Allosteric Signaling in Proteins: Development of a Molecular Dynamics Based Pipeline

Yizhuang Lin[1,2,4,5] and Kelly M. Thayer[1,2,3]

[1]College of Integrative Science,[2]Department of Mathematics and Computer Science, [3]Department of Chemistry, [4]Quantitative Analysis Center [5]ylin05@wesleyan.edu

Wesleyan University, Middletown CT 06459

Abstract

Allosteric signaling, the phenomenon of an effector molecule to modulate the activity at a distal active site, has been known for some half a century in molecules such as proteins. However, how that signal is transmitted remains a debated topic. One method posited to identify a network of residues transmitting the signal is sector analysis. This identifies a group of residues covarying evolutionarily; these residues are termed a sector. Based on this, our lab has developed a similar method, MD sectors, based on the covariance of the residues in molecular dynamics (MD) simulations. Examining the networks from model systems such as PDZ and p53 has indicated that the networks themselves change based on the liganded state, and we have called upon MD simulations to gain insights into this observation. However, to perform such analysis, the convergence of the simulations is imperative. To this end, our current project focuses on both streamlining our pipeline analysis and evaluating the extent to which convergence has been ascertained. Here, we present the steps used in our analysis, as well as the development of metrics to assess the convergence of the trajectories to ensure the robustness of the conclusions.

Background

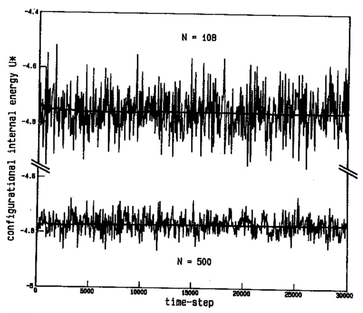

Fig. 1. Magnitudes of internal energy fluctuating within a specific range. N stands for atoms numbers for two Lenard-Jones fluid. [1]

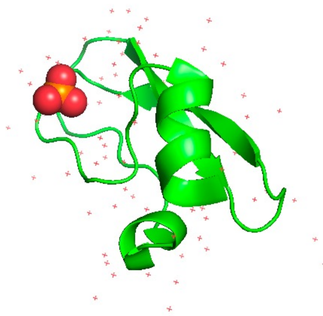

Fig. 2. Performing Molecular Dynamics on BPTI protein (pdbid: 6pti) as a test for pipeline.

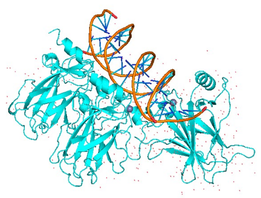

Fig. 3. Previous sector analysis done on p53. MD simulation indicates potential change on liganded state.

Methods

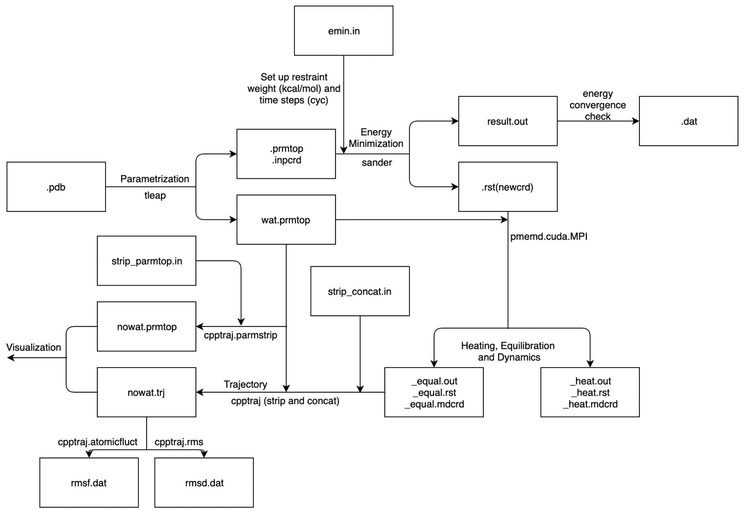

Fig. 4. Pipeline of molecular dynamics simulation running with Amber. Generated trajectory file will be used for various analysis.

Results

Energy Minimization

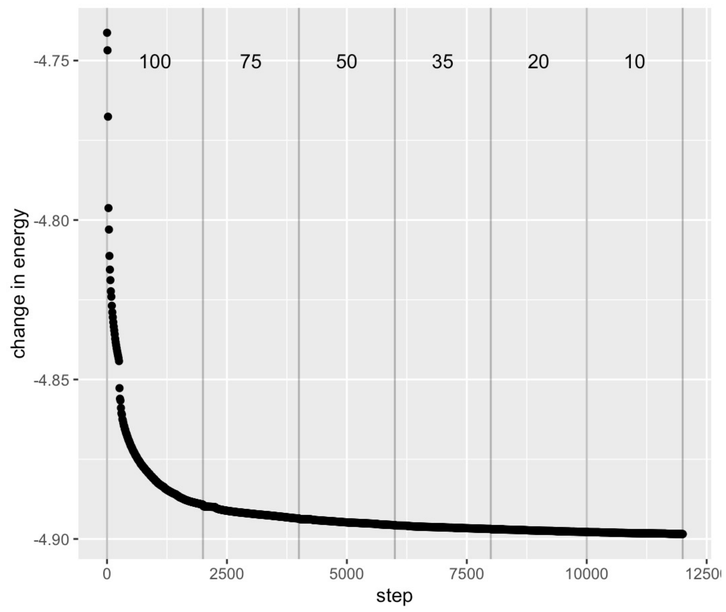

Fig. 5. Energy minimization with 100, 75, 50, 35, 20 and 10 kcal/mol restraint. The semi-log graph of potential energy after 12000 steps of minimization indicates convergence.

References

1. J. M Haile. *Molecular Dynamics Simulation: Elementary Methods*. 208. (1992).

Results

RMSD/RMSF

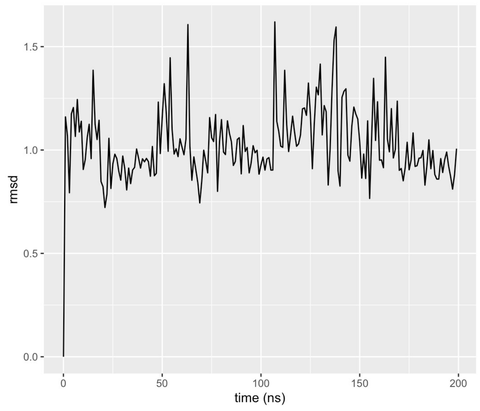

Fig. 6. RMSD value is under 2 for the entire run of the simulation, demonstrating stability in the previous run.

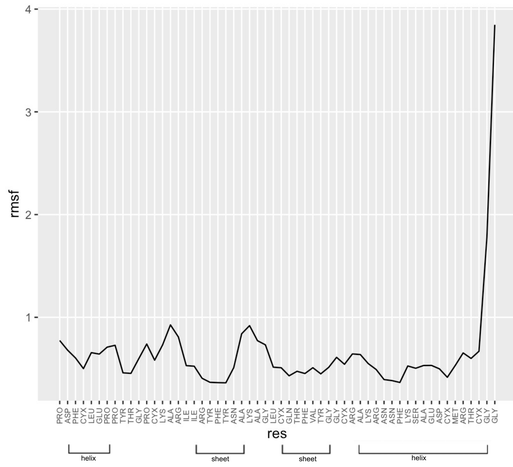

Fig. 7. Average RMSF graph with respect to residual numbers.

Conclusion and Future Directions

- The pipeline runs the molecular dynamics simulation for a simple structure BPTI as well as checking whether each step runs correctly by examining the convergence of energy minimization and mean square deviation/fluctuation of residues in the end result.
- The pipeline will be tested for more complex molecules within the lab, and furthered improved to allow user parametrization.
- Algorithms may be developed to help determine the correct parametrization, alleviating the need for human inspection.
- A potential implementation of graphical user interface.

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