Introduction to the Schrodinger Bioluminate package

Session 1: Maestro

Learning goals:

By the end of this workshop, participants will be able to:

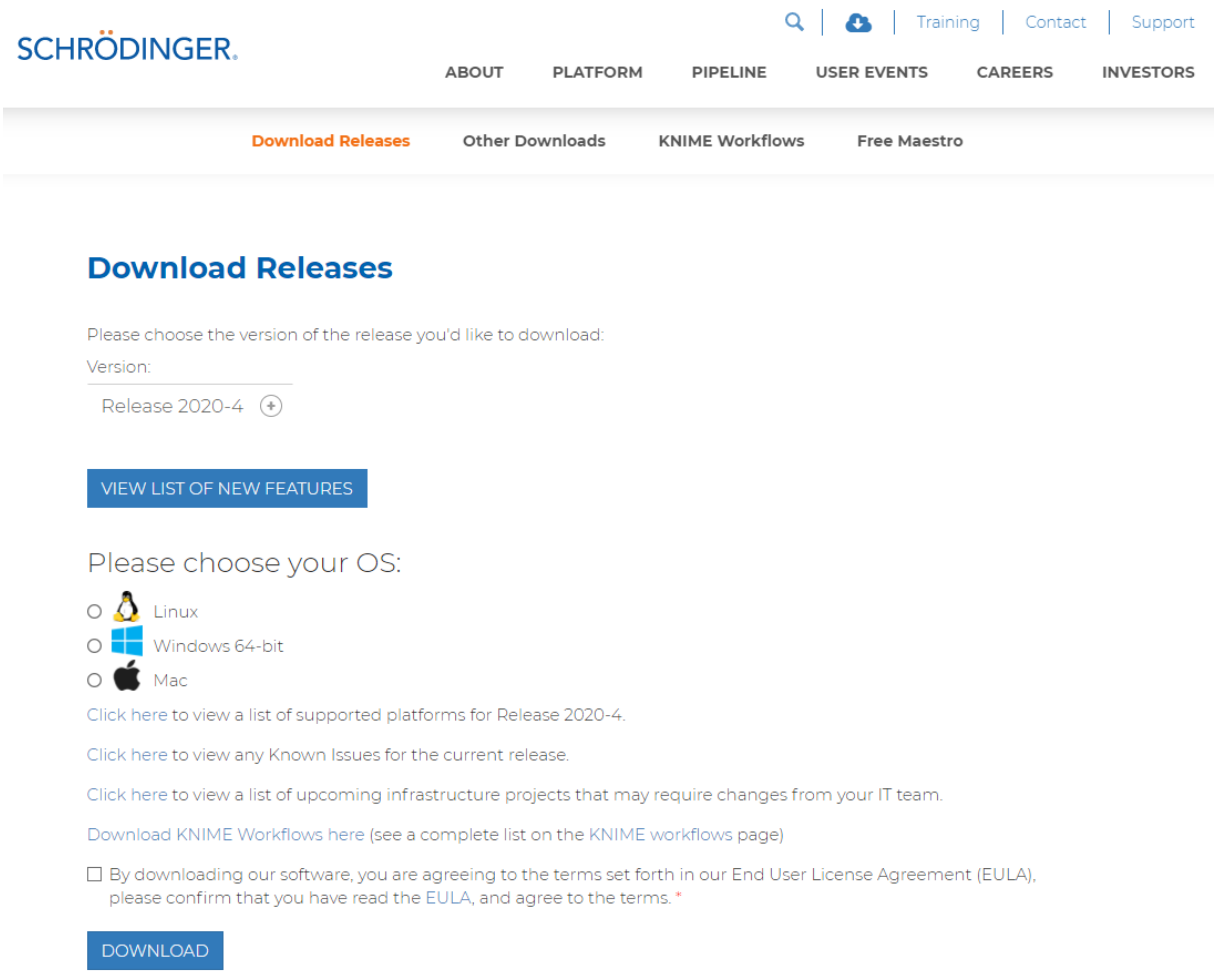
- Know where to find additional resources for learning about Schrodinger functionality.
- Know where to find and how to use the commands for selecting, editing, and rendering molecules.
- Import and prepare a protein for further analysis.
- Create new macromolecules using the Maestro interface.

Contents:

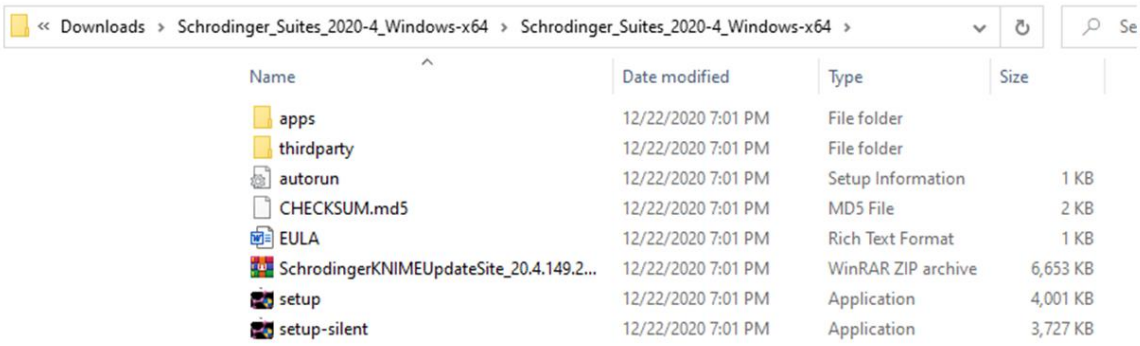
1. Intro to Schrodinger
2. Schrodinger resources: Where to find them and how to use them
3. Learn the Maestro interface:
    a. Demonstration of importing pdbs + user interface
    b. Try it yourselves
    c. Demonstration of protein preparation & analysis
    d. Try it yourselves
4. Evaluation

Download and Install Bioluminate

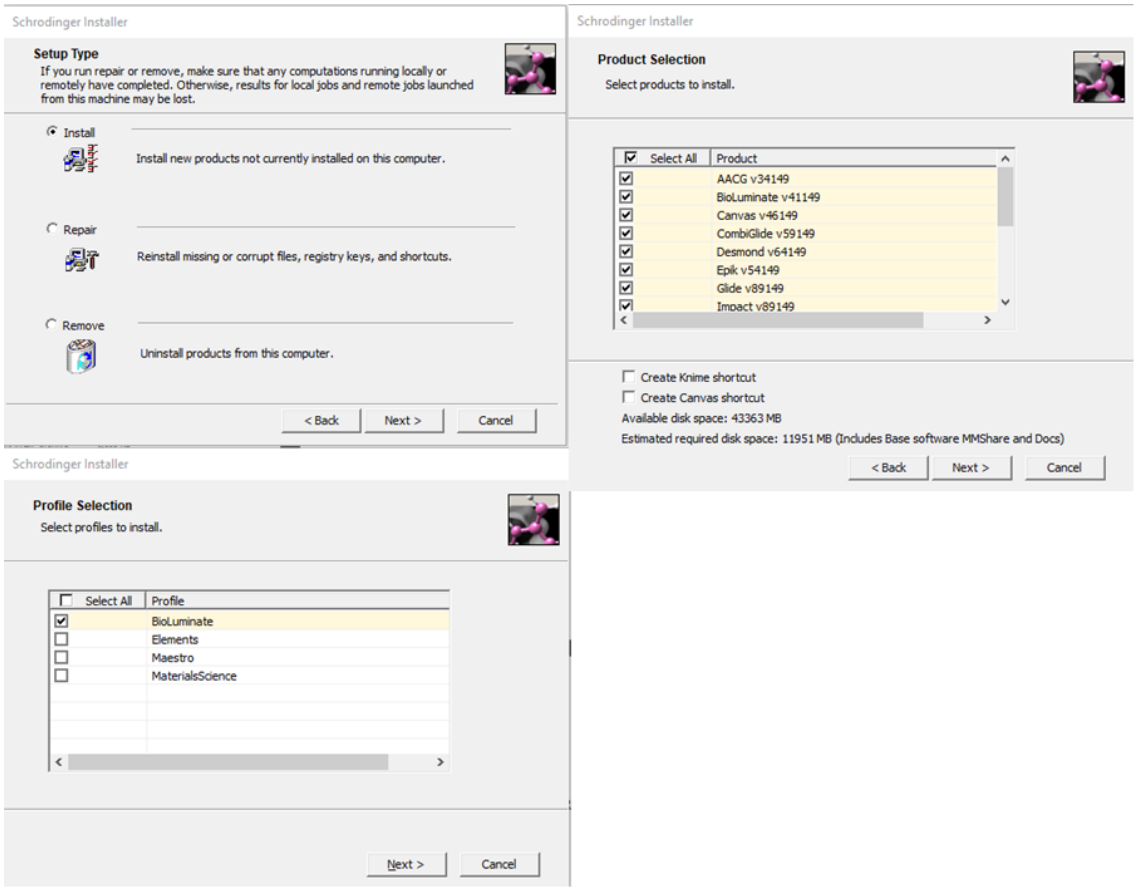
1. Go to www.schrodinger.com and create an account.
2. Click the download button in the top menu.
3. Choose the latest version and your operating system. Check the license agreement (EULA) box and click DOWNLOAD. You will need at least 6 GB of free disk space to download the full suite.
4. When the download is done, double-click the downloaded package to extract the software.



5. Enter the extracted folder and double-click the setup file to start the installation.



6. Choose the Install option and select the products to install.

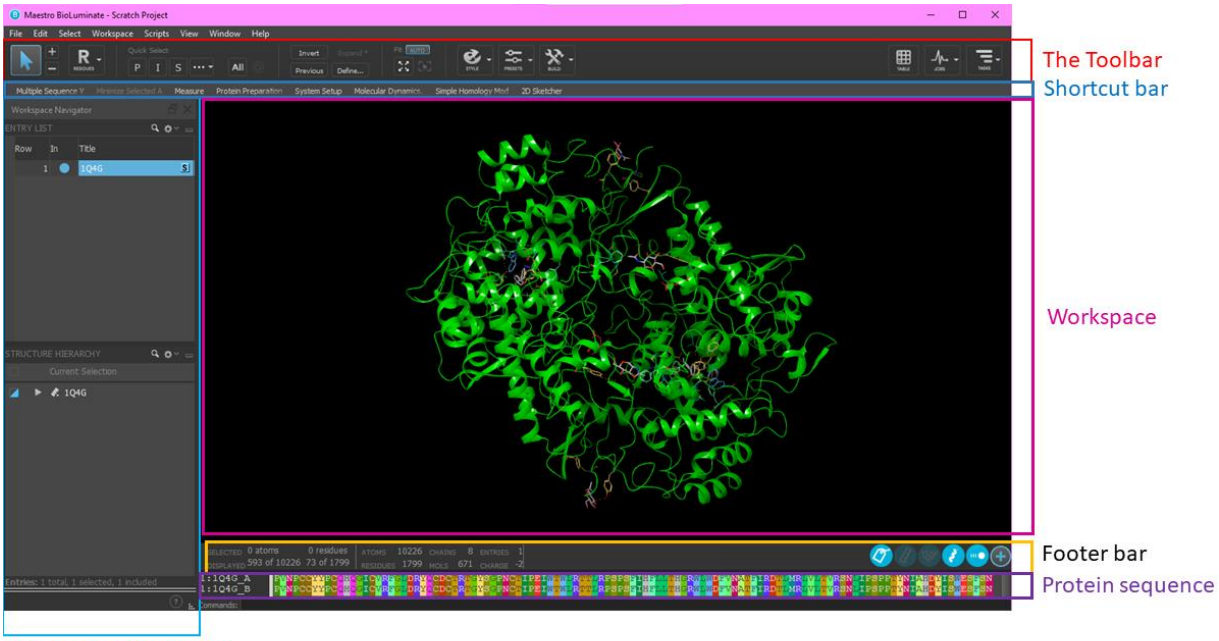


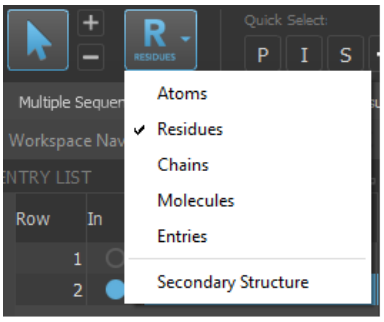
You will need almost 12GB of disk space to install the whole package. If you don't have enough free space you can install Maestro (4.3GB) for now.

Quick guide to other useful Schrodinger packages we will be using in other sessions:

Canvas	Tools for chem/bioinformatics. For finding and building libraries of substructures.
Desmond	Molecular dynamics simulation engine
Epik	pKa predictions
Glide	Molecular docking
Jaguar	Ab initio Quantum mechanics
Macromodel	Force-field based molecular modeling
Prime	Homology modelling

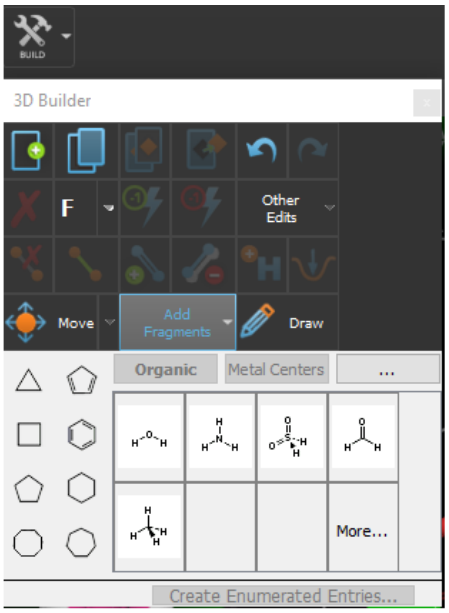
The Maestro interface



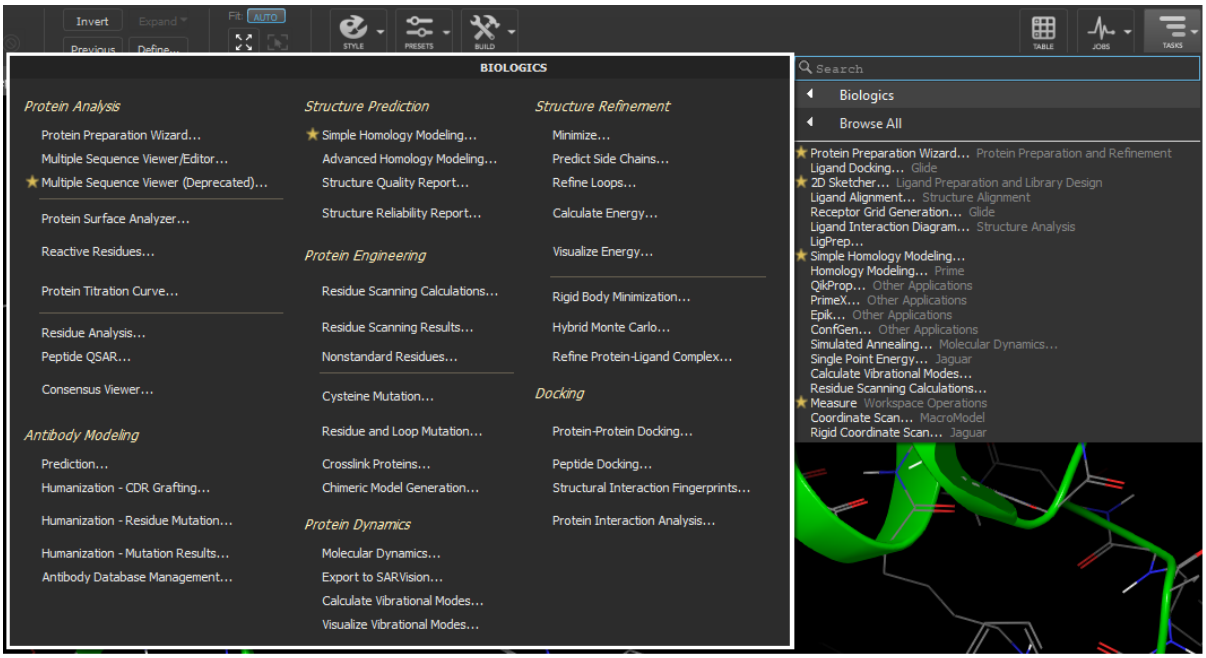


Select/ Picker

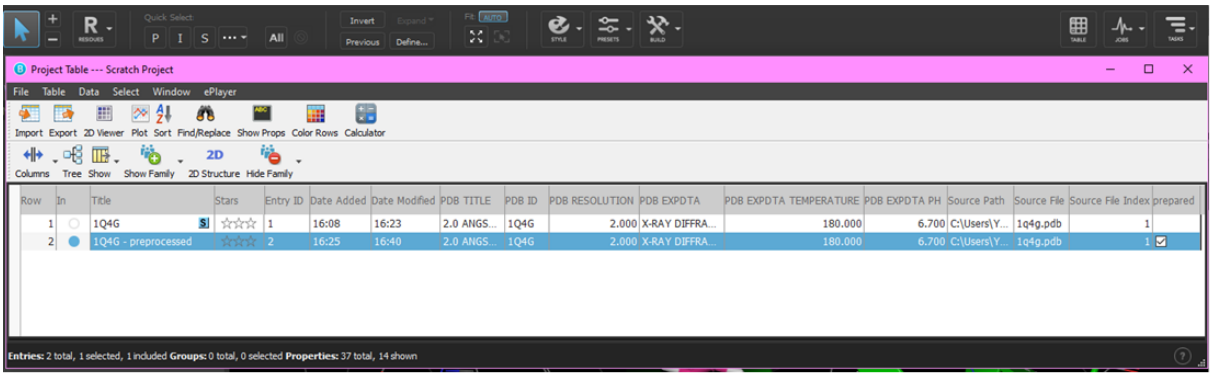
Apply styles



Builder /edit structures



Tasks finder & Search bar



Project table

The basics

Using the mouse:

Left click: Pick atoms/residues

Shift + left click: Pick atoms inside the formed box

Scroll: Adjust the pane clipping

Middle click + move mouse: Translate the view

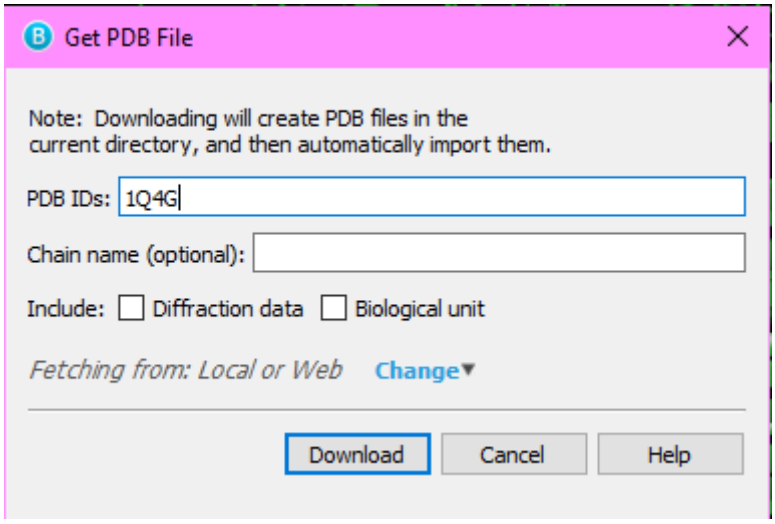
Right click: Opens menu options for the clicked structure

Right click + move mouse: Zoom

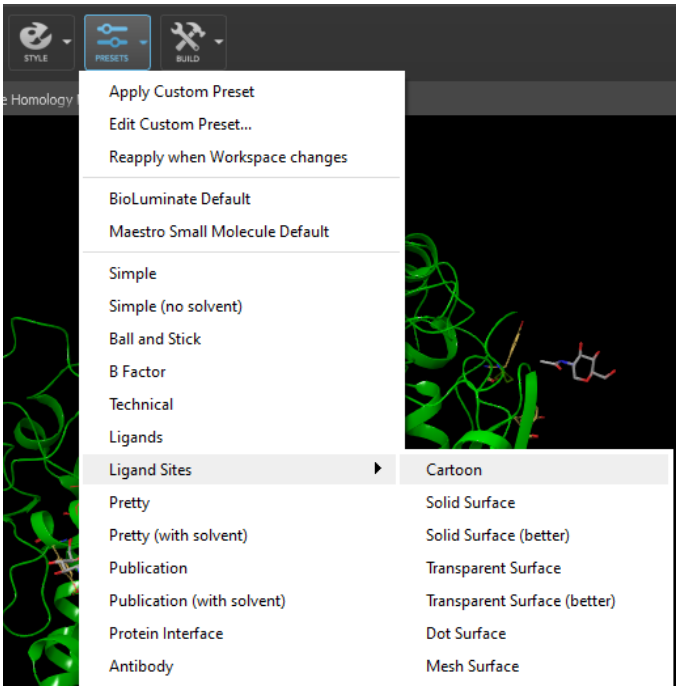
What do combinations of left, middle and right clicking and movements do?

Get to know the Maestro user interface

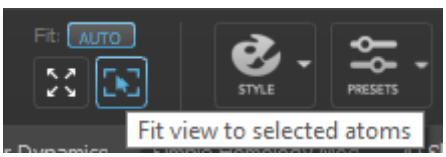
1. Create a directory on your desktop and change the working directory to it (File -> Change Working directory).
2. Import the 1Q4G structure (File -> Get PDB).



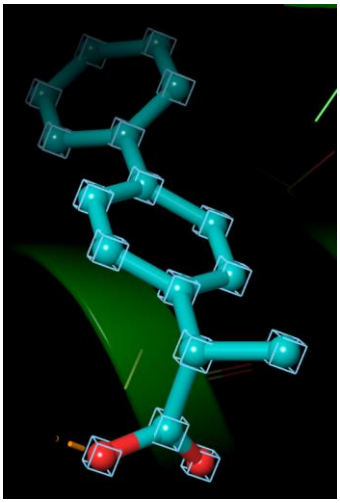
3. Change the look of the protein using the presets. Try out different ones until you find something that you like.



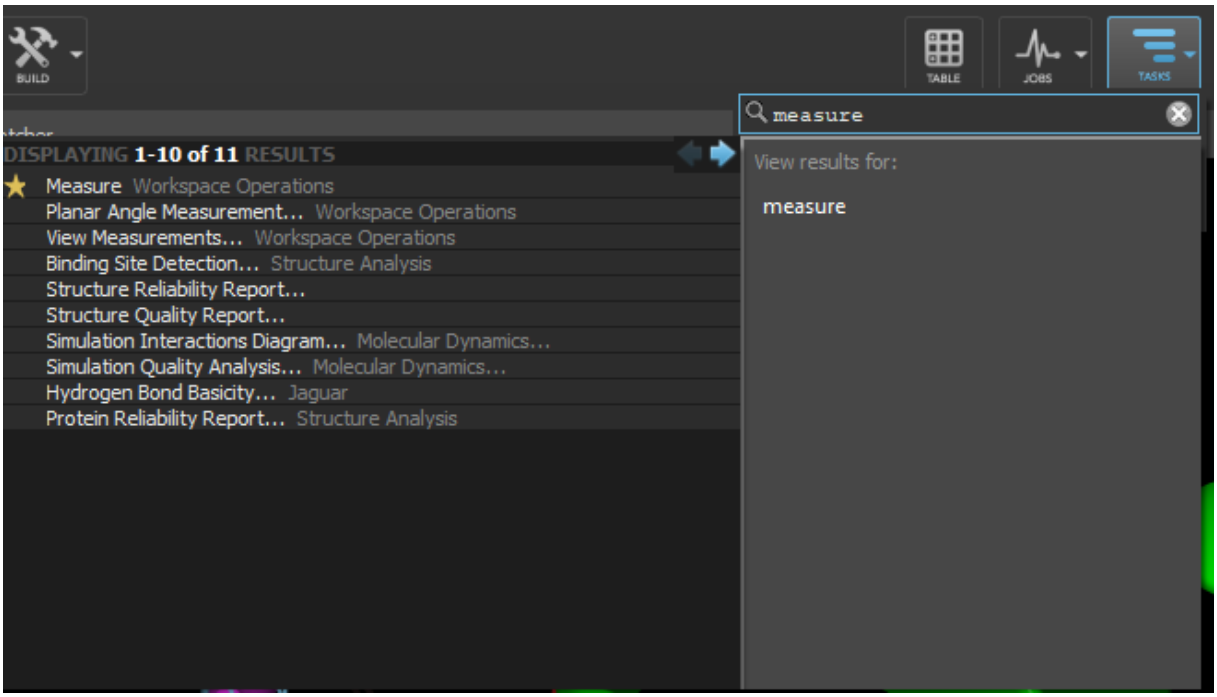
4. Find a ligand, select it and fit the view on it (see previous page for mouse controls).



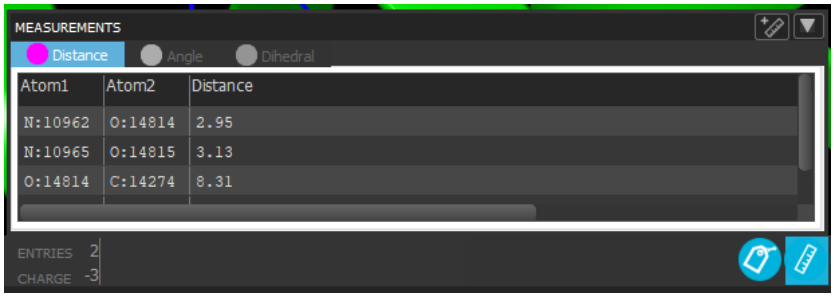
5. Change the color and line thickness of the ligand.



6. Use the search bar to find the measurement tool. Measure the distance between the carboxylate oxygens and the Arginine nitrogen. **Which other measurements can you make using this menu?**



7. You can see all your measurements if you click the three dots above the measurement icon (the ruler). Delete a measurement.

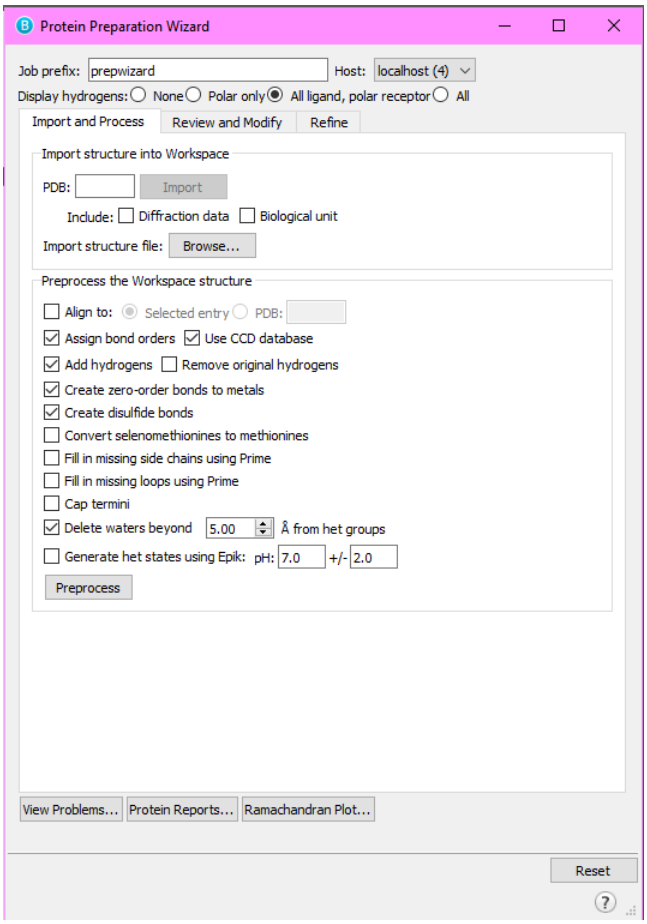


8. Try the interactions toggle to see if the ligand has any interactions with the surrounding protein. Clicking the three dots above the toggle will open a window that tells you what kind of interactions this ligand has. **What kind of interactions does it have? What kind of intramolecular interactions does it have?**

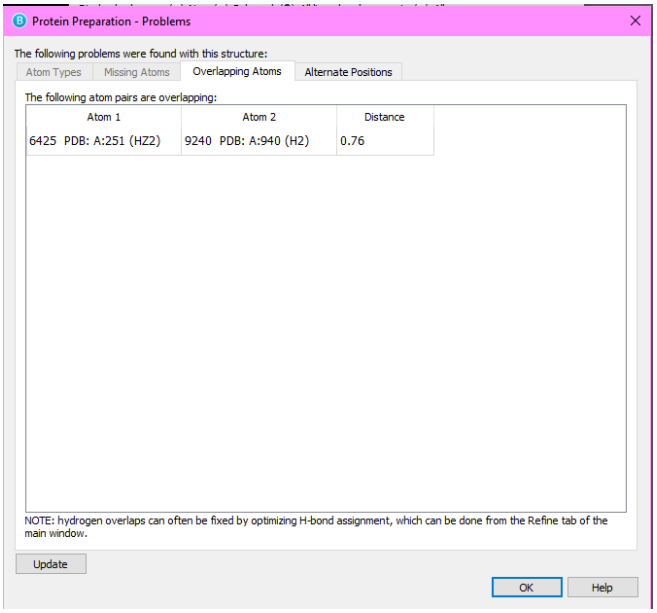
9. If you have time left: explore the workspace and click at random buttons to see what they do!

Prepare the structure with prepwizard

1. Search for the prepwizard in the Tasks menu and start it. If you haven't installed the Epik package, uncheck the "Generate het states using Epik" box. Then click Preprocess.

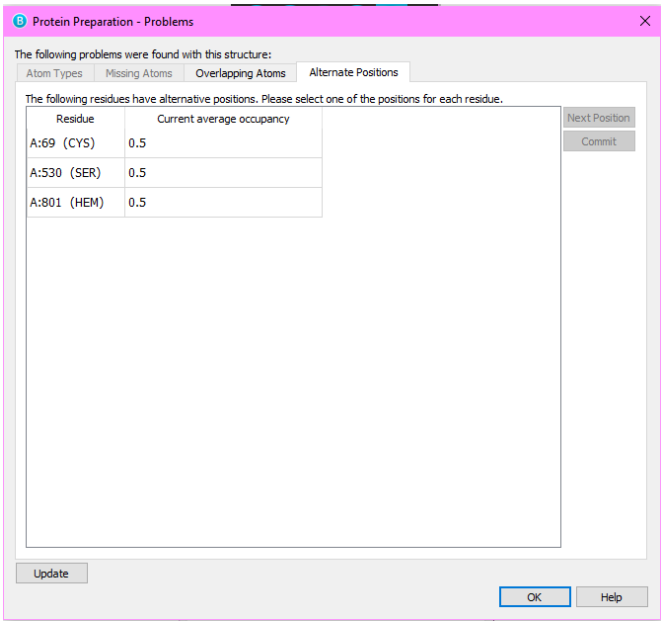


2. Fix the problem that came up by double-clicking the row and see what's wrong in the workspace.

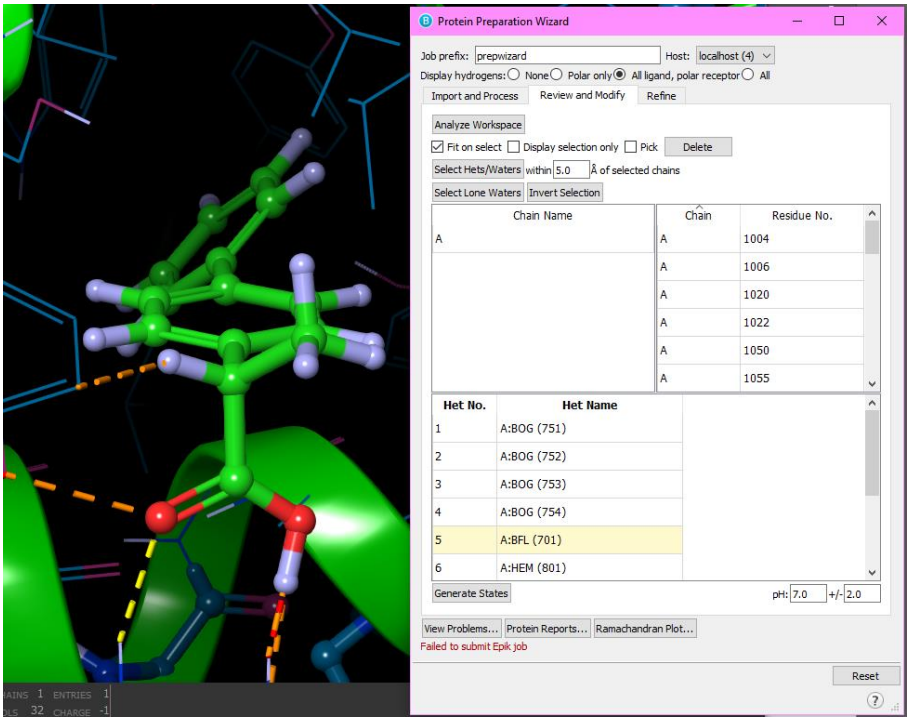


When you have fixed the problem, go back to the problem window and click Update to see if it was resolved.

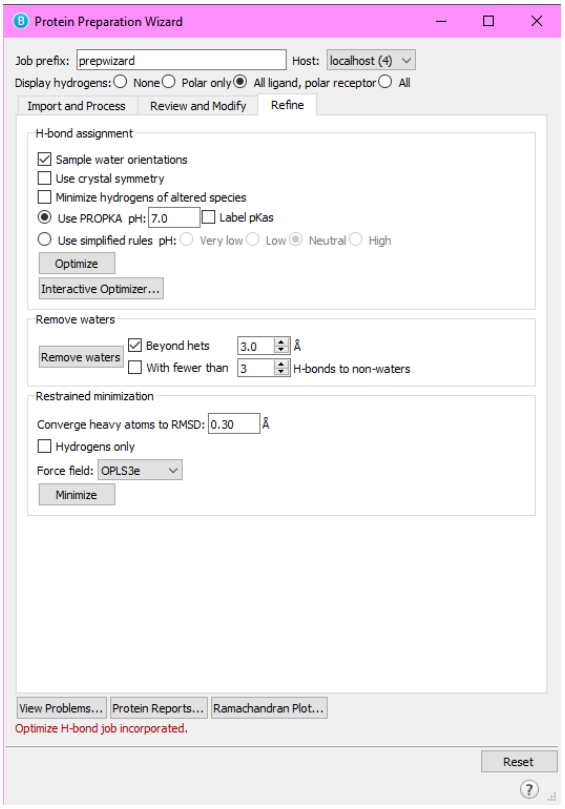
3. Move on to the alternate positions tab in the same window. These residues have at least two different orientations. Decide which one is the most appropriate orientation and click the Commit button on the right-hand side. When there are no more issues, click the OK button.

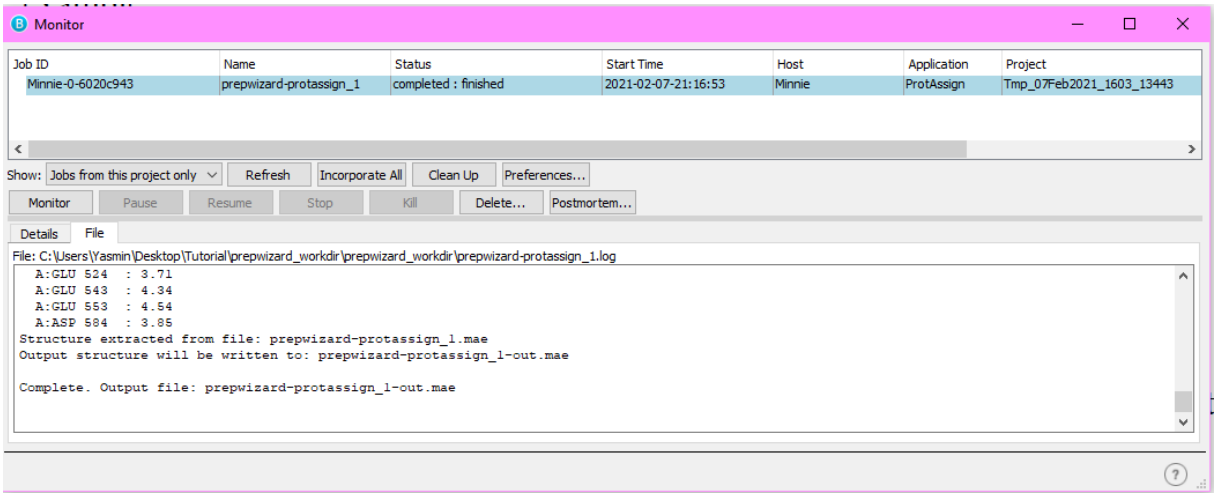


4. Go back to the Protein Preparation Wizard window and click the Review and Modify tab. Take a look at BFL. This molecule is supposed to have a deprotonated carboxylate with a negative charge. Use the build menu to fix it. Don't forget to choose the right picker!



5. Check that your ligand has the correct charge by labelling it according to its formal charge. (Try right-click)
6. Go back to the Protein Preparation Wizard window and choose the Refine tab. Click Optimize. While the job is running (ca 2 min), monitor the output by going to the Monitor pane.





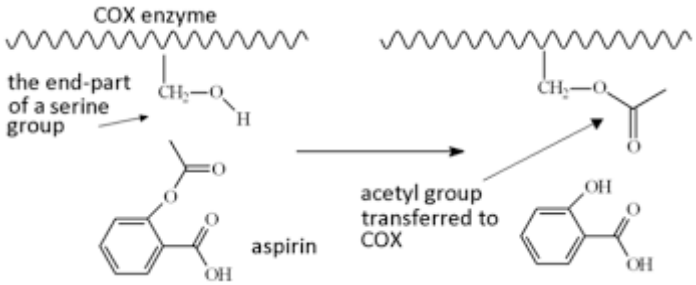
What did optimization do to the structure? Do you agree with the changes?

To compare more easily when moving between different entries, you can save the current view by going to the main menu (View -> Save Camera View). To restore the view go to View -> restore camera view.

7. Convert the neutral Glutamate to a charged one.

Create an acetylated COX-1 in complex with salicylic acid from 1Q4G

1. COX is irreversibly acetylated by aspirin, which acetylates Ser530 and results in salicylic acid. **Build the new complex based on the current structure. Don't forget the hydrogens!**



2. Export your new complex using the name AcetylatedCOX-1.mae