Tarakanova Group Undergraduate Research Projects – Fall 2018

Principal Investigator: Prof. A. Tarakanova

Our group specializes in molecular modeling & simulation to study biomaterials, biomechanics and biophysical processes associated with the body's function in health and disease. We are always interested in mentoring self-motivated undergraduate students from diverse backgrounds.

Interested students should email a resume/CV and a brief cover letter to anna.tarakanova@uconn.edu indicating which project(s) they are interested in and why they would be a good match for their chosen research. Please indicate whether you are interested in the Fall semester or both Fall & Spring.

Project #1: Cracking Protein Clumps

Amyloids are sticky protein aggregates linked to the development of dozens of diseases, including Type II diabetes, Alzheimer's and Parkinson's. Amyloid plaques form from many different proteins and polypeptides, folding into well-ordered nanofibrils, disrupting the function of healthy tissues and organs. Recent work has identified that metabolites, small molecules produced as intermediate products of the body's metabolic processes, may also undergo amyloid-like aggregation, though they are much smaller than proteins associated with amyloid fiber formation. For example, physiological accumulation of the amino acid phenylalanine in body tissues, urine, and plasma is associated with phenylketonuria (PKU), a single-gene disorder characterized by mental retardation, epilepsy, organ damage and unusual posture. In this project, we will use molecular modeling approaches to build a library of disease-linked, small-molecule metabolites and characterize their propensity for self-assembly into amyloidal nanoarchitectures. Biomechanical properties and stability of the aggregates will be evaluated. Following structural and mechanical characterization, we will build molecular models of metabolite aggregates interacting with the lipid bilayer of the cell to predict cellular toxicity mechanisms.

In this project, the student will gain experience in molecular model development, atomistic modeling, coarse-graining approaches, molecular simulation setup and implementation on supercomputers, molecular visualization software, MATLAB/Python scripting, and scientific writing. The student will have a chance to participate in a collaborative project with an experimental group, and if successful, contribute to a scientific publication.

Project #2: Secrets of the (Extracellular) Matrix

The elasticity of tissues such as blood vessels, lungs, skin and ligaments derives from an interconnected network of elastic fibers spanning extracellular space. Biomechanical requirements of different tissues dictate the tissue-specific arrangement of elastic fibers. These fibers form an insoluble fiber system within connective tissues, and are comprised of a fibrillin-rich microfibril scaffold fixing an elastin protein core. Elastic fibers are formed through a complex process whereby tropoelastin, the precursor to elastin protein, is deposited on preformed fibrillin microfibril bundles. The interaction between

fibrillin and tropoelastin has a key influence on elastic fiber assembly, maturation and resultant biomechanical properties. Recently, an important interaction between a segment of fibrillin 1 and tropoelastin has been identified. In experiment this interaction has been shown to support tropoelastin aggregation and assembly into an elastic fiber. However, the molecular mechanisms of this process remain elusive. In this project, we will develop molecular models of fibrillin 1 and fibrillin 1-tropoelastin complex to identify the structural changes produced as a result of this interaction, and characterize the downstream behavior of elastic fiber assembly, aggregation and molecular mechanics in response to this interaction.

The student will learn to build and simulate molecular and coarse-grained protein models through *ab initio* structure prediction and protein folding, homology modeling, advanced sampling algorithms, and molecular-dynamics-based approaches to characterize large proteins. The student will gain experience in implementing molecular simulations on supercomputers, molecular visualization software, MATLAB/Python scripting, and scientific writing. The student will have a chance to participate in a collaborative project with an experimental group, and if successful, contribute to a scientific publication.

Project #3: Tissue Biomechanics from Bottom Up

Tropoelastin, the precursor molecule of elastic fibers, is one of the stretchiest natural materials. Its molecular structure confers elasticity to the fibers that drive life: lungs that expand and contract to allow breathing, arteries that engorge as blood courses through the body, and pliable skin shielding your organs from the outside world all depend on elastin for their function. Throughout the elastic fiber assembly process (cf. Project #2), significant chemical cross-linking occurs as tropoelastin is deposited onto a microfibrillar scaffold. The presence and distribution of these crosslinks along the full span of the molecule is poorly understood. In this project, we will study how the elasticity of elastin and elastic tissues is regulated by the presence of crosslinks, to examine how local chemistry informs mechanical properties across length scales, starting from the single molecule. The project will involve chemical parameterization of lysine-based crosslinks within a molecular modeling framework and simulations of molecular stretch for mechanical behavior characterization.

The student will learn to build and simulate molecular protein models through molecular-dynamics-based approaches, including molecular force field parameterization, simulation setup and implementation on supercomputers. The student will also gain experience in molecular visualization software, MATLAB/Python scripting, and scientific writing, and if successful, will contribute to a scientific publication.

Project #4: Supernatural Resilin

Nature has engineered some of the most remarkable materials currently known: from seashells of exquisite strength and toughness, to the spider's strong and lightweight spider silk and the grasshopper's rubbery jumper's joints. How can we learn from Nature and build "super-natural" materials for energy harvesting, conversion and storage; for example, hyper-extensible materials inspired by the rubber-like resilin protein in the wings and cuticles of insects? To do this, we can mimic Nature in its creative process, starting like it does, from a single molecule, and building the material up.

In this project, we will develop an *ab initio* molecular model of resilin to understand the basis of its remarkable mechanical properties. The goal of this project is twofold: 1) to build a macroscale molecularly-tunable resilin-like material and 2) to decompose the resilin molecule into its building blocks to identify molecular elements that result in superior stretch and characterize associated mechanisms. The project will be in collaboration with an experimental group.

The student will learn to build and simulate molecular and coarse-grained protein models through *ab initio* structure prediction and protein folding, advanced sampling algorithms, and molecular-dynamics-based approaches to characterize large proteins. The student will gain experience in implementing molecular simulations on supercomputers, molecular visualization software, MATLAB/Python scripting, and scientific writing. The student will have a chance to participate in a collaborative project with an experimental group, and if successful, contribute to a scientific publication.

Project #5: Molecular Clues into Loose-Skin Disease

Understanding diseases due to mutations in extracellular matrix proteins poses a unique challenge due to the fibrous, hierarchical nature of these protein assemblies, as well as the complexity of isolating contributions from extracellular matrix and cellular processes. A number of diseases, including cutis laxa, emphysema, and supravalvular aortic stenosis are associated with mutations within elastin or improper function of elastic fibers. Mutations in the elastin monomer influence multiple levels of structural hierarchy within the elastic fiber assembly cascade. In this project, we will consider mutations associated with cutis laxa, which includes a collection of disorders characterized by loose, wrinkled and inelastic skin, as well as complications including hernias, aortic aneurysm, and emphysema. We aim to expose disease mechanisms from the molecular scale up, modeling how mutations affect structure, binding domains, mechanical properties and assembly, and resultant co-polymerization through the fiber assembly process and into the tissue scales. Our ultimate goal is to provide a detailed dynamic multiscale structural model associated with disease phenotypes to expose treatment targets.

The student will learn to build and simulate molecular and coarse-grained protein models through *ab initio* structure prediction and protein folding, advanced sampling algorithms, and molecular-dynamics-based approaches to characterize large proteins. The student will gain experience in implementing molecular simulations on supercomputers, molecular visualization software, MATLAB/Python scripting, and scientific writing. The student will have a chance to participate in a collaborative project with an experimental group, and if successful, contribute to a scientific publication.

Helpful experience for all projects: Familiarity with scripting in the Linux environment, molecular modeling, basic MATLAB.

Preferred coursework: Differential Equations/Linear Algebra, Physics I: Mechanics/Statistical Physics, Biochemistry.