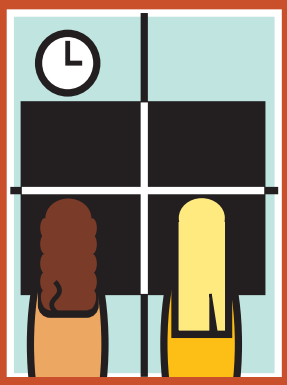
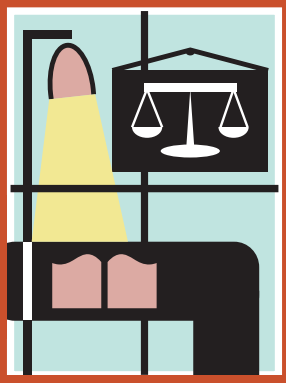
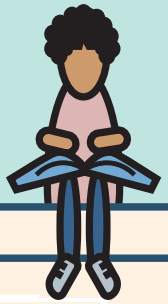
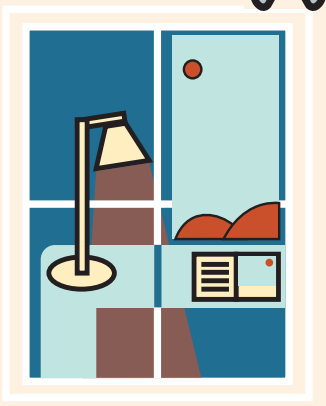
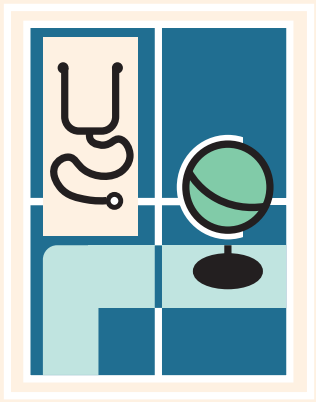


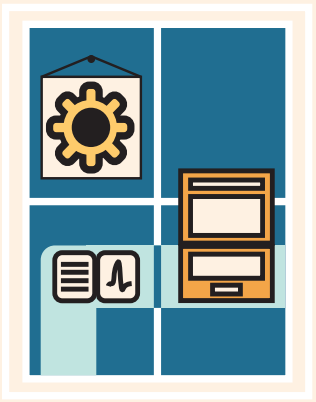


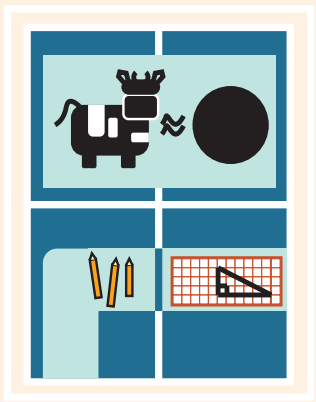
HSURV ABSTRACTS

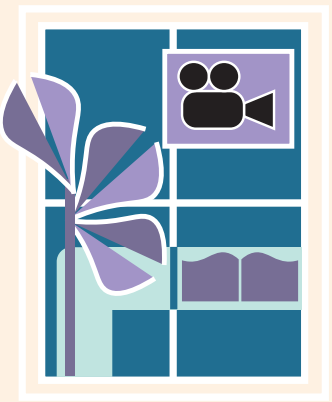


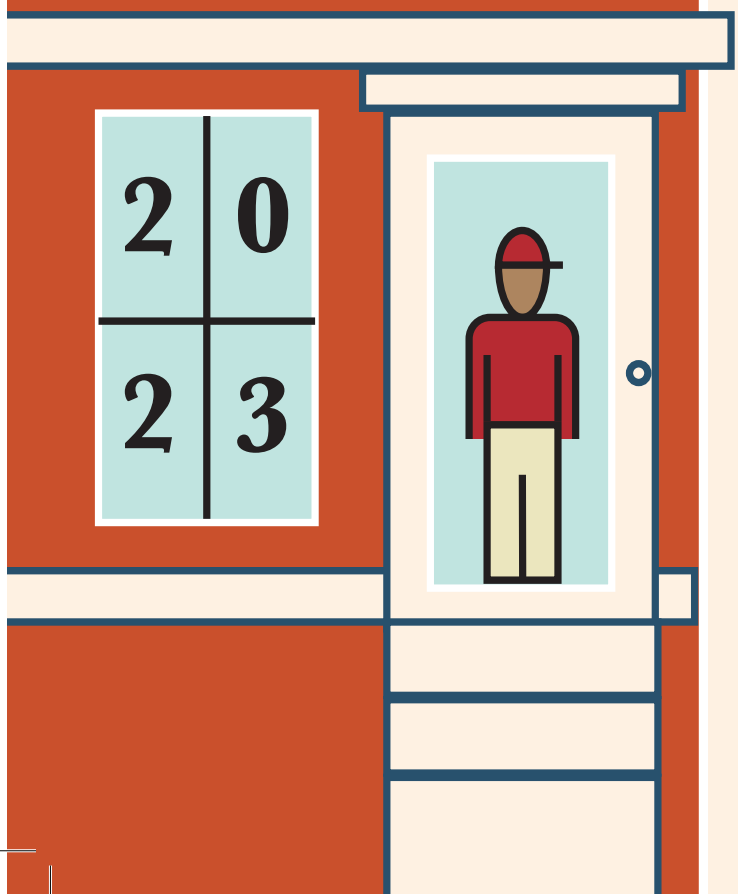












Harvard Summer Undergraduate Research Village 2023 Abstract Book

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PARTICIPATING PROGRAMS
Program for Research in Science and Engineering (PRISE)
Build Learning through Inquiry in the Social Sciences (BLISS)
Program for Research in Markets and Organizations (PRIMO)
Summer Humanities and Arts Research Program (SHARP)
Summer Undergraduate Research in Global Health (SURGH)
Summer Program for Undergraduates in Data Science (SPUDS)

Office of Undergraduate Research and Fellowships
Harvard University
Cambridge, Massachusetts

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Letter from the Director

Dear Harvard Summer Undergraduate Research Village Fellows,

I am thrilled to introduce the Abstract Book, a volume culminating the scholarly experiences of the fellows in the 2023 Harvard College Summer Undergraduate Research Village, our 18th summer. The Village (in order of program inception) is comprised of PRISE (Science and Engineering), BLISS (Social Sciences), PRIMO (Markets and Organizations, co-hosted by Harvard Business School), SHARP (Humanities and Arts), and SURGH (Global Health, co-hosted by the Harvard Global Health Institute), and our most recent addition to Research Village programs, SPUDS, the Summer Program for Undergraduates in Data Science, co-hosted by the Harvard Data Science Initiative.

Since the beginning of PRISE in 2006, we have collected a remarkable history of Harvard College students' research: over 3,000 abstracts across the full disciplinary range, from literature, to physics, to medicine, sociology, and beyond. Also noteworthy is the number of projects over time that are thoroughly interdisciplinary in their approach, a harbinger of the collaboration and adroit thinking that will be necessary to develop and deeply explore the world and the universe for generations to come. Over these years, it has been gratifying to witness the extraordinary degree to which our students have accomplished significant growth as researchers over the relatively brief ten weeks of our time together. Imagine the creativity they are capable of as their intellectual trajectory further evolves—truly exciting and inspiring!

I very much appreciate and am grateful for the tireless efforts of our amazing proctors and program assistants who have stewarded an impressive schedule of activities and opportunities for everyone to meet and engage throughout the summer. Further, our collection of abstracts here would not have been possible without the dedication and fortitude sustained by the group of Research Village editors whose voluntary charge has been to collect, organize, and publish the works of all the fellows. I would especially like to thank program assistant Soy Choi for taking the initiative and seeing this important project through.

To the Summer Undergraduate Research Village fellows of 2023: I admire the degree of bonhomie, inclusivity, and energy you have put into your ten weeks together this summer. I am confident the connections you have made here will endure through your undergraduate years and beyond. I wish you the best of success and hope that you will consider sharing (and hosting!) like experiences in your own residential and academic communities going forward.

All best wishes,

Gregory A. Llacer
Director, Harvard College Office of Undergraduate Research and Fellowships (URAF)

Letter from the Editors

Dear Research Village Community,

Congratulations to all villagers on a wonderful summer of research!

I feel like our 10 weeks together have flown by so quickly. It must be true that time flies when we are having fun. I recall that at our Opening Dinner Greg mentioned to all of us that the Harvard Summer Research Village experience is often "the best summer" one can have. Having previously only been a part of the virtual village, I was not sure what to expect.

Now, as our summer comes to a close, I realize the truth in Greg's opening speech. This was indeed one of "the best summers." Each and every day of this summer was filled with the budding of new relationships, the collection of unforgettable memories, and the accumulation of new enlightenments and reflections.

Relationships
This summer has been a pleasantly fruitful season of meeting new friends, hearing novel perspectives, and learning about the valuable connections that bring us all together. I have met, conversed, and bonded with some very special people this summer, which in itself has made my summer worthwhile. My conversations with fellow villagers inside and outside of Leverett House have been invaluable. At the end of each day, I think about how much I would have been missing out if I did not develop these precious relationships with each of these lovely individuals, and I am eternally grateful that our research village has brought us together.

Memories
With great relationships come great memories. This summer was full of exciting social events and outings. From watching the Jagged Little Pill at the Citizens Bank Opera House to visiting Six Flags for experiential learning of physics concepts, our time was jam-packed with unforgettable events that were made even more special by our company. A special thanks to our wonderful proctors, program assistants, and HSURV staff that helped make many memories this summer.

Enlightenments
And of course, research! We all spent much of our time conducting a vast range of research. It has been an exhilarating opportunity to learn about such a diverse range of topics from many of you. I believe that the research village not only provides you with the opportunity to grow within your research background but also expands the breadth of your knowledge through the fellows around you. Furthermore, the various esteemed guest speakers, panel discussions, and fellow-run groups served as a canvas for constant learning and growth. We sincerely thank all of our wonderful guest speakers.

Additionally, a special thank you to Elizabeth Perten from URAF, who shared her support, time, and advice in helping us make the 2023 Abstract Book a reality. A heartfelt thank you to Greg Llacer, Tom Hamel, Ariel Lepito, and the rest of the wonderful URAF staff for working tirelessly to create an intellectual and social community where we could learn, grow, and thrive. We will always remember and be grateful for your generosity and kindness.

Last but surely not least, fellow fellows, there is so much gratitude to each and every one of you for co-creating the welcoming community we all enjoyed together this summer.

Sincerely,

Soyoun Choi
Editor-in-Chief
On behalf of the 2023 HSURV Abstract Team

Letter from the Artists

“Stories of Students”

This is one of the first relatively normal iterations of Harvard’s research village since March 2020. With subdued pandemic anxieties, we student researchers enjoyed social summers, engaging in program-related activities alongside friends old and new. Our home — Leverett House — seemed to embody a resurgence of human connection and the summer fun that’s typical of younger generations. For this reason, we chose a front cover depicting Leverett House playfully, with bright, saturated summer colors and an eclectic composition. However, we chose a contrasting back cover of Leverett House at night with cool tones and a simpler geometry — even in the revival of busy, social lives, for many of us these post-pandemic years carry on the lesson that quiet reflection can be just as enjoyable and important. In Leverett’s windows, you’ll find illustrations of disciplines related to each of HSURV’s programs, and as you flip through this book, you’ll see those same windows, bigger and more detailed, introducing each program’s abstracts. We hope our artistic perspective captures the unique character of each program, and that something about our designs — whether it’s their content or their form — will resonate with you.

Sincerely,

Your grateful designers
Maria Alejandra Cuervo, Emily Dial, Amanda Dynak, April Keyes, and Niki Nair

Program Descriptions

The Program for Research in Science and Engineering (PRISE) seeks to build community and stimulate creativity among Harvard undergraduate researchers in the life, physical/natural, engineering and applied sciences. Selected fellows work on projects with Harvard-affiliated researchers and participate in extremely rich evening programming that includes both social and academic activities within a diverse, vibrant intellectual and social community.

The Program for Research in Markets and Organizations (PRIMO) aims to build community and stimulate creativity among Harvard undergraduate researchers in business and related fields. Fellows are placed with pre-designed faculty projects at Harvard Business School, working in research areas which span diverse topics (finance, organizational behavior, marketing, etc.), disciplines (Psychology, Economics, Sociology), as well as methods (quantitative or qualitative). As part of the residential community of researchers, students participate in enrichment activities such as faculty lectures, professional development workshops, presentation opportunities, and social events.

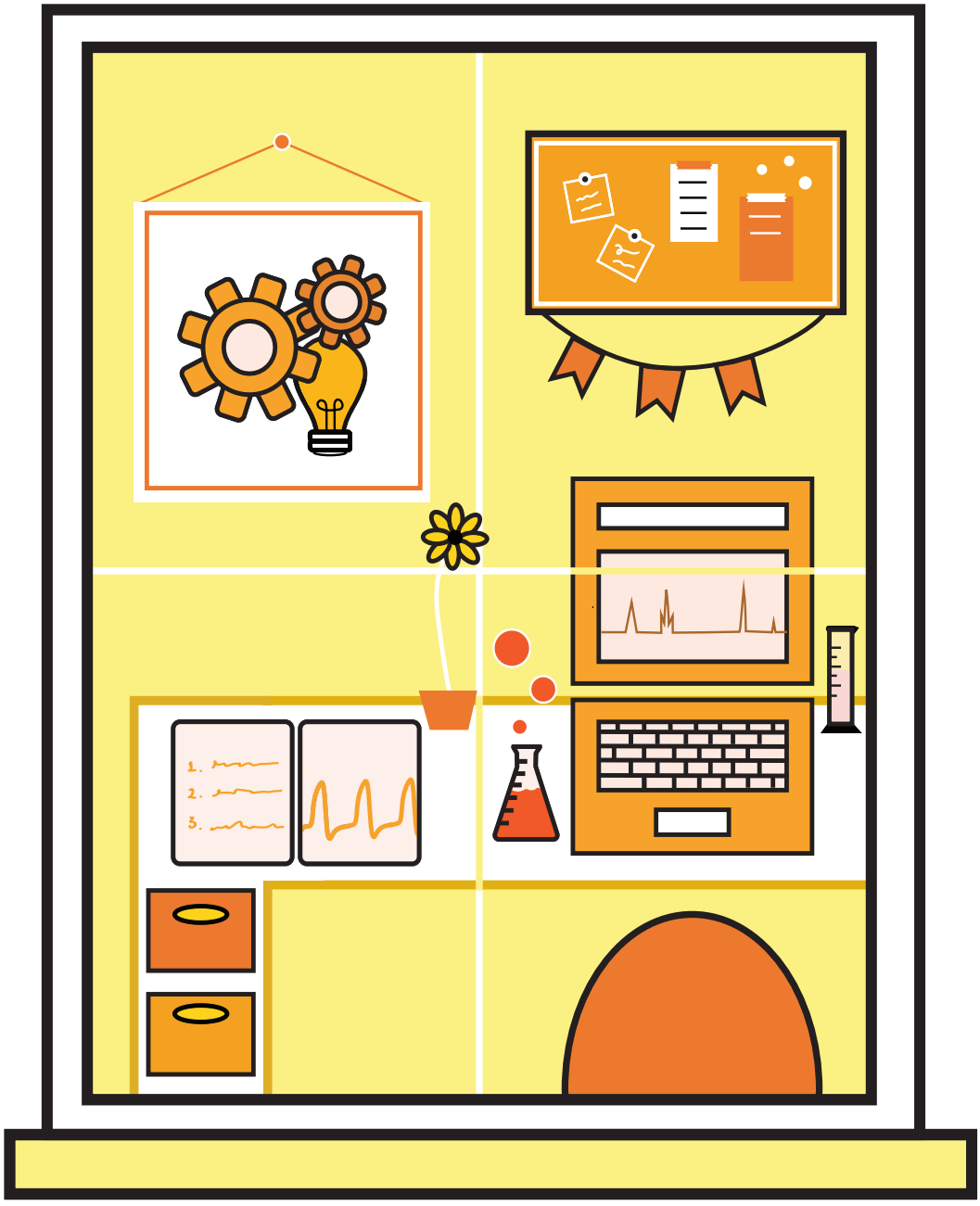
Build Learning through Inquiry in the Social Sciences (BLISS) is designed to provide a formative and substantive social science research experience and to promote community, creativity, and scholarship. A diverse cohort of BLISS Fellows works on pre-designated research projects led by Harvard faculty, and lives in one of the Harvard College houses with the other fellows in the Summer Undergraduate Research Village. In addition to conducting full time research, BLISS Fellows participate in a rich variety of programming, including both social and academic activities.

The Summer Humanities and Arts Research Program (SHARP) strives to build community and stimulate creative thought among a small cohort of Harvard undergraduate researchers in the humanities and arts. Students work on pre-designed research projects with Harvard-affiliated faculty, researchers, and senior library and museum staff. Fellows live together in one of the Harvard College houses and participate in rich evening programming with social and academic activities.

The Summer Program for Undergraduates in Data Science (SPUDS) aims to provide a formative and substantive data science research experience and to promote community, creativity, and scholarship amongst Harvard College students. SPUDS will support Fellows with interests in computer science, mathematics, and statistics, including those who are interested in data science applications across the arts, humanities, sciences and more. As part of SPUDS, fellows will participate in rich evening programming, including both social and academic activities, and become members of a vibrant intellectual and social summer community.

The Summer Undergraduate Research in Global Health (SURGH) program endeavors to build community and stimulate creativity among a small cohort of Harvard undergraduate researchers in global health. SURGH fellows work on pre-designed research projects with Harvard-affiliated faculty and researchers. Students live together in one of the Harvard College houses and participate in rich evening programming including both social and academic activities.

PRISE



Investigating Structural Changes in the Axolotl Brain During Limb Regeneration

Anika Allen
Neuroscience, 2024
Harvard College, Adams House
PI/Advisor: Jessica Whited
Mentor: Noah Lopez

Nearly 60 million people worldwide are living with the loss of a limb due to traumatic causes, and this number is continually increasing. The role played by the central nervous system (CNS) in the limb regeneration process remains unclear. In human amputees, there is evidence of structural and organizational changes in the brain following amputation, but how this relates to any latent or unproductive attempts to regenerate the limb remains unexplored. While humans have extremely limited regenerative ability, the Mexican axolotl (*Ambystoma mexicanum*) has remarkable regenerative abilities and can regrow entire limbs, making it a useful model system for tetrapod regeneration. Our project utilized NISSL staining of histological sections of axolotl forebrains to investigate changes in the gray matter composition at various stages of both successful and unsuccessful limb regeneration. If our initial hypothesis is supported, we expect to see a decrease in gray matter associated with unsuccessful regeneration, and no significant changes when regenerating successfully. Future work concerning a potential causal relationship between regeneration and structural changes in the brain can continue to develop an understanding of successful regeneration that may eventually be used to enhance human healing capabilities.

Enhanced Butyrylcholinesterase Based ELISA Testing Technique Using Ion-Selective Electrodes

Ahmad Alsheikh
Chemistry & Government, 2024
Harvard College, Quincy House
PI/Advisor: George Whitesides
Mentor: Khaled Abdelazim

Enzyme-linked immunosorbent assay (ELISA) rose in prominence during the COVID-19 pandemic to conduct serological testing of SARS-CoV-2 antibodies. ELISA is an analytical biochemistry assay used to measure antibodies in the blood. Traditional ELISA is typically analyzed via spectrophotometry and relies on the activity of the enzyme horseradish peroxidase (HRP). However, HRP is beleaguered with light-sensitivity and efficiency issues. To address its shortcomings, we test the activity of non-traditional enzyme Butyrylcholineesterase (BChE) using Ion Selective Electrodes (ISEs). ISEs are electrochemical sensors that measure electric potential based on the Nernst equation. While previous literature has used BChE-based ELISA and ISEs to monitor reactions independently, there have been no reports in the literature of these improvements being integrated with one another. The ISEs are manufactured to be selective for a particular ion and to perform potentiometric measurements, contrasting with traditional HRP-based colorimetric methods. The newly developed BChE-based ELISA was found to offer a significant improvement in efficiency over HRP-based ELISA in all protein concentrations ranging from 6.14 pg/mL to 1500 pg/mL. These findings may enable speeding antigen testing and enable point-of-care testing in healthcare settings.

Characterization of DNMT1 Binding to Nucleosomes With Post-Translationally Modified H3 Tails

Adelina Andrei
Mathematics & Molecular and Cellular Biology, 2026
Harvard College, Currier House
PI/Advisor: Phil Cole
Mentor: Sam Whedon

DNMT1 (DNA methyltransferase 1) fulfills the critical role of converting hemi-methylated DNA to fully-methylated DNA during genome replication. Ultimately, this activity helps to maintain a stable epigenetic state, thus ensuring normal cellular function. Recently, studies identified the recruitment of DNMT1 to chromatin occurs through the RFTS (replication foci targeting sequence) domain, which binds to two mono-ubiquitinated lysines, as well as to trimethylated lysine K9 of histone H3. However, whether lysine ubiquitination and methylation modifications of histones exert cooperative, redundant, or antagonistic effects on DNMT1 affinity remains unknown. In the study, we aim to characterize the binding of DNMT1 to nucleosomes composed of 185 bp of DNA wrapped around a histone octamer, with histone H3 carrying combinations of these possible modifications involved in recruitment. To do so, we synthesized histone H3 tails made up of 34 amino acids carrying two mono-ubiquitinations at different combinations of lysines K14, K18, and K23, with some of the tails also containing lysine K9 trimethylation. The incorporation of ubiquitin at these desired lysine sites was performed using a chemo-selective ligation of ubiquitin (1-75) thioesters with histone tails bearing Lys Nε-Cys isopeptides. The desulfurization of these cysteines created alanines, a close mimic of the natural ubiquitin (1-76) modified tails. Ultimately, we linked the synthesized tails to the nucleosomes through an engineered sortase ligation reaction. Then, using a fluorescent label, either on the nucleosome DNA or DNMT1, we will measure the affinity of these modified nucleosomes to DNMT1 by microscale thermophoresis and by electrophoretic mobility shift assay. These experiments will uncover what nucleosome modifications most significantly contribute to DNMT1 binding to chromatin, potentially identifying new druggable sites influencing DNMT1 activity, and thereby different diseases linked with abnormal DNA methylation patterns.

Investigation of the Relationship Between MITF and A-syn Expression Levels Through the Administration of SIK Inhibitors and siRNA

Alin Asim
Molecular and Cellular Biology, 2026
Harvard College, Eliot House
PI/Advisor: David E. Fisher
Mentor: Nicholas Theodosakis

Dyspigmentation is a clinical challenge that disproportionately affects people of color. The accumulation of insoluble melanin aggregates resistant to dermal macrophage clearance has been hypothesized to play a key role in its pathogenesis. One of the components of LBs in Parkinson's disease is Alpha-synuclein (a-Syn). a-Syn is thought to play a role in skin pigmentation, as suggested in the preliminary histological studies demonstrating the localization of a-Syn to melanocytes, specifically melanosomes. This study aims to investigate the potential role of α-Syn in the pigmentation process, in part focusing on its regulation by the transcription factor MITF: the master regulator of human pigmentation. We designed a time-course experiment where we monitored the expression of MITF and a-Syn in response to stimulation of the tanning pathway with HG-9-91-01, a small molecule inhibitor of salt-inducible Kinase (SIK). After treating primary melanocytes with SIK inhibitors, we extract RNA from the cells and perform real-time quantitative PCR to measure expression levels. Future experiments include using siRNA to silence the expression of MITF, which we hypothesize decreases a-Syn levels. We also plan to investigate MITF's role in activating the autophagy pathway in melanocytes to remove UV-induced aggregates. We expect normal aggregate removal under regular conditions and impaired removal under autophagy inhibition, which could potentially be rescued by MITF activation.

Rescuing Rett Phenotype in Mice Models Using Small Molecule X

Nicole Asiryan
Human Developmental and Regenerative Biology, 2025
Harvard College, Currier House
PI/Advisor: Jeannie Lee
Mentor: Yuka Takeuchi

Individuals with Rett syndrome, an X-linked disorder that causes developmental regression at an early age, harbor a heterozygous loss-of-function mutation in the MECP2 gene. Since Rett syndrome currently has no cure and treatment relies mainly on the alleviation of symptoms, an epigenetic approach to treatment will allow for a more permanent solution. Xist, a long noncoding RNA, inactivates one of the X-chromosomes at random in XX females by recruiting silencing factors; the selected X-chromosome could harbor the healthy copy of the Mecp2 gene, depleting cells of normal Mecp2 expression levels. This study used Xist antisense oligonucleotide (Xist-ASO), which binds and inhibits Xist, and small molecule X, a DNA methylation inhibitor, to restore Mecp2 expression and rescue the Rett phenotype in Rett mouse models. The ASO was administered via intracerebroventricular injection (ICV) to allow the treatment to cross the blood-brain barrier while the small molecule was delivered via intraperitoneal injection (IP). Small molecule X shows increased in vivo drug tolerability compared to FDA-approved nucleoside-analog hypomethylating agents that have been historically used for DNA hypomethylation. Small molecule X interacts with a DNA methyltransferase directly instead of incorporating into the DNA. Behavioral analyses using the open field apparatus, elevated plus maze test, Catwalk test, and the Three-Chamber test showed that Rett mice treated with small molecule X experienced significant recovery when compared to the untreated Rett mice, yielding results similar to that of the wild-type mice. These results demonstrate possible treatments for human females with Rett syndrome that can be tested in clinical trials. Additional experiments to test changes in overall gene expression between untreated and treated cell populations will be performed in the future to analyze Mecp2 expression and possible off-target effects.

Changes in Autophagic Flux Caused by Inactivation of Host Factors Involved in Membrane Repair During Mtb Infection

Zach Baskir
Bioengineering, 2025
Harvard College, Currier House
PI/Advisor: Amy Barczak
Mentor: Pooja Uchil

Mycobacterium tuberculosis (Mtb) is the deadly intracellular pathogen that causes tuberculosis- an infectious disease with an estimated annual death toll of 1.6 million people. When a person inhales a Mtb-containing droplet, the bacterium is transported into the lungs where it is engulfed by alveolar macrophages. One core role of macrophages is to clear ingested invaders through progressive maturation of phagosomes and fusion with lysosomes, which can kill and digest most bacteria. However, Mtb is exquisitely adapted to inhibit macrophage functions by creating holes in the phagosomal membrane. The pathways by which the bacterium affects this phagosomal damage are relatively well known, but the host factors that repair damaged phagosomes are less well understood. Two of the factors known to contribute to phagosomal membrane integrity are the endosomal sorting complex required for transport (ESCRT) and autophagy. In previous work using a CRISPR whole genome screening approach, the Barczak laboratory identified new candidate host factors that contribute to repair of the Mtb-containing phagosomal membrane. Two of the most promising hits from the screen were the phosphoinositide kinase PIKFYVE and Vacuolar protein sorting-associated protein 18 (VPS18). We hypothesize that each of these factors contribute to either membrane repair or participate in recruitment of autophagy machinery to clear severely damaged phagosomes. My project seeks to test the second hypothesis by investigating whether VPS18 knockout macrophages or macrophages treated with PIKFYVE inhibitors have impaired autophagic flux under different conditions including Mtb infection. Through Western blotting of autophagic markers LC3B and p62 we will investigate autophagic flux. Additionally, fluorescent microscopy images of Mtb infected cells will be analyzed to quantify LC3 and Mtb colocalization. Preliminary results show that the VPS18 knockout cells show enhanced basal autophagy which is consistent with a model in which VPS18 is part of a distinct repair mechanism from autophagy.

High-Voltage Power Supply for Size, Weight, and Power (SWaP)-Constrained Systems

Arjun Batra
Electrical Engineering, 2025
Harvard College, Adams House
PI/Advisor: Gage Hills

Miniaturized devices deployed in reduced-resource settings demand unprecedented constraints on size, weight, and power (SWaP) that cannot be met by conventional hardware systems. Such constraints impose challenges on developing compact high-voltage circuitry to drive actuation because typical power circuits use discrete/bulky components too large for SWaP systems. Using an integrated circuit approach, our research focuses on SWaP-optimizing high-voltage circuit topologies. We modeled the Dickson and Cockcroft-Walton high-voltage charge pumps through discrete transition matrices that determine output voltages with 90% accuracy. This algebraic model takes hundredths of a second and is 10,000x faster than conventional LTSpice differential equation circuit simulations, enabling rapid exploration of the design space. From this model, we devised an output-resistance-based circuit optimization algorithm for a given output voltage and load current. This algorithm was applied to the SWaP case study of powering the high-voltage piezoelectric actuators of RoboBee, a centimeter-scale flying microrobot from Professor Robert Wood's laboratory. With constraints from X-FAB's XT018 integrated chip fabrication process, we optimized the circuit size (measured by area) across various output voltages and load currents up to RoboBee's upper-bound flight requirements (200 V output voltage and 1 mA load current). This optimized design space reveals circuit-size trends in the context of the robot's piezoelectric material thickness. At 1 mA load current, the model demonstrates that an output voltage drop from 200 V to 100 V (caused by a 2x decrease in piezoelectric material thickness) corresponds to a 4x smaller Dickson optimal area and 8.5x smaller Cockcroft-Walton optimal area. Therefore, piezoelectric material thickness is a significant factor for co-optimizing charge pump size with the robot's mechanical designs. We plan to analyze and compare analogous optimized design spaces for other power circuit topologies (boost converter, flyback converter, etc.), enabling further electrical and mechanical co-optimizations for power converters in SWaP-constrained systems.

Using Human Cerebral Organoid Model to Investigate the Effects of Mutations in Autism Spectrum Disorder-risk Gene SHANK3

Uyanga Batsaikhan
Neuroscience, 2026
Harvard College, Quincy House
PI/Advisor: Paola Arlotta
Mentor: Rafaela Sartore

Cortical development is a protracted process spanning embryonic and postnatal life which involves the orchestration of cellular events, such as proliferation, differentiation, migration, and maturation. The precise execution of these processes at the right time and place are crucial to guarantee proper cortical development, and alterations during these processes may lead to neurodevelopmental disorders (NDDs). Autism spectrum disorder (ASD) is a childhood-onset NDD, affecting around 1 in 36 children, and is characterized by impaired social interaction and communication, repetitive behaviors, and atypical sensory processing. The severity of phenotypic manifestations can widely vary due to the complex and polygenic nature of the disease. Whole-exome sequencing data shows that hundreds of loci contribute to increased genetic risk for ASD. However, how mutations in this vast and heterogeneous collection of risk genes converge to phenotypic features found in ASD remains poorly understood. The three-dimensional cerebral organoid model, derived from pluripotent stem cells, closely recapitulates the structural complexity, cellular diversity, and gene expression patterns observed in in vivo brain tissue during embryonic development, which cannot be observed in typical animal models. Cerebral organoids also offer a platform for disease modeling when applying cell lines that are genetically engineered to possess disease-related mutations. Mutations in SHANK3, which encodes a scaffolding postsynaptic protein, are among the most prevalent in individuals with ASD and intellectual disability, occurring in 1 to 2 percent of patients. In this project, we are probing cerebral organoids derived from SHANK3 heterozygous mutant and isogenic control cell lines at different stages of development through single RNA sequencing in order to understand the effects of SHANK3 mutation on cellular composition, gene expression, and functionality of the neuronal network. By developing a comprehensive understanding of the genotype and phenotype correlations in ASD, we can untangle the nuanced genetic interactions that underlie the pathophysiology of ASD.

Investigating Salivary Inflammatory Biomarkers for the Prediction of Neonatal Sepsis

Kathleen Bellon Pizarro
Molecular and Cellular Biology, 2024
Harvard College, Mather House
PI/Advisor: David Walt
Mentor: Justin Rolando

Neonatal sepsis, a systemic inflammatory disease provoked by infection, is a leading cause of mortality in infants. Currently, diagnosis relies on serial blood measurements, which can be difficult to perform on these individuals with limited blood volumes. Investigating inflammatory markers in saliva has been proposed as a safer, noninvasive alternative. However, quantifying inflammatory proteins can be difficult due to the greater variation in their salivary concentrations compared to blood. Given the ability of the single-molecule array (Simoa) platform to detect analytes in biofluids at a sub-femtomolar level, we seek to utilize this ultrasensitive platform to quantify various inflammatory markers in neonatal saliva. In combination with clinical and demographic data of over 1,000 neonates, we plan to generate predictive models that can aid in the diagnosis of neonatal sepsis. Previously, our laboratory successfully detected a panel of ten cytokines in saliva and generated a k-nearest neighbors (k-NN) based predictive model with moderate sensitivity and specificity (78% and 80%, respectively). To improve upon these parameters, novel inflammatory biomarkers, including chemokines and adipokines will be incorporated and tested for their detection. To our knowledge, none of these inflammatory markers have ever been detected in saliva; therefore, we will also establish normative reference values for these proteins in healthy neonates. These results will not only provide a closer look into the proteome of neonatal saliva but will potentially guide future clinical diagnostics for neonatal sepsis.

A Study on the Formation and Growth Properties of Black Hole Seeds Based on Recent JWST Discoveries

Bruna Biz
Astrophysics, 2026
Harvard College, Mather House
PI/Advisor: Fabio Pacucci

In recent months, the James Webb Space Telescope (JWST) has discovered an unprecedented number of high-redshift galaxies - many having a signature of a black hole at their center. Due to the size and redshift of these black holes, it is not known how they grew from the formation, or seed, stage at redshift $z > 20$ up to the observed state at $z \sim 8$-12. In particular, we focused on two models for the formation of black hole seeds: light seed, formed from the collapse of the first population of stars, or heavy seed, formed by more exotic high-z mechanisms. In this work, we performed a statistical study based on the most distant black holes discovered so far. Our goal is to infer the formation and growth properties of the first black hole seeds formed in the Universe. In particular, we focus on four properties: the initial seed mass, the average Eddington ratio, the duty cycle, and the matter-to-radiation efficiency. Based on the detection mass of these black holes, estimated from their spectral properties, we performed Monte Carlo simulations to calculate the probability distribution functions of their initial masses and the average accretion rate leading up to their observed stage. We found that, in the light seeding case with an average mass of 300 solar masses, the average accretion rate is 60% higher than the Eddington one. In the heavy seed case with an average mass of half a million solar masses, the typical accretion rate is only 0.37 times the Eddington rate. Building on our findings of the seed properties, we are also investigating the limiting redshift where we would be able to detect the growth of these seeds with current and future X-ray observations.

Incremental Slow and Sparse Representation Learning of Form and Motion

Alexander Cai
Computer Science & Statistics, 2025
Harvard College, Currier House
PI/Advisor: Cengiz Pehlevan

How does the human brain develop a representation of three-dimensional space? Understanding this ability is critical for understanding other neural functions including vision, proprioception, and motor control. A reasonable model must satisfy many criteria: It should support object recognition, depth and pose estimation, and scene extrapolation. It should also be robust to perturbations, support a biologically plausible learning process, and rely on two-dimensional visual input. To our knowledge, no existing model satisfies all of these requirements. One promising algorithm, however, is slow feature analysis (SFA), which exploits the intuition that entities in a natural scene typically undergo slow changes. Variations of SFA have achieved success on tasks such as human action recognition, change detection, and video segmentation. However, SFA is not generative: the learned representation cannot be used to extend a natural video. In this work, we seek to remedy this by coupling SFA with continuous transformation learning (CTL), which learns explicit representations of the physical transformations that objects undergo. The space of transformations is assumed to form a Lie group so that an object's trajectory can be described by a generator from the underlying Lie algebra. In particular, we learn object representations using Kernel SFA and transformation representations (in feature space) using CTL. Our method requires no supervision and is fully online. We impose sparsity constraints on both the object representations and transformation coefficients to simulate biological energetic constraints. We find that the learned SFA features qualitatively resemble biological neural codes, supporting the conjecture that slowness is a learning principle of the visual cortex. We also find that the learned transformations can extend toy scenes in a plausible and controllable way. Our findings contribute to the understanding of spatio-temporal representation learning in the human brain. We seek to investigate biologically plausible implementations in future work.

Automated Measurement of Social Touch in Animal Models of Autism

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The American Psychiatric Association characterizes autism spectrum disorder (ASD) as a complex developmental condition marked by sensory hyperreactivity and hyporeactivity, making deficits in social touch detrimental in maintaining close relationships and personal wellbeing. However, research findings studying these atypical reactivities in ASD patients are nascent despite the plethora of clinical data reporting such behaviors. Autism behavioral phenotyping studies are beginning to use rat models to better understand how complex behaviors and sociality works in mammals. We developed a technique to quantify social touch in freely moving rats that leverages modern technologies in animal pose estimation and 3D behavior modeling. This technique models the distribution and intensity of social touch within an ASD model pair by relating points of contact with social behaviors. To begin, we recorded the natural social behavior of two Long-Evans rats. We then utilized DANNCE, a powerful 3D pose estimation technique, to track the motor behaviors of six ASD rat models and fit a deformable mesh model that estimates the points of contact between the two animals. Ultimately, we determined that each strain has different quantifiable social touch behaviors. Given the phenotypic and genotypic diversity of animal behavior, we can continue improving these models of measurement for potential use in the quantification of regional touch deficit. These findings produce novel deep behavioral phenotyping modeling data that can ultimately begin to characterize the multifaceted behaviors of developmental disorders such as ASD.

Investigating β Cell Senescence in Type II Diabetes

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Cellular senescence, a key hallmark of aging, is a complex state in which cells remain metabolically active despite cessation of cell proliferation. While even young mice have some population of senescent cells, the number of senescent cells within pancreatic islets increase with age and obesity. Type 2 diabetes is a disease characterized by hyperinsulinemia and hyperglycemia, and aging is one driver of this disease. To further study the relationship between senescence and age related type 2 diabetes, we utilized mitochondrial transport proteins as a proxy to understand the role of mitochondria in maintaining homeostasis and in signaling pathways involved in cellular senescence. Using a transgenic mouse model, we allow the mice to naturally age to mimic the typical progression of type 2 diabetes, then locally knockout a gene responsible for a specific protein of interest using CRISPR-Cas9. Afterwards, we assessed the blood glucose and insulin levels in transporter-null mice. Simultaneously, we use both overexpressed and knockout cell lines of the protein of interest, chosen for its role as a primary transporter of NAD^+ within the mitochondria, to assess the molecular mechanisms underlying augmentation of the inner mitochondrial membrane protein. Senolytic agents, an emerging therapeutic, aim to ameliorate age-related pathologies by eliminating senescent cells. One challenge, however, is the gap in knowledge regarding the molecular mechanisms tying β-cell senescence and markers of senescence to observed phenotypic changes. The preliminary results of this study suggest an upregulation of the inner mitochondrial protein of interest, meaning additional research is needed to determine whether this serves as a compensatory mechanism for decreasing levels of mitochondrial NAD^+ associated with aging or indicative of dysfunction of the mitochondrial protein due to oxidative stress and cellular senescence. The results of this study have the potential to inform novel therapeutic approaches in attenuating age-related pathologies.

Development of Molecular Tools to Investigate Subcellular Molecular Networks in Growth Cones of Distinct Cortical Projection Neuron Subtypes

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Growth cones (GCs) are specialized subcellular compartments that integrate extracellular signals to control axon extension, critically enabling construction of precise neural circuits. Previous research has shown that GCs respond rapidly to changes in their local extracellular environment (seconds to minutes), whereas responses via signals from their parent somata take much longer (hours to days). Despite this semi-autonomous nature of GCs, previous studies have investigated GCs via whole-neuron perturbations, instead of manipulating molecular abundances directly in GCs. We developed a molecular system that targets a fluorescent protein to stage- and subtype-specific GCs. Now, we propose to extend this approach by trafficking hfCas13d, a targeted RNA degrader, to GCs, enabling knockdown of candidate transcripts with subcellular specificity. GapPal43, an axonal targeting motif, was fused upstream of hfCs13d to traffic this protein towards GCs, thereby enabling manipulation of candidate transcripts (e.g. *Mmp24* and *Pcdhαc2*) directly in GCs. mEGFP was also fused downstream of hfCas13d to enable subcellular specific visualization. Preliminary results indicate that hfCas13d localization is detected through mEGFP fluorescence. To assess if fusion of GapPal43 and/or mEGFP alters the RNA degradation activity of hfCas13d, qPCR of transfected N2A cells *in vitro* was performed. The results indicate that abundance of *Mmp24* and *Pcdhαc2* in cells transfected with the hfCas13d fusion construct is higher than those transfected with the control (unmodified hfCas13d), suggesting mEGFP fusion inhibits hfCas13d activity. Finally, we are investigating *in vivo* effects of this construct in mice. I expect to observe a decrease in abundance of *Mmp24* and *Pcdhαc2* transcripts in GCs, but not in cell bodies, and will visualize potential circuit defects that might result from this subcellularly specific knockdown via microscopy. Since specific GC molecules are implicated in disease, identifying molecules that function subcellularly in GCs to enable proper neural circuitry formation is critical for development of novel targeted therapies.

Towards a Regulatory and Mechanistic Framework for RarA-Mediated Carbapenem and Multidrug Resistance Phenotypes

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Carbapenems are a class of antibiotics critical to treating multidrug resistant (MDR) infections. However, escalating levels of carbapenem-resistant Enterobacterales pose a significant global concern. Studying clinical strains of common MDR pathogen *Klebsiella pneumoniae*, our lab observed that overexpression of RarA, a transcription factor from the XylS/AraC family, contributes to MDR and high levels of carbapenem resistance beyond what is expected from genotyping common resistance markers. However, in addition to exacerbating resistance, RarA overexpression creates a considerable fitness cost to growth. Our project, therefore, aims to clarify the regulation of RarA expression, define its regulon of co-expressed genes, and disentangle which molecular pathways link RarA to resistance and fitness cost phenotypes. To address these aims, we used in vitro evolution, base editing, and plasmid complementation to assemble a library of 26 *K. pneumoniae* strains with various genetic perturbations in RarA, its putative repressor OqxR, and several putative downstream targets. We then conducted broth microdilution assays to examine these strains' susceptibility to carbapenems and other antibiotics across a wide range of bacterial inocula. The resultant resistance profiles suggest that RarA contributes to resistance by downregulating porins to decrease permeability and upregulating efflux pumps to increase drug removal, with each mechanism contributing variably to resistance to different antibiotics. Analyzing gene expression with RT-qPCR confirmed that nearby transcription factor OqxR represses RarA and RarA activates expression of efflux pump genes OqxAB. These findings suggest a new possible model for OqxAB regulation: Instead of OqxR directly repressing OqxAB as previously thought, OqxR may impact OqxAB expression via repression of RarA. Further, kinetic growth assays revealed that a significant component of RarA's fitness cost is mediated by its upregulation of OqxAB. Future directions for this research include comprehensive exploration of RarA's regulatory network via RNA-Seq and how this network interacts with related, MDR-associated transcription factors.

Controlling Oscillations to Treat Alzheimer's Disease: Anatomical Survey of Cortical cFos Expression in Response to Treatment With 40Hz Optogenetic Excitation of Basal Forebrain Parvalbumin Neurons

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Alzheimer's Disease (AD) is a devastating neurodegenerative disease that causes those affected to have memory impairment, changes in personality and behavior, and difficulties with thinking and reasoning. AD is believed to arise due to the build-up of amyloid-beta (Aβ) protein in the brain, causing a cascade of other pathologies such as tau hyperphosphorylation, neuroinflammation, and neurodegeneration, and is additionally associated with aberrant gamma oscillations. Evidence suggests that evoking 40Hz gamma oscillations may have therapeutic benefits in the context of AD. Indeed, our research has shown that 40Hz optogenetic excitation of basal forebrain parvalbumin neurons (BF PV) evokes potent 40Hz gamma oscillations in the medial prefrontal cortex (mPFC) and dorsal hippocampus (dHPC) and additionally increases microglial Aβ uptake in forebrain samples from 5xFAD amyloidosis model mice. Our current research project focuses on expanding our understanding of the neural mechanism of 40Hz BF PV excitation treatment with an anatomical survey of cortical cFos expression, a commonly used marker for neural activity, in wild-type mice. We first performed brain surgery to equip mice for optogenetic treatment and implanted ipsilateral local field potential (LFP) recording electrodes in mPFC and dHPC or motor cortex (MC) and visual cortex (VC) to measure oscillatory activity. Eight weeks after surgery, we treated mice with either 40Hz BF PV excitation or 40Hz laser stimulation (control group) for one hour and analyzed cFos expression in the cortex using immunohistochemistry. LFP analysis shows that 40Hz BF PV excitation evokes 40Hz gamma oscillations in all four regions (mPFC, dHPC, MC, and VC). Analysis of cFos expression is in progress. This study will guide future projects aimed at elucidating molecular mechanisms by identifying cortical regions where treatment benefits are likely to be most prominent. This, in turn, can inform future projects to treat human AD patients.

Detecting Pathological Node-Positive Breast Cancer Patients With Machine Learning

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Identifying pathological node positivity in patients would provide greater clarity for decision-making regarding the use of neoadjuvant treatments, A recent study found that approximately 14% of early-stage triple-negative breast cancer (TNBC) patients with clinically node-negative disease have pathologically positive nodes and approximately 20% of HER2+ patients that underwent upfront surgery were pathologically node-positive. This study seeks to improve the identification of pathologically node-positive patients in early-stage TNBC and HER2+ diseases, enhancing decision-making and the efficacy of neoadjuvant treatments. We aim to utilize clinical records and diagnoses to develop a predictive model using machine learning methodologies. We aspire to exceed the predictive accuracy of existing approaches such as the MDACC Breast Cancer Nomogram. Our research proposal has been approved, and we're currently undergoing an ethics review and preliminary data cleaning, anticipating results by the end of summer. This research has the potential to transform the understanding and management of pathological node positivity in breast cancer, thereby optimizing patient outcomes and treatment efficiency.

Development of Soft Robotic Sensors for Local Strain Detection in Grippers

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The functions of grasping and manipulation are vital features for humans, animals, and robots alike. 'Grasping' is the ability to pick up and hold an object against external disturbances, while 'manipulation' refers to the ability to exert forces on an object and thus cause its rotation and/or displacement from the reference point. The broad aims of this project are to improve human-like touch sensations in robotic grippers in order to improve performance on delicate tasks such as utilizing kitchen utensils with appropriate manipulation techniques and placing objects accurately in the correct orientation. Within this broader context, developing sensors for soft robotic systems that can measure local strains within a single sensor device is crucial. These stretchable, capacitive sensors will be attached to the finger structures of mechanical grippers and allow for the grasping of objects of different shapes and rigidities successfully. Specifically, after designing a library of soft sensors to differentially detect local strain within robotic grippers, the various geometries of sensors were fabricated by spraying layers of carbon nanotubes (CNT)/carbon black (CB) onto silicone and then encapsulating these layers with additional layers of silicone (Dragon Skin 10) to create a parallel-plate capacitor structure. The sensors were then interrogated at a single interface across a range of excitation frequencies (100Hz to 20kHz) to resolve the spatial distribution of strain. If multiple elements can be interrogated using a single electrical interface, this reduces the complexity of high-deformation sensor arrays. In application, this leads to increased manufacturability and reliability of the deformable systems that utilize these sensors. However, considering that the response of the sensors to strain is not a simple function, the goal is to train an artificial neural network that can accurately reconstruct strain states based on the curves of capacitance and resistance across the frequency sweep.

Untitled Project

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Most photonic devices are silicon based, but silicon does not exhibit a Pockels effect, which means that the silicon's refractive index does not change with an applied electric field. However, the Pockels effect is necessary in designing photonic devices such as a high speed light modulator. In contrast to silicon, $BaTiO_3$ is a ferroelectric material that exhibits a Pockels effect. The enhanced photonic properties of $BaTiO_3$ depend on its ferroelectric microstructure. In this project, we study the ferroelectric polarization domains of scanning transmission electron microscopic images of $BaTiO_3$ thin films. The films were synthesized on $GdScO_3$ substrates through reactive-oxide molecular beam epitaxy. We first verify that the unit cells of the thin film have orthorhombic distortions, which means that the in-plane and out-of-plane lattice constants are inequivalent. Then we map the polarization domains of $BaTiO_3$ thin films using the displacement of the titanium atom from the center of mass of its nearest barium neighbors. We find that the polarization vectors largely have a consistent orientation and magnitude in defect-free regions. Understanding the polarization domain structure of the films can lead to an improved understanding of how an applied electric field can affect the optical properties of the $BaTiO_3$ thin films.

Synthesizing Hypervalent Organoiodide Cluster Compounds as Environmentally Friendly Redox Catalysts

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Mentor: Khashayar Rajabimoghadam

Transition metals often exhibit unique properties that enable them to perform reactions, often as industrial redox catalysts, that are otherwise inaccessible using only organic reagents. However, they have several issues, including scarcity and supply chain instabilities, toxicity and regulatory burden, and environmental pollution. These concerns naturally motivate research on organic compounds that could replace them or serve as alternatives. Our work aims to create organic compounds that mimic the properties that make transition metals such useful catalysts. This project puts forth the idea of organoiodide compounds, particularly di-, tri-, and tetraiodide scaffolds that force iodine atoms together in a locked configuration. Positioning these huge iodine atoms in extreme spatial proximity creates a large amount of repulsion between their electrons, forming a more reactive catalyst that works with milder oxidants. The delocalization of electrons across multiple redox-active iodine atoms also greatly expands the range of accessible oxidation states and offers the compound greater stability. Our analysis of cyclic voltammetry data has shown that 1,8-diiodonaphthalene is much more readily oxidized than the mononuclear compound 1-iodonaphthalene. Moreover, 1,8-diiodobenzene, a similar compound to 1,8-diiodonaphthalene, has also been shown to effectively catalyze an intramolecular arene C–H amination reaction, whereas 1-iodonaphthalene could not. We have also synthesized several polyiodide compounds using techniques such as dilithiation and Sandmeyer reactions and are currently evaluating them as catalysts for olefin functionalization. However, synthesis of these polyiodide compounds is difficult due to the iodine-iodine repulsion, so several modified structures utilizing steric or electronic factors are also being tested to favorably form other viable polyiodide compounds. Synthesizing these polyiodide catalysts will enable many pollution-intensive industries to become more environmentally friendly and sustainable.

Quantifying Wildfire Smoke Exposure and Health Impacts in the Western United States

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Mentor: Tianjia Liu, Makoto Kelp

Smoke particulate matter ($PM_{2.5}$) pollution from accelerating wildfire activity in the Western United States poses a significant threat to public health, especially to low-income populations and to individuals with existing cardiovascular and respiratory conditions. However, in preparing for future fires, land managers face considerable challenges quantifying these health risks. We develop a novel framework to evaluate the relative sub-regional contributions from Western U.S. wildfires to smoke exposure and health impacts on nine regions across the contiguous United States. This framework incorporates historical and projected fire emissions, land cover types, variability in fire recurrence, and wildfire smoke transport to generate a relative rank-based smoke risk index at $0.25° \times 0.25°$ spatial resolution. Results from our risk index suggest that our projected high smoke-risk areas for 2018 and 2020 align well with ground-truth burned area data for the 2018 and 2020 fire seasons. In the 12 months following the 2020 fire season, we estimate that excess mortality attributable to smoke $PM_{2.5}$ exposure in the Western United States approached 50,000 deaths. We deploy the risk index on an online software tool, allowing land managers to analyze smoke risk under various burned area and fuel consumption scenarios. Ongoing and future work includes conducting further scenario analyses and developing mortality estimates for individual large fires. Ultimately, use of our risk index will enable land managers to direct fire prevention resources towards areas that contribute heavily to smoke exposure, furthering efforts to safeguard low-income communities and other high-risk populations from excess smoke $PM_{2.5}$ exposure.

Characterization of CRAF Functional Mutations

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Mentor: James Woods

The mitogen-activated protein kinase (MAPK) pathway controls cell growth and proliferation. When dysregulated the MAPK pathway can result in tumorigenesis; in fact, the upstream RAS proteins (including isoforms KRAS, NRAS and HRAS) are mutated in around 30% of all human cancers. Among members of the pathway, the protein CRAF has been established as essential to tumor growth in RAS mutant cancers. Our research aims to elucidate CRAF functionality through base editing and the identification of CRAF inactivating mutations. To characterize mutations as either functional or protein degrading, our research relies on a knock-in of the green fluorescent protein (GFP) into CRAF. We cloned both a homology directed repair (HDR) template and appropriate CRISPR Cas9 guide plasmids. We then transiently transfected these two plasmids into H358 cells, a non-small cell lung cancer cell line possessing a KRAS mutation. To optimize protocols for the lipid-mediated transfection we tested a GFP expressing plasmid. Combining 0.125 million cells, 300 nanograms of DNA, and 1.5 microliters of the transfection reagent (lipofectamine), transfection efficiency reached 22.58%, as measured by flow cytometry as the percent of GFP positive cells. We applied this transfection protocol to create the GFP knock-in. Next we will introduce a CRAF tiling library to introduce mutations throughout the protein and sort the knock-in cells by GFP signal. This will distinguish between functional and protein destabilizing mutations. In the future this work can be used to identify regions of CRAF that could be targeted by small-molecule probes. Given CRAF's essentiality to tumor growth, developing a specific CRAF inhibitor – that prevents tumor growth without abrogating normal MAPK activity – would address a critical, unmet need.

Identifying and Characterizing Variable Responses of Acute Myeloid Leukemia Single-Cell MOLM13 Clones to Nutrient Depletion and Chemotherapy

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Acute myeloid leukemia (AML) is a heterogenous, high-relapse hematologic malignancy with a very poor prognosis. Malignant, genetically identical leukemia cell clones that escape the selective pressure of induction chemotherapy drive disease relapse and demonstrate resilience indicative of their fitness for survival under stress. While the genetic landscape of AML at diagnosis and recurrence is documented, the mechanisms driving clonal selection independent of recurrent mutations are incompletely understood. We hypothesize that metabolic diversity plays a role in the dominance of and selection for certain leukemic cell clones over others. Controlling for genetic variation through the human AML cell line, MOLM13, we isolated and expanded single-cell clones that we defined by their resistance to stress conditions, including treatment with clinical chemotherapy drugs and conditions such as hypoxia and serum and amino acid starvation. We seek to define metabolic pathways that characterize and distinguish chemo-resistant clones from their sensitive counterparts and reveal key mechanisms allowing certain AML cells to resist chemotherapy and cause relapse, potentially revealing avenues for new treatments that target these metabolic vulnerabilities.

Targeting SKP2 and CDK1/2 in Kaposi's Sarcoma Herpesvirus-Induced Oncogenesis: A Potential Novel Treatment Approach

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Kaposi sarcoma herpesvirus (KSHV) is the causative agent of Kaposi's sarcoma (KS), an endothelial tumor with a high incidence in sub-Saharan Africa. Current treatments include combination antiretroviral therapy to manage HIV infection and invasive procedures such as surgery, radiation and chemotherapy. Previous research has shown that KSHV induces oncogenic transformation of endothelial cells through downregulation of microRNA (miRNA)-127-3p, a tumor suppressive miRNA that directly inhibits the oncogene SKP2 to induce cell cycle arrest (Soo Mi Lee, Kaye and Slack, 2021). In this study, we hypothesized that by directly inhibiting SKP2 and its downstream target CDK2, cell proliferation would be suppressed, thus providing a novel therapeutic option for this disease. We treated KSHV-infected human endothelial cells (LTC) with Dioscin, a potent SKP2 inhibitor and CDK2-IN-73, a specific CDK2 inhibitor, and the cells were imaged 24 and 48 hours after treatment. We then carried out a BrdU cell proliferation assay to determine the percentage of proliferating cells. Our preliminary results showed a significant decrease in cellular proliferation in LTC treated with the SKP2 inhibitor. However, treatment with the CDK2 inhibitor alone did not have a significant effect likely due to compensation by CDK1 (Adhikari et al., 2012). Therefore, we simultaneously treated LTC with RO-3306, a CDK1 inhibitor, and observed a significant decrease in cellular proliferation, indicating that CDK1 can compensate for CDK2. We will conduct a more in-depth cell cycle analysis to determine the specific cell cycle phase in which the cells are arrested. Should our hypothesis be supported *in vivo*, inhibiting both SKP2 and CDK1/2 could provide a promising treatment option for KS. The understanding gained from studying KS and its association with miR-127 may shed light on similar mechanisms underlying other virus-induced cancers such as those caused by Epstein-Barr Virus (EBV).

Modifying Morphology of the Iron Metal Organic Framework

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Metal-organic frameworks (MOFs) are crystalline materials formed by linking organic and inorganic units. MOFs are a growing field of major interest due to their unique properties, such as high porosity, conferring them multiple applications like energy and gas storage. Most well-known MOFs have limited water stability and are infiltrated by water molecules when dispersed in it. Contrastingly, our project focuses on the study of the Fe2(bdp)3 MOF, which has around 80% oxygen capacity and is stable when immersed in water. The ongoing aims consist of modifying the morphology of MOF to make it nano-sized and isotropic while maintaining its porosity. Through a literature review, we determined the best methodology is adding modulators to the synthesis process, as modulators compete with the ligand for metal coordination, intervening in crystal growth. Previous studies have shown that for other MOFs, morphology is correlated to the presence of electron donating groups, electron withdrawing groups and bulky functional groups in the modulator. Accordingly, we chose four modulators: Pyrazole, 3-Methylpyrazole, 3-(Trifluoromethyl)pyrazole and Indazole. The Fe2(bdp)3 was synthesized with each of these, and SEM imaging was performed. The MOF with the pyrazole modulator produced crystals 300 nm wide and 20 nm long. 3-Methylpyrazole modulator produced crystals 2.5µm long and 500 nm wide. 3-(trifluoroMethyl)pyrazole modulator produced two distinct groups, one of 400 nm long and 100 nm wide crystals, and another of 1.5µm long, 400 nm wide crystals. We are currently working on taking SEM and measuring the MOF with the indazole modulator. The initial results show new trends between modulator and morphology, indicating trends vary depending on MOF's chemical nature. This project contributes to the fundamentally interesting inquiries around MOF design, synthesis and morphology control so that the process can be adjusted to specific applications.

Investigating the Evolutionary Trajectory of PROM-1 Through Conservation Analysis in the Context of Sterol Biosynthesis

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Prominin-1/CD133 (Prom1) is an integral membrane protein that is highly conserved among animals and widely expressed in human tissues, with clinical significance in several types of cancer as well as retinal degeneration and stem cell differentiation. Prom1 regulates membrane bending and induces protrusions and the formation of extracellular vesicles (EVs) from the plasma membrane. The stable binding of Prom1 to cholesterol regulates its membrane bending and scaffolding functions as well as EV formation. In order to identify which species express prominins, we performed an evolutionary breadth search and found that prominins can be found in non-metazoan Opisthokonts such as fungi, SAR, and choanoflagellates, all of which lack cholesterol expression. Our goal is thus to investigate the evolutionary trajectory of Prom1 in the context of the transition from cholesterol to different sterols and test how it affects known Prom functions. We performed conservation analysis to identify residues in the transmembrane region that might correspond to this transition and are therefore hypothesized to play an important role in cholesterol-dependent Prom functions. We then mutated these sites (W795, L161, G454, N791, and C135), and tested their impact on EV formation and partner protein binding. We found that all mutants produce approximately similar-sized EVs but they may have different Prom1 densities which suggests that they may have different levels of Prom1 activity. In addition, W795L and C135S show a defect that significantly decreases the co-trafficking of Prom1 with Pcdh21. Our next steps will include replicating our results as well as testing stable cholesterol binding, glycosylation, oligomerization, and membrane bending, as well as characterizing EV populations. These assays will help us identify the differences in phenotype between the wild type and mutant Prom1 which is critical for understanding the function of the mutated residues and developing a stronger mechanistic understanding of Prom1 function.

Supercooled Phase Change Material Microcapsule as a Rapid Heating Agent

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Phase change materials (PCMs) such as certain salts hold a multitude of opportunities for green energy applications in temperature-controlled systems due to the large latent heat they exude when undergoing phase changes. This may be utilised in heating applications. While supercooled, the salt may be triggered to crystallise with external activation. Particularly interesting is the ability to encapsulate these salts so that they are the correct size to travel through the bloodstream, a few micrometres. A future application for these capsules would be in organ transplants. Microcapsules could be injected into the bloodstream then externally activated via ultrasound to heat the donor organ to body temperature. Therefore, ultrasound was initially investigated as a trigger for crystallisation. It was found that 53 wt% of water in sodium acetate trihydrate salt solution was the ideal concentration, to be triggered if undercooling was greater than 20ºC. Polymethyl methacrylate was chosen as the biocompatible coating. Two synthesis techniques were considered. For the direct evaporation method, salt solution was homogenised in acetone at 60ºC, using span-80 as a surfactant. For the interfacial polymerisation technique, initially salt solution and toluene was homogenised. A monomer in acetone solution was then added dropwise for polymer formation. The latter was considered the more successful technique as polymer precipitated directly on water droplets rather than forming a film. Both methods required use of surfactant to create stable emulsions. Several surfactants were investigated, adapting the hydrophilic-lipophilic balance. Resulting capsules were analysed using optical microscope for quality check, DSC to ensure peak from supercooled salt, then XRD to confirm composition. We hope to detect microcapsules which do not dissolve in water, indicating successful encapsulation. Future goals would be to improve yield and control of particle size, via altering the ratios of reactants and testing alternative salts.

Nanopatterning Bi2Sr2CaCu2O8+δ Superconductor

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Mentor: Kevin Hauser

Nanoscale fabrication techniques have revolutionized electronics, but advanced materials like superconductors have not received sufficient attention. In this project, we address the local degradation of superconductivity when Bi2Sr2CaCu2O8+δ (BSCCO) comes into contact with thin chromium overlayers, and aim to create nanopatterns on BSCCO for potential use in next-generation quantum computers and other technologies. To attain this objective, I made use of clean-room nanofabrication and nanoscale imaging techniques. Using photolithography techniques and reactive ion etching (RIE) I created a recipe to etch trenches on silicon oxide chips that would yield vertical walls, while optimizing parameters like the correct photoresist, dosage, defocus, and etching time. Additionally, depositing chromium was an issue since it oxidizes quickly when in contact with air. In solving this issue I used a protective layer of gold which can be removed with aqua regia, an acidic solution that does not react with chromium due to chromium passivation. For future directions in verify the effectiveness of the device in locally degrading superconducting activity, I used the physical properties measurement (PPMS) machine to measure the resistivity of the material at different places and temperatures.

Understanding the Effects of CAHS-2 Proteins on Cellular Stress Tolerance

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Mentor: Samuel Lim

Extremotolerant organisms such as tardigrades are known to survive in harsh environments due to production of intrinsically disordered proteins (IDPs). Because of their lack of tertiary structure, IDPs exhibit several mechanisms that protect cells from stress, including vitrification and water replacement, which mostly function by forming protective compartments around the toxin or around critical areas of the cell. In this project, we investigate the effects of the CAHS-2 protein, which is found in tardigrades, in human and bacterial cell lines. Specifically, we predict that CAHS-2 proteins facilitate the formation of phase-separated condensates in human cells to protect the cells from various stresses. We further hypothesize that cysteine disulfide bonds present in the CAHS-2 protein are responsible for the formation of these granules, and thus that cells containing a cysteine-knockout mutation will not exhibit the protective phenotypes. We performed MTS assays to measure cell viability when exposed to various stresses. Preliminary results suggest that cells expressing CAHS-2 proteins form protective granules when exposed to arsenite-induced oxidative stresses. Future directions include the introduction of self-assembling coiled-coil domains as well as additional cysteine residues to tune the biophysical properties of the condensates and determine the relationship between condensate properties and the protective phenotype of the CAHS-2 proteins expressed in vivo in E Coli. These findings could provide critical insights to enable the engineering of cells with enhanced tolerance to extreme weather events and disease.

Agency and Arousal

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Past literature suggests that one's feeling of being "in control," or the sense of agency, is related to emotional arousal. However, this past work has mixed findings; while some studies suggest a positive correlation between sense of agency and arousal, others show the opposite trend. In this study, we seek to further understand the relationship between agency and arousal by measuring human participants' explicit and implicit sense of agency under conditions of varied arousal, while passively measuring pupil size as a readout of arousal. To measure explicit agency, we have participants complete an agency judgment task where they indicate whether or not they believe they caused an unrewarded outcome. To measure implicit agency, we have participants complete a sensory attenuation task based on prior work showing that perceptions of sensory information are dampened when people believe they caused it. And to systematically vary arousal, we have participants perform identical tasks under both the threat and absence of uncomfortable but painless shock. We expect arousal and agency to be negatively correlated. Under threat of shock (i.e., increased arousal condition), we expect to see an increase in pupil size, a decrease in sensory attenuation (implicit), and a decrease in agency judgments (explicit). These results may indicate that as arousal increases, sense of agency decreases. By illuminating the relationship between arousal and sense of agency, our results will help us understand the mechanisms behind the phenomenology of agency which may have important implications for patients with pathologies related to the sense of agency, such as depression, anxiety, and psychosis. In the future, a similar study which directly manipulates physiological arousal using the drug propranolol may illuminate whether or not arousal plays a causal role in modulating sense of agency.

Investigating T-Cell Mediated Glaucomatous Neurodegeneration

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Glaucoma, characterized by optic nerve damage and retinal ganglion cell (RGC) degeneration, is the predominant cause of irreversible blindness throughout the world, affecting approximately 80 million people worldwide. Furthermore, one important disease risk factor is high intraocular pressure (IOP), and lowering high IOP is currently the only way to treat glaucoma clinically. However, high IOP alone is not the sole cause of glaucoma, nor is it necessary for causing glaucoma. Recent studies show the involvement of T-cells specific to heat shock proteins (HSPs) and suggest that glaucoma may be an autoimmune disease related to inflammatory responses. Specifically, HSP60 and HSP27 have been linked to RGC loss in mice and have previously been detected in glaucomatous patients and animal models. To further define the T-cell subtypes involved, we utilized triple-immunolabeling and flow cytometry to detect CD4+ T-cells and T-cell subsets which infiltrate the ganglion cell layer (GCL) in murine glaucomatous retina. These include interferon- γ (IFN-γ) corresponding to TH1 T-cells, CD25 and FoxP3 corresponding to Treg T-cells, and interleukin-10 (IL-10) and LAG3 corresponding to Tr1 T-cells. Further studies may lead to greater mechanistic understanding of cytokine production due to HSP specific T-cell infiltration systemically in glaucomatous mice and humans with primary open-angle glaucoma (POAG). Such findings may have broader implications for neurodegenerative diseases and inflammatory diseases such as Alzheimer's disease, and may provide greater gateways to potential therapy treatments, which target immune-related disease mechanisms.

Pain and the Brain: Using fMRI to Identify the Cortical and Subcortical Brain Representation of Experimentally-Induced Secondary Mechanical Hyperalgesia in Healthy Volunteers

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Pain is considered neuropathic when it is associated with a lesion or disease of the somatosensory nervous system, and is also considered chronic when it lasts for three months or longer. Individuals with chronic neuropathic pain often experience hyperalgesia, increased pain to normally painful stimuli. Primary hyperalgesia is the exacerbation of pain directly where a noxious stimulus is applied, whereas secondary hyperalgesia is enhanced pain that occurs outside of the area of direct stimulation. This implies a change in how the central nervous system (CNS) processes nociceptive signals, though the mechanisms behind secondary hyperalgesia are not fully understood. To address this, the capsaicin-heat pain (C-HP) model was developed to model neuropathic pain. C-HP can induce secondary hyperalgesia to pinprick stimuli in healthy subjects. We used event-related fMRI to identify the cortical and subcortical brain structures that respond to painful pinpricks to the leg, and how they change following C-HP exposure in 30 healthy adults (17 females, 27±6 years old). Before and after C-HP, subjects underwent fMRI and experienced a series of 27 weighted pinprick stimuli, with nine repeated probings of three forces: 128 mN, 256 mN, and 512 mN. Subjects rated pain intensity using a numerical rating scale (0-100) for each pinprick weight after each fMRI session. A two-way repeated measures ANOVA detected: 1) a significant main effect of condition, indicating that C-HP successfully induced secondary hyperalgesia ($F=4.643$, $p=0.040$), and 2) a significant main effect of stimulus intensity, showing that we were able to elicit different levels of pain ($F=19.314$, $p<0.001$). fMRI analysis will explore neural activation patterns within the brain evoked by pinprick stimuli before and after C-HP. By identifying the regions responsible for processing secondary hyperalgesia, we can further develop therapeutic treatments that mitigate the effects of chronic neuropathic pain.

Oxidative Stress Response: Identification of Small Molecules Triggering NRF2 Induction

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The human gut hosts trillions of microbes, many of which release small molecules that interact with human cells. There are many cellular pathways that respond to these small molecules. Oxidative Stress Response (OSR) is one of the important pathways that can potentially get affected by these small molecules. OSR regulates levels of reactive oxygen species within the cell, protecting biomolecules such as DNA and RNA from degradation. NRF2 is a transcription factor that plays a pivotal role in the OSR by activating important genes responsible for responding to oxidative stress. In existing literature, some molecules are shown to activate NRF2; however, gut microbiome-associated molecules have not been studied in detail. There is a need for a high-throughput readout of OSR conducive to evaluate many microbially-derived small molecules for their ability to impact oxidative stress. To this aim, I built a luciferase-based reporter to detect changes in NRF2 induction. I tested six reporter designs for their strength of response to sulforaphane, a known inducer of OSR, to validate the reporter design. Future directions using this tool include a chemical screening on different cell types such as human colonic epithelial cell line (HT-29) and human embryonic kidney cell line (HEK 293T) to identify a novel microbiome derived molecule that activates the OSR. This research has profound implications for future studies such as enabling high throughput screening for molecules that form the link between OSR-related diseases and the gut microbiome and may one day inspire drug design for OSR-linked diseases.

Optimization-Based Game Engineering for Attaining Desired Nash Equilibria

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In a mathematical game involving strategic interactions between two or more players, the Nash equilibrium is a state in which no player can improve their payoff by changing their strategy, while the other players keep their strategies unchanged. This concept is fundamental in understanding the outcomes and analyzing the long-term behavioral patterns in game theory, with extensive applications to cell biology, politics, behavioral sciences, and economics. However, there are situations where the existing game's Nash equilibrium does not align with desired outcomes, emphasizing the need to develop engineering systems that facilitate the attainment of new equilibrium states when the current equilibrium state is undesirable. We aim to bridge this gap through game engineering: our computational model identifies optimal perturbations to the current game that allow the transition from undesirable Nash equilibria to more desirable Nash equilibria. We formulate an optimization problem aimed at minimizing such perturbations with custom software tools that reach the solution within well-defined constraints that encode the necessary conditions for Nash equilibrium. Our results show that this robust framework effectively modifies the payoff matrix of our game to achieve desired pure-strategy Nash equilibria efficiently, achieving linear time in the number of payoff entries. Furthermore, the software can be applied to games with diverse player and strategy configurations. Notably, our introduction of accumulative constraints within our optimization model allows for the attainment of distinct perturbation combinations, thereby obtaining multiple unique solutions that attain the desired Nash equilibria. Future directions include expanding the scope of our optimization-based approach to handle games with incomplete or imperfect information, providing more comprehensive solutions to real-world scenarios, and incorporating mixed-strategy Nash equilibrium games.

Skeletal Homeostasis During Aging: Defining celsr1a Adult Skeletal Stem Cells in the Zebrafish

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Stem cells replenish cells lost to age and injury and are crucial to maintaining tissue structure in a post-embryonic organism. During aging, stem cell function and quantity decrease with time, resulting in diminished homeostasis and tissue degeneration throughout the body. A recently emerged zebrafish model with a nonfunctional cadherin EGF LAG seven-pass G-type receptor 1a (celsr1a) gene appears aged at just 10-12 weeks of age due to diminished stem cell-mediated tissue homeostasis across multiple body systems. celsr1a is necessary to activate quiescent stem cell populations that are key to the long-term maintenance of tissue structure in adult zebrafish. Gaining genetic control of these stem cells would allow us to model human age-related diseases. This aging model presents a useful and efficient system for studying organism-wide aging, but developing tissue-specific genetic regulatory mechanisms for celsr1a is necessary to more specifically detail the genetic and physiological aging of different organ systems. As celsr1 in humans is associated with decreased bone density, we aimed to identify an enhancer that regulates celsr1a in zebrafish skeletal stem cells. We compared areas of open chromatin in resting and regenerating bone to areas of histone mono-and-tri-methylation adjacent to the celsr1a locus to identify regions of enhancer activity. Of these, C1a-A emerged as a candidate enhancer sequence active in bone in small, dispersed cell populations consistent with the characteristics of quiescent stem cells. I hypothesize that the C1a-A putative enhancer is a tissue-specific regulator of celsr1a expression in stem cells of the adult zebrafish skeleton and is necessary for skeletal stem cell activation during long-term homeostasis. Unlocking the ability to control stem cell populations in the skeletal system using enhancers would allow us to gain a deeper understanding of how bone tissue degenerates with age and how to maintain our bone health as we become older.

Hyper-Volatile Entrapment in Interstellar Ice Analogs

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Planets and planetesimals acquire their volatile reservoir through ice and gas accretion in protoplanetary disks. The distribution of volatiles between solid and gas states within these disks thus determines the quantity of volatiles accreted onto a solid core or gaseous atmosphere of planets forming throughout different disk regions. The entrapment of hyper-volatiles in less volatile ices allows the hyper-volatile to remain solid beyond its sublimation temperature, producing more complex chemical profiles and different snowline locations in disks compared to what would otherwise be expected. This study uses laboratory experiments to explore the ability of several abundant interstellar ices, H2O, CO2, NH3, CH3OH, and C2H6 to trap key hyper-volatile components, 13CO, CH4, 15N2, and Ar. The entrapment efficiencies of these ices are measured for each hyper-volatile through temperature programed desorption (TPD). During the TPD, the ice is heated at a rate of one Kelvin per minute, and the desorption of both the hyper-volatile and ice species is detected using a quadrupole mass spectrometer (QMS) and further monitored by infrared (IR) spectroscopy. Preliminary results find entrapment efficiencies around 60% for all ices and essentially no statistically significant difference between ice matrix or hyper-volatile species, with perhaps the exception of C2H6, for which current results indicate a much lower entrapment efficiency. These results suggest an entrapment mechanism that operates independently of the chemical properties of both the hyper-volatile and ice species, with perhaps an exception for ethane. Further investigation into the hydrocarbon entrapment mechanism is likely warranted to completely understand entrapment as a whole, and provide the framework to explain and predict the volatile ratios in protoplanetary disks and their subsequent planets.

A High-Throughput *In Vivo* Assay for Magnesium Transport

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Membrane transporter proteins play an important role in maintaining cell homeostasis by governing what molecules enter and exit the cell based on their ability to distinguish between substrates. We are investigating substrate selectivity in DraNramp, a model bacterial metal transporter from *Deinococcus radiodurans*. DraNramp imports rare transition metals like manganese while excluding abundant alkalines like magnesium, but homologous proteins have been identified with altered substrate selectivity. To profile the effects of mutations on substrate selectivity in this model transporter, we need high-throughput assays that couple the import of metal to a readout on which cells can be sorted. To that end, we designed a novel assay that couples magnesium import to fluorescence in *E. coli*. The magnesium reporter leverages a native magnesium-responsive riboswitch, an RNA regulatory element, to activate expression of a fluorescent protein upon magnesium binding. As all known magnesium-responsive riboswitches repress downstream expression, we engineered a "double-negative" system that inactivates a repressor protein responsible for repressing production of a fluorescent protein. This setup allows for magnesium binding to trigger expression of the fluorescent protein. As predicted, we observed increasing fluorescence with increasing magnesium concentration for a magnesium-transporting DraNramp variant, while observing no change in fluorescence for the canonical DraNramp. These initial data indicate that the assay is effectively reporting on magnesium import, and we are currently optimizing the assay for cell sorting applications before testing DraNramp variants. This magnesium assay, in combination with an existing manganese uptake assay, will advance our understanding of the sequence and structural features influencing DraNramp substrate selectivity. Additionally, the engineered reporter strain has broad applications for studying magnesium homeostasis in bacteria and as a platform for designing fluorescence assays with other regulatory elements.

Investigating the Effect of cAMP Modulation on KLF2 Expression in Cultured Human Endothelial Cells

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Atherosclerosis is a complex cardiovascular disease (CVD) characterized by endothelial dysfunction, chronic inflammation, and plaque buildup within the arteries. Dysfunction of the endothelial lining of blood vessels is driven by low levels of expression of Krüppel-like factor 2 (KLF2). KLF2 is a transcription factor crucial in maintaining endothelial integrity and vascular homeostasis and in curtailing pro-inflammatory processes critical in atherogenesis. Thus, understanding how the expression of KLF2 can be upregulated may lead to innovative therapies for CVD. Recently, our laboratory has identified the activation of several G-protein coupled receptors (GPCRs) as an upstream event in the upregulation of KLF2 expression. This project aimed to elucidate the impact of levels of cyclic adenosine monophosphate (cAMP), a second messenger released in response to the activation of GPCR, on KLF2 expression. cAMP is generated by adenylate cyclases and degraded by phosphodiesterases. To this end, we first cultured human umbilical vein endothelial cells with forskolin, a cAMP pathway activator (treatment), or dimethyl sulfoxide (DMSO; control) at specific time points: 15 minutes, 30 minutes, 1 hour, 2 hours, and 3 hours. These experiments showed that the maximum increase in KLF2 expression is achieved after 1 hour of treatment with forskolin. Therefore, a secondary investigation involved pretreating cells with 3-isobutyl-1-methylxanthine (IBMX), a phosphodiesterase inhibitor, for one hour, followed by treatments with forskolin or DMSO at the same time points to analyze KLF2 expression. Our data demonstrated that KLF2 expression is further increased at the one-hour time point when IBMX is also used. Collectively, these experiments documented that increasing cAMP levels results in the upregulation of KLF2 expression in cultured human endothelial cells. Our research has significant implications for future studies on atherogenesis. Moreover, understanding the molecular mechanisms associated with KLF2 expression may contribute to identifying novel therapeutic targets for the prevention and treatment of CVD.

Identifying Mediators of Regenerative Versus Fibrotic Wound Repair Mechanisms in Mammalian Skin

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Mammalian skin is uniquely susceptible to full-thickness wounds which may result from burns, physical trauma, or surgery. While adult skin repairs the epidermal barrier, vital skin cell types and structures are permanently lost and replaced by fibrotic scarring. Scarring affects over 100 million patients annually in the U.S. and causes functional impairment (e.g. growth restriction, joint contraction). By contrast, fetal wounds heal scarlessly, regenerate diverse cell types, and completely restore skin function. While scarless healing in the fetus is well documented, the cellular and molecular mechanisms underlying this loss of regenerative capacity remain poorly understood. This project aimed to identify and functionally characterize specific genes driving the skin's switch from regenerative to repair mechanisms in fetal and adult murine skin, respectively. Bulk RNA-sequencing was previously performed on fibroblasts and macrophages isolated from postnatally wounded skin, embryonically wounded skin, and unwounded age matches. Genes that were highly (transcripts per million > 10) and differentially expressed (log2 fold change > 1) were selected for in vivo functional testing. To determine if genes specifically upregulated in embryonic wound healing were sufficient to induce regeneration in postnatal skin, adeno-associated viruses (AAVs) were used as a vector to overexpress candidate genes in postnatal wounds. After intradermal injection of AAVs containing candidates, full-thickness wounds were created on P5 mice and harvested 14 days post-wounding. Formation of key skin appendages such as hair follicles, arrector pili muscles, and neurons was assessed via immunofluorescence staining. Wounds treated with the genes Ptn and Ccn3 exhibited faster rates of wound closure and increased angiogenesis compared to saline-treated wounds. We plan to verify expression of candidate genes and angiogenesis-related genes via qPCR and further visualize the wound bed via whole mount staining. Ultimately, findings from this work can inform future therapeutic strategies to reactivate fetal-like regenerative pathways in adult wounds.

Nociceptor-Specific Gene Therapy for Chronic Pain

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Chronic neuropathic pain is a condition that affects up to 10% of the US population. It occurs when nociceptors (pain-sensing neurons) fire in the absence of painful stimuli, causing pain perception. The pain itself can be temporarily controlled through various medications and procedures, but no cures or therapies exist that target the underlying cause of the condition. A proposed way to treat chronic pain is by turning off these overactive nociceptors through targeted gene therapy, delivered via injection of a viral vector containing a drug driven by a nociceptor-specific promoter. Current gene therapies for other conditions utilize promoters that do not discriminate between cell types, and would thus result in serious off-target effects if used for chronic neuropathic pain. The proposed study aims to identify promoters that are nociceptor-specific and could thus eliminate pain in patients while allowing them to retain other sensations. To do this, we tested the specificity of different promoters that ATAC-seq data previously identified to us as possibly nociceptor-specific. Mice were injected with constructs containing different promoters derived from the mouse genome and GFP. Dorsal root ganglia (bundles of sensory neurons located in the peripheral nervous system in close proximity to the spinal cord transmitting sensory information) were sectioned and fluorescent in situ hybridization was performed. Nociceptors were identified following Tac1 labeling and neurons infected by the viruses were labeled with GFP. GFP positive cells from each image were segmented and categorized based on GFP and Tac1 expression levels. So far, we have identified a potential candidate virus that mostly targets nociceptors but also infects other types of cells to a small extent. We hope to identify other potential promoters that could lay the foundation for development of a nociceptor-specific gene therapy to combat chronic pain.

Reduction of Prion Protein Formation in U251MG Cells Through the Use of Base Editors

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Mentor: Meirui An

Infectious, misfolded prions can cause various fatal diseases in mammals, such as Creutzfeldt-Jakob disease and bovine spongiform encephalopathy, none of which currently have a cure. Prion protein (PrP) is a nonessential protein encoded by the *PRNP* gene in humans. Previously, delivery of antisense oligonucleotides targeting *Prnp* in the brains of adult mice has been shown to reduce cellular *PrP* levels and be protective against prion disease symptom onset and death. In 2016, the Liu Lab developed cytosine base editors (CBEs), a fusion of CRISPR-Cas9 and cytidine deaminase enzyme that enables the conversion of C•G DNA base pairs to T•A base pairs. A guide RNA (gRNA) directs CBE to the target gene locus for editing. Using CBEs, we seek to install single base pair edits within the *PRNP* gene that will result in nonfunctional or shortened *PrP* and therefore decrease the formation of misfolded prions. Plasmids encoding CBE and gRNA were introduced to U251MG human glioblastoma cells via transfection, but high-throughput sequencing of the *PRNP* amplicon revealed no editing of the gene. We aim to optimize conditions for introducing the gRNA and CBE plasmids to these cells via nucleofection, a technique that uses an electric current to create pores in the cell membrane, allowing DNA to enter the cell. We will then perform high-throughput sequencing of the *PRNP* amplicon to quantify editing efficiency, then determine percent *PrP* level change relative to untreated cells using a western blot or flow cytometry. The results of this project will help determine whether base editing can feasibly decrease *PrP* in human cells as a potential therapeutic for prion disease.

Characterization of Jurkat Cell Based Assays for PD-1/PD-L1 mAb Analysis

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Upon activation, CD4+ and CD8+ T cells express PD-1. PD-L1 is a PD-1 cell surface ligand that recruits PD-1 near the T cell receptor and CD28, leading to T cell inactivation. Certain cancer tumors overexpress PD-L1 allowing them to evade immune responses. To combat this, PD-1 and PD-L1 inhibitory monoclonal antibodies have been developed and shown to be effective in treating cancer. However, in the context of autoimmune diseases, agonizing PD-1 and inhibiting T cell activation has therapeutic potential. Therefore, the PD-1/PD-L1 pathway is a potential target in treating cancer and autoimmune conditions. Through in silico, in vivo, and in vitro methods, this project aims to expand upon PD-1/PD-L1 immunobiology and discover novel antibodies that show clinical promise in agonizing or antagonizing PD-1. To establish an effective model for T cell activation, this project seeks to characterize the properties of a Jurkat cell model. The results show that Jurkat IL-2 luciferase reporter mPD-1 cells contain the cell surface proteins necessary for them to be effective in a T cell activation model. To measure T cell activation, Jurkat NFAT luciferase reporter or IL-2 luciferase reporter cells were added to wells seeded with mPD-L1+ and mPD-L1- CHO-TCR activator cells. Luminescence was measured as it serves as an estimator of T cell activation in this model. The data shows that the NFAT model is more sensitive to the inhibition of PD-1-PD-L1 interactions, whereas the IL-2 model shows dependency on both the blocking of PD-1-PD-L1 interactions and the engagement of CD28. However, through experimentation with B7 agents, we determined that the Jurkat assay was not effective in detecting PD-1 agonism. Future experimentation includes testing of antibody effectiveness in transducing or blocking a PD-1 signal in a mouse model, and the modeling of these agents or antibodies using AlphaFold2-Multimer for structure prediction.

A Molecular Phylogenetic and Morphological Analysis of Percnon Crabs (Brachyura, Percnidae)

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Mentor: Paula Rodriguez-Flores

Percnon crabs (Brachyura, Percnidae) were considered a genus under the family Plagusiidae, until 2005, when they were established as their own family, Percindae. Percnon crabs consist of seven extant species across all oceans. Previous studies have created molecular phylogenies for Brachyura crabs, but none have evaluated Percnon at a species level. This study aims to provide the first species-level molecular phylogeny of Percnon. In this study, the phylogeny was constructed based on ultra-conserved elements (UCEs) and the DNA barcoding system using mitochondrial gene segments and was supported by morphological characteristics. The taxa were photographed, illustrated, and imaged using micro-computed tomography (microCT). The implications of this phylogeny will support the classification of Percnidae as monophyletic and highlight the morphological structures that support the vast geographical spread of the seven Percnon species. Future studies may investigate the specific identified morphological traits and how they might result from evolutionary adaptations to new geographic locations.

Characterizing Ubiquitin Inclusions in X-Linked Dystonia Parkinsonism

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Mentor: Christine Vaine

X-linked dystonia parkinsonism (XDP) is a rare neurodegenerative disease that is characterized by a combination of hyper- and hypokinetic features typical of dystonia and parkinsonism, respectively. Analysis of post-mortem XDP patient brains reveals a progressive loss of medium spiny neurons in the striatum, and unpublished preliminary studies from the Bragg Lab have identified inclusions in XDP post-mortem brain tissue that are immunopositive for ubiquitin and p62, suggesting the possibility that the inclusions may play a role in XDP neuron death. In this study, we developed a method to isolate ubiquitin-bound proteins for future mass spectrometry by performing immunoprecipitation using human post-mortem brain tissue. In parallel, we are performing immunofluorescence staining for ubiquitin and p62 on various regions of XDP and control brains to confirm previous findings and inform our choice of brain region for pulldown experiments. Thus far, the pulldowns for cerebellum and BA9 region samples have stained positive for ubiquitin on a Western blot, suggesting that immunoprecipitation using brain tissue lysates was successful. Subsequent staining for p62 shows no significant differences in ubiquitination of the protein between control and XDP samples. Preliminary results of the post-mortem tissue staining show a slight increase in the amount of ubiquitin and p62 inclusions in all regions of XDP tissue compared to control tissue, which confirms previous findings. Furthermore, we are currently generating neurons via induction of XDP patient and control iPSCs as well as direct conversion of XDP patient and control fibroblasts to retain epigenetic markers. Immunofluorescence staining of ubiquitin and p62 with these neurons will help to determine whether these cell models exhibit the same dysregulation of proteins as post-mortem brain tissue. Confirmation of these results in the cell models would allow for future studies to further probe mechanisms underlying the ubiquitin and p62 protein deposits.

A Novel Immunosuppressant for the Treatment of Graft-Versus-Host Disease

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Graft-versus-host disease (GvHD) is a complication that can occur after allogeneic stem cell transplant, in which immune cells originating in donated graft recognize and attack host tissues. Prophylactic and therapeutic regimens utilizing conventional immune suppressants have reduced the incidence and significance of GvHD for many transplant patients. However, these drugs can be ineffective, induce adverse side effects, and be challenging to manage clinically. Preliminary in vitro and in vivo data indicate that eliglustat, a glucosylceramide synthase inhibitor currently used to treat Gaucher's disease, inhibits T cell proliferation and expands regulatory T cell populations in mice. Its effect on human T cells, however, has not been characterized. This study aims to elucidate the effect of eliglustat and ibiglustat, another glucosylceramide synthase inhibitor, on human T cell proliferation and cytotoxicity in vitro. It further examines the impact of these compounds on the proliferative activity of hematopoietic stem cells. By determining to what extent human T cells are suppressed by glucosylceramide synthase inhibitors, this work could motivate further investigation into the effect of these compounds on animal GvHD models. Together, these studies will indicate whether systemically delivered glucosylceramide synthase inhibitors represent a potential treatment for hematopoietic stem cell transplant-associated GvHD.

Effects of Developmental Microbial Depletion on Neural Circuits of Gastrointestinal Pain

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Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Disease (IBD) are chronic, potentially debilitating disorders characterized by severe gut pain and general gastrointestinal (GI) dysfunction. Although IBS and IBD affect many millions of people worldwide, not much is known about the neurological circuits underlying GI pain, nor how other factors such as the gut microbiome affect the development of these circuits. This project utilizes a wild-type mouse line treated with a set cocktail of oral antibiotics throughout the prenatal and early developmental period to elucidate how microbial depletion in the gut impacts the development of gut-innervating dorsal root ganglion (DRG) neurons. Following antibiotic treatment, we perform behavioral analyses at the adult time point to investigate the influence of developmental microbial depletion on sensations of pain in the colon. To analyze visceral hypersensitivity in the mice, we administer animals with a colorectal gavage of capsaicin and score them for pain-related behaviors. We then perform immunohistochemistry (IHC) to visualize cFos activation patterns in the dorsal horn of the lumbosacral spinal cord for analysis of innervation patterns of colon-innervating DRG neurons. While tissue processing and behavioral analysis is still underway for this cohort of mice, results may point towards a greater role of the gut microbiome in development of neural circuits of GI pain. Should these findings prove to be significant, it will open doors for future research into the molecular pathways underlying connections between neuronal development and the gut microbiome.

Examining Transcriptional Heterogeneity in Response to Antibiotic Perturbation on a Single-Cell Resolution

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Antibiotics have revolutionized the ability to treat bacterial infections, greatly improving life expectancy and the quality of medical care. However, the emergence of antibiotic resistance and persistence has jeopardized this intervention, representing a global crisis that is projected to cause nearly ten million deaths annually by 2050. Antibiotic efficacy is evaluated by the median lethal dose concentration (LD50), representing a key benchmark in understanding the distinct bacterial responses within infections. Unlike bulk RNAseq, which lacks the resolution to differentiate between the responses of individual bacteria, single-cell RNAseq is able to identify sub-populations of interest. Through the use of BacDrop, a bacterial single-cell RNA sequencing (scRNAseq) method, our lab has studied the transcriptomics of bacterial populations and identified transcriptional heterogeneity in *Klebsiella pneumoniae*. Our lab has also identified sub-populations that demonstrate the bacterial persister phenotype when exposed to antibiotic stress. We now apply BacDrop to clinical isolates of *Escherichia coli* to study the heterogeneity that allows 50% of a population to survive in a given concentration of antibiotics while 50% die. We aim to identify clusters of genes that are expressed or repressed during antibiotic stress. Such gene regulation may be linked to antibiotic resistance or persistence. Currently, our work has been directed towards successfully performing BacDrop with treated *E. coli* and constructing a complete cDNA library for deep sequencing. Preliminary results may reveal potential treatment targets by identifying biological pathways linked to stress responses.

Mechanisms of Species-Specific Engagement of LPS Inflammasome Caspases by NLRP11

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The aim of this study is to investigate the determinants of NLRP11 binding, a lipopolysaccharide (LPS) pattern recognition receptor discovered in human macrophages. It is known that NLRP11 binds and activates the human caspase 4 inflammasome complex but fails to do so with its mouse homolog caspase 11. Understanding the determinants of these binding interactions will provide important insights into species-specific responses to LPS, especially given that mice have less sensitivity to LPS compared to humans. The goal of this project is to create an improved mouse model with modified NLRP11–caspase 11 that increases LPS sensitivity to a level comparable to humans. The first objective was to define the domains and residues of caspase 4 required and sufficient for interaction with NLRP11. To do this we have created chimeric constructs interchanged with the CARD, p19, and p10 domains of caspase 4 and 11 utilizing PCR, restriction endonucleases, and Golden Gate cloning. Next, we validated our constructs using DNA sequencing and successfully tested expression of each construct through transfection of HEK 293T cells through western blot analysis. Currently, we are utilizing immunoprecipitation assays for each chimeric construct with FLAG tagged NLRP11 in HEK 293T cell lysates, allowing for the identification of the domains of caspase 4 required for binding to NLRP11. Once we have narrowed down the domains of interest for caspase 4, we will identify specific residues that are required and sufficient for binding by aligning the domain(s) of interest with wild-type caspase 4 and caspase 11, allowing for non-conservation analysis and targeting of specific residues for individual or multiple substitution with QuikChange ll. Overall, these findings will provide a basis for developing potential therapeutic approaches for the treatment of inflammatory diseases and contribute to our understanding of the innate immune system through an improved mouse model.

Dissecting the Functional Relevance of Intratumoral HER2 Heterogeneity in Breast Cancer

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Accounting for 20% of breast cancer cases, HER2-positive breast cancer is a molecular subtype characterized by the amplification of ERBB2, the oncogene encoding human epidermal growth factor receptor 2 (HER2). In the past few decades, targeted therapies including anti-HER2 antibodies (e.g., trastuzumab), antibody-drug conjugates (e.g., T-DM1 and T-DXD), and small molecule inhibitors (e.g., neratinib, tucatinib, and lapatinib) have been developed to inhibit HER2 signaling and consequently mitigate tumor growth. However, resistance to treatment poses a significant concern, especially for patients with heterogeneous tumors. Our lab has shown that intratumoral heterogeneity for ERBB2 amplification and HER2 overexpression is associated with a lack of response to HER2-targeted therapies. This project aims to study the functional relevance of HER2high and HER2low subclones in breast tumors. In order to model this HER2 heterogeneity, we identified two HER2-positive human breast cancer cell lines with distinct and stable HER2high and HER2low subpopulations, tagging each with a fluorescent marker to enable live tracking in cell culture. We used functional assays, immunofluorescence, and western blots to characterize these subpopulations individually and in co-culture, specifically in regard to drug response. Our preliminary results indicate that HER2low cells promote the growth of HERhigh cells in co-culture, suggesting that the subpopulations may be engaging in cell-cell communication. Moreover, HER2low cells are resistant to some HER2-targeting therapies while interestingly responsive to others despite having low numbers of the HER2 receptor on their surface. Further research will look to elucidate the interaction between the two cell subpopulations as well as guide the development of effective combination therapies for cancer patients with HER2-heterogeneous tumors.

An Investigation of the Role of Astrocytes in Alzheimer's Disease Pathogenesis Through Astrocyte Ablation

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Alzheimer's Disease (AD) is the most common form of age-related dementia, characterized by progressive memory loss and cognitive impairment. Two pathological hallmarks of AD are amyloid plaques, which are composed of the amyloid-β protein (Aβ), and neurofibrillary tangles (NFTs), composed of filamentous accumulations of hyperphosphorylated tau (p-Tau). The amyloid hypothesis of AD posits that accumulation of Aβ leads to NFTs. Astrocytes regulate the synaptic transmission, protect neurons against toxins, and provide metabolic support for the function of neurons. Attempts have been made to explore astrocytes' role in AD pathogenesis in AD transgenic mice. However, there is still limited understanding of astrocytes in the context of Aβ and tau pathologies in human AD. In this project, we utilize three-dimensional (3D)-AD cell culture models, consisting of neurons and astrocytes differentiated from human neural progenitor cells. These 3D-AD cultures overexpress familial AD-associated APP$_{Swedish/London}$ mutations or both APP$_{Swedish/London}$ and PS1δE9 mutations. Of note, these cultures recapitulate many of the key aspects of AD, including Aβ aggregation and increased p-Tau. This project seeks to understand the role of astrocytes in human AD through astrocyte ablation using L-α-aminoadipic acid, an astrocyte-selective gliotoxin. We will confirm astrocyte ablation by western blot analysis using astrocyte marker proteins (GFAP and S100β antibodies). We will examine Aβ pathology by measuring Aβ40 and Aβ42 levels in the conditioned media and 3D gel lysates using Meso Scale Discovery's (MSD) V-PLEX Plus Aβ Peptide Panel Kit. Furthermore, tau pathology will be assessed using MSD's Phospho(Thr231)/Total Tau Kit and western blots using PHF-1 (Ser396/Ser404), AT8 (Ser202/Thr205), and total tau antibodies. Expected results would provide insight into astrocytes' role in the AD pathogenesis. Elucidating the mechanisms by which astrocytes contribute to AD pathology is crucial to better understand this disease, eventually providing an effective treatment strategy.

Elicitation of Rare, Broadly Neutralizing Influenza Antibodies via Rational Immunogen Design

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There is an urgent need to develop next-generation influenza vaccines that provide improved protection against seasonal influenzas as well as emerging, potentially pandemic, viruses. Rational, structure-based immunogen design leverages protein engineering to advance vaccine candidates that elicit broadly neutralizing antibodies (bnAbs) targeting conserved regions on the influenza hemagglutinin (HA). Recent strategies have used hyperglycosylation to design influenza HA immunogens engineered to elicit bnAb responses that target the conserved receptor binding site (RBS) on HA. Our work investigates how modifying glycosylation patterns on HA can design immunogens that bind bnAbs targeting the RBS. Preliminary data suggests that our initial, engineered immunogens, can be recombinantly expressed, with biophysical characterization (e.g., biolayer interferometry [BLI], ELISA) ongoing. Successfully characterized immunogens will be advanced towards subsequent in vivo characterization in the murine model. Following immunization, serum, as well as lymph node samples, will be collected for single B-cell analyses and used for biochemical and biophysical assays to assess immune-focusing on the RBS. This subsequent serological profiling, as well as B cell sorting, will show how our designed immunogens will elicit responses to the conserved HA RBS. These immunogen design strategies will ultimately provide protection against pre-pandemic influenzas and serve as templates for next-generation viral vaccines.

Understanding the Structural Determinants of Interleukin-1β and Crystallin γS Interaction in Neuroinflammation in the Eye

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Glaucoma and age-related macular degeneration (AMD) affect the eyesight of millions yearly. In efforts to resolve this issue, it has been found that crystallin γS (CrygS) protein modulates interleukin-1β (IL1β) signaling through regulating an inflammatory cascade that causes retinal neuroinflammation. Preliminary experiments suggest that retinal injections of CrygS recombinant protein have prevented retinal inflammation in mice by interacting with IL1β (Dr. Eleftherios Paschalis Ilios, PhD). However, the structural factors that govern the chemical interaction between CrygS and IL1β proteins have not yet been resolved. Wildtype CrygS and IL1β proteins have been expressed and purified using bacterial cells under denaturalized conditions (6M guanidine) that cause them to unfold. Pure proteins were refolded and purified using overnight dialysis and size exclusion chromatography (SEC) to determine their oligomeric, or structural, states. After SEC experiments, proteins were mixed into a 1:1 ratio for protein crystallization using a vapor diffusion method at 4°C for crystal formation, where diffusion of water vapor from protein solution creates an equilibrium between protein and precipitate preferable for crystal formation. To date, promising crystals have been observed that will be sent for X-ray diffraction analysis in order to resolve the potential structure of the complex CrygS+IL1β. If the IL1β and CrygS proteins are successfully bound, a deep analysis of the structure will provide a better understanding about the binding interface between CrygS and IL1β proteins. This information could help us to design molecules that could modulate such complex formation in vitro as well as neuroinflammation in the eye.

Additively-Manufactured Gradient TPMS Silicon Anodes for Solid-State Batteries

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Silicon (Si) anodes have piqued the interest of the solid-state battery (SSBs) industry due to their high specific capacities, promising improved performance while maintaining cycling durability. 3D triply periodic minimal surface (TPMS) morphologies have likewise been known to carry highly desirable properties for energy storage, with their high surface areas, morphological uniformity, structural stability, and interlocking nature. Combined, Si anodes and TPMS structures offer a synergistic blend of advantages that promise to break free of the limitations of traditional interdigitation. This work provides a stepping stone toward such fully-integrated TPMS batteries by studying stacked, "2.5D" SSBs with TPMS Si anodes, where only the anode is three-dimensionally structured. The TPMSs were synthesized via vat-polymerization (VP) based additive manufacturing (AM), using a custom feedstock comprising Si powder and a wax-based photopolymer binder. A variety of TPMS structures are assessed, including gyroids, lidinoids, diamonds, and split-ps, as well as gradient TPMSs of varying densities. Results indicate measurable energy and power density advantages as compared to traditionally-manufactured cells, with minimal losses in long-term cycling durability. These findings bode well for the future of TPMS SSBs, paving the way toward fully-integrated, atmospheric-pressure TPMS SSBs that fully leverage morphological synergies. Such TMPS SSBs would prove to be compelling alternatives to conventional lithium-ion batteries in a range of space-, performance-, and durability-prioritizing applications.

Enteric Neurons Prime Systemic Immunity

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Mentor: Rahmeh (Ro) Othman

The enteric nervous system (ENS), also known as the "second brain," plays a pivotal role in regulating the physiology of the gastrointestinal tract (GI), including peristalsis and nutrient absorption. Recently, our lab has highlighted the role of the ENS as a key regulator of GI immunity. Interestingly, the ENS is unique as it can synapse with the central nervous system, leading to bidirectional communication between the gut and the rest of the body. We hypothesize that enteric neurons are poised to sense disruptions in intestinal immunological homeostasis and can convey this information peripherally. By artificially stimulating the ENS in transgenic mice, we show that the ENS can indeed drive the expression of immunomodulators in peripheral immune organs, to prime and protect the body from systemic infection. Furthermore, by challenging mice with an intestinal *Salmonella* Typhimurium infection (Stm), followed by a secondary systemic infection, we identify that mucosal infection primes peripheral immunity. Of note, this protective response is lost after GI denervation. Interestingly, cytokine profiling in the blood of mice whose ENS was stimulated, artificially or through Stm, showed an upregulation of proteins involved in neutrophil trafficking and activation axes, suggesting a putative mechanism of action underlying this response. Neutrophil expression and distribution were validated by immunostaining using a neutrophil marker (Ly6G) and a neural structural marker (β-Tubulin 3), showing an increase in neutrophils upon neuronal stimulation. To confirm this, we are currently quantifying neutrophil expression in various organs, including the blood, liver, spleen, and bone marrow using flow cytometry. Altogether, this work unravels an essential role of the ENS in "rapidly" detecting infection in the GI to alert, prime, and protect the body against microbial invasion.

Force-Measuring Cuff for Wearable Shoulder Robot

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Researchers at the Harvard Biodesign Lab have developed a soft pneumatic wearable robot to support the arm at the shoulder, reducing fatigue when performing tasks with raised or extended arms. Because of the complicated nature of the shoulder joint and pneumatic actuators, there is currently no way to measure the exact amount of force the robot is exerting on a wearer's arm. Determining this force is crucial in order to ensure the wearer's comfort when using the robot or to adapt the robot for medical and rehabilitative applications. This study began the process of developing a specialized cuff with an embedded force-sensing load cell to be worn between the arm and the robot's actuator. The cuff is intended to measure the force that the robot exerts throughout its motion. The best type of load cell for this application was determined using a bench test. This test used a pneumatic piston to apply angled and off-axis point loads, simulating non-ideal loading conditions on the robot, to evaluate load cell accuracy under such conditions. A prototype cuff was designed to interface the load cell with the wearable shoulder robot and accommodate the unique constraints of each. Further development will include research into the accuracy of this force cuff during use of the robot to determine the ultimate viability of this concept.

Investigating the Effect of Forskolin in Human Neural Cells Expressing Membrane-Avid Synuclein Mutant

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α-Synuclein (αS) is a 140-amino acid protein that binds to neuronal vesicle membranes and governs synaptic health. Imbalances in its dynamic equilibrium contribute to neuronal loss in Parkinson's disease (PD), which presents as progressive loss of motor control, and other related synucleinopathies. We previously showed that excess αS at the membrane leads to cytotoxicity, decreased tetramer:monomer ratio, and abundance of inclusions, which colocalize with vesicle markers and lipid droplets. In cellular and mouse models, interfering with fatty acid metabolism via stearoyl-CoA desaturase (SCD) ameliorates PD-relevant phenotypes. Here, we tested the effect of the lipid droplet altering drug forskolin on inclusions and lipid droplets in the engineered αS '3K' neuroblastoma cell line, which models the membrane:cytosol imbalance by amplifying the familial PD-linked mutant E46K. Mutant 3KY αS expression was induced with doxycycline addition, and inclusion formation was monitored by live cell microscopy using automated Incucyte from Essen BioScience. Forskolin treatment resulted in reduction of inclusions as well as a reduction in lipid droplet size. Increased phosphorylation is often used as a pathological marker for PD. We find that forskolin treatment led to a significant decrease in phosphorylated αS at S129. Our results suggest that forskolin has potential to alleviate abnormal αS phosphorylation by altering lipid droplet dynamics. Future directions include elucidating the mechanism by which forskolin improves cellular health of 3KY-expressing cells by co-treatment with etomoxir, which inhibits shuttling of fatty acids into the mitochondria and thus interferes with fatty acid oxidation and energy production. Through our research, we hope to provide a pathway toward Parkinson's relief.

Overcoming *ALK* Resistance Through Covalent Inhibitors

Christine Lee
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Mentor: Stefan Harry

EML4-ALK, the fusion between echidnoderm microtubule like protein (*EML4*) and anaplastic lymphoma kinase (*ALK*), plays a key role in the development of non-small cell lung cancer for tens of thousands of patients worldwide. Historically, drugs targeting this fusion protein have centered around non-covalently inhibiting *ALK*, aiming to outcompete ATP as a kinase substrate and ultimately reduce protein function and cancer proliferation. However, as the world of precision medicine has painfully learned, the rapid evolution of mutations constantly renders drugs ineffective, presenting the need for the development of novel drug modalities. To this end, the aim of the project is to develop a suite of covalently binding inhibitors targeting outside the kinase domain. Through proteome-wide mapping and high-content screening, we have discovered that *EML4-ALK* contains highly ligandable cysteines and have also identified several molecules with specificity for the fusion protein. Our studies ultimately define a roadmap for systematically uncovering previously unfound small molecule targets, offering a platform that leverages a new modality for covalent targeting *EML4-ALK*.

Asymmetric Hydrogen-Bond-Donor Catalyzed Synthesis of P-Stereogenic Compounds

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Mentor: Marcus Sak, Gabriel Lovinger

Phostines, compounds belonging to the hydroxy-oxaphosphinanes family, possess anticancer properties and notably exhibit chirality at phosphorus. Medicinal chemistry studies have demonstrated that the biological activity of hydroxy-oxaphosphinanes depend on the compounds' relative and absolute stereochemistry at phosphorus and carbon. Currently, the synthetic production of phostines results in four different diastereomers,of which only one is biologically active. Hypothesizing that the stereoselective synthesis of these phostines can be achieved by stereospecific derivatization of an *H*-phosphinate building block, we synthesized a protected arabinose sugar as the starting material. In parallel, we envision preparing a series of dual-hydrogen-bond-donor catalysts to assess both their abilities to prepare enantioenriched *H*-phosphinates as well as their potential use in other asymmetric organocatalytic reactions. These catalysts include an aminothiourea catalyst and an arylpyrrolidine-thiourea scaffold, employing a state-of-the-art synthetic route to construct the enantioenriched arylpyrrolidine ring. This work is being conducted with a view towards applying these catalysts to catalytic reactions, including those that prepare P-stereogenic compounds in enantioenriched fashion. By extension, implications for this research include improving the ratio of the biologically active phostine that is produced and understanding the mechanism behind diastereoselectivity of this particular reaction.

Synthesis of a Novel Lipid Nanoparticle for Transfection of Exocyst-Silencing Small Interfering RNA Against Immune Evading Adenocarcinoma Cells

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Mentor: Tanmoy Saha

Cancer cells expand oxidative phosphorylation capacity through directional transfer of mitochondria presented by natural killer T (NKT) cells via physical nanotube structures. As an immune evasion strategy, the expansion of phosphorylative capacity metabolically hinders immune cells' ability to promote CD8+ tumor surveillance and limits the effectiveness of commonly administered immune checkpoint inhibitors (ICI) drugs for cancer. The exocyst complex responsible for nanotube formation is an octameric protein complex of Sec proteins which interact with Rho and Ral GTPase during actin remodeling. To limit organelle transfer and prevent further metabolic loss in NKT cells, the colocalization of Sec3 and Sec5 at the site of cytoskeletal recruitment constitutes a potential therapeutic target. In this study, a novel lipid nanoparticle (LNP) synthesized with an ionizable cationic amino lipid is utilized as a transfection agent for small interfering RNA (siRNA)-mediated knockdown of Sec proteins and monitored for long-term stability against particle aggregation and fluctuations in electrical potential surrounding colloidal dispersion. Preliminary results suggest the novel lipid nanoparticle readily undergoes efficient cellular delivery based on fluorescein-conjugated scramblase sequence internalization in the human mammary adenocarcinoma cell line, MDA-MB-231. The LNP's subsequent endosomal escape is further demonstrated by in vitro knockdown of Sec5 validated through immunoblotting and ongoing work to quantify respiratory capacity post-delivery and further optimize lipid composition for maximal transfection. This work holds promise for LNP-based therapeutic siRNA for clinical translation that only requires the target primary nucleotide sequence, thus enabling streamlined drug design and further providing a premise for investigating the mechanistic pathogenesis of mitochondrial channeling to increase T cell capacity in breast cancer patients.

The Vocal Communication Network in the Canine Brain

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Vocal communication is prevalent across the animal kingdom. Studying the vocal communication network in other species' brains provides valuable insight both into their cognitive processes and into the evolution of the human language network. In the human brain, a white matter tract called the arcuate fasciculus connects Broca's area (speech production) and Wernicke's area (speech comprehension). The arcuate fasciculus is implicated in human language. This study assesses whether domestic dogs possess a white matter tract analogous to the arcuate fasciculus and whether this tract shows breed-specific variation. MRI scans from domestic dogs were analyzed using diffusion tensor imaging to look at connectivity between brain regions involved in vocal comprehension and vocal production. The caudal ectosylvian gyrus and rostral ectosylvian gyrus served as regions of interest for vocal comprehension and the precruciate gyrus and polar gyrus served as regions of interest for vocal production. We looked for a ventral pathway connecting the caudal ectosylvian gyrus to frontal regions and a dorsal pathway connecting the rostral ectosylvian gyrus to frontal regions. Our tractography results were compared to the human language network and were assessed for breed specific differences. These findings represent the first study using DTI to look for a pathway similar to the arcuate fasciculus in the domestic dog and to examine how artificial selection for different behaviors and cognitive abilities may have shaped its anatomy differently in different breeds. As a non-primate outgroup, dogs give insight into how vocal communication shapes the mammalian brain, and through domestication, dogs provide a unique opportunity to study how intense selection for behavior and appearance alters neuroanatomy.

Development of an *In Vitro* Model of Bioprosthetic Heart Valve Macrophage-Derived Vesicle-Mediated Calcification

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The demand for bioprosthetic heart valves (BHVs) is projected to triple to 850,000 by 2050. The lifespan of BHVs is limited as they are prone to calcification. The role of adherent and infiltrating macrophages in BHV calcification is unknown. Macrophage-derived extracellular vesicles (EVs) are important in native cardiovascular tissue calcification. This study aims to determine the role of EVs in BHV calcification by developing an *in vitro* model of macrophage-derived leaflet calcification. We first conducted leaflet disk incubation tests in normal (1 mM calcium, 5 mM phosphate), pro-calcific (2 mM calcium, 3 mM phosphate), and osteogenic (2 mM calcium, 11 mM phosphate) media for 14, 21, 28, and 35 days. To optimize THP-1 cell culture conditions, we performed adhesion tests to determine the extent of monocyte/macrophage attachment to culture plastic versus bovine pericardium. Different cell concentrations, centrifugal forces, incubation times, and washing steps were examined. Results were obtained by staining cells with calcein and performing plate reader fluorescence and confocal imaging. Based on optimization results, we cultured phorbol 12-myristate 13-acetate-stimulated (PMA) THP-1 monocytes exposed to basal or osteogenic media on culture dishes and pericardium. Macrophage secreted EVs were collected and enriched for characterization. Nanoparticle Tracking Analysis, western blot and alkaline phosphate measurements determined EV count and size, presence of EV markers, and calcific potential. Cell adhesion tests revealed dose-dependent increases of attachment. With higher centrifugal forces, cells were concentrated surrounding pericardium disks. Varying incubation time had little effect on adhesion. Washing steps reduced the number of adherent cells. Based on optimization, final cultures were performed at a density of 1.5×10^6 cells/mL and stimulated with PMA for 48 hours with no centrifuge step. Media incubation and EV characterization experiments are ongoing. Developing a BHV calcification model will increase understanding of mechanisms of calcification mediated by host cells.

Exploring the Evolution of Oligomerization in the DNA Methyltransferase DNMT3A

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Mentor: Emma Garcia

The *de novo* cytosine methyltransferase DNA methyltransferase 3A (DNMT3A) is a critical regulator of gene expression and development. DNMT3A is able to oligomerize, with its oligomerization state modulating its enzymatic activity. Loss-of-function mutations to DNMT3A are associated with hematopoietic diseases such as acute myeloid leukemia and clonal hematopoiesis. We have shown that the loss-of-function hotspot mutation R882H located in one of the known oligomerization (RD) interfaces reduces DNMT3A activity by causing formation of macro-oligomers. However, we found that the wild-type homolog of DNMT3A in *Octopus bimaculoides* contains a histidine at the residue corresponding to human R882. Studying the oligomerization of DNMT3A homologs may provide insight into correcting loss-of-function DNMT3A mutants in the context of human disease. We performed sucrose gradient ultracentrifugation to find that S878R+A884R, a double mutant designed to mimic the RD interface of *O. bimaculoides* DNMT3A, rescues macro-oligomerization of R882H. We will repeat this experiment with each single mutant to elucidate the residues required to rescue R882H oligomerization. We will also perform this experiment with wild-type *O. bimaculoides* DNMT3A to determine its oligomerization state. Additionally, data from sucrose gradient ultracentrifugation indicates that the histone reader (PWWP) domain of DNMT3A is required for oligomerization. Thus, this project also uses protein sequence analysis tools to elucidate the evolution of the PWWP domain and mechanisms of oligomerization in DNMT3A variants. Through generating and analyzing multiple sequence alignments and phylogenetic trees, we identify additional DNMT3A homologs corresponding to common disease mutations and characterize clades containing and lacking PWWP domains. Ultimately, we hope to create a predictive model of DNMT3A variant oligomerization to understand the roles of R882H and the PWWP domain in oligomer formation. By using experimental and computational techniques to study DNMT3A homologs, we can elucidate the biochemical underpinnings of oligomerization and inform treatment of R882H and other disease mutations.

Strategies to Improve iPSC-Derived Cardiomyocyte Maturation *In Vitro*

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Mentor: Nivedhitha Velayutham

Heart disease is the leading cause of death worldwide. Because mature cardiomyocytes (CMs) do not have the capacity to proliferate, the adult human heart cannot regenerate lost tissue after acute injuries, such as myocardial infarctions. Developing stem cell therapies has the potential to replace lost tissue in hearts after such injuries and reduce heart failure. Thus, human induced pluripotent stem cell (hiPSC)-derived cardiac organoids hold great promise in regenerative medicine. Current protocols have successfully differentiated induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), creating highly pure beating cardiomyocyte populations *in vitro*. However, these hiPSC-CMs often struggle to thrive in *in vivo* conditions and are at risk of causing cell death or arrhythmias when injected into hearts to test stem cell-based strategies. We tested multiple small molecule treatments to promote proliferation and maturation in hiPSC-CMs, contributing to the decades-long investigation to develop hiPSC-CMs *in vitro* that better mimic the structures and beating patterns of mature cardiomyocytes *in vivo*. One such small molecule treatment examines the role of Harmine, an inhibitor of the protein DYRK1a. DYRK1a is upstream of the DREAM complex and is involved in regulating the DREAM complex's activity in cell cycle and quiescence mechanisms. When activated and functioning properly, the DREAM complex helps drive cell proliferation. To observe cardiomyocyte proliferation induction by Harmine, RT-qPCR methods were used to measure the levels of cell cycle gene expression, including *CDK2*, *CDK4*, *CDK6*, *CCNA1*, *CCND3*, and *CCNE1*. At the same time, the expression of genes such as *HCN4*, *TNNT2*, *MYH6*, *MYH7*, and *MKI67* was also noted to measure different stages of cardiomyocyte maturity. The results of these experiments will be used to construct a model for Harmine's effect on cardiomyocyte transcriptional profiles, which will then be used to identify downstream gene targets useful for future DREAM complex, proliferation, and maturation studies.

Differentially Private Probit Regression

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Mentor: Elbert Du

The probit, or "random effects," model is a type of generalized linear model that is useful for making predictions involving human behavior. It is commonly used in conjoint analysis, which models choices made by people among a finite set of discrete alternatives (e.g. type of healthcare, choice of transportation, which college to go attend), and in the learning of other reward models. Attributes of the respondents are often utilized when learning individual and population preferences, so when individuals are asked to participate in these surveys, they may be worried that their information will be leaked or used inappropriately. Our work focuses on studying the probit model under differential privacy, such that predictions about individuals can be made in a privacy-preserving manner. We show that the assumption of normal random effects allows the probit model to integrate smoothly with certain differentially private methods that work by inserting Gaussian noise into the data because the additive noise gets enveloped by a scaling of the coefficients. Combining this procedure with a random perturbation of the binary predictions, we bound the expected losses of the private estimators. Our results show that we can get a similar tradeoff between privacy and learning performance when the data collector is untrusted as current state-of-the-art techniques that assume a trusted centralized server.

Shape Changing Dielectric Elastomer Actuators Using UV Light

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Dielectric elastomer actuators (DEAs) are soft, electrically powered actuators of growing interest in the field of soft robotics due to their mechanical properties, which closely resemble those of mammalian muscles. A simple DEA consists of a soft elastomer layer sandwiched between two electrode layers. When a voltage is applied across the electrodes, the coulombic attraction between the charged electrodes causes a compression in the elastomer. This results in an elongation perpendicular to the applied electric field. By stacking alternating electrode and elastomer layers we can then produce multilayer DEAs with increased actuation. Typically, fabricating the DEA layers involves spin-coating each layer of elastomer onto a substrate and then stamping carbon nanotube electrodes onto the elastomer surface, repeating the process until the desired number of layers is met. However, this process only creates DEAs in the form of flat sheets or rolled-up cylinders, limiting the possible applications of DEA devices. This project aims to use a new class of elastomers to overcome this limitation and produce curved DEA geometries. Recently developed photoswitchable covalent adaptive network elastomers, or photo-CAN elastomers, possess the ability to rapidly and reversibly alter their stiffness when exposed to UV light under ambient conditions, enabling permanent shape change. In this project we demonstrate the successful fabrication of a multilayer DEA using a photo-CAN elastomer. The standard method was adapted by using a base of PET plastic in order to increase the overall stiffness of the DEA and improve its ability to hold its shape. By leveraging the photoswitchable properties of the photo-CAN elastomer, we then achieved new cylindrical actuator shapes, changing the actuation direction based on the new curvature. These findings open up new possibilities for DEA geometries in soft robotics, where intricate and non-planar shapes are desired.

Understanding the Role of CHAMP1 in Replication Stress in Cancer Cells

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Mentor: Amira Elbakry

A recently discovered protein, CHAMP1, has been identified to be involved in DNA repair as a positive regulator of homologous recombination (HR). CHAMP1 plays this role by promoting double-strand break end resection, a critical step for HR to occur. PARP inhibitors (PARPi) induce replication stress in BRCA1-deficient cells, as seen in various cancers, and upregulation of CHAMP1 expression was observed as a mechanism of acquired PARPi resistance in both experimental cell lines and clinical cases. Moreover, knocking out CHAMP1 in BRCA1-deficient cells showed increased sensitivity to PARPi, suggesting the significance of CHAMP1 in the replication stress response. Replication stress is typically found in cancer cells due to defective DNA repair and uncontrolled growth signaling. The replication stress response is vital for genomic stability and preventing DNA damage, so the response must be functional for cancer cells to survive. Since HR factors are also involved in the replication stress response at replication forks, we are investigating the role of CHAMP1 at this site. By inducing replication stress to wild type and CHAMP1 knockout cells with hydroxyurea or ATR inhibitors (ATRi), we can measure the strength of the replication stress response at the replication fork via measuring levels of signaling proteins involved in the response, such as CHK1, KAP1 and RPA, in Western blots, or cell viability assays, correlating with cell survivability. Using these methods, we expect CHAMP1 knockout cells to show higher levels of replication stress. The significance of the role of CHAMP1 in the replication stress response is the potential for CHAMP1 to function as a biomarker of replication stress in cancer cells, such that cancer cells overexpressing CHAMP1 should be targeted with replication stress inhibitors, such as ATRi.

Generative Modelling Using Matchgate Circuits

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Mentor: Hong-Ye Hu

In recent years, machine learning has become increasingly prevalent, with its applications ranging from image classification to natural language processing. Recent popular machine learning models such as DALL-E and ChatGPT are generative, meaning that they are capable of creating new instances of the data that they were trained on. On the other hand, quantum computing has emerged as a rapidly growing field, with the potential to significantly accelerate certain classical computing algorithms. However, the current state of quantum computing is referred to as the "noisy intermediate-scale era," due to the significant error rates and limitations in the number of qubits apparent in even the world's best quantum computers. To better understand its performance and characteristics, we turn to classical simulation.In particular, we studied generative models in the context of quantum computing, aiming to uncover potential quantum speed-ups in machine learning tasks. Building upon previous work done by other members of the Yelin group, we utilized a particular class of quantum gates called matchgates, which are not only efficiently simulatable on a classical computer but also exhibit deep connections to ideas from free fermion theory. Matchgates are promising both from a theoretical and a practical perspective, for their use in quantum machine learning models has yet to be realized. Using Python and Julia, we first implemented parametrized quantum circuits exclusively using matchgates. Since the circuits were parametrized, we were able to utilize classical optimization algorithms to train them on the MNIST dataset of handwritten digits. Once trained, we will be able to generate entirely new pictures of handwritten digits. Ultimately, we want to benchmark the performance of matchgates on generative tasks to see how quantum computing with a large number of error-free qubits performs.

Understanding Retinoic Acid Dysfunction in Colorectal Cancer Initiation

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Colorectal cancer (CRC) in the United States today remains the third deadliest out of all cancers, with more than 80% of cases harboring the loss of the APC gene. Loss of APC has been shown to faithfully recapitulate CRC model. Although new cases and deaths of CRC are steadily declining due to early detection guidelines, CRC is responsible for an alarming trend amongst the younger population. Primary treatment today consists of aggressive chemotherapy that is high in toxicity with limited benefits, still disease progression and malignant transformation regarding CRC remains poorly understood. Sethi lab has shown that the transcription factor *SOX9* is overexpressed in CRC initiation and drives an aberrant cell state with failure to differentiate. *SOX9* overexpression negatively regulates the retinoic acid (RA) signaling pathway in CRC initiation. RA functions as a ligand for the complementary RA nuclear receptor that governs the transcription of important developmental genes in embryos and has been shown to be imperative in the induction of cellular differentiation and proliferation. Single cell RNA and single cell ATAC analysis in the mouse model of CRC ($Apc^{-/-}$) identified loss of key RA metabolic enzyme Aldh1a1 in adenoma compared to normal tissue. We hypothesized that the addition of the terminal RA ligand will recuperate Aldh1a1 levels and RA metabolism. However, upon addition of RA ligand, ATRA, in $Apc^{-/-}$ organoids, reduced RA-signaling output was observed. Together, this data implicates that dysregulated RA-metabolism and signaling is conserved in $Apc^{-/-}$ adenomas. These preliminary results suggest a repressor mediated downregulation of RA-signaling in adenomas. Directly targeting this repressor to study RA dysfunction in CRC models will give insight for new therapeutic approaches that will restore proper differentiation of colon cancer cells in CRC patients.

Efficient Human Germ Cell Specification and Meiosis Induction From Stem Cells via Combinatorial Expression of Transcription Factors

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Advancements in our understanding and manipulation of germ cell development hold promising prospects for the future of human reproduction and infertility solutions. The successful production of *in vitro* gametes, especially oocytes, could alleviate a majority of infertility cases. However, the practical application of current methods for inducing primordial germ cell (PGC) and oogonia formation is restricted by intrinsic technical limitations concerning their methodologies, throughput, and yield. Transcription factor (TF)-based methods offer a promising alternative, having shown potential in identifying pivotal regulators of germ cell development, including primordial germ cell-like cell (PGCLC) formation, meiotic entry, and oocyte maturation. Our research builds upon this method by examining 94 oogenesis-relevant TFs to demonstrate their impact on PGCLC and oogonia formation. We previously found that the co-expression of *ZNF281*, *LHX8*, and *SOHLH1* enabled direct oogonia-like cell formation from human induced pluripotent stem cells (hiPSCs) in a feeder-free culture condition. Additionally, we found that genome-wide demethylation, achieved through DNA methyltransferase inhibitors and modulating factors involved in epigenetic reprogramming, aids in expressing germ cell-specific factors, like *DDX4*. Nevertheless, a pivotal step absent in our in vitro oogenesis is the induction of meiosis; our induced germ cells have yet to enter meiosis and develop into oocytes. Accordingly, we adopted the same TF-overexpression methodology to induce meiosis. Our preliminary data suggested that a co-expression of three transcription factors significantly enhanced the expression of *REC8*, a marker specific to meiosis. In sum, our results lay the foundation for the targeted generation and genetic screening of human germ cell types via TF-guided differentiation. Looking ahead, our research will probe further into the activation of additional meiosis-specific genes, including *SYCP3*. Moreover, our work on meiosis induction opens the door to potential pathways for deriving haploid human stem cells, thus fostering advancements in chromosomal engineering, genetic screening, and other state-of-the-art technologies.

Restoring BLM Expression Through the Use of Adeno-Associated Viruses

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Adeno-associated viruses (AAVs) are a rapidly emerging therapy in the treatment of chronic and genetic diseases. These synthetic viruses allow for cellular delivery of any gene within a 4.7kb limit. My study proposes the use of AAVs as a gene therapy for Bloom syndrome, a disease caused by a genetic mutation that results in systemic loss-of-function of the DNA helicase BLM. This loss of function leads to an increased rate of cancer due to inability to repair DNA damage, shown by elevated sister chromatid exchanges and downregulation of the 45S ribosomal subunit. Though AAV therapy holds great promise for Bloom syndrome, the delivery of the full BLM gene through AAVs is limited by its protein size. The coding sequence of BLM is 4.2kb, which exceeds capacity when considering regulatory elements necessary for expression. To address this, I generated multiple miniaturized BLM proteins to fit within the AAV limit while preserving the protein's core helicase and nuclear localization sequence. I then tested the activity of each protein variant. To assess the activity of each protein, a Bloom syndrome patient cell line was nucleofected with the protein coding plasmids. Subsequently, the cells were sorted for plasmid incorporation and assayed for number of sister chromatid exchanges and relative rRNA expression, compared to empty vector transfection controls. The selection of the most active protein will be determined by the lowest number of sister chromatid exchanges and the highest levels of rRNA expression. Following selection, the protein will be integrated into AAVs in order to evaluate gene therapy in mice with Bloom syndrome. This research opens up the possibility of AAV gene therapy for Bloom syndrome and potentially other cases with size constraints, paving the way for more accessible and effective gene therapies for genetic disorders.

Machine Learning for Two-Dimensional Strongly-Correlated Quantum Lattice Models: Graphene, Kagome, and the tJ Model

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Strong localization of electrons in real space gives rise to dispersionless electronic bands in momentum space and provides an ideal system for exploring emergent, strongly-correlated phenomena. Flat bands can naturally arise in geometrically frustrated lattices, such as moire bilayer graphene and the kagome lattice, and yield rich many-body physics such as density-wave instabilities, quantum spin liquids, and unconventional superconductivity. This motivates the use of a many-body approach employing machine learning (ML) with the t-J model to study graphene and kagome lattices in order to explore strongly correlated phases. The intensive computational aspect of the project requires the deployment of new methods and tools, such as neural networks, which can exploit the symmetries of the lattices to permit larger and more complex systems to be probed. Prior studies show that the computational cost of ML scales linearly with the system size $(O(N))$, while that of quantum mechanical simulations scales as the cube of system size $\left(O(N^3)\right)$. As such, ML empowers simulations with quantum mechanical accuracy while restricting computational cost and provides a promising vehicle to mitigate the simulation scalability-accuracy dilemma. Due to their extraordinary expressive power when trained with sufficient data, neural models can reach quantum mechanical accuracy in energy and magnetic order evaluations. Once the tJ model on graphene and the kagome lattice is fully understood, a more elaborate neural model can be devised to study many-body phenomena in related systems, such as superconductivity in moire bi-layer graphene.

Characterizing Spinal Cord Injury in *Oryzias latipes*

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The Japanese rice fish known as medaka (*Oryzias latipes*) is an emerging model organism for comparative analyses of regeneration in vertebrates. Although medaka are physiologically similar and phylogenetically related to zebrafish (*Danio rerio*), they exhibit an uneven regenerative capacity across different organ types, whereas zebrafish can fully regenerate several organs including heart, brain, fin, tendon, retina, and spinal cord. In response to stab wounding in the brain, medaka, like mammals, form a glial scar, a dense accumulation of glial fibers around the injury site that inhibits new tissue growth and axonal extension. Currently, the medaka response to spinal cord injury (SCI) is unknown. To characterize this response, we performed immunohistochemistry (IHC) across different time points in injured and uninjured embryonic medaka to determine if and when a glial scar forms after SCI. We used an anti-GFAP antibody to mark radial glia and an anti-GFP antibody to mark neurons in the Tg[Kif5Aa:GFP] transgenic line with GFP+ neurons. We will perform EdU cell proliferation assays in combination with IHC to quantify the number of newly formed neurons around the injury site and will additionally stain for Coro1a to quantify recruited leukocytes. In the future, we will perform single-cell RNA sequencing in injured and uninjured medaka to analyze changes in gene expression and investigate the behavior of immune cells during the SCI response through IHC and live imaging with transgenically-labeled macrophages. This characterization of SCI in medaka creates an initial framework through which wound healing in a scarring species can be assessed. Further research will attempt to enhance medaka wound healing via transplantation from zebrafish or ectopic expression of regeneration-associated genes. Later, these molecular and cellular mechanisms in medaka and zebrafish can be applied to mammals, potentially providing insight into improving the human response to SCI.

Computational Modeling of Janus Transition Metal Dichalcogenide Bilayers

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One of the fastest growing areas of condensed matter physics explores ”twistronics.” By stacking sheets of two-dimensional materials, and then twisting the sheets relative to each other, large-scale moiré patterns emerge in the overall lattice. Most research in the field has focused on the properties of twisted graphene bilayers. We explored the electronic properties of a less studied category, the twisted ”Janus” transition metal dichalcogenide (TMD) bilayers. TMDs are a category of 2D material with a layer of transition metal atoms between two layers of chalcogen atoms. They are called ”Janus” when the chalcogens on each side of the sheet are different. We developed a computational framework to explore the behavior of these materials over a variety of twist angles and stacking configurations. Using this computational model, we examined the parameters that produce a host of valuable phenomena, including superconductivity and unique charge density distributions. The resulting properties were displayed for a large number of materials and published in a collaborative materials science database.

Effects of Ionizing Radiation on Osteoclast Precursor Survival and DNA Repair Activity

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Mentor: Yukako Otani

One of the biggest risks that astronauts face during space travel is high-energy proton, heavy ion, and photon radiation. While the dose rate of space radiation is typically low, the effects are cumulative. Proton and photon irradiation are also common treatment methods for many types of cancer, and recent studies have shown a higher incidence of bone fractures in patient populations after proton therapy in comparison to photon therapy. This issue naturally extends to astronauts because exposure to space-based radiation and microgravity can weaken skeletal integrity. We aim to elucidate the mechanisms behind increased fracture rates by analyzing the direct effects of protons and X-rays on osteoclasts, the bone-resorbing cells that mediate skeletal remodeling. We also investigate the efficacy of parathyroid hormone (PTH) in protecting bones against irradiation, as it has been shown to reverse skeletal deterioration. Preliminary results show that osteoclast precursor cells do not show significant difference in surviving fraction between X-ray and protons for 1-8 Gy doses of radiation. Rather, they appear less sensitive to radiation than osteocyte cell lines and even show increases in proliferation at 2 Gy. Further, the quantity of 53BP1 DNA repair foci in osteoclast precursors after irradiation show no significant differences between X-ray and proton radiation, with and without PTH treatment. However, a 47% increase in average foci intensity due to protons, as compared to X-rays, was observed 1 hr after irradiation. This is consistent with the higher linear energy transfer of protons, likely producing more complex and clustered double strand breaks (DSBs). Future work includes exploring the mechanisms by which osteoclast precursor proliferation increases at low doses and the differential nature of the DSBs caused by proton and photon radiation.

Elucidating the Coordination of Peptidoglycan Synthesis and Lipopolysaccharide Transport

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Some bacteria's first line of defense against harmful environmental assaults is their three-layered cell envelope. This envelope, characteristic of a type of bacteria labeled Gram-negative, consists of a symmetric phospholipid bilayer at the inner membrane (IM), an asymmetric outer membrane (OM), and a thin layer of peptidoglycan cell wall interlaced between the two membranes. Lipopolysaccharide (LPS), a crucial component of the OM, is transported via a seven-membered protein bridge composed of LptBFGC-A-DE from its site of biosynthesis in the IM to the outer leaflet of the OM, requiring transport through the cell wall— a process that is poorly understood. LPS is first extracted from the inner membrane by LptBFG, loaded onto the bridge composed of LptC, periplasmic LptA, and LptD, and then inserted into the OM by LptDE. As LPS transport and cell wall expansion must be tightly coordinated, we hypothesized that this process may be regulated by space-making peptidoglycan endopeptidases. We have observed that over-expression of LptA or LptA fused to the C-terminus of LptC results in a lysis phenotype indicative of cell wall hydrolysis. Our initial results suggest that LptA forms direct interactions with at least one cell wall endopeptidase, which may explain the increased hydrolysis of peptidoglycan peptide cross-links at sites of LPS transport. Additionally, the data suggest that increased hydrolysis requires LptA to be in a full-bridging state where all seven Lpt proteins are associated. As both LPS transport and peptidoglycan biosynthesis are crucial for cell viability in most Gram-negative bacteria, understanding the mechanisms behind their coordination could reveal novel drug targets for the treatment of antibiotic-resistant bacterial infections.

Identifying Potential for AI Bias in CT Scan Analyses

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When developing AI algorithms that analyze medical images like CT scans, people believe they can prevent bias by excluding demographic information (such as sex) from the input. However, if certain traits inherent to a CT scan allow a patient's sex to be reliably predicted, these features can act as a proxy factor. Algorithms may still learn to differentiate sex based on these indicative traits. This can cause replication of historical gender bias without taking gender into account directly. This project investigates whether a machine learning algorithm can identify the sex of a patient from a head CT scan. This classification task was performed with a transfer-learning based 3-D convolutional neural network (CNN) using the language Python and the deep learning framework PyTorch. CT data from 299 comatose cardiac arrest patients were used. The dataset was split into training (n=178), validation (n=60), and testing (n=61) cohorts on a patient level to avoid data leakage. The resulting training data consisted of 465 CT scans (some patients underwent multiple exams), including 320 scans from men and 145 from women. Transfer learning was used to finetune a residual CNN (ResNet) model pre-trained on medical images. Early stopping and a weighted loss function were used to counter the data imbalance. Hyperparameter optimization was performed through 51 experiments. If the network exhibits successful learning, it will suggest that classifying a patient's sex from a CT scan is possible. Those developing CT scan analysis algorithms should be aware of the potential for bias, even without gender as a direct input, and take steps to mitigate it. Future work could explore mitigation methods, such as skull stripping, to investigate their potential to reduce the vulnerability to bias.

Your Brain on Space: Examining the Effects of Microgravity on the Cerebellum

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Over the last ten years, the frequency and duration of human voyages have exponentially increased, leading to the demand for more studies investigating astronaut health and the physiological effects caused by microgravity. In microgravitational environments, astronauts often report facing difficulty with balance and coordination. Our work aims to examine the cerebellum, known for its role in balance and coordination, to see if there were any notable activity or structural changes. Our lab partnered with the Hindlimb Unloading (HU) NASA studies which use a pelvic harness to suspend the hind limbs of rats simulating partial weight bearing. With this analog HU rodent model, we collected brains from two groups of female rats: one group with no load bearing and one group with full load bearing. The brains are currently being analyzed using immunohistochemistry staining and PCR analysis to identify areas of the cerebellum with inflammation and abnormal activity using c-FOS and GFAP markers. The precerebellar regions in the brain stem, including the inferior olive and the lateral reticular nucleus (LRN) are also under review. These potential abnormalities are thought to result from disuse in the lumbar region, as astronauts don't need to use their legs in space. These results will help better understand the modulations human bodies undergo while on and off this planet. Efforts to combat these modulations will not only help treat future astronauts with spaceflight, but could additionally aid in creating solutions for people experiencing balance and coordination issues on Earth.

Investigating OSK as a Prospective Model of Enhanced Axonal Regeneration Following Spinal Cord Injury

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Corticospinal neurons (CSN) are excitatory projection neurons that connect the cerebral cortex to the spinal cord to enable fine motor control. During normal development, CSN axonal growth is guided by growth cones (GCs), specialized subcellular compartments at the leading ends of growing axons that integrate intracellular and extracellular cues to establish precise circuitry. While CSN are capable of reliably finding distant targets during development, they cannot regenerate to find these same targets after injury such as spinal cord injury (SCI). Critical to translational progress, we aim to understand GC-specific molecular mechanisms underlying increased capacity of CSN in mouse genetic models of increased regeneration. My project investigates potential enhanced CSN regeneration via overexpression of *Oct4*, *Sox2*, and *Klf4* (OSK), three genes associated with inducing pluripotency in terminally differentiated cells. OSK overexpression has been shown to increase regeneration in retinal ganglion cells, but is yet to be tested in CSN. To this end, I constructed a plasmid insert including both OSK and mClover (mC), a fluorescent protein. After insert sequence verification, I subcloned OSK-mC into two doxycycline inducible (Tet-off) backbones, one of which contains inverted loxP sites to make insert expression Cre-dependent (FLEx). Whole-plasmid sequencing confirmed that DNA sequences were intact and appropriately oriented. I then transfected cultured HEK293 cells with both OSK-mC and control mC plasmids. The OSK-mC transfected cells produced green fluorescence indicating effective OSK-mC overexpression. As expected, the FLEx-OSK-mC plasmid only generated green fluorescence when it was co-transfected with a Cre vector. In future experiments, I will quantify OSK expression in the presence and absence of doxycycline via qPCR and western blotting, to assess 'leakiness' of the construct. I will then proceed to *in vivo* testing of the constructs as well as assessing CSN growth after SCI upon OSK overexpression.

Developing a CAR-DC Engager Platform to Enhance CAR-T Cell Treatment Efficacy

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CAR-T cells are genetically engineered immune cells that express chimeric antigen receptors (CARs) to recognize and target specific cancer cells for immunotherapy. CAR-T Cell therapy has transformed blood cancer treatment. Still, its efficacy in solid tumors remains limited because of the immunosuppressive tumor microenvironment that hinders CAR-T cell infiltration and function, the lack of tumor-specific antigens, and the difficulty in effectively targeting solid tumors without causing off-target toxicity to normal tissues. We propose an off-the-shelf CAR-dendritic cell (CAR-DC) engager platform to address this challenge. The platform seeks to improve CAR-T cell treatment by enabling interaction between CAR-T cells and dendritic cells, thus enhancing co-stimulatory signals through DC engagement protein. This approach seeks to overcome the decline and disappearance of CAR-T cells in solid tumors. Additionally, we study changes in the tumor immune microenvironment (TIME) and lymphoid organs after CAR-DC treatment through cytometric analysis techniques, such as flow cytometry, to assess the frequency, distribution, and activation status of various immune cell populations in response to CAR-DC therapy. By analyzing the expression levels of key immune markers and cytokines, we seek to unravel the intricate immune response dynamics induced by the CAR-DC platform, focusing on CD4+ CAR-T cells' response. Understanding these dynamics can allow us to optimize CAR-T cell therapy.

Deep Learning as a Method to Solve the Time-Dependent Schrodinger's Equation in One Dimension

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Schrodinger's equation is a second-order complex partial differential equation that describes particles' behavior in quantum mechanical systems. Solutions to this equation, known as wavefunctions, determine the probability of finding a particle at a specific position and time. Schrodinger's equation depends on the particle's potential energy and has analytical solutions for some simple potentials. Only numerical solutions exist for many potentials, which approximate solutions and cannot propagate over a large range. Deep learning techniques have recently been applied to physical problems without closed-form solutions. By training neural networks using a loss term derived from Schrodinger's equation, one can obtain time-evolving differentiable solutions for arbitrary potentials. The network takes position and time as inputs and returns the real and imaginary components of the wave function. The network can take other parameters of the equation as inputs, allowing the network to return families of solutions that cover a range of parameters. The outputs are multiplied by a Gaussian position envelope and a linear time-dependent term to ensure adherence to the problem's boundary conditions. The algorithm calculates the loss function from the parameterized network. We successfully applied this technique to the infinite square well potential, quantum harmonic oscillator potential, and Morse potential, all of which have closed-form solutions. The algorithm calculated the root mean square error from the true solutions to measure accuracy. Then we applied the method to the Lennard-Jones potential, which does not have a closed-form solution. The network successfully modeled the time evolution under this potential for initial conditions that approximated eigenfunctions and superpositions of those eigenfunctions. These results demonstrate the network's ability to create accurate solutions across a wide position and time range. The goal is to apply this technique to more complicated and realistic potentials, making deep learning a valuable tool in materials modeling and many-body quantum problems.

PET Imaging as a Novel *In-Vivo* Diagnostic Method for Tissue Cancers and Diseases

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Imaging inflammation has promising implications for enhancing the diagnosis, treatment, and prognosis of various medical conditions, encompassing infections, cancer, cardiovascular, liver, gastrointestinal diseases, neurological disorders, and autoimmune diseases. For tumorous cancers and autoimmune diseases, *in vivo* imaging has the potential to be a superior replacement for tissue biopsies. Nevertheless, the lack of a reliable inflammation imaging probe has impeded progress, curtailing its utilization in research and clinical management. To address this gap, we introduce a novel approach: a positron emission tomography (PET) imaging technique tailored for inflammation detection. Our study demonstrates the remarkable sensitivity and clarity of PET imaging in detecting inflammation across diverse inflammatory models, encompassing lung, liver, colon, and syngeneic tumor models. Furthermore, we have developed a human-specific PET probe, identifying inflammation in a preclinical mouse model of graft-vs-host disease. The efficacy of this probe was tested in humanized immunodeficient mice with various cancer forms, which showed promising results. The PET imaging approach holds significant clinical potential, enabling physicians to make well-informed therapeutic decisions based on precise individual and temporal inflammation biology and severity evaluations. In direct comparison with tissue biopsy, PET imaging carries the potential for earlier, more accurate, and more widespread detection of malignancies in many locations. As a result, the application of PET imaging in inflammation research and clinical settings is set to advance considerably.

Midnolin Localizes to Chromatin to Promote IEG Protein Degradation

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Immediate early genes (IEGs) encode transcription factors that are rapidly transcribed in response to extracellular cues including developmental, immunological, and neuronal signals. The transient induction and rapid turnover of IEGs, such as c-fos and EGR1, are critical for neurodevelopment and neuronal plasticity. While the mechanism behind the rapid degradation of IEGs has been unclear, the Greenberg lab recently identified a novel protein, midnolin (MIDN), that is able to degrade numerous nuclear proteins including IEGs in a ubiquitination-independent and proteasome-dependent manner. However, it remains unclear where midnolin-bound proteasome localize to facilitate the degradation of midnolin targets. Immunofluorescent staining of endogenous midnolin protein suggests its nuclear localization, which is consistent with its targets being mostly nuclear proteins crucial for transcription. Since IEG proteins are well-characterized midnolin substrates and directly bind chromatin, we hypothesize that midnolin can be recruited to chromatin by IEGs to degrade them. Using the chromatin immunoprecipitation (ChIP) assay, we isolated epitope-tagged midnolin-bound chromatin following IEG induction and sequenced the chromatin to determine regions of DNA enriched with midnolin. Preliminary results show that midnolin-binding regions highly enrich the binding-domain DNA sequence of IEGs. As an alternative approach to investigate the chromatin-binding capacity of midnolin, we performed subcellular fractionation of epitope-tagged *MIDN* cells followed by western blot analysis. We found that both midnolin and IEGs show similar expression patterns and accumulate largely in free nuclear and chromatin-bound fractions. These results suggest that midnolin is capable of promoting substrate degradation on chromatin, potentially explaining the rapid turnover and regulation of IEGs. Ongoing ChIP experiments aim to determine whether midnolin association with chromatin is dependent on its substrates including IEGs. These experiments set a premise for further investigating the coupling of protein degradation and transcriptional activity of midnolin targets on chromatin.

Carbon Capture With Oxygen and Electrochemical Stable Quinones

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Climate change is a growing issue with each passing year and direct air capture (DAC) is a popular candidate for mitigating climate change. However, carbon capture has a sizable energy and monetary cost, and current methodology of capturing carbon dioxide straight from the atmosphere is an even more energy intensive process. An attractive approach for DAC is to use electricity to control the capture and release of CO_2 because of low energy requirements and future availability of electricity using renewables. Redox active organic molecules (RAOMs), that have two oxidation states, the first of which possesses high affinity to CO_2 and while the other state possesses low affinity, are attractive to facilitate this electrical process. Most reported systems of RAOMS are sensitive to oxygen, thus lowering efficiency and limiting the practicality of the process. In this project, several quinones, cyclic molecules that easily gain or lose electrons, were synthesized to assess their viability towards electrochemical direct carbon capture. In order to assess the viability of a molecule, multiple experiments were conducted with the molecule. Cyclic voltammetry was conducted to demonstrate the redox ability of these molecules and to find its reduction potential. Solubility in water was measured by UV-Vis spectroscopy to screen for molecules displaying high solubility in aqueous environment for practical application. The electrochemical stability of these molecules were assessed by cycling the molecule in a flow cell in oxygen-free conditions. Afterwards, controlled CO_2/N_2 was introduced in a second test to assess the molecule's ability to capture carbon dioxide reversibly. Finally, a promising candidate is subjected to a flue gas simulated condition to characterize its stability against oxygen. These tests would give knowledge about the stability and kinetics of these molecules, thus insight to the molecule's potential application in DAC.

VRK1: A Possible LSD1 Demethylase Substrate

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Post-translational modifications represent key regulators of protein function and gene expression. The LSD1-CoREST complex comprises the lysine demethylase LSD1 and the scaffolding protein CoREST. Presently, methylated Lys-4 of histone H3 is the only well-established LSD1 demethylase substrate site and this demethylation is associated with transcriptional silencing. Our research investigates whether LSD1 can demethylate a non-histone protein (VRK1) and the physiological significance of this. The VRK1 kinase possesses a histone-like N-terminal motif with methylated Lys-4 and residues mimicking histone H3 and Snail, the substrate and a strong competitive inhibitor of LSD1, respectively. Moreover, VRK1 resides in nuclei and directly engages nucleosomes. Hence, it appears a plausible target for LSD1 demethylation. The wild-type unmethylated VRK1 and a methionine mutant (a methyl-lysine mimic) were overproduced and purified from *Escherichia coli*. These recombinant proteins were incubated with LSD1-CoREST and binding was assessed using size exclusion chromatography. However, they eluted independently, indicating a lack of strong binding. Protein semisynthesis was then employed to prepare a VRK1 N-terminal peptide with site-specific Lys-4 methylation. This 11-residue peptide was linked to truncated VRK1 (Δ1-11) using a chemoselective ligation reaction between an N-terminal cysteine and C-terminal thioester, producing semisynthetic VRK1 containing methylated Lys-4 and only one other amino acid change, Cys-12. With methylated VRK1 we shall pursue LSD1-CoREST enzymatic studies to determine whether it is indeed an LSD1 substrate. Additionally, extensive computational modelling was employed to investigate binding to LSD1-CoREST. Encouragingly, AlphaFold's structure prediction placed VRK1 at LSD1's active site. Subsequently, Rosetta FlexPepDock was used to calculate the optimum docking location using Monte Carlo sampling. This ongoing modelling suggests Lys-4 methylation greatly improves active site targeting. In summary, this project will advance our understanding of VRK1's ability to serve as an LSD1 substrate and provides an approach to generate modified forms of VRK1 for biochemical analysis and demethylation assays.

Connecting Dystonia to the Disruption of the Nuclear Envelope and Subnuclear Machinery Through Super-Resolution Microscopy

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Hereditary dystonias are hyperkinetic movement disorders caused by various genetic mutations and involve abnormal postures and movements that are often worsened upon initiation of voluntary movement. Due to an abundance of genes causing hereditary dystonia, it has been difficult to identify a clear mechanism for its pathology on a cellular level. However, a commonality amongst many of the causal genes of dystonia is that they affect nuclear function at some capacity (i.e. nuclear transport, gene expression, nucleo-cytoskeletal integrity); hence, one theory has related dystonia to dysfunction of the nuclear envelope (NE) and subnuclear machinery involved in gene expression. To test this theory, we plan to use antibodies that target subnuclear machinery (i.e. RNA-binding proteins that interact with transcription factors) and nuclear envelope (NE)-resident proteins in human induced pluripotent stem cell (iPSC)-derived neurons with known dystonia genotypes, which will be imaged via immunofluorescence. Differences between patient and control iPSC-derived neurons will be captured via super-resolution microscopy. Imaging of this magnification has not been performed on these kinds of dystonia cell lines. The cell lines of interest include DYT-*TOR1A* and X-linked dystonia-parkinsonism (XDP), two forms of hereditary dystonia that are caused by mutations in a NE-resident protein and a transcription factor, respectively. These images will help determine whether there is mislocalization or disruption of both NE-resident proteins and subnuclear machinery in DYT-*TOR1A* and XDP iPSC-derived neurons. This data would indicate a shared mechanism between two distinct types of hereditary dystonia, making it possible that different hereditary dystonias share a common mechanism of disrupted nuclear function in neurons.

Improving Spin State Readout Fidelity in Ensemble of Nitrogen-Vacancy Centers

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Mentor: Weijie Wu

Quantum technology has gained significant attention for its application of fundamental principles from quantum mechanics to real-world scenarios. Nitrogen-vacancy (NV) centers in diamonds have emerged as a promising platform for quantum technology, thanks to their ability to utilize electronic spin states as highly sensitive probes for quantum metrology and information processing. Improving the quantum-state detection fidelity is hence one of the central tasks to develop an NV center as an efficient and reliable quantum system for practical use. At room temperature, the detection of quantum states in NV centers relies on a non-resonant fluorescence readout scheme, where we detect the difference in the number of emitted photons when different spin states decay into their ground states. However, the readout fidelity of this scheme is limited due to the relatively short timescale before the quantum state information is lost. Our research aims to improve the readout fidelity of the electronic spin state in NV centers in an ambient condition by utilizing the nuclear spin state of a nitrogen atom as an ancillary device to record the initial electronic spin state. By mapping the electronic spin state to the nitrogen nuclear spin, which has a longer coherence time, one can extend the readout timescale and thus achieve a higher detection fidelity. The improved readout fidelity will showcase the potential of NV centers as a promising tool for experimentally verifying our theory of scalable spin-squeezing in condensed matter systems, and more generally, it will provide a benchmark for enhanced sensitivity with quantum algorithms in ensembles of quantum sensors.

Generating Cortical Organoids Representative of Specific Areas

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Mentor: Xuyu Qian

Understanding cortical arealization, a fundamental process in cerebral cortex development, is crucial for elucidating the pathogenesis of neurodevelopmental disorders. However, a lack of representative models has been a major obstacle. This study aimed to bridge this gap by investigating the genetic mechanisms underlying the induction of areal identities in organoids derived from human pluripotent stem cells (hPSCs). To this end, we generated cortical organoids, which were exposed to various agonists and antagonists targeting key signaling pathways to induce arealization. Immunostaining of organoids revealed differential expression of area markers such as SP8, indicative of the successful development of distinct areal identities. Subsequent analysis demonstrated consistent changes in marker expression patterns, with FGF pathway activation causing a shift suggestive of an anterior identity. These organoids were then benchmarked against human fetal cortex data using RNA-seq, with preliminary results showing promising correlations. Upon completion, this analysis could offer substantial insights into arealization and potentially provide a robust model for studying disorders resulting from abnormal cortical development.

Investigating the Activation Mechanism of Insect Chemosensory Receptor Proteins

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Mentor: Sanket Walujkar

Insects use a diverse array of odorant receptor proteins (ORs) to detect small, volatile odorant molecules. Odorant receptor 5 from the jumping bristletail *Machilis hrabei* (*Mh*OR5) can detect a broad range of odorants including DEET (a common insecticide), eugenol (found in cloves), and benzaldehyde (a simple aromatic aldehyde). *Mh*OR5 is a homotetrameric ligand-gated ion channel with seven transmembrane helices in each monomer. While recent high-resolution structures of *Mh*OR5 in ligand-free and ligand-bound forms have identified important binding site residues, the mechanism by which ligand binding results in opening of the channel pore and ion conduction is still unknown. To investigate this, we conducted molecular dynamics simulations, which calculate and apply forces on individual atoms to make predictions about both intramolecular and intermolecular motions. Based on electron densities in the structure of *Mh*OR5, we hypothesized the existence of and modeled four lipids in the membrane bilayer that are embedded between protomers, with lipid heads pointed into the pore, thus likely contributing to the ion conduction properties of the channel. The presence of electron densities suggest these lipids occupy this position a majority of the time. Preliminary simulations support this hypothesis, and we are interested in understanding their dynamics and what can influence these dynamics. We also plan to analyze the differences between the simulations of *Mh*OR5 in ligand-free and benzaldehyde-bound form to understand how ligand binding changes protein conformation. These results may also reveal the mechanism of gustatory receptors (GRs), a related family of ligand-gated ion channel proteins that share a similar seven-transmembrane-helix topology. These insights may be valuable as there are currently no published structures of any GR. Furthermore, since GRs have no mammalian homologs, understanding the mechanism of GR proteins may facilitate development of high precision pesticides to protect agriculture and human health.

Contact Engineering of Transition Metal Dichalcogenide Devices via Modulation Doping

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Mentor: Elise Brutschea, Shivangi Shree

Semiconducting transition metal dichalcogenide (TMD) monolayers are two-dimensional (2D) materials whose direct band gaps when thinned down to the monolayer limit allows for enhanced light-matter interactions. Thus, TMDs, such as WS_2, WSe_2, and $MoSe_2$, are promising for studying 2D condensed matter physics and show potential applications in optoelectronics, such as single-photon emitters and photovoltaic cells. However, experiments exploring such properties have been limited due to the high resistance in metal-TMD junctions, resulting in low quality electrical contacts. A phenomenon where the metal's Fermi level becomes locked to an energy level within the TMD's band gap due to metal-induced gap states, called Fermi-level pinning, causes these poor contacts. Such contacts in turn make analysis of electron transport measurements difficult due to a nonlinear current-voltage relation and a low signal-to-noise ratio. To better carry out transport measurements,we designed novel van der Waals heterostructures with thin α-$RuCl_3$ in proximity to WSe_2 monolayers in the region contacted by Pt metal. The α-$RuCl_3$ acts as a modulation doper, decreasing the Schottky barrier width by tuning the Fermi level of the TMD, such that a doping density triple that of conventional contact gates can be achieved. We hope this allows for electron tunneling through the metal-TMD barrier and ultimately lower the contact resistance. We fabricated multiple devices using a stamp made by adhering a polycarbonate (PC) film to a polydimethylsiloxane (PDMS) block, including a four-terminal device. This should allow measurement of the contact resistance separate from the channel resistance, while the channel was not covered by α-$RuCl_3$ to independently dope with a channel gate and to study transport at low charge densities. To benchmark this design, we will perform four-terminal transport measurements on the α-$RuCl_3$ device and compare its contact resistance to that of devices with only contact gating.

Identifying Effects of Vaccine Misinformation and Correction Across Different Populations

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During the later stages of the COVID-19 pandemic, the central goal for public health officials was to vaccinate as much of the population as possible. Unfortunately, they faced a formidable opponent: misinformation. Now, an emerging area of interest is how vaccine misinformation and subsequent correction of this misinformation affects different subpopulations. By observing how different subpopulations respond to misinformation and correction, public policymakers can respond more efficiently to vaccinate a greater portion of the population. In our study, we focused on how misinformation and correction affects subjects' confidence in their own knowledge about the COVID-19 vaccines. More specifically, we conducted an experiment (N = 15325) on a survey to observe the effects of asking subjects to evaluate the accuracy of commonly-held misinformation statements and of subsequent correction. We found that on average, subjects' confidence decreases in response to misinformation. In a sense, misinformation has a confounding effect: it prompts subjects to doubt their own prior knowledge about the vaccines. Further, on average the effect of correction is weak and unable to recover subjects' confidence to levels prior to misinformation exposure. Across many different variables (party, age, vaccination status, education, concern), we find that those more likely to have preconceived beliefs are less responsive to both misinformation and subsequent correction. This means that the populations most vulnerable to misinformation are the ideologically insecure. Thankfully, this population is also generally the most responsive to correction. For public health officials, this result outlines the relevant subgroups in their effort to combat misinformation. So far, our efforts in modeling treatment effect heterogeneity have been parametric. Currently, we are implementing the causal forest algorithm, which discovers treatment effect heterogeneity non-parametrically, in hopes that it will confirm our existing findings and illuminate unexpected diversity.

A Bayesian Multiple Imputation Procedure to Quantify Uncertainty due to Privacy Protection

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Due to the scarcity of existing data, a rapidly growing scientific effort seeks to harness machine learning models to predict health and poverty outcomes at high temporal and spatial resolutions using satellite images. An impediment to these models' performance is that some of their training data consists of household surveys whose geographic information has been perturbed to protect the confidentiality of human respondents. To account for this privacy protection, we propose a Bayesian multiple imputation procedure that computes a posterior distribution $\pi(\mathbf{a}|\mathbf{a}')$ for the true geographic data $\mathbf{a}$ given the observed, perturbed geographic data $\mathbf{a}'$. From this posterior, one can draw m multiply-imputed datasets $\mathbf{a}_1, \mathbf{a}_2, \ldots, \mathbf{a}_m$ on which m predictors $f_1, f_2, \ldots, f_m$ can be trained. The variance of these predictors can be used to measure uncertainty due to privacy protection, and their average can give a more robust estimate of a given location's poverty level. Since the imputation posterior $\pi(\mathbf{a}|\mathbf{a}')$ relies on a continuous likelihood $p(\mathbf{a}'|\mathbf{a})$ and a discrete prior $\pi(\mathbf{a})$, they cannot be integrated using Bayes' theorem. We demonstrate different ways to remedy this resolution mismatch: extending the prior to a continuous distribution or alternatively discretizing the likelihood using imprecise probability theory. Currently, we are quantifying the impact of using different continuous priors and discretized likelihoods by comparing their corresponding posterior imputation distributions through simulation. These results will inform the difficult task of working with privacy protected geospatial data and allow for the development of robust algorithms that give more meaningful insights into sustainable development.

Refining the Electrical Design and Function of a Soft, Active Shoulder Exosuit

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Mentor: David Pont

Workplace overuse injuries due to repetitive tasks are incredibly common, particularly in industrial settings, with the shoulder being one of the most susceptible body parts to such trauma. In order to assist automotive factory workers with their daily tasks while reducing risk of injury, a soft, active exosuit has been developed that utilizes pneumatic actuators to provide the proper support to the shoulder joint. It was determined that the pressure in the actuators, which serves as an input for the device's circuitry through the use of a pressure sensor, needed to be adjusted to fit a compatible output voltage range so as to not overload the following analog to digital converter (ADC) within the device. A circuit that would fit the voltages from the pressure sensor over a range of 0.18 V to 1.8 V given an input pressure range of 0 psi to 20 psi was theorized, designed, built, and tested. The final design utilized both amplification and cutting to ensure that the following part of the electronic system had an appropriate range of input values. This work will improve both the safety and quality of the device's function by protecting the ADC channel of the device's microprocessor and establishing accuracy in the measurements.

Enhancing Formal Verification of Coq Theorems With Large Language Models: A Tactics- and Goals-Embedded Fine-Tuning Approach

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In light of the increasing demand for efficient and reliable formal verification processes in software engineering and mathematics, this research delves into the potential of Large Language Models (LLMs) for verifying Coq theorems. This project introduces a unique approach that integrates fine-tuning (with regard to tactic prediction from previous and desired goals) and subgoal-based demonstration prompting. This methodology simplifies complex theorems into manageable subgoals and embeds these, along with relevant tactics, into the LLM training process, thus augmenting the model's capacity to manage intricate theorem proofs. By leveraging the nuanced understanding of embedded tactics and goals during fine-tuning, the LLM is better equipped to generate accurate and complete proof scripts. This project reveals considerable advancements in the LLM's capability to accurately verify Coq theorems, underscoring the potential of this approach to foster more robust artificial intelligence (AI) integration in formal verification tasks. The advancements brought about by this research have the potential to significantly transform the field of formal verification, rendering it more efficient and less prone to error. This research promises future implications for software engineering and mathematics, cryptographic protocol design, and critical systems development, where verifiable accuracy is crucial. Moreover, this approach sets the stage for further exploration into the integration of AI in complex problem-solving tasks, potentially paving the way for more autonomous AI systems capable of tackling high-level abstract thinking tasks.

Investigating the Native Substrates of the E3 Ligase Substrate Adaptor Cereblon

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The E3 ligase substrate adaptor cereblon positions substrates for ubiquitination and enables their subsequent degradation via the proteasome, a complex of enzymes that digests proteins to their amino acid building blocks. In pharmaceutical contexts, immunomodulatory drugs (IMIDs) such as thalidomide and its derivatives induce ternary complex formation between cereblon, the drug, and a neosubstrate to enable neosubstrate degradation. These IMIDs mimic C-terminal cyclic imides, formed by cyclization of asparagine or glutamine, which have recently been demonstrated to serve as cereblon degrons. The endogenous substrates that carry this C-terminal degron, however, and the processes that induce degron formation on those substrates, remain unknown. A particular challenge of identifying these substrates is the 22-24 hour half life of the C-terminal cyclic imide, meaning that a stable population of proteins carrying this degron within the cell does not exist. As a way to better identify and understand these native substrates of cereblon, we have worked towards the manipulation of MccB, an enzyme found in bacteria that promotes the C-terminal cyclization and adenylation of its heptapeptide substrate MccA. If MccB can be mutated such that this cyclization step is isolated from the adenylation step, MccB can then be used *in vivo* to promote C-terminal cyclization of other proteins in human cell lines, opening the door for more comprehensive analysis of cereblon substrates by providing a more stable C-terminal cyclic imide substrate population. As a preliminary step, we have worked this summer to mutate MccA and test these mutants in activity assays with MccB to interrogate the activity of MccB on more diverse substrates.

Investigating the Correlations Between Metabolic Similarity and Metabolic Pathway Similarity

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Mentor: Jennifer Dawkins

A healthy microbiome is crucial for well-being. This includes the gut skin, vaginal, nose, mouth, and lung microbiomes, which each perform essential functions in the human body. The disruption of these microbial communities, dysbiosis, can result in deleterious outcomes, including pro-inflammatory responses, immune dysregulation, and increased susceptibility to pathogenic microbial infections. Previous studies have focused on the compositions of these microbiomes to predict susceptibility to infection. However, accurate and high-throughput analysis of human microbial communities is difficult and has limited efforts to define functional connections between microbial strains and host phenotypes. Additionally, in many cases, the presence of specific microorganisms can't accurately predict disease outcomes compared to other biomarkers. One important way that human microbiomes influence host physiology is through the production of small molecules called metabolites, which can be converted into metabolic fingerprints based on the presence of certain structural and molecular properties. Our project integrates metabolic and microbial composition data in a computational model to make interpretable predictions of host-microbial interactions, utilizing many features, such as microbial interactions and metabolite effects on hosts, and only a few samples. Using the Tanimoto distance metric to calculate distance matrices of metabolite fingerprints from a C. Difficile infection recurrence dataset, we demonstrated the relationships between metabolites and the human body and visualized them in phylogenetic dendrograms. We then extracted the related metabolic pathways and explored patterns between metabolic similarity and pathway similarity. Understanding these patterns will allow us to better exploit existing microbial and metabolomic data in our model to predict disease outcomes for patients using metabolomic profiles.

Using Simulation Studies to Improve Small Area Estimation Techniques in Forestry

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Within the United States Forest Service, the Forest Inventory and Analysis (FIA) program tracks the status and trends of the nation's forests. Under FIA's sampling and estimation paradigm, Small Area Estimation (SAE) is a burgeoning field allowing FIA to accurately estimate important forest characteristics on increasingly smaller scales — scales that prove vital towards understanding the impact of land use change, forest fires, and more on the forests of the United States. Using simulated population inventory data from ecoprovince M333, the Northern Rocky Mountain Forest-Steppe-Coniferous Forest-Alpine Meadow Province, this study simulated 2,500 samples from the population and tested various SAE techniques over each sample, comparing their precision, accuracy, and confidence interval coverage to a simulated truth. Specifically, this study compares the FIA's current SAE technique of Post-Stratification to General Regression models (GREG) and Unit- and Area-level Empirical Best Linear Unbiased Predictors (EBLUP). As these estimators are all model-assisted or model-based, this study relies on remotely-sensed auxiliary data to pair with inventory data for model-building, and the study also explores variable-selection for these estimators. The study demonstrates that without other domains to borrow strength from, a GREG fitted on a single strong predictor variable best balances computational efficiency, accuracy, and precision. When other areas can be borrowed from, area-level EBLUP models perform the strongest. These results suggest that with the suite for SAE techniques, there is not a standard estimator, and depending on the circumstances, the FIA may turn to different estimation methods to most accurately, precisely, and easily estimate these forest characteristics over a variety of small areas.

Machine Learning Modeling for High Critical Temperature Superconductor Discovery

Dries Rooryck
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Mentor: Jason Hoffman

Superconducting materials, materials that conduct electricity without resistance, have many commercial applications, including in magnetic resonance imaging (MRI) systems, electromagnets, and nuclear fusion reactors. Known materials only superconduct at low temperatures, which makes them impractical to operate and expensive to cool. In recent years, computational methods to predict new superconductors that function at higher temperatures have significantly progressed. Machine learning (ML) methods have become a focal point of this effort. In our work, we have preprocessed and featurized a subset of materials from the Japanese Materials Data Repository 'SuperCon' database. It contains 26,000 experimentally observed superconductors with their critical temperatures (Tc). We have expanded on previous literature to create a supervised regression approach, and have been successful in predicting the Tc of *known* superconductors with an out-of-sample accuracy of ±9.1 K based on root-mean-squared-error (R2=0.91). In particular, we utilize a wider array of 360+ calculated features based on stoichiometry and constituent-element data, and we attempt both a gradient-boosted decision tree model and a neural network using TensorFlow. Our initial approach does not take into account lattice structure, which is known to play a role in governing superconducting properties in many material systems. We are now focusing on developing a classification model capable of identifying promising candidate materials for high-Tc superconductivity using both compositional and structural properties. Such a model will represent crystal lattices as approximated graphs and apply convolutional neural networks to accurately reflect the role that disorder plays in high-temperature superconductivity.

Sputtering Metallic MoO_2 Thin Films

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Discovering new superconductors remains a continued interest in the field of condensed matter physics. Potassium-doped MoO_2 has demonstrated superconductivity, although the mechanism of superconductivity is unknown. Synthesizing MoO_2 as a thin film allows for the exploration of more possible superconducting materials, as thin films can behave differently than the same material in bulk form. Epitaxial (100) MoO_2 thin films were formed on (0001) Al_2O_3 substrates using sputtering. The films were sputtered at 500°C and 4 mTorr using an Mo metal target with oxygen flow. The resulting films were metallic MoO_2. X-ray diffraction, atomic force microscopy, and X-ray photoemission spectroscopy were used to characterize the quality and content of our films, in terms of purity and surface roughness. A physical property measurement system was used to determine the level of conductivity and magnetism exhibited by the films. A large increase in the magnetoresistance of our MoO_2 occurs below 10K. Based on this change in magnetoresistance, growing oxygen deficient MoO_2 or MoO_2 doped with other alkali metals and measuring their conductivity and magnetism may provide more insights into the mechanisms of superconductivity in the future.

Characterizing the Distinct Morphology of Monkeyflower Nectary Tissues

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Mentor: Yan Gong

Nectaries are specialized tissues in the flowers of angiosperms, or flowering plants, that produce and deposit nectar, a sugary solution that acts as the major reward for pollinators. Because successful pollination ultimately enables angiosperms to occupy a vast range of geographic habitats, nectaries subsequently play an outsize role in the survival and diversification of this plant lineage, which accounts for nearly 90% of all extant plant species. However, little is known about the genetic circuitry controlling nectary development. The objective of this project is to better understand the genetic controls underlying nectary development in the *Mimulus* (monkeyflower) model system by characterizing nectary development in four different *Mimulus* species (*lewisii*, *cardinalis*, *verbenaceus*, and *parishii*) via scanning electron microscopy (SEM) and periodic acid-Schiff (PAS) staining histology studies. Imaging results confirmed the existence of nectaries across all species studied, with nectary structures being most pronounced in the hummingbird-pollinated *cardinalis* and highly reduced in the self-pollinating *parishii*. In addition, phytogenetic analysis and reverse transcription PCR confirmed the existence of orthologs of the *CRABS CLAW* (*CRC*) gene, a known nectary regulator in several eudicot lineages, in the nectary tissues of all *Mimulus* species. We aim to then characterize the spatial-temporal expression pattern of *CRC* by creating transcriptional and translational reporter constructs of the *cardinalis* and *parishii CRC* orthologs with fluorescent protein tags and performing an *Agrobacterium*-mediated stable transformation protocol. This research will lay the basis for future exploration of CRC expression dynamics in *Mimulus* nectary development and will help further untangle the complex genetic circuitry underlying nectary development in angiosperms.

Development of Machine Learning Models to Reduce Racial Disparity in Kidney Function Testing

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Glomerular filtration rate (GFR) is commonly used as a measure of renal function and, therefore, for diagnosing chronic kidney disease (CKD). Direct measurement of renal function is inefficient, so formulas are employed, using demographic variables such as patient age, sex and race as well as biomarkers such as serum creatinine concentration to estimate GFR. Whilst GFR estimated from clinical biomarkers closely tracks measured GFR (mGFR) at a population level, sizeable inter-individual variability causes significant individual-level discrepancies. In addition, while race is widely used in clinical predictions, it is a highly unreliable and crude predictor of biological variation between individuals. To address this, we developed a supervised machine learning model to improve accuracy in estimating GFR, beyond the capabilities of current clinical equations. In this study, we analyzed data from the Chronic Renal Insufficiency Cohort Study (CRIC) and 18 years of data from the National Health and Nutrition Examination Survey (NHANES) conducted by the Centers for Disease Control and Prevention (CDC). We applied supervised machine learning techniques to create models that estimate mGFR from commonly available blood laboratory biomarkers. We demonstrate that mGFR can be inferred accurately without the use of race as well as without using sex and age. Finally, we pilot a semi-supervised learning framework to integrate both labeled data (i.e. with mGFR) and unlabeled data (i.e. without mGFR) and integrate data from CRIC and NHANES to further improve eGFR. These results suggest that commonly available biomarkers can be used to improve eGFR without relying on problematic demographic variables like race. Removing race from eGFR calculations would allow for increased diagnosis in Black adults, and reclassification to more advanced stages of CKD, allowing earlier access to specialist treatment.

Investigating the *In Vitro* and *Vivo* Potential of Photodynamic Oncolytic Herpes Simplex Virus (PD-OV) Therapy in Glioblastoma (GBM)

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Medicine, 2024
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Mentor: Fatma Turna Demir

Glioblastoma is the most common and aggressive primary brain tumor. Effective therapy remains elusive, with median patient survival only 14.6 months after surgery followed by radiation and temozolomide. G47Δ is a triple-mutated, third-generation oncolytic Herpes Simplex type 1 virus (oHSV-1) that selectively infects and lyses tumor cells. Found to increase 1-year survival in phase II clinical trials, it is approved in Japan as a promising malignant glioma immunotherapy. However, clinical data suggests OV monotherapy is insufficiently effective, prompting rational attempts to produce recombinant OVs that selectively deliver additional therapeutics. To investigate the translational significance of armed OVs, we generated a recombinant G47Δ armed with membrane-bound Killer Red (KR) photosensitizer protein. Photo-activated by 585nm wavelength (amber) light, KR produces damaging ROS including superoxide. We expect this to enhance tumor-selective cytotoxicity and increase anti-tumor immune responses by modulating the tumor microenvironment (TME). In our project, we interrogate the hypothesis that KR-driven PD-OV therapy more effectively destroys GBM cells than OV monotherapy using *in vitro* and *vivo* assays. Building on proof-of-concept trials showing increased regression and macrophage infiltration in athymic nude mouse flank tumor models using human U87 GBM stem cells (GSCs), we investigate the effects of four different exposures (saline controls, OV without light, light delivery as LED or laser, and PD-OV therapy combining G47Δ-KR and light) on 005 and C3 murine, and MGG8 and MGG23 human GSCs. *In vitro* experiments use CellTiter Glo viability and Cytotox Glo cell death assays to evaluate therapeutic effects. Critically, *in vivo* survival trials monitor symptoms of immune-competent C57BL/6J mice with 005 or C3 brain tumors after each exposure, using cranial windows to deliver laser to the brain. These studies will help characterize PDOV therapy's anti-GBM effects, and its impact on the TME. Future preclinical research directions include developing less invasive laser delivery protocols.

Interpolation for Veronese Embeddings and Semi-Stability of Their Normal Bundles

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Veronese varieties $\upsilon_{n,d}$ are n-dimensional projective varieties sitting inside of an ambient projective space of dimension $\binom{n+d}{d} - 1$, given by linear series $|\mathcal{O}_{\mathbb{P}^n}(d)| : \mathbb{P}^n \hookrightarrow \mathbb{P}^{\binom{n+d}{d}-1}$ for every $n, d \geq 0$. This project attempts to understand two questions involving Veronese varieties: interpolation and semi-stability. The first question relates to an old enumerative problem: given $\binom{n+d}{d} + n - 1$ general points in $\mathbb{P}^{\binom{n+d}{d}-1}$, does there exist a Veronese variety $\upsilon_{n,d}$ intersecting every such point? In the case of $n = 1$ and arbitrary d, it is well-known that given any general $d + 3$ points in $\mathbb{P}^d$, there exists a unique rational normal curve $\upsilon_{1,d}$ satisfying interpolation. In 1920, Arthur Colbe provided a solution for $n = 2$, $d = 2$. Through any 9 general points in $\mathbb{P}^5$, there exists exactly 4 Veronese varieties $\upsilon_{2,2}$ intersecting them. For all other cases, the solution to this enumerative problem is unknown. One goal of this project is to prove or disprove existence of nonzero finitely many Veronese varieties interpolating any $\binom{n+d}{d} + n - 1$ general points in $\mathbb{P}^{\binom{n+d}{d}-1}$. The second question of this project concerns semi-stability of the normal bundles $\mathcal{N}_{\upsilon_{n,d}}$, in the sense of Mumford's geometric invariant theory. In the case of $d = 2$ and arbitrary n, we conjecture that $\mathcal{N}_{\upsilon_{n,d}}|_{RNC} \cong \bigoplus_{i=1}^{n(n+1)/2} \mathcal{O}_{\mathbb{P}^1}(2n + 2)$, where RNC denotes any rational normal curve on $\upsilon_{n,d}$. If this conjecture is true, this would prove semistability of the normal bundles $\mathcal{N}_{\upsilon_{n,2}}$. In other words, these normal bundles are represented by points on the moduli scheme representing the appropriate moduli functor.

Acoustic Twisted Harmonic Oscillators

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Mentor: Benjamin November, Harris Pirie, Stephen Carr

The discovery of twisted van der Waals (vdW) heterostructures hosting moiré lattices has opened a parameter space of materials and twist angles too vast for direct exploration. Acoustic metamaterials can be used to mimic the behaviors of vdW heterostructures, serving as cheap and rapid prototypes for their expensive and laborious quantum counterparts. For example, twisted bilayer graphene (TBG) has already been successfully translated into the field of acoustics. While TBG is known to feature isolated flat bands due to the hybridization of dispersive Dirac states, it is also possible to manifest a ladder of flat band harmonic oscillator states originating at the parabolic band edges farther from the Fermi level. Using COMSOL Multiphysics, a finite-element analysis simulation software, we discover emergent harmonic oscillator modes in acoustic twisted bilayer graphene, and we simulate their real space distribution. The twist angle and interlayer coupling strength of our metamaterial can be easily tuned to control the energy spacing of the flat bands and their localization across the moiré lattice supercell. Our metamaterial may serve as a tunable platform for emergent phenomena such as second harmonic generation.

Quantifying Viral Load and Rebound in HIV-1 Patients Using the Antigen p17

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Mentor: Tyler Dougan

Human Immunodeficiency Virus 1 (HIV-1) is an incurable viral infection that requires lifelong treatment and disease monitoring, as a lapse in treatment can lead to viral resurgence. The current standard for monitoring viral rebound in HIV-1 patients involves measuring nucleic acid copies. However, existing technologies fail to capture accurate information regarding the reservoirs where the virus is harbored. A potentially more effective viral rebound detection method would measure the levels of specific viral antigens required for active HIV infection as disease biomarkers. One such antigen is p17, which is essential to viral replication cycles and elicits strong immune responses from host organisms. The single molecule array (SiMoA), developed at the Walt Lab, is an ultrasensitive assay platform that uses antibody-bead sandwich pairs and is capable of detecting analytes at femtomolar levels. My thesis project therefore seeks to develop an ultrasensitive assay using SiMoA that can detect p17 antigens in human samples to quantify viral load and potential for rebound in HIV-1 patients. I cross tested forty-two different antibody-bead pairs for my proposed SiMoA assay, with five pairs showing high signal to background ratio values and limit of detection values at picogram levels. The assay is currently undergoing optimization steps to improve sensitivity for detection of the target antigen and reduce background noise before being used on human plasma samples.

Allometric Scaling in Bones and Feathers Structures Migration-Associated Variation in Wing Morphology in Song Sparrows (*Melospiza melodia*)

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Mentor: Subir Shakya

The association of avian migration with wing lengthening and narrowing, as quantified by hand-wing index, is one of the most robust relationships in ecomorphology. Despite this, the specific integumentary and osteological components of the avian wing that drive this relationship remain unknown. In this study, we investigate how scaling in the individual flight feathers and bones of Song Sparrows (*Melospiza melodia*) determines variation in overall wing morphology between the species' many phylogenetically independent migratory and sedentary populations. We integrated traditional hand measurement with micro-CT scanning, including a novel method for extracting feather lengths from these scans, to analyze museum study skins. We characterized hand-wing index, primary feather lengths, and the morphology of the carpometacarpus and phalanges for $\sim$ 2020 individuals across the geographic distribution of this diverse species. We verify a significantly higher hand-wing index in migratory populations and demonstrate that this lengthening is driven by the lengthening of the primaries and second digit while the size of the first digit and carpometacarpus are conserved. These results show how geographic adaptation in a macroscale morphological trait is structured by complex allometry between differentially conserved components. We plan to expand the number of birds measured and scanned to encompass all subspecies and to perform a landmark-based Procrustes analysis to build a granular, continuous map of morphological variability and conservation across the entire wing.

Bootstrap Diagnostics for Irregular Estimators

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Researchers often use normal approximations of estimators in order to summarize and communicate uncertainty about their findings. When such approximations are unreliable, they can lead consumers of scientific research to make misguided decisions. We propose to measure the quality of the normal approximation for a given estimator by the maximum vertical distance between the empirical CDF of a bootstrap distribution and the normal distribution implied by the point estimate and standard error. Our approach applies to estimators of linear and nonlinear models, and can diagnose failures of normality due to limited information, estimates near a boundary, and other sources. We show that our methods are especially easy to implement in the many situations in which a bootstrap is used to compute the standard error. In a sample of recent papers published in top economic journals that use a bootstrap to compute standard errors, we show that failures of normality are common. An accompanying python package facilitates adoption of our proposals.

Cell Response to Highly Entangled (HE) Hydrogels

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Mentor: Nicholas Hesse

Highly entangled (HE) hydrogels, which incorporate long single-network polymer chains with minimal crosslinking, show promise for in-vivo applications as surgical adhesives and drug delivery devices. HE hydrogels possess favorable mechanical properties compared to traditional hydrogels, having higher crosslinking ratios that tend to be swell-resistant yet embrittled. However, their biological compatibility is not very well understood and therefore requires thorough evaluation before utilization. In this study, HE hydrogel biocompatibility was assessed through cytotoxicity, cell spreading, and proliferation analyses. To investigate cytotoxicity, we exposed 3T3 fibroblasts to HE-hydrogel-conditioned media at varying dilution ratios (1:1, 1:10, 1:100, and 1:1000) on the WST-1 assay. Additionally, we measured cell proliferation and viability using the MTT assay with identical dilution ratios. A polyacrylamide-only (PAAM) gel with a high crosslinking ratio underwent the same cell conditions as the HE hydrogel for comparison and control purposes. Preliminary findings indicate that the individual components used in forming the HE hydrogel do not exhibit cytotoxic properties, as can be supported by the WST-1 assay. However, we hypothesize that the unique structure of the HE hydrogel, characterized by long dangling polyacrylamide chains, may impede the firm adhesion and proliferation of 3T3 fibroblasts. If our hypothesis is confirmed, our results will suggest the necessity of supplementary polymer adhesives to promote cell spreading and expansion on the HE hydrogel effectively. Nevertheless, further investigation on long-term cell integration and behavior is needed to enhance the safety and efficacy of HE hydrogels as potential adhesives and drug-delivery devices in biomedical applications.

Ōura Ring Validation Study

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Sleep tracking devices are becoming more widely used, yet few devices have been validated to ensure that the data they present to users is accurate. This study evaluated the performance of a popular sleep tracker, the Ōura Ring, and two competitor devices, the Apple Watch Series 8 and the Fitbit Sense 2, against the gold standard sleep measure, in-lab polysomnography. We recruited 35 healthy participants, ages 20-50 years old. Recruitment weights were used to ensure the sample reflected the racial and ethnic composition of Massachusetts, according to US Census estimates. All participants completed one night of in-lab polysomnography preceded by one week of outpatient ambulatory sleep monitoring using a MotionLogger (CamNtech Inc.) to confirm the patient's habitual sleep-wake schedule. During the in-lab visit, the participant wore two Ōura rings (one on each hand), a Fitbit on one wrist, and an Apple Watch on the other during the overnight polysomnography, in accordance with their habitual sleep-wake schedule. Measurements regarding sleep stages, sleep efficiency, sleep latency, and heart rate variability were captured from the Ōura rings, the Fitbit, and the Apple Watch, and each was compared to one another and to polysomnography. Epoch-by-epoch analyses revealed sensitivity between polysomnography and the devices as follows: Ōura (0.99), Fitbit (0.92), and Apple Watch (0.90). Of the commercial trackers, Ōura performed the best in terms of sensitivity to polysomnography, while FitBit was the next most sensitive device. In controlled settings, wearable sleep trackers showed promising performance, reinforcing their viability as research-grade technologies. Though these devices might not provide the depth of insight offered by polysomnography, our study showed that wearable trackers provide robust and reliable measurements in field settings.

scFLARE2-Halo Tag: A Molecular Tool for Time-Tagging Neuronal Activity

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To study the cellular mechanisms of complex brain functions, such as memory, it would be ideal to have high resolution, temporally precise imaging of neural activity below the brain surface (e.g., hippocampus) over large fields-of-view. A current approach is to use molecular reporters that enable *in vivo* labeling of transiently active neuronal circuits, which can be read out via *ex vivo* microscopy for imaging, characterization, and manipulation. However, many integrators can only resolve activated neuronal circuits at a single time point. Here, we validated the scFLARE2 system, a light and calcium gated molecular reporter of neuronal activity, in cultured neurons and genetically modified it to enable time stamping of neuronal activity. We designed a genetic construct that replaces scFLARE2's mCherry reporter of neuronal activity with a self-labeling protein tag, HaloTag, which can bind fluorescent dyes of different colors. In the presence of blue light stimulation (temporal gate of the experimental window) and elevated calcium (proxy for neuronal activity), HaloTag proteins will be expressed in activated neurons and bind to the fluorescent dye injected within that experimental time window. The dye color is a marker of neuronal activity at that particular time point. After providing stimuli at various time points, *ex vivo* microscopy will be used to identify the color of the neurons, which can be inferred to have been activated by the stimulus provided in the same time window as the colored dye. We are validating our novel tool in cultured neurons and preparing it for *in vivo* testing in the mouse hippocampus. Once validated, our tool can be applied to record neuronal dynamics at different time points in previously inaccessible areas of the brain, which can provide insight on the neuronal mechanisms underlying complex phenomena, such as memory formation.

Deciphering the Activation of KLF2 Expression Through CRISPR-Cas9 Knockout Studies

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The vascular endothelium, the single-cell-thick lining of blood vessels, experiences varying biomechanical forces generated by the flow of blood; therefore, endothelial cells are equipped with signaling pathways that protect against adverse humoral and hemodynamic environments. A vital gene that is activated by flow-mediated signaling pathways is the transcription factor Kruppel-like factor 2 (KFL2), which is responsible for vasoprotective functions in endothelial cells. Due to the importance of KLF2 in protecting endothelial cells, our project aims to understand KLF2 expression by finding the genes that affect its expression under flow conditions. In order to understand KLF2 expression, the lab conducted a genome-wide CRISPR screen using two sgRNA libraries, totaling 6 guides/gene. Our analysis of the results of this screen pointed to 406 statistically significant genes that decreased KLF2 expression when knocked out. To narrow down to the most significant genes, we studied the 406 genes in reference to a myriad of gene libraries and already established pathways to better understand the function of these genes and draw connections with KLF2 expression. After pathway analysis, a few gene families and unique genes appeared to be significant in endothelial cells with potential novel connections to the KLF2 pathway in endothelial cells. These include several G-protein coupled receptors (GPCR) and downstream signaling. With these genes, we will next validate their connection to KLF2 by conducting individual CRISPR-Cas9 knockout studies. This validation will significantly add to our understanding of endothelial mechano-activated signaling pathways, which is critical for the development of novel therapeutic approaches for cardiovascular diseases, including atherosclerosis.

The Genetic Basis of Behavior: Olfaction in Deer Mice

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Mammals rely on olfactory receptors to detect odors that indicate the presence of predators. Thus, mutations in olfactory receptor genes may impact a species' ability to detect predators. Understanding the impact of these genetic differences and their evolutionary history is crucial for understanding the interplay between genetics and behavior. Here, we investigate the impact of genetic variation in olfactory receptor genes on predator detection capabilities in deer mice (*Peromyscus maniculatus*). To accomplish this, we developed an automated pipeline that takes the lab mouse (*Mus musculus*) genome, the *Peromyscus* genome, and a *Mus* gene of interest as input, compares the two genomes to find the orthologous sequences in *Peromyscus*, and searches for variation in the identified gene among *Peromyscus* populations. This allows us to identify any mutations in the sequence that might affect the functionality of the olfactory receptor corresponding to the gene of interest across different *Peromyscus* populations. Next, in an effort to link genotype and phenotype, we will test multiple *Peromyscus* populations exhibiting variation in the gene for variation in behavioral responses to predator scents. These variations could indicate evolution to local predator regimes. While originally developed to assess olfactory receptor variation in *Peromyscus*, our flexible pipeline can also assess variation in any target gene using any two species. Understanding the relationship between genetics and behavior is vital for diverse fields, including evolutionary biology, conservation, and human health. The bioinformatic pipeline that we have created will allow for broader investigations into the evolutionary relationships and interplay between genetics and behavior.

The Dynamics of Mating in a Penis Fencing Worm

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The phylum Xenoacoelomorpha likely represents an outgroup to all other organisms with bilateral symmetry. Despite this evolutionarily informative position, there have not been rigorous studies characterizing the life histories of these animals. Some acoels are believed to use hypodermic insemination, or "penis fencing," to mate, a mode of copulation that has not been quantitatively studied. Using *Hofstenia miamia*, an acoel worm and emerging model organism, I developed a staining procedure to label sperm and then injected sperm at different sites along the body. The result of this experiment will reveal where sperm are stored following mating. Additionally, by using subsequent egg-laying as a sign of insemination success, it can be determined whether the worm's female reproductive system can accommodate sperm injection at any site. I also used a behavioral filming rig to capture egg laying. These videos revealed that *Hofstenia* lays eggs out of its mouth, marking a novel method of egg deposition and the first video of acoel egg deposition. I also analyzed mating events I filmed previously using the pose estimation software DeepLabCut. This will yield a mathematical model of penis fencing that reveals the structure of this behavior. Together, the results of these experiments will greatly increase our understanding of acoels, broadening our knowledge of the diversity of animal life and evolution. Future histological studies will supplement this work to enable a deeper understanding of acoel anatomy and physiology.

Metamaterial Implant for Deep Brain Stimulation

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Deep brain stimulation (DBS) has become an increasingly common therapeutic procedure, providing remarkable advancements in the treatment options for various neurological and neuropsychiatric conditions. Through implanted electrode implants (leads) that send controlled electrical impulses to specific targets in the brain, DBS has been shown to treat a range of illnesses from Parkinson's disease to epilepsy. Unfortunately, this success is limited by the implant's poor compatibility with magnetic resonance imaging (MRI), a standard tool used in medical diagnoses. During an MRI exam, these leads act as an electrical antenna, absorbing substantial amounts of radio frequency (RF) energy and delivering it to surrounding tissue, often causing serious burns and other heat-related injury. This project aims to design a novel lead design that reduces this antenna effect, effectively "scattering" this energy away rather than absorbing it, leading to decreased tissue heating from an MRI exam. Using a combination of computational modeling and experimental measuring, an RF-transparent prototype was created, optimized, and tested in a gel phantom during an MRI scan to ensure a decrease in heating, cost-effectiveness, and greater biocompatibility compared to current commercial DBS leads. The proposed design may be able to grant many patients with DBS implants the diagnostic benefits of MRI while not compromising the efficacy or cost of their implant.

Defining Genetic Changes in PDAC Precursors Using Single Cell Transcriptomics

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Mentor: Katie Aney, Woo-Jeong Jeong

Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease, with a five-year survival rate of just 11.5%. Surgery offers the only chance of cure, which makes early detection especially important for survival. One of the precursor lesions to PDAC is pancreatic intraepithelial neoplasia (PanIN). While PanIN precursors and PDAC histologically resemble ductal cells, they are thought to originate from transdifferentiated acinar cells through acinar ductal metaplasia (ADM). ADM is a rate-limiting step in PDAC progression and also occurs when acinar cells respond to stress or injury. To examine early PDAC and the ADM transition at a detailed timescale, we performed scRNA-seq on the pancreas of a genetically engineered mouse model (GEMM) at multiple timepoints soon after activation of a *Kras* mutation, the initiating mutation in almost all cases of PDAC. Because acinar cells produce high levels of RNases and digestive enzymes, the pancreas is a challenging context for transcriptomic analysis. We therefore devised a novel technique using a reversible crosslinker that achieved lower cellular stress signatures and celltype capture that more closely resembled the composition expected from histology. Downstream analysis of differentially expressed genes, receptor-ligand pathways, and trajectory inference resulted in the formulation of an ADM gene index comprising 17 genes, providing a way to quantitatively determine the extent of ADM transition following perturbation such as pancreatitis or cancer. After one week, no significant transcriptomic changes were observed following a *Kras* mutation. However, dramatic histologic changes including metaplasia appear at eight weeks, defining a time window in which we will investigate the earliest events mediating ADM, building a better understanding of how the gene networks of early precursor lesions — ADM and PanINs — develop and illuminating potential targets for PDAC early interception and detection strategies.

A Dilated CNN Model for Prediction of Retinopathy of Prematurity in Preterm Infants

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The rapid advancement of deep learning and the widespread adoption of electronic health record (EHR) systems inspire novel integration of the two to transform the current practice of medicine. When employed by deep-learning approaches, these EHR data can enhance our understanding of diseases and improve methods for their diagnosis, prevention, and treatment. In this study, we developed a novel dilated CNN model to accurately diagnose retinopathy of prematurity (ROP) using longitudinal patient vital signs, ECG, and monitor data. ROP is a prevalent disorder affecting preterm infants, characterized by the abnormal development of blood vessels in the eyes, which can progress to retinal detachment and blindness. Current screening guidelines for ROP involve timely examinations of preterm infants by ophthalmologists trained in ROP, a very costly and inefficient process, particularly in under-resourced areas. Recent attempts to aid ROP risk prediction suffer from low specificity or rely fully on quality retinal images, which can be difficult to obtain without trained ophthalmologists. Thus, our approach is to harness the potential of deep learning architectures in medicine to develop a model trained on real-time monitoring data already collected by neonatal intensive care units (NICUs) to develop a new class of screening tool for ROP that is more efficient, accurate, and accessible than existing options. Specifically, we are currently developing and evaluating a model based on WaveNet architecture originally designed to generate raw audio waveforms given the similarity of audio waveform data to ECG waveform data. With this adapted architecture, we can then encode longitudinal patient monitoring and waveform data to predict risk for ROP. Ultimately, we hope that this implementation can aid physician understanding of a patient's risk for ROP using vital signs and monitoring data already collected as a function of staying in the NICU to reduce overall incidence of ROP.

Investigating the Role of Transcription Factor MAFF in Inflammation-Induced Dysfunction of Brain Endothelial Cells

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Mentor: Mary H.C. Florido

The aging brain experiences increased levels of neuroinflammation and metabolic dysregulation. These changes lead to dysfunction of the blood-brain-barrier (BBB), the structure that strictly regulates which molecules are permitted to cross between the blood and the brain. However, the exact mechanisms leading to BBB dysfunction are not fully understood. In this project, we focus on MAF bZIP transcription factor F (*MAFF*), which we previously identified to be significantly upregulated in aged versus young mouse brain endothelial cells, the main barrier-forming cell type of the BBB. Our single-cell RNA-seq dataset also showed impaired mitochondrial pathways and the upregulation of inflammatory pathways in brain endothelial cells, suggesting an unhealthy cell state. While previous studies have implicated *MAFF* in the regulation of inflammation and metabolism in other cell types, its role in the aging brain remains unknown. Thus, we hypothesize that when brain endothelial cells experience pro-inflammatory conditions in the aging brain, the resulting upregulation of *MAFF* causes endothelial cell dysfunction. We treated brain endothelial cells derived from human induced pluripotent stem cells with the pro-inflammatory cytokine TNF-α, whose levels are elevated in the brains of elderly individuals and patients with Alzheimer's disease. Preliminary results show that this treatment is sufficient to upregulate *MAFF*. Future experiments using reverse transcription-quantitative polymerase chain reaction (RT-qPCR), immunofluorescence imaging, and various apoptosis and endothelial cell functional assays will further probe the mechanisms induced by *MAFF* upregulation. Our results will improve the field's understanding of how inflammation, metabolic dysregulation, and BBB dysfunction are related. Ultimately, this project could provide evidence that *MAFF* can serve as a therapeutic target to improve overall BBB function in elderly individuals or patients with age-related neurodegenerative diseases.

Noninvasive Testing to Diagnose Uterine Fibroids

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Uterine leiomyomas, also known as uterine fibroids, are the most common benign pelvic tumors in reproductive-aged women that arise from the overgrowth of the smooth muscle stem cells of the myometrium. While many individuals with fibroids remain asymptomatic, some experience symptoms, such as excessive menstrual bleeding that lead to anemia, pelvic pain, and urinary incontinence. Prior research has found that exon 2 of the *MED12* gene, which is part of a mediator complex that controls gene-specific and global transcription by guiding regulatory DNA components to the RNA Polymerase II initiation complex, harbors pathogenic variants in 70% of uterine leiomyoma patients. We hypothesize that *MED12* variants can be detected through deep sequencing of DNA in cells shed into peripheral blood. To determine this, we enrolled women prior to uterine fibroid surgery, extracted DNA from paraffin sections of patients' fibroids, and performed PCR amplification of exon 2 of the *MED12* variant selected. Next, we will perform deep sequencing from the patient's peripheral blood to match the *MED12* variants from patients' fibroids. Peripheral blood samples will be collected from patients without uterine fibroids to serve as controls. Our study will provide a road to noninvasive identification of uterine fibroids, which will allow further study of the genes that predispose women to develop uterine fibroids and optimize future diagnostics and management of the condition.

Airway Epithelial Microfold Cells Sample, Deliver, Process, and Present Antigens to Activate a Robust Local Adaptive Immune Response

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The airway epithelium is under constant dynamic exposure to airborne environmental allergens and pathogens. In addition to forming an intact barrier, the cells of the airway epithelium must sample antigens and communicate with the immune system to mount appropriate antigen-specific responses. Microfold (M) cells, first identified in the intestines, are antigen-sampling epithelial cells that uptake diverse luminal antigens and transcytose them to underlying mononuclear phagocytes and lymphocytes, activating robust local adaptive immune responses. Having been recently identified in the lower respiratory airways, the antigen delivery mechanisms of airway M cells remain unexplored. Furthermore, whether airway M cells can directly process and present antigens to immune cells is not known. We hypothesize that airway epithelial M cells not only deliver antigens to antigen-presenting dendritic cells but also activate T cells through MHC II-dependent antigen presentation and MHC I cross-presentation. In this study, we used several model antigens, including solubilized ovalbumin and particulate microspheres in an in vitro air-liquid interface (ALI) model of the murine airway epithelium to evaluate the antigen sampling potential of airway M cells. We observed that M cells failed to uptake soluble ovalbumin but efficiently endocytosed particulate beads of 0.1, 0.5 and 1.0 um diameter. We now seek to further investigate the antigen-processing ability of airway M cells using DQ-conjugated microspheres. DQ, a quenched BODIPY dye, is homeostatically non-fluorescent but fluoresces under proteolytic conditions that liberate fluorescent peptides, allowing for direct visualization of antigen processing. Our next step will be to develop a novel a novel in vitro M cell-immune cell co-culture model using matrigel diluted in 804G to thoroughly investigate M cell antigen delivery to antigen-presenting dendritic cells and B cells as well as the processing and presentation necessary to directly activate the T cells of the local adaptive immune response.

Investigation of the Pro- or Anti-Fibrotic Effect of GDF11 in Cardiac Fibrosis

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Growth Differentiation Factor 11 (GDF11) is a member of the transforming growth factor-β superfamily (TGF-β) involved in several biological processes such as cell survival, differentiation, apoptosis, and inflammatory and reparative responses. These cytokines are also known to be involved in cardiac remodeling after an infarction via the modulation and regulation of inflammation and heart repair. Among all of the characterized functions of GDF11, this protein has also been shown to have both an antifibrotic and profibrotic effect in the heart, which begs the question of why it can have such differential effects and what determines whether it has an antifibrotic or profibrotic effect. GDF11 signals through the SMAD2/3 pathways, which are implicated in the later stages of fibroblast activation. Interestingly, it can activate either the SMAD2 or SMAD3 pathways more strongly; this can lead to different gene expression. Activation of SMAD2 has an antifibrotic effect by decreasing the expression of *Collagen1* and upregulating the gene MMP2, resulting in the degradation of the extracellular matrix. Conversely, activation of SMAD3 has a profibrotic effect by upregulating *Collagen1* expression and thereby causing further production of the matrix. To further investigate this, we treated human cardiac fibroblasts and a co-culture of cardiomyocytes/fibroblasts or cardiomyocytes/endothelial cells/fibroblasts with different concentrations of GDF11 (0, 25, 50, 100 ng/μL) and exposed them to these treatments for 3 different time lengths (6, 24, 96 hours). We aim to analyze the differential expression of *Col1* and *MMP2* to see which genes are being activated downstream by GDF11 stimulation and the phosphorylation of SMAD2 and SMAD3 in response to GDF11 treatment relative to the global amount of SMAD2/3. Ultimately, this will allow us to better understand GDF11's activation of the SMAD2/3 pathways in the heart and its potential role in treating atrial fibrosis.

What Does Social Interaction Look Like in Brains: A Hyperscanning Project

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Hyperscanning is an emerging technique in which the brains of two interacting individuals are simultaneously recorded. While established for human EEG studies, hyperscanning experiments in mice remain limited. We aim to establish methods using fiber photometry and behavioral assays to investigate neural activity associated with social behavior in Shank3-deficient mice, an established Autism Spectrum Disorder (ASD) animal model. We employed fiber photometry, an optogenetic technique, to initially record neuronal response in the striatum. Multiple C57BL/6J (wildtype) mice were stereotaxically injected with different viral vectors encoding fluorescent probes to detect either redox activity, dopaminergic neuron activity, or intracellular calcium concentrations. To characterize the fluorescence efficiency of each, freely behaving animals were recorded after two or more weeks of viral expression, by alternating 470-405 nm wavelength light passed through a surgically implanted optical fiber. With regard to social behavior, the tube test, an established assay for determining social dominance in mice, was conducted using heterozygous Shank3fx (+/-) mutants in pairwise bouts against wildtype controls. Dominance was determined by which animal successfully pushed the other out of the tube. Fluorescence was observed in fiber photometry signals for each of the viral probes in vivo. In the tube test, Shank3fx mutant mice won significantly more bouts over wildtype controls (χ^2 = 6.25, df = 1, p-value = 0.012). Our results revealed a striking social dominance of ASD model mice. Future experiments will assess neural activity associated with these behavioral differences by concurrent fiber photometry recordings of the prefrontal cortex (ACC) during pairwise interactions across the dominance hierarchy. Signal coherence between interacting animals will be assessed for synchronization or other time-locked relationships, which could provide novel intrinsic correlates of ASD-related social behavior.

Homogeneous Nucleation of Colloidal Crystals

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Mentor: Will Wang

Crystal nucleation is an ubiquitous process underlying many phenomena from the fabrication of semiconductors to the formation of ice crystals in the atmosphere. Classical Nucleation Theory (CNT) is the working theory to describe these systems. Under CNT, crystal nuclei form due to small structural fluctuations in a liquid, with probability of growth determined by their Gibbs free energy. When these nuclei are small, they are unlikely to grow, but above a critical radius, they develop rapidly into crystals. We study this system with hard spheres, where CNT is in good agreement with experiments when the number density of particles is sufficiently high. At lower densities, however, we see a discrepancy between theory and experiment of hundreds of orders of magnitude. To address this problem, we aim to investigate homogeneous nucleation using novel techniques. Specifically, we are measuring the homogeneous nucleation rate of colloids, which are micron-sized polymer hard spheres immersed in a liquid. They are small enough to stay suspended in liquid strictly due to Brownian motion, yet are still large enough to be imaged under a confocal microscope. We imaged these colloids under a confocal microscope, allowing us to track the movement of millions of them as the crystals develop over time. Based on this data, we render a 3D image, and using crystal identification algorithms, can track the crystals as they grow or shrink over time. In doing so, we will determine nucleation rates and critical radii, which will be compared to earlier results and the predictions of CNT, hopefully resolving this decades-old question.

Investigating the Role of the SOX9 Protein in the Initiation of Colorectal Cancer via Interaction With BAF Complex Assemblies

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The objective of this project is to elucidate the precise role of the SRY-box transcription factor 9 (SOX9) protein in the initiation of colorectal cancer, particularly in relation to the BAF (BRG1/BRM-associated factor) complex. Our work follows up on preliminary observations that suggest a significant involvement of SOX9 with the BAF complex, a versatile assembly comprising diverse subunits that form various assemblies such as ncBAF, PBAF, and cBAF. The assemblies have previously been shown to promote oncogenesis via different mechanisms, so SOX9's preference for a specific assembly can provide insights into its role in colorectal cancer initiation. We employ two approaches to understand the molecular mechanism of SOX9's interaction with the BAF complex. The first approach is to employ immunoprecipitation with SOX9 as the bait, followed by Western Blot analysis to identify the specific BAF subunits interacting with SOX9, thus inferring the assembly it potentially belongs to. The second approach is to utilize base editors to modify a critical region of the SOX9 gene previously identified as essential for BAF complex interaction through knockout constructs. This genetic manipulation aims to shed light on the intricacies of the SOX9 gene, particularly the critical regions for BAF complex interaction. Preliminary results suggest that SOX9 shows a predilection for interaction with certain BAF subunits, potentially implying its role within specific BAF assemblies. These findings, although preliminary, suggest that SOX9 promotes colorectal cancer initiation by inhibiting the differentiation pathway of intestinal epithelial cells. Future directions of our research include completing the analysis of SOX9 gene alterations and refining our understanding of the SOX9-BAF interaction. These outcomes have potential implications not only for improving our understanding of colorectal cancer initiation but also for the development of targeted therapeutic strategies.

Towards an Open-Source XR Development Platform for FPGA-Accelerated tinyML

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Tiny machine learning (tinyML) is a computing paradigm in which machine learning hardware, software, and algorithms operate on the edge, permitting power- and resource-constrained use cases on the respective orders of milliwatts and kilobytes. The need for high-performance computing resources in traditional models has confined most machine learning applications to the cloud. However, by training, pruning, and quantizing models prior to deployment and eliminating dynamic memory allocation, we enable extremely small-scale microcontroller-based embedded devices to perform stable on-device, real-time inference, while also preserving accuracy, bandwidth, and data privacy. In particular, we focused on the deployment of a keyword spotting convolutional neural network (CNN) model on the Monocle, an open-source extended reality (XR) optical device. We implemented, trained, and memory-optimized the CNN in TensorFlow and compiled it to MicroPython bytecode for onboard integration. To prevent irrecoverable OOM events, we allocated RAM for the glibc heap, thereby enabling class allocation on the MicroPython heap and preventing their garbage collection. We deployed the custom firmware encapsulating the CNN onto embedded flash memory chips. Likewise, we were interested in hardware acceleration of the CNN leveraging the on-device Field-Programmable Gate Array (FPGA). Through a paradigm similar to CFU Playground, an open-source framework for tinyML acceleration on FPGAs, we implemented and integrated a model-specialized CPU instruction set similar in principle to the AVX extension of the x86 ISA used by modern Intel processors. Our procedure and findings provide groundwork and a comprehensive proof-of-concept for future work on building an open-source XR development platform for hardware-accelerated tinyML.

Exploring Electrical Activity in an Inducible Brain Organoid Model of Alzheimer's Disease

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Mentor: Matthias Hebisch

Alzheimer's disease (AD) is the most common cause of dementia globally and is the sixth-leading cause of death in the United States. The disease is characterized by amyloid-β (Aβ) plaque buildup, tau neurofibrillary tangle accumulation, neuroinflammation, and progressive loss of synapses and neurons. Previous electrical studies using animal and cellular models of AD reveal a higher frequency and a lower threshold of action potentials firing, indicating possible neuronal hyperactivity in AD neurons. Moreover, experiments with AD organoid models display enhanced extracellular action potential firing rate, suggesting that neuronal hyperactivity may precede AD hypoactivity and neuronal death. The Kim lab, aiming to develop a relevant and accurate AD model, developed a cortical organoid model of AD from human-induced pluripotent stem cells (hiPSCs) with doxycycline-inducible overproduction of Aβ42 (I45F) or Aβ40 (I47F) that exhibits Aβ-driven pathology and neurodegeneration. Whether these cortical organoid models show electrical hyperactivity and synaptic impairment commonly associated with AD needs to be tested. First, we matured cortical organoids with the mutations and controls for 2-4 months, then we plated whole organoids and live organoid sections on both 2D and 3D extracellular multi-electrode arrays (MEAs) to monitor populational neural activity and neurocircuit activity. We detected spontaneous electrical activity matching neuronal action potentials but plan to further improve neuronal maturation and firing rate in order to assay aberrant electrical activity and synaptic impairment within our AD models. Our study hopes to determine whether the current cortical organoid models of AD can be useful platforms to explore electrical and synaptic impairments in AD. Future drug-screening efforts can then be guided towards protecting circuit function and preserving cognition instead of biomarker modification in order to dramatically improve screening efficiency.

Investigating the Molecular Mechanism of SMOC1 in Alezheimer's Disease Pathogenesis Using Patient-Derived Neurons

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Mentor: Zach Augur

SMOC1 is a secreted protein expressed ubiquitously in humans and present at high levels in the brain. It is involved in many biological functions, including cell adhesion, angiogenesis, and development. Molecularly, studies suggest SMOC1 activates the TGF-β signaling pathway and inhibits the BMP signaling pathway. In both cases, SMOC1's pathway regulation may be mediated by Smad proteins. SMOC1 is an attractive biomarker for Alzheimer's disease (AD) because it has been shown to be significantly elevated in AD brain tissue, cerebrospinal fluid, and plasma. Additionally, it has been shown to partially co-localize with β-amyloid plaques, a hallmark of AD, in human frontal cortex tissue. However, the mechanism causing SMOC1 upregulation in AD remains unknown. Our preliminary TMT-MS proteomics analysis confirmed a significant upregulation of SMOC1 protein in TBS-soluble brain extracts from AD patients and non-cognitively-impaired (NCI) individuals displaying high AD neuropathology compared to NCI individuals displaying low AD neuropathology. We validated these results with Western blot analysis of SMOC1 levels using the same brain extracts. To further analyze the functions of SMOC1 in AD, we will use neurons and astrocytes derived from induced pluripotent stem cells from older and genetically-diverse individuals. These individuals span the full spectrum of AD pathology, facilitating our exploration of SMOC1 in an AD context. We will generate both wild-type and SMOC1-knockout neurons and astrocytes with our cell differentiation and CRISPR-Cas9 protocols. We will then perform proteomic analysis and assay for AD-relevant proteins (e.g. β-amyloid and tau) and SMOC1-relevant pathways (i.e. TGF-β, BMP, and Smad proteins) in these cell types. Ultimately, by investigating the mechanism of SMOC1 upregulation in AD brains, our research will reinforce the relevance of SMOC1 as an AD biomarker and facilitate a better understanding of the disease's multifactorial pathogenesis.

PRIMO

Intercollegiate Varsity Athletes: Diversity and Athletic Performance

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Current literature examines the role athletics has when determining the college majors and career outcomes of student athletes in major athletics conferences in the National Collegiate Athletics Association (NCAA). However, this research project aims to compare the college majors and career outcomes of student athletes relative to non-athletes in the Ivy League. Since the difference in academic capability between athletes and non-athletes when admitted to Ivy League schools is much smaller between these two groups than that between these two groups admitted to schools in other athletic conferences, we can better identify whether factors exogenous to academic intellect may lead to the success of either group. To investigate this, we used data that scraped the LinkedIn information of individuals and provided information relevant to this research project such as an individual's college major, the sport(s) they played while in college (if applicable), and their first job post-graduation. Using this information, we statistically computed the differences of factors such as wage, first industries post-graduation and "seniority", the median time it takes one to attain a certain job title in a particular industry, of Ivy League athletes versus non-athletes. Some initial results found that economics and history were the two most popular college majors for both athletes and non-athletes alike. However, the results also found that athletes tend to earn higher wages than non-athletes on average, and are also more likely to pursue careers where they can achieve a higher level of "seniority", which is highly dependent on the industry one works in. We are still determining whether we have conclusive data to suggest that skills such as teamwork and perseverance, which can be referred to as "human capital", are developed by athletes while they participated in athletics which help them progress along their careers.

Economics of the Space Sector

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Private investment in space totaled over $270 billion over the course of the past decade, according to data from Space Capital (2023). Its possibilities as a frontier are endless. Yet little attention has been devoted to studying the unique environment of space commerce and to facilitating market-based solutions to its development. By considering the history of railroad development as an imperfect analog for the stimulation of space commerce in the present, we hope to chart a path forward for policymakers and firms seeking to expand into space. Our review finds that railroads had a substantial impact on economic development in the U.S. in the 19th century, validating in part the extensive and controversial public-private partnerships characteristic of the time. At the same time, we found that land grants, often viewed as a historical paragon of smart subsidy, positioned railroad companies as both real estate and transportation firms, industries with misaligned incentives. They also failed to efficiently time the delivery of capital to firms. Additionally, our findings suggest a role for the public sector in designing a favorable environment for firms. Early investments in railroads by local governments were generally motivated by access to an expanded network of markets, which is also a driving cause of economic growth resulting from railroad development. While this makes the connection between railroads and space more tenuous, as space has no existing market structure, it underscores the importance of network effects: once initial projects are underway, subsequent projects will be more strongly incentivized. This suggests initial space investments may be underprovided, possibly implying a role for the public sector in correcting this market failure.

Aligning Incentives for Improved Jobs and Firm Performance

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As firms brace for another recession, one topic on the mind of all employers and employees alike is how the employment landscape will change to accommodate the challenges and opportunities of the coming years. Our project aims to address a fundamental question: Are there methods to align the incentives of employers and employees to promote financial prosperity and increase job quality? Through intersecting case studies, literature review, and qualitative data analysis, we find strong evidence to support that such an arrangement is not only possible but also essential to meet the complex challenges of firms in today's financial and sociopolitical environment. By creating pathways to higher education and providing employees with a greater financial stake in their firms, employees can experience greater loyalty to firms while driving profit. The research we have conducted has enduring implications for both the public and private sector, with notable opportunities for collaboration between the two sectors. Future research aims include applying the key strategic and financial takeaways acquired through our findings to devise policy solutions to mounting social and financial inequity in the United States.

Varieties of Capitalism

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Varieties of capitalism (VoC) is a theoretical framework that examines the diverse institutional arrangements and economic systems across countries. It recognizes that nations adopt different approaches to capitalism, resulting in Liberal Market Economies (LMEs) and Coordinated Market Economies (CMEs). LMEs are characterized by market-driven mechanisms, individual autonomy, and limited state intervention, while CMEs are characterized by coordinated relations between the state, firms, and other stakeholders. Some influential factors that contribute to the formation and development of these varieties of capitalism include historical events, cultural norms, gender dynamics, natural resource endowments, and migrant labor patterns. One such dynamic that has shaped the varieties of capitalism is nationalism. Nationalism, as a cultural, political, and social force, often impacts economic governance and policies within nations. By examining the interplay between nationalism and varieties of capitalism, this paper seeks to understand how nationalistic sentiments influence the adoption of specific economic models. Using comparative analysis, the study investigates historical examples and case studies to explore how nationalism has shaped economic systems in various countries. It will examine the impact of nationalist ideologies on industrial policies, trade strategies, state intervention, and the role of institutions and governance structures in fostering specific varieties of capitalism. This research opens avenues for exploring how the interplay of nationalism and changing global dynamics, such as shifts in migration patterns and evolving cultural norms, may further shape the varieties of capitalism in the future.

Tech for All

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Despite the benefits of technology, its rewards are unevenly distributed, leaving a majority of the world's population, including several minority communities, underserved. With the rise of generative AI technologies and escalation of data-driven transformations, understanding technology's impact and developing tools for equitable distribution both in the private and public infrastructure is crucial for fostering inclusive innovation. As a part of our study, 2500 Kenyan entrepreneurs were trained to use a generative AI tool developed to seek business advice. Initial surveying evaluated socio-demographics and business performance while the final survey, involving 1300 respondents, gauged efficiency, innovation, and management practices, allowing for those provided with an AI tool to be compared to those with business manuals. The ongoing study explores differences in performance and advice quality between the AI tool and traditional manuals. This contributes further to dialogue on the benefits of the generative AI tools, particularly in regions bereft of expert information. Crucially, the results highlight potential enhancements for the AI tool paving way for subsequent deployment and subject expansion. Parallel to this, the advent of robust Digital Public Infrastructure (DPI), instrumental in the creation of an accessible legal identity and digitization of daily activities globally, is exemplified by the India Stack. This suite of open APIs has significantly fostered innovation, financial inclusion, and data network access across India. Our report explores and evaluates leading startups leveraging the India Stack, intending to identify markers that measure the stack's impact on diverse users and sectors, including e-commerce, healthcare, and education. The goal extends beyond identifying disparities in India's digital public goods distribution. It aims to contribute to discourse on enhancing and securing DPI's foundational elements, particularly in emerging markets and underserved communities.

The Impact of ChatGPT on Consultants

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Generative artificial intelligence (AI) tools, such as those built upon generative pre-trained transformer (GPT) language models like ChatGPT, have rapidly become one of the most influential topics in business. Their potential to displace jobs and revolutionize the way that people work could have large-scale implications for the future of many organizations and subsequently the economy. By partnering with a large consulting firm in this project, we conducted a large-scale randomized controlled experiment to evaluate the usefulness of generative AI as a tool for writing and problem-solving tasks, investigating how the use of GPT impacted performance on functions relevant to the daily work of consultants. For both tasks, our work found that most respondents given access to GPT retained a significant portion of the content that GPT returned to them in its responses, with users often choosing to copy the text in its entirety while only making minor modifications. This led participants assigned the writing task with access to GPT to score substantially higher than their previously measured baseline performance and higher than a control group without access to GPT. However, it also led to worse performance for those given access to GPT in the problem-solving task since GPT would often lead the user to an incorrect solution. In both cases, access to GPT significantly reduced the amount of time that participants spent on the given tasks, suggesting the potential for increased productivity when leveraged properly as a companion for human workers. The next phase of this project involves another experiment that explores how generative AI might augment the skills of data scientists, where individuals are already technically fluent. These findings help demonstrate the potential influence of generative AI on high-skill professions and better inform business leaders about how companies can leverage AI in the workplace.

Pharmaceutical Drugs and Payment Systems in the US

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Mentor: Olivia Zhao

Prescription drug spending in America exceeds that of any other country and is largely driven by a small number of very expensive drugs. These costs matter for pharmaceutical industry competition and patients, who may face financial barriers to accessing essential care. To assist patients in purchasing expensive brand name drugs, pharmaceutical companies offer copay assistance through drug coupons. Our research focuses on maximizer programs, which are designed to extract the maximum manufacturer assistance available to benefit the commercial health plan provider without changing or reducing patients' out-of-pocket costs. Insurance plans implemented these programs in response to the higher cost burden of patients choosing high-priced brand name drugs, often over lower-cost brand or generic options. Using pharmacy claims data from a large self-insured employer, we analyze copay assistance following the implementation of a maximizer program, at the drug level. The objective is to learn about the share of drug spending involved in a copay maximizer program, the types of drugs included, and the share of enrollees involved. To determine what factors are predictive of the amount of assistance offered, we explore the association between the amount of assistance collected per prescription and the drug price, the number of rivals in that therapeutic category, and orphan status (an alternative proxy for the level of competition a drug faces). Additionally, we assess medication adherence by measuring the proportion of days patients have medication accessible over a specified period before and after implementation of the maximizer program. Understanding the factors driving copay assistance availability and generosity and the impact of maximizer programs on patients' drug spending and medication adherence holds significant implications for policy on pharmaceutical drugs and payment systems in the United States. This research can also be extended to the spillover effects on utilization of non-targeted drugs and other healthcare services.

What Are the Characteristics of Firms That Purchase Carbon Offsets?

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The market for carbon offsets has grown significantly in recent years. In order to meet internal deadlines or comply with industry standards for achieving carbon neutrality, many companies purchase carbon offsets to balance their emissions and reach their net zero goals. However, the types of carbon offset projects and their respective qualities vary greatly, from low-quality avoided deforestation credits to high-quality investments in carbon capture technology. This study explores the efficacy of carbon offsets as a method of determining whether carbon offsets are used to reach net zero carbon emissions or if they allow firms to procrastinate their own decarbonization efforts. Using CDP (formerly named the Carbon Disclosure Project) data from 2009-2021, this research investigates the market for carbon credits through case studies and analyses of the relationships between firm characteristics (financial variables, total emissions, decarbonization investment, etc.) and firms' practices of purchasing carbon offsets. The preliminary findings suggest a relationship between buying any credits and greater emissions reduction, greater investment in decarbonization, and higher Environmental, Social, and Governance (ESG) scores. Similarly, firms that buy a greater number of credits are also predicted to have greater emissions reduction, greater investment in decarbonization, and higher ESG scores while also having lower price volatility. These early results suggest a positive correlation between acquiring carbon credits and some markers for firms' likelihood to commit to environmental sustainability.

How Parents Build Relationships at Work

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The COVID-19 pandemic significantly disrupted working arrangements in the United States, with an increase in remote and hybrid work options. Existing studies paint a bleak picture of parents' experiences—especially mothers'––due to increased childcare and housework responsibilities while working from home. However, changing dynamics at work and in work relationships alongside these home changes remains less studied. This study aims to explore how mothers and fathers navigate work relationships throughout the pandemic, investigating the lasting effects of these changes on work relationships among them. Using an iterative, mixed methods approach, we conducted three rounds of surveys and interviews over a two-year period. The survey sample comprised 1032 individuals surveyed in May 2020, May 2021, and May 2022, with a focus on changes in working arrangements, household activities, personal and professional relationships, satisfaction levels at home and work, and gender attitudes. We restricted analysis to cisgender individuals in heterosexual couples, resulting in a final sample of 1023 participants, consisting of 52% women and 48% men. Additionally, 117 participants were recruited for interviews, and across three rounds of interviews—again spanning 2020 to 2022—we conducted 244 semi-structured interviews, including both parties in 20 couples. These interviews explored the impact of these changes on work activities, household tasks, childcare responsibilities, and maintenance of personal and professional relationships. By examining the evolving dynamics at home and work throughout the pandemic, this study aims to uncover lasting implications of the interplay between relationships, gender roles, and changing work arrangements.

The Handbook of Labor Economics: Recent Advances in Personnel Economics, Incentives and Compensation

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The Handbook of Labor Economics, released once a decade, provides an authoritative overview of the labor economics literature and proposes new lines of research. For this edition of the Handbook, we review new lenses through which work in personnel economics has expanded upon one-principal, one-agent models and relational incentives in repeated games. Specifically, we highlight the behavioral literature on monetary incentives, the role of imperfect information on agents' unobservable characteristics, and the optimal design of incentives for innovation and teamwork. Theoretical work has suggested that monopsonistic competition for workers increases the prevalence of output-based pay; we suggest that this line of research is fruitful and deserving of more empirical work. We emphasize other gaps in the literature, such as why firms provide general skills training. With more data inside firms than ever before, now is a great opportunity for field experiments to enrich the practice of human resource management as well as the academic literature on industrial organization, game theory, and monopsony in labor markets.

Accounting Fraud in Socially-Responsible Firms

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Anecdotal evidence suggests that managers are strongly incentivized to avoid the reporting of earnings decreases and to maintain consistent increases in earnings. Past research provides evidence that 30% to 44% of firms with slightly negative pre-managed earnings exercise discretion to report positive earnings. In this research project, we sought to explore ways in which socially-responsible firms behaved differently than firms that were not labeled as socially-responsible. Our research explores whether companies that have higher ESG (environmental, social, and governance) ratings are less likely to engage in accounting fraud. One key aspect we focused on was earnings data. We gathered net income data from all companies who filed an annual report to the U.S. Securities and Exchange Commission (SEC) between 1950 and 2022. We plan to split the data by high ESG ratings (top 50 percentile) and low ESG ratings (bottom 50 percentile), and create two earnings density distributions to compare the prevalence of accounting fraud in more socially-responsible companies with that of less socially-responsible companies. The presence of accounting fraud may be detected when there are unusually low frequencies of small decreases in earnings and unusually high frequencies of small increases in earnings. Our findings can contribute to the elucidation of whether ESG ratings primarily serve as a form of virtue signaling or if companies with higher ratings exhibit a stronger moral conscience.

How Generative AI Is Shaping the Future of Human Crowdsourcing

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Mentor: Miaomiao Zhang

Generative Artificial Intelligence (AI) has transformed the very essence of work for individuals and society–but what does this shift entail for businesses? Our research project aims to explore the capabilities of Generative AI as a tool for generating creative business solutions in comparison to conventional human-centered crowdsourcing models. In collaboration with VentureLabs.AI and Freelancer.com, a crowdsourcing challenge titled ”Creating a Sustainable Future: Harnessing the Potential of a Circular Economy” was organized. This challenge attracted 310 human participants, from which 125 viable solutions were identified after filtering for expertise in circular economy. Concurrently, we leveraged the power of GPT-4, an advanced language model, to generate AI solutions by simulating six different problem-solving scenarios using prompt engineering techniques. These techniques involved prompting GPT-4 with various contexts like emulating a certain persona or real-life expert (ex. “You are Elon Musk, an expert in the space technology industry”). We then engaged 145 evaluators from Prolific.org to assess a randomized sample of 234 human and AI solutions. The results present an intriguing tradeoff: human solutions demonstrated greater novelty, while AI solutions excelled in terms of environmental and financial impact. This study sheds light on the possibilities and limitations of both human crowdsourcing and AI in generating innovative business solutions, laying the foundation for a potential integrated approach to problem-solving. Given the tradeoff of AI versus human output, in the future we hope to establish scalable and robust evaluation methods that can effectively assess AI solutions across various contexts.

The Effect of Management on Workplace Productivity

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Mentor: Raffaella Sadun

The dynamic landscape of technological progress has spurred novel interest in training programs to ensure that employees are able to continue to contribute relevant skills. We investigate the value of training team members using administrative data from a fast-food company, car company and retail company. We argue that managers play a key role in skilling, reskilling and upskilling workers, and identify good managers as the top 50% of all managers based on training completed by their team. This study takes advantage of exogenous demand shocks, namely the introduction of an ordering/delivery platform and increased production requests from upper level management. Using an event study set up, we find that exogenous positive demand shocks result in increased absenteeism and turnover rates and decreased productivity. However, teams with "good managers" are significantly less affected by the increased stress at work; there is less absenteeism, lower turnover, and higher productivity than teams under poor management. Hence, this study implies that access to training, and by extension a team's ability to reskill and upskill, creates a more resilient workforce.

Rebranding Museum Visitor Experiences: A Behavioral and Experimental Approach

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PI/Advisor: Alison Wood Brooks, Ryan Buell, Leslie John, Michael Norton, Ting Zhang, Jimin Nam

Museums are institutions that collect and display a community's shared knowledge and experiences, playing critical roles in the preservation, education, and scholarship of their respective fields. Yet, despite their meaningful contributions to society, many museums increasingly struggle to attract and engage visitors. To understand and reconcile this disparity between museums' societal value and public engagement, this project uses survey data and field experiments through a partnership with the Harvard Museums of Science and Culture (HMSC). From our preliminary surveys, we have identified two themes central to memorable museum experiences: novelty and companionship. Indeed, memorable visits tend to be characterized by learning or experiencing new concepts and/or exploring the museum with close companions. Going forward, we plan to conduct field experiments that use control-treatment conditions based on novelty and companionship to test their effects on dependent variables such as attendance numbers and level of engagement during visits. Through this behavioral and experimental approach, our project aims to advance discourse on museum experiences, an area that has traditionally relied heavily on the individual discretions of museum staff, and discover actionable insights that museums can utilize to revitalize their audience engagement.

Davivienda Bank Reskilling Evaluation

Gabriela Lahera
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By the year 2025, 50% of the global workforce will need retraining, underscoring the inevitability of digital transformation, including the seamless integration of automation technologies. The advent of artificial intelligence (AI) and its necessary implementation in diverse business domains raises concerns surrounding the displacement of human labor. To understand the impact on internal structures and task assignments, we evaluate the outcomes of a reskilling program as a response to the introduction of a new technology in a bank in Colombia, with the dual aim of understanding the key attributes that yield successful outcomes for employees and its impact on overall company productivity. The literature reveals that contrary to popular apprehension, AI does not invariably supplant human labor, but rather displaces mundane and routine tasks, affording human capital the liberty to focus on more intricate and value-driven endeavors. We expect to observe similar outcomes when implementing classical empirical methods that rely on granular data at the worker, office and client level, such as difference-in-difference, regression discontinuity, and event studies. However, the data was not always internally consistent, thus we implemented several cleaning techniques to ensure the implementation of methods. As companies strive to stay competitive, our study offers valuable implications for crafting effective reskilling strategies and driving sustainable economic growth in the digital age.

Round Number Patents

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Numerous studies from disparate fields have consistently demonstrated the influence of anchors on individuals' decision-making. Defined as the first pieces of information given regarding an object or topic, these anchors are often represented by notable labels such as round numbers and play important roles in diverse domains ranging from real estate bidding to financial trading in fixed income and equity markets. In this study, we aim to investigate this seemingly inherent human inclination and its intersection with the realm of intellectual property, specifically focusing on the United States Patent & Trademark Office (USPTO) and its allocation of patent numbers, which subsequently reflect the actual innovations involved. Our exploration encompasses various facets of round numbers; that is, numbers that are salient for particular reasons, such as having four or more trailing zeros. To do so, we dive into the intricate details surrounding assignment processes, associated media attention, assignee groups, funding sources, and the realization and subsequent development of further innovative ideas. By diving into the USPTO's patent number assignment process through an empirical end-to-end natural language processing analysis, we aim to shed light on the significance of round numbers and their implications within the intellectual property landscape. Through this project, we aim to deepen our understanding of the underlying mechanisms behind anchors' power in decision-making and to provide valuable insights into the dynamics of intellectual property management, thus contributing to the broader body of knowledge in this domain.

Oversharing: A Review of Information Disclosure in the Domains of Secret-Keeping and Difficult Conversations

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Conventional wisdom often suggests that oversharing is a harmful habit that should be avoided. Our project seeks to assess the veracity of this argument, investigating the various circumstances in which sharing information can prove to be more beneficial than harmful. The present work explores this through a series of literature reviews of the various contexts in which sharing information may be used. Preliminary findings from the reviews suggest that secret-keeping and giving difficult feedback to employees are two domains in which sharing information may be favorable. Research into secret keeping has consistently demonstrated the deleterious effects of concealment on one's well-being. When one is practicing concealment, their mind tends to wander more frequently to what they are keeping a secret and this negatively impacts their well-being. Conversely, confiding information to another person seems to lead to less frequent mind-wandering. Similar positive effects have also been found for self-disclosure (i.e., sharing personal experiences) in conversations between supervisors and employees. Literature in this field suggests that self-disclosure on the part of the supervisor can have positive effects on the relationship between supervisor and employee, particularly in situations where the employee is struggling. The disclosure of personal information or experiences seems to strengthen the bond between the supervisor and employee and encourages authenticity on the employee's part. Building upon these early findings, our project will continue to explore other areas in which sharing information is beneficial and tackle the potential misconception that oversharing is always bad.

Acquisitions and Innovation in Financial Services

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Previous research has found that mergers and acquisitions (M&As) of innovative firms increases innovation on the market level. However, it has been argued that in the pharmaceutical industry, M&As hurt innovation, with such acquisitions denoted as "killer acquisitions." Little research has examined the effects of M&As on subsequent innovation in the financial services sector. We aim to compare the innovativeness of financial firms before and after M&A activity against a synthetic control group, controlling for industry subclass, location, and year. We first create a novel dataset of all innovative financial firms and their patents from 2000-2018. We then develop an innovation measure through machine learning based textual analysis methods. While currently developing our innovation measure, we expect to see a change in the innovativeness of firms post M&A activity in the financial services sector. The results of our research have implications for the corporate development strategy of innovative financial firms, the regulation of M&A activity in the financial sector, and policies to promote financial innovation.

China as Global Financier: State Goals and Local Entanglements

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PI/Advisor: Meg Rithmire

China, as the world's second largest economy, has transitioned from a global capital importer to a global investor and financier, serving as an alternative to western-led international financial institutions as well as an emerging superpower willing to engage in helping developing countries that are usually neglected by the West. Although the United States has accused China of using a political tactic called "debt-trap diplomacy" to exert its geopolitical influence, most China-initiated projects are characterized by low interest rates or grants. In this study, we look at the entirety of Chinese economic activities, including foreign direct investment, lending, and aid, covering firms from both public and private sectors as well as business conducted in all industries in Pakistan and Sri Lanka. In addition to collecting data and analyzing the array of Chinese investments and lending projects, we also collect local media reports aiming to extrapolate local attitudes towards various Chinese projects taking place in host countries over time. Then, this study will utilize geographic information system (GIS) mapping to incorporate the collected data into an interactive map to examine how interactions with China have become politicized and what effects they have. Lastly, the study will place an emphasis on China's foreign direct investment in Pakistan and Sri Lanka and use the aforementioned data to answer the ultimate research question: do higher investment in host countries lead to better terms of leading?

Age of Early Hires for Startups

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Contrary to the popular belief that successful start-ups are predominantly founded by young individuals, this research takes an in-depth look at the age demographics of early hires in startups. Existing literature has, for the most part, focused on the founders' ages, often overlooking the significance of early team members in driving a start-up's growth. The gap our research aims to fill lies in scrutinizing these vital contributors, their ages, and the potential impact on the success trajectory of the startups. This study uniquely probes into the age demographics of early hires in startups, a relatively uncharted territory within current academic literature. While numerous studies have examined the correlation between founder age and startup success, the crucial role of initial hires remains under-explored. Therefore, our project seeks to fill this research void by centering on early employees, their demographics, and their influence on startup success. Previous research (Azoulay et al., 2020) suggests that renowned young founders like Bill Gates and Steve Jobs represent exceptions rather than the norm. In light of this, our research proposes to question if such a view might be incomplete or skewed, considering the lack of comprehensive analysis on the early hires. The trajectory of our research, depending on the discovery of potential skewness in age demographics, would lead us towards an extensive examination of data. We aim to investigate whether younger entrepreneurs or team members possess unique qualities that drive superior outcomes within the startup ecosystem. If our study aligns with this hypothesis, it could imply that young entrepreneurs like Gates and Allen might not be outliers, but potential exemplars. Future directions may include advising venture capitalists to favor younger innovators due to their potential to steer startups towards heightened success. This would represent a profound shift in understanding and investing in the startup ecosystem.

Leadership and the Value of Persistence

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Research and development firms must choose only a small subset of a variety of different projects to pursue, and success is generally unknown until after these firms invest significant time into any given project. The decision of whether to persist with or terminate a project that has been unsuccessful initially is of prime importance to leaders at these firms because persistence strategies can impact firm profitability. Yet, persistence behavior could have second-order downstream effects as well due to impacts on employees. Persisting with projects could signal to project managers that the firm leader senses their project is high-value and hence induce more effort from their subordinates; alternatively, persistence could incentivize project managers to work harder on projects they care little about because they realize that the only method of receiving new and more interesting projects is by finishing their current work. This research uses a two-agent infinite-time period model to examine how a firm leader's persistence impacts their employee's effort level. In the model, compensation for both the leader and project manager is tied directly to project success, and both agents optimize for their profits. The model indicates that persistence can be used as a leadership tool to effect higher levels of effort from project managers when asymmetric information is present about project value, or when projects are expected to return low values to the firm. A mathematical analysis reveals under what conditions stationary equilibria for the leader's persistence strategy and employee's effort strategy exist. Using the model as a basis, we created a computer program to find stationary equilibria for effort-persistence strategies for different model parameters.

Measuring Corporate Purpose Using Machine Learning

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Deep purpose companies embed their purpose into every aspect of their organization. This study evaluates how companies narrate the relationship between their purpose, their strategy, and their identity in annually published 10-K statements. The way that companies portray themselves can lend insight into how their purpose penetrates throughout the whole firm. Using recently published 10-K data, we examined the degree to which company success is relational to company purpose, self-described company identity, and overall strategy. To isolate this concept, we created a codebook and labeling procedure to standardize definitions and subcategories of the three focus areas found in the 10-Ks. From the codebook, we independently coded over 150 10-K documents for these topics and validated our methods through an inter-reliability check of the labeled excerpts. To scale this process, the excerpts were used to train a Natural Language Processor to identify the concepts in thousands of statements and calculate the degree of purpose within a company. Preliminary findings imply that companies who state a purpose statement also include references to their purpose through company implementation of strategy and core values. As a result, the measured degree of purpose centered companies is compared against overall company success.

Building Purposeful Ventures

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Any company can boast a catchy purpose statement in their annual report, but in order to be truly purpose-driven, their purpose must be deeply aligned with every aspect of their operations. The role of corporate purpose has often been questioned, with some arguing that it may be a mere distraction from profit-focused objectives. However, this research project takes a different approach by exploring the possibility that deeply embedded purpose within a company could, in fact, lead to increased profitability. We aim to investigate the relationship between purpose orientation and corporate performance, building upon Ranjay Gulati's book Deep Purpose: The Heart and Soul of High-Performance Companies. Employing natural language processing models to analyze 10-K statements, this study introduces an innovative metric to quantify the purpose orientation of firms. We assess purpose intensity by examining the proximity and alignment of purpose with the organization's strategy, identity, and culture as conveyed in the 10-K statements. Additionally, the research delves into the concept of a "purpose vector," a measure of the focal point of the organization's purpose, whether it centers on employees, customers, stakeholders, or shareholders. This study investigates purpose as a management ethos and has the potential to influence the way companies view and embrace purpose as a vital element in their pursuit of both social and financial goals. soy

Managing Miscarriage at Work

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Miscarriage is a common experience among working women that detrimentally affects a significant portion of the workforce. However, limited research has been conducted to better understand the emotional and social implications of this topic, primarily due to the societal taboos surrounding it. In the face of a stigmatizing social environment and insufficient organizational support, women often experience *disenfranchised grief* after miscarriage—referring to the emotional anguish following the loss of an unborn child, which society fails to perceive. Our aim is to understand the intricate interplay between personal and professional aspects concerning miscarriage by examining how women navigate their miscarriage experiences at work, encompassing disclosure or concealment strategies and the impact of co-workers' trustworthiness. Through semi-structured interviews with 33 full-time working women who experienced a miscarriage, we propose a theory which identifies two coping pathways, influenced by organizational and cultural norms, as well as key work relationships. Pathway 1, Independent Coping, involves women managing their grief independently, seeking solace within work by engaging in self-directed actions and preserving professionalism. Pathway 2, Relational Coping, focuses on seeking emotional recognition and support from others through communication with supervisors and colleagues. There appears to be a trade-off between the two coping pathways where the level of support from the work environment significantly impacts the coping process and outcome in terms of the emotional toll of their miscarriage experience. This framework contributes to addressing knowledge gaps on disenfranchised grief experiences and provides insights for supporting women who have experienced pregnancy loss in the workplace. While our current study has limitations in offering evidence-based strategies, future research may focus on implementing interventions and analyzing cross-cultural contexts to enhance our understanding of post-miscarriage grief, and develop practical organizational strategies addressing working women's miscarriage challenges.

Can Framing Interventions Improve the Psychological Experience of Low Wage Work?

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Each day, employees complete seemingly unimportant tasks that lack an overarching purpose. Past research has established that social purpose interventions can be useful in practical careers with clear external benefits like social work. However, little is known about whether these interventions can be effective in jobs or tasks that do not have direct benefits for society, such as doing mundane or routine tasks (i.e., data entry). Furthermore, low-wage workers are underrepresented in management research. Thus, we propose the following question: How can we improve the work experiences of those in low-wage jobs who perform mundane routinized tasks? To address this question, we are exploring three routes to improving the employee experience: establishing a social purpose, connecting with others, and making the task easier. We will post two job descriptions using the platform Upwork, recruiting freelancers to complete text coding or data entry tasks for a research project. Participants will be assigned to one of four experimental conditions: control, active control, purpose, or superordinate framing (i.e., thinking about how their tasks build on other tasks to achieve a broader purpose). In the active control condition, we will not provide reframing strategies, but AI assistance, such as ChatGPT will be allowed. This condition provides a strong test of whether psychologically informed interventions improve well-being. After each workday, participants will complete an end-of-day survey assessing task enjoyment, meaning and motivation, cognitive engagement, and the positive impact they believe their work has on others. We predict that the superordinate framing condition will be more effective than the other conditions as it will harness employees' social connection motives and help workers feel as if they are a part of a bigger team that is accomplishing their otherwise mundane work. The current study seeks to improve workplace conditions for low-wage workers through reframing seemingly "unimportant" tasks in a positive light.

Scaling New Ventures: A Path Dependent View

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The success of startups is largely dependent on their ability to scale their operations and expand their market presence. However, there are conflicting views on the path by which companies achieve scalability. The "lean startup" methodology advocates for prioritizing sales and customer growth while product development undergoes an iterative, experimental process that accelerates as the company gains more traction over time. Facebook's transformation from an exclusive website for Harvard students to the world's largest social networking platform serves as a notable example of the efficacy of this approach. Conversely, the "nail it, then scale it" approach argues for significant investment in product development, ensuring a high-quality offering before scaling and growing the consumer base. Dyson's emphasis on meticulously developing exceptional vacuum cleaners with immense time and capital investments exemplifies the potential success of this strategy. Clearly, there is merit in both methods of achieving scale, but there are also risks and tradeoffs associated with each approach. Our research endeavors to explicate the optimal scaling strategies for entrepreneurs by studying 1,787 B2B SaaS (business-to-business software-as-a-service) companies. We analyze their scaling patterns using complete employee data, a panel of customers growth over time, and firm outcomes in various scenarios to calculate the odds of success of each approach in different circumstances, through which we aim to provide data-driven insights that guide entrepreneurs in their scaling decisions. Furthermore, we explore how a series of external factors, such as market concentration, network effects, and entrepreneur risk preferences influence the selection of scaling strategies. We hypothesize that new market opportunities that rely on network effects are more suited for the "lean startup" approach, while the "nail it, then scale it" strategy prompts higher chances of success for startups entering an existing market with high production costs.

Analysis of Market Entry Across Geography and Market Segment in the Wireless Product Industry

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The wireless product industry is comprised of a wide range of technologies, ranging from Wi-Fi and Bluetooth products, to other products on the unlicensed radio frequency spectrum. This project examines the entry and exit patterns of firms in the wireless product industry, and documents the distribution of firms across U.S. geographic regions and market segments. Prior to entering the U.S. market, firms apply for product approval from the Federal Communications Commission (FCC). We utilize this application data from the FCC, subsetting on U.S. based firms from 1997 to 2021, to analyze three key patterns: how firms are distributed across U.S. geographic regions, how firms are distributed within different sectors of the manufacturing industry, and how the composition of firms in the market changes over time. First, we find that despite Silicon Valley being the technological hub of the U.S. since the 1970s, wireless product firms are dispersed throughout the country, including major presence in New York City, Los Angeles, and Chicago. Then, we find that within the manufacturing industry, a few sectors dominate the wireless product market, including radio and television broadcasting, and computer equipment. Finally, while the geographic and industry distribution patterns persist over time, the individual firms that are present in the market do not. We observe high rates of turnover among smaller firms, and only large industry players such as Samsung, LG, and Garmin remain consistent over time. These conclusions imply that the wireless product market heavily benefits populated cities and is primarily composed of large technology firms, and helps characterize these previously unknown aspects of the ever-growing wireless industry.

Disclosure in Romantic Relationships

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Romantic relationships give people the greatest happiness and deepest sorrow, yet people are constantly trying to be involved in and maintain romantic relationships. It is difficult for people to decide whether, how, and when to disclose in relationships: Should we confess our feelings? How and when to break the silence? Our current project uses literature review to answer such questions. Prior research shows that people who confess their feelings, even when their love is unreciprocated, have more positive affect compared to people who are being confessed to or rejecting others. People who confess have more positive feelings, including a deep sense of relief; while people who reject others feel guilty about hurting someone. Other literature focuses on stonewalling, the phenomenon of being emotionally withdrawn and refusing to communicate in a relationship, and strategies to break the silence. We found interesting gender differences in the phenomenon: while men are more likely to "stonewall" their partner, women report more negative experiences in relationship silences, which further predicts less relationship satisfaction and higher rates of divorce in the future. Further literature review and experimental studies will be conducted in order to examine the role of confession and silence in romantic relationships, which will give the general population advice on when and how to better communicate.

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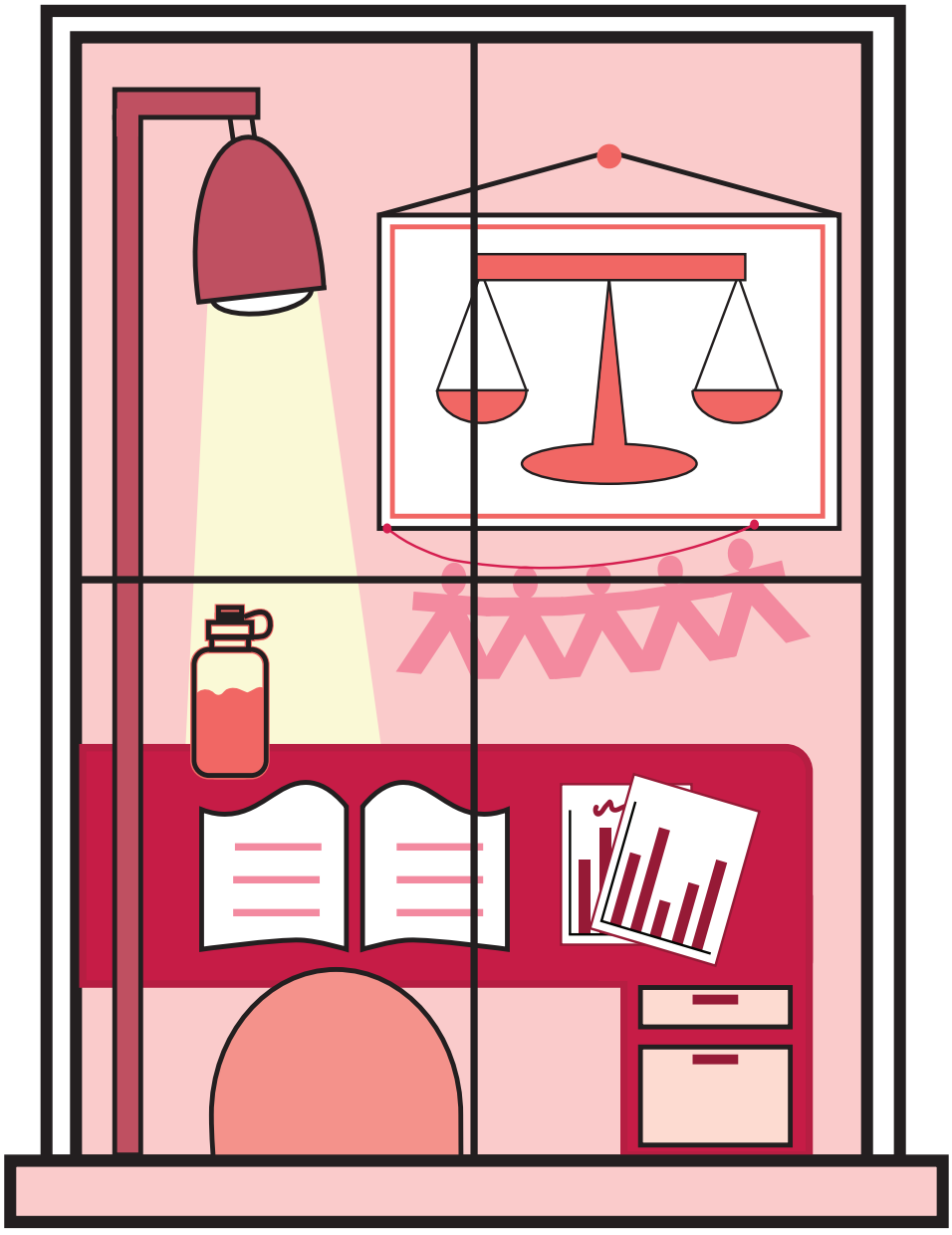

Children's Understanding of Possibility Concepts

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Mentor: Irene Canudas Grabolosa

The cognitive development of possibility concepts, such as "might" or "could," is a significant focus in developmental psychology, crucial for educational methods, scientific research, and epistemological theory. Our current research explores how 3-year-olds reason about multiple possibilities. A previous study presented children with two sets of opaque cups, one set containing one cup and the other multiple cups (2 or 6). One coin was hidden in one cup from each set, concealed from the child's view. Opting for the singleton maximizes expected rewards, as it is certain to contain a coin, whereas it is merely possible that 1 of the 6 cups or 1 of the 2 cups contain a coin. In this experiment, both 3-year-olds and 2.5-year-olds chose the singleton at a rate higher than random chance (33%). However, 3-year-olds selected the singleton at nearly 60%, which is an interesting increase from the rate observed in 2.5-year-olds, who, like chimpanzees, select the singleton around 50% of the time. Notably, chimpanzees' preference for the singleton increases as the number of cups in the other set increases, and the subsequent possibility of a coin being in one of the cups in the set decreases ($1/2$ vs $1/3$ vs $1/4$ etc.). The same trend is not observed with 2.5-year-olds. Yet, chimpanzees were tested with a different method (showing the coin going into the cup, followed by occlusion and shuffling), hence the two results could not have been compared. Our ongoing study integrates investigation of all aforementioned factors, comparing 1 vs. 2 cups and 1 vs. 6 cups scenarios, as well as occluded hiding (previously used with children) and shuffling (previously used with chimpanzees). This multifactorial study enables novel comparison of possibility concepts among young children and non-human primates, while informing our model for the development of these cognitive abilities.

Willingness to Exert Effort in Exchange of Information Resolving Risk and Ambiguity

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Mentor: Haoxue Fan

Humans have the tendency to seek information including in situations where the information does not have instrumental value. This intrinsic valuation of information resolves uncertainty, which most humans find aversive. These circumstances of uncertainty can be put into two categories: risk (known probabilities) and ambiguity (unknown probabilities). We aim to analyze how people value information that resolves risky vs. ambiguous situations. Specifically, we aim to probe the valuation process by quantifying the amount of effort they're willing to exert in exchange of information. Participants in the study—from the Harvard SONA study pool—encounter a variation of "lotteries," with possible outcomes of $0 and $10, simulated using bags containing different ratios of red to blue chips (100 in total). There are either 'risky' lotteries with exact probabilities shown, or 'ambiguous' lotteries with a gray bar hiding the full probabilities. To elicit people's true preference, we implemented a Becker–DeGroot–Marschak auction mechanism: after seeing the lottery, participants indicate ('bid') how much effort they are willing to exert in exchange of the outcome information by squeezing a hand dynamometer. The computer then randomly generates an effort level, which participants must hold ('pay') for 3 seconds in order to see the outcome of each given lottery. We are at the beginning stages of data collection, but expect to see a variety of responses from participants—no bidding, consistent bidding, or variation depending on the lottery type. Despite the likelihood of a multitude of response types, we hypothesize that participants will generally expend more effort in lotteries with high uncertainty, which can be quantified in a variety of ways including higher willingness to exert effort. Once completed, these results will contribute to the existing literature on information-seeking and effort, as well as humans' behavior difference under different types of uncertainty.

The Effect of Perceived Control on What Comes to Mind

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Mentor: Fred Callaway

This study investigates the impact of perceived control on possible outcomes that come to mind during decision-making. Building on computational models, we hypothesize that when individuals perceive control over outcomes, they tend to think mostly of good outcomes. Conversely, when individuals lack perceived control, they tend to think of extremely-valued (i.e., very good and very bad) outcomes. To test this hypothesis, we devised an interactive word game that assigned scores to words based on their letter combinations. Participants were recruited on Prolific and were randomly assigned to either the high or low control condition. In each of the three game rounds, low control participants could choose between randomly generating a word or earning fixed points, while high control participants could create their own words or earn fixed points. Participants also reported the words that came to their mind during decision-making. Consistent with the model predictions, preliminary results suggest that low control participants are more likely to think of words with letters of very high and very low scores, whereas high control participants predominantly think of high-scoring letters. These findings may shed light on the relation between perceived control and cognitive sampling and offer insights into the cognitive mechanisms underlying anxiety and depression.

Evaluating and Improving the Effectiveness of Youth Mental Health Care

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PI/Advisor: John Weisz
Mentor: Josh Steinberg, Katherine Venturo-Conerly

Roughly 25% of youths will be diagnosed with at least one psychiatric disorder (e.g., an anxiety, depressive, or conduct-related disorder) before adulthood, thus leading to a large global burden of disease. Over recent decades, there have been crucial developments in the treatment of mental health problems among children and adolescents, but treatment outcomes for many of these individuals remain poor. Therefore, we aim to explore different methods for improving the effectiveness of youth psychotherapies. Our work includes updating a database of randomized controlled trials (RCTs) of youth mental health interventions to be used in meta-analyses that examine which treatments work best for which mental health challenges. This database of youth psychotherapy RCTs that focus on treating anxiety problems, depressive problems, conduct/misbehavior problems, and ADHD problems includes studies published between January 1960 and 2020. We will also gather and analyze data from 6 RCTs of a well-known transdiagnostic youth psychotherapy, the Modular Approach to Treatment for Children with Anxiety, Depression, Trauma, or Conduct Problems (MATCH-ADTC), to determine the effectiveness of specific treatment elements. Moreover, this work will test how both demographic and clinical characteristics of youths and their families interact with the effects of each treatment element. For both projects, the primary outcome measures will be reductions in the symptoms of these mental health problems. The results of this work could serve to guide future psychotherapy research and clinical practice, as clinicians can adopt more personalized and empirically supported treatment approaches for their young clients.

Symbolic Math Games to Improve Children's Mathematical Skills?

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Mentor: Akshita Srinivasan, Cristina Sarmiento

Early childhood mathematics skills correlate with academic achievement throughout elementary school. However, children from low socioeconomic backgrounds are often at a higher risk of not reaching their academic potential. Previous interventions centered on nonsymbolic math games for children from low-income families resulted in improved intuitive math abilities yet failed to improve their formal math abilities. Therefore, while beneficial, improved intuitive math skills alone did not translate to improved learning outcomes in school. This study explored the effects of introducing symbolic math games as an alternative intervention. The study occurred on a medium scale in a home-based setting. To assess the impact, 64 participants underwent remotely administered and equally difficult pre and post-tests with formal math and reading questions. Participants and their parents played the at-home games directly after the pretest and immediately before the post-test about 14 days later. The treatment group received symbolic math games, whereas the active control group received reading games. We hypothesized that the children who play the symbolic math games will show greater improvement in formal math skills, whereas those who play the reading games will show greater improvement in reading skills. Confirming our hypothesis, which we have done halfway by verifying the treatment group's higher growth in math scores, could have broader implications for educational efforts and large-scale randomized controlled trials in developmental economics. Schools may implement symbolic math games into their curriculum for extended periods, increasing the difficulty of the games as the children's skills develop. These game-like interventions might enhance formal math learning and make the process more engaging compared to current curriculums. Children in the developing world may significantly benefit from incorporating symbolic math games into schooling. Better math skills would encourage children from low socioeconomic backgrounds to participate longer in school, fostering upward mobility and increasing their future worker productivity.

The Institutional Determinants and Challenges of Infrastructure Investment in Latin America

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Political scientists believe that democracies with weak states, meaning countries that lack a strong set of administrative, legal, and coercive institutions, struggle to build large infrastructure projects. Yet, according to the International Monetary Fund, the percentage of GDP invested in infrastructure projects has increased in developing economies during the last 20 years. What has pushed governments in the "emerging" economies to shift their political programs to the infrastructure sector? Why do politicians promise to build infrastructure when many of these large projects will not be finished during their time in office? We compiled a database with infrastructure projects in Colombia, Ecuador, and Peru to observe how the political logic behind infrastructure investment changes with the strength of institutions. We also looked at judicial cases to understand the corruption and campaign finance benefits that might lead politicians to invest in such projects. This project argues that the political rewards from infrastructure projects do not come from project inaugurations, where politicians aim to finish projects, but instead, they come from assigning the associated contracts. Due to public-private partnerships (PPPs), governments can contract work to the private sector, which can bring more resources, experience, and transparency. However, politicians can manipulate contracts to hide project costs and pass them on to future administrations, avoiding negatively affecting their political campaigns and capturing short-run rents. We look at how PPPs have changed the way political campaigns are financed and help explain why politicians build large infrastructure projects in weak institutional environments. Looking at the data, we expected to find an increase in the assignment of contracts before electoral periods to ensure campaign donations. It will help us see private infrastructure companies as actors in the political arena, dependent on institutional determinants while moving with the desires of political parties to gain contracts and have fewer regulations.

Racial Disparity in Covid Prison Admission Freezes

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PI/Advisor: Elizabeth Hinton, Brandon Terry
Mentor: Brennan Klein

Mass incarceration in the United States is characterized by decades of increasingly long sentences and pervasive racial disparities. In recent years, however, the percent of incarcerated people who are Black has been steadily decreasing. This trend reversed during the COVID-19 pandemic, despite a rapid decrease in the overall number of incarcerated people. Previous studies suggest that these disparities were a reflection of pre-pandemic sentencing disparities based on race. Our research builds on these findings, using individual-level data from state prisons in Texas, Illinois, and the Federal Bureau of Prisons (FBOP) to better understand the mechanism linking sentencing disparities and the Covid-era demographic makeup of the incarcerated population. We find that racial differences in sentence length distributions have predictable effects on changes to prison population demographics. On average, we find that Black people are given longer sentences than white people for the same crimes. As a result, Black people have a lower churn rate (people admitted divided by people incarcerated) than white people. As long as admissions continue, demographics can stay stable (though disparate) because the number of people being admitted to and released from prison stays relatively constant. However, when prison admission halted, as they did in most states during the first months of the pandemic, the percent of the prison population made up by Black people spiked. Ultimately, these results shed new light on the state of U.S. mass incarceration. Specifically they provide evidence that disparities in admissions and departures rates may make seemingly neutral policies, like an admission moratorium, cause racially disparate impacts.

Walnuts and Watermelons: Improving Population Parity in Algorithm-Assisted Redistricting Simulations

Lucy Ding
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PI/Advisor: Kosuke Imai

Simulations for legislative redistricting have become widely used to approximate distributions of all possible district maps drawn under a set of redistricting rules. These simulations have been used to support legislative bodies in drawing their maps, as well as courts to determine the legality of the maps drawn. However, for computational and practical reasons, simulation algorithms are typically applied using precinct-level data while most enacted plans are based on the census block data. This means that the plans drawn by the simulation algorithms usually have a population parity of several hundred people. While this disparity suffices for the evaluation of redistricting plans, simulated plans themselves may not satisfy the legal requirement of ”one person one vote.” We introduce a computational algorithm to significantly improve the population parity of simulated plans. The proposed algorithm first uses integer linear programming to find optimal transfers of populations between districts. It then repeatedly applies the subset sum algorithm, which finds subsets of precincts that sum up to the optimal transfer values, to reduce the population difference between a pair of districts first at the precinct level and then at the census-block level. In our empirical applications, we find that the proposed algorithm often brings the population parity, or difference in population between the districts, down to, on average, less than ten people. This algorithm will make drawing block-level redistricting plans easier, supporting legislative bodies, courts, and researchers alike.

The Gender and Race of Armed Self-Defense

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Women, Gender, and Sexuality Studies, 2024
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PI/Advisor: Caroline Light

Contemporary rhetoric in the United States holds that the criminal justice system is beyond the race and gender issues of our society; some even hold that we have overcome these issues entirely. However, race and gender issues have not disappeared from our society nor our criminal justice system. Our research seeks to illuminate one of the covert ways in which gender and race impact the public perception, litigation, and outcomes of cases of armed self-defense in the U.S. In self-defense cases, there are typically two factors at issue: imminence and necessity. We focused on how the definition of imminence, while presumed to mean immediacy, in practice can be twisted to disadvantage marginalized communities. For example, a female domestic violence survivor's self-defense claim may be denied because she had the hypothetical ability to avoid the danger regardless of how immediate the danger was; it wasn't "imminently necessary" for her to use force. This has concerning implications for women defending themselves from domestic or intimate partner violence as they're expected to retreat even from their own homes before protecting themselves. To conduct our research, we studied legal reviews, case documents, and public facing articles focusing on cases in which imminence was a relevant issue. Our preliminary results confirm that the gender of the perpetrator or victim in cases of armed self-defense alters how imminence is applied, typically increasing the standards women must meet to prove their self-defense claims in comparison to men. In the future, we hope to present evidence as to how race and other identity markers, such as one's sexual orientation (real or perceived), also impact the argumentation, outcome, and public perception of self-defense cases. Our ultimate goal is to propose directives that can be implemented by courts in self-defense cases to prevent these disparities.

Data Management for the History of Punishment

Pierre Lamont-Dobbin
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Harvard College, Adams House
PI/Advisor: Adaner Usmani

The goal of this summer's work is to assist in building a dataset for the History of Punishment project. The objective of this larger endeavor is to provide a comparative historical analysis of crime and punishment across nations. The project encompasses data sources dating as far back as the year 1200. As such, data sources are wide ranging in their procurement, format, and language. The primary objective of this sub-project is to collect diverse data sources into a general spreadsheet format. This process involves scanning physical sources, running them through optical characterization software (OCR), and reading the result into tables using Python and R. The latter objective proved difficult due to the limitations of the scan quality of the documents and of the software packages available to render information into tables. Further work requires manual entry or analysis of the faults that optical character recognition (OCR) makes in reading the documents, likely using machine learning and customizing software accordingly.

What We Can Learn From 8th Graders About How to Teach Civics?

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PI/Advisor: Katie Giles
Mentor: Natalie Sew

In 2018, Massachusetts passed legislation requiring 8th graders to take a year-long civics class including a student-led project designed to involve youth in civic action. The Democratic Knowledge Project (DKP) at the Edmond & Lily Safra Center for Ethics developed a civics curriculum and has been piloting and revising it every year since the legislation was implemented. In an effort to continue improving the curriculum and prioritize youth voices, this summer we facilitated a Youth Advisory Board (YAB) composed of 8th graders from across Massachusetts who finished the civics class in June, with the goal of collecting student feedback and co-designing resources for teachers and families in future iterations of the curriculum. Each session of the YAB targeted a different theme, with questions and activities designed to solicit youth perspectives about the influence of civics class on their lives and their perceptions of themselves as civic actors. These questions are critical, as the country faces increasing polarization and only 30% of people younger than 40 consider it essential to live in a democracy. Early results indicate that students find it important to talk about their own identities and values in civics class, wish adults took their political opinions more seriously, and plan on voting when they're old enough. In response to these findings, the DKP is developing guidance for teachers about how to make students feel more comfortable discussing their identities in class and for adults about how to have reciprocal conversations with youth about government and politics at home, as well as other resources for teachers and families.

Moral Tethers: Strategic Uses of Gender in Social Movements

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Sociology, 2025
Harvard College, Mather House
PI/Advisor: Jocelyn Viterna
Mentor: Catharina O'Donnell

This study analyzed thousands of emails sent by social movements, such as Black Lives Matter, Make America Great Again, and Planned Parenthood. The focus is to identify and analyze the use of moral tethers by these social movements. Specifically, this project aims to understand how movements, even those that are considered progressive, draw upon traditional moral concepts, such as ideas of 'protecting' femininity or family, to further their goals. This project utilizes a combination of quantitative and qualitative approaches through the use of softwares such as R Studio and NVivo. Initial analysis of emails considers organization outreach differences, such as the number of emails sent, the average number of words in each email, and the date of the first sent email. Exploratory textual analysis through Tidyverse and TF-IDF yielded lists of the top words used by each organization within their emails. Within these lists, words alluding to moral tethers were flagged, such as those relating to family, women, and children. These findings and the way in which top words differ between organizations has major implications for how different movements can grow and gain support. Findings can also shed more insight into how certain traditional moral concepts are reinforced. Future steps will involve qualitative analysis through NVivo to better understand the context of these most commonly used words and how they are actually being used.

Can Adults and Children Use Context to Adapt Their Lexical Predictive Processes?

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Mentor: Margaret Kandel

During language comprehension, listeners continuously make predictions about what concepts, structures, or words will come next. When listeners predict a specific word, they may preemptively activate its features: meaning, morphemes, or even sounds. Such pre-activation facilitates processing of the predicted word if it later appears in the input. Prior research suggests that adults generate more predictions when context makes it a logical strategy to do so. The current study investigates whether children between five and six also possess this flexibility. In this study, participants hear pairs of words. Within each pair, the words can be related (e.g., umbrella–rain) or unrelated (e.g., omelet–rain). The proportion of trials with related pairs was manipulated (high-proportion condition: 80%, low-proportion condition: 20%). Participants' brain waves are recorded using electroencephalography (EEG). Participants' N400 response to the second word in each pair (i.e., the target) will be analyzed. The amplitude of the N400 reflects how easy a word is to process. Therefore, N400 amplitude will be smaller when participants predict the target word and processing is facilitated. The context (frequency of related pairs) warrants prediction of the target word more in the high-proportion condition than the low-proportion condition. The analyses will investigate whether the difference in N400 amplitude for target words in related pairs vs. unrelated pairs is larger in the high-proportion condition, suggesting that participants modulated their generation of predictions based on relatedness proportion. Furthermore, if this pattern is found in both adults and children, it will indicate that children can also adapt their linguistic predictive processes to context. This study will enhance understanding of whether flexibility in predictive processing develops with language experience or is an innate ability of the language comprehension system (present early in development). Future studies might examine whether linguistic prediction differs across age groups or in bilinguals.

Marijuana and Arlington Heights: Challenge Racism in the Law Through History, Legal Theory, and Data Science

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History & Statistics, 2026
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Mentor: Brennan Klein, Elizabeth Ross

In 1970, after the Supreme Court declared the 1937 Marihuana Tax Act unconstitutional, Congress passed the Controlled Substances Act (CSA). This sweeping law placed federally regulated drugs into five schedules. Moving contrary to recommendations from the National Commission on Marihuana and Drug Abuse, Congress put marijuana in Schedule I alongside heroin and methaqualone. Black people have been incarcerated for marijuana-related charges at significantly higher rates than White people since the CSA's passage. Yet, it remains in effect today. This research project investigates the drafting and passage of the CSA, and its impact on racial groups, following the empirical and interpretive questions set by the Supreme Court's precedent in Village of Arlington Heights v. Metropolitan Housing Development Corp., which declares that a violation of the Equal Protection Clause may be shown by demonstrating both disparate impact on racial groups and discriminatory intent of lawmakers. Hence, our scholarship explores the extent of the disparate impact of the CSA's marijuana provisions on Black people and the discriminatory intent of policymakers, including the Nixon administration. Proving the CSA's disparate impact has, thus far, been challenging for scholars due to incomplete datasets throughout the 1970s. However, by utilizing federal sentencing records, Uniform Crime Reports, and focusing on the more complete data from the 1980s, we have demonstrated significant racial disparities in marijuana arrest and sentencing rates through numerous graphs and heatmaps. These visualizations illustrate the racially disparate impact of marijuana criminalization in aggregate and geospatially. Additionally, we utilized historical and archival research in government records to reveal key legislators' racist intent. This research program not only aids legal challenges on behalf of those impacted by this law, but also furthers a more wide-ranging theory of change that relies on combining history, legal theory, and data science to challenge racially discriminatory laws and their unjust outcomes.

Understanding McCarthyism Through Language Modeling

Julia Shephard
Applied Math & Economics, 2026
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PI/Advisor: Melissa Dell
Mentor: Emily Silcock

Historical analyses of newspaper coverage and media sentiment can be colored by historical memory and the limitations of examining source material manually. The Dell lab has developed a pipeline to automate such analyses by performing optical character recognition (OCR) on several million American newspaper articles from 1920-1977. This database facilitates the development of neural methods for large-scale analysis of historical newspaper data. Fine-tuning RoBERTa, a language model, we develop topic classifiers on the red scare, civil rights movement, labor unions, and antitrust laws, allowing us to quantitatively assess the extent of coverage of these topics. Moreover, we select the Red Scare as a case study for combining tools developed by the lab to replicate or disprove the findings of historians and political scientists. Previous literature suggests that Joseph McCarthy manipulated press timelines to circulate unsupported claims of government infiltration by Communists in the 1950s. We further this work, finding that articles referencing McCarthy are reprinted at a substantially higher rate than their counterparts. Extracting articles that reference the same newspaper story using neural methods, we also work on developing classifiers that identify degrees of sensationalization and slant in Red Scare headlines and articles. We plan to use these tools to more comprehensively understand how American media reacted to McCarthyism and produce others, such as fact-checking classifiers, for wider newspaper use.

Moral Tethers

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Mentor: Catharina O'Donnell

Why do essentialized and hierarchical notions of race, gender, and other forms of identity persist despite the success of progressive social movements? This study analyzed one potential explanation: that social movements increase their appeal by reaffirming long-held cultural structures and morals in their rhetoric. To identify and examine this "tethering" to fundamental values, we utilized a database of over 13,000 email newsletters from both progressive and conservative social movements. Our work relied on RStudio, most notably the Tidyverse and Dplyr packages, to conduct a quantitative analysis of the top words in the database. This analysis offered insight into the most common topics organizations addressed in their emails, as well as the rhetoric different organizations utilized to appeal to followers. In the first stage of analysis, we utilized Tidyverse to calculate a list of the most common words used in an organizations' newsletters. From there, Term Frequency – Inverse Document Frequency analysis (TF-IDF) was used to calculate the frequency that a word is used in an organization's emails relative to how commonly used it was across all organizations' emails. TF-IDF helped uncover words that were specific to an organization's rhetoric, such as appeals to religious or family values. While style across organizations' emails was often distinctive, comparing lists of top words and TF-IDF words uncovered rhetorical commonalities across emails from organizations of all social movements and ideologies. Our next step is to identify which organizations engage in "tethering" by examining the moral and gendered language in our lists. Randomly sampled emails from these organizations will then be analyzed qualitatively to examine instances of "tethering" to traditional structures and values, and the implications of "tethering" on reingraining identity-based hierarchies.

The Politics of Genomic Science: 3 Cases, 3 Countries, at Least 3 Controversies

Samantha Williams
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PI/Advisor: Jennifer Hochschild

Recent advancements in genomics are expected to revolutionize the fields of medicine, reproduction, and criminal justice, yet it is still unsettled how these new technologies will be understood, regulated, and legislated across the world. The U.S., the U.K., and Germany, three countries at the forefront of innovation, are in the midst of establishing a preliminary policy framework to simultaneously encourage and regulate genomic progress, while accounting for salient ideas in public discourse. Regarding tendencies in biopolitics, Americans center the debate on the sanctity of life concerns, Britons focus on class inequalities, and Germans unify against the shadow of neo-eugenics. This project and its exploratory findings at large aim to shape a comprehensive survey project that will underlie the project's theoretically novel three-part framework: interrogating what each country's public knows, what they believe, and what particular experiences, ideologies, and identities motivate their beliefs. In a literature review, I cataloged over 200 articles from across mainstream journalism, including the Atlantic, Scientific American, and The Economist, to identify what key information about genomics was disseminated by the media internationally over the past five years. Using this information, I identified 50 trusted authorities with influence in the broad socio-political discourse to be interviewed at a future date. Exploring major themes of genomics and personal autonomy, I evaluated the findings and methodology of over 100 public opinion polls conducted across the U.S. and the E.U. over the past 70 years to trace evolving global opinion trends. Early research suggests that while the media and the public are excited at the prospect of biotechnological progress, many are wary of potentially immoral applications. By laying the foundation in this field of study, this project will preempt the maturation of controversial technologies and prepare the public and policymakers to navigate the new, nuanced landscape.

Legal Anthropology Matters

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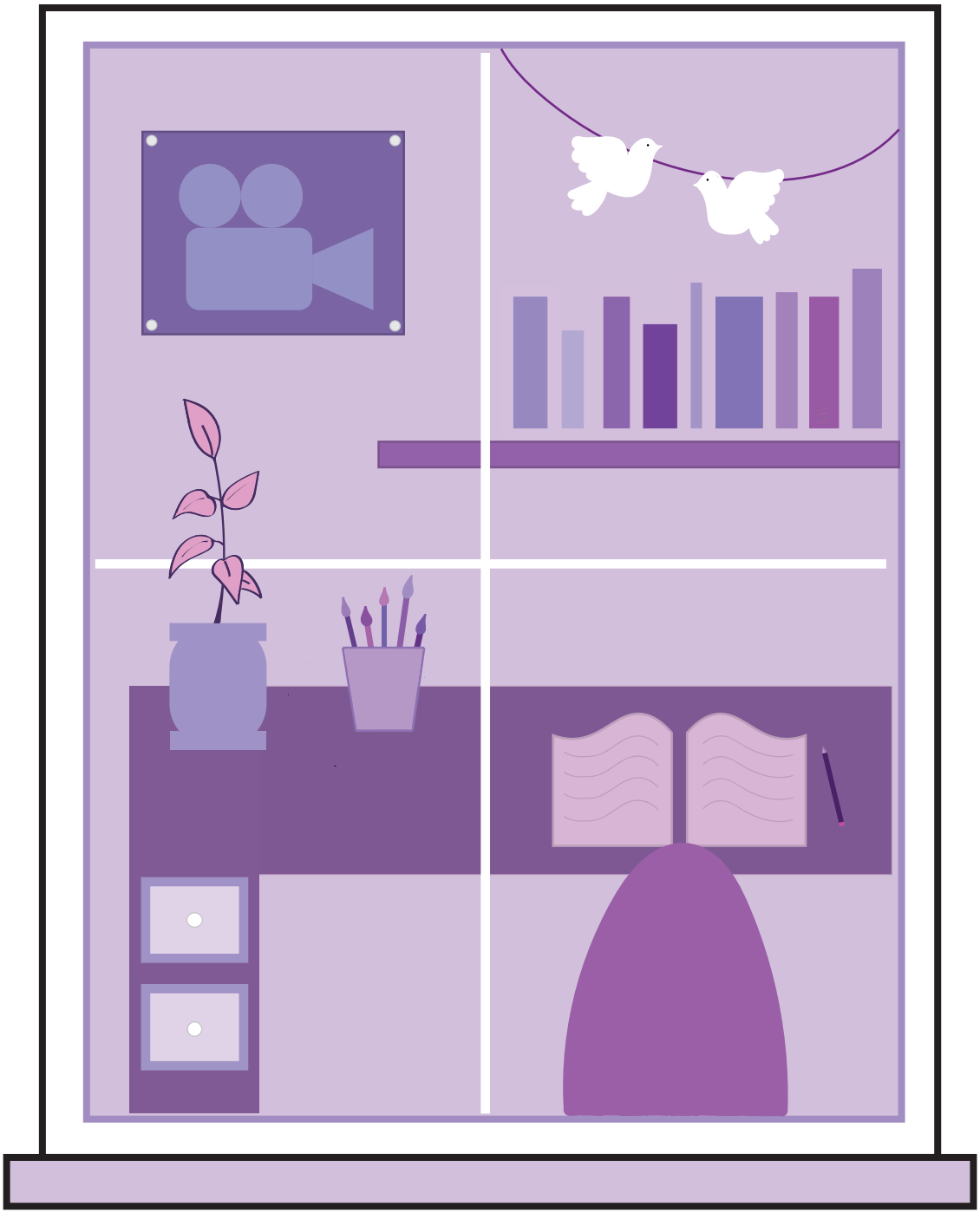
Government, 2025
Harvard College, Eliot House
PI/Advisor: Malavika Reddy

The prevailing canon in legal anthropology often reflects a narrow and depoliticized perspective, diminishing the importance of social and political trends at large in informing the field. It is thus necessary to critically reassess the teaching materials and reorient the pedagogical approach toward more inclusive and diversified syllabi. Through an extensive literature review of various key themes within legal anthropology, this project seeks to create a new standard for the subdiscipline through placing greater emphasis on pedagogy rather than theory. Leveraging a variety of sources including academic texts, blog posts, and poems, we scrutinize the dominant narratives that form the backbone of legal anthropology education in universities, and inform potential new approaches with perspectives from professors and students. Our research reveals biases, gaps, and outdated and irrelevant themes within traditional undergraduate legal anthropology syllabi. Building on these findings, we propose an innovative curriculum model that encapsulates a wider array of existing literature and more relevant focuses within the field today, thereby presenting students with a more comprehensive outlook on legal anthropology.

SHARP



Digitally Mapping the Movement and Concealment of Ancient Wealth

Sage Barnes
Government & Classics, 2024
Harvard College, Leverett House
PI/Advisor: Michael McCormick, Reed Morgan

Rich information about the ancient past is found in what people have left behind, whether that be their remains, homes, graves, or even their wealth. Through the Initiative for the Science of the Human Past (SoHP), this project is creating an interactive digital map of ancient Roman coin hoards throughout the early Byzantine Period in the Balkans and Asia Minor. Visualizing these coin hoards can give insight into ancient migration patterns as well as potential patterns relating to important historical events, including the Slavic invasion of Greece and the Justinian pandemics. To build this interactive tool, we have created a geodatabase mapping the 368 coin hoards found in *Les trésors monétaires byzantins des Balkans et d'Asie Mineure (491-713)* by Cécile Morrisson, Vladislav Popović , and Vujadin Ivanišević. The end result, a publicly available interactive map, will have multiple applications within many fields whether scientific, historical, or archaeological. Ultimately, it may reveal previously undiscovered knowledge about this time period and the people who lived in it.

Fisheye Femmes in Search of New Constellations

Mila Barry
English, 2025
Harvard College, Lowell House
PI/Advisor: Eleanor Craig

As the effects of climate change become increasingly tangible—and the need for action becomes increasingly urgent—climate literature grows robust. There's a vital collective desire to express what's at stake. My project—a short poetry zine—offers a contribution to the conversation focused specifically on the emotional experience of ecological grief: what it feels like to hold space for despair as well as authentic hope and awe in a time of environmental crisis. It's also deeply concerned with my body's relationship to the natural world, and how organic metaphors can be used to term gender, specifically womanhood, in expansive ways. Fundamentally, this zine is a personal journey; a reflection of the daily ups and downs of continually turning away from fear to find love and compassion for a self and a world in pivotal flux. What does imaginative adaptation amidst uncertainty look like? These poems aim to help readers draw a connection between the practice of empathetic self building, relation building, and future building while holding space for the painful and contradictory feelings that come along with doing that in a society that is deeply flawed. They draw from the thematic and stylistic techniques of many immensely talented and generous contemporary writers, most notably Victoria Chang and Mei-Mei Berssenbrugge. The longer list of inspirations includes Franny Choi, Pauline Alexis Gumbs, adrienne maree brown, Alan Pelaez Lopez, Mary Oliver, Joy Harjo, Donika Kelley, and Kinsale Drake. The end goal is to inspire people away from apathy and abject cynicism by opening up an invitation to see both individual and collective futures on non-static, creative, and spacious terms.

Mapping Asian American Poetry

Niyathi Chagantipati
English & Government, 2026
Harvard College, Lowell House
PI/Advisor: Christopher Spaide

Since its first publication over a century ago, Asian American poetry has significantly increased in its prolificness; however, there have still been few attempts at anthologizing this vast body of literature, necessitating the existence of this project. This project consists of three parts. The first is to compile a dynamic document that tracks those who identify as Asian American or disseminate Asian American poetry: not only work by East, Southeast, and South Asian Americans but also Pacific Islanders, West Asian Americans, Arab Americans, and a wider Asian diaspora. The second is to visualize this data using ArcGIS to discover any recurring patterns. The final part is to use this newly mapped data to address research questions: for example, which American coasts produce the most Asian American poetry? How does an urban, suburban, or rural landscape affect poetic themes? When have there been upticks in the publishing of Asian American poetry? Using Juliana Chang's Quiet Fire as a case study, we mapped where each poet she includes traces their family origins and where they lived in America (urban, suburban, or rural) with the aim to uncover deeper relationships between geography and a poet's contribution to the Asian American poetic tradition. The creation of this database will serve as an expansion on previous attempts at anthologizing, aiding further scholarship and serving as a resource for future work on the nuanced work of a diverse range of Asian American poets.

Urban Futures in History

Emma Fang
Comparative Literature, 2025
Harvard College, Leverett House
PI/Advisor: Bruno Carvalho

Conversations in urban planning naturally shift with different historical contexts. Analyzing the archives of *The American City* publications between the years of 1909-1920, early twentieth-century American urban planning seemed to emphasize creating comprehensive development plans that prioritized adaptability to future growth and needs. This sentiment arose from simultaneous acknowledgement of the unpredictability of the future and optimism for its potential. Further, many looked to Europe in discussions of the direction that development should take. Letchworth Garden City in England, German alterations on English precedents, and the emergent "garden suburb" or "garden village" models were particularly inspiring amidst increased concern for beauty, sanitation, and general want of more natural environments and lifestyles. In addition, these conditions were rarely spoken about as ends in themselves but were often intertwined with grandiose notions of bettering the "human race". Gardens were strongly advocated for in schools, and garden contests were common in neighborhoods. With regard to sanitation, dust produced by the increasingly popular automobile's travel on roads designed for horse-drawn traffic emerged as a pressing issue. Publications reported on experimentation with alternative construction materials to address both the dust problem as well as the automobile's more vigorous wear of the roads. While the automobile presented challenges to existing infrastructure, it allowed rapid innovation in the realm of firefighting technology. This research will support arguments presented in Professor Carvalho's book *The Invention of the Future*, which uses a historical perspective to provide insights about the future of urbanization and urban environments.

Poetry in America

Julia Garcia Galindo
Sociology, 2025
Harvard College, Cabot House
PI/Advisor: Elisa New, Hogan Seidel

Long before the COVID-19 pandemic forced many schools to go virtual, the education nonprofit Poetry in America was already experimenting with online/hybrid models of education. Through its various online literature courses, Poetry in America is able to, as its mission states, "bring poetry into living rooms and classrooms around the world." Furthermore, its education team is constantly aiming to innovate within the educational sphere, seeking to address gaps in access to quality education through its virtual offerings. I worked with Poetry in America's education team as they finished developing their newest offering, a course on the Health Humanities. One of my main tasks was providing feedback on the current draft of the curriculum. In giving feedback, I looked for gaps, areas that may not be as accessible to some learner population(s) or could be expanded upon. Some of my other tasks included participating in team meetings and creating materials to meet the gaps I identified. In addition to my work on their Health Humanities course, I also revised their recurring courses and suggested new course prompts. Through these experiences, I've gained course development skills, and have been exposed to the special considerations required for online/hybrid course offerings.

"A Winter's Tale: Karen Blixen in America"

Aidin Kamali
History, 2025
Harvard College, Lowell House
PI/Advisor: Thomas Wisniewski

In the winter of 1959, Karen Blixen, the Danish author of *Out of Africa*, *Babette's Feast*, and *Seven Gothic Tales*, made her first trip across the Atlantic to meet her American readers. This piece of literary history is the focal point of my HSURV research for an upcoming documentary film that tells the story of this trip and Blixen's legacy in the United States: "A Winter's Tale: Karen Blixen in America." To that end, I have throughout the summer compiled archival video, audio, and photos from 1959, including Blixen's performances in New York and Boston. In my research, I draw on a range of biographies, documentaries, first-hand accounts, and newspapers to construct a three-month timeline of the trip. I give a close look at Orson Welles' screenplay adaptations of her work (and sole completed feature film), as well as his interviews and writing on Blixen, to highlight Blixen's cinematic legacy. Drawing on secondary scholarship and Blixen's fiction and nonfiction, I contribute original writing to the development of the documentary on topics including postcolonial critiques of Blixen's work, inspired by Kenyan writer Ngũgĩ wa Thiong'o, and the cinematic legacy of work, as seen in *Babette's Feast* and *Out of Africa*. As the documentary moves from research and development into production, I will continue to work with a team of Harvard students and researchers to incorporate my own writing and analysis of archival materials into the script.

Annotations in *A Homer Commentary in Progress*

Elena Lu
Classics, 2026
Harvard College, Mather House
PI/Advisor: Gregory Nagy

Since the publishing of the work of Milman Parry and Albert Lord on oral poetics almost a century ago, the study of Homer has found new life, with the discovery of traditional style allowing scholars to pursue new avenues of inquiry while equipped with a new set of methods. The editors of the collaborative and ever-evolving *A Homer Commentary in Progress* conduct synchronic and diachronic analyses of the *Iliad*, *Odyssey*, and *Homeric Hymns* to argue that the surviving texts of the poems do, as the works of Parry and Lord have contested, originate from a formulaic system of oral poetry. As an editor, I focus primarily on the *Iliad*, analyzing how its formulas serve as the foundation from which the poem builds its conflict, and contributing annotations to the *Commentary* based on this analysis. My annotations, though based on a reading of the entire poem in its original Greek, focuses specifically on four passages: Bellerophon's genealogy in *Il*.6, Hector and Ajax's duel in *Il*.7, Idomeneus' *aristeia* in *Il*.13, and the *theomakhia* of *Il*.21. In my contributions to the *Commentary*, I pay particular attention to the poetics of conflict both verbal and physical, examining the role of traditional language as it defines and navigates the social world that lies between the Achaeans' thousand ships and the high walls of Troy. With a better understanding of each of these passages, the tapestry our *magnus poeta* has woven unfurls to reveal an artwork as worthy of glory as its heroes.

Harvard Square and Cambridge History

James McAffrey
Government & History, 2026
Harvard College, Leverett House
PI/Advisor: Suzanne Blier

The goal of this project is to create a resource for community members and visitors to learn more about the history of Cambridge beyond Harvard and MIT. There are tons of tours for both Harvard and MIT, but that does not create a full picture of the real impact that Cambridge has had on the world beyond those institutions. Using several interviews, meetings, books, archival, and other materials, there were two walking tours created about the history of East Cambridge and Harvard. Each walking tour focuses on a neighborhood in Cambridge, including Harvard Square and East Cambridge. These tours contain a set of locations, each with a small blurb summarizing the importance of the area. In addition to the walking tours, there were three videos introducing the basic history of each of these areas. The Harvard Square video introduces the early history of Cambridge and the East Cambridge introduces the industrial era in Cambridge. Through this research, I have attempted to summarize a large portion of Cambridge history to make an easy introduction for viewers. These tours will help reveal some of the basic history of the city and Harvard by attempting to reveal the fact that Harvard was built as a school used to 'civilize' Native Americans.

"Until a Name and All Its Connotations Are the Same": Literary Form in the Poetry of Elizabeth Bishop and AI

Liv Oster
English, 2025
Harvard College, Eliot House
PI/Advisor: Kristine Grieve, Zoe Hill

Artificial intelligence and, more specifically, the large language models (LLMs) behind sites like ChatGPT currently dominate public discourse. My project aims to recenter the discussion of these emerging technologies around literary form, which I take as the culturally sensitive "container" of words that generate context-specific expectations and experiences. Composed of compact arrangements of language, poetry proves a particularly useful site for this exploration. Accordingly, in my paper I conduct a close analysis of poet Elizabeth Bishop's drafts; her laborious editing process and participation in the 20th-century convergence of both formal and antiformal movements make her an ideal case study for examining the interdependence between poetic form and content. I use a combination of examples from Bishop and AIs to suggest that form has the advantage of allowing us to evaluate the limitations of LLMs while simultaneously revealing how literature bridges mere linguistic representations of the world with the actual experience of those representations in reality. Given LLMs' construction as statistical predictors (an underlying fact that has not changed despite their significant advancement in recent years), they are unable to engage with the nuanced historical and ideological conditions that grant form a stake in the meaning-making process. Their failure to bring texts into conversation with the structures that comprise our social conditions reveals not only why human authorship must endure, but also helps us think in more sophisticated terms about what exactly it is that humans do when they create meaningful art. More broadly, this study aims to demonstrate how scholars can use AI technologies to inform and redefine traditional literary studies, revealing through their limitations the complex nature of human creativity.

Reconstructing Life After Deindustrialization in the U.S. and France

Arjun Purohit
Social Studies & Philosophy, 2025
Harvard College, Lowell House
PI/Advisor: Lizabeth Cohen

Scholars have investigated how African-Americans were discriminated against by steel companies and unions in the Rust Belt after migration into the urbanized North in search of mobility. However, less has been documented about how the economic and social consequences of deindustrialization interacted with civil rights activism and black community organizing to impact the personal lives of steel workers and their families. Our project aims to compare deindustrialization and its implications for communities of color in Youngstown and Pittsburgh. By drawing from newspaper materials and oral testimonies in the form of personal memoirs and interviews, we aim to examine how *de facto* segregation affected schooling, racial protests, and public facilities in the Rust Belt. In particular, our research, in which we use eye-witness accounts and local reporting from *The Pittsburgh Courier* and *Youngstown Vindicator*, explores how racial violence in 1968 galvanized vicissitudes in law enforcement deployment, policy reform, and youth organizing. We seek to illuminate the context behind the protests in Pittsburgh and Youngstown, including the particular issues raised, the scope of the riots themselves, efforts to restore order on the part of both black and white Pittsburghians, black-white community relations, and finally the extent to which progress was made after the disorder in the eyes of black community organizers. This endeavor will bring focus to how urban renewal and the decline of steel production in Eastern Ohio and Western Pennsylvania affected black workers and their communities and in doing so, help explain how minority communities endure in the post-industrial era through grassroots activism and local organizing.

Negative Grounding Facts and Anti-Essence

Anna Pauliina Rumm
Philosophy, 2025
Harvard College, Eliot House
PI/Advisor: Selim Berker

We often explain facts by appealing to more fundamental facts that underlie them. For instance, we may use facts about chemistry to explain facts about biology, facts about neurology to explain facts about our emotional states, and facts about an action's non-moral features to explain facts about its moral features. However, while much research in contemporary metaphysics has attempted to understand what enables facts to stand in such explanatory relations, another closely related question has been largely neglected. Namely, why is it that some facts *cannot* explain certain other ones? For example, why cannot biological facts be explained by political ones or facts about quantum mechanics be explained by those about morality? In my paper, I answer this question by developing an account of *anti-essence*, which is meant to capture the intuitive idea that objects, properties, and other such entities are all in certain ways limited and constrained. In the first part of the paper, I motivate the need for such an account by showing that negative explanatory facts cannot be explained just in terms of truths about essences; and so, unless we are willing to accept the existence of anti-essences, it is unclear how we should explain a whole host of facts that require explaining. In the second part of the paper, I develop the theory of anti-essence further. More specifically, I suggest that an object's anti-essence characterizes it in an inherently negative manner and is constituted by certain propositions about it that must be necessarily false if the object is to be the sort of thing that it is. Finally, I show that, not only can such a theory of anti-essence provide an attractive account of what explains negative explanatory facts, but it can also be used to illuminate questions about modality, identity, and ontological dependence.

Robert Morris, Jr., and a Boy Called Bernardo: Two Case Studies in Abolitionist Child-Rearing

Jonathan Schneiderman
History & Literature, 2025
Harvard College, Dunster House
PI/Advisor: Kristine Greive, Zoë Hill

Drawing inspiration from the microhistorical work of Saidiya Hartman and Mary Elizabeth Perry, this paper considers two case studies in which New England abolitionists of the mid–nineteenth century had occasion to see to the education and rearing of individual Black children: (1) the case of Robert Morris, Jr., the son of the Black Boston lawyer Robert Morris; and (2) the case of a Cuban boy named Bernardo who came into the care of a New England abolitionist network. My primary method is close-reading letters by and about Morris, Jr., and Bernardo to understand what attitudes these adolescent's caretakers had toward them and what these caretakers prioritized in their rearing, using philosophical, sociological, and educational theory to help understand how these people may have been thinking in ways they did not make explicit. The paper devotes particular attention to the identification of paternalism and to the effect of interpersonal (as distinguished from structural) racial prejudice on a person's education. I argue that nearly all the guardians in these case studies were attentive caretakers intent to protect the children from prejudice, but that Morris, Sr., was more attuned than were the abolitionists caring for Bernardo to the dangers of prejudice. Today, when books with titles like *For White Folks Who Teach in the Hood* become bestsellers, progressives struggle with the question of what the education of Black children demands—if, indeed, it demands anything different from the education of children generally. As these cases show, progressives have been struggling with this question for nearly two centuries; understanding how these particular progressives answered it in the 1850s can help us understand both the normative question of how progressives might answer it today and the descriptive question of what concerns they are thinking about when they do.

Collective Reconstructions: Genre and Historical Trauma in Argentinean Cinema

Gibbi Sepulveda Rabago
History of Science, 2024
Harvard College, Eliot House
PI/Advisor: Jennifer Alpert

Collective Reconstructions: Genre and Historical Trauma in Argentinean Cinema is an upcoming book by Jennifer Alpert that will examine the cultural role of motion pictures in resisting state-sponsored violence and upholding democracy in Argentina. The country serves as a key case study given its tumultuous history, marked by six periods of dictatorship since the 1930s, with the most recent lasting seven years and ending in 1983. This latest dictatorship, at the helm of a junta of military commanders, abducted, tortured, and murdered tens of thousands of people, 30,000 of whom were never to be seen again. The project examines Argentinean genre cinema's role as a powerful form of resistance, and argues that it has provided a platform for people to navigate through the complexities of trauma, reconstruct the country's identity, and forge a strong collective memory in the aftermath of dictatorship. The project analyzes nationally produced mainstream fiction films and archival cultural primary sources, such as periodicals, journals, and testimonies. I largely engaged with the latter, finding, reading, and analyzing reviews, interviews, and ephemera such as film festival catalogs through close reading to understand the discourses surrounding these films and their afterlives. In addition, I digitized related uncatalogued materials that shed further light on the dictatorship's relationship to civilians and institutions that serve marginalized populations in the country. The book serves as a poignant reminder of culture's enduring role as a critical tool in resisting tyranny and providing refuge in the hope of a brighter future. As far-right-wing movements resurface across the world, *Collective Reconstructions* comes at a timely juncture as it underscores the profound impact of fiction in elaborating historical trauma, ultimately reaffirming the enduring relevance of cinema in shaping societal consciousness.

Reconstructing Egyptian Papyri From the Pyramids Age (2300 BCE)

Elijah Visio
Anthropology, 2026
Harvard College, Mather House
PI/Advisor: Victoria Almansa-Villatoro

Many are captivated by ancient Egyptians and the various artifacts they left behind. Although incomplete, we have an appreciable understanding of Egyptian history from the second millennium BCE and onwards, due to the recovery and analysis of primarily royal artifacts. Less is known, however, about the Old Kingdom era (c. 2700-2200 BCE). In this project, we analyze an archive of Old Kingdom provincial hieratic papyri from the island of Elephantine. This unpublished and untranslated archive gives rise to many questions: 1) how did the hieratic system of writing and the ancient Egyptian language evolve throughout the Old Kingdom; 2) will it reveal the function of the Elephantine Pyramid, a structure that lacks a burial chamber; 3) does it give insight into the everyday life of an ancient Egyptian household; and 4) does it contain the oldest non-royal mortuary or religious texts written on papyri? To answer these questions, we first need to discern what the archive says. We started this process by editing each fragment's photo in Adobe Lightroom to accentuate better the hieratic signs, grain texture, and color of the fragments. Then, we utilized Microsoft Powerpoint to construct plates of all the fragments. Next, we identified essential papyri fragments that contained particular ink, names of gods, and names of people/households. Finally, we transcribed these key fragments to gain an overall sense of the archive's content. As this project advances, the entire archive will eventually be reconstructed, transcribed, transliterated, and translated as completely as possible. Our current hypothesis is that the fragments are letters and accounts from an affluent household, possibly mixed in with religious texts or temple administrative documents. Since the archive is non-royal and provincial, understanding its contents may reshape our understanding of Old Kingdom Egypt by challenging the informational bias presented by royal artifacts.

Equal Educational Opportunity: Aesthetic and Moral Dimensions

Graham Weber
Social Studies, 2025
Harvard College, Cabot House
PI/Advisor: Gina Schouten, Samantha Matherne

Careful examination of a diverse array of philosophy, from 18th-century letters to contemporary analytic philosophy, has given way to an intellectual map that charts diverse, disparate, and overlapping ways of thinking about and understanding topics in education. From Mary Wollstonecraft's 1792 *A Vindication of the Rights of Woman* to Kenneth Howe's 1997 *Understanding Equal Educational Opportunity: Social Justice, Democracy, and Schooling*, these texts, which cut across continents, centuries, and methods, serve as a fertile source of inquiry into the nature of aesthetic education and the notion of equal educational opportunity. The aesthetic dimension of this research consists of excavating the roles that not only various forms of art, design, and literature but also beauty, sublimity, and the ways people dress, speak, and interact with the environment play in education. The moral dimension, often living in the world of Rawlsian theory, involves investigating the meaning and various constructions of the principle of equal educational opportunity as well as the complicated and uncertain road that leads to implementing it. Compiled into short essays and discussed at length, examinations of these texts and ideas serve as a survey of deeply intertwined and vitally important disciplines of philosophy, which serve as springboards to explore questions like the nature of the self, the relationship between the individual and society, the limits of personal agency, and the development of the social fabric. This research sets the stage for deeper philosophical intervention from Professors of Philosophy Gina Schouten and Samantha Matherne, who are in the early stages of scholarship on these subjects.

SPUDS

Decoding Smad2/3 Transcriptional Responses: Investigating Whether the Activating Ligand Affects Transcriptional Output

Karla Avalos
Applied Mathematics, 2024
Harvard College, Leverett House
PI/Advisor: Rosen Vicki, David E. Maridas
Mentor: David E. Maridas

Osteoporosis, a chronic disease characterized by bone loss and weakness, costs more than five trillion dollars in the US, Canada and Europe alone. One critical step towards developing effective therapeutics for osteoporosis includes developing a better understanding of the pathways involved in maintaining skeletal mass and strength. Excessive Smad2/3 phosphorylation has been shown to contribute to osteogenesis imperfecta, also known as brittle bone disease, where bones easily fracture in mice. Moreover, circulating levels of ligands, that activate Alk4 and Smad2/3 signaling, are positively associated with age, and preliminary results have shown that their inhibition decreased bone loss in mice. However, there are multiple ligands that can activate Alk4 in bone, including Activin A, Myostatin and GDF11. In this project, we investigated if the transcriptional output resulting from Smad2/3 signaling is dependent on the activating ligand by treating W20 cells with Alk4 binding ligands and TGFβ. TGFβ is selected as a comparative control as it activates Smad2/3 signaling without using Alk4. RNA sequencing will be performed to compare transcriptional outputs across treatments. We hope to establish this cell culture assay to investigate the transcriptional output of each Alk4-binding ligand and provide potential therapeutic targets for addressing osteoporosis.

Using the Brief Observation of Social Communication Change to Measure Longitudinal Changes in Social Communication Behaviors

Diamante C. Balcazar
Neuroscience, 2025
Harvard College, Pforzheimer House
PI/Advisor: Susan Faja
Mentor: Aiko Jones

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition usually diagnosed early in childhood and characterized by differences in social communication skills and restricted and repetitive behaviors. The benchmark diagnostic assessment for ASD is the Autism Diagnostic Observation Schedule (ADOS), but it insufficiently tracks changes in individual behaviors over time. The Brief Observation of Social Communication Change (BOSCC) was developed to objectively measure individual differences in social communication over time. This project evaluates the BOSCC's accuracy when measuring changes in social communication in children with varying language abilities over a 2 year period, as its reliability has not been explored when paired with children who use phrase speech or better and at longer lengths. Forty-four 2-to-7 year olds on the autism spectrum and their parents participated in a 10 minute-long recorded parent-child interaction (PCI) and were instructed to freely play with toys. Each recording was segmented into halves and scored using the BOSCC coding battery, featuring social affect (SA), restricted/repetitive behaviors (RRB), and overall scores. We found none of the children reached maximum or minimum BOSCC scores, reflecting neither ceiling or floor effects across varying language abilities and time points. Sixty-three percent showed progress in social communication ability reflected through their BOSCC score, with no significant correlation between BOSCC change scores and ADOS equivalents. Our preliminary results show changes undetected by the ADOS may be tracked using the BOSCC. This suggests the BOSCC is a valid measure to document change in social communication skills amongst autistic children with varying language levels longitudinally.

Better Post-Processing for Multiaccurate Classifiers

Alexander Glynn
Applied Mathematics, 2024
Harvard College, Quincy House
PI/Advisor: Flavio Calmon
Mentor: Carol Long

From mortgages to stock trading, many important decisions today rely on machine learning models, so auditing for and improving fairness in the models is essential. Classifiers, a type of model predicting whether an entry is a member of some class, have been the subject of rich study on fairness. Our work contributes to this by expanding our understanding of post-processing for multiaccuracy (or related properties), a process in which a pre-trained model, accessed only as a black-box, has a transformation applied to its outputs based upon only few data. Multiaccuracy, one property we wish to impose through a transformation, insists that for each group of entries in the data, where the groups are in some defined family, the expected difference between the predicted and the true class across entries in that group is small, meaning it is unbiased. Our research novelly relates multiaccuracy and related notions to underlying statistical mechanisms, such as integral probability metrics, unlocking new tools for the study of multiaccuracy. We then find a function space whose functions serve as the methods of grouping data and use a property of kernel functions to gain an efficient method of discovering regions where multiaccuracy is not achieved. This provides a method of auditing for multiaccuracy, revealing entries that do not satisfy it, which shows promising results in testing. Using the auditor, we then plan to propose a novel algorithm to post-process for multiaccuracy. We will evaluate this algorithm against existing methods in terms of time complexity, how well fairness is satisfied, and accuracy. This research will contribute to creating models that are fair for everyone, and continues to link different aspects of information theory, statistics, and machine learning together.

Efficient High-Dimensional Gaussian Approximation

Kenneth Gu
Statistics & Mathematics, 2025
Harvard College, Currier House
PI/Advisor: Morgane Austern

In statistics applications, there is often an interest in bounding the probability that an estimator is more than t away from the corresponding estimand. In the high-dimensional setting, we may be interested in bounding the probability that the maximum difference between a collection of estimators and their estimands is greater than t. The law of large numbers indicates that both probabilities should converge to zero as the sample size or t grows, but existing probabilistic tools only provide very weak bounds. Our approach combines modern probabilistic techniques like Stein's method with existing work in the one-dimensional setting. We develop explicit bounds for the Wasserstein-p distance – a common metric for probability distributions – between the distributions of the maximum of several empirical averages and the maximum of a multivariate Gaussian random variable, the latter of which has been extensively studied in the past. The bounds developed in our work can then be applied to form concentration inequalities that are valid in finite samples and asymptotically efficient.

Small Area Estimation for Forest Inventory Application

Lal Kablan
Economics & Psychology, 2025
Harvard College, Adams House
PI/Advisor: Kelly McConville
Mentor: Grayson White

The U.S. Forest Inventory and Analysis Program (FIA) regularly collects plot data pertaining to diverse forest attributes, ensuring the ongoing monitoring of the nation's forests and their changing trends. As the demand for more accurate estimates increases, particularly for smaller ecological regions like eco-subsections, there arises a need for a comprehensive set of estimation tools on more granular scales. Small area estimation (SAE) is a statistical method, commonly employed in national forest inventories, that combines ground plot data with remotely sensed information to generate more precise estimates of forest parameters such as biomass and carbon content. This research presents two distinct yet interconnected projects aimed at utilizing SAE techniques to further refine estimates of forest features and their ownership attributes. Project one focuses on simulation studies within an artificial population of M333 Northern Rocky Mountain Forest-Steppe-Coniferous Forest-Alpine Meadow Province. Using SAE, we investigate an array of small area estimators of biomass in terms of statistical properties including variance and bias. We aim to gain insight into the performance and limitations of different tools such as Hierarchical Bayesian, EBLUP, and GREG estimators. Project 2 focuses on the National Woodland Owner Survey (NWOS), a different component of the FIA program. While the NWOS provides valuable information on private forest owners at a broader geographic scale such as at state-level, it lacks the necessary spatial resolution for tactical implementation and understanding forest owner characteristics at finer scales like county and congressional district-level. This project aims to test SAE techniques, more specifically Area-level EBLUP and HB estimators, with the NWOS data to produce precise estimates of ownership attributes at county and similar scales. Through both projects we aim to enhance forest resource management by equipping decision-makers with improved estimation techniques and actionable insights for program development, policy formulation, and service implementation.

PM 2.5 & Absolute Mobility

Sophie-An Kingsbury Lee
Environmental Science and Engineering, 2026
Harvard College, Mather House
PI/Advisor: Francesca Dominici

Exposure to PM 2.5, fine particles with a mass median aerodynamic diameter under 2.5 μm, causes cardiac and respiratory issues with reduced productivity, and has been associated with decreased educational attainment. PM 2.5 levels vary widely across the contiguous United States, and recent studies have demonstrated the racial, ethnic, and economic disparities in exposure. While studies have found an association between PM 2.5 on economic mobility, to our knowledge, none provided evidence of a causal effect. Here, we attempt to use three causal inference models to provide strong evidence for a causal link between childhood PM 2.5 exposure and future earnings for low-income children. In addition, we divide the contiguous United States into four Census regions and repeat analyses to understand the spatial distribution of PM 2.5 and absolute mobility. Moving forward, we also plan to analyze if racial or ethnic disparities may exist in the effects of PM 2.5 on economic mobility.

Profiling EdgeBERT: An Accelerator Designed for NLP Inference

Joshua Park
Computer Science & Mathematics, 2025
Harvard College, Currier House
PI/Advisor: David Brooks, Gu-Yeon Wei
Mentor: Abdulrahman Mahmoud, Thierry Tambe

With the introduction of the attention and transformer models, large language models (LLMs) have taken the world by storm. Models like BERT and GPT-4 have had wide implications in the field of natural language processing. While their impact is undeniable, these transformer-based models require large amounts of memory and energy, often containing hundreds of millions of parameters. Thus, running inference using these models is a very memory and energy-intensive task. To decrease the memory and energy needs for running inference, EdgeBERT, an accelerator designed specifically for natural language processing (NLP) inference was designed. EdgeBERT incorporates various features that aim to improve on energy and memory. First, EdgeBERT uses the novel AdaptivFloat data type to quantize values, allowing for a greater range in weights and activations. Furthermore, it allows for early exit for each transformer layer, so that inference can possibly be terminated early. Finally, it contains a bitmask encoding to save memory on the accelerator. Now, we aim to profile EdgeBERT's performance on the A Lite BERT (ALBERT) model, a variant of the BERT model. Preliminary results have shown that EdgeBERT's design improves runtime, while using limited amounts of memory. These improvements will allow LLMs to run more efficiently on platforms that have significant memory constraints. By allowing these computations to be done directly on these platforms, we can reduce the amount of computation that needs to be done on the cloud, improving latency and user privacy.

Odor

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Mentor: Shanshan Qin

With modern microscopy, we can study how the brain stores and processes information at the level of single neurons, allowing the construction of a complete structural map of the *Drosophila* cortex. We aim to use the connectome to elucidate how the olfactory system encodes odors. This process begins with a palette of olfactory receptor neurons (ORNs) on the antenna. When odorous chemicals bind to receptors, the neurons spike, transmitting information through a layer of Projection Neurons (PNs) to a collection of 2000 Kenyon Cells (KCs) in the mushroom body, a region which encodes olfactory input. While structurally similar chemicals usually have highly correlated responses from ORNs, this correlation rarely persists in the high-dimensional KC space. Evolutionarily, decorrelation is thought to allow flies to differentiate between related odors which require distinct behavioral responses, i.e. ripe versus rotten fruit. Yet, the mechanism of this decorrelation is not understood. Through computational modeling of this system, we consider the anterior paired lateral neuron (APL), a large GABAergic interneuron in the mushroom body, as the mediator of decorrelation. Calcium imaging shows compartmentalized activity by the APL, meaning that inhibition of individual KCs is disproportionately a function of their own activity. We explore the impact of localized APL activity and Fly Wire connectome data on a baseline model with uniform inhibition and random connections from PNs to KCs and find evidence of decorrelation. Because the stimuli in our model were synthetic, it remains unclear the extent to which nonuniform inhibition accounts for the lack of randomness in true representations. Using a more exhaustive collection of ORN recordings as inputs to our model would allow us to look for specific patterns of decorrelation in, for example, food odors or pheromones. Ultimately, our model reveals the necessity for direct interrogation of APL behavior in realistic contexts.

Driver Speed With Endogenous Congestion: A Novel Model for Urban Traffic

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Traffic jams are a major problem in densely populated urban areas across the world. To better understand these phenomena, many economists have tried to model individual driver speeds. We propose a new model that focuses on the effect of an individual driver's neighboring drivers on their own behavior. We utilize sightings from traffic cameras across the city of Rio de Janeiro, Brazil, to develop this model. This project consists of four steps. First, we construct vehicle trips through combining consecutive sightings of vehicles and saving the travel time. Next, we utilize these trip durations to run a fixed effects regression, which captures individual driver preferences. We then implement a nonlinear regression based on a microeconomic model that ultimately allows us to determine how surrounding driver preferences affect each individual driver's speed. We find that there is a positive coefficient in this regression once we condition on location-time fixed effects. We are still looking to estimate the heterogeneity coefficient, which tells us how much we weigh the effects of surrounding cars depending on their preferences.

Interpreting MLP Blocks in Transformers Using Geometric Dictionary Learning

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PI/Advisor: Demba Ba

Deep artificial neural networks have fueled the current AI revolution but generally lack interpretability of their output. Neural networks with ReLU nonlinearities lead to piecewise approximations of smooth functions. Supervised K-Deep Simplex (KDS) provides an alternate, more interpretable parametrization of piecewise linear functions, consisting of two sets of weights, called atoms, associated with the domain and codomain of a function of interest, respectively. The atoms in the domain define simplices that allow every input to be expressed as a convex combination of the atoms defining the simplex to which it belongs. The output is then interpreted as the same convex combination of those atoms in the codomain. I implemented Supervised KDS, tested it on the MNIST handwritten digit dataset, where it achieved upwards of 97% test accuracy while learning interpretable atoms, and used it to gain insight into the functions of individual MLP blocks in transformer models. In particular, I trained a 500-atom Supervised KDS model to predict the output activations of the first MLP block in Facebook's OPT-small model from the input activations, achieving $R^2 = 98.5\%$ and a KL divergence of 0.0981 in the next token predictions. Many of the atoms are readily interpretable in the domain. Perhaps most strikingly, many conjunctions and prepositions have their own dedicated atoms, including: and, or, for, as, in, if, but, that, by, on, at. I have proposed a method for interpreting the output weight for each atom (and hence the action of the MLP block) that infers the relative importance of all its destinations using mean ablation, but its implementation is yet to be completed.

A Spatial Analysis of Air Pollution and Mortality in the American Medicare Population

Leo Vanciu
Statistics & Mathematics, 2026
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PI/Advisor: Francesca Dominici
Mentor: Dafne Zorzetto

Numerous epidemiological studies have highlighted the association between mortality risk and social-economic disparities, as well as mortality risk and exposure to fine particulate air matter (PM2.5). However, few studies have investigated the spatial distribution of these associations across the entire United States. We aim to address this gap by performing a comparison of Bayesian hierarchical models to estimate the mortality risk in the U.S. Medicare population across more than 25,000 ZIP codes in 2016, including several socio-economic characteristics and PM2.5 exposure. Disease mapping models provide a framework for analyzing spatially correlated data and have been widely used to model disease risk across geographic areas. Their application to the study of air pollution and health outcomes can allow for the assessment of the relationship between annual average PM2.5 exposure and mortality rates while accounting for socio-economic and other confounding factors in a spatial context. Preliminary results suggest that the association between mortality risk and PM2.5 exposure as well as some socio-economic characteristics varies spatially across the continental United States, particularly in the 85+ years old group. A stratified analysis by sex and age underlines a characteristic spatial correlation between these variables and mortality risk across the nine Census divisions in the United States.

The Social Science of Science

Henry Wu
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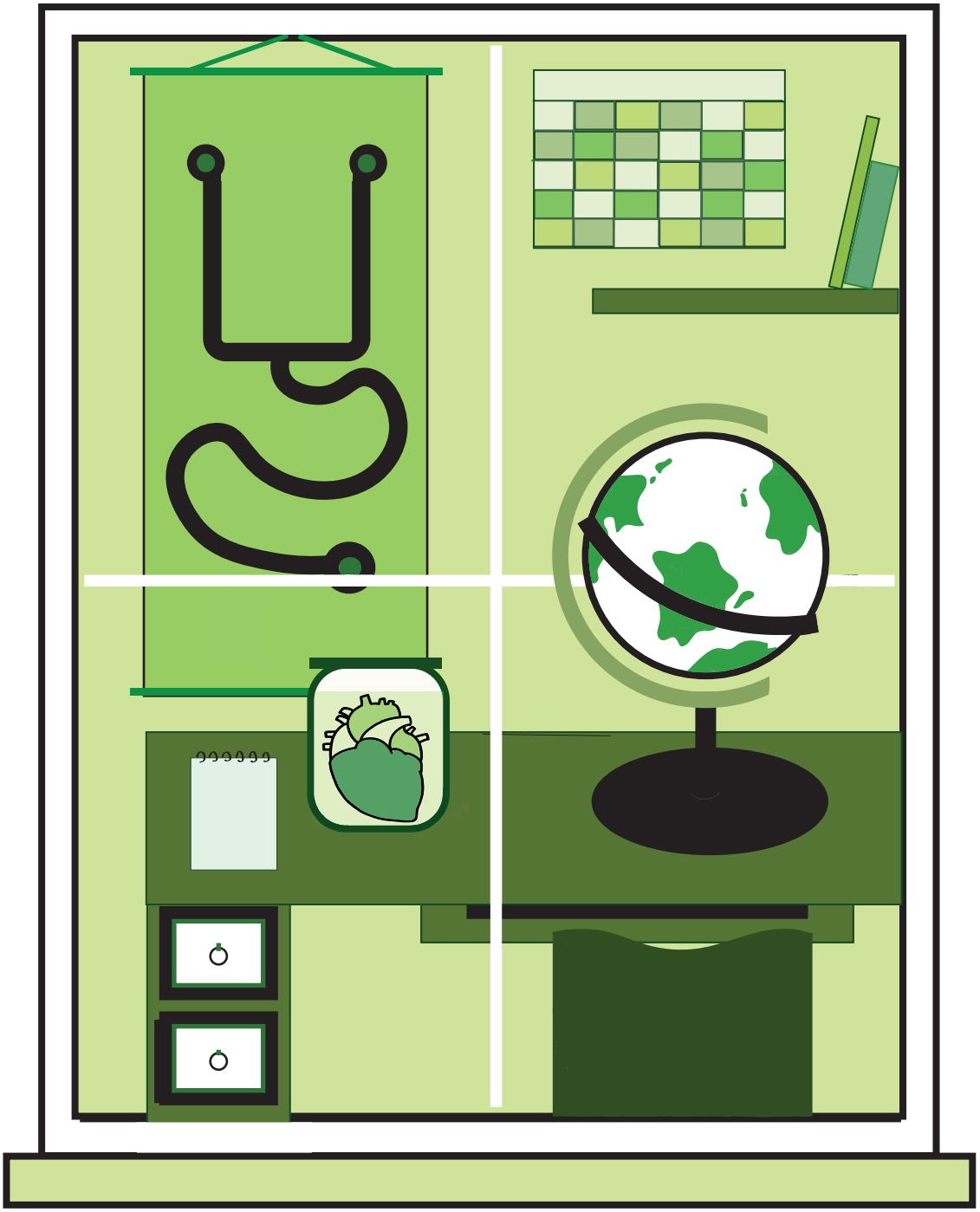
Mentor: Casey Petroff

Science has led to remarkable improvements in health, wealth, and quality of life, but it is unclear how exactly scientists have come together to form such successful institutions. We hypothesize that science has worked to accelerate progress because of the incentives of its novel social organization. We conducted a network analysis of the people cited in the scientific and alchemical works of Isaac Newton. This enables us to test our hypothesis that science, unlike other scholarly disciplines, is uniquely reliant on cooperation and competition to generate progress. Alchemy, unlike its modern descendant chemistry, had a tradition of suppressing rather than sharing information and methodologies. Thus, Newton, who was active in both modern science and alchemy, represents an ideal case in which to test this hypothesis. We scraped the website of The Newton Project for the full texts of Newton's works (173 scientific and 69 alchemical) and used a combination of named entity recognition and hand-coding to compile a list of 481 names cited in those works. We then created two separate co-citation networks of people cited in the two different types of works, with an edge connecting two people if they were cited in the same work. We found that Newton's scientific works, on average, contain significantly more citations, unique people cited, and citations per word than his alchemical works. Furthermore, the scientific co-citation network is more dense and has a larger connected component than the alchemical co-citation network, suggesting that Newton's scientific work relied on a greater variety of sources that were placed in comparison with each other. These findings have implications for the success of emerging fields of research in the present, and future work could be directed toward more recent discoveries or toward co-authorship networks covering broader historic alchemical and scientific communities.

SURGH



Improving Access and Usage of Evidence-Based Resources in African Medical Schools

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Many current and future medical clinicians in developing countries lack access to evidence-based resources associated with improved patient care. The Better Evidence (BE) team is trying to reduce these gaps in resources by partnering with UpToDate, an organization that provides a digital clinical support tool, to give free subscriptions to medical schools across Africa. Research has shown, though, that simply giving students access to UpToDate does not guarantee use, so BE started to work with faculty members, known as Champions, at each school to scale the program and have a greater impact. However, after noticing that Champions were using different methods and achieving different results in spreading UpToDate, the BE team decided to standardize the Champion program more. To ensure Champions have the same knowledge of the platform and are implementing it most effectively, the BE team is developing a curriculum. This curriculum will familiarize Champions with UpToDate, teach them best practices for spreading it at their schools, and help them understand how to measure their progress. The curriculum will be online and consist of eight modules, each one hour or less, that will have informative videos, materials, and resources to help Champions learn how to fulfill their responsibilities. While the curriculum has not been released yet, it is expected to improve registration rates and increase daily usage of UpToDate for medical schools that partner with the BE team in the future. The long-term benefits of spreading UpToDate are expected to be significant because the earlier people use evidence-based tools, the more they use them throughout their career, which has the potential to influence innumerable clinical decisions and patient lives.

Investigating the Impact of Digital Tool Access on the Health Workforce in Underserved Regions

Nneka Arinzeh
Molecular and Cellular Biology, 2025
Harvard College, Adams House
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Mentor: Sara Pellegrom

Access to the latest medical information is essential for health care workers to make the best decisions for their patients and the community. However, in low-resource settings, where some of the most vulnerable populations reside, access to reliable clinical information is limited. This limitation hinders the ability for healthcare workers to provide optimal care. The Better Evidence Team at Ariadne Labs focuses on addressing this issue by providing free access to UptoDate, a leading electronic clinical decision support tool, to current and future health workers serving underserved populations worldwide. The goal of our project is to broaden access to evidence-based clinical tools for medical students and clinicians in low-resource settings and assess the tools' impact on healthcare delivery. To evaluate the outcomes and effectiveness of UptoDate implementation, qualitative analysis is being performed on a comprehensive database containing about 65,000 self-reported testimonies received from clinicians between 2022 and 2023. In these testimonies, clinicians expressed a need for reliable clinical information and documented their experiences and outcomes following the use of UptoDate. To date, our analysis reveals that clinicians utilizing UptoDate have benefited most from enhanced decision-making accuracy, expedited diagnosis or treatment, and an expanded scope of care. In efforts to expand our initiative's reach, our team is documenting and analyzing medical schools across Africa. By filling gaps in available data on these schools, we aim to bolster the development of medical educational facilities across the continent. Our outcomes will offer valuable insights into the impact of access to reliable medical information for clinicians in low-resource settings, informing policy changes and program outreach efforts. Our vision is to further support the current and future health workforce by continuing to extend access to a larger network of clinicians and medical schools in underserved regions, ultimately leading to improved global health equity.

Following Longitudinal Outcomes to Understand, Report, Intervene, and Sustain Health of Infants, Children, and Adolescents Who Are HIV-Exposed Uninfected (FLOURISH) Cohort Study

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Chronic health conditions, including HIV, can contribute to poor mental health. We sought to understand the prevalence of poor mental health by HIV status, identify risk factors associated with poor mental health, and to assess outcomes of mental healthcare referrals among mothers living with and without HIV participating in the observational Botswana-based FLOURISH study. Participants were screened for depression and anxiety using standardized instruments, PHQ-9 and GAD-7. Poor mental health was defined as screening positive for depression (PHQ-9 score $\geq$ 5) or anxiety (GAD-7 score $\geq$ 5). Prevalence was compared by HIV exposure status. Unadjusted and adjusted logistic regression models were fit to identify risk factors for poor mental health. Of 1,087 mothers screened for anxiety and depression, 819 (75.3%) were living with HIV. Mothers living with HIV (MLHIV) were older, with lower educational attainment, income, and food security levels. The prevalence of poor mental health was 11.5% among MLHIV compared to 6.6% among HIV seronegative mothers (p = 0.02). In unadjusted analyses, HIV-exposure status and severe food insecurity were significantly associated with poor mental health [Odds ratio (OR) 1.8 (95% Confidence Interval (CI) 1.1, 3.1)] and [OR 2.3 (95% CI 1.4, 3.9)] (p = 0.002) respectively, but only severe food insecurity [OR 2.4 (95% CI 1.4, 4.2)] was significantly associated with poor mental health after adjusting for HIV status and maternal age. Of 76 FLOURISH participants who provided feedback post-depression referral, 36 (47.4%) participants opted not to seek mental health care, another nine (11.8%) attended a health facility but did not receive support, and four (5.3%) participants received support but were dissatisfied with the support provided. Our team recommends developing a national campaign to destigmatize mental health care, scale up mental health support services, and enhance social protection programming, including food assistance programs, particularly for MLHIV.

Characterization of ORFs Within the *Shigella flexneri* T3SS Virulence Plasmid

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Molecular and Cellular Biology, 2026
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Mentor: Janice Nieves-Bonilla

Many pathogens utilize complex secretion nanomachines to propagate and invade cells. One such machine is the needle-shaped type III secretion apparatus (T3SA). This apparatus is part of the type 3 secretion system (T3SS), a larger system of effector proteins and chaperones that play a crucial role in carrying out pathogenesis. The T3SS and effectors are encoded on a virulence plasmid. This plasmid also encodes a large body of open reading frames (ORFs), genes of unknown function. Utilizing a deletion collection of M90T *Shigella flexneri* bacteria, we investigated how the deletion of certain ORFs influences secretion of effectors in comparison to the wild-type strain M90T WT. We chose eight effectors, four first wave effectors (OspC1-OspD3, OspC2, IpgB2, and IpgD) and four second wave effectors (OspD1, IpaH9.8, OspE1-IpaH1.4, IpaH7.8) to represent the 20+ effectors that are produced and secreted via T3SS. Current understanding of the model shows a hierarchy within effector secretion, creating a distinction of first wave and second wave effectors. First wave effectors have been well studied and are characterized by their earlier secretion but also their dependence on chaperon proteins for secretion. In contrast, second wave effectors currently lack any known chaperones and are secreted after first wave effectors. The eight effectors are FLAG-tagged and introduced to the mutant and wild-type strains via a pCMD136 plasmid. Through secretion assays, it was found that two mutant strains, Δorf131a and Δorf131b, exhibited increased secretion of IpaH7.8, IpaH9.8, and IpaH1.4 effectors with a slight drop in IpgD and IpgB2 effectors compared to WT *Shigella*. This suggests that the genes of *orf131a* and *orf131b* play a role in enforcing the hierarchy of secretion. Greater investigation is needed to further understand the secretion hierarchy and would allow for improvements on the current T3SS model and future medical applications.

Child-Friendly Catholic Schools Study in Zimbabwe

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Mentor: Amiya Bhatia

Teachers' use of corporal punishment remains widespread and underreported in Zimbabwe. Additionally, children experience high rates of sexual abuse from peers and staff at school. To address this issue, the Zimbabwe Catholic Bishops Conference (ZCBC) developed the Safe Schools Programme: an intervention that employs school- and community-based activities over 18 months aimed at preventing violence in Catholic primary schools through the involvement of administrators, teachers, parents, church leaders, and learners in grades 4, 5, and 6. To assess the effectiveness of this intervention, researchers at the London School of Hygiene & Tropical Medicine (LSHTM), in collaboration with ZCBC and other international partners, developed a study consisting of qualitative research conducted alongside the development of the intervention, a process evaluation, and an impact evaluation. The impact evaluation takes the form of a cluster randomized controlled trial, whereby collaborators in Zimbabwe will conduct quantitative surveys with students and teachers at 20 intervention schools and 20 control schools at two time points: a) at baseline prior to the intervention and b) at endline after the end of the intervention. Drawing from validated tools, our team is generating the measures for the baseline and endline learner surveys. These measures focus on the study's primary and secondary outcomes, including students' perceptions of school climate and their experiences of violence by peers and school staff, as well as other topics addressed in the intervention materials, such as students' perceptions of gender norms and their sense of empowerment to enact change in their school. Findings from a pilot intervention conducted in March of 2022 provide promise for the intervention's success. Importantly, as one of the first studies to evaluate a school-based violence prevention intervention in the context of the Catholic Church, this study has the potential to inform future intervention development and scale up within Zimbabwe and globally.

Social Media for Advocacy Organizations: Fenway Health Policy & Advocacy

Lauren Murphy
History of Science, 2025
Harvard College, Mather House
PI/Advisor: Carrie Richgels

The Policy & Advocacy Division of Fenway Health develops high quality healthcare and research that supports the LGBTQIA+ community by addressing the social and political barriers to care and creating a larger public awareness of Fenway Health's mission and the issues the institution addresses. The role of Policy and Advocacy Division Social Media Intern was created to help Fenway Health to reach a larger audience through an impactful social media presence. The project will culminate in a social media implementation guide for Fenway Health that will utilize relevant research on social media as an advocacy tool. The main goals of this project are to grow engagement and expand impact on our follower base in order to generate greater support for legislation promoting inclusive healthcare. This project will allow Fenway Health to communicate more effectively with patients and community members to ultimately mobilize more citizens to actively support policy and advocacy efforts.

Determining Genes Responsible for Drug Resistance in *Mycobacterium Abscessus*

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Mentor: Mark Sullivan

Mycobacterium abscessus, a species of bacteria distantly related to *M. tuberculosis*, is innately resistant to most classes of antibiotics, including β-lactams, macrolides, and tetracyclines. *M. abscessus* is commonly responsible for many open-wound skin infections and, separately, lung infections in patients with preexisting respiratory complications, such as COPD, cystic fibrosis, and HIV. Treatment of patients with *M. abscessus* infections centers around multi-drug injections given intravenously. The current treatment recommendations include a combination of the antibiotics amikacin, clarithromycin, and imipenem. However, although this regimen has proven success in some patients, it has also failed in many other instances. Tigecycline, a novel drug that inhibits protein translation, has shown promising efficacy against *M. abscessus*, though the reasons behind tigecycline's effectiveness are still being explored. This project seeks to analyze *M. abscessus* survival under tigecycline pressure as well as under the combination of tigecycline, amikacin, imipenem, and clarithromycin, to determine if tigecycline synergizes with the other commonly-used antibiotics against *M. abscessus*. Our study utilizes transposon sequencing (tn-seq) to determine the genes responsible for drug resistance in *M. abscessus*, in both tigecycline and the four-drug combination. Future research includes removing the genes found in our study and testing bacterial growth to confirm essentiality and conducting biochemical assays to determine gene function. Determining the genes essential for drug resistance in *M. abscessus* will provide more insights on bacterial drug resistance as well as future drug delivery targets.

EMPOWER: Building the Mental Health Workforce: A Pilot Study of a Digital Training Program in Texas

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Mentor: Natali Carmio

Task sharing models have shown strong evidence for improving mental health care access, particularly in low and middle-income countries. However, scaling these models remains a challenge, and there are limited successful examples of their execution in the United States. To address this, EMPOWER aims to combat the mental health crisis by employing digital tools to train non-specialist providers (NSPs) towards mastering and delivering evidence-based brief psychosocial interventions for community settings. EMPOWER's training includes the Foundational Skills of Mental Health Counseling course, covering evidence-based common factors in psychotherapy, and the Behavioral Activation program, covering an evidence-based intervention for adult depression, both adapted from India to the US-English context. To evaluate the acceptability and feasibility of the digital training platform in the United States, a pilot study was conducted with 54 providers recruited from a Texas health system, 62.3% of which had no prior mental health training. The study utilized various methods, including assessing participants' pre and post-training knowledge through a validated questionnaire and conducting eight focus groups to assess feasibility and acceptability of the training content. Thus far, focus group findings have indicated high training relevance, indicating the program's applicability to the participants' professional development. Among the 54 enrolled participants, the findings reveal an overall improvement in post-training knowledge by 5.4%, even after accounting for training completion (40 completed, 9 partially completed, and 5 did not start the training). The promising results from the pilot study showcase the potential impact of EMPOWER in enhancing provider knowledge and competencies. Additional pilot study results will be used to directly inform next steps for training providers and supporting care delivery in Texas and other national settings.

911, This Is a National Emergency: Reforming Healthcare in Critical Times

Hana Rehman
History and Science, 2025
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Mentor: Arissa Ruano, Clare Smith

As health care costs rise across the United States, our nation's health care system continues to fail the most vulnerable patients, such as the homeless, the elderly, and those in the criminal justice system. The University of Chicago's Health Lab strives to improve health outcomes for these populations by conducting evaluations of public health interventions rolled out by civic and community leaders. One of these evaluations is for Chicago's Crisis Assistance response and Engagement (CARE) program, which seeks to reframe the city's 911 response by creating a system of mental health services embedded throughout the crisis response system. I am conducting a literature review in CARE to study evidence-based tools and models created by other alternative responses. After assessing other community violence intervention programs, we plan to help develop protocols for mental health clinicians to use while redirecting patients at times of crises. This will help reduce liability for clinicians and increase the effectiveness of their involvement in emergencies. Our lab is also conducting an evaluation of the Critical Time Intervention (CTI) model that aims to understand the impact of CTI for people with serious mental issues who are experiencing homelessness. We are also performing a narrative literature review to understand engagement in homeless services by people with serious mental illness. The implications of this research will help inform how successful CTI's involvement has been with helping homeless populations compared to other services like Rapid Rehousing or Permanent Supportive Housing.

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