PRISE BLISS PRIMO SHARP SURGH SPUDS

# HSURV

## ABSTRACTS

2021

HARVARD SUMMER UNDERGRADUATE RESEARCH VILLAGE

# ABSTRACT BOOK 2021



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*

# Contents

# Letter from the Director

With the production of this volume, I am delighted to introduce the sixteenth collection of research abstracts from the 2021 Harvard College Summer Undergraduate Research Village, 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 the Research Village fold, SPUDS, the Summer Program for Undergraduates in Data Science.

This second summer of the coronavirus pandemic presented us once again with a completely uncharted range of variables in thinking about how to define our community. Neither "in person" or "remote" in its entirety, HSURV indeed was made up of every permutation among its constituents: living on-campus, living away from campus, conducting in-person projects as well as remote research. Particularly considering these inherent variations, I am gratified by the high degree of flexibility and adaptation among all the fellows, especially those who were many time zones away from campus. And while the experience was not what any of us would have expected or otherwise would want, I very much appreciate and am grateful for the tireless efforts of our amazing proctors and activity organizers who have stewarded a full schedule of opportunities for everyone to meet and engage throughout the summer.

Our collection of abstracts here would not have been possible without the outstanding, determined work of the group of Research Village editors whose voluntary charge has been to collect, organize, and publish the works of all of the Fellows. I would especially like to thank Karina Ascunce González for taking the initiative and seeing this important project through.

To the Summer Undergraduate Research Village Fellows of 2021, I hope you have found your research projects compelling and that living in the unusual circumstances we have experienced this summer was buffeted by our lively community, in Cambridge and beyond. I very much appreciate your enthusiasm and inclusiveness, and hope you have been able to develop meaningful personal and collegial relationships with your peers that extend beyond the Research Village going forward.

Sincerely,

Gregory A. Llacer

Director, Office of Undergraduate Research and Fellowships

# Letter from the Editors

Dear HSURV,

This summer, we finally had a chance to breathe. Those of us in Cambridge were able to take off our masks and inhale the scent of flowers, rain, and HUDS spicy chicken. We breathed sighs of relief as Harvard began to open its doors. In our hybrid situation, fellows proved flexible and eager to relish the uncertainty. Laboratories opened, allowing some fellows to work in person, while those continuing remote work tried to find the best work spots in Cambridge or in their hometowns. With the resurgence in social activities, assisted by the reopening of Harvard common spaces and the creativity of the proctors and fellows, fellows had more opportunities to meet serendipitously and ask the commonly heard question: "What's your project?" From these encounters, fellows learned about the variety of fascinating research projects their peers were working on as part of the Research Village.

As this last year of global pandemic and continued racial disparities exposed real rifts and problems in our society, fellows entered this summer's village with an aim to find solutions, heal divisions, and build community through research. Fellows sought answers to serious problems through exploration of science, social science, economics, art, and humanities. Our first cohort of SPUDS (Summer Program for Undergraduates in Data Science) fellows spent this summer exploring the ways data could provide answers to these problems.

This abstract book serves as a testament to the perseverance of the fellows and their commitment to advancing knowledge in a complicated and changing environment. Our faculty mentors and advisors are responsible for nurturing our learning and growth in this time of uncertainty. They encouraged us to embrace uncertainty as part of the research process, to be inquisitive, to think critically, and to cultivate intellectual pursuits in a collaborative environment. Our program assistants and HSURV staff enlivened our days with social interactions, personal support, and incredible talks from scholars. We would like to express our thanks to Chris Kabacinski, for answering hundreds of logistical emails and seeing to it that fellows' basic needs were met, while supporting a wide array of outings, innings, and social and educational activities. To the dining and building management staff, thank you for keeping fellows well-fed and comfortably housed. We owe an enormous debt of gratitude to Greg Llacer, for overseeing the entirety of the research village. All of these efforts have been essential in fostering a vibrant intellectual community where friendship and intellectual growth naturally meld.

Sincerely,
The 2021 Abstract Book Team

# Program Overview

According to the Office of Harvard Undergraduate Research and Fellowships, the 2021 Harvard Summer Undergraduate Research Village is a 10-week residential community that comprises Research Fellows from the following programs:

**PRISE:** The Program for Research in Science and Engineering (PRISE) is a 10-week summer program that aims to build community and stimulate creativity among Harvard undergraduate researchers in the life, physical/natural, engineering and applied sciences. To participate in PRISE, you must find a research position on your own, and apply to PRISE separately. (NOTE: it is not necessary to have secured a research position by the PRISE application deadline). Selected fellows work on projects with Harvard-affiliated researchers and get to live with other PRISE fellows in one of the Harvard College houses and participate in extremely rich evening programming (that includes both social and academic activities). In addition to receiving free lodging and being members of a diverse, vibrant intellectual and social community, fellows also receive a nominal stipend, and partial board.

**BLISS:** Build Learning through Inquiry in the Social Sciences (BLISS) is a 10-week summer residential program for Harvard undergraduates, 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 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 fulltime research, BLISS Fellows participate in rich variety of programming, including both social and academic activities. To participate, undergrads in good standing must apply and be selected to work on one of the pre-designated BLISS research projects.

**PRIMO:** The Program for Research in Markets and Organizations (PRIMO) is a 10-week summer program that aims to build community and stimulate creativity among Harvard undergraduate researchers in business and related fields. To participate in PRIMO, you must apply and be selected to work in one of the research areas which span diverse topics (finance, organizational behavior, marketing, etc.), disciplines (Psychology, Economics, Sociology), as well as methods (quantitative or qualitative). Successful fellows will be placed with pre-designed faculty projects at Harvard Business School. As part of the residential community of researchers, students will participate in enrichment activities such as faculty lectures, professional development workshops, presentation opportunities, and social events. PRIMO fellows are offered Harvard campus housing, a partial board plan, and modest research support.

**SHARP:** The Summer Humanities and Arts Research Program (SHARP) is a 10-week immersive summer program that aims to build community and stimulate creativity among a small cohort of Harvard undergraduate researchers in the humanities and arts. SHARP fellows work on 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 that includes both social and academic activities. To participate in SHARP, you must apply and be selected to work on one of the available SHARP research projects.

**SURGH:** The Summer Undergraduate Research in Global Health (SURGH) program is a 10-week summer program that aims to build community and stimulate creativity among a small cohort of Harvard undergraduate researchers in global health. SURGH fellows work on research projects with Harvard-affiliated faculty and researchers. Fellows live together in one of the Harvard College houses and participate in rich evening programming which includes both social and academic activities. To participate in SURGH, you must apply and be selected to work on one of the pre-designated SURGH research projects (usually announced in mid-January).

**SPUDS:** The new Summer Program for Undergraduates in Data Science (SPUDS) is a ten-week summer program, co-sponsored by Harvard College and the Harvard Data Science Initiative (HDSI), that 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. We also encourage SPUDS projects that focus on or emphasize ethical practices in data science research. To participate in SPUDS, prospective fellows should seek a research collaboration with a Harvard faculty host, and apply to SPUDS directly through the Office of Undergraduate Research and Fellowships. It is not necessary to have secured a research position by the SPUDS application deadline. Fellows will work with Harvard-affiliated researchers and live in one of the Harvard College houses with other fellows in the Summer Undergraduate Research Village. 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.

# ENGINEERING AND APPLIED SCIENCES

# APPLIED MATH

## Understanding Causes of Death for Bacteria in Starvation Using Mathematical Models

**Edward Athaide**
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*Mentor:* Severin Schink

Aging organisms invariably exhibit senescence, a state in which cells stop growing and eventually die. The causes of death for senescent cells are complex. Nutrient-starved bacteria, however, serve as useful model organisms in understanding cellular death due to their relative simplicity. Recent unpublished experiments on *E. coli* cells have suggested that the immediate cause of death is pressure buildup due to damage to the cell's outer membrane, but they have not revealed what long-term factors determine whether pressure will build up in an individual cell at a given moment. To further understand what might cause pressure buildup and death, we developed mathematical models of pressure dynamics inside bacterial cells and used MATLAB to simulate the macroscopic behaviors that these models would predict. The models made different sets of assumptions about the internal parameters of the system, and their predictions were compared with experimental observations. By studying these models, we hope to better understand the degree to which various parameters determine a cell's lifespan under starvation. Of particular interest is whether lifespan is affected more strongly by internal conditions in the cell prior to starvation or by stochastic events during starvation. Preliminary results suggest that shorter-lived cells have their lifespan largely determined by their initial state, while the survival times of longer-lived cells may exhibit more uncertainty due to the effects of stochastic processes. These results could lead to both predicting and understanding the uncertainty around the lifespans of aging bacterial cells, with further research developing similar models for organisms of higher complexity.

## Diamond Etching for Atomically Flat (111) Surfaces

**Soyoun Choi**
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Diamond is known for its superior physical and electronic characteristics. Due to its high chemical stability, plasma processes are usually used for diamond etching. The downside of this method is the deterioration of device performance from defects created in the diamond surfaces and subsurfaces. Surface roughening from this process is also problematic. For future electronic device developments in diamond, it is vital to have smooth, low density substrate materials for utmost device performance. Compared to the etching process of conventional semiconductor materials, processing technologies associated with plasma-etching diamonds remain immature. Thus, the goal of this research study is to experimentally identify the ideal temperature and method of diamond etching. Diamonds used in this experiment were SC Macle Type 1b diamonds (4.0 x 4.0 x 3.0 mm, 1.0 mm thick). These samples were grown by the High Pressure High Temperature (HPHT) synthesis processes. Specifically, using these diamond samples, two types of etching tests were performed. Ni-catalyzed etching in $H_2O$ vapor was applied to the first cohort. This method is a form of anisotropic diamond etching through the thermochemical reaction between Ni and diamond in high temperature water vapor. Bare diamond etching in $H_2O$ vapor was applied to the second cohort. Each tested diamond had its own unique defects, so both temperature and defect interactions were observed in each test group. The objective was to identify the etch rate at different temperatures and determine how unique defects of each diamond sample affect the etch rate. Based on results, it was found that bare diamond etching in $H_2O$ vapor without depositing nickel at the temperature of 1000 °C results in the smoothest form of etching. More specifically, large defects etching and round pitting were suppressed at 850 °C. Various confounding variables remain for further investigation. Diamond is a wide-bandgap semiconductor material for next-generation high-power, quantum, chemical electronic, and optoelectronic devices which makes this research valuable for future development.

## Automating Evolutionary Distance Computation to Interpret Homology Search Error Detection

**Frank D'Agostino**
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*Mentor:* Caroline Weisman

Sequence homology searches with computational tools like BLAST and HMMER are fundamental, but there is a limit to the power of any homology search tool to successfully find homologs. When homologs are not detected, there remains a question of how to interpret this absence; for example, a lack of detectable homologs in species outside some clade is often interpreted as support for de novo origination of a gene. A new computational method from our lab, abSENSE, determines the probability that a homology search program is expected to fail to find an ortholog for a given gene simply from expected lack of search sensitivity (e.g. for rapidly evolving or short genes). Currently, abSENSE requires user input of precalculated evolutionary distances between the source and target species, and the original paper only precalculated distances for two well-studied clades (yeasts and *Drosophila*). Here, we developed a fully automated method to precompute the necessary evolutionary distances among any set of input species. This method identifies available protein annotations from reference databases, locally downloads the necessary files, identifies well-conserved genes, and uses them to calculate the desired evolutionary distances. This addition makes it easier to apply abSENSE analyses to different target species genomes.

## Robust Quantile Regression in Financial Markets

**Aditya Dhar**
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*Mentor:* Scott Kominers

The celebrated quantile regression Koenker-Basset estimator is used to estimate the conditional quantile of a feature variable rather than the mean. Despite quantile regression models being used when conditions of linear regression such as homoscedasticity and linearity are not met, they, like other traditional financial econometrics, deteriorate under thick tailed predictors. This paper proposes a robust estimator of the linear quantile model that is simple to compute under existing software and has a bounded influence function, making it less vulnerable to non-Gaussian conditions frequently found in financial markets. This paper describes statistical properties of this estimator, empirical results when this estimator is applied to markets, and several extensions. Specifically, we provide novel methods to make regression differentially private, a mathematical privacy tool that ensures individuals are not identifiable when data analysis is performed. Moreover, we discuss how thick tailed predictors affect traditional economic models that assume normality, focusing on how financial market equilibria change. The results of this research are particularly useful in developing stronger predictive techniques in finance and social sciences more broadly, where privacy is of greater concern.

## Neoadjuvant Immunotherapy and Chemoradiation Followed By Esophagectomy for Esophageal Cancer: A National Analysis of Short- and Long-Term Outcomes

**Beverly Fu**
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*Mentor:* Nikhil Panda

Treatment of locally advanced esophageal cancer includes neoadjuvant chemoradiation followed by esophagectomy. It is unclear whether the addition of neoadjuvant immunotherapy to current induction regimens is safe. We evaluated the perioperative and oncologic outcomes of patients who underwent neoadjuvant immunotherapy and chemoradiation (chemoRT+I/O) followed by esophagectomy for esophageal cancer. Adults who underwent esophagectomy following neoadjuvant chemoRT (without immunotherapy) or chemoRT+I/O for T1-4, N0-3, M0 esophageal cancer were identified from the National Cancer Database (2010-2018). Unadjusted, propensity-score-matched, and Cox proportional hazards analyses were used to compare perioperative outcomes and three-year overall survival (OS) between patients who underwent esophagectomy following neoadjuvant chemoRT versus chemoRT+I/O. Factors associated with receipt of neoadjuvant chemoRT+I/O were identified using the lasso penalized logistic regression estimator. Among 14,065 patients, 158 (1.1 percent) received neoadjuvant chemoRT+I/O. ChemoRT+I/O patients had larger tumors with predominantly adenocarcinoma histology. Factors associated with the receipt of chemoRT+I/O included younger age and year of diagnosis. There were no differences between the chemoRT and chemoRT+I/O cohorts regarding lymph nodes resected, margin positivity, 30-day readmission, 30-day mortality, 90-day mortality, and 3-year OS. A propensity score-matched analysis of 226 patients showed a greater proportion of nodal upstaging among chemoRT+I/O patients, but no differences in short-term outcomes and 3-year OS between cohorts. In conclusion, recent data supports the feasibility of adding immunotherapy to induction regimens; however, further evidence is needed regarding the impact on long-term oncologic outcomes.

## Investigation of Novel Matching Models with Complex Preferences

**Andrew Garber**
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*Matching theory* studies how agents can match to each other given their preferences over one another. This field has been instrumental in the design of the program used to match medical residents to hospitals in the United States, as well as school choice programs all around the world. We investigate two problems in matching theory. First, we examine matching markets in which agents have complex preferences over contracts with prospective match partners. For example, when firms hire workers, the workers have preferences not only over the firms they wish to work for, but also over the salaries they receive. It is a well-known result that a *stable matching*—a matching of firms and workers to contracts such that no workers or firms have an incentive to strike deals outside the matching market—need not exist given arbitrary firm and worker preferences. Previous literature has derived restrictions on firms' preferences that guarantee the existence of a stable matching in matching markets with contracts. We instead tackle the problem from the other side: We prove that if workers' preferences are *harmonious*—roughly, that they agree on a ranking of the firms—then a stable matching exists regardless of the firms' preferences. Moreover, harmonious worker preferences are necessary for there to always be a stable matching. These results expand the set of necessary and sufficient conditions for stable matchings to exist in matching markets with contracts. Second, we examine elections in which candidates run for multiple positions as a problem in matching theory. For example, in club elections, candidates might run for both President and Treasurer. A problem is to determine good—that is, less manipulable—ways to match candidates to their and the voters' preferred positions. The inclusion of a vote introduces novel strategic incentives to such markets, depending on the design. For example, candidates can improve their chances of obtaining their preferred positions by running for positions they do not want, e.g., by splitting the vote in other elections. Improved designs can thus lead to more robust and transparent elections.

## Development of Multivariate Statistical Models for the Cross-Sectional and Longitudinal Analysis of Microbiomic Data in Infants at Risk of Celiac Disease

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Celiac disease (CD), a long-term autoimmune disease characterized by the inability to consume gluten due to resulting damage to the small intestine, affects millions of individuals, young children in particular, around the world. Many factors contribute to the development of CD, including genetics; environment; bacteria in the gut, more formally the gut microbiota; and metabolites. The Celiac Disease Genomic Environmental Microbiome and Metabolomic Study is a prospective longitudinal cohort study at Massachusetts General Hospital that follows infants from birth through five years of age, collecting numerous biospecimens and data from the host and their gut microbiome; in particular, fecal samples undergo metagenomic sequencing and metabolomics to profile microbes, pathways, and metabolites present in each sample. Analysis of this data unleashes the potential to evaluate the role of pre-disease gut microbiota alteration, on the establishment of autoimmunity characteristic of CD. However, few statistical models and methods exist for the longitudinal analysis of microbiomic data while taking relevant covariates and matched case-control pairs into account. Thus, it becomes essential to develop new statistical models for the multi-omics cross-sectional and longitudinal analysis of microbiome data, utilizing linear mixed-effect models. These models allow for seamless adjustment of groupings, covariates, and other dependencies, to subsequently infer longitudinal patterns in each microbiome feature and unravel the links between features both cross-sectionally and over time. Building these statistical models ultimately helps shed light on how the gut microbiome and metabolome contribute to the development of CD, to better streamline the identification of pre-onset biomarkers of CD in the gut microbiome and thus allow for the development of targeted CD prevention and intervention strategies. While CD was used as a paradigm in this study, these models can be further applied to study the role of gut microbiota in all other diseases.

## Reinforcement Learning Drift Diffusion Modelling and Links to Neural Data in Clinical v. Healthy Groups

**Sanjana Ramrajvel**
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Modeling at the intersection of behavioral and neurological processes is the future of treatment for psychiatric disorders. Currently, the standard diagnostic/classification system for mental disorders, DSM-5, is largely description-based and can often over-simplify the complexity of human behavior; data analysis in this field can allow us to shift towards more targeted treatment methods. We were particularly interested in how the decision-making process works in the brain, and how this might look differently for individuals with symptoms of depression. The two types of models we used to analyze our choice experiment data are the reinforcement learning (RL) model, which assumes the brain codes and updates expected values of choice based on a reward prediction error, and the drift diffusion model (DDM), which assumes evidence accumulates in the brain until a certain decision threshold is reached. However, individually, RL models tend to underestimate the choice process by failing to account for reaction times, and the DDM struggles to describe learning over time. In our study, we showed that a combination model, where the DDM is used as the choice rule for the RL model, produces a better fit for our data than either of these models alone. Going forward, we aim to identify associations between the neurological processes and behavioral outcomes by using regression modeling with our reinforcement learning drift diffusion model parameters, as well as EEG and fMRI data collected during these choice experiments to better understand the relationship between brain activation and resulting behavior. Specifically, we are looking to study these processes in individuals with varying BDI (Beck's Depression Inventory) scores by splitting our dataset into subgroups based on the severity of depression symptoms. This could allow us to establish a relationship between dysfunction in a cognitive or motivational process and the underlying neural mechanisms.

## Morphological Metrics for Generative Design

**Howard Timlin**
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*Advisor:* Andrew Witt

Generative design is a new field of computational design where machine learning is used to generate novel figures and design motifs from existing datasets or reference material. Generative design applications typically work by training a generative adversarial network to produce a landscape of convincing examples interpolating between the points of a given dataset. Then, traversing this landscape around points of interest reveals new designs consistent with the imputed dataset. However, this landscape typically exists in very high dimensional space and is often fraught with garbled or otherwise unusable outputs. Researchers at the Harvard Graduate School of Design are working to alleviate these issues for generative design of 3D figures by leveraging tools from topology and the study of 3D shape comparison. By synthesizing different notions of shape from these fields, researchers have been able to compute a variety of descriptors summarizing important geometric properties of three-dimensional shapes. They are working to use these descriptors to train and organize the output of the *shapegan* generative adversarial network with the ultimate goal of developing a plugin for the *Rhinoceros 3D* computer-aided design software allowing designers to efficiently generate novel designs with specific geometric properties consistent with the imputed dataset. This software serves as a step towards a future where machine learning seamlessly augments creativity and enables designers to conceive of new forms with unprecedented speed, ease, and efficiency.

## Lost in Translation

**Ethan Wang**
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*Mentors:* Yifei Wei, Kyle Schirmann

Scientific research on a global scale, accelerated by the connectivity of the Internet Age, has led to many technological innovations. However, the fact that English is the de facto language of scientific communication may disadvantage ideas from non-native English-speaking countries. Not only do scientists from these countries need to learn English in the first place, but non-native speakers may also find it more difficult to proficiently write up their ideas in English. Poor writing might mask good ideas. As a consequence, we expected differences in writing quality to partially explain why researchers from non-English-speaking countries–especially developing countries–received far fewer citations to their academic articles than scientists in English-speaking regions. To test this idea, we gathered over 10,000 research papers from PubMed and then used Grammarly's AI writing tools to estimate writing quality scores for these articles. While we find a robust association that native English-speaking scientists have higher writing quality scores, we find no relationship between writing quality and future citations. Our regressions accounted for factors such as word count, publication journal, year, country of origin, Medical Subject Heading classification, and research funding type. In addition, we utilized Natural Language Processing techniques like Latent Dirichlet Allocation, Term Frequency–Inverse Document Frequencies, and Weighted Log-Odds Ratios to account for the impact of certain words or topics on the regression. In the end, our results demonstrate that there is no significant positive relationship between writing quality and paper citation count in biomedical research topics. This is an important result because it shows biomedical innovations from non-English-speaking countries are rarely or minimally underrepresented due to discrepancies in writing ability. A promising area of future research may be to apply similar analysis techniques to other academic fields, both STEM and non-STEM, to see if this null result holds elsewhere.

## Real-time Monitoring and Forecasting Dengue Activity at Multiple Spatial and Temporal Resolutions Using Novel Data Sources, Machine Learning, and Ensemble Approaches

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*Mentors:* Lucas M. Stolerman, Leonardo Clemente

Dengue fever is a mosquito-transmitted viral disease that has become a leading cause of death and hospitalization in many tropical countries. Currently, many countries' public health departments lack access to timely and accurate surveillance reports on Dengue fever outbreaks. For this reason, Dengue forecasting models using diverse data sources are a potential solution for providing policymakers with more accurate understandings of the true Dengue incidence in their regions. In this project, we study the individual performances of several models designed for Dengue activity prediction in provincial and city-level locations at both weekly and monthly time horizons. Specifically, our modelling techniques include a novel dynamically-trained Susceptible-Infected-Recovered (SIR) model, a Seasonal AutoRegressive Integrated Moving Average (SARIMA) model, and an AutoRegressive with GOogle search queries as exogenous variables (ARGO) model. All of our models are trained on historical Dengue incidence, and the ARGO model is also trained on Dengue-related Google search query frequencies. For certain locations, preliminary results suggest that our individual models can predict Dengue incidence with 20 percent - 30 percent less error than a baseline naive persistence model at monthly time horizons. Next, we construct ensemble approaches combining input from all three short-term forecasting models to generate more accurate and robust predictions. We explore the extent to which the voting ensemble approaches are capable of further reducing prediction error in comparison to individual forecasting models, and we study their ability to deliver stable estimates. Future work includes combining our short-term individual and ensemble models with mid-term climate-based forecasting models to predict Dengue activity at longer time horizons.

## Quantifying Data Quality for Estimating Population Extremes

**Jason Zhou**
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*Advisor:* Xiao-Li Meng

As we delve deeper into the digital age, it becomes increasingly critical to understand the effect of data quality on our statistical results. This project extends the work by Meng (2018, *Annals of Applied Statistics*) on quantifying data quality from estimating population averages to population extremes, essential for understanding risks of extreme events, such as major financial crashes or devastating natural disasters. Estimators for extremes are mathematically more complicated because they are nonlinear functions of data. Nevertheless, we found a novel identity via data spacings that parallels the critical identity given in Meng (2018), decomposing the estimation error into three main factors: data quality, data quantity, and problem difficulty. This new identity allows us to examine how sampling schemes affect the estimation error through both data quality and data quantity. We provide explicit results for special cases, such as the benchmark of simple random sampling without replacement. Through both theory and simulation, we also compare the estimation of extremes to the estimation of means. Collectively, these results shed light on what affects the estimation error of extremes, and how intuitions based on data size alone can be very deceptive.

# COMPUTER SCIENCE

## Verification of Differentially Private Algorithms

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*Mentor:* Michael Shoemate

The notion of differential privacy, as first introduced by Dwork et al. in 2006, constitutes a rigorous mathematical definition of privacy. Informally, an algorithm is "differentially private" if, by observing the output, an outsider cannot distinguish whether or not any particular individual's data was included in the original dataset. Differentially private tools can be used for releasing public statistics about sensitive data and quantifying the incurred privacy loss. Since its inception, differential privacy has become a very active research area spanning multiple disciplines, from cryptography to law. In recent years, several community efforts have emerged to bridge the gap between theory and practice in the field of differential privacy. One such effort is the OpenDP project, which is currently building trustworthy software tools for the analysis of sensitive private data. These include an open-source library of differentially private algorithms aimed at practitioners. However, beyond their code implementation, such algorithms require an accompanying proof that demonstrates their utility and privacy guarantees. To that end, we provided mathematical proofs for the different algorithms implemented in the library, as well as a contributor proof guide and similar supporting documents for future code contributions. Our proofs follow a unified treatment when developing notation and mathematical techniques. This lays the groundwork for OpenDP to have a systematic proof verification process, with a hybrid of human and machine verification confirming the correctness of more complex algorithms built with and contributed to the library.

## Understanding the Geometry of ICU Data

**Zad Chin**
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*Mentor:* Peniel Argaw

Various machine learning models have shown that a patient's vital sign in the first 48 hours of admission has a significant effect on readmission and mortality in intensive care units (ICU). However, many of these models did not explicitly explore the importance of those vital features in contributing to higher readmission or mortality rate. Our work proposes a new framework in understanding the geometry of ICU data with the goal of recognizing unique patient trajectories in the first 48 hours of admission that leads to negative outcomes such as readmission and mortality. A total of 10,184 patients in ICU are sourced from comprehensive, longitudinal clinical data from the MIMIC-III, a health-related Electronic Health Record data of more than 40,000 patients in the Intensive Care Units (ICU) of the Beth Israel Deaconess Medical Center between 2001 and 2012. The seven common features related to readmission and mortality that were included are respiratory rate, heart rate, mean blood pressure, sodium, creatinine, fraction inspired oxygen, albumin, bilirubin, blood urea nitrogen and hematocrit. We then used density-based spatial clustering of applications with noise algorithm to cluster the patients with varying numbers of features. Initial findings from the algorithm indicated that the data might not consist of clusters. We further investigated the data by plotting the number of connected components against varying features, epsilon values, and methods of standardization. The results suggested that the highly-dimensional data is sparsely related, and presents itself in the form of spectrum rather than clusters. Future work concerning deeper analysis on the geometry of ICU data with different methods and algorithms would make for valuable contributions in augmenting clinical decision-making for ICU specialists.

## Deep Reinforcement Learning for Atari Economics

**Matt Fu**
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*Advisor:* David Parkes
*Mentor:* Matthias Gerstgrasser

Atari games, such as Space Invaders, have been used as a benchmark for an AI technique called reinforcement learning, which allows an AI to independently discover how to accomplish tasks such as playing a video game. Space Invaders can be converted into a multiplayer environment by running multiple games concurrently; this environment serves as a useful condition through which one can understand resource allocation mechanisms in dynamic environments with both AI and human participants. The goal of this work is to enable this *AtariEconomics* framework to serve as a benchmark for understanding these kinds of allocation problems, and, in turn, examining multi-agent behaviors together with suitably optimized mechanisms. We show that the PyTorch and TensorFlow frameworks are able to suitably train agents in our custom environments, which were altered for this multi-agent setting. By building PyTorch models we are able to use RLLib to explore Deep Q-learning, Rainbow, and other Q-learning variants in our custom environment. The creation of our Torch models also opens up the future exploration of state of the art Ape-X and QMIX algorithms and opens up new directions for multi-agent reinforcement learning.

## Who is Most Vulnerable? Causal Inference and Machine Learning Approaches to Estimate Health Effects and Health Care Costs of Air Pollution in the United States.

**Daniela Garcia**
SPUDS Fellow
Statistics, 2024
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Causal subgroup identification is a powerful statistical tool for determining vulnerabilities in a population with respect to a particular treatment or environmental agent. For example, in the context of exposure to air pollution or climate change related disasters, we want to identify the subgroups most or least vulnerable to a policy intervention. As causal inference and machine learning provide an efficient and accurate means for data-driven subgroup identification, software packages are proving an essential tool to broadly disseminate and reproduce these algorithms. As a result, we wrote the "CRE" R Package, which implements the Causal Rule Ensemble (CRE) algorithm, a flexible and interpretable method for denovo subgroup discovery. The CRE approach focuses on identifying drivers of treatment heterogeneity in observational or randomized studies in the presence of an intervention. The R package we developed is centered on one function, cre(), that implements the entire CRE algorithm given a dataset and a series of input parameters from the user. For example, for the estimation of Individual Treatment Effects, users can select from a list of methodologies that vary with respect to their speed and precision, such as Bayesian Causal Forests or Bayesian Additive Regression Trees. The cre() function then calls on a number of our helper functions to conduct discovery and inference subsample analysis. The final output of the cre() is a list of selected causal rules that identify the subgroups with higher effect heterogeneity and a matrix of estimated Conditional Average Treatment Effects for each rule. We intend to apply the method to a dataset linking air pollution (PM2.5) data to Medicare mortality data across the United States. Our overarching goals are to identify the most vulnerable communities, inform policymakers on how to mitigate the negative health and economic effects on these subgroups, and reduce inequality.

## Earthquakes and Oil Production at the Wilmington Oil Field: a Coupled Flow and Geomechanics Model

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While earthquakes have long been attributed to tectonic processes and natural stress changes underneath the Earth's surface, there is reason to believe that anthropogenic, man-made triggers may be responsible for some seismic activity. Fluid injection related to oil and gas production, geothermal energy extraction, and carbon capture and storage (CCS) are activities potentially causing subsurface stress changes and inducing earthquakes. In this project, the area being studied is the Wilmington oil field in the Los Angeles Basin, which overlays the Wilmington thrust fault capable of inciting strong earthquakes of magnitudes 6.3 to 6.4. The goal is to determine the effect of Wilmington oil production and water injection on the stability of pre-existing geological faults. Studying this could demonstrate whether such sub-surface changes pertaining to fluid pressures are affecting seismicity, while also informing energy policies. We are building a coupled multiphase flow and geomechanics simulation in MATLAB to model Wilmington's historical oil production and water injection, utilizing data from 1936 to 2020. The overarching model is coupled because changes in reservoir rock pore pressures cause changes in its volume that can induce normal/shear stress changes along the Wilmington fault (multiphase flow fluid dynamics model). Together, the changes in fluid pressure and stress could trigger earthquakes, and may also cause vertical motions of the ground surface. We intend to determine the impact on the reservoir rock's pore pressures and deformation; additionally, we aim to look at how the changes in shear and normal stresses along the Wilmington fault compare with the maximum fault strength, thereby analyzing the stability of the fault overtime.

## Remote Protein Homology Detection Using Locally Enriched Transformer Models

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One of the central problems in computational biology is the identification of *homologs*, which are evolutionarily related biosequences that often share elements of conserved structure and function across species. Of particular interest are highly-diverged sequences called remote homologs, which capture very ancient evolutionary trajectories. Modern homology search tools such as HMMER and BLAST help scientists link novel sequences to known homologous sequences, providing insight into structure and function. Yet due to inherent context-simplifying assumptions that make inference more tractable, these tools can struggle to identify more elusive homologs such as remote homologs with low sequence similarity. We developed a sequential-context based approach, based on the novel Transformer model from natural language processing, to detect these remote homologs. We designed and implemented several deep neural network models using the Transformer architecture to learn representations of "local context" within proteins. Using a masked-language modeling task, we trained these models to encode salient features of each residue's local environment, such as the complex physicochemical interactions in the native tertiary structure. The resulting contextual features were fed into a downstream Transformer model to produce global embeddings of each protein in high-dimensional Euclidean space, and a standard dynamic-programming pipeline was used to align similar sequences and identify homologs. We observed promising initial results from validation on alignments in the Pfam database. Ultimately, we envision that machine-learning models incorporating sequential context will represent the next generation of homology search tools.

## Conformal Inference in Batched Bandits

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We consider uncertainty quantification in the setting of batched bandits of batch size $n$ and time horizon $T$ by constructing distribution-free prediction intervals at test-time (i.e., prediction intervals of the reward of a single batch element at time $T+1$). We first extend the paradigm of conformal inference under covariate shift [Tibshirani et al. (2020)] to the most general setting in which the joint distribution over covariates may be arbitrary—rather than having to be exchangeable within train and test datasets—and then apply our extension to batched bandits to construct a conformal band for the next time-step. We then show that, surprisingly, the quality of conformal inference (even in non-bandit settings) is severely degraded if the distribution of non-conformity scores is too light-tailed. Additionally, we show that exact computation of conformal bands in batched bandits in $poly(n, T)$ time across the class of all bandit policies is impossible unless $\#\mathbf{P} = \mathbf{FP}$ (which would imply $\mathbf{P} = \mathbf{NP}$). Thus, we resort to randomized algorithms to construct the conformal bands, empirically demonstrating via simulation that a combination of Simple and Importance Sampling Monte Carlo algorithms enjoy at most quadratic sample complexity across various local asymptotic regimes on the reward margin in bandit algorithms including $\epsilon$-greedy, explore-then-commit, Thompson Sampling, and UCB1.

## Uncovering Genetic Privacy Risks in Gene Expression Data

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A genetic sequence is a unique identifier of individuals and can reveal potentially sensitive information about their traits, such as disease susceptibility. Recent advances in sequencing technologies and molecular assays have led to an explosion of functional genomic datasets such as gene expression and epigenetic profiles. Despite strict policies regarding the privacy and responsible sharing of genomic and health-related data, the biomedical community lacks an understanding of the extent to which one can reveal sensitive genetic information from functional genomic data, such as gene expression profiles, which are often publicly shared. In this project, we develop a model for predicting individuals' genotypes from their publicly available gene expression profiles and explore its predictive power. Our model leverages information from large public reference panels of genotypes to refine posterior probabilities at sensitive genotype positions. Specifically, we (1) train an ordinal regression model to predict a subset of the genome and (2) separately train a hidden Markov model to impute the rest of the genome, using the public reference panel as the set of hidden states for this model. We show that certain regions of the genome are easier to predict than others—namely that those with higher density of correlated SNPs (eQTLs) are easier than less dense regions. We further show that off-the-shelf imputation software is not well suited for our task, and, as such, explore our own imputation and posterior refinement methods leveraging the public reference panel. On a holdout set of 292 anonymized genotypes and gene expression profiles, our method is able to reidentify a greater percentage of people (67 percent) than previously published methods, suggesting a need for stronger regulations for genomic data sharing. We are now exploring stronger models to perform imputation and prediction jointly, as well as mitigation strategies for future data releases.

## Verifying Differentially Private Transformations for OpenDP

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Data scientists work with large-scale sensitive data, which inevitably leads to privacy risks. Differential Privacy (DP) is a mathematical definition of privacy that aims to mitigate privacy risks inherent in data analysis and machine learning. DP is a rapidly growing field adopted by the industry and government (Apple, Facebook, Census) yet there lacks a generalizable implementation that is usable to the general public. OpenDP, an open-source software DP tool, allows the government, industry, and academic institutions to share sensitive data to researchers or the public while preserving privacy. To ensure that the OpenDP code is trustworthy to the public, we proved the correctness of basic functions, whose privacy properties extend to more complex DP programs. A transformation, which is one of the essential building blocks of complex DP programs, is a deterministic function from datasets to datasets. In this paper, we prove the correctness of fundamental OpenDP transformations (is_equal, impute, row transform) with mathematical analysis and statistics. Our approach can be extended to ensure the validity and mathematical properties for randomized DP transformations.

## Predicting Chemical Skin Permeability with Molecular Graph Encoders and Transformers

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Accurate prediction of the permeability of chemicals through the skin is critical to advancing the potential of transdermal drug delivery and improving the safety of cosmetics. Current models for predicting permeability face difficulty generalizing to new chemicals due to their reliance on simple mathematical and statistical models and small sets of heterogeneous data with little consideration of varied experimental protocol. Deep learning approaches such as directed-message passing neural networks (D-MPNNs) and graph neural network transformers (GNN transformers) have shown promise in various molecular property prediction tasks, including in limited data settings, and have yet to be applied to skin permeability. In this study, we compiled an expanded dataset of skin permeability coefficients ($\log K_p$ values) alongside experimental condition data. With our dataset, we identified appropriate $\log K_p$ thresholds for aggregating permeability data from separate experiments. We evaluated a collection of baseline models on the aggregation thresholds and compared their accuracy with deep learning model architectures, using root mean square error (RMSE) as an evaluation metric. Our findings suggest that the optimal $\log K_p$ aggregation threshold for a given chemical is $\pm 0.8$ from its mean $\log K_p$. Of the architectures evaluated, random forest with D-MPNN graph encodings plus experimental information performed on par with random forest with molecular fingerprinting, outperforming random forest with only graph encodings and supervised D-MPNNs (GNN-ERF-0.75, RF-0.75, GNN-RF-0.84, D-MPNN-0.77). Though the small dataset size limits the D-MPNN's ability to generalize, graph representations of molecules with experimental data appear to be a promising alternative to molecular fingerprints. To address these limitations, we are investigating the efficacy of self-supervised GNN transformers, pre-trained on a large corpus of chemicals and fine-tuned on our $\log K_p$ dataset. Ultimately, our goal is to create an optimal ensemble of models to accurately screen a large dataset of small-molecule drugs for transdermal delivery potential.

## Analyzing COVID-19 Indirect Impact on High-Risk and Low-Income Communities Based on Hierarchical Linear Models

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With ramifications extending far beyond the economy and medical system, the COVID-19 pandemic has uprooted traditional priorities and shifted efforts towards urgent care for patients with the disease. Surges of COVID-19 infection cases can cause hospital overcrowding and lead to delays and cancellations of the health care for non-COVID patients, which could result in complications and even fatalities. Less evident is the specific effect of the pandemic on patients in low-income communities and/or who suffer from underlying conditions; in such cases, individuals may be unable or hesitant to receive in-person routine treatments due to decreased access to treatment and increased concern over contracting COVID-19. To better understand this effect, we carried out a statistical analysis to determine the extent to which the medical treatment of patients with underlying conditions and in areas with high income inequality has been disrupted by the COVID-19 pandemic. Analysis using hierarchical linear models with data from 7696 hospitals across the US indicated that the frequency of in-person treatment relates closely to the Gini Coefficient, a measure of income inequality of a region, in such a way that the average distance traveled by patients to hospitals increased by 1226.6 meters for every 0.1 increase of the Gini Coefficient between 2019 and 2020. In addition, we found that during the period there were on average 225.6 fewer visits to each hospital for every 0.1 increase in Gini. These results were robust, not changing significantly even after considering other factors including random variation between states and counties, percent of ethnic minority groups, median household income, and percent with health insurance. Together, these results suggest that factors like income inequality and underlying conditions may exert a meaningful influence on individuals' treatment patterns, health, and subsequent medical access following the onset of epidemics like COVID-19 in the US.

# ENGINEERING SCIENCES

## Understanding Immunization in South Africa: Qualitative Analysis of the Road to Health Application

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More than one million children are born in South Africa (SA) every year with the hope that they can grow up with equal opportunities for health and success. Unfortunately, inequities persist for these children, limiting their ability to achieve a healthy lifestyle and leading to detrimental economic, physical, and educational outcomes. By providing interventions that address health equity, the playing field can be made more level by expanding access to success, happiness, and health for children from all backgrounds. The Road to Health program is a key intervention available to babies upon vaccination in SA. The Road to Health booklet is used from birth to ensure safety from disease, record vaccinations, and measure healthy growth via weight and height. The Road to Health Application (RTHA), previously in booklet form, now exists as a digital application that facilitates interactions between healthcare services and caregivers, provides safe, reliable childcare information, and allows for easier updating and viewing of childrens' health records status. This digitization of the progress made by the physical Road to Health booklet mitigates the risk of loss of paper booklets and may help address some other challenges to immunization in the African region. Although the RTHA is available for wide-scale use, additional work is required to assess user feedback that will inform marketing, increase the number of active users, and improve health outcomes, especially for children. To ensure a user-engaged approach this study surveys existing and future users of the RTHA using serial interviews to identify potential areas for improvement of the application. The results of this study will guide application developers to improve the RTHA, inform policy around resources to achieve comprehensive immunization in SA, and contribute to existing knowledge about the Road to Health program's effectiveness.

## 3D Organoids for the Study of Esophageal Cancer

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Despite considerable advances in research and oncology, survival for esophageal cancer remains poor, with 5 year survival approximately 20 percent. Esophageal cancers are mainly divided among two subtypes: squamous cell carcinoma and adenocarcinoma. In the latter case, chronic gastroesophageal reflux disease (GERD), including both acid and bile reflux, and the development of Barrett's esophagus are risk factors for its development. Despite these known risk factors for the development of esophageal adenocarcinoma, it is still unknown what mechanism underlies this transition into cancer. Both animal models and 2D monolayer cultures have been used to study molecular pathways involved in this process, but both have their own kinds of restrictions. Mouse models, although helpful, lack some physiological relevance due to anatomical differences between the murine and human upper gastrointestinal tract. 2D monolayer cultures have also been at the core of many studies, but are unable to fully recapitulate the interactions between cells and the environment of the esophagus in a way that mimics that of a patient. As a solution, 3D cell culture methods in the form of organoids can be used to remedy the shortcomings of both of the previously mentioned approaches, allowing for more faithful modeling by reproducing the various epithelial cell layers and innate intracellular signaling of the native esophageal stratified squamous epithelium. Studies on the effects of GERD, and the consequent chronic exposure of esophageal cells to acid and bile salts, in 3D organoids could thus reveal key insights into the development of esophageal cancer in the setting of chronic reflux.

## Design of a High Compliance, Semi-Rigid Joint for Exosuit Applications

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Soft robotics in the form of exosuits has emerged as a powerful technology to assist the movement of individuals with motor disabilities, such as those post-stroke or with cerebral palsy, as well as augmenting people's normal functioning to lower the metabolic cost of locomotion and assisting with repetitive motions found in daily life. Current cable-driven soft exosuits augment locomotion by pulling in parallel with muscles beneath the suit interface, allowing for low-profile construction. However, these suits are anchored to soft tissue rather than a rigid skeleton, resulting in hysteresis and high compliance issues. As such, they often need to be tightened to an uncomfortable degree to overcome shear forces, decreasing usability and practicality for long term use. In this project, we aim to explore novel flexure designs to limit the shear forces experienced by the user and to maintain the low profile of current exosuit designs while implementing benefits found in hard exoskeletons. Current flexure designs focus on low-range of motion, high precision applications which do not allow for the compliance or range of motion necessary for use in an exosuit. We propose an experimental prototype of a novel high compression compliant mechanism (HCCM) designed specifically for application on the hip joint, allowing for 180° of rotational motion in flexion-extension and 45° of rotational motion in abduction-adduction while resisting translational forces both horizontally and vertically. We observe promising results in simulated CAD modeling, dimensional analysis, and real world prototype analysis, with the preliminary design achieving full range of motion in flexion-extension and tensile force loads exceeding predicted load requirements. Initial findings show that the class of HCCM designs may be capable of movement in all degrees of motion while also supporting a hip extension-flexion force load greater than current exosuit systems. Further development of the design shows potential to expand the use of flexures in other applications requiring high range of motion and tolerance to high compression. Expansion in this joint design can allow for more transparent, more comfortable exosuits in the future.

## Machine Learning to Predict Antibiotic Mechanism of Action from Molecular Fingerprints

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Antibiotic-resistant bacterial infections are a rising threat to public health as the rate of resistance evolution outpaces antibiotic discovery. New antibiotics are ineffective if bacteria are already resistant to the mechanism of action, so antibiotics with novel mechanisms are needed to combat multidrug-resistant bacteria. Moreover, for newly discovered antibiotics, there is a need to characterize the mechanism of action before clinical development. However, experiments for elucidating antibiotic mechanisms of action are costly and labor-intensive. Recently, a deep learning model predicted antibiotics from molecular structure and discovered a broad spectrum antibiotic renamed *halicin*, so we hypothesized that machine learning could also predict and guide the experimental determination of antibiotic mechanisms of action. Thus, we trained shallow and deep multiclass classification models to predict eight major antibiotic mechanisms of action from molecular fingerprint representations of antibacterial compounds. We collected and labeled 2,835 antibiotics using the Shared Platform for Antibiotic Research and Knowledge database and other curated literature. The best model had high test accuracy (0.938), macro-averaged area under the receiver operating characteristic curve ($0.985 \pm 0.038$), and macro-averaged average precision ($0.957 \pm 0.114$). We performed t-SNE, Tanimoto similarity, and chemical scaffold analyses to examine the models' ability to generalize to new chemical spaces. Preliminary results show that a Gaussian process model outperforms random forest, support vector machine, *k*-nearest neighbor, and graph neural network classifiers. After validation with both external datasets and experimental mechanism determination, the best model can be deployed to characterize antibacterial compounds and enable faster development of antibiotics to treat drug-resistant bacteria.

## Conductivity, Uptake, and Water Activity of Nafion 117 Membranes Soaked in Donor Solutions of Potassium Hexacyanoferrates at Varying pH and Concentration

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Ever-increasing carbon emissions and the resultant climate catastrophe have created a massive need for innovation in the renewable energy space, specifically vast energy storage infrastructure to remedy the intermittency and unpredictability of wind and solar. In the last several years, aqueous redox flow batteries (RFBs) have emerged as a contender to meet this need. These batteries consist of aqueous electrolytes stored in external reservoirs and two electrodes separated by an ion exchange membrane. The electrolytes undergo redox reactions at each electrode, causing electrons to flow through an external circuit and ions to be transported across the membrane. Understanding membrane properties in an RFB, such as conductivity, water content, and electrolyte uptake, of the membrane in an RFB is critical to optimizing performance. For example, conductivity is influenced by uptake and water content, and in turn conductivity affects energy efficiency in a battery. In this study, Nafion 117 cation exchange membranes were equilibrated with donor solutions of varying pH and concentrations of both potassium ferri- and ferrocyanide, technologically relevant positive electrolytes in aqueous RFBs. Conductivity measurements were taken via electrochemical impedance spectroscopy using a Gamry 3000 potentiostat. Electrolyte uptake in the membrane was found via mass analysis and spectrophotometry. Higher electrolyte concentration in donor solutions was associated with higher uptake and, subsequently, decreased conductivity in Nafion 117. These results will aid future research, as this characterization allows other, potentially more effective membranes to be quantitatively compared to Nafion 117, the currently most widely used cation exchange membrane in RFBs. Furthermore, this will allow for electrolytes to be engineered to optimize RFBs which employ Nafion 117.

## Designing 3D Nanofiber Scaffolds to Promote Cardiac Tissue Infiltration

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In tissue engineering, researchers have used fiber scaffolds to mimic the extracellular matrix for culturing cells in a three-dimensional (3D) format. Scaffolds that are densely packed with fibers do not allow cells to integrate into the 3D structure, while loosely packed scaffolds will not form a single tissue. Our goal in this project is to maximize cell infiltration into gelatin nanofiber scaffolds by altering the porosity of the scaffolds, while still forming a single tissue. Here, we used focused rotary jet spinning to create scaffolds made of aligned gelatin nanofibers, and we adjusted the porosity of the scaffolds by incorporating porogens (soluble salts or sugars) during nanofiber spinning. The porogens were dissolved away after scaffold creation, leaving varying sizes and amounts of pores in the scaffold. We then seeded neonatal rat ventricular myocytes onto the scaffold and cultured them for 6 days. To assess cell infiltration and cardiac functionality, we performed contractile analysis and immunostaining on the scaffolds. If our hypothesis is supported, we will record increased contractility in scaffolds that have the correct pore size. We expect to see contractility increase as more porogens are added during scaffold creation and a decrease in contractility as the scaffold becomes too porous. Therefore, we will be able to find the porosity level that results in the strongest contractility, and we will quantify the cell infiltration at that level using immunofluorescent staining. Overall, this project will quantify cell infiltration into scaffold bases, where improved infiltration can lead to more physiologically relevant platforms for pharmaceutical testing and disease modeling.

## Ultrasound-Triggered Red Blood Cell Delivery of Thrombin to Induce Targeted Hemostasis

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Persons with hemophilia and other bleeding disorders suffer from inefficient blood clotting, resulting in excessive bleeding upon injury or damage. Thrombin, the final enzyme in the blood coagulation cascade, can directly cleave fibrinogen to clot blood. However, systemic delivery of thrombin to treat bleeding may result in lethal thrombosis such as pulmonary embolism. A noninvasive, targeted form of thrombin delivery is needed to treat bleeding in areas not easily accessible. To this end, red blood cell carriers were engineered to deliver a payload of thrombin upon targeted activation by ultrasound. Three separate methods of creating red blood cell carriers from human blood and thrombin were used and compared. An ultrasonic water bath was used preliminarily to activate the carriers. We show that thrombin is fully enveloped by the red blood cell carriers and that thrombin release can be triggered by ultrasound. Future work would involve *in vitro* coagulation assays in human plasma and *in vivo* studies in mice to evaluate hemostasis after injury.

## Generating Growth Factor Gradients to Guide Vascular Sprouting from Kidney Organoids

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Three-dimensional (3D) kidney tissue models have the potential to recapitulate human renal physiology *in vitro* for drug screening, disease modeling, and, ultimately, repair and regeneration. Recently, kidney organoids have emerged as a promising 3D model. While they possess an endogenous microvasculature, they are not addressable via perfusion *in vitro*. Here, we explore how growth factor gradients may be harnessed to direct vascular sprouting from kidney organoids to nascent blood vessels. We first created a microfabricated device for screening growth factors, which consists of a thin layer of gelatin-fibrin matrix onto which kidney organoids are seeded. The organoid-seeded gel is placed between two fluid reservoirs with different growth factor concentrations, giving rise to the desired gradient for stimulating cell migration and vascular sprouting. Preliminary results demonstrate the rapid formation of linear gradients across the organoid-seeded gel. Migration of cells from the kidney organoids into the gel is directly observed in the presence of a linear gradient of vascular endothelial growth factor. Ultimately, the results obtained from these experiments will allow one to identify the ideal growth factor type and gradients needed to promote vascular sprouting from kidney organoids used for drug screening and other applications.

## Affordable Static CT Scanner

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The computed tomography scanner is an important diagnostic tool used by physicians that allows for precise imaging of everything from internal wounds to cancers. However, access to this life-saving technology is limited due to the immense cost of such scanners, which can easily reach millions of dollars. This limited access leaves some developing nations with only 1 percent the number of CT scanners per million the US has. To address this disparity in access to CT-scanner technology, a low-cost CT scanner module was independently designed and prototyped. In order to create the X-rays a CT scanner needed for imaging, it was critical to have high voltage that can spark across a vacuum-sealed chamber. A receptor was also necessary to capture images. A voltage of approximately 120,000 V was generated using a power supply along with a ZVS driver and flyback converter, a translucent air-tight chamber suitable for a vacuum was developed using additive manufacturing, and an iridium spark plug and grounded metal bolt were used as electrodes. This was then connected to a vacuum pump. A scintillator screen was used to convert the X-rays into visible light that could be captured by a Raspberry-Pi-based camera system. This X-ray emitter-receptor device, with further development on the vacuum seals, would be able to capture one-dimensional X-rays of objects. Upon circular replication of this module, a highly robust solid-state CT scanner can easily be created that would cost much less than and also have comparable results to the CT scanners of today.

## Developing Improved Cognitive Testing for Identifying and Measuring Delirium

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Delirium is a state of serious mental disturbance often resulting in mental confusion and reduced awareness. In elderly patients in particular, the disease not only increases the risk of cognitive decline but can also lead to death. Although numerous methods to assist in diagnosing delirium currently exist, it continues to be underdiagnosed in up to 88 percent of patients. The implementation of current diagnostic methods is more or less limited to specialists and research protocols and usually requires patient history that is often unavailable to the clinician at the time of evaluation. This project ultimately seeks to iteratively design, test and refine a new diagnostic strategy for delirium consisting of tasks assessing various cognitive markers with rapid administration that requires minimal training.

Patients at the Beth Israel Deaconess Medical Center are being tested using the current version of the diagnostic tool. In addition, a subset of the tool evaluating memory was released on a wide scale to quantify the population baseline for cognitive memory.

While testing of this diagnostic tool is ongoing, current results have provided insight into how markers such as short term memory and attention in delirious patients compare with delirium free patients. In addition, these results are being used to validate and improve the current version of the tool using a numerical model previously developed by the team.

## Endolysin-Loaded Lipsomes as a Transtympanic Drug Delivery System for Otitis Media

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Otitis media (OM), an ear infection mainly caused by *Streptococcus pneumoniae*, affects millions of children each year. The oral antibiotics traditionally used to treat OM come with many side effects and are becoming less effective. This study investigates if liposomes loaded with MSlys endolysin, a protein found to have antipneumococcal activity, can act as an effective transtympanic drug delivery system to treat OM and other infections of the middle ear. Recombinant *Escherichia coli* was used to produce endolysin before it was labeled with fluorescein isothiocyanate. The protein was then encapsulated in two different types of liposomes, L alpha-lecithin and sodium cholate (L.SC) and L-alpha-lecithin & PEG2000 (L.PEG), and a permeation assay was performed, using Franz diffusion cells and porcine skin as a model of the hydrophobic tympanic membrane. After samples were collected at 24, 48, and 72 hours, their fluorescence was measured to determine protein concentration and their values were compared to a control sample of PBS. Results from the first study were not very consistent, but higher fluorescence measurements for L.SC and L.PEG samples may suggest that the liposomes are more permeable to the membrane than free endolysin, as expected. Because one of the L.PEG samples carried the most fluorescence, this may also suggest that L.PEG is more effective at delivering the drug than L.SC. In a second study, we're working to improve the results by increasing the concentration of endolysin in all samples and using thinner, more uniform skin samples. Along with this, next steps will include permeation assays with sheep tympanic membranes and, eventually, *in vivo* models with chinchillas.

# LIFE SCIENCES

# MOLECULAR AND CELLULAR BIOLOGY

## Antigen Based PET Imaging of CD19 CAR T-cells.

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Chimeric antigen receptor (CAR) T-cell therapy is the first engineered cellular therapy for cancer. CAR T-cell therapy has shown impressive results against hematologic malignancies. However, this targeted living drug therapy is still faced with several unknowns; CAR T-cells expansion and localization need to be closely monitored to prevent off target effects as well as to manage associated toxicities such as neurotoxicity. The improvement of CAR T-cell therapies is dependent on the ability to monitor their in vivo dynamics. Therefore, there is a need for monitoring of CAR T-cells to maximize the benefits of the therapy while minimizing its adverse effects. Current tools such as blood analysis are invasive and have limited monitoring capacity of T-cells relative to the targeted tumor. Immuno-positron emission tomography (immunoPET) imaging is a promising noninvasive platform for longitudinal monitoring of CAR T-cells and their localization relative to the targeted tumor. Here, we developed a CD19 PET imaging probe to monitor CD19-CAR T-cells. After designing the imaging probe, we expressed the ectodomain of the human CD19 in Escherichia coli (E. coli) BL21 cells and purified it. Then, we installed desferrioxamine (DFO), a chelator used to incorporate $^{89}$Zr for PET imaging, to CD19 using Sortase technology. Next, we PEGylated the construct to improve its solubility and decrease its immunogenicity. Our results showed that this construct can bind CD19-CAR T-cells. We have also shown that this imaging agent does not affect the activity of CAR T-cells. In the future, we will load the PEGylated CD19-DFO imaging probe with $^{89}$Zr and use it to image CD19-CAR-T cells targeting pancreatic ductal adenocarcinoma expressing human CD19 in mice. Antigen-based imaging of CD19-CAR T-cells would enable a rapid improvement of CAR T-cells therapies since it has a translatable protocol to other currently available and investigational CAR T-cells.

## Quantifying Rho3 Expression in the Obligate Human Parasite *Trichomonas vaginalis*

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Trichomoniasis is the most common non-viral sexually transmitted infection worldwide. With an estimated 200 million cases annually, this disease is caused by the obligate protozoan parasite *Trichomonas vaginalis*. This human parasite often harbors one or more trichomonasviruses, a genus of double-stranded RNA viruses of the family *Totiviridae*. These viruses persistently infect the parasite and are not typically cleared over extended times in culture. While viral infection appears benign to the parasite host, trichomonasviruses have been shown to exacerbate disease severity in the human superhost. Genes responsible for establishing and maintaining these persistent viral infections remain undetermined, and so we sought to measure differential gene expression between infected and uninfected parasites. Using publicly available RNA sequencing datasets, transcripts encoding a putative Rho3 homolog were identified as significantly upregulated in the presence of virus among the samples analyzed. Although not yet studied in *Trichomonas vaginalis*, Rho3 is well characterized in yeast species *Saccharomyces cerevisiae* as a GTPase that regulates the actin cytoskeleton and exocytosis. To further investigate the correlation between *rho3* transcript levels and trichomonasviruses, we extracted total RNA from uninfected, singly infected, and co-infected *Trichomonas vaginalis* isolates and are currently measuring *rho3* expression using reverse transcriptase quantitative polymerase chain reaction (RT-qPCR). If our initial hypothesis is supported, namely, that the presence of trichomonasviruses correlates with upregulation of Rho3, future studies can determine the role of Rho3 in viral infection. For instance, knockdown or knockout experiments of *rho3* using siRNAs or CRISPR-Cas9 could indicate if and how Rho3 is involved in antiviral or proviral mechanisms. Considering the impact of trichomonasviruses on human disease, we expect that unraveling the response of *Trichomonas vaginalis* to viral infection will help to elucidate the biology of an important human pathogen.

## Understanding the Neuronal Membrane Proteasome

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Protein homeostasis, or proteostasis, is essential for maintaining cellular health. In neurodegenerative diseases such as Alzheimer's Disease or Parkinson's Disease, failures of neuronal proteostasis can lead to deleterious outcomes such as protein aggregation or cellular death. One of the major regulators of proteostasis is the proteasome, a protein complex that breaks down polypeptides. Recently, the Ramachandran lab has identified a novel proteasome, the neuronal membrane proteasome (NMP). Dysregulation of the NMP has been implicated in several neurodegenerative diseases. The NMP is unique from other proteasomes in several ways, including its ability to degrade its substrates in a ubiquitin-independent manner and its activity's dependence on neuronal stimulation. To determine the mechanism that the NMP uses to break down proteins, we are generating endogenously tagged NMPs for purification and super-resolution imaging and measuring how NMP localization is modified in isogenic cell lines from patients with neurodegenerative disease. Once determined, the degradation pathway could be targeted in neurodegenerative disease to enhance degradation of potentially toxic protein species. This research explores an entirely novel process for regulating neuronal proteostasis, which could have broad implications for human brain health.

## Determining the Impact of *TSC2* Loss and mTORC1 Activation on Mitochondrial Dynamics

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Tuberous Sclerosis Complex (TSC) is an autosomal dominant disease characterized by tumors in multiple organ systems. TSC is caused by a loss-of-function mutation in one of two genes, *TSC1* or *TSC2*, and affects 1-2 million people worldwide. TSC mutations result in mTORC1 hyperactivation, thereby promoting cell growth, alongside changes in mitochondrial function. Based on preliminary studies, targeting aberrant mitochondrial metabolism holds promise as a TSC therapy. Thus, this project explored the impact of hyperactivated mTORC1 on mitochondrial dynamics *in vitro*. First, we overexpressed a mitochondria-targeted plasmid containing a hemagglutinin (HA) tag and a GFP sequence in HeLa cells. Then, we used CRISPR-Cas9 to knock out *TSC2* in these cells and confirmed that *TSC2* was successfully deleted using western immunoblotting. Low serum media conditions amplified mitochondrial morphology differences between control and knockout cells. After 0 and 24 hours of growth in this media, GFP-tagged mitochondria were imaged using confocal microscopy, and their morphology classified as fragmented, intermediate, or fused. Interestingly, we observed a significant 4-fold increase in the amount of fragmented mitochondria in *TCS2*-knockout cells compared to the wild type after 24 hours in low serum media ($p < 0.05$). To elucidate the mechanisms through which loss of *TSC2* leads to mitochondrial fragmentation, we used western immunoblots for mitochondrial dynamics proteins. In particular, we found that Aurora A kinase inhibition reduced the expression of the key mitochondrial fission protein *DRP1*. Furthermore, we optimized a mitochondrial immunoprecipitation protocol and isolated GFP-tagged mitochondria from HeLa cells by using anti-HA tag magnetic beads. We will validate the purity of the mitochondrial fraction with western immunoblotting and examine mitochondrial dynamics using proteomic and metabolomic approaches. This project will help reveal more about mitochondrial dynamics in TSC, and may lead to new strategies for TSC treatments.

## Exploration of the mechanism by which PACT inhibits PKR

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Protein Kinase R (PKR) is one of four stress response kinases that converge to phosphorylate the eIF2$\alpha$ pathway. PKR binds to double-stranded RNA as a defense mechanism against viral infection leading to activation of the eIF2$\alpha$ pathway which shuts down translation in the cell. PKR consists of two double-stranded RNA binding domains and one kinase domain. When double-stranded RNA is introduced into the cell, it binds to the double-stranded RNA binding domains and activates the kinase activity domain of PKR. PKR is active as a dimer, which has been a basis for hypothesizing experiments involving PKR. Through collaboration with the Gray lab, the Hur lab has been able to test conjugated inhibitors that, through proximity and binding affinity to PKR, can potentially activate PKR by helping to facilitate dimerization. Initial western blot analysis has not yet shown significant activation with these conjugated constructs.

## Investigating the Negamycin Biosynthetic Pathway

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Negamycin is a peptide-based antibiotic produced by bacteria that targets Gram-negative and Gram-positive bacteria by binding to ribosomal subunits and inducing miscoding. Moreover, its analogs are under active investigation for treating muscular dystrophy. Biochemically, this pathway is interesting since negamycin features an unusual nitrogen-nitrogen bond called a hydrazide group, which is key to its function. Previous bioinformatics work allowed us to identify a putative negamycin gene cluster due to the presence of a member of a nitrogen-nitrogen bond forming enzyme family. Through my research, I hope to characterize the enzymes that are encoded within the negamycin gene cluster. By understanding the enzymes which form negamycin's nitrogen-nitrogen bonds, other bacteria that produce valuable hydrazide-containing compounds can be discovered through genome mining. To investigate negamycin's biosynthetic pathway, I first tried to heterologously express the proposed negamycin gene cluster from *Kitasatospora purpeofusca* in *Streptomyces lividans*. I tested a variety of media for optimal negamycin production and took numerous time points after inducing expression of the gene cluster. I have not yet detected negamycin through mass spectrometry, so further optimization, such as increasing the concentration of the compound for induction, will be required to increase likelihood of negamycin production and detection. In parallel, to investigate the function of NegJ, the key enzyme hypothesized to form the nitrogen-nitrogen bond, I knocked out the gene encoding NegJ through a genetic recombineering system that couples with $\lambda$-Red and CRISPR-Cas9 technology and validated the knockout via sequencing. Once I detect negamycin in the unaltered system, I can probe the effects of the NegJ knockout. Ultimately, this research will help us gain a deeper understanding of the negamycin pathway and the roles of individual enzymes within it, as well as facilitate identification of more valuable hydrazide-containing antibiotics.

## Characterizing the Role of Stromal Cells in T cell Infiltration of a Zebrafish Melanoma Model

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T cell infiltration is a known predictor of immunotherapeutic response in melanoma, but the mechanisms that govern T cell infiltration of tumors are not well understood. We hypothesize that stromal cells in the tumor microenvironment critically regulate the ability of T cells to infiltrate a tumor. Our work aims to identify tumor-specific stromal cell subpopulations and test candidate stromal cell genes for their role in regulating T cell infiltration in a zebrafish model of melanoma. We analyzed preliminary 10x single-cell RNA-sequencing data of sorted stromal cells from tumors and normal skin to identify subpopulations specific to tumors. The tumor-derived stromal cells clustered separately from the normal skin-derived cells, indicating that there is a tumor-activated transcriptional state. From this data, we were able to narrow down a list of 6 tumor-enriched genes, including 2 positive control genes, that are our candidates for stromal regulation of T cell infiltration in melanoma. For each candidate gene, we plan to verify its expression in tumor stromal cells using quantitative PCR and characterize its effect by knockout or overexpression. Additionally, we created a plasmid with a stromal cell-type-specific promoter (*cxcl12a*), upstream of a gene encoding E. Coli nitroreductase (NTR), an enzyme that catalyzes the metabolism of the prodrug Nifurpirinol (Nif) to produce a cytotoxic product. By establishing a transgenic line of zebrafish with the *cxcl12a*:NTR construct, we plan to determine the effect of *cxcl12a*+ stromal cells on T cell infiltration at multiple stages of tumor development using inducible ablation of *cxcl12a*+ cells. Understanding whether stromal cells inhibit or promote T cell infiltration, and what stromal cell genes regulate this interaction, would have implications for determining what tumors would best be treated by immunotherapies and suggest new therapeutic co-targets to increase the proportion of responders to immunotherapy.

## Iron-Driven Ecological Dynamics of Vaginal Microbiota

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The community of microorganisms that colonize the cervix and vagina, the cervicovaginal microbiome, is an important determinant of female sexual and reproductive health. Recent studies have identified the presence of "optimal " vaginal microbial communities to be dominated by the *Lactobacillus* genus, whereas higher microbiome diversity is linked to adverse reproductive outcomes, including HIV susceptibility, preterm birth and bacterial vaginosis. Yet, neither the drivers of bacterial community composition nor the factors shaping ecological interactions in the vaginal microbiome are fully understood. This project aims to interrogate whether a frequent source of interspecies competition among bacteria, iron acquisition, can be manipulated to induce an optimal microbial community composition. In the case of the cervix and vagina, iron is a nutrient of particular interest as there are significant fluctuations in free and protein-bound iron in the environment during menstruation and infection. In response to these fluctuations, the human body naturally regulates free iron in bodily fluids through iron-chelating proteins, such as lactoferrin, to prevent cytotoxicity and minimize microbial growth. I predict that because the beneficial *Lactobacillus crispatus* is found to grow independently of environmental iron compared to the anaerobic bacteria associated with adverse health outcomes, inducing iron stress will supply a select advantage for the *L. crispatus* to outcompete other anaerobic bacteria. By mapping the innate growth kinetics of 10 bacterial strains endogenous to the female genital tract with varying concentrations of lactoferrin in isolation and within a mock bacterial community, this project will demonstrate possible interactions between lactoferrin and bacterial strains, potentially supporting *Lactobacillus* dominance. Ultimately, understanding the role of bioavailable iron in regulating vaginal bacterial community composition will inform methods to therapeutically modulate the cervicovaginal microbiome.

## Clinical Genotype and Phenotype Analysis of Males with Filamin-A Mutations

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Loss-of-function mutations in the X-linked gene Filamin-A (*FLNA*) are known to cause periventricular nodular heterotopia, a neuronal migration disorder linked to epilepsy and developmental delay. As with X-linked diseases, *FLNA*-positive males were thought to die *in utero* or shortly after birth; however, little is known about surviving males with *FLNA* mutations. We aim to characterize the clinical and genetic phenotypes of *FLNA*-positive males. We created a cohort of all surviving *FLNA* males with confirmed mutations from the literature and the existing Boston Children's Hospital patient registry. Patient demographics and medical information was abstracted from the literature and chart review. A genotype-phenotype correlation was undertaken. 139 males, with a median age of 7 yrs (range 0-65 yrs) with *FLNA* mutations formed our cohort. 82 percent (114/ 139 had confirmed germline mutations. 35 percent (49/ 139) of our cohort had died (median age: 6.0 mo, range: 0-57 yrs). The most common cause of death was respiratory failure (n=8, median age: 2 days, range: 0-3 yrs), followed by cardiac failure (n=6, median age 8.8 yrs, range: 2 mo-46 yrs). Most males presented with multi-organ anomalies. Skeletal dysmorphisms were the most common, presenting in 75 percent of patients, followed by neurological (60 percent), cardiovascular (60 percent), and gastrointestinal (52 percent) abnormalities. Consistent with severe presentation, the highest number of mutations affected the highly conserved actin binding and dimerization domain of the protein. This is the first study to conduct clinical genotype-phenotype analysis of all known males with *FLNA* mutations. Frequently, males have severe disease and a wider spectrum of multi-organ phenotypes, shedding light on unique insights into *FLNA*, and providing clinicians with a basis to diagnose and treat filaminopathies in surviving males.

## Characterizing METTL3 Regulation in Chemotherapy-Treated Cancer Cells

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Chemotherapy in cancer treatment can effectively kill cancer cells, but some cells survive treatment. These chemoresistant cells can lead to relapse, and their resistance to the initial chemotherapy makes them harder to treat. However, the way that cancer cells regulate gene expression to promote chemoresistance is not well understood. One potential mechanism is through RNA modification, as chemoresistant cancer cells have increased levels of RNA modifying enzymes. One such enzyme is METTL3, the methyltransferase responsible for modifying RNA with m6a methylation marks. The goal of this project is to characterize the regulatory pathway responsible for METTL3 upregulation in chemotherapy-treated cancer cells. BT549 triple negative and MCF7 hormone-positive breast cancer cells were treated with different doses of chemotherapy drugs, such as gemcitabine or paclitaxel, or with drugs affecting stress response pathways, such as Sal003. Cells were exposed for up to 24 hours in time course experiments, and Western blot analysis was used to quantify protein expression of METTL3 and the stress response proteins over time. Expression patterns associated with activation of the integrated stress response pathway were upregulated along with METTL3 in chemotherapy-treated cancer cells. Additionally, treating cells with integrated stress response agonists alone upregulated METTL3. These results suggest that the integrated stress response is responsible for METTL3 upregulation in chemotherapy-treated cancer cells. Therefore, targeting the integrated stress response could provide an avenue for reducing chemoresistance, which would result in improved chemotherapy outcomes.

## Sustainable Congenital Heart Disease Infrastructures for Low and Middle Income Countries

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The Boston Children's Center for Applied Pediatric Quality Analytics (CAPQA) promotes excellence in applied predictive analytics and healthcare innovation research to improve pediatric health outcomes. CAPQA hosts the International Quality Improvement Collaborative (IQIC) for Congenital Heart Disease, a project centered on reducing the mortality rate for pediatric patients with Congenital Heart Disease (CHD) in low and middle income countries (LMICs). The severity of a CHD diagnosis varies depending on the resources available to a medical facility. While survival rates for CHD cases are quite high in the United States, these rates in LMICs are much lower due to lack of resources available to provide effective treatment. With over 70 sites in 25 countries worldwide, IQIC focuses on initiatives that promote patient safety and sustainable strategies for improving pediatric CHD care. IQIC schedules regular audits with partner sites to verify that data provided is accurate. I aided in the creation and organization of the annual benchmarking reports which details the results of the audits and suggestions for improvement; the data from all of the sites is compiled, allowing each site to see not only its growth in comparison to other sites, but also overall annual trends in catheter and surgical procedures. I also organized key site contact information to streamline communication with IQIC stakeholders, allowing for more rapid dissemination of crucial information. Thus, IQIC models the importance of global collaboratives in improving pediatric care, especially CHD.

## Testing Novel Drugs to Overcome PARP Inhibitor Resistance in Ovarian Cancer

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Ovarian cancer remains the most lethal gynecologic cancer, yet FDA-approved targeted drugs to treat specific ovarian cancer subtypes are limited. Poly (ADP-ribose) polymerase inhibitors (PARPi) are one highly effective treatment option, especially in cancers deficient in homologous recombination (HR), a key DNA repair pathway. They are also oral drugs, well-tolerated compared to conventional chemotherapy, and combine well with other agents. However, HR-deficient cancers frequently develop PARPi resistance, causing relapse, or return of the cancer. Combinatorial therapy that harnesses synthetic lethality, or cell death resulting only from a combination of deficiencies, suggests a potential solution to this problem. PARPi resistance may be overcome by drugs targeting alternative pathways on which cancer cells develop dependency, such as alternative non-homologous end joining. The goal of this study was to test novel drugs thought to demonstrate synthetic lethality based on DNA repair pathways. These included combinations of PARPi, Ataxia telangiectasia and Rad3-related (ATR) protein inhibitors, and Ubiquitin Specific Peptidase 1 (USP1) inhibitors, treated in cell lines that exhibit genetic deficiencies common in ovarian tumors, including those linked to PARPi resistance. Clonogenic and Cell-titer Glo assays examined drug response, and biomarkers for resistance mechanisms, DNA damage, and replication stress were investigated via Western Blot. Preliminary findings bolster evidence for efficacy of PARP inhibitors Olaparib and Niraparib; suggest synergy between an ATR and USP1 inhibitor in *p53/BRCA1/53BP1* knockout cells, and between Niraparib and an ATR inhibitor in PARPi resistant cells; and indicate additional replication stress in *p53/BRCA1* knockout cells treated with a combination of PARP and USP1 inhibitors compared to single drugs. While further experiments are necessary to support drug synergism, these findings represent promising advancements in precision medicine for ovarian cancer, a field lacking sufficient targeted therapies, and are implicated in treatment of other solid tumors and DNA damage diseases.

## Characterization of Mutant Population Dynamics in the Long-Term Stationary Phase

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Long-term stationary phase (LTSP) is a state in which bacteria can live without an external food source for many years at near-constant population size, surviving by recycling nutrients from dead bacteria. As a dynamic environment of bacterial growth and death, LTSP is an excellent model system for microbial evolution. We combined experimental and computational efforts to determine the parameters that govern bacterial behavior under these conditions. One manipulable evolutionary pressure arises from the fact that bacteria often produce nonessential proteins. Intuitively, under starvation conditions, we expect evolutionary selection against this excess protein expression, allowing the bacteria to conserve their limited energy. To test this, we experimentally introduced a plasmid with an overexpressed protein into *E. coli* strains to increase their protein burden, and observed that cultures with high plasmid overexpression experienced selection against those loads: mutant strains having reduced or no expression of the plasmid came to competitively exclude the parental strain. In parallel, we observed similar results through computational modeling: in simulations with constant excess loads, the strain with the lowest load always competitively excluded all other strains. However, computational analysis also showed that given an original strain with a constant excess load, a new strain with an oscillating load of a slightly higher average can coexist with, or even competitively exclude, the original strain. The advantage of oscillation could provide an explanation for a past experimental observation that the excess loads of bacteria can "pulsate" — go through small time spans of high nonessential protein production, followed by long periods of lower load. In the future, we plan to fit our model to the experimental data and to investigate whether the unexpected benefit of oscillating protein expression could also occur *in vivo*.

## Elucidating the Structure of NRAMP-like Transporters Through X-Ray Crystallography

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Natural resistance-associated macrophage proteins (NRAMPs) are transmembrane transporters that import divalent transition metal ions, such as iron and manganese, into cells. NRAMPs are present in nearly all forms of life and help organisms maintain homeostasis by preventing an overload or deficiency of transition metals. Structural and biochemical studies in a few bacterial NRAMPs reveal that they have a conserved transition metal binding site consisting of aspartate, asparagine, and methionine residues. Sequence analysis of 6712 NRAMPs by Sam Berry, a PhD candidate in our lab, further identified a group of NRAMP-like proteins whose metal-binding-site sequence deviates from the canonical NRAMPs. We hypothesize that NRAMP-like proteins transport substrates other than the divalent transition metals. In this project, I aim to structurally determine two primary bacterial NRAMP-like proteins from *Eggerthella lenta* using X-ray crystallography, and compare them with known bacterial NRAMP structures to identify structural differences and potential substrates. For that purpose, I transformed the gene of interest into competent *E. coli* cells and overexpressed it. Additionally, I harvested the cells and purified the NRAMP-like protein using affinity and size exclusion chromatography. I then prepared the purified protein for crystallization trials with commercially available conditions containing various buffers, salts, and precipitants known to induce protein crystallization. Using the LCP crystallization technique, which provides membrane proteins with a membrane-mimetic environment, I obtained preliminary crystal hits. Based on the initial conditions, I prepared refinement screens to obtain better quality crystals. My next step will be to test the crystals using an X-ray beam. Once we obtain high quality X-ray diffraction data, we can determine the 3D structure of the protein. These findings will help us identify key structural components that impact metal binding, selectivity, and function in the NRAMP-like family.

## Exploring Catechol Dehydroxylation in Microbes by Characterizing Hydrocaffeic Acid Dehydroxylase from *Gordonibacter pamelaeae*

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Catechols are an important class of compounds that contain a benzene ring with two adjacent hydroxyl groups. The catechol motif is typically found in neurotransmitters, food, and drugs. Catechol dehydroxylation has been widely observed in human microbiome and other microbial environments, wherein a hydroxyl group is replaced by a hydrogen atom. Comprehensive understanding of this metabolism is important in modulating the activity of the human gut microbial community to combat diseases and improve human health. The enzymes responsible for this metabolism, catechol dehydroxylases, have been identified. However, characterization of these enzymes has been challenging due to their oxygen sensitive nature. Recently, hydrocaffeic acid dehydroxylase (Ghdh) from *Gordonibacter pamelaeae* (G3C) has been shown to be an air-stable and highly reactive homolog, providing opportunities to study this enzyme in more detail. Characterizing Ghdh will provide insight into the mechanism of catechol dehydroxylation and give insight into how microbes metabolize catecholic compounds. Efforts to heterologously express catechol dehydroxylases have been unsuccessful. As such, preparation of Ghdh rely solely on the native organism, *G. pamelaeae*. The primary goal of this project has been to determine the optimal growth conditions to produce Ghdh on large scale (2 to 10 L). This includes evaluation of medium supplements, culture agitation, and incubation temperature. The success of each condition was determined by assessing two main factors: (1) the metabolism of hydrocaffeic acid by the culture and (2) the catalytic activity of Ghdh in culture lysate. This summer, we have optimized the growth conditions to yield active Ghdh protein and will proceed with scaling up this protocol. Purification, followed by native gel, and Inductively coupled plasma mass spectrometry (ICP-MS) experiments will be conducted to investigate the size of the Ghdh complex, and the metal content of Ghdh, respectively. Further characterizations of Ghdh will be conducted in the Fall of 2021.

## Determining Metal Substrates of the *Eggerthella lenta* Nramp-like Proteins

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Transition metals are important for diverse biological processes in all organisms. To help maintain metal homeostasis, organisms import divalent transition metal ions using the natural resistance-associated macrophage proteins (Nramps). The substrates and roles of a few model bacterial and human Nramps are understood. However, two groups of homologs closely related to the Nramps, termed the Nramp-like proteins, remain poorly studied. To better understand the function of the Nramp-like proteins, I aim to determine the physiological metal substrates of two such proteins from the bacterium *Eggerthella lenta*, EleD and EleG, using a proteoliposome assay. In the assay setup, I embedded the proteins into phospholipid vesicles containing ion-sensitive fluorophores, forming proteoliposomes that can signal metal transport using fluorescence. I purified EleD and EleG with minimal contaminants and used these proteins in proteoliposome assays to test $Cd^{2+}$ and $Mn^{2+}$ transport under different voltages. My results suggest that EleD transports $Mn^{2+}$ under high voltage conditions ($-80$ mV and $-120$ mV) but not $Cd^{2+}$ while EleG transports neither metal under any conditions. The observed voltage dependence in EleD transport resembles that of specific Nramps. Many metals, including divalent non-transition metals and non-divalent transition metals, remain to be tested. Further research into metal transport in EleD and EleG will provide insight into the key substrates and role of Nramp-like proteins while opening future study into more examples of these divergent proteins.

## Investigating NF-$\varkappa$B as a Mediator of Endothelial Cell Barrier Integrity in Sturge-Weber Syndrome

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Sturge-Weber Syndrome (SWS) is a sporadic neurocutaneous disorder occurring in approximately 1 in 20,0-50,0 children and is characterized by leptomeningeal, choroidal, and cutaneous capillary malformation (CM). A somatic activating mutation in *GNAQ* (R183Q), which encodes the G-protein subunit Gαq, causes 90% of SWS cases. This mutation is enriched in endothelial cells (ECs) within SWS lesions on the skin and within the brain. We hypothesize that the R183Q mutation may compromise the endothelial barrier by disrupting the ability of ECs to sense laminar shear stress, potentially explaining the development of CMs and the observed degeneration of tight junctions. Since increased endothelial permeability accompanies elevation of nuclear factor-kappa B (NF-$\varkappa$B), a regulator of the inflammatory response, the goal of this project was to investigate NF-$\varkappa$B as a mediator of EC barrier integrity in SWS. Bortezomib, a proteasome inhibitor, ultimately halts translocation of NF-$\varkappa$B to the nucleus, where it would canonically initiate transcription of pro-inflammatory factors. To test the efficacy of Bortezomib, endothelial colony-forming cells (ECFCs) were treated with $20\,\mathrm{ng\,ml^{-1}}$ of tumor necrosis factor alpha (TNF-$\alpha$) to induce inflammation and expression of endothelial-specific surface marker, E-selectin. Verified by flow cytometry, E-selectin expression was attenuated following pretreatment and administration of different concentrations of Bortezomib, confirming it as a potent inhibitor of NF-$\varkappa$B and warranting additional consideration. Ongoing trials will utilize transendothelial electrical resistance (TEER) to assess EC barrier integrity by providing real-time measurements of impedance across cultured cells on a semipermeable membrane. In our next steps, unconditioned ECFCs and ECFCs transduced via lentiviral vector to express either wild-type or mutant *GNAQ* will be treated with Bortezomib and subjected to the TEER assay. NF-$\varkappa$B may be implicated as a mediator of EC barrier integrity and perhaps direct further SWS research.

## Sea Star Sensory Systems

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Marine ecosystems are among the most extreme on earth; as such, the animals that have come to inhabit these systems display an interesting and complex organization of their sensory systems. Echinoderms, in particular, have a higher complexity of photoreception and mechanoreception than was initially expected. Construction of the Sea Star transcriptome returned 3 genes of interest in their tube feet and sensory tentacles. *Piezo*-type mechanosensitive excitatory ion channels that are able to transduce mechanical stimulation biological signal. Rhodopsin-like olfactory receptors that transduce chemical ligands into biological signals. Retinal rod rhodopsin-sensitive cGMP that facilitates the transduction of photostimulation into biological signal. Behavior experiments with live and empty mussels demonstrated patterns in behavior where the sea star engages each sensory system. In these experiments, sea stars were found to detect the presence of prey through olfaction but used photo sensation to hunt that prey down. The sea star then used tactile information to identify whether or not the prey was still alive. These findings are important for understanding the predation behaviors in sea stars and can be used to help inhibit the predation of coral colonies in reefs.

## Growth Rate Regulation in Rod Shaped Bacteria

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How bacteria couple the rate they build cell walls to their rate of growth is not understood. However, it is known that one filament forming protein, MreB, is essential to the growth of rod shaped bacteria. MreB forms 250 nm long filaments that rotate around the circumference of the cell. These filaments move circumferentially as MreB associated enzymes insert material into the cell wall. One MreB associated protein, RodZ, is likely to control MreB polymerization. RodZ is a transmembrane protein with a cytoplasmic domain that binds to MreB monomers. The goal of this study is to understand how bacteria regulate the number of MreB filaments to match the nutrient conditions so the cell inserts the correct amount of material to match the growth rate. To test if and how RodZ affects MreB filaments in *Bacillus subtilis*, RodZ expression was titrated while mNeonGreen-MreB filaments were observed microscopically using the Elyra 7 at the HCBI. The filaments were tracked in 3D with 65 nm resolution. Combining these *in vivo* observations with computational analysis allowed us to count the number of MreB filaments per cell and also determine their rate of appearance, disappearance, and overall lifetime. By testing how different levels of RodZ expression affect these parameters, it is expected that increased RodZ expression will either increase the rate of appearance, indicating RodZ is a nucleator, or decrease their rate of disappearance, suggesting RodZ is a filament stabilizer. RodZ's activity is also modulated by phosphorylation by PrkC, so in future experiments these parameters will be assayed in cells containing phosphomimetic and phosphoablative RodZ mutants. Together, this study will give the first insight into how these essential bacterial cytoskeletal filaments are regulated by the cell, so it can coordinate its rate of cell wall growth to match the external nutrient conditions.

## Structural Characterization of 7SK snRNP Bound to HEXIM1 and, Alternatively, HIV-1 Tat Protein

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*Mentor:* Vincent Pham

Human immunodeficiency virus-1 (HIV-1) remains a prevalent public health concern, and advancements in our understanding of its replication cycle are crucial to our ability to improve treatment. HIV transcription requires host transcription factors that are normally sequestered by host 7SK small nuclear ribonucleoprotein (7SK snRNP). To release these transcription factors from 7SK, HIV Tat protein binds to 7SK snRNP, displacing the transcription factors as well as HEXIM1 protein. Currently, there is no structural data of the 7SK snRNP for these stages of protein binding. The interaction between two proteins associated with the 5′ and 3′ ends of 7SK snRNP— methyl-phosphate capping enzyme (MEPCE) and La-related protein 7 (LARP7), respectively— may have hindered the D'Souza lab's previous attempts to detail the structure of full 7SK snRNP complex bound to HEXIM1 and HIV Tat. During these attempts, wild-type 7SK snRNP spontaneously formed helical polymers where the LARP7 of one snRNP binds to the MEPCE of another snRNP, preventing the high-resolution reconstruction of isolated (monomeric) 7SK snRNP. Therefore, we expect that increasing the ratio of 7SK snRNP monomer to polymer would allow us to generate insightful cryogenic electron microscope (cryo-EM) images and deduce the full structure when bound to HEXIM1 or HIV Tat. The "open" conformational state of 7SK snRNP prevents the interaction between LARP7 and MEPCE and is thought to be a single snRNP particle that binds both HEXIM1 and P-TEFb. Therefore, we have hypothesized that the use of a MEPCE VLD(447-449)AAA mutant that is known to disrupt the MEPCE-LARP7 interaction in vivo will increase the formation of the monomeric 7SK snRNP by breaking apart the helical arrays that precluded structural elucidation. The characterization of these structures could prove useful in verifying the functions of specific regions and improving the treatment of HIV infection.

## Pharmacological Inhibition of 2-Hydroxyglutarate Production in IDH-Mutant Murine Glioma Cell Lines

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Gliomas are the most common and aggressive form of primary brain cancer in humans. The metabolic gene isocitrate dehydrogenase (IDH1) is commonly mutated in a large proportion of low-grade gliomas (LGG). The oncometabolite, 2-hydroxyglutarate (2HG), produced by the IDH mutation has been shown to modulate the immune response in gliomas. In this project, we aimed to establish a syngeneic preclinical model of the IDH-mutant tumor immune microenvironment using the murine glioma cell lines, CT2A and GL261. Culturing cells in DMEM, 10 percent FBS and 1 percent penstrep, we successfully transduced CT2A and GL261 parental lines with cDNA encoding either the wild-type IDH1 or the mutant IDH1R132H. Clonal selection of IDH-expressing cells was achieved by use of antibiotics (blasticidin). We then treated the cells with either DMSO (control) or 2uM of the IDH-inhibitor, AGI-5198, for 72 hours. Western blot and the 2HG assay were used to evaluate expression for mutant IDH and production of 2HG, respectively. We confirmed the protein expression of IDH1R132H in mutant cell lines using a western blot, while cell lines transduced with the IDH1 lentivirus did not express the mutant IDH. 2HG analysis showed that the AGI-5198 treatment significantly abrogated the production of 2HG in the mutant-IDH cell lines. IDH-mutational status represents the most important distinction when stratifying glial tumors and is associated with differential antitumor immunity. We successfully generated two isogenic cell lines for both GL261 and CT2A that differed only in IDH-mutational status. We also demonstrated that AGI-5198 decreased the levels of 2HG production in our engineered mutant-IDH cell lines. From these results, we intend to study the immune modulating effect of AGI-5198 in an experimental in-vivo system.

## The Role of Glycolysis and NAD+/NADH Ratio in Beta Cell Stress Resistance

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Type 1 diabetes is a chronic disease characterized by insulin deficiency due to autoimmune destruction of insulin producing pancreatic beta cells. Treatment for type 1 diabetes currently involves constant blood glucose monitoring and frequent injections of insulin in order to keep blood glucose levels within a healthy range to prevent complications. Beta cell replacement therapy using autologous stem cell-derived beta cells has emerged as a promising path to achieving insulin independence for type 1 diabetics, but subsequent autoimmune destruction of the newly implanted cells presents a significant challenge. Recently, our lab has shown that the deletion of the gene that encodes for the enzyme Renalase (Rnls) protects beta cells from autoimmune destruction and intracellular stress. There has been increasing evidence that intracellular stress could play a role in triggering the autoimmune killing of beta cells, however, it is not known how this deletion renders these beta cells more stress resistant. Not much is known about the role of Rnls in the body, but it has been shown to be an oxidase capable of converting isoforms of NAD(P)H to NAD(P)+. Preliminary data from our lab shows higher glycolytic activity for *Rnls* knockdown cells. Thus, we hypothesize that this shift towards glycolysis and/or a change in the intracellular NAD+/NADH ratio play critical roles in stress resistance in beta cells. To investigate this, we intend to measure the beta cell response to ER stress and cell viability after inhibiting glycolysis and challenging the cells using an ER stressor. We also intend to manipulate NAD+ availability and measure the stress outcomes in beta cells. Collectively, these approaches will provide evidence into how altering beta cell metabolism could reduce activation of stress pathways that lead to beta cell death in type 1 diabetes.

## Differentiation Block is an Early Conserved Event in Colorectal Cancer

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Genomic alterations that dysregulate intestinal stem cell differentiation are central to the development of colorectal cancer (CRC), and identification of functional molecular mediators are key in developing effective therapeutic treatments. Having already identified SRY Box Transcription Factor 9 (*SOX9*) as functionally important to CRC in previous studies, a genetically engineered mouse model was used to further investigate the role of stem cell differentiation in early CRC progression with a special interest in the role of *SOX9*. Preliminary results demonstrated that impeding normal intestinal cell differentiation and aberrant *Sox9* expression are early events in CRC progression. Single cell RNA-sequencing (scRNA-seq), a next-generation sequencing technology that analyzes gene expression of individual cells, revealed that loss of *APC*, a tumor suppressor gene commonly mutated in CRC, leads to a distinct, aberrant transcriptional state with enrichment of select canonical intestinal stem cell activity, including elevated *Sox9* expression. Initial findings showed three distinct substates within this distinct transcriptional state, and we intend to further investigate the characteristics and functionality of these substates. Furthermore, scRNA-seq of adenomas from a patient with familial adenomatous polyposis, an inherited disorder characterized by mutated *APC* in all colon cells, validated these results, showing a distinct stem-like transcriptional state with upregulation of *SOX9* as well as three distinct substates within this aberrant transcriptional state. In addition, enrichment of embryonic pathways, including *Ly6a/Sca1*+ upregulation, was observed in a genetic mouse model and validated in human FAP adenoma samples. Finally, scRNA-seq of a mouse model with heterozygous deletion of *Sox9* validated *SOX9* as a necessary event in colon cancer formation, as reducing *Sox9* expression increased intestinal differentiation and lowered expression of the aberrant, stem-like transcriptional state. These studies establish differentiation blocks as an early event in CRC and carry important implications for developing therapeutics directed at inducing intestinal differentiation.

## Novel Implications of Non-CoV-2 Antigens in Determining COVID-19 Disease Severity

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COVID-19 disease severity varies widely across infected individuals: many present no symptoms, while others require oxygen support or even succumb to the virus. Variations in disease severity are correlated with demographics, social health determinants, and basic immunological correlates (e.g. neutralizing antibodies, Fc-effector activity). However, specific immunological underpinnings of severe disease are yet to be discovered. After observing high antibody titer specific to *non*-SARS-CoV-2 pathogens in COVID-19 patients, we hypothesized SARS-CoV-2 induced broad immune responses for non-present or latent pathogens to evade destruction. We performed a multi-cohort analysis of COVID-19 patient serum samples. We ran Luminex and functional assays, including antibody-dependent cellular/neutrophil phagocytosis (ADCP/ADNP) and antibody-dependent complement deposition (ADCD). Luminex assays form fluorescent antigen-antibody complexes to measure antibody levels via high-throughput flow cytometry. Functional assays measure phagocytic activity of various immune cells. By measuring the products and byproducts of immune recognition, we elucidate the ability of antibodies to drive effector functions in vitro. Together, these assays quantified antigen-specific antibody (IgG, IgM, IgA) and FcR antibody binding (FcR2a/b, FcR3a/b) levels for a wide variety of pathogens, helping us visualize the magnitude and nature of each immune responses. Pathogens of particular interest included Human Cytomegalovirus (CMV), as well as pathogens with vaccine protection (i.e. Measles, Diphtheria). Preliminary results indicate significant differences in CMV FcR2/3a, and Tetanus IgG1 responses between individuals who experienced moderate, severe, or fatal SARS-CoV-2 infection. Our findings may provide novel, immunology-grounded methods of predicting disease outcomes in COVID-19 patients, allowing providers to prepare resources (i.e. ventilators) for those at-risk. This would help lower patient mortality and morbidity, and enable hospitals to more adeptly triage COVID-19 patents. Through further research, we aim to understand the mechanism by which SARS-CoV-2 overwhelms

the immune system and leads to severe disease.

## Deciphering the Role of Mitochondrial Cargoes in Extracellular Vesicles in Promoting Breast Cancer Growth and Chemotherapy Resistance

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Cancer cells employ bidirectional cell communication to maintain growth and metastasis in the tumor microenvironment. One mechanism of communication that has become increasingly appreciated is the secretion of extracellular vesicles (EVs), heterogeneous multi-signal messengers that support cancer dissemination through the transfer of biomolecules such as oncoproteins and noncoding RNA species. However, little is understood about EVs in relation to chemotherapy resistance. In this study, we profiled two different breast cancer cell lines: 1) BT549 (triple negative), treated with gemcitabine (DNA replication inhibitor) and paclitaxel (microtubule nucleation inhibitor), and 2) MCF7 (hormone-positive), treated with palbociclib (CDK 4/6 inhibitor) and fulvestrant (estrogen receptor degrader), compared to their wild-type states. EVs were collected from these chemotherapy-exposed cells using tangential flow filtration and quantified using Brownian motion-based nanoparticle tracking analysis and microfluidic resistive pulse sensing, and subsequent profiling of RNA and peptide markers was completed through RT-qPCR and Western blotting, respectively. Initial data showed that representative mitochondrial ribosomal genes *mt12S* and *MRPS14* were among the most upregulated RNAs in our drug-exposed EV samples, indicating that extracellular transfer of mitochondrial materials plays a role in cancer growth under chemotherapy stress. These findings were supported by prior genetic research at the Vasudevan Lab, in which a set of mitochondrial ribosomal proteins was found to be upregulated in chemoresistant acute monocytic leukemia cells, as well as by the recent discovery of mitovesicles, a novel population of EVs that originate from mitochondria as opposed to the plasma membrane. Through additional efforts to isolate further subtypes of EVs, the mechanisms by which these mitochondrial cargoes promote chemoresistant phenotypes may be identified.

## NAD+ Accumulation Confers Resistance to Poly(ADP-Ribose) Polymerase Inhibition in Breast Cancer

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Poly(ADP-ribose) polymerase (PARP) is a class of multifunctional proteins that acts as a DNA damage sensor in the base excision repair pathway in cancerous tissues, preventing cell death. PARP inhibitors (PARPi) such as Olaparib have become a therapeutic strategy against cancer, especially against those which lack higher forms of DNA damage repair pathways such as homologous recombination, as is the case for *BRCA*-deficient cancer. All cancers eventually develop resistance to PARPi, resulting in ineffective treatment. Because PARP functions by catalyzing polymerization of nicotinamide adenine dinucleotide ($NAD^+$). We hypothesize that the buildup of $NAD^+$ as a direct result of PARPi results in a shift from equilibrium in other NAD-dependent biochemical pathways, resulting in the synthesis of biomolecules that may promote cell survival. This study aims to determine the combination of metabolic inhibitors and conditions in which PARPi is most effective to treat breast cancer cell lines with and without *BRCA1* mutation. To observe the potential role of glycolysis and the TCA cycle (two of the most prevalent and well-understood NAD-dependent pathways) in promoting tumor survival, we manipulated glucose concentrations and oxygen availability, simulating the hypoxic conditions within the tumor microenvironment. The effects of these pathways were then quantified using viability, ATP measurement, and Luciferase assays. Initial findings showed that a decrease in glucose concentration in hypoxic conditions contributes to cancer cell proliferation in the presence of Olaparib, implicating that a decrease in glycolysis activity contributes to PARPi resistance and chemosurvival due to the presence of separate NAD-dependent pathways. Further experimental work is needed to better characterize these pathways so that they can be therapeutic targets for the treatment of cancer.

## Comparative Analysis of Taxonomic Assignment Tools for Environmental Microbiome Characterization

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As sequencing becomes cheaper, metagenomic shotgun sequencing has become increasingly popular for characterizing microbial communities. However, it can be more challenging to interpret when used in diverse environments containing many uncharacterized microbes (as compared to e.g. the well-studied human microbiome). Here, we compare three popular methods for taxonomic profiling – MetaPhlAn 2, MetaPhlAn 3, and mOTU2 – on five shotgun sequencing data sets comprising 188 environmental microbiome samples ranging in geography, climate, and chemical conditions to determine their applicability in such settings. Comparing predicted taxonomic abundance, we found that MetaPhlAn 2 and mOTU2 predicted more similar abundances than any other pair of profiling tools, but which tool was used still explained more variance in the estimated abundances than even the samples' environmental contexts (univariate PERMANOVAs on Bray Curtis distances; all q-values $< 0.1$). Furthermore, in 10.1 percent of samples, all three methods labeled $> 90$ percent of the relative abundance as unknown or unclassified. Comparing predicted taxonomic assignments, on average, only 4.1 percent of genera assigned to a sample were assigned by all mOTU2, MetaPhlAn 2, and MetaPhlAn 3, and 76.7 percent of genera assigned to a sample were assigned by only one tool. To test whether this observed 4.1 percent of overlapping assignments among all three tools was more than expected by chance, we developed a new method for calculating cumulative distribution functions from conditional hypergeometric distributions four thousand times faster than previously possible. This showed that in the 64 percent of samples with at least one three-way assignment overlap, the probability of seeing the observed number of overlaps or more by chance was between 0.004 and $< 1 \times 10^{-16}$, indicating genera assignment was indeed still associated among all three tools. This research calls out the undercharacterization of most types of environmental microbial communities and identifies areas for improvement in analyzing them via shotgun metagenomics.

## Identifying Enhancers to Interpret Genomic Imprinting of Kcnk9 and Birk-Barel Syndrome

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Genomic imprinting is an epigenetic mechanism resulting in gene expression from only one of the two parental alleles. Having only one functional gene copy makes humans more susceptible to genetic disease. Furthermore, imprinted genes are highly expressed in the brain; thus, when a functional allele copy is mutated, phenotypes such as intellectual disability can arise. For example, *Kcnk9* is a potassium leak channel exclusively expressed from the maternal allele in neurons. Maternally inherited mutations within *Kcnk9* cause Birk-Barel syndrome with cognitive dysfunction. Reactivating the intact, imprinted paternal allele in patients could serve as a potential therapy, however, the mechanisms by which the paternal allele is silenced are not known. The Whipple lab has recently identified potential enhancers that interact with the *Kcnk9* promoter specifically on the maternal allele. Enhancers are regions where transcription factors bind, leading to augmented transcription of distal genes. Structural differences in the paternal allele prevent these enhancer-promoter interactions. Thus, we hypothesize that *Kcnk9* alleles are regulated by enhancer activity. We tested if the potential enhancer regions can amplify distal gene expression using a luciferase reporter assay. Plasmids each containing a different putative enhancer followed downstream by the luciferase gene were incorporated into mouse embryonic stem cells (ESCs) as well as ESCs differentiated into neurons. If the putative enhancers do have enhancer activity, the luciferase gene will be transcribed and emit light only in the induced neurons, as *Kcnk9* is neuron specific, indicating the enhancer activity must also be neuron specific. If the hypothesis is correct and the putative enhancers are both canonical and neuron specific, this study supports an enhancer based model of *Kcnk9* imprinting. Through this experimentation, the neuronal function of *Kcnk9* will be better understood, furthering therapies for Birk-Barel syndrome through enhancer reactivation of imprinted alleles.

## An Analysis of Batch Effects in Cancer Mutational Signatures

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Some of the most widely studied changes in genes that are associated with cancer evolution are somatic single nucleotide variants (SNVs), single nucleotide changes in cancer DNA. Different cancers preferentially harbor different types of SNVs, meaning that different mutational processes generate characteristic mutational signatures. The accumulation of these SNVs leaves its own imprint or "signature" in the tumor DNA, known as mutational signatures. Current signatures have been identified using high throughput sequencing data generated from cancer genomes using non-negative matrix factorization (NMF), which models data by additive combinations of non-negative basis vectors. Mutational signature analysis has arisen as an emerging field in cancer detection and poses potential clinical value as tumor diagnosis, treatment guidance, and predictor of the therapy response in cancer. Previous research has focused on characterizing signatures and their relationship to different cancer types; however, little is known about how batch effects, non-biological factors that can cause changes in the data produced, could be potentially influencing our current understanding of these mutational signatures. These effects can arise from minor technical differences in sequencing protocols and are common in computational research. As such, this summer I have been investigating and characterizing the role of batch effects in cancer signature mutational analysis by subsetting data from the Catalogue Of Somatic Mutations In Cancer (COSMIC) database in order to acquire SNV mutation data from different liver cancer projects, such as the International Cancer Genome Consortium. I used signeR, a package that provides an empirical Bayesian approach to mutational signature discovery to analyze the signature mutations that arise from different batches by comparing the resulting signatures and exposures across different projects. If batch effects are affecting our current characterization of signature mutations, methods to potentially correct for these effects need to be explored.

## Crystallizing an Alternate Crystal Form of Protein Tyrosine Phosphatase 1B

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X-ray crystallography is a powerful structure determination method for macromolecules that frequently achieves atomic resolution and thus produces high quality structures. However, some aspects of these structures may be artifacts of the crystallization process. One such artifact is the formation of stabilizing interactions between macromolecules, or crystal contacts, within the crystal packing environment. These interactions can give rise to visually compelling structures or correlations within a protein that are not biologically relevant. However, by varying the packing environments, it is possible to differentiate novel and relevant protein structures from such artifacts. In protein tyrosine phosphatase 1B (PTP1B), these contacts have complicated attempts to resolve correlated motions within the protein that are important for its function. PTP1B is a validated drug target for type II diabetes and breast cancer so harnessing these motions is imperative in designing effective therapies. Previous work has hypothesized that the catalytic loop of PTP1B and a loop over 20 Å away are coupled, but these conclusions are only drawn from the P $3_121$ crystal form. PTP1B has been shown to crystallize in the P $2_12_12_1$ crystal form, which exhibits different crystal contacts than the P $3_121$ crystal form, and early attempts at the isolation of P $2_12_12_1$ crystal form have been promising. By screening and optimizing crystallization conditions through trial and error, novel crystallographic methods like electric field stimulated X-ray crystallography (EFX) may disentangle these artifacts and lead to a more rigorous understanding of the correlated motions in PTP1B and how they relate to the protein's function and its role in disease.

## Identifying and Investigating lncRNAs Crucial to Neurodevelopment

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Long-non-coding RNAs (lncRNAs), broadly defined as RNAs over 200 nucleotides in length and lacking the ability to code for proteins, are thought to have important biological functions. However, the specific ways in which lncRNAs contribute to cellular processes remains unknown. In neurodevelopment, the disruption and dysregulation of certain lncRNAs is associated with various diseases, such as autism spectrum disorder (ASD). The purpose of this study was to identify lncRNAs that regulate the differentiation of neural progenitor cells (NPCs) and gene expression in the developing brain. To this end, we employed a CRISPR screen using Cas13 machinery and single guide RNAs (sgRNAs) which target specific lncRNA sequences and disrupt them via knockdown in cultures of NPCs. To create a stable line of Cas13 expressing cells, we inserted Cas13 into the NPC genome with a Tet promoter that requires activation by doxycycline. We found high expression of Cas13 within 6 hours of treatment with doxycycline. This finding indicates that doxycycline can be used for temporal control over the expression of Cas13 in NPCs. Moreover, we plan to transfect NPCs with constructs containing sgRNAs that target the lncRNA *SOX2OT* to investigate the effects of *SOX2OT* disruption on NPC differentiation. We will then conduct a large screen of lncRNAs thought to be involved in neurodevelopment and investigate the phenotypic variations of NPC cultures that have specific lncRNAs knocked down. This research will be important for identifying the specific lncRNAs crucial to neurodevelopment, as well as elucidate the larger roles lncRNAs play in cellular processes in the developing brain.

## Examining the Association of Mitochondrial Characteristics with the Functioning of CD8+ T Cells During HIV Pathogenesis

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CD8+ T cells, a type of effector immune cell, play a critical role in the defense against HIV infection. Although several studies have focused on the role of CD8+ T cells in eliminating infected CD4+ T cells from the peripheral blood, the gastrointestinal (GI) mucosa contains the body's largest reserve of CD4+ T cells. HIV-associated GI epithelial barrier disruption is an early hallmark of HIV infection, and CD8+ T cells have been shown to mediate this GI epithelial cell apoptosis, driving systemic inflammation. Since mitochondrial metabolism is known to impact the functional capacity of CD8+ T cells, the goal of this project is to determine if HIV pathogenesis induces the dysregulated mitochondrial metabolism of peripheral blood and GI mucosal CD8+ T cells. To this end, I will be investigating the metabolic function of peripheral blood and GI mucosal CD8+ T cells in antiretroviral therapy (ART) treated, HIV infected; ART-naive, HIV infected; and HIV uninfected cohorts. To compare the mitochondrial characteristics of the three cohorts, I have begun measuring the mitochondrial mass and membrane potential of peripheral and GI mucosal CD8+ T cells using flow cytometry. I will next examine the metabolic function of GI mucosal CD8+ T cells through measurements of key indicators of mitochondrial metabolic pathways, such as the fatty acid oxidation rate. Thus far, I have found that peripheral blood derived CD8+ T cells from ART-treated, HIV infected individuals exhibit greater mitochondrial hyperpolarization compared to CD8+ T cells from HIV uninfected subjects. These results suggest that even with ART treatment, CD8+ T cells display poor mitochondrial health. Further work will elucidate the association between mitochondrial characteristics and metabolic signaling upon HIV infection, as well as compartmental differences between CD8+ T cells of the GI mucosa and the peripheral blood.

## Improving Antigen Presentation Through Induction of B2M and MHC-I Expression in Human Cancer Cell Lines

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Major histocompatibility complex class I (MHC-I) is involved in the immune system, specifically in cell surface antigen presentation and in the recognition by T cells. $\beta$-2 microglobulin (B2M) is a component of MHC-I, and the downregulation of B2M has been shown to strongly correlate to immune checkpoint blockade treatment. Moreover, downregulation of MHC-I and B2M has been observed in many primary and metastatic tumors. The human leukocyte antigen system (HLA) is a complex of genes that encode cell surface molecules which are specialized in antigen presentation to T cells. A previous study demonstrated that complete or near-complete loss of MHC-I expression in forty-three percent of melanoma cases was related to the transcriptional repression of the HLA and B2M genes before immunotherapy; they showed that patients with MHC-I downregulation developed primary resistance to anti-CTLA4 therapy, a type of cancer immunotherapy which seeks to inhibit the T cell-activation suppression behavior of the CTLA4 protein. B2M mutations and loss of heterozygosity were additionally observed in melanoma patients who did not respond to immunotherapies. This highlights the significance of tumor MHC-I expression in response to immune checkpoint blockades. In the current project, a drug previously used to treat HIV was unexpectedly found to upregulate B2M expression. We found that incubation of this repurposed HIV drug in multiple human melanoma, lung, and pancreatic cancer cell lines significantly induced B2M and MHC-I expression. Functional T cell assays also showed increased IFN-$\gamma$ (a cytotoxic T cell activation signal) was released by co-incubated T cells following treatment with this drug in melanoma and pancreatic cancer cell lines. Ongoing studies are examining the mechanism of the response. These results demonstrate a potentially promising strategy to improve antigen presentation and thereby enhance clinical responses to immunotherapies in patients with multiple cancer types.

## Role of *Enterococcus*-unique Hypothetical EF1909 in Intrinsic $\beta$-lactam Resistance

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The enterococci have emerged as leading antibiotic-resistant hospital-acquired pathogens, but the genetic basis for the factors that facilitate their survival and transmission in the hospital remains largely unknown. EF1909 is a protein of unknown structure and function that is unique to and ubiquitous within the genus *Enterococcus*. A genome-wide screen called Tn-seq indicated that EF1909 is essential for growth in the presence of $\beta$-lactam antibiotics. Furthermore, in the genome of the hospital pathogen *E. faecalis*, EF1909 is encoded adjacent to EF1908, a key enzyme for cell wall synthesis. Taken together, this suggests that EF1909 fundamentally alters the enterococcal peptidoglycan by a poorly-characterized mechanism. This alteration may result in the intrinsic $\beta$-lactam resistance observed in enterococci. We have developed and implemented an allelic replacement strategy to make a clean deletion of EF1909 in *E. faecalis* that fuses translational start and stop sequences to avoid polar effects. We have also designed a complementation vector starting from the tightly regulated expression vector pCIE which will be used to express EF1909 in the knock-out to prove that lack of EF1909 results in the phenotype found. In addition, we conducted a bioinformatic analysis of the genetic context of EF1909 throughout all enterococci which indicates that the synteny of EF1909 and the genes that surround it is conserved within but not between the four major clades of enterococci. These approaches promise the verification and further characterization of the unique but conserved protein EF1909 within the enterococci and how it may confer $\beta$-lactam antibiotic resistance to this genus. If EF1909 is central to the intrinsic $\beta$-lactam resistance of enterococci, identification of EF1909 inhibitors could, for the first time, render enterococci broadly susceptible to this widely available antibiotic class, which would be an advance of the utmost importance.

## Structural Basis for Translation Initiation in *Leishmania major*

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About 20 species of the *Leishmania* protozoan parasites cause one million new cases of leishmaniasis annually. Few therapies are available, and significant side effects and parasite resistance limit their effectiveness. Most gene expression in *Leishmania* is regulated post-transcriptionally, mainly during translation. In mammalian cells, translation initiation requires coordinating the interaction of many initiation factors (eIFs). A crucial step in this process includes recognizing the $m^7$GTP cap structure, located at the 5′ end of messenger RNAs, by the cap-binding protein eIF4E. eIF4E also interacts with the scaffold protein, eIF4G, which recruits the large multisubunit complex, eIF3, associated with the small ribosomal subunit. Translation initiation is less well characterized in *Leishmania*, which encode various isoforms of most of the eIFs. The *Leishmania* cap-binding isoform 1, LIF4E-1, is the only isoform that maintains its cap-binding activity in the human host. LIF4E-1 was recently shown to interact with the subunit "a" of LIF3. This interaction has never been observed in orthologous systems, and its molecular details are yet to be described. For this project, we focused on expressing and purifying LIF3a to biophysically characterize the interaction between LIF4E-1 and LIF3a. Using a bacterial system, we expressed recombinant versions of LIF3a and LIF4E-1. These proteins were purified over Nickel-NTA resin, followed by size exclusion chromatography. We used native gel shift analysis and other biophysical techniques to characterize the LIF4E-1 and LIF3a interaction. As we previously determined an LIF4E-1 and L4E-IP1 crystal structure, we used L4E-IP1 as a positive control in these experiments. Our preliminary results show an interaction between LIF3a and LIF4E-1. This work will set the fundamental grounds to further characterize a unique protein-protein interaction in *Leishmania* parasites, and this information, in turn, could guide the development of specific translation initiation inhibitors against these parasites.

## Identifying Causal Genes in Fibroblast Aging

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Aging shares underlying mechanisms with several prevalent chronic diseases, for which it is also a major risk factor. Evidence that genetic mutations can affect both the lifespan and healthspan of organisms supports a genetic approach to therapeutic age reversal. Progress in understanding how to modulate aging has been slow, since aging is a complex process. Age-related expression changes in thousands of genes make it difficult to select relevant targets. To better predict gene targets, we adapted a network-based algorithm to identify candidate aging genes that could induce a young transcriptome in an old cell. Our analysis showed that the network-scoring method, which selects for influential genes in highly differentially expressed local gene networks, generates a ranked list of targets that has a significantly high enrichment of previously discovered and putative aging genes. In comparison, popular target selection methods such as traditional differential gene expression analysis did not show any significant enrichment of known age-related genes. We are validating the network-based method by testing an overexpression library of the highest-ranked genes for their effects on cellular aging in three differently-aged cell lines. We are performing single gene screens to study individual gene effects in the transcriptome and cell function, which is evaluated using assays for cellular senescence and mitochondrial potential. We are also performing pooled library screens to investigate how combination of genes can affect cell function in concert. Preliminary results from the pooled assay showed that cells with high and low staining for our aging assays had enrichment of certain factors, indicating that some of our genes might be inducing these phenotypes. Furthermore, RNA-Seq from initial single gene tests showed our target overexpression induced age-related gene expression changes. Completion of this study will identify target genes for the development of age-reversal therapies and provide a widely applicable network-based approach for scoring highly influential genes involved in complex phenotypes.

## Immunomodulatory Properties of the IMiDs versus Dipeptide Analogues

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The transcription factor interferon regulatory factor 4 (IRF4) is required for the survival of myeloma cancer types. Its downregulation by canonical immunomodulatory drugs (IMiDs), such as lenalidomide, serves to inhibit the growth of myeloma and lymphoma cells. Additionally, lenalidomide possesses immunosuppressive effects through the suppression of tumour-necrosis factor alpha (TNF-alpha) and NF-kappa Bdown-regulation. Recently, the Woo lab discovered a set of dipeptide-based ligands that can functionally engage cereblon (CRBN) in the $CRL4^{CRBN}$ E3 ubiquitin ligase. Some of the compounds in this library have also demonstrated potency to downregulate IRF4 production similar to IMiDs but possess different substrate degradation and immunosuppressive profiles. In addition, the dipeptide analogues differ from lenalidomide in the cell lines they target, as confirmed by survival assays. Thus, this project entailed using myeloma, lymphoma, and leukemia cell lines to investigate the nature of this anti-cancer activity. This project entailed conducting cell viability assays to observe the effect of the dipeptides in different cell lines, then degradation assays to see the effects of these compounds on the IRF4 transcription pathway. It is likely that these novel ligands may have a mechanism for IRF4 downstream regulation independent of neosubstrate degradation, leading to a different inhibitory profile in IRF4-dependent cell lines. This project serves to elucidate an alternative route of small molecule cancer therapy through the deactivation of the IRF4 pathway while preserving immunogenic activity, thus offering a tolerable, effective modulator of myeloma cancer types.

# An evolutionary path from prebiotic to modern biochemistry: adapting ribozymes that catalyze ligation of RNA activated with the 'prebiotic' 2-aminoimidazole group to the 'modern' pyrophosphate-activated RNA

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The RNA world hypothesis proposes that early life was dependent on RNA molecules that performed the dual function of carrying genetic information and performing enzyme catalysis. To support an RNA-based biology, RNA enzymes, or ribozymes, must have played a central role in assembling complex RNA molecules from simpler monomeric or oligomeric building blocks. Ribozymes that catalyze ligation of RNA oligomers activated with the prebiotically-plausible, 2-aminoimidazole (2AI) group would have been instrumental in building up molecular complexity in the RNA world by facilitating the transition from chemical to biocatalytic RNA assembly. However, modern RNA is made by protein enzymes (RNA polymerases) from building blocks activated with a pyrophosphate moiety (nucleoside triphosphates) which suggests that at some point these RNA enzymes would have evolved the capacity to use pyrophosphate-activated RNA building blocks to create longer RNA molecules. We used *in vitro* evolution to identify ribozymes that catalyze ligation of pyrophosphate-activated RNA oligomers by starting with a partially mutagenized 2AI ligase ribozyme sequence. We sequenced the RNA pools from six rounds of selection and analyzed the selected sequence space by custom computational tools. We mapped the emergence of new ribozymes during selection which coincided with the disappearance of parent AI ligase-like sequences. We discovered mutational pathways between the parent AI ligase ribozyme sequence and the most abundant sequences that emerged from the current selection. Our results show that the fitness landscapes of the 'source' phenotype (ligation of 2AI-activated RNA) and 'target' phenotype (ligation of pyrophosphate-activated RNA) approach each other closely and even intersect at certain sequences. Bifunctional ribozymes could be drivers of RNA evolution by allowing neutral networks of distinct phenotypes to intersect in genotype space. Collectively, our computational and experimental analyses will reveal how interconnected distinct RNA functions are in sequence space and illuminate viable paths toward evolutionary diversification of RNA enzymes.

# NEUROSCIENCE

## Assessment of Conductive Presbycusis in Humans

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Age-related hearing loss, or presbycusis, is a commonly experienced and described condition that affects most of the elderly population. Presbycusis is commonly considered to be of inner ear origin, but there is emerging evidence that a portion of age-related hearing loss may be mechanical (conductive) in nature. Conductive presbycusis results from dysfunction of the outer and/or middle ear and may be characterized by an isolated high-frequency hearing loss. Despite its prevalence, there is no clear way to identify and localize conductive presbycusis. Currently used techniques are inadequate for identification of high frequency conductive pathology. The goal of this study was to identify noninvasive methods to reliably diagnose high frequency conductive hearing loss. Extended frequency air conduction (9-16 kHz) and bone conduction (6-16 kHz) hearing tests were performed, along with Wideband Acoustic Immittance and Laser Doppler Vibrometry tests. Subjects included those with normal hearing and those with previously diagnosed presbycusis. Through these non-invasive tests, both air and bone conduction at extended frequencies and vibrational properties of the middle ear were determined, allowing for comparison between participants with normal hearing and those with presbycusis. We expect to find a subset of patients with presbycusis to have lower thresholds in bone conduction than air conduction by 10dB or more, which will support the notion of clinically relevant conductive presbycusis. Characterization of conductive presbycusis from noninvasive hearing tests may lead to noninvasive methods of identifying specific causes of hearing loss, contributing to improved patient-centered care overall.

## Cortical Interneuron Development is Disrupted in an NMDA Receptor Hypofunction Model of Schizophrenia

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Schizophrenia (SZ) is a chronic and severe neurodevelopmental disorder that affects 0.5-1 percent of the population worldwide. Disruption in the control of excitatory neurons by cortical inhibitory interneurons (CINs) is thought to underlie altered processing of cortical information in SZ, however, mechanisms that regulate CIN development are still being elucidated. The Balu laboratory focuses on how glutamate N-methyl-D-aspartate receptor (NMDAR) hypofunction contributes to the pathophysiology of SZ. Various studies show that SZ patients have functional deficits in parvalbumin-expressing (PV+) CINs. Furthermore, preclinical studies show that genetic deletion of NMDARs in PV+ causes brain and behavioral abnormalities consistent with SZ pathophysiology. Evidence suggests that NMDAR activity plays a role in CIN development. For activation, NMDARs require the binding of the agonist glutamate and D-serine at the co-agonist modulatory site. D-serine is racemized from L-serine by the neuronal enzyme serine racemase (SR). We found that SR mRNA colocalizes with the GluN1 subunit of the NMDAR at embryonic and early postnatal timepoints. Our main objective is to determine whether D-serine-mediated NMDAR activity regulate the development of PV+ CINs. To answer this question, we use a transgenic mouse model that causes NMDAR hypofunction via deletion of SR (SR-/-). I show changes in the proliferation of embryonic IN progenitor cells, and reduced CIN neurotransmission markers (such as GABA transporter (GAT1) protein) in the medial prefrontal cortex at early postnatal time points in SR-/- brains. Next, we will look at the effect of SR deletion on the embryonic Nkx2.1+ progenitors and postmitotic Lhx6+ cells, which ultimately give rise to PV+ CINs postnatally. This research is significant because it will provide important insight into pathophysiology of SZ, particularly during sensitive developmental time periods. Future studies will investigate whether the administration of D-serine during embryonic development can restore NMDAR function and reverse the CIN abnormalities.

## Developing Human Stem Cell Models to Probe Mechanisms of Therapeutic Psychedelics

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Psychedelic drugs are predominantly known for their effects on cognition and sensory experiences, but a growing body of research suggests that they have therapeutic potential. Neuroplasticity, the ability of the brain to reorganize and adapt, is impaired in psychiatric illnesses such as major depression and post-traumatic stress disorder. The therapeutic effect of psychedelic compounds is hypothesized to occur via promoting neuroplasticity by acting on the serotonin system, particularly the serotonin 2A (5-$HT_{2A}$) receptor. However, a deeper understanding of mechanisms of action of these compounds is necessary for the development of precision psychedelic medications. The current study aims to establish a human neuronal model that will be used to evaluate psychedelic-induced neuroplasticity. To address this, neural progenitor cells derived from human induced pluripotent stem cells (iPSCs) were differentiated for up to 6 weeks and validated for expression of mature neuronal markers at different time points. Once the model was established, a panel of serotonergic compounds, including psychedelics, was screened for effects on neuroplasticity, quantified by changes in the density of immunostained synapses. Compounds were also screened for effects on cell death and cell viability. Western blots confirm that the 5-$HT_{2A}$ receptor is expressed in iPSC-derived neurons at each differentiation timepoint, and antibody concentrations for immunostaining experiments have been optimized. Results from the neuroplasticity and cell death/cell viability studies are forthcoming, and additional experiments are required to validate the functional activation of 5-$HT_{2A}$R in response to psychedelic compounds. To our knowledge, this is the first panel of human iPSC-derived neurons used to screen psychedelic compounds; the development of this model paves the way towards future high-throughput *ex vivo* drug screens.

## fMRI Study: Neural Representations of Opinions and Knowledge

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In a highly polarized political climate, distinguishing between matters of fact and matters of opinion is paramount. Through the advent of technology, the public has greater access to information than ever in the forms of both opinions and data. Despite this, people struggle to differentiate between factual and opinion statements they encounter in this vast informational landscape. This phenomenon feeds into the development of a polarized political landscape: when opinions are treated as knowledge, the political attitudes and policy positions of individuals are further polarized. This fMRI study investigates the neural representations of statements about the world. Participants reviewed political and non-political propositions phrased as either opinions or factual statements, and made explicit judgments about the type of each statement (opinion statement or factual statement). Neural representations were extracted from the consideration period for each statement and visualised using fMRI. Whole-brain representational similarity analysis and multivariate cluster analyses were then used to evaluate the relationships between the different statements, leading to the conclusion that participants have significantly more difficulty in parsing fact and opinion statements in political contexts than in apolitical ones. While data collection is still in progress, result from this study could impact both our philosophical understanding of knowledge and provide insight on how the brain codifies information.

## Understanding the Transgenerational Epigenetic Effect of Maternal Psychosocial Trauma Exposure on Infants via lncRNA-sequencing

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Pregnant women and children are particularly vulnerable to psychosocial trauma and its consequences, which places them at higher risk of posttraumatic stress disorder (PTSD), major depressive disorder (MDD), and comorbid PTSD and/or MDD. Several prospective mother and child cohort studies have found that children exposed to maternal psychological depression, stress, or anxiety during the prenatal period are at greater risk of developing behavioral and or emotional problems in the future. However, an understanding of the biological mechanisms that underlie the vulnerability of these children due to maternal exposure is still limited. Since perinatal stress can affect children into adulthood, this study aims to bridge the gaps in current knowledge, advance understanding of the negative effects of perinatal exposure, and further outline signs for early detection. To do this, we have examined RNA-mediated epigenetic factors of the Drakenstein mother and infant cohort. A unique cohort with only trauma exposed participants. Specifically, we will examine lncRNA and lncRNA-mediated epigenetic effects at birth of infants exposed in utero to maternal PTSD/MDD. Then, we will explore the stability of lncRNA-mediated epigenetic factors associated with exposure to maternal PTSD/MDD at birth and at ages 2 and 5 years. Finally, we will examine the correlative relationship of the lncRNA expression profiles on behavior and developmental measures of the infants at ages 2 and 5 years. We hypothesize that that expression in lncRNA regulatory pathways is reduced in newborn infants' case vs. control. Additionally, we expect epigenetic effects to persist throughout childhood and impact early developmental stressors. Such results would indicate that stress induced alterations of lncRNA networks is a potential therapeutic target for negative behavioral and developmental outcomes in trauma exposed children.

## Threat Perception Determines Hypothalamoseptal Activity and Physiological Responses to Environmental Threats

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Experiences shape perceptions about our external world to guide behavior. Threat perception can influence different defensive behavioral outcomes in response to threatening stimuli. Using in vivo calcium imaging, our lab has shown that neurons expressing the stress-related neuropeptide receptor gene, Crfr2, in the lateral septum (LS), a forebrain limbic structure, influence and encode distinct aspects of the threat response: threat detection, arousal, and outcome prediction. Additionally, glutamatergic afferents from the Supramammillary nucleus (SuMVglut2) to the LS, also track with pupil-linked arousal and innate threat detection. Interestingly, when mice are trained to associate either a controllable or an inescapable punishment with a tone, the mice that perceive the threat as inescapable display larger neural responses in LSCrfr2 and LS-projecting SuMVglut2 neurons. Given these two subsets of neurons track closely with physiological arousal, we hypothesized that distinct threat perceptions could be responsible for evoking distinct global arousal states that may underlie differences in neural activity. Using video tracking and a pulse oximeter capable of detecting biological metrics such as heart rate, respiratory rate, oxygen saturation, movement and pupil size, we found that mice that perceived the threat as inescapable had increased pupil dilation, lower velocity, lower heart rate, and increased O2 saturation in response to the threat cue, compared to mice that learned they could avoid the threat. These results suggest the perception of inescapable threat leads to enhanced physiological indices of arousal, as compared to the perception of controllable threat. Together, we postulate that differences in threat perception, directed by experience, can differentially influence bodily and brain states, likely to guide the most adaptive behavioral response. Ongoing studies will dissect the input-output anatomical organization of the SuM-LS circuit to understand how this node is embedded in a broader threat and arousal network.

## Lateral Septum Crfr2+ Neurons Modulate Internal Arousal States via Polysynaptic Connections to the Cortex

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Responses to environmental stimuli are modulated by internal arousal states, which allow animals to quickly transition between quiescent states and hypervigilant states that are necessary for survival. However, excessive arousal can be maladaptive and is a common symptom of human anxiety disorders. The lateral septum (LS) is a largely understudied subcortical brain region that has been implicated in regulating such internal arousal states through putative indirect connections to cortical regions. Previous research has suggested that the *Crfr2*+ expressing subset of neurons within the LS respond to external threats and that their activity is sufficient to drive changes in arousal states. Even so, the exact neural circuit mechanisms by which LS *Crfr2*+ neurons regulate defensive behaviors via changes in global arousal states remain unknown. Given the putative associations between the LS *Crfr2*+ neuronal subset and arousal, we hypothesized that the underlying neural pathway may involve connections of a polysynaptic nature. Using a combination of experimental approaches and computer vision techniques, we have indeed identified neural circuitry in mice that drive arousal in an indirect, polysynaptic manner. Specifically, we first conducted a series of ramp-up startle response experiments using in vivo calcium imaging, which demonstrated how increasing salient stimuli drives increases in behavior but not in LS *Crfr2*+ activity. This suggests that LS *Crfr2*+ activity is not correlated with a specific behavior (e.g. freeze or flight) but rather modulates global arousal in response to the detection of threatening stimuli in the environment. Follow-up anterograde transneuronal circuit mapping with Herpes simplex virus 1 led to anatomical validation of an indirect pathway into the cortex that may be involved in regulating internal arousal states. Further confirmation of the relationship between internal arousal states and cortical connections will require additional investigations of both the behavioral and anatomical data, which we plan to perform using wavelet analysis and computational models, respectively.

## Effects of Cannabis Usage and Childhood Trauma on Cortical Gyrification Across Psychotic Disorders

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Cortical gyrification is the pattern and degree of brain folding. Studies of gyrification in schizophrenia, schizoaffective disorder, and bipolar disorder type 1 report discordant findings. Here, we directly compare gyrification across these disorders and assess the influence of cannabis and childhood trauma as possible mediators of cortical folding in psychosis. Participants were recruited within the Bipolar-Schizophrenia Network of Intermediate Phenotypes consortium. All participants received MRI and clinical assessment. A subset (controls, n = 239; Schizophrenia, n = 170 ; Schizoaffective, n = 171; Bipolar1, n = 150) completed the Childhood Trauma Questionnaire (CTQ) and reported cannabis use. Gyrification was measured using Freesurfer 7.1.0. Group comparisons were conducted in R adjusting for age, sex, race, scanner, and total intracranial volume. p values below 0.05 after false discovery rate correction were considered significant. Group comparisons indicated significant hypogyria across probands compared to controls. Effect sizes indicated more severe hypogyria in subjects with schizophrenia and schizoaffective disorder than those with bipolar disorder. Subjects with bipolar disorder showed hypergyria of the left frontal-occipital lobes compared to subjects with schizophrenia and of the right cingulate compared to subjects with schizoaffective disorder. Age of first cannabis use and CTQ score affected hypogyria differently by diagnosis; hypogyria was more extensive in subjects with schizophrenia than schizoaffective disorder, and no effect was found for subjects with bipolar disorder-1. We found widespread hypogyria in all control-proband comparisons. Between-proband findings indicated a pattern of increasing hypogyria from probands with bipolar to schizoaffective to schizophrenia disorders, providing novel data on gyrification in psychotic disorders. There were indications of cannabis and trauma effects on gyrification in probands with schizophrenia and to a lesser extent with schizoaffective disorder. We will further investigate the effect of illness duration on gyrification and the relationship between gyrification and cognition and clinical symptomatology.

## Investigating the Effects of RIMS2 Depletion in Primary Cortical Neurons

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Parkinson's disease (PD) is a major neurodegenerative disorder characterized by preferential loss of dopaminergic neurons in the substantia nigra. Recently, the Scherzer Lab discovered a genetic locus strongly linked to accelerated progression of Parkinson's Disease (PD). Individuals with genetic variations in the gene known as regulating synaptic membrane exocytosis 2 (RIMS2) showed signs of dementia significantly earlier than noncarriers. The RIMS2 protein is involved in vesicle docking and priming, playing a crucial role in synaptic transmission. The protein's critical functions in the presynaptic terminal suggests that impairment of RIMS2 function could destabilize the active zone — potentially accelerating neuronal dysfunction and progression of PD. This research will investigate how loss of RIMS2 function may enhance the progression of PD. To determine the effect of RIMS2 in the brain, we performed a series of mechanistic experiments to assess the consequences of RIMS2 knockdown (KD) in rat primary neurons. Rat primary neuronal cultures were transfected with a small interfering RNA (siRNA) cocktail that targets the RIMS2 gene for silencing. Cultures are quantitatively assessed using immunocytochemistry, western blotting, and quantitative PCR. Techniques that allow for analysis of protein and mRNA content. Future work aims to determine if RIMS2 KD affects the levels of alpha-synuclein (a-syn); a protein whose aggregates are the major pathological hallmark for PD. We hypothesize that KD of RIMS2 may perturb a-syn homeostasis, potentially enhancing neurodegeneration. Generally, our work aims to unravel the molecular mechanisms of Parkinson's allowing for more accurate prediction of disease progression and the development of new treatments.

## Immunofluorescence Performed with Adult Human Glioma Tissue Samples Yields Signals for Excitatory and Inhibitory Neurotransmitter Receptor Subunits

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Gliomas are the most common primary central nervous system tumor, representing 81% of all intracranial malignancies. With a median overall survival of about 15 months, high mortality and morbidity characterize high grade gliomas despite their relatively rare occurrence. Thus understanding the molecular drivers of glioma is crucial to finding therapeutic targets that would improve patient survival and clinical prognosis. High grade gliomas are thought to be driven by a few key somatic alterations in the genome such as mutations in isocitrate dehydrogenase 1 *IDH1*, telomerase reverse transcriptase *TERT* promoters, and *p53* tumor suppressors. However less is known about the effect of neuronal activity on glioma cell proliferation and migration. In this study we sought to qualitatively characterize the distribution of neurotransmitter receptors in samples of supratentorial glioma tissues from human adults via an immunofluorescence assay. Primary antibodies were used to target the NMDA glutamatergic receptor GluN1 subunit, the AMPA glutamatergic receptor GluA1 subunit, and the ionotropic GABA(A) receptor beta subunit. We determined via preliminary qualitative analysis that glioma cells yield signals for all three subunits, with the NMDA and GABA(A) subunits yielding a stronger overall signal. These findings elucidate the potential for neuronal impact on the development of glioma cells. These findings elucidate the potential for neurotransmitter action on glioma cells via receptors which might impact cell proliferation and migration. Future research will focus on identifying the impacts of classical neurotransmitters glutamate and GABA on glioma cell proliferation *in vivo*.

## Building a Computational Pipeline to Quantify Adult-Infant Interactions in Mice

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Until recently, the analysis of animal behavior in research was restricted to manual scoring by humans. The development of deep neural networks in the form of pose estimation software such as DeepLabCut has facilitated the task of scoring behaviors through quantitative means. This project aims to create a computational pipeline that uses spatiotemporal body tracking data from adult and infant mice produced by DeepLabCut to classify occurrences of salient adult-infant interactions (infant retrieval, infant investigation, huddling, etc.). Kinematic features were extracted from this data using custom Python scripts to algorithmically calculate aspects of adult-infant interactions, such as movements of the adult, distance between the adult and infant, and the angle formed by different points on the adult's body. These features were then used as inputs to train several RandomForestClassifier models (a type of machine learning model), each of which are intended to classify the occurrences of predetermined adult-infant interactions on new adult-infant interaction data. Thus far, we have developed a model that is successfully able to classify the number of times an adult retrieves an infant, along with the specific time points at which retrieval is occurring. While progress has also been made on feature extraction and models for the classification of infant approach, infant investigation, and adult huddling, initial results have been promising in showing that a computational pipeline provides a fast, reliable, and reproducible method for quantifying important adult-infant interactions in mice compared to manual scoring.

## Inflammation and Blood-Brain-Barrier Leakage Associated with Microhemorrhage in Cerebral Amyloid Angiopathy

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Cerebral amyloid angiopathy (CAA) is a small vessel disease found in over 33% of general autopsies and 90% of those with Alzheimer's disease. It is a leading cause of symptomatic intracerebral hemorrhage and a major contributor to age-related cognitive decline. However, the mechanisms leading to hemorrhage in CAA remain largely unknown. CAA is characterized by the deposition of amyloid β (Aβ) in the walls of cerebral blood vessels. Recent work has shown that ruptured blood vessels have evidence of Aβ removal and vessel wall remodeling, potentially driven by inflammatory processes. In this study, we used serial sectioning and histopathological analysis to evaluate perivascular inflammation, blood-brain barrier (BBB) leakage, and vessel integrity on a single vessel level across different degrees of CAA severity. Using adjacent 6μm sections localized at areas of confirmed microbleeds by ex-vivo MRI, immunohistochemistry was performed against Aβ, fibrin(ogen), smooth muscle actin (SMA), reactive astrocytes (GFAP), and activated microglia (CD68). Individual vessels were graded using a previously defined CAA severity system, and a blinded sholl analysis was performed to quantify levels of inflammation in surrounding tissue. Across vessel grades, BBB leakage, SMA coverage, and perivascular inflammation were assessed. Our results indicate that increased CAA severity in individual vessels is associated with BBB leakage, SMA loss, and perivascular inflammation. These findings suggest that BBB leakage and inflammation may play a critical role in CAA pathogenesis and introduce new potential therapeutic targets.

# Molecular RNA and Protein Machinery within Subtype-specific Corticospinal Synapses as Potential Underpinnings of Selective Vulnerability in ALS

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that affects both corticospinal neurons (CSN: "upper motor neurons") and spinal motor neurons (SMN: "lower motor neurons"), leading to spasticity, diffuse and respiratory muscle weakness, paralysis, and death. In the neocortex, neuronal subtypes diversity is very important for understanding ALS, because this disease centrally affects these two specific neuronal populations–CSN (a subtype of sub-cerebral projection neurons) in the brain's neocortex, and SMN (their indirect or direct synaptic partners, which directly innervate muscles) in the spinal cord. This selective vulnerability is despite the fact that mutations causing familial ALS are present in every neuron type and cell type in the body, including closely related cortical subtypes that do not degenerate. Given that CSN and SMN are both key components of corticospinal circuity, the disturbances of the normal functionality of corticospinal synaptic nerve terminals might contribute to the disease. This project aims to adapt and optimize state-of-the-art synaptosome purification and enrichment approaches to investigate CSN subtype-specific synaptic transcriptomes/proteomes that might contribute to selective vulnerability in ALS, using the human mutation $hSOD^{G93A}$ ALS mouse model. We isolated cortical and spinal synaptosomes of 6-week-old mice via ultracentrifugation and sucrose density gradients. We then performed western blots, testing for enrichment of presynaptic markers and de-enrichment of nonsynaptic markers. We have confirmed both enrichment and protease protection of pre- and postsynaptic markers, indicating isolation of at least partially intact membrane-bound synaptosomes. These results indicate that synaptosomes can be isolated with membranes remaining at least partially intact after ultracentrifugation. We next aim to apply this optimized approach to isolate and analyze CSN subtype-specific synaptosomes in $hSOD^{G93A}$ ALS model mice. The research promises to identify proteins/RNAs with altered abundances at CSN synapses in ALS model mice, which might uniquely inform future mechanistic investigations into ALS pathology, and CSN selective vulnerability in ALS.

# ORGANISMIC AND EVOLUTIONARY BIOLOGY

## Analyzing Ancient DNA to Better Understand the Population History of the Indian Subcontinent

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Ancient DNA has revolutionized the study of the human past. For instance, it has demonstrated that ancient human populations frequently migrated and interbred with neighboring populations, upending the idea that ancient communities were inclined to stay in one place. By improving our understanding of human evolutionary history, ancient DNA research has helped us better understand recessive diseases, especially in the Indian subcontinent, which consists of many population subgroups. This summer, I analyzed ancient DNA from individuals in India and Pakistan to better understand the population history of the Indian subcontinent. I used standard methods such as PCA (principal component analysis), f3 statistics, four-population tests, admixture analyses, and FST analysis to understand the evolutionary history of several groups of individuals on the subcontinent.

## The Influence of Soil Characteristics, Water Availability, and Topography on the Spatial Distribution Patterns of Tall Trees in the Southeast Asian Tropics

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In tropical forests, tall trees (top 1-5 percent in height) are known to have a disproportionate influence on forest dynamics and play a large role in carbon sequestration. Tall trees have to overcome a number of challenges in order to reach and sustain their large size. Water transport through the xylem becomes increasingly harder as trees get taller and consequently tall trees are more vulnerable to climate change impacts. In addition, tall trees are often selectively targeted for logging. The outsized role and vulnerabilities of tall trees make understanding and conserving them important, especially in light of the rapidly changing climate. However, little is known about the environmental conditions that enable these trees to reach their extreme heights. To investigate this, I analyzed relationships between forest canopy height and a series of environmental attributes, including topography, distance to the nearest stream or river, and soil texture and chemistry, hypothesizing that tall trees are more likely to occur at lower elevations, near water, and in nutrient-rich soils. The findings from this study can inform targeted conservation plans that support the persistence of these important individuals.

## Metabolic outcomes of early-life gut microbiome disruption with antibiotics

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Early life disruptions in the gut microbiome have been linked with alterations in host metabolism, leading to conditions such as obesity, though the extent of these adverse physiological consequences is not well understood. We now show that low- and high-dose antibiotic treatment in specific pathogen free mice during early life development causes perturbations in the gut microbiome that lead to symptoms of metabolic dysregulation. Here, we measured energy harvest during early life, mouse body composition (via EchoMRI), oral glucose tolerance in adults, and lifelong fecal microbial composition (via 16S sequencing). We found that any disruption of the gut microbiome with antibiotics (both low and high doses) altered growth rate and body fat in a sex-specific manner compared to controls. To date, there was no distinguishable difference in glucose tolerance. However, 16S sequencing data revealed statistically significant perturbations in gut microbial communities between experimental and control mice. These studies highlight key physiological consequences in adults of early life gut microbiome disruptions and have implications for our understanding of the critical role of the gut microbiome during growth and metabolic development.

## Mechanical and Genetic Dynamics of Villus Development in the Chicken Hindgut

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Villi are protrusions into the intestinal lumen that increase surface area to aid nutrient absorption. Villus development in the midgut of the chicken (*Gallus gallus*) relies on global mechanical constraints generated by alternately oriented layers of smooth muscle, while mouse (*Mus musculus*) midgut villi likely develop due to local signals from cell clusters that result from inherent mesenchymal contractility. However, the chicken hindgut develops disorganized villi, and the contributions of mechanical forces or mesenchymal signals are unclear. In this project, perturbations of tissue constraints and analysis of RNA-seq data were carried out to elucidate the interplay of mechanical and signaling factors in hindgut villus morphogenesis. We implemented a new explant protocol, in which hindguts were dissected from chicken embryos and grown *in vitro* to enable physical and chemical perturbations. Hindguts were cut in patterns that relieved circumferential or longitudinal mechanical constraints, or both. Hindguts were treated with small molecules to reduce smooth muscle contractility or to inhibit non-muscle myosin to prevent mesenchymal clustering. Preliminary data suggest that the circumferential but not the longitudinal muscular constraint is key to hindgut villus development. Inhibiting mesenchymal contraction also disrupts villification, suggesting that hindgut villi also require local mesenchymal signals. To address genetic factors underlying hindgut villification, we carried out RNA-seq data analysis to compare gene expression levels in hindguts and midguts that were posteriorized using viral overexpression of the posterior homeobox gene *HOXD13*. Analysis of differentially expressed genes in posteriorized midguts and hindguts suggests the involvement of angiogenesis and TGF$\beta$ related genes in hindgut morphogenesis. These genes are being validated via *in situ* hybridization. The explant protocol that we developed and this suite of genes will enable future mechanical and genetic perturbations to better resolve the relationship between circumferential stress and cluster signals in hindgut villus development.

## Genetic Basis of Behavioral Evolution in Peromyscus Burrowing

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Little is known about the genetic basis of behavioral variation and evolution, in part, due to challenges in quantifying behavior. Two sister species of deer mice, *Peromyscus maniculatus* and *Peromyscus polionotus* are good models to examine the genetic basis for behavioral evolution as they are interfertile and have strong differences in burrowing behavior. *P. maniculatus* dig short burrows and *P. polionotus* dig longer burrows with an escape tunnel. Both species' burrowing is innate and has a strong genetic component. Previous research using forward genetic mapping suggested that a locus on chromosome 4 of *P. polionotus* contributes to a longer burrow length of approximately 3cm. To characterize the specific effects of the chromosome 4 locus, we backcrossed mice to create a congenic line of *P. maniculatus* mice that contain the chromosome 4 locus of *P. polionotus*. This congenic line of mice was then placed in a tube assay where their burrowing behavior was recorded. Using the video recordings, the specific burrowing behaviors the mice performed, such as forelimb digging and pushing, were noted and quantified for each mouse. This data will be analyzed to determine which behaviors are performed most frequently, how much time is spent on each behavior, and the sequence of the behaviors. The results from these analyses will determine whether the chromosome 4 locus significantly contributes to a longer burrow length and if so, which specific behaviors and behavioral patterns are associated with the chromosome 4 locus.

## Computational Analyses of Vocal Evolution in Deer Mice

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Vocal behaviors are diverse across mammals, but the genetic and neural mechanisms underlying this diversity are poorly understood. Unlike traditional models of vocal behavior, deer mice (genus *Peromyscus*) exhibit natural vocal variation. Furthermore, the rodent group is abundant across various North American habitats and interfertile among distinct species, providing a unique opportunity to study the evolution of vocalization. Yet, their vocal ontogeny lacks quantitative description, data necessary to uncover genetic and neural causes of natural variation in vocalization. This summer, I recorded vocalizations from mice belonging to 9 *Peromyscus* species at 1, 3, 5, 7, 9, 11, and 13 days of age and adolescents at 3 to 5 weeks of age. I then built a computational bioacoustics pipeline to detect, quantify, and compare vocal syllables across development and between species. This data set lays the foundation for genetic mapping and tissue staining, among other tools, to be used to identify genetic and neural differences underlying natural variation in vocal behavior. This work will ultimately contribute to our understanding of animal behavior evolution and may also provide insights into human language and speech pathology.

## High Temperature and Pressure Cultivation of a Complex Microbial Community from a Hydrothermal Vent Environment Could Increase the Known Upper Temperature Limit of Life

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The current upper temperature limit of life (UTLL) of 122 °C is likely underestimated, as microbial consortia are known to live in metabolic syntrophy around hydrothermal chimneys with *in situ* temperatures above 300 °C. This study hypothesizes that syntrophy increases microbes' experimental tolerance to high temperature and pressure (HTP), but because of HTP conditions around hydrothermal vents *in situ* assessment of this hypothesis is difficult. This study incubated hydrothermal sulfide chimney samples collected from the East Pacific Rise at 120°, 122°, 125°, and 130 °C; 20.68 MPa; and a $H_2$, $CH_4$, and $H_2S$ gas mixture dissolved in artificial vent water medium with $^{13}C$- and $^{15}N$- labeled aqueous tracers. Daily subsampling was performed to monitor reduction potential (Eh), pH, and dissolved gas composition, which might indicate microbial metabolism if either a decrease in Eh or oxidation of reducing gases was observed relative to a sterile control. Direct cell counting, fluorescent *in situ* hybridization (FISH), and nanoscale secondary ion mass spectrometry (nanoSIMS) imaging were used to assess, respectively, microbe abundance, taxonomy, and metabolism. While data is forthcoming, results would indicate a new UTLL if nanoSIMS-imaged cells were directly observed with isotopically heavy biomass indicating non-equilibrium incorporation of $^{13}C$- and $^{15}N$-labeled tracers. Community compositions and hypothesized metabolisms of these hyperthermophiles would then be parsed via metagenomics and targeted tracer experiments enriching for defined metabolisms. The hypothetical "most" HTP-tolerant microbe(s) could be chemolithoautotrophic (i.e., metabolizes inorganic matter) or rely on more complex syntrophic interactions among species. Additionally, a higher UTLL would widen the known habitable zone of life on Earth and imply expanded habitability in geothermal settings on other ocean worlds (e.g., Jupiter's moon Europa and Saturn's moon Enceladus).

## Cooperative Behavior and Competition in Acacia Ants

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Cooperative behavior is essential to social insects such as ants for foraging, nursing, hygiene and nest defense. Although cooperation between workers in ant colonies is well known, changes in levels of cooperation during the development of a colony or in response to changing environmental conditions have not been well-studied. To analyze potentially adaptive changes in cooperation, the behavior of seven colonies of *Crematogaster mimosae* and *C. nigriceps* will be compared. These closely related species are native to East Africa where they compete to inhabit specialized swollen thorn domatia on trees of the plant *Vachellia drepanolobium*. To characterize each colony's behavior, either twelve ants of the same species or six of both species, were placed inside a ring of agarose gel, presenting the challenge of how to escape from a small compartment. A camera recorded the ants' movements, and tracking software translated each of these movements into distinct behavior patterns. During the excavation, the expansion of the gel's inside perimeter represented the escape speed. Preliminary results suggested high levels of cooperation within species, as both species dug one wide tunnel rather than narrow individual ones. Future trials will test behavioral differences within species, whose colonies vary in size and age, and between species. I hypothesize that older and more experienced workers in colonies of the same species will be more likely to cooperate, thereby facilitating faster escape than workers from colonies of different species who will be less likely to cooperate. Differences in behavior between ants from competitive and non-competitive environments will provide insights into how competition influences cooperation. On a broader scale, differences in behavior that depend on colony characteristics such as age, size, and experience will also provide insights into the evolution of sociality and the extended phenotype exhibited by nest construction and habitat modification.

## A Global Phylogenetic Structure of the Female Genital Tract Microbiome Improves Host-Microbe Associations

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HIV is a worldwide health crisis that affects an estimated 38 million people. In sub-Saharan Africa, one of the epicenters of the global pandemic, infections disproportionately occur in young women, with over 90 percent of transmissions following heterosexual sex. The mucosal surfaces of the female genital tract (FGT) are the primary site where HIV infection is established. Certain bacterial communities in the FGT are associated with an elevated risk of HIV acquisition, likely due to increased local mucosal tissue inflammation as measured by increased inflammatory cytokines in genital secretions. Previous attempts to identify the specific bacteria mediating this inflammation reached only limited resolution and could not clearly track correlations between precise bacterial strains and cytokine levels. We hypothesized that breaking up traditional species into more stringently-defined species genome bins (SGBs) based on phylogenetic distances would improve associations with host inflammatory cytokines. Leveraging a comprehensive genome catalogue for the FGT and high throughput shotgun metagenomic sequencing, we built a novel taxonomic profiling tool to determine relative abundances of FGT microbes in samples from young women in sub-Saharan Africa and validated the tool against simulated communities. Focusing on species that split into multiple SGBs, we performed downstream statistical analyses including ordination, clustering, and other multivariate data analysis methods to integrate bacterial abundances with coupled cytokine profiles. We found that taxonomic differences do improve associations between the FGT microbiome and local inflammation. These findings may be used to develop more targeted antibiotic and probiotic interventions to disrupt high-risk bacterial populations and subsequently reduce HIV acquisition risk for women in sub-Saharan Africa.

# STEM CELL AND REGENERATIVE BIOLOGY

## Investigating Functional Regionalization in the Human Uterus

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The plasticity and regenerative capacity of the human uterus are unmatched — throughout the average reproductive window, the uterine lining sheds and renews itself over 400 times, and during pregnancy the uterus undergoes drastic changes in size and cellular makeup to accommodate the growing blastocyst. Yet while the basics of uterine anatomy are well-understood, the ways in which differences in the localization and prevalence of different cell types across the uterus may influence the organ's outstanding capabilities are not. In particular, unexplained functional differences have been observed along the two main axes of the uterus. Along the endometrial-serosal axis, only the stratum functionalis layer sheds and renews while the stratum basalis layer remains unchanged, hinting at the existence of an unidentified endometrial stem cell. Meanwhile, rates of successful blastocyst implantation vary widely along the fundal-cervical axis. This project aimed to investigate regional differences in cellular makeup across these axes, in the hopes of elucidating potential cellular-level bases for these functional differences and identifying candidate endometrial stem cells. Three uteri were obtained from brain-dead adult donors and each regionalized along the fundal-cervical axis; each region was then sectioned and subjected to repeated rounds of immunofluorescence to stain cell markers and thus visualize different cell types. Each section provides a snapshot of tissue along the endometrial-serosal axis, while comparison of sections from different regions offers two-dimensional insight into differences along the fundal-cervical axis. Significant preliminary results indicate that expression of N-cadherin and SSEA-1, antibodies proposed to be markers of the endometrial stem cell, is too nonspecific to support this potential role. Next steps include whole-mount staining to obtain a three-dimensional look at cell type localization and prevalence, as well as Slide-seq to simultaneously examine transcriptomic and positional information about sampled cells.

# ICAM-1 as a Potential Target for the Immune Protection of Stem Cell-Derived Beta Cells

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Type 1 Diabetes (T1D) is a disease marked by the autoimmune destruction of insulin-secreting, pancreatic $\beta$-cells. While $\beta$-cells can be derived from a renewable source (stem cells) *in vitro*, they are subject to immune attack once transplanted into a diabetic patient. Thus, a remaining challenge in the field is to engineer stem cell islets that are resistant to immune destruction. Most immune-protection strategies focus on limiting end-stage islet destruction, yet less is known about the events underlying the initial immune cell recruitment to the islet. Furthermore, how $\beta$-cells respond to an inflammatory milieu, and how this response shapes immune cell infiltration remains ill-defined. Pro-inflammatory cytokines mediate crucial interactions between islet cells and immune cells in T1D. To determine whether $\beta$-cells promote immune cell recruitment in an inflammatory context, we analyzed RNA-sequencing data from primary human islets treated with cytokines. We observed that islets cells significantly upregulate intercellular adhesion molecule 1 (ICAM-1). ICAM-1 aids in the formation of the "immunological synapse" between a T lymphocyte and an antigen-presenting cell, by polarizing the peptide-MHC complex and allowing for productive interactions with a T cell receptor. Furthermore, mice deficient in ICAM-1 are normoglycemic and resistant to developing diabetes. We hypothesized that ICAM-1 is necessary in T-cell mediated $\beta$-cell destruction. We first verified that ICAM-1 is highly upregulated on the surface of stem cell-derived $\beta$-cells (sc-$\beta$ cells) in the presence of cytokine stimuli. Then, to determine whether ICAM-1 blockade could blunt T cell effector responses, we co-cultured sc-$\beta$ cells with matched patient T cells, treated with an ICAM-1 monoclonal blocking antibody. Our end goal is to produce an ICAM-1 KO sc-$\beta$ cell line via CRISPR-Cas9 engineering to determine whether ICAM-deficiency protects $\beta$-cells from immune destruction *in vivo*. Accomplishing this would mark ICAM-1 as a promising target toward the goal of producing immune-evasive $\beta$-cells.

# The Development of an Axolotl Limb Explant Culture

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Currently, around two million people in the United States live with limb loss. Driven by an ageing population and an increased prevalence of cardiovascular disease, this figure is expected to double by the year 2050. Unfortunately, no viable treatment option exists for such patients outside of prosthesis. Of primary focus is the identification of factors early in the regenerative process that alert an organism to limb loss and subsequently activate regeneration. However, the lack of an *in vitro* system modeling limb regeneration has severely limited progress towards elucidating such mechanisms. Here, we describe a novel method for culturing limb explants from *Ambystoma mexicanum*, a species of salamander capable of fully regenerating lost or injured limbs within weeks. Importantly, these three-dimensional explants largely maintain cellular viability upwards of five days post culture, as evidenced through apoptotic staining (TUNEL). Moving forward, such a model will allow cheaper, faster, and higher throughput assays for investigating limb regeneration in the axolotl salamander, and hopefully, inform the development of future therapeutics.

# Study of Early Initiators of Aging in Mouse Hindlimb Skeletal Muscle to Modulate Healthspan

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Skeletal muscle in mammals shows a progressive decline in regenerative function with age. This decline is partially driven by changes in satellite muscle progenitors—the resident stem cell population in muscle tissue responsible for repairing damaged muscle—and their respective niche cells. While many studies have characterized the changes these cell types undergo with advanced age, understanding the early pathology of age-related decline remains an open area. Numerous studies have reported specific timepoints of interest for looking at early initiators of tissue degeneration within C57BL/6 mice. These time points are characterized by significant changes in gene and protein expression across multiple cell types and multiple key regulatory pathways. These changes result in either the increased presence of proteins correlated with aged phenotypes or the decreased expression of proteins associated with healthy tissues. To further characterize these changes, mice ranging from eight to sixteen months will be analyzed to identify early differential changes in gene regulation that modulate the healthspan of hindlimb skeletal muscle. Identifying early modulators of age-associated degeneration will open up new translational avenues for preventing drastic, debilitating declines in tissue health and function.

# PHYSICAL AND MATHEMATICAL SCIENCES

# CHEMISTRY

## Carbon Monoxide Oxidation on Platinum Powder in a Temporal Analysis of Products Reactor

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Platinum is an important catalyst for many industrial oxidation and reduction reactions, and it is used in essential technologies such as catalytic converters. One of the most common reactions performed over platinum catalysts is the oxidation of carbon monoxide to carbon dioxide. This reaction has been well studied using a variety of techniques, but it is still poorly understood and has not been extensively studied using a temporal analysis of products (TAP) reactor. TAP experiments can be used to precisely determine the kinetics of gas-solid catalytic reactions, providing accurate measurements of kinetic coefficients such as activation energies. In order to study the reaction between carbon monoxide and oxygen on platinum, a mixture of the two reactant gases was pulsed over the catalyst at varying temperatures and ratios. Additionally, uptake and temperature programmed desorption experiments were conducted for both carbon monoxide and oxygen to see the different types of active sites on the catalyst surface and to see in which order those sites are filled up. In stoichiometrically-balanced or oxygen-rich reaction environments, the carbon dioxide production rate was observed to be different when heating and cooling the reactor over the temperature range of 25–300 °C. In an oxygen-poor environment, carbon dioxide production was the same when heating and cooling. The uptake and desorption experiments for carbon monoxide and oxygen showed that there are multiple different active sites on the platinum catalyst. For oxygen, the first active sites filled were those that require the highest temperatures to desorb the gas from the catalyst surface. These experiments will increase the breadth of knowledge of this important catalytic reaction and inform our further study of carbon monoxide oxidation on platinum in an ambient pressure flow reactor, allowing improved efficiency of industrial systems and technologies.

## Investigating Chronic Pain Signalling: $Na_v1.7$ Selective PET Probes

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Chronic pain is one of the most common ailments amongst adults today, leading to significant consequences. Voltage-gated sodium channels ($Na_v$) have been implicated in pain sensory pathways and chronic pain conditions. In particular, the isoform $Na_v$ 1.7 has been implicated in chronic pain signalling. Unfortunately, as of yet there are no non-invasive techniques to image $Na_v1.7$ *in vivo*. A non-invasive technique, such as positron emission tomography (PET), could provide a powerful tool to understand the regulation of chronic pain and advance potential treatment. To this end, the literature was searched for previously identified $Na_v1.7$ selective compounds. These compounds were processed in the *in silico* molecular docking software Schrödinger to create pharmacophores, a map of the features of a ligand that are necessary for biological activity. The pharmacophores were used for the quantitative structure-activity relationship screening of molecule databases for potential $Na_v1.7$ selective ligands. Multiple pharmacophores were created using various groups of $Na_v1.7$ selective ligands, including altering the presence of non-sulphonamides (sulphonamides have been identified as a major group of $Na_v1.7$ selective compounds). A pharmacophore was also created from the $Na_v1.7$ protein, as opposed to the ligand-based approach. These pharmacophores were then used to screen libraries in order to identify promising PET probe candidate molecules. It was found that for allosteric binders such as the $Na_v1.7$ selective ligands, a ligand-based pharmacophore approach results in higher recovery of active ligands. While the inclusion of the relative efficacy of molecules as IC50 values does result in higher enrichment, the additional specification of non-active molecules does not. Our findings also suggest that using a more varied group of ligands to build the pharmacophore yields higher recovery of active ligands.

# Inhibition of a Gut Bacterial Pathway for Levodopa Metabolism

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Parkinson's disease is a neurodegenerative disorder with life-threatening symptoms. While the cause of Parkinson's is currently unknown, a low concentration of dopamine in the brain is typically observed. Dopamine does not pass the blood-brain barrier, preventing direct administration. Instead, levodopa (L-dopa) is employed since it can pass the blood-brain barrier, and subsequently be converted to dopamine in the brain by the human enzyme aromatic amino acid decarboxylase. However, the majority of L-dopa does not reach the brain due to the presence of decarboxylases elsewhere in the human body. This unproductive metabolism is mitigated by administering Carbidopa, a decarboxylase inhibitor, in combination with L-dopa. Unfortunately, vast variability among patient response remains a major challenge. Recent work in the Balskus lab revealed that a tyrosine decarboxylase (TyrDC) from the human gut bacterium *Enterococcus faecalis* can metabolize L-dopa in the gut. These studies also demonstrated (*S*)-α-fluoromethyltyrosine as a promising inhibitor for L-dopa decarboxylation by *E. faecalis*. The further optimization of inhibitors targeting this microbial pathway may eventually lead to better Parkinson's disease treatment. We aimed to test various inhibitors with purified TyrDC and structurally characterize the protein to further guide the inhibitor development effort. First, we heterologously expressed TyrDC in *Escherichia coli* and purified the isolated protein. Thus far, our inhibitor assays have been consistent with the whole-cell assays suggesting TyrDC is a crucial part of the *E. Faecalis* metabolism of L-dopa and that the inhibitor is correctly targeting TyrDC rather than other mechanisms such as transport. Further inhibitor optimization will be guided by structural biology. Our efforts to structurally characterize TyrDC employed multiple approaches: X-ray crystallography, homology modeling, and mutagenesis experiments. The results of these studies will be combined to explore the active site of TyrDC and its role in catalysis of L-dopa decarboxylation, which is crucial in inhibitor development.

# The Effect of Ligand Design in Metal–Bis(acetamide) Glasses

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Glasses are critical to technologies that support our modern lifestyle, but, in contrast to crystalline solids, the realization of new glasses is limited by their lack of long-range order. Forming metal–organic glasses by quenching liquid phases of metal–organic frameworks (MOFs), which are extended networks of metal centers bridged by organic ligands, presents opportunities to achieve tunable glass materials. However, most MOFs' high melting temperatures preclude formation of stable liquid states. Excitingly, the Mason group developed a series of MOFs with record low melting temperatures, primarily containing polymethylene (n = 2, 4, 6) bisacetamide bridging ligands. Here, we focused on expanding the library of metal–bisacetamide frameworks with accessible glass states by adjusting polymethylene chain length to explore whether a systematic odd-even effect exists and by introducing ligand rigidity to increase free volume. As such, we synthesized multiple organic bisacetamide ligands, with n = 3 and 5 polymethylene chains or with more rigid cyclohexane or benzene rings between the acetamide groups. For polymethylene ligands, we then conducted vapor diffusion crystallizations to synthesize the frameworks under an inert atmosphere and x-ray crystallography for structure determination. For rigid ligands, we conducted mechanochemistry syntheses and infrared spectroscopy to confirm metal–ligand coordination. The thermal stability and melting behaviors of the new compounds were characterized by thermogravimetric analysis and differential scanning calorimetry, and powder x-ray diffraction measurements confirmed the amorphous nature of their glassy phases. With these new compounds, we not only diversified the structural library of metal–organic glasses but also explored their processability into functional materials. For example, we fabricated both glassy and crystalline thin films, whose optical and mechanical properties were tested through techniques like ultraviolet-visible spectroscopy. Furthermore, we identified compounds with reversible crystal–glass transitions, which have potential applications as temperature-controlled switches in areas such as computer memory and photonics.

## Creation of Molecular Nitrogen in Comets via UV Irradiation

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In 2014, Comet 67P Churyumov–Gerasimenko passed by Earth. The *Rosetta* probe, sent by the European Space Agency, completed a detailed compositional analysis of Comet 67P showing the presence of molecular nitrogen ($N_2$). The origin of this volatile material was unclear; other groups theorized that it may indicate a very cold comet-formation temperature or be due to abundant ammonium salts ($NH_4^+$) as alternative sources of $N_2$. We intend to discern if the molecular nitrogen present in Comet 67P could have formed *in situ* via ultraviolet irradiation of more-common ammonia ($NH_3$) ices. This work aims to gain insight into the creation, presence, and behavior of molecular nitrogen as one of the fundamental building blocks of life on an early Earth. In order to mimic the properties of space in the lab, we utilize a Surface Processing Apparatus for Chemical Experimentation to Constrain Astrophysical Theories (SpaceCAT), which creates a low-pressure, low-temperature environment in which layers of ice can be built and irradiated for extended periods. Irradiation of $NH_3$ ices should allow the N-H bonds to break, facilitating the formation of $N_2$. Infrared spectroscopy and mass spectrometry are used throughout the irradiation process and subsequent sublimation to measure the production of $N_2$ and destruction of $NH_3$. The $N_2$:$NH_3$ proportion that is formed in our experiments is compared to Comet 67P. Our preliminary results indicate a lower proportion of $N_2$ creation in the lab than in Comet 67P, possibly meaning that irradiation of $NH_3$ ices may not be the main origin of molecular nitrogen in Comet 67P. Our continuing research will further investigate the viability of ammonia ice irradiation as a source of $N_2$ in comets, and will have implications in our understanding of the origins of nitrogen compounds in space.

## Pulsed Laser Ablation Product Selectivity in Organic Solvents and Supercritical CO2

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Developing new catalysts that harness renewable resources in a sustainable fashion has never been more important as slowing global climate change requires the complete elimination of $CO_2$ emissions by 2050. The development of earth-abundant, highly active electrocatalysts that are capable of converting feedstocks to fuels, pharmaceuticals, and other value-added chemicals is one crucial route to reducing $CO_2$ emissions. A promising technique to synthesize new electrocatalysts is pulsed laser ablation in liquids (PLAL) since it can yield surfactant free nanoparticles (NPs), which is a challenge when using wet chemical methods. One fluid of interest for PLAL is supercritical $CO_2$ as the density can be varied over a wide range without having to undergo phase transitions from liquid to gas, which can be useful when attempting selective fabrication of NPs. Our preliminary findings have shown that a selectivity between metal oxide and carbide NPs is tunable depending on the density of supercritical $CO_2$ when paired with an organic solvent. In our next phase, we will use a wider range of densities for supercritical $CO_2$ and examine the NP selectivity when pairing supercritical $CO_2$ with different solvents. As productivity improves with laser synthetic methods, understanding the mechanism behind the selective synthesis of NPs will be crucial to the development of new electrocatalysts with unique surface properties to power the planet and reduce $CO_2$ emissions in a timely and economical fashion.

## On the Emergence and Spatial Localization of Simple Acid-Base Reaction Networks

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One unanswered question in research concerning the chemical origins of life research is how nominally disordered chemical reactions became spatially and temporally coupled into the processes resembling life, such as metabolism. In this work, we hypothesize and demonstrate that spatial gradients in both pH and temperature could contribute to the localization of chemical reactants and reactions–specifically by exploiting the fluid flow arising from these gradients. We employed thiol-based reaction networks as a model system for exploring how these pH and temperature gradients are coupled together and can be used to generate life-like processes. Specifically, we used a reaction network composed of cystamine, maleimide, and alanine thioester and examined the reactivity of this reaction network in unbuffered reaction conditions. Using a pH-meter (proton-selective electrode), we measured the effects of acidic or basic pHs on the reactions–modifying the pH of the solution using HCL or NaOH respectively. Preliminary results from these experiments suggest that, upon reaching an initial pH of 11.0 or higher, the reaction network achieved oscillatory behavior–similar to what one might expect in a proto-metabolic system. Based on these findings, the higher pH solutions were synthesized on a larger scale and placed in a petri dish along with a glass plate coated with a photocatalytic substance of either $TiO_2$ or pyrite with varying levels of ultraviolet light shone onto the dish and, later on, variant levels of thermal energy applied instead. Initial data from these trials seemed to imply that pH gradients may have developed between reactive regions with high thermal energy and less reactive regions with lower thermal energy. This would suggest that heat, such as from subterranean vents or the sun, may have played a role in the initial spatial localization of reaction networks in the prebiotic world that would eventually become the biochemical networks we see today.

## A Novel Reaction Type For Olefin Nitrosations

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The chemistry of olefins (hydrocarbons containing at least one carbon-carbon double bond) has long represented a greater ability to better understand chemical transformations that relate to the optimization of chemical bonding along this $\pi$-$\pi$ plane. This summer, our research has employed triflyl nitrite generated *in situ* from tetra-*n*-butylammonium nitrite and triflic anhydride in $CH_2Cl_2$ solution to serve as an effective nitroso agent for a wide range of unsaturated substrates for nitroso compound formation. These nitrosations (the addition of $NO^+$to the aforementioned unsaturated substrates) have unearthed a new type of nucleophilic-olefin attack, where these nitrosyl-additions have led to the formation of allylic and vinyl nitroso compounds depending on the substrate type. Moreover, this substrate-conditions pathway has illuminated a novel cyclization pathway that has generated stable, 4-membered ring substrates. This surprise development shifted the focus of our research in order to better investigate the methodology behind this novel, highly reactive reagent. By employing retrosynthetic pathway techniques, we were able to synthesize several new scaffolds that model this cyclic-ring structure; which ultimately proffer a potential unique, rigorous mechanism for organic chemistry.

## Activity and Stability of Nanoporous Bimetallic TiCu Catalysts

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The addition of hydrogen gas to α,β-unsaturated aldehydes to afford an unsaturated alcohol is extremely relevant to organic syntheses in chemical industries, but the process' unfavorable thermodynamics require the addition of a metal catalyst. In this study, a class of nanoporous Cu (npCu) and nanoporous TiCu (npTiCu) catalysts, formed from dealloying $Cu_{30}Mn_{70}$ and $Ti_2Cu_{28}Mn_{70}$ in acidic media, was reported. The choice of dealloying solution controlled the final composition of npCu and npTiCu materials; $Cu_{30}Mn_{70}$ in 1 M hydrochloric acid afforded $npCu_{98}Mn_8$ catalyst, and in 1 M ammonium sulfate produced $npCu_{95}Mn_5$. Similarly, $Ti_2Cu_{28}Mn_{70}$ in 1 M hydrochloric acid resulted in $npTi_{0.5}Cu_{90}Mn_{9.5}$ and in 1 M ammonium sulfate generated $npTi_4Cu_{81}Mn_{15}$. For each catalyst, a summary of its activity between 30 °C and 400 °C was produced via hydrogen/deuterium exchange (HDX) trials, in which hydrogen and deuterium gases are flowed onto the catalyst surface, where $H_2$ molecules undergo an isotopic substitution to form HD. The pressure of HD, a bellwether of catalytic efficacy, was monitored via in-line mass spectroscopy. Preliminary results showed that $npTi_{0.5}Cu_{90}Mn_{9.5}$ catalysts used at low temperatures (<300 °C) promote the most stable and predictable conversion to HD. HCl-dealloyed catalysts showed no HDX activity until 300 °C, suggesting residual chloride ions may poison the catalyst after preparation. Catalysts dealloyed in $(NH_4)_2SO_4$ solutions fared much better up to 250 °C. Temperatures above 300 °C also caused severe and irreversible deactivation, which may be because these high temperatures approach the decomposition temperature of manganese oxides. In all, low wt percent Ti in npTiCu was more active compared to npCu, which encourages future characterization of these catalysts using CO as a probe molecule for diffuse reflectance infrared spectroscopy to study the adsorption mechanism further.

## Semi-Synthesis of Next-Generation Lincosamides

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Semi-synthesis, the process of synthesizing chemicals using natural starting materials, is a common strategy used for the development of antibiotics. The lincosamide class of antibiotics, including lincomycin and clindamycin, is characterized by a northern thiooctose linked to a southern proline moiety by an amide bond. Lincosamides bind to the bacterial 50S ribosomal subunit, prohibiting protein synthesis and thus inhibiting bacterial growth. Clindamycin was semi-synthesized from lincomycin, a natural bacterial fermentation product, through a stereoinvertive deoxychlorination of the northern half of the molecule. Despite its approval by the US Food and Drug Administration over fifty years ago for exhibiting better inhibitory activities than lincomycin, clindamycin remains to be the most recently approved and one of the widely-used lincosamides today. While clindamycin is effective against gram-positive and anaerobic bacteria, its inactivity towards many gram-negative strains limits the drug's clinical utility. Its association with life-threatening *Clostridioides difficile* colitis (inflammation of the colon) is also a major liability. As antibiotic resistance is one of the greatest global health challenges, the synthesis of next-generation lincosamides with enhanced antibacterial activities against varied species is essential. Starting with economical and easily-accessible (*D*)-galactose, we aim to synthesize intermediates of the northern half of the compound that can be rapidly diversified to further investigate the structure-activity relationship in lincosamides.

# MATHEMATICS

## Analyzing the robustness of a feedback control method for preventing bifurcations and chaos

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It is often desirable in practical applications to be able to suppress unwanted oscillations and stabilise a fixed point of the system. For instance, alternation of cardiac action potential duration can have fatal consequences if not remedied. There have been control methods that suppress such oscillations which have been successfully implemented experimentally. However, the theoretical understanding of these methods has been limited to numerical computation as well as local stability analysis. The latter fails to provide information about the *basin of attraction*, which is the set of initial conditions for which the system eventually converges to the fixed point. The goal of this project is to derive analytical results about the sets of parameters and initial conditions that are required for particular control methods to succeed. We studied the discrete logistic map $x_{n+1} = \mu x_n(1 - x_n)$ (DLM) due to its simplicity and its ability to display oscillatory behaviour. We applied the simplest control method, *time-delay autosynchronization* (TDAS), which perturbs the parameter $\mu$ by an amount proportional to the difference between the two most recent iterates. By applying local stability analysis, we characterized the parameters such that TDAS stabilizes the otherwise unstable fixed point of DLM. Using computer simulations, we were able to plot basins of attraction for various parameter choices, enabling us to make conjectures regarding the size and shape of these basins. While progress has been made towards proving some of these conjectures, the matrix obtained by linearization of the DLM has a high condition number, which presents challenges. However, the area-contracting and trapping properties of the DLM in the basin give good reason to believe the conjectures are true. We are currently attempting to use the method of Lyapunov functions to gain more information about the basin.

## Sparse Signal Recovery in Beta Models

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Networks form the basis of modern understanding of many interactions, such as Facebook friends, cellular interactions, and ecological systems. One particular network of interest is the beta model, which consists of abnormal and normal nodes. The abnormal nodes are few, or sparse, and have significantly higher interaction probability with other nodes than normal nodes. A concrete example would be spam bots in a network of email users, where interactions are defined as emails between users. Therefore, a major concern would be detecting and identifying which are the abnormal nodes. Previous literature on this particular model has focused on the question of discovering which parameter regimes would we be able to detect the presence of these abnormal nodes, and this work will expand upon the literature by answering the question of discovering which parameter regimes would we be able to actually identify these abnormal nodes. We used sharp moderate deviation inequalities for Gaussian-like variables in order to obtain upper and lower bounds on the parameters.

# PHYSICS

## Sensitivity Study of a proposed Small Satellite Wide-Field X-ray telescope for detecting a new class of Black Hole X-ray Binaries

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A black hole X-ray binary consists of a black hole and a "normal" star orbiting one another. The black hole will accrete mass from the "wind" (outflow of matter) from its binary companion star and then be detectable by the X-rays produced by the extreme energy released in the accretion disk around the black hole. Recently, a new class of black hole X-ray binaries was discovered by my advisor and his colleagues, where the black hole accretes mass from "weak winds" of a relatively cool O star. An O star is the hottest type of star, but in this "weak wind" case, the temperature is nearly as low as the next class of massive stars (B stars). A "weak wind" O star is not only relatively cool but is also on the "main sequence" part of its lifecycle. The current project's goal is to detect more examples of this type of black hole X-ray binary class by proposing (to NASA) a small satellite (SmallSat) to be launched into space with an X-ray imaging telescope. In order to achieve this goal, the imaging X-ray detectors for the telescope must be tested inside a thermal vacuum chamber mimicking conditions in space and calibrated using X-ray source catalogs to account for the background of relatively bright X-ray sources that are already known. With the telescope's proper functioning ensured, it will be possible to correctly interpret signal detections once the satellite has been launched. The satellite, beyond just aiding in the discovery and understanding of more of the new class of black hole X-ray binaries, will also contribute to other scientific endeavors, such as the detection of black hole mergers and the first direct detection of the universe's very first stars revealed by their Gamma-Ray Bursts.

## Acoustic Metamaterials

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The arrangement of the $CuO_2$ plane in cuprates into a Lieb lattice gives rise to a flat band which is thought to contribute to the strong correlations that lead to high temperature superconductivity. Thus, exploring the origin of this flat band and ways to engineer flatter, more isolated bands in this geometry would be help to understand the cuprates. However, synthesis of cuprates is time-consuming and making structural changes to the $CuO_2$ planes would be difficult. We therefore study the Lieb lattice in acoustic metamaterials which have recently emerged as a rapid, tunable, and widely accessible platform for the study of arbitrary tight-binding models. We simulate air cavities in plastic in the Lieb lattice geometry using COMSOL Multiphysics in both a simplified tight-binding model using identical s-modes at all sites and a more realistic tight-binding model to the cuprates, involving the coupling between d and p modes at neighboring sites. We then 3D print our Lieb lattices and experimentally measure the acoustic band-structure and find it matches our theoretical predictions. Our work opens the door for making modifications to the Lieb lattice to enhance the flat band properties to rapidly prototype potential systems to explore in the quantum analogues. Additionally, by driving the acoustic source with large enough amplitude, non-linearities can be added to the system, allowing for fast and easy exploration of correlations in the Lieb lattice.

## Effects of Cytoskeletal Networks on Intracellular Condensates

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The nucleus, mitochondria, and Golgi bodies are all important cellular components enclosed in membranes. Another important cellular component is the cytoskeleton, a network of filamentous proteins that provide structural support to cells. In addition to these cellular structures, there are also intracellular condensates, which are membraneless organelles. Intracellular condensates contain proteins and can expedite or halt chemical reactions by facilitating cellular organization. It remains unclear how the cytoskeletal networks affect the self-assembly and growth of intracellular condensates. The goal of my project is to understand how condensates and the cytoskeleton interact. Previous studies show that elastic networks inhibit the growth and movement of intracellular condensates. To examine the effects of cytoskeletal networks on condensates, I analyzed confocal microscope videos taken of biomolecular condensates in the presence of microtubules, a type of cytoskeleton, and compared with the case where microtubules are disassembled. The videos are prepared by our collaborators. I used the software Fiji to locate and track intracellular condensates. To understand their growth rate, I binarized and cropped individual condensates from the microscope images. Using Python, I wrote code to extract the center of mass of the condensates. From my initial study, the average size of condensates with microtubules assembled is actually larger than that of the cells with microtubules disassembled. I am still analyzing the effect of the cytoskeleton on velocity, but preliminary results show that condensates actually move faster in the presence of microtubules. This could be because microtubules can transport the condensates. Further research is needed to increase our understanding of the effect of the cytoskeleton on intracellular condensates. Possible applications of this research are therapeutics and drug delivery.

## Generation of tunable femtosecond laser pulses using noncollinear optical parametric amplification at visible frequencies

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Ultrafast laser pulses tuned to the resonant frequencies of specific lattice vibrations have recently been shown to have a tunable effect on electronic phases in quantum materials. The characterization of these phonon-driving pulses, with oscillation periods on the order of tens of femtoseconds, require even shorter probe pulses produced via nonlinear processes. Here, we aim to generate pulses of 10 fs in duration, tunable from 500 nm to 800 nm in wavelength by constructing a noncollinear optical parametric amplification device (NOPA). Using the NOPA, the spectrum of an incoming 800 nm beam is broadened into the visible range using a sapphire crystal through white light generation. The resultant signal is then amplified using a more intense second harmonic generation before being compressed into femtosecond pulses by a series of chirp mirrors. Guided in part by the methodology of Kaindl et al., we compare beam profile quality and energy conversion efficiency to optimize efficiency between 18 percent and 20 percent while retaining beam profile integrity in the far field. Altogether, the NOPA enables the characterization of electronic excitations in quantum materials with phase-stable pulses, and further paves the way to observing novel forms of light-induced electronic dynamics.

## Noise Characterization in the New Small Wheel of the CERN ATLAS Detector

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One of the primary goals of many particle physics research initiatives such as the ATLAS experiment at the Large Hadron Collider at CERN is to search for evidence of a theory beyond the well-known Standard Model. Evidence for a popular theory known as supersymmetry is suspected to consist of new unstable particles with high masses and long lifetimes. In order to find such rare particles, the ATLAS detector needs to be able to collect massive amounts of data from proton-proton collisions. However, a major barrier to effective and precise data collection is the difficulty of separating electronics noise from tracks left by ionizing particles in the detector. In particular, very little is understood about the level of noise in the New Small Wheel, a section responsible for detecting and tracking muons. The goal of this research is to identify the noise in the detector and characterize its size by looking at clusters of charge left behind after a passing muon. Common characteristics of noise such as cluster position, cluster timing, and cluster charge as well as their correlations are identified and plotted in test runs of muons from cosmic showers. It has been observed that these clusters do not have characteristics typical of noise and may be associated with real physical processes instead. This work has helped focus the next endeavor to determine how much, if any, information on noise can be extracted from these clusters and how to successfully separate it from the relevant data.

## Accounting for Tau Energy Losses with nuSQuIDS

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Using the software package Neutrino Simple Quantum Integro-Differential Solver ($\nu$-SQuIDS), it is possible to simulate neutrino propagation under a variety of circumstances and track how various parameters evolve over a given neutrino's trajectory, most notably its energy. As a neutrino propagates through a medium, it loses energy due to numerous electromagnetic interactions; a neutrino's potential to give rise to more neutrinos over the course of its trajectory complicates attempts to track the evolution of energy. Under the current implementation of $\nu$-SQuIDS, neutrinos arising in this manner spontaneously decay without losing any energy, which is an appropriate approximation for a range of energies. However, for high energies above 10 PeV, this approximation no longer holds, and it becomes necessary to track derived neutrinos. This project endeavors to extend the functionality of $\nu$-SQuIDS to properly account for the propagation of tau neutrinos by estimating the energy losses associated with any derived neutrinos using Monte Carlo methods made available in the Proposal software package. This project will comment on the quality of the results afforded by this estimation, possibly discussing any trade-offs with regard to computation time and memory.

## Scalable Implementation of Quantum Algorithms with Modular Quantum Hardware

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Quantum computing is believed to be a powerful tool capable of significantly improving the algorithmic run-time of solutions to hard problems. However, while quantum algorithms are theoretically feasible, they have yet to be implemented at scale due to the large number of errors introduced by experimental imperfections. As such, it is crucial to design algorithms that can be seamlessly implemented on realistic quantum hardware. In particular, a recent paper (Anikeeva et al, PRX Quantum 2, 020319 (2021)) designed a quantum gate called an oracle for solving an NP-hard problem with quadratic speedup in a cavity QED system. However, the protocol given would additionally require nonlocal interactions to be applied to large problems. In other words, a procedure for implementing additional nonlocal gates is required for the scalability of the protocol. In this work, we develop such scalable strategies for implementing oracles. Our protocol can be applied to multiple experimental settings. Specifically, we consider a distributed quantum network, where each cavity has a limited number of spins, and a central spin model relevant for Rydberg atom arrays. The central spin model consists of a central ancilla atom and multiple other atoms at exact distances from the central one, such that these distances encode the parameters of the NP-hard problem. We implement detailed numerical simulations of our protocols, allowing us to benchmark their performance in a realistic setting for systems of up to 20-30 qubits. If successful, the tools we develop should serve as the basic building blocks for realistic implementation of quantum algorithms.

## Molecular Spectroscopy of Polyatomic Molecules for Laser-Cooling Applications

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Laser-cooling is the process by which laser light is used to remove a particle's energy. This method has been quite successful at cooling gases of single atoms, and more recently, researchers have utilized laser-cooling to cool molecules as well. These ultracold systems have applications in quantum information, quantum chemistry, and physics beyond the Standard Model. However, the internal complexity of molecules, specifically the addition of vibrational and rotational states, makes them more difficult to laser-cool than atoms. Understanding a molecule's spectrum of states is necessary to laser-cool it. For this reason, we began development of an algorithm to analyze dispersed fluorescence spectroscopy data and estimate a molecule's vibrational branching ratios. These properties relate to a molecule's spectrum and provide valuable information not only in determining whether a molecule is a good candidate for laser-cooling but also in constructing a relevant laser-cooling scheme. The algorithm will be used to analyze data from large polyatomic molecules such as CaCCH. Additionally, we began building a laser system to collect spectroscopy data for a separate molecule, SrOH. Though SrOH is a prime candidate for laser-cooling, experimental data is required before an attempt to cool the molecule is undertaken, motivating the construction of an external cavity diode laser that will be used to excite a specific molecular transition in SrOH. Through analysis and the construction of this laser, we hope to contribute to the measurement of molecular spectra and, more broadly, to future attempts at laser-cooling large polyatomic molecules.

## Building an Optical System for the Calibration and Frequency Stabilization of Lasers

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In atoms, electrons can be promoted to higher energy states via an energy source, such as the photons from a laser. Because such transitions require a specific amount of energy, the ability to measure and stabilize the frequency of lasers to a resolution that is on the order of Megahertz is crucial for observing and driving the transitions efficiently. Moreover, many spectroscopy experiments require the use of multiple lasers simultaneously. To address this challenge, I have built an optical system which is designed to measure the frequencies of up to eight lasers on a laser wavelength meter (wavemeter), and can be further used to stabilize and lock the frequencies of these lasers. Specifically, eight pathways for the lasers were prepared on an optical breadboard, and a galvanometer was used to point the different pathways into the wavemeter via an applied voltage. A function generator is used to control the voltages applied to the galvanometer, and trigger the wavemeter to commence the exposure to light. Once the wavemeter receives a reading, it is transmitted to a computer, where values are stored for logging and correction of a given laser. I have finished the optical alignment of the paths on the breadboard, and created code to display readings from the wavemeter in real time. Once complete, this setup could be used by the Ni lab to tune their lasers and prepare them for future experiments.

## Determining the Contribution of Black Hole-Neutron Star Mergers to r-Process Enrichment in Ultra Faint Dwarf Galaxies

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With the advent of the Laser Interferometer Gravitational-Wave Observatory (LIGO), astronomers can now devise multi-messenger studies to answer unsolved questions in compact object astrophysics. LIGO's most recent detections of GW200105 and GW200115 provide the first conclusive evidence of black hole-neutron star (BH-NS) mergers in the universe. BH-NS binaries follow one of two inspiral tracks on their path to merging: either the NS plunges into the BH entirely, or the NS is tidally disrupted by the BH, forming an accretion disk and an ejecta of neutron-rich material outside the BH. It is expected that BH-NS ejecta, like the ejecta of NS mergers, may be a site of heavy element formation via r-process nucleosynthesis. The Dark Energy Survey identified several Ultra Faint Dwarf (UFD) galaxies, the oldest class of galaxies in the universe, that show r-process enrichment; however, binary NS mergers likely do not account for the r-process material in UFD galaxies because of their high kick velocities. Simulations of BH-NS mergers were performed to determine if disrupting BH-NS binaries could play a role in the r-process enrichment of these galaxies. Using 15 population synthesis models, which each make different assumptions about the dynamics of binary stellar evolution, realistic samples of BH-NS parameters are simulated, including the BH and NS masses and the NS radii. These parameter distributions are combined with a model to identify which BH-NS systems undergo disruption and form an ejecta. With the model's calculations of the systemic center of mass velocities and inspiral times of the BH-NS systems, the fraction of BH-NS that form an ejecta, a potential r-process site, within the average UFD galaxy's virial radius can be determined, taking into account the relatively low escape velocities of UFD galaxies. Two of the models are found to yield formation rates that are consistent with UFD galaxy enrichment.

## Simulating Bilayer Graphene under Uniform Magnetic Field in Acoustic Metamaterials

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Acoustic metamaterials have recently emerged as a rapid, tunable, and widely accessible platform for the study of single-particle physics. Specifically, much progress has been made of late in mimicking van der Waals (vdW) heterostructures, stacked layers of 2-d materials which interact only though van der waals forces, allowing for the creation of acoustic analogues of bilayer and twisted bilayer graphene. Additionally, it is known that a tri-axial lattice strain in graphene can be used to mimic the effects of a uniform magnetic field on the band structure, even in non-electronic systems, opening the door for the investigation of vdW heterostructures under magnetic fields using acoustic metamaterials. Building on previous work in the Hoffman group, we numerically simulate acoustic metamaterial AA- and AB-stacked bilayer graphene, composed of interconnected air cavities in two stacked steel plates connected through a high density polyethylene (HDPE) membrane, under various strengths of a uniform pseudo-magnetic field. Our acoustic analogue of bilayer graphene under magnetic fields reproduces the expected landau quantization at the K point, showing both sub-lattice polarization of the zeroth level and the expected $\sqrt{n(n-1)}$ level scaling. Additionally, our model can achieve magnitudes of pseudo-magnetic fields on the order of 100T, allowing us to explore extreme regimes of phase space inaccessible in the quantum system.

## Search for $WVZ$ production at ATLAS with machine learning

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The Standard Model is a particle theory that describes all known elementary particles and their interactions. The ATLAS experiment uses proton-proton ($pp$) collisions at CERN's Large Hadron Collider to experimentally test Standard Model predictions. Within Standard Model physics, the production of the $WVZ$ triboson process, containing three massive vector $W$ and $Z$ bosons, requires rare higher-order self-interactions of $W$ and $Z$ particles and occurs infrequently in $pp$ collisions. Experimental measurements of the true likelihood of these high-energy decay modes may help constrain the limits of the Standard Model and achieve a more complete understanding of particle physics. We investigated the 4-lepton final state signature targeting the decay channel $WWZ \rightarrow 4\ell$, where the lepton flavor is either an electron or muon. Selections, or "cuts," are made on particular properties of events to distinguish the desired signal process from similar background events; however, the complexity of the $WVZ$ signal's multi-lepton final state signature complicates direct selection of a single best set of cuts. Using Monte Carlo simulations of ATLAS events, we explored the lepton identification quality of the two leptons most likely to have decayed from the two $W$ bosons. Our preliminary findings indicated that a looser requirement on lepton quality for certain decay channels may improve the discrimination significance between 4-lepton signal and background events. We intend to train machine learning models on simulation data, including a deep neural network and a boosted decision tree, to improve upon these nominal findings with a multivariate analysis optimization. This analysis will enable us to experimentally determine the cross section, or frequency, of the Standard Model $pp \rightarrow WVZ$ decay process. These measurements of Standard Model physics will allow us to continue testing and refining predictions of rarer particle physics processes.

# Calculating the Solar Atmospheric Neutrino Flux

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When cosmic rays — charged particles such as protons traveling near the speed of light — hit the Solar atmosphere, the collision produces particles like neutrinos. This solar neutrino flux has never been measured, but researchers have made theoretical predictions using Monte Carlo models. However, these calculations did not account for the effects of the Solar magnetic field. Low-energy cosmic rays, in the 100 GeV range, can be trapped in the magnetic field, which increases the probability that they hit the Solar atmosphere. This effect increases the expected neutrino flux as compared to if the particles traveled undeflected. To construct the Solar magnetic field, we use the Potential-Field Source Surface model, which takes magnetogram data from the Global Oscillations Network Group and numerically solves Maxwell's equations in the region $R_\odot < r < 2.5R_\odot$. Here $R_\odot$ is the radius of the Sun and $r$ is the distance from the center of the Sun. Then, by solving the equation of motion due to the Lorentz force, we simulate cosmic rays traveling in the solar magnetic field and track which ones hit the Solar atmosphere. Finally, known models of proton-proton interactions can predict the number of neutrinos produced and the number expected to be observed on Earth. When the simulation is complete, this work will be the first theoretical prediction of the solar neutrino flux that accounts for magnetic field effects and will serve as a baseline for when the flux is finally observed experimentally.

# Optimizing $SrLaAlO_4$ Substrate Preparation for Epitaxial Growth of Superconducting $La_{2-x}Sr_xCuO_4$ Films

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A superconductor is a material that both conducts electricity without loss and expels magnetic fields. These properties make superconductors useful for applications such as high speed trains and magnetic resonance imaging. However, currently known superconductors maintain such properties only at extremely low temperatures that are unfeasible for widespread usage. For instance, the compound $La_{2-x}Sr_xCuO_4$ (LSCO) loses its superconductivity above the critical temperature ($T_c$) of 25 K. Molecular beam epitaxy can be used to grow LSCO for studying its electric and magnetic properties. However, epitaxial growth of superconducting LSCO films requires an atomically-flat and singly-terminated substrate with lattice constants that are well-matched to that of bulk LSCO. Pairing LSCO with a $SrLaAlO_4$ (SLAO) substrate can increase its critical temperature to 49 K. Preparing SLAO is challenging because its Ruddlesden-Popper structure allows for termination at multiple planes, making it difficult to achieve consistent step heights and identify the termination. While procedures for obtaining acceptable SLAO substrates have been reported, finding the exact experimental parameters requires further inquiry since the quality of as-received substrates as well as our equipment access varies. In this project, we experimented with annealing and etching techniques to obtain a precise procedure for preparing high-quality SLAO substrates. We used atomic force microscopy to characterize the topography of our samples, as well as X-ray diffraction to study the crystallinity. We find that annealing SLAO in a cation-rich environment provided by $La_2O_3$ powder yields half-unit-cell height terraces optimal for LSCO film growth. In future work, we will use reflection high-energy electron diffraction to further characterize the substrate crystallinity and determine if miscut angle is a crucial factor in the resulting surface quality.

## Effective Configuration Space Continuum Model for Phonons in Incommensurate Twisted Bilayer van der Waals Heterostructures

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Bilayered two-dimensional materials, such as bilayer graphene and transition-metal dichalcogenides (TMDCs), exhibit widely varying electronic and optical properties when the two layers are twisted relatively by a small angle into a moiré crystal. In this research, we study the structure of phonon dispersions and fields in such systems. We develop a twisted bilayer phonon model, using a continuum approximation with angle-dependent relaxation in the configuration space of incommensurate materials that describe the local environment, bypassing the need for large supercell calculation and periodic approximation. We show that configuration space is a natural space to calculate phonon spectra due to its correspondence to reciprocal moiré space. In configuration space, phonon frequencies exhibit symmetries analogous to those of their generalized stacking fault energy (GSFE), though force constants often break the pristine lattice symmetry. We transform such calculations in configuration space to analyze the variation of phonon dispersions with twist angle.

## Quantum sensing with nitrogen-vacancy centers in diamond nanostructures

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Nuclear magnetic resonance (NMR) spectroscopy is a noninvasive method, capable of revealing the chemical structure of proteins and other applications from biochemistry to material science. However, this method can only be applied to bulk materials, requiring a very high number of identical copies of the sample molecule. This comes from the limited sensitivity of the technique and prevents detection of single molecules. Atomic scale quantum sensors provide an alternative path to overcome this limitation. In this project, the nitrogen-vacancy (NV) center in diamond is employed as a quantum sensor. NV centers are formed when carbon atoms in the diamond lattice are replaced with a nitrogen atom and an adjacent vacancy. The spin state of an NV center can then be optically read out, creating a highly sensitive atomic-scale quantum sensor. With NV centers close to the diamond surface, it becomes possible to detect NMR signals from nanoscale sample volumes. This represents a fifteen order of magnitude improvement compared to conventional NMR spectroscopy. Some challenges of this NV based technique is the low spectral resolution and nondeterministically localization of sensor and sample, hindering straightforward application of the technique. In this project we resolve these challenges by fabricating nanostructures in the diamond. This enables the nanoscale trapping of samples close to the quantum sensors. We characterize the nanofabricated diamonds and spin properties of the NV centers. For the sensing, different pulse sequences are applied with the goal of detecting the nanoconfined samples. Ultimately the goal is to demonstrate chemical analysis on the nanoscale of arbitrary liquid state samples. This would allow structure determination of single proteins and highly sensitive detection of biomarkers in solution. With the NV centers, we have so far successfully detected $^{13}C$ spins. Next, we plan to detect fluorine and Gadolinium spins inside the nanostructures.

## Optimizing Indium Oxide Growth

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Transparent conducting oxide (TCO) thin films play an important role in the development of optoelectronic devices. In order to serve as contacts and interfaces, these materials need to be electronically conductive, while maintaining optical transparency. Indium tin oxide (ITO) is a widely used TCO. However, a challenge in the synthesis of indium-oxide based films is achieving a sufficiently high crystalline quality and smooth surface morphology, which has complicated their integration into next-generation nanoscale devices. Here, we use oxide molecular beam epitaxy as well as sputter deposition to explore the optimal growth parameters for both undoped and doped indium oxide. Using post-deposition x-ray diffraction and atomic-force microscopy, we improve the smoothness of our films as an important step to facilitate their integration in optoelectronic devices.

## On Compounding of Error Unitaries over Pulse Sequence for NV System Control

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Nitrogen-vacancy centers (NV), which consist of a single nitrogen atom adjacent to a vacancy in the carbon lattice of diamond, feature quantum mechanical coherence even at room temperature and can strongly interact with each other. Due to these characteristics, NV ensembles can be utilized as quantum sensors or as simulators of quantum many-body dynamics. For both applications, controlling the interaction and disorder of the NV ensemble is critical. In order to control the system, a sequence of magnetic field pulses, known as dynamical decoupling, is typically applied to the system. While this has led to significantly longer coherence time in such systems, the limiting factors to this technique in experiments are not fully understood. Recent experiments have suggested that the compounding of individual errors over multiple cycles can be a significant limiting factor, motivating detailed modeling and understanding of how such effects occur. This research project developed code to compute the resulting final error unitary from a measured control waveform and examine the structure of the error as a function of the waveform phase. Results revealed a pronounced periodicity of the error in both experimentally measured waveforms and ideally generated square waveforms, suggesting the presence of underlying structure in observed pulse errors. Further extending this code to the case of multiple pulses, we will be able to better understand how individual errors compound for specific phases and frequencies of the applied pulses, which may point to better strategies for suppressing such errors and achieving higher fidelity spin control.

# Visualization of Optical Lattice Geometry for Use in Quantum Simulation and Control Experiments

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In recent years, optical lattices have become an important tool in implementing quantum simulation and control experiments. The simplest optical lattice is produced by orthogonal, counter-propagating laser beams; the resulting interference intensity pattern consists of periodic potential wells. These wells trap molecular entities by capitalizing on the electric dipole moments induced by the light field. By altering the configuration of the laser beams, different lattice geometries can be achieved, thus allowing for the study of different quantum phases. To this end, a program is developed to aid in the determination of the appropriate experimental set-up given a desired lattice geometry. Written in MATLAB, it is designed to accept variable polarization, frequency, intersection angle, and quantity of lasers as input. The user-friendly program then calculates the intensity pattern and produces a visual of the optical lattice. As this program allows researchers to efficiently consider new trap geometries when designing experiments, it will facilitate the investigation of new quantum properties and interactions.

# Radiative Properties and Selection Criteria for Wandering Intermediate-Mass Black Holes in the Milky Way Galaxy

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Black holes have a mass distribution spanning almost 10 orders of magnitude, from stellar-mass to super-massive black holes. Intermediate-mass black holes (IMBHs), with a typical mass between $10^3$ and $10^5\,M_\odot$, have been found in the central region of some dwarf galaxies, but they are generally challenging to detect. Recent studies suggest the presence of wandering IMBHs in the Milky Way (MW) galaxy, formed either by a collision between smaller black holes or by capture from external galaxies. These objects have, thus far, escaped our detection. Here, we used analytical models for advection-dominated accretion flows (ADAF) to compute the typical accretion rates onto IMBHs of $\sim 10^5\,M_\odot$. We used five models for realistic environments in the MW galaxy and specifically tailored code to compute the spectral energy distribution for black holes accreting in ADAF regimes. We found that both in the infrared and in the X-ray domain, predicted fluxes span $\sim$ 20 orders of magnitude, from $10^{-30}$ to $10^{-10}\,\mathrm{erg\,s^{-1}\,cm^{-2}}$, with the brightest fluxes predicted in molecular clouds or cold neutral medium. We predict that $\sim$ 2 percent of these sources can be detected in the X-ray with the Chandra X-ray Telescope, while the upcoming Roman Space Telescope could detect up to $\sim$ 9 percent of sources in the infrared. We also investigated some selection criteria to facilitate the identification of promising sources in surveys. Specifically, we computed the sub-mm to optical ratio, and the X-ray to optical ratio in terms of the $\alpha_{ox}$ parameter, finding a peak value of $\alpha_{ox} \sim 1.9$ for accretion rates $10^8$ times lower than the Eddington rate, decreasing to $\alpha_{ox} \sim 0.5$ for rates of $\sim$ 1 percent the Eddington one. These predictions will offer invaluable guidance for upcoming searches of IMBHs in our Galaxy and will be fundamental to understanding the demographics and the cosmological evolution of IMBHs.

## A Tensor Network Model for AdS Black String Geometry with a Gravitating Bath

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The discovery of the *Page curve* has significantly advanced our understanding of quantum information in black hole radiation and has provided an avenue towards resolving the black hole information paradox. In particular, it has been shown that constraints on the entropy of radiation relative to the entropy bound of its originating black hole require an increase and subsequent decrease of entanglement entropy at the *Page time*, rather than a monotonic increase, as previously predicted by Hawking. Recent work has shown that in a Karch-Randall (KR) braneworld, a system with a gravitating bath and AdS black string exhibits phase transitions of the Page curve under changes of brane angle with respect to the AdS boundary: If a brane is placed just beneath the so-called *critical angle*, its Page time vanishes. Above the *critical angle*, entanglement entropy between the branes is a time-independent constant, and the Page curve becomes irrelevant. Existing independent work shows that the tools used to understand entanglement entropy in the KR setup, namely holography via the AdS/CFT correspondence and the quantum Ryu-Takayanagi formula, can be mutually understood using a tensor network model in AdS. In this project, we aim to construct a tensor network model for the black string system in hopes of recovering the phase transition from the aforementioned work within a primarily quantum-mechanical theory. If successful, this would support tensor networks as a powerful tool in our understanding of quantum gravity.

## Epitaxial Growth of $Sr_{n+1}CrnO_{3n+1}$ Homologous Series

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Complex oxide materials display a wide range of electronic, magnetic and optical properties and are leading contenders for integration in next-generation devices. Most studies to date have investigated complex oxides in powder form and involve materials that have yet to be stabilized in thin-film form. It is difficult to perform measurements on the powder-form due to lack of a domain crystal structure; grain boundaries can dominate the observed properties and obscure the underlying ground state. As a result, we focus on the growth of thin film strontium chromate Ruddlesden Popper superlattices ($Sr_{n+1}Cr_nO_{3n+1}$) using Molecular Beam Epitaxy. These materials are thought to host a range of exotic physical states such as orbital ordering. Strontium chromate ($SrCrO_3$) was grown on neodymium gallate at high temperature and high vacuum with a low partial pressure of oxygen using a shuttering method to control stoichiometry and dose. We were successful in n = 2 and n = 3 heterostructures synthesis and to our knowledge, this is the first time these systems have been grown as thin films. This growth achievement will enable us to do high resolution imaging of the films using scanning transmission electron microscopy in order to examine the crystal layering orientation. We also plan to perform SQUID measurements and in-house transport measurements to investigate the magnetic and electrical properties and try to uncover the expected orbital and spin orderings.

## Empirical Model for the Size Growth of Galaxies

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Since the timescales for galaxy evolution are too long to follow observationally for individual galaxies, empirical models provide a powerful tool to constrain the physical processes that drive galaxy growth. Here, we present an empirical model that comprehensively captures the principal drivers of galaxy evolution through star formation and stellar mass growth on spatially resolved scales, allowing us to describe morphological evolution with cosmic time. In the model, star formation and stellar mass evolve based on the star-forming main sequence, which relates the star-formation rate and stellar mass of a galaxy. The model incorporates fluctuations relative to the main sequence relation to account for natural variations in growth throughout a galaxy's lifetime. Star formation is suppressed probabilistically to produce the quiescent galaxy population. The morphological evolution is captured by assuming that the star formation is distributed in an exponential disk. The exponential disk profile has a free parameter for the scale length of the exponential shape, $R_s$, whose temporal and evolutionary dependencies we investigate. Analytical results from the model about the dependencies of $R_s$ make novel contributions to understanding galaxy morphological evolution. We use the model to numerically construct a simulated sample of galaxies and their star formation and stellar mass evolution, and compare it to observational measurements of galaxy sizes. From this comparison, we learn how individual galaxies grow while they are star-forming, quenching, and in their quiescent phase.

## Dynamic 3D Simulations of Tree and Network Sea Fan Structures

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Sea fans are a variety of corals structured in a flat fanlike pattern of numerous cylindrical polyps. Their morphology has been previously studied through 2D images and digitized data points depicting different structures have been obtained. The project employs polymer physics and Molecular three-dimensional simulations to study two samples of tree-like and network structures and analyze differences in their dynamics. The sea fans' motion was initially simulated in the Large-scale Atomic/Molecular Massively Parallel Simulator (LAMMPS) molecular dynamics software package by connecting the data points (viewed as discrete particles) through harmonic bonds and modulating the flexibility of the structures introducing bending stiffness through an angle potential between three particles. Next, hydrodynamics was integrated using the Smooth Particle Hydrodynamics and the Constant Energy Dissipative Particle Dynamics LAMMPS packages, which allow for laminar or turbulent flow in the simulations. Varying the parameters allows the inclusion of different environmental factors, which in turn facilitates accurate, real models. Preliminary analysis of the simulation output through local density, connectivity, and particle displacements computations suggests that tree structures tend to be more dynamic than networks and that the greatest displacements correspond to outer particles, a result consistent with previous data. Further analysis of all available 2D structures is necessary to conclusively find the correlation between the morphology of sea fans and the corresponding environment.

# Dynamics of Intermediate-Mass Black Holes Wandering in the Milky Way Galaxy

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The detection of Intermediate-Mass Black Holes (IMBHs) in dwarf galaxies is of paramount importance to closing the gap in the wide mass distribution of black holes ($\sim 1 - 10^{10}\,\mathrm{M}_{\odot}$). IMBHs originally located at the center of dwarfs that later collide with the Milky Way (MW) could potentially be wandering, thus far undetected, in our own Galaxy. We used the cosmological simulation IllustrisTNG to study the dynamics of IMBHs in a MW-analog galaxy. We showed that $\sim$ 84 percent of the IMBHs studied drift inward, and $\sim$ 13 percent reach the central $1\,\mathrm{ckpc\,h^{-1}}$ of the MW within a Hubble time. The radial velocity of sinking IMBHs was found to have a median value of $\sim 0.38\,\mathrm{ckpc\,h^{-1}\,Gyr^{-1}}$ and a positive dependence on the black hole mass. The median radial velocity of the most massive $\sim$ 10 percent of sinking IMBHs was $\sim$ 2.3 times larger than that of the least massive $\sim$ 10 percent. A simple physical model including gravitational and drag forces was developed to describe the system and explain why radial velocity decreases towards the galactic center. These findings constrain the spatial distribution of IMBHs, suggesting that future searches should focus on the central regions of the Galaxy. Additionally, we studied the distribution of the 3D velocities of IMBHs with radial distances between $0 - 30\,\mathrm{ckpc\,h^{-1}}$ from the MW center. The velocity distribution with respect to the galactic center is well-fitted by Gaussians, with a mean of $\sim 180\,\mathrm{km\,s^{-1}}$ and larger variance as the radial distance decreases. Remarkably, the velocity distribution relative to the local gas (for radial distances $\gtrsim 5\,\mathrm{ckpc\,h^{-1}}$) shows much lower values, with a mean of $\sim 87\,\mathrm{km\,s^{-1}}$. These results are crucial for predicting the accretion and irradiation properties of IMBHs, facilitating their detection with future multi-wavelength surveys.

# A Young Mini-Neptune in the AB Doradus Moving Group

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The discovery and characterization of young planets is an essential part of the quest to understand the mechanisms that create and shape exoplanetary systems, as signatures of these processes can be lost over time to tidal interactions and stellar irradiation. Neptune-sized planets (around 4 Earth radii) can be found around 30-50 percent of sunlike stars, making them an important planetary demographic to understand through the study of young systems. Using data from NASA's Transiting Exoplanet Survey Satellite, the star TIC 464646604 was identified as a candidate planet host via detection of a dimming in the stellar brightness characteristic to a planetary transit. In collaboration with the European Space Agency, the space telescope CHEOPS was employed to obtain additional photometric observations of the star in order to confirm the existence of a planet and constrain its parameters. Additionally, analysis of the star's kinematics placed it in association with the AB Doradus moving group, which is believed to be around 50 million years old. After conclusive false-positive analysis and modeling of the data using modern simulation techniques, TIC 464646604b was confirmed as a newly discovered planet with a radius of $3.13 \pm 0.33 R_{\oplus}$ and orbital period of $7.7125 \pm 0.0007$ days. As one of the smallest young planets ever discovered, and due to its host star's brightness ($V = 8.31$), TIC 464646604 is an excellent candidate for follow-up observations and study to further explore how planetary systems form.

# Calculating Detector Responses of Detector Arrays

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Radiotherapy uses ionizing radiation to kill cancer cells and shrink tumors. In external radiotherapy, doses are delivered via a linear accelerator (LINAC). In recent years, medical LINACs have advanced to highly complex machines, consisting of dynamically moving and dose rate shaping components. Nonetheless, a comprehensive, LINAC-integrated, and reliable beam monitoring system has not been developed for medical LINACs. Challenges facing such beam monitoring include reliability, affordability, and resilience to radiation. To address some of these difficulties, this project investigated two similar detector arrays called remote sensing array (RSA) and resistive electrode (RE). In RSA, strip electrodes are located at the perimeter of the beam. Notably, the beam does not directly interact with the electrodes, and currents in the electrodes are generated by ions in air. In RE, there is a large, grounded central electrode juxtaposed between two electrodes that are at a voltage bias. Ionization of the detector panel creates multiple readouts and injections. This project focused on theoretically computing detector responses to pencil beams and comparing such calculations results to experimental measurements. The calculations required numerically solving Laplace's equation with appropriate boundary conditions to determine electric fields and employing Shockley–Ramo theorem to compute current induced on electrodes. Once the response function is fully understood, it will be convolved with the beam shape to obtain the overall response for the entire field. The eventual goal is to optimize clinical beam parameters that will aid in the development of a functional, remote sensing detector.

# SOCIAL SCIENCES AND HUMANITIES

# ART HISTORY

## Brandywine Workshop and Archives Exhibition

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Founded in 1972, The Brandywine Workshop and Archives (BWA) aims to educate and introduce a diverse community of artists to the medium of offset lithography through artist residencies and programs. Artists of all backgrounds and training, from Faith Ringgold to Edgar Heap of Birds, have been invited to practice at BWA. In 2018, Harvard Art Museums acquired over 100 prints from BWA to establish a "satellite collection," and curators Elizabeth Rudy and Sarah Kianovsky have been preparing the works for an upcoming show titled *Prints from the Brandywine Workshop and Archives: Creative Communities*. The exhibition will focus heavily on artist experience and the legacy of BWA, and it required written and recorded interviews from all represented living artists. I contacted the 25 living artists represented in the show for interviews and compiled templates based on the Museums' holdings, artists' recorded time at BWA, and conservation reports under the guidance of Museum staff. In addition to artist interviews, the team also consulted archival materials, recordings, media, and advice provided by BWA founder Allan Edmunds in discussions of programming and exhibition design. The interviews I conducted helped the team construct a timeline and narrative of the BWA residency program over the past few decades, including the creative inspirations and influences of artists before and after residency. Research into the works and their artists contributed to the digital tool and accompanying exhibition programming alongside the use of interview material for the physical exhibition. The opening of *Prints from the Brandywine Workshop and Archives: Creative Communities* at the Harvard Art Museums will mark the inaugural introduction of this important collection of prints, as well as give the public new access to the historical impact and legacy of the BWA.

## Devour the Land: War and American Landscape Photography since 1970

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*Devour the Land: War and American Landscape Photography Since 1970*, an upcoming photography exhibition at the Harvard Art Museums, will examine the ecological impact of military activity in the United States. The effects of American battlefield pollutants, such as Agent Orange in Vietnam, are well-studied. However, environmental historians often overlook military destruction on the home front. Military materials production, mobilization, and training activities produce chemicals that threaten nearby populations. There are 136 major sites of military contamination in the country; in addition, the petrochemical, coal, electronics, and heavy metals industries that support military activities contribute hundreds more. Interviews with photographers, a review of EPA Superfund sites, and archival research on local activists and historians revealed three centuries of tension between the military-industrial complex and affected citizens, who often struggled to find legal support. The findings will culminate in an article supporting the exhibition's claim that citizen activism is crucial for environmental progress. Additionally, information on activism will aid in programming and outreach, and Superfund site profiles and additional historical contextual research will provide supplemental content for the exhibition website and social media.

## "Works in Progress" Podcast

**Kristian Hardy**
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Oftentimes society views art solely as a finished product. An entity to be viewed, analyzed, and consumed. What would happen if this perspective was challenged and the value of art was found in process rather than product? The Harvard ArtLab, a unique arts-based laboratory for interdisciplinary research and experimentation, poses this question daily. Even still, a gap remained as the majority of the work ArtLab artists in residence completed stayed within the facility walls. Enter *Works in Progress* , a new podcast from the Harvard ArtLab. *Works in Progress* aims to expose the creative evolution of some of the industry's most innovative emerging artists and cultivate conversation among Harvard faculty, students, and fellows.

The pre production tasks for this podcast included crafting an efficient work model, researching key artists, and writing scripts for each episode. I spent a large chunk of time scouring through artists' portfolios, CVs, and even social media profiles to ensure that the podcast would not only touch on their accomplishments, but the research they did to make those moments a reality. On a broader scale, this podcast intends to expand the arts landscape at Harvard University and the world at large. Research and art typically are not put into the same realm, but *Works in Progress* will uplift artists that are committed to researching some of the world's most pressing issues and honing that knowledge through creative expression.

## Illuminating the *Divine Comedy*: a Vision of Dante's Cosmos

**Madeleine Klebanoff O'Brien**
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Dante Alighieri's *Divine Comedy* is a luminous text, in two senses of the word. Dante's cosmos is a manifestation of divine light: it coheres through illumination. It also has a rich tradition of illumination populated by artists such as Botticelli, Gustave Dore and Salvador Dali. Last summer, I studied both the theory and the practice of illumination to create my own cosmographical map of the *Comedy*, accompanied by a set of artist's notes. This summer, I am creating an interactive website to house my work. Users can click on regions of the map to see the corresponding notes, which consist of explanatory text, quotations from primary sources, and diverse visual references, many of them drawn from Harvard special collections. With its distinctly visual format, this project is an amalgam of art and scholarship, encouraging exchange between creative and academic methodologies. It is a playful, twenty-first century addition to the rich tradition of illustration and commentary that surrounds the *Comedy*.

## Civil War through Modernism: Graphic Design & Video Editing

**Marcus Knoke**
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Poetry in America
*Advisor:* Elisa New
*Mentor:* Hogan Seidel

Harvard professor Elisa New created Poetry in America (PIA) in 2016, launching a multi-platform educational initiative and teaching American poetry to thousands of students globally. In 2018, the organization released a public television series with the same name nationwide. The show, met with acclaim, aired its second season in April of 2020. I worked with the education department at PIA, where I prepared content for a course on American poetry from the Civil War through Modernism, scheduled to be taught in the spring of 2022. I designed a graphic for the Canvas website of the course and edited historical photographs for lecture videos. I built an interactive timeline that contained syllabus and historical information for students unfamiliar with American history. My photo and video editing turned historical photographs into moving pictures, as I adjusted depth and perspective in Adobe editing programs to create interesting optical dynamics. The content that I created will enhance students' learning experience in the course. Young students' of poetry are technologically-savvy, and require content that plays to those strengths. With online courses such as this one, content also needs to be attention grabbing and aesthetically pleasing. I met these goals with my work at PIA. Professor New, through her work with Poetry in America, has made poetry education accessible to a new audience of eager students, in classrooms and living rooms. Courses in American poetry will continue to diversify and update their content to dynamically respond to the desires of poetry students. Poetry in America brings in new learners and teaches them to critically interpret important poems for the first time, inviting silenced voices to the table and telling them that anyone can interpret a poem and provide valuable ideas.

## Seeing Clear Through: Studio Research on the "Shadowgraphs"

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Shadowgraphs, x-rays of artworks, have been primarily used in art history and conservation as scientific tools. In 1925, Alan Burroughs systematically took x-rays of artwork from key collections in the US and Europe for the Fogg Museum. In line with other applications of the x-ray since its discovery in 1895, like the diagnostic use of medical x-rays or the exploratory nature of astronomy x-rays, these shadowgraphs served as technical tools aiding the art critic or conservator in viewing the layers, materiality, and history of artwork. While shadowgraphs have been standardly understood as resources to uncover forgeries or observe great masters' painting styles and the development of a work, they have been less frequently considered in unconventional and imaginative ways. This project combined speculative art historical and studio arts research through examining the collection, analyzing literature, researching artists, and creating studio art. Readings drew from art history, astronomy, medicine, forgery, and concepts inspired by the studio work, which consisted of drawings, paintings, and prints on a variety of media such as rice paper, windowpane, and plexiglass. These explorations corresponded both directly and obliquely with the shadowgraphs, focusing on their qualities as potential artworks while maintaining a sense of their capabilities as forensic objects. Reading outside of art history and integrating literary research with creative art-making, we considered the history of shadowgraphs while investigating possible associations for the contemporary viewer, such as questions about the composition of the body, the deterioration of materials, and the dissolution of boundaries like the inside and outside, past and present, visible and invisible. With a creative and expansive type of research to understand these objects differently, the project illustrates that this archive does not exist as a closed record, but instead as a source of inspiration generating discovery across many disciplines.

# CLASSICS

## Critical Text of the Vita Sancti Facii de Cremona

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This paper presents the first critical text of the *Vita Sancti Facii de Cremona*, the 13th-century Latin hagiography of northern Italian lay saint Facio of Cremona. To produce this text, readings were compared directly between the 16th-century manuscript Cremona Sez. Ia, cass. 11, whose text was imperfectly transcribed in Vauchez 1972 and which is most commonly referenced in published scholarship as containing the only surviving text of the *Vita*, and the 13th-century manuscript Harvard Ms Riant 22, which is rarely mentioned in published scholarship and whose text has hitherto been unpublished. This paper is the first both to correct Vauchez's imperfect transcription of Cremona and to present Harvard's new readings for the *Vita* that are both variant to and absent from the text of Cremona. Within the introduction of this paper, Harvard Ms Riant 22 itself, the characteristics of the manuscript's text, and the manuscript's provenance from Italy to France to the United States are discussed; within the critical text itself, the best (and, from Cremona, corrected) readings from both manuscripts are presented of the *Vita*; and finally, within the apparatus criticus, variant readings for the text are presented and conjecture made by Vauchez on the basis of Cremona alone is discussed within the new context of Harvard's readings. By so comparing a corrected text of Cremona Sez. Ia, cass. 11 to the text of Harvard Ms Riant 22, an edition of the *Vita Sancti Facii de Cremona* has been produced wherein is presented the most comprehensive and current text of the *Vita* to date, including complete readings that would be impossible to reconstruct without the complementary witness of both manuscripts.

# ECONOMICS

## Energy Research

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How can innovation in the clean energy sector be promoted? Two possible approaches that we examine are: one, we can increase the supply of new researchers by expanding and investing in graduate training programs; or two, the existing set of researchers can be redirected with taxes and subsidies to conduct research in clean energy topics.There needs to be more people to study and invent new methods of energy creation, storage, and usage in order to mitigate the impact energy consumption has on climate change. We hope to determine which of these two approaches would be more efficient in increasing the amount of research on energy; in other words, should the government invest in graduate training programs or re-directive R&D policies? We plan to use natural experiments that will allow us to analyze the costs and benefits of the two policy mechanisms being considered. Historical data on birth rates and PhD graduates in the U.S. can be used to investigate the former. The latter can be analyzed by collecting data on energy-specific research subsidies and energy-related product taxes. The effect of these exogenous variables on researchers and the type of energy research they are conducting may provide insight on which approach is most effective. We are also able to generate new data on the distribution and evolution of PhD-trained energy researchers to look at general trends in researchers studying energy-topics.

# Collegiate Student-Athletes and Professional Career Success

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Collegiate varsity student-athletes often encounter a vastly different university experience compared to that of their non-athlete peers. Demanding practice and competition schedules take considerable time away from a student-athlete's academic pursuits and may negatively impact both academic performance and, hence, career advancement. This study examines the correlation between intercollegiate varsity athletic participation and future career success outside of professional athletics. While the considerable time taken up by athletic pursuits might negatively impact academic performance, there are many other potential benefits to student-athlete career outcomes. Rigid schedules of student-athletes can serve to enhance focus, discipline and goal-setting, enabling students to better tackle new challenges. Such discipline gained by student-athletes may potentially extend into enhanced life skills like advanced preparation, diligence, the ability to work in teams, and scheduling skills. In addition, future career success might be enhanced by the connections that athletics provide inside and outside of school. The primary goal of the study is to understand whether participation in varsity intercollegiate athletics prepares young adults for the challenges of the real world. Are they better off for their participation? The data utilized in this study includes the identification of more than 380,000 intercollegiate varsity athletes from forty-five colleges and nearly 3.5 million non-athletes from those same forty-five colleges. EMSI has provided comprehensive resume data for these 3.8 million individuals that allows the examination of career choice and career success. There are many factors including graduation year, gender, sport, school, and athletic conference that impact a student-athlete's likelihood of finding future career success excluding professional play. This project discovers new ways to sort and classify characteristics of these athlete profiles, so they can be used as a measure to study student-athlete career success. Using resume data identifying former student-athletes' selected career industries as well as home assessment data on the value of their current residence as a measure of personal wealth will allow the estimate of career success of athletes vs. non-athlete peers. Through this research, we can better understand the effect of a person's focus on the mastery of a skill or ability on the outcome of their life's successes.

## Do Financial Advisers Give Good Advice?

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In the United States, citizens plan on privately funding a large portion of their retirement above and beyond the support from Social Security. Given that current estimates suggest that Social Security Administration funds may be depleted in the next fifteen years, the responsibility only falls heavier on citizens to financially support themselves during retirement. Given this autonomy, we are interested in how investors save for retirement in defined contribution plans. Our research uses data on over 70,000 different defined contribution plans where we observe the investment menu, holdings, and fees for each plan. We look at how retirement plans vary across industries and over time and examine patterns of risk-taking in investment. We are particularly interested in the influence of industry and occupation wage and fatality rate on investment decisions. We use data on investor portfolio choices to learn about how they plan for retirement and infer about their beliefs and risk preferences. Further research may provide valuable insight as to how the United States should attempt to reform retirement planning.

## Racial Diversity in Financial Services

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This paper examines diversity in the financial services industry, with special attention to the employment of African-Americans. In contrast to the significant progress observed in reducing gender gaps in employment, we measure substantially slower gains in the employment of African-Americans. The paper first documents the proportion of African-American workers in financial services over time, drawing insights from Current Population Survey data. We measure the disparity in employment across various types of jobs within finance, finding that desegregation is particularly slow within high-level jobs such as managers, quantitative analysts, etc. Second, we investigate potential explanations for this continued disparity, including group differences in educational background and skill difference. We find some evidence that, initially, differences in educational background drove lack of diversity but, over time, an increasing proportion of the disparity in financial services is unexplained by observed group differences. Finally, we employ intergenerational survey data to estimate the effect of connections, networks, and family wealth, finding evidence of intergenerational transmission of employment in finance.

## The Vietnam War and Trust in Public Institutions

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The distribution and dissemination of news media have a profound effect on how we interact with and understand our societies and their contemporary issues. While the existing literature has worked to broaden our understanding of the impact of news media, it is severely limited by a lack of comprehensive, high-quality data. Leveraging deep learning and natural language processing (NLP) methods from computer science, we are working to digitize over 12 million US newspaper editions from over 7000 American newspapers published since 1850. From the more than 100 million resulting articles in the database, sentiment analysis, geographic tagging, content origination, and a variety of other NLP analyses will provide rich output for further downstream tasks. The outputs, to be published as the *American Communities Computable Newspaper Database* (ACCND), will additionally be made public for outside researchers and general audiences.

The role of the media in the Vietnam War is just one example of the ACCND's potential to provide valuable insights on the influence of news dissemination. The Vietnam War was not only the first widely covered American war, but it also witnessed the dramatic erosion of American public confidence in the government. Several interesting questions immediately arise. By exploiting sentiment in coverage towards Vietnam War protests, we might ask whether trust in government declined continuously throughout the war or if it fell as a series of precipitous declines around watershed moments such as the Tet Offensive, the Pentagon Papers, and the Watergate scandal. With a list of pro and anti-war publications along with supervised sentiment analysis, we can use topic clustering to understand whether pro-war and anti-war newspapers presented different accounts of the same stories or simply chose to cover different events during the war.

## Diversity in Private Capital

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The presence of homophily among private investors causes minority entrepreneurs to face difficulty raising capital because of their racial identity. This research corroborates that compared to non-minority-owned capital funds, minority-owned funds have fewer investors, take longer to raise funds, and are ineffective at estimating the size of their follow-on funds based on their performance. However, these patterns reverse during periods of high racial awareness, HRA. This study investigates how awareness of racial issues affects investors' willingness to fund minority-owned firms. For this research, we define a firm as minority-owned if at least 50 percent of its founders or senior partners are Black or Hispanic. To capture the racial sensitivity, we use crowdsourced data on fatal encounters between police and Blacks or Hispanics. If the ratio of all fatal encounters between police and minorities in a state is above the median fraction of fatal encounters of all states, then HRA equals 1. The results indicate that the relation between performance and ability to fundraise for minority entrepreneurs is substantially strong during high attention to racial issues. Minorities struggle less with fundraising during periods of high racial awareness, but only if the fundraising occurs in a state with a high allocation of public pension funds to private equity. The limited representation of Black- and Hispanic-owned firms in private equity was due to a lack of demand from investors rather than a lack of supply of available high-quality or diverse fund managers.

## Using Computational Methods to Study Communication Patterns in a Hybrid-Remote Workplace

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The recent COVID-19 pandemic has forced many companies to embrace hybrid workspaces and working-from-home arrangements (WFH), practices that seem likely to continue post-pandemic. However, there is little literature addressing how such arrangements affect communications between workers who are not jointly colocated in office, with most prior studies focusing on purely virtual work. We seek to bridge this gap by taking advantage of a field experiment conducted with a large firm based in Bangladesh as pandemic restrictions began lifting. Randomizing the number of days per week workers worked in office versus working from home, we collected performance evaluations and email data from the employees involved. Applying machine-learning topic-modeling methods to the email communications, we find that the topics discussed between employee dyads with above versus below median joint colocation in office have a high degree of semantic difference, providing the first causal evidence that WFH has a substantive impact on information sharing between coworker dyads. Our results have important implications for companies implementing WFH models, who must think carefully about structuring communication channels to ensure that information silos do not develop within company divisions and teams that are geographically distributed.

## Secular Stagnation and the Space Frontier

**Connor Haskin**
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Slowing economic growth rates in high-income countries in recent decades have revived discussions of secular stagnation, a Depression-era concept which posits that a combination of high savings and low investment levels generate consistently low interest and growth rates. Some suggested causes for secular stagnation include a decline in capital-intensive investment in innovation and the absence of a frontier economy to justify and encourage high capital investments. We investigated the possibility of addressing secular stagnation through the emerging commercial space economy, whose activities demand high investment levels in capital-intensive research and new technologies. We closely examined existing literature on secular stagnation, distinguishing between theoretical models that focus on exogenous shocks, such as deleveraging shocks, as a cause of stagnation and models centered on endogenous factors, such as investment in innovation and productivity growth. Using the endogenous model approach as a framework, we then evaluated data on growth rates and research and development (R&D) investment in the United States to see if the actual recent trajectory of the national economy is in line with the characteristics of secular stagnation as described in theory. We intend to determine on this empirical basis if capital-intensive investment in the commercial space economy can realistically address secular stagnation in the United States as well as in other high-income regions experiencing slowed growth like the European Union and Japan.

## Early Warning Signs of Stock Bubbles

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A security price bubble is characterized by an irrational price increase followed by a predictable price decline. The efficient markets hypothesis states that security prices reflect all available information, which makes the prediction of price bubbles impossible. There has been no evidence that the popping of a bubble and its timing are systematically predictable. We look for leading indicators of industry-level asset bubble pops, specifically using the 2000's internet bubble as a case study. We evaluate analyst forecasts, early firm-level failures, investor holdings, and share issuances. While analyst forecasts lag stock returns, we find the divergence between analyst forecasts to be contemporaneous with the bubble pop. We also find no predictive power in early firm failures or changes in investor holdings. Using scraped SEC filings, we find predictive power in share issuance announcements, which spike in both frequency and magnitude preceding a bubble pop. These findings regarding share issuance provide some evidence contrary to the efficient markets view that asset price bubbles are impossible to predict ex ante.

## The Impact of Management Practices of Nursing Homes on Nursing Homes' Health-Related Outcomes During COVID-19

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A large share of nursing homes in the United States experienced outbreaks of the Coronavirus Disease 2019 (COVID-19). The goal of this research was to better understand how the management practices of nursing homes affect nursing homes' health-related outcomes during the pandemic. The first phase of this research was conducting literature review, looking in particular at intermediate inputs related to management practices (e.g. staff ratios, use of performance reviews). We are currently investigating whether differences in policies and regulations across US states may help explain differences in management practices and performance across nursing homes, focusing in particular on regulations related to the management of staff (e.g. staffing levels, structure, wages of nursing staff), equipment and delivery of care (e.g. personal protective equipment, home health care), and Medicaid reimbursements. This research will inform the analysis of novel data on management data across nursing homes collected by the U.S. Census prior to the pandemic.

## The Effects of Wage Change Through Time on Political Unrest by US County

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Macroeconomic conditions such as wage growth, unemployment rates, and inflation have long been cited as drivers of political unrest. Central to this idea is the concept that negative changes experienced at the individual level can influence population-level increases in political tension. This project investigates the effect of changes in worker wages on several measures of political unrest and minority sentiment. Income data from the Bureau of Labor Statistics' Quarterly Census of Employment and Wages provided highly granular annual wage data for US counties, which were adjusted for inflation to obtain changes in real wages over the study period of 2010 to 2016. Political unrest and sentiment, a commonly-used metric of turmoil within US communities, was quantified with the FBI's Hate Crime Reporting statistics available by jurisdiction. Ordinary Least Squares (OLS) regression results indicate a significant correlation ($\alpha = 0.05$) between a relative decrease in wages compared to surrounding counties and an increased incidence of racially and ethnically motivated hate crimes. If the relationship were to hold under controls, this would support the theory that localized economic impacts can create an upwelling of political animosity. Further analysis may involve sentiment analysis on tweet datasets as well as Google search trends for divisive speech terms as more comprehensive indicators of political sentiment. These data sources have been shown to provide more detail and be more responsive to wage growth than conventional data sources.

## The Effects of Expanded Unemployment Insurance on Job Search during the COVID-19 Pandemic

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In response to the labor market disruptions caused by the COVID-19 pandemic, the United States federal government enacted a series of historic expansions to unemployment insurance (UI) programs. In addition to increasing the duration of benefits and loosening eligibility requirements, the federal government also supplemented state UI payments to a level that exceeded what most recipients earned while working. Proponents argue that these benefits are necessary to sustain households kept out of work due to labor market conditions or health risks; critics suggest that expanded UI has disincentivized reemployment in light of growing numbers of job openings that go unfilled. Several states have decided to end federal supplements early, but the resulting effects on employment are still inconclusive.

Using individual and county-level data from the Current Population Survey and Opportunity Insights, this project studies the effect of UI payments on job search using three identification strategies. First, it compares states with different UI schedules, leveraging the haphazard timing of rollout and some states' early cancelation of federal supplements. Second, it compares recipients for whom benefits constituted a different fraction of their prior earnings. Third, it compares people who lost their jobs and are eligible for UI with first-time job seekers who are ineligible. The relationship between UI and job search is then broken down by age, education, occupation, and local COVID-19 risk to examine potential disparities by group, which will contribute to the literature on labor incentives and optimal UI design.

## Human Capital In Mutual Fund Professionals

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With $24 trillion in assets under management, mutual funds have been among the largest investors in the financial market. While numerous academic literature focus on sell-side analysts, buy-side analysts in mutual funds have long been ignored due to the lack of data and information. As mutual funds gain popularity and become more exposed to the public view, we hope to explore factors that determine the success of mutual funds as well as the success of analysts within the funds. Specifically, we determine the success of the funds by measuring the return, CAPM alpha, and common performance ratios such as the Sharpe ratio. The success of analysts is measured by the number of years for them to become portfolio managers as well as the success of the funds they belong to. Some factors that we are exploring include age, gender, education, past working experience, and social networks of the analysts, and the diversity and age of the funds. Building off of a novel private dataset which allows us to identify buy-side analysts, we utilize LinkedIn to gather detailed information about each individual including their educational background, past working experience, and social network. Then, by cleaning the data and doing some regression analysis, we hope to identify one or more factors that affect the success of analysts and mutual funds. Our research will contribute to the overall literature surrounding mutual fund performance from a human capital perspective.

## Who Do They Hire and When? Investigating How Algorithm-Enabled Startups Successfully Scale

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Many companies are using algorithms or artificial intelligence to scale the accessibility of domain specialists, such as lawyers, personal stylists, or financial advisors. Little research has been done into how these algorithm-based startups scale successfully. To investigate this idea, the composition of each startup's employees will be analyzed, specifically to determine whether they hire employees with artificial intelligence expertise or with a specific domain expertise, such as law, fashion, or finance. We will also look at whether the order in which employees are hired and the past experience of the employees has any bearing on the startup's trajectory. Specifically, we will use the LinkedIn job titles and descriptions of employees at around 500 algorithm-enabled startup companies as data. We expect there to be some relation between the company's pattern in hiring employees with domain expertise and the eventual growth of the startup. These findings could be relevant to emerging startups with algorithm or AI-enabled business models, particularly with helping them decide whether to hire more domain specialists or computer scientists.

## A Machine Learning Approach to Startup Pitches and Entrepreneurial Performance

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Startup founders write pitches to describe their business idea to potential investors and attract funding. These pitches can affect how millions of dollars are allocated. This study uses a dataset of 2156 startup pitches from 24 phases of a business plan competition at a top tier business school in the mid-Atlantic between the years 2006 and 2015. We use Natural Language Processing machine learning models from Hugging Face's open source libraries as well as pitches' word and page counts to explore, first, features that correlate with a startup's attractiveness to investors and, second, features that correlate with actual success. By identifying features that are associated with higher ratings in the competition and a higher likelihood of receiving funding but that are not associated with startup success, our results may reveal biases investors have in evaluating startups. Investors can use our conclusions to improve their ability to invest in startups with the greatest likelihood of success, and entrepreneurs can use our results to improve the potential of their pitches.

## What is the Impact of Financial Incentives on Inference from Surveys?

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How do financial incentives impact survey response rates, respondent characteristics, and inference about population-level statistics? We examine these questions in the context of small business respondents, using a panel dataset of small business responses to surveys administered in 2020 through the Alignable network that asked about the impact of COVID-19 on business operations. Small businesses were selected from a larger network of businesses in the Alignable network and were randomly assigned to receive no financial incentive, a $25 gift card whether or not they completed the survey, a $25 gift card after completing the survey, or a $50 gift card after completing the survey. We observe response rates, defined as the proportion of businesses that finish the survey, between about 10 percent and 40 percent, and conditional response rates, defined as the proportion of businesses that finish the survey conditional on starting it, between about 60 percent and 85 percent. Preliminary findings suggest that treatment groups that receive financial incentives have higher unconditional and conditional response rates compared to the control group. In addition, preliminary results suggest that the types of answers that small businesses give are not statistically significantly different between treatment groups, suggesting that financial incentives do not cause heterogeneity in the collected data. Financial incentives thus appear to improve statistical power by increasing sample sizes but do little to alter inference. We plan to further analyze response and respondent characteristics to determine the extent to which respondents are representative of population parameters. A potential area of further research is examining whether increased response rates justify the monetary cost of providing financial incentives.

# Financial Conversation

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Financial conversations (e.g. how to split finances, what expenses to prioritize, how much to spend and save) are difficult undertakings, but they are entirely necessary in romantic relationships. Miscommunication about finances can and does lead to marital conflict and loss of household wealth. Currently the most common methods for romantic couples to improve their financial collaboration are marital counseling and financial advising. But most marital counseling is connected to religious institutions (and therefore not pursued by secular couples), and financial advising does not address the communication issues that underlie financial mismanagement in romantic relationships. Thus, there is a need to methodize how couples can approach financial conversations to improve their collaboration and ultimately, their marital health.

This research aims to explore how households can healthily and productively engage in financial conversations. In this study, 113 romantic couples ($N$ = 226) were recruited to complete two financial tasks: a debt repayment simulation and an investment task. Their interactions were video recorded and analyzed to determine how their communication affected their collaborative and objective performance on the tasks. In the debt repayment simulation, the couples were tasked with paying off 6 debts, each with a different balance and interest rate, over the course of 25 rounds (where each round equaled one year). Their performance was evaluated based on how much debt they had left by the end of the 25 rounds, with the lowest possible amount being $12,000. This task was incentive-compatible as couples were awarded a bonus payment based on their objective performance (couples who ended the game with the lowest debt balance were paid a higher bonus payment). The second task asked couples to make investment decisions in bonds or stocks, with the goal of accumulating as much returns as possible. Initial analyses using LIWC software to assess conversational sentiment, revealed that financial performance on both tasks was predicted by less negative conversational exchanges ($p$ <. 001) and marginally improved by a greater proportion of positive conversational exchanges ($p$ = .07). Further, financial conversations tend to be asymmetrical (i.e. one party speaks longer and more frequently than the other), especially in heterosexual relationships, wherein the male partner is more dominate in the discussion. Couples exhibiting these dynamics tended to perform worse ($p$ = .003), indicating that couples with higher degrees of collaboration and more equal contributions from both parties lead to more productive conversation and better financial outcomes. A future intervention study is planned to introduce a collaborative intervention by having female partners initiate the financial discussion and to require a financial 'check-in' after every third round of the debt repayment simulation to assess whether more frequent involvement of both conversation partners will improve objective performance.

## The Anatomy and Evolution of ESG Reports

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Environmental, Social, and Governance (ESG) reports are among the fastest growing voluntary disclosure phenomena in recent history. Despite rising interest among firm stakeholders for ESG disclosures, they remain unaudited and lack uniformity in both quality and content. This study provides the first detailed examination of a large-scale hand collection of ESG reports of all firms in the S&P 500 from 2010 to 2020. Using machine learning algorithms to characterize the contents of the ESG reports, we study the extent to which regulatory guidance has shaped the evolution of these reports and create an index measuring the extent that financially material information is contained in firms' voluntary ESG disclosures. In the data analysis phase of this assessment, we have built a topic model and machine-readable understanding of the ESG reports. With this topic model, we will examine the evolution of ESG reports and quantify the disclosure quality of ESG reports relative to what is expected as defined by industry-specific regulatory guidance. Successful completion of this study will provide an understanding of the role of voluntary standards on voluntary disclosures and a transparent, scalable index to determine disclosure quality of ESG reports.

## Understanding Privacy Preferences Around the World

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As data-intensive economies become dominant in the digital landscape, privacy is becoming increasingly important. Understanding individual privacy preferences is a necessary component to understanding individual economic behaviors. However, understanding privacy preferences is complicated and often contradictory. Prior studies on privacy indicate that most Americans are worried about surveillance by governments and private industry, yet, on an individual level, people can be unwilling to take the steps necessary to protect it. In fact, Americans are sharing more of their lives online than at any other point in history. To examine these trends through an economic lens, we constructed a survey to measure three aspects of privacy preferences and behavior: individual privacy preferences, perceived costs and benefits of privacy-related actions, and social attitudes toward regulating data access by governments and corporations through collective action. We sent a pilot survey to 50 American participants to elicit data on each of these components. Then, we scheduled interviews with participants to gain further insight into their perceptions of privacy actions and social attitudes toward privacy. After this pilot round, we plan to release this survey to a larger group of participants beyond the United States in order to compare privacy preferences between countries and within countries. This is the first study to examine privacy-related preferences, beliefs, and behaviors comprehensively and rigorously, which will allow policymakers, individuals, and business leaders alike to make informed decisions about privacy in economic decision-making.

## Editorial Decision Making in Scientific Publishing

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Authors, reviewers, and editors each play an essential role in the editorial decision-making process of scientific publishing. However, there is limited knowledge upon the criteria that experts use in their determination of whether to publish a manuscript into their journal as well as whether editorial biases impact how likely a paper is to be published and cited. It is important to understand how papers are subjected to critique because potentially valuable information could be withheld due to these biases of reviewers and editors. We took existing data with over 27.000 observations of manuscripts and tracked their progression from their initial submissions through revision to their final decisions along with the experts' comments to one another explaining their decisions. The preliminary results of our research indicate that the most frequently published topics include DNA and cancer research, papers are always more commonly rejected than accepted, and there is a positive trend from 2013 to 2018 in the proportion of papers transferred to a different journal than accepted/rejected papers in the originally submitted journal. In addition to these initial findings, we intend to discover whether a relationship between the level of formality in the communication between reviewers and editors and whether consensus among reviewers affects the likelihood that a paper gets published. Our findings on bias and preference in the publishing process can provide insight into the standard to which research is held in the determination of publication.

# GOVERNMENT

## Impact of Covid-19 on Views about and Votes for President Trump

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It is well-established that intense partisan motivated reasoning can lead people to filter new information through a combination of already-existing beliefs, perceptions, and identities so that this new information reinforces partisan loyalties instead of changing them. This paper leverages spatial and temporal variation in the spread of the COVID-19 pandemic to investigate how, when, how much, and in what situations new information reinforces or undermines partisan proclivities. It develops and tests six frameworks for understanding how perceptions of the pandemic affect pandemic-related behaviors and presidential and congressional vote choice: direct experience, community experience, national experience, use of information, partisanship, and new narratives. We analyze three main sources of evidence: public opinion surveys of geolocated American adults throughout 2020; COVID-related behavior, such as mask-wearing and movement outside of the home, of geolocated American adults throughout 2020; and Republican and Democratic vote shares in the 2020, 2018, and 2016 presidential and congressional elections. Highly preliminary results suggest that new information about and experiences with COVID-19 do cause Americans' partisan loyalties and partisan-affected behavior to change a little.

## Redesigning Civic Education in Massachusetts for the Modern World

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Toxic dialogue? Insurrection? The end of democracy? These and other buzzwords have come to represent the decline and fall of civic engagement in the United States over the past twenty years. The Democracy Knowledge Project Design Studio (DKP), a design, research, and implementation hub based at the Edmond J. Safra Center for Ethics (EJSCE) at Harvard University, works to integrate ethics and civics into curricula at all levels; and ensure that a new generation of leaders can think holistically and responsibly about the power in their hands. Our team analyzed, assessed, and redesigned the DKP eighth grade civics curriculum taught in thirteen districts across Massachusetts. Using a custom mapping tool to assess existing curriculum resources around seven core project-based learning concepts, and feedback from educators who have previously implemented the curriculum, the team was able to identify curriculum redesign priorities to better meet DKP's deeper civic learning framework and state civics standards. The mapping tool, combined with observed implementation data, highlighted several pedagogical recommendations needed to create an accessible and engaging learning environment for students. Furthermore, several redesign seminars with six pilot teachers confirmed the mapping findings and resulted in new curricula proposals to be implemented for the upcoming school year, specifically in the areas of civic identity, civic knowledge, and civic skills. More broadly, we are continuing our assessment and redesign work to uncover weaknesses and trends within the landscape of civic education in Massachusetts, and eventually offer a curriculum that can be taught in a diversity of districts across the state and be an exemplar for curricular adaptation and creation nationally. The results of this work will assist teachers and administrators in strengthening civics curricula to better educate and prepare students to be authentic, informed, and skilled civic participants.

## Lawyers as Lobbyists: How Banks Influence Financial Regulation

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How do large financial institutions mobilize legal expertise to influence federal rulemaking processes? What are the effects of these efforts upon the favorability of regulatory outcomes and on firm performance? This project examined these questions in the context of Federal Reserve-enforced provisions of the Dodd-Frank Act of 2010, which sought to reform and stabilize the financial industry after the crisis of 2007-09. We argued first that traditional conceptions of lobbying fail to consider the role of lawyers who, particularly in technical rulemaking matters, effectively act as lobbyists for their clients despite not being officially registered as such. We then explored this phenomenon of 'lawyers as lobbyists' in the context of Dodd-Frank rulemaking, an area where large banks often had a significant financial stake. To do so, we developed original datasets of all notice-and-comment submissions and meeting participants with the Federal Reserve on Dodd-Frank rulemaking, spanning over 15,000 interactions. These datasets demonstrated extensive engagement on behalf of large banks by lawyers who were *not* registered as lobbyists, as well as a highly disproportionate skew in lawyer representation for large financial institutions relative to smaller banks or public interest groups. To demonstrate the effects of this phenomenon, we integrated previous work to show that banks which deployed legal expertise in Dodd-Frank rulemaking experienced sustained stock price increases upon the announcement of new rules relative to competitors who did not. Several detailed case studies on interactions between banks, white-shoe law firms, and financial regulators reinforced the idea that large banks gain materially from having lawyers act effectively as lobbyists on their behalf. This research pointed to the central and understudied role of lawyers in shaping administrative politics, bolstered our understanding of the role of money in regulatory affairs, and exposed new dimensions of political inequality in the design and implementation of regulation.

## Lawyers as Lobbyists: Regulatory Advocacy in American Finance

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Regulatory lobbying, the practice of advocating to regulatory agencies in the executive branch on behalf of another party, is much less known than traditional legislative lobbying, and even neglected by some political scientists. Congress regularly delegates agencies with writing and enforcing rules to implement the goals of legislation it approves. This delegation gives agencies significant discretion in deciding how to define and enforce policy, and presents an opportunity for individuals to influence regulators and advocate for a client's position. This study describes the role that lawyers play in regulatory advocacy of agencies tasked with financial regulation. We examined rules promulgated by federal agencies as a part of the Dodd-Frank Act of 2010 and the individuals that participated in those procedures. To do so, we collected publicly available comments submitted to agencies regarding specific rules, as well as data on meetings between private individuals and agency officials before and after rule announcements. We combined this data with the Open Secrets and LinkedIn databases to obtain data on which commenters were lawyers, which were lobbyists, and which lobbied on Dodd-Frank. To examine the mechanisms at play more closely, the study also examined the particular case of Rodgin Cohen, the executive managing partner of Sullivan & Cromwell, a white-shoe law-firm at the top of corporate law. The data indicates that corporate lawyers are some of the most regular participants in the rulemaking procedures of federal agencies. In addition, plausible estimates indicate that the number of lawyers engaged in regulatory advocacy could be comparable or even surpass the number of registered lobbyists. Furthermore, expenditures on regulatory advocacy by Bank Holding Companies could equal or even surpass their expenditures on traditional lobbying. These findings suggest that current definitions of lobbying may be overlooking a significant and important portion of lobbying activity in government.

## State Legislative Redistricting: A Case Study of Pennsylvania

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Legislative district maps serve as the connection between voters and their corresponding representation in government. Subtle changes in district maps can alter the political make-up of a state legislature, and thus have large impacts on policy outcomes. Via sequential and markov chain monte carlo methods we sample potential legislative maps for the Pennsylvania state legislature according to varying sets of geographic and policy oriented constraints. When comparing enacted maps to simulations, we find evidence of both "packing" and "cracking," particularly on the borders of population dense areas; certain districts are extremely dense in both minority and Democrat leaning voters, while in others, their vote share is diluted. One objective is to increase the number of Democrat leaning districts to combat the disadvantages the party faces due to geography and gerrymandering. Increasing the number of Democrat leaning districts requires districts that cross city and county limits, with larger gains possible in smaller cities compared to already extremely Democratic Pittsburgh and Philadelphia. We find that to increase the number of majority minority districts (as suggested by the Voting Rights Act to improve representation), it is also often necessary to cross geographic boundaries such as city limits or county lines; in contrast to creating Democratic districts, there are more opportunities for majority minority districts in Philadelphia and Pittsburgh due to greater minority populations. The two goals of majority minority districts and Democratic leaning districts are often in tension. Drawing majority minority districts limits the ways maps can be drawn due to the geographic distribution of the minority population, locking in a less than maximal number of Democratic leaning districts around many cities in Pennsylvania. These findings are consistent with results from other states like Georgia and Louisiana. Future research will connect these patterns to the changing demographics of suburban areas.

## Do Strong Property Rights Hinder Public Infrastructure Investment?

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Neoclassical and institutional political economies often highlight the importance of secure property rights for economic development. Property rights reduce transaction costs and provide security to owners, allowing individuals and companies to make long-term investments that they will benefit from. Similarly, well-defined property rights allow governments to purchase land for public projects more easily. However, they can also increase transaction costs to acquire land for public investment when there is disagreement on the sale. In reality, in places with unmet distributional needs, property rights can be used by individuals and communities to demand a price higher than the market value or even make "opportunistic" claims regarding public and social goods. We study the mechanism by which property rights might hinder public infrastructure investments by conducting a cross-country qualitative analysis of property rights regimes. We examine Peru's property rights in light of its eminent domain and prior consultation legislations and compare it to two countries with similar income levels but that differ in property rights security: Colombia and Ecuador. After that, we analyze a survey experiment in Colombia with 1005 respondents to test the role of formal property rules in motivating claims isolated from other factors like private sector involvement. The treatment effects study suggests that respondents' perceived bargaining power against the state and their willingness to file legal claims and demand higher compensation are higher when they are told they have a more comprehensive set of property rights. This research contributes to the understanding of how property rights might affect the ability of developing countries to carry out major public infrastructure projects that are often seen as crucial for economic development. The study of how specific bargaining claims impact infrastructure projects also helps elucidates how states can improve their capacity to implement those projects and better address related distributional needs.

## Debate Participation in Presidential Elections

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In countries with less well-established democratic systems, the organization of and participation in presidential debates is less regular and less well studied than in the United States or European countries. Our research aims to assess the effect of candidates' debate participation on electoral outcomes in presidential elections, especially in low-income countries: Do candidates who choose to participate in the debate see an increase in their support compared to those who do not? In order to assess this effect, we are gathering data from polls, prediction markets, and social media websites. We focus on 73 presidential elections in 25 countries across Latin America and Africa. We first analyze the factors that correlate with a candidate's decision to attend the debate or not, such as their incumbency, standing in the polls, and demographic characteristics. We then consider the effect of this debate participation on the range of outcome variables. Of particular interest are the differential effects of debate participation on candidates depending on incumbency, gender, and pre-debate polling strength. So far, much of our work has been cleaning the polling data and gathering prediction market and social-media data. We use a difference-in-difference design to assess the effect of participation on the outcome variables.

# HISTORY

## Urban Futures in History

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Over the last 250 years of rapid urbanization, cities have been arenas for competing visions of the future from different planners, politicians, artists, corporations, and commonplace people. For example, some advocated for segregated suburbs, while others advocated for egalitarian, concentrated urban areas. As part of Professor Bruno Carvalho's new book-length project, I investigated a variety of online oral histories of primarily nineteenth–twentieth century immigrants, women, and freed slaves, interrogating their experiences and of the east coast cities of the United States and their expectations for the future. I have also researched fictional representations of cities in various twentieth century advertisements. Thus far, this information presents a correspondence between optimism, the state of the economy and US foreign affairs, access to prosperity, and race, class, gender, and citizenship. These patterns from people of the past reveal that at best, humans have a mixed success rate at predicting the future and that as such, the right change in policy, culture, and the arts can influence the people of today to reimagine their own future cities, especially with regard to the role of cities in climate change and the catastrophic vision many hold regarding the future of the planet's climate.

## The Amendments Project

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The goal of the Amendments Project is to create a searchable database of proposed amendments to the US Constitution that can be used for empirical analysis by both scholars and activists. To that end, we combined the National Archives' record of nearly 12 000 constitutional amendments proposed in Congress between 1787 and 2014, compiled from Congressional documents, with amendments proposed by citizens and political organizations, discovered through archival research. We primarily used the Comparative Constitution Project's topic ontology to tag each amendment proposal, making the database searchable by topic category even as the language of proposals changed over time. While the archival research and the topic-tagging will take years to complete, the work done this summer is suggestive. Analyzing amendments related to K-12 education reveals sustained debate over the constitutional limitations on religion in schools; this debate has persisted from nineteenth-century movements to restrict public funding for parochial schools, through strife over teaching evolution in the early twentieth century, to modern conflict about prayer in school. I studied 581 of these proposals, sorting them chronologically and by subject matter to track sustained efforts to alter the religiosity of publicly-funded education; the first, banning appropriations to parochial schools, dates to 1870; the most recent, concerning voluntary prayer in public school, was proposed in 2013. These amendments arise at the intersection between the Establishment Clause and the "parental rights" movement, highlighting the role of public schools in mediating (or, perhaps, escalating) tensions between individual liberty and institutional authority. Although this "data story" may not be widely applicable, it demonstrates how our dataset can be an effective tool for longitudinal historical analysis. More broadly, the creation of a tagged and searchable database could be a powerful resource for both researchers and activists to track historical and contemporary patterns of efforts for constitutional change.

## Mapping the Past for a Better Future: Next-Generation Research into Past Pandemics, Places, Photography, Philology

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A slave society with roughly 5 million slaves—10 to 15 percent of its total population—ancient Rome maintained a complex and ever-evolving system for supplying, subjugating, and circulating enslaved populations. While other, later slave-trading societies have been studied in-depth, and databases have been made available for study to researchers, there does not exist such a database of forced movement for the Roman Empire. This project compiled a Geographic Information System (GIS) database containing information on forced movements of populations in the Mediterranean from approximately 500 B.C. to 600 A.D. Database entries were extracted from secondary sources that summarize ancient accounts of forced movements. This database enables an empirical look into how forced movements in ancient Rome changed over time: shifts in trade routes, market locations, and the circumstances of enslavement are all given quantitative grounding. More than 360 entries have revealed a highly complicated, voracious, and horrific scene of ancient Mediterranean supply and trade of human beings. A survey of these entries showed that ancient Rome's supply of slaves came through methods ranging from conquest to reproduction and infant exposure (e.g., abandonment at a garbage dump). Moreover, towards Late Antiquity, there emerged the consolidation of a trans-Saharan trade network with populations being enslaved in Mauritania, Ethiopia, and Numidia (modern Tunisia, Libya, and Morocco); secondary sources indicate that the Christian Church played a central role in facilitating and justifying this then-nascent trade connection. These two interrelated developments—slave trade out of Africa, and enslavement predicated on race—formed in the late Roman Empire, and became the cultural underpinnings for slave societies in the modern world (Brazil, Caribbean, the United States).

## Climate Futures & Fiction: Two Short Stories

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The growing genre of climate creative writing, shortened to "cli-fi" in the world of fiction, maintains strong ties to the apocalyptic, imagining the definitive end of the planet, or, in stories populated with warring refugee communities, plagues, and resource empires, spectacular ends to life as most know it today, at least. Apocalyptic narratives often hold within their images of destruction the notion of a sanitary ending: a point of no return, beyond which the world stops turning and life follows, falling away. This project, comprising two short stories set in a fast-approaching future, draws on Houghton Library's collections, in particular, on the papers of Wole Soyinka and W. G. Sebald, to imagine a world made and unmade by global temperatures soaring past a two degree inflection point. The stories mark a departure from the tradition of cataclysm, turning their attention, instead, toward the everyday experiences of living in a constant state of climate disaster. The Wole Soyinka papers, which include boxes of the playwright's drafts and annotated manuscripts, news clippings, and correspondence, stage a number of contemporary environmental and political conflicts and, further, articulate various approaches to imagining the transnational and trans-special alliances that make tenable otherwise hostile habitats. The stories turn toward the future, toward ecological disaster and its evolving intensities, through irruptions of the past, making use of Houghton's holdings on W. G. Sebald: drafts of his prose narratives and letters exchanged with Michael Hulse, responsible for English-language translations of three of Sebald's works. This project considers life beyond apocalypse, beyond the easy notion of any definitive ending, then, through the political, aesthetic, and philosophical strategies articulated in the papers of Sebald and Soyinka, two writers greatly concerned with the siren call of progress, with disaster and memory, and with what shapes history takes as time moves onward.

## Deindustrialization and Its Impact in the US, the UK, and France

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In the past few decades, social scientists have dedicated much attention to deindustrialization, a process by which manufacturing and related industries move out of a region. Deindustrialization is typically accompanied by high unemployment, outmigration, depressed wages, and other markers of economic decline, especially in small, specialized economies. Our project aimed to develop a comparative outlook of deindustrialization in France, the United Kingdom, and the United States; we focused on characteristic communities in each country—namely the Meuse Valley and surrounding areas in northeastern France, Sheffield and greater South Yorkshire in the United Kingdom, and the Mahoning Valley in the United States. Thus far, our research—in which we relied on local resources, government data, and the work of other social scientists—has uncovered patterns in the economic, social, and political postindustrial lives of these communities. In particular, our early work has focused on these communities' efforts to revitalize their economies through public investment and their more recent shifts toward right-wing populism. We plan to further investigate both the causes and effects of deindustrialization, particularly as they relate to the pasts and futures of places that have experienced its impact. We hope this research can spotlight the challenges faced by the many towns left in deindustrialization's wake.

## Deindustrialization and Its Impact in the US, the UK, and France

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Beginning in the 1970s, steel mills and automobile factories across the industrialized world closed their doors. Since then, these abandoned communities in the United States, the United Kingdom, France, and elsewhere have reckoned with deindustrialization's economic and cultural consequences. While scholars of various disciplines have studied deindustrialization and its legacies within individual countries, this project provides a historical, book-length, comparative analysis. Drawing on oral history interviews and memoirs of former workers—including women, immigrants, and workers of color—we explore how workers and their families coped with factory closures, and how their local communities and governments attempted to address their concerns and rebuild their economies. Because industrial decline leaves a legacy well beyond the workers themselves, we also explore how deindustrialization has been portrayed to the broader public. By reviewing everyday representations of working-class life—in museums, documentaries, and even creative projects like plays, photographs, and songs—we can better understand deindustrialization's place in our collective memory. This project, grounded in the experiences of workers and their communities, will help us grapple with industrial decline as it continues and help us think about the future of post-industrial work, workers, and communities.

## Amend & Annul: Constitutional Amendment Proposals as a Response to Supreme Court Decisions

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The U.S. Constitution can be amended through either judicial interpretation or the formal amendment ratification process. But what is the relationship between these two types of constitutional change? This research aims to examine the connection between landmark judicial decisions handed down by the Supreme Court and the attempt to correct or override them by constitutional amendment. It derives from an in-depth study of the National Archives dataset of amendments to the Constitution proposed in Congress from 1787 to 2014 and Landmark Cases' list of landmark Court decisions. To determine the number of amendment proposals that sought to overturn a Court decision, each relevant National Archives entry within one year of a particular decision was counted. Additionally, combining this research with Harvard law professor Vicki C. Jackson's scholarship, this paper also assesses the role that the perceived difficulty of amendment played in the quantity of judicial backlash amendment proposals. An analysis of the data demonstrates that the majority of landmark decisions throughout legal history have had little to no reactionary Congressional amendment proposals that aimed to nullify them, with the culture war period of the 1960s to 1990s serving as the strong exception. The cases leading to the most backlash during this period were *Engel v. Vitale* (1962) with over 60 amendment proposals, *Miranda v. Arizona* (1966) with 5 amendment proposals, *Roe v. Wade* (1973) with over 35 amendment proposals, and *Texas v. Johnson* (1989) with over 55 amendment proposals. Since 4 of the Constitution's current 27 amendments were ratified during this same period, the high frequency of judicial backlash amendment proposals lends credence to Jackson's contention that the perceived ease of the amendment process can lead to its increased use. However, this paper further argues that the fact that most culture war amendment attempts endured well after a year of their triggering Court decisions — and the fact that judicial backlash amendment proposals were sparse throughout the rest of U.S. history — points towards the role that increased polarization and the utility of amendment proposals as strategic political markers also play in amendatory culture.

# PHILOSOPHY

## Moral Development at American Colleges and the National Ethics Project

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Ethical questions pervade our personal, professional, and civic lives, and they often cross these domains, as the past year of public health, economic, and political challenges has vividly illustrated. Colleges and universities need to prepare their students to successfully grapple with these questions, but it is unclear how they are doing so or with what degree of success. How do American colleges and universities promote the moral development of their students? Where and how is ethics taught to undergraduate students? As part of the National Ethics Project, I am inquiring into these questions through two main approaches. First, a literature review aims to describe the existing scholarship on theories of moral development, various pedagogies for promoting moral development within college classrooms, and activities and initiatives that promote moral development beyond the classroom. Second, a mixed method study across Harvard, Stanford, and the New Jersey Institute of Technology Computer Science and Engineering programs that aim to teach "public interest technology" explores student and instructor experiences with ethics through qualitative and quantitative analysis of interview and survey data. The ultimate goal of these two efforts is to fill the gaps in the literature about the most effective ways to teach ethics to, and facilitate the moral development of, college students at American undergraduate institutions.

# PSYCHOLOGY

## Underestimating the Desire for Feedback

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Why do most people avoid giving feedback even when it is clear that someone else would benefit from receiving feedback? What stops people from giving feedback even in obvious and urgent situations? A thorough read of the research text points to two factors that possibly deter the desire of people to give feedback even while constructive in motive. One reason is based on personal experience with past discomfort or affected relationships, and another reason is based on considerations about the receiver's experience in a case of the value of the feedback, or anticipated discomfort of the receiver. In a field study, survey administrators placed food or markers on their face as they approached unsuspecting participants for a survey random request, and in this study, only 2.6% voluntarily provided feedback about the administrator's face. Several experiments were conducted with a purpose to understand people's reasons for underestimating others' desire for feedback. The results demonstrated the implications of a decline in the desire to give feedback span across public speaking, professional conversations and multicultural interactions.

## Diversity & Discrimination in the Digital Age

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Recently, the prevalence and accessibility of social media has brought to the public's attention the disparities in customer service that minorities face at the hands of frontline workers. However, these events are not new. Prior research has shown that, across industries, Black customers receive less quality service, higher price quotes, and experience higher incidents of being racially profiled based on their names, than their White counterparts. Naturally, due to this, there is now an interest in crafting interventions to discrimination in customer service that will ensure that all patrons receive equitable service across the board. This project aims to contribute to existing literature on racial prejudice, which has shown that customer-based discrimination can be mitigated by equity-emphasizing company mottos and clear customer status. In the present research, we are testing the use of job function reminders that are either self-imposed or are expressed by management, reminding participants, in this study acting as the frontline workers, to provide equitable service or not. These surveys will be conducted on Amazon Mechanical Turk through Qualtrics XM. We hypothesize that those participants randomly assigned to the conditions promoting equity will display less bias against customers of color than those assigned to the discriminatory conditions. If our hypothesis is supported, then job function reminders could be used as an intervention to decrease discrimination against customers and create more just customer service practices.

## The Carrot or the Stick? Low-Status Workers and Perception of Employee Motivation

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There is increased attention towards the treatment of low-wage workers. In this project, we are exploring whether managers use different strategies to motivate workers to improve in low-status occupations (i.e., jobs that are viewed as less prestigious and valuable in the United States) vs. high-status occupations. Using a between-subjects experimental design (n = 581), participants recruited on Amazon's Mechanical Turk, an online platform to crowdsource jobs or survey responses, were randomly assigned to read about a group of employees in either a low or high-status position in the same industry (either a cashier or a marketer for a grocery store). Participants were asked to draft a strategy to motivate a subgroup of employees experiencing low customer satisfaction ratings. The performance and demographics of employees were held constant across both conditions. We developed coding schemes that captured the most prevalent strategies and coded responses based on whether they did or did not include each strategy. Participants were significantly more likely to recommend using financial incentives for workers in low- versus high-status jobs. Participants who reported that workers in low-status jobs were less intrinsically motivated were more likely to suggest financial incentives for low-status jobs. Participants were also significantly more likely to use money-based words in the low-status condition and to use achievement-based words in the high-status condition. These results suggest that managers might overestimate the importance of extrinsic rewards and underestimate the importance of intrinsic rewards when motivating low-wage workers. In future work, we will continue to explore differences in how mangers incentivize employees in low-status occupations to improve their performance and why these differences exist.

## Are Toddlers Curious About What They Can Do?

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Previous research on children's exploratory play has shown that children express interest in uncovering information about the world around them. They test conceptual theories and spend more time playing with toys that behave in surprising ways. However, little research has examined whether children are also curious to learn about themselves. To test the hypothesis that children seek out activities that tell them about their own abilities, we plan to conduct an experimental study. Children will play two games, one independently and the other with a caregiver, that involve fine motor skills. They will then be asked which game they would like to play independently. If our hypothesis is supported, then we expect children to choose the game they had previously played with their caregiver because they are unsure whether they can play the game successfully on their own. The findings of this work could have important implications for future studies of curiosity and exploratory play and may contribute to researchers' understanding of when and how children learn about what they can do. As a first step, we gauged parents' intuitions about what motor skills their children have. We surveyed parents of children ages 2-4 (planned N = 75 parents) on whether their children can do a range of tasks that involve fine motor skills, such as using scissors, pouring liquids, and eating with a spoon. The results from this survey will help us design games for the experimental study that are both challenging and attainable for toddlers.

## Algorithm-Induced Biases

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The use of artificial intelligence (AI) algorithms in several industries, from consumer service to supply chain predictions, has increased dramatically over the past few decades. This rising reliance on AI has raised concerns about potential racial and gender biases it can perpetuate in advertising, hiring, and pricing (Bigman et al., 2020; Lambrecht & Tucker, 2019; Zettelmeyer & Morton, 2001). While, in many cases, the role of AI is to support human decision-makers, most of the limited research on algorithmic biases has focused on the bias of algorithms themselves, ignoring potential biases that perfectly objective algorithms can induce in human judgment. This research explores how subjects interpret recommendations from an AI algorithm differently, depending on the gender of the individual who communicates the advice. Specifically, in one preregistered study (n = 1,774), we find that participants are significantly more likely to accept advice from a financial adviser if the advice based on an AI algorithm comes from an adviser who is male. However, using an AI algorithm does not seem to make a difference for female advisers. Our findings have important implications for AI's role in potentially widening the gender gap in different contexts (e.g., personal selling) even when algorithms are not biased.

## Sarcasm and Context-Cue Dependency

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Sometimes utterances cannot be taken at face value, but instead are meant to be taken as *sarcasm*. What may differentiate sarcasm from other metaphorical language like irony and satire is the interplay of background context and cues (vocal or physical) to both communicate and comprehend the hidden message. Previous research and personal experience has shown that in some situations, sarcasm fails. The current study will aim to isolate the roles of context (that is, the background probability that the utterance is true) and cues (that is, prosodic signals) in the use and understanding of sarcasm by manipulating and presenting these elements to naive participants. Participants will be shown a series of four videos (counterbalanced using four lists in a Latin Square design) in which they are exposed to either context *and* cues, context *or* cues, or *no* context and *no* cues. Participants will then be asked to report the likelihood of truth of the target utterance. Comparing the likelihoods from the same scenarios between participants may allow us to identify whether it is context, cues, or a mix of both that has the strongest influence on the success or failure of an utterance in communicating the sarcasm and its message. The main hypothesis is that- if provided a combination of sufficient context and cues- participants will be able to more clearly detect sarcasm in the utterances provided; cues or context alone will lead to weakened interpretation with sarcasm. If this hypothesis is supported, participants are predicted to report more polarized likelihoods (closer to either 0 or 100 percent) in the "cues and context" and the "no cues no context" conditions. The study aims to provide a more in-depth understanding of what is necessary for sarcasm, as a linguistic device, to be effective.

## Decision-making, Introspection, and Morality

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Accurate introspection is one's ability to explain the rationale behind their actions. It has long been identified as a key component of self-assessment and awareness. Yet, the field of psychology continues to lack a reliable, objective measure of introspective accuracy. This project seeks to address this gap in the literature by attempting to develop such a measure in the form of an easily administered, 15-item questionnaire. Each item in this questionnaire will prompt participants to make a choice or judgment and subsequently identify what factors they believed influenced their decision-making process. These self-reported factors will then be compared to those proven by the social and cognitive literature to influence decision-making, thereby producing an estimate of introspective accuracy. Currently, the test is in the development stage with plans to undergo pilot testing prior to general use. Once fully developed, the test is expected to allow for between-group comparisons of introspective accuracy, which may serve as the basis for identifying demographic variations in introspective accuracy, assessing the effectiveness of different introspection training techniques, and other fruitful areas of study.

## TransCare: Utilizing Community-Based Participatory Research Methods to Assess Access to Healthcare for Transgender Individuals

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Access to healthcare for transgender individuals is rarely studied as minimal literature exists on the topic. LGBTQ communities experience significant health disparities as there is a lack of understanding surrounding their experiences with healthcare systems, which could further inform future reform. The objective of the TransCare study is to utilize community-based participatory research (CBPR) methods alongside an intersectionality approach to understand the experiences of transgender individuals in accessing and navigating healthcare and mental health services in India before, during, and after COVID-19. To understand their experiences, transgender individuals were interviewed using a standard questionnaire, and their interviews were consequently transcribed. Open coding, a form of qualitative analysis, was performed on the transcriptions to retrieve major themes and codes emerging from the study such as "passability as a cis person" for example. Analysis is currently being conducted to document the primary themes and preliminary conclusions. Focus group discussions were concurrently performed as a data collection tool to obtain feedback and community participatory workshops were held as a part of the CBPR approach to obtain feedback and input at every stage of the research process. Furthermore, training workshops were organized for co-learning with the community and capacity building on gender-sensitive research conduct. The study found that mental health has been significantly impacted and current disparities exacerbated due to the COVID-19 pandemic.

## The Implementation of Help-Seeking Interventions using Community-based Methods in Goa, India

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Increasing patient engagement with appropriate care to tackle mental health burdens remains a difficult task in all nations, regardless of income level, resulting in limited engagement with treatment across the world. Sangath works primarily in India, a low-and-middle-income country, and the IMplementation of evidence-based facility and community interventions to reduce the treatment gap for depRESSion (IMPRESS) project aims to reduce the treatment gap by addressing both supply and demand side barriers. The project combines two interventions previously developed by Sangath: the scaling up of the Healthy Activity Program (HAP), a manualized psychological treatment for Depression, and the VISHRAM Program, a community-based mental health intervention working to enhance mental health literacy. First, we developed a systematic review that will look at interventions aimed to improve help-seeking behaviors, attitudes, and intentions of individuals facing mental health conditions in all countries. After comprehensively searching a series of databases, this systematic review will synthesize the results of studies published over the last five years through a narrative and statistical analysis, serving as an update to the Xu et al. (2018) review about the same topic. Simultaneously, we consolidated Sangath manuals and other literature to outline and build a set of online modules to train the IMPRESS community agents in sharing accurate information about mental health and debunking misconceptions. Preliminary database searches have shown that several new interventions have been conducted to improve help-seeking in a variety of contexts, and initial module development has revealed that the modules must be specific to the community agents' needs and include layperson terms for mental health, while encompassing a strong foundational healthcare background. Ultimately, the conclusions from systematic review and the training modules will be used to inform and test IMPRESS interventions and enhance help-seeking in India.

## Decision-Making in Modular Youth Psychotherapy

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Therapists must make complex treatment decisions throughout the process of providing psychotherapy to each client. From unique therapist and client circumstances to patient preferences to possible comorbid mental disorders, deciding on the best course of treatment for each patient is a complex process. Though decision-making is an essential aspect of clinical practice, little research has examined which decision points arise in psychotherapy and the processes used to make optimal decisions. This review aims to address this gap. Specifically, we focus on modular youth psychotherapy – a flexible form of therapy consisting of rearrangeable intervention components with opportunities for decision-making regularly throughout the treatment protocol. By conducting a scoping review of existing modular psychotherapies as a representative form of clinical practice, we seek to understand the key decision-points in everyday treatment and what guidance and evidence is provided to clinicians to make these decisions. Using the study characteristics gathered from this review, we intend to create counts and visual representations, including flowcharts and tables, to represent the decision-making processes present in youth modular psychotherapies. From these results, we aim to support clinicians in their own everyday decision-making for their patients, as well as to provide recommendations for future research related to implementing clinically effective decision-making guidance.

## The Desire for Direct Experience: Advice-Seekers Overvalue Expertise Gained through Direct Experience

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Who do we choose to seek advice from? People often assume that those with personal, direct experience have more expertise and will provide better advice than advisors who have learned vicariously. However, we find that people show a "direct experience bias" - they overvalue advice from those with direct experience, even when doing so makes them worse off. In Study 1, we use historic data from the NBA, NFL, and NHL to demonstrate that people prefer a coach with prior professional playing experience, as well as overestimate the chances of having a winning record with a coach with prior professional playing experience compared to a coach with no professional experience. In Study 2, we replicate people's preference for an advisor with direct experience over an advisor with vicarious experience across a number of domains, including negotiation, finance, and public speaking. In Study 3, we collect real advice from advisors with direct and vicarious experience and find that people overestimate the quality of advice from those with direct experience, compared to actual ratings of advice quality. Finally, in Study 4, we use a car negotiations scenario to demonstrate that individuals favor advice from those with direct experience, even when doing so leaves people worse off. Taken together, these findings demonstrate that advice-seekers use the source of advisor knowledge as a misguided heuristic when making estimates about whether to seek and adopt their advisors' recommendations.

# SOCIOLOGY

## Immigrant Founders and Venture Capitalists/Career Paths in Entrepreneurship and Venture Capital

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Over the past several decades, venture capitalists in the United States have taken a prominent role in the development of well-known startups all over the nation. The Venture Capital ecosystem is also investing in immigrant-founded startups that have stacked the US against other countries that also competitively seek to invest in the next generation of immigrant entrepreneurial talent. However, in the US, immigrant entrepreneurs with college degrees have been outpaced – in terms of founding a company in a shorter amount of time – by their American counterparts. As a result, an age gap between when immigrants graduate college and when they found their companies has formed and continues to grow. Thus, by means of empirical analysis, the goal of this study is to analyze why immigrant founders are less likely to pursue paths in entrepreneurship earlier on in their career paths than the average American, holding that both groups are college educated and have similar experience levels in the industries wherein they found their companies. We rely on EMSI data - EMSI is a labor analytics firm that locates data through reliable government sources - and platforms like LinkedIn to assess the profiles of immigrant entrepreneurs to quantify the causes of this growing age gap taking place in the United States and, in the long term, seek solutions to remedy this problem.

## Courageous Leadership

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Great teams often make courageous decisions. This project explores the antecedents of such courage. I examine three cases (the Massachusetts 54th Regiment, the Fellowship of the Ring, and the Kamikaze pilots of WWII Japan) in which courage was displayed by a team. Through analysis of primary sources, I find a range of sociological processes can help promote courageous action. Applications to cases of business leaders will also be discussed.

## Understanding Cultural Change Through Newspapers

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A core challenge in the study of cultural persistence and change is identifying the best means of measuring it historically. Why do some issues rise and fall in relevance, while others remain more stable? Newspapers are a crucial source of political, financial, and social information for local, national, and global communities that date back centuries. They are also a novel data source that have been underutilized in the current literature surrounding culture. Utilizing databases of digitized articles may provide new and deeper insights on old questions. During this project, we collected and analyzed newspaper data to understand cultural shifts in the United States and across the globe over time. Initially, we assessed the popularity of 15 sports over time in 112 countries as measured by the number of newspaper mentions for each sport in a given year. Through this process, we hope to identify trends in the popularity of certain sports across countries and cross-reference this information with other cultural measures in order to better understand the underlying societal factors a given sport's popularity may reflect. Later, our process involved compiling information to form a database not currently available in the literature, which contains newspaper data from the twentieth and twenty-first centuries. This project will next apply machine learning and word-embedding techniques to the compiled database in order to understand how distinct social issues have been conceptualized over time and which have been the most salient. One additional application of newspaper data within this project has been using archival materials to better understand changing portrayals of the prototypical entrepreneur and their role in American culture over time.

## Village China

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China's rapid modernization is self-evident in its increasing influence as a world power. However, the sustainability of this rapid growth depends on China's ability to extend its benefits to the group fueling it: China's majority rural population. The Chinese state claims that it has adapted in ways that benefit its rural population through opportunities for urban labor, educational reforms, poverty alleviation campaigns, and policies such as the One Child Policy. In reality, however, the complex reactions of rural families to these policies bring into question whether the state's policies have helped or hindered rural development. This research aims to address this through probing issues such as eldercare, gender and labor markets, and education through the lens of the family. This was done through literature review of existing research on rural China, as well as archival work in oral history databases of Chinese interviews. For example, market and education reforms have given women more job opportunities in cities, but the view that the investment return of education in daughters is a good marriage to an urban man shows almost a clear step backwards for women's rights. Jobs in urban areas seem to offer better earning opportunities for rural people, but because of institutional barriers to public services, laborers and their families are barred from settling down in cities, leading to divided families and a drain of human capital from the countryside to the cities. China must ensure security for its rural population through state-funded welfare and institutional reforms that support villagers no matter whether they choose to settle down in urban or rural areas. If the state continues to socioeconomically leave-behind rural families, rural loss of potential human capital and faith in the state will threaten the stability of China as a whole.

## American Mass Incarceration in Comparative and Historical Perspective

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The United States imprisons more of its people than any other country in the world. While American mass incarceration is a profound social issue that has been studied in many ways, the investigation into its characteristics and causes has focused mostly on America. This project was motivated by the view that we can learn more about American mass incarceration by studying the rest of the world and the period before mass incarceration. To do this, we collected crime, prison, policing, and spending data for nearly all sovereign and some colonial countries for the modern period (c. 1800 to the present). We gathered this data from a variety of multinational sources, such as government reports, academic studies, and reference books. While this data collection is still underway, one initial finding is that, proportional to penal spending, the United States spends considerably less in social welfare than do other developed countries. Such a result suggests that American mass incarceration is a consequence of America's disproportionate reliance on penal rather than social policy. The ambition of this project is to develop a general theory of the penal state in modern societies, with the hope of explaining not just the extreme case of American mass incarceration but also helping us understand punishment and policing more generally.

## Piloting the Use of the 4Ms Age-Friendly Bundle to Enhance Care of Older Adults

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As the US population ages, physicians, medical trainees, and healthcare systems must be prepared to care for older adults and their unique challenges within the healthcare system and society. While scientific treatments and innovation have fought hard to promote the quantity and longevity of life, it is essential that society centers the quality of life of the later years of life to the forefront of our agenda. To address the complexity of the health-related issues that older adults face, the Age-Friendly Health System Initiative has developed the 4Ms Framework to inform the care of older patients, focused on what Matters, Medication, Mentation, and Mobility for each older adult. This study presents a feasibility pilot of an Age Friendly 4Ms bundle for hospitalized older adults implemented by internal medicine residents.

We developed and piloted a Age-Friendly 4Ms "bundle" to be implemented by internal medicine residents to improve the care of older adults admitted to the hospital. For new hospital admissions of patients over age 65 at the West Roxbury VA Medical Center, housestaff conducted a brief review of the following information for each patient:

Mentation: baseline delirium screen such as the Ultra-Brief-2 Screen and baseline cognitive status

Mobility: functional and ambulatory status, including assistive devices needed

Medications: a flag of any high-risk medications that are potentially inappropriate

Matters Most: personalized advanced directives and goals of care

The feasibility and usability of the 4Ms bundle was tested through an anonymous survey as well as individual semi-structured interviews. Based on preliminary studies, the Age-Friendly 4Ms bundle is a feasible tool to help internal medicine residents care for older adults and clarify the many complex issues that older adult patients often face. Limitations include a small sample size at a single institution. Future studies will investigate the impact of the Age Friendly 4Ms bundle on the care and health outcomes of hospitalized older adults.

## Data Analytics in Action

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New data analytics tools shift how people make decisions and relate to one another within the information economy. By understanding how organizations use people analytics tools to inform decision-making in an organizational context, firms will identify and observe mechanisms and trends relating to management and human behavior. They will also have the unique opportunity to quantify the impact of specific management practices on individuals throughout a period. Our previous work has shown that firms are quickly adopting this technology for the management of their employees. But how exactly does the use of analytics shape and change management practices? That is still largely unknown, and a gap in the literature we aim to fill through this inductive, mixed-methods research project. A means towards answering the question is understanding and contextualizing the literature and data at a high level. To this end, we conducted a literature search on how managers use data analytics in the workplace. This review of the literature will serve as a foundation for a multi-year study currently in the design stage with a multinational energy company. The findings of this project will shed light on how access to data analytics tools can influence managers' behaviors and the environments in which they work.

## A Mixed Methods Analysis of How Children Felt Being Interviewed About Violence

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While various stakeholders study violence against children, little is known about how children feel participating in surveys where they are interviewed about violence. The Violence Against Children (VACS) surveys conducted in Nigeria, Zambia, Zimbabwe, and Malawi interviewed children about physical, emotional and sexual violence. These surveys also included questions about children's interview experiences. This mixed methods study aimed to understand how children reported their interview experience, how talking about difficult situations made them feel, and, when applicable, the reasons they felt upset or stressed answering questions.Researchers conducted sex-stratified descriptive quantitative analyses of four questions about participating in the survey. Researchers also reviewed responses to two open-ended questions, identified themes as close to the respondent's original language as possible, and developed two qualitative codebooks. The first was used to code emotions felt when describing difficult questions into positive, negative, neutral, and other categories and the second to code specific reasons for feeling upset or stressed into nine categories. Two researchers independently coded responses and discrepancies noted by a third coder were resolved as a group. Sentiment analysis, word correlation, and word clouds on R supported qualitative analysis.
Preliminary quantitative results showed that the majority of boys and girls found it worthwhile to answer questions about violence. The qualitative results suggested more variation in sentiment, ranging from negative feelings like regret, pain, or shyness, to positive feelings like being encouraged, excited, or relieved after talking to an interviewer about violence. Some common reasons respondents felt upset or stressed included the content of questions (e.g. questions about sex, HIV/AIDS, or suicide), concerns about disclosure, and the survey's length and design. These findings underscore the value of asking children about their experiences participating in violence research and will inform conversations about conducting ethical research that is as harmless as possible.

## Hot Off the Press! The Problem of Women at Work

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The cultural response that once victim-shamed and vilified Monica Lewinsky now champions the stories surrounding the #MeToo movement merely two decades later; so what changed? This project explores the US media coverage of sexual harassment in the workplace, spanning from 1979 to 2019. This research adopts a novel inductive approach to studying the social discourse surrounding women's employment, using machine learning techniques to sort through a corpus of 4,657 historical newspaper articles from three news publications: *The New York Times, Washington Post,* and *Wall Street Journal*. This project involved extensive processing of the historical newspaper archives in addition to several reviews on the literature surrounding sexual harassment, the adoption of newspaper datasets, and the application of natural language processing to the corpus of newspaper articles. We examine and analyze results that suggest that public sentiment and emotionality have shifted over the 40-year period. Given that the hypotheses were not assumed a priori, the research utilizes a nuanced perspective on the social construction of sexual harassment, openly exploring how change in understandings of sexual harassment have occurred across various industries and generations.

## Understanding Cultural Change Through Newspapers

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Culture is highly multidimensional and thus a complex concept to quantitatively measure; it usually requires a large dataset to historically capture cultural trends that are difficult to comprehend without direct empirical evidence. Newspapers have been an essential part of our lives for centuries and can provide a time-transcending tool to study cultural changes across the world. Our project investigates cultural change by looking at patterns of topics covered in different newspapers across the world, including the US. To do so, we built a novel database of newspaper articles and leveraged this database through analyzing cultural trends with machine learning and word-embedding models. Preliminary findings from an extensive sub-dataset on the popularity of fifteen different sports, measured by how frequently the sports were mentioned in newspapers in over one hundred nations, showed that soccer has become more popular almost universally in every investigated country. Our next step in the project will be to examine what this trend might tell us about cultural changes within those societies. We also intend to continue expanding our database by extracting articles from a range of American newspapers to study why certain social issues were salient in different periods of time in history. We propose using formal text analysis as a promising methodology to recover understandings of cultural change from historical populations no longer available for direct observation, and thus produce an addition to a rather new area of the literature that capitalizes on word embedding and machine learning in sociological research.

## Crisis and Culture: How American College Students Adapt Cultural Tools and Membership in Response to Uncertainty

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Young Americans face growing uncertainty in a society dominated by heightened inequality, social divisions and unrest, and unstable institutions. Exacerbated by the pandemic and the recent crisis around racial injustice, this uncertainty has worsened the mental health of young adults. This project considers how American college students mobilize cultural tools in response to the threat of uncertainty. Our team conducted and coded two waves of interviews with eighty college students living in the Northeast and the Midwest, before and during the pandemic, focusing on ways they respond to challenges, find sources of hope, and plan for the future. We produced frequency counts to identify salient cultural trends. Results suggest that respondents mobilized braided cultural repertoires which contribute to retaining hope and a sense of agency. By braiding certain cultural repertoires and rejecting others, students create new cultural values centered around three key concepts: expanding the American dream, pursuing social impact-driven careers, and creating a "Gen Z" cohort narrative built on inclusion, activism, and social justice. Young adults mobilize specific cultural tools as a means of building social resilience. We compared white middle class and racialized working class respondents and found that the second group relies more on personal experiences of hardship and collective identity to overcome crisis. An analysis of braiding and the process of building social resilience reveals the contributions and limitations of cultural repertoires in providing accessible, adaptive resources for young adults facing increasingly uncertain times.

# STUDIES OF WOMEN, GENDER, AND SEXUALITY

## Towards a Feminist Museum History

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Harvard's Fogg Museum directors referred to the museum as a "laboratory for art," because of its role as a training ground for museum professionals during the first half of the twentieth century. Paul J. Sachs taught his "Museum Course" to a total of 388 students, 160 of whom went on to hold careers in museum work. Although nearly half of Museum Course students were women, there is documentation of only 30 of them going into the field. This project explores the lives of these women who did and did not continue to work in museums, to elucidate the barriers that existed for them. Through an examination of archival materials, including oral histories, the correspondence between Paul Sachs and his students, and Harvard's institutional records, this project places women museum workers in the context of a museum world and university with discriminatory policies and attitudes towards women. This context includes rules that women could not become curators, hiring practices that overlooked them, constant requests to type up their male colleagues' papers, even a lack of women's bathrooms. To facilitate engagement with a broad public, the researcher has created a series of videos featuring these women's stories.

## A Study of HIV Prevention Through Policy and Practice

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It has been established by previous studies that people living with HIV, who receive and adhere to antiretroviral therapies, are able to suppress their viral load to numbers that are undetectable, resulting in a massive reduction or elimination of the possibility that they will transmit the virus to another person. Although this is an exceptional advancement in the treatment of HIV infection and transmission, other preventive action is still needed if the goal of zero new HIV diagnoses, zero stigma, and zero AIDS-related deaths is to be reached. To advance HIV prevention, we focused our approach on advocacy and legislative action. We took a community centered educational approach to advocate for people living with HIV and groups who are disproportionately affected and at a greater risk by hosting sex education webinars and designing engaging materials and guides to learn more about HIV related issues such as systemic racism, housing insecurity, injection drug use, and sex work. We also supported legislative action by presenting research panels, hosting legislative briefings, and creating informative resources that encouraged the passage of bills in Massachusetts. These bills would implement preventive measures, increase community involvement in ending the HIV epidemic, and improve accessibility to resources, treatment, and knowledge. After each event, we collected evaluations from our participants and found that a majority of participants learned new information and were inspired to get involved with advocacy efforts related to HIV prevention. These preliminary results demonstrated the impact that legislative action and advocacy can have in informing the public and increasing preventive HIV measures.

# Intersectional Analysis of NVDRS Defensive Gun Use

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In recent decades, the "gun rights" lobby revitalized gun culture by reframing firearms as necessary tools for self-defense. The underlying rhetoric around defensive gun use draws on the fear-based criminalization of predatory strangers, the "protection" of women against violence, and the heroic trope of a "good guy with a gun." However, each of these tropes is infused with gendered and racialized notions of criminality and vulnerability. Given that a majority of states have passed "Stand Your Ground" legislation since 2005, self-defense laws provide legal immunities for lethal violence and license to kill discriminatorily. Recent research has investigated the impacts of "Stand Your Ground" laws, but few studies have sought to understand *both* the gendered and racialized implications of defensive gun use. Through an intersectional lens, this project analyzed the CDC's National Violent Death Reporting System (NVDRS), a comprehensive state-based surveillance dataset from 2003 to 2018 that includes extensive information on violent deaths and their circumstances. We conducted statistical analyses of the dataset to examine trends surrounding justifiable homicide, armed women, homicide location, and racial differentials. We used and coded law enforcement and medical examiner narratives found in the NVDRS to question potential biases ingrained in the data itself. The preliminary results validate that women primarily defend themselves against intimate partners, not illusory strangers, and that significant differences exist when comparing justifiable homicide rates along racial and gender lines. It seems likely that the "stranger danger" rhetoric simply stirs up public fear and does not have factual basis, instead exacerbating racial disparities in gun violence.

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