Introduction to the Schrodinger Bioluminate package

Session 4: Desmond

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Version 1.0

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Learning goals:

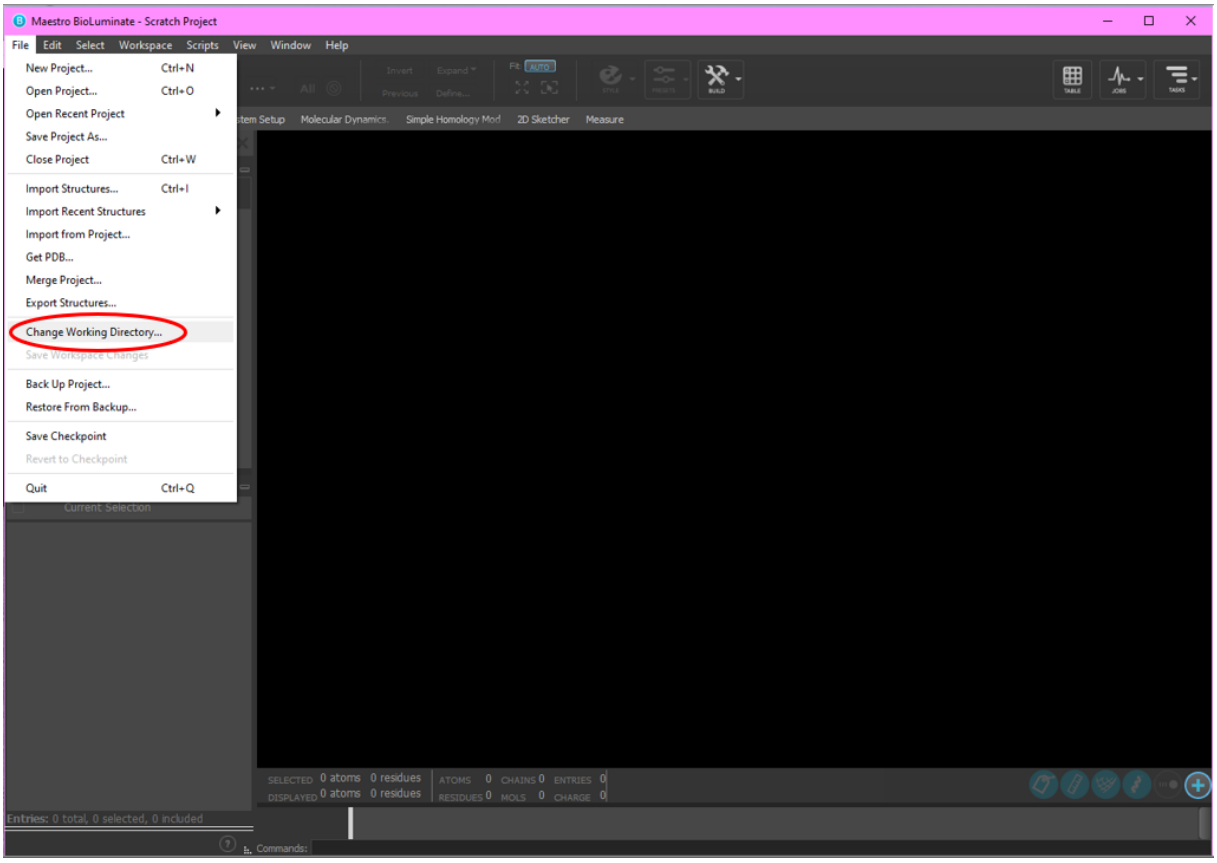
By the end of this session participants should:

- Understand the underlying concepts of molecular dynamics (MD) simulations and the adjustable parameters in Desmond
- Independently prepare a system for MD simulations in Desmond
- Analyze MD trajectories and know how to extract information from the simulations.
- Explain how changes in parameters affect simulation results

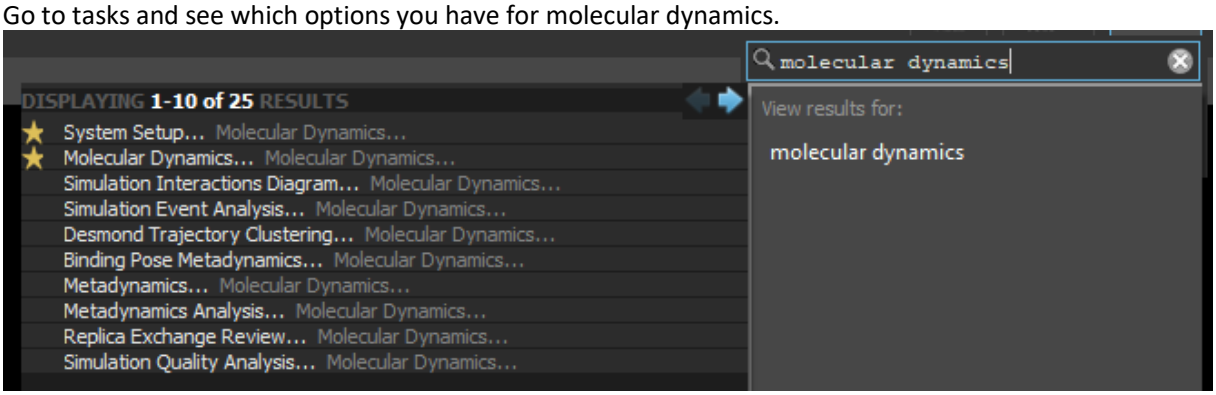
Contents:

Getting started with DESMOND

1. Create a new folder on your Desktop called DESMOND.
2. Move the folder with the created homology models and your docked ligands from the previous workshop to the new DESMOND folder. If you used an open conformation, copy the folder from the Boxer Google Drive (G:\Shared drives\Chemistry Boxer Lab - Current Members\General BoxerLab Folders\Schrodinger_Workshop) and place it in your DESMOND folder.
3. Change the working directory to your DESMOND directory on the desktop:



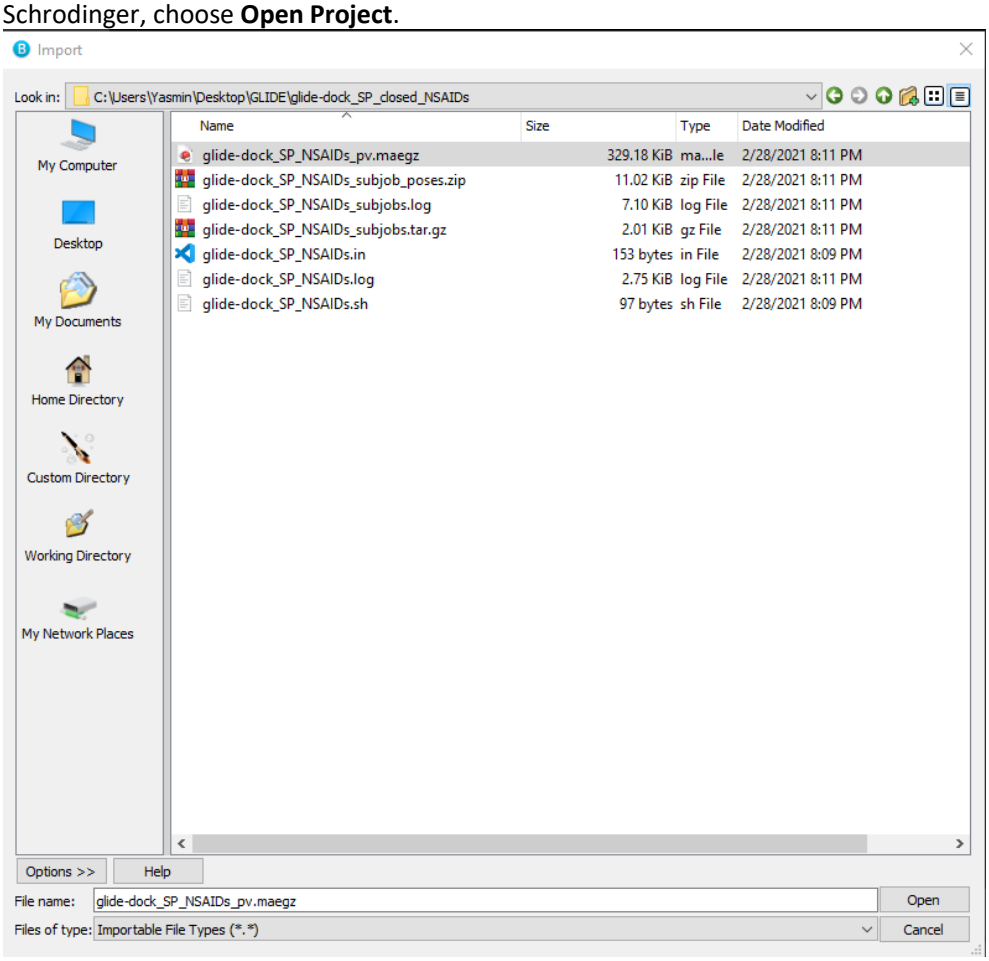
4. Go to tasks and see which options you have for molecular dynamics.



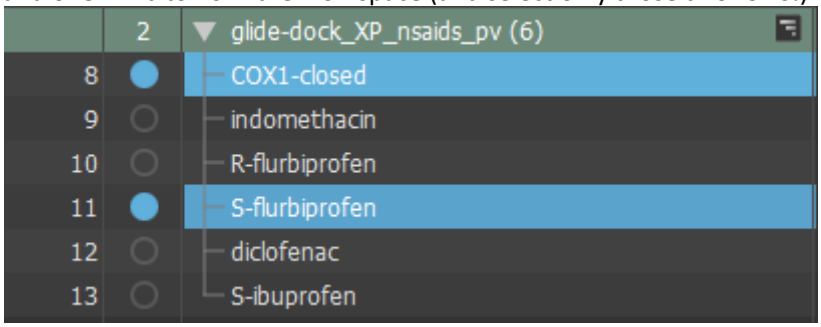
Preparing your MD simulations

Each member of the group will work on only one protein structure and two NSAIDs: R-Flurbiprofen and Ibuprofen. To save time, you will only prepare the flurbiprofen-enzyme system and to get ahead of the queue on the computational cluster we will first prepare the systems and submit them before going back and looking at the different options available.

1. Import the protein and the docked structures from your previous workshop. If you don't have a good structure you can copy the DockedStructures.prj file from the Google drive (G:\Shared drives\Chemistry Boxer Lab - Current Members\General BoxerLab Folders\Schrodinger_Workshop\4.Desmond-molecularDynamics) to your Desmond folder. In Schrodinger, choose **Open Project**.

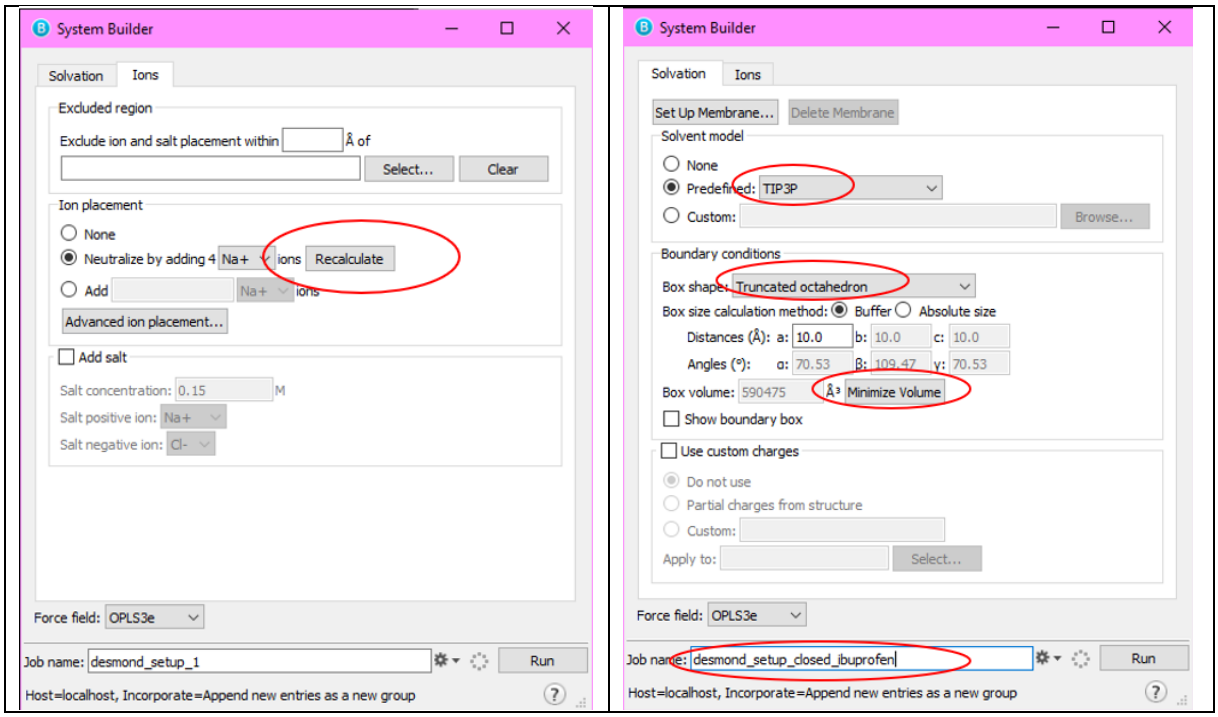


2. Before you can run your simulation you need to create a simulation box. Make sure that only your protein and one inhibitor is in the workspace (and select only those two rows!)

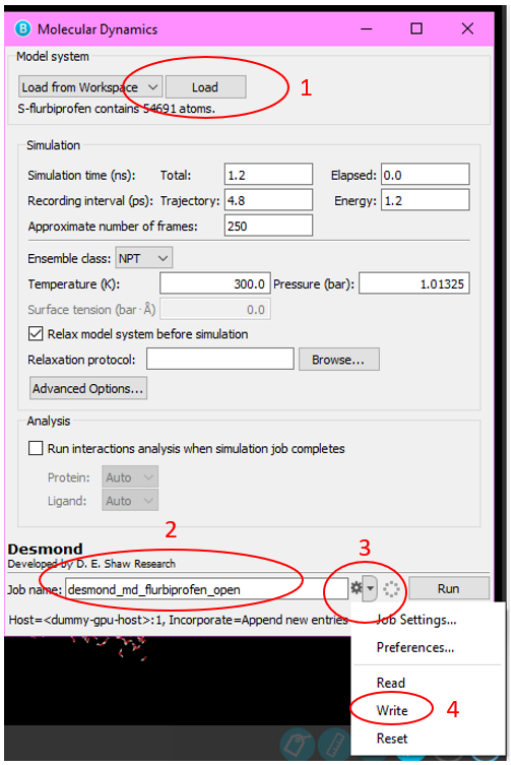


3. In the Tasks pane, search for molecular dynamics and pick **System Setup… Molecular Dynamics.**

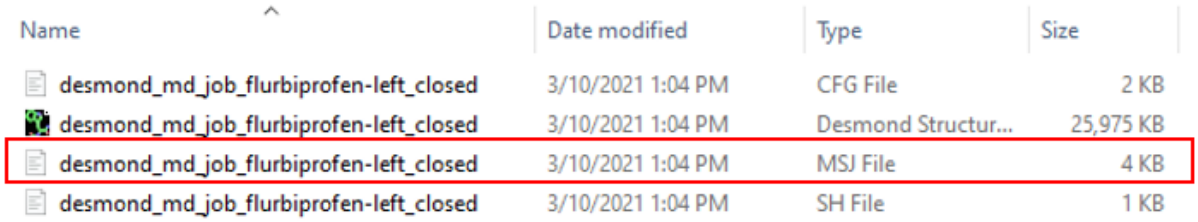
   Go to the Ions tab and click Recalculate. **How many Na+ will be added?**



4. Go to the Solvation Tab and Choose the Predefined **TIP3P** solvent model and the **Truncated octahedron**. Click **Minimize Volume**. Then set an appropriate name for your job and hit **Run**.
5. Wait for the run to get incorporated (ca 5 min). Click **View in Project** to see your box. Do not click anywhere in the Entry list or the workspace! **What was added to your system in this step?**
6. Open **Molecular Dynamics… Molecular Dynamics** in the Tasks pane. Click **Load** to load the structure that was just incorporated into your workspace.



7. Leave all values at their default. Choose an appropriate name for your enzyme-ligand system and save by clicking the arrow next to the cogwheel and choose **Write**.
8. There is a bug in the 2020-2 version of Schrodinger, which is the current one used on Sherlock. To get around the bug you need to open the .msj file in your newly created folder.



Name	Date modified	Type	Size
desmond_md_job_flurbiprofen-left_closed	3/10/2021 1:04 PM	CFG File	2 KB
desmond_md_job_flurbiprofen-left_closed	3/10/2021 1:04 PM	Desmond Structur...	25,975 KB
desmond_md_job_flurbiprofen-left_closed	3/10/2021 1:04 PM	MSJ File	4 KB
desmond_md_job_flurbiprofen-left_closed	3/10/2021 1:04 PM	SH File	1 KB

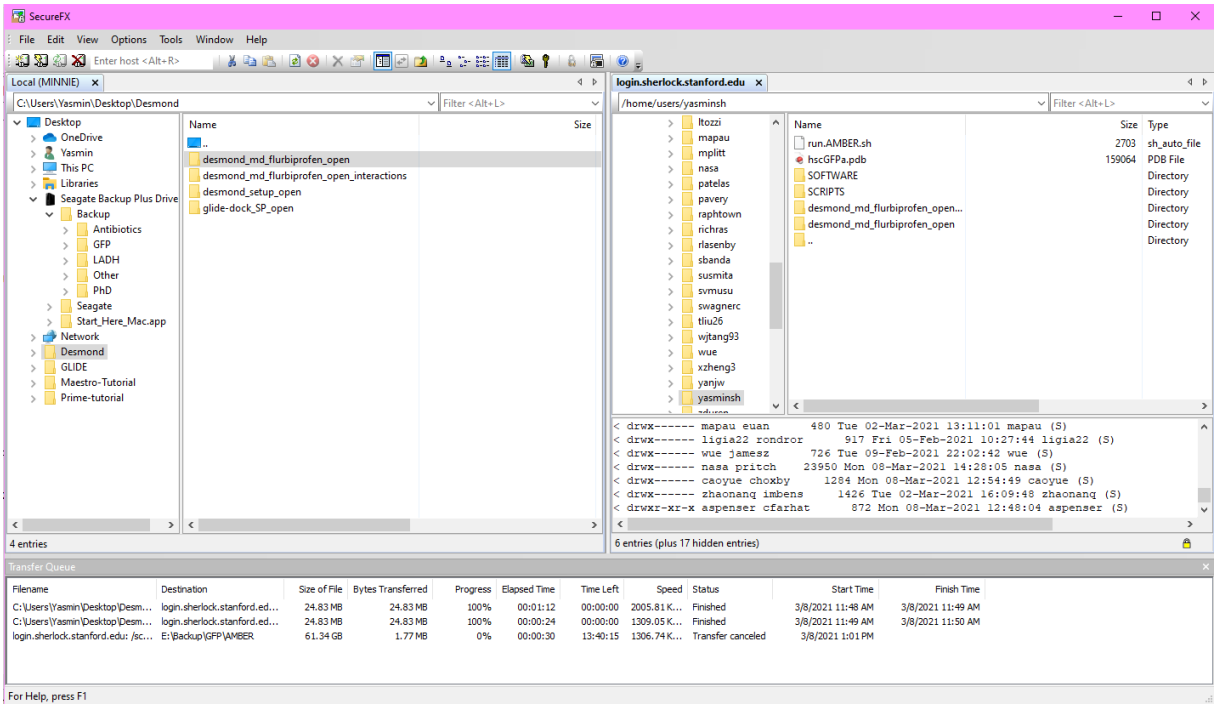
9. Use a text editor like notepad or Visual Studio Code to open your file (do not use Microsoft Words or similar editors!)
10. Add the following at the beginning of your file: **backend.is_for_fep = false**

```
task {
    task = "desmond:auto"
    set_family = {
        desmond = {
            checkpt.write_last_step = no
            backend.is_for_fep = false
        }
    }
}
```

Save the file and close it.

Uploading files to and working on Sherlock

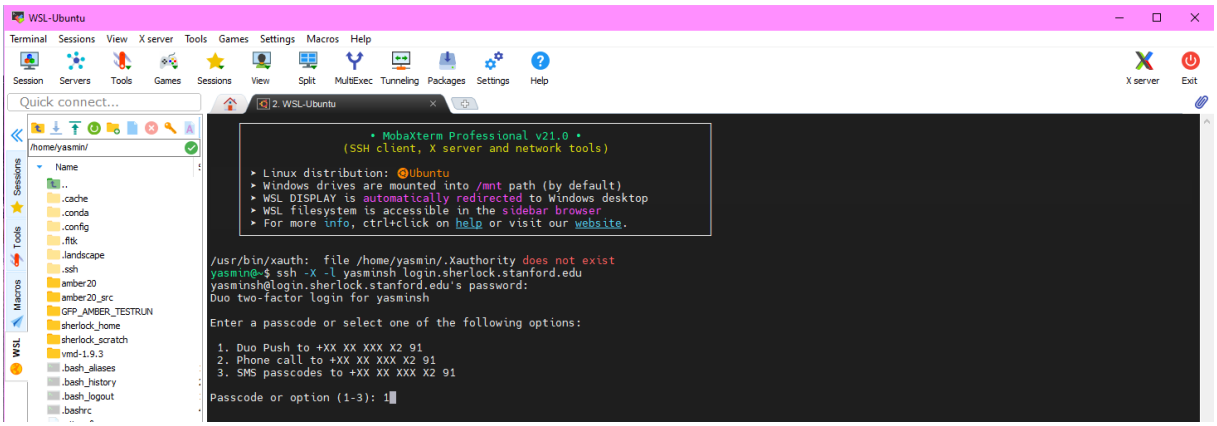
1. Upload your newly created folder to Sherlock using an ftp program. Drag your file into your home folder:



2. SSH into Sherlock in a terminal window. Example command:

```
ssh -X -l USERNAME login.sherlock.stanford.edu
```

Or in MobaX:



When logged in you should see the welcome screen in the terminal:

When you log into Sherlock you should land in your HOME directory. You will know that you are in the right place if you look at the prompt- you should see the tilde (~) character:

```
[yasminsh@sh03-ln02 login ~]$ mkdir SCHRODINGER
```

1. Create a new directory in your home directory using the **mkdir** command mkdir SCHRODINGER.
   Ensure that the spelling is exactly as in this document, otherwise the script will not work.
2. Move your uploaded directory to the newly created SCHRODINGER directory using the **mv** command (mv FILE_TO_BE_MOVED NEW_FILE_LOCATION):

```
[yasminsh@sh03-ln02 login ~]$ mv desmond_md_flurbiprofen_open SCHRODINGER/
```

   Hint: You don't need to write out the whole name. After writing the first couple of letters you can use the Tab key on your keyboard to autocomplete (this reduces spelling errors too!).

3. In our group folder $GROUP_HOME there is a bash file containing a script you will run to start your simulations. Copy it to your $HOME directory using the cp command:
   cp $GROUP_HOME/runSchrodingerGeneral.sh .
   Note: There has to be a space between the file name and the dot at the end of the command. The dot means "to here".

```
[yasminsh@sh03-ln02 login ~]$ cp $GROUP_HOME/runSchrodingerGeneral.sh .
```

4. Run the script using the bash command:

```
[yasminsh@sh03-ln02 login ~]$ bash runSchrodingerGeneral.sh
```

Check that the simulation has started by using the squeue command. Change the username at the end for your username (seen in green at the start of your prompt).

```
[yasminsh@sh03-ln02 login ~]$ squeue -u yasminsh
```

Running simulations are denoted R in the fourth column. Queueing runs are denoted PD:

```
[yasminsh@sh03-ln02 login ~]$ bash runSchrodingerGeneral.sh
Submitted batch job 19919433
Submitted batch job 19919434
[yasminsh@sh03-ln02 login ~]$ que
             JOBID PARTITION     NAME     USER ST       TIME  NODES NODELIST(REASON)
          19919433 gpu,hns,i desmond_ yasminsh PD       0:00      1 (Resources)
          19919434 gpu,hns,i desmond_ yasminsh PD       0:00      1 (None)
[yasminsh@sh03-ln02 login ~]$ que
             JOBID PARTITION     NAME     USER ST       TIME  NODES NODELIST(REASON)
          19919433       hns desmond_ yasminsh CF       0:12      1 sh01-27n21
          19919434       hns desmond_ yasminsh CF       0:12      1 sh01-27n21
[yasminsh@sh03-ln02 login ~]$ que
             JOBID PARTITION     NAME     USER ST       TIME  NODES NODELIST(REASON)
          19919433       hns desmond_ yasminsh  R       0:34      1 sh01-27n21
          19919434       hns desmond_ yasminsh  R       0:34      1 sh01-27n21
```

You should receive an e-mail when the simulation starts and when it has finished, so keep an eye out for e-mail notifications.

While you are waiting for the simulation to finish (ca 25 min), fetch a simulation of ibuprofen in your protein conformation (closed, open or mutant) from the group folder on Sherlock: **/home/groups/sboxer/Schrodinger_Workshop/SCHRODINGER/**

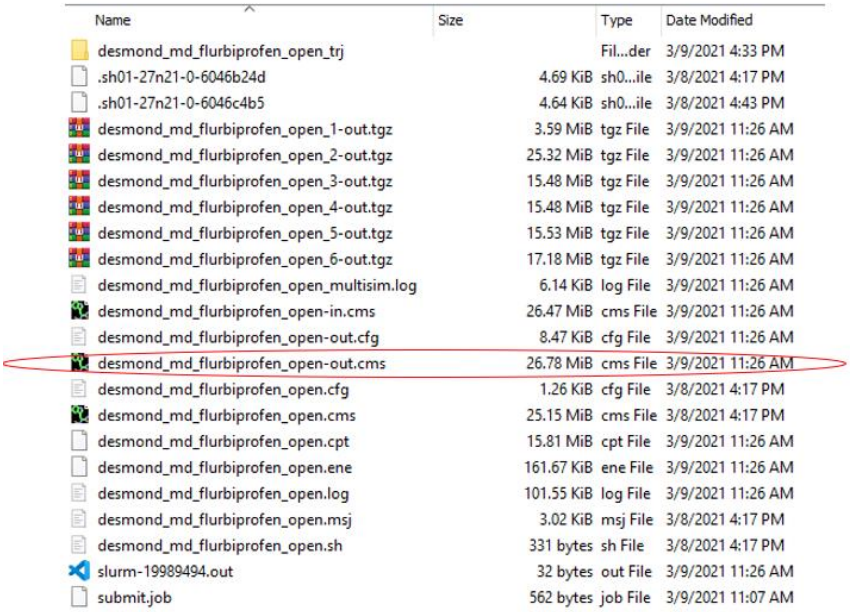
Download the whole folder to your Desmond folder. It will take a couple of minutes to download these folders. Come back to the main room for a brief discussion on what you did and which options are available to you. While waiting for everyone to come back, try to answer the following questions with the other group members in the main room:

1. When generating your box you got the option of changing the water model, the box shape, and the number of ions added to your box. The choice of water model affects the behavior of the simulations, while the box shape affects the simulation time. **Why were ions added to the system?**
2. In the MD simulations box you had the opportunity to change simulation times, temperature and pressure. **What do you think would happen if you increase the temperature of the system?**
3. Which parameters can you change in the **Advanced Options** in the MD simulations box?

Analysis of simulations

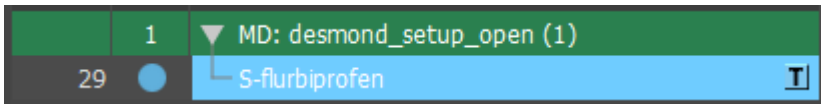
We will start analyzing the ibuprofen structure. Find the ibuprofen folder and import the structure.

1. **Import Structure …** Choose the **FILENAME-out.cms file:**

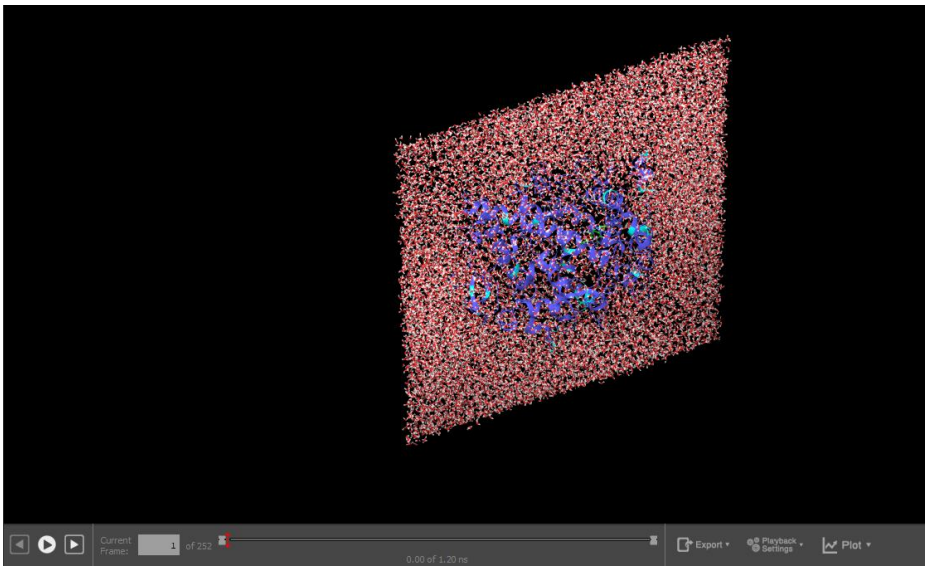


Name	Size	Type	Date Modified
desmond_md_flurbiprofen_open_trj		Fil...der	3/9/2021 4:33 PM
.sh01-27n21-0-6046b24d	4.69 KiB	sh0...ile	3/8/2021 4:17 PM
.sh01-27n21-0-6046c4b5	4.64 KiB	sh0...ile	3/8/2021 4:43 PM
desmond_md_flurbiprofen_open_1-out.tgz	3.59 MiB	tgz File	3/9/2021 11:26 AM
desmond_md_flurbiprofen_open_2-out.tgz	25.32 MiB	tgz File	3/9/2021 11:26 AM
desmond_md_flurbiprofen_open_3-out.tgz	15.48 MiB	tgz File	3/9/2021 11:26 AM
desmond_md_flurbiprofen_open_4-out.tgz	15.48 MiB	tgz File	3/9/2021 11:26 AM
desmond_md_flurbiprofen_open_5-out.tgz	15.53 MiB	tgz File	3/9/2021 11:26 AM
desmond_md_flurbiprofen_open_6-out.tgz	17.18 MiB	tgz File	3/9/2021 11:26 AM
desmond_md_flurbiprofen_open_multisim.log	6.14 KiB	log File	3/9/2021 11:26 AM
desmond_md_flurbiprofen_open-in.cms	26.47 MiB	cms File	3/9/2021 11:26 AM
desmond_md_flurbiprofen_open-out.cfg	8.47 KiB	cfg File	3/9/2021 11:26 AM
desmond_md_flurbiprofen_open-out.cms	26.78 MiB	cms File	3/9/2021 11:26 AM
desmond_md_flurbiprofen_open.cfg	1.26 KiB	cfg File	3/8/2021 4:17 PM
desmond_md_flurbiprofen_open.cms	25.15 MiB	cms File	3/8/2021 4:17 PM
desmond_md_flurbiprofen_open.cpt	15.81 MiB	cpt File	3/9/2021 11:26 AM
desmond_md_flurbiprofen_open.ene	161.67 KiB	ene File	3/9/2021 11:26 AM
desmond_md_flurbiprofen_open.log	101.55 KiB	log File	3/9/2021 11:26 AM
desmond_md_flurbiprofen_open.msj	3.02 KiB	msj File	3/8/2021 4:17 PM
desmond_md_flurbiprofen_open.sh	331 bytes	sh File	3/8/2021 4:17 PM
slurm-19989494.out	32 bytes	out File	3/9/2021 11:26 AM
submit.job	562 bytes	job File	3/9/2021 11:07 AM

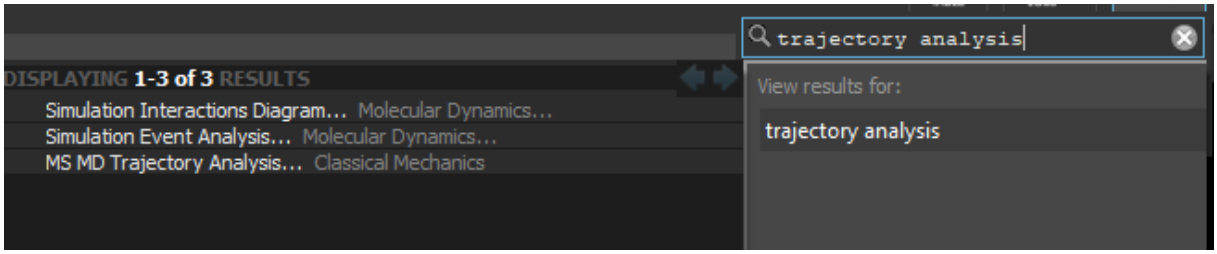
2. After importing your file you should see the new file in your workspace and the file in the Entry List. In the Entry list you can now see a small box with a T inside on the row of your imported structure. Double-clicking this T will load the trajectory of the simulation into the workspace.



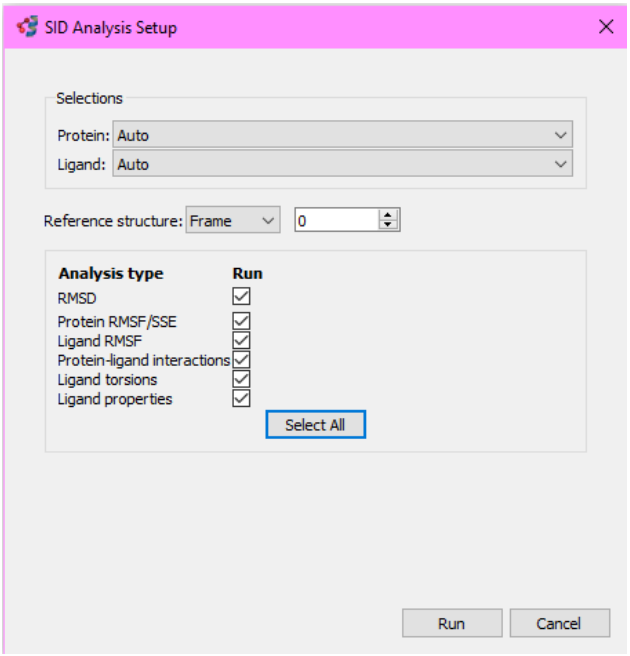
3. Using the handle, you can choose which part of the simulation you want to visualize, or you can play it like a video. Zoom in on the drug and display Leu531, Ser530, and Arg120. Then run your trajectory. Do you see any changes in the structures at the beginning compared with at the end of the simulation?



4. Schrodinger has a built-in trajectory analysis tool. Open the **Simulation Interactions Diagram**



Open the panel and Load… your output file. Choose Select All in the next window and Run.



What do you see? Just from the RMSDs, would you say that the protein is stable? How about the ligand? What are the average RMSDs (roughly)?

5. Go to the P-RMSF tab and check C-alphas, Side chains and Ligand contacts. How stable are the residues that are interacting with the ligand?
6. Go through the different tabs in the window and experiment with toggling different checkboxes.
7. By now your simulations should have finished so you can download it.
8. While you are downloading, take some screenshots of your simulation interaction diagrams so you can compare them with your simulations.

Answer the following questions:

1. Are there any differences in how the proteins and ligands behave in the different systems?
2. Which system was more stable?
3. Which residues moved the most?
4. Which atoms on the ligand moved the most?
5. What were the top 5 ligand-protein interactions?
6. Are there any stable water bridges in the binding pocket?