Rana Ashkar, Ph.D. 2021 Awardee
Department of Physics
Virginia Polytechnic Institute and State University

"Reversing Pathology through Informed Molecular Regulation of Lipid Rafts"

Project Summary: Multidrug resistance (MDR) is a major obstacle to effective treatments of cancers and infectious diseases, two leading threats to global public health. Among the potential cellular targets for reversing MDR are small signaling domains within the cell membrane, known as lipid rafts. Lipid rafts are rich in cholesterol and harbor a variety of proteins, including ABC transporter proteins which actively export drugs out of diseased cells. Anomalies in raft growth and clustering are also implicated in the migration and metastasis of cancerous cells. Thus, the ability to regulate raft formation, growth, and clustering provides a promising and exciting approach for the cure and prevention of disease.

This proposal focuses on a novel, molecular-based approach using sterol-modified (SM) lipids as molecular regulators that can effectively control undesired raft formation or growth in unhealthy cells. These lipids are expected to frustrate differential segregation of cholesterol into rafts, thereby providing a molecular mechanism for reversing raft-related pathological conditions. The lipids can be delivered to diseased cells through liposomes by simply fusing with membranes of diseased cells and imparting their raft-disruptive capabilities. However, given the novelty of this approach, it is unknown how SM-lipids interact with the molecular components of the target cells, i.e. lipids and cholesterol. It is also unknown what ratio of SM-lipids is necessary to achieve regulation of raft formation, growth, and clustering – processes that occur over multiple length scales. To address these questions, we will take a mutually informative computational and experimental approach as outlined in the specific aims (SA):

SA-1: *Use Coarse-Grained Molecular Dynamics Simulations to uncover the molecular mechanisms of raft regulation by SM-Lipids.*

SA-2: *Utilize high-resolution experiments to determine the effects of SM-lipids on molecular packing and raft clustering.*

SA-3: *Identify the role of SM-lipids in controlling the size and stability of lipid rafts on the nanoscale.*

Elyas Bakhtiari, Ph.D. 2021 Awardee

Department of Sociology

College of William and Mary

"Using Machine Learning to Study Middle Eastern and North African Populations in Health Disparities Research"

Project Summary: Populations with ancestry from the Middle East and North Africa (MENA) have been understudied in research on health and mortality disparities, in part due to their ambiguous ethno-racial classification in the United States. Formally considered white according to the Office of Management and Budget, individuals with MENA ancestry are often "statistically invisible" in vital statistics reports, health records, Census data, and other sources of existing data. However, recent research suggests MENA Americans experience many social determinants that shape health disparities for other populations, including ethno-racial discrimination. This study aims to incorporate MENA populations into health disparities research by developing a machine-learning algorithm for categorizing MENA individuals using given name and surname information in administrative data. The two-part classification algorithm will match names unique to MENA origin countries and also detect linguistic and ethnic naming patterns based on textual characteristics of full name sequences using a long short-term memory model. The algorithm will be applied to two datasets spanning 20 years in order to study both adult mortality and birth outcomes in Virginia, which has one of the largest MENA populations in the United States. The results will not only advance our epidemiological understanding of MENA population health outcomes, but it will also contribute to a growing literature on the links between discrimination, stress, and health. The final step of the analysis will rely on a natural experimental research design to test the effects of heightened discrimination on birth outcomes in two key periods—the months following September 11, 2001 and the months following a 2017 executive order banning travel from select Muslimmajority countries.

Stephanie Coster, Ph.D. 2021 Awardee

Department of Biology

Randolph-Macon College

"Surveying Pollinator Assemblies and Modeling Occupancy at Native Plant Gardens, a Comparative Approach"

Project Summary: Pollination is an essential ecosystem service that supports the reproduction and propagation of over 87% of the world's flowering plants. The dramatic decline in pollinators, especially insect pollinators, due to climate change and pesticide use threatens not only our food supply, but also the diversity of native plants. Urban and suburban areas, if well managed, can serve as corridors and reserves for pollinator species and benefit agricultural and natural ecosystems well beyond the urban environment. In this study, we aim to explore the characteristics of urban and suburban native plant gardens that maximize native pollinator richness to inform recommendations for natural resource management. To do this, we will employ the common monitoring methodology of visual surveys in collaboration with the innovative application of using environmental DNA (eDNA) in a community metabarcoding analysis. We will then build a novel occupancy model that uses site and survey covariates to evaluate the variables that maximize pollinator richness and use this model to investigate detection biases associated with each monitoring method.

Sepideh Dolatshahi, Ph.D. 2021 Awardee

Department of Biomedical Engineering

The Rector and Visitors of the University of Virginia

"A Systems Immunology Approach to Uncover Key Maternal and Placental Immune Regulatory Mechanisms Differentially Affecting Antibody Transfer During Pregnancy across Racial Groups"

In the United States, 2018 mortality rates were 2.44 and 2.36 times higher among black compared to white infants and neonates, respectively. The disparity in mortality rates between white Americans and black Americans are larger today than in 1850. Our central hypothesis is that the trans-placental transfer of antibodies varies during gestation and its selectivity and efficiency is controlled by glycosylation, subclass and antigen-specific repertoire of maternal antibodies, and the changes in cellular composition and receptor expression on the placental barrier. We further hypothesize that racial groups exhibit immune phenotypic differences reflected in these maternal, cord, and placental features that might be transcriptionally and epigenetically regulated. Our proposed project aims to take a system immunology approach to combine systematic sample collection during pregnancy and at birth with multiplexed measurements and computational analysis to study the regulation of maternal humoral response during pregnancy, at the maternal-placentalfetal interface and in cord blood. To this end, we propose to (1) Identify key glycosylationmediated immune phenotypic regulators of antibody transfer during gestation using (1A) comprehensive quantitative profiling of immunoglobulin G (IgG) antibodies, (1B) quantitative characterization of cellular and receptor expression profiles of placental tissue using the multiplex immunohistochemistry and (1C) the development of a mechanistic mathematical model that integrates these multiplexed experiments. We will then (2) develop and use multivariate computational statistical learning approaches to identify key features that differentially affect the transfer of antibodies in black and white populations. Finally, we will (3) investigate the transcriptional regulatory mechanisms underlying the identified differential immune phenotypes. Given emerging data that vaccination may direct antibody glycosylation, our study provides insights for the development of next-generation maternal vaccines designed to elicit antibodies that will most effectively promote neonatal health and alleviate the disparities in child health outcome in black and white infants.

Gillian Eastwood, Ph.D. 2021 Awardee

Department of Entomology
Virginia Polytechnic Institute and State University [Virginia Tech]

"Assessing Tick-borne viruses circulating in Virginia through a One- Health lens"

Of the multiple tick species present in Virginia, at least two common ticks are competent vectors of viral pathogens. Such arboviruses (i.e. Powassan, Heartland, and Bourbon virus) are capable of causing fatal clinical infections or long-term neurological sequelae, and exist in neighboring U.S. states. Yet while Lyme disease is well-recognized, little is known about the prevalence of tick-borne viruses circulating in the United States. Our broad long-term objectives take a One Health approach (integration of human, animal and ecosystem health) to understand the presence of tick-borne viruses in the western Virginia region, and mathematically simulate how prevalence varies in species and geographical region. Incorporating undergraduate researchers, the project will monitor active infection or evidence of past exposure to these tick-borne viruses in ticks, potential wildlife mammal hosts, and livestock, in at least four regions of the Commonwealth.

Our Specific Aims are:

1: To sample for evidence of tick-borne virus circulation in at least four regions of the Commonwealth, in i) cattle sera, ii) potential small-mammal wildlife hosts, iii) tick vectors in the environment of Fauquier, Augusta, Roanoke and Patrick counties.

2: Calculate the prevalence of each virus, and simulate the relative risk of exposure in key species (of livestock, wild-mammal, ticks) by region and season, developing a network ordinary differential equations model.

3: Generate better awareness of emerging tick-borne viruses, and act as a platform for outreach by educating the participants involved in this project; including enhanced VT Extension tick products and student curricula, as well as undergraduate research capacity. The proposed project centers on monitoring for emerging infectious diseases and ensuring healthy populations of people in Virginia.

Michelle Gervasio, Ph.D. 2021 Awardee

Margaret Jones Wyllie '45 Engineering Program
Sweet Briar College

"Monte Carlo Simulation of Microplastic Suspension Behavior in the Presence of Coagulants"

Microplastics have become of great environmental and human health concern in recent years as the production and use of inexpensive, single-use plastics has increased. Much research has been conducted in the hopes of identifying protocols for removing aqueous microplastics and while some mathematical models have been proposed in order to model the behavior of microplastics, one area ripe for further study is the development of models that do so in the presence of coagulants. Such a model would enable rapid, preliminary evaluation of coagulants and potentially offer insights into improving existing coagulation protocols.
This study hopes to accurately capture and predict the coagulation behavior of synthetic organic polymer particles that are suspended in water in the presence of coagulating agents by using a modified DLVO model to drive a constant-number Monte Carlo simulation. The total interaction parameters between particles will be calculated as superposition of Van der Waals, electric double layer, and depletion forces. Once the total interaction potential between each particle pair is known, Smoluchowski coagulation theory will be employed to determine the agglomeration frequency for all possible pairs. The agglomeration frequency will be used to construct a probability density function from which the particle pair to be agglomerated will be selected. The amount of simulated time that "passes" for each agglomeration event will be based on the average agglomeration frequency across all particle pairs. Considerations for Brownian motion and Stokes settling will also be included.
The simulation will be validated by comparing the final predicted sedimentation and final particle size distribution with physical experiments of suspended poly(ethylene) particles in the presence of Fe(OH)3 or Al(OH)3 salts. If successful, the model would shed light on the coagulation process and pave the way for discovering novel coagulants to aid in the removal of microplastics from our water.

Lucas RF Henneman, Ph.D. 2021 Awardee

Civil, Environmental, and Infrastructure Engineering

George Mason University

"Detailed Emissions in Virginia (DEVA): Identifying air pollution sources for environmental justice"

We propose a project to inform ongoing efforts by Virginia lawmakers to address air pollution health impacts and inequities through environmental and energy regulations. Using data assimilation and emissions modeling, will create the most detailed air pollution emissions inventory available in Virginia between 2011-2020. With this dataset, we will quantify the extent that emissions source categories (e.g., power plants, automobiles, and various industries) each contribute to environmental injustice by disproportionally affecting some population groups more than others. The specific aims are:
1. Develop computational data aggregation methods to estimate time-resolved, spatially fine-scale air pollution emissions from multiple air pollution sources (e.g., automobiles, power plants, industry, agriculture, etc.) using publicly available data from 2011-2020 in Virginia
2. Develop source-specific equity measures to evaluate the equity implications for proximity to emissions from specific air pollution source categories
3. Document the approach, data procurement, and analysis code in a publicly available repository for ease of future use and extension to future studies of Virginia air quality equity

The work will require reproducible data integration methods due to the many sources of information from which we will draw relevant data—we will acquire and assimilate publicly available data on power generation, vehicular populations, industrial activity, and more. Using state-of-the-art data science techniques and code version tracking software, we will document the approach to ensure reproducibility. This will ensure the results are available to policymakers charged with ensuring a healthy, equitable Virginia.

Caitlin E. Martin, MD MPH 2021 Awardee

Obstetrics and Gynecology

Virginia Commonwealth University

"An investigation of how social determinants of health and sex intersect to impact the health of Virginia Medicaid members with opioid and other substance use disorders"

Over the past decade, females have witnessed more rapid rates of increasing mortality due to substance use disorder (SUD) than males, including in the year after pregnancy. SUD treatments, including medications for opioid use disorder (MOUD), effectively reduce morbidity and mortality. However, SUD treatment outcomes vary by sex and other variables, such as race/ethnicity and geography. Evidence is lacking on how to devise sex-informed SUD interventions. Having a better understanding of how SUD outcomes differ by sex, as well as how multi-level factors impact outcomes differentially for males and females, would guide adaptations of SUD policies and treatments to individuals' needs. SUD-related morbidity and mortality has skyrocketed in Virginia with Medicaid members being a highly vulnerable population for these adverse outcomes, likely due to amplified negative effects of social determinants of health (SDH). We propose a novel approach to investigate sex-specific impacts of SDH on SUD outcomes among Virginia Medicaid members. Our hypothesis is that sex is an important modifier of associations between SDH and SUD outcomes. We will conduct sex-stratified analyses of Medicaid claims data (2016-2020) for the outcomes of SUD treatment utilization and SUD-related acute care use in relation to SDH measures. Additionally, for females with OUD undergoing a live birth, we will investigate how MOUD receipt evolves by SDH through the postpartum period. We will utilize a novel SDH measure, the Virginia Health Opportunity Index (HOI): a state-of-the-art method to quantify community wellbeing. We also will employ innovative computational methods to bring together disparate data sources to construct SUD outcomes and area-level SDH measures. Completion of these aims will inform identification of opportunities for implementation of evidence-based, sex-informed public health, health policy and clinical care interventions for SUD treatments. Such advancements will inform the critical next steps to eradicate health disparities for Virginia Medicaid members with SUD.

Allison H. Moore, Ph.D. 2021 Awardee

Mathematics & Applied Mathematics
Virginia Commonwealth University

"Advancing theory and exploring applications of unknotting to molecular biology"

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This proposal seeks to advance our mathematical understanding of knots and links, to explore the relationships between invariants of knots and three-manifolds, and to leverage these developments toward knot-theoretic models of DNA recombination mediated by enzymes and entanglement in biopolymers. The central hypothesis of the proposal is that knot theory provides a rigorous mathematical framework with which to investigate molecular knotting and entanglement in DNA. The proposed mathematical projects center around the study of local operations on knots and knot invariants. In particular, Heegaard Floer homology and Khovanov homology are powerful new theories that have had striking impact in the study of knots, links and smooth manifold topology. The two mathematical aims of the proposal are (1) to develop Floer and Khovanov-theoretic tangle invariants to solve core problems in knot theory and (2) to investigate knot graphs and develop the theory of unknotting in spatial graphs. The PI will use techniques in geometric topology, Heegaard Floer theory, Khovanov homology, and graph theory to advance these two aims.
The two mathematical aims of the proposal inform the third aim, focused on the application of knot theory to molecular biology. In the third aim, the PI proposes to uncover new connections between knotting phenomena and the mathematical modeling of enzymatic actions and entanglement in DNA and RNA molecules. In particular, crossing changes and band surgeries along knots model strand passage and recombination in circular DNA mediated by type II topoisomerases and site-specific recombinases. Spatial graphs are relevant in modeling intermediary structures in DNA replication. The proposed projects have been designed to involve undergraduate researchers in nontrivial aspects of computational and combinatorial topology while significantly supporting their academic and professional development.

Camilla W. Nonterah, PhD 2021 Awardee

Psychology Department
University of Richmond

"Development of the Barriers in Access to Transplantation Scale (BATS)): Developing a culturally relevant psychometrically sound measure for identifying high-risk renal patients."

Patients diagnosed with end-stage renal disease (ESRD) are more likely to experience better health outcomes with transplantation relative to prolonged dialysis. Many barriers in access to transplantation such as insurance issues, medical mistrust, lack of referrals, and poor health literacy impede patients' successful completion of the steps to transplantation. Given the high prevalence of ESRD patients, especially among those who identify as racial/ethnic minorities, it is essential that these barriers are reduced to increase access to kidney transplantation. While many researchers and transplant centers have developed a variety of interventions to help reduce these barriers, a significant problem that continues to exist is the lack of uniformity in assessing these barriers. Transplant centers typically employ their own methods of assessment, and the majority of these assessments are not valid and/or reliable. Moreover, many patients face multiple impediments, and most interventions target the most apparent barrier and do not address others that produce compounding effects. The proposed study seeks to develop a culturally relevant, psychometrically sound measure of barriers in access to transplantation, "The Barriers in Access to Transplantation Scale (BATS)." This will be achieved through three phases of a study in which the initial items of the BATS assessment tool are tested and refined. Statistical analyses such as exploratory factor analysis, confirmatory factor analysis and regressions will be used to examine different iterations of the measure to create the final version. The BATS will be able to be administered in both English and Spanish and could be used in transplant centers in Virginia as well as other parts of the country. The development of a measure of this nature will facilitate the systematic examination of barriers in access to transplantation to enhance transplant-specific research, and will enable the development of tailored interventions focused on creating parity in access to transplantation.

Jonathan Richardson, Ph.D. 2021 Awardee

Biology Department

University of Richmond

"Quantitative Assessment of the Environmental and Social Determinants of Rodent-borne Zoonotic Disease Risk in Richmond, Virginia"

Norway rats are a globally-distributed pest species that causes billions of dollars in property damage and food contamination annually. This species also carries dozens of pathogens and parasites known to cause zoonotic diseases in people. This is a particular concern in rapidly expanding urban areas. Municipalities are in dire need of information that will allow them to accurately predict where zoonotic disease risk is highest for its residents. For diseases vectored by rats (e.g., leptospirosis, typhus, hantavirus, etc.), this means also being able to predict where rats will occur in a city, and what aspects of the urban environment make "good" rat habitat. Here, we propose two objectives that will allow us to address the rat-borne disease concerns in Richmond, Virginia – a city that has not had any research done on rats and their disease potential since the 1940s, and has marked heterogeneity in social attributes, creating inequities in disease risk among its residents. (1) We will trap and sample rats at 32 locations across Richmond, and using metagenomic and bioinformatic protocols we have developed to identify the zoonotic pathogens and parasites carried by each rat. Lastly, we will assess the level of chronic immune challenge faced by these rats in their environment. (2) With the data from Objective 1, we will model the habitat suitability of the study area for rats, identifying the environmental variables most associated with rat abundance. We will also generate maps of zoonotic disease risk based on the pathogen/parasite prevalence data. Socioeconomic variables will be included in each model to characterize how social factors may be linked with rat presence and disease risk. From our work in other cities, it is clear that public health agencies need this sort of information on spatial disease risk. We aim to provide the first such information for the city of Richmond.

Nick Ruktanonchai PhD 2021 Awardee

Population Health Sciences
Virginia Tech

"Mobility-based Outbreaks in Virginia Early Response System (MOVERS): Using real-time mobility data to develop an infectious disease outbreak early warning system for Virginia"

Human mobility data have transformed how we understand and predict the transmission of infectious diseases such as COVID-19, partly because they can measure changes in population mixing without the logistical and epidemiological delays associated with obtaining case data. Fundamentally, mobility drives transmission by influencing where, when, and how much population mixing occurs. Many different mobility datasets exist, however, and knowing which metrics derived from various datasets are best for predicting future transmission remains an open question, and further depends on the social, cultural, and economic context of the population being studied.

Here, we use machine learning techniques and mathematical modeling approaches to address these key questions for both mathematical epidemiology broadly, and for understanding COVID-19 transmission in Virginia. Specifically, we will identify the mobility metrics that best predict near-future transmission, and quantify how far into the future these metrics can effectively predict changes in COVID-19 cases. First, we will use machine learning approaches to define key mobility indicators (KMIs) that best predict change in COVID-19 transmission at varying time scales across each pandemic wave in Virginia. Then, we will implement these KMIs within an existing epidemiological model of COVID-19 transmission (BEARmod, available on GitHub at https://github.com/wpgp/BEARmod) to predict cases several weeks into the future and identify potential high-risk areas over this near-term period. Because these mobility data are available in near-real time, we will package model results into an early warning system provided to New River Health District and Virginia Department of Health collaborators, benefiting the health of all Virginians.

By rapidly updating this model and predictions over time, we can improve response to emerging COVID-19 cases, outbreaks of vaccine-resistant strains, and potential emergence of similar respiratory diseases. Lastly, we have further outlined several smaller, adjacent research questions throughout each aim that undergraduates can undertake.

Peter Schauss, Ph.D. 2021 Awardee

Department of Physics

University of Virginia

"Computational and Experimental Study of Repulsive Pairing as a Precursor to Superfluidity in Triangular Lattice Hubbard Systems"

In modern society, where electricity is ubiquitous, losses in electric power transmission are of critical concern. Superconductors allowing loss-less power transmission are a potential solution, but are unfortunately not yet practical for widespread applications, due to the cryogenic temperatures required. Understanding and designing superconductors that can operate at higher temperatures is one of the biggest challenges in the field of condensed matter and material physics. Conventional low-temperature superconductivity relies on pairing of electrons to so-called Cooper pairs that then condense and propagate without resistance through the material. A rigorous quantum treatment explains the pairing via electron-phonon interactions, that is, as the result of a coupling between the moving electrons and vibrations of the host lattice. One of the big open questions is whether other microscopic pairing mechanisms exist that do not rely on phonons and allow pairing at higher temperatures. Indeed, such mechanisms may be responsible for high-temperature superconductivity that has been observed but is not currently understood. The complex behavior of these systems, while not tractable using conventional computers, can be simulated using extremely cold, interacting atoms trapped in optical potential arrays created by laser light. Motivated by that prospect, we will perform numerical calculations of a model system and compare them to experimental quantum simulation data to understand how pairing can occur in a repulsively interacting system. Undergraduate students will perform these calculations under the PI's supervision. Our project has the potential to revolutionize the commonly accepted view on superconductivity using a new interdisciplinary approach. The understanding we gain will pave the way towards designing room-temperature superconductors. Practical room temperature superconductors would enable lossless power transmission, leading to a more stable electric network and lower prices, thereby revolutionizing the existing power grid for the benefit of people in Virginia and across the globe.

Rong Tong, Ph.D. 2021 Awardee

Department of Chemical Engineering

Virginia Polytechnic Institute and State University

"Deep Learning Discovery of Efficient Catalysts for Electrochemical Synthesis of Degradable Polyesters"

The extensive use of commercial synthetic polyolefin polymers has created economic and environmental problems, because these non-degradable polymers are made from non-renewable sources and lead to environmental pollution. Polyesters have a leading position as biodegradable polymers, and some of them have been industrially produced and are approved by FDA. However, their utility for applications that demand mechanical properties such as high stiffness, ductility, and tensile strength is greatly limited by the lack of side-chain functionality in polyesters and in their monomers. Additionally, the production of polyesters is energy extensive, which requires high-temperature polymerization processes. To address these problems, we have recently developed a new synthetic strategy to prepare functionalized polymers from amino acids-derived monomers using energy-saving electrochemical polymerization methods. A grand challenge for improving such an electrochemical polymerization process is to identify efficient redox-active catalysts in an immense materials space, which demands a new approach instead of conventional trial-and-error methods. Herein we propose to develop an integrated experimental and deep-learning approach to accelerate the discovery of new redox-active electrochemical catalysts for efficient electrochemical polymerization to prepare functionalized degradable polyesters on large scales. We propose to combine state-of-the-art Bayesian deep learning algorithms with precise synthesis to address the below aims:

1. Benchmark the reactivity and redox capability of electrochemical metal catalysts for polymerization
2. Develop deep learning models to predict and validate optimal catalysts

The success of the proposed work will lead to an integrated experimental-computation-data analytical framework that enables systematically uncover mechanistic parameters impacting the polymerization process, and accelerate the polymerization optimization and scale-up process for degradable polymer productions.

Julie Zinnert, Ph.D. 2021 Awardee

Department of Biology

Virginia Commonwealth University

"Coastal resilience and sea-level rise: computationally modeling ecological and physical processes and their interactions"

Coastal dunes and barrier systems comprise the first line of defense against ocean flooding and storm surge. The importance of ecological processes and feedbacks are recognized in coastal systems, but current barrier models are dominated by physical processes. There is a need to incorporate **bio**geomorphic processes into models that accurately predict future scenarios for management planning. Protecting and enhancing green infrastructure like natural coastal barriers is a priority goal in the 2020 Virginia Coastal Resilience Master Plan. Two biogeomorphic states have been identified from previous studies. These states develop from feedbacks among vegetation, topography and overwash disturbance. Low, flat topography increases the likelihood of future overwash, affecting interior dynamics in disturbance-reinforcing states. Low vegetative cover allows for sediment to migrate inland and new communities to establish. In contrast, disturbance-resisting states are dominated by grasses that form linear dune ridges and enhance topographic roughness that resists overwash. Higher vegetative cover in the swale, often woody plants, increase resistance of sediment transfer, resulting in higher rates of shoreline erosion. Currently we do not have models that are able to handle ecological processes in coastal evolution. These configurations of dune-swale topography and vegetation patterns ultimately determine dune and island response to sea-level rise and storms. By combining mesocosm studies, field measurements, and modeling, we enhance our mechanistic understanding of how vegetation dynamics influence coastal dune and barrier island evolution. This project will allow us to fine tune a coastal biogeomorphic model to secure future funding that incorporates SLR and storm events. The proposed research will focus efforts at the Virginia Coast Reserve and will answer the following questions:
1. How do sediment dynamics change spatially and temporally with elevation, distance from shoreline, and vegetative cover?
2. How do interactions among biotic and abiotic processes affect the evolution of barrier islands?

Ryan Brindle, Ph.D. - 2020 Awardee
Hazel Thorpe Carman and George Gay Carman Trust
Department of Cognitive and Behavioral Science
Washington and Lee University

"Modeling Energy Regulation Under Stress: A Possible Mechanism Linking Stress and Disease?"

Depression and cardiovascular disease impact over 1.5 million Virginians annually. Mental stress significantly contributes to the development and progression of depression and cardiovascular disease. However, the mechanisms linking mental stress to disease remain poorly characterized and methods for identifying at-risk individuals are lacking. The proposed project seeks to combine basic physiological monitoring with advance group-based trajectory modeling to test the hypothesis that functional energy regulation is compromised under stress, a condition that if maintained over time could lead to disease.

In this project heart rate (HR), blood pressure (BP), and oxygen consumption (VO2) will be simultaneously measured during exercise and mental stress. During exercise HR and BP are tightly coupled to VO2 to ensure adequate muscle function. However, during mental stress VO2 does not change but HR and BP change dramatically. HR and BP become uncoupled from VO2; energy regulation becomes dysfunctional. We will calculate the metabolic appropriateness of the HR and BP responses during mental stress and it is expected that individuals will vary in the degree to which they exhibit dysfunctional energy regulation. Using group-based trajectory analysis, a modelling approach that simultaneously identifies latent groups of individuals in data and adequately models that dynamic nature of the cardiovascular system, we will be able to identify individuals that have particularly dysfunctional energy regulation strategies during mental stress. It is hypothesized that these individuals will display preclinical signs of depression and cardiovascular disease, measured in this study by self-reported depression symptoms and arterial stiffness, respectively.

Stress is ubiquitous in modern life and depression and cardiovascular disease are two of the most prevalent and debilitating diseases. By combining basic physiological measurement with advanced group-based trajectory modeling, this proposal is ideally suited to simultaneously test a candidate mechanism linking stress to these outcomes and make meaningful advances in identifying at-risk individuals.

Lane Carasik, Ph.D. - 2020 Awardee
Department of Mechanical Engineering
Virginia Commonwealth University

"Accelerating the Deployment of Advanced Energy Systems by Improving Heat Transfer Equipment"

Advanced energy systems such as concentrated solar, nuclear, or geothermal energy use heat transfer equipment (heat exchangers) to transfer heat from heat generation components to power conversion components. Commonly, heat exchangers consist of two working fluids that are separated by tubes, plates, or other surfaces. These surfaces can be modified through heat transfer enhancements (HTE) to increase the heat transfer and overall efficiency of the heat exchanger. Any meaningful increase in the efficiency of heat exchangers can lead to improved economics (capital, operating & maintenance costs) of the advanced energy system. In this project, we will use a combined experimental and computational effort that will integrate state-of-the-art additive manufacturing and mathematical models for investigating new and existing HTEs in tubular molten salt heat exchangers. The experimental effort will build upon our previous work in the integral measurements of heat transfer and pressure drop in heat transfer enhanced tubes through the integration of additively manufactured tubes. The computational effort will involve state-of-the-art computational fluid dynamics (CFD) tools such as the Department of Energy's Nek5000 code for predicting integral and whole field information in the HTEs.The results of this work will: (1) expand the design space information (pressure drop & heat transfer) of the selected heat transfer enhancement, (2) integrate additive manufacturing of plastic components and set the foundation for metallic additive manufactured parts, (3) validate methodology for using computational fluid dynamics to predict integral behavior of the selected HTE and (4) provide the foundation for future CFD investigations of additional HTEs made possible through additive manufacturing.

Yana Cen, Ph.D. - 2020 Awardee
Department of Medicinal Chemistry
Virginia Commonwealth University

"Determining Enzyme Transition State Using Kinetic Isotope Effects and Computational Analysis"

The Sir2 enzyme from Plasmodium falciparum (PfSir2) is essential for the antigenic variation of this parasite, and its inhibition is expected to have therapeutic effects for malaria. Knowledge of enzymatic transition state (TS) provides sufficient information to synthesize mimics that bind tightly to their cognate enzymes. The coupling of kinetic isotope effects (KIEs) to computational chemistry has the potential to provide details about enzymatic TS to guide the design of TS analogs. When TS features can be approximated into chemically stable mimics, inhibitors with femtomolar dissociation constants have been obtained. The objective of this proposal is to solve the TS structure of PfSir2 catalyzed deacetylation using a combination of KIE measurement and computational analysis. This will be accomplished by two specific aims. In Aim 1, our effort will be directed at the synthesis of isotopically labeled NAD substrates and the determination of KIEs at positions that are expected to experience bond change at the TS using competitive radiolabel strategy. The experimental KIEs will be corrected for remote effects and commitment to determine the intrinsic KIEs for PfSir2 catalyzed reaction. In Aim 2, Gaussian03 quantum mechanical approaches will be used to iterate systematically through possible TS structures to find a TS with the nearest match of the intrinsic KIEs. Subsequently, electrostatic potential surfaces will be calculated from the wave functions of the reactant and TS. The information gained in the computational analysis will guide the future inhibitor design. This unique combination of experimental and computational access to TS information permits not only the design of TS analogs as powerful enzymatic inhibitors, but also the exploration of protein features linked to the TS structure as well as the analysis of ensemble atomic motions involved in achieving the TS.

Stefano Colafranceschi, Ph.D. - 2020 Awardee
Department of Mathematical Sciences
Eastern Mennonite University

"Improving the State-of-the-art of Particle Detectors by Using a Novel Additive Manufacturing Technique and by Developing Computational Methods for Performance Analysis Testing"

Particle detection technology has a crucial impact on scientific development and on our society. In this study, we address the need to develop a new particle physics detector technology for the Compact Muon Solenoid (CMS) Experiment. This is a giant machine that seeks to uncover the origin of the universe by colliding two high-energy proton beams, to recreate the primordial conditions that existed right after the Big Bang. The Resistive Plate Counter (RPC) detector technology is one of the most used to ensure a correct and reliable data-taking. Since it is fundamentally important to keep the RPCs working efficiently, this project focuses on a new implementation of RPCs with enhanced capabilities and ultimate performance.

The two major specific aims of this work are hereby listed: 1) to design and implement a new 3D printed Resistive Plate Counter particle physics detector, 2) to develop a Data acquisition system (DAQ) for detector characterization.

The initial hypothesis is that 3D printing, applied to instrumentation for physics, will enhance detector performance and capabilities, cutting construction costs and improving standardization over large scale productions. By fully optimizing the entire design and by implementing the construction via additive manufacturing, the expectation is to achieve a standardized detector, mechanically more resistant/resilient and electrically more stable if compared to the state-of-the-art. During the second phase, a data acquisition system will be developed to readout the detector anodic charge and to produce the large datasets needed to study the detector behavior and performance. The analysis is going to be performed using machine learning techniques on GPU hardware.

The successful implementation of this project has the long-term objective to impact not only the physics domain but also the security (cargo imaging and general-purpose scanners) and healthcare (tomography machines) domains, where particle detectors are widely adopted.

Amanda Gibson, Ph.D. - 2020 Awardee
Department of Biology
University of Virginia

"Modeling the Evolution of Disease Resistance in a Variable World"

Individuals vary dramatically in their ability to resist parasites, and this variation has a strong genetic basis. Given this, it seems obvious that alleles associated with parasite resistance should spread in host populations experiencing parasite outbreaks. Yet results from natural host populations often fail to support this intuition. The very opposite can happen – alleles associated with parasite susceptibility can increase in frequency during epidemics. Theoretical models suggest that these unexpected results arise because the fitness advantage of a resistance allele varies with environmental context. In particular, host diet can influence the benefits conferred by resistance alleles and the energetic costs associated with resistance. Building on this idea, we propose to test the central hypothesis that resistance alleles are more advantageous under high quality diets than low quality diets, where the costs of mounting parasite defense may outweigh the benefits. We take advantage of near-isogenic lines of the model nematode Caenorhabditis elegans that allow us to measure the environmental sensitivity of two different alleles that confer resistance to the natural microsporidia parasite, Nematocida parisii. In Aim 1, we will quantify environmental variation in multiple traits linked to the fitness of individual resistance alleles. In Aim 2, we will develop theoretical models to predict the evolutionary trajectories of resistance alleles based on these empirical data. This synthesis of theory and data is required to disentangle the joint effect of multiple, potentially opposing evolutionary forces. In Aim 3, we will test the predictions of these evolutionary models using experimental evolution of parasite resistance under different dietary conditions. This work will contribute to our long-term goal of developing a predictive framework for variation in the advantage of resistance alleles and promote applied efforts to identify and exploit the genetic basis of health phenotypes.

Kristine Grayson, Ph.D. - 2020 Awardee
Department of Biology
University of Richmond

"Forecasting the Spread of an Invasive Forest Pest"

Biological invasions can be highly damaging and costly, leading to large-scale management efforts to contain the spread of these species and mitigate their harm. The majority of invasive species management is reactive, occurring after an invasive species has already become established. The ability to accurately predict where and when an invader will further spread would enable managers to more efficiently allocate limited resources and deploy pre-emptive actions. Using the gypsy moth invasion of Eastern North America, this proposal advances two complimentary objectives to enhance spread modelling efforts for invasive species: 1) Quantify larval cold tolerance for populations across the invasive range and predict geographic climatic suitability for gypsy moth; and 2) develop and test a spread forecasting system for this destructive forest pest. In objective 1, we will perform experiments on cold tolerance using 9 populations from across the invaded range to complete our knowledge on variation in thermal performance traits across the gypsy moth invasion front. We will use these measures of local adaptation in thermal physiology to improve predictive maps of the areas with climatic suitability for gypsy moth in the United States. In objective 2, we will develop a spread forecasting system and evaluate the performance of three candidate forecasting models, focusing on how forecast accuracy is affected by the level of detail included in the model on gypsy moth biology and its interactions with the environment. Our work advances a synthetic understanding of the processes determining gypsy moth spread and has specific applications to invasive species management.

Hongzhi Guo, Ph.D. - 2020 Awardee
Department of Engineering
Norfolk State University

"Towards Autonomous Underwater Target Detection And Monitoring Using Swarm Robotics"

Exploration of the vast underwater environment is dangerous and dull. Underwater swarm robotics using robots with computation, communication, and sensing capabilities can move cooperatively to accomplish complex tasks that cannot be done by any one individual. The objective of this project is to develop formal computational and quantitative methods to efficiently design and prototype underwater swarm robotics systems that can accurately detect underwater targets and transmit high-volume data to above water environments. The ultimate goal of this project is to automate the underwater target detection and monitoring by using swarm robotics which can find optimal trajectories to locate and identify targets and send high-resolution real-time videos to above water wireless infrastructures. This project is divided into three intertwined tasks. First, this project will develop magnetic induction communication prototypes for underwater robots to transmit control signals. Also, underwater visible light communication prototypes will be built which can support high-speed data communication. Theoretical and experimental visible light communication channel models will be developed to plan robots' trajectories and coordinate their motions. Second, this project will adopt deep convolutional neural networks and federated learning algorithms to optimally and adaptively train the target detection model. Robots will work cooperatively to identify targets from different angles and share their local machine learning model parameters to find optimal global parameters. The joint design of robots' motion and target detection will be performed to find the optimal distribution of robots to improve detection performance. Lastly, this project will develop optimal trajectories for robots to find, identify, and monitor targets. Wireless communication and networking performance will be considered when designing robots' trajectories to ensure that high-resolution videos can be transmitted successfully by the robotic network.

Feng Lin, Ph.D. - 2020 Awardee
Department of Chemistry
Virginia Polytechnic Institute and State University

"Development of Integrated Experimental and Computational Approaches to Empower Structurally Disordered, Sustainable, and High-Capacity Battery Materials"

The lithium ion battery technology has impacted nearly every human being on this planet. The increasing energy demand calls for a paradigm shift in how we design novel electrode materials that can fundamentally disrupt the ordered ion-intercalating electrode materials in today's lithium ion batteries. Most lithium ion batteries use cobalt as the main redox active element. The high cost and relative scarcity of cobalt, as well as ethical quandaries involving use of child labor in the Democratic Republic of Congo, where most cobalt is mined, make development of low-cobalt or cobalt-free alternatives to conventional cathodes particularly urgent. Cobalt-free, cation-disordered rocksalt oxides represent a new class of cathode materials with theoretical capacity and energy well beyond the state-of-the-art layered oxides. However, these new materials suffer from poor battery lifetime and low power density. The proposed research aims to advance the fundamental insights into the multiscale chemical, structural, and redox properties of cobalt-free, Li-rich disordered rocksalt oxide cathodes through a suite of synchrotron methods and computational methods. The ultimate goal is to develop design principles that will make disordered rocksalt oxide materials superior to the state-of-the-art cathodes in terms of cost, sustainability, energy density, and safety. The proposed project will take a fundamental materials chemistry approach based on electrochemical diagnostics, density functional theory calculations, dynamics simulations, and synchrotron X-ray analyses. Our specific aims are (1) quantitatively investigating the dependence of redox chemistry and performance degradation on chemical composition, local coordination environment, and electrochemistry, (2) understanding Li kinetics and diffusion pathways using density functional theory calculations and kinetics Monte Carlo simulations, and (3) establishing approaches to tailor the cathode surface chemistry for improving battery performance. The successful outcome of this project will provide critical insights into designing higher energy, higher power and more stable Li ion batteries.

Michael Norris, Ph.D. - 2020 Awardee
Department of Chemistry
University of Richmond

"Understanding the Reduction of CO2 to Methanol Catalyzed by Simple Amines with a Combined Computational and Experimental Approach"

The reduction of carbon dioxide to useful fuels is part of a solution to the current global energy crisis. Finding a way to generate methanol from CO2 would represent an important breakthrough in curbing global warming and providing a carbon-neutral energy source compatible with our current infrastructure. We plan to interrogate the ability of simple chemical systems to affect this transformation of CO2 to methanol. We will evaluate amines, hydride donors, and Lewis acids as components that allow for the activation and reduction of CO2 by a total of 6 electrons and 6 protons to the methanol oxidation state.

Specific Aim #1: Utilize a computational model to understand key factors that result in the reduction of CO2 to methanol and make predictions about effective chemical systems.

Specific Aim #2: Develop a systematic chemical approach that will complement the computational data and allow for the observation of reaction intermediates and products.

A detailed understanding necessitates a cross-disciplinary approach that will require both sophisticated computational modeling of the individual mechanistic steps as well as an experimental approach to test a set of well-defined variables in order to elucidate the effect of several important factors.

Joonsuk Park, Ph.D. - 2020 Awardee
Department of Mathematics and Computer Science
University of Richmond

"Understanding the Impact of Argumentative Structures on Helpfulness of Online Product Reviews"

Reading product reviews has become a crucial component of online shopping. Whether they are purchasing a $2 pen or a $2,000 laptop, consumers often rely on the product reviews they read. This is because product reviews can contain a convenient overview of strengths and weaknesses of the products, as well as persuasive opinions based on anecdotal evidence. Unfortunately, though, not all product reviews are helpful; and with ever increasing number of product reviews available online, the need for automatic identification of helpful reviews is rising. Existing work on automatic helpfulness prediction leveraging superficial aspects of reviews, e.g. the number and lengths of sentences, words expressing emotions, review history of the reviewer and the star rating, among others.

We hypothesize that argumentative structures--the types of premises and conclusions, as well as how they work together to form an argument--have a direct impact on the helpfulness of product reviews and that they are more reliable indicators of helpfulness than simple features used in previous work. The hypotheses will be investigated through three main tasks: (1) identifying argumentative structures that positively, or negatively, impact the helpfulness of product reviews, (2) building a state-of-the-art helpfulness predictor using patterns of argumentative structures found in Task 1, and (3) investigating if automated feedback on argumentative structures can help improve the helpfulness of product reviews.

The proposed work will lay a foundation to study the relationships between argumentative structures and different measures of quality, such as helpfulness, clarity, and persuasiveness. Also, this work will pave the way for machine-assisted construction of arguments, where a natural future work includes incorporation into peer-assessment so that students will provide more helpful feedback to one another. Lastly, if and when deployed in large scale, this technology can help improve the overall quality of textual content available online to everyone.

B. Daniel Pierce, Ph.D. - 2020 Awardee
Department of Biology
University of Richmond

"Determining the Precise Molecular Interactions Between Plant Phenols and the Agrobacterium Receptor VirA"

The plant pathogen Agrobacterium tumefaciens (also known as Rhizobium radiobacter) causes crown gall tumors in its host through inter-kingdom gene transfer. Pathogenesis is initiated when the Agrobacterium receives signals from a wounded host plant, which then mobilizes the protein machinery for the multiple steps of DNA transfer. The histidine kinase receptor VirA is critical for signal reception, coordinating two molecular signals—sugars and phenols—and initiating a two-component phosphorelay cascade to transcribe the virulence genes. The VirA protein contains four regions (Periplasmic, Linker, Kinase, and Receiver) and its Linker region is implicated in its interaction with phenols. Homology predictions have led to a modeling of the Linker region as a GAF domain; in other species, these domains bind small molecules. We hypothesize that the Linker region interacts directly with phenols, and this proposal is designed to identify and characterize this interaction. We aim to solve the structure of the Linker region in the presence and absence of phenol using x-ray crystallography and analysis using computational software. In addition, we have used modeling simulations to predict possible phenol binding sites in the Linker region. We will refine these predictions and mutagenize VirA Linker residues to determine the phenol-protein interaction. Finally, we will use fluorescence-based thermal shift assays and microscale thermophoresis with phenol and purified Linker region to measure this interaction biochemically. By defining the Linker/phenol interaction, we will gain insight into the molecular mechanism of the initiation of Agrobacterium pathogenesis.

Joshua Puzey, Ph.D. - 2020 Awardee
Department of Biology
College of William & Mary

"A Machine-learning Approach to Identify Plant-root Microbiomes That Increase Plant Fitness"

The world's food supply is in crisis -- a crisis that will only intensify with continued population growth and a rapidly changing climate. The Food and Agriculture Organization of the United Nations has estimated that agricultural productivity needs to increase by 70% by 2050 to keep pace with population growth. Moreover, climate change is predicted to negatively impact the agricultural outputs of some markets by 15-30% making this goal more difficult to reach. Beyond just increasing yield to feed the human population, there is a need to achieve this goal without further harming our planet. It has been suggested that optimization of below-ground interactions, between plant roots and soil microorganisms, might be our best hope for further increasing yield. One of the primary findings of recent soil microbiome research is that variation in the soil microbiome community is highly variable; differing as a function of both abiotic and biotic factors. The premise of this study is that modeling variation in plant-microbe interactions in natural contexts, where plants and soil microbes have evolved together, will lead to innovative strategies for maximizing the benefit of this relationship in applied agricultural contexts. Here, we propose to generate an extensive data of plant quality metrics and soil metagenomic data from a wide variety of soil types across the entire state of Virginia. Using this dataset, the primary goal of this study is to develop a machine-learning based approach to efficiently and effectively screen hundreds of naturally collected soil-microbiome datasets to identify which specific combinations of microbiota improve plant fitness in low nutrient soils. The long-term goal of this project is to use this information to develop applied strategies for sustainable agricultural settings.

Bin Ren, Ph.D. - 2020 Awardee
Department of Computer Science
College of William & Mary

"A General, Real-time DNN Execution Framework on Mobile Devices"

Deep Neural Networks (DNNs) have been evolved as the core enabler of many applications, such as smart health devices, wearable devices, robotics, image or video processing, etc., that broadly exist in many research fields ranging from medical science, biology to geoscience and environmental science. Considering the latency, privacy, and security requirements of these applications, real-time DNN execution on edge devices is desired. Unfortunately, this is still challenging, specifically if both real-time execution and high inference accuracy are in demand. This is because the increasingly large model size and complex model structure of high-accuracy DNNs usually require tremendous computation and memory resources that are not available on resource-constrained edge devices.

This project proposes a novel, fine-grained structured pruning called Block-based Column-Row (BCR) pruning that can achieve low inference latency and high accuracy for DNN executions on mobile platforms, simultaneously. Based on BCR pruning, it also proposes to build an end-to-end DNN acceleration framework, BPDNN that consists of two stages: a compiler-based stage to generate optimized DNN execution codes by leveraging BCR pruning, and an optimization framework to determine the block size for BCR pruning.

Project scope and relevance to this call. This project fits in the scope of Jeffress Trust Award due to two major reasons: 1) real-time DNN execution on mobile devices is increasingly on-demand in many domains, e.g., combining motion sensors and high-precision DNN inferences to support short-latency motion recognition can enable a real-time Parkinson treatment, and 2) the optimization framework of BPDNN relies on a classic mathematical model called ADMM (Alternating Direction Method of Multipliers), providing a pioneering attempt to benefit the model pruning from ADMM.

Yuhao Zhang, Ph.D. - 2020 Awardee
Department of Electrical and Computer Engineering
Virginia Polytechnic Institute and State University

"Machine Learning Enhanced Material-Device Co-Design for Power Electronics"

Power electronics, processing over 50% of world's electric energy, are used ubiquitously in electric vehicles, data centers, and smart grids. Recently, a new generation of power de-vices based on wide-bandgap (WBG) materials have demonstrated unprecedented per-formances and seen early applications by companies like Tesla, Google, and Amazon. However, their performances are still far away from the theoretical limits. Their design practices mostly rely on empirical experiences which often lead to non-optimum designs. While machine learning (ML) could efficiently traverse the material/device design spaces, it is prohibitively costly and time-consuming to obtain large experimental data for ML training. Additionally, there still lacks an effective ML model suitable for material-device co-design.

This project aims to develop a novel and computationally efficient framework, which comprises advanced ML models and a data-generation scheme that utilizes Technology Computer-Aided Design (TCAD) simulations to augment the experimental data. The cali-brated TCAD simulations will be used as a 'low cost' tool to generate extra device data (10-to-100-fold larger than experimental data). Reservoir computing (RC), a recent ML paradigm with enhanced performance but significantly lower size and power budgets, will be used to construct deep learning models. The TCAD-ML framework will be explored to correlate the material/device designs to the device performance metrics in both forward process and inverse process. The computational framework will be validated experimen-tally.

A highly interdisciplinary team with the leading experts in WBG materials and devices, power electronics, TCAD simulation, ML, has been assembled. Silvaco, a world's leading EDA/TCAD company, will collaborate with the team. This project also highlights a unique and interdisciplinary undergraduate research training on materials, devices, data science, TCAD, and ML. This project will greatly advance the development of WBG devices and ML-embedded simulators as well as the mathematical/statistical understanding on the ML application into physical electronic systems.

Huiyuan Zhu, Ph.D. - 2020 Awardee
Department of Chemical Engineering
Virginia Polytechnic Institute and State University

"Deep Learning Discovery of 2D MXenes for Electrochemical Ammonia Synthesis"

Electrochemical ammonia synthesis coupled with renewable electricity can serve as a sustainable alternative to the conventional energy- and carbon-intensive Haber-Bosch process. It can operate at a much smaller thus more distributed scale compared with the large infrastructure of the Haber-Bosch plant, avoiding high "well-to-wheel" costs. A critical bottleneck here is the sluggish electrochemical nitrogen reduction reaction (NRR), calling for the development of high-performance electrocatalysts. Here we study an emerging class of two-dimensional (2D) layered materials with transition metal carbides/ nitrides chemical compositions, i.e., MXenes, as the NRR electrocatalysts because of their excellent electron conductivity and structural diversity. A grand challenge of optimizing MXenes for the NRR is to tailor the desirable properties in an immense materials space, which demands a new approach rather than traditional trial-and-error methods.

We propose to develop an integrated experimental and deep learning approach to accelerating the discovery of MXenes for the efficient NRR to ammonia. We will combine state-of-the-art deep learning algorithms with precision synthesis and advanced characterizations to address two specific aims:
1. Benchmark activity and selectivity trends of MXenes for the NRR; and
2. Develop deep learning models for the prediction and validation of optimal catalysts.

The catalytic properties of MXenes will be tailored by the composition, surface groups, defects, and surface doping. We will integrate operando spectroscopic probing of reaction intermediates and quantum-chemical modeling to provide the quantitative relationship between free formation energies of key NRR intermediates and the activity/selectivity of MXenes toward ammonia. We will then develop deep learning models using the convolutional neural networks to predict optimal MXenes followed by experimental validation.

Success in this project will pioneer the development of a holistic framework and design strategy that develops highly efficient NRR electrocatalysts, and shed new light on the design of a sustainable, low-carbon, low-cost, and decentralized ammonia synthetic route.

Xianming Bai, Ph.D. - 2019 Awardee
Department of Materials Science and Engineering
Virginia Polytechnic Institute and State University

"Designing Next-Generation Batteries for Extreme Conditions from First Principles, Defect Science, and Machine Learning"

Next-generation batteries are expected to operate under extreme conditions such as harsh radiation, high temperature, and high pressure. The proposed research aims to develop a knowledge base for designing novel rechargeable batteries for operations under extreme conditions, such as under radiation. Our central scientific objective is to understand the interplay between the radiation-induced defect chemistry and the battery performance of layered oxide materials through atomistic modeling, machine learning, and experiments. The successful outcome of the project will create enormous opportunities to enable autonomous electronics and robotics in the nuclear power industry, as well as outer space exploration. Under these extreme conditions, many different types of defects can be created in materials, including interstitials, vacancies, dislocations, and antisite defects. On one hand, defect evolution can lead to complex microstructural evolution and may degrade the battery properties. On the other hands, defects may serve as ionic transport carriers and channels and thus enhance the battery performance. The true role of defects on the battery performance is unknown. In this work, a combined computational and experimental approach will be conducted to study the role of defects on battery performance. High-concentration defects will be introduced into sodium layered oxide battery materials, a model system, by ion irradiation at various doses. The defect chemistry will be characterized using advanced synchrotron X-ray spectroscopy and imaging techniques that are sensitive to the local defect chemical and structural environments. Atomistic modeling such as density functional theory and molecular dynamics will be conducted to study defect production and stability. The ion reaction kinetics and battery performance will be characterized as functions of ion radiation and defect chemistry. The atomic-level defect properties will be correlated with experimental battery properties through machine learning to explore the key factors that govern the performance of batteries under extreme conditions.

Hunter Bennett, Ph.D. - 2019 Awardee

Department of Human Movement Sciences
Old Dominion University Research Foundation

"An Innovative Interdisciplinary Examination Of Movement Efficiency For Youth With Autism Spectrum Disorder, A Pilot Study"

Motor domain deficiencies have emerged as a critical factor impeding the physical activity engagement of youth with autism spectrum disorder. However, few biomechanics studies have been performed in this population, and little is known about underlying biomechanical or energetic mechanisms of their motor domain deficiencies. The creation of a physiology-based model for predicting physical activity could provide new insight into why individuals with autism spectrum disorder are at risk for being physically inactive. Therefore, the overarching objective of the proposed research study is to define a normative database of walking and running movement patterns, movement efficiencies, body composition, and physical activity in youths with autism spectrum disorder. The specific aims of the proposed research are 1) compare movement efficiency between physically active and inactive youths with autism spectrum disorder and 2) create a model using physiological measures to predict physical activity level. This project will utilize both on-site and off-site data collections of 50 youth participants with autism spectrum disorder. On-site, three-dimensional motion capture, force data, electromyography, and accelerometry will be collected during walking and running tasks at standard speeds. The on-site data will fully describe the movement patterns, forces, and muscle activity during these common modes of physical activity for youth with autism spectrum disorder, which are currently unknown. Additionally, these measures will be used to calculate walking/running efficiency, which details the effectiveness of recycling muscle efforts to reduce cardiovascular loads. Off-site, participants will wear accelerometers for a seven day period to measure habitual physical activity levels. From the experimental data, a best-fit model based on physiological measurements will be designed to predict physical activity levels. This project will provide the framework for future research in biomechanics, exercise physiology, adapted physical activity, and engineering fields to increase physical activity and improve health-related measures for this typically physically inactive population.

Prateek Bhakta, Ph.D. - 2019 Awardee
Department of Mathematics and Computer Science
University of Richmond

"Towards Robust and Fair Allocation Policies for Liver Donations"

The purpose of this project is to design and test allocation policies for donated livers in the US. Livers are typically donated at the death of the donor, and are only viable for a short time after donation. This fact adds logistical and scheduling constraints to the choice of the eventual recipient of that liver, as the donations can't be scheduled in advance and the livers cannot travel more than a few hundred miles to their recipient.

In general, we would prefer donating to sicker people, however, the policy of always donating a liver to the sickest person it can viably reach is provably suboptimal in some cases. For example, people in rural areas may have far fewer opportunities to receive a liver than do people near cities. The current US policy has an additional significant drawback: geographical disparity in liver donation due to local demographic differences. This disparity privileges wealthy patients who can afford a second residence in advantageous districts. In addition, people could choose to register at favorable transplantation centers if they knew in advance that they would be one of the sickest people at that center.

The aim of this project is to design a policy for allocating donated livers in a way that optimizes social good and resists manipulation by those with insider information about waiting lists in the country. We seek provable results about the fairness and robustness of our proposed allocation strategies, and empirical verification of these strategies via simulation. Most importantly, we hope to contribute meaningfully to public policy. Similar algorithmic improvements on paired kidney donation have led to real changes in public policy, and we hope to effect change in a similar way.

This project touches on many areas of computer science, industrial engineering, and operations research, as well as medicine.

Phoebe Chappell, Ph.D. - 2019 Awardee
Department of Ocean, Earth and Atmospheric Sciences
Old Dominion University Research Foundation

"Exploring A Pelagic N2 Fixation "Hotspot" Along The Mid-Atlantic Bight Continental Shelf"

This project will combine innovative quantitative and bioinformatic approaches to explore the temporal extent and biogeography of biological dinitrogen (N2) fixation in a recently discovered "hotspot" of N2 fixation along the Northern Outer Banks with a special focus on interactions between N2-fixing symbionts and marine diatoms. This work capitalizes upon recent sampling efforts that measured unexpected elevated rates of N2 fixation in North Carolina shelf waters in a region with elevated abundance of a diatom known to harbor N2 fixing symbionts, low surface nitrate concentrations, and reduced salinity. The project will support monthly sampling at a coastal site near the hotspot in addition to seasonal transects offshore from this site with two transects in the seasons N2 fixation rates are predicted to peak (summer and fall). Sampling will include N2 fixation rate measurements, molecular characterization of both the N2-fixer and phytoplankton communities, and additional hydrographic parameters including temperature, salinity, nutrients, and chlorophyll. In addition to providing valuable data about both the extent (temporal and spatial) of coastal N2 fixation in a region where few measurements exist, the matrix of environmental data will be analyzed using correlative measures to help explore different potential influences on both carbon and nitrogen cycling in the region. It will address these specific aims:
1) Determine how long this hotspot persists throughout the year and estimate how much additional productivity it may be supporting.
2) Determine which N2 fixing group is responsible for high rates of N2 fixation at the hotspot.
3) Determine how the eukaryotic phytoplankton community changes at the hotspot throughout the year.
4) Perform correlative and factor analysis to identify potential linkages between environmental variable(s) and elevated N2 fixation rates in the region.
5) Examine metatranscriptome samples from August 2016 for evidence that N2 fixation activity alleviated nitrogen limitation in diatom symbiont hosts.

Tong Chen, Ph.D. - 2019 Awardee
Department of Engineering Systems and Environment
University of Virginia

"Modeling Energy & Emissions of Autonomous Electric Vehicles"

Increasingly, experts agree that the future of transportation will be autonomous and electric. However, the way which autonomous electric vehicles (AEVs) will be adopted by travelers and fleet operators remains highly uncertain. Predictions of the impacts of AEVs on transportation energy and emissions range from optimistically utopian (most trips will be rideshared, thereby reducing overall vehicle miles traveled [VMT] and congestion) to borderline dystopian (single occupant trips will dominate, and VMT will increase with AEVs traveling empty to avoid parking fees, pick up subsequent travelers, etc.). We propose forming a team with experience in modeling travel demand and transportation network operations in the context of AEVs from University of Virginia and Virginia Tech to develop a decision-support model to enable proactive planning for a sustainable energy future with AEVs. Instead of waiting to react to what may happen, this tool allows decision-makers to proactively anticipate the travel behavior shifts associated with AEVs and assess the magnitude of pricing policy impacts on AEV energy and emissions reduction. Specifically, this tool aims to address:

• In terms of travel demand, how will private AEV ownership rates and shared AEV adoption rates affect trip patterns?

• In terms of planning for a sustainable future with AEVs, what types of travel taxes and parking charges/incentives motivate travelers and fleet operators to shift travel demand and operational strategies to minimize transport-related energy consumption and emissions, and to what degree?

Samy El-Tawab, Ph.D. - 2019 Awardee
Department of Integrated Science and Technology
James Madison University

"Independent Mobility for the Elderly: Machine-Learning-Based Passenger-Aware User Interfaces for Autonomous Vehicles"

The transportation industry is currently undergoing a drastic shift towards autonomous vehicles (AV) and processes. It is likely that autonomous transportation systems will be deployed within retirement communities significantly sooner than they are available to the general public: these communities have a particularly acute need for assisted mobility, and the controlled environment of a retirement campus simplifies many of the technical problems related to autonomous control. The elderly population has a relatively high prevalence of physical, sensory and cognitive limitations that must be addressed in the design of an AV system. We believe that a successful user interface in this domain will require a high level of passenger awareness. External and in-vehicle sensors will monitor the position, activities and mental state of passengers. The user interface will use that information to guide passenger interactions. For example, raising the volume of spoken instructions if a passenger is having difficulty hearing, or calling for assistance if a passenger is having difficulty entering or exiting the vehicle. The central research questions that we consider are 1) How can machine learning models be used to extract relevant passenger information? 2) How should an AV user interface incorporate passenger monitoring data to provide safe and reliable mobility service for the elderly? In earlier work, we developed an autonomous golf cart that provides the key capabilities required for autonomous passenger transport. The proposed work will build on that foundation to address the research questions outlined above. We propose to: 1) Equip our autonomous vehicle with a sensor suite that will enable the collection of passenger data suitable for training machine learning models. 2) Develop and train machine learning models to extract passenger information that can be used by the user interface. 3) Prototype a passenger-aware user interface. 4) Validate the user interface design through user trials.

Keigo Fukumura, Ph.D. - 2019 Awardee
Department of Physics and Astronomy
James Madison University

"Modeling Hard X-Ray Obscuration in Active Galactic Nuclei with Accretion Disk-Winds"

Supermassive black holes (BHs) are thought to be energetic central engines (aka. active galactic nuclei or AGN) in very luminous galaxies by accreting plasma to power various components of spectroscopic signatures primarily observed in X-ray. In hard X-ray band (2- 10 keV), the observed continuum component is often found to be partially (if not fully) absorbed by a putative obscurer of some column density (e.g. Nh ~ 1e23-1e25 1/cm^2) within the local system. From a detailed observation of the blue-shifted absorption lines, on the other hand, it is believed that a large fraction of accreting plasma (e.g. ~50% or more) is actually ejected from the BH accretion disk in the form of ionized winds.

In this project we will test our hypothesis that an ionized disk-wind can obscure the primary X-ray continuum to produce the observed spectrum in AGNs and investigate their physical correlations. Specifically, we plan to calculate the so called "absorption function" – a fractional AGN distribution as a function of AGN X-ray luminosity – by numerically modeling theoretical spectra in the context of magnetohydrodynamic (MHD) outflow models. This function depends on a number of model parameters; e.g. accretion-rate, observer's viewing angle, density profile, X-ray luminosity.

To this end, we will simulate a family of MHD-driven disk-wind solutions, which will intercept and absorb hard X-ray photons, by numerically solving the MHD equations. For radiative transfer process between ions in the wind and radiation field, we will utilize the xstar photoionization code. Predicted absorption functions will be compared with the observed function obtained from a large sample of X-ray surveys available. Our final goal is to deliver a set of wind variables consistent with data.

Three JMU undergraduates will be supported by this program in collaboration with two unfunded external astrophysicists at NASA/GSFC.

Dipankar Ghosh, Ph.D. - 2019 Awardee
Old Dominion University Research Foundation

"Quantitative Understanding Of The Role of Dielectrophoretic Forces (DEP) In The Synthesis Of Ice-Templated Hierarchical, Directionally Porous Ceramics And Structure-Property Relationships"

Mechanically robust open-cell porous ceramics are critical for a variety of engineering endeavors, ranging from aerospace, automotive, biomedical, energy, national security, and structural applications. Many applications involve fluid flow and ion transport through the porous ceramic; however, random pore orientation in conventionally processed open-cell porous ceramics leads to highly tortuous pathways impeding its transport properties. Another limiting factor is the weak mechanical behavior of open-cell ceramic foams. These requirements can be met by the newly emerging ice-templating technique, which enables the synthesis of directionally porous, hierarchical ceramics with low pore tortuosity. However, processing innovations in templating are in urgent need for improved process control and enhancement of mechanical properties and functionalities, to accelerate the deployment of this technology for practical implementation.

This research aims to develop an innovative methodology by incorporating dielectrophoresis into the existing ice-templating process for the synthesis of directionally porous ceramics. Specifically, this research will investigate the fundamental role of dielectrophoretic (DEP) forces, which generate in colloidal suspension due to application of an external AC electric field, in the synthesis of ice-templated ceramics and in the structure-mechanical property relationship of the resulting materials. Under Specific Aim 1, this research will develop the proposed methodology, and investigate the effects of AC field on microstructure and compressive mechanical properties of the synthesized porous ceramic materials to develop processing-microstructure-mechanical property relationships. Under Specific Aim 2, this research will develop a transient multiphysics model under the thin electric double layer assumption, in which the fluid flow field, AC electric field, and motion of finite-size particles will be simultaneously solved using an Arbitrary Lagrangian-Eulerian numerical approach. The model will thus serve as a versatile tool to design hierarchical ice-templated ceramic materials. Long-term goal of this research is to fundamentally change the way porous ceramic materials are designed and processed for various applications.

Oleksandr Kokhan, Ph.D. - 2019 Awardee
With support from the Hazel Thorpe Carman and George Gay Carman Trust
Department of Chemistry and Biochemistry
James Madison University

"Regulation of Substrate Binding in the bc1 Complex"

Ubiquinol-cytochrome c oxidoreductase (bc1 complex, complex III) is a key membrane enzyme involved in respiration. It is known to be one of the major producers of reactive oxygen species (ROS) in mitochondria. Our overarching hypothesis is that there are at least two overlooked bc1 regulations mechanisms. Specifically, our first aim is to use a combination of computational and experimental techniques to test anti-cooperative substrate binding in the bc1 complex. This effect was suggested based on available X-ray crystal structures but was not experimentally tested. Our second hypothesis is that lipid membrane composition and lipid charge can regulate substrate binding affinity. This project will use a combination of computational and experimental techniques to predict molecular level bc1 regulation mechanisms and to test them experimentally. We will use long all-atom molecular dynamics (MD) simulations of bc1 in different lipid environments to predict structural changes associated with different occupancy of the substrate binding sites and to guide our experimental work on detergent-solubilized and nanodisc-embedded bc1. We will use isothermal calorimetry (ITC) to test substrate binding in vitro, and to measure binding stoichiometries, association constants, and thermodynamic parameters as a function of ionic strength and lipid charge. We will use small-angle X-ray scattering (SAXS) to independently verify the ITC results, to confirm the locations of substrate binding sites, and to construct low-resolution solution-state structures of the enzyme-substrate complexes. Laser-induced time-resolved optical spectroscopy will be used to measure changes in the charge transfer rates as response to changes in lipid environment and substrate binding regulation. Finally, we will use kinetic spectroscopy to study the roles of lipid membranes and intermonomer interactions within the bc1 complex dimer on the catalytic turnover rates and the rate of ROS production. Overall, this interdisciplinary approach will advance understanding of bc1 regulation and will test the two predicted regulation mechanisms.

Justin Lemkul, Ph.D. - 2019 Awardee
Department of Biochemistry
Virginia Polytechnic Institute and State University

"Towards Computational Drug Design Against DNA G-Quadruplexes"

G-quadruplexes (GQs) are noncanonical nucleic acid structures that form in both DNA and RNA, serving important functional roles in telomere maintenance and regulation of both transcription and translation. Given these essential roles, GQs are emerging as novel targets for small-molecule therapeutics against neurodegenerative disorders and cancer. Structural studies have thus far indicated that most GQ structures are unique, raising the possibility that each structure can be targeted specifically and with high affinity. However, despite this structural evidence, little is known about how GQs fold and remain stable. It is known that ions, typically K+, are required for GQ folding, but it is not known how these ions may affect important loop regions that dictate GQ topologies, or how they affect the electronic structure of GQ stems, which are composed entirely of Hoogsteen hydrogen-bonded guanine bases. Molecular dynamics simulations can provide such insights, but many theoretical investigations to date have suffered from insufficiently accurate potential energy functions, failing to account for electronic polarization, which is essential for K+ binding to GQs. We propose to investigate DNA GQs using a cutting-edge polarizable force field based on the classical Drude oscillator model, which we have demonstrated yields stable GQ structural ensembles and K+ coordination. In this project, we aim to (1) characterize the interactions of ions with DNA GQs in terms of discrete binding sites and ion condensation and (2) define the conformations adopted by loop regions that exist between the guanine tetrads that comprise the GQ stem. This information is critical for understanding accessible structural motifs on DNA GQs that can be targeted with putative drug molecules to modulate their stability and dynamics, towards modulation of gene expression at the nucleic acid level. In so doing, we seek to advance therapeutic specificity and efficacy for a range of diseases.

Kendra Letchworth Weaver, Ph.D. - 2019 Awardee
Department of Physics and Astronomy
James Madison University

"Determining Nanoscale Interfacial Structure by Integrating Quantum and Statistical Mechanics with Experimental Characterization"

Theoretical and computational methods are well-developed for inorganic solid materials and for statistical physics of liquid molecules. However, the interface between the two regimes proves challenging for predictive theories. Electronic energy levels determine chemical reactivity and dictate interactions between light and matter at a solid surface, but at the same time, charge screening and steric effects of the surrounding liquid environment critically impact the electronic structure of the surface. Connecting with experimental measurements requires bridging the length and time scales between traditional first principles methods for the solid phase and statistical methods for reacting molecules on the surface. In the proposed project, we will obtain a realistic, multiscale computational description of interfaces by combining quantum and statistical mechanical methods and utilizing techniques and algorithms from data science to make connections to experimental measurements. Undergraduate students will be involved in theory and software development, predictive simulations, and experimental measurements to compare with theoretical predictions.

The project entails developing and utilizing innovative, scale-bridging computational techniques such as density-functional theory (DFT), molecular dynamics, and machine learning to integrate predictions with experimental measurements. Advances in modeling will create opportunities for experimental collaborators to address fundamental questions in interfacial science. Our team will investigate the structural and electrochemical properties of metallic and semiconducting surfaces and the impact of liquid or interphase regions on surface chemistry. At JMU, we will utilize temperature programmed desorption, microscopy, and spectroscopy informed by the proposed computational work to determine morphology and reactivity of catalyst surfaces. At Argonne National Laboratory, collaborators will perform X-ray reflectivity measurements of the structure of aqueous interfaces for direct comparison to theoretical predictions. Novel insights into these cross-cutting basic science problems will aid design of technology in catalysis, renewable energy generation, and water purification.

Xu Liu, Ph.D. - 2019 Awardee
Department of Computer Science
College of William and Mary

"Supporting Efficient Execution of Computational Models"

Inefficiencies abound in complex, layered software (e.g., highly parallelized scientific applications). A variety of inefficiencies show up as wasteful memory operations. Many existing tools instrument every load and store instruction to monitor memory, which significantly slows execution and consumes enormously extra memory.

In this project, we will develop a piece of computer software—HPCProf, a lightweight inefficiency- detection tool that measures the execution performance of computer software widely used in the domain of various computational sciences. HPCProf will sample consecutive accesses to the same memory location by exploiting two ubiquitous hardware features: the performance monitoring units (PMU) and debug registers. HPCProf will perform no instrumentation. Hence, client tools built atop HPCProf will be able to detect a variety of software inefficiencies while introducing negligible slowdown and insignificant memory consumption. As a mathematical component in this project, we will quantify and improve the measurement accuracy. We expect that HPCProf will yield similar accuracy to the ground truth. HPCProf will guide code optimization that will efficiently map scientific simulation code to modern and emerging computer architectures, which will both increase the productivity of the scientific researchers and reduce the energy consumption of the computer system.

This project falls in the interest of Jeffress Trust Award mainly due to two reasons. (1) HPCProf will directly benefit computational sciences to improve their code performance. (2) As a research component, HPCProf will employ a mathematical model to improve its analysis accuracy.

Eyleen O'Rourke, Ph.D. - 2019 Awardee
Department of Biology
University of Virginia

"Pan-modeling of Animal Metabolism: The C. elegans Project"

Animals are integrated networks of interacting organs systems with a critical subcellular organization ruled by genes. Genetic or environmental perturbation of the intracellular gene networks disrupts the interactions between cells, tissues, and organs leading to a cascade of system failures and ultimately disease or death. There are currently no models that can represent animal life with its major levels of organization: gene, cells, and organs (3D modeling). Without 3D models it is not possible to anticipate the distinct effects of drugs on different organs, to design tissues or organs our bodies would not reject, or simply to understand health and disease at the molecular level. However, 3D modeling of an entire animal has remained out of reach, mainly due to the lack of technologies to: 1) define the level of metabolic-enzyme activity across all tissues of an animal in physiological and pathological conditions; 2) reconstruct in silico the cell, tissue, and organ networks that compose an animal; and 3) perform genome-scale experimental testing of model predictions with tissue or organ resolution in living animals. Using the proven model of human disease Caenorhabditis elegans, with a team of collaborators, we developed whole-animal single-cell transcriptomics allowing us to infer the level of activity of metabolic enzymes across all C. elegans tissues, and automated genome-scale tissue-specific RNA interference so that we can experimentally test the impact that each metabolic enzyme has on each tissue and organ, and ultimately on whole-animal metabolism. Here, we propose to use these technologies to assist the development of in silico models for all 27 C. elegans cell-types and of tools to integrate these cell-specific models into an experimentally-validated single-cell resolution platform for predictive modeling of the metabolism of an entire living animal. Whole-animal metabolic modeling is expected to accelerate the discovery of disease mechanisms and new treatments.

Tara Pelletier, Ph.D. - 2019 Awardee
Department of Biology
Radford University

"Long-term Impacts Of The Mountain Valley Pipeline On The Physical Habitat, Water Chemistry, And Biodiversity Of Mill Creek, Roanoke County, Virginia"

We have three main aims that integrate methods from field ecology, environmental chemistry, and genomics & bioinformatics for assessing biodiversity at the Mill Creek watershed in Virginia. Factors such as population dynamics, community dynamics, and environmental change are vital factors that shape current biodiversity patterns. Consequently, identifying these complex processes is an ongoing challenge for biologists. A particularly useful approach evaluates the fit of multiple models given the data. We will combine disparate data types in a unified framework using data simulation, hypothesis testing, and predictive modeling. We will 1) Develop baseline data for long-term ecological assessment; 2) Compare measures of biodiversity and community composition from field surveys and molecular environmental DNA; and 3) Use machine learning to determine the most important environmental variables (water chemistry and physical habitat) for predicting several measures of biodiversity. This project will provide valuable interdisciplinary research experiences for four undergraduate students, such that they are highly competitive for professional and/or graduate programs. Our proposal to use both field and lab techniques will give us more precise measurements of biodiversity by detecting rare, ephemeral, and cryptic species that are hard to identify morphologically, and assess the ability for molecular techniques and bioinformatics to estimate species abundance. This biodiversity assessment will help to address a paradigm shift in conservation biology to protect less-charismatic species that are necessary for ecosystem functioning by assessing species composition and richness in aquatic insects after an extreme habitat modification. In summary, we will assess biodiversity changes in relation to physical habitat, water chemistry and the implementation of the Mountain Valley Pipeline in southwest VA. Additionally, this study will construct novel predictive models to evaluate the succession of invertebrate species in aquatic systems, and guide future management plans.

Emily Rivest, Ph.D. - 2019 Awardee
Department of Biological Sciences
College of William and Mary

"Fast Food On High-Speed Real Estate – A Bioindicator For Effects Of Climate Change On The Virginia Coast Barrier Island Ecosystem"

Shorebirds rely on Virginia's barrier islands as pit stops along their bi-annual migration routes. Refueling their energy reserves, the birds rely on bivalve recruits (young juveniles) as prey. Ocean acidification may alter the availability and quality of bivalve recruits as a valuable prey resource. Using an innovative, interdisciplinary, quantitative approach, we will explore the use of blue mussels (Mytilus edulis) and coquina clams (Donax variabilis) as indicators of ocean acidification and co-stressors in the Virginia Coast Reserve barrier island ecosystem. First, we will collect oceanographic data as juvenile mussels and clams recruit to the barrier islands. Using seasonal variation in water conditions as a natural experimental framework, we will establish mechanistic relationships between changes in water chemistry and bivalve traits. Second, we will analyze biological samples from a historical collection of bivalves from our study sites, extending back 13 years, to quantify long-term trends in bivalve traits. We will apply our mechanistic relationships to historical time series to quantify present-day impacts of climate change. Finally, we will develop a computational model to predict future changes in bivalves and their shorebird predators as a result of future ocean acidification and co-stressors. Many of the shorebirds that use this Virginia Coast Reserve to refuel are highly imperiled, including the federally threatened red knot (Calidris canutus rufa). Understanding how ocean acidification affects, now and in the future, prey quality is critical for designing flyway-level conservation measures. Our work linking ocean acidification processes to bivalve prey and shorebird predators will also serve as a model for other studies of ecosystem impacts of ocean acidification in the Virginia Coast Reserve and other locations around the globe.

Navid Tahvildari, Ph.D. - 2019 Awardee
Department of Civil and Environmental Engineering
Old Dominion University Research Foundation

"An Integrated Computational Framework for Hydrodynamic and Biological Processes in Seagrasses"

Seagrass meadows are crucial ecosystems that improve water quality, provide habitat for fisheries, reduce ocean acidification, and stabilize sediments. They can also mitigate coastal storm impacts by attenuating storm waves and surge. There is growing interest to preserve seagrasses for their ecological services, and mitigation of climate change impacts such as ocean acidification. Furthermore, aquatic vegetation is increasingly been considered as part of nature-based solutions for storm damage reduction. Seagrass meadows have had drastic losses due to water quality deterioration and science-based models are needed to develop effective strategies for their restoration. This project aims to address some critical gaps in our capability to numerically model flow-vegetation interaction and simulate seagrass production. In particular, the capability to simulate seagrass blade-blade interactions and quantify their impacts on currents and waves is lacking. Furthermore, biophysical models for seagrass growth assume vertically uniform flow which is a substantial oversimplification of real conditions. We propose to develop a flow-vegetation interaction model that in addition to computing velocity profile and wave attenuation rate, can simulate seagrass blade-blade interactions, and compute instantaneous blade bending angle which is influenced by the aforementioned factors. The model will be tightly coupled with a seagrass biophysical model so that it can compute seagrass photosynthesis at a high temporal rate. To validate the modeling framework, datasets of hydrodynamic variables and plant properties will be acquired from a temperate and a tropical site. The distinct hydrodynamic and seagrass species in the two sites will enable validating the model over a wide realistic parameter space. The project will develop a tool that predicts how seagrasses affect hydrodynamics and identifies flow conditions where seagrasses can thrive. Thus, it will support optimal strategies for seagrass restoration and their utilization as a natural solution for coastal mitigation.

- **Liang Zhao, Ph.D.**
  Assistant Professor – 2019 Awardee
  George Mason University

"Evaluation of Molecular Structures via Deep Learning"

Protein Structure Prediction (PSP) is to predict the three-dimensional structure of a protein from its amino acid sequence. As the protein structure is essential in determining its function, PSP has become an increasingly important domain in molecular biology for crucial applications like drug design. Until now, there is still no generative/mechanistic model that directly calculates out protein structure from its sequence. To sidestep this challenge, existing works routinely resort to optimization-based frameworks that search for protein's native structure guided by predefined scoring function and under various constraints in a vast searching space (e.g., with size over 10^{60}). Despite great progress over decades, however, such frameworks for PSP are approaching a saturation point with diminishing return, partly due to the inherent algorithmic bottleneck in balancing the exploration and exploitation in sophisticated searching space. Also, until now there still lacks unbiased scoring functions. Currently, around 99% proteins' structures have not been accurately confirmed and the gap is still increasing.

To overcome the bottlenecks, this project aims at charting a radically new pathway towards a potentially more fundamental solution to PSP, by directly modeling the protein folding by most recent advancement of deep graph generative models. This research is buoyed by the most recent remarkable success in Artificial Intelligence (AI) for creating complex-structural data such as text, images, music, and molecule structures. These advancements provide unprecedented opportunities to directly modeling the underlying generative process of protein structure from a sequence. The investigators will bring together their complementary expertise on generative and interpretable deep learning (from Zhao), and biomolecular modeling (from Shehu). Innovative heterogeneous graph encoders and decoders will be developed for representing and generating protein molecules, with explainable modeling and predicting process. The proposed research will deepen our understanding in protein folding, with far-reaching contributions to graph deep learning, explainable AI, biological molecular.

Christopher Berndsen, Ph.D. - 2018 Awardee
Department of Chemistry and Biochemistry
James Madison University

"Connecting Active Site Dynamics to Reaction Chemistry During Ubiquitin-Like Protein Activation"

Protein post translational modifications regulate most cellular pathways. The timing of the modification, target identity, the enzyme mechanisms and regulation of the enzymes that perform these modifications are of key interest for understanding the complex biochemical networks that control cellular functions. The modification of cellular proteins with ubiquitin or ubiquitin-like proteins is primarily associated with protein degradation however this modification also functions to regulate DNA damage repair, endocystosis, and other essential cellular processes. Less is known about the enzymatic mechanism(s) of modification and how enzyme dynamics function in modifying other proteins with ubiquitin and ubiquitin-like proteins. The first step in attaching ubiquitin and ubiquitin-like proteins is called activation and is executed by the activating family of enzymes. These enzymes catalyze ubiquitin/ubiquitin-like activation in 3 apparently discrete reactions. Dynamic structural changes to the enzyme have been suggested by crystallography, however the timing of these changes relative to the reaction chemistry is not clear. In addition, some E1 activating enzymes are missing part of a catalytic domain required for activation and it is not clear if the chemistry of catalysis differs in these structurally non-canonical enzymes. Given the essential functions of the E1 enzymes in cells, our lack of a complete mechanism and a clear sense of the biochemical differences between the canonical and non-canonical E1 enzymes represents a significant knowledge gap. The proposed experimental plan will biochemically characterize a representative member of the activating enzyme family in order propose the first chemical mechanism of catalysis for this enzyme class. Through biochemical, and computational methods we will identify when and where structural changes are occurring in the E1 enzymes relative to the reaction chemistry. These data will demonstrate how the dynamic E1 active site stabilizes and facilitates the reaction chemistry and lead to further comparative study of this enzyme family.

Lauren Childs, Ph.D. - 2018 Awardee
Department of Mathematics
Virginia Polytechnic Institute and State University

"Modeling Immunological Memory: a Combined Biological and Mathematical Approach to Understanding T Helper Cell Differentiation"

During the course of an infection, specialized immune cells called T helper cells proliferate and secrete cytokines to orchestrate the immune-mediated elimination of invading viruses, bacteria, or parasites. As pathogen is eliminated, the number of T helper cells is reduced to avoid potentially dangerous autoimmune responses. However, long-lived 'memory' T helper cells survive and are maintained in the body to form an important branch of immunological memory. This process allows the immune system to respond more quickly and robustly to repeat infections, and is the basis for a number of modern medical therapies including vaccination. Due to the importance of memory T cells to human health, there is intense interest in understanding how these vital cells are formed.

It is recognized that the generation of memory T cells is mediated by numerous cell-extrinsic and -intrinsic influences, including both the cytokine environment and proteins called transcription factors that regulate changes in gene expression required for memory cell development. However, as this is a complicated and multi-step process, many questions remain regarding the mechanisms that promote memory cell formation. Due to this complexity, the generation of novel, interdisciplinary experimental approaches is required to answer these questions. Therefore, we will employ combined cutting-edge mathematical modeling approaches, next generation sequencing platforms, and highly tractable T helper cell differentiation systems to define how cell-extrinsic cytokine signals and cell-intrinsic transcription factor activities are integrated to properly regulate memory T cell differentiation decisions. Collectively, the findings generated through this proposal will be significant, as they will generate critical understanding necessary for the informed design of increasingly effective vaccines, and provide the molecular building blocks for the development of novel immunotherapeutic strategies surrounding immunological memory formation.

Cristian Danna, Ph.D. - 2018 Awardee
Department of Biology
University of Virginia

"Computational Modeling for the Discovery of Pathogen Metabolites Critical to Plant Infection"

Plant infectious diseases account for 42% of the global-annual losses of the six most important food crops. The bacteria Pseudomonas syringae is an economically important plant pathogen that causes disease in several crops grown in the Commonwealth of Virginia, including soybeans, tomato, tobacco, cotton and pepper. PI Danna recently discovered a critical, yet uncharacterized, defense mechanism against P. syringae: plants that resist P. syringae infection withhold nutrients from the sites where this pathogen would otherwise grow, triggering a starvation response in P. syringae that halts its growth and prevents it from causing disease. As all pathogens need nutrients from their host plants, it is reasonable to predict that programmed microbe starvation is a viable biotechnological strategy to produce crops with durable resistance against a broad range of pathogens (not just P. syringae). To exploit pathogen starvation to improve plant productivity, it is essential to identify the critical metabolites that microbes need to successfully infect a host. However, plants produce thousands metabolites, and any of them, or combinations of them, could define the success of the pathogen. Therefore, computational models that can predict which metabolites would be critical for pathogen growth are needed. However, predictive models of plant-pathogen metabolism are currently lacking. We will fill this gap through: Aim 1) Metabolic network reconstruction of P. syringae metabolism; and Aim 2) Predictive modeling and experimental testing of in vivo P. syringae nutritional requirements. We anticipate that predictive metabolic-network modeling of P. syringae will: 1) enable the generation of testable hypotheses about the critical nutrients and metabolic pathways defining the success of P. syringae to infect a host plant, 2) facilitate the discovery of mechanisms of disease in a wide range of plant-pathogen interactions, and ultimately, 3) contribute with foundational knowledge to develop programmed starvation as a novel strategy to reduce crop losses.

Sanket Deshmukh, Ph.D. - 2018 Awardee
With support from the Hazel Thorpe Carman and George Gay Carman Trust
Department of Chemical Engineering
Virginia Polytechnic Institute and State University

"Machine-Learning Accelerated Computational Design of MOFs for Drug Delivery"

Cancer continues to be one of the leading causes of morbidity and mortality around the world. Among various available anti-cancer drugs, curcumin has shown potential for the treatment of many cancers via its effect on a variety of biological pathways involved in mutagenesis, cell cycle regulation, metastasis, apoptosis, tumorigenesis, and oncogene expression. However, the use of traditional direct administration route to deliver curcumin is very challenging due to its low solubility, chemical stability, and bioavailability. Here, we propose to design a biocompatible and biodegradable metal-organic framework (MOF) as a drug carrier that can load a biologically relevant amount of curcumin, and release it only under the right physiological conditions, for example the pH in the tumor micro-environment. Ideally, a MOF structure can be separated into three basic building blocks: a metal node, an organic linker, and a functional group decorating a MOF. In principle, one can alter the combination of these building blocks, and tune their pore diameter/size, pore geometry, stability, and chemical environment. Although, the vast number of building blocks provide a great opportunity to design a new MOF, exploring this combinatorially large and multidimensional materials space through experimental, trial-and-error approach can be very inefficient and laborious task. To overcome this challenge, we propose a rational design route led by computational approach, which will utilize machine learning models along with the state-of-the-art molecular modeling methods and simulations to accelerate the discovery of new MOFs. The three specific aims (SAs), which will be validated experimentally are:

SA-1: Design new hypothetical MOFs (H-MOFs -- MOFs that can be practically synthesized in a laboratory but have not yet been synthesized).

SA-2: Investigate the mechanisms of curcumin adsorption/desorption in H-MOFs.

SA-3: Identify H-MOF features responsible for their adsorptive properties to develop predictive models to accelerate the design of new H-MOFs.

Miles Johnson, Ph.D. - 2018 Awardee
Department of Chemistry
University of Richmond

"An Integrated Synthetic-Computational Approach to Developing a Quantitative Model for Proazaphosphatrane-Enabled Cross-Coupling"

The rational development of transition metal-catalyzed cross-coupling methods is essential for the synthesis of pharmaceutically relevant compounds. Despite the essential nature of these transformations in medicinal chemistry, quantitative predictive models for reaction outcomes remain rare, hindering the optimization of known reactions and the discovery of new transformations. Ground-breaking methods now exist for the parameterization of catalysts using both computational and experimental measurements, but these technologies have only been applied to the study of reaction outcomes without investigating catalytic intermediates. Our laboratories will undertake an integrated approach to studying the reaction parameters that affect cross-couplings involving proazaphosphatrane ligands. These structurally complex ligands exhibit exceptional performance in numerous cross-coupling reactions yet the properties that engender high reactivity under mild conditions remain unknown. For these reasons, catalytic intermediates involving these ligands will be prepared and characterized experimentally with simultaneous structural and electronic parameterization of these organometallic compounds through density functional theory (DFT) methods. Multivariate correlation of parameters with reaction outcomes will then be conducted to elucidate what factors yield ideal catalyst performance. This combined synthetic-computational study will be conducted with two goals in mind:

Specific Aim #1: Construct a quantitative and predictive model for proazaphosphatrane-supported palladium-catalyzed cross-coupling reactions.

Specific Aim #2: Develop sustainable cross-coupling methods using earth abundant metals and simple hydrocarbon feedstocks.

Not only will this work result in highly quantitative models to explain previously observed reaction outcomes, it will provide a predictive tool to rationally achieve desired results in novel transformations. Importantly, the in-depth understanding of proazaphosphatrane ligands garnered from these studies will inform the critical development of environmentally benign catalysts designed to modify substrates from renewable chemical sources (e.g. biomass).

Nathanael Kidwell, Ph.D. - 2018 Awardee
Department of Chemistry
College of William and Mary

"Experimental and Computational Analysis of Atmospheric Brown Carbon Photolysis in the Gas and Particle Phases"

Organic carbon molecules in the atmosphere are emitted by both plants and humans and play a key role in atmospheric chemistry, air quality, and climate. Most organic molecules can absorb UV and infrared but do not absorb much in the visible region of the solar spectrum. Recently, studies have focused on organic molecules with chromophores that can absorb in the near UV (300-400 nm) and visible regions, termed "brown carbon" (BrC). These molecules are found in both the gas phase and in the condensed phase in aerosols and cloud droplets. Direct absorption of solar radiation by gas phase BrC molecules can lead to the formation of radicals that can further oxidize other atmospheric organic molecules. In the condensed phase, BrC can warm and help evaporate cloud droplets as well as drive secondary reactions with other condensed phase organic material. These impacts are relatively unconstrained in climate models now due in part to a lack of data on the sources, source strengths, and lifetimes of these molecules in the atmosphere. The research outlined in this proposal will pursue an experimental and computational analysis of the photochemical processing of three classes of BrC molecules: nitrophenols, nitroguaiacols, and nitrocatechols. We will investigate (1) the photolysis lifetimes of these molecules in both the gas and condensed phases with modeling at atmospherically relevant solar fluxes, pressures and temperatures, (2) the solar photochemical reaction dynamics in the gas phase integrated with electronic structure calculations and computed potential energy surfaces, and (3) the effects of secondary photolysis reactions on the composition of dissolved organic material in combination with a statistical oxidation model.

Oleksandr Kravchenko, Ph.D. - 2018 Awardee
Department of Mechanical and Aerospace Engineering
Old Dominion University Research Foundation

"Computational Modeling to Inform Manufacturing of Advanced Hybrid Composites"

One of the main challenges with composites manufacturing is the certification of these new materials. The complex morphology of composites, arising from layup of continuous fibers or composites produced by molding of platelet or short fiber reinforcement, complicates design and manufacturing. A robust and repeatable manufacturing process is essential to composite manufacturing. Therefore, the development of new composite materials with targeted mechanical properties, especially for automotive and aerospace applications, requires predictive capabilities that can capture intrinsic variability of composite mechanical behavior due to the complex morphology and the effect of manufacturing processes on resulting mechanical properties. This proposal is focused on developing a computational damage mechanics model to analyze the structural response of hybrid composites, which consist of continuous fiber and discontinuous fiber reinforced platelets systems. The hybrid configuration offers unique opportunities in balancing performance and manufacturability allowing for greater versatility in designing composite structures with targeted properties. Currently, the design practices of hybrid systems are primarily empirical, which adversely affect time and cost of the initial design. Therefore, establishing the computational framework that captures comprehensive failure modes of composite is the focal point of this project to enable wider adoption of the hybrid systems.

The project is focused on two interconnected tasks of establishing a computational model for predicting structure-property relationships of the hybrid system and experimental validation of the proposed model using experimental mechanical testing. Once the computational model is validated, it will be used to investigate how various parameters related to processing temperature conditions, platelet initial configuration, and volume fractions of the continuous and discontinuous component affect the overall mechanical response of the composite. The combination of computational modeling and experimental validation will provide a high fidelity framework that will connect with the next step of the project in design and manufacture of the automotive structural component.

Song Li, Ph.D. - 2018 Awardee
Department of Crop and Soil Environmental Sciences
Virginia Polytechnic Institute and State University

"Unveiling the Mystery of Innate Immune Cell Memory with Single Cell Sequencing and Machine Learning"

Low dose lipopolysaccharide (LPS) treated monocytes leads to a low-grade, non-resolving inflammation. Long-term accumulation of such low-grade inflammation could lead to tissue damage, which is associated with multiple chronic diseases. Most research has been focused on the transient response of monocytes to high dose LPS, which is an indicator of bacterial infection. However, little is known about the regulatory mechanisms underlying the non-resolving inflammation caused by low dose LPS activated monocytes.

The long-term goal for this project is to identify key regulators of cell fate decision and stress response in monocytes. We approach this problem by integrating machine learning with advanced, single cell genomic experiments. Traditional RNA sequencing experiments using millions of cells failed to capture sub-population of activated monocytes. We have developed a novel microfluidic device for single cell sequencing, which reduce the cost of sequencing by 30-fold while increasing the detection sensitivity by more than two-fold as compared to other published approaches. Using this device, we could sample hundreds of cells and detected sub population that represents as low as 2% of treated monocytes.

The aims of this project are: 1) Perform time-course, single cell sequencing experiments at four time points that span the time frame of monocyte activation. 2) Apply ensemble machine learning methods to predict gene regulatory networks by integrating existing knowledge of gene regulation with newly generated single cell gene expression data. We will identify subpopulations that responded to low LPS treatments at each time point. The machine learning method will identify the key target genes that are responsible for low LPS responses. This project will provide valuable research experience for four undergraduate students in an interdisciplinary research team. The tools developed in this project can be applied to finding target genes in other complex human disorders and plant diseases.

Daniel Miller Runfola, Ph.D. - 2018 Awardee
Department of Applied Science
College of William and Mary

"Evaluating the Impact of International Aid on Ecological Processes by Integrating Computational and Experimental Methods"

Over $8 billion dollars of international aid is allocated to environmental protection each year, representing a 250% increase since 2000. Despite many localized case studies, the multi-directional impact of this aid on ecological systems is poorly understood at the global scale. This knowledge gap is driven by many factors, but a critical limiting factor to date has been that the processes driving the impact of aid on ecological systems illustrate strong heterogeneity across geographic regions. Here, we propose research which can capture such heterogeneity at the global scale by employing a novel approach to machine learning - Causal Trees (CT). Building on previous research, we will integrate a database of approximately 10,000 geographic locations at which international environmental aid was distributed with satellite and other spatial data recording relevant outcomes (i.e., forest cover) as well as dozens of variables containing relevant covariate information (i.e., temperature, distance to roads). Following the CT approach, each of these locations will be matched - spatially and temporally - to an area of similar characteristics which did not receive environmental aid, and the dimensions along which impacts vary most will be identified. Finally, a Random Causal Forest (RCF) will be employed to estimate the importance of different variables in driving the effectiveness of aid by examining the resultant purity scores from each forest iteration. If successful, this approach will enable researchers to identify the contexts in which aid changes environmental processes without the a priori specification of interaction terms, as well as the directionality of impact. The lessons learned regarding CTs and RCFs will be highly applicable outside of this study, as similar machine learning models are seeing nascent application in clinical trials, online web advertising, and a range of other disciplines where quasi-observational and randomized control trials are of high importance.

Benjamin Ramage, Ph.D. - 2018 Awardee
Department of Biology
Randolph-Macon College

"Effects of Disturbance on Species-Specific Feedbacks, and the Implications for Forest Diversity"

Two critical drivers of forest diversity are disturbance and conspecific inhibition. Disturbances are discrete events that kill or remove biomass such as hurricanes, fires, and timber harvest. Conspecific inhibition, a form of species-species negative feedback, is defined as a reduction in performance when "conspecific" (same species) densities are high, typically owing to the local accumulation of species-specific enemies. While the importance of both of these phenomena has been recognized, they have rarely been considered simultaneously. This is a surprising research gap, as several lines of evidence suggest that disturbance likely alters the strength of conspecific inhibition, and that complex interactions between disturbance and conspecific inhibition may drive diversity. The proposed work seeks to answer the following questions: (1) Does disturbance alter the strength of conspecific inhibition? and (2) How are diversity patterns generated by the interaction of these two phenomena? Our proposal develops a novel quantitative framework for simultaneously investigating conspecific inhibition and disturbance, and then details a research plan involving both field experiments and computer simulations. Fieldwork will occur in central Virginia and focus on planting tree seedlings in areas with and without: a) conspecific canopy trees and b) recent disturbance. Field measurements of seedling performance will be used to create response surfaces, which will enable the seamless integration of our empirical data and our newly developed quantitative framework. Our simulations, parameterized in part with our field data, will allow us to explore a broader range of variables and scenarios, and to consider spatial and temporal scales that cannot be investigated empirically. Simulations are particularly important for studying diversity dynamics given that shifts in diversity often manifest at timescales ranging from decades to millennia. Our work will provide crucial insights about how to best manage biodiversity in forest ecosystems imperiled by threats ranging from climate change to habitat fragmentation.

Phiala Shanahan, Ph.D. - 2018 Awardee
Massachusetts Institute of Technology
Massachusetts Institute of Technology

"Quark and Gluon Structure of Nucleons and Nuclei"

The proposed research program will reveal new aspects of the structure of the atomic nuclei which constitute more than 99% of the visible mass in our universe. It is known that this complex structure emerges from the interactions of the quarks and gluons described by Quantum Chromodynamics (QCD), the Standard Model theory of the strong force. Nevertheless, making quantitative predictions for nuclear physics processes from this fundamental theory remains a defining challenge bridging particle and nuclear physics research, high-performance computing and data science. Such predictions are not only the key to interpreting observations of nature in terms of the currently-accepted fundamental theory, but are essential to inform experimental searches for new physics, from explorations of the high-energy frontier at the Large Hadron Collider, to direct and indirect dark matter searches. One aspect of nuclear structure which is poorly understood at the present time is the role of gluons, the particles which carry the strong force, in the structure of protons and neutrons and the emergence of complex nuclear structure in Nature. The specific aims of this project are to provide quantitative theory predictions for aspects of the gluonic structure of protons, neutrons and light nuclei from the Standard Model for the first time. In particular, first QCD calculations of the gluon radius of the proton and of exotic glue in nuclei will be performed. This will be achieved using method known as lattice QCD, involving large-scale numerical simulations of QCD on a discrete four-dimensional space-time, using the world's largest supercomputers. The results will provide essential information for current and future nuclear physics experimental programs, in particular at Thomas Jefferson National Accelerator Facility and for the planned electron-ion collider, designed to measure the gluon structure of nucleons and nuclei with unprecedented precision over the next decade.

Robert Brinkerhoff, Ph.D. - 2017 Awardee
Department of Biology
University of Richmond

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

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. - 2017 Awardee
Department of Engineering
Sweet Briar College

"Water Treatment In Context: Appropriate Technology and Water Quality"

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. - 2017 Awardee
Department of Chemistry
University of Virginia

"Modeling The Effect Of An Oscillatory Cellular Environment On Protein Folding"

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. - 2017 Awardee
Department of Physics
Virginia Polytechnic Institute and State University

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

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.

Gaurav Giri, Ph.D. - 2017 Awardee
Department of Chemical Engineering
University of Virginia

"Creating High Performance Flexible, Transparent Electronics Using Solution Shearing and 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. - 2017 Awardee
Department of Plant Pathology, Physiology, and Weed Sciences
Virginia Polytechnic Institute and State University

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

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. - 2017 Awardee
Department of Chemistry
University of Richmond

"Experimental And Computational Investigations Of MEMO1 And Its Role In Breast Cancer"

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.

Patrick Sachs, Ph.D. - 2017 Awardee
Department of Medical Diagnostics & Translational Sciences
Old Dominion University Research Foundation

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

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.

Robert Waters, Ph.D. - 2017 Awardee
Department 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"

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. - 2017 Awardee
Department of Electrical and Computer Engineering
University of Virginia

"Perceptually Aware Model Training for Image Reconstruction"

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.

Sen Zhang, Ph.D. - 2017 Awardee
Department of Chemistry
University of Virginia

"Advanced Electrocatalysts Through Core-Shell Nanostructures"

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.

Laura Barnes, Ph.D. - 2016 Awardee
Department of Systems and Information Engineering
University of Virginia

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

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. - 2016 Awardee
Department of Chemistry
University of Virginia

"Harnessing the Power of Bacterial Populations"

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. - 2016 Awardee
Department of Biology
University of Richmond

"Using Genome-Wide Association Models to Determine the Genetic Architecture of an Invasive Forest Insect"

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. - 2016 Awardee
Brown Student Center
Hampden-Sydney College

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

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. - 2016 Awardee
Department of Physics
University of Richmond

"Properties of Aligned Electrospun Nanofibers"

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. - 2016 Awardee
Department of Biology
Virginia Wesleyan University

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

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. - 2016 Awardee
With support from the Hazel Thorpe Carman and George Gay Carman Trust
Department of Chemical Engineering
University of Virginia

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

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.

Sara Maxwell, Ph.D. - 2016 Awardee
School of Interdisciplinary Arts and Sciences
University of Washington

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

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.

Shengfeng Cheng, Ph.D. - 2015 Awardee
Department of Physics
Virginia Polytechnic Institute and State University

"A Computational Model to Study the Self-assembly of Microtubules"

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.

Takeshi Fukao, Ph.D. - 2015 Awardee
Department of Crop and Soil Environmental Sciences
Virginia Polytechnic Institute and State University

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

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. - 2015 Awardee
Department of Biology
University of Richmond

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

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. - 2015 Awardee
Department of Mechanical and Aerospace Engineering
Old Dominion University Research Foundation

"Developing Quantitative Measures of Mechanical Coherence in Epithelial Tissue"

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. - 2015 Awardee
Department of Psychology
University of Virginia

"Biophysical, Dynamical-Systems Models of Neurons that Recognize Complex Acoustic Patterns"

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.

Helen Murphy, Ph.D. - 2015 Awardee
Department of Biology
College of William and Mary

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

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.

Kendra Sewall, Ph.D. - 2015 Awardee
Department 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"

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. - 2015 Awardee
Department of Biology
University of Virginia

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

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. - 2015 Awardee
Department of Chemistry and Biochemistry
James Madison University

"Computational and Biochemical Determination of the Mechanism of Thioester Aminolysis"

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.

Linda Columbus, Ph.D. - 2014 Awardee
Department of Chemistry
University of Virginia

"Using Hybrid Computational and NMR Structure Determination to Study Host-pathogen Interactions at the Molecular Level"

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.

David Gauthier, Ph.D. - 2014 Awardee
Department of Biological Sciences
Old Dominion University Research Foundation

"Advanced Phylogenomics of the Human and Animal Pathogen 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. - 2014 Awardee
Department of Biology
Eastern Mennonite University

"High-Salt Diet-Induced Regulation of NFAT5 in Hypertension"

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. - 2014 Awardee
Department of Biology
James Madison University

"Developing an Innovative Mathematical Simulation Model to Inform Recovery Strategies for the Endangered James Spinymussel (Pleurobema collina)"

The James Spinymussel (Pleurobema collina) is the top priority species for recovery of all Endangered Species in Virginia. Spinymussels 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 Spinymussel 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.

Michael Shirts, Ph.D. - 2014 Awardee
Department of Chemical Engineering
University of Virginia

"Understanding and Predicting Pharmaceutical Binding to Blood Plasma Proteins"

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. - 2014 Awardee
Department of Mechanical Engineering

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

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 cryogens 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 than 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.

Michel Audette, Ph.D. - 2013 Awardee
Department of Modeling, Simulation and Visualization Engineering
Old Dominion University Research Foundation

"Development of Patient-Specific Spine Modeling and Surgery Simulation"

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.

Grace Lim-Fong, Ph.D. - 2013 Awardee
Department of Biology
Randolph-Macon College

"Genomic and Transcriptomic Analyses of an Unculturable Marine Bacterial Symbiont"

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. - 2013 Awardee
Department 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"

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 nucleic (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. - 2013 Awardee
Department of Physics
College of William and Mary

"Computational Tools for Controlling Thin Films Properties for Optoelectronics and Nanotechnology Applications"

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 inohomogeneities 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 inhomogenous 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 requires 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. - 2013 Awardee
Department of Biological Systems Engineering
Virginia Polytechnic Institute and State University

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

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.

Eugene Wu, Ph.D. - 2013 Awardee
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"Studies of DNA Polymerase Mechanism and Thermostability using Molecular Dynamics Simulations and 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.