DOCKING OF RIGID MACROMOLECULES USING AUTODOK

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Abstract-

Molecular docking is a kind of bioinformatics modelling which involves the interaction of two or moremolecules to give the stable adduct. Depending upon binding properties of ligand and target, it predicts the three dimensional structure of any complex. Molecular docking generate different possible adduct structures that are ranked and grouped together using scoring function in the software. This exercise again demonstrated a crucial importance of the correct local legand geometry for the overall success of docking. Knowledge of the preffered orientation in turnmay be used to predict the strength of association or bindingaffinity between two molecules using,for example scoring funstions. In the field of molecular biology,selected ligand can act as good drug lead and can be further go for clinical trial.

Introduction

Molecular docking is used for study of protein-ligand interactions and for drug discovery,synthesis and development. Actually the process starts with a target of known structure of an enzyme of medicinal interest. Docking is then used to predict the bound conformation and binding free energy of small molecules to the target. Single docking experiments are useful for exploring the function of the target, and virtual screening, where a large library of compounds are docked and ranked, may be used to identify new inhibitors for drug development.
AutoDock is a suite of free open–source software for the computational docking and virtual screening of small molecules to macromolecular receptors. The suite currently includes several complementary tools:

AutoDock Vina: a turnkey computational docking program based on a simple scoring function and rapid gradient-optimization conformational search. 1
AutoDock: a computational docking program based on an empirical free energy force field and rapid Lamarckian genetic algorithm search method2,3.

Raccoon2: an interactive graphical tool for virtual screening and analysis4.

AutoDockTools: an interactive graphical tool for coordinate preparation, docking and analysis.5

AutoLigand: a program for predicting optimal sites of ligand binding on receptors.6

The AutoDock suite, including source, is freely available, and has been widely used in research and drug discovery.

MATERIALS

Required Data

Coordinate file for receptor (in a variety of formats, including pdb, mol2, cif & sdf)

Coordinate file for ligand (in a variety of formats, including pdb, mol2, cif & sdf)

Several files are available in Supplementary Data for use as a tutorial for each of the protocols: 1iep_receptorH.pdb (coordinates of c-Abl kinase domain from PDB entry 1iep, with hydrogen atoms added in AutoDockTools), 1iep_ligandH.pdb (coordinates of imatinib from PDB entry 1iep, with hydrogen atoms added in AutoDockTools), 1fpu_receptorH.pdbqt (coordinates of c-Abl kinase domain from PDB entry 1fpu, in PDBQT format), imatinib.pdbqt (coordinates of imatinib in PDBQT format), NCIdivII_subset (a folder that includes 499 compounds from the ZINC library, formatted as PDBQT files)

Hardware and Software
Computer: Linux, Macintosh, or Windows PC; Internet access

For virtual screening with Raccoon, a Linux cluster/HPC with either a PBS or SGE scheduler

PROCEDURE

Coordinate Preparation with AutoDockTools - timing 10 min

Generate the ligand coordinate file. A coordinate set that includes hydrogen atoms is required. This may be obtained in a variety of ways, including experimental coordinates from the Protein Data Bank (www.pdb.org) or Cambridge Crystallographic Database (ccdc.cam.ac.uk), or structure generation methods such as the CACTUS server (cactus.nci.nih.gov/translate). The file 1iep_ligandH.pdb is provided for use as a tutorial for this protocol (all example files are supplied in Supplementary Data) it includes ligand coordinates taken from PDB entry 1iep, to which all hydrogen atoms have been added and manually adjusted to the known protonation state. Start AutoDockTools (ADT) (Figure 1) and set the working directory by clicking “File->Preferences->Set”. Type your working directory path name into the “Startup Directory” box and click “Set”. Click “Dismiss” at the bottom of the window.

Read the atomic coordinates. To do this, first select “Ligand->Input->Open” and use the “Files of type” menu to choose “PDB files”. Click on your coordinate file, in this case, 1iep_ligandH.pdb, and click “Open”. ADT will read the coordinates, add charges if necessary, merge non-polar hydrogens, and assign appropriate atom types. At this point, the ligand will be displayed in the viewer window, with aromatic carbons in green. Click “OK” on the popup to continue.

VITAL STEP Prepare a PDBQT file by selecting “Ligand->TorsionTree->DetectRoot”, this will define the center of the torsion tree. Selecting “Ligand->TorsionTree->ChooseTorsions” will launch a window that allows choice of torsional degrees of freedom. Rotatable bonds are in green, rigid portions are in red, and potentially rotatable bonds that are currently set as “not rotatable” (such as the peptide bond at the center of imatinib) are in magenta. Clicking on bonds will switch the rotation flexibility on and off. When finished, click “Done”. Click “Ligand->Output->SaveAsPDBQT”, then select “Save” to write the file 1iep_ligandH.pdbqt.

If your coordinate set does not include hydrogen positions, click “File->Read Molecule” and choose your coordinate file. Then, by clicking “Edit->Hydrogens->Add”, you will add all hydrogens by default. Select “Ligand->Input->Choose” to choose the ligand molecule

Error Detection
Generate the receptor coordinate file. A receptor coordinate file with all hydrogen atoms is required. If you are using experimental structures (for instance, from the PDB), use a text editor to remove water, ligands, cofactors, ions, etc. that should not be included in the receptor. The file 1iep_receptorH.pdb is provided for use as a tutorial for this protocol andit includes receptor coordinates taken from PDB entry 1iep. Open the file by

selecting "Grid->Macromolecule->Open", use the "Files of type" menu to choose "all files". Click on your coordinate file, in this case, 1iep_receptorH.pdb, and click "Open". ADT will read coordinates, add charges, merge non-polar hydrogens, and assign appropriate atom types. Click "OK" to accept the changes. A window will pop up to write the PDBQT file. Click "Save" to write a file 1iep_receptorH.pdbqt

Error Detection

If your coordinate set does not include hydrogen positions, Click "File->Read Molecule" and choose your coordinate file. Then, selecting "Edit->Hydrogens->Add" will add all hydrogens by default. Click "Grid->Macromolecule->Choose" to choose the receptor molecule.

Methods for Docking Simulation

Once receptor and ligand coordinates are formatted, the AutoDock suite provides a number of methods for docking simulation. This protocol includes six methods, ranging from a simple docking to advanced methods, as described in the following table.

Option	Method	Description
A	Single docking experiment with AutoDock Vina	Basic docking method for study of a single ligand with a single receptor
B	Single docking experiment with AutoDock	Basic docking method for study of a single ligand with a single receptor, with explicit calculation of affinity maps.
C	Virtual Screening with Raccoon2 and AutoDock Vina	Virtual screen of a library of ligands with a single receptor, often used for drug discovery
D	AutoDock Vina with Flexible Side Chains	Docking method for a single ligand with a single receptor, incorporating limited receptor flexibility
E	Active Site Prediction with AutoLigand	Method for analysis of receptor binding sites, for prediction of drugable sites
F	Docking with Explicit Waters	Advanced docking method for a single ligand with a single receptor incorporating explicit bridging water molecules

Result And Disscussion

Molecular Docking reaults show that selected ligand showing least energy confirmation which indicates good docking. The molecular docking studies with inhibitor into the binding cavity of target showed that autodock has more binding affinity with better docking score. The results of this current study can be useful for the design and development of new drug inhibitor that can accordingly be used to manage disease.

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