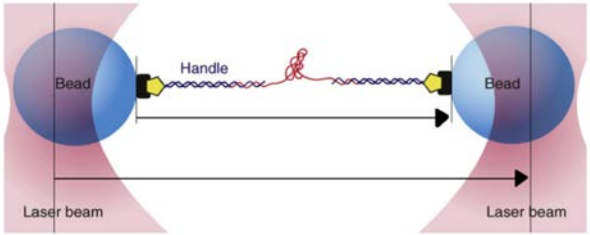
Nonequilibrium Optimization in Single-Molecule Pulling Experiments

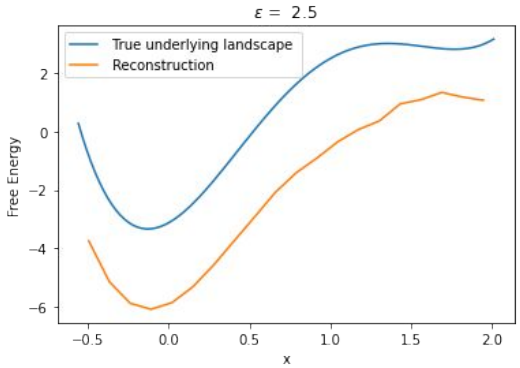
Zofia Adamska[1], Megan C. Engel[2], Michael P. Brenner [2]
[1]California Institute of Technology, [2]Harvard University

Complex biomolecules must fold into specific shapes to carry out their functions. Understanding this folding process has profound implications for drug design and treatment of many diseases. Viewing this problem through the lens of statistical physics provides us with a framework in which the folding process is treated as a search through a free energy landscape, where the minima correspond to the most probable configuration of the biomolecule.

The simplest experiments used for obtaining free-energy landscapes involve applying a constant tension and pulling the molecule between two stable configurations whilst still in equilibrium. However, some molecules have very high energy barriers, making the equilibrium experiments impractical. In these cases, we can implement non-equilibrium methods based on the Jarzynski equality. The estimates obtained with these methods have errors which can be minimized by finding optimal protocols that describe the velocity of pulling the molecule during the experiment. Using Automatic Differentiation (AD) and Molecular Dynamics (MD) simulations, we found optimal protocols for devising free-energy landscapes of DNA hairpins. We verified that our approach yields reliable results by reproducing findings of papers that used different methods.

Compared to these previous methods, our approach works for more complicated systems that can be driven farther from equilibrium. We then devised an iterative algorithm that uses simulations along with experiments in order to improve the accuracy free energy landscapes reconstructions.





Reconstructing free-energy landscape from a single-molecule pulling experiment. Top image taken from Woodside, M. T., García-García, C. & Block, S. M., 2008.

Nonequilibrium Optimization in Single-Molecule Pulling Experiments

Zofia Adamska[1], Megan C. Engel[2], Michael P. Brenner [2]
[1]California Institute of Technology, [2]Harvard University

Zofia Adamska is a rising sophomore at Caltech, majoring in Physics and Mathematics. After graduation, she plans to pursue a Ph.D. in theoretical physics.

I have had an amazing experience during the REU program this summer. My group consists of very passionate individuals who inspired me to keep unraveling the mysteries of our universe. My mentor has provided me with great support and invaluable insights. Through my research, I have deepened my knowledge of statistical mechanics and learned how to apply it to biological systems. I have also gained more experience in machine learning and molecular dynamics simulations. Altogether, the program has helped me grow as a person and a scientist, and I'm incredibly grateful for all the opportunities that it has offered.

Zofia Adamska (left) with her research mentor, Megan Engel (right), in front of a blackboard in Pierce Hall, Harvard.