Introduction to the Schrodinger Bioluminate package

Session 3: GLIDE

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Learning goals:

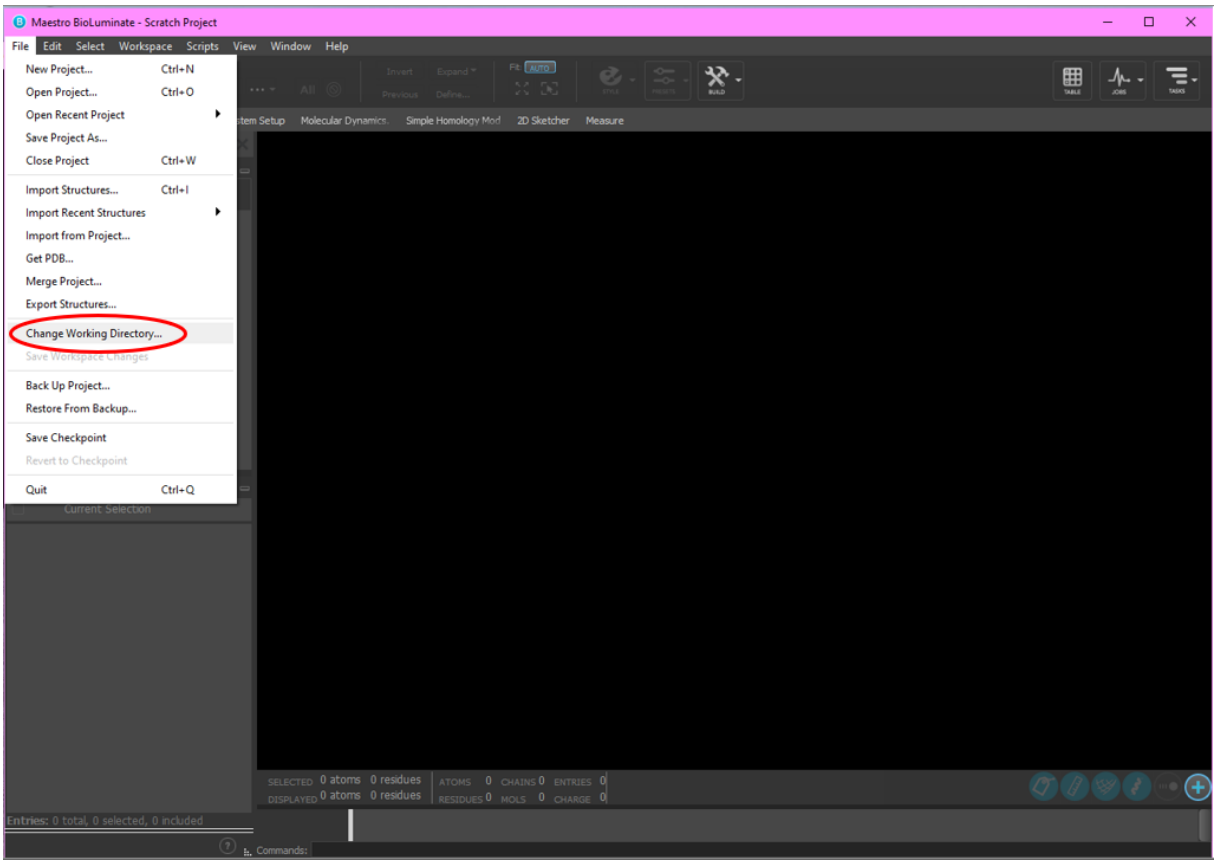
By the end of this session participants should:

- Know the scoring functions used by GLIDE
- Understand the underlying concepts of molecular docking and the limitations of the method
- Independently dock ligands to a protein
- Assess the quality of docked structures.
- Explain how changes in parameters affect docking results
- Design ligands with maximized docking scores

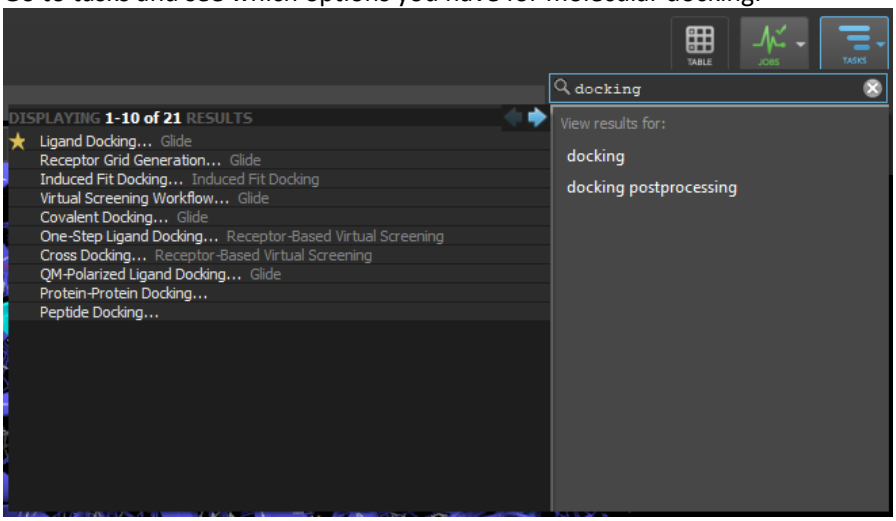
Contents:

Getting started with GLIDE

1. Create a new folder on your Desktop called GLIDE.
2. Move the folder with the created homology models of the open and closed structures from the previous workshop to the new GLIDE folder.
3. Change the working directory to your GLIDE directory on the desktop:



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



Docking your structures

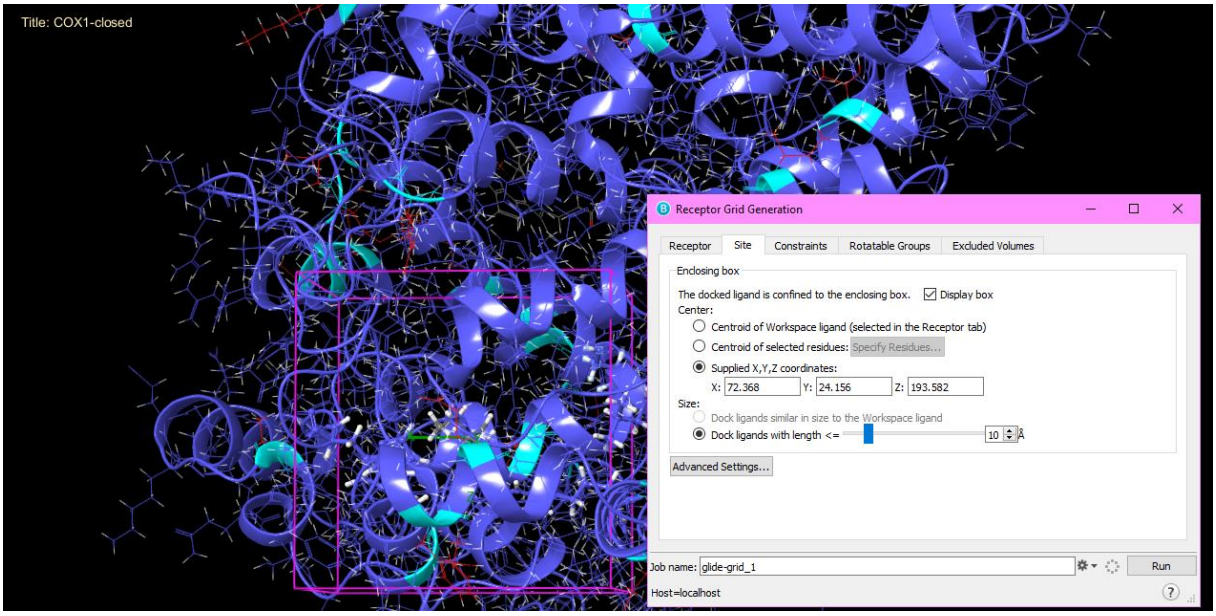
Each member of the group will work on a different structure. The person with the name that would come first in the dictionary will run the closed structure, the next one will dock the open structure. For 3-person-groups the next one will run the Ile523 to Val523 mutant. Note if it is the open or closed version! In 4-person-groups the final member will do the other version of the mutant.

1. Before you can dock your structure you need to generate a receptor grid. Choose the **Receptor Grid Generation… Glide** option.

   Read the options in each tab to see what your options are. Today, we will use the coordinate of the gate-keeping residue Ile/Val523 as our center point for the grid, specifically the CB atom. You can find the coordinates in the .mae file you generated (Open in a text editor to see it):

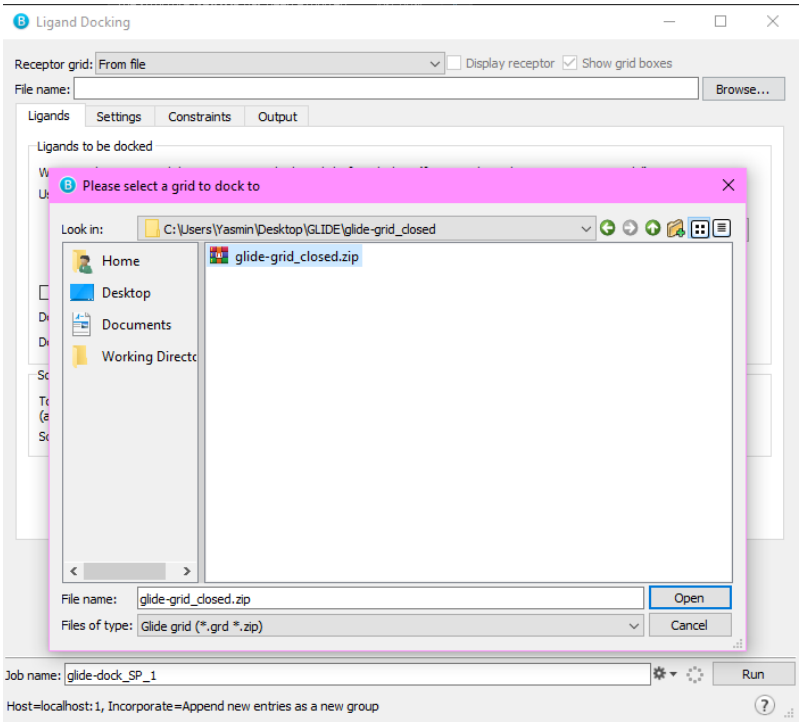
   ```
   72.368000 24.156000 193.582000 522 I A 44 "ILE " " CB " "
   ```

   What happens in the workspace when you drag the toggle next to the Dock ligands with length…?

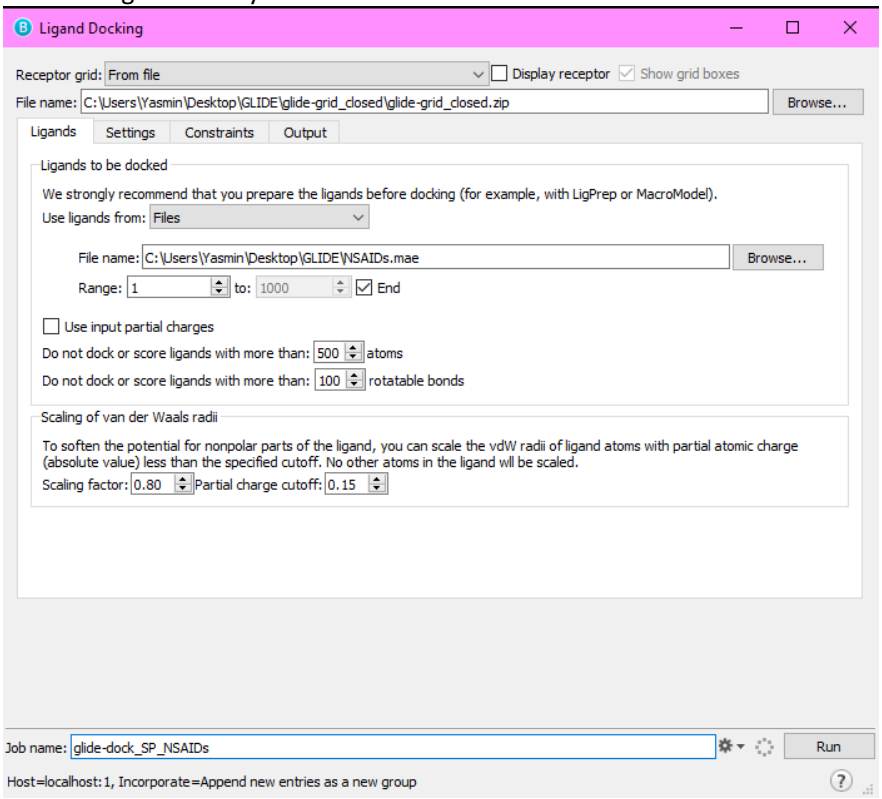


5. Use a box side of 10Å. Edit the job name so you know which grid this was for. Example: glide-grid-closed. Then hit Run and wait for the job to finish (ca 2 min). Check that you have a folder with your grid in your folder (compressed file). Note: This file can be shared with other people so that they can dock to the exact same structure as you.
6. Next, you will start to dock some ligands into your binding pocket. Your test ligands are in the Schrodinger folder/GLIDE on the Google Drive (NSAIDs.mae). Copy it to your GLIDE folder.

7. Start your docking session by opening the Ligand Docking window. Browse and select your grid file.

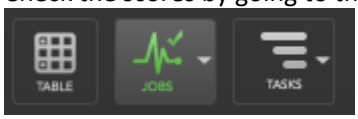


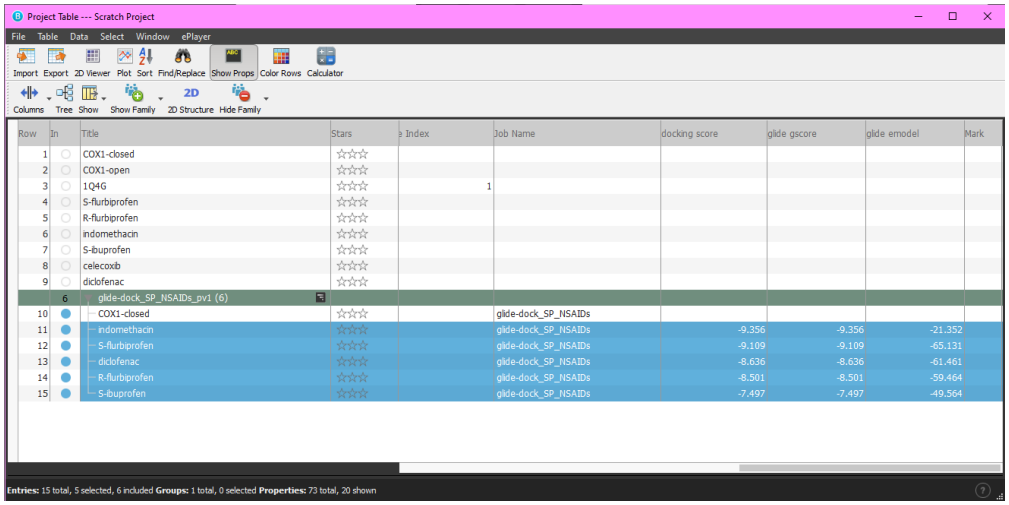
Load the ligands that you want to dock. The file contains 6 different NSAIDs.



Check the other tabs to see what the options are. Keep all the standard settings and choose a suitable name for your file. Hit Run and wait for the job to finish (ca 2 min).

8. Analyze your results.
    a. Check the scores by going to the Table and scrolling to the far right.





Experimental values and structures for these ligands have been published according to this table:

Ligand	Instant inhibition IC50 (µM) (Laneuville, 1994)	Pre-incubated inhib. IC50 (µM) (Warner, 1999)	Your docking scores SP	XP	Crystal structure
Indomethacin	13.5	0.013			4COX
Flurbiprofen (racemic mixture)	0.5	0.075			1EQH, 3N8Z
Diclofenac	2.7	0.075			3N8Y, 1PXX
Ibuprofen	4	7.6			1EQG
Celecoxib	Assumed similar to pre-incubated values.	1.2			3KK6

Did your docking results match experimental data? How did they rank? Why do you think you got these results?

Crystal structures of these inhibitors (or similar ones) are available in the RCSB database. They can be imported for comparison.

Do the ligands have any similarities or differences? Do the docking poses you got look reasonable (check at least one crystal structure per person in the group)? Are you missing any structure? Why do you think that is?

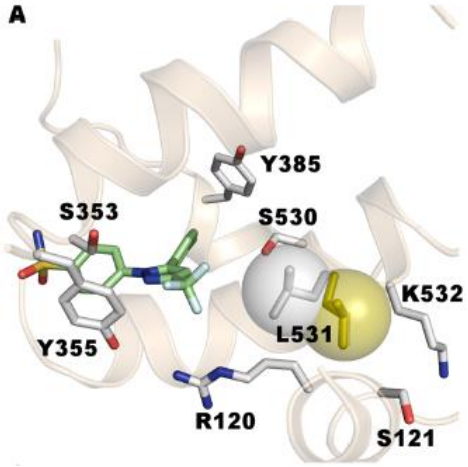
9. Repeat the docking using the XP scoring function (you can re-use the grid).

Was there any difference in the docking scores? Did the internal rankings of the ligands change? Why/ why not? Which scoring function and model seems to rank the ligands more closely with experimental data? Why do you think that is?

10. If you have undockable ligands you can try adjusting parameters to force the program to dock it and give you a score. Try different methods within the group and see if you can find a good way to get it to work.

A drug design project

Now that you know how a docking program works, why not use your newly found knowledge to design the best next-generation drug possible? In your groups, design your own high-affinity NSAIDs and test them. When you have found the best candidate you will present it to the other groups. The group presenting the best drug (according to the scoring functions) will win a prize!



For today, we will assume that the mutated Ile523 to Val523 is a good approximation of COX-2. When you have found your ideal drug, note the docking scores in both SP and XP in all your enzyme models and send them to me. I will collect the results and present them. Be ready to explain why your drug is the most optimized (think of how the scoring functions work, and which interactions you have maximized when designing your molecule).

Breakout room number / Drug name	Closed conformation		Open conformation		Val523 mutation (closed)		Val523 mutation (open)	
	SP	XP	SP	XP	SP	XP	SP	XP

Hint: You can analyze your docked ligand interactions with the enzyme by keeping them in the workspace together with the protein and opening up the 2D panel.

References:

Laneuville, O.; Breuer, D.K.; Dewitt, D.L.; Hla, T.; Funk, C.D.; Smith, W.L. Differential inhibition of human prostaglandin endoperoxide H synthases-1 and -2 by nonsteroidal anti-inflammatory drugs. *J. Pharmacol. Exp. Ther*. **1994**, *271*, 927-934.

Warner, T.D.; Giuliano, F.; Vojnovic, I.; Bukasa, A.; Mitchell, J.A.; Vane, J.R. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: A full ***in vitro*** analysis. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, *7563-7568.*