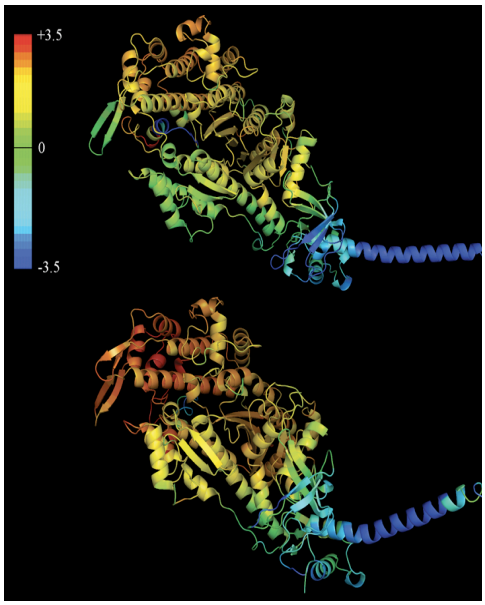
Computational Physics: Discovering simplicity in complexity – Professor Donald Jacobs

My research is primarily concerned with applying statistical and computational physics to model and investigate thermodynamic, mechanical and dynamic properties of proteins and polypeptides in solution, and to study the thermodynamic properties of aqueous solutions. Proteins are macromolecular machines that carry out biological functions in living organisms – making them an important biomolecule to study because their existence is critical for supporting life on Earth.



Comparing the dynamical motions in myosin V that are exhibited in two stable conformational states along the pathway for the transduction of chemical energy to mechanical work.

Understanding how proteins function in terms of its structure and its detailed dynamics as a physical process resulting from intramolecular interactions and its interactions with solvent is a necessary step toward the ability to perform molecular engineering with applications to drug discovery. For example, molecular dynamic simulations are performed to wiggle protein and solvent atoms to detect correlated motions. One approach is to integrate equations of motions described by Newtonian mechanics. For numerical accuracy, the integrating time step must be in femtoseconds, requiring more than 10^{12} numerical integration steps to probe the motion of each atom on a millisecond time scale. Such a trajectory represents one instance of possibilities. From a large number of such trajectories, thermodynamic properties can be calculated. While this brute-force method is ideal to study motions on short-time scales, it is inefficient to get thermodynamic response. But is this the only way?

My research program has developed a novel modeling scheme (two US patents recently issued) to accelerate this sampling process by using mechanical constraints to model molecular interactions. The approach allows for rapid estimate of the conformational entropy without requiring explicit simulations. This is achieved by constructing a free energy functional involving probabilities for various fluctuating constraints to be present or not, and minimizing this functional numerically. By feeding the information about fluctuating constraints into geometrical simulation yields a complete picture of conformational motions and quantitative stability/flexibility relationships. Herein, the discovered "simplicity" found in the protein/solvent system that exhibits complicated behavior is *network rigidity* – a long-range mechanical interaction. By using rigidity theory, otherwise hidden mechanical correlations are identified, making it possible to rapidly calculate the free energy landscape of a protein as a function of thermodynamic/solvent conditions. Knowing mechanical correlations at the atomic level allows the non-additive *free energy reconstitution* (FER) of energy and entropy components defined in terms of pre-calculated model parameters based on a *free energy decomposition* (FED) scheme. Interestingly, the model parameters renormalize to different values as a result of interactions between component parts. This idea is similar in spirit to how the electron mass renormalizes from its bare value in free space to an effective value when it is in a crystal depending on direction of motion due to its interactions with other electrons & phonons. The calculation is very rapid because as a general rule it is best to use as many pre-calculations and partial analytical results as possible. Finally, with the free energy landscape readily available, long-time motions are simulated efficiently via free energy driven geometrical simulation. Myosin (top right picture) is a large motor protein that is difficult to explore its motions using brute-force simulation. Many research projects are available to study conformational pathways to identify thermo-mechanical mechanisms governing energy transduction in different classes of myosin proteins, and with disease causing mutants. More projects include similar studies on other proteins and study of solvent properties.