Weighted-Ensemble Brownian Dynamics Simulation

Amanda McCoy, Harvard University
Daniel M. Zuckerman, Ph.D., University of Pittsburgh, Department of Computational Biology

I. Introduction

The ability to determine protein structure has made great advances in recent years due to vast improvements in the technology and techniques of protein isolation. These new developments provide an additional host of coordinate data that is useful for more detailed study of protein function in biology.

However, proteins are dynamic molecules and rarely remain in one conformation, but must move between different conformations in order to function. Unfortunately documentation of all the possible conformational structures a protein might exist in is not yet available. The task of determining the structures of rare protein conformations is daunting, because it is difficult to isolate proteins in their high energy states for a period long enough to acquire an accurate structure. Since the structures of these high energy conformations cannot be determined experimentally, a dynamics simulation is next best option for resolving these mysteries. A variety of dynamics simulation methods have been proposed to capture proteins in their high energy states, yet none have been able to give a satisfactory solution. [1]

Current algorithms for dynamical modeling fail in their inability to simulate a protein for a period long enough to observe a large-scale conformational change. [2] The massive number of parameters and iterations required to accurately model a reasonably-sized protein at atomic resolution are beyond even a supercomputer's processing abilities, and scientists are often "waiting a very long time for an unlikely event to occur." [2]

A real-life example of this problem is the often-studied protein, myosin, a large motor protein responsible for muscle contraction. It binds to filamentous actin and uses ATP hydrolysis as an energy source to walk along the filament towards the positive end. [3] Myosin exists in many conformations, however, only few conformational structures have been determined. However, the beginning and ending conformations of myosin as it travels along its reaction pathway are well-known. With this knowledge and the proper algorithm, it should be possible to dynamically model myosin as it traverses its reaction pathway.

Huber and Kim's weighted-ensemble Brownian (WEB) dynamics simulation method is an appropriate tool to address this problem.

II. Weighted-Ensemble Brownian Dynamics Simulation Model

As discussed above, the problem of attempting to simulate protein dynamics using a standard Brownian method, [4] is that computers cannot generate the number of iterations necessary to reveal a protein changing from one conformation to another in a reasonable amount of computing time. The WEB method is capable of producing the same length of real-time for a simulation as a standard Brownian method, but at a fraction of the computing time (10^{-4} to 10^{-3}). [2] In order to validate the WEB method against a standard Brownian, it is convenient to revert back to one and two dimensional particle systems and then work back up to the larger protein system.

For simplicity, we will look at a two dimensional particle system comprised of an energy barrier and "reactant" and "product" surfaces as a model to investigate the differences between the standard Brownian and WEB methods. The calculation of interest for this two dimensional system is the expected time for a particle to surmount

the energy barrier and reach the product surface. [5] A standard Brownian method demands that each particle trajectory is simulated using successive numeric integrations, thus each trajectory provides the time it takes for the particle to reach the product surface; these times are then averaged to calculate the expected time for a particle to reach the product surface. However, using a standard Brownian method, it is possible that a particle will never surmount the energy barrier and reach the product surface; therefore, it is near impossible to calculate the average value.

The alternative WEB method provides for an initial probabilistic distribution of particles throughout the configuration space. Once the simulation begins, as each particle surmounts the energy barrier and reaches the product surface, it is automatically reintroduced back into the system on the reactant surface while conserving the systems' probability distribution. Different from a standard Brownian method, the value of interest in the WEB method is the steady-state flux of the particles across the product surface. From this value, the expected time for a particle to reach the product surface can directly be calculated. Yet the problem with the WEB method is similar to the one encountered in a standard Brownian method: particles arrive at the product surface too infrequently on the simulation time-scale to calculate an accurate flux. This problem is remedied by endowing particles with smaller statistical weights to allow more particles to surmount the reaction energy barrier on a more reasonable time-scale. Thus, despite the statistically small size of the particles reaching the product surface, it is possible to calculate the flux on a reasonable time-scale. [2]

III. Methodology [2]

There are many ways to go about a WEB dynamics simulation, but the process that we will undertake goes as follows:

- Divide the configuration space into a number of bins of equal size.
- Assign each bin a distinct probability based on the Boltzmann distribution.
- Step particles forward on a general Brownian algorithm.
- At each iteration, reevaluate the probability space and modify (split, combine, or destroy) the statistical weights of particles reemerging on the reactant surface to conserve probability.

IV. Research Objectives

It is our objective to produce a WEB dynamics simulation using the methodology outlined above for the following systems in the order of increasing complexity:

- **Objective 1:** Simulation of a one-dimensional configuration space using 100 bins and 100 particles per a bin.
- **Objective 2:** Simulation of a two-dimensional configuration space using 100 bins and 100 particles per a bin.
- **Objective 3:** Simulation of a dipeptide comprised of two leucines in full atomic detail. We will use an empirical potential model to determine the initial probability distribution of the individual atoms.

For each objective, we will compare our WEB dynamics simulation results to data produced from standard Brownian simulations.

V. Conclusion

Refinement of the WEB dynamics simulation method will provide for in-depth exploration the dynamics of complicated proteins and systems. Soon, it will be possible to simulate proteins and other large systems, far more complicated than dileucine, a powerful lens for examining the protein fundamentals of chemistry and biology. This improved understanding of protein and other system dynamics may prompt new

discoveries in medicine that will provide a better quality of life to all. However, in order to understand the potential that WEB dynamics simulation method will bring to the life sciences communities, small reproductions of the WEB dynamics simulation method, such as the objectives we propose to undertake, must be accomplished before moving on to larger projects. In fact, the WEB dynamics simulation method may soon be capable of resolving the complex, conformational mysteries of myosin.

VI. References

1. Weiss, J.N., Z. Qu, A. Garfinkel. 2003. "Understanding Biological Complexity: Lessons from the Past." *Journal of the Federation of American Societies for Experimental Biology*. Vol 17 (1): 1-6.

2. Huber, Gary A. and Sangtae Kim. 1996. "Weighted-Ensemble Brownian Dynamics Simulations for Protein Association Reactions." *Biophysical Journal*. Vol 70: 97-110.

3. Hofmann, W.A. and P. de Lanerolle. 2006. "Nuclear Actin: To Polymerize or Not to Polymerize." *Journal of Cellular Biology*. Vol 172 (4): 541-552.

4. Northrup, S. H. and H. P. Erickson. 1992. "Kinetics of a Protein-Protein Association Explained by Brownian Dynamics Computer Simulation." *Proc. Nat. Acad. Sci. USA*. Vol 89: 3338-3342.

5. Northrup, S.H. and J. A. McCammon. 1980. Efficient Trajectory Simulation Methods for Diffusional Barrier Crossing Processes. *Journal of Chemical Physics*. Vol 72: 4569-4578.