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2017 Award Recipients

• **Robert Brinkerhoff, Ph.D.**

Assistant Professor of Biology
University of Richmond

“Quantitative Genomic Analysis of Black-legged Tick Populations in Virginia to Identify Processes Associated with Increased Lyme Disease Incidence”

Key Words: Epidemiology, RADseq, Infectious disease, Mathematical modeling, Computational genetics, Zoonotic disease

Lyme disease, transmitted by the black-legged tick, is expanding in Virginia and throughout North America. Environmental change and increasing deer populations are likely drivers of growing tick populations, but mechanisms to account for spatial disease spread and invasion of new localities are unidentified. Publication of the black-legged tick genome and recent developments in DNA sequencing technology have allowed for unprecedented opportunities to identify fine-scale evolutionary patterns that may explain spatial variation in disease risk. We will use a restriction site associated DNA sequencing (RADseq) approach to explore gene flow and demographic and evolutionary patterns in Virginia black-legged tick populations to identify potential dispersal corridors and genomic markers of expanding populations. This approach will also allow us to test hypotheses related to population genomic structure that can tell us about recent evolutionary history and thus make predictions about continued spatial and demographic expansion. We will also use behavioral experiments to link host-seeking phenotypes with specific genomic markers to tick populations associated with high disease risk. These analyses will also allow for future investigations of specific genes or genetic pathways associated with specific host-seeking or host-sensing behaviors. We will also use statistical and computational geospatial analyses to identify predictive habitat and landscape variables associated with genomic profiles that are linked to high encounter risk tick behaviors. In summary, we will leverage advanced technologies to gain insights into expanding human risk to Lyme disease. In addition to learning about the state of Lyme disease emergence in Virginia, we will gain insights into the potential continued spatial expansion of tick-borne disease risk and develop a framework for exploring fine-scale population genomic structure that can be applied to other locations. We will also develop a method for characterizing spatial variation in Lyme disease as a function of host-seeking behavior as characterized by population genomic profile.

- **Bethany Brinkman, Ph.D.**

Assistant Professor
Sweet Briar College

“Water Treatment In Context: Appropriate Technology and Water Quality”

Key Words: Filtration, Appropriate technology, water quality, concrete

Approximately 748 million people worldwide do not have access to safe drinking water. When addressing this problem, engineers should focus on local resources, capabilities, and cultural dynamics in an interdisciplinary effort rather than just applying the most efficient technology. This research proposes to develop simple concrete filters as a step towards establishing an affordable means of treating water in the developing world. The porous concrete filters will be created in reusable housings that can also serve as water storage containers. The composition of the concrete filters will be varied by water content and aggregate size and composition (as determined by X-ray diffraction) to obtain at least a 90% removal of fecal coliforms and organic matter from the source water. Filter efficacy will be tested with seasonal waters from sites within the George Washington National Forest and on the campus of Sweet Briar College. Spatial and temporal changes in water quality can clog a filter, so the system must function in varying conditions. Water quality parameters will be determined and modeled with a total organic carbon analyzer, UV/Vis spectroscopy, and excitation-emission matrices while fecal coliforms will be counted by the Rapid 7-Hour Fecal Coliform Test. From this research, quantitative correlations will be established between water quality, concrete mix composition, and filtration success. These correlations could then help the filter systems be implemented in the field by suggesting specific times at which to collect water or a particular type of rock to use as aggregate in the concrete. Future research will continue to investigate variations in water quality with respect to land use and season by continuing to monitor existing sites and selecting new ones, including those that are more impacted by human activities. More importantly, additional locally available materials such as clay will be investigated for their suitability as disc filters.

- **Kateri DuBay, Ph.D.**

Assistant Professor of Chemistry
University of Virginia

“Modeling The Effect Of An Oscillatory Cellular Environment On Protein Folding”

Key Words: Protein Folding, Cellular Environment, Environmental Oscillations

The hereditary information stored in DNA is translated into a functional form via proteins. Most of these long chains of amino acids fold up into stable, 3-dimensional structures, with this native fold determined by the specific sequence of those amino acids. Understanding how these polymers fold rapidly and reliably into their native states has been the focus of an intense research effort. During these investigations, folding proteins are most often observed or simulated within relatively simple solvent environments in vitro and in silico. However, in vivo, folding occurs in a more complex setting, and that complexity influences folding -- in ways that appear both unintentional and designed. As an example of the former, the crowding within the cellular environment has been shown to influence folding behaviors, while, in an example of the latter, highly evolved protein complexes known as chaperonins serve as nano-scale factories that assist with the folding of certain proteins. We intend to explore yet another feature of the cellular environment whose influence on protein folding has not yet been determined -- variations and oscillations in the concentrations of different chemical species in the cell. Interestingly, very recent theoretical work on the self-assembly of colloids demonstrates that assembly within an oscillating environment can differ significantly from assembly within a static environment. Since folding can be thought of as a self-assembly process, we hypothesize that cellular oscillations may also influence protein folding in vivo. Therefore, we propose to use atomistic simulations to investigate the extent to which cellular oscillations can influence the folding of small, globular proteins.

- **Bartlett Douglas Edmonds, Ph.D.**

Adjunct Assistant Professor

Virginia Polytechnic Institute and State University

“Determining the Time-dependent Photoionization Structure of Mass Outflows in Active Galactic Nuclei”

Key Words: Active galactic nuclei, AGN, Seyfert galaxy, Quasar, Quasar outflow, AGN outflow

Active galactic nuclei (AGN) ubiquitously show outflows. It is now widely recognized that these outflows are key components in the evolution of super-massive black holes and their host galaxies. As important as these outflows are, we still lack sufficient understanding of their structure and energetics. Variability of absorption line spectra is a powerful tool in determining the physical properties of AGN outflows. In order to properly interpret variable data, we must have a strong understanding of time-dependent photoionization models. Three major findings have come out of simulations so far: 1) An outflow that appears to be heterogenous (e.g., dense knots in a diffuse wind) when ionization equilibrium is assumed may be a homogeneous outflow that is far from equilibrium; 2) A non-equilibrium plasma is over/under ionized with respect to the radiation field. By tracking a time-dependent ionization parameter (a measure of the plasma response) and comparing it to changes in the radiation field, we can determine the density of the plasma; 3) Chemical abundances tend to be over/under predicted for nonequilibrium plasmas.

These indicate that the assumption of equilibrium could lead to incorrect results. This impacts galactic and cosmic evolution scenarios that include AGN feedback. In this proposed study, we plan to study time-variability and time-dependent photoionization in simulations in order to develop methods for applying non-equilibrium models to data. This is especially difficult when spectroscopic observations are limited. A combination of Monte-Carlo simulations and genetic algorithms will be used to produce a robust and efficient method to fit data of variable outflows. These methods will be tested for efficacy on two well-monitored and well-studied AGN: NGC 4151 and NGC 3783.

- **John Friend, Ph.D.**

Assistant Professor of Biochemistry
Washington and Lee University

“Translational Control at the Boundary between the Pluripotent and Differentiated State”

Key Words: Embryonic stem cells, Growth factor-free medium, Messenger RNA translation initiation and decay

Stem cells have remarkable therapeutic potential since they can differentiate into many cell types. They are also outstanding models for human disease; for example, patient-derived, induced pluripotent stem cells have been used to study multiple sclerosis and Alzheimer's disease.

In addition to differentiation, stem cells must self-renew to retain their stem cell identity. The transition from self-renewal to differentiation requires differential gene expression, but little is known about how mRNA translation is regulated as stem cells differentiate. We will use mouse embryonic stem cells (mESCs) to investigate differential mRNA translation initiation in self-renewing versus differentiating mESCs since we have observed regulated translation initiation at the boundary between self-renewal and differentiation in mESCs. We will also investigate the connection between mRNA translation and mRNA decay in mESCs. We expect a global increase in mRNA translation rates as stem cells differentiate based on our previous work, and higher mRNA translation rates are known to promote mRNA decay. We will ask whether the increase in global translation rate promotes mRNA clearance during early differentiation as the second goal of our proposal. In both cases, we will use a combination of high-throughput sequencing and extensive bioinformatics approaches to address these questions.

We also have preliminary data that translation inhibition prolongs stem cell self-renewal, so the final goal of our proposal is to replace expensive stem cell growth factors with chemical inhibitors that maintain mESC self-renewal. We propose a targeted approach with chemicals previously known to promote self-renewal and, if necessary, a chemical genetics approach. Previously, the network governing pluripotency has been computationally modeled, and our findings will be incorporated into existing models to simulate mESC responses to growth factors.

By thoroughly investigating the mRNA translational response at the boundary between mESC self-renewal and differentiation, we propose to conduct targeted replacement of mESC growth factors.

- **Gaurav Giri, Ph.D.**

Assistant Professor of Chemical Engineering

University of Virginia

“Creating High Performance Flexible, Transparent Electronics Using Solution Shearing and Multiscale Modelling”

Key Words: Organic electronics, Solution shearing, Multiscale modelling

Organic electronics using thin film organic semiconductors (OSCs) are currently being explored for large area, flexible and transparent electronic applications, such as bendable displays and flexible photovoltaics. To enable large area processing, flow coating methods have been previously used in other industries such as textile manufacturing and printing. The flow coating method called solution shearing has shown that rapid deposition of thin film OSCs onto diverse substrates such as paper, plastic and glass is possible, while still yielding high performance electronics. However, due to the large parameter space available during solution shearing, trial and error methods are currently utilized to create OSC thin films for electronic applications. The thrust of this project is to use multiscale modelling to understand how fluid dynamics and evaporation conditions during solution shearing gives rise to different OSC thin film morphologies, and the impact of these morphologies in the electrical performance. This project will be completed in three steps. We will first create a novel solution shearing machine with controllable parameters that affects the fluid dynamics and thin film crystallization. Then, this machine will be complexed with high speed, optical and X-ray scattering methods so that millisecond resolution data of fluid dynamics and crystal growth can be recorded. Finally, this data will be utilized to create a multiscale model that spans from the large area fluid dynamics down to the molecular interactions. We will then verify our predictions by using the solution shearing methods on novel OSCs to find new areas of high performance accessed using solution shearing. The eventual outcome of the project will enable researchers to predict the parameter space that enables high performance organic electronics without using trial and error methods. The prediction of thin film crystal growth will be applicable to other fields such as sensors, separation membranes, and photovoltaics.

- **David Haak, Ph.D.**

Assistant Professor of Plant and Microbial Genomics
Virginia Polytechnic Institute and State University

“Do RNA Viruses Hijack Host Alternative Splicing Machinery for Infections? A Bioinformatician's View”

Key Words: Alternative Splicing, Viral–Host Interactions, Potyvirus, Pathogen, Stress, Defense Response, Turnip Mosaic Virus, *Nicotiana benthamiana*, Arabidopsis

Plant pathogens cause large losses in agricultural production annually and therein constitute a major threat to global food security. Efforts to improve crop production have traditionally focused on plant protection from stressors/pathogens and this focus has become particularly poignant in recent years due to higher demands for increasingly limited inputs (e.g., water, arable land, etc.). Thus, improving plant protection by targeting natural mechanisms of plant–disease interactions provides a sustainable avenue toward increased global food security.

This interdisciplinary collaboration, leverages emerging computational and biological tools to begin unpacking the 'black–box' of stress induced alternative splicing in plants. The project will identify mechanisms and key isoforms associated with virus infection. Notably, this study takes advantage of recent insights on viral replication dynamics—wherein viral proteins are directly targeted to the spliceosome—coupled with known spliceosome mutants in Arabidopsis, to begin a mechanistic dissection of virus–spliceosome interactions. The aim is to determine, 1) the role of viral proteins in manipulating alternative splicing by 'hijacking' host spliceosomal machinery for viral replication, 2) spliceosomal components important to pathogen–mediated alternative splicing and viral infection, and 3) the virus–mediated alternative splicing landscape across two evolutionarily divergent plant lineages.

The primary outcomes of this project will significantly advance our understating of virus–host interactions, the role of alternative splicing in response to pathogen stress, and finally the complex regulation of alternative splicing in plants. These findings will be an important step toward elucidating targetable mechanisms for enhancing crop protection from environmental stresses. This project will also generate community tools including a template for testing similar mechanisms in human viral pathogens, and a wealth of genomic data which can be used for further analysis, in particular, these data can also be immediately expanded by subjecting virus–infected tissues to metabolomic analysis for a broader dissection of the alternative splicing regulatory network.

- **Julie Pollock, Ph.D.**

Assistant Professor of Chemistry and Biochemistry
University of Richmond

“Experimental And Computational Investigations Of MEMO1 And Its Role In Breast Cancer”

Key Words: Phosphorylation, Breast cancer, protein–protein interactions, Virtual screening, Cancer migration, Drug development

Regulation of phosphorylation markers is essential in signaling cascades and many aspects of cellular biology. Consequently, abnormal phosphorylation has been linked to human diseases including many types of cancer. Although protein kinases and phosphatases are responsible for facilitating the addition and removal of phosphates, there are other scaffolding proteins known as phospho–binding proteins that participate in the regulation of these phosphorylation sites. MEMO1, a recently discovered phosphotyrosine–binding protein, is upregulated in almost half of human breast tumors and has been linked to cell motility and metastasis. The cellular targets and molecular interactions of MEMO1 have not been fully characterized. This project will combine the power of experimental and computational biochemistry to establish the binding interface of MEMO1 at a molecular level and determine residues essential for phosphate–binding. In addition, in silico and in vitro screening will be used to identify small molecule inhibitors of MEMO1 binding. These results will allow us to probe the role of MEMO1 in breast cancer and establish if it is a viable target for the development of new cancer therapeutics.

- **Wanli Qiao, Ph.D.**

Assistant Professor of Statistics

George Mason University

“High-dimensional Statistics and Biomolecular Modeling as a Powerful Microscope over Pathogenic Mutations in Proteinopathies”

Key Words: Human Disorders, Pathogenic Mutations, Molecular Mechanisms, Protein Dysfunction, Energy Landscape, Structure Space, Spatial Data Analysis, High-dimensional Statistics, Biomolecular Modeling, Stochastic Optimization.

The objective of this pilot study is to uncover the organization of the structure space (and accompanying energy landscape) of a biomolecule so as to obtain quantitative thermodynamics- and structure-based descriptors/markers of the impact of (DNA) mutations on protein dysfunction in human disorders. This is an inherently interdisciplinary study that brings together a young, energetic principal investigator (Qiao) with a strong research record on the statistics and geometry of high-dimensional, spatial data and a mid-career co-investigator (Shehu) with a prolific research record on the algorithmics of biomolecular modeling.

The driving scientific question pursued here is how mutations percolate to dysfunction in proteins. The hypothesis put forth is that the phenotypic impact of a pathogenic mutation can be quantified via automated analysis of the energy landscape that governs a molecule's equilibrium structural dynamics. The investigators will bring together their complementary expertise on high-dimensional geometry and statistics, manifold theory, and biomolecular modeling to extract descriptors of high-dimensional landscapes. The latter will not only allow a principled comparison of healthy and disease variants of a protein, but will also allow building discrete models via which to simulate the meso-scale dynamics of a protein in silico.

The contribution of this collaborative project and our immediate interest is in understanding and quantifying how DNA mutations change protein energy landscapes and in turn the function of a disease-central protein. The mathematical formulations and automated tools expected to result from the proposed research, however, have farther-reaching applicability in other domains of science where perturbations of a dynamic system can be compared in terms of the impact on complex state space dynamics. Hence, this pilot study launches a joint research activity expected to span the course of many years, with NSF, NIH, the Keck foundation and other foundations promoting interdisciplinary basic science research as principal funding sources.

- **Patrick Sachs, Ph.D.**

Assistant Professor

Old Dominion University

“Three-dimensional Bioprinting for High-throughput In-vitro Modeling of Asymmetric Stem Cell Divisions”

Key Words: Induced pluripotent stem cells, 3D Bioprinting, Asymmetric cell division, Stem cell niche

It has been proposed that a key component of asymmetric divisions is the coordinated segregation of sister chromatid pairs bearing uneven epigenetic markings. The result is the inheritance of specific transcriptional profiles within each daughter cell allowing one cell to be "primed" for differentiation. Determining by direct means whether daughter cells of asymmetric divisions have differential transcriptional profiles has not been possible in human systems due to experimental limitations. This proposal seeks to overcome these obstacles through the use of bioprinting. A custom 3D bioprinter with single cell printing resolution will be used to generate artificial microenvironments that drive coordinated asymmetric divisions of human induced pluripotent stem cells (iPSCs) into neuronal progenitor cells (NPCs). The system will provide high-throughput analysis of transcriptional profiles between daughter cells of asymmetric divisions. Therefore, the objectives of this study are to optimize a 3D bioprinting system to study asymmetric divisions in high throughput and to test the hypothesis that differential transcriptional profiles occur between daughter cells during human asymmetric stem cell divisions. This will be accomplished by: 1) optimizing efficiency of 3D bioprinter and pluripotent hydrogel systems; 2) determining inherited transcriptional differences between daughter cells of iPSC asymmetric divisions. Asymmetric divisions will be generated in high throughput by printing naïve iPSCs in contact with WNT3A conjugated fluorescent beads in differentiation conducive medium. Daughter cells will be isolated by laser capture microdissection and gene expression profiles determined by ion-torrent transcriptome analysis. The Database for Annotation, Visualization, and Integrated Discovery (DAVID) will be used to generate computational models of differences in activated gene ontologies and pathways between daughter cells. These findings will determine if daughter cells of asymmetric divisions contain differential transcriptional patterns, and if those patterns contribute to specific differentiation. The findings from this proposal have major implications for developmental biology and regenerative medicine.

- **Burak Tanyu, Ph.D.**

Assistant Professor of Geotechnical Engineering
George Mason University

“Evaluating the Potential of Bio-Inspired Soils to Enhance Nature Based Coastal Resiliency Systems by Combining Experimental and Computational Methods”

Key Words: Ground improvement, Bio-inspired soils, coastal resiliency

Hurricanes are one of the most costly natural disasters in the U.S and flooding from storm surge accounts for the greatest damages around coastal areas worldwide. Geotechnical engineers provide solutions for coastal protection via levees, dikes, and sheet piles, however these structures are extremely costly and require extensive maintenance over time. Currently, there is an increasing interest to develop coastal wetlands as natural alternatives to traditional methods. However, coastal erosions due to extreme events pose significant threats to this nature-based protection methods. The overarching goal of this project is to investigate a new paradigm for coastal protection and infrastructure resilience by integrating bio-inspired soils and nature-based features into a high-performance computational framework for extreme weather engineering design in coastal areas. This project will yield a significant, novel advancement in our understanding and modeling of bio-inspired, green infrastructure and its potential to create a natural first line of defense along coastal areas to protect civil infrastructure. The research will combine geotechnical engineering, water resources, environmental, biological and agricultural engineering, and computational analyses to support regional resilience for extreme events. The research is potentially transformative and will have two major advantages: (1) it will improve the stability of the soil substructure in regions where wetlands already exist, while minimizing disturbance of the existing and established wetland buffer zone and (2) provide a secondary mechanism for coastal stability in the form of bio-inspired soils, which when combined with wetland infrastructure, yields a redundant, more resilient and sustainable defense against natural hazards. The Sustainable Environmental-Geotechnical Action (SEA) team of five undergraduate students will engage in field, laboratory and high-performance computational studies to develop a novel, student-driven and previously unexplored approach to coastal resiliency combining microbiology and phytology with geotechnical engineering in the context of computational modeling.

- **Robert Waters, Ph.D.**

Assistant Professor of Biology
University of Mary Washington

“Visualizing Big Data to Determine the Effects of Physical Exercise on Social Ethology, Social Rank and Neurophysiology in Laboratory Mice”

Key Words: Social Ethology, Automated animal tracking, Neuropeptides, Physical exercise

Laboratory mice are social animals that exhibit specific patterns of behavior during social interactions that result in the formation of dominance hierarchies. Reciprocally, a mouse's hierarchical rank influences the temporal and behavioral characteristics of its ethology. These behavioral characteristics are strongly influenced by central neuropeptides expressed in brain regions that control appetitive and stress related behaviors. Understanding how these neurobiological systems influence, and are influenced by, social interactions will allow us to form a holistic picture that relates physiology and behavior to evolutionary fitness.

Voluntary wheel running (VWR) is a model of aerobic activity that is performed spontaneously and robustly by laboratory mice. This activity has profound effects on the ethology and neurophysiology of mice, which extends to social interactions and neuropeptides. The direct influence of VWR on social rank however, has not been reported.

The research proposed here explores the connections between ethology, social rank, and neuropeptides, and how these traits are influenced by physical activity. We will use radio-frequency identification (RFID) tags to track the position of mice living in a social colony, and use these data to perform a long-term, high-resolution assessment of the social behavior of mice. We will accomplish this by constructing Java functions and visualization software to create heat maps and vector maps that indicate the ethological patterns of each mouse in the social colony. We will then use RFID gated tubes to allow selective access of individual mice in the colony to a running wheel, which will allow us to assess the influence of VWR on behavioral patterns and social rank.

Following our behavioral assessment, we will collect brain tissue to assess differences in neuropeptide systems that may result from social interactions and social rank. These systems include oxytocin, vasopressin, neuropeptide Y, and corticotropin releasing factor.

- **Daniel Weller, Ph.D.**

Assistant Professor of Electrical Engineering
University of Virginia

“Perceptually Aware Model Training for Image Reconstruction”

Key Words: Image Reconstruction, Magnetic Resonance Imaging, Cardiac Imaging, Image Quality, Signal Modeling

Cardiac magnetic resonance imaging is routinely used to diagnose coronary artery disease, myocardial infarction, and other cardiac events. However, conventional exams are time consuming and uncomfortable for patients. New image reconstructions are needed to produce high quality, detailed images from accelerated acquisitions. Data-driven model-based regularization is an important ingredient in such reconstructions. The proposed research aims to train these data-driven models robustly when available training data are of varying quality, and use these models to reconstruct high quality cardiac magnetic resonance images. By measuring the quality of each training image, dictionary learning can account for these quality differences within the model regression. The resulting data-driven model will be richer, more robust, and less biased to features found in individual images. Such models will be employed in state-of-the-art model-based parallel-imaging reconstructions of cardiac images and compared against both ground truth (complete acquisitions) images and existing model-based reconstructions.

Perceptual image quality measures are the key innovation to achieving this goal. Recent work with relative quality indexes suggest structural coherence and texture complexity are important for assessing the relative quality of an image patch. Undergrads will adapt these measures to the dictionary learning problem, and compare the approximations of training data using the resulting dictionary against those using conventionally trained dictionaries. Then, for a large set of cardiac images acquired by physicians, the undergrads will compare images reconstructed with the best trained dictionaries against existing methods. A subset of these reconstructions will be graded visually for quality, while the whole set will be compared versus ground truth using cross validation, to comprehensively assess the proposed model. The principal investigator will use the results of this project to propose future innovations in computational medical imaging.

- **Jie Xu, Ph.D.**

Assistant Professor

George Mason University

“Increasing Power Grids Resilience To Weather Via Optimal Power Line Hardening”

Key Words: Power Grids, Weather Resilience, Hardening, Simulation, Optimization

Severe weather is the leading cause of power outages in the United States. The annual costs of power outages caused by severe weather was estimated to be \$18 billion to \$33 billion in a 2013 report by the Executive Office of the President. Cascading outage is of particular concern because of the large geographic area that may be affected as a result of an initial small disturbance.

Severe weather poses challenges to traditional grids security analysis known as the "N-1" policy, and requires new mitigation methods. The "N-1" policy ensures that the grid would remain connected after the loss of any power line. However, severe weather like thunderstorms frequently leads to the loss of multiple power lines within a short amount of time because of heavy winds. Such multiple failure scenarios are out of the scope of "N-1" policies and have larger chances to lead to a cascading outage.

This project aims to increase the power grids resilience to weather by optimally hardening power lines to mitigate cascading outage risks in preparation for severe weather conditions with days-ahead forecasts. The specific aims are:

- Establish a new simulation optimization with auxiliary information (SOAI) methodology to optimize power line hardening plans using a recently developed high-fidelity cascading simulator, with an objective to minimize loading shedding in preparation for severe weather given day-ahead forecasts.
- Develop a parallel SOAI (P-SOAI) algorithm that can dramatically reduce the wall-clock time to solve large-scale problems by utilizing parallel computing power in a scalable way.
- Evaluate the performance of P-SOAI by extensive experiments on both benchmark IEEE-39/118 bus systems and real-life problem instances.

This project will provide three undergraduate students with advanced training in interdisciplinary computational and engineering research methods, and motivate them to pursue a career in science/engineering.

- **Sen Zhang, Ph.D.**

Assistant Professor of Chemistry
University of Virginia

“Advanced Electrocatalysts Through Core–Shell Nanostructures”

Key Words: Core–Shell, Nanoparticles, Electrocatalysts, Fuel Cells, DFT, QM–MM Simulation, Energy

Proton exchange membrane fuel cells (PEMFCs) have been recognized as a clean, economical, and highly efficient energy conversion technology to meet the sustainability of human society, running with renewable feedstocks such as hydrogen and biomass derived compounds. However, the commercialization of PEMFCs still requires a substantial improvement on their performance, durability, and cost-effectiveness. This project focuses on reducing the Pt group metal (PGM) usage in the fuel cell cathode reaction (oxygen reduction reaction (ORR)) catalysts while maintaining high activity and durability by using rationally designed and precisely synthesized core–shell nanoparticles (NPs). Success in this project will significantly reduce the PEMFCs catalysts cost and increase the efficiency and life time, and also shed a light on the design and preparation of Pt based core–shell nanocatalysts for many other catalytic reactions.

A key concept in this research is the search of NPs with an ideal non-precious-metal-based core and an ultrathin Pt shell. To achieve such a goal, we propose to systematically integrate computational simulations/calculations with controlled chemical synthesis and advanced characterizations. Using Density Functional Theory (DFT) and Quantum Mechanics–Molecular Mechanics (QM–MM) simulations, we will identify the most active and stable core–shell structures for ORR in acidic media, which will be further translated into a practical nanocatalyst using controlled colloidal chemical synthesis. The interdisciplinary approach in this project will lead to a better understanding of the structure–catalysis correlation on core–shell Pt-based electrocatalysts, demonstrate an improved synthetic methodology for the atomic-level controlled nanostructure fabrication, and establish an theoretical and practical guidance for the future catalyst design for low-cost and high-performance PEMFCs.

2016 Award Recipients

- **Laura Barnes, Ph.D.**

Assistant Professor

University of Virginia

“A Novel Computational Framework for Prediction of Severe Sepsis and Response to Therapy”

Key Words: Predictive Models, Sepsis, Hyperlactatemia, Medical Informatics, Temporal Data Mining, Precision Medicine

Sepsis, the systemic response to infection, is the leading cause of in-hospital mortality and is associated with significantly higher costs. Severe sepsis (sepsis complicated by organ dysfunction) strikes more than 1 million Americans and has a 30% mortality rate. Furthermore, those patients who survive severe sepsis are more likely to have permanent organ damage, cognitive impairment, and physical disability. The best chance of survival of severe sepsis is earlier and more aggressive treatment response. In fact, recent studies suggest that every one-hour delay in treatment of severe sepsis/shock with antimicrobials increases a patient's mortality probability on average by 7.6%. Many of the sepsis related deaths could be postponed or averted if better early warning score (EWS) were in place. However, current methods for identifying and predicting severe sepsis are biased and inadequate. Many institutions use systemic inflammatory response syndrome criteria to identify patients at risk for severe sepsis, but this strategy is not validated and misses 1 out of 8 cases. Furthermore, the best therapy for patients with severe sepsis remains unknown despite several recent randomized studies of protocolized care. The goal of the proposed work is to overcome the limitations of existing systems such as the SIRS criteria by developing a new computational framework for the prediction of severe sepsis including the early identification of severe sepsis and predicting the individualized response to therapy post diagnosis indicators using patient demographics and commonly available clinical laboratory values and vital signs. We hypothesize that patients at risk for severe sepsis with bloodstream infections can be identified earlier and with greater sensitivity and specificity by employing sophisticated computational modeling techniques for prediction. Furthermore, we hypothesize that we can better predict and quantify response to therapy based upon historical clinical data and individual patient attributes.

- **Andreas Gahlmann, Ph.D.**

Assistant Professor of Chemistry
University of Virginia

“Harnessing the Power of Bacterial Populations”

Key Words: Bacteria, biofilms, microbial fuel cell, super-resolution microscopy, image segmentation, graph theory

Most bacteria found in nature form dense multicellular communities called biofilms. Yet, the majority of our knowledge of microbiological life has been obtained from isolated cells in solution. The large number of cells found in a biofilm enables bacteria to have a measurable impact on the macroscopic world. For example, biofilms of electron producing bacteria can metabolize chemical compounds found in waste water and thereby generate electrical power in microbial fuel cells. This ability of bacterial populations, if successfully harnessed, could provide enough power to make waste water bioremediation energy neutral and remotely deployable. However, the cellular level mechanisms of electricity conduction within biofilms are still poorly understood. The goal of the proposed research is to shed light into the single-cell dynamics within microbial communities. A critical barrier to progress in biofilm research is the inability of current methods to visualize the behavior of individual cells over many generations with sufficient resolution. Here, we propose to integrate newly-developed lattice light-sheet microscopy with fluidic fuel cell growth chambers that contain electrode substrates and enable electrical power measurements. Without perturbing the biofilm, we will visualize how individual bacterial cells in pure- and mixed-species community cooperate to generate electrical currents throughout the biofilm. To extract quantitative and statistically significant information from the obtained image sequences, graduate and undergraduate students in the Dept. of Chemistry and the Dept. of Electrical and Computer Engineering at the University of Virginia will work together to develop the required computational data analysis framework. This combined experimental and computational approach will lead to a mechanistic understanding of how the capabilities of bacterial populations can be harnessed to generate electrical power. At the same time, these results will also inform potential strategies to control biofilms in medical, industrial, and agricultural applications.

- **Kristine Grayson, Ph.D.**

Assistant Professor of Biology
University of Richmond

“Using Genome–Wide Association Models to Determine the Genetic Architecture of an Invasive Forest Insect”

Key Words: Adaptive traits, Genome–wide association mapping studies (GWAS), Gypsy moth, Invasion dynamics, Population divergence, Single–nucleotide polymorphism (SNP) markers

Understanding the ecological and economic impact of invasive species requires estimating the potential range of spread in a new habitat. An underappreciated component of spatial spread in invasive species is the process of adaptation at a range edge, where changes in phenotypic traits can overcome previous limits on climatic or habitat suitability. Examining the genetic architecture of these traits is the next frontier for studies of life history adaptation. Next generation sequencing now allows detailed investigations of the genetic structure underlying observed phenotypic differences and ecologically–relevant adaptations. We use the North American invasion of the European gypsy moth (*Lymantria dispar*), a highly destructive forest pest, to examine the genomic basis of range–wide variation in developmental and life history traits. We will conduct a genome–wide association study to map genetic differences between established and invasion front populations and test for local adaptation in phenotypic traits associated with gypsy moth persistence and spread. Specifically, this study uses bioinformatics methods to test for selection on high temperature tolerance at the southern invasion front in Virginia. At this dynamic range edge, gypsy moth populations are continuing to spread through the Appalachian Mountains, but may be experiencing temperature–associated limits on further spread in the Coastal Plain region. The novel contributions of this study include using genomic approaches to understanding the process of invasive species spread. While methods in genome–wide association mapping are well–characterized for model species, this will be the first application of these methods in an invasive species. Our results will assess whether a damaging insect pest can adapt to new climatic environments at an invasion front, which is important for understanding whether invasive species will shift their distribution under changing climates.

- **Kristian Hargadon, Ph.D.**

Elliott Assistant Professor of Biology
Hampden-Sydney College

“Bioinformatic Analysis Of CD8+ T Cell Differentiation In Tumor-free Versus Tumor-involved Lymph Nodes”

Key Words: Bioinformatics, Tumor immunology, CD8+ T Cell, Differentiation, Melanoma, Immune Regulation, Cancer Immunotherapy

Melanoma, the 6th most common fatal malignancy in the United States, is the most lethal form of skin cancer because of its propensity to metastasize to several vital organs. Many cases of progressive melanoma are also associated with anti-tumor CD8+ T cell dysfunction. The nature of this immune dysfunction remains poorly understood, and it is unclear how tumor burden and lymph node involvement by melanomas impact T cell responses to this cancer. Using a murine model of metastatic melanoma, we will investigate the differentiation and function of CD8+ T cells isolated from tumor-free versus tumor-involved lymph nodes. Undergraduate students will perform whole genome expression microarray analyses on CD8+ T cells responding to the highly tumorigenic B16-F1 melanoma that metastasizes to tumor-draining lymph nodes and the poorly tumorigenic D5.1G4 melanoma that is immunologically controlled and lymph node noninvasive. Linear modeling of normalized microarray data will be applied to identify by Volcano plot filtering differentially expressed genes in CD8+ T cells responding to these melanomas, and gene set enrichment analysis will be performed in limma in conjunction with Gene Ontology and KEGG databases to identify molecular processes, cellular functions, and biologic pathways exhibiting a significant enrichment of differentially expressed genes in these tumor-specific CD8+ T cells. These analyses will guide pathway-focused gene and protein expression arrays aiming to address how lymph node involvement by melanomas impacts the quality of CD8+ T cell responses to both tumor-derived and cancer vaccine-associated antigen. This bioinformatics approach to study CD8+ T cells activated in tumor-free versus tumor-involved lymph nodes will significantly improve our understanding of anti-tumor immune dysfunction and may suggest therapeutic strategies for interfering with its induction. Moreover, the interdisciplinary nature of these studies will enhance STEM training of undergraduate students preparing for graduate education and careers in bioinformatics and the biomedical sciences.

- **Christine Helms, Ph.D.**

Assistant Professor of Physics
University of Richmond

“Properties of Aligned Electrospun Nanofibers”

Key Words: Electrospinning, electric field, mechanical properties, Young's Modulus, nanofibers, AFM

Electrospun nanofibers have potential importance in a vast array of fields including filtration, medicine, and energy. However, applications in these fields often need particular mechanical properties along with fiber alignment. Little is known about the effect of alignment on individual electrospun fiber properties.

In the proposed research we aim to model the electric field used to produce aligned fiber during parallel plate electrospinning and measure the mechanical properties of aligned and nonaligned electrospun poly(ethylene oxide) fibers.

We hypothesize that alignment of electrospun fibers by the electric field will affect the mechanical properties of the fibers through increased modulus, increased strength, decreased extensibility, decreased elasticity and altered failure mechanism. Specifically our aims are:

Aim 1: Computationally model the electric field used to align the electrospun fibers.

We will solve Laplace's equation using 4th order Runge–Kutta method.

Aim 2: Measure, quantify and compare the modulus, strength, extensibility, and elasticity of aligned and non–aligned fibers. We will use an atomic force microscope to manipulate and measure force exerted by individual fibers as well as their diameters.

Aim 3: Determine the method of failure of aligned and non–aligned fibers by imaging stretched fibers with scanning electron microscopy and transmission electron microscopy.

The combination of our electric field model and fiber data has the potential to provide insight into the mechanism causing the change in fiber properties and may act as a predictive tool for electrospun fiber properties. Also the individual fiber properties can be used in network model for electrospun fiber device design. Additionally the project will provide undergraduates the opportunity to experience scientific research first hand using cutting edge equipment and present their finding to the scientific community.

- **Eric Johnson, Ph.D.**

Assistant Professor of Biology
Virginia Wesleyan College

“Enigmatic Proteins in Ancient Cell Types: Identifying a Role for Arabinogalactan Proteins in Moss Spermatogenesis.”

Key Words: Arabinogalactan proteins, Physcomitrella, Bryophyte, Plant Spermatogenesis, RNA-seq

Arabinogalactan proteins (AGPs) are a diverse family of glycosylated, hydroxyproline-rich glycoproteins unique to plants that play widespread roles in plant reproduction, growth, and development; yet the molecular mechanism by which they function continues to be debated. These proteins have been identified in male gametes of diverse plant lineages, including the motile cells of ferns to those encapsulated in the pollen of flowering plants. This research aims to identify these mysterious proteins in the moss *Physcomitrella patens* and align their presence with developmental events within sperm cells. This moss is an emerging model system representing one of the oldest lineages of plants, arising 450 Mya, that is proving to be an excellent system for molecular studies because it is easy to culture and is amenable to targeted genetic manipulations. Using the Illumina HiSeq 2000 platform to quantify transcriptome-level changes throughout spermatogenesis, a thorough quantitative analysis will allow us to map changes in gene expression for 165 putative AGPs over four time points. These data will be confirmed using both qRT-PCR and a transgenic approach to localize expression within the plant. We will also utilize the high efficiency of homologous recombination in *Physcomitrella* to target the four most involved AGP encoding genes for labeling and deleting, which will allow protein-level characterization at key time points during spermatogenesis. This project will provide ample opportunity for undergraduate training in both molecular and quantitative techniques, including an RNA-seq analysis workshop at the Bioinformatics Core Facility at the University of Virginia, incorporation of data into a molecular techniques course at Virginia Wesleyan College, and provide support for up to five students to conduct and disseminate this research. Ultimately this project will develop a system that can be used to continue to probe the functional mechanisms of AGPs in an evolutionarily important cell.

- **Kyle Lampe, Ph.D.**

Assistant Professor of Chemical Engineering
University of Virginia

“Simulation And Synthesis Of Engineered Extracellular Matrix Proteins For Neural Tissue Engineering”

Key Words: Biomaterials, Engineered protein, Tissue engineering, Molecular dynamics, Simulation, Central nervous system, Stem cell

The loss of neurons and associated glial support is a hallmark of neurodegenerative disease. Recent attempts at restoring damaged neural tissue involve engineering 3D microenvironments that regulate neural stem cell (NSC) proliferation and differentiation. These microenvironments are often designed to mimic essential properties of the native extracellular matrix (ECM), including elasticity, proteolytic remodeling, and cell-adhesive sites. However, creating an appropriate microenvironment that retains many such biological functions remains a challenge for protein engineering. An effective protein engineering--based biomimicry strategy would enable design of stimuli-responsive and multifunctional biomaterials that could deliver stem cells and allow precise control of their behavior for neural tissue regeneration. Because of their physicochemical similarities to the ECM, elastin like proteins (ELPs) can be utilized as NSC carriers for targeted delivery. Using state-of-the-art computational chemistry approaches, including atomistic molecular dynamics simulations, we will examine the structural stability of a laminin-mimetic elastin-like (LG-ELP) protein scaffold. Though computationally intensive, MD simulations are less costly and labor-intensive than manually screening the properties and solution-state behavior of large families of LG--ELP constructs. Simulating a system in silico affords a view of its structural stability and bulk (thermodynamic) properties. Thus, computer simulations represent a potentially powerful new route in our protein engineering/design workflow; enabling identification and screening of non-folded candidates before costly expression and purification. With this approach we aim to 1) engineer proteins that respond autonomously to small temperature shifts as a mechanism of gelation, 2) create hydrogels that support and regulate cell function as a controllable substitute for normal physiological microenvironments, and 3) train multiple undergraduates trans-disciplinarily in computational protein design and experimental protein synthesis techniques. This proposal will provide a foundation for more effective (structurally-guided) approaches to engineering new matrices, thereby accelerating the iterative design process toward minimally invasive cell-matrix delivery to diseased brain areas.

- **David Lattanzi, Ph.D.**

Assistant Professor of Structural Engineering
George Mason University

“Connecting 3D Imaging and Computational Mechanics for Next-generation Civil Infrastructure Assessment”

Key Words: civil infrastructure, computer vision, mechanics, pattern extraction

The National Academy of Engineering recently declared the maintenance and restoration of urban infrastructure as one of the Grand Challenges for Engineering in the 21st Century. Innovations that improve life-cycle infrastructure assessments will play a major role in addressing this challenge.

With the advancement of 3D imaging technologies, such as light detection and ranging (LIDAR), geometric changes in structural components due to damage can be measured. However, 3D imaging does not provide information regarding how damage has altered the performance of a component and the result is that the use of 3D imaging for assessments is currently limited.

The goal of this research program is to establish a quantitative link between 3D imaging and computational mechanics through a multidisciplinary coupling of computer vision, pattern analysis, and finite element modeling. Specifically, the research program aims to achieve the following:

- Create new 3D image analysis and pattern extraction techniques.
- Establish a methodology for updating computational models of structures based on extracted information.
- Validate the approach using real-world specimens.

The will be accomplished using comparative point-cloud analysis techniques in tandem with pattern segmentation algorithms tailored for use with finite element models. The investigation will establish and explore this coupled analysis method, using a series of laboratory tests for prototyping. The methodology will then be validated on components from a recently decommissioned bridge on the George Mason campus. The research program will also provide undergraduate students valuable training in the interdisciplinary methods and technologies that underpin modern engineered systems.

This imaging-mechanics linkage will enable engineering communities to quantitatively leverage 3D image data in new ways, with subsequent and long-reaching economic and public safety benefits. The research program will also serve as a first step in a larger effort on the analysis and monitoring of in-service bridges and buildings across the Commonwealth of Virginia.

- **Sara Maxwell, Ph.D.**

Assistant Professor

Old Dominion University Research Foundation

“Seabird Collision Risk Models to Balance Ecological Protections and Access to Clean Energy”

Key Words: wind energy, seabird, ecological sustainability, human health, Bayesian hierarchical state-space models, distribution models, habitat suitability modeling, animal behavior

Development of clean, renewable energy is vital to human and ecosystem health, and is predicted to stimulate economic and job growth in Virginia and the Mid-Atlantic region. Wind energy is considered one of the cleanest energy sources, however, it is not without impacts that must be mitigated under a variety of US laws. The construction and operation of offshore wind turbines can cause impacts on seabirds through collision with moving turbine blades, and avoidance responses may result in displacement from key habitats or increase energetic costs, and many species in the mid-Atlantic region are listed as protected under a variety of state and federal laws. This may affect birds migrating through the area, and particularly those that may use wind energy lease areas as important foraging habitat. To quantitatively assess risk, risk models must be developed for seabirds and requires information on their spatial distribution, flight altitude, and animal behavior (e.g., foraging or transiting) to determine the likelihood of co-occurrence with the wind energy. The goal of this research is to develop quantitative, robust spatially-explicit collision and disturbance risk models. The researchers will use satellite tracking on a population of individual birds across three protected species to empirically determine flight heights, animal behavior and habitat distribution. To highlight areas of high and low risk of wind turbines to seabirds, the data components will be integrated to create individual- and multi-species collision and disturbance risk models. Additionally, the project aims to train undergraduate students to undertake the field and analytical techniques of this project. This project will provide essential information for understanding the potential risk of offshore wind energy developments, and can help to balance ecological protections and clean energy development, as well as develop a workforce in Virginia with expertise in clean energy.

- **Carolina Salvador Morales, D.Phil.**

Assistant Professor of Bioengineering
George Mason University

“Using Computational Modeling for the Design and Optimization of Novel Cancer Theranostics”

Key Words: Computational Fluid Dynamics, Simulations, Patchy Particles, Cancer Theranostics,

This proposal aims to develop sophisticated computational methods such as computational fluid dynamics simulations (CFD) to design and optimize the synthesis of lipid-polymeric patchy particles, potential novel theranostic devices for the treatment of breast cancer.

Patchy particles have anisotropic surface domains that can be remarkably useful in diverse medical and industrial fields because of their ability to simultaneously present two or more different surface chemistries on the same construct. Breast cancer is the second leading cause of death in women after lung cancer. Therefore, we need to create new and more effective treatments for this devastating disease. Our patchy particles can be particularly advantageous for the creation of novel theranostic devices because they can uniquely perform imaging and therapeutic functions at once. For example, because of the cluster effect of the patch, an imaging signal can be enhanced, while the polymeric core can be tuned to render specific drug release kinetics.

The first specific aim is to determine the role of the shear stress rate in the particle's external and internal morphology using novel CFD. This goal will be achieved by varying key parameters in the particle's synthesis such as the gap size between the inner diameter of the homogenizer's workhead and the rotor-shaft, and geometry of these two homogenizer's parts. Additionally, we will conduct CFD to track the fluid dynamics trajectory of the two main particle's components: lipid-polymer based functional groups and poly (lactic-co-glycolic acid) polymer.

The second specific aim is to optimize the physicochemical properties of patchy particles, assess in vitro the efficacy and toxicity of the engineered patchy particles and validate the CFD simulations results. We will achieve this goal by applying a multifactorial chemical approach, conducting cellular uptake studies, and measuring the photoacoustics signal of patchy particles when the particle's internal and external structure is varied.

- **Woon-Hong Yeo, Ph.D.**

Assistant Professor

Virginia Commonwealth University

“Ultrathin, Nanomembrane Electronics for Quantitative Monitoring of Sodium Intake”

Key Words: Nanomembrane electronics, Quantitative mechanics, Biocompatibility, In vitro measurement, and Sodium intake.

Hypertension (high blood pressure) is the most common chronic medical problem prompting visits to primary health care providers in the US. In 2010, the direct and indirect costs of hypertension was estimated at about \$94 billion and is expected to rise to \$150 billion by 2020. Although about 80% of hypertensive individuals are aware of their condition, adequate control of salt intake has been challenging, mostly due to the lack of home monitoring/management devices that can be easily operated by users.

To address those issues, we will develop a nanoelectronic device that includes ultrathin, ion-selective sensors and the circuit interconnect for batteryless, wireless, quantitative sodium recording. Once embedded in a soft elastomeric membrane, this device can be mounted in the oral cavity like the conventional dental retainer.

The specific aims are to 1) conduct a quantitative computational study to design a mechanically stretchable nanomembrane electrode and circuits, 2) fabricate a device including soft membranes, circuit interconnects, and chip components, using a newly developed technique of materials integration and transfer printing, 3) quantitatively measure cell viability on the nanomaterial to demonstrate biocompatibility and structural safety, and 4) study the device feasibility via in vitro, quantitative monitoring of sodium intake. Completion of a working prototype device would represent the first demonstration of real-time monitoring of sodium intake in the human oral cavity. This project will lay the groundwork for other low-profile, implantable nanoelectronics applications needed for the next-generation biomedical systems.

This project will train two undergraduate students via a multi-school research team including Dr. Yeo (Engineering; expertise in nano-micro systems), Dr. Costanzo (Medicine; expertise in smell and taste sensing), Dr. Cheng (Computer Science; expertise in smartphone applications), and Dr. Coffey (Dentistry; expertise in prosthodontics).

2015 Award Recipients

- **Shengfeng Cheng, Ph.D.**

Assistant Professor of Physics

Virginia Polytechnic Institute and State University

“A Computational Model to Study the Self-assembly of Microtubules”

Key Words: Microtubules, Tubulin, Self-assembly, Dynamic Instability, Coarse-graining, Molecular Dynamics, Cytoskeleton

The long-term objective of my research is to understand the nonequilibrium self-assembly of complex building blocks into dynamic superstructures, using microtubules as a model system. As a major component of the cytoskeleton, microtubules are hollow cylinders made of dimeric tubulin proteins. The aim of this proposal is to construct a coarse-grained model of the tubulin dimer (called CG dimer) that can be used to study the self-assembly of microtubules. Based on our previous wedge model of tubular structures, we expect to use 50–70 CG sites to represent each tubulin dimer. The CG dimer should capture both the dynamics and conformation (shape) of tubulin in order to describe both the self-assembly and biomechanics of microtubules. We will exploit the recently available atomistic structures of microtubules. First, atomistic molecular dynamics modeling will be performed on a microtubule segment. A method called essential-dynamics coarse-graining will be used to analyze the atomistic trajectory and identify dynamic domains, the center of mass of which the CG sites will be assigned to. The interactions between CG sites will be harmonic potentials with spring constants parameterized such that the dynamics and shape of tubulin are roughly preserved. The dimer-dimer interactions will occur via surface binding CG sites with strengths matching those of tubulin-tubulin interactions from the atomistic simulation. Our immediate specific aim is to produce microtubules in the self-assembly simulations starting with a solution of free CG dimers, which will yield fresh insights on the kinetics, dynamics, and pathways of microtubule self-assembly and help answer long-standing questions regarding the structure of microtubules. The CG dimer will also enable us to study biomechanics of microtubules, a field attracting substantial interests recently. Our long-term goal is to reproduce dynamic instability in silico with the CG dimer and to test a variety of hypotheses on its molecular mechanisms.

- **Daniel Conway, Ph.D.**

Assistant Professor of Biomedical Engineering
Virginia Commonwealth University

“Measurement of Mechanical Tension on the Nuclear Membrane”

Key Words: Mechanotransduction, Nucleus, Nesprin, Fluorescence resonance energy transfer

Significant mechanical forces have been measured across both cell–matrix and cell–cell adhesions. Despite the availability of techniques to measure forces at the perimeter of the cell, almost nothing is known about how these forces are propagated onto intracellular structures, such as the nucleus. This limitation in knowledge is largely due to a lack of experimental techniques to measure intracellular forces.

We have developed a new technique to measure the mechanical forces applied onto the nucleus, by inserting a fluorescence resonance energy transfer (FRET) tension biosensor in the protein nesprin–2, a nuclear membrane protein that connects the nucleus to the actin cytoskeleton. This technique is based on previous successful sensors to measure mechanical forces across cell–cell and cell–matrix adhesions and we have confirmed functionality of the new nesprin sensor.

Using the sensor in living cells we show that the nucleus is subject to significant mechanical tension and that the magnitude of force is dynamic. In these proposed studies we will use the sensor to investigate two aspects of nuclear forces: 1) the relationship of nuclear force to externally applied forces at the perimeter of the cell and 2) the relationship of nuclear force to the geometry of the nucleus. The sensor will allow for real–time, spatial measurements of the forces applied onto the nucleus. Experimental results will then be used to develop and validate mathematical models that can explain force transmission between the cell surface and the nucleus, and also how nuclear forces regulate nuclear shape. Because nearly every cell contains a nucleus, we anticipate our results will be applicable to the entire field of cell biomechanics.

- **Takeshi Fukao, Ph.D.**

Assistant Professor

Virginia Polytechnic Institute and State University

“Small RNA-mediated Transcriptional Regulatory Networks Governing Adaptation to Submergence and Reoxygenation in Rice”

Key Words: Rice, Environmental stress, Transcriptional regulation, Climate change, Food security

Rice is the staple food for more than half the world's population, including 640 million undernourished people in Asia. Rice is also a fast-growing food staple in Africa and Latin America. Indeed, over one billion people depend on rice cultivation for their livelihood worldwide. Rice is suited to wet environments. However, complete submergence is a major constraint for rice production, resulting in annual losses of over \$1 billion in tropical and subtropical regions. A major regulator of submergence tolerance, SUBMERGENCE-1A (SUB1A), was identified in tolerant rice varieties. Our studies revealed that SUB1A, a plant-specific transcription factor, restricts carbohydrate consumption and elongation growth through transcriptional and hormonal regulation, thereby avoiding energy starvation during submergence. After floodwaters subside, submerged rice encounters re-exposure to oxygen, inducing reoxygenation injury. Recent studies demonstrated that SUB1A also contributes to reoxygenation tolerance. The long-term goal is to elucidate the mechanism of SUB1A-mediated tolerance to submergence and reoxygenation at molecular, cellular, and whole-plant levels. During the one-year of this study, we will dissect small RNA (sRNA)-mediated transcriptional regulation that coordinates submergence and reoxygenation tolerance using a combination of state-of-the-art genomic and computational tools. The specific aims are to 1) determine genes and splice variants that are up- or down-regulated by submergence and reoxygenation in a SUB1A-dependent manner by mRNA-Seq, 2) identify sRNAs that are differentially regulated by SUB1A using sRNA-Seq, and 3) construct sRNA-mediated transcriptional regulatory networks governing submergence and reoxygenation tolerance through integrated analysis of mRNA- and sRNA-Seq data. This study will determine how SUB1A controls expression of genes associated with acclimation to submergence and reoxygenation via sRNA-mediated regulation, providing valuable information for the development of new varieties with further enhanced tolerance. This project will train two undergraduate students at the forefront of interdisciplinary research, spanning the fields of plant physiology, molecular biology, genomics, and bioinformatics.

- **Angela Hilliker, Ph.D.**

Assistant Professor of Biology
University of Richmond

“Using Next Gen Sequencing to Identify Suppressors of Ded1, an RNA ATPase that Promotes Translation”

Key Words: Gene expression, DEAD-box ATPase, Translation regulation, mRNA storage, Yeast genetics, Next gen sequencing

Cells constantly alter gene expression in response to their environment and signals from other cells. One quick and reversible way to alter gene expression is through translation. Under many stresses, most translation is inhibited and mRNAs are stored in cytoplasmic mRNA granules. After stress, some mRNAs quickly return to translation. How mRNAs move between translation and storage is unclear, but the RNA-dependent ATPase, Ded1, promotes this process. Ded1 performs two sequential roles to move mRNAs from storage into translation, in an ATP-dependent manner. We will combine the power of yeast genetics with advances in deep sequencing to identify genes that influence Ded1 function. We have well-characterized mutations in Ded1 that affect each of its two functions and will use these mutations as bait in a genetic screen to find loss-of-function suppressor mutations of ded1 mutants. However, classical ways of identifying suppressors are labor intensive and inefficient. Instead, we will back-cross the suppressors to the parent strain and force the cells to go through meiosis, essentially shuffling all the mutations in the suppressor strain. We will sequence the genome of several spores from meiosis and compare their sequence to the parent strain. The mutation(s) that correlate with the suppression phenotype will reveal the mutation that is responsible for suppression, identifying a new gene that interact with Ded1. By finding regulators of Ded1, we will increase our understanding of factors that are involved in deciding whether mRNAs are translated or stored. Additionally, Ded1's human ortholog, DDX3, is misregulated in a host of cancers and is utilized by Hepatitis C and HIV viruses as they invade human cells. By using yeast to identify regulators of Ded1, we may illuminate new genetic pathways that are relevant to viral infections and cancer progression.

- **Venkat Maruthamuthu, Ph.D.**

Assistant Professor

Old Dominion University Research Foundation

“Developing Quantitative Measures of Mechanical Coherence in Epithelial Tissue”

Key Words: Epithelial Tissue, Cell Biomechanics, Traction Force Microscopy, Particle Imaging Velocimetry, Correlation, Cancer, Finite Element Method

Nearly 85 percent of all cancers occur in epithelial tissue. Moreover, 90 percent of cancer-related deaths are due to one or more cancer cells breaking off from the primary tumor and spreading the cancer. Despite decades of research on the biochemical basis of cancers, the mechanical basis of cancer progression is still unclear. This is largely because very little is known about the mechanical coherence of epithelial tissues themselves, which is determined by the forces exerted among the cells within the tissue.

In this project, we propose to determine quantitative measures of the mechanical coherence of an epithelial cell sheet, using a combination of experiments and multiple computational approaches. We will extend our prior work using high-resolution traction force microscopy to determine the forces exerted by cells within a cell pair to much larger photo-patterned epithelial cell sheets. We will use several computational approaches including particle imaging velocimetry, correlation methods and finite element modeling to determine quantitative metrics of epithelial tissue coherence.

In Specific Aim 1, we will engineer epithelial cell sheets on flexible substrates and measure the deformation caused by cell generated forces in the substrate beneath.

In Specific Aim 2, we will compute the displacement field as well as the traction force field of the substrate due to the epithelial sheet.

In Specific Aim 3, we will first use correlation methods to determine a model-free metric of cell-to-cell mechanical coordination in the epithelial sheet. We will also model the epithelial sheet as an elastic medium and compute inter-cellular forces at individual cell-cell interfaces within the epithelial cell sheet.

Our work will set a quantitative base line for the computed measures of mechanical coherence in epithelial tissue. Understanding how these measures are affected when genes that advance cancer are activated is expected to lead to novel therapeutic targets in the future.

- **C. Daniel Meliza, Ph.D.**

Assistant Professor of Psychology
University of Virginia

“Biophysical, Dynamical–Systems Models of Neurons that Recognize Complex Acoustic Patterns”

Key Words: Sensory neuroscience, Auditory recognition, Neuron models, Dynamical systems

The brain's ability to identify speech sounds in noisy and complex acoustic environments is necessary for language, but the computational principles used to solve this task are poorly understood. Songbirds are a useful model for neural mechanisms of sensory pattern recognition because they also use highly structured and variable vocalizations to communicate. The caudal mesopallium (CM), a region of the avian auditory cortex where learned objects are first extracted from sound stimuli, contains several distinct classes of neuron. Our goal is to determine how these neurons function together to perform this computation by constructing biophysical models that can represent the complex, nonlinear dynamics of the circuit. These models are not easily fit to experimental data, so we are adapting novel statistical data assimilation methods developed for chaotic physical systems. The aims of the proposed research are (1) to use these methods to determine which ionic conductances characterize each class of CM neuron and (2) to use pharmacological and gene expression data to validate these inferences and further develop the data assimilation methods for use with neural systems.

To address these aims, we will make whole–cell recordings from neurons in slices of zebra finch CM and inject current waveforms that activate a broad range of voltage–gated ion channels. The recorded voltage is used to estimate unmeasured states and parameters of Hodgkin–Huxley–form conductance models using nonlinear optimization software developed in collaboration with the Abarbanel group at UC San Diego. Completed models are internally validated by predicting voltage responses to novel injected currents and externally validated with pharmacology and single–cell gene expression data. Progress in this research will yield insight into the function of CM, demonstrate the feasibility of this approach for future study of neuron circuits, and contribute to development of general tools for the study of nonlinear systems.

- **Hua Min, Ph.D.**

Assistant Professor of Health Informatics

George Mason University

“Applying the Ontology-guided Machine Learning to Analyze the Surveillance, Epidemiology, and End Results Program–Medicare Health Outcomes Survey (SEER–MHOS) Linked Database”

Key Words: Personalized Medicine, Data Analysis, Machine Learning, Ontology, Unified Medical Language System

Personalized evidence-based medicine, along with the unprecedented growth in volume and complexity of biomedical Big Data, calls for the use of new intelligent technologies. While many computational researchers in the areas such as Machine Learning (ML) or Data Mining (DM) focus on the ability to process massive amounts of data and build accurate models, the complexity, heterogeneity and semantics of biomedical data are often outside of the mainstream research. Healthcare is particularly rich in domain knowledge and that knowledge has been formally represented by using biomedical ontologies such as the Systematized Nomenclature of Medicine–Clinical Terms (SNOMED–CT), International Classification of Diseases (ICD), and Unified Medical Language System (UMLS). Unfortunately, there is a gap between computational methods and biomedical knowledge. This proposal aims at advancing computational and machine learning methods by leveraging medical ontologies in order to achieve better applicability in real-world healthcare applications. Specifically, the goal is to develop an ontology-guided ML method to promote the effectiveness and efficiency of data analytics in healthcare. The ontology-guided ML involves the use of ontology and verifiable inferences based on the ontology to effectively analyze the complex and heterogeneous biomedical data. The developed method will be applied to a large and complex linked dataset called Surveillance, Epidemiology, and End Results Program–Medicare Health Outcomes Survey (SEER–MHOS).

- **Helen Murphy, Ph.D.**

Assistant Professor of Biology
College of William and Mary

“Exploring the Evolutionary and Molecular Dynamics of Mixed Biofilms to Disrupt their Stability”

Key Words: Biofilms, Microbial community, Cooperation, Cheat, Social evolutionary strategies, Spatial stochastic population modeling, RNA-seq data analysis

Rather than being solitary and free-living, many microorganisms are now recognized as existing in biofilms. These complex communities are attached to a surface and enmeshed in extracellular structures that confer protection to environmental stresses, including antibiotics. Biofilms are found in aquatic and terrestrial systems, in living and dead tissues, even on medical devices. Within these communities, individuals excrete products used by all members. This scenario could favor individuals who do not produce "public goods", but reap the benefit, which leads to the question: How could such cooperative systems evolve and maintain stability, when cheating phenotypes can potentially invade? Indeed, introducing engineered microbial "cheats" to disrupt stable communities, thus making them more susceptible to other interventions, has been proposed as a strategy for combating biofilms when they pose public health risks. Yet this strategy has not been tested due to the difficulty of studying most microbes. Recent work has shown that natural and clinical isolates of the yeast *Saccharomyces cerevisiae* develop complex biofilm colonies. While the genetic underpinnings of this trait are being uncovered, the evolutionary dynamics have yet to be explored. Using lab-based and computational approaches, we will study multi-strain *S. cerevisiae* biofilm communities— an exciting new direction for this model organism. First, using RNA-seq, a quantitative approach to measuring gene expression, we will characterize cells communicating with non-related individuals in a cooperative community, and identify targets for engineering "cheaters". Second, we will use a combination of stochastic spatial population modeling and lab-based experiments to explore a "Trojan Horse" strategy that we designed to disrupt stable communities: introduce a strain engineered to produce both a toxin which kills susceptible cells, and a self-protective anti-toxin. This research will allow us to better understand fungal biofilms and to explore whether disrupting cooperative communities using an evolutionary strategy is feasible.

- **Joseph Reiner, Ph.D.**

Assistant Professor of Physics

Virginia Commonwealth University

“Single Molecule Forensic DNA Analysis with Laser-Induced Nanopore Heating”

Key Words: DNA, Nanopore Sensing, Single Molecule, Laser Heating, Autocorrelation Analysis, Forensic Science, Human Identity, Short Tandem Repeats

Forensic DNA analysis relies on costly and time consuming techniques that can yield incomplete or very complex results, based on the number of people contributing to the sample. This creates a need to develop rapid screening methods that provide previews of the genotype(s) in the sample. Each person has a unique genome that yields differently-sized DNA fragments upon amplification. Determining the number of these fragments in solution can indicate the number of individuals with their DNA on the evidence. Our proposal describes a new approach that can provide this "preview genotype" of the sample, utilizing laser heating in conjunction with nanopore-based resistive pulse sensing. Our initial results show that laser-based heating greatly increases the difference in interaction times between the pore and different sized fragments of DNA. We will utilize this effect to characterize mixtures of differently-sized DNA, which will enable the development of a rapid and cost effective method for prescreening DNA samples for forensic applications. The project will focus on three specific aims: demonstrate that the technique works for sufficiently long DNA molecules, apply the technique to synthesized DNA from a common forensic locus and finally, demonstrate that the technique has real-world applicability by analyzing samples derived from mock forensic evidence.

To achieve these specific aims, we will couple nanopore sensing to laser heating and continue from our preliminary results, which demonstrated successful analysis on 20 and 30 nucleotide long DNA mixtures. The quantitative portion of the project will focus on applying a new type of data analysis to nanopore sensing that utilizes autocorrelation functions. Experimentally, we will explore temperature and voltage parameter space to maximize the difference in sensor interaction times for similarly sized DNA with a target DNA size on the order of commonly used forensic loci (60–100 nucleotides).

- **Kendra Sewall, Ph.D.**

Assistant Professor of Biological Sciences

Virginia Polytechnic Institute and State University

“Using Social Network Models and Manipulations of Glucocorticoids to Understand How The Social Environment Impacts Neural Function”

Key Words: Neural plasticity, Social modulation, Glucocorticoids, RFID

The broad aim of this research is to characterize the direct impacts of social interaction on brain function. We know that social contact is essential to normative brain function because it provides enrichment and learning opportunities. However, social interactions are also one of the best-documented sources of chronic "stress," and can induce high levels of stress hormones (glucocorticoids). At very high levels glucocorticoid can impair neural plasticity, thereby compromising brain function. Individuals differ in their experiences of the benefits of social contact and detriments of socially-induced glucocorticoids, so quantifying the impacts of social interaction on brain function requires manipulating both variables and measuring outcomes in an animal model. The proposed work will manipulate social contact by housing animals in large (high contact) or small (low contact) groups and glucocorticoid levels (using sham or hormone implants) in a social bird, the zebra finch (*Taeniopygia guttata*), using a full factorial design. Zebra finches are a compelling study system because they live in groups of varying size and are an established neurobiological model. Importantly, because individuals experience differing levels of social contact or socially-induced "stress" within their social groups, independent of the experimental manipulation, we will use RFID (radio frequency identification) technology for tracking individuals to generate mathematical models of social dynamics, to identify factors underlying individual variation in brain measures. Subjects' brain function will be evaluated using three cognition assays and measures of neuronal survival, neuron density, and synaptic plasticity. Thus, the proposed study is highly interdisciplinary and integrates work from molecular and cellular neurobiology, cognitive neuroscience, and stress physiology with mathematical modeling, to better understand the effects of the social environment on brain function. Undergraduate researchers will contribute to all aspects of the research and be trained in computational approaches, cognitive neuroscience, and cellular and molecular neurobiology.

- **Karsten Siller, Ph.D.**

Research Assistant Professor
University of Virginia

“Intelligent Microscopy: Self-guided Image Acquisition and Quantitative Analysis in Neural Stem Cell and Neuronal Degeneration Research”

Key Words: Light microscopy automation, Quantitative image analysis, Stem cells, Neuronal degeneration

Technological advances in light microscopy facilitate the investigation of molecular and cellular mechanisms underlying tissue development in normal and disease states, including stem cell behavior and neuronal degeneration. A challenge in microscopy is the imaging of sparsely distributed cells at unknown positions, which either requires laborious search for "regions-of-interest" (ROIs), or tiled imaging of the encompassing area, creating an overhead of insignificant images without cells of interest. Time-lapse microscopy may be particularly challenging when attempting to capture rare cellular events in a preselected single ROI, because chosen cells may never exhibit the "event-of-interest" during the time of observation. We developed a software tool, AutoImage, for the widely used open-source Micro-Manager software package that converts "conventional" microscopes into automated imaging platforms. The specific project goals are: 1) Extension of AutoImage function to enable "intelligent acquisition" modes where acquisition parameters are dynamically adjusted using realtime image analysis for self-guided "region-of-interest" or "event-of-interest" imaging; 2) Utilization of AutoImage for quantitative investigation of cellular mechanisms controlling neuronal degeneration and neural stem cell migration; and 3) Interdisciplinary training for undergraduate students in computational science and biology involved in the here proposed project. In the long-term, our results are expected to advance our mechanistic insights into these biologically important processes, which may lead to new future therapeutic acute spinal cord injury intervention therapies and a better understanding of abnormal stem cell migration events such as tumor metastasis. Furthermore, we will disseminate AutoImage bundled with the widely used open-source Micro-Manager microscope control software package, thereby facilitating the broad utilization of our software free of charge on a wide range of microscope systems in the scientific community.

- **Isaiah Sumner, Ph.D.**

Assistant Professor of Chemistry and Biochemistry

James Madison University

“Computational and Biochemical Determination of the Mechanism of Thioester Aminolysis”

Key Words: Post-translational modification, Acetylation, Ubiquitin, Molecular dynamics, Metadynamics, QM/MM

Protein post-translational modification (PTM) is a rapid method for cells to respond to changes in internal or environmental stimuli. Despite the prevalence of PTMs in regulating all cellular pathways, the mechanisms used by the enzymes that carry out the modifications are relatively unknown. We propose to combine computer simulations with experimental biochemistry to uncover the mechanisms used by enzymes that catalyze two types of modifications: ubiquitination and acetylation. Defects in the enzymes catalyze these PTMs can result in neurological disorders, anemia, cancer, insomnia, and viral infection. Therefore, a better understanding of the enzymes' mechanisms could lead to treatments for these diseases. However, there are currently no studies on these enzymes which conclusively show the reaction pathway. It is currently assumed that both ubiquitin and acetyl transferases use the same mechanism despite significant differences in their amino acid sequences and overall structures. Namely, both enzyme families are proposed to proceed through a charged, tetrahedral intermediate. However, there is no direct evidence for this structure and recent studies suggest that alternate intermediates are possible. Therefore, we aim to determine and compare the reaction pathways for representative members of the acetyl and ubiquitin transfer family of enzymes. First, we will use ab initio molecular dynamics (computation) to predict the transition states for each enzyme class. Second, we will provide information on transition structures with biochemical assays (experiment). This interdisciplinary approach is necessary to reach unambiguous conclusions since the biochemical experiments will confirm the accuracy of the modeling and the modeling will eliminate alternate interpretations of the experimental data. Finally, this study will be the first of its kind directed at determining the reaction mechanism for these two families of enzymes and is the first in a planned series of studies targeting the myriad of enzymes that catalyze these deceptively simple chemical reactions.

2014 Award Recipients

- **Linda Columbus, Ph.D.**

Associate Professor of Chemistry
University of Virginia

“Using Hybrid Computational and NMR Structure Determination to Study Host–pathogen Interactions at the Molecular Level”

Key Words: Membrane proteins, Molecular recognition, Protein dynamics

Many pathogenic bacterial membrane proteins hijack human cellular pathways by mimicking or manipulating the host machinery. The outer membrane opacity-associated (Opa) proteins of *Neisseriae* exemplify this by binding to specific receptors and inducing engulfment of the bacterium even in non-phagocytic host cells. Receptor recognition by Opa proteins provides an example where structural plasticity is key to biological function. This plasticity is not easily investigated with standard methods, so we have developed a hybrid computational approach to provide a more complete view of the dynamic structural ensemble with which Opa proteins recognize their receptors. This computational approach maintains consistency with the NMR data but, compared to the standard NMR refinement methods, provides a more detailed physical model and more extensive sampling of conformational space. In this refined ensemble, the extracellular loops of Opa60 are dynamic and not folded into a well-defined structure, yet they display transient interactions. Since Opa–receptor interactions differ among variants, we hypothesize that the high degree of plasticity is required to allow diverse sequences to engage a common set of receptors. We aim to test this hypothesis using computational studies of three Opa proteins, as well as with Opa–receptor complexes. The results of these aims, the dynamical and structural data obtained from investigating the variety of Opa sequences and their interactions with human receptors, will enrich our understanding of molecular recognition and also significantly contribute to the field of protein–protein interactions. In addition, the field of structural biology is shifting and evolving beyond static structures and incorporating state-of-the-art computational analysis and dynamics into the understanding of the protein function. The proposed investigations will be at the forefront of this evolution and provide methodological platforms for structure calculations and analysis.

- **Denis Demchenko, Ph.D.**

Associate Professor

Virginia Commonwealth University

“Microscopic Mechanisms of Defect Luminescence in Wide Bandgap Semiconductors”

Key Words: Gallium Nitride, Solid-state lighting, Photoluminescence, Semiconductor dopants

Current energy efficient fluorescent lighting sources contain mercury, produce unnatural light spectrum, and have limited lifetime. In contrast, solid-state light emitting devices can be made from benign and abundant materials, produce almost ten times more light per watt, and last about one hundred times longer. GaN is an exceptional semiconductor that can be used in a wide range of devices, including bright blue and UV light-emitting devices and laser diodes. However, the properties and reliability of these devices significantly depend on point defects in the materials. The proposed computational/experimental program attempts to identify a number of point defects commonly present in GaN and to obtain a clear and comprehensive understanding of their luminescence properties. This will improve our basic understanding of point defects in semiconductors, the mechanisms of radiative and nonradiative recombination, as well as lead to significant improvements in device performance for solid-state lighting applications.

The computational part of this project will guide the experimental collaborators to perform specific experiments in defect identification. Our recent results on the yellow band in GaN [Physical Review Letters 110, 087404 (2013)] indicate that including bound defect complexes in computational modeling is crucial to capture the defect physics. Therefore we propose to advance this field by introducing uniaxial pressure PL measurements, where lattice deformation would lead to measurable PL changes, which can be immediately compared to the accompanying hybrid functional calculations. The anisotropic complexes will produce a much stronger uniaxial pressure response (i.e. changes in PL polarization), and therefore PL due to defect complexes can be distinguished from that of the isolated defects. This integration of experiment and theory would significantly optimize the investigation by reducing an array of possible defect structure candidates that need to be calculated and compared with experimental measurements.

- **David Gauthier, Ph.D.**

Associate Professor of Biological Sciences

Old Dominion University Research Foundation

“Advanced Phylogenomics of the Human and Animal Pathogen *Mycobacterium marinum*”

Key Words: High-Throughput Sequencing, Genomics, *Mycobacterium marinum*

Mycobacterium marinum is a significant bacterial pathogen of fishes and other animals, and causes major losses in wild populations and aquaculture. *M. marinum* and related bacteria are also zoonotic human pathogens and can cause severe skin infections requiring lengthy antibiotic therapy and/or surgery. In Chesapeake Bay, USA, these bacteria cause a major disease of striped bass, or rockfish (*Morone saxatilis*), an economically and ecologically important fish species. In this work, we will perform whole-genome Illumina sequencing of at least 24 *M. marinum* strains and related species from human, animal, and environmental sources. Genomic information will be used to determine relatedness within the group and examine genetic and metabolic patterns of evolution from free-living bacteria to obligate animal pathogens. This information will allow us to sensitively track infection outbreaks in humans and animals, which will aid in control and prevention of disease. Whole-genome information on this bacterial group will also be useful for vaccine development in humans and animals, including potential use of the striped bass pathogen *M. shottsii* as a vaccine or vaccine vector against *M. tuberculosis*. Assembly of mycobacterial genomes from high-throughput sequence data is complicated due to genomic repeat regions, therefore we propose to develop novel, open-source algorithms to guide genome assembly and finishing. One such algorithm, the Correlative Algorithm for Repeat Placement (CARP), will use raw sequence reads to both identify and accurately place problematic repeats, thus minimizing expensive manual finishing and improving efficiency of prokaryotic genome finishing. This project is therefore highly interdisciplinary between biological and computer sciences. Undergraduate researchers will play a central role in the proposed work, and will be cross-trained in advanced DNA sequencing and analysis, as well as advanced computational methods. These students will therefore be highly competitive for advanced careers in biotechnology and STEM-related fields.

- **Julia Halterman, Ph.D.**

Assistant Professor of Biology
Eastern Mennonite University

“High-Salt Diet-Induced Regulation of NFAT5 in Hypertension”

Key Words: High-salt diet, Hypertension, Blood pressure, RNA expression, NFAT5

Currently in the United States, 1 out of every 3 adults suffers from hypertension (high blood pressure [BP]). Diet and nutrition influence the expression of proteins within the body, and unhealthy diets can increase tissue inflammation, raise BP, and produce dysfunction within various organ systems. It is understood that sustained consumption of a high-salt diet (HSD) in humans increases the risk and prevalence of hypertension; however, the molecular mechanisms behind how high-salt diets alter organ function are unknown. Nuclear factor of activated T-cells 5 (NFAT5) is the only known mammalian transcription factor sensitive to changes in salt concentrations. Although NFAT5 expression has been extensively studied under high-salt concentrations in vitro, it is unknown how dietary salt consumption in vivo will alter systemic expression of NFAT5 and how this adaptation contributes to hypertension. We hypothesize that consumption of a HSD increases tissue-specific expression of NFAT5, resulting in the upregulation of NFAT5-dependent genes involved in elevating BP in hypertension. The aims of our research are two-fold: 1) To determine how consumption of a HSD alters tissue-specific NFAT5 expression and BP in rats, and 2) To identify the genes regulated by NFAT5 in hypertension. Rats will be placed on a high-, intermediate-, or normal-salt diet for 6 weeks and injections of an anti-NFAT5 antibody will test the effects of NFAT5 activity on BP regulation. Daily BP measurements will be recorded, and 16 tissues will be analyzed for NFAT5 expression using quantitative real-time PCR. A computational cross-analysis of microarray datasets will identify novel salt-sensitive genes putatively regulated by NFAT5 in hypertension. Rat tissues from the in vivo studies will be used to further validate these genes as NFAT5 targets in HSD-induced hypertension. These pilot studies will provide the first understanding as to how diet alters NFAT5 expression, BP control, and gene expression in hypertension.

- **Christine May, Ph.D.**

Assistant Professor of Biology

James Madison University

“Developing an Innovative Mathematical Simulation Model to Inform Recovery Strategies for the Endangered James Spiny mussel (*Pleurobema collina*)”

Key Words: Freshwater mussels, Detection probabilities, Occupancy modeling, Endangered species

The James Spiny mussel (*Pleurobema collina*) is the top priority species for recovery of all Endangered Species in Virginia. Spiny mussels frequently burrow into the substrate, rendering them unavailable for observation, and when this low detection rate is combined with its rarity the result is an inability to determine the species occurrence and trends in abundance.

The objectives of the proposed study are to: (1) develop a mathematical simulation model to quantify temporally variable detection probabilities used to determine whether the species is present in an area and to rigorously quantify population trends, and (2) identify survival probabilities by tracking individually marked mussels in different habitats. To address these objectives we propose a combined strategy of experimentation, field observations, and innovative mathematical and statistical computations.

The first objective will utilize experimental stream channels to quantify how frequently mussels are exposed at the surface of the streambed and visible to an observer. This information will be used to establish detection probabilities, and how these probabilities are affected by temperature and stream discharge. A mathematical simulation will mimic this experimental set-up, and a statistical model will be developed to estimate the combined effect of these variables. This knowledge will be used to distinguish between the true absence of the species versus failure to detect its presence, and allow for accurate estimates of population trends.

For the second objective, individual mussels will be uniquely marked and tracked through time. Based on relevant habitat conditions a statistical analysis will detect temporal trends in survival probabilities in different habitats. Without this basic ability to decipher habitats with high survival, recovery of the James Spiny mussel is severely limited.

This study will serve as an example of how to use quantitative methods to assist in Endangered Species recovery and will be developed into a teacher's case study.

- **Suzanne Robertson, Ph.D.**

Assistant Professor

Virginia Commonwealth University

“The Impact of Temporal Variation in Host Life–Stage Abundance on the Regional Transmission and Control of West Nile Virus”

Key Words: West Nile virus, Mathematical epidemiology, Differential equation, Stage–structure

West Nile virus (WNV), a vector–borne pathogen, is an annual public health problem in Virginia. Although the timing of WNV outbreaks coincides with the end of the avian nesting season, no specific connection between this event and the mechanism responsible for seasonal amplification of the virus in the mosquito population has yet been demonstrated.

Heterogeneity among host species is known to structure WNV transmission, but within–host variability such as age or life–stage differences has not been well explored. Nestlings, newly hatched birds, are extremely vulnerable to mosquitoes and may receive a disproportionately high number of bites over other avian age classes (fledglings and adults). Although the total avian population size increases throughout the season, nestling abundance decreases at the end of the brooding season. This may concentrate mosquitoes on the last few remaining nestlings, significantly increasing the vector–host contact ratio and potentially leading to the amplification of the virus in the vector population.

We propose to develop and use a novel ordinary differential equation model for WNV in avian and human hosts, incorporating avian stage–structure with stage–specific vector feeding preferences, to gain insight into the ecological mechanisms responsible for the observed seasonal outbreaks in Virginia and to determine the extent to which temporal fluctuations in specific host stage abundance influence WNV transmission.

We will gather local data on avian nesting parameters, perform a sensitivity analysis to determine how model parameters such as biting preference, vector abundance and nesting phenology affect the timing and magnitude of WNV transmission, and use optimal control theory to determine the most effective combination of mitigation strategies throughout the season to reduce West Nile virus cases and guide regional public health interventions for WNV.

- **Michael Shirts, Ph.D.**

Assistant Professor, Chemical Engineering

University of Virginia

“Understanding and Predicting Pharmaceutical Binding to Blood Plasma Proteins”

Key Words: Blood plasma proteins, Molecular simulation, Molecular dynamics, Biophysics, Free energy calculations, Drug design

The purpose of this project is to develop computational methods for the quantitative prediction of drug binding to human serum albumin (HSA) and other blood serum proteins as part of the drug design process.

Understanding how small molecule pharmaceuticals interact with blood plasma proteins is a necessary step in making an effective drug. Blood plasma proteins play a central role in the pharmacokinetics of virtually all drugs entering the bloodstream. Drugs binding too tightly to these proteins will not be available to take action in the body. However, drugs that are not naturally soluble in blood or are cleared from the body quickly can be stabilized if they bind moderately to these proteins.

There are no good existing computational methods to predict a putative drug's serum protein binding. This means that significant time and money is lost in the drug development process on trial-and-error experimentation. We need improved computational methods to determine to what extent small molecules will bind to these proteins even before they are synthesized.

In this project, we will simulate at atomic resolution the interactions of HSA, the most abundant blood serum protein, with drug molecules of interest. The computations are enabled by a set of molecular simulation algorithms we have recently developed. This level of simulation allows us to explore interactions of the drugs over the entire protein surface. We will use these simulations to predict binding locations and the network of molecular interactions between the drug molecules and HSA, as well as the overall binding affinity. We will start with a small, carefully curated experimental data set and then move on to larger datasets and blind predictions. If successful, this research will yield tools for fast and accurate prediction of HSA binding and substantially reduce the costs of new drug development.

- **Ryan Taylor, Ph.D.**

Assistant Professor of Mechanical Engineering
Virginia Military Institute

“Investigation of Internal Thermally Active Oscillating Flows using Computational Fluid Dynamics and Non-Contact Laser Imaging”

Key Words: CFD, Oscillating Flow, Heat Transfer, Laser Imaging, MTV&T

The goal of our research is to advance the understanding of internal, thermally active oscillating gas flows allowing for development of next-generation thermal transport technology. This specific type of flow is unique as thermal energy can be transported from cold to warm regions using an oscillating pressure wave. Problems that plague this type of flow stem from boundary layer and buoyancy driven hydrodynamics coupled with thermal convection linked to the hydrodynamic field. Presently, these advanced hydrodynamic and thermal phenomena are not well understood and advances in understanding will aid the use of oscillating gas flows for thermal transport. Impacts of this work include development of more efficient heat transport systems and advancement of cryogenic cooling technology aiding the next generation of IR space satellites aiding weather prediction, high-speed communication systems, and minimize reliance on liquid cryogenics for low temperature applications.

Our research advances the knowledge of internally, thermally active oscillating flows using detailed computational modeling validated with non-contact laser flow measurements. Computational modeling is performed using a developed high-fidelity three-dimensional computational fluid dynamic model capable of capturing all relevant physics (boundary layer transport, buoyancy driven convection, and hydrodynamic stability). This model is used to perform a parametric study of internal, thermally active oscillating gas flows over an oscillating Reynolds number range that spans six orders of magnitude. Validation of the modeling predictions is achieved using Molecular Tagging Velocimetry and Thermometry (MTV&T) in a custom oscillating test flow facility. The MTV&T technique allows for simultaneous measurement, in a non-contact manner, of the velocity and temperature of the oscillating gas using the phosphorescent emission of a tracer gas. Correlations will be developed using the validated results for energy transport as a function of an oscillating Reynolds number and gravitational orientation for the greater research community to aid next generation thermal transport applications.

- **Natalia Toporikova, Ph.D.**

Assistant Professor of Biology and Neuroscience
Washington and Lee University

“Using Gene Expression and Mathematical Modeling to Uncover the Effects of Diet-induced Obesity on Reproductive Hormone Cycling and Fertility”

Key Words: Western diet, Diet-induced infertility, Reproductive hormones, Prolactin, Luteinizing hormone, Gene expression

Obesity can lead to irregularities in the menstrual cycle, reducing conception rates in both therapeutically assisted and natural reproduction. Proper reproductive hormone signaling requires coordination between the central nervous system and peripheral tissues such as ovaries. Diet-induced obesity disrupts the amplitude and timing of hormone surges; however, the mechanism underlying these changes remains unclear. Therefore, we propose a novel investigation of the physiological and molecular mechanics that underlie the adverse effects of obesity on female fertility. Rats are a compelling model for studying reproductive hormones, physiological effects of diet-induced obesity, and regulation of gene expression in the nervous system and reproductive tissues. Although the effects of diet on gene expression in a variety of tissues have been well characterized in male rats, the molecular events associated with diet-induced changes in female reproductive hormone signaling are not well described. Consequently, we will create a model of diet-induced obesity by feeding juvenile female rats either a control or Western-style diet. Ovaries will be removed from all of the animals (OVX) and then half will be implanted with slow-release estradiol pellets (OVXE). This creates a simplified model of hormonal surges which allows us to isolate the contribution of the central nervous system in the absence of signaling from peripheral tissue. These physiological observations will be combined with gene expression analysis of relevant tissues (RNA-Seq). This analysis will identify regulatory systems that are specifically modulated in response to both diet and the reproductive hormone cycle. Finally, we will integrate physiological and gene expression signals into our current mathematical model of hormonal signaling in OVX and OVXE animals. Our ultimate goal is to develop a working model for the effects of obesity on hormonal signaling at the physiological and molecular levels in order to predict therapeutic targets that might be utilized to mitigate diet-induced infertility.

- **Qi Wei, Ph.D.**

Assistant Professor of Bioengineering
George Mason University

“A Novel Computational Model to Study Human Eye Movement Disorders”

Key Words: Computational modeling, Biomechanical simulation, Ultrasound imaging, Eye movement, Strabismus

The objective of this project is to develop novel data-driven computation models to simulate eye movement in three dimensions, critical to elucidate the underlying mechanism and improve treatment of eye movement abnormalities. Strabismus is a prevalent eye movement disorder causing binocular misalignment. According to the American Academy of Ophthalmology, strabismus affects approximately four percent of the US population. The causes of strabismus are complicated, making effective diagnosis and treatment difficult. Our long term goal is to use data-driven computational simulation to advance our understanding of the generation of eye movement under both normal and abnormal conditions, which will potentially improve the quality of life of millions of strabismus patients.

Computational models of the ocular biomechanics are known to be necessary to reveal the underlying mechanism of eye movement, and are complementary to experimental studies. However, existing models are either biomechanically unrealistic or limited to static simulation of eye fixation. Leveraging previous work by the investigators, we propose to develop a data-driven ocular biomechanics simulator integrating ultrasound measurement that overcomes many drawbacks of published models.

The first specific aim is to research and develop a multi-scale computational model of the oculomotor plant, which will be the first biomechanical model capable of simulating eye movement dynamics. We will use the model to: (a) simulate important yet controversial hypothesis on the eye kinematics and (b) predict whether separate neural control in two dimensions is sufficient to drive the oculomotor plant. The second aim is to research novel ophthalmic ultrasound techniques to measure extraocular muscles (EOM) deformation in vivo. Quantified EOM kinematics will be integrated in eye movement simulation and used to validate the model. The third aim is to develop a patient-specific biomechanics simulator for strabismus diagnosis and surgical treatment planning.

2013 Award Recipients

- **Michel Audette, Ph.D.**

Assistant Professor

Old Dominion University Research Foundation

“Development of Patient-Specific Spine Modeling and Surgery Simulation”

Key Words: Surgery Simulation, Anatomical Modeling, Patient-Specific, Discectomy, Open-Source Software, Haptics, Biomechanics

Surgical efficacy can be improved by simulation-based training, but the latter generally does not address the requirements of spine surgery, despite a clinical need. Existing work is limited to commercial simulation emphasizing needle insertion and generic anatomy, while spine surgery requires anatomically faithful, biomechanically predictive volumetric simulation. There is strong justification for simulation of spine therapy that is predictive and interactive, patient-specific, and extensible to radiotherapy and emerging therapies. Inter-vertebral disc degeneration afflicts approximately 100 million Americans, while intervention is also indicated for spinal metastatic tumors and spinal cord injury. Simulation could improve in all areas the efficacy of residents and experienced surgeons mastering new therapies.

This project, part of a broad haptics and GPU-based neurosurgery simulation effort, will lay the groundwork for a patient-specific spine surgery simulator, through minimally supervised anatomical model computation and simulation of minimally invasive discectomy. We also exploit open-source Simulation Open Framework Architecture (SOFA) and strategic collaborations.

The first aim of this project is a multi-surface spine model, through active multi-surface simplex modeling and particle filter-based tractography. Boundaries will include vertebrae, inter-vertebral disks, meninges, spinal cord and spinal nerves. The simplex is an active surface mesh model governed by pseudo-physical forces. Spinal nerve identification will build on particle filtering and tractographic MRI diffusion data. A neurosurgeon will provide clinical oversight.

The second aim is the simulation of resection of herniated disc, leveraging preliminary work on meshless cutting and ellipsoidal forceps bite modeling. The bite model represents a family of bite shapes that account for various opening angles, with the correct shape looked up in real-time from haptic opening angle. This project will build on research conducted by graduate and undergraduate students, whose work will be potentiated by open-source software tools including SOFA, in conjunction with the PI's development of ODU classes built on these tools.

- **David Edwards, Ph.D.**

Assistant Professor of Statistics

Virginia Commonwealth University

“The Truth about Bacterial Metagenomics: Uncovering Bias using Mixture Effect Models”

Key Words: Design of Experiments, Mixture Effect Models, Metagenomics, Microbiome

Complex microbial communities are present in every ecosystem on earth. However, our understanding of how microbial diversity varies over space and time is lacking, hampering our ability to forecast potential alterations in community structure and ecosystem function that may result from disease or global climate change. Characterization of the diversity and composition of the metagenome of a community is currently hindered by the introduction of bias during the processing of a metagenomic sample. This project, through designed experiments and computational modeling, will identify the sources of bias and quantify their impact. The resulting models can be applied to environmental samples to predict true quantities of bacteria based on the observed quantities. An experimental and computational protocol will be developed for future investigations in bacterial metagenomics, enabling scientists to make more precise comparisons between bacterial communities.

The specific aims of this project are to answer the following questions:

1. What contributes to bias in 16s rRNA based characterization of metagenomic samples?
2. Does the presence of a certain bacterium increase or decrease the observed proportions of other bacteria?
3. Can computational models predict the true proportion of bacteria in a sample based on observed proportions?

To answer these questions, mock communities will be designed and community amplicons sequenced using the Illumina platform. The resulting data will be analyzed using mixture effect models to isolate and quantify different aspects of sample processing bias. Possible sources of bias include differences in cell lysis efficiencies, nonlinear PCR amplification, differences in 16s rRNA copy number, and bias introduced during amplicon sequencing. Mixture effect models will be fit to answer the questions in the specific aims. Moreover, by designing a soil relevant mock community, the results generated by this project are applicable to the next microbial ecology challenge: characterization of the earth microbiome.

- **Celso Ferreira, Ph.D.**

Assistant Professor of Civil Engineering
George Mason University

“Protecting Virginia from Hurricane Storm Surge with Wetlands Ecosystems: Can Nature Help to Reduce Hurricane Flood Risk?”

Key Words: Hurricane flooding, Wetlands ecosystems, Flood protection

Hurricanes are one of the most costly natural disasters impacting the US coastal areas and the State of Virginia has historically faced severe impacts from these storms (e.g., Isabel [2003] and Sandy [2012]). Although coastal areas are predominantly at risk from storm surge flooding, areas along the Chesapeake Bay and its tributaries are also extremely vulnerable to hurricane flooding. It is believed that coastal wetlands, besides its ecological importance, might help to reduce the impact of storm surge, acting as a natural protection against hurricane flooding, especially for small hurricanes and tropical storms. Here, we propose to develop a novel framework integrating high performance computing of hurricane storm surge flooding, hydrodynamics characterization of flow through natural wetlands ecosystems and critical infrastructure inventory to investigate the potential of wetlands to reduce hurricane flooding, improving our basic understanding of natural hazards and our capability to expand the State resilience to such events. To improve our fundamental knowledge of tide and storm surge hydrodynamics in wetlands ecosystems, four study sites in the eastern shore will be equipped with sensors to thoroughly monitor water levels within wetlands ecosystems and field survey will be performed in these sites to measure vegetation structural characteristics contributing to flow resistance (i.e. height, diameter and stem density). The field campaigns information will support the development and calibration of computational models to simulate storm surge flow over wetlands specifically designed to represent Virginia's aquatic vegetation. A multi-model, multi-scale, multi-resolution approach will be developed to integrate High Performance Computing (HPC) of large scale and high resolution hurricane storm surge modeling and small scale high fidelity models to evaluate the benefits of wetlands ecosystems to reduce storm surge and related damage to critical infrastructure quantified using geospatial analyses. Quantifying these benefits will provide sound scientific information to support planning and decision making.

- **Grace Lim-Fong, Ph.D.**

Assistant Professor of Biology

Randolph-Macon College

“Genomic and Transcriptomic Analyses of an Unculturable Marine Bacterial Symbiont”

Key Words: Systems biology, Symbiosis, Genomics, Transcriptomics, Constraint-based modeling, Bryozoan, Bryostatin, Unculturable bacteria

Symbiotic bacteria residing in marine invertebrates are the source of many bioactive metabolites. However, the inability to culture these symbiotic microbes has hampered the development of the bioactive metabolites into pharmaceutically useful compounds. Our long-term goal is to understand the evolution and ecology of bioactive metabolite symbiosis. The proposed project is a collaborative effort between a marine microbial ecologist trained in natural product symbiosis and a systems biologist with expertise in genomic analysis and metabolic modeling to address a newly emerging research opportunity catalyzed by the declining cost of DNA sequencing and advances in computational methods. These techniques allow us to investigate a previously intractable microbe that makes a promising drug candidate. In this proposal, we seek to sequence the genomes of four unculturable bacterial symbionts using high-throughput sequencing technology. These symbionts, called *Candidatus Endobugula*, are found in the marine bryozoan genus *Bugula* and are the source of bryostatins, a family of polyketides which have anti-cancer, anti-Alzheimer's and anti-HIV properties. Genome sequencing will not only reveal the genes required for bryostatin biosynthesis and other functions that the symbiont may serve, but will also provide the framework to develop and test hypotheses regarding the ecology and evolution of the symbiosis. Using information from the annotated genomes, we will also apply the constraint-based modeling approach to construct genome-scale metabolic models to uncover active and missing pathways in the symbionts, from which insights regarding the host contribution to the symbiosis can be gleaned. The metabolic interaction between the host and symbiont will be further dissected by analyzing the meta-transcriptome of one symbiotic pair: *B. neritina* and *Ca. E. sertula*. Three undergraduates will be recruited to participate in this interdisciplinary project, which broadly spans the fields of natural product chemistry, marine ecology, and computational biology.

- **Thomas O'Halloran, Ph.D.**

Assistant Professor of Environmental Science
Sweet Briar College

“Predicting Aerosol Nucleation Events and their Contribution to Climatologically Significant Atmospheric Particles in Central Virginia using Field Measurements and Modeling”

Key Words: Aerosol, aerosol nucleation, New particle formation, Particulate matter, Nanoparticles, Classification and regression tree, Symbolic regression, Data mining

Atmospheric aerosols are significant because they can be harmful to human health when inhaled, they reduce visibility, and they are important modulators of Earth's climate, but their complex climate effects are poorly understood. Depending on their size, chemical composition, and location in the atmosphere, aerosols can have either a warming or cooling effect on climate. Aerosols that are large and hydrophilic can act as cloud condensation nuclei (CCN), and thereby affect the radiative properties of clouds and their ability to produce precipitation. New particle formation via aerosol nucleation is a major source of aerosols to the atmosphere, yet the physical and chemical processes comprising nucleation are poorly understood. This study will contribute new knowledge regarding the controls on aerosol nucleation by measuring nanoparticle formation events in ambient air using scanning mobility particle sizers, as well as meteorological variables and precursor gas concentrations at a site in rural central Virginia. Research will take place during summer 2014 with the assistance of undergraduates at Sweet Briar College, a women's liberal arts college in Amherst County, Virginia. Sweet Briar's 3,250 acres contain over 1,500 acres of predominantly oak forest, which are among the strongest emitters of natural volatile organic compounds (VOCs) of any forest type in the world. These natural VOCs combine with local and upwind sources of air pollution to produce the summer hazes that are characteristic of the southeast, and rival the optical thickness of hazes observed worldwide. This project will develop a new statistical framework for predicting the occurrence of aerosol nucleation events by employing state-of-the-science modeling techniques drawn from data mining, including classification and regression tree analysis, and symbolic regression. These nonparametric techniques should be ideal for predicting the highly nonlinear processes involved in new particle formation, which includes tree physiological processes, atmospheric dynamics, and heterogeneous atmospheric chemistry.

- **Enrico Rossi, Ph.D.**

Assistant Professor of Physics
College of William and Mary

“Computational Tools for Controlling Thin Films Properties for Optoelectronics and Nanotechnology Applications”

Key Words: Thin Films, Vanadium Dioxide, Electronic Properties, Metal–Insulator Transition, Ultrafast Optics, Heterogeneous Systems, Disorder

The goal of the proposed research program is to develop a computational tool to model the electrical and optical properties of realistic thin films in close synergy with an experimental effort. While thin films are important in a very wide range of applications, their properties are hard to predict, since traditional theoretical approaches meet significant difficulties accounting for the effects of inhomogeneities that are intrinsic for most thin films due to stresses, doping, and impurities. The proposed research will apply a novel approach to the problem that will take into account the realistic inhomogeneities of a film.

The proposed program will focus on producing an accurate model that will describe the properties of VO₂ films during the insulator-to-metal transition that can be induced in this material thermally or optically. This material (especially in thin film form) has many potential applications in electronics, telecommunications and environmental designs. Yet, a complete theoretical description of its properties still does not exist.

Various computational approaches will be verified through a thorough experimental characterization of various samples. This synergy between computational and experimental work will ensure the accuracy, versatility, and immediate applicability of the resulting computational tools.

The outcome of the proposed research will be a theoretical–experimental approach that will provide the revolutionary capability to characterize the inhomogeneous electronic structure of a system using only far–field measurements.

This project is also an excellent tool for involving advanced undergraduate students in high–level scientific research. Both computational and experimental work will require significant training provided by the PIs and the involved graduate students and therefore offer a unique research and training experience for the undergraduate participants.

- **Ryan Senger, Ph.D.**

Assistant Professor

Virginia Polytechnic Institute and State University

“Engineering a De Novo Biosynthetic Pathway to Make the Valuable Building Block Chemical 2-Pyrrolidone”

Key Words: Synthetic biology, De novo biosynthetic pathways, Renewable biochemicals, Sustainability

This research will produce a model-guided platform to enable high productivity of novel chemicals by de novo biosynthetic pathways installed in microbial chemical factories. Over the past decade, synthetic biology has enabled the production of non-native chemicals by microbes. These efforts must expand dramatically if society is to obtain its chemicals, pharmaceuticals, and materials from renewable resources. The proposed model-guided platform relies on (i) de novo biosynthetic pathway discovery using a novel algorithm and (ii) molecular docking and dynamics simulation studies to determine interactions of existing enzymes with non-native substrates and identification of optimal variants and enzyme engineering targets. In this research, the platform will be used to produce the high-value building-block 2-pyrrolidone from crystalline cellulose substrate. Over 700 differently substituted pyrrolidones with industrial and pharmaceutical value can be derived from this building-block. To achieve high levels of production of 2-pyrrolidone, candidate de novo biosynthetic pathways to 2-pyrrolidone (from 1-pyrroline-5-carboxylate) will be evaluated through molecular docking and dynamics simulations to select optimal variants and identify potential amino acid modifications. While 2-pyrrolidone is an important chemical product, the methodology derived in this research will apply broadly to all newly derived de novo biosynthetic pathways.

- **Amarda Shehu, Ph.D.**

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“Probabilistic Search Algorithms Meet Statistical Mechanics: Powerful Novel Tools for Peptide Modeling”

Key Words: Peptide Modeling, Structural Diversity, Function Modulation, Stable and Semi-stable Structural States, Structural Transitions, Probabilistic Search, Statistical Mechanics, Energy Surface, Free Energy, Stability Estimation

The objective of this pilot study is to establish a novel and unified computational framework to advance modeling and simulation of biological peptides central to disease and therapeutic treatment by providing a detailed characterization of the structure–function relationship. The study establishes seminal interdisciplinary collaborative research integrating cutting–edge computational approaches in Shehu's lab (PI) for modeling protein structures and motions with rigorous quantitative approaches in Blaisten–Barojas's lab (CoPI) for estimating stability and accessibility of molecular states.

The driving application here is the poorly understood role of structural diversity in modulating functional mechanisms of peptides central to disease and treatment. One such system is Met–enkephalin (Met–Enk), an endogeneous peptide switching between different structures to bind different receptor classes. Interest in Met–Enk is great due to its potential role in pain inhibition, alcoholism, and cancer treatment. Macroscopic wet–lab measurements are available for validation of the research proposed here, but a detailed microscopic treatment is currently missing.

The proposed research activities will provide a detailed microscopic treatment of Met–Enk by elucidating structures and structural transitions modulating biological activity. Building on Shehu's expertise, an evolutionary–inspired probabilistic search algorithm will map the peptide energy surface. Building on Blaisten–Barojas's expertise, free energy estimations will identify stable and semi–stable states in this surface. Building on Shehu's expertise, a robotics–inspired probabilistic search algorithm will then map pathways between identified states. Building on Blaisten–Barojas's expertise, pathways will be enhanced with dynamics to identify states accessed by the peptide to tune functional mechanisms.

The study will lead to better understanding of Met–Enk and elucidate diverse structural states leading to potentially unknown functional mechanisms. Data obtained in this pilot study will position the investigators for substantial funding from NSF and NIH on a general framework advancing the state of modeling and simulation on peptides and proteins.

- **Eugene Wu, Ph.D.**

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“Studies of DNA Polymerase Mechanism and Thermostability using Molecular Dynamics Simulations and X-Ray Crystallography”

Key Words: DNA polymerase, Molecular dynamics, X-ray crystallography

Template-directed DNA synthesis, an essential reaction for all of life, is catalyzed by DNA polymerases. DNA polymerases are not only important in the stability of all genomes, but also in biotechnology, where they play essential roles in revolutionary techniques such as PCR and DNA sequencing. The process of copying the genetic material with high fidelity involves an intricate mechanism.

Broad objective: Here, we propose to gain a better understanding at the atomic level of the moving pieces as a function of time using long (microsecond time scale) molecular dynamics (MD) simulations.

Aim 1: Three key states, "open", "ajar", and "closed", in the nucleotide selection mechanism of *Bacillus stearothermophilus* (Bst) DNA polymerase have been structurally characterized. Upon binding one of four deoxynucleoside triphosphate (dNTP) substrates, the enzyme-DNA complex is believed to transition from the open to the ajar state, wherein the incorrect dNTPs are initially distinguished. We propose to simulate the very fast (sub-millisecond) open to ajar transition with MD simulations of Bst DNA polymerase. These studies will reveal the order of movements by the various moving parts and perhaps show additional conformational states not yet observed crystallographically.

Aim 2: A conservative isoleucine to leucine mutation to DNA polymerase I from *Thermus aquaticus* far from its active site renders the enzyme less active at room temperature. Our recent crystallographic studies indicate that the conservative mutation rearranges the polymerase such that the template strand loops back to block the active site. We propose to probe the stability of this unusual conformation using MD simulations and solution fluorescence at low and high temperatures. These studies will shed light on the activity and stability of enzymes at low and high temperatures and provide valuable information for structure-based engineering of improved DNA polymerases for biotechnology.