PRISM 2019 Project Descriptions

Faculty Mentor – Dr. Dale Beach

Exposing the Hidden Genetic Character of Non-Model Organisms

The expanse of living organisms populating the earth is undeniably linked by the DNA content within the cell. All organisms utilize the same 4 letter alphabet of DNA to encode the molecule blueprints of life, providing the complex information to produce the essential proteins of the cell in a tightly regulated environment. Molecular Biology techniques and DNA sequencing methods allow us to decode DNA and use this information to better understand the physiology and function of the cell as well as establish unique "serial codes" to taxonomically categorize organisms. For non-model organisms, those creatures that are not commonly used in laboratory studies, targeted DNA sequencing is used to determine genetic variation and unique cellular properties. For example, genetic sequences from the pathogenic bacteria, Salmonella, collected from a chicken house or a natural stream can indicate resistance to antibiotics or the traits linked to lethal infections in humans. Our group uses molecular techniques to purify and sequence DNA from naturally isolated organisms for identification and determination of genetic characteristics. Primarily, members of the fungal genus Pilobolus and the bacterial genus Salmonella are collected for study via whole genome analysis and single gene sequencing methods. Computational analysis of the sequence information facilitates comparisons within a known species and to other species in the genus. In general, research projects determine DNA sequence information to establish the genetic variation and characteristics within the genomes of newly-identified, non-model organisms.

Faculty Mentor – Dr. Julian Dymacek

Constrained Non-negative Matrix Factorization

Our previous work (PRISM 2017) developed a novel constrained, non-negative matrix factorization algorithm and Monte Carlo Markov chain simulation to identify underlying patterns in mRNA and miRNA gene expression data. To keep up with the growing size of available data sets, we created a hybrid system (PRISM 2018), allowing for a reduction in computation time and an increase in accuracy. Building on this previous work, we propose to modify our system in three additional ways:

1. build tools for visualization of patterns and results,
2. optimize tools for visualization of patterns and results,
3. handle additional constraint types and error metrics.

We originally built this system to analyze a very specific kind of biological data, but these modifications focus on adapting our work to be user-friendly for external audiences and diverse projects. Our previous work has focused solely on the efficiency of the program to analyze mRNA data. Now that we have developed a very fast system, we can work backwards to fine tune other aspects to make it more complete for analyzing patterns in general time-series data (climate/weather, images and facial recognition, etc.). These proposed

modifications have been suggested by interested collaborators both internal and external to LU. Our work from PRISM 2017 was recently presented at one of the top international conferences on bioinformatics and published in the peer reviewed conference proceedings as the only paper with an undergraduate co-author.

Faculty Mentor – Dr. Kathy Gee

Evaluating Control and Mitigation Techniques for Mosquitoes in Rainwater Harvesting Systems

Mosquitoes are associated with the spread of diseases such as the Zika and West Nile viruses. Government and health officials recommend the elimination of standing water to prevent the breeding of mosquitoes that carry these viruses. Previous research has shown that rainwater harvesting (RWH) systems in humid regions tend to be underutilized, thereby creating a source of standing water that could potentially harbor mosquitoes and their larvae. During PRISM 2017, the prevalence and relative abundance of mosquitoes were investigated in 64 RWH cisterns throughout Virginia and North Carolina. Of the 64 systems sampled, 47% contained mosquitoes; the predominant species found was Aedes albopictus, a potential carrier of Eastern Equine Encephalitis, LaCrosse Encephalitis, West Nile virus and Zika virus. These results made it apparent that owners of RWH systems need to be made aware of the potential problem of mosquitoes and recommendations need to be made regarding mitigation methods when mosquitoes are found in RWH systems; however, which mitigation methods are most effective? This study aims to answer that question by implementing and evaluating several design and/or maintenance modifications to RWH systems containing mosquitoes. The efficacy of each modification will be evaluated and the results used to produce design and maintenance recommendations for RWH system owners.

Faculty Mentor – Dr. Maxwell Hennings

An Analysis of Neurogenesis in a Mouse Model of Chemotherapy Related Cognitive Impairment

Adjuvant chemotherapy has been associated with cognitive decline in breast cancer survivors. The deficits can last for years and can have a deleterious impact on survivor quality of life. The etiology of chemotherapy-related cognitive impairment remains relatively unknown and interactions between genetics, epigenetics, and the environment/life history of individuals complicate studies of the effects of chemotherapy on cognition in humans. Animal models of chemotherapy-induced cognitive impairment and neurotoxicity may facilitate progress in elucidating the etiology of “chemobrain” and will facilitate the development of preventative treatments. Recent studies show that a number of chemotherapy agents used in the treatment of breast cancer can cause cognitive/memory impairments in rodents. In addition, chemotherapy agents can have short-lasting neurotoxic effects. While there is limited evidence that chemotherapy agents such as fluorouracil can cause a short-term decrease in neurogenesis (formation of new neurons) and cause short-term myelin damage, the research literature has not systematically explored these effects. During the summer PRISM session, the selected student will work with me to process brain tissue from animals previously perfused during the summer of 2018. The selected student will receive training in cryosectioning and immunohistochemistry techniques. By the end of summer, the student will analyze levels of neurogenesis across the processed tissue and previously collected datasets. The goal is for the PRISM student to develop skills in quantitative reasoning, scientific research, scientific writing, and training in neuroscience methodology by the conclusion of the project.

Faculty Mentor – Dr. Brandon Jackson

Shake a tail feather: finding the function of bird tails in slow flight

The evolution of major animal groups is often punctuated by changes in locomotor styles and related novel morphologies. In vertebrates, this pattern is best illustrated by birds with wings, which are well studied. Bird tails are similarly unique and potentially just as important. A small body of literature has shown that passively controlled tails function similarly to those of airplanes when birds fly at cruising speeds. However, birds appear to actively spread and contract their tails during landing, taking off, and in slow-flight competitions. Only one published study has evidence for a possible function of the tail of a single species. While studies of tail function are extremely limited, even simple descriptions of tail pulsing in slow flight are limited to a few species and behaviors. This project aims to determine the usage and function of this unique, important, yet poorly understood morphological trait. American Goldfinches (*Spinus tristis*) and Black-capped Chickadees (*Poecile atricapillus*) are active at feeders and partake in aggressive flights with other birds. Observations of both species show that they actively pulse and fan their tails during these flights. However, what determines the presence, the magnitude, the timing of, or variation between species regarding such pulses is unknown. Using multiple high-speed video cameras, we will measure three-dimensional tail, body, and wing movement during a variety of flight behaviors in both species to determine when tails are most active. The movement will be further analyzed with mathematical models to elucidate the aerodynamic function.

Faculty Mentor – Dr. Sarah Porter

Spectroscopic and Chemometric Analysis of Petroleum Products for Forensic, Environmental, and Industrial Applications

The analysis of petroleum products and ignitable liquids is a critical area of research in forensic and environmental chemistry and in the petroleum industry. In forensic chemistry, ignitable liquids are used to deliberately start fires in cases of arson, and most of these ignitable liquids are petroleum-based products, including gasoline, kerosene, and lighter fluids. Oil spills, tailpipe emissions, and contamination from fueling stations are a few of the environmental concerns that arise from the widespread use of petroleum products. Finally, quality control in the production of petroleum products from crude oil requires reliable, standardized analysis techniques. All of these areas can benefit from robust, rapid, inexpensive analytical methods for the identification or classification of an unknown sample or the characterization of specific properties of a sample (for example, octane rating for a fuel). The goal of the proposed project is to use spectroscopic methods, including Fourier transform infrared spectroscopy (FTIR) and X-ray fluorescence spectroscopy (XRF), combined with chemometric data analysis as alternatives to the more widely used gas chromatographic analyses that dominate the field of petroleum analysis. Chemometrics, broadly defined, is the application of mathematical and statistical modeling to chemical data. We will combine simple, readily available algorithms with few computational steps for rapid and robust analysis of spectroscopic data. The developed methods will be validated using gas chromatography-mass spectrometry (GC-MS) and other established, standard test methods. The validated methods will be shown to be widely applicable for multiple applications (environmental, forensic, and industrial).

Faculty Mentor – Dr. Troy Purdom

A Randomized Double-Blind, Placebo-Controlled Crossover Study of Low-Dose Creatine on Cognitive Function Before and After Athletic Competition

High intensity exercise has been shown to stress the body and the brain due to the high intensity nature of the exercise. High intensity exercise places significant demand on the oxygen transport capacity of the cardiovascular system and bioenergetic processes that supply the brain with available energy. The reduced cognitive function due to the hypoxemic state has been shown to negatively affect cognitive function. Reduced cognition due to the hypoxemic state could put athletes at risk temporarily due to impaired cognition. Creatine supplementation has been shown to have performance and cognitive benefits in a variety of populations, including the mentally impaired, youth, and the elderly. Low dose creatine supplementation is a stark contrast to the creatine loading studies conducted previously. Creatine dosages of 30g/day have been shown to be safe and well-tolerated in healthy populations throughout the lifespan without any long-term deleterious effects. Furthermore, short term (5 days) and long-term studies (5 years) have shown to be both safe and effective. The available research shows that a dose range of (0.3g/kg/dy - 0.8 g/kg/dy) or 56g/dy for a 70kg person is safe and effective for a period of five years. Therefore, the purpose of this study is to investigate if low-dose creatine has an effect on cognitive function in college age athletes pre and post high intensity exercise.

Faculty Mentor – Dr. Erin Shanle

Investigating the effects of bromodomain cancer mutations on the activity of p300

In eukaryotic cells, DNA is wrapped around histone proteins that regulate gene expression in part through chemical modifications, such as acetylation. Histone acetylation can serve as binding sites for 'reader' proteins that contain highly conserved regions known as domains. 'Reader' proteins recruited to the histone-DNA complex can act as co-activators for gene expression and promote transcription of neighboring genes. The protein p300 helps activate gene expression by binding acetylation through its bromodomain (BD) and further increasing acetylation using the neighboring catalytic core domain. Importantly, p300 is often mutated in cancer cells but the functional significance of BD mutations has not been fully explored. My previous research demonstrated that mutations in p300-BD impaired the interaction with histone acetylation, suggesting that these mutations may affect the neighboring catalytic core and function of p300 in cancer cells. The goal of this project is to develop a system to test the effects of BD mutations on the catalytic activity of p300 using CRISPR-Cas9 targeting to a specific location in the genome of human cancer cells. First, mutations in p300 BD mutations will be made using site-directed mutagenesis of pcDNA3.3-Nm-dCas9-p300-Core, a DNA sequence that induces expression of enzymatically inactive Cas9 (dCas9) fused to the catalytic core domain of p300. Next, genomic regions will be identified to develop guide RNA sequences that can target dCas9 fused to wild-type or p300 catalytic core to that specific genomic region. Finally, RNA levels of the neighboring genes will be compared in cells expressing normal or mutant dCas9-p300-core proteins.

Investigating the effects of cancer mutations on DNA damage response proteins in yeast

In cancer cells, an array of genetic changes occur that allow cells to bypass normal growth and support uncontrolled proliferation. Our understanding of the genetic changes involved in the development of cancer has rapidly expanded because of the advent of technologies in DNA sequencing and bioinformatics. The Catalogue of Somatic Mutations in Cancer (COSMIC) database contains detailed information about genetic

changes that have been observed in over 500,000 different tumors. Although thousands of mutations are observed in different tumors, it is challenging to determine the impacts of cancer mutations protein function. The goal of this project is to use the budding yeast *Saccharomyces cerevisiae* as a model to screen cancer mutations for deleterious effects using the DNA damage response gene *CHK2* as a candidate. The DNA damage response is highly conserved, from yeast to humans, and human CHK2 protein will complement the yeast homolog so it may be possible to use yeast for screening cancer mutations that disrupt the normal functions of CHK2. To achieve this goal, mutant and wildtype human CHK2 protein will be expressed in yeast cells lacking the yeast homolog of CHK2 (*rad53-null*), which are sensitive to DNA damage because they cannot regulate the normal response to DNA damage. Mutations that do not rescue the sensitivity observed in *rad53-null* cells are likely important for the function of CHK2. By using yeast as a model organism, this study will quickly characterize cancer mutations for further study in human cancer cells.

Faculty Mentor – Dr. Benjamin Topham

Chemical design of single molecule electronic device

Since their inception, electronic devices have continually been made smaller and more powerful, while new functions and applications have been pursued. A key contributor to this progress has been the development of new materials. One recent example is the use of organic electronics in consumer products, such as organic light emitting diodes (OLEDs) in TV and phone displays. The field of molecular electronics proposes to transform the electronics industry by reducing the size of active components to a single molecule. This idea has gathered momentum as the ability to fabricate devices has improved, but there is still a need to better understand device performance before this technology can be used more broadly. Computational chemistry can play an important role in the development of single molecule electronic devices by enabling large numbers of molecules to be screened without needing expensive and sensitive equipment to make the corresponding measurements on actual devices. The central issue of molecular electronics is the control of electrical current through a molecule. It has been assumed that chemical modification is a straightforward way to enact this control, but recent studies have shown that this may not be as straightforward as originally conceived. We will use computational chemistry to investigate how electron transmission through a molecular device can be controlled through chemical modification for optimal device performance.

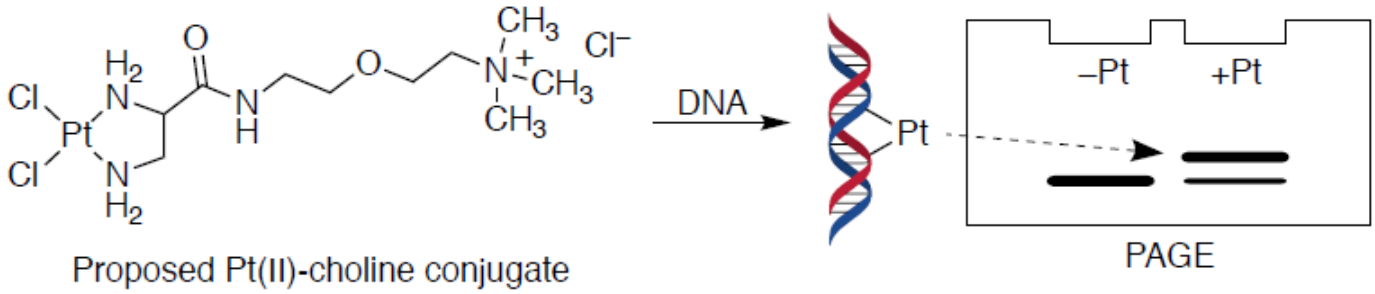
Faculty Mentor – Dr. Jonathan White

Synthesis of a cancer-targeting, choline-appended Pt anticancer therapeutic and characterization of its DNA target binding and cellular toxicity

Cancerous cells are characterized by numerous metabolic re-programming events, and many of these phenotypes have increasingly been utilized as avenues for targeted drug therapies. Among a broad class of cancers, numerous oncogenes are overexpressed that are crucial for the anabolism of choline. Despite an overwhelming majority of cancers expressing enhanced choline metabolism, relatively little effort has explored potential avenues for “hijacking” choline metabolism for targeted cancer therapies. Such strategies might utilize, for example, small molecule drugs covalently tethered to a quaternary ammonium cation, mimicking the structure function relationship of choline and enhancing cellular uptake in tumor cells.

Currently, the mainstay of small-molecule anticancer therapeutics remains the platinum-based drugs. Many cationic Pt complexes have been generated from modifying existing drugs in order to improve solubility and enhance delivery and target binding; however, none of these compounds have demonstrated superior efficacy

in vivo. I propose to synthesize and investigate a novel, hybrid cationic Pt compound—a choline-conjugated Pt(II) compound—incorporating the potential cancer cell targeting of choline metabolites and enhanced solubility and target binding of a cationic Pt complex. We will use established synthetic protocols to synthesize a small Pt(II)choline conjugate, then quantify its binding to model DNA. Improved DNA binding by Pt-choline is anticipated due to more favorable electrostatic interactions. We will then quantify cellular toxicity using S. cerevisiae as a model organism and compare the activity to unmodified Pt drugs.



Proposed Pt(II)-choline conjugate

Faculty Mentor – Dr. Thomas Wears

The Geometry of Curves in Surfaces in 3-dimensional Lie Groups

The aim of this project is to study the geometry of curves and surfaces in 3-dimensional Lie groups equipped with a geometric structure determined by a left invariant metric. After an initial review of the geometry of curves and surfaces in Euclidean 3-space, we will then introduce the necessary algebraic and geometric structures on 3-dimensional Lie groups of interest, such as the 3-sphere and other 3-dimensional Lie groups which are topologically equivalent to Euclidean 3-space. Of particular interest in our study will be surfaces which can be built from curves in the Lie group through use of the corresponding group operation. Working in 3-dimensional spaces throughout the study will allow for the use of computer graphics and animation to develop and sharpen intuition. This project will be accessible to any student who has completed MATH 280 and MATH 361.