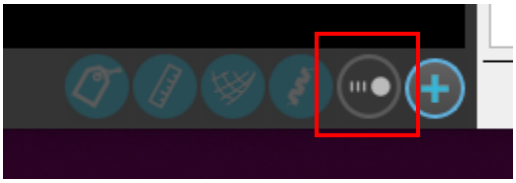
5.3 Set a hydrogen bonding constraint
Step 8. If you choose the wrong atoms, a pop up window will say something like "this is not the right atom." And you can choose again, so don't be afraid that you'll choose the wrong atoms. There are only 2 correct oxygen atoms. Continue picking until the program accepts them.

6 Docking a ligand
Step 1. Search "ligand docking" in the search bar if you can't find it under browse.
Step 2. The zipped file is in the folder glide-grid_1fjs
Step 4. This is in the ligprep_1fjs folder.
Step 6. Depending on your version, you may see "constraints" tab, and then you see the "receptor" tab instead of the "grid-based" tab. As long as you see the constraints (the 2 oxygen atoms) there, it is ok. Also, go to "output" tab, and select "write per-residue interaction scores" so that you can view the interactions later in the viewing panel.
Step 10. The pose viewer panel may not automatically appear. If that's the case, open the project tree (ctrl + T), right click on "glide-1fjs_cognate_pv(5) entry, and select "open pose viewer panel."

8.2 Apply a preset style

Step 2. Pretty may be under “Presets > Legacy > Pretty,” depending on your version

8.3 Visualize interactions
Step 1. The interactions panel is called out from the bottom right of your workspace. A blue icon like this:



8.5 Generate a 2D interaction diagram
Step 3. depending on your version, it may be under the gear icon > LID legend. LID = ligand interaction diagram.