Preparation for Docking with Glide

Ligand Preparation

Run LigPrep with the default settings (for details, see Chapter 5 of the *Glide User Manual*):

- Desalt, generate tautomers, stereoisomers, retain specified chiralities
- Ionization: generate possible states at target pH 7.0 +/- 2.0

Protein Preparation

For details, see Chapter 4 of the *Glide User Manual*.

1. Molecules to keep/remove (see the *Glide User Manual*, p. 40)
   - Metal ions—keep (usually catalytically or structurally important).
   - Cofactors—keep.
   - Water— keep to a minimum. Keep only when coordinated to a metal ion or if critical for ligand binding. If a new ligand could potentially displace the water, prepare the protein with and without the water present and dock into each of the prepared structures.
   - Other solvent molecules and counterions—remove.
2. Correct bond orders, formal charges, atom names (see *Induced Fit Docking*, p. 42)
   - Choose Assign Bond Orders from the Tools menu to fix bond orders of the ligands, cofactors, and any nonstandard residues (colored in orange). Check that assignments are correct.
   - Inspect formal charges and make changes as needed.
   - If blue residues are present, check and correct PDB atom names using the Build panel.
   - Add hydrogens.
   - Delete bonds to metals, set formal charge on metal.
3. Add missing side chains and residues (see *Induced Fit Docking*, p. 45)
4. Run the `protassign.py` script to optimize the H-bond network in the binding site:
   - Geometry adjustment: determine if O and N atoms of Gln and Asn residues should be flipped.
   - Adjust protonation and tautomerization: check for the correct protonation and tautomerization of His residues.
   - Position hydroxyl and thiol hydrogens.
5. Check the protonation states of Asp, Glu, Lys, and Arg. Check for occurrences of two basic or two acidic groups that are close to each other: one of the side chains may be better modeled as the neutral form.
6. Perform refinement (see the *Glide User Manual*, p. 52)
7. Test the structure (see *Induced Fit Docking*, p. 47)

Grid Calculation and Glide Docking Tests

For details, see Chapter 6 and Chapter 7 of the *Glide User Manual*.

- Redock the cocrystallized ligands in their protein structure to check the protein structure preparation.
- Cross-dock the cocrystallized ligands in other protein structures:
  - Structures that perform well in cross-docking experiments are preferred for docking runs.
  - Those that do not do well in such experiments may be good candidates for Induced Fit Docking studies.
- Enrichment studies with known active molecules:

  Structures that yield the best docking results are preferred
- Induced Fit Docking (see the *Induced Fit Docking* manual): Generate other conformations of the binding site based on known active ligands that don't bind in the available protein structures.