

# Elucidating the Structural Dynamics of Proteins by Simulations

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All-atom molecular dynamics simulations provide a vehicle for capturing the structures, motions, and interactions of biological macromolecules in full atomic detail. Recent years have seen substantial advances in both the timescales accessible to molecular dynamics simulations and in the quality of the force fields used in such simulations. Together, these developments have led to dramatic improvements in the ability of molecular dynamics simulations to capture the structure and dynamics of proteins.

Access to longer timescales and the improved sampling of conformations has been enabled by progress in a number of areas. I will in particular focus on how a specialized computer for molecular dynamics simulations, called Anton, has allowed us to access long-timescale (up to 1 millisecond) dynamics in proteins using all-atom simulations with an explicit representation of solvent molecules.

The last five years have also seen substantial improvements in the force fields used in molecular dynamics simulations. In this area, NMR spectroscopy has played a central role by providing a wealth of experimental data reporting on a broad range of structural and dynamical properties of peptides and proteins; such data are ideally suited to validate molecular dynamics simulations.

Having access to long and accurate molecular dynamics simulations, it is in turn possible to provide new insight in to the dynamical properties of proteins. In the case of folded proteins, I will describe how our millisecond-long simulations of two proteins, BPTI and ubiquitin, have provided insight in to the long-timescale dynamics of proteins. Historically, it has been difficult to obtain accurate and well-converged unbiased all-atom molecular dynamics simulations of unfolded proteins, and I will also describe our results on gauging the ability of state-of-the-art simulations to probe the structural dynamics of unfolded proteins.

In the area of protein folding, we have used simulations to describe the general principles of how fast-folding proteins fold. In simulations of 12 structurally diverse proteins, representing all three major structural classes, we observe the proteins to spontaneously and repeatedly folded to their experimentally determined native structures. I will present the results of the analyses we performed to identify the common principles that underlie the folding of these proteins.