docking parameters

January 30, 2023

1- Ligan preparation with LigPrep

The molecules were optimized with RDKit were taken as the input and further optimized with Schrödinger's LigPrep [1]. The settings for the ligand preparation were the following:

- Force field: OPLS4.
- Generate possible states at target pH: 7.4 ± 2.0; Using Epik.
- Desalt.
- Steroisomers:

  → Determine chiralities form 3D structure.

- Output format: maestro. Afterwards, the receptor was prepared

2 - Protein preparation

Protein preparation was done with the protein preparation wizard module of the Schrödinger suite [2]:

- Assign bond orders.

- Add Hydrogens.
- Create zero-order bonds to metals.
- Create disulfide bonds.
- Fill in missing side chains using Prime.
- Cap termini: Since the missing loops are not near the binding site we are interested in analyzing, we will simply use the cap termini option. This option adds ACE (N-acetyl) and NMA (N-methyl amide) groups touncapped N and C termini.
- Generate het states using Epik, at pH=7.4 ± 2.0. Then, potassium and calcium atoms present in the structure were removed, as well as POV and LMT ligands, which are located near the top of the structure, where the protein interacts with the membrane, and thus are of no interest for this docking simulation, as they are not part of the binding site we are interested in exploring.

3 - Docking box:

For the glide simulation, a 15Åx15Åx15Å box was created, whose center was the centroid of the residues that make up the binding pocket: 19F, 32L, 51M, 54E, 55V, 63I, 68F, 71M, 72M, 75K of chain G and residues 184A, 185L. For now, flexibility of the receptor amino acids was not considered

4 - Docking calculations:

Docking calculations were performed with Glide [3]:

- Ligands Panel:

  → Do not dock or score ligands with more than: 500 atoms.

- → Do not dock or score ligands with more than: 100 rotable bonds.
- → Scaling factor: 0.8.
- → Partial charge cutoff: 0.15.

- Settings Panel:
  - → Precision: XP (extra precision)
  - → Ligand Sampling: Flexible
- Sample nitrogen inversions
- Sample ring conformations
- Bias sampling of torsions for: All predefined functional groups.
  - → Add Epik state penalties to docking score.
  - → Reward intramolecular hydrogen bonds.
- Output Panel.
  - → File type: Pose viewer file (includes receptor)
  - → Write out at most: 1 poses per ligand
  - → Perform post-docking minimization
- Number of poses per ligand to include: 10
- Threshold for rejecting minimized pose: 0.5 kcal/mol
- Apply strain correction terms
  - → Write per-residue interaction scores
- For residues within 12Å of grid center.
  - → Compute RMSD to input ligand geometries