

Tutorial for LeWater

LeWater can be used to filter docking poses and/or integrated into a scoring function to improve the accuracy of predicted binding affinity.

Here we use BRD4 bromodomain (PDB code 4PCI) as one example. The top 2 docking poses of the crystal ligand are wrong, but the last two are within 0.5 Å of the crystal poses. We will go through the procedures from preparation of an input file for LeWater to analysis of the results. As the VMD plugin for LeWater will be used to generate an input file, VMD shall be installed in advance. Otherwise, please use the example input file (lewater.in) instead.

The example input and output files can be found in the directory [example_output](#)

Open a terminal:

1. `$ cd work`
2. `$ vmd pro.pdb`
Protein shall have hydrogen atoms added and has no ligand inside the binding site
3. Open VMD Tk console: Extensions → Tk Console
4. In Tk Console: `source ../vmd_plugin_for_lewater/input_lewater.tcl`
5. `lewaterin -proid 0 -xmin 4 -xmax 19 -ymin -1 -ymax 15 -zmin -6 -zmax 9 -weight_donor 0.5 -weight_acceptor 1.0 -sasa_limit 0.5 -sasa_probe 1.2 -hbond_dis 3.6 -hbond_angle 60 -box_zoom 4`

The following will be output:

Pocket

0.00 23.00 -5.00 19.00 -10.00 13.00

Donor

A81 N HN 0.5

...

Acceptor

A81 O 0

...

END

6. Copy the above output and save it in a file “lewater.in”
7. Back to the terminal: \$ `ls lig*pdb >poses.list`
8. \$ `lewater lewater.in pro.pdb poses.list`
9. The output is written in the file “filter”. \$ `cat filter`

```

lig_dock001.pdb      2.332  P: 2.100  L: 0.232  Dpro: 0.0 0.0 0.0 0.0 0.0 0.7 0.0  Apro: 0.0 0.5 0.0 0.0 0.0 0.0 0.0 0.0 0.0
lig_dock002.pdb      2.262  P: 2.047  L: 0.215  Dpro: 0.0 0.0 0.0 0.0 0.0 0.8 0.0  Apro: 0.0 0.6 0.0 0.0 0.0 0.0 0.0 0.0 0.0
lig_dock003.pdb      0.000  P: 0.000  L: 0.000  Dpro: 0.0 0.0 0.0 0.0 0.0 1.0 0.0  Apro: 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0
lig_dock004.pdb      0.000  P: 0.000  L: 0.000  Dpro: 0.0 0.0 0.0 0.0 0.0 1.0 0.0  Apro: 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0

```

Analysis

Values in the second column are H-bonding penalties, with 1 corresponding to a penalty of about 1.5 kcal/mol in the free energy of binding. The penalty score multiplied by 1.5 can be added to the docking score (or affinity predicted by other scoring functions) to rescore the poses. LeWater evaluates the geometry of H-bonds between the ligand and protein as well as the solvation status of polar atoms at the protein-ligand interface to output a penalty score. The precision level of such calculations is usually higher than that of molecular docking. It is recommended that docking poses are subject to further energy minimization by a force field e.g., CHARMM before LeWater calculation. Values in the fourth and fifth column are penalty divided into protein and ligand.

Values in the following columns are fitness of H-bonds between the ligand and protein polar atoms listed in the LeWater input file with the same order. None zero value indicates a H-bond including acidic CH as H-bonding donor. The value of 1 means a perfect H-bond. If there are conserved H-bond(s) among known ligands, such H-bond(s) can be used as filter to remove poses that are unlikely to be true.