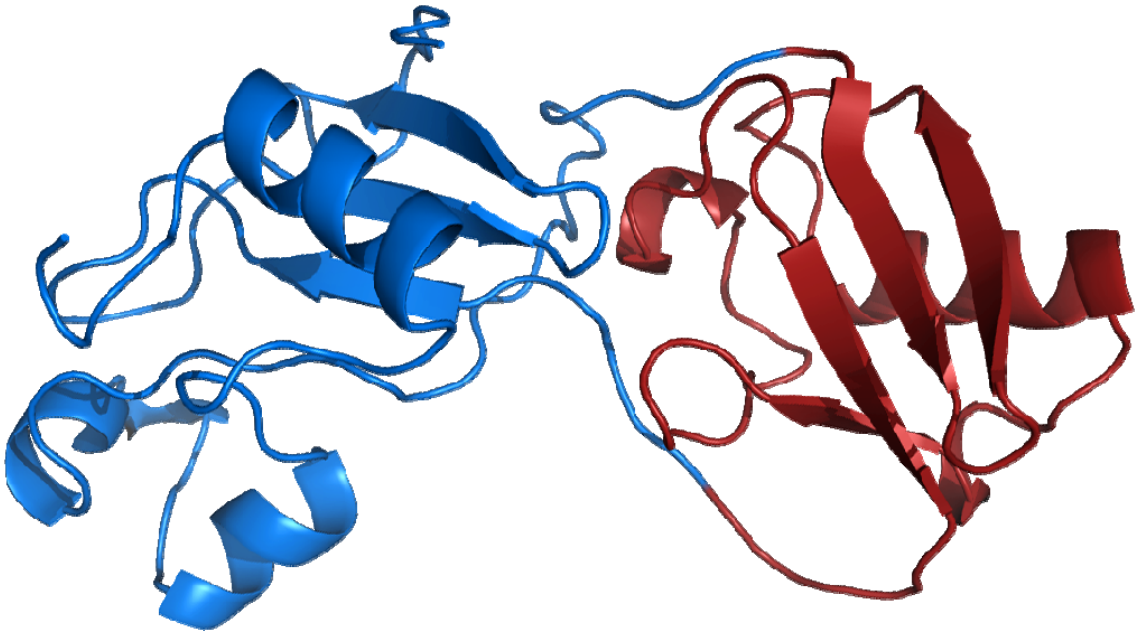
Mechanically-Induced Unfolding in All-Atom Simulations of a Molecular Switch

Brandon M Mills, Lillian T Chong
University of Pittsburgh

Enzymatic proteins have their activity tightly regulated, often via conformational switching (shape-changing) events which can turn them on or off in a reversible fashion. A change in shape at one location on a protein can induce a change at another location. The Loh Group at SUNY Medical School has engineered a model system for studying such changes in molecular switches by inserting a guest protein (ubiquitin) into a host (barnase). The two protein domains become coupled and undergo a thermodynamic struggle which is concluded by the mechanically-induced unfolding (and deactivation) of one domain. It has been shown that through changes in environmental conditions or the addition of effector molecules, the unfolded domain can refold by unfolding its competitor. Engineered switches may have practical applications as biological assays.

However, structural information for these molecular switches is limited due to their partially-unstructured nature. Therefore, we have conducted all-atom, unforced Langevin dynamics simulations in order to gain structural insight into the mechanism of mechanically-induced unfolding. Simulations and experiments have shown that placing flexible linker residues between the two domains reduces the degree of coupling between the domains, and also that unfolding is not limited to regions near the domain insertion site.



Pictured: A starting model for the barnase-ubiquitin fusion protein with both domains folded. Simulations allow the tug-of-war between the two domains to commence.