EPSDock User Manual

Version 1.0

1. Introduction

EPSDock is an advanced docking program based on an enhanced variant of particle swarm optimization technique derived from artificial been colony algorithm and the energy scoring function of Autodock 4.20 program. The docking process is divided into two main stages: the pre-calculation of affinity grids for the receptor and the actual docking simulation. This manual provides a step-by-step guide to performing a complete docking experiment using EPSDock.

2. System Requirements & File Overview

Before starting, ensure you have the following installed:

- **AutoDock Tools (ADT):** Essential for preparing the necessary input files.
- **EPSDock Suite:** Includes the autogrid and epsdock executables.

A typical EPSDock project requires these key files:

1. **Receptor File (Receptor.pdbqt):** The 3D structure of the target such as RNA receptor, with added charges, solvation parameters, and atom types.
2. **Ligand File (Ligand.pdbqt):** The 3D structure of the small molecule to be docked, prepared with flexible torsions, charges, and atom types.
3. **Grid Parameter File (Receptor.gpf):** Contains instructions for autogrid to pre-calculate the affinity maps around the receptor.
4. **Docking Parameter File (Docking.dpf):** Contains all parameters that control the EPSDock docking simulation (e.g., algorithm, number of runs, energy evaluations).
5. **Docking Log File (Result.dlg):** The output file containing all docking results, including binding energies, coordinates of docked poses, and cluster analysis.

3. Step-by-Step Workflow

Step 1: Prepare the Receptor and Ligand Files

The first step is to convert your input PDB files into the PDBQT format required by EPSDock.

1. **Open AutoDock Tools (ADT).**
2. **Prepare the RNA Receptor:**
    - Go to File > Read Molecule and select your receptor structure file (e.g., RNA.pdb).

- In the Edit menu, select Hydrogens > Add to add polar hydrogens.
- In the Edit menu, select Charges > Compute Gasteiger to calculate atomic partial charges.
- Check for any missing atoms or structural issues. The RNA structure should be complete.
- Go to Grid > Macromolecule > Choose and select your prepared RNA molecule. Save the file as Receptor.pdbqt.

3. **Prepare the Ligand:**
   - Go to Ligand > Input > Open and select your small molecule ligand file (e.g., Ligand.pdb or Ligand.mol2).
   - ADT will guide you through ligand preparation. Set the Root and Detect Root options automatically or manually.
   - In the Torsion Tree window, define the **flexible torsion bonds** by selecting them. It is crucial to choose bonds that allow the ligand to explore realistic conformational space. Click Done.
   - Go to Ligand > Output > Save as PDBQT to save the prepared ligand as Ligand.pdbqt.

Step 2: Generate the Grid Parameter File (GPF) and Affinity Maps

The grid file defines a 3D box where the affinity maps will be calculated. This box should encompass the expected binding site on the RNA.

1. In ADT, make sure your Receptor.pdbqt is loaded.
2. Go to Grid > Macromolecule > Choose and confirm the selection of your receptor.
3. Go to Grid > Grid Box. A new window will appear.
4. **Set the Grid Box:**
   - Adjust the box center (center_x, center_y, center_z) to the coordinates of your RNA's binding site (e.g., an active pocket).
   - Adjust the box dimensions (size_x, size_y, size_z) to be large enough to accommodate the ligand but focused on the region of interest to save computation time. A typical size is 60x60x60 points with a default spacing of 0.375 Å.
5. Go to Grid > Output > Save GPF to save the grid parameters as Receptor.gpf.
6. **Run AutoGrid:** Execute the following command in your terminal or command prompt to generate the affinity maps (e.g., Receptor.maps.fld). For instance:

   Bash# Autogrid4 -p receptor.gpf -l grid.log

Step 3: Set Up the Docking Parameter File (DPF)

This file configures the EPSDock docking simulation.

1. In ADT, ensure both your Receptor.pdbqt and Ligand.pdbqt files are loaded.

2. Go to Docking > Macromolecule > Set Rigid Filename and choose Receptor.pdbqt.
3. Go to Docking > Ligand > Choose and select your Ligand.pdbqt.
4. Go to Docking > Search Parameters > to set the docking parameters. Key parameters include:
    - For instance, below is a set of detailed searching parameters typically used in the EPSDock docking (key numbers are highlighted):

pso_c1 **2.05**	# the first confident coefficient
pso_c2 **2.05**	# the second confident coefficient
pso_k **50**	# max number of particles informed by a given one
pso_swarm_moves **2500000**	# total swarm moves
pso_size **50**	# swarm size
pso_n_exec **10**	# number of requested PSO runs
sw_max_its **50**	# iterations of Solis & Wets local search
sw_max_succ **2**	# consecutive success before changing rho
sw_max_fail **2**	# consecutive failures before changing rho
sw_rho **1.0**	# size of local search space to sample
sw_1b_rho **0.01**	# lower bound on rhon
ls_search_freq **0.06**	# probability of performing local search on individual
set_psw1	# set the above pseudo-Solis & Wets parameters

5. Go to Docking > Output > Enhanced particle swarm (or other algorithm) > Save DPF to save the docking parameters as Docking.dpf.

    It is highly recommended to open the Docking.dpf file in a text editor to verify and fine-tune parameters.

Step 4: Run the EPSDock Docking Simulation

With all input files ready, you can now run the docking calculation.

Execute the following command (suppose you have fully compiled the EPSDock executables):

Bash# epsdock -p Docking.dpf -l docking.log

- -p Docking.dpf: Specifies the Docking Parameter File.
- -l docking.log: (Optional) Saves the text output to a log file for debugging.

The simulation may take from several minutes to hours, depending on the system size and parameters.

Step 5: Analyze the Docking Results

The primary results are stored in the Result.dlg file.

1. **Open the DLG file in ADT:**
    - In ADT, go to Analyze > Docking > Open and select your Result.dlg file.
    - The interface will display a list of docking poses (conformations), typically ranked by **Estimated Free Energy of Binding (ΔG)** in kcal/mol. Lower (more negative) values indicate stronger binding.
    - Poses are also grouped into **clusters** based on spatial similarity. The cluster with the most members (lowest RMSD from each other) often represents the most stable predicted binding mode.
2. **Extract and Save Poses:**
    - In the Analyze window, you can select individual poses or entire clusters.
3. **Advanced Analysis:**
    - For detailed energy breakdowns and conformational analysis, the Result.dlg file can be parsed using custom scripts or other analysis tools to extract specific data like intermolecular energies, internal energies, and torsional free energy.

4. Troubleshooting Tips

- **Poor Results:** Ensure the grid box correctly covers the binding site. Incorrect box placement is a common cause of failure.
- **File Errors:** Double-check that all file paths in the GPF and DPF are correct and that the PDBQT files were generated without errors in ADT.

For further assistance, please consult the EPSDock documentation or contact our support team.

EPSDock source code download website:

https://github.com/Lorentz-force-coder/EPSDock

Contact the supporting team:

Dr. Xuan Chen, E-mail: xuanchen@mail.dlut.edu.cn
Prof. Yongliang Yang, E-mail: everbright99@163.com