Discovery Challenge
Promoting cross-disciplinary collaboration

Fifth Annual Campus-Wide Research Competition

Wednesday, April 6, 2016 | Noon – 5 p.m.
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ABSTRACT BOOKLET

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#1

**Side Effects: The Unintended Consequences of Health Reform on Public Hospitals**

**Simon F. Haeder**  
Graduate Student  
*Political Science*

Long before the establishment of Medicaid or the passage of the Affordable Care Act, California counties provided their poorest residents with access to relatively comprehensive medical care. This paper analyzes the creation and closure of public hospitals in the State of California from the 1840s until today. It combines both qualitative historical research and event history analysis to assess what led first to the creation of the nation’s most comprehensive public health network and then to its gradual demise. A particular focus is on the role of Medicaid, which unintentionally accelerated this demise, and the lessons that can be drawn for the implementation of the Affordable Care Act. I find strong evidence that the creation and implementation of Medicaid in California significantly altered the calculus of local governments with regard to the operation of public hospitals. In particular, Medicaid shifted county hospitals from the realm of allocational, perhaps even developmental, to that of redistributive politics. Subsequently, reforms at the state and federal level further encouraged this development. Because of this shift, many counties decided to close their hospitals. Moreover, as expected for redistributive policies, the operation of public hospitals is not driven by need but instead merely the result of fiscal ability: counties that can afford public hospitals continue to maintain them while poorer counties with objective need close their doors. Developments under the ACA may further exacerbate this situation, as may the creation of two new medical schools.

#2

**Mouse TM EM 135 Mutation Reveals an Age-Related Macular Degeneration (AMD) Mechanism Involving Mitochondrial Dynamics**

**Wei-Hua Lee**  
Postdoctoral Researcher  
*Medical Genetics*
Age-related macular degeneration (AMD) affects ~15 million Americans and causes a progressive loss of vision. Particularly for “dry” AMD, the most common type of macular degeneration affecting 90% of the people who have the condition has no proven medical treatment available. Whereas aging itself is the most major risk factor for developing AMD, the molecular mechanisms underlying the aging process and how they relate to the disease-causing mechanisms are yet to be clearly understood. In this study, we searched for a model system in which the close relationship between mitochondrial dynamics, oxidative stress, aging and age-related diseases could be clearly analyzed. We screened for, and identified an ENU-induced mutant mouse strain showing accelerated retinal aging phenotypes. We aimed to positionally clone the gene responsible for these early aging phenotypes, and identify the molecular function of the gene product. Methods: Phenotypic characterization of FUN025 mice was performed by histological analyses. Genetic mapping and high-throughput sequencing techniques were used to identify the genetic mutation in FUN025 mice. Localization of TMEM135 was determined by immunofluorescence, immunoelectron microscopy, and western blot in mouse, monkey and human cells as well as in the mouse retina. The role of TMEM135 in mitochondrial dynamics was studied in mouse fibroblasts (MFs) from wild-type, FUN025 and Tmem135 transgenic mice that overexpress wild-type Tmem135. Mitochondrial functions in MFs were measured using Seahorse XFe24 Extracellular Flux Analyzer and flow cytometer. Results: We observed lipofuscin accumulation, enhanced inflammation, and photoreceptor degeneration in the FUN025 retina, which are common signs in AMD. By positional cloning, we identified a mutation in the gene encoding transmembrane protein 135 (Tmem135), previously known as a longevity gene in C. elegans. Our studies using the cell culture system revealed that TMEM135 proteins form punctate structures on mitochondria within the cell. Analysis of the mitochondria from FUN025 MFs and MFs that overexpress wild-type Tmem135 indicated that TMEM135 is involved in mitochondrial fission mechanism. Mitochondrial functions were impaired in primary cells derived from FUN025 mutant mice as well as from Tg-Tmem135 mice. The level of oxidative stress and the sensitivity to oxidative stress were increased in cultured FUN025 mutant cells and mutant retina. Conclusion: In summary, we show that Tmem135 is a mouse gene of previously unknown function involved in the regulation of the balance between fission and fusion of mitochondria. Our results suggest that the regulation of mitochondrial dynamics via TMEM135 is critical for protecting cells from environmental stress and controlling the progression of the aging process. Unbalanced mitochondrial dynamics may lead to impaired mitochondrial function, and thus increase the risk of developing age-related retinal diseases. TMEM135 reveals a molecular link between the aging process and age-related diseases, and a possible molecular mechanism leading to ‘dry’ AMD.
A Survey: Demographics and the Rebound Effect in Vehicle Fuel Efficiency

James Mahoney
Graduate Student
Civil & Environmental Engineering

One of the pressing problems facing humanity in the 21st century is a changing climate. Modern society relies comprehensively on the combustion of fossil fuels, with the transportation sector emitting approximately a quarter of all emissions. Efforts to reduce emissions from transportation fall into two camps: market-based approaches of increasing fuel prices by way of a fuel tax or other means and by improving fuel efficiency standards through legislation. The economic principle behind a fuel tax is to increase price and create a consequent decrease in demand, resulting in fewer miles driven and lower levels of emissions. Alternately, producing vehicles with improved fuel efficiency allows consumers to travel a given distance using less fuel, also decreasing emissions. An important consideration while quantifying the fuel savings from more efficient vehicles is to determine the rebound effect. The rebound effect occurs when an increase in the efficiency of a good leads to increased consumption of either that good (direct rebound) or of other goods (indirect rebound). This study will estimate the rebound effect as it applies to improved fuel efficiency in vehicles to show what percentage of the theoretical fuel savings from increased efficiency is realized. This determination will offer insight into whether regulations pertaining to efficiency will in practice lead to overall fuel savings. To gain an understanding into the rebound effect as it applies to vehicle fuel efficiency, consumer surveys were administered to gather data on driving habits, motivations for purchasing new vehicles, and demographics. This study utilized the data to estimate a quantification of the transportation rebound effect for various groups of participants. Groups were established based on demographic data, such as comparing rural households to urban households, various income levels, and single-vehicle households verses those with multiple vehicles. The variations in the magnitudes of the rebound effect among the groups were analyzed to investigate factors that influence driving behavior and to what extent they influence fuel price elasticity. It is anticipated that comparing the rebound for households on different ends of particular demographic categories will reveal significant differences in the magnitudes of their respective rebound effects. Of particular interest was comparing rural households and urban households and investigating the differences in the respective rebound effects. An important factor in this comparison is the availability of alternate modes of transportation, or lack thereof; when fuel prices increase, urban households can readily adopt alternate transportation or revert from it when fuel prices fall, whereas rural households may not have that opportunity. These findings can be used to identify how different groups of drivers respond to improvements in fuel efficiency. Better understanding this behavior will provide discernment into the efficacy of using fuel efficiency mandates to reduce transportation emissions.
Competition, Price Dispersion and Capacity Constraints: The Case of the U.S. Corn Seed Industry

Cornelia Ilin
Graduate Student
*Agicultural and Applied Economics*

The economic theory and empirical analysis proposed in this study add insight into the effect of competition on price dispersion, and contribute to the understanding of the relationship between product availability and pricing. In the proposed theoretical model we argue that the effect of competition on price dispersion is contingent on the ability of firms to satisfy market demand. Our comparative static results show that competition among firms with symmetric capacity-constrained levels leads to a price decrease in the lower tail of the distribution and a price increase in the upper tail. In contrast, competition among firms with symmetric capacity-unconstrained levels, or among firms with asymmetric capacity levels leads to a price increase at each quantile of the distribution function. The results also show a positive relationship between product availability and pricing. To investigate these findings, we use a novel data set from the U.S. corn seed industry in which firms competing in the market are either capacity-constrained or capacity-unconstrained. The data provides firm-level sales information for conventional and genetically modified corn seeds sold between 2004 and 2009. We estimate the empirical model using a new methodology, the IV Quantile Regression, and show that competition among seed firms with symmetric capacity-unconstrained levels, or asymmetric capacity levels competing in a region where corn is the predominant crop, leads to a price increase at each quantile of the distribution function. The analysis also show that capacity-unconstrained seed firms charge a price premium, confirming the positive relationship between product availability and pricing.

Development of a Pd-Bi-Te/C Catalyst (PBT) for Aerobic Oxidation of Alcohols to Carboxylic Acids

Maaz Ahmed
Graduate Student
*Chemistry*
David S. Mannel (chemical and biological engineering); Thatcher W. Root (chemical and biological engineering)

The need for economical, selective oxidative transformations remains an ongoing challenge in organic chemical synthesis. Carboxylic acid are an important target functional group due to their prevalence various pharmaceuticals, agrochemicals, and larger-scale chemicals. We have recently developed a heterogeneous Pd catalyst promoted by Bi and Te for the aerobic oxidative methyl esterification of diverse alcohols, including both activated and unactivated examples. This catalyst also is effective for conversion of primary alcohols to the carboxylic
acids. The inclusion of both Bi and Te enhances the activity and selectivity of the catalyst. The demonstrated substrate scope and functional group tolerance are the widest reported for oxidation to carboxylic acids with a heterogeneous catalyst. The catalyst has been implemented in a packed bed reactor with 99% yield of benzoic acid maintained throughout a two-day run. Biomass derived 5-(hydroxymethyl)furfural (HMF) is also oxidized to the di-acid with a yield of 95%.

Inhibition of JAK/STAT and BCL-2 Synergistically Enhances Anti-Tumor Effects in a Model of T-Cell Acute Lymphoblastic Leukemia (T-ALL)

Kirsti L. Walker
Graduate Student
Pediatrics; Cellular and Molecular Pathology (CMP) program
Sydney N. Olson (pediatrics); Myriam N. Bouchlaka (pediatrics)

T-cell Acute Lymphoblastic Leukemia (T-ALL) is an aggressive hematologic malignancy comprising 15% of pediatric and 25% of adult cases of ALL. With current treatment options, T-ALL survival rates have reached 50-60% in adults and 85% in children. Despite great strides in the treatment of this malignancy, T-ALL still shows resistance to first-line therapies in over 50% of adults and 25% of children, and relapse is often chemorefractory. Mutations in the J anus Activating Kinase / Signal Transducer and Activator of Transcription (JAK/STAT) pathway are highly linked to the progression of T-ALL, and to treatment resistance. Our lab demonstrated that the JAK1/STAT1 pathway is critical in preserving graft-versus-leukemia effects after bone marrow transplant. An anti-apoptotic protein, Bcl-2, was recently discovered to be directly linked downstream of the JAK/STAT pathway, and it is often upregulated in hematologic malignancies. Our hypothesis is that inhibiting both the JAK/STAT and Bcl-2 pathways with inhibitors; Ruxolitinib and Venetoclax will inhibit T-ALL growth and survival. Proliferation and viability of T-ALL was assessed by MTT assay, trypan blue and flow cytometry at 24, 48 and 72-hour time points post-treatment. Single-drug dose responses were conducted for both inhibitors. Six doses of both Ruxolitinib and Venetoclax were tested from a range of 0.156uM – 5uM for Ruxolitinib and 1.56nM– 50nM of Venetoclax. A response was seen for the three highest doses of both inhibitors (1.25uM, 2.5uM, and 5uM for Ruxolitinib and 12.5nM, 25nM, 50nM for Venetoclax). Synergism was achieved for all three assays at both 48 and 72 hours post-treatment with the combination dose of 1.25uM Ruxolitinib and 25nM Venetoclax (CI<1). This optimal in vitro combined dose significantly lowered proliferation and viability of jurkat cells compared to no treatment, vehicle control and the single-drug dose control groups (all at a P<0.0001). Targeting both the JAK/STAT and Bcl-2 pathway with orally available inhibitors could provide a novel alternative treatment for patients who are resistant to first-line chemotherapeutic regiments.
Kinetics and Mechanism of Formation and Stabilization of the RNA Polymerase-Promoter Open Complex

Munish Chhabra
Graduate Student
Biophysics
Raashi Sreenivasan (biochemistry, chemistry and biophysics programs); Emily Ruff (biochemistry, chemistry and biophysics programs); Mikaela Poulos (biochemistry, chemistry and biophysics programs); Cece Wang (biochemistry, chemistry and biophysics programs); Irina Artsimovitch (microbiology, The Ohio State University); Tom Record (biochemistry, chemistry and biophysics programs)

Specific binding of E. coli RNA polymerase holoenzyme (RNAP; α2ββ’σ70) to promoter DNA sets in motion a series of conformational changes that advance the initial closed complex (RPC), open 12-14 bp including the -10 region and the transcription start site, and at some promoters then stabilize the initial open complex dramatically. Our research focuses on the kinetics and mechanism of these conformational changes at different promoters, using Förster resonance energy transfer (FRET) and protein induced fluorescence enhancement (PIFE) together with fast footprinting and filter binding assays to determine the kinetics of open complex formation and dissociation, and to obtain structural and thermodynamic information about key intermediates. FRET and PIFE results to date demonstrate the importance of wrapping of upstream promoter DNA on RNAP for efficient bending of the downstream duplex into the active site cleft to form the advanced closed complex which is opened by RNAP in the rate limiting step. The initial open complex is found to be unstable, and is subsequently stabilized at some but not all promoters by conformational changes and interactions of in-cleft and downstream mobile elements of RNAP, directed by the discriminator sequence of the promoter. Dissociation kinetic studies with PIFE, FRET and filter binding assays are being used to probe the mechanism of these conformational changes in open complex stabilization.

Genetic Screen of Artificial Transcription Factors to Reprogram Cells

Asuka Eguchi
Graduate Student
Biochemistry; Cellular and Molecular Biology
Matthew J. Wleklinski (biochemistry); Mackenzie C. Spurgat (biochemistry); Evan A. Heiderscheit (biochemistry); Catherine K. Vu (biochemistry); James A. Thomson (cell and regenerative biology); James R. Dutton (Stem Cell Institute, University of Minnesota); Aseem Z. Ansari (biochemistry)

The purpose of this study is to identify gene regulatory networks that regulate cell fate conversions using artificial transcription factors (ATFs). Master regulators can profoundly alter the transcriptional dynamics of a cell to the extent that the cell adopts a new cell fate. For
example, transcription factors, Oct4, Sox2, Klf4, and c-Myc, can reprogram a differentiated cell type to convert to an induced pluripotent stem (iPS) cell state. With the right cocktail of transcription factors or small molecules that alter transcription, one can also differentiate pluripotent cells or progenitors into a particular cell type with a specified function. However, the process of discovering master regulators or combinations of factors that control cell fate choices is challenging because testing natural transcription factors by trial and error is often labor-intensive and cost-prohibitive. Moreover, transcription factors function in a specific cellular milieu and trigger appropriate gene expression in response to specific cues that might not be reproduced in cellular systems where they are being tested. To overcome these challenges, we developed a library of gene-activating artificial transcription factors with the complexity to target an array of 9-bp sequences in the genome. We used this ATF library to screen for factors that can turn on an Oct4 reporter in mouse embryonic fibroblasts. We identified three combinations of ATFs that can activate the pluripotency network without exogenous expression of Oct4. In conclusion, we demonstrate that ATFs can serve as versatile tools for perturbing transcriptional networks that drive cell fate changes. This forward genetics approach enables cell type conversions in an unbiased manner.

#9

A Dynamic Framework for Metabolic Engineering of the Branched-Chain Amino Acid Biosynthesis Pathway in E. coli

Anna Kropornicka
Graduate Student

Genetics; Biochemistry

Devesh Bhimsaria (electrical & computer engineering); Xiaolin Zhang (cellular and molecular biology); Christopher Pai (biochemistry); Jennifer Reed (chemical & biological engineering); Parameswaran Ramanathan (electrical & computer engineering); Aseem Ansari (biochemistry and chemical & biological engineering)

Metabolic engineering, in combination with synthetic biology, has been used to produce a number of valuable resources, including biofuels and pharmaceutical precursors. The goal of metabolic engineering is to harness an organism’s metabolism to create a product of interest, which is generally at odds with the cell’s primary objective of maximizing biomass production. In the branched-chain amino acid (BCAA) biosynthesis pathway, the overproduction of valine indirectly causes accumulation of a toxic byproduct in Escherichia coli cells. This opposition makes it extremely difficult for metabolic engineers to manipulate such systems. To bypass the cell’s opposition, computational methods are used to predict where regulatory perturbations should be made to maximize the production of a desired molecule and simultaneously optimize cell growth. The modular design principles of natural transcription factors can be harnessed to create artificial transcription factors (ATFs), such as Transcription Activator-Like Effectors (TALEs), that target any specified sequence and perturb metabolic networks with temporal control. Combining in silico modeling with a design amenable to high-throughput production of TALEs provides a dynamic method of regulating metabolic networks. As a proof of principle, we showed that the valine biosynthesis pathway could be optimized with rationally engineered TALEs. Our ATFs have proven to be specific and effective repressors.
BeamSwipe: A Case for mmWave Imaging Via Swiping Device in the Air

Sanjib Sur
Graduate Student
Electrical and Computer Engineering
Parameswaran Ramanathan (electrical and computer engineering); Xinyu Zhang (electrical and computer engineering)

Every day in America, we navigate the threat of gun violence. This threat percolates all corners of the country, from shady street alleys to even inside the school campuses and classrooms. A recent report showed gun violence has killed more Americans in the past 50 years than in every single American war - from George Washington's Colonial Army defeat of the British in 1781 to Operation Enduring Freedom in 2014. While we understand that everyone has the right to conceal and carry gun for whatever reasons, we also strongly believe that allowing a nearby person to be at least aware of the situation, may enable better judgement and safety decisions. With this philosophy in mind, we propose our system BeamSwipe that allows a nearby person to "see-through" the clothing and image small to medium-sized metallic objects like guns/knives that is hidden under it. BeamSwipe operates on similar fundamental principle as in airport security scanners, but unlike using the cumbersome scanning equipment, a user holding/wearing a smart device (e.g. smart-phone or smart-watch) can image the nearby hidden object with as simple as a swiping motion of hand in air. BeamSwipe system leverage the reflected millimeter-wave radio signals from the object and a novel algorithm that enables an ad-hoc imaging capability on hand-held devices. We have prototyped BeamSwipe in our experimental platform that shows high accuracy in imaging a gun hidden under clothing of a person even from a 1.5 meter distance.

Full-Field Stress Analysis of Orthotropic Composite Plates Containing Geometric Discontinuities Using a Single Component of Displacement

Narin Sara Fatima
Graduate Student
Mechanical Engineering

A simple but accurate hybrid method is illustrated to determine the stresses at and near any discontinuity in loaded, orthotropic plate using a combination of conformal mapping, analytic continuation, complex airy stress functions, and least square methods. This hybrid technique provides reliable stress/displacement data around the edge of the cutouts, only using a single component of measured data away from the cutouts. Using only a small amount of recorded displacement data in either the loading direction or transverse to the loading direction, this
method is capable of evaluating a full field stress analysis of the plate, the results of which are independent of the input variables used. The results from this hybrid technique are validated using FEM. Using Digital Image Correlation (DIC) recorded displacements, the hybrid technique gives excellent full field stress analysis of the structure without physically needing to differentiate the measured displacements or requiring accurate data near the boundary of the cutout; both of which are challenging in real life.

#12

Combination of Chemotherapy and Targeted Therapy Promises Potential Therapy for Prostate Cancer

Bao Le
Graduate Student
School of Pharmacy
Yutong Tam (pharmacy); Glen Kwon (pharmacy)

Advanced prostate cancers that are resistant to all current therapies create a need for new therapeutic strategies. One recent innovative approach to cancer therapy is the simultaneous use of multiple FDA-approved drugs to target multiple pathways. The main challenge of this approach is caused by the different solubility requirements of each individual drug, resulting in the need for a drug vehicle that is non-toxic and capable of carrying multiple water-insoluble antitumor drugs. Micelles have recently been shown to be a new candidate drug solubilizer for anti cancer therapy. This study set out to examine the potential use of multi-drug loaded micelle system, referred as DR17, for prostate cancer treatment in preclinical models including cell line and mouse models heterozygous and homozygous for Pten deletion. Specifically antimitotic agent Docetaxel, mTOR inhibitor Rapamycin, and HSP90 inhibitor 17-N-allylamino-17-demethoxygeldanamycin (17-AAG) were incorporated into the micelle system (DR17) and tested for enhanced antitumor efficacy. In vitro growth inhibition of prostate cancer cells was greater when all three drugs were used in combination compared to each individual drug. At the molecular level DR17 targeted simultaneously several molecular signaling axes important in prostate cancer including androgen receptor, mTOR, and PI3K/AKT. In a mouse genetic model of prostate cancer in vivo DR17 treatment decreased prostate weight, which was achieved by both increasing caspase-dependent cell death and decreasing cell proliferation. These results suggest that combining these three FDA-approved cancer drugs in multi-drug loaded micelles may be a promising strategy for prostate cancer therapy.
Topical Application of Chitosan-Based Nanoformulated Green Tea Polyphenol EGCG Ameliorates Imiquimod-Induced Psoriasis-Like Skin Lesion in Mice

Jean Christopher Chamcheu
Postdoctoral Researcher
Dermatology

Imtiaz A. Siddiqui; Vaqar M. Adhami; Shah-Johan Dodwad; Dhruba Bharali; Gary S. Wood; Shaker Mousa; Hasan Mukhtar

Psoriasis is a chronic and currently incurable inflammatory skin disease characterized by hyperproliferation, aberrant differentiation and inflammation, leading to disrupted skin barrier function. The use of natural agents that possess the ability to abrogate these effects could be useful for the treatment of psoriasis. Earlier studies have shown that treatment of keratinocytes and mouse skin with the green tea polyphenol, epigallocatechin-3-gallate (EGCG), increased the expression of caspase-14 that is involved in epidermal differentiation and cornification. However, dose and bioavailability restrict the therapeutic development and application of EGCG in the treatment of psoriasis. To overcome these limitations, we developed fully characterized, chitosan-based nanocarrier to encapsulate EGCG (hereafter termed as nanoEGCG) suitable for topical delivery. Here, we assessed the efficacy of nanoEGCG (48mg/animal) using an IMQ-induced mouse psoriasis-like skin model and compared the effects to free EGCG (1mg/animal). Treatment with nanoEGCG resulted in significant (p<0.01) amelioration of pathological markers of psoriasiform lesions including reduction in i) ear and skin thickness, erythema and scales, ii) proliferation (Ki-67), iii) infiltratory immune cells (mast cells, neutrophils, macrophages and CD4+ T cells), iv) angiogenesis (CD31), and v) increase in the protein expression of caspase-14, early (K1 and k10) and late (filaggrin and loricrin) differentiation markers and AP-1 factors (junB and cJun), and (v) modulates several psoriasis-related inflammatory cytokines and chemokines analyzed compared to high dose of free EGCG (p<0.05). Taken together, topical application of nanoEGCG was found to ameliorate IMQ-induced Balb/c mouse psoriasis-like lesions with greater than 25-fold dose advantage over free EGCG. Our observations warrant further in vivo efficacy studies of this unique nanoEGCG formulation in robust inducible and genetic models of psoriasis.

Bioreversible Modification of Proteins by Diazo Compounds

Kalie A. Mix
Graduate Student
Biochemistry; Molecular Biosciences Training Program

The O-alkylation of carboxylic acids with diazo compounds provides a direct method for labeling proteins via an ester linkage. This linkage is cleaved by cellular esterases in a manner reminiscent of prodrugs. The modification of protein using diazo compounds has been limited,
however, by lack of chemoselectivity of highly reactive compounds. We present a modular scaffold for systematically tuning the reactivity of the diazo compound that also provides a synthetically simple means of imparting functionality. The optimized diazo compound labels proteins more efficiently than any other known diazo compound, and enables the bioreversible modification of proteins. Using this diazo compound to attach cell-type targeting, cell-penetration, and pharmacokinetic enhancing moieties to proteins in a bioreversible manner could broaden the utility of proteins whose activities diminish upon irreversible modification.

**Brain Tissue Microstructure Is Altered in Healthy Older Adults and Is Associated with Early Cognitive Dysfunction**

Andrew Merluzzi
Graduate Student

*Medicine and Public Health; Neuroscience Training Program Neuroscience and Public Policy Program; Alzheimer’s Disease Research Center*

Douglas C. Dean III (Waisman Laboratory for Brain Imaging and Behavior); Nagesh Adluru (Waisman Laboratory for Brain Imaging and Behavior); Gaurav S. Suryawanshi (Waisman Laboratory for Brain Imaging and Behavior); Ozioma C. Okonkwo (medicine and public health); Jennifer M. Oh (medicine and public health); Bruce P. Hermann (Wisconsin Alzheimer’s Institute); Mark A. Sager (Wisconsin Alzheimer’s Institute); Sanjay Asthana (Geriatric Research Education and Clinical Center, William S. Middleton Memorial Veteran’s Hospital); Hui Zhang (computer science, Centre for Medical Image Computing, University College, London); Sterling C. Johnson (medicine and public health); Andrew L. Alexander (medical physics); Barbara B. Bendlin (medicine and public health)

Background: Normal human aging is accompanied by progressive alterations in brain structure in both white and gray matter. However, our ability to detect these changes has traditionally relied on post-mortem histology or on brain imaging techniques that lack sensitivity for the underlying microstructural phenomena that occur. However, novel diffusion-weighted imaging techniques might be able to resolve these age-related changes more clearly. One recent model for diffusion-weighted imaging is neurite orientation dispersion and density imaging (NODDI), which is capable of measuring the density of axons and dendrites, the degree to which they disperse away from each other or remain in coherent bundles, and the level of unhindered water diffusion throughout the brain. In conjunction with neuropsychological testing, NODDI may be able to resolve early brain changes and their relation to cognitive functioning with more specificity than traditional brain imaging techniques. In turn, this could aid in the differentiation between healthy aging and the pathological processes underlying Alzheimer’s and other dementias.

**Methods:** One-hundred and seventeen late middle aged, cognitively healthy participants (average age 61.7; range = 45-72) with increased risk for Alzheimer’s disease (AD) underwent a diffusion-weighted MRI scan and a neuropsychological battery. The three NODDI parameters were examined in relation to age after controlling for the covariates of sex, family history of AD, and the AD risk gene, APOE ε4. Correlational analyses were used to examine the relationship between the NODDI parameters and neuropsychological scores, controlling for effects of education and vascular health in the brain.

**Results:** Widespread increases in isotropic water diffusion were observed throughout the gray matter of the brain with increasing age, likely reflecting age-related atrophy and increased
diffusion from adjacent compartments of cerebrospinal fluid. Additionally, localized decreases
in neurite density in frontal white matter regions were observed with increasing age, and
decreased neurite density in the dorsomedial and ventromedial prefrontal cortex was
associated with poorer performance on tests of memory and executive function. Conclusion:
These results suggest that NODDI is capable of measuring age-related brain changes and
subclinical signs of cognitive impairment in an otherwise cognitively healthy sample of older
adults. These findings are largely in agreement with post-mortem histological studies as well as
other diffusion-weighted imaging techniques, but allow greater sensitivity for detecting early
microstructural brain changes. In sum, this study sheds light on the processes underlying
normal brain development in the 5th through 8th decades of life, knowledge that is critical for
differentiating healthy aging from the pathology associated with Alzheimer’s disease and other
dementias.

#16

Fall-Triggered Airbag Hip Protector to Reduce Hip Fracture Risk

Bjoern Buehring
Postdoctoral Researcher

School of Medicine and Public Health; Institute on Aging

Ellen Fidler (Institute on Aging); James Hermus (biomedical engineering); Cameron Hays (biomedical engineering); Patrick Cummings (biomedical engineering); Catherine Finedore (biomedical engineering); Austin Scholp (biomedical engineering); Paul Thompson (biomedical engineering)

Background: Hip fractures are the most devastating osteoporosis related fractures because
they lead to significant disability, morbidity, and mortality. For example, the 1-year mortality
rate for an older adult who sustains a hip fracture is 20-30%. From a public health perspective
hip fractures are common (more than 250,000 hospitalizations for hip fracture per year in the
US alone) and very expensive costing more than $10 billion per year. More than 90% of hip
fracture occur after a fall. As such, prevention of hip fractures can target increasing bone
strength or reducing fall risk. Additionally, hip protectors have been developed to reduce the
impact of a fall in individuals at high risk for hip fractures. Although hip fractures have been
shown to reduce forces at the hip success to reduce hip fracture risk in clinical trials has been
limited. One factor is very poor adherence (around 30% in some trials). This is due to the fact
that current designs are very hard to put on and take off which makes them unattractive to
older adults with limited mobility and incontinence. Design: Inspired by news reports on an
airbag bike helmet we develop an airbag hip protector belt that would inflate during a fall but
would not have the limitations of the current hip protector pants. To do so we develop our own
algorithm for the fall detection, designed and produced a belt that contains the airbag and
devised our own deployment mechanism and used a 3D printer to produce this device. The
current prototype works by using a microcontroller and an accelerometer to collect
acceleration data. The fall detection algorithm determines when a fall has occurred using a
threshold combined with a multi-window approach. The microcontroller sends a signal to a
solenoid, which releases a latch restraining a CO2 cartridge. The CO2 cartridge is pulled into a
nail by two extension springs in parallel to puncture the cartridge. The cartridge is punctured
and the gas fills the airbag. Results: Initial testing of this prototype proves that we can detect
falls with a low rate of false positive airbag deployment. The algorithm was found to have a sensitivity of 100% and specificity 93.3%. The airbag deploys in 300 to 400 msec, which is before ground impact and is able to reduce the impact force. The belt is easy to strap on and take off and less burdensome than other available designs. Conclusion: Our fall-triggered airbag hip protector is a promising design because system offers unique abilities that make it more effective as well as more attractive for older adults to wear. We think that our device has a big potential to benefit individuals as well as public health as hip fractures are common, have very negative health outcomes and the health care costs associated with hip fractures are so large.

#17

**Stochastic Particle Models for Complex Systems**

**Wai-Tong (Louis) Fan**  
Postdoctoral Researcher  
*Mathematics; Statistics and Operations Research*

Amarjit Budhiraja (statistics and operations research, UN C-Chapel Hill); Zhenqing Chen (mathematics, University of Washington); Rick Durrett (mathematics, Duke University)

Mathematicians and scientists use interacting particle models to gain understanding of the emergence of macroscopic phenomena from microscopic laws of nature. In this poster, I will illustrate the use of these powerful tools by practical examples including the transport of charges in solar cells and the evolution of randomly growing cancer tumors. To connect the microscopic mechanisms with the macroscopic behaviors at two different scales, we obtain the functional law of large numbers for these systems. The limiting objects are described by partial differential equations and stochastic partial differential equations.

#18

**A Defined System for the Derivation of Brain Microvascular Endothelial Cells from Human Pluripotent Stem Cells**

**Tongcheng Qian**  
Postdoctoral Researcher  
*Chemical and Biological Engineering*
**JAK2/STAT3 pathway Is Upregulated in Canine Diffuse Large B Cell Lymphoma and JAK Inhibitors Decrease Canine B Cell Lymphoma Cell Growth In Vitro**

Hannah Ruetten  
Graduate Student  
*Medical Sciences, School of Veterinary Medicine; Carbone Cancer Center*  
Paulo Jark (medical sciences and Carbone Cancer Center); Courtney Hong (medical sciences and Carbone Cancer Center); Nathan Bollig (medical sciences and Carbone Cancer Center); Marie Pinkerton (pathobiological sciences); Xuan Pan (medical sciences and Carbone Cancer Center)

Non-Hodgkin lymphoma (NHL) is the fifth leading cause of human cancer death in the United States. NHL is also the most common canine malignancy, accounting for up to 24% of all reported neoplasms in dogs. Similar to humans, the majority of canine NHL (60-80%) arise from malignant B cells, most representing diffuse large B-cell lymphoma. Canine diffuse large B cell lymphoma (c-DLBCL) also shares with humans a similar response to chemotherapeutic treatments. For these reasons c-DLBCL is often used as a large animal model for human NHLs. The Janus Kinase (JAK) and signal transducer and activator of transcription (STAT) pathways play important roles in the proliferation and pathogenesis of hematologic malignancies. Activated JAK2-STAT3 signaling pathway promotes the growth and survival of a variety of lymphomas in humans. There is a great demand for understanding JAK-STAT pathway in c-DLBCLs and evaluating the therapeutic potential of JAK inhibitors. Our study aims to evaluate the expression and activation of JAK2-STAT3 pathway in c-DLBCLs and to assess the impact of AZD1480 and CYT387, two novel JAK inhibitors, on c-DLBCL cell growth.

Immunohistochemistry was performed in forty-two c-DLBCLs lymph node (LN) samples, ten reactive and ten normal LNs as controls, with primary antibodies against STAT3 and phosphorylated STAT3 (pSTAT3). Immunolabelling for STAT3 and pSTAT3 was evaluated by percentage of positive cells. To evaluate the therapeutic effect of novel JAK inhibitors, canine DLBCL cell line CLBL-1 and canine normal kidney cell line MDCK were treated with doses of 1M, 2M, and 5M AZD1480 or CYT387 with 100% DMSO as treatment control. Trypan blue viability and apoptosis assays were performed post treatment. There was a significant increase in expression of STAT3 and pSTAT3 (mean percentage of positive cells per patient sample) in c-DLBCLs (76%, 15%) compared with the normal lymph node control (49%, 3.9%), (p<0.05).

There was no significant difference between c-DLBCLs and reactive LNs. Both AZD1480 and CYT387 inhibited canine DLBCL cells viability in a dose dependent manner. MDCK viability was mildly inhibited only at 5M. Percentage of early apoptotic cells increased in a dose dependent manner with both JAK2 inhibitor drugs, compared to DMSO. There were no significant changes of early apoptotic cell percentage in the AZD1480 or CYT387 treated MDCK cells. This is the first study to evaluate the JAK2/STAT3 pathway in canine DLBCLs. Understanding JAK2-STAT3 activity in canine DLBCLs will enable us to explore the therapeutic potential of JAK inhibitors. The identification of a dose dependent cell growth inhibition by novel JAK inhibitors in this study provides rationale for future studies of the underlying mechanism.
Metabolic Profiling in the Plasma of Rats in Response to Aging and Ischemic Stroke by Nuclear Magnetic Resonance Spectroscopy

Vijesh Bhute
Graduate Student
Chemical and Biological Engineering

Umadevi V. Wesley (neurological surgery); James F. Hatcher (neurological surgery); Robert J. Dempsey (neurological surgery)

Introduction: Metabolic dysfunction is a common hallmark of aging, and it influences the neurodegenerative diseases including stroke incidence and outcome. Several metabolomics-based studies have revealed metabolite biomarkers in stroke patients and yet metabolic changes as a result of aging and focal ischemia/reperfusion (I/R) time are not completely elucidated. In this study, we examined the dysregulation of metabolites in the plasma as a function of age and cerebral ischemic injury. Methods: We compared the metabolic pattern in young (3 months) and older rats (12 months) before, and 2 days after I/R injury. Stroke was induced by middle cerebral artery occlusion. For time course study, plasma samples from younger animals were collected at day 2, 3, 7, and 14 of I/R (n=3). We used Nuclear Magnetic Resonance spectroscopy and compared the metabolite peaks using spectral binning and targeted profiling. The data was analyzed using one way analysis of variance, principal component analysis (PCA) and hierarchical clustering. Pathway enrichment and topological analysis tools were used to identify the age and stroke responsive metabolic pathways. Results: PCA revealed global differences in plasma of naïve young and old rats, with old rats showing significantly lower glucose levels, and higher formate levels. Also, older animals showed reduced levels of proline, threonine and tyrosine and high levels of isoleucine, leucine, phosphocholine and valine 2 days after I/R. Younger rats showed significant differences starting from day 3 onwards with lower glucose, lactate, citrate, succinate, fumarate and glutamate concentrations and increased creatine, formate, isoleucine, leucine, lysine, and glycine concentrations, which remained at a higher level on day 7 of I/R. Interestingly, the metabolic profile of plasma at day 14 of I/R showed similar pattern as that of control naïve animals. Pathway enrichment analysis revealed enrichment of citric acid cycle and glycine, serine and threonine metabolic pathways in older animals as early as 2 days after I/R. However, younger animals showed a delayed metabolic response after day 3 of I/R. Conclusion: We have demonstrated that the metabolic profile of plasma is altered as a function of age, ischemic stroke and time of reperfusion. These results suggest an important role for imbalance in metabolites in stroke pathogenesis.
#21

**Subclonal Diversity Arises Early Even in Premalignant Colorectal Tumors and Contributes to Differential Growth Fates**

Chelsie K. Sievers
Graduate Student

*Medicine; Cellular and Molecular Pathology Graduate Program; Oncology*

Luli Zou (medicine); Perry J. Pickhardt (radiology); Kristina Matkowskyj (pathology and laboratory medicine); Dawn Albrecht (medicine); David Kim (radiology); Michael Newton (statistics)

Basic and clinical scientists believe that benign polyps in the colon progress to cancers through the slow, stepwise accumulation of mutations. Interestingly, only a small percentage of all polyps progress, whereas a significant number remain static in size, regress, or resolve completely. The mechanisms underlying these differential fates are unknown, and currently there are no biological characteristics that can reliably predict which polyps will grow or progress into a deadly cancer. To identify molecular predictors, the mutational landscape of early polyps was determined using targeted next generation sequencing. This study was unique because the growth rate of each polyp had been assessed by interval imaging with CT colonography. Patients were scanned at the University of Wisconsin in Madison and Walter Reed National Military Medical Center in Bethesda, MD. To determine spatial location of identified mutations within a polyp, micro-dissection was performed followed by quantitative PCR to validate low frequency mutations. The mutational landscape of small polyps is varied both within and among individual polyps. Polyps carried 0-3 pathogenic mutations with the most frequently altered genes being APC (67%, 32/48), KRAS/NRAS (17%, 8/48), BRAF (17%, 8/48), FBXW7 (10%, 5/48), and TP53 (8%, 4/48). Additionally, 13% (6/48) contained driver mutations at varied mutant allele frequencies, indicating the presence of subclonal populations. In silico modeling of tumor growth was used to determine the likely size at which additional driver mutations arose to account for the observed frequencies. This model of tumor growth in the colon utilized Approximate Bayesian Computation (ABC) and three-dimensional mathematical modeling to generate tumors that acquire subclonal mutations, which may change the fitness positively or negatively, and the lineage from these mutant subpopulations was tracked during tumor growth. In silico polyps were then sectioned and mutant allele frequency was recorded and compared to the frequencies observed from the targeted sequencing of human polyps. Contrary to the postulated step-wise accumulation of mutations, these data indicate small polyps can have multiple pathogenic mutations in crucial driver genes that arise as a tumor is just beginning to form and become established. Understanding the molecular pathway of tumorigenesis and clonal evolution in polyps that are at risk for progressing to invasive cancers will allow us to begin to better predict which polyps might be more likely to progress into cancers and which patients are predisposed to developing advanced disease. Furthermore, understanding the process of neoplastic transformation at the cellular population level could lead to novel tumor prevention strategies.
High-Throughput Touch Stimulus Device for Controlling Plant Growth and Development

Richard Barker
Postdoctoral Researcher
Botany
Caleb Fitzgerald (industrial and systems engineering); Amit J. Nimunkar (biomedical engineering); Simon Gilroy (botany)

Under current methods of indoor growth, plants do not receive the touch stimuli they experience growing in the wild. There are no changing winds, rains, or animals brushing against them. By creating a device that systematically provides touch stimulus to plants, such as the model plant Arabidopsis thaliana, we will be able to approach both fundamental and applied questions about the regulation of plant growth. Mechanical stimulation is known to alter agronomically/horticulturally important plant features such as pathogen resistance and time of flowering. Indeed, greenhouse-grown plants are prone to a range of reduced mechanical-stimulation related issues such as increased susceptibility to pathogen attack and reduced stress tolerance. The use of fans and even of employing people to walk through growth facilities brushing every plant with a cane is often used as an attempt to solve this issue but the plants remain weak and frail compared to the equivalent wild plants. In addition, the mechanical stimulation is highly heterogeneous and poorly controlled using these approaches. This results in less output in terms of usable plants for food and horticulture and an increased use of pesticides. The commercial use of a scalable, regulated touch stimulus device would provide a low labor approach to manipulate plants and alleviate many of these issues. We have been able to develop a device that creates controlled, intermittent touch stimulation to plants and have tested it to the level of documenting physiological responses that are distinctly different in touch-related Arabidopsis mutants. The current prototype is limited in the ability to control outlying variables such as light or wind and in providing feedback control for individual plants. Our next iteration aims to bring the current device into a controlled, all-inclusive device that can target individual plants for stimulation. This next iteration of the equipment will consist of four parts: (1) an enclosure and watering system to maintain control of abiotic factors such as wind, water, and light; (2) a more robust frame and motor to stimulate the plants consistently and systematically at certain time intervals of the day; (3) an interchangeable contact surface that allows for the implementation of soft materials to contact the plants as well as harder materials for experimentation on wounding responses; and (4) the addition of thermal, GFP fluorescence and/or NVDI imaging system to develop a feedback biomonitoring system controlling a piezo-driven stimulator individually addressable to each plant. By incorporating imaging and individual plant addressability, the system will add flexibility to the greenhouse systems where, e.g., plant flowering in different zones could be optimized to provide successive cropping from a single growth space through the ability of touch stimulation to delay flowering. Similarly, pest resistance could be tuned to prevailing or expected conditions through touch stimulation-triggered defense responses in an entirely pesticide-free approach. The device under development will also provide the critical data from the imaging systems and touch stimulation responses to begin to develop and optimize algorithms to help growers mechanically “tune” the health and productivity of their plants.
Automated Full-Range Spectroscopic, Thermal and Laser Plant Scanning System

Richard Barker
Postdoctoral Researcher

Botany
Aditya Singh (forest and wildlife ecology); Amit Nimunkar (engineering); John Couture (forest and wildlife ecology); Clayton Kingdon (forest and wildlife ecology)

Remote monitoring of plant physiology and biochemistry holds enormous potential for both understanding and manipulating plant growth and development in settings ranging from the laboratory to the field. Indeed, reflectance spectroscopy is rapidly emerging as a highly effective and practical approach for the rapid, non-destructive estimation of a wide variety of plant chemical, biophysical and metabolic traits in living tissue. The technique uses variations in leaf optical properties that arise from the interaction of light and chemical bonds. Measurement of absorbance and reflectance features in the visible spectrum and out into the infrared (~400-2500 nm) are used to directly estimate foliar structure as well as plant chemical composition, water content and even metabolic status. Some spectral features are known to be associated with specific chemical or stress responses, yet these spectra also remain a rich resource of information to be mined, with many features of plant physiology and chemistry awaiting to be extracted from the data. While such spectroscopic imaging techniques offer huge potential, they also raise many practical issues that currently limit applications. For example, scheduling collections for multiple spectroscopic measurements across many samples and over many time points is often logistically difficult and even prohibitively time consuming. These become important issues for the analysis of plant responses which tend to change rapidly in response to environmental or biotic stressors (requiring time-course data collection) and also to vary widely between different plant species or genotypes (requiring sampling from many individuals). We have therefore begun to develop a high-throughput, automated, full-range spectroscopic, thermal and laser scanning system that addresses these difficulties. The equipment is based around computer control of a mobile scanning head and is applicable to the investigation of many different plant types. The system under development uses a commercial spectrometer but we plan to integrate other imaging modalities to provide an even deeper set of structural and chemical data to monitor plant performance. Thus, a parallel thermal imaging system will allow assessment of changes in the critical parameters of transpiration and photosynthetic capacity and a laser scanner will further enable the assessment of changes in foliar structure and biomass across experiments. The automated positioning system adds the ability to integrate these types of data across multiple plant samples and represents a major increase in the capacity of these kinds of spectroscopic and imaging-based analytical tools. Previous research has shown that using spectral image analysis we can measure upregulation of plant defense compounds in milkweed stimulated by caterpillar feeding and detect the presence of bacterial infections in Arabidopsis thaliana well before any visual symptoms are observed. We have also been successful in modelling plant metabolism (carboxylation capacity of RubisCo, and its sensitivity to temperature) on scales ranging from leaves to fields. The automated nature of the equipment currently under
development will move these kinds of measurements into a new realm of highly temporal- and multi-specimen-oriented analysis. This new depth of measurement will in turn provide an unprecedented view into how plants dynamically respond to their environment.

#24

**NVDI Imager for Analysis of Plant Productivity**

**Richard Barker**  
Postdoctoral Researcher  
*Botany*

Kyle Schneider (industrial and systems engineering); Amit J. Nimunkar (biomedical engineering); Simon Gilroy (botany)

Remote sensing through the imaging of plants has immense potential to aid in understanding plant responses in settings ranging from the farmer’s fields through to the research laboratory. Images from normal cameras can gather key data on plant growth and development but recently, analysis of images taken outside the range of visible wavelengths has proven an extremely powerful analytical tool. For example, such spectral imaging at wavelengths longer than 700 nm can generate images that show the intensity of plant photosynthetic capacity in real time. The significant drawback of such an approach is cost. “Normal” hyper-spectral cameras cost upwards of $30,000, moving the equipment out of the range of most researchers and farmers. However, it is now possible to minimize this expense through the use of cameras that cost less than $150. The core piece of hardware making such equipment development feasible is the Raspberry Pi minicomputer. This $30 computer has the power to run Normalized Difference Vegetation Index (NDVI) imaging code in real time and an NDVI-compatible (near infra-red detecting) camera is available for ~$120. This system allows real time recording of plant photosynthetic capacity/health (as plants become stressed, photosynthetic capacity drops, visible within the NDVI images). We are developing this low cost system as a research tool to follow the development of the plant Arabidopsis as a proof of concept for a potentially wider usage. To minimize expense, we are developing a system where one camera can follow plants growing in 6 separate Petri dishes. In this approach, the Raspberry Pi controls a motor which has the camera on it. This allows the camera to sequentially take images of each of the 6 different Petri dishes. Arranging the Petri dishes in a circle instead of in a line with the camera on a linear mount, minimizes space, providing a robust, scalable device with a small footprint within the laboratory. The NDVI analysis will be integrated with classical quantitative plant growth image analysis using software packages such as Root Trace. This combination of measurements will allow dissection of relationships between stress, growth and photosynthetic capacity. It will also provide a further proof-of-concept for more widespread application of this cheap quantitative NDVI imaging approach. NDVI is already in use for surveying agricultural productivity from satellite imagery but a cheap, well validated system could open up a wide array of applications such as with drones or for use with plants in the home. One further application we are extremely interested in exploring is the potential use of such systems as reliable monitors for plant growth and health in extreme environments, such as on board the International Space Station and during deeper space flight. Use of plants as part of a bio-regenerative life support system will absolutely require efficient, and reliable monitors of plant health and productivity. Our experience with such experimentation indicates a reliable, cheap
and well validated imaging approach would be a key addition to current plant monitoring capabilities during spaceflight.

#25

Linear Automation of Time-Lapse Photography with Variable Light Environments

Richard Barker
Postdoctoral Researcher

Botany

Ben Cox (Morgridge Institute for Research); Shyamal Anadkat (computer science and electrical engineering); Patrick Masson (genetics); Simon Gilroy (biomedical engineering)

This project focuses on developing a high-throughput time-lapse photography system for quantifying the growth kinetics of plant growth. Further, incorporating fluorescence imaging to the system will also allow correlation of growth behaviour with monitoring of the real-time dynamics of biochemical signaling. The analytical capabilities of the equipment are currently focused on proof-of-concept, using the model plant Arabidopsis, but the equipment is scalable and the technology transferable to other plants such as crops. The system provides a high degree of control of its environment including flexibility in the lighting regime and facilitating measurement at high temporal resolution. This equipment will allow research that is currently extremely hard to perform. For example, it is difficult to isolate gravity and other stimuli (especially interactions with light) that affect plant growth but this equipment allows highly quantitative control of both light direction and of light quality (color, intensity, duration) as plants are reoriented with respect to gravity. Other applications include exploring interactions between plants and their physical environment such as growth medium hardness or mineral composition. The prototype hardware consists of a camera programmed to capture time lapse photographs. The camera is mounted on a motorized track allowing it to be programmed to visit a set of linearly mounted plant growth stations. These stations are placed at set distances along the length of travel of the camera and each consists of a novel RGB variable LED lighting array that surrounds, and holds a Petri dish with each plant sample. The variable LED light boxes allow an unparalleled control of the plant’s light environment, individually controlling illumination intensity, direction, duration and spectrum for each sample. The design and circuitry of the six independent lighting boxes utilizes microcontrollers and multi-channel PWM drivers to set the RGB LEDs at the desired color and brightness. The lighting is controlled by custom software bundled into a convenient custom graphical user interface. The system has been prototyped to the level of being tested with plants with known responses or lesions in their light response capabilities, including genetic knockouts in specific color receptors of plants. The setup of the system allows the direction, quality, and quantity of light to be attuned around a 360 degree rotatable plant chamber, allowing us to also test for the interaction between directional responses to gravity and to light. Future work will involve implementing some practical enhancements that have emerged as desirable from the prototype testing including: addition of wireless modules to the microcontrollers in order to allow remote access to the light boxes’ variables, upgrading the software to extend timing and lighting controls and improving the camera tracking system. However, a further key element to be added is a new capability. Fluorescence imaging is proving an immensely powerful tool to follow plant
biological responses in real time and we plan to implement both a fluorescence and Forster Resonance Energy Transfer imaging system to greatly extend the equipment’s capabilities.

#26

Investigating Distribution, Stability and Dose Response Following Intranasal Targeting of Antibodies and Their Fragments to the Central Nervous System

Geetika Nehra

Graduate Student

School of Pharmacy

Niyanta N. Kumar (Pharmacy); Jeffrey J. Lochhead (Clinical Neuroengineering Training Program); Eric Brunette (National Research Council of Canada, Institute for Biological Sciences); Danica B. Stanimirovic (National Research Council of Canada; Institute for Biological Sciences); Robert G Thorne (Pharmacy, Clinical Neuroengineering Training Program, Center for Neuroscience & Neuroscience Training Program and Cellular and Molecular Pathology Graduate Program)

The ability to deliver therapeutic macromolecules to widespread areas in the CNS has been demonstrated to occur in as little as 30-60 minutes following intranasal administration. This rapid transport of nasally administered molecules to the brain is thought to occur via distribution within potential extracellular pathways associated with the olfactory and trigeminal nerves that innervate the nasal mucosa as well as the perivascular spaces surrounding cerebral blood vessels. An intranasal approach featuring non-invasive, chronic application may offer a particularly attractive option for antibody-based drugs. In the current study, we intranasally administered non-targeted radiolabeled or fluorescently labeled full-length antibodies (IgG ~150 kDa) or antibody fragments such as single domain antibodies (sdAb ~ 15 kDa). We then analyzed their distribution in the brain, cerebrospinal fluid (CSF) and periphery. We also investigated the potential of matrix metalloproteinase-9 to improve intranasal delivery of antibodies to the CNS. Our results revealed that at least low to mid-picomolar concentrations of antibodies are achievable in widespread brain areas following intranasal administration. The highest concentrations were observed at brain entry sites (olfactory bulbs and trigeminal nerves) and cerebral perivascular spaces. At doses which produced similar end point blood concentrations, intranasal delivery resulted in significantly higher concentrations in the CSF and the brain than systemic delivery. Our findings represent the first study to compare both the distribution of antibodies in the brain, CSF, blood and periphery following intranasal delivery versus systemic delivery. The results suggest that intranasal delivery may offer a non-invasive chronic immunotherapy approach for CNS disorders.
#27

Utilizing the Wisconsin Idea to Empower a Community and Enhance Individual and Environmental Health

Mike Geiger  
Graduate Student  
*Horticulture*

Park Falls, located in the Flambeau River valley, is home to almost 2500 Wisconsin residents, including more than 1000 elementary, middle, and high school students. Recent research and local dialogue highlight the need for a focus on healthy eating and renewable resources throughout the community. In response, the Flambeau River Community Growing Center has been developed to utilize waste streams from the Flambeau River Paper Mill while establishing a strong relationship between University of Wisconsin–Madison and the Park Falls community. Collaborators include plant scientists from UW–Madison, engineers from Flambeau River Paper Mill, outreach staff from UW–Extension, educators from Chequamegon School District, and the broader Park Falls community. This has been a unique opportunity to introduce a UW presence in a northern Wisconsin community. Ultimately, we have embraced the Wisconsin Idea in order to empower a community and enhance individual and environmental health.

#28

Investigating the Whole Brain Distribution of Intrathecally Applied Antibodies and Antibody Fragments Using Ex Vivo Fluorescence Microscopy and In Vivo Magnetic Resonance Imaging

Brynna Wilken-Resman  
Graduate Student  
*School of Pharmacy, Division of Pharmaceutical Sciences*

Michelle E. Pizzo (pharmaceutical sciences and Clinical Neuroengineering Training Program); Daniel J. Wolak (pharmaceutical sciences and Clinical Neuroengineering Training Program); Eric Brunette (Institute for Biological Sciences, National Research Council of Canada); Melanie-Jane Hannocks (Institute of Physiological Chemistry and Pathobiochemistry, Muenster University); Christina M. Lewis (medical physics); M. Elizabeth Meyerand (Clinical Neuroengineering Training Program, medical physics and biomedical engineering); Lydia Sorokin (Institute of Physiological Chemistry and Pathobiochemistry, Muenster University); Danica B. Stanimirovic (Institute for Biological Sciences, National Research Council of Canada); Robert G. Thorne (pharmaceutical sciences, Clinical Neuroengineering Training Program, Neuroscience Training Program, Cellular and Molecular Pathology Graduate Program and Institute for Clinical and Translational Research)

It is currently not well understood what transport processes govern the distribution of macromolecules between the cerebrospinal fluid (CSF) and the brain interstitial fluid (ISF). Studies suggest that diffusion primarily governs transport in the ISF-filled 40-60 nm wide...
extracellular spaces (ECS) of the brain (Sykova & Nicholson. Physiol Rev 2008; Thorne et al. PNAS 2006 & 2008), but convective flow may occur in CSF compartments and perivascular spaces (PVS) surrounding cerebral blood vessels (Iliff et al. Sci Trans Med 2012 & J Clin Invest 2013). The perivascular compartment is thought to play a role in waste clearance, homeostasis, and immune function, but could also provide an underappreciated path for drug delivery. However, the anatomical boundaries of the PVS and its role in CSF/ISF exchange remain unclear. Here, anesthetized rodents received intracisternal infusions of labeled, non-targeted antibodies and antibody fragments. Whole brain distribution was characterized using ex vivo fluorescence microscopy and in vivo 3D magnetic resonance imaging. Immunostaining and confocal microscopy were used to clarify the distribution of antibodies in the PVS and define the anatomical pathways of CSF/ISF exchange using various basement membrane markers (Yousif, Russo, & Sorokin. Cell Adh Migr 2013). Diffusion parameters from integrative optical imaging (Wolak, Pizzo, & Thorne. J Control Release 2015) yielded the apparent hydrodynamic diameters of the various antibodies (4.5 – 10 nm) and demonstrated their size-dependent diffusional hindrance in brain ECS. Intrathecal infusions of the antibody tracers resulted in fluorescent signal distributions consistent with both diffusion across the pial brain surface to the underlying parenchyma and penetration to deeper brain regions through apparent convective transport within the PVS of cerebral blood vessels, occasionally reaching as far as microvessels. MRI revealed a complex distribution of gadolinium-labeled antibody through the subarachnoid spaces and cisterns of the midbrain and forebrain as well as a time-dependent distribution in compartments associated with leptomeningeal blood vessels. Finally, immunofluorescence staining for different laminin isoforms and other markers was used to differentiate between blood vessel types and to begin to molecularly characterize the PVS compartments accessed by the antibodies. Our findings better define the role of diffusion and convection in CSF/ISF exchange and suggest perivascular transport is important for antibody distribution within the brain. These results may have high relevance for immunotherapies aimed at CNS pathology.

#29

Detection of Prostate Cancer Cells Using Electrochemical Biosensing Method

Rajesh Seenivasan
Postdoctoral Researcher

Biological Systems Engineering
Chandra K. Singh (dermatology); Nihal Ahmad (dermatology)

Prostate cancer is one of the most prevalent and second leading causes of cancer death among men in the United States. Therefore, early cancer disease diagnosis and detection is of significant prognostic value and helps to study therapeutic outcomes of cancer treatment. However, current methods to detect cancer are complex, expensive, lack the required specificity and sensitivity, and suffer from producing false-positive and false-negative results. Therefore, developing simple, label-free, cost effective, and highly specific and sensitive method that requires only small sample volume to detect cancer cells is needed for early diagnosis and treatment of cancer. We report such a method through electrochemical biosensing. In our method, we use functionalized gold nanoparticles (AuNPs) to modify working electrode surface patterned on an indium tin oxide (ITO) glass for biocompatibility and
The Effectiveness of Generating Drawings When Learning with Visual Representations in Chemistry

Sally Wu
Graduate Student

*Educational Psychology; Interdisciplinary Training Program for Education Sciences (ITP)*

Martina A. Rau (educational psychology)

In science, technology, engineering, and mathematics (STEM), students learn by integrating conventional visual representations with their own mental models. However, students face difficulties when learning with representations and require instructional support. Prompting students to draw can help them externalize their mental models and integrate them with conventional visual representations. We conducted an experiment with 72 undergraduates to investigate the effectiveness of drawing prompts in an educational technology for chemistry. We compared (1) students who received drawing prompts throughout instruction, (2) students who received drawing prompts only before and after, and (3) students who did not receive drawing prompts (i.e. control condition). Quantitative results from a delayed posttest show that drawing prompts lead to higher learning gains only when provided throughout instruction. Qualitative analyses of students’ drawings suggest that drawing prompts throughout instruction help students compare their mental models and revise them to align with conventional representations. Future work will investigate the cognitive processes that students engage in while drawing throughout instruction. Taken together, the results have implications for how and when to effectively implement drawing prompts when students learn with visual representations.
A Blood Brain Barrier Neurovascular Unit Model Derived with Brain Microvascular Endothelial Cells, Neurons, and Astrocytes from Human Stem Cells

Scott Canfield  
Postdoctoral Researcher  
Chemical and Biological Engineering  
Eric V. Shusta (chemical and biological engineering); Sean P. Palecek (chemical and biological engineering); Matthew J. Stebbins (chemical and biological engineering); Bethysmarie S. Morales (chemical and biological engineering); Shusaku W. Asai (chemical and biological engineering); Gad D. Vatine (Regenerative Medicine Institute, Cedars-Sinai Medical Center); Clive N. Svendsen (Regenerative Medicine Institute, Cedars-Sinai Medical Center)

Detecting Anisotropy in Attenuation Coefficients of In Vivo Human Breast Tumors

Haidy Nasief  
Graduate Student  
Medical Physics  
James Zagzebski (medical physics); Sarah Kohn (radiology); Timothy Hall (medical physics)

Purpose: Quantitative ultrasound (QUS) provides acoustic parameters that describe tissue microstructure and sound wave propagation. A commonly-estimated acoustic property is the attenuation coefficient that quantifies the rate at which an ultrasound beam loses energy as it propagates through tissue. Using (clinical) array transducers, the ultrasound beams can be steered over a range of angles. Averaging QUS parameter estimates from multiple angles can provide more reliable estimates. However, if the parameters are anisotropic, averaging the estimates among steered beams can induce bias. Therefore, we are interested in developing methods to detect anisotropy in attenuation estimates. This study outlines a methodology for detecting anisotropic attenuation and reports preliminary results on a small data set of in-vivo breast tumors. Methods: This IRB-approved, HIPAA compliant study recruited subjects who were scheduled for core biopsy of a suspicious breast mass. A Siemens S2000 scanner equipped with linear array transducers was used to acquire radiofrequency echo data at beamsteered angles from -10º to 10º from the normal to the transducer face in both radial and anti-radial planes (along and across the breast ducts, respectively). Echo signals were also obtained from a reference phantom using the same settings. Radiofrequency echo data from 16 human subjects were used to estimate the “specific attenuation coefficient” (SAC; attenuation coefficient versus frequency slope) within the tumor using a reference phantom method. Ten of these subjects were found to have fibroadenomas and the rest were carcinomas. Acoustic attenuation was estimated for each beam steering angle in both radial and anti-radial directions. A power-law fit was applied to the estimated attenuation and the
value at 6 MHz was calculated for each beam steering angle. If the SAC estimates are equivalent (within twice the standard deviation among estimates at that angle) at all steering angles then the parameter appears isotropic. If there is a trend in attenuation estimates from positive to negative angles in either the radial and anti-radial scan planes, then the parameter estimates are anisotropic. When parameter values appear to be isotropic estimates from multiple view angles can be averaged (a technique referred to as “spatial compounding”) to obtain lower variance estimate of the SAC within the tumor. Results: The results suggest that 70% of fibroadenomas showed attenuation anisotropy in the anti-radial direction and 50% showed anisotropy in the radial direction. Roughly equivalently, 50% of carcinomas showed anisotropy in either the radial or anti-radial views. However, a larger study is needed to understand cause for anisotropy in breast tumors. A larger data set and complementary methodologies, such as diffusion-weighted MRI, nonlinear optical microscopy, and other QUS parameters, are needed for more detailed investigation. Conclusion: Anisotropy in acoustic attenuation was detected in both fibroadenomas and carcinomas. Since most in-vivo breast tumors showed attenuation anisotropy, compound averaging of attenuation from multiple angles can induce a bias.

#35

**Distributed Optimization and Active Learning for Smart Refrigerators**

**Sejal Chauhan**

Graduate Student

*Computer Science*

**Mihir Shete**

With the recent advances in Machine Learning and Image Processing it is possible for computers to recognize various objects. Our objective is to use the advances in these fields with the compute power available on embedded systems to make an ecosystem of products and services centered around a smart refrigeration system. In the USA, organic waste is the second highest component of landfills, which are the largest source of methane emissions and accounts for 30-40% of the total food supply. We believe that preventing food wastage begins in the home itself, and our approach to tackle this issue is by making the refrigerators smarter using low cost embedded systems. These systems will run active learning and image processing algorithms to detect food items in the refrigerator and predict how long they will stay fresh. The core algorithms can be used to build an ecosystem of applications, like showing the inventory of the refrigerator to the owner when he is shopping for grocery so that he can decide what needs to be bought. By getting information on the freshness of food items the refrigerator can suggest some recipes which can be made from items which are about to go stale, and if the owner cannot eat the items about to go stale in a couple of days the refrigerator can take actions like contacting services like Copia which donate surplus food to those in need. Our proposed idea is a small embedded device which can be attached to any commodity refrigerator, the device comes with a few camera modules which can take pictures of items in the refrigerator. The raw data will be stored on a central server for our prototype, but we will leverage the processing power of the embedded system attached to the refrigerator and pre-process images to extract various features for our machine learning.
algorithms. Our goal is to run the machine learning algorithms on the embedded systems themselves to prevent large scale data processing on the servers and thus lower the cost of overall solution with these distributed optimizations.

#36

**Discovering Social and Political Events with Topic Modeling of Twitter Data**

Frederick Boehm  
Graduate Student  
*Statistics*  
Bret Hanlon (statistics); Robert Turner (statistics)

Social media platforms enable users to discuss current events. Over time, topics, such as the Super Bowl, may arise in social media conversations. Some of these topics persist over time, while others are short-lived. We propose machine learning methods to identify hidden themes (or topics) that characterize communications on social media. We build on existing topic modeling strategies, such as latent dirichlet allocation (LDA) and its extensions, to uncover unobserved topics at distinct time points. Initial explorations focused on detection of themes that related to the 2015 Super Bowl football game. Our current methods include an automated pipeline for continuous collection of tweets from the Twitter API and a workflow for processing raw tweets and performing LDA on tweets from a single day. Due to the high volume of tweets that we collect (on the order of 4000 per minute), we have been forced to limit inputs to each topic model to a single day’s tweets. We collected tweets by repeatedly querying the Twitter API on the days surrounding the 2015 Super Bowl football game. We implemented LDA with existing software in the R statistical environment. We used a cross-validation strategy to identify the number of topics in each model. We visualized our models using freely available R software. One major limitation of our initial strategy is that we’re fitting distinct models for each day within our time period of interest. Future directions include explicit modeling of topics over time. Ideally, we’d like to extend LDA-based strategies to develop models that incorporate time and allow for the dynamic evolution of topics. Our dynamic topic models will be useful to researchers in the social sciences, humanities, and biological sciences.

#37

**A Search for Unnatural Biomimetic Catalysts**

Melissa MacDonald  
Postdoctoral Researcher  
*Chemistry*  
David R. Walt (Tufts University)

The search for synthetic catalysts that rival the remarkable efficiency of enzymes has been a long-term goal of the chemical community. An enzyme's activity depends on adoption of a specific tertiary structure, and it can be assumed that oligomers with unnatural backbones will
have to display comparable folding behavior in order to manifest enzyme-like catalytic properties. However, very little is known about the relationship between subunit sequence and higher-order conformation for unnatural backbones. Therefore, we have pursued a structure-agnostic approach to catalyst discovery. Specifically, we have begun to search the chemical space available to backbones containing mixtures of α and β amino acid residues by combining unique synthesis and screening methods to seek catalysts for challenging hydrolytic reactions. High-density optical arrays allow us to analyze complex oligomer mixtures at the single-molecule level for the presence of catalytically active sequences. Progress towards the goal of finding unnatural oligomer catalysts will be discussed. 1. Goodman, C. M.; Choi, S.; Shandler, S.; DeGrado, W. F. Nat. Chem. Biol. 2007, 3, 252. 2. Zhang, H.; Nie, S.; Etson, C. M.; Wang, R. M.; and Walt, D. R. Lab on a Chip, 2012, 12, 2229.

#38

**Biosensing for Determining the Microbial Safety of Environmental Waters**

**Youngsang You**

Graduate Student

*Biological System Engineering*

Simple and rapid detection of pathogen is crucial for preventing and treating infectious diseases. Detection of foodborne microorganism, even in water, is essential to secure the safety of health. Although culture-based colony-counting and polymer chain reaction (PCR)-based genetic identification methods are popular, the time-consuming nature and/or the need for sophisticated instrumentation of those methods limit their on-site applications. The use of nanotechnology and specifically, gold nanoparticles (AuNPs) has facilitated the development of biosensors that can potentially be used on-site because they provide a colorimetric output. We have developed a novel highly sensitive and visible detection method based on aggregation of AuNPs that does not require any readout device. The biosensor consists of streptavidin-functionalized gold nanoparticles (stAuNPs), which can produce a visually recognizable color change, and biontinylated anti-bacteria antibody (bAb) as switchable linker (SL). A two-step procedure is used for the SL to function as a crosslinker to bind to the target bacteria present, and thus produce a visible colorimetric signal based on the quantitative relationship between the amount of SL used and the number of stAuNPs in the system. When SL is mixed with the test sample (the first step in our assay) the immunogenic function of the SL leads to antibodied binding to the surface antigens of the target bacteria. Subsequently, when stAuNPs is added (the second step) the crosslinking of AuNPs produces a visible color change. We used this biosensing system to detect Escherichia coli (E.coli) in tap water and lake water. Series of tests employing anti-E.coli antibody and stAuNPs produced visible color change in response to the presence of E.coli as few as 3 CFU/mL. The bacterial loads tested were confirmed by plate-counting. The color change happens within about 15 min without requiring any enzyme or other amplification techniques.
Intimate Partner Sexual Violence Among Men Who Have Sex with Men in Delhi, India

Mridu Markan
Graduate Student
Gender and Women Studies
School of Human Ecology

Male to male sexualities in India are highly nuanced and diverse. The National AIDS Control Organization, 2011 elucidates how MSMs include self-identified gay men (Western acculturated), kothis (men who tend to be the receptive male partner in anal and oral sex and typically have more effeminate mannerisms), panthis (men who tend to be the insertive male partner in anal and oral sex), and double deckers (men who are both receptive and insertive partners). While MSM may self-identify as kothi, the terms panthi and double-decker are generally given by kothis to their male partners based on their sexual roles. On the other hand, Hijras (Male to Female Transgender) voluntarily seek initiation into the Hijra community and in accordance to the community norms, customs and rituals which may vary from region to region. Sexual violence faced by Men who have Sex with Men (MSM) and Transgenders often mirrors intimate partner violence that women experience—the perpetrator uses violence as a way to maintain power and control over the victim, and often the victim takes on the more effeminate role in the relationships. Due to this, violence against MSMs and Transgenders can be considered a form of gender-based violence. Effective HIV prevention interventions and violence reduction programs face tremendous challenges as homosexuality is mostly a taboo subject in the Indian civil society and for the government. This exploratory study aims to contribute towards the nascent scholarship examining sexual violence within MSM community in India. The purpose of this exploratory study is to understand the nature intimate partner sexual violence faced by MSMs in New Delhi, India. New Delhi, is the national capital of India, witnessing a high HIV prevalence among MSMs and remains home to a large populace of the community (National AIDS Control Organization, 2011). To explore this phenomenon, the focus was to gather insights on 12 months and lifetime prevalence of unwanted sexual episodes faced by MSMs along with identification of risk factors which make them vulnerable towards intimate partner sexual violence. The data is collected at one site-Mitr Trust, which is a community based organization working to safeguard rights of MSMs in New Delhi, India. The Trust provides HIV prevention interventions to a sizable population of MSMs by implementing a government-funded Targeted Interventions project in New Delhi under the National AIDS Control Programme of the Ministry of Health & Family Welfare, Government of India. This study is an attempt to highlight the limitations of idealizing hegemonic masculinity and gender relations as heterosexual, while acknowledging the plurality of Indian masculism and advocating the need for intimate partner violence support services.
Do Different Crustal Rocks Creep and Respond the Same Way Under Stress?

Cecilia S.N. Cheung
Postdoctoral Researcher
Civil and Environmental Engineering; Geological Engineering

Understanding the long-term time-dependent behavior of rocks, or creep, is important in predicting long-term performance of various geomechanical engineering systems such as mines, waste disposals, and reservoirs. However due to the slow nature of the phenomenon, it is often difficult to gain micro-mechanical insights of the process from laboratory investigations and results are oftentimes described phenomenologically. Many experimental studies therefore either applied large differential loads relative to their rock strengths (e.g. >80%) or imposed high strain rates compared to those observed in nature, in order to promote the micromechanical process and expedite the creep deformation. Few studies attempt to perform creep experiments at in-situ load and strain rate conditions. Thus the application of laboratory findings to natural settings and extrapolation beyond laboratory time-scales remain challenging. Rock creep of different rock types are also typically studied independently. Since different rocks and minerals exhibit creep due to different physical processes, experiments are designed according to the rock/mineral type. It is rare that creep behavior of different rock types are compared under identical loading conditions. In minimization of variability among different equipment that may overshadow the variability of such behavior of our interest, we started a creep experiment where samples of different rock types (i.e. granite, sandstone, shale, limestone) are loaded in series by a dead weight load. Strain in the load-parallel and load-perpendicular direction is monitored by strain gauges to compare the volumetric response to the applied differential load. Taking advantage of the steady dead weight load, the creep deformation will be monitored for over several months and more. Deformation mechanics itself is a subject of broad interest among other engineering disciplines (Mechanical Engineering, Engineering Physics). Specifically, creep deformation has been studied extensively in other materials of interest (e.g. metals, piles) (e.g. Soil Mechanics, Material Science and Engineering). Not limited to experimental studies, but to theoretical and computational efforts (e.g. Finite Element Modeling, Discrete Element Modeling). Furthermore, our studies would immensely be benefitted with constructive ex-situ micro scale imaging resolving techniques (e.g. Scanning Electron Microscopy, Transmission Electron Microscopy, X-ray Microtomography). Therefore, we hope to establish new connections through the WARF Discovery Challenge.
Development of Human Pancreatic ECM Platforms for Promoting Endocrine Specification and Function from hPSCs

Daniel Tremmel
Graduate Student
Surgery – Transplantation; Cellular and Molecular Biology graduate program; Molecular Biosciences Training Grant program
Sara Dutton Sackett (surgery-transplantation)

Stem cell-based therapies, such as the differentiation of beta-cells from human pluripotent stem cells (hPSC), hold great potential for the treatment of Type I diabetes. Despite recent progress and improved in vitro differentiation protocols, emphasis on producing consistent physiological function in vitro is necessary in order to extend a stem cell-based therapy to patients with diabetes. Extracellular matrix (ECM) plays an important role during human embryonic development by actively regulating cell behavior through structural support and biochemical stimulation. Tissue-specific ECM has been proposed for use in a number of regenerative strategies for tissue and organ replacement. However, few studies have explored the potential of using human pancreatic ECM (P-ECM) to specifically enhance the differentiation of hPSCs into functional beta-cells. Through application of decellularization techniques to human pancreas we are able to generate acellular, 3D biological scaffolds competent for seeding with cells differentiated toward pancreatic cell lineages. We employed homogenization, perfusion and spin techniques using different nonionic and ionic detergents to systematically remove cellular content while retaining ECM components. The decellularized P-ECM was examined for preservation of ECM proteins, such as laminin, fibronectin and collagen, for glycosaminoglycan content and ultrastructure integrity by scanning electron microscopy. Using this information, we developed an optimized decellularization protocol for producing P-ECM scaffolds and hydrogels from human pancreatic tissue. The resultant P-ECM was processed to create a variety of platforms for seeding cells as an alternative to the 2D culture platforms presently used in most differentiation culture conditions. These P-ECM platforms include intact P-ECM slices, moldable sponge-like scaffolds, and hydrogel. These platforms introduce an amenable tissue culture environment, which recreates the native pancreas extracellular milieu and can be easily manipulated for use in a variety of culture and transplantation systems. We hypothesize that through incorporation of tissue-specific ECM into an in vitro culture system or transplantation models, we can enhance the production of functional beta-cells from hPSCs. These materials may also enable future tissue engineering strategies for treating diabetes.
Improving Active Delta-Tj Control of Switching Power Semiconductors

Timothy A. Polom
Graduate Student
Mechanical Engineering; Wisconsin Electric Machines and Power Electronics Consortium (WEMPEC)
Boru Wang (mechanical engineering and WEMPEC)

Switching power semiconductors enable power conversion supporting industrial and research applications, such as aircraft, renewable energy systems, and traction. The discrete components of semiconductors – e.g. direct-bond copper (DBC) substrates, silicon chips, and wire bonds – are generally comprised of dissimilar materials, and have mismatching coefficients of thermal expansion. Conduction and switching losses manifested as heat thus cause differential expansion during power cycles, resulting in high thermal-mechanical strain at interconnects. Spatial temperature gradients within and between the discrete components especially amplify the strain-related issues. Despite thermal-mechanical vulnerabilities, device lifetime targets are tens of years. Thus, regulating the thermal plant of power electronic systems is a prudent controls task. Specifically, analyses of semiconductor failure modes quantify how limitation of average and maximum junction temperature (Tj), and the load cyclic, temporal change in junction temperature (Delta-Tj) can increase the usable life of power semiconductors. The objective of this research is to add precision and dynamic capability to a controller of Tj and, especially, the Delta-Tj state to support reliability goals. This research leverages recently developed sensing methods to extract temperature information non-invasively and at high sensing bandwidth for closed-loop control, contrasting with sensing methods utilizing low bandwidth substrate temperature sensors and thermal models to estimate Tj and Delta-Tj. Using the high bandwidth Tj information, a region-based controller has been created to regulate values of Tj and Delta-Tj to remain within critical thresholds, reducing thermal-mechanical strain within power devices. The developed active thermal control methods adjust power semiconductor conduction and switching frequency to manipulate losses and reduce the magnitude of Delta-Tj during power cycling. A need for collaboration exists to allow the closed-loop system to achieve controls design goals without throttling manipulated electrical inputs and thus potentially degrading system-level performance. Additional degrees-of-freedom are sought which can facilitate adequately fast heat transfer to regulate Delta-Tj during power cycles found in realistic applications of power converters. For instance, it is anticipated that the developed control methods are compatible with state-of-the-art, device-level dynamic cooling methods, such as two-phase or direct impingement cooling, to further extend device lifetime. Power conversion literature documents control laws which manipulate electrical inputs for dynamic control of Delta-Tj, and shows steady-state applications of device-level dynamic cooling methods. The opportunity exists, however, to develop a controller which utilizes the desirable properties of both dynamic cooling methods and the developed loss manipulation Delta-Tj controller. The partitioning of controller tasks between a slower, more powerful dynamic cooling manipulated input and the faster, less powerful loss manipulation is a topic seen especially worthy of exploration. By achieving dynamic regulation of thermal cycling and strain without sacrificing system-level
performance, the described project aims to lead significant advances in the fields of controls and power electronics. These advances would help to decelerate mechanical fatigue, potentially removing reliability concern as reason not to fashion renewable energy conversion systems and, more generally, expedite electrification. Compared to traditional de-rating of power semiconductors, the described project also enables power converters to be operated at their thermal limitations, enhancing the utilization of silicon.

The Antidiabetic Drug Metformin Increases Pro-apoptotic Effect of TRAIL Therapy by Reducing X-Linked Inhibitor of Apoptosis Protein (XIAP) Levels in Triple-Negative Breast Cancer Cells

Dmitry Malin
Postdoctoral Researcher
Medicine
Elena Strekalova

Most metastatic tumors, such as triple negative breast cancer (TNBC) respond poorly to conventional chemotherapy. We have previously demonstrated that targeting TNF-related apoptosis-inducing ligand receptor-2 (TRAIL-R2) might be an effective pathway against metastatic TNBC. However, many TNBCs are resistant to TRAIL receptor agonists. Here we demonstrate that diabetes drug metformin, previously linked to preventing and treating several types of cancer, enhances sensitivity of TNBC cells to recombinant TRAIL and TRAIL-R2 agonistic humanized monoclonal antibody (lexatumumab)-induced apoptosis. We have demonstrated that combination of metformin with lexatumumab or TRAIL augments response to TRAIL therapy and reduce cancer cell viability via induction of apoptosis and inhibiting long-term survival of three different metastatic TNBC cell lines. Intriguingly, metformin treatment also sensitized transformed MCF10A-RasV12 cells, but not untransformed MCF10A-Vector cells, to TRAIL agonist therapy. This effect was associated with reduction of X-linked Inhibitor of Apoptosis Protein (XIAP) levels after metformin treatment. Similar to metformin treatment, inhibition of XIAP by small interfering RNA sensitized breast cancer cells to TRAIL-induced apoptosis. Moreover, metformin treatment in combination with lexatumumab more efficiently inhibited primary tumor growth and lung metastases in orthotopic model of TNBC. Overall, our results demonstrate that dietary methionine restriction in combination with targeting TRAIL-R2 receptor may be a good strategy to augment the antitumor effects of TRAIL receptor agonistic therapy and provide the foundation for a clinical trial combining dietary metformin and TRAIL-R2 agonists.
Graphene-Based Electrochemical Aptsensor for Pathogen Detection

Jiehao Guan
Graduate Student
Biological Systems Engineering
Rajesh Seenivasan (biological systems engineering); Yi-Cheng Wang (biological systems engineering)

The presence of pathogens such as bacteria, virus etc. in food, water, and other sources pose serious threat to our health. Electrochemical methods for the detection of pathogens are becoming increasingly popular due to their several inherent advantages such as fairly inexpensive, label free, high sensitivity, specificity, stability, and rapidity. The ability to integrate with both antibody-based immunoassay and DNA oligonucleotide (aptamer)-based aptasensor makes electrochemical detection even more promising. We employed differential pulse voltammetry (DPV) to detect Escherichia coli (E. coli) using designed aptamer sequence. This aptamer probe was designed by randomly selecting a 50 base sequence of single-stranded DNA oligonucleotides (Apt), which would specifically bind the target region between 971-1020 of 16S rRNA gene for E. coli strain 11775. The aptamer was immobilized on cysteine self-assembled gold nanoparticles (AuNPs) incorporated with graphene (Gr) films on the surface of screen-printed carbon working electrode (SPE). Gr films were grown by chemical vapor deposition on copper (Cu) foils. The surface of Gr-Cu foil was coated with poly-methyl methacrylate (PMMA), and Gr film was removed by dissolving Cu in 0.5 g/mL iron nitrate solution. Then the Gr film was transferred onto the SPE. During electrochemical detection, the specific binding between the aptamers and the target pathogens interferes with redox reaction of [Fe(CN)6]3−/4−, which is converted into corresponding electrical signal. When the target DNA is present in the test sample it specifically binds with aptamers on the SPE, which hinders the electron transfer reaction and the resulting change in the electrical signal is used to quantify the amount of target pathogen present. The pathogen detection process is fairly rapid, taking less than 15 min. The aptasensor could be regenerated by immersing it in 2 M NaCl solution for one hour.

Plunge Force Stability on Friction Stir Welding of Aluminum 6061_T6

Bandar Aloyaydi
Graduate Student
Mechanical Engineering

Friction stir welding (FSW) is defined as a solid state welding technology. Indeed, FSW is considered as environmentally friendly technology and has lower energy consumption compared to the arc welding. However, to achieve good weld quality, the heat input to the weld zone must be carefully controlled to maintain the physical and mechanical properties of
the welded material. Many researchers have investigated the relationship between the process input variables and process output variables in FSW. The input variables include the tool features (e.g. shoulder diameter, pin length, travel angle... etc.), which are not changeable during the welding process, and the process parameters (e.g. plunge depth, traverse speed, spindle speed), which can be manipulated during the welding. Experimentally, the process parameters have been shown to have a significant influence on the stability of the process output variables (e.g. plunge force, traverse force, and lateral force). The objective of this work is to experimentally determine the optimal process input parameters, focusing on the effects of traverse speed and spindle speed such that we stabilize and minimize the resulting plunge force while maintaining good quality weld. Stabilizing the plunge force is highly desirable for both force control applications and robotic friction stir welding in general.

#46

**Air Copula Constructions for Semicontinuous Longitudinal Data with Application to Insurance Experience Rating**

**Lu Yang**  
Graduate Student  
*Statistics*  
Peng Shi (risk and insurance)

In non-life insurance, insurers use experience rating to adjust premium to reflect the policyholder's previous claim experience. Performing prospective experience rating can be challenging when the claim distribution is complex. For instance, insurance claims are often semicontinuous in that a fraction of zeros is associated with an otherwise positive continuous outcome from a right-skewed and long-tailed distribution. Practitioners use credibility premium that is a special form of the shrinkage estimator in the longitudinal data framework. However, the linear predictor is not informative especially when the outcome follows a mixed distribution such as the insurance case. In this project, we introduce a mixed vine pair copula construction framework for modeling semicontinuous longitudinal claims. In the proposed framework, a two-component mixture regression is employed to accommodate the zero inflation and thick tails in claim distribution. The temporal dependence among repeated observations is modeled using a sequence of bivariate conditional copulas based on a mixed D-vine. We emphasize that the resulting predictive distribution allows insurers to incorporate past experience into future premiums in a nonlinear fashion and the classic linear predictor can be viewed as a nested case. In the application, we examine a unique claims data of government property insurance from the state of Wisconsin. Due to the discrepancies between claim and premium distributions, we employ an ordered Lorenz curve to evaluate the predictive performance. We show that the proposed approach offers substantial opportunities for separating risks and identifying profitable business when compared with alternative experience rating methods.
Electrochemical Imnosensing of Mycotoxins Fumonisin B1 and Deoxynivalenol

Lin Lu
Graduate Student
Biological Systems Engineering
Rajesh Seenivasan (biological systems engineering); Yi-Cheng Wang (biological systems engineering); Jae-hyuk Yu (bacteriology and genetics); Sundaram Gunasekaran (biological systems engineering)

Mycotoxins such as aflatoxin, deoxynivalenol (DON), fumonisin B1 (FB1), ochratoxin A, and zearalenone are a group of toxic secondary metabolites produced by certain fungi. They naturally contaminate foods and feeds, which lower the product quality, pose severe health risk to humans and animals, and cause profound economic losses worldwide. Due to the widespread prevalence of multiple mycotoxins in foods and feeds, a rapid and effective method for highly sensitive and selective detection of mycotoxins is an urgent need to ensure the safety of our food and feed supply. We developed an electrochemical immunosensing method for selective detection of FB1 and DON in a real matrix even when these mycotoxins co-exist. A disposable screen-printed carbon electrode (SPE) was used as the sensing platform. The working electrode part of SPE was modified by gold nanoparticles (AuNPs) and polypyrrole (PPy) and electrochemically reduced graphene oxide (ErGO) nanocomposite film for effective anti-toxin antibody immobilization, enhanced electrical conductivity, and biocompatibility. Specific antibodies were immobilized for capture target toxins and the electrochemical signal response was recorded for determining the toxin concentration. Under optimized test conditions, the limit of detection and linear range achieved for FB1 were 4.2 ppb and 0.2 to 4.5 ppm (%RSD=4.9%); and the corresponding values for DON were 8.6 ppb and 0.05 to 1 ppm (%RSD=5.7%). The sensor performance exhibited high sensitivity and low matrix interference when tested using extracts obtained from spiked corn samples. Hence, our electrochemical immunosensing scheme can be adopted for highly sensitive and rapid detection of multiple co-contaminant mycotoxins in food and feed products. This biosensing platform can be integrated with a microfluidic system to allow for low-cost detection and quantification of multiple mycotoxins simultaneously.

Correlation Between ACL Graft Geometry and Tibiofemoral Kinematics

Michael Vignos
Graduate Student
Mechanical Engineering
Jarred Kaiser (mechanical engineering); Geoffrey S. Baer (orthopedics and rehabilitation); Richard Kijowski (radiology); Darryl G. Thelen (mechanical engineering and biomedical engineering)
INTRODUCTION: The inability of ACL reconstruction (ACL-r) to restore normal knee kinematics, which leads to abnormal cartilage loading, is theorized to be a cause of the high incidence of osteoarthritis in these patients (>50% at long-term follow-up)[1,2]. Indeed, studies have shown greater external tibia rotation and progressive anterior translation in ACL-r knees[3]. It is important to assess how ACL graft placement may contribute to such asymmetries. Studies investigating relationships between graft geometry and knee mechanics have taken two approaches. The first is to use cadaveric experiments to study these relationships under simple loading conditions[4]. However, cadaver studies are unable to consider functional loading scenarios. A second approach is to compare joint mechanics in ACL-r subjects during locomotion[5]. However, with complex tasks it is difficult to determine which factor produces a change in mechanics, suggesting it may be preferable to study links between ACL-r geometry and kinematics using simpler tasks. In this study, we used static and dynamic MR imaging to investigate the relationship between ACL-r graft geometry and tibiofemoral kinematics during a knee flexion-extension task. We hypothesized that graft orientation would be the best predictor of bilateral differences in anterior tibia translation and external rotation. METHODS: We collected static, bilateral MR images of 12 subjects’ knees that underwent a primary, unilateral ACL-r (5M/7F, 24.8+/-4.4yrs). Each subject then lied supine in the MR scanner with their lower leg secured to a loading device. Subjects performed cyclic knee flexion for 5min against an inertial load at 0.5Hz while SPGR-VIPR images were collected[6]. Bone and ACL geometries were segmented for both knees from the static images. We then measured the area and location of the ACL attachments and the orientation of the ACL relative to the tibial plateau in the sagittal and frontal planes. Bilateral differences were computed as the reconstructed minus the contralateral value. Six degree of freedom tibiofemoral kinematics were measured using model-based tracking[6]. Bilateral differences in the tibiofemoral translations and rotations at peak flexion and in the translation and rotation ranges of motion were computed for each subject. Correlations between the bilateral differences in ACL geometry metrics and bilateral differences in kinematic metrics were computed (significance of p<0.05). RESULTS AND DISCUSSION: Bilateral differences in kinematics were most significantly correlated with sagittal plane ACL orientation. At peak knee flexion, an increase in sagittal plane orientation was positively correlated with anterior and medial tibia translation and internal rotation. Sagittal plane orientation was also correlated with internal rotation range of motion. This suggests a more vertically oriented graft may produce greater anterior-posterior and rotational laxity. The initial results in this study suggest that ACL geometry may be predictive of knee kinematics under in vivo loading conditions. However, increased subject numbers are needed to assess the robustness of the relationships observed. Further analysis is also needed to consider potential multifactorial interactions. REFERENCES: 1.Linden,M et al. Arthroscopy, 2008. 2.Andriacchi,TP et al. AnnBiomedEng, 2004 3.Tashman,S et al. AmJ SportsMed, 2004 4.Zavras,TD et al. KneeSurgSportsTraumatolArthro, 2005 5.Scanlan,SF et al. AmJ SportsMed, 2009 6.Kaiser,J et al. MRM 7, 2013.
Characterizing Objective Quality of Life and Normative Outcomes in Adults with Autism Spectrum Disorder: A Latent Class Exploratory Analysis

Lauren Bishop-Fitzpatrick
Postdoctoral Researcher

Waisman Center; Waisman T32 Training Program in Intellectual and Developmental Disabilities Research

Jinkuk Hong; Leann E. Smith; Renee A. Makuch; Jan S. Greenberg; Marsha R. Mailick

Background: There is little consensus about how best to assess normative outcomes and objective quality of life (QoL) in adults with autism spectrum disorder (ASD). Past outcome research has found that very few adults with ASD achieve the conventional markers of adulthood – becoming employed and self-supporting, living independently, developing a network of friends, contributing to the community. Some have called for a reconceptualization of QoL for adults with ASD, but little empirical research has been conducted that can inform such a reconceptualization or identify strategies for improving the QoL of adults with ASD.

Objectives: The current study aims to construct a unified definition and conceptualization of normative outcomes and objective QoL for adults with ASD by: (1) characterizing the heterogeneity of normative outcomes and objective QoL; and (2) identifying predictors of positive normative outcomes and good objective QoL.

Methods: 180 adults with ASD between the ages of 23.72 and 60.47 (M=34.06, SD=7.99) were drawn from a longitudinal study, the Adolescents and Adults with Autism Study. Three indicators of normative outcomes (employment, independent living, social engagement) and four indicators of objective QoL (physical health, quality of neighborhood, family contact, mental health issues) were assessed using a dichotomous scale and entered into an exploratory latent class analysis to determine groups of adults with ASD who were similar in their normative outcome and objective QoL profiles. A multinomial logistic regression then tested the association between intellectual disability (ID) status, age, daily living skills, autism symptomatology, executive functioning, maternal criticism, and maternal warmth. Results: Exploratory latent class analysis findings identified three discrete groups – Greater Dependence, Good Health, and Greater Independence – of adults with ASD in terms of normative outcomes and objective QoL. The Greater Independence group experienced the most favorable normative outcomes, while the Greater Dependence group experienced the worst. The Good Health and Greater Independence groups experienced the most favorable objective QoL while the Greater Dependence group experienced the worst. In addition, findings indicate that better daily living skills (Good Health vs. Greater Dependence: \( \exp(B)=1.110, p<.001 \); Greater Independence vs. Greater Dependence: \( \exp(B)=1.175, p<.001 \)) and better executive function (Good Health vs. Greater Dependence: \( \exp(B)=.966, p<.05 \); Good Health vs. Greater Independence: \( \exp(B)=.964, p<.10 \), and higher maternal warmth (Good Health vs. Greater Independence: \( \exp(B)=1.857, p=.022 \)) are associated with membership to outcome groups with better outcomes, when controlling for ID status, age, and autism symptomatology.

Conclusions: This research proposed a broad conceptualization of normative outcomes and objective QoL that takes into account many facets of life, is long-term in nature, and may be variable over time.
Our findings indicate that normative outcomes and objective QoL for adults with ASD may be quite nuanced; having good normative adult outcomes may not necessarily lead to good QoL, and vice versa. Notably, there appears to be a relatively strong association between better daily living skills and membership to a group with improved normative outcomes and objective QoL. Findings have important implications for future research and for interventions designed to improve outcomes and QoL in adults with ASD.

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Mapping the Myelin G-Ratio During Neurodevelopment

Douglas C. Dean III
Postdoctoral Researcher
Waismann Center

J. O’Muireachartaigh (neuroimaging, King’s College London, and Institute of Psychiatry, London); Brittany Travers (Waismann Center and kinesiology); Nagesh Adluru (Waismann Center); E. Croteau-Chonka (Advanced Baby Imaging Lab, Brown University); H. Dirks (Advanced Baby Imaging Lab, Brown University); S.C.L. Deoni (Advanced Baby Imaging Lab, Brown University, pediatric radiology, Children’s Hospital Colorado, and radiology, University of Colorado Denver)

Target Audience: Researchers interested in early brain maturation, myelination, white matter imaging and quantitative magnetic resonance imaging (MRI). Purpose: Myelination is a critical process of white matter development. While several neuroimaging techniques have been used to study white matter development, no prior studies have directly examine the microstructural properties of myelin. The myelin g-ratio, defined as the ratio of the inner axonal diameter to the total outer diameter of the fiber, may provide a novel contrast of the myeloarchitecture. Recently, models relating quantitative magnetization transfer and neurite orientation dispersion and density imaging (NODDI) parameters to the myelin g-ratio have emerged thereby providing a method to measure this fundamental property in vivo. In this work, we present an alternative approach, combining multicomponent relaxometry and NODDI data, to measure the myelin g-ratio. To highlight this method, we demonstrate myelin g-ratio measurements in typically developing children and, for the first time, provide developmental trajectories of myelin g-ratio. Methods: MRI Acquisition: 19 typically developing infants (102-2713 days, corrected for gestation) were imaged using a 12 channel head RF array on a Siemens Tim Trio scanner during non-sedated sleep. Multi-flip angle SPGR and bSSFP images were acquired and three-pool mcDESPOT post-processing was used to calculate myelin water fraction (VFM) parameter maps. A two-shell diffusion imaging protocol (b=700 s/mm2, b=2000 s/mm2, 30 diffusion encoding directions each) was also acquired and NODDI parameters were calculated using the available MATLAB toolbox. VFM maps and the volume fractions of the intra-cellular (vicvf) and isotropic compartments (vviso) were combined to calculate the myelin g-ratio. Mean VFM, vic, vicio, and g-ratio across white matter was calculated for each subject and plotted against the subject’s gestation-corrected age. Results: VFM appears to follow a sigmoidal trajectory, vicvf and vicio have a linear relationship, while the myelin g-ratio follows a decreasing logarthmic trajectory. Discussion: The observed changes in VFM and g-ratio reflect the progressive development of myelinated white matter. Theoretical models suggest that for maximal axonal efficiency, the optimal g-ratio of the developed brain is between 0.6-0.81. Here, calculated g-ratio values are larger, however, values appear to approach these conjectural values as the brain develops over time. Conclusion: In this work, we have described
an approach to quantifying the myelin g-ratio by combining the mcDESPOT and NODDI imaging techniques and for the first time have presented developmental trajectories of the myelin g-ratio during early childhood. This presented work provides an important step for understanding the developmental patterns of white matter microstructure and the myelin g-ratio. Future research will investigate the utility of the g-ratio as a biomarker of neurodevelopmental and neurological disorders as well explore the relationships between the myelin g-ratio and cognitive/behavioral outcome.

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**Automatic Stop in NICU Admit Order Set Lowers Antibiotic Exposure**

**Maria Corazon Astorga**  
Postdoctoral Researcher  
*Pediatrics: Fellowship Training Program, Neonatology*

Pamela J. Kling (pediatrics and Meriter UnityPoint Health Hospital); Ann M. Ebert (PharmD and Meriter UnityPoint Health Hospital); Steven C. Ebert (PharmD and Meriter UnityPoint Health Hospital); Kyle J. Piscitello (Meriter UnityPoint Health Hospital)

Background: Suspected neonatal sepsis is a common diagnosis in the NICU. Increased antibiotic exposure pose risks in both term and preterm infants. Standard practice includes treating neonates on rule out sepsis with antibiotics for 48 hrs pending results of cultures. Based on clinical rounding times, antibiotic dosing can exceed 48 hrs. As part of a stewardship initiative, a 48-hr automatic (auto) antibiotic stop was placed in the electronic admit order.  

Objective: Antibiotic orders 1 yr before and after institution of a 48-hr autostop was assessed. The admit order set included autostop times for Ampicillin (Amp) and Gentamicin (Gent). We hypothesized that antibiotic exposure per patient(pt), per patient(pt) days and overall unit exposure would decrease.  

Methods: Data on NICU patients receiving antibiotics were obtained from electronic medical records for 1 yr before and after the autostop initiative. Dosage data on Amp, Gent, Vancomycin (Vanc), Cefotaxime (Ceftx), Metronidazole (Metro) were analyzed. Clinical patient acuity measures were ascertained from Vermont Oxford Network (VON) data.  

Results: Early (0.6%) and late onset sepsis (0.9%) were uncommon in combined pre/post groups. Chorioamnionitis, early and late onset sepsis cases did not differ between pre- and post-autostop initiative. Only the number of surgical neonates decreased in the post-autostop group (p=0.048). Total doses given per pt or per pt days were lower post-autostop (p<0.0001). Amp and Gent doses were lower per pt and per pt days post-autostop (p<0.0001 on both). Other doses/pt or doses/pt days not in the autostop initiative also dropped: Vanc, Metro and Ceftx (p<0.0001 for all) with highest percentage drop seen in Vanc.  

Conclusion: Using antibiotics beyond 48 hrs is a common phenomenon in NICUs. Most antibiotic orders for presumed infection are placed on admission. It is common to wait for culture negativity before stopping antibiotics, a practice that may promote unnecessary extra doses. Despite unchanged pre-post acuity indicators, dramatically decreased antibiotic usage was observed. Fewer doses of Ceftx, Metro, Vanc were given post-autostop; we can surmise that this was because of provider awareness of the antibiotic stewardship initiative. Electronic order sets are valuable resources in execution of stewardship goals.
Cellulose Nanofibril (CNF)–Reduced Graphene Oxide (RGO)–Carbon Nanotube (CNT) Hybrid Aerogels for Highly Flexible and All-Solid-State Supercapacitors

Qifeng Zheng
Graduate Student

*Materials Science and Engineering; Wisconsin Institute for Discovery*

Zhiyong Cai (Forest Product Laboratory); Zhenqiang Ma (electrical engineering); Shaoqin Gong (biomedical engineering)

There is an ever-increasing demand for high-performance energy storage systems due to the rapidly growing market in wearable and portable electronics such as roll-up displays and electric paper. Lightweight, high power and energy density, high flexibility, and low cost, as well as environmental friendliness, are some principal requirements of these energy storage devices. A novel type of highly flexible and all-solid-state supercapacitor using cellulose nanofibril (CNF)–reduced graphene oxide (RGO)–carbon nanotube (CNT) hybrid aerogels as electrodes and H2SO4–poly(vinyl alcohol) gel as the electrolyte was developed and is reported here. These solid-state flexible supercapacitors were fabricated without any binders, current collectors, or electroactive additives. Due to the porous structure of the CNF/RGO/CNT aerogel electrodes, and the excellent electrolyte absorption properties of the CNFs present in the aerogel electrodes, the resulting flexible supercapacitors exhibited a specific capacitance of 252 F g-1 at a discharge current density of 0.5 A g-1, and remarkable cycle stability with more than 99.5% capacitance was retained after 1000 charge–discharge cycles at a current density of 1 A g-1. Furthermore, the supercapacitors also showed extremely high areal capacitance, areal power density, and energy density, which were 216 mF cm-2, 9.5 mW cm-2, and 28.4 μWh cm-2, respectively. The study reported here provides a simple and environmentally friendly method for fabricating porous electrode materials based on an abundant and sustainable natural polymer (i.e., CNF) and carbon materials, which possess desirable electrical and mechanical properties for flexible all-solid-state supercapacitor for energy storage.

Nile Red Functionalized Partially Oxidized Graphene Based Sensor for Selective Detection of Iron (III)

Omer Sadak
Graduate Student

*Materials Science Program; Biological Systems Engineering*

Ashok K. Sundramoorthy (biological systems engineering)

Nile Red (NR) is a red phenoazone dye that preferentially binds with Fe3+ over other cations such as Fe2+, Cu2+, Pb2+, Hg2+, Mn2+, Ni2+, Zn2+, Co2+ and Cd2+ in DMF/water solution.
at room temperature. We found that the color of NR in DMF/water solution changes from purple to dark brown with increasing Fe$^{3+}$ concentration. Thus, NR was employed as an indicator for the detection of Fe$^{3+}$ in the range of 30 - 1000 µM using UV-vis absorption spectroscopy with a limit of detection (LOD) of 24.9 nM. In addition, we prepared functionalized partially oxidized graphene (po-Gr) with NR. The NR treated po-Gr flakes (po-Gr-NR) were characterized by UV-vis spectroscopy, FT-IR, Raman, and FE-SEM. The po-Gr-NR film was deposited on glassy carbon electrode (GCE) surface (po-Gr-NR/GCE) and used for electrochemical measurement of Fe$^{3+}$. Using differential pulse voltammetry (DPV), Fe$^{3+}$ was detected from 35.6 nM to 34.2 µM in 0.05 M HCl + 0.05 M KCl at po-Gr-NR/GCE, with an LOD of 16.4 nM. A practical application of this sensor was tested by measuring Fe$^{3+}$ content in a red wine sample. The accuracy of the sensor was studied by Fe$^{3+}$ recovery analysis, which produced satisfactory results. Thus, we believe our sensor can serve either as a visual indicator for the detection of Fe$^{3+}$ or for selective and sensitive measurement of Fe$^{3+}$ in biological and environmental samples.

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**Interactions Between Residues in the Voltage-Sensor Pore Interface of the Shaker Potassium Channel Are Involved in the Energy Transduction from the Close to the Final Open State**

Ana I. Fernandez-Mariño

Postdoctoral Researcher

*Neurosciences; Biomolecular Chemistry*

Kevin Oelstrom (neurosciences and biomolecular chemistry); Baron Chanda (neurosciences and biomolecular chemistry)

In excitable cells, the final opening process of the voltage-gated ion channels (VGICs) depends on changes in the membrane potential, but also of the energy transmitted to the channel gate. Side chain interactions and backbone movements have been proposed, amongst others, as the responsible entities of the signal propagation from the voltage-sensors to the channel gate within this VGICs. However the precise molecular mechanisms underlying the final opening process, have been difficult to ascertain. Median voltage measurements were recently shown to be a useful and reliable parameter to estimate the charge-voltage relationship of VGICs. Those measurements can be used to derive the net free energy changes (DG$_{net}$) which is directly associated with their voltage-dependence of activation. The combination of this approach with mutant-cycle analysis allow us to identify the residues that are energetically coupled and subsequently, will contribute to the final activation process. In the present study, we systematically analyze paired residues in the interface between the voltage-sensor and the pore domain within the Shaker potassium channel. This approach will give more insight of how the initial signal propagates form one region to the other. We will discuss our results in the context of the electromechanical coupling in VGICs.
Machine Learning Methods As a Tool to Catalyse the Systems Biology Workflow

Sanjan T.P. Gupta
Graduate Student
Chemical and Biological Engineering
Prashant Kumar & Paul A. Adamczyk (chemical & biological engineering); Parmesh Ramanathan (electrical & computer engineering); Jennifer L. Reed (chemical biological engineering)

Functionalized Single-Walled Carbon Nanotube Based Electrochemical Sensor for Selective Detection of Caffeine

Ashok K. Sundramoorthy
Postdoctoral Researcher
Biological Systems Engineering

Single-walled carbon nanotubes (SWCNTs) are useful for preparing electrochemical sensing devices due to their extraordinary conductivity, large-specific surface area, and biocompatibility. When SWCNTs were covalently functionalized with 8-aminopyrene-1,3,6-trisulfonic acid (APTA), they became soluble in water without any other surfactants. The nature of binding between APTA and SWCNTs was confirmed as covalent using Raman, FT-IR, and UV-visible-near infrared (UV-Vis-NIR) spectroscopies. APTA-functionalized SWCNTs (APTA-f-SWCNTs) conducting thin films were prepared on polyethylene terephthalate (PET) substrate and glassy carbon electrode (GCE) to study their electrochemical properties. We found that the APTA-f-SWCNTs film had high electrocatalytic properties to oxidation of caffeine with relatively high peak current observed at +1.37 V. But, both pristine SWCNTs film and bare-GCE did not reduce the over potential of caffeine oxidation, which takes place at a higher potential of +1.47 V in 0.3 M HClO4 solution. To test the selectivity of the sensor, we added other common electroactive interferents such as dopamine (DA) and ascorbic acid (AA) into caffeine solution. Well-defined oxidation peaks (with high currents) of DA (+0.49 V), AA (+0.53 V) and caffeine (+1.47 V) were observed at APTA-f-SWCNTs film, but not with bare GCE. Thus, the APTA-f-SWCNTs film is useful for selective detection of caffeine in the presence of DA and AA. We also demonstrated selective detection of caffeine in fruit juices.
Gold Nanoparticles/Biopolymer-Based Visible Time-Temperature Indicator for Monitoring Quality of Foods and Other Perishable Biomaterials

Yi-Cheng Wang
Graduate Student

Biological Systems Engineering

Lin Lu (biological systems engineering); Jiehao Guan (biological systems engineering)

Foods that require time and temperature control for their safety are capable of supporting rapid growth of toxigenic and infectious microorganisms. These foods include a wide range of raw, processed, and cooked foods. In addition, high-value biomaterials such as stem cells, plasma, enzymes, antibodies etc., and pharmaceuticals are also perishable and sensitive to temperature. Therefore, it is critical to develop a cost-effective and user-friendly time-temperature indicator (TTI) to monitor the thermal history of the perishable foods and biomaterials. We employed green synthesis methods to fabricate a TTI using alginic acid, a biopolymer, and gold nanoparticles (AuNPs). The alginic acid-mediated AuNPs synthesis produced visible color change as the system was exposed to different temperatures and for varying durations, due to the change in localized surface plasmon resonance of the evolving AuNPs. The optimal TTI synthesis involves mixing hydrogen tetrachloroaurate with alginic acid solution at 90 °C for 2.5 min. When this TTIs is stored at different temperatures (0, 4, 23, and 40 °C), their colors changed with time from almost transparent to light grey; the color change becomes deep grey when stored at higher temperature. The TTIs prepared with different compositions exhibit different sensitivities to the same storage conditions. The TTIs were characterized by UV-vis spectroscopy and transmission electron microscopy to understand the potential behavior of the gold nanoparticles. Thus, the AuNPs/alginic acid TTIs could be designed as systems for real-time, continuous, and visual monitoring of thermal history and the attendant quality changes in foods, biomaterials, and pharmaceuticals.

MDM2 Inhibition Rescues Neurogenic and Cognitive Deficits in Fragile X Mice

Yue Li
Postdoctoral Researcher

Waisman Center; Neuroscience

Michael E. Stockton (Waisman Center); Ismat Bhuiyan (Waisman Center); Brian E. Eisinger (Waisman Center); Yu Gao (Waisman Center); Jessica L. Miller (Waisman Center); Anita Bhattacharyya (Waisman Center); Xinyu Zhao (Waisman Center and neuroscience)
Experimental Studies of Solidification Phenomenology in Fluoride Salt Mixtures

Jarett Kallas
Graduate Student
Nuclear Engineering; Engineering Physics

Louis J. Chapdelaine (nuclear engineering and engineering physics); Kazi K. Ahmed (nuclear engineering and engineering physics)

Fluoride salt mixtures have demonstrated excellent performance as nuclear heat transport fluids and are; therefore, being considered as primary coolants for advanced reactor designs like the Fluoride Salt High Temperature Reactor (FHR). The FHR is a Generation IV reactor concept which combines three major pre-existing technologies in a revolutionary design to maximize efficiency and safety while minimizing time required for licensure and deployment. A tristructural, isotropic pebble bed fuel design is combined with robust, high temperature molten salt cooling and high efficiency air turbines to capitalize on several inherent safety features, such as buoyancy driven flow at atmospheric pressure, to enable the economic design of passive safety systems. Coolant salt in the FHR operates in a bulk temperature range of 600°C to 700°C allowing for coupling with more efficient thermal conversion cycles inaccessible to water cooled reactors such as the Open, Air-Brayton Cycle. This power conversion cycle is also employed by modern, high efficiency natural gas plants, lending itself to the application of power peaking through natural gas co-firing. Overcooling transients resulting in localized freezing of the primary coolant are part of the design considerations unique to advanced coolant reactors and must be thoroughly investigated to prevent corrosion damage to the reactor and loss of coolant circulation. To date, little analysis of this class of transients has been performed and the computational methods and tools for modeling liquid-solid phase change in thermal-hydraulic system codes are limited. A fluoride salt freezing experiment is being conducted at University of Wisconsin Madison in order to investigate the solidification phenomena of fluoride salts. This experiment is to be conducted with eutectic salt mixtures LiF-BeF2 (FLiBe) as well as LiF-NaF-KF (FLiNaK). This study, along with scaling analysis, will investigate whether simulant fluids can be successfully used to reproduce overcooling transients of FLiBe, at reduced temperature and scale with non-toxic fluids. The results of modeling the freezing front propagation in fluoride-salt cooled systems will also be presented. The experimental data are to serve as a validation problem for the modeling. The models are then used to quantify scaling distortion for the proposed simulant fluids. One of the solidification phenomena of interest is supercooling. Some indication that FLiBe experiences significant supercooling below its melting point has been observed, but never quantified in controlled experiments. Literature about supercooling in other fluids suggests that variables such as cooling rate and sample volume may have a measurable effect on supercooling. Cooling rate will be varied in the solidification experiment by controlling the ambient bulk temperature and thus the heat flux from the sample to determine the quantitative relationship on FLiBe supercooling. Prior to the bench-scale experiment, initial studies were performed using differential scanning calorimetry (DSC). The DSC measurements indicate that this is not an appropriate tool for the study of supercooling transients, though useful in the determination of temperature-dependent thermo-physical properties of molten salt mixtures.
Small Molecule-Based Epigenome Editing to Reverse Friedreich’s Ataxia

Graham Erwin
Graduate Student
Biochemistry
Matthew P. Grieshop (biochemistry)

The lethal neurodegenerative disease Friedreich’s ataxia is caused by a hyperexpansion of AAG repeats in the first intron of the frataxin (FXN) gene. This expansion leads to ~80-90% transcriptional repression and subsequent reduced protein levels. The repeat expansion induces a repressive chromatin state at the FXN locus that blocks RNA polymerase from elongating through the gene. Because the repeat expansion occurs in the intron, patients with Friedreich’s ataxia express normal FXN protein, albeit at reduced levels. Thus, chemical approaches to re-activate frataxin expression would be extremely promising. To directly address the reduced FXN expression, we designed and synthesized a new class of small molecule-base epigenome editors. These bifunctional molecules composed of a DNA-binding polyamide that targets AAG repeats, and a ligand that recruits a chromatin remodeler, potently and selectively activate FXN expression in cell lines derived from patients. Furthermore, this molecule fails to activate expression in a genetically matched cell line from a healthy individual who has a normal number of AAG repeats, providing further evidence for on-target mechanism of action. Importantly, a control molecule, designed to target an unrelated DNA sequence, failed to activate FXN expression. To our knowledge, this molecule is by far the most potent activator of FXN levels reported to date. These results suggest that small molecules that selectively edit the epigenome may be useful therapeutics to treat Friedreich’s ataxia.
Development of Nylon-3 Polymers Targeting Clostridium Difficile

Leslie Rank
Graduate Student
Chemistry
Naomi Biok (chemistry); Emily Woods (microbiology and molecular genetics); Sarah Anderson (microbiology and molecular genetics); Shonna McBride (microbiology and immunology); Samuel H. Gellman (chemistry)

Clostridium difficile colonizes the gastrointestinal tract of humans and other animals, resulting in severe toxin-mediated intestinal disease, known as C. difficile infection (CDI). It is estimated that there are ~500,000 cases and roughly 20,000 deaths due to CDI in US hospitals alone per year (1). C. difficile is resistant to a wide range of antibiotics (1). Treatment of CDI is further complicated when one considers that C. difficile exists in various morphological stages within the host GI tract, and these morphological stages have different susceptibilities to antibiotics (1). C. difficile spores enter the body via the fecal-oral route and germinate within the intestine to vegetative cells, after which a subset of cells revert back to spores to be secreted by the host. Current therapies target the vegetative form of C. difficile. The research described herein will discuss the development of a nontraditional antimicrobial therapy for C. difficile based on synthetic nylon-3 copolymers. Nylon-3 copolymers have a polyamide backbone, with subunits derived from beta-amino acids, offering increased biocompatibility and proteolytic stability (2). Nylon-3 copolymers have previously been developed with Minimum Inhibitory Concentrations (MIC) for vegetative cells and Outgrowth Inhibition Concentrations (OIC) for spores comparable to the host-defense peptide LL-37 (2). This poster will discuss our efforts to design new nylon-3 copolymers with enhanced potency and ability to target spore viability with low toxicity towards mammalian cells. 1. Rupnik, M.; Wilcox, M. H.; Gerding, D. N. Nature Reviews Microbiology 2009, 7 (7), 526-536. 2. Liu, R. H.; Suarez, J. M.; Weisblum, B.; Gellman, S. H.; McBride, S. M. Journal of the American Chemical Society 2014, 136 (41), 14498-14504.

Single-Cell, Real-Time Detection of Antimicrobial Peptide Action on Live Escherichia Coli

Zhilin Yang
Graduate Student
Chemistry
Heejun Choi

Antimicrobial peptides (AMPs) are an important bacterial population regulator in the host of all living organisms. Understanding bacteria-AMPs interaction will help to understand bacterial imbalance causing human chronic inflammatory diseases. In addition, unlike small molecule antibiotics, AMPs are multifunctional and less susceptible to develop bacterial resistance,
serving as a platform to design a new class of peptide-based antibiotics. To obtain the complete picture of AMP action, I will use single-cell, time-lapse quantitative fluorescence microscopy with various fluorescent indicators and E. coli model system to directly observe cellular responses to AMPs attack. These include outer and cytoplasmic membrane permeabilization, and reactive oxygen species (ROS) formation. Compared with bulk assays, single-cell, time-lapse studies reveal cell response heterogeneity and enable correlation of different phenomena in space and time, rendering clues of interactions between different AMP mechanisms. For the newly discovered ROS mechanism, so far, we already discovered that for some synthetic and natural AMPs, such as CM15, polymer, LL-37 and Melittin, the killing and growth-halting activity are oxygen-sensitive, and can induce a burst of ROS in the E. coli. Existing results indicate that Electron Transport Chain (ETC) is important for the generation of ROS, and the cytochrome oxidase bo3 in the ETC seems to be important for some AMPs to form ROS in the E. coli and contribute to the lethality of AMPs.

Massive Parallel Texts Comparison of Harry Potter

Hong Yan

Graduate Student

East Asian Languages and Literature; Linguistics

Xin Li (linguistics)

This project is a parallel text analysis of Harry Potter series, which aims at discovering the different phonological properties of languages and culture variances behind the language by comparing translations of proper names in the texts of different languages. Parallel texts are texts in different languages that can be considered translational equivalent. Parallel texts have played an essential role in philology. In the era of big data, this method can be applied to the typological research with massively parallel texts available. By using "Massively parallel text" (MPT), we can build up a database of existing translated texts of Harry Potter. These texts represent written language, and mostly standardized registers. Through the process of translation, there can be inference from the source language. The current project combines the method of parallel texts comparison and big data analysis, which is the first project in the field of linguistics including all available translations texts in different languages. The results will reveal the inner mechanism of human languages. The most popular modern linguistic theory Generative Grammar claims that there is a universal grammar (UG) across all human languages, which suggests that although languages differ at the surface level, they have the same mechanism underneath superficial language properties. However, the evidence for or against this argument is limited because it is almost impossible to exhaust all languages by human intelligence. With the assistance of programming, we can make use of MPT to analyze large data sets and find either positive or negative evidence of UG, and eventually draw a big picture of human languages. The database can be further used by researchers in different fields, such as ethnology, anthropology, and sociology for other related research interests.
A Dual-Selective Sensor for Iron in Different Oxidation States

Kari Jordan
Graduate Student

Biological Systems Engineering

Sundaram Gunasekaran (biological systems engineering); Ashok K. SundraMoorthy (biological systems engineering); Bhagya S. Premkumar (SRM University)

We have developed a dual-selective sensor for the detection of iron at different oxidation states (Fe2+ and Fe3+). The sensor is composed from reduced graphene oxide (rGO) dispersed into a poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS) polymer that is then deposited as a hybrid film onto a glassy carbon electrode (GCE) surface. The intercalation of rGO sheets in PEDOT:PSS film shows high electrocatalytic activity for Fe2+/Fe3+ redox reaction. The structure of the rGO/PEDOT:PSS film was evaluated by Raman spectroscopy, UV-Vis-NIR spectroscopy and scanning electron microscopy. Using amperometry, with controlled applied potential, we determined that the sensor responds linearly to Fe2+ from 20 to 833 µM (at 0.6 V) and to Fe3+ from 1 to 833 µM (at 0.4 V) in 0.5 M KCl + 0.05 M HCl. At its current rGO/PEDOT:PSS film thickness, detection level is in the micromolar concentration range. The signal was tested to confirm that it is not disrupted by other select common interfering metals and organics such as Cu2+, Co2+, Ag+, Pb2+, Cd2+, Zn2+, Mn2+, Ni2+, Hg2+, L-glycine, L-cysteine, L-tyrosine, glucose, KCN, guanine, uric acid, xanthan, salicylate, tartrazine, and naphthol yellow. Successful measurements of Fe2+ and Fe3+ contents in a red wine sample and iron supplement tablets with this sensor show potential for its wide use. We also demonstrated the use of this sensor for determining the oxidation kinetics of Fe2+ using hydrogen peroxide and measuring Fe3+ by differential pulse voltammetry (DPV).

Efficient Methods for Finding All Power Flow Solutions

Zachary Charles
Graduate Student

Mathematics

Nigel Boston (mathematics and electrical and computer engineering); Alisha Zachariah (mathematics); Dan Wu (electrical and computer engineering)

Power flow study is a numerical analysis of the flow of electric power in a power system. The principal information (or “solution”) obtained from studying the power flow problem is the magnitude and phase angle of the voltage at each bus, and the real and reactive power flowing in each line. Many methods have been developed to find a single high-voltage power flow solutions. However, we are often interested in finding all power flow solutions. Two common applications for which the ability to find multiple solutions is needed, are the quick
considerable research was conducted in the 1980s on finding all the solutions. Theoretical bounds on the possible number of solutions were found (and conservatively high), and practical methods for calculating the solutions were sought. Research needs waned after 1993 when a numerically efficient algorithm to find all the solutions to the load flow equations was published that utilized topological properties of the solution set. In 2013 Lesieutre and Molzahn demonstrated that this algorithm did not capture every solution, and interest in this topic has been renewed. The challenge is to design a practical algorithm to calculate all the solutions. General methods for finding all the solutions to equations are impractical, and can only be used on very small system models. An efficient solution to this problem would have significant practical applications. Suboptimal operation of power systems costs billions annually, while the annual cost of power interruptions can cost up to $79 billion annually. Both of these are addressed by the ability to solve power flow equations efficiently. We propose a novel projective homotopy continuation method, based on existing continuation methods for finding roots, to find all power flow solutions. The combination of work in the fields of algebraic geometry and power systems, two areas with historically little overlap, is vital to this our project. The physical realities of the problem require expertise in the area of power flow study, while the mathematical work allows us to foresee and avoid pitfalls encountered by previous algorithms. Our method uses techniques from algebraic geometry to guarantee convergence to all solutions and should eliminate the issues in the 1993 algorithm. The method should also scale according to the actual number of solutions instead of commonly used large upper bounds, making it more computationally feasible than other methods. We also propose methods to find all power flow solutions when the associated power network forms a tree. These methods use the topology of the network to solve the system efficiently by reducing it to systems of linear equations and real univariate polynomials. By utilizing the special structure of the equations we differentiate our work from existing techniques and hope to improve our ability to solve the power flow problem.

# 66

Novel Drug Target for Cancer Metastasis: The Exosome Release Pathway

Scott Messenger
Postdoctoral Researcher

Biochemistry

Steve Bruinsma (biochemistry); SangSu Woo (biochemistry)

Development and homeostasis in multi-cellular organisms is dependent on proper intercellular communication. Dysregulation of intercellular signaling is an underlying factor in cancer progression and successful anti-cancer therapies depend on our understanding of cancer cell communication with other cells. Exosomes are a recently identified form of communication that uses small lipid bilayer membrane vesicles to transfer biologically active material between cells. Exosome formation allows specific incorporation of cytoplasmic DNA, RNA, proteins and lipids, to enter the exosome which maintain topological organization thereby directly delivering this material to the target cell cytoplasm. Cancer cells use exosomes during tumor progression in numerous ways: oncogenes loaded into exosomes are transferred to healthy tissue; exosomes
travel to distant organs to make the environment suitable for colonization; the extracellular matrix surrounding a tumor is degraded by exosomes allowing initiation of metastasis; and exosomes stop the immune system from killing cancer cells. Blocking exosome release is crucial to stopping the spread of cancer however; the underlying mechanisms for exosome release are poorly classified. Here we provide evidence of a novel exosome release pathway that is highly active in breast, pancreatic and lung carcinoma cell lines. We further identify a specific inhibitor to block exosome release. The small lipid bilayer exosomes are found inside a large lipid bilayer vesicle called the multivesicular body (MVB). MVB fusion with the plasma membrane (exocytosis) releases exosomes to the environment. The mechanisms of regulated exocytosis are conserved across all vesicle types where the coiled-coil containing SNARE-proteins interact to provide the energy to fuse lipid bilayer membranes in a process stimulated by increases in intracellular Ca2+. Munc13-4 is a Ca2+-dependent SNARE- and membrane-binding protein required for Ca2+-dependent secretory granule exocytosis in hematopoietic secretory cells. Data from the cBioPortal, showed Munc13-4 is overexpressed in breast, pancreatic, and lung cancers. Elevation of intracellular Ca2+ increased exosome release by 5 fold in breast, pancreatic and lung carcinoma cell lines. shRNA down-regulation of Munc13-4 fully inhibited exosome release in these cell lines and prevented extracellular matrix degradation in breast cancer cells. A recently identified small molecule inhibitor of Munc13-4 blocked exosome release similar to depletion of Munc13-4. Our results identify a novel Ca2+-stimulated exosome release pathway as a potential therapeutic target to block tumor progression and metastasis. Future collaborative work is required to determine if the chemical structure of the small molecule inhibitor can be altered to increase potency, test the pharmacological properties of this small molecule in cancer models and determine the molecular make-up of Ca2+-stimulated exosomes.

#67

A Map of DNA Methylation Transferase Enzyme Expression in the Mouse Prostate During Development and in Response to Prostate Injury

Diya Binoy Joseph

Graduate Student

Comparative Biosciences; Cellular and Molecular Biology Graduate Program

Kimberly Keil (comparative biosciences); Lisa Abler (comparative biosciences)

DNA methylation is a chemical reaction catalyzed by DNA methyltransferase enzymes (DNMTs). DNA methylation patterns are heritable, but also affected by an individual’s environment and age. Abnormal DNA methylation patterns have been implicated in several diseases including schizophrenia, cancer, obesity and diabetes. We are examining the role of DNA methylation in prostate proliferative growth, which in conjunction with male hormones has been linked to prostate cancer and benign hyperplasia. Understanding the underlying cause of these diseases is important because existing therapies are not effective. We used fluorescently labeled antibodies to visualize DNMT1 and DNMT3A in actively dividing cells under three experimental conditions that trigger prostate proliferative growth: prostate development, castration, and inflammation. DNMTs in the fetal prostate were concentrated in
actively dividing cells at the tips of prostatic ducts. Castration (depletes male hormone concentrations needed for prostate cell survival) reduced DNMT abundance while treatment of castrated mice with testosterone increased the number of proliferating prostate cells and restored DNMT expression. Prostate inflammation (linked to urinary complications of benign prostate disease and to prostate cancer in men) increased mouse prostate cell proliferation and DNMT1 and DNMT3A abundance. Our results support a role for male hormones in controlling prostate DNMT abundance and identify prostate inflammation as a factor that potentially alters prostate DNA methylation. Whether altered prostate DNA methylation underlies benign hyperplasia and prostate cancer, and whether preventing these alterations will be therapeutically beneficial, are areas of future investigation. Supported by NIH GRANT R01DK099328.

#68

Remaining Useful Life Prediction Based on the Mixed Effects Model with Mixture Prior Distribution

Raed Al Kontar  
Graduate Student  
Industrial Engineering; Statistics

Junbo Son (industrial and systems engineering); Chaitanya Sankavaram (General Motors Research & Development); Yilu Zhang (General Motors Research & Development); Xinyu Du (General Motors Research & Development)

Modern engineering systems are gradually becoming more reliable and pre-mature failure has become quite rare. As a result, degradation signal data used for prognosis are often imbalanced as most units are reliable and only few tend to fail at early stages of their life cycle. Such imbalanced data may hinder accurate remaining useful life (RUL) prediction especially in terms of detecting pre-mature failures as early as possible. This aspect is detrimental for developing cost effective condition-based maintenance strategies. In this paper, we propose a degradation signal-based RUL prediction method to address the imbalance issue in the data. The advantageous features of the proposed method are demonstrated through a numerical study as well as a case study with real world data in the application to the RUL prediction of automotive lead-acid batteries.

#69

Investigating the Mechanism of Dynein-Based Axonal MT Polarity

Sihui Yang  
Graduate Student  
Biochemistry; CMB (Cell Molecular Biology program)

The establishment and maintenance of a polarized microtubule (MT) cytoskeleton is essential for neuronal polarity. In fly neurons, axonal microtubules are oriented uniformly plus-end-distal
relative to the cell body, whereas microtubules in dendrites are largely minus-end-distal. The microtubule minus-end directed motor dynein and its cofactor NudE are required for the uniform axonal microtubule polarity. The mechanism, however, is not understood, and our current work aims to elucidate how dynein controls axonal microtubule polarity using a combination of genetics, genome engineering, and live-imaging approaches.

The Just and Merciful Community

Lai Wong
Graduate Student

Educational Psychology; Wisconsin Collaborative Education Research Network (the Network); School of Medicine & Public Health

Matthew Hirshberg (educational psychology); Linghua Jiang (educational psychology); Jichan Kim (educational psychology)

Can we thrive together as a just and merciful community? Too often groups operate only from the virtue of justice, which can be too cold and uncaring. In contrast, groups in a just and merciful community tend to be of service to others because they operate on both the principles of fairness and mercy. Mercy involves love, kindness, compassion, generosity, forgiveness and benevolence. As mercy recognizes persons as ends in and of themselves, mercy balances fairness and humanizes justice. A just and merciful community is needed in our world today because many of us are confronted with bullying, violence, social stereotyping, and as well as other conflicts due to differences across abilities, languages, cultures, incomes, social status, race, gender, sexual orientation, religion and so forth. The importance of cultivating a just and merciful community is apparent to Dr. Robert Enright as he and his research teams, for the last 30 years, conducted the social scientific study of forgiveness in different parts of the world, including contentious regions such as Belfast, Northern Ireland and Milwaukee, Wisconsin. In 2000, a research study was launched to examine how the new concept of a just and merciful community would influence school climate and disciplines. The study involved a structured, open-ended survey with about 69 school teachers in mid-west region. In 2015-6, the study is repeated to examine the evolution of the concept. While the 2015-6 study is still in process, the survey in 2000 shows a promising future for the just and merciful school community even though schools (84% of survey participants) operate under a justice model. There were high levels of support (84%) for more mercy in schools with a commonly held belief that including more mercy in schools would improve the school environment. Many participants (66%) agreed that student learning and development would be enhanced. As they said, students could feel empowered (#73), start afresh (#42), become self-regulated (#35) and motivated to improve (#47 & 42). As a teacher participant (#13) who worked in a just and merciful school community said, “Kids love it here. They can fail, learn and grow.” Being less self-centered, more respectful and cooperative, students would have a better balance and happiness in life in a just and merciful community (#2, #45 & #53). There are still a whole lot to explore for the application and implementation of a just and merciful community. While we hope to learn more as the latest research is completed, we realize that a just and merciful community goes beyond the boundary of a school. Indeed it can manifest to the extent as we are all willing as a community such as a neighborhood, an interest group, a
cultural group, a city, a county, and so forth. Therefore we would like to invite other disciplines to explore the concept of a just and merciful community together with us. Would you join us to explore the just and merciful community together?

#71

**Engineering Biomass-Degrading Microbial Consortia Using Synthetic Ecology Principles**

Camila Carlos  
Postdoctoral Researcher  
*Bacteriology*  
Gina R. Lewin (bacteriology)

Synthetic ecology is a branch of synthetic biology in which the main approach is to manipulate microbial communities, by combining different populations to achieve a complex function. Synthetic ecology is a promising approach for improving biotechnological processes, such as the conversion of lignocellulosic biomass to biofuels. Production of lignocellulosic biofuels requires the deconstruction of plant cell wall polymers (cellulose, hemicellulose, pectin and lignin) into fermentable monomers and high-value co-products. Microbial species co-exist in stable and robust communities in most natural environments. The mechanisms of co-existence of species in wild communities can be used as design principles for engineering stable microbial consortia for target applications. We established 20 microbial consortia, derived from four distinct environmental sources, through consecutive weekly transfers in minimal media with filter paper, AFEX-treated switchgrass, Cu-AHP treated-poplar, FMT-5 zip lignin poplar mutant, or WT-zip lignin poplar as the sole carbon source. We isolated and identified around 50 bacteria from those microbial consortia, of which 11 isolates presented cellulolytic activity. Six of the cellulolytic isolates belong to the Cellulomonas genus, while five belong to the Cellulosimicrobium genus, both belonging to the Actinobacteria phylum. In addition, we are currently characterizing the ability of the 50 isolates to grow on hemicellulose components, such as arabinan, mannan and xylan, and also pectin and lignin, in order to select the best degraders of each component. Moreover, we are using a culture-independent approach by sequencing the 16S rRNA gene using MiSeq Illumina to characterize the community structure of each consortia, and by using co-occurrence networks to investigate ecological interactions among the community members, such as competition and synergy. We will conduct quantitative assays to compare the efficiency of biomass degradation between synthetic and wild type communities. Our goal is to design stable synthetic microbial consortia able to deconstruct lignocellulosic plant biomass by using the information from the ecological interaction. The knowledge generated in this study can be used for the development of a microbial consortium able to integrate all the biologically mediated transformations necessary to convert lignocellulosic biomass to biofuels, an approach called consolidated bioprocessing.
Use of SIM to Evaluate Resident Performance During Complex Scenarios in Urinary Catheter Insertion

Jay Nathwani
Postdoctoral Researcher
Surgery
Bridget O'Connell-Long (medicine); Rebecca Ray (surgery); Rebekah Fiers (surgery); Shannon DiMarco (surgery)

Introduction: Urinary catheter insertion is a common procedure performed in hospitals. Improper catheterization can lead to unnecessary catheter associated urinary tract infections and urethral trauma, increasing patient morbidity. To prevent such complications, guidelines were created by the American College of Surgeons on how to insert and troubleshoot urinary catheters. As nurses have an increasing responsibility for catheter placement, resident responsibility has shifted to more complex scenarios. This study examines the clinical decision making skills of surgical residents during simulated urinary catheter scenarios. We hypothesize that during urinary catheterization, residents will make inconsistent decisions relating to catheter choices and clinical presentations. Methods: Forty-five general surgery residents (PGY 2-4) in Midwest training programs were presented with three of four urinary catheter scenarios. Scenarios varied in difficulty: A) female trauma patient with a bladder injury, B) female patient with labial constriction, C) male patient with complete obstruction of the urinary tract, and D) male patient with benign prostatic hypertrophy with partial blockage of the urinary tract. Residents were allowed 15 minutes to complete three scenarios. Scenario A was performed by all residents. Residents were presented with five different catheter choices and the option to consult an on-call Urologist. A Chi Squared test was performed to examine the relation between initial and subsequent catheter choices and to evaluate for consistency of decision making for each scenario. Results: All (N=45) residents performed scenario A; 45% performed scenario B; 67% performed scenario C and 82% performed scenario D. For scenario A-C, the 16 French Foley catheter was the most common choice (38%, 54%, 50%, p's<.001) for the first catheter. For scenario D, the 16 French Coude was the most common choice (37%, p<.01). Variation in first choice of catheters is shown in Table 1. Residents were most likely to be successful in achieving urine output in the initial catheterization attempt (p<.001). Chi-Square analyses showed no relationship between residents’ first and subsequent catheter choices for each scenario (p’s >.05). Conclusion: Evaluation of clinical decision making shows initial catheter choice may have been deliberate based on patient background, as evidenced by the most popular choice in scenario D. Analyses of subsequent choices in each of the catheterization models reveal inconsistent decisions. These findings suggest a lack of competence or inadequate training in clinical decision making with regards to urinary catheter choices in complex scenarios.
Sigma Receptor Ligands Inhibit Kv2.1 Currents Independently of Sigma Receptors

Yingmei Fu
Postdoctoral Researcher
Surgery

Sigma-1 and Sigma-2 receptors are potential drug targets for treatment of cancer and neuronal diseases. Previous reports show that Sigma receptors modulate the activity of multiple channels via direct interactions. We investigated possible Sigma receptor modulation of Kv2.1, a K+ channel abundant in retinal photoreceptors, by using established Sigma receptor ligands. Surprisingly, Sigma-1 antagonists inhibited Kv2.1 currents in both wild type and Sigma-1 knockout HEK293 cells that we engineered using the CRISPR/Cas9 technology. Moreover, Sigma-2 agonists inhibited Kv2.1 in Sigma-1 knockout cells as well, but this action was not blocked by Sigma-2 antagonists. These results indicate that the Kv2.1-inhibiting function of these Sigma ligands is not Sigma receptor dependent, and suggest a direct effect of these ligands on the Kv2.1 channel.

Poplar as a Model for Dissecting Early Mycorrhizal Signaling in Woody Perennials

Kevin R. Cope
Graduate Student
Bacteriology
Cellular and Molecular Biology Program

Two ecologically and economically important mycorrhizal symbioses are arbuscular mycorrhizae (AM) and ectomycorrhizae (ECM). Significant advances have been made in elucidating the molecular mechanisms controlling mutual recognition between AM fungi and their host plants. In contrast, our understanding of these mechanisms in ECM associations is still limited. In AM associations, the fungus releases various signaling molecules that are recognized by the host plant, including lipochitooligosaccharides (LCOs) and chitooligosaccharides (COs). We hypothesized that similar signaling molecules are released by ECM fungi and that they too are perceived by plant roots leading to changes in root architecture and gene expression. We performed root hair deformation assays with Medicago truncatula and Vicia sativa to test for the presence of LCOs in the exudates of several ECM fungi. For all ECM fungal species tested, root hair deformations occurred similar to those induced by purified LCOs. We therefore tested the ability of various types of LCOs to regulate lateral root formation in hybrid poplar (Populus tremula x alba). Non-sulfated LCOs induced significantly more lateral roots per length of primary root compared to sulfated LCOs and the negative control. We therefore performed an RNA sequencing experiment on poplar roots treated with isolated fungal signals (LCOs and COs) as well as AM and multiple ECM fungal
exudates to identify similar transcriptomic responses. Some similarities existed between treatments thus suggesting a potential role for LCOs as signaling molecules in ECM associations. Future work will focus on determining if ECM fungal exudates trigger nuclear calcium spiking in poplar roots, a characteristic response during AM symbiosis in other plant species. We will also test if this response is dependent on genes involved in the common symbiotic signaling pathway.

#75

**DHEA Targeted Delivery Protect the Retina from NMDA Induced Neuronal Injury Using CTB Conjugated Nanoparticle**

Lei Zhao  
Postdoctoral Researcher  
*Surgery*

Retinal ganglion cell death is a characteristic of glaucoma. Although the underlying mechanism is not completely known, activation of NMDA receptor, a glutamate receptor subtype, is involved in neuronal excitotoxicity mechanisms and thought to be an underlying mechanism of glaucoma induced neuronal cell death. DHEA and its related pharmacological compound have been demonstrated to reduce axonal loss and preserve ganglion cell function in glaucoma model. However, one key challenge is how to deliver the drugs specific to retinal ganglion cells to exhibit its protective effect. In this study, using NMDA induced retinal ganglion cell death as a model system, we optimize CTB conjugated Nanoparticle as vehicle to targeted deliver DHEA to retinal ganglion cell layer. Compare to non-targeted nanoparticle, after 14 days of injection, targeted nanoparticle still exhibits protective effect to retinal ganglion cell. Furthermore, using targeted nanoparticle, lower dose of drug is need and longer term of availability is observed, in compare to DHEA drug only.

#76

**Genetic Analysis of the Periaqueductal Gray: Genes Linked to Protein Breakdown Show Altered Expression in the Pink1-/- Rat Model of Parkinson Disease**

Cindi Kelm-Nelson  
Postdoctoral Researcher  
*Surgery, Division of Otolaryngology-Head and Neck Surgery; Communication Sciences and Disorders*  
Michelle R. Ciucci (surgery, Division of Otolaryngology-Head and Neck Surgery, communication sciences and disorders and Neuroscience Training Program)
Voice disorders in Parkinson disease (PD) manifest in the early stages of the disease, occur in 90% of individuals, and have significant negative impacts on patient quality of life. PD pathology is widespread including not only the hallmark central dopamine loss, but early-onset neuropathology including alpha-synuclein aggregation. However, the underlying pathology that contributes to early-onset vocal dysfunction is poorly understood. We use a genetic rat model of PD, Pink1 knockout (−/−), to model early-onset vocal deficits. Rats produce social 50-kHz ultrasonic vocalizations and our recent data show that male Pink1 −/− rats exhibit early, progressive deficits compared to non-affected wildtype (WT). Within the brainstem, the periaqueductal gray (PAG) is responsive during the production of vocalizations and is hypothesized to be involved in the central coordination of vocalizations as well as integration of motivational state. Our recent data show significant aggregations in insoluble alpha-synuclein within the PAG, suggesting a possible link to the observed vocalization deficits. To gain insight into the mechanism related to parkinsonian vocal deficits, we investigated changes in genetic expression within the PAG. At 8 months of age, microdissected brain tissue from Pink1 −/− rats and age-matched WT controls was collected for (A) microarray analysis and (B) real time qPCR. A targeted RNA sample was used in an Affymetrix WT Plus Expression Gene Microarray (Rattus norvegicus RaGene 2.0 ST Hybridization). Data was extracted and processed using Affymetrix Command Console version 4.0.0.1567G Expression Software and the dataset was normalized using Robust Multi-Array Analysis (RMA) and processed with BioConductor package Limma. qPCR mean Ct values for each sample were transformed via the Pfaffl Method to yield individual relative expression normalized to reference genes. Our data demonstrate that Pink1 −/− rats have mRNA expression levels of alpha-synuclein comparable to WT. However, Pink1 −/− rats have significantly decreased levels of Atp13a2, a transmembrane lysosomal P5-type ATPase suggesting a potential mechanism for the observed abnormal aggregation. We found no difference in the expression of glucocerebrosidase (Gba) or the CASP8 and FADD-like apoptosis regulator (Cflar). Further, we show that mRNA expression levels of dopaminergic markers including TH, D1 and D2 receptor as well as GABA signaling markers including GABA-A and glutamate decarboxylase 2 (GAD2) do not differ between genotypes. However, we found that glutamate decarboxylase 1 (GAD1) is significantly reduced in this PD model suggesting a possible disruption of neurotransmission within the PAG. These results are the first to suggest that alpha-synuclein aggregation in this model is not a result of increased transcription, but rather a deficit in the breakdown and clearance, and that the observed vocal deficits may be related to impaired neural transmission. Our results suggest novel therapeutic pathways, including the lysosomal degradation pathway, which can be used in understanding the pathogenesis of and improving treatment for vocal dysfunction PD.

#77

Blocking BET Epigenetic Readers Rescues Retinal Degeneration

Jun Li
Postdoctoral Researcher
Surgery

Introduction: Retinitis pigmentosa (RP) is a group of retinal degenerative diseases resulting from rod and cone photoreceptor cell death and is a major cause of blindness in adults. Recent
reports show that JQ1, a specific Bromo and Extra-Terminal (BET) family inhibitor, potently suppresses inflammatory responses. In this study, we investigated the effect of JQ1 on retinal inflammation and photoreceptor apoptosis in RD10 mice, an animal model of RP. Method: Postnatal (P14) RD10 mice were intravitreally injected with JQ1 (2mM) and DMSO (control). Eyeballs were collected 10 days after injection. Retinal degeneration was determined by counting photoreceptor nuclei; inflammation was evaluated by immunostaining of Iba-1 and qPCR of inflammatory cytokines; apoptosis was measured by TUNEL and caspase-glo; retinal function was determined by ERG. Results: JQ1 reduced retinal inflammation and apoptosis, and preserved retinal morphology and function in RD10 mice compared to WT mice. Conclusion: Epigenetic drug JQ1 rescues photoreceptor cells from degeneration in RD10 mice, likely by suppressing inflammation.

#79

Cooling Cows for Less with Biofeedback Controls

Ian Atkins
Graduate Student
Biological Systems Engineering
Mario Mondaca (medical sciences)

When cows produce more heat than they can dissipate, they suffer from heat stress, which reduces productivity and threatens animal health. While advancements in genetics, nutrition, and management have increased milk production, heat stress is being exacerbated because high-producing dairy cows also generate more heat. To allow for this high level of productivity and also to allow for the expansion of the dairy industry into extremely hot climates, many dairy producers have built facilities that provide evaporative cooling and high air velocity. Operating these cow cooling systems, however, requires additional costs and resource consumption. For example in Saudi Arabia, a recent study measured water use for cooling at nearly 100 gallons per cow per day. Yet, current cow cooling systems are typically controlled using only temperature, which falls short of optimal for several reasons. One is that additional environmental parameters such as humidity, air velocity and solar radiation also affect a cow’s level of heat stress. Another is that the susceptibility of a herd to heat stress depends greatly on its productivity, as well as breed, age, and a slew of other factors. One approach to more optimal cow cooling system control is to measure a greater number of environmental variables and more thoroughly quantify the factors that influence an individual cow’s susceptibility to heat stress. A much simpler approach is to directly monitor the cow. As cows become heat stressed, they display well-documented physiological responses, including increased body, skin, and udder temperatures, as well as increased respiration rates. We propose using this ‘biofeedback’ to determine when cooling systems should be engaged and to what degree, allowing the system to effectively cool the cows, but not waste resources. Remote sensors will monitor a number of representative cows, and one or several physiological responses will be chosen for cooling system control depending on the reliability, practicality, and cost of their measurement.
Force, Adhesion, and Motion in the Cell Monolayer

Aashrith Koundinya Saraswathibhatla
Graduate Student
Engineering Physics

Cell monolayers play a pivotal role in many biological processes of multicellular organisms such as wound healing, cancer metastasis, and embryogenesis. Research in collective cell migration has intrigued not only biologists but also engineers because of the complex connections between intercellular signaling, active force generation, and mechanical interaction with the surrounding environment. Together, these complex connections cause each cell to apply forces to the substrate beneath it and to its neighbors. These cell-substrate and cell-cell forces generate cellular motion. Interestingly, the collective motion is characterized by the presence of back-and-forth phase transitions between an unjammed fluid-like layer, in which cells move freely with respect to their neighbors, and a jammed solid-like layer, in which cells lose the freedom of motion. This apparent phase transition is similar to the physics of soft glassy materials such as colloidal suspensions, foams, and polymers near to a glass-transition. Intrigued by this complex behavior, we and others have developed various experimental and computational tools to investigate the underlying physical mechanisms. Cell displacements and velocities are measured by applying image correlation techniques to time lapse images captured by optical microscopy. The principle of force equilibrium is used to calculate the cell-substrate and cell-cell forces. Force equilibrium is also employed to estimate the intercellular adhesion energies and the phase—solid-like or fluid-like—caused by these energy changes. We now look to apply these tools in studying the role of mechanics of the monolayer in filling a damaged area during wound healing, in directional migration during an organ development, and in permeability of endothelial barriers.

When Does Accurate Encoding of the Equal Sign Help? The Role of Power Dynamics in Collaboration

Sarah Brown
Graduate Student
Psychology; Interdisciplinary training program in educational sciences
José Fransisco Gutiérrez (mathematics education)

We report a qualitative analysis of elementary school students engaged in collaborative problem solving involving mathematical equivalence tasks. We build on previous research showing that students often use strategies based on either operational or relational understandings of the equal sign. We closely analyze three cases and identify nuanced aspects of the social interaction that influence whether and how students develop and use operational or relational strategies toward a final solution. Students’ demonstrated understandings of the equal sign during collaboration aligned with those identified in past research. We argue that a
social-mathematical power dynamic was co-constructed in each of the dyads, and the ways students navigated that dynamic affected the quality of individual engagement and therefore learning.

#82

**Preliminary Results of an Ongoing Randomized Clinical Trial Evaluating No-Treatment of Culture Negative Cases of Clinical Mastitis on Somatic Cell Count and Milk Production**

**Maria J. Fuenzalida**

Graduate Student  
*Dairy Science*

Cecilia Baumberger (dairy science); Pamela L. Ruegg (dairy science)

Mastitis is an intramammary infection and is the most common and costly disease affecting dairy cows. Mastitis can present with clinical or subclinical symptoms. Clinical mastitis (CM) is the most frequent occurring disease of dairy cows and the most common reason antibiotics are used. The majority of antimicrobial treatments of CM are not targeted based on etiology which increases societal concerns about antimicrobial usage in dairy farms. One method to reduce and guide antimicrobial usage is on-farm culture (OFC) programs which are based on use of selective media to arrive at limited microbial diagnoses that allows targeted use of antimicrobial therapy. The objective of this paper is to report initial results based on the first 40 cases enrolled in an on-going randomized clinical trial study evaluating non-treatment of culture negative cases of CM. Preliminary results of quarter-level somatic cell count (SCC) and milk production of treated and non-treated non-severe cases of culture-negative CM during a follow-up period of 12 weeks are presented. Non-severe CM cases (i.e., abnormal milk with or without signs of inflammation in the udder) are eligible to be enrolled in the study. Severe cases of CM (i.e., fever, off-feed, depressed) are excluded. Duplicate milk samples are collected from affected quarters to inoculate an OFC biplate. After the inoculation of the biplate, the remaining milk in that sample is preserved using bronopol for SCC analysis. Twenty-four hours after inoculation, plates are observed for growth and culture-negative cases are randomly assigned to either treatment (n=19) or control (n=21). Cases that are culture positive are not enrolled. Aseptic duplicate quarter milk samples are collected 1, 2, 4, 9 and 12 weeks after enrollment. Daily milk production data is collected until 90 d post CM. Repeated measures analyses was performed to analyze SCC quarter-level changes and daily milk production through time between treatment groups. No significant differences in quarter-level SCC were observed between treated and not-treated culture-negative cases from day of CM to 12 weeks after enrollment. After occurrence of culture-negative cases of CM, SCC rapidly decreased and remained low in both treated and non-treated cases. No significant differences were observed in daily milk yield between treated and not-treated culture-negative cases from day of CM until 90 days after enrollment. Similar trends in SCC quarter-level between treated and not-treated cases of CM emphasize the importance of OFC to reduce antimicrobial treatment in non-severe culture-negative cases. These results should be interpreted cautiously as they represent a small number of initial cases in the on-going study. However, if these preliminary results are validated at the end of the study, they provide evidence that
antimicrobial therapy is not justified for treatment of most cases of non-severe culture-negative clinical mastitis. Moreover, these preliminary results could result in a 30% reduction in antimicrobial used for treatment of clinical mastitis on dairy farms.

#83

**Workload Balancing - Staffing Ratio Analysis for Primary Care Redesign**

Xiang Zhong  
Graduate Student  
*Industrial and Systems Engineering*

Xiang Zhong (industrial and systems engineering); Hyo Kyung Lee (industrial and systems engineering); Jingshan Li (industrial and systems engineering); Molly Williams (University of Wisconsin Medical Foundation); Jeffery Sleet (University of Wisconsin Medical Foundation); Richard Welnick (University of Wisconsin Medical Foundation); Lori Hoschild (University of Wisconsin Medical Foundation); Sally Kraft (Dartmouth-Hitchcock)

The objective of this work is to investigate the optimal staffing composition of chief care provider (e.g., physician (MD)) and support care provider (e.g., medical assistant (MA)) under various task assignment settings. Specifically, we investigate the effects of workload shifting and identify the proper ratio between MAs and MDs to achieve effective and efficient service level. Based on an analytical framework characterizing care providers' activities during patients' primary care clinic visits, analytical investigation and numerical experiments were conducted. The results articulate that the optimal staffing ratio is achieved when the workloads of MDs and MAs are balanced. To validate the findings under general primary care clinic settings, discrete event simulation models were developed and extensive experiments were carried out. The sensitivity study elucidates that the balanced-workload optimality is not affected by system variations such as different patient volumes, and arrival and service time distributions.

#84

**Spatially Explicit Life Cycle Optimization of Cellulosic Ethanol Supply Base: Case Study in South Central Wisconsin**

Mahmoud A. Sharara  
Postdoctoral Researcher  
*Biological Systems Engineering; Wisconsin Energy Institute*

Keith Cronin (Wisconsin Energy Institute); Troy Runge (biological systems engineering)

Utilization of crop residue and grasses in ethanol production can help achieve strategic, economic, and environmental objectives; namely, the diversification of fuel/energy base, boosting local economy through supporting new production sectors, in addition to maintaining ecological sustainability and resilience. To achieve these goals, however, a precise evaluation
of the biomass supply base is necessary to ensure process viability and avoid unintended negative impacts to ecosystems, and to related production systems. Economic and environmental sustainability metrics, such as life cycle analysis (LCA), are useful tools to evaluate the impacts of current or future products or processes. This study presents a decision-making methodology to assist stakeholders in evaluating supply base choices in cellulosic ethanol production using life cycle optimization. The proposed methodology consists of an optimization routine that combines economic costs with the environmental impacts of supplying biomass to cellulosic ethanol facilities. The environmental impacts considered were: global warming potential, eutrophication, soil erosion, and soil carbon loss. The optimization outputs represent the supply base decisions, i.e., fields to harvest, storage facility locations, and pretreatment technologies, which minimize the total environmental impacts and costs incurred in meeting a certain biomass demand level. To demonstrate this methodology, a case study was developed to model corn stover utilization towards cellulosic ethanol, with the supply base limited to a 4-County region in South Central Wisconsin: Dane, Sauk, Iowa, and Columbia Counties. Spatially explicit yields and environmental impacts of biomass production were modeled using the Environmental Policy Integrated Climate (EPIC) model. Transportation cost and environmental impacts were modeled using road and railway transportation models. Biomass storage and pretreatment facilities were modeled to represent capacity and transportation accessibility limitations, as well as costs and environmental impacts. It is our goal to adapt and expand this tool, in the next stages, to incorporate multiple biomass sources, as well as larger supply base scenarios, i.e., multi-State, and multi-Biorefinery. We plan to present this methodology as a nucleus for current and future collaboration, between agronomists, soil scientists, engineers, mathematicians and sustainability experts. The outcome will be a robust decision-making tool to inform investments and policies towards the sustainable development of cellulosic biofuels and bio-products.

#85

Pharmacological Targeting of Receptor Interacting Kinases (RIPKs) in Necrotic-Eye Diseases

Kartik Gupta
Graduate Student
Surgery
Qiwei Wang (surgery); Noel Phan (surgery); Kirsti Walker (surgery)

Death of cells in the retina is the major pathological feature associated with the loss of vision in multiple genetic, traumatic and infectious diseases, including retinitis pigmentosa, retinal-detachment and herpes simplex virus-induced acute retinal necrosis, respectively. Consistent with the observations in other tissues, the trauma and infection-related cell death pathway-necroptosis- is also found to be activated in these retinal diseases. Recent studies have discovered the molecular cascade that controls this form of programmed necrosis (necroptosis) which, by the virtue of being regulated, is an attractive target for pharmacological therapy. The key regulators in this pathway include members of the receptor interacting kinases (RIPs/RIPKs)—RIP1 and RIP3. While small molecule inhibitors to RIP1 have been instrumental in probing the role in necroptosis in multiple disease models, targeting RIP3 is believed to have broader applications. However, the few known inhibitors for RIP3 are not suitable for in-vivo
applications. To identify new RIP3 inhibitors, we screened three small-molecule chemical libraries comprising of 1,141 kinase inhibitors using MOVAS cells that were induced to undergo necroptosis, and also performed a virtual screen for the compounds with highest affinity for RIP3. We identified a group of compounds represented by C9 which was subsequently found to bind to the kinase domain of RIP3 with a K(d) of 130nM. Further, we identified that C9 was minimally cytotoxic compared to the previously reported RIP3 inhibitors, as well as more efficacious at preventing necroptosis in a cell-culture model of mouse SMC cells. Finally, using the novel technique of cellular thermal shift assay (CETSA) that identifies drug-interactions in-vivo in cells, we observed interesting pharmacodynamics and target engagement attributes of this compound. Preliminary data from the lab demonstrates that the drug also ameliorates other diseases associated with necroptosis namely abdominal aortic aneurysm in a rodent model. As a logical extension to our findings, we surmise a beneficial role of C9 compounds or its analogs in treating the diseases associated with retinal-necrosis and want to test this in a rodent model of retinal-necrosis. Results from these pre-clinical studies will be essential for harnessing the translational potential of the new RIP3 inhibitors.

#86

Physical Activity at the Recommended Level May Be Protective Against Brain Atrophy in Adults at Risk for Alzheimer’s Disease: Collaborative Findings from Kinesiology and the ADRC

Ryan J. Dougherty
Graduate Student

Kinesiology; Wisconsin Alzheimer’s Disease Research Center

Stephanie A. Schultz; Elizabeth A. Boots; Dorothy F. Edwards; Sterling C. Johnson

Within the department of Kinesiology the Exercise Psychology laboratory is focused on understanding the psychobiology of exercise with the primary goal of determining the relationships between physical activity (PA) behaviors and cognitive health. Investigators at the Wisconsin Alzheimer’s Disease Research Center (ADRC) conduct basic, clinical, and behavioral research with the long-term goal of finding a way to cure and possibly prevent Alzheimer’s disease (AD). Through a collaborative effort, the department of Kinesiology and the ADRC are working together to explore the effects of exercise and PA on cognitive health in individuals with either genetic and/or familial risk for AD. Alzheimer’s disease affects over 5 million Americans and that number is projected to nearly triple by 2050. A hallmark feature of AD is brain atrophy, which typically precedes the onset of symptoms and is a predictor of future cognitive impairment. Physical activity may mitigate brain atrophy as it has been positively associated with brain volume in older adults. However, the optimal dose of PA remains unknown. The Department of Health and Human Services along with the American College of Sports Medicine and the American Heart Association recommends accumulating 150 minutes of moderate-intensity, or 75 minutes of vigorous-intensity, or an equivalent combination of moderate and vigorous physical activity (MVPA) per week to promote health in all adults. Whether the current physical activity recommendations (PAR) impart substantive brain health
benefit is not currently known. The temporal lobes atrophy with age, and this atrophy can predict cognitive decline to AD. Thus, the present study investigated temporal lobe volumetric differences between older adults strictly categorized as having met PAR and those who were insufficiently active. Ninety-one enrollees from the Wisconsin Registry for Alzheimer’s Prevention (WRAP) participated in this study. The WRAP is a longitudinal registry composed of more than 1500 cognitively healthy adults at-risk for AD. Participants were a triaxial accelerometer on their hip for seven consecutive days to quantify their PA behaviors. Participants were instructed to wear the device during all waking hours, with the exception of when showering, swimming, or bathing. Participants also underwent a T-1 anatomical magnetic resonance imaging scan to determine temporal lobe volumes. Participants were categorized as either having met current PAR or not based on the recommendation of 150 minutes of MVPA per week. Results demonstrated that older adults who met PAR possessed significantly greater inferior ($\eta^2_p = .050$) and anterior ($\eta^2_p = .055$) temporal lobe volumes compared to those who did not ($p < .05$). Using an objective assessment of PA behaviors, this study suggests that weekly PA at or above PAR is not only beneficial for overall health, it may be an important way for older adults to preserve temporal lobe volume using natural, affordable methods that are safe and accessible.

#87

A Bayesian Unfolding of the Cosmic-Ray Energy Spectrum Measured with HAWC

Zigfried Hampel-Arias
Graduate Student
Physics

We present results and methods of a measurement of the all-particle cosmic-ray energy spectrum above 10 TeV with the High-Altitude Water Cherenkov (HAWC) Observatory. HAWC is a ground based air shower array deployed on the slopes of Volcán Sierra Negra in the state of Puebla, México. It comprises 300 large light-tight water tanks covering an area of 20,000 square meters. Each tank is instrumented with four photomultipliers to detect particles from extensive air showers produced by cosmic rays upon entering the Earth's atmosphere. HAWC is sensitive to hadronic air showers in the TeV energy range, allowing for a detailed measurement of the cosmic-ray flux from 10 TeV - 1 PeV. The primary cosmic-ray energy is estimated with a maximum likelihood approach, using the particle density as a function of distance to the shower core. The true energy distribution is then measured with an unfolding procedure that uses Bayes’ theorem to get the best estimate of the true distribution in an iterative fashion, using the posterior from the previous iteration as the prior for the next. We will report on the energy resolution of the technique and the results of the unfolding.
Single-Molecule Tracking of Elongation Factor P in Live E. coli Cells

Sonisilpa Mohapatra
Graduate Student
Chemistry; Physical Chemistry
Heejun Choi (Janelia Research Campus)

Efficient peptidyl transfer during the translation elongation is required for proper cell growth. Due to the low reactivity of secondary amines, the rate of proline incorporation into an elongating peptide is slow, especially when there is a stretch of prolines. In E. coli, this process is accelerated by elongation factor P (EF-P), which associates with the exit site of the ribosome when it is empty. Since polyproline stretches are more frequent in metabolic enzymes, transporters, and regulatory transcription factors, the interaction between EF-P and ribosomes is critical for efficient cell growth. Our lab specializes in performing super-resolution microscopy, a non-invasive technique on live bacterial cells. We are interested in understanding the spatial and temporal organization of Elongation Factor P using super-resolution microscopy. To begin with, we have constructed a K-12 strain whose chromosome expresses EF-P with the photoswitchable fluorescent protein mEos2 appended to the C-terminus. The growth rate of this strain is comparable to a standard K-12 strain confirming the viability of the strain. Using single-particle tracking by photoactivation-localization microscopy (spt-PALM), we are able to study the subcellular diffusion and spatial distribution of EF-P in live cells at high resolution. Tracking of single molecules of EF-P-mEos2 yields a mean diffusion coefficient of 2.5 μm²/s. The spatial distribution shows evidence of ribosome association. To further augment their association with ribosomes, we pretreated the cells with translation halting drug, Chloramphenicol and transcription halting drug, Rifampicin in separate experiments. These experiments have been instrumental in further confirming association of EF-P to ribosome. In vitro experiments have shown that K34 in EF-P is extremely essential for action of EF-P. We have constructed a K-12 strain with a plasmid expressing EF-P (K34A) to investigate the role of K34 in the activity of EF-P. The spatial distribution of EF-P (K34A) shows no obvious ribosome association. Tracking of single molecules of EF-P (K34A)-mEos2 yields a mean diffusion coefficient of 3.6 μm²/s which is about 1.5 times higher than wild-type EF-P. The increased diffusion coefficient hints towards reduced ribosome association and therefore, the role of K34 in association of EF-P to ribosomes. We are also interested in quantifying the time scale of wild type EF-P association to ribosomes. We have performed experiments at different tracking speeds, the results of which will be discussed. Interestingly, at 30 ms tracking speed, wild type EF-P shows very strong membrane association and we are yet to understand the possible reasons for this.
Industrial Streptomyces Strains Engineered for Heterologous Secretion of Lignocellulolytic Enzymes Acquire Enhanced Capabilities to Consume Lignocellulosic Materials

Robert J. Stankey
Postdoctoral Researcher
Bacteriology; Great Lakes Bioenergy Research Center
Emily T. Beebe (biochemistry); Evelyn Wndt-Pienkowski (bacteriology); Adam J. Book (bacteriology); Brian G. Fox (biochemistry); Cameron R. Currie (bacteriology)

NoFAQ: Synthesizing Command Repairs from Examples
Michael Vaughn
Graduate Student
Computer Science

The command-line provides a robust and powerful text-based interface for interacting with computer systems. However, command-line tools are confusing and hard to use for novice programmers due to their cryptic error messages and documentation that is frequently either extremely complex or non-existent. Inexperienced users often resort to online help forums for finding corrections to their buggy commands, but have a hard time in searching precisely for posts that are relevant to their problem and then applying the suggested solutions in their context. We present the tool NOFAQ that uses a set of repair rules to suggest possible fixes when users write buggy commands that trigger commonly occurring errors. The rules are expressed in a language called FIXIT and each rule pattern matches against the user’s buggy command and the error message and uses them to produce a possible fixed command. Our main contribution is an algorithm for synthesizing FIXIT rules from examples of buggy and repaired commands. This algorithm allows developers to insert more rules in NOFAQ without having to manually encode them. For each command bug, a user simply needs to present several examples of the incorrectly used command, the corresponding error message, and the fixed command. From these examples, NOFAQ is able to synthesize a candidate repair rule in under a second. We present the evaluation of NOFAQ on 92 benchmark problems and show that NOFAQ is able to instantly synthesize rules for 81 benchmark problems in real time and using just 2 input-output examples for each rule.
High-Throughput Machine Learning from Electronic Health Records

Ross Kleiman
Graduate Student

*Computer Sciences; CIBM - Computation and Informatics in Biology and Medicine; CPCP - Center for Predictive Computational Phenotyping*

Paul Bennett (computer sciences, CIBM and CPCP); Peggy Peissig (Marshfield Clinic and CPCP); Scott Hebbring (Marshfield Clinic); Richard Berg (Marshfield Clinic); Michael Caldwell (Marshfield Clinic); David Page (computer sciences, CIBM and CPCP)

The use of Electronic Health Record (EHR) systems has increased dramatically in recent years. This vast digitization of medical data allows for new ways to predict diseases that were not possible with paper charts. In our research, we develop thousands of predictive classifiers across ICD-9 diagnoses codes present in the Marshfield Clinic EHR system. This pan-diagnostic approach yields inference on the health landscape of both individual patients and patient populations. In order to achieve results at such a large breadth, this work leverages the vast computational power of the HTCondor high throughput computing platform developed at UW-Madison. Our results showcase predictive performance across diagnoses at both 1 and 6 month prediction windows. Additionally, we perform a prospective study that simulates the efficacy of this predictive system in practice. The results of our retrospective study are shown both quantitatively, as predictive accuracies, as well as qualitatively by clustering ICD-9 codes based on their predictive outputs. Furthermore, we discuss the potential for the creation of a patient education tool that leverages the predictive models to provide individual patient risk profiles spanning the ICD-9 diagnosis code hierarchy. This work supports an increase in the use of decision support systems in the healthcare setting. Instead of only targeting a small number of well understood diseases, this research shows machine learning techniques can be used to help predict the broad spectrum of diagnoses a patient may receive. Acknowledgements: The authors acknowledge support of the NLM training grant: 5T15LM007359 and the NIH BD2K grant: U54 AI117924.

Influenza Virus Hijacks Human Protein Kinase C-Delta to Phosphorylate Viral Nucleoprotein and Regulate Viral RNA Synthesis

Arindam Mondal
Postdoctoral Researcher

*Medical Microbiology and Immunology*

Anthony Dawson (medical microbiology and immunology); Gregory Potts (chemistry); Josh Coon (chemistry); Andrew Mehle (medical microbiology and immunology)
Influenza virus infections are one of the most widely spread diseases, causing significant health and economic burdens to the world population on an annual basis. Upon infection, viruses must avoid host immune responses while at the same time exploiting host co-factors for their own benefit. Targeting these virus:host interactions could serve as a potent approach to develop new anti-viral therapeutics against these deadly human pathogens. The influenza virus nucleoprotein (NP) is the major structural component of the ribonucleoprotein complex (RNP) that performs transcription and replicates the viral genome. NP expressed alone binds cellular RNA non-specifically and oligomerizes spontaneously into non-productive aggregates, yet it is selectively incorporated into viral RNPs during infection. We have recently shown that reversible phosphorylation of NP regulates its oligomerization and controls its assembly into viral RNPs, thereby playing a critical role in virus replication. Influenza virus does not encode a kinase; therefore it must rely on cellular enzymes to perform this regulatory function. Here we identify protein kinase C (PKC) as the host kinase that phospho-regulates NP oligomerization. We showed that isozymes PKCδ, PKCη and PKCβ2 specifically phosphorylated NP and their overexpression suppressed NP:NP interactions in cells, consistent with the phospho-regulation of NP oligomerization. Whereas NP is the target of several PKC isozymes, our data reveal that a specific subunit in the viral polymerase selectively binds PKCδ and recruit it to NP for phosphorylation during infection. We verified the role of PKC by generating CRISPR-mediated PKCδ knockout cells. Quantitative mass spectrometric analysis showed that phosphorylation of the regulatory positions in NP was selectively reduced in the knockout cell lines. The knockout cells supported normal levels of primary transcription, but exhibited defects during genome replication, a step in the viral life cycle dependent upon controlled NP oligomerization and de novo RNP assembly. Moreover, replication of multiple strains of influenza virus was impaired in the knockout cells, implicating PKCδ as a master regulator of NP phosphorylation, RNP formation and virus propagation. Overall, this work establishes PKC as a proviral host factor and hence a new therapeutic target for the treatment of influenza virus infections.

Healthy Communities Evaluation: Reflections from Co-researchers with Intellectual Disabilities on the Benefits and Importance of Inclusive Research

Brittany St. John
Graduate Student
*Occupational Therapy Program, Kinesiology; Waisman Center*
Iulia Mihaila (human development and family studies)

An emerging body of literature has called on researchers to expand practices to overcome established power differentials between researchers and participants. A variety of inclusive research methodologies are on the rise to address this concern, specifically the participation of research subjects as co-researching partners. Research and disability communities are advocating for flexibility and accommodation in methodologies for various levels of participation on the part of co-researchers with disabilities. Despite the call for inclusion of co-researchers, there remains a large literature gap detailing their actual participation, identifying the supports needed to ensure their success, and exploring how their participation impacts
them individually as well as the research outcomes. An in-depth exploration of the inclusion of three co-researchers with intellectual disabilities in a qualitative study of the Special Olympics Healthy Communities programs is presented. Co-researchers with intellectual disabilities completed an individualized training program on the research objectives and process. Each co-researcher then administered interviews to peer athletes with the support of a research team member. Using a case-study approach, the integration of these individuals on the research team will be described, including their individual training, overall research processes, and the supports needed to allow for their successful collection of interview data collection with peer athletes. In addition, their reflection on participation will be shared to provide a unique look at how the presence of co-researchers changed the research process as well as how it impacted them personally. Each participating co-researcher was interviewed about their experience and perceptions of the need for inclusive research. A thematic analysis was applied to the interviews with four main themes emerging: the importance of the shared experience of disability, value and contribution of co-researcher participation, support and preparation necessary, and individual skills learned by the co-researchers. The strengths and challenges of implementing this methodology will be discussed, including considerations for planning the integration of co-researchers with intellectual disabilities in future studies.