

Motion defines us. We must dynamically respond to our environments in order to survive and become the bustling, adapting, moving creatures that we are. Mechanochemical enzymes, i.e. enzymes that convert chemical energy into mechanical energy, mediate cellular motion. In muscle, the motor protein myosin uses the energy derived from ATP hydrolysis to generate force along filamentous actin, ultimately producing muscle contraction. The structural mechanism of energy transduction in muscle, with an emphasis on ***myosin structural dynamics***, is the focus of my research.

Why study molecular dynamics? Macromolecules sample a rich diversity of structures whose relative stabilities and transitions between are dictated by their energy landscapes. The shape of the landscape is determined not only by the sequence of structural building blocks (amino acids, nucleotides, etc.) but also by interplay with other macromolecules and the chemical environment. Macromolecules and their complexes are in constant motion, with measureable, functionally significant structural fluctuations occurring on the femtosecond to microsecond timescales. Atomic level structure determination by nuclear magnetic resonance (NMR) and X-ray crystallography has undoubtedly led to great insights into the relationship between structure and function. However, to limit discussions of structure to isolated structural states is an oversimplification that diminishes our ability to understand and predict macromolecular function. It is crucial to move beyond static structural views toward a view that encompasses ***dynamic disorder and structural disorder*** of both macromolecules and their complexes.

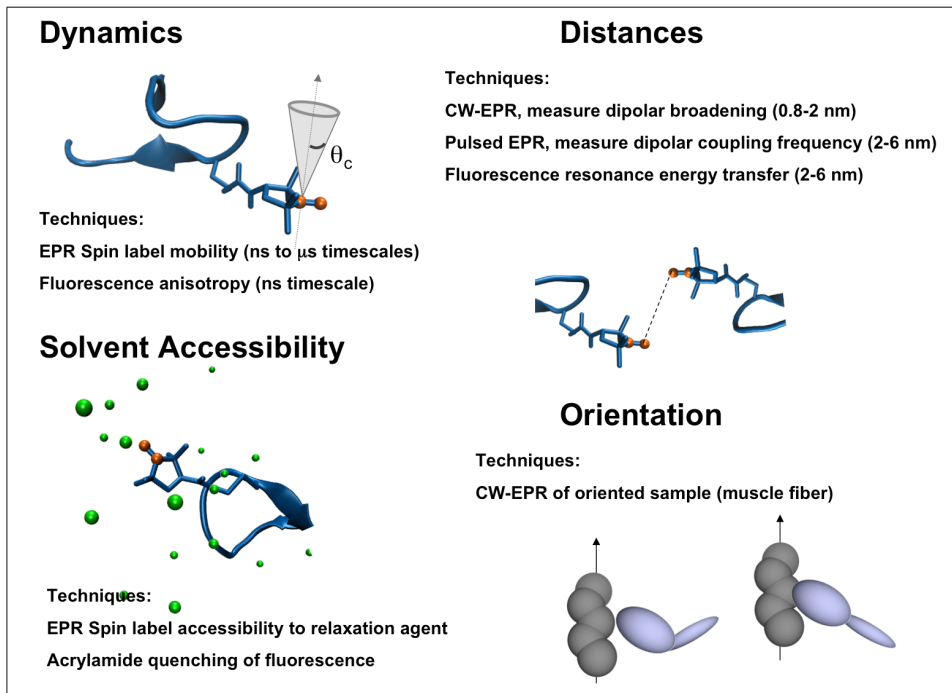


Figure 1. Spectroscopy experiments are used to measure protein structure and dynamics, even in large complexes.

**Spectroscopy.** We specialize in biophysical techniques that can be used to measure Å-resolution structure, molecular dynamics, and static disorder under biochemical conditions challenging or impossible to achieve using X-ray crystallography (membrane-embedded proteins, protein complexes, muscle fibers) or NMR (large proteins, protein complexes). Site-specific labeling in combination with electron paramagnetic resonance (EPR) and/or fluorescence spectroscopy can be used to measure biophysical properties of proteins that include nanometer distances, solvent accessibilities, and nanosecond to microsecond dynamics. Our approach to creating proteins containing site-specific labeling sites includes site-directed mutagenesis combined with robust protein expression systems. In order to test and refine existing structural models, we have developed tools to simulate spectroscopic data from molecular dynamics trajectories of labeled proteins. This method has been successfully used to detect and resolve multiple protein structures in solution, muscle fibers, and membranes, yielding a more comprehensive understanding of the relationships between structure, function, and molecular/cellular environment.

## Selected Abstracts and Publications

**Klein, Jennifer C.**, Piechowski, Nicole, Titus, Margaret A. and David D. Thomas (2010) Structural Impact Of Myosin Methionine Oxidation. *Biophysical Journal*, Volume 98, Issue 3, Supplement 1, January 2010, Page 145a.

**Klein, Jennifer C.**, Lin, Ava Yun, Titus, Margaret A. and David D. Thomas (2009) Myosin II Trapped In A Weak Actin-binding State Through A Chemical Crosslink Across The Actin-Binding Cleft. *Biophysical Journal*, Volume 96, Issue 3, Supplement 1, February 2009, Page 492a.

**Klein, Jennifer C.**, Burr, Adam R., Svensson, Bengt, Kennedy, Daniel J., Titus, Margaret A., Rayment, Ivan, and David D. Thomas (2008) Actin-Binding Cleft Closure in Myosin II Probed by Site-Directed Spin Labeling and Pulsed EPR. *PNAS*. 105(36): 13397-13402.

**Klein, Jennifer C.**, and Thomas Sibley (2003) Taking the Sting out of Wasp Nests: A Dialogue on Modeling in Mathematical Biology. *College Mathematics Journal*. 34(3): 207-215.

## Current Projects:

### Experimental Biochemistry and Molecular Biophysics

We cannot survive more than minutes without oxygen—nor have we escaped vulnerability to oxidative stress. **Disease and biological aging** are familiar contexts in which the role of **oxidative ‘damage’** to DNA, lipids, and proteins has been recognized, even popularized by the promotion of antioxidants for longevity and disease resistance. Under normal conditions, too, cells sensitively detect and respond to cellular redox state to maintain balance. Our goal is to understand **how molecules sense, respond, and are eventually damaged by oxidative stress**.

We will examine how post-translational protein modifications associated with oxidative stress **trigger functional and structural changes** in the proteins involved in **muscle contraction**. We will also test the role of antioxidant systems in recovering protein function after oxidative modification.

Undergraduate projects will focus on the impact of oxidative stress on **protein structure and function** using a variety of

techniques that include molecular biology to create proteins for site-directed spectroscopy, *Dictyostelium* cell culture and protein expression, carrying out biochemical assays, mass spectrometry and biophysical spectroscopy.

Qualifications include pursuit of a degree in biology, chemistry or physics.

### Computational Biochemistry

Undergraduate projects include carrying out **molecular dynamics simulations** of muscle regulatory and contractile proteins. The project will involve *in silico* modeling of post-translational modifications, molecular dynamics simulations, and the option to carry out related experiments in the laboratory. The oxidative modifications we will study are related to the progression of **biological aging, skeletal muscle disease and heart disease**.

Qualifications include pursuit of a degree in biology, chemistry, physics or mathematics/computer science, with a strong interest in computational biology.

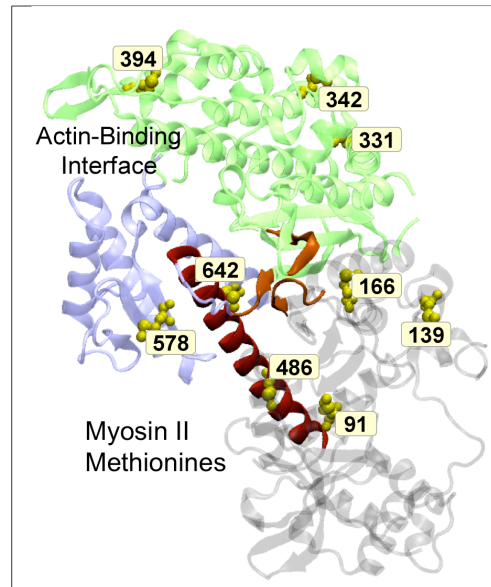


Figure 2. Myosin methionines (yellow) are targets of oxidative modification.