ANAKIN-ME: Coupled Ligand-Protein Dynamics

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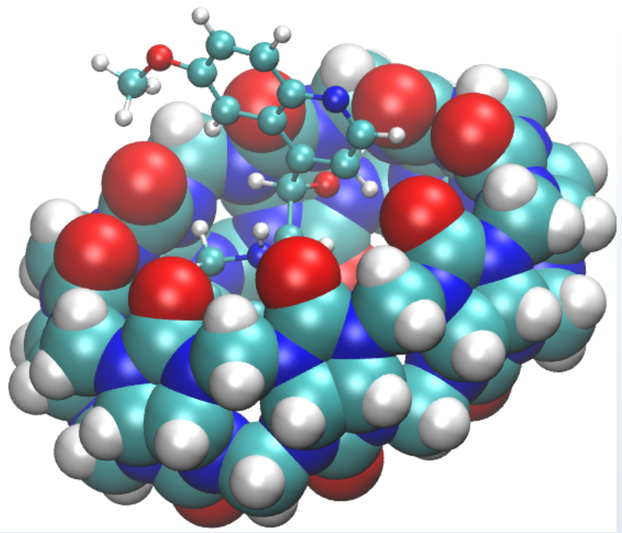
Introduction

Through the study of protein-ligand dynamics, simulations are performed with the intent to enhance the accuracy of drug development. Normally, these simulations are ran using classical molecular dynamics where topologies are fixed. For this project, we instead utilize a new force field, Anakin-ME (ANI), to perform these simulations. ANI was developed with the capabilities of using both quantum mechanical and classical molecular dynamics aspects. This allows the topologies to change throughout the course of the simulation while still performing with near classical speeds. Being trained on a set of Human Genome Databases, we used ANI to predict the forces and energies of our system. We then will run deprotonation simulations to see if we can identify any changes to the topology while under these instances and eventually run binding and unbinding simulations as well. Although ANI is slower than classical MD, we hope this will method pave the way for more accurate simulations to be used during drug discovery.



The system used throughout the project *Host-Guest*

Objectives

- Determine benchmarks for Anakin while running simulations.
- Implement ASE as a runner within WEPY
- Demonstrate through simulations the deprotonation of molecules within the system.
- Further deepen the accuracy within simulations for drug development.

Discussion

From the results of total energy over one picosecond, it was determined from the change in total energy, all time steps would be suited to use for the course of our simulations. Due to the changes in energy being negligible and the time steps chosen not causing significant impact on the energy. This being stated, we chose the two highest femtoseconds as to have faster simulations for our project.

Methods

ASE- Atomic Simulation Environment is used to set up, run, visualize, etc. atomistic simulations

Modules used within ASE are:
- NPTBerendsen: a thermostat to keep temperature constant
- Velocity Verlet: an integrator to keep energy constant

Weighted Ensemble Python (WEPY)
- WEPY is a computer program which uses algorithms to read trajectories and find outliers within them.
- REVO- Algorithm used to which goal is to optimize a function (spread function) which is performed to enhance rare events within simulation. This is set up by a distance metric we give.

$$S = \sum_i \sum_{j>i} (d_{ij})^{d-power} \times wtfac_i \times wtfac_j$$

$$DM = \sqrt{alpha} \times \frac{d_1}{d_2} \times \cos\theta$$

Results

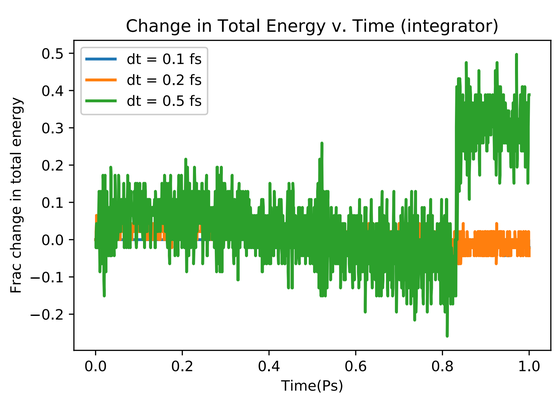


Figure 1. The change in total energy over the course of one picosecond viewed between three different time steps to determine if total energy remains constant. The Velocity Verlet integrator was used.

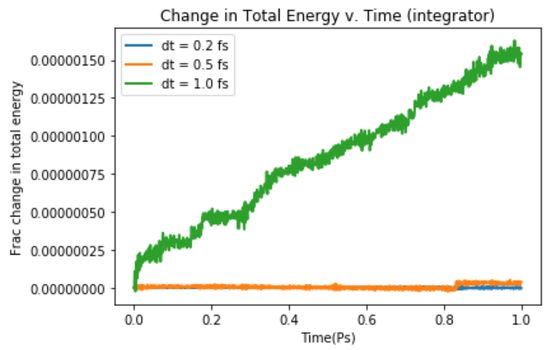


Figure 2. The change in total energy over the course of one picosecond viewed between three different time steps to determine if total energy remains constant. The Velocity Verlet integrator was used.

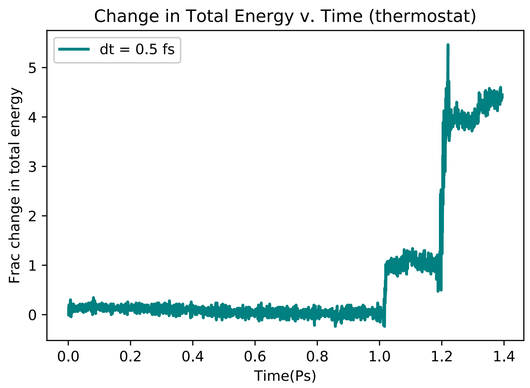


Figure 3. The change in total energy over the course of the simulation with the NPTBerendsen thermostat in place of a total energy integrator. (half a femtosecond)

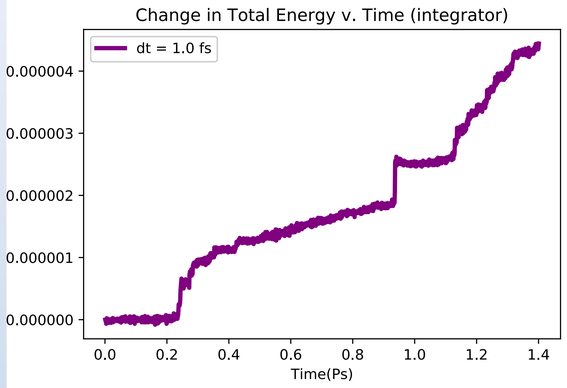


Figure 4. The change in total energy over the course of the simulation with the NPTBerendsen thermostat in place of a total energy integrator. (one femtosecond)

Future Work

After debugging ASE runner within WEPY, there are many opportunities for future work:

Run the deprotonation simulation.
- Implement the distance metric (DM) within REVO to perform deprotonation simulations with our system.
- If determining the distance metric within REVO is not enough to perform the deprotonation, then we can look at making changes to the pH of the system.

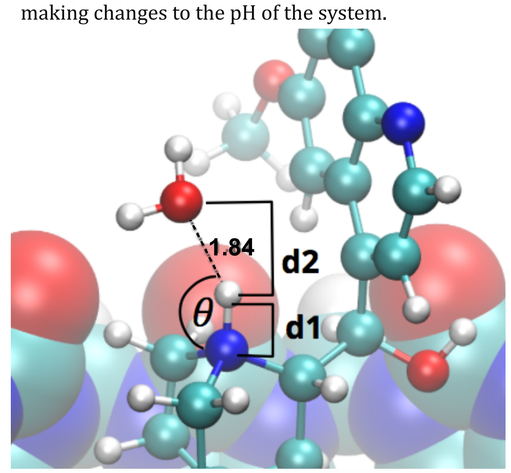
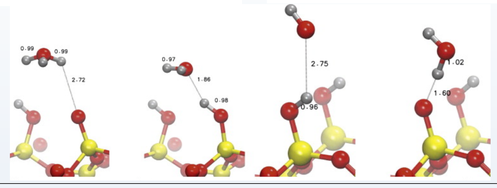


Figure 5. Displays the distance between the donor atom (Nitrogen) , the Hydrogen, and the acceptor atom (OH).

$$H_3O^+ + RO^- \rightarrow H_2O + ROH \qquad OH^- + ROH \rightarrow H_2O + RO^-$$



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