Protein-ligand docking using the AutoDock suite of programs

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Introduction

The goal of this project was to dock 46 sesquiterpine lactones into the active site of various conformations of 9 different proteins using the AutoDock suite of programs from the Scripps research institute. This required researching the active site of each protein, preparing the protein PDB files in AutoDockTools (ADT) and then running two programs called AutoGrid4 and AutoDock4. In some cases it was beneficial to use a utility of ADT called AutoLigand. These programs/utilities will all be described, and the results of the docking will be shown. At the end of this project an alternative to AutoDock4 and AutoGrid4, called AutoDock Vina was found and was also evaluated.

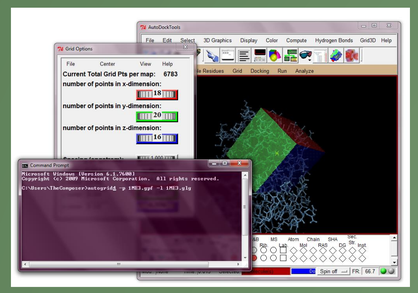

Figure 1: A general view of the AutoDock suite being used. In particular the AutoGrid portion.

Background

Ways to save humans from disease have always been at the forefront of scientific goals. Some current diseases lacking consistent and safe cures are Chaga's Dissease and African Sleeping Sickness. These diseases are caused by two strains of the Trypanosoma bacteria Cruzi and Brucei, respectively. So it is of interest presently to find a way to kill these bacteria without harming humans in the process. Recently, it has been shown that a series of sequiterpine lactones will bind to the active site of key proteins in the parasites life cycle. We know that these lactones have been shown to be anti-parasitic; however, the way in which the molecules bind and the strength of the binding is not exactly known. In order to narrow down the actual experimenting, 46 lactones were experimentally docked into 8 different proteins (in various conformations) in an attempt to narrow down which lactones do and do not strongly bind to a particular protein.

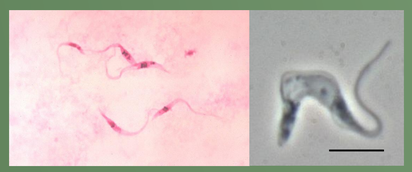

Figure 2: Trypanosoma Cruzi on the left and Brucei to the right

Conclusion

Now that the dockings have been run in AutoDock, the data needs to be compared to the original data that inspired the project from Dr. Thomas Schmidt of The University of Muenster. In addition the runs should be compared to runs done in AutoDock Vina. These two comparisons will conclude something about the accuracy and would then need to be compared to actual lab experiments for a sort of final conclusion on which docking simulation seems to be the most accurate in these situations. After the most accurate on average docking have been determined that program should also process the ligands against the human protein counterparts of the bacterial proteins to conclude which sesquiterpine lactones will bind to the bacterial proteins strongly over the human counterparts. In the event they bind to the human proteins over the bacterial ones, humans would die rather than the bacteria. Hopefully, the research into these lactones will lead to results in safe cures for Chaga's disease and African sleeping sickness.

AutoDockTools

AutoDockTools, or MGLTools, is a suite of programs created by the Scripps Institute that allow manipulation of proteins and ligands. It allows the user to create flexible residues, denote rotatable bonds, visually inspect the grid, analyze results, and utilize various other tools that aide in the manipulation of molecules.

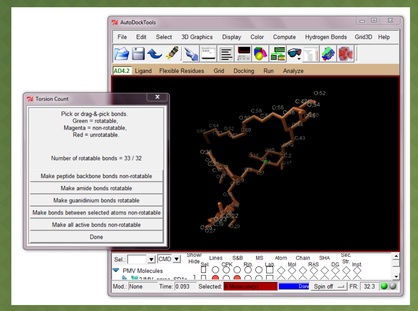

Figure 3: An extremely flexible ligand showing the way ADT deals with rotatable bonds in the ligand.

AutoDock Vina

Vina is a newer alternative to AutoGrid and AutoDock. The program wasn't noticed until the end of the research program. It uses a different algorithm to dock the ligand into the protein and includes the map calculations in the same program as the docking algorithm. It achieves accurate results about two orders of magnitude faster than the time needed to get an accurate solution using AutoDock. However as shown it gives differing solutions sometimes to AutoDock and neither can be said to be more accurate in every situation.

Source:
http://onlinelibrary.wiley.com/doi/10.1002/jcc.21334/abstract

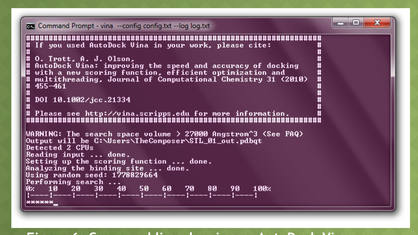

Figure 6: Command line showing an AutoDock Vina run.

AutoLigand

AutoLigand is a utility that that allows the user to inspect areas on a molecule that have a higher possibility of being active sites, and allows the user to inspect the areas visually. This utility can be customized to cover different volumes of area about the surface of the molecule.

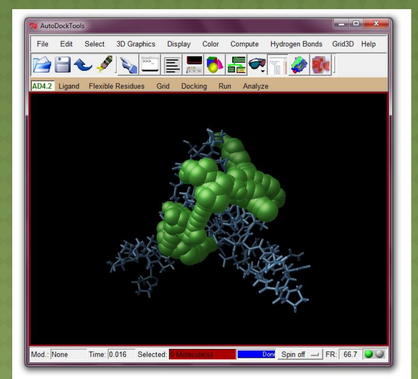

Figure 4: The results of AutoLigand being run on a portion of a protein. This AutoLigand run covers a much larger area than is standard, and shows a likely bonding area on the protein.

AutoGrid & AutoDock

AutoGrid and AutoDock are two executable programs that can be run independently of the ADT Suite; however, ADT can be used to help visualize the commands that can be given in the configuration files for the two programs. Autogrid prepares several files called maps that hold values for all of the differing atoms within each molecule. AutoDock actually performs the docking process/calculation.

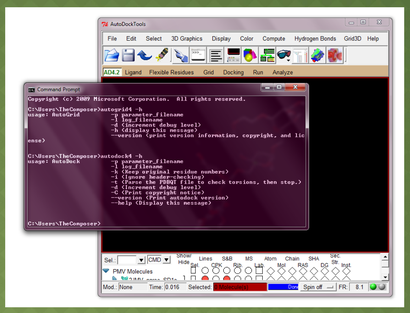

Figure 5: Command line showing both AutoDock and AutoGrid and their relative options.

Analysis & Results

Using ADT it is possible to visually inspect your results and compare conformations that were calculated using AutoDock or Vina.

This shows the results of AutoDock4 and Vina on the first protein and first lactone ligand used (1ME3 protein). The results are not identical and it would be impossible to tell with only this data which is correct or the most correct. However, by running it in multiple simulations in a lab, it can be determined. In either case, this is useful information. One of these two could be the right answer and it gives us insight into a more probable and standardized possibility. This negates the process of attempting each one in a lab and running multiple tests on it. Results like this exist for nearly all of the protein-ligand pairs (excluding some that ran into errors with AutoDock4). Only preliminary work has been done with AutoDock Vina.

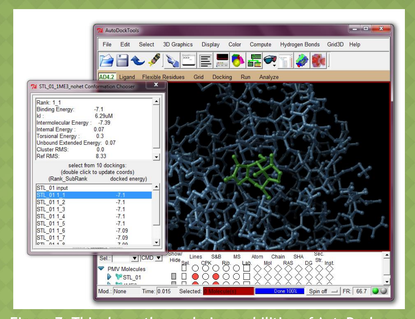

Figure 7: This shows the analysis capabilities of AutoDock runs.

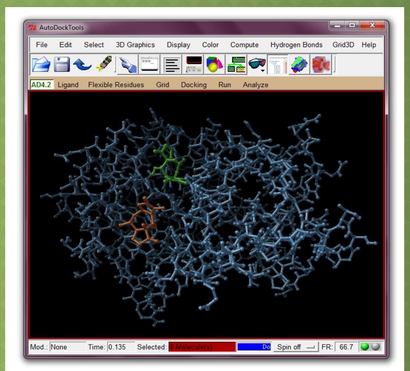

Figure 8: This shows the difference between the results of an AutoDock4 and Vina run on the same molecule. Vina is in orange and AutoDock4 is in green.

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