AutoDock Tools Molecular Docking Guide

Required Software/Tools

1. **AutoDock Tools (ADT)**:
    - **Purpose**: Prepares input files (protein, ligand, grid) and analyzes docking results.
    - **Why**: ADT is the main interface for setting up and running AutoDock simulations.
2. **MGLTools**:
    - **Purpose**: Provides utilities for AutoDock, including ADT.
    - **Why**: MGLTools is required to install and run ADT.
3. **PyMOL**:
    - **Purpose**: Visualizes protein-ligand interactions and converts file formats.
    - **Why**: PyMOL helps in visualizing the 3D structure of proteins and ligands and preparing ligand files.
4. **Open Babel**:
    - **Purpose**: Converts molecular file formats (e.g., SDF to PDB).
    - **Why**: AutoDock requires specific file formats (e.g., PDBQT), so conversion tools are necessary.
5. **PrankWeb**:
    - **Purpose**: Predicts binding sites on the protein.
    - **Why**: Helps identify the region where the ligand is likely to bind, which is crucial for defining the grid box.

Prerequisite Files

1. **autodock4.exe** and **autogrid4.exe**:
    - **Purpose**: Executables for running docking and grid calculations.
    - **Why**: These are the core programs that perform the docking simulations.
2. **AD4.1_bound.dat** and **AD4_parameters.dat**:
    - **Purpose**: Parameter files for AutoDock.
    - **Why**: These files contain force field parameters and other settings required for docking.

3. **Protein from PDB**:
    - **Purpose**: The 3D structure of the target protein.
    - **Why**: The protein is the target molecule for docking.
4. **Ligand from PubChem in SDF format**:
    - **Purpose**: The small molecule to be docked into the protein.
    - **Why**: The ligand is the molecule whose binding affinity and orientation are being studied.

Setting Up the Working Directory

- **File > Preferences > Set Startup Directory**:
    - **Purpose**: Sets the default folder where AutoDock will look for input files and save output files.
    - **Why**: Ensures all files are organized in one location, making the workflow more efficient.

Protein Preparation

1. **File > Read Molecule > Select protein.pdb**:
    - **Purpose**: Loads the protein structure into ADT.
    - **Why**: The protein must be loaded to prepare it for docking.
2. **Edit > Delete Water**:
    - **Purpose**: Removes water molecules from the protein structure.
    - **Why**: Water molecules can interfere with docking calculations.
3. **Edit > Hydrogen > Add Polar Only**:
    - **Purpose**: Adds hydrogen atoms to polar atoms (e.g., oxygen, nitrogen).
    - **Why**: Hydrogen atoms are necessary for accurate energy calculations and hydrogen bond formation.
4. **Edit > Charges > Add Kollman Charges**:
    - **Purpose**: Assigns Kollman charges to the protein.
    - **Why**: Charges are essential for calculating electrostatic interactions during docking.
5. **Grid > Macromolecule > Choose Protein > Save as protein.PDBQT**:
    - **Purpose**: Saves the prepared protein in PDBQT format.

- **Why**: PDBQT is the required format for AutoDock.

6. **Edit > Delete > Delete All Molecules**:
    - **Purpose**: Clears the workspace.
    - **Why**: Prepares ADT for the next step (ligand preparation).

Ligand Preparation

1. **Open PyMOL, open ligand.sdf, save as ligand.pdb**:
    - **Purpose**: Converts the ligand file from SDF to PDB format.
    - **Why**: AutoDock requires the ligand in PDB format for preparation.
2. **File > Read Molecule > Select ligand.pdb**:
    - **Purpose**: Loads the ligand into ADT.
    - **Why**: The ligand must be loaded to prepare it for docking.
3. **Ligand > Input > Choose Ligand**:
    - **Purpose**: Selects the ligand for docking.
    - **Why**: Specifies which molecule will be docked into the protein.
4. **Ligand > Output > Save as PDBQT**:
    - **Purpose**: Saves the prepared ligand in PDBQT format.
    - **Why**: PDBQT is the required format for AutoDock.

Grid Preparation

1. **Grid > Macromolecule > Open protein.PDBQT**:
    - **Purpose**: Loads the prepared protein into the grid setup.
    - **Why**: The grid must be centered around the protein.
2. **Grid > Set Map Types > Open ligand.PDBQT**:
    - **Purpose**: Loads the ligand to define the grid parameters.
    - **Why**: The grid box should encompass the ligand's binding site.
3. **Set the spacing to 0.5 angstroms**:
    - **Purpose**: Defines the resolution of the grid.
    - **Why**: A smaller spacing increases accuracy but requires more computational resources.
4. **Enter X, Y, Z coordinates from PrankWeb**:

- **Purpose**: Defines the center of the grid box.
- **Why**: Ensures the grid box is focused on the binding site.

5. **Grid > Grid Box > Save grid.GPF**:
   - **Purpose**: Saves the grid parameter file.
   - **Why**: The grid file is required for running AutoGrid.
6. **Run > AutoGrid**:
   - **Purpose**: Runs AutoGrid to generate grid maps.
   - **Why**: Grid maps are used by AutoDock to calculate interaction energies.

Docking

1. **Docking > Macromolecule > Set Rigid Filename > protein.PDBQT**:
   - **Purpose**: Loads the protein for docking.
   - **Why**: The protein is the target for the ligand.
2. **Docking > Ligand > Open ligand.PDBQT**:
   - **Purpose**: Loads the ligand for docking.
   - **Why**: The ligand is the molecule being docked.
3. **Docking > Search Parameters > Genetic Algorithm (GA)**:
   - **Purpose**: Sets the search algorithm to Genetic Algorithm.
   - **Why**: GA is efficient for exploring the conformational space of the ligand.
4. **Docking > Output > Lamarckian GA**:
   - **Purpose**: Uses the Lamarckian GA algorithm.
   - **Why**: This algorithm combines GA with local search for better results.
5. **Docking > Save > dock.dpf**:
   - **Purpose**: Saves the docking parameter file.
   - **Why**: The DPF file is required for running AutoDock.
6. **Run > AutoDock**:
   - **Purpose**: Runs the docking simulation.
   - **Why**: Performs the actual docking calculation.

Post-Docking Analysis

- **Purpose**: Analyze the docking results (e.g., binding poses, interaction energies).
- **Why**: Determines the most likely binding mode and affinity of the ligand.