Alex Dickson

Assistant Professor, Departments of Physics and Astronomy, CMSE, and Department of Biochemistry and Molecular Biology
alexd@msu.edu | 517.884.8985 | 603 Wilson Rd., Room 316

BIO SKETCH

Alex Dickson joined the Michigan State University faculty in 2015, with joint appointments in the Department of Computational Mathematics, Science and Engineering, and the Department of Biochemistry and Molecular Biology.

Dr. Dickson received his Ph.D. from the University of Chicago under Prof. Aaron Dinner. There he developed new computational approaches to enhance the sampling of simulations that are driven out of equilibrium. Applications spanned from biomolecular systems, such as an RNA unfolding in a flowing solvent, to model systems from physics, such as sheared Ising models.

In 2011, he began as a postdoctoral researcher with Prof. Charles L. Brooks III at the University of Michigan, where he continued developing new enhanced sampling methods for application to atomistic biomolecular systems. A novel method, "WExplore," allows for enhancement of sampling in an undirected fashion, and has been used to observe a wide variety of rare biomolecular phenomena. He also developed a set of analysis techniques that can help visualize the entire space of possible biomolecular conformations in a network plot.

RESEARCH INTERESTS

Intrinsic disorder in molecular systems; protein-protein interactions; drug design; molecular dynamics; rare event modeling; network theory; non-equilibrium processes

LAB(S)/GROUP(S)

Dr. Dickson's group will employ a wide range of computational tools to address fundamental questions in molecular biology and medicinal chemistry. Using approaches that explicitly simulate the motions of drug receptors, his group will: find small molecules (drugs) that are designed to block flexible protein-protein interaction sites, and examine off-target binding of currently approved drugs to flexible protein sites that are critical to cell function.

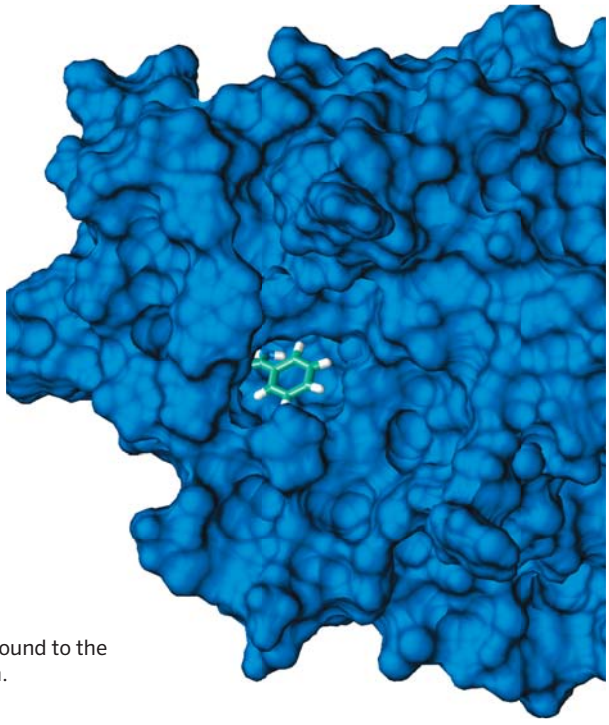

FIGURE 1. Benzamidine bound to the binding pocket of trypsin.

WEBSITE

https://cmse.natsci.msu.edu/directory/faculty/alex-dickson/

COLLABORATORS

J. Karanicolas (Kansas), W. Pomerantz (U. Minn.), D. Hatters (U. Melbourne)

CURRENT RESEARCH FOCUS

At the atomic level, the molecules in our bodies are in constant motion, and are undergoing constant change. The motions are incredibly rich; they range from the isomerization of side-chains, to the formation and destruction of large intermolecular complexes, to the birth and death of the molecules themselves. A deep understanding of these motions can radically improve our understanding of health and disease through rational design, where drugs target specific receptors, which are chosen for a specific molecular impact.

In my lab I use computational techniques such as molecular dynamics to simulate the motions of biomolecules (protein, RNA, and DNA). These numerical experiments extend our knowledge beyond the "snapshots" provided by x-ray crystallography and NMR, and provide the entire landscape of conformations accessible to a molecular system. My goal is to use this technique to gain a deep understanding of the binding of small molecule drugs, which will be used to design small molecule therapeutics.

I also use larger-scale network models of biological processes to gain an understanding of processes that involve many different molecular species, such as chaperone action in the cell. This allows a much broader reach, and can synthesize findings from simulation and experiment into a coherent biological model. Working in both worlds simultaneously allows for a multiscale disease-targeting strategy that is detailed enough to capture atomic-level perturbations, and broad enough to capture the cell-level consequences of disease.

1. Accessing complete binding and unbinding pathways of drugs to receptors. Historically, drug-receptor interactions were studied using static techniques, such as docking, where a small-molecule drug is fit into a binding pocket like a puzzle piece. In addition to the fully docked state, there are many other transient drug-protein conformations that can impact the kinetics of the binding process. Unbinding from a pocket is

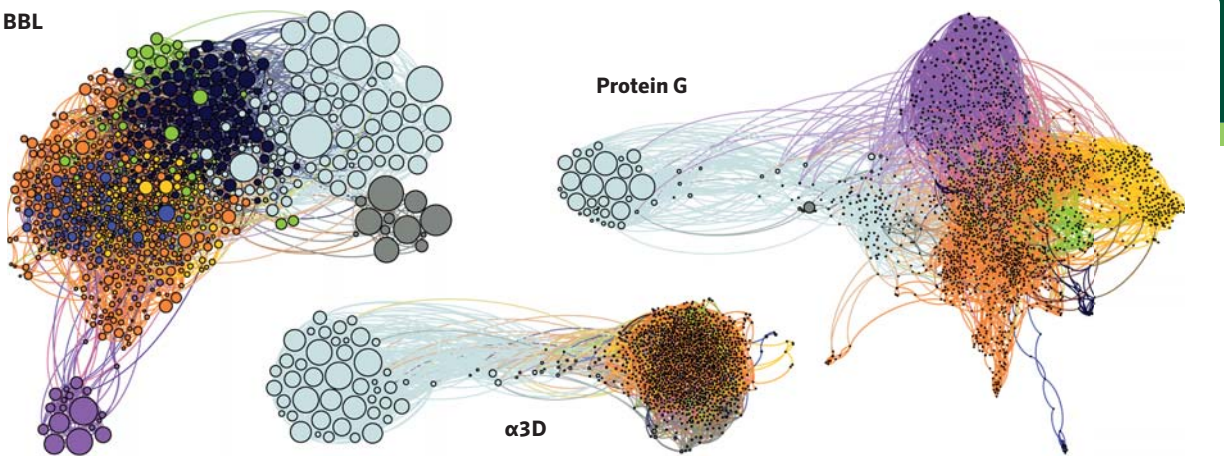

FIGURE 2. Conformation space networks of three fast folding proteins. The light blue states are folded, and the other colors make up the unfolded ensemble.

an extremely rare event that occurs on a long timescale; only recently have full, unbiased unbinding pathways been captured, and for only a very small number of systems.

Using an enhanced sampling method I developed ("WExplore"), we can generate unbinding pathways without using a biasing potential. We can determine the kinetics of unbinding, as well as the set of relevant transition states that can determine kinetics. As this technique is based on the parallelization of multiple trajectories, it is also much more parallelizable than standard "vanilla" molecular dynamics, and ready to exploit large-scale computing infrastructures.

In addition to visualizing known drug-receptor interaction pathways, WExplore can also be used for drug design. This goes far beyond docking-based approaches, and takes advantage of the entire ensemble of ligand-accessible protein conformations.

2. Visualization of entire free energy surfaces with conformation space networks. After any large molecular simulation is performed, another challenge presents itself: how do we analyze and digest the massive quantity of data produced? Using clustering techniques and network modeling, I employ conformation space networks to visualize entire free energy surfaces. The nodes of these networks represent specific molecular conformations, and the links (or "edges") in the network show which conformations can interconvert. As the network graph is created, nodes that interconvert are pulled together, and others are pushed apart, which reveals the underlying structure of the free energy landscape without having to project onto a chosen set of variables.

This gives us new ways to visualize dynamics, providing an easy way to judge the impacts of different environmental factors such as pH, temperature, or molecular crowding.

3. Connecting outward from molecular simulation. Experimental advances in parallel data collection and the standardization of data have led to a "database culture": databases of protein-protein interactions, genetic diversity across populations, drug-protein interactions, somatic mutations in cancers, and biological pathways are all freely-available, and constantly growing. However, although advances in molecular dynamics extend our ability to determine thermodynamic and kinetic information for one- and two-body systems, methods to extend these results to their many-body, biological consequences are not well-developed.

In my lab I aim to incorporate kinetic data from simulation into biological reaction network models. This will fundamentally extend the reach of simulation to larger timescales and system sizes by building up holistic models from individual reaction components. By using simulation to calculate intermolecular reaction rates, we obtain a view of the interactions at unprecedented detail. This allows perturbations to the on- and off-rates resulting from genetic mutation to be estimated using a Hamiltonian perturbation technique, and allows key transition states to be identified and targeted for inhibition by small molecules.

In the long term, this strategy will allow for a connection of genotype to phenotype, which could provide a pathway to knowledge-based personalized medicine.

RECENT PUBLICATIONS

A. Dickson, L.S. Ahlstrom, C.L. Brooks III, "Coupled folding and binding with 2D Window-Exchange Umbrella Sampling," *Journal of Computational Chemistry* (2015).

A. Dickson, A.M. Mustoe, L.S. Salmon, C.L. Brooks III, "Efficient in silico exploration of RNA interhelical conformations using Euler angles and WExplore," *Nucleic Acids Research*, vol. 42, pp. 97–110 (2014).

A. Dickson, C.L. Brooks III, "WExplore: Hierarchical Exploration of High-Dimensional Spaces Using the Weighted Ensemble Algorithm," *Journal of Physical Chemistry B*, vol. 118, pp. 3532–3542 (2014).

A. Dickson, C.L. Brooks III, "Quantifying Chaperone-Mediated Transitions in the Proteostasis Network of *E. coli*," *PLoS Computational Biology*, vol. 9, pp. e1003324 (2013).