Conformational Network and Residence Time Estimation of Trypsin-Benzamidine Unbinding Pathways

Alex Dickson*+ and **Samuel D. Lotz** *
*Dept. Biochemistry & Molecular Biology and +Dept. of Computational Mathematics, Science and Engineering
Michigan State University, East Lansing, MI

Introduction

Most molecular events of biological importance take place on time scales which are inaccessible to current simulation methods, such as ligand (un)binding. The development of faster computers and algorithms for sampling the vast conformational landscape of protein systems has begun to make some of these events accessible and deliver dynamical information at an unprecedented level of detail. Dynamic portraits of sampled phenomenon can take the form of conformation networks, whose topology is determined by the pathways taken across conformational space by a system, such as the unbinding of a ligand. This opens up the possibility for predicting kinetic constants from simulation data, as opposed to the thermodynamics determined from the starts and ends of these pathways.

One such kinetic parameter of interest to drug design is the residence time of a drug, which has been shown in some cases to be more indicative of efficacy than the affinity of binding (a thermodynamic quantity). We applied weighted ensemble enhanced sampling (by the WExplore algorithm) to molecular dynamics simulations of the trypsin-benzamidine receptor-ligand model system and observe the ligand unbinding conformational network and estimate the residence time. We estimate residence time to within an order of magnitude, and we discover a novel unbinding pathway.

Conformational Network of Trypsin

The sampled dynamics of trypsin-benzamidine system show 3 distinct pathways for unbinding to occur. The ligand becomes more unbound as the solvent accessible surface area (SASA) of the ligand increases.

Network Communities

Modularity metric confirms intuitively determined regions and uncovers novel regions of potential importance (B* & P3*).

Residence Time Estimates

Across multiple WExplore runs average residence time agrees to within 1 order of magnitude.

Conformational Space

Once the (arbitrary number of) dimensions of the space are determined it is divided up into regions by Voronoi polyhedra.

As trajectories of the system evolve they cross the boundaries to other regions, which is measured by a distance metric. This avoids the need to define explicit reaction coordinates and may not be known or obvious to define.

WExplore: Weighted Ensemble Sampling

Parallel trajectories sample the conformations in each region. As trajectories make it to new regions sampling effort is redistributed while the overall statistical weight is rebalanced and kept normalized. This allows observation of high free energy regions.

Network Construction

Once trajectory data is collected it is clustered by some meaningful metric related to the process. This greatly reduces the dimensionality of the data.

Clustering

After clustering, the sum of the weights in each cluster determines the weight of the node and the number of interconversions the edge weight, defining the conformational network.

Weight Assignments

Low Probability Pathways Discovered

The WExplore algorithm is able to detect unbinding pathways of very high free energy. While the lowest free energy pathway (P1) is the most important, at long time scales high free energy pathways (P2 & P3) may also be important.

Literature Cited

1. Dickson, A., & Brooks, C. L. (2014). J Phys Chem B, 118(13)
2. Beauchamp, K. A., et al. (2011) Journal of Chemical Theory and Computation, 7(10).
3. Huber, G. A., & Kim, S. (1996) Biophys J, 70(1).
4. Copeland, R. A. (2016). Nat Rev Drug Discov, 15(2), 87–95.
5. Blondel, V. D., et al. E. (2008). Journal of Statistical Mechanics: Theory and Experiment, 2008(10), 10008.
6. Guillain, F., & Thusius, D. (1970). Journal of the American Chemical Society, 92(18).
7. Dickson, A., Tiwary, P., & Vashisth, H. in press