Glide Docking

This sheet summarizes the process of docking a set of compounds (ligands) from a file to a PDB target that has a cocrystallized ligand. The process involves preparing the protein, preparing the ligands, setting up a grid, and docking the compounds. Preprocessing is necessary because modeling requires 3D, all-atom structures with hydrogens.

Preparing the Protein

1. Choose Tasks → Protein Preparation or Applications → Protein Preparation Wizard.
2. In the Import and Process tab, enter the PDB ID into the PDB text box, and click Import.
3. Choose options for preprocessing the protein structure (other than the defaults).
   - If you don't want to keep waters in the active site, enter `0` in the Delete waters beyond text box.
   - If you want to convert selenium atoms to sulfur, select Convert selenomethionines to methionines.
4. Click Preprocess.
5. Address any problems reported in the Protein Preparation - Problems dialog box.
   - If the problems are far from the active site, select the Fill in options and Cap termini, and click Preprocess again.
   - If the problems are in or near the active site, run a Prime Refinement for the problem side chains and loops.
6. Delete unwanted parts of the system (chains, solvent molecules, etc.) in the Review and Modify tab.
7. Optimize the H-bond network in the Refine tab.
8. Click Minimize to run a restrained minimization on the structure.

Preparing the Ligands

1. Choose Tasks → Ligand Preparation or Applications → LigPrep.
2. Set Use structures from to File, and click Browse to find and select your ligand file.
3. If you have Epik installed, under Ionization select Using: Epik.
4. If the protein has a metal in the binding site, select Add metal binding states (requires Epik).
5. Click Start to run the job. If the ligand file is large, distribute the job over multiple processors if possible.

Generating the Receptor Grid

1. Choose Tasks → Docking → Grid Generation or Applications → Glide → Receptor Grid Generation.
2. Display the prepared receptor in the Workspace.
3. Pick the ligand to define the grid center.
4. Adjust the size of the active site in the Site tab to accommodate larger ligands, if necessary.
5. Add any constraints in the Constraints tab.
6. Pick any rotatable hydroxyl or thiol groups in the active site if such groups could rotate during docking.
7. Add any excluded volumes to exclude atoms from regions other than the receptor.
8. Start the grid generation job.

Docking the Ligands

1. Choose Tasks → Docking → Glide Docking or Applications → Glide → Ligand Docking.
2. Specify the receptor grid to use.
3. Select the docking precision:
   - HTVS for initial screen of millions of compounds (limited conformational search but fast)
   - SP for thousands of compounds (better coverage of conformational space)
   - XP for tens or hundreds of compounds (high accuracy on docked poses)
4. If you chose XP, select Write XP descriptor information if you want to visualize interaction terms.
5. Select Add Epik state penalties to docking score, if Epik was used in ligand preparation (especially for metalloproteins).
6. Specify the ligand file to use, in the Ligands tab.
7. If you want to set up constraints to a reference ligand core or calculate RMSD to this core, you can do this in the Core tab.
8. Select the receptor constraints you want to use in the Constraints tab, and supply any required information.
9. If the ligands are very flexible, you can apply constraints on ligand torsions in the Torsional Constraints tab, to reduce the torsional degrees of freedom.
10. Set the number of poses per ligand and total number of poses in the Output tab.
11. Use post-docking minimization if you want to improve pose geometries.
12. Select Write per-residue interaction scores for residues within N Å of grid center if you want to examine interactions of ligand poses with the receptor, and set the cutoff distance.
13. Run the job. If the ligand file is large, distribute the job over multiple processors if possible.

Examining Poses

1. Import the pose file *jobname*`_pv.mae` into Maestro. Ensure that the option For pose viewer files, turn on pose viewing is selected.
2. In the View Poses panel, turn on display of H-bonds and contacts. If you wrote out per-residue interaction scores, select Display in the Per-residue interactions section.
3. Use the LEFT ARROW and RIGHT ARROW keys to step through the poses, and examine their interactions with the receptor.
4. When you have finished examining poses, right-click on the receptor entry in the Project Table and choose Unfix to exit the pose viewing mode.