Harvard Summer Undergraduate Research Village
PRISE | BLISS | PRIMO | SHARP | SURGH

Harvard College

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2019 Abstracts

PRISE BLISS PRIMO SHARP SURGH

2019

ABSTRACT BOOK

Harvard Summer Undergraduate Research Village
2019 Abstract Book

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Summer Humanities and Arts Research Program (SHARP)
Summer Undergraduate Research in Global Health (SURGH)

Office of Undergraduate Research and Fellowships
Harvard University
Cambridge, Massachusetts

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Letter from the Director

Dear Harvard Summer Undergraduate Research Village Fellows,

Indeed, I am privileged to introduce the 14th volume of HSURV research abstracts from the collective programs 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). The 2019 cohort of 186 outstanding undergraduate scholars have done exceptional work guided by Harvard faculty, postdocs, graduate students, and other investigators across the Harvard universe, including affiliated teaching hospitals and research enterprises across Boston and Cambridge. Combined with the energetic residential community that quickly evolved at Winthrop House, the Summer Undergraduate Research experience is an enduring testimony to the compelling value of developing strong social and intellectual ties among emerging young researchers across the full range, breadth, and diversity among scholarly interests and pursuits in a rich, vibrant environment.

This collection of abstracts could not have been possible without the outstanding and indefatigable effort of the group of Research Village editors whose mission it has been to collect, organize, and publish the works of all of the Fellows. Along with this summer's Program Assistant Fellows, who have helped with all of the fellow-initiated activities, I would like to thank this group especially for taking on the particular challenge to record the research projects of the Research Village community this summer.

To the Summer Undergraduate Research Village Fellows of 2019, I wish you every success in your further intellectual growth and academic trajectory and hope your research and fellowship experience is a springboard that further serves your manifest curiosity and creativity. I cannot tell you how impressed I have been by your spirit and energy (and stamina!) over these ten weeks, which have flown by way too quickly. Your engagement, enthusiasm, and inclusiveness are inspiring, and I hope the personal and collegial relationships you have cultivated during our time together continue to grow and flourish long after your HSURV summer.

All best wishes,
Gregory A. Llacer
Director, Harvard College Office of Undergraduate Research and Fellowships (URAF)
Director, Harvard College Program for Research in Science and Engineering (PRISE)

Letter from the Editors

Dear HSURV Community,

This summer has been an incredible and humbling experience for us all. Whether getting to learn about the unique, inspiring characters that make up each summer program or working alongside pioneering researchers for the last ten weeks, every day brought something new and exciting. HSURV has helped build a new, meaningful community all while pushing us to explore our academic interests as undergraduate researchers.

While HSURV has been filled with adventures to amusement parks, beaches, chocolate shops, and cities across New England, we all endured the heat and humidity of a summer in Cambridge to conduct research. Spanning from neurons and neutrons to art history and gender equality, it has been incredible to learn about the fascinating projects that can make a person light up with excitement. Wanting to celebrate the research that came out of long hours writing, coding, or in a lab, we are proud to share each person's abstract in this book.

This summer has been incredible thanks to the hard work and dedication of many people. We would like to say thank you to the faculty, mentors, and fellow students who have welcomed us into the world of research. Thank you to the program assistants and HSURV staff who have strived to make each day special for the fellows. Elizabeth Perten from URAF has played a large role in helping us make this abstract book a reality. A huge thank you is in order for Greg Llacer, Chris Kabacinski, and the rest of the URAF staff who have helped everything run so smoothly. And lastly, we would like to say thank you to the fellows who made up the research community for making this summer so special.

Sincerely,
The 2019 Abstract Book Editorial Board

Program Descriptions

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

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

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

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

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

Engineering and Applied Sciences

Applied Math
Computer Science
Engineering Sciences

Antibiotic Resistance Phenotyping with Machine Learning and Mycobacterium tuberculosis Genome Sequencing

Michael Chen
PRISE Fellow
Applied Mathematics, 2020

Harvard Medical School
Kohane Lab
Advisors: Andrew Beam, Maha Farrhat, Isaac Kohane

With the increasing use of antibiotics, multi-drug resistance in tuberculosis remains a global health threat. Current culture-based susceptibility testing is lengthy due to the slow growth of Mycobacterium tuberculosis. Also, molecular tests often rely on a few mutations to determine antibiotic resistance, which limits test sensitivity. Machine learning methods have shown promise in providing an accurate and quick new alternative. We sought to build an updated machine learning tool to predict antibiotic resistance. We collected a large dataset of Mycobacterium tuberculosis whole genome sequences with a high proportion of multidrug resistant strains. We then fit a variety of neural network architectures to the genome sequencing data and assessed predictive performance of the algorithms for four anti-tubercular drugs. We also analyzed the relative importance of mutational position within genes of interests and surrounding intergenic regions. Preliminary testing has shown that predictive performance for the neural network models is comparable to baseline methods. The relative importance analysis for mutational position suggests an agreement with our current understanding of the drug mechanisms for each of the four drugs. Further testing is required to determine if more complex machine learning algorithms trained on a large dataset can increase predictive accuracy for antibiotic resistance in tuberculosis.

The Origin of Celtic Languages: Exploring British History with Ancient DNA

Michael Isakov
PRISE Fellow
Mathematics and Statistics, 2022

Harvard Medical School
Reich Lab
Advisors: Nick Patterson, David Reich

The Indo-European language family contains most extant European languages and encompasses more than 3.2 billion native speakers. While the arrival of Indo-European into Eastern Europe around 2800 B.C.E. is well-known, its differentiation after this point is less clear. A major subfamily of Indo-European is Celtic, and by the Iron Age (1000 B.C.E. – 0 C.E.), archaeological data and place names indicate that languages in this group were spoken in what is now modern-day Britain, France, Italy, and Spain. Despite this wide distribution, there is no consensus about when and where proto-Celtic originated or how it spread. For instance, hypotheses about when proto-Celtic speakers first arrived in Britain range from as early as 2300 B.C.E. to as late as 500 B.C.E. Using ancient DNA from individuals living in Iron Age Britain, cis-Alpine Gaul, and Iberia, we attempt to shed light on the genetic shifts which define this period and how they may relate to the spread of languages in this region. The data gleaned from these samples represent millions of known variable positions in the human genome, and by comparing these variations across populations and time, it is possible to reconstruct viable patterns of migration and genetic interchange. Preliminary results suggest a previously unknown migration into Britain during the Middle-Late Bronze Age (about 1300 B.C.E. to 1000 B.C.E.), which may represent the advent of proto-Celtic speakers on the island. The genetic affinity of these migrants appears to align most closely with Bronze Age Iberians, contrary to earlier hypotheses that Celtic originated in central Europe. Thus, ancient DNA, together with linguistic and archaeological evidence, illuminates the population dynamics which led to the current distribution of languages in Europe.

Efficient Guarantees in the Multi-Unit Assignment Problem: Theory and Application to Course Allocation at Harvard

Jimmy Lin
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Mathematics, 2022

Mathematics Department
Advisors: Scott Duke Kominers, Shengwu Li

The multi-unit assignment problem involves allocating bundles of objects to agents with heterogeneous preferences, such as assigning shifts to workers or players to sports teams. We study mechanisms for allocating courses to students, under which students receive a fixed number of courses, and courses may have different capacities.

The only course allocation mechanisms that are both strategy-proof and Pareto efficient are *serial dictatorships*, which are typically viewed as unfair. We thus seek to modify our incentive and efficiency goals so that we can design mechanisms with fairness in mind.

We introduce the notion of a student's *guarantee*, which corresponds to the best worst-case outcome the student can achieve regardless of how other students act. A mechanism *mildly dominates* another mechanism if everyone's guarantee is never worse off; it *strictly dominates* if anyone's guarantee is also strictly improved. A mechanism has *efficient guarantees* if no mechanism strictly dominates it. In the case that all courses have one-seat capacities (i.e. all objects are unique), we show that every picking order has efficient guarantees, and all neutral mechanisms are mildly dominated by some picking order. However, in the general case, even common picking orders like the snake draft used at Harvard Business School (HBS) may have inefficient guarantees. We show that there always exist picking orders with efficient guarantees, and we characterize them by developing an algorithm for computationally determining them. These results suggest that HBS's course allocation mechanism can be improved. More generally, our framework of efficient guarantees can help market organizers design fair and efficient mechanisms while helping agents strategize more optimally.

Multi-Agent Sensor Coverage and Exploration Algorithms

Victor Qin
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Electrical Engineering, 2021

School of Engineering and Applied Sciences
Li Lab
Advisor: Lina Li

Multi-agent algorithms and optimization play important roles in the future of robotics, from the coordination of autonomous cars collectively mitigating traffic, to robotic search and monitor missions that investigate and collect data. However, many algorithms, while great in theory, are only validated for robustness when tested on physical systems subject to true environmental noise. This summer, I developed a multi-agent robotics platform for the Li lab to test and demonstrate reinforcement learning algorithms, using Turtlebot3 robots and the ROS software architecture. We are designing a zeroth-order sensor coverage algorithm to maximize the observation of interesting sources across large distances. In the future, we will further pursue and demonstrate algorithms in autonomous driving and sensor coverage.

Identification of Spatially Associated Subpopulations by a Cell-type Focused Hidden Markov Random Field Model

Arpan Sarkar
PRISE Fellow
Molecular and Cellular Biology and Statistics, 2020

Dana Farber Cancer Institute
Yuan Lab
Advisors: Guo-Cheng Yuan, Qian Zhu

Multicellular organisms demonstrate organization at several levels, including tissues, organs, and organ systems. Cells in complex tissues are organized by distinct microenvironments and anatomical structures. The spatial organization and architecture of cells is considered to be important for the specialized functions of individual cells and, on a larger scale, tissues. The recent and rapid development of novel spatial transcriptomic technologies that can profile several hundreds to thousands of single-cell transcriptomes in situ while accounting for cells' spatial coordinates provide an opportunity to study the interactions between cells and their native microenvironment, specifically spatially organized structures in tissue. This project aims to develop a cell-type-focused hidden Markov random field (HMRF) model to detect the spatial organization of cells in tissue. HMRF models are an example of an undirected probabilistic graphical model, and they are often used for pattern recognition. My approach will rely upon modifying an existing HMRF method based of continuous gene expression data to run on discrete neighboring cell-type data. Given a user input of K distinct spatial domains, the model will classify each cell as belonging to one of the K domains based on the distributions of the cell's neighboring cell-types, where a cell's neighbors are determined by a Euclidean distance threshold. The project aims to prove that a cell-type-based HMRF model can isolate distinct spatial domains that a gene expression-based HMRF model may miss, and this model will be tested on data generated from multiplexed smFISH from the adult mouse visual cortex.

Expanding a Clinical Decision Support Tool to Improve Cancer Risk Estimates

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PRISE Fellow
Applied Mathematics, 2021

Dana-Farber Cancer Institute
Bayes Mendel Lab
Advisor: Danielle Braun

ASK2ME is a decision support tool for clinicians that estimates an individual's risk of relevant cancers over their lifetime based on the results of genetic panel testing. The models that support this tool do not currently use a patient's race to inform their risk estimates. Since susceptibility to cancer can vary significantly with race, we sought to add this information to ASK2ME to better tailor risk estimates to individuals. This required the establishment of a new database to hold race-specific data for both carriers and non-carriers of deleterious genetic mutations, along with a significant rewrite of the functions used to estimate carrier risk. During this update, efforts were also taken to streamline the code and to generalize functions that were previously designed for specific combinations of genes and cancers. These changes promote easier implementation of future updates and extensions. For example, it will allow for the number of genes and cancers analyzed by ASK2ME to grow more efficiently. Because the publications used to inform ASK2ME report risk in a variety of ways, and often do so for specific populations, extra care was taken to record and reduce assumptions when using published findings to inform our models. Efforts are underway for determining the best way to extrapolate the cumulative risk for carriers of one race to accurately model carriers of another race, given the known relationship between non-carrier risk estimates for each. Further updates to the database structure and models are ongoing, with the end goal of producing a risk estimation tool for gene carriers that can be rapidly expanded and updated.

Improved Machine Learning Algorithms for Animal Pose Estimation

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PRISE Fellow
Computer Science, 2022

Rowland Institute, Faculty of Arts and Sciences
Mathis Lab
Advisors: Alex Mathis, Mackenzie Mathis

The field of human and animal pose estimation involves using computer vision techniques to determine the locations of human and animal joints in images and videos. The current state of the art algorithm for animal pose estimation is DeepLabCut. With an ImageNet trained ResNet-50 backbone, DeepLabCut is a deep convolutional neural network that can be trained to estimate the pose of any animal. Although DeepLabCut is generally effective, its limitations reflect broader issues in the machine learning and computer vision community: a lack of generalizability and an inability to correct for image noise and occlusions. With this in mind, I have explored different architectural adjustments and additions to improve DeepLabCut. For one, different methods for denoising data were tested as potential options for correcting inaccurate animal poses that DeepLabCut produces. Out of the various algorithms applied, the denoising autoencoder was the most effective. In general, a denoising autoencoder is a deep neural network made up of multiple fully connected layers. In our case, it was the best algorithm for correcting random noise and for estimating the locations of occluded joints based on the positions of other joints. In addition, other changes to DeepLabCut's backbone algorithm based on state of the art machine learning techniques are currently being tested to improve its generalizability. Not only does this work improve upon a state-of-the-art animal pose estimation algorithm, but it indicates the general importance of careful network design for improved machine learning performance.

Implementing a Differentially Private Synthetic Data Generation to PSI

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PRISE Fellow
Mathematics, 2022

School of Engineering and Applied Sciences
Privacy Tools Lab
Advisor: Salil Vadhan

The Privacy Tools lab developed the Private data Sharing Interface (PSI) tool to allow people without Differential Privacy expertise to privately share or use data. Differential Privacy is a mathematical guarantee for privacy where when an algorithm satisfies the definition, the output of the algorithm on any dataset is approximately the same as what it would have been if we change one row in the data. We have added a synthetic data generation algorithm for high dimensional data to the functionalities of this tool. This problem is known to be NP-hard, so we used a modified version of McKenna et. al's graphical model approach as a heuristic. The algorithm is as follows:

We first determined which relationships between variables are important to capture. We allowed the user to input part (or all) of the important relationships, and then we privately learned the rest of the relationships using the exponential mechanism with a new method. Then, for each relationship, we privately computed the value of the marginal query by constructing a DP histogram. Finally, we converted this to a graphical model which we sampled from to generate synthetic data.

By adding an implementation of this algorithm to an easily accessible interface for use by data scientists, it will become much easier in the future, especially for social scientists, to release the data used in their studies while preserving the privacy of individuals in their data. Being able to release synthetic data privately is especially important for analysis such as Machine Learning which requires input that looks like a row of the data.

Immersive Sports Analytics with Augmented and Virtual Reality

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Computer Science, 2022

School of Engineering and Applied Sciences
Visual Computing Group
Advisors: Johanna Beyer, Hanspeter Pfister

Within the world of sports, coaches are often overwhelmed by the abundance of performance analytics and are required to make sense of the data. Thanks to recent advancements in scalable augmented reality (AR) and virtual reality (VR) technology, however, immersive analytics has become an emerging field for data visualization within immersive AR and VR environments. In this design study, we leverage immersive analytics to help coaches better visualize player performance. To characterize the visualization problems for different sports, we performed a requirement analysis in which we interviewed domain experts in several sports teams, including Harvard's baseball, soccer, crew, and tennis teams. Collaborating with Harvard Women's Tennis, we piloted an immersive sports analytics application on the Microsoft mixed-reality HoloLens, programming in C# on the Unity game engine. In this application, AR is used to embed virtual data representations of player serve placements onto the real-world tennis court, while VR immerses the coach in a virtual world in which data is represented in 3D and scaled to the real world. The coach, when wearing the HoloLens, can then watch a tennis match with these virtual representations of player statistics overlaid on the actual court in a spatially reasonable manner, thus helping them to easily spot player weaknesses and effectively direct players to improve, both during games and during training. Upon further development of this prototype, this augmented and virtual reality coaching technology can potentially transform the ways in which professional sports teams across the nation train and improve athlete performance.

A Holistic Framework for Measuring Similarity Across Short Stories

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Harvard Business School
Laboratory for Innovation Science at Harvard
Advisors: Karim Lakhani, Shreyas Sekar

Recent advances in Natural Language Understanding (NLU) have allowed computers to read a passage and draw conclusions beyond the scope of the text, but these methods are limited to explanatory writing and only capture literal meaning. Consequently, they are better suited for snippets of reviews or wiki entries rather than fiction. In this work, we design a measure of similarity across flash-fiction, a type of length-restricted fiction that often relies on implied information to deliver a story. We model a flash-fiction story as a combination of its (i) genre, (ii) themes, and (iii) information flow and train the model to determine if texts are similar across any of these three story elements. The model relies on pre-trained InferSent sentence embeddings as base features that capture the semantic meaning of the text. Then, it extracts meaningful story-level representations through unsupervised methods trained directly on the sentence embeddings and supervised methods that rely on spatial properties of the sentence embedding. We also curate an annotated dataset of themed stories and plan to evaluate the model's similarity predictions against labels provided by human readers. Preliminary test results indicate that our methods outperform the state-of-the-art. Our experiments demonstrate the limitations of transferring NLU methods to fictional text and the potential of extracting features specific to a literary device.

Approximate Learning and Planning Algorithms for Predictive State Representations with Uncertainty

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Mathematics and Computer Science, 2022

School of Engineering and Applied Sciences
Advisor: Finale Doshi-Velez

Predictive state representations (PSRs) allow an agent to sufficiently describe the state of the world in partially observable Markovian domains. While much research has focused both on learning algorithms for PSRs as well as exact and approximate algorithms for planning with them, we consider the setting in which prediction vectors possess a degree of uncertainty. That is, given, instead of a single initial prediction vector, a distribution over initial prediction vectors, we propose parametric and non-parametric learning and planning algorithms. In the parametric case, we are able to naturally extend the Point-Based Value Iteration (PBVI) algorithm of Pineau et al. (JAIR 2006) developed for partially observable Markov decision processes, whereas in the non-parametric case, we estimate prediction vector updates directly from a blind policy. Furthermore, we build off of work by Boots et al. (UAI 2013) which focuses on embeddings of PSRs in reproducing kernel Hilbert spaces to extend our work to continuous action and observation spaces. Finally, we evaluate our model on two tasks: first, a synthetic toy model, representing a simplified version of the task of hypotension management, in which an agent is given the dynamics of the system and need only recover a near-optimal policy; and second, on real data from electronic health records, in which the agent must learn and develop an approximately optimal policy with the goal of maintaining the patient's heart rate at a healthy level.

VolRen: A Lightweight Web-Based Volumetric Data Explorer

Zev Nicolai-Scanio
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Computer Science, 2022

School of Engineering and Applied Sciences
Visual Computing Group
Advisors: Johanna Beyer, Hanspeter Pfister

Image-based investigation of structures and connectivity within the human brain is an important and rapidly growing field of study within neuroscience. The theoretical underpinning is that by mapping the connectome — the full schematic of the neurons in the brain and their connections — biologists can gain insight into the function and development of the brain, and medical practitioners will be better able to model and treat given pathologies. Thanks to an explosion in high throughput neural imaging technologies such as electron microscopy and volume reconstruction and segmentation algorithms, researchers have been able to accumulate and process an increasing amount of raw imaging data. This wealth of data, however, means there is a pressing need for techniques to quickly preview, visualize, and analyze the resulting volumetric datasets. To address this need we developed VolRen, a cross-platform web-based application that allows users to easily explore their volumetric data in a browser and avoids the need for performance computing or specialized desktop applications. We made use of the new WebGL 2 API and adapted state-of-the-field volume rendering techniques so that they could be implemented in the supported subset of the OpenGl ES 3.0 specification. We conducted a survey of current interface designs in the literature and used this to inform our construction of VolRen intuitive and responsive user interface. Able to run in modern browsers on all systems, VolRen allows users to seamlessly upload their datasets and launch the interactive renderer. Researchers can then explore the result in three dimensions, slice and clip the volume, and export views. Rendering and stylization of the volumes can be customized using the intuitive transfer function editor feature. For segmented volumes, users can also manage selective display and clipping of individual features. This combination of widespread support for the application, intuitive usability, and powerful analytics features provides neuroscientists with a platform to more effectively collaborate and explore their ever-growing datasets.

Snapshotting, Restoring, and Migrating Virtual Machines with User-Level Networking

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Computer Science and Mathematics, 2021

School of Engineering and Applied Sciences
Advisor: Eddie Kohler

As hardware costs decrease and computing abstractions improve, more and more computational services have moved to the cloud. Traditionally, cloud providers offer resources in the form of stateful virtual machines that house an entire Windows or Linux operating system. Typically, these virtual machines are slow to boot, costly to replicate, and locked to a single datacenter, or even a single machine. Recently, lots of cloud computing has moved to a stateless, serverless paradigm. Serverless functions have the advantage of being simple to program and quick to spin up, but they lack persistent storage and fulfill limited use cases due to their stateless nature.

We are working on a partial implementation of a new paradigm of stateful, and serverless computing called Alto. We aim to provide a powerful runtime that allows for snapshot and restore capabilities, live migration between datacenters, and transparent replication and failure recovery. To provide these guarantees, we ensure that Alto virtual machines (VMs) keep a small memory footprint and minimize their kernel state. This requires implementing networking support in userland rather than the kernel. User-level networking in virtual machines is promising because migrating virtual machines becomes equivalent to simply snapshotting and restoring their memory, and ongoing network connections are uninterrupted. Similarly, implementing our own user-level networking stack allows us to buffer network output from VMs, ensuring transparent replication and recovery of VMs in the case of hardware failure. We have benchmarked several user-level networking stacks on both throughput and latency, and are now implementing snapshot and restore functionality.

Metrical Task Systems with Online Machine Learned Advice

Kevin Rao
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Computer Science, 2021

School of Engineering and Applied Sciences
Advisor: Michael Mitzenmacher

With the rapid development and improvement of machine learning methods comes the natural problem of using these tools to solve traditional problems. Machine learning algorithms are designed to make accurate predictions of the future based on existing data, while online algorithms seek to complete their objectives with minimal cost and no knowledge of the future. Lykouris and Vassilvitskii propose augmenting online algorithms with a machine learned oracle to improve their performance when compared to full knowledge offline algorithms.

In this work we apply the idea of a machine learned oracle to the online metrical task system problem, which was put forth by Borodin, Linal, and Saks as a general model for dynamic systems processing tasks in an online fashion. We treat the oracle as a black box and only concern ourselves with the worst case guarantees on the quality of the predictions to show that low error oracles lead to improved competitive ratios.

A task system is characterized by a set of processing states S, tasks T, and a distance matrix d, where tasks are requested at discrete time steps. Each task is a size $|S|$ array that gives its processing cost at each state, and the distance matrix satisfies symmetry and the triangular inequality. The goal of the algorithm is to produce a schedule that minimizes the total processing costs and state transfer costs. We propose a randomized algorithm that uses the information provided by the oracle that compared to the optimal oblivious algorithm, performs better, given a good oracle and within a constant factor, given a bad oracle.

Incentives in Proof-of-Stake Mining for Blockchains

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EconCS Group
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Blockchains have rapidly increased in popularity in the past decade, with implications for fields ranging from global finance to healthcare, real estate, and more. The most widely-used means of constructing blockchains involves proof-of-work (PoW), a protocol which uses wasteful computation in order to achieve distributed consensus. This protocol has led miners of the popular cryptocurrency Bitcoin to consume as much electricity as medium-sized countries such as Austria and Colombia. It remains an open question whether distributed consensus can be reached without either a trusted third-party or proof-of-work, and answering this question is important in understanding the future of blockchain technology. Proof-of-stake (PoS) protocols, which seek to allow distributed consensus without wasteful computation, are one possible approach. In this project, we analyze the incentive-compatibility of proposed PoS protocols, especially the Ethereum 2.0 proposal. For this, we develop a stylized model of the consensus protocol as a Markov Decision Process (MDP), and seek an approximate or exact optimal strategy for a selfish miner. This builds on related approaches that have been developed for studying PoW mining (Sapirshtein et al., 2016). If successful, we will learn whether or not the intended mining strategy for PoS is an equilibrium.

Supervision Focused Latent Dirichlet Allocation

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Computer Science, 2020

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DTAK
Advisor: Finale Doshi-Velez

Topic models are statistical models effective at finding low-dimensional topics that capture structure hidden in high-dimensional data. In supervised contexts, existing topic models struggle with discovering topics that are both interpretable and discriminative. We introduce supervision focused latent Dirichlet allocation (sfLDA), a dual-channel topic model that allows for focused, discriminative topics via vocabulary selection. We derive a connection between our model and the prediction-constrained objective for sLDA introduced by Hughes et al. (2018). Inference for sfLDA relies on variational methods common for latent variable models. So far, we demonstrate effective prediction on text sentiment analysis and qualitatively observe that sfLDA finds much more sentiment-focused topics. We plan on applying our model to electronic health record tasks and hope to do some more quantitative analysis of results.

Hierarchical Reinforcement Learning for Open-Domain Dialog

Abdelrhman Saleh
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Computer Science, 2020

MIT Media Lab
Advisors: Natasha Jaques, Rosalind Picard

Reinforcement learning has recently been applied to dialog generation with promising results. Under a reinforcement learning framework, a dialog system, like Alexa, interacts with its users and learns to maximize a set of predefined rewards. For example, a dialog system can learn to hold more empathetic conversations through interaction if it is rewarded for producing positive sentiment responses. Reinforcement learning has traditionally been applied at the word generation phase, meaning that systems get rewarded for specific word choices. However, not all of conversation happens at the word level. Engaging dialog requires longer-term planning and higher-level decision-making across multiple conversation turns. Therapy applications, for instance, require shifting a patient's perspective, a task that requires reasoning over many responses. In this study, we leverage this fact by applying hierarchical reinforcement learning to dialog generation. We propose a novel approach for rewarding dialog systems for making better high-level decisions. We do this by treating hidden representations deeper within the model as continuous action spaces and propagating rewards through them. We hypothesize that learning better deep representations before the word generation phase will lead to effective conversation level control. We plan to carry out human evaluation to test our models against strong baselines and quantify the strengths and weaknesses of our proposed approach. We expect that hierarchical reinforcement learning would result in similar improvements when applied to other natural language generation tasks such as machine translation and summarization.

A Software Platform for the Automated Analysis of Animal Behavior

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Computer Science, 2020

Molecular and Cellular Biology Department
Murthy Lab
Advisor: Venkatesh Murthy

As digital storage becomes cheaper, researchers are increasingly able to record and store video of animal behavior in quantities too large to analyze manually. In the past few years, researchers have largely solved a fundamental problem in automated behavioral analysis, automatic tracking of animal body position, by training neural networks which can quickly localize animal body parts in large amounts of video. To fully automate the analysis of behavior, researchers must now develop techniques to convert body position data into visualizations and statistics which meaningfully quantify behavior. To aid behavior researchers, we develop a software application to automate the process of constructing ethograms (time series data indicating the intervals during which a behavior occurs) from animal body positions. Our application offers researchers two avenues for analyzing behavior. First, we implement a system to allow researchers to compose higher-order behaviors from trees of basic, vectorized mathematical operations over body positions (e.g. derivatives, norms, and angles). Second, we develop a suite of algorithms which can identify stereotyped behaviors in mice (e.g. mouse body configuration, mouse social interactions, and basic parenting behaviors). Our system additionally provides researchers the ability to review and edit ethograms by dynamically rendering editable ethograms alongside a video display. Further, the system can compute and display basic visualizations showing ethograms and behavior frequency from the user-constructed behavior data. All data is stored in an SQLite database which can be shared and loaded back into the system for further analysis. Our system aims to provide researchers with a toolbox which can efficiently produce accurate and standardized analyses of large quantities of animal behavior, which can be leveraged to answer fundamental questions in ethology, neuroscience and elsewhere.

The Hardness of Statistical Difference

David Xiang
PRISE Fellow
Mathematics, 2021

School of Engineering and Applied Sciences
Advisor: Madhu Sudan

It is known that interaction with a third-party prover greatly increases what can be proved. For example, in the most general setting of interaction it is known that all problems in PSPACE possess interactive proofs. One can then restrict the model of interaction, such as limiting the amount of communication or randomness used. The class of problems possessing efficient statistical zero-knowledge proofs (informally, ones that leak little information to an outside observer), known as SZK, is particularly interesting because it is known to possess complete problems. In particular, the Statistical Difference problem, which consists of determining whether two distributions C_0, C_1 satisfy $\mathsf{SD}(C_0, C_1) < \alpha$ or $\mathsf{SD}(C_0, C_1) > \beta$ is known to be complete for SZK when $\alpha < \beta^2$. We explore the computational complexity of the statistical difference problem in the remaining space of parameters, and attempt to rule out black-box reductions in these cases to SZK.

Design and Control of New Soft Robotic Mechanisms

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In recent decades soft robotics has gained unexpected attention among the scientific community worldwide. Soft robots combine non-metallic materials with non-electrical inputs, making them greatly resourceful where traditional robots fail. They can be integrated with natural or biological systems and are employed in a growing number of applications, spanning from industrial tasks to support duties during natural disasters. It has been previously established that elastic inflatables are effective actuators: not only are they soft and light, but their non-linear pressure–volume (p – V) characteristics allow multiple inflatables to be actuated by a single input. By controlling dimensions, ensuring viscous flow between inflatables and adding inflation constraints, intelligence is embedded in the hardware, creating complex sequenced motions. I aim to create a crawling robot using sequenced balloons with one input. Constrained balloons connected rigidly in series and sequenced asymmetrically exhibit longitudinal displacement after each cycle due to the differential friction coefficient between the latex and constraining material. This mechanism is enhanced by connecting the balloons to an auxetic origami structure known as the Yoshimura pattern, a 2D tessellation of a degree-6 vertix with two perpendicular planes of mirror symmetry. We expect that this pattern, following geometric optimization, will amplify the balloon crawling. This opens new avenues for soft robotic design that is applicable over a wide range of scales and is highly adaptable. Additionally, I plan to improve the actuator design by creating a kirigami balloon, comprising a tough kirigami skin embedded in a silicone rubber layer. The kirigami pattern can precisely control the p – V behavior, with the aim to create a bistable structure. This provides an energy minimum that may correspond to a pressure minimum, which will be tuned and harnessed to design the sequenced inflation. This could provide complex and consistent performance for various soft applications.

3D Reconstruction of the Elephant Ear: Towards development of finite element models

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Elephants are large mammals found throughout sub-Saharan Africa, South Asia, and Southeast Asia who rely on sounds, often below the human hearing frequency range, for communication over distances greater than 1.5 km. The normal air conduction pathway in most terrestrial mammals is through the middle ear to the cochlea. An alternate pathway is bone-conduction hearing, where sounds reach the cochlea through skull vibrations. It has been proposed that long-distance communication in elephants is facilitated not just through the air but also through ground vibrations that travel through the feet, the body, and ultimately the inner ears. However, little is known about the elephant's hearing mechanisms.. Given the rarity of obtaining cadaveric elephant temporal bones for experimentation, one key objective is to create computational models of the elephant inner and middle ear physiology that can be studied and manipulated virtually. In this project, a previously obtained microCT image stack of an African elephant cadaveric temporal bone was segmented in software (Simpleware, Synopsys) to create a 3D reconstruction of the middle and inner ear structures, including the tympanic membrane, ossicles and their suspensory attachments, middle ear muscles, and cochlea. Creation of the model has already revealed unique anatomical differences compared to humans: division of the middle ear cavity compartment into two by the tympanic membrane; malleus-incus complex buried in soft tissue; and lack of a clear tensor tympani muscle. These differences raise questions as to what functions they may contribute to low frequency hearing. The segmented anatomy will be used to create a finite element model tested and refined with ongoing 3D laser Doppler vibration measurements in the lab. Ultimately, comparisons with human anatomy and physiology may deepen our understanding of what factors may lower the elephant's low-frequency limit and hearing threshold for air-conducted and bone-conducted sounds below that of humans.

Mock Circulatory Loop Development for Arterial Physiological Flow Modelling

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Advanced heart failure is characterized by weakening heart muscle and the inability to sufficiently pump blood through the body, and affects approximately 5 million people in the United States. Mechanical circulatory support (MCS) devices like Impella and ECMO (extracorporeal membrane oxygenation) are mechanical devices that can be positioned in the circulatory system to compensate for inadequate pumping. However, the specific interactions of these devices with the circulatory system are not well defined, limiting the efficacy of these support systems. To enable studying the interaction of an MCS with the body, the cardiovascular system is often modelled by mock circulatory loops using the Windkessel model, which models blood flow as having resistance to flow and having compliance to accommodate changing volume. Our loop also aims to simulate physiologic conditions and waveforms through a more anatomically correct aortic tree, rather than solely through the conventional discrete resistance and compliance components. The variable compliance and resistance along the length of the model enables studying realistic flow and pressure patterns along the vasculature. Pressure data was recorded at the model left ventricle, carotid, renal, and femoral arteries, and data was analyzed and plotted using MATLAB. To use this model to accurately determine the effects of the MCS, data was compared to physiologic flows and major discrepancies were discovered and eliminated. To increase physiological accuracy and reduce noise, modifications included changing the input waveform, testing different aortic valves, and reducing the distance between the pump and model left ventricle. The model also had paravalvular leakage around the aortic valve which required repositioning the valve and designing 3D-printed casings to prevent movement during flow or pressure changes. Ultimately, the Impella and ECMO will be inserted into the model and the changes in pressure and flow waveforms will be analyzed at different points along the vasculature.

A Magnetic Cell Sorting Procedure for Use in Directed Evolution of Biosensors

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Protein-based fluorescent biosensors are useful for imaging biological systems. This is especially evident in neuroscience, where Ca^{2+} sensors and membrane voltage indicators can be used to study the dynamics of the brain *in vivo*. These fluorescent sensors must be developed and optimised through successive rounds of mutagenesis and high-throughput screening. The main challenge with optimising biosensors is that mutants must be selected based on favourable dynamic properties (e.g. kinetics), rather than static ones (e.g. fluorescence intensity). Most currently available cell sorting techniques, such as fluorescence-activated cell sorting (FACS), only sort by static properties. The Cohen lab has recently developed a photo-selection technique for directed evolution of biosensors. The cells expressing the mutant library are characterised by their dynamic properties. A photoactivable or photoconvertible fluorescent protein is co-expressed in these cells. The cells showing favourable phenotypes are labelled through patterned illumination to create a fluorescent marker for FACS. An inherent limitation of this method is that the spectrum of the photoactivable/convertible protein cannot overlap with that of the biosensor of interest, thus leaving a limited optical window for biosensors. To overcome this problem, I am therefore developing a magnetism-based cell isolation system. A micromirror device is used to pattern light onto mammalian cells in the presence of a photocrosslinking reagent (biotin-nitrophenylazide, i.e. photobiotin). The illuminated cells are thus modified with biotin. Streptavidin-coated magnetic beads are then selectively attached to the biotin-coated cells, enabling separation using a magnet. Experiments are currently underway to optimise the optical dose required for efficient crosslinking. Once the method is perfected, it may facilitate the development of novel biosensors for a wide range of applications.

Reactivity and Selectivity of Diazirine-Containing Photoaffinity Labeling Tags

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In the last half-century, photoaffinity labeling (PAL) has become an essential method of studying drug-protein interactions and elucidating the molecular interactions taking place at drug binding sites. PAL involves the photo-induced covalent linkage of a drug to its protein target, followed by affinity purification and identification of not only the protein but also its binding sites. The diazirine functional group is a widely used photoaffinity label. Despite the widespread use of diazirines in PAL, the reactivity of diazirines in biological systems remains unclear. Physical chemistry studies suggest that diazirines can form both a diazo intermediate and a carbene, but this reactivity is unknown in biological systems. Recent evidence from the Woo Lab has shown that certain diazirines possess selectivity to acidic amino acids via the unstable diazo intermediate. My project investigates the effects of electronics on the stability of this diazo intermediate. By first synthesizing two diazirine-containing tags with unique electronics, then carrying out small molecule interactome mapping by photoaffinity labeling (SIM-PAL) experiments, the relative reactivity of the diazo intermediate of these two PAL tags can be compared. It is expected that the diazirine tag with stabilizing electron withdrawing groups at the alpha position of the diazirine will reduce the amino acid bias of the diazo form. The results of this research will reveal the effects of changing tag electronics on reactivity and labeling, and will provide further evidence about the extent to which the diazo form of the diazirine creates a reactive bias towards acidic residues. This project contributes to understanding the reactive pathways of diazirines in biological systems and will clarify the mechanistic ambiguities that underlie PAL experiments involving diazirine-containing tags. This clarification of the reactivity of diazirines will accelerate drug discovery pipelines.

Evaluation of Acoustic Properties of Various Tympanic Membrane Grafts

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The tympanic membrane (TM), or eardrum, is a crucial structure for hearing. Being a thin structure, the TM can rupture when exposed to trauma such as blasts or foreign objects. If the perforation is too large, a surgical operation called a tympanoplasty is required to close the hole. Worldwide, there are approximately 26 million people with chronically perforated eardrums, most of whom live in third-world countries with limited access to the skilled surgeons and microscopes needed to perform this surgery. Surgeons use either autologous graft materials harvested from the body during surgery or non-autologous materials. Unfortunately, these materials do not remodel into the circular and radial architecture of the human TM. Thus, despite successful perforation closures, many people lose low or high-frequency hearing after. A new biodegradable, 3D-printable graft material was designed to program complex print patterns that can be remodeled into native tissue resembling the print path. The objective of this research was to study the in vitro acoustic properties of these various grafts, including various print architectures of the new, 3D-printable graft, to better understand how the TM structure relates to its ability to conduct sound across frequencies important for human hearing. For the acoustic testing, we used two tests: Digital Opto-Electronic Holography (DOEH) and Laser Doppler Vibrometry (LDV), along with a custom 3D-printed holder to clamp the grafts similar to how they would vibrate post-tympanoplasty. We hypothesize that by mimicking the architecture of the native TM through 3D-printed TM grafts, we will observe improved high-frequency sound-induced velocity, while maintaining the low frequencies. We hope to improve the audiometric outcomes for patients undergoing tympanoplasties. In the future, we hope that our easy-to-manipulate, non-autologous graft material will make tympanoplasties accessible to resource-limited populations, so that more people may regain efficient middle ear sound conduction and therefore optimal hearing outcomes.

Use of Biofeedback to Analyze Post-Stroke Gait Biomechanics to Improve Device Effectiveness

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Post-stroke gait is slow, asymmetric, and energetically inefficient. Soft robotic exosuits have been previously shown to improve paretic ankle function by delivering mechanical dorsiflexion, or backward flexion, to assist in ground clearance and mechanical plantarflexion, or the extension of the ankle, to enable better forward propulsion. Trailing limb angle is an important determinant of propulsion in post-stroke gait. We hypothesize that a reduced trailing limb angle is a less optimal position for push-off, potentially limiting the ability of the individual to leverage the plantarflexion assistance from the exosuit. Biofeedback has been previously implemented in various studies to influence gait components including propulsion, symmetry, and kinematics. This study uses real-time, visual biofeedback enabling systematic variation of the trailing limb angle to analyze the importance of post-stroke gait biomechanics on the human-exosuit system. Data collected on the biomechanics of gait include joint kinetics and kinematics obtained through motion capture, and muscle activity measured by electromyography. Our study also focuses on the generation of center of mass power during step transitions, which has shown to be correlated with increased walking speed, a measure that the exosuit seeks to improve in clinical populations. Such data will help determine the relationship between individual gait patterns and device effectiveness as measured by the changes in power delivered by the exosuit.

Development of a Human Shoulder Test Rig for Soft Actuator Characterization

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Soft robotic exosuits offer wide-ranging capabilities to aid and enhance human performance in industrial applications, military environments, and physical therapy post injury or illness. The use of soft components and actuators allows for safer and more compliant movement to better interact with and support humans using the devices. However, due to their soft nature, it is difficult to accurately characterize the performance of these actuators over a natural range of motion to allow for comparison between different actuator designs. This project has developed a statically poseable test rig with kinematic sensors to replicate the multiple degrees of freedom in the movement of the human shoulder over a range of motion similar to the biological joint. When locked in place, this system allows for quasi-static torque measurements around the joints to characterize the performance of different actuator designs for use in assistive exosuits. The shoulder test rig will be skinned in a combination of foam and thermoplastic to represent the compliance of human tissue. On top of this layer it will feature mounts for force sensitive mats to measure the contact regions of the soft actuators. Additionally, we are exploring the use of the test rig in a dynamic configuration to aid in control systems development. This configuration would allow for high levels of repetition of specific movements to calibrate sensors and train controller models without requiring extensive test participant time. Ultimately, this test rig will allow for better optimization of actuator design and would result in improved performance and comfort of the soft exosuits.

Establishing a Disease Model to Assess Immune-Mediated Nephrotoxicity in Kidney Organoids

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Immunotherapy drugs have shown great promise in cancer treatment by enlisting the patient's own immune system to target and attack cancerous cells. However, safety and efficacy testing proves challenging in animal models, for the human immune system cannot be fully recapitulated for assessing the toxicity of drugs directed against human antigens. Although new human models have emerged, such as kidney organoids, boasting functionally mature nephron structures, these technologies remain inadequate for preclinical testing. The difficulty of producing and accurately measuring robust, reproducible drug effects from the organoid's diverse cell populations have hampered the biomimetic benefits of these models compared to traditional 2D assays. We seek to overcome these limitations by developing a robust killing assay to examine immune-mediated nephrotoxicity of a T-cell bispecific antibody-based drug in our human kidney organoids. Towards this aim, we have used a previously developed millifluidic chip culture system to assess organoid viability in response to varying lymphocyte ratios and drug doses, and quantification techniques to evaluate input and output cell populations. Specifically, an image analysis method was developed to quantify the input organoid cells by measuring organoid cross-sectional area as an indicator of total cell count, while output live/dead organoid cells and activated T-cells were measured using flow cytometry. Preliminary normalization results have revealed significant variation in input organoid counts and greater organoid proliferation in perfusion over static culture, demonstrating the precision of our new quantification methods. These findings have since led to the development of more rigorous organoid seeding protocols to normalize input cell population. This quantification will also allow us to identify an optimal immune effector to organoid target cell ratio with maximal T-cell activation and off-target killing to facilitate viability screening for a future dose-response curve. Ultimately, we strive to establish this kidney organoid model as a robust drug testing platform for cancer immunotherapeutics.

Improving Anatomical Understanding of the Human Tympanic Membrane Through Histologic Processing and 3D-Printing of a Custom Holder

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The human tympanic membrane (TM) is an conically-shaped, thin layer of tissue in the middle ear that receives sound vibrations from the outer ear and transmits them into the inner ossicles. Diseases resulting from TM perforations, such as chronic otitis media, affect more than 10 million people yearly and can transform into fatal infections. Although some perforated TMs can self-heal, others are unable to close themselves up. Even when distant from the perforation, a large part of the structural layer is often missing in these TMs. Through histological processing of human TM specimens, we hope to improve anatomical understanding of the tympanic membrane's self-healing capacity in future research and clinical projects. Currently, TMs extracted from patients undergoing tympanoplasties are clipped between two pieces of wax for structural stabilization in preparation for processing. However, this flattens the collected tympanic membrane, causing it to show unrealistic anatomical results when analyzed. TM tissue can also shear, creating difficulties with characterizing fiber alignment. To address this, we designed a custom 3D-printed holder using stereolithography to mimic the natural size and shape of the human TM, allotting extra space for patient variations. A solid perimeter aligns the TM in place, while a porous mesh interior allows chemicals to seep into the TM during fixation and staining. After histological processing, samples are embedded into paraffin blocks and sliced into ribbons. Every tenth slide is stained with hematoxylin and eosin (H&E). Hematoxylin stains cell nuclei blue and eosin stains proteins pink, allowing us to visualize fiber structure in specific tympanic membrane layers. Future directions include optimizing print material and design of the TM holder, as well as performing full-graft analysis on the TM slides. By better understanding how perforations of the human tympanic membrane heal themselves, we can vastly improve hearing loss and ear infection treatment.

Life Sciences

Molecular and Cellular Biology
Neuroscience
Organismic and Evolutionary Biology
Psychology
Stem Cell and Regenerative Biology

Identifying a New Drug Target in Babesia

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Babesia are parasites that infect almost all animals and are emerging as a disease in humans. Currently, the treatments for babesiosis are not ideal; most patients receive a cocktail of anti-malarial drugs or, in severe cases, exchange transfusion. The goal of this study was to locate a new viable drug target across *Babesia* species. Previously, an alkaline phosphatase (PhoD) was identified as a potential target for novel inhibitor (MMV019266) derived from the Medicines for Malaria Ventures Malaria Box. This protein is predicted to be in the apicoplast, a unique organelle that synthesizes isopentenyl diphosphate (IPP). Inhibition or destruction of the apicoplast leads to parasite death; however ,this can be reversed using several fatty acids. To test if PhoD was in the apicoplast, we completed a series of drug assays using *B. bovis* and *B. divergens*, and *P. falciparum* and *P. knowlesi* as controls. Atovaquone was used as the negative control, actinonin for *Plasmodium* and fosmidomycin for *Babesia* were used as the positive controls, and MMV019266 was the drug in question. With each drug, IPP and geranylgeraniol were added as rescue agents. With *Plasmodium*, there was evidence of a slight rescue with the addition of IPP when the parasites were treated with MMV019266. This suggested that PhoD is located in the apicoplast. Thus, we endeavored to tag and localize the PhoD protein using reverse genetics. We cocnstructed a plasmid containing an ACP-GFP fusion protein and PhoD-HA tagged protein. ACP is known to localize to the apicoplast, allowing for us to make the organelle green, allowing for co-localization with the HA tagged PhoD. If our hypothesis proves to be correct, both tags should show up in the same location. Future experiments would address the function of PhoD.

Structural Determination of Clade B Nramp Transporters

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Many physiological cellular processes, such as energy metabolism and oxygen transport, require metal ions. Natural resistance-associated macrophage proteins (Nramps) are transmembrane transporters that facilitate movement of divalent metal ions across cellular membranes using a proton gradient. Nramps are found in all kingdoms of life and transport various essential metals like iron and manganese, whilst preventing toxic concentrations of these metals from accumulating in the cell. Bacterial Nramps have been divided into different clades (clade A, B and C) based on their sequence similarity.

I investigated clade B Nramps, a less well-studied subfamily whose amino acid sequence indicates an alternative proton pathway in comparison to the studies done with bacterial Nramps from clade A and C. Moreover, these Nramps have not been explored structurally or functionally. I tested the expression of a subset of clade B Nramps using western blotting to find potential candidates for large-scale expression and purification. Clade B Nramps from Bacteroides fragilis and *Chlorobaculum tepidum* expressed best and I am currently optimizing their purification protocol to obtain high protein yields. Such purified protein can then be used for X-ray crystallography to elucidate the structure of clade B Nramps, and for in vitro functional assays to study their metal and proton transport properties. I am also performing in-cell metal uptake assays to determine the metal ion selectivity of clade B Nramps. These results will help better understand the alternative proton pathway used by clade B Nramps and how these transporters selectively take up metals essential for cellular physiology.

Elucidating the Function of the H3K27M Mutation in DIPG Proliferation

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Diffuse Intrinsic Pontine Gliomas (DIPGs) are a subset of pediatric high grade gliomas (pHGGs) that originate in the brain stem. Approximately 300 children are diagnosed with DIPGs every year, and 90% die within a year or two of being diagnosed. From biopsies, it was discovered that 78% of DIPGs have a heterozygous mutation in the histone 3 tail, which results from an amino acid substitution of lysine to methionine (H3K27M). The H3K27M mutant histone is a marker specific to pHGGs and necessary for their proliferation. Previous research has shown that the mutant H3K27M histone tail globally inhibits EZH2, which is responsible for the mono-, di-, and tri-methylation of H3K27, facilitating transcriptional repression. Although it is clear that the H3K27M mutant histone competes with the wild type tail for binding in the catalytic pocket of EZH2, thereby inhibiting EZH2 catalytic activity, it is not known whether H3K27M-mediated oncogenesis in DIPG cells is solely due to its interaction with EZH2. As such, the goal of my research is to determine the necessity of this interaction by identifying an EZH2 mutant protein resistant to H3K27M-mediated inhibition. Using CRISPR-Cas9 technology, I designed single guide RNAs (sgRNAs) to target specific regions of the EZH2 catalytic site, and I transfected EZH2 dependent malignant rhabdoid tumor cells with the sgRNAs. After introducing the H3K27M mutant histone into the cells, I expect that any cells that do not die from frame-shift mutations caused by the sgRNAs will instead have resistance mutations to the H3K27M mutant histone. This resistant EZH2 protein could then be introduced into DIPGs to determine if the cells are still able to proliferate in the absence of the mutant histone tail interaction with EZH2. DIPG dependence on the interaction between EZH2 and the H3K27M mutant histone would indicate that potential therapies for patients with DIPGs could include small molecule drugs that target and reverse this interaction.

Non-Coding Regulation of Cardiac Remodeling

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Heart failure is a chronic and progressive health condition that currently affects approximately 6 million Americans and is expected to become significantly more prevalent in coming years. Consequently, much research has been focused on heart failure in recent years. Particular emphasis has been placed on elucidating how the condition arises and progresses, and much of this research has been driven by the observation that an increase in heart mass commonly precedes the chronic pathological condition. However, very little is known about possible means to achieve regression of heart size, which might provide the key to reversing the pathological development that drives heart failure. Noncoding microRNAs (miR) are highly conserved across species and have been shown to play important roles in cardiac development. We hypothesize that miRs also regulate the transcriptional mechanisms that drive cardiac regression. To test this hypothesis, deep RNA sequencing was performed to generate a profile of the transcriptome of multiple vertebrate models of cardiac regression. The results were used to curate a list of candidate miRs associated with cardiac regression and thus might have a regulatory role. We developed an in vitro cell size assay to test the effects of candidate miRs on cell size, morphology, and gene transcription. Assay efficacy and reproducibility were then established by using it to assess the effects of phenylephrine, a cardinal pharmacological agent known to induce cardiac hypertrophy in cells and whole hearts. A consistent 21.5% ± 11.2% increase in cell size was observed in phenylephrine-treated cells compared to controls ($p = 0.005$, $n = 2472$). We will then use agomiRs (synthetic miRNA activating agonists), and antagomiRs (synthetic miRNA antagonists) of candidate miR to assess their in vitro effects on cardiomyocytes.

The Effects of the R4 Regulatory Enhancer of the Gdf5 Gene on the Development of Osteoarthritis in Mice

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Recent genetic studies have illuminated that the Gdf5 gene is involved in the development of hindlimbs, their respective joints, and osteoarthritis,the degeneration of cartilage in joints, most commonly in the knees. In vivo studies in mice have elucidated the Gdf5 gene's cis-regulatory architecture and shown that downstream sequence is required for proper knee joint morphology. We found the appearance of knee osteoarthritis in mice with an experimentally genetic deletion of the R4 enhancer as the joint regulatory element, including a loss of articular cartilage glycosaminoglycans on all joint surfaces or severely damaged joint surfaces in some individuals, and at P30 and 1 year, R4 loss led to significant changes in key morphological features of the distal femur and proximal tibia. In this study, we hoped to determine how a deletion of the binding site of this R4 enhancer affects the development of the knee using mice models. Thus far, chondrocyte cells from the articular cartilage in the knee have been collected. Total RNA will be purified, and RNA sequencing will be performed to determine the transcriptional levels of the genes. In the next phase, the study will focus on comparing the transcriptional differences between R4 deletion homozygous, heterozygous, and wild type mice at 16.5 days of gestation, newborn, 30 days old and one-year old. The expectation is to figure out the corresponding transcriptional changes of signaling pathways affected by R4 deletion in our mouse model, which would determine how the R4 enhancer plays as a risk factor in the development of osteoarthritis in the knee joints. This finding would further encourage research to understand the mechanism of osteoarthritis and ways to prevent or cure this pervasive disease.

Effects of Electrical Signaling on Embryonic Patterning

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Pattern formation is the process by which equivalent cells in a developing tissue in an embryo take on complex forms and functions. This process is genetically controlled and involves each cell identifying its position along a chemical signaling gradient. A cell's identity is determined based on its position, and these different identities give rise to patterns.

One such patterning system, the paraxial mesoderm, is divided into distinct segments (called somites), which later give rise to the characteristic segmented body plan that is common to all vertebrate organisms. It has been proposed that a signaling gradient coupled with an oscillatory gene regulatory network called segmentation clock underlies the process of segment formation. However, whether other signaling mechanisms such as electrical signaling may control this process is poorly understood.

Electrical signaling is typically associated with action potentials: spikes in membrane voltage that return to baseline. However, electrical signaling has recently been shown to be associated with stable spatial patterns similar to its chemical counterpart. Here, we investigate whether spatial changes in membrane voltage can affect segment formation. Using all-optical electrophysiology, we attempt to measure membrane voltage across different regions of a 3D differentiation system derived from human iPS cells that recapitulate paraxial mesoderm development and form morphologically distinct segments in vitro. Mapping the membrane voltage will allow us to make direct comparisons between observed morphological patterns and spatial changes in resting potential.

Dissecting the Mechanism of Ionocyte Differentiation

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Cystic fibrosis (CF) is a genetic disease caused by deleterious mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which disrupt its ion-transport function. We and others recently discovered a very rare cell - the ionocyte - present in both mice and humans that produces most of the CFTR in the airways and lungs. However, the rarity of this cell type makes it hard to study, as both the tissue itself and in vitro epithelial tissue cultures produce few to no ionocytes. Since it is likely that any achievable cure to CF would require the fixing of CFTR in ionocytes, here, we aim to elucidate how to culture higher numbers of ionocytes. Our approach focused on the use of a set of genes computationally identified as being at the center of ionocyte-specifying gene regulatory networks. We conducted weighted gene co-expression network analysis (WGCNA) to identify candidate genes using data from the large mouse sc-RNAseq dataset we previously published. From this list, we chose 7 genes, including Foxi1, Ascl3, and Stap1 to clone into doxycycline inducible vectors that we then packaged into AAV2 serotyped virus. We infected mouse Foxi1-GFP+ basal cells separately with these viruses and co-cultured each one mixed with wildtype basal cells in air-liquid interface (ALI) culture. We induced expression of each of the genes with doxycycline for either the initial 4 days or all 14 days of culture. After 14 days, we collected mature samples and validated induction of each gene of interest using qPCR. Finally, we assayed for any effect on the number of ionocytes by each gene overexpression using the Foxi1-eGFP reporter.

Evolutionary Adaptation to an Altered Cell Cycle Regulation Linked to Genetic Instability

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Genetic instability, the heritable increase in the rate of genetic mutation, is a key source of genetic variation that drives tumor evolution. Defects in cell cycle regulation machinery can cause genetic instability and are prevalent in cancer, but the relationship between the two processes and evolutionary fitness is unclear. Here, we explore this relationship using experimental evolution on mutants with cell cycle defects and is genetically unstable. This approach allows for unbiased detection of molecular processes critical to determining genetic instability, fitness, and the robustness of cell cycle regulation. Candidate mutants were selected by constructing mutants with alterations in key G1 regulators whose human equivalents are commonly altered in cancer including whi5Δ, sic1Δ, and overexpression of CLN3. The sic1Δ mutant, which lack the S-phase cyclin inhibitor Sic1, was selected for experimental evolution as it spends significantly less time in G1, has a 10-fold higher gross chromosomal rearrangement (GCR) rate, and has a fitness defect of 13% compared to WT. Populations of sic1Δ cells that had been evolved for 300 generations showed 6-9% fitness improvements compared to the ancestor. Although most populations had lower point mutation and GCR rates, some demonstrated no change in genetic instability despite fitness improvement. Surprisingly, the fraction of cells in G1 was significantly decreased in all evolved populations compared to both WT and the sic1Δ ancestors ($p<0.05$). Our preliminary results suggest that restoring normal cell cycle progression is not the preferred evolutionary route for improving fitness and genetic instability in sic1Δ cells. Further exploration of evolved strains is needed to determine the molecular changes that alter genomic fidelity, cell cycle regulation, and growth.

The Effect of Early Life Stress on Social Behavior of Female Mice

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The brain is especially susceptible to environmental cues during the developmental period, meaning Early Life Stress (ELS) can affect adult social behavior. This phenomenon has been replicated in multiple studies, including mice-model studies, but limited research has been done on female mice because their hormonal cycles complicate analysis of behavior in adulthood. We conducted multiple behavioral assays on female mice who have experienced ELS via the fragmented care (FC) approach. The FC approach calls for minimizing the amount of nesting provided to the mother, which induces anxiety and prevents the mother from properly caring for her new pups. The first behavioral assay performed was the Tube Test, which tests for dominance between an FC mouse and a control care (CC) mouse that had normal parental care. The second behavioral assay was a 3x3 Interaction Assay, in which three FC mice and three CC mice were put into an open field box. Interactions between the mice are recorded and scored by a computer. The third assay was a Sucrose Preference Test, which is used as an indicator of anhedonia, or lack of incentive to seek pleasure, one of the hallmark symptoms of depression. Because a bias toward a sweetened drink is typical, no bias between the sucrose solution and water suggests depressive behavior. The assays suggest that female FC mice are submissive to female CC mice and that FC mice have an aversion to interactions compared to their CC counterparts. The Sucrose Preference Test did not show a significant difference between FC mice and CC mice. Taken together, these results indicate that FC mice exhibit behavioral disruption compared to CC mice. The next steps of this project would be to explore the underlying mechanisms of these behavioral disruptions and connect them to adult human behavior.

Characterizing the Interaction Between Fatty Acid-Binding Proteins and Eicosanoid Synthetic Complexes

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Arachidonic acid (AA) is metabolized to produce inflammatory lipid signaling molecules called eicosanoids, including prostaglandins (PGs) and leukotrienes (LTs). PGE synthesis requires cyclooxygenase (COX)-1 and -2, and prostaglandin E synthases (PGES). 5-lipoxygenase (5-LO) oxygenates AA to begin LT production and 5-LO activating protein (FLAP) is believed to be a scaffold protein for LT synthetic complex formation. Preliminary FLIM-FRET and microscopy data indicate that FLAP also interacts with COX-1, COX-2, and mPGES-1. We hypothesize that FLAP and eicosanoid synthetic enzymes form complexes on the nuclear membrane that produce prostaglandins and/or leukotrienes, dependent on the inflammatory stimuli, and that fatty acid-binding proteins (FABPs) transport AA to these complexes. We aim to characterize FABP interaction with FLAP and eicosanoid synthetic enzymes using FLIM-FRET and analysis of single-molecule localization data from stochastic optical reconstruction microscopy (dSTORM). Control or LPS-stimulated RAW264.7 cells were used for all experiments. PGE2 production was measured by ELISA. FABP4 and -5 relocation to nucleus was observed in stimulated cells using epifluorescence microscopy, consistent with each possessing an inducible nuclear localization signal. Decreased FLIM-FRET donor lifetimes on the nuclear envelope were observed for FABP4/FLAP and FABP5/FLAP in stimulated cells versus control. FABP3, -4, and -5 were imaged with FLAP using 2-color dSTORM and data were analyzed using Clus-DoC, an algorithm to quantify cluster properties and colocalization of molecules. Significant increases in FABP5 clusters/µm2 and percentage of FLAP colocalized with FABP5 were observed on the nuclear envelope, providing additional evidence for interaction. dSTORM to characterize FABP/COX-2 colocalization is being performed. FABP interaction with LT synthetic enzymes will then be explored. Eicosanoid production by leukocytes incites a range of inflammatory diseases; demonstrating that FABP4 or -5 is directly involved in eicosanoid production would strengthen their status as therapeutic targets and contribute to understanding cellular lipid trafficking mechanics.

The YAP Pathway Interprets Hemodynamic Forces from Blood Flow to Signal Hematopoietic Stem Cell Fate in Endothelium during Embryogenesis

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Hematopoietic stem cells (HSCs), formed from endothelial cells in the ventral dorsal aorta (VDA) during development, are responsible for generating all circulating blood and immune cells into adulthood. Because HSCs are able to maintain life-long production of each blood cell type, they are sought-after for transplant therapy to treat hematological diseases and cancer. Due to low success rate and cell loss in donor HSC transplantation, a beneficial treatment strategy would be to generate healthy HSCs in vitro from a patient's endothelium. Blood flow is one central factor necessary to stimulate HSC formation during development, but we have yet to characterize the pathway in which hemodynamic force is translated into a genetic signal that instructs blood vessel endothelium to become HSCs. In this ongoing project, we are studying a particular regulatory factor, YAP, that responds to mechanical signals and instructs cell fate-change genetic programs. We hypothesized that YAP is implicated in translating mechanical blood flow stimulus to genetic signals promoting HSC formation. Our preliminary work—using loss-of-function in vivo zebrafish lines, heat-shock overexpression techniques, and morpholino silencing during zebrafish embryogenesis—implies YAP activation as an enhancer of HSC production, and piezo1 as an upstream component of the YAP pathway. Yap loss-of-function mutants exhibit decreased markers for HSC emergence (runx1/cmyb) after blood flow initiates, while heat-shock overexpression of yap enhances runx1/cmyb expression, HSC production, and partially rescues hematopoietic potential in silent heart (sih) zebrafish embryos lacking heartbeat. Cyclic stretch–a hemodynamic force which promotes HSC emergence–can sustain HSC signal even in the absence of wall shear stress (WSS), but loses this capacity in mutants for piezo1—-a stretch-specific cation channel known to promote YAP activity. Our current results underscore the importance of the YAP axis in implementing the hemodynamic force conditions of embryogenesis in order to recapitulate HSC emergence in vitro.

Identifying Novel Diazo-Containing Products Through Biochemical Characterization of CreM Activity in *Mycobacterium abscessus*

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The diazo group is a highly reactive chemical group consisting of two doubly-bonded nitrogen atoms at the terminal position of an organic molecule. Diazo compounds have been harnessed as DNA-damaging chemotherapy drug candidates and powerful tools in synthetic chemistry, but their biosynthetic pathways are poorly understood. The cre gene cluster encodes the pathway for the diazo-containing cytotoxin cremeomycin in *Streptomyces cremeus*. Similar genes have been identified in *Mycobacterium abscessus*, indicating the presence of a putative diazo-containing natural product. *M. abscessus* is a common multi-drug resistant pathogen that causes lung, skin, and soft tissue infections. We are interested in examining the role of CreM, an ATP-dependent diazo-forming enzyme, and its unidentified diazo product on *M. abscessus* viability. Preliminary experiments focused on designing and optimizing a heterologous expression system for *M. abscessus* CreM in *Escherichia coli* to maximize protein production. Ultraviolet-visible light (UV-Vis) spectroscopy and mass spectrometry assays were developed to confirm diazotization of substrates of CreM homologs. These assays allowed us to compare enzymatic activity while varying reaction conditions. Using the cremeomycin precursor 3,2,4-AHMBA as a substrate for *M. abscessus* CreM, we saw non-enzymatic cremeomycin formation under acidic and high-temperature conditions, complicating initial assays. However, UV-Vis and liquid chromatography-mass spectrometry assays developed while troubleshooting provided necessary tools to monitor diazo synthesis over the course of the reaction, yielding valuable information on the mechanisms and kinetics of catalyzed diazotization. Although the native *M. abscessus* CreM substrate has yet to be recovered in vivo, we selected chemically synthesized substrate candidates based on predicted upstream *M. abscessus* gene cluster products. Engineering alternatively-tagged CreM analogs will generate enough functional protein to draw connections between CreM structure and enzymatic activity. Continued analysis of the CreM product may guide further in vivo studies on the pathogenicity of *M. abscessus*.

Development of a Ring Chromosome to Study Oncogene Evolution in Liposarcoma

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Well-differentiated liposarcoma is the most common human sarcoma. These tumors are cytogenetically characterized by a supernumerary ring-shaped chromosome that contains genes from chromosome 12q. This ring structure contains many additional copies of oncogenes overexpressed in liposarcoma, such as MDM2. It has previously been shown that ring chromosomes are unstable during mitotic cell division, and it has been hypothesized that the ring structure promotes evolution of oncogene amplification. To test this hypothesis, two ribonucleoproteins (RNPs) were designed to induce double-stranded breaks (DSBs) in chromosome 12, and a DNA repair plasmid was added and repair the DNA in a ring structure connecting the chromosome between the two DSBs. The RNPs and plasmid were transfected into HEK293T cells using Lipofectamine CRISPRMAX reagent or Nucleofection, and these methods of transfection were compared in efficiency. Thus far, only the 2 RNPs have been transfected into the cells. Transfection attempts have been made with both Lipofectamine CRISPRMAX and Nucleofection with the Lonza 4D Core Unit. Nucleofection was determined to be the more efficient method of transfection using a fluorescent protein reporter. Future experiments will optimize efficiency of CRISPR/Cas9 induced DNA double-strand breaks. Upon verification of efficient double stranded cutting, the 2 RNPs and the repair plasmid will be transfected simultaneously to yield a ring chromosome derived from chromosome 12 in HEK293T cells. These cells could then be used as a model to test the hypothesis that the ring structure promotes evolution of oncogenes in well-differentiated liposarcoma.

Finding Lost JAK2 Driver Cancer Mutation in First Reported Cured Patient of Polycythemia Vera

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Polycythemia vera (PV) is a type of chronic blood cancer that is caused by a mutation in the JAK2 gene in blood cells. It is not well understood how the mutation allele frequency impacts clinical outcome. Examining case studies, however, may lead to a greater understanding of this relationship. In 2017, a 53-year old PV male became presumably the first recorded patient to lose the JAK2 mutation — along with the disease's symptoms — after three years of treatment not including a bone marrow transplant. We have identified the possibility that the patient in 2017 still had the mutation just like in 2014, but at an allelic frequency below existing diagnostic detection limits. To test this hypothesis, I am constructing a protocol for detecting point-mutations with frequency as low as .09% by optimizing the existing Duplex Sequencing (DS) method to be compatible with this JAK2 mutation region. Standard clinical Sequencing methods' sensitivity is limited to about 5% by the formation of artificial mutations as a result of sequencing preparation. These artificial mutations become indistinguishable from actual mutations in the blood cells of the patient. However, DS allows us to identify these artificially created mutation, bypassing this problem. DS relies on the ligation of sequencing adapters harboring complementary double stranded unique molecular identifiers (UMI) to the sample DNA of interest. This allows mutations not occurring in both strands of DNA with the same UMI to be discarded as non-real mutations. I am also using targeted enrichment probes to selectively isolate duplex adapter-ligated DNA fragments containing sequences in the JAK2 region to maximize the number of sequencing reads mapped on the mutation site. Once the protocol's sensitivity is tested on serially diluted cell-extracted DNA with mutations of known frequency, JAK2-Specific Duplex Sequencing will be run on the 2017 bone marrow sample of the patient to determine whether the patient truly lost the mutation and whether he is truly cured genetically. Uncovering the truth behind the patient's apparent deep remission will shed light on a disease affecting over 100,000 people in the United States.

The Role of FAM55A and FAM55D in Mediating Intestinal Homeostasis and Inflammatory Bowel Disease

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Inflammatory bowel disease (IBD) is a chronic inflammatory condition affecting the gastrointestinal tract, encompassing disorders such as ulcerative colitis and Crohn's disease. Although IBD etiology has both environmental and genetic components, large genome-wide association studies (GWAS) have highlighted the contribution of genetics through the identification of multiple risk variants. This project will focus on FAM55A and FAM55D, two uncharacterized genes identified through GWAS as having variants associated with ulcerative colitis. Through sequencing analysis, FAM55A and FAM55D have been determined to be members of the GDSL/SGNH esterase superfamily and the PC-esterase family of proteins. Our preliminary research into this topic has shown that both enzymes are expressed exclusively in colonic goblet cells, the cells generating the mucus that lines epithelial surfaces. Therefore, our aim in this phase of the project was to generate knockout organoid cell lines in order to facilitate future functional studies. Using techniques including molecular cloning, lentiviral production, and CRISPR-mediated gene deletion, we engineered single, double, and triple knockout organoids of the genes FAM55A and FAM55D as well as the paralog FAM55B; the genotypes were validated using amplicon sequencing and Western blot. Further validation experiments using immunostaining revealed endogenously lower levels of mucus secretion in FAM55A-/- and FAM55D-/- organoids, further suggesting a role of FAM55A and FAM55D in mediating mucosal immunity. Future studies will continue characterizing the mechanistic implications of FAM55A and FAM55D knockout in organoid-derived goblet cells and mouse models and investigating the specific modifications carried out by these enzymes, with the ultimate aim of establishing the relevance of FAM55A and FAM55D to intestinal homeostasis and immunity.

Developing a Universal Off-Target Detection Method for CRISPR Nucleases and Base Editors

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CRISPR RNA-guided nucleases and base editors have gained widespread adoption as tools used to further basic science research, advance bioengineering, and to better understand the function of various genetic elements. The specificity of the editing these systems induce varies, in part because guide RNA designed to bind to a specific, on-target sequence can tolerate binding to sites differing from this sequence by up to several base pairs, resulting in the introduction of unintended mutations at off-target sites. As this technology begins to be translated into potential therapeutic applications, it is particularly critical that benchtop-accessible, highly specific, and highly sensitive methods to detect the off-target effects of gene editing are developed. Existing methods for off-target detection have generally been experimentally laborious and required sequencing capabilities and levels of DNA input likely inaccessible to most labs. This summer I have assisted in the late-stage validation of a universal off-target detection method that aims to improve upon these shortcomings. In anticipation of downstream clinical applications, I am also working to expand the sensitivity of this method to enable the enhanced characterization of genomic sites of particular therapeutic relevance. As the first class of CRISPR-based therapeutics enter clinical trials, the urgency to widely adopt a highly reliable off-target detection method is underscored. A robust off-target detection regimen, such as that my lab has developed, must accompany the development and implementation of any human therapeutic leveraging gene editing, in order to protect patients undergoing such treatments from experiencing unintended, potentially detrimental effects stemming from the introduction of off-target editing.

Binding of the Novel Inhibitory Receptor KIR-X to its Ligand HHLA2 Negatively Regulates T cell Activation

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Cancer immunotherapies have become a prominent treatment method in the last decade through the use of antibodies to prevent inhibitory receptors from binding to their ligands. Human endogenous retrovirus-H long terminal repeat-associating protein 2 (HHLA2) is a novel B7 family member and ligand often expressed on cancer cells, and it has the ability to contribute to both T cell stimulation and inhibition. By binding to transmembrane and immunoglobulin domain-containing protein 2 (TMIGD2), HHLA2 is able to stimulate T cells, but the lab recently identified KIR-X as a potential inhibitory ligand for HHLA2. The goal of this project was to confirm that KIR-X is an inhibitory ligand and to test a panel of antibodies for their effect on HHLA2-mediated T cell activation. We believe that blocking KIR-X will be valuable for stimulating T cells in cancer, while blocking TMIGD2 has potential in deactivating T cells in autoimmune disease. My goal is to find an antibody that blocks KIR-X-mediated inhibition while leaving TMIGD2 mediated T cell activation alone. To measure T cell stimulation, KIR-X and TMIGD2 were separately expressed on Jurkat cells with an NFAT or IL2 luciferase reporter which luminesced when the T cell was active, and they were put in wells with CHO cells expressing HHLA2. The bioluminescence produced by the firefly luminescence reporter reflects NFAT or IL2 transcriptional activation. T cell stimulation and inhibition mediated by the TCR and HHLA2 signal were measured. The antibodies were tested for the capacity to affect the HHLA2-mediated effect on T cell activation. My results show that the anti-KIR antibodies 2D8, 2F11, 2H1, and 1G7 and the anti-HHLA2 antibodies 4D1, 2C4, 6D10, and 6F10 successfully resulted in T cell activation. The anti-HHLA2 antibodies 6F10 and 4D1 prevented TMIGD2-mediated T cell activation. These assays showed that there was good correlation between physical blocking ability and effect on signaling of T cell activation.

The Role of Microbial Bioproducts in Modulating the Response of Macrophages to Gluten in Celiac Disease Patients

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Celiac Disease (CD) is an autoimmune enteropathy that affects approximately 1% of the worldwide population. In genetically predisposed individuals, small intestinal inflammation is triggered by gluten protein ingestion, which can cause serious complications. Its rising incidence in recent years suggests that additional environmental factors other than gluten may contribute to disease onset and pathogenesis. Although the adaptive immune pathway is well understood, the innate response is less explored. Particularly, macrophages (MΦ) are thought to be implicated yet remain understudied. Therefore, we sought to investigate the MΦ response to pepsin-trypsin-digested gliadin (PTG), a component of gluten, both alone and with microbial-derived metabolites, which can influence the phenotype and function of immune cells.

Monocytes isolated from whole-blood samples of CD and non-CD patients were differentiated into mature MΦ before undergoing a 24-hour stimulation with PTG, lactate or butyrate, or PTG and either metabolite in combination. Pro- and anti-inflammatory cytokine mRNA expression was determined via real-time reverse-transcription polymerase chain reaction. Supernatants from MΦ cultures were collected and cytokine production was measured via enzyme-linked immunosorbent assays (ELISAs). Preliminary findings indicate that both butyrate and lactate lead to a slight decrease in production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β in PTG-stimulated cells in both groups of patients. Many cytokine expression levels were not statistically different, however, and therefore, ongoing experiments are assessing the effect of metabolites in a dosage-dependent manner.

Given the diversity of intestinal microflora, future directions could involve culturing cells with other microbial bioproducts or multiple metabolites at once. Additionally, flow cytometry will be used to determine phenotypic differentiation of MΦ. This research could provide a more comprehensive understanding of the mechanistic link between gluten and metabolite exposure in the innate autoimmune response in CD patients.

Analyzing Cis P-tau in Hypoxia Models of Trophoblast Stress

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Traumatic brain injury (TBI) is a major cause of death, disability, and lifelong impairment in the United States. People with TBIs are at greater risk of developing Chronic Traumatic Encephalopathy (CTE) and Alzheimer's disease. A pathological hallmark of these diseases is the accumulation of tangles of phosphorylated tau proteins, particularly those of the cis conformation (cis p-tau). Cis p-tau causes cell death and neurodegeneration by interrupting mitochondrial transport and microtubule assembly, known as cistauosis. A useful model for cis-p tau accumulation is the trophoblast, or placental cell. In pre-eclampsia, a serious complication affecting the placenta during pregnancy, trophoblasts are impaired by protein misfolding and aggregation, similar to the aggregation seen in Alzheimer's disease. Furthermore, prior research shows that cis p-tau is induced in stressed trophoblasts. To induce cis p-tau expression, trophoblasts were cultured in high, medium, and low stress conditions: 0.5% oxygen hypoxia without fetal bovine serum (FBS) cell growth supplement; normoxia without FBS; and normoxia with FBS. Cells were collected at 0-, 24-, and 48-hour timepoints for comparative analysis. By using cis p-tau-specific antibodies, relative amounts of cis p-tau expression were determined using immunostaining and western blotting. Image processing software allowed for quantification of cis p-tau expression. Results showed that high levels of cis p-tau are induced when cells are exposed to hypoxia or serum starvation, compared to the very low levels of cis p-tau that are induced in cells in desirable oxygen and serum conditions. Time also positively correlated with increased stress and cis p-tau. Given that pre-eclampsia prevents sufficient blood flow to the uterus and placenta, the results indicate that cis p-tau likely is involved in poor placentation and harm done to babies and mothers suffering from pre-eclampsia. This research shows that cis p-tau may play a major role in the degenerative effects of both traumatic brain injury and pre-eclampsia.

Role of the Wnt Gatekeeper Sfrp4 in the Maintenance of the Pool of Periosteal Stem Cells/Progenitors

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The periosteum, a thin cellular layer surrounding long bones, which plays a critical role in cortical bone expansion and homeostasis, has regenerative capabilities and responds to anabolic drugs. However, despite its clinical significance, our basic understanding of periosteal cellular characteristics, local or paracrine regulatory factors, is incomplete. Thanks to powerful new sequencing technologies, a periosteal population of cells labeled by Cathepsin K (Ctsk+), which include bona fide periosteal stem cells (PSCs) and non-stem periosteal progenitor (PP1 and PP2) cells, has been recently identified, providing a great opportunity for studying the regulation and significance of the periosteum in skeletal phenotypes. Loss of function mutations of SFRP4, a known inhibitor of the Wnt signaling pathway, were identified in our previous studies as causing Pyle's disease (OMIM-265900), a rare skeletal disease characterized by skeletal deformities and bone fragility. Using a knockout mouse model, we uncovered that Sfrp4 mediates cortical bone homeostasis primarily through repression of non-canonical Wnt signaling. The purpose of this project is to explore Sfrp4's role in periosteal function. To this aim, we first assessed the colony-forming unit potential of periosteal cells lacking Sfrp4 and found that Sfrp4 deficiency decreased the colony formation ability of fibroblasts and osteoblasts and decreased their differentiation into osteoblasts. Transcriptome analysis revealed high Sfrp4 expression in PP1 and PP2 cells. FACS analysis showed that SFRP4 deletion led to a marked decrease in the percent of PSCs and increase in the percent of PP2 cells. A decreased percentage of more mature osteochondral lineage cells was also observed. Together, this suggests that Sfrp4 deletion promotes the differentiation of PSCs into PP2 progenitors while preventing their progression from PP2 into more mature cells. Further analysis of the pathways that govern these cells may improve our understanding of the role of the periosteum and have applications to diseases affecting cortical bone.

Development and Evaluation of SHERLOCK-based Diagnostic Panel for Respiratory Viruses

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Acute respiratory infections are correlated with significant disease burden worldwide and are the leading cause of death among children under five years of age in developing nations. Respiratory infections and influenza-like illnesses are particularly difficult to diagnose, as many pathogens present with very similar clinical manifestations. State-of-the-art commercial multiplexed PCR systems are able to detect dozens of viral targets simultaneously, but many of them have prohibitively expensive per-sample costs and have difficulty differentiating between closely related species. In the past year, CRISPR-Cas13 based nucleic acid detection platforms, such as SHERLOCK, have proven to be highly sensitive and specific. SHERLOCK leverages Cas13's collateral cleavage of a fluorescent RNA reporter to detect the presence of a viral target in a patient sample. The goal of our project was to develop a SHERLOCK-based panel to detect 18 respiratory viral targets. Genome sequences were obtained from NCBI, and a bioinformatics pipeline was used to identify conserved regions. Primers and CRISPR RNAs were designed to ensure that the panel captured at least 95% of all known sequence diversity. Pooled PCR amplification was performed on 18 synthetic viral targets, followed by SHERLOCK detection reactions. Optimization of enzyme concentrations, PCR protocol, and primer designs was performed to maximize fluorescent signal. Our panel was able to detect the presence of 16 synthetic viral targets down to 1 copy/µL. Further work will involve testing the panel on clinical samples and spatially multiplexing the Cas13 detection, enabling clinicians to perform high-throughput, low-cost, and highly-sensitive diagnosis of patients who present with respiratory illness.

CRISPR-Engineering of Circulating Tumor Cells as a Therapeutic Strategy for Primary and Metastatic Tumors

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The search for new and innovative ways to treat cancer is at the forefront of modern research and medicine, leading to profound discoveries in cancer therapies. As a result of emerging technologies including gene-editing tools, medical imaging, and drug development, cancer cells, in and of themselves, can be mobilized to target tumors and have the potential to treat various types of cancers. Yet, oftentimes, these cancer cells are invasively isolated from tumors that are well established and the process to genetically engineer these cells can be time-consuming. Time is very valuable to cancer patients considering how lethal end-stage cancer is and so, the search for cancer therapies that allow for early diagnosis and treatment is a necessity. Circulating tumor cells (CTCs) offer a potential solution as CTCs can be detected in the early stages of a patient's cancer, which can allow for enough time to use gene editing tools and to implement the therapy before a patient's condition gets extremely fatal. This research project seeks to isolate circulating tumor cells from mouse models with established tumors expressing fluorescent bioluminescent markers. CTCs will be isolated and modified using CRISPR-Cas9 technology to knock out cell surface receptors and ultimately engineered to express cell surface receptors targeted pro-apoptotic ligands and a prodrug-activatable suicide system. These therapeutic cancer cells will be tested for their efficacy in different mouse tumor models. If successful, this project could demonstrate the effectiveness of new cancer therapies that employ genetic engineering of tumor cells derived from cancer patients.

Exploration and Optimization of Trehalose Dimycolate Hydrolase in Permeabilizing the Cell Wall of Mycobacteria

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Mycobacterium tuberculosis, the causative agent of tuberculosis (TB), remains to be one of the biggest threats to global health, causing more than one million deaths annually. Despite being largely treatable, the current regime for treating active TB requires multi-antibiotic treatment for at least six months. This leads to low patient compliance and therefore an increased risk of drug resistance development. The characteristic lipid-rich cell wall of *M. tuberculosis* not only makes TB hard to treat but also hinders biological research on the bacterial physiology. Current techniques that break through the cell wall, either chemically or mechanically, would inevitably destroy the intracellular architecture, which is a major limitation for studying the molecular basis of both mycobacteria physiology and pathogenesis. Therefore, finding a method which permeabilizes the mycobacterial cell wall while preserving the intracellular molecular integrity is greatly needed in order to continue understanding the inner workings of mycobacteria. According to previous literature, an enzyme encoded by mycobacteria themselves, trehalose dimycolate hydrolase (TDMH), could degrade the lipid-rich mycobacterial outer membrane in physiological conditions. The purpose of this study is to explore and maximize the effectiveness of the enzyme TDMH in killing *Mycobacterium smegmatis*, a fast growing, non-pathogenic mycobacteria species. First, a strain of *E. coli* will be genetically engineered to produce and excrete TDMH. This will be done by tagging TDMH with proteins normally excreted by *E. coli*, such as OmpA. Secondly, the TDMH expressing E. coli strain will be co-plated with *M. smegmatis*, anticipating a lack of mycobacteria growth where the TDMH is secreted. Finally, through directed evolution and the co-plating killing assay we aim to find TDMH mutants with enhanced mycobacterial cell wall degrading activity. This project could potentially provide an improved mycobacterial cell wall permeabilizing agent which could facilitate future development of research tools to understand the intricate molecular biology of mycobacteria.

Investigating the Regulatory Function of Human Accelerated Regions in Autism Patients

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Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that affects 1 in 59 people worldwide. There is strong evidence for the role of coding mutations in ASD, but the contribution of non-coding mutations is not well understood. One particular type of non-coding regions of interest is Human Accelerated Regions (HARs). HARs are non-coding regions of the genome that have been kept unchanged across many different species, but show an accelerated rate of divergence specifically in humans. Importantly, previous work has demonstrated that in consanguineous populations, individuals diagnosed with ASD were found to be enriched for biallelic mutations in HARs. When tested functionally, HAR mutations found in affected individuals exhibited a significant change in regulatory activity in brain tissue compared to healthy individuals. This study aims to use a new assay being developed in the lab to more systematically assess which HARs possess regulatory activity and which portions of the HARs are responsible for its function. The method captures DNA sequences of interest and then inserts them into a DNA barcoded reporter assay that allows us to test for regulatory activity in thousands of sequences at the same time. Many HARs are long, and one advantage of the technique is that it is able to test in parallel regions 500 bp in length, which is 4-5x more than current methods. Furthermore, we are combining this high throughput reporter assay with mutagenesis to gain a better understanding of which portions of the HARs are responsible for regulating gene expression. Through this approach, we hope to systematically test whether variants in HARs in ASD patients change regulatory activity, as well as gain insight on how this fits in the broader context of the role of HARs in the development and vulnerabilities of the human brain.

Optimization of Antibody-Dependent Cellular Phagocytosis Assay on Murine J774 Macrophage and HMC3 Cell Lines

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Cell lines are well established cell cultures that replicate indefinitely if grown in proper environmental conditions. These immortal cells are often used in place of primary tissue given their cost effectiveness, ease of use, and their ability to allow researchers to avoid possible ethical concerns involved in working with animal and human tissue. We attempt to take advantage of the various benefits of cell lines by performing and optimizing the antibody-dependent cellular phagocytosis assay (ADCP) to better understand an in vitro model of the phagocytic immune response. Using the murine J774 monocytic and the human microglial clone 3 (HMC3) cell lines, we sought to understand and optimize their phagocytic response to Zika virus (ZIKV) non structural protein 1 (NS1) and Ebola virus (EBOV) glycoprotein (EBOV GP) specific monoclonal antibodies respectively. Bead based assays such as ADCP require cells to recognize and attack an immune complex made of antibodies bound to an antigen coupled fluorescent latex bead, which are then used to calculate a phagocytic score using flow cytometry. We found that in the murine J774 macrophages, performing the assay in cell medium RPMI 10 opposed to DMEM 10 substantially improved the reproducibility of our assay. Interestingly, flow cytometry analysis of the J774 cell line reveal two independent monocyte populations. We hypothesize that one of such populations represents activated cells that interact with the ZIKV immune complex, whereas the other population are the remaining inactivated cells. Furthermore, given that HMC3 cells are derived from the brain, these cells are not primarily phagocytic in the way that macrophages are. Future assays and adjustments must be performed in order to optimize the HMC3 cell line for this ADCP assay.

Genetic Analysis to Determine the Function of MreD, a Conserved and Essential Protein Required for Bacterial Cell Shape Determination

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The peptidoglycan cell wall, composed of glycan strands connected with short peptides, is an essential feature of most bacteria. It acts as an exoskeleton by protecting the bacteria from internal osmotic pressure and maintaining the cell shape. Because the cell wall is essential for bacterial survival, its biogenesis is also an important target for many antibiotics, such as penicillin. Therefore, a complete understanding of how the cell wall is synthesized may reveal new ways of targeting its assembly for the development of novel antibiotics, which are sorely needed due to the increasing incidence of resistant infections. Two multiprotein complexes,the rod complex and divisome, are required to build the cell wall of rod-shaped bacteria. MreD is a protein of unknown structure and function in the rod complex and is conserved among all rod-shaped bacteria and essential for E. coli survival. In this project, I have been generating mutations in mreD and characterizing their effect on its function. The results are helping us to understand the role of MreD in cell wall biogenesis by the rod system and to identify portions of the protein that are essential for its activity.

Quantifying miRNAs in Systemic Lupus Erythematosus

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Systemic Lupus Erythematosus (SLE), an autoimmune disease impacting many key organs, has no cure. Many researchers, having realized the importance of timely diagnosis in implementing interventions, have focused on one key component of SLE, T cell dysfunction. SLE patients experience lower regulated cell death and cytotoxicity. One explanation for this irregularity is low expression of the SRSF1 gene, which is essential to T cell function. Antibody stimulation of T cells, an *in vitro* model for SLE, decreased SRSF1 protein levels, but did not change corresponding mRNA levels. Thus, my preliminary research quantified SRSF1-specific miRNAs, which downregulate protein expression by binding to the SRSF1 mRNA's 3' untranslated region (3'UTR) in stimulated T cells. An extensive literature search using miRSystem, miRbase, and TargetScan was done to analyze the role of miRNAs in the diseased T cell state and to identify target miRNAs that bind to the SRSF1 3' UTR. Primers for these miRNAs were designed and miRNA expression was measured in stimulated T cells using RT-qPCR, which was confirmed with a DNA agarose gel. Results suggest that miRNAs, hsa-miR-200b and hsa-miR-10b, are highly expressed in stimulated T cells. Using this data, future studies can transfect cells with mimics of these two miRNAs and plasmids of the SRSF1 3' UTR region to investigate how these miRNAs contribute to the lack of correspondence between SRSF1 mRNA and protein levels.

Mechanism of Amphiregulin-Induced Modulation of Muscle Satellite Cell Expansion

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Chemical and Physical Biology, 2020

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Sarcopenia, the loss of muscle tissue as part of the aging process, is a growing burden on the healthcare system. In 2000, the estimated direct healthcare cost of sarcopenia in the United States was $18.5 billion. Therapies that could lead to even a 10% reduction in the prevalence of sarcopenia would save the United States $1.1 billion/year. To discover novel treatments, foundational research into muscle development, regeneration and function is necessary. One exciting avenue of research is the role of the immune system in regulating muscle regeneration. Foxp3+ CD4+ regulatory T cells (Tregs) are a heterogenous population of lymphocytes critical for suppressing pathogenic immune responses. Recent studies suggest Tregs may also be involved in promoting muscle repair. However, despite accumulating evidence, the mechanisms by which Tregs exert this pro-regenerative effect remain elusive. One Treg-produced candidate, Amphiregulin (Areg), partially recapitulates the pro-regenerative effects of Tregs. We set out to determine if Areg signaling changes the rate of muscle satellite cell proliferation. Moreover, we sought to determine if Areg treatment could attenuate the reduced self-renewal and differentiation capacity of aged muscle satellite cells. We isolated muscle satellite cells by fluorescence activated cell sorting (FACS) as PI−, Calcein+, Sca1−, CD45−, Mac1−, Ter119−, β1-integrin+, CXCR4+ cells. We used fluorescence imaging to detect nuclear staining, EdU (5-ethynyl-2´-deoxyuridine) incorporation, and MyHC expression to measure cell number, proliferation and differentiation, respectively. If our hypothesis is correct and Areg can attenuate the age-associated reduction in muscle satellite cell self-renewal and differentiation capacity, Areg could have therapeutic value as a treatment for muscle wasting diseases such as sarcopenia.

Selective Therapeutic Targeting of IDH-mutant Biliary Tract Cancer

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Intrahepatic cholangiocarcinoma (ICC) is an aggressive cancer of the liver bile ducts, commonly exhibiting mutations in the metabolic isocitrate dehydrogenase (IDH) gene. Our group sought to identify new treatment strategies against IDH-mutant ICCs by testing tumor-derived cell lines for sensitivity toward a large set of drugs. These studies identified the small molecule drug N1603 as being highly effective at selectively killing IDH-mutant ICC cells. Though the cellular target of N1603 is unknown, we found, using mass-spectrometry-based protein expression analysis, a very strong correlation between N1603 sensitivity and expression of Sult1a1, an enzyme known to bioactivate certain drugs. We thus hypothesized that Sult1a1 activates N1603 such that it becomes capable of killing the cancer cells. To test this hypothesis, I deleted the Sult1a1 gene from IDH-mutant ICCs using a CRISPR-Cas9 genome editing construct packaged in a viral delivery system. I confirmed the deletion via immunoblot and treated the Sult1a1-deleted IDH-mutant cell lines with N1603 alongside unmodified control cells. Notably, I observed that the Sult1a1-deleted IDH-mutant cell lines were completely resistant toward N1603. In parallel, I designed a Sult1a1 expression-promoting plasmid and introduced it into IDH-wildtype ICCs that are normally insensitive to N1603 and show low expression of Sult1a1. These cells became hypersensitive toward N1603 compared to unmodified control cell lines, further supporting our hypothesis. Although the N1603 drug mechanism downstream of Sult1a1 activation, as well as the possible functional significance of Sult1a1 in IDH-mutant ICCs, have yet to be elucidated, all current evidence points to Sult1a1-mediated activation as a prerequisite for N1603-induced cell death. Collectively, our studies suggest the application of a novel, highly specific chemotherapy for IDH-mutant ICCs and other Sult1a1-rich cancers.

Targeting Radiation-induced Secreted Factors for Improved Responses to Radiotherapy

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Radiation therapy is a common form of breast cancer treatment which uses high-energy particles or x-rays to damage cancer cell DNA, thereby promoting cell death. Recent studies suggest that while tumor cells undergo radiation-induced DNA damage and cell death, simultaneous activation of regenerative processes may facilitate acquisition of advanced tumor properties within surviving cells. Preliminary *in vitro* experiments have indicated that radiation-naive mouse mammary carcinoma cells, after being cultured in media conditioned by irradiated cells, exhibit enhanced migratory properties and expression of stem cell antigen 1 (Sca1). These results suggest that products secreted from irradiated tumor cells play an important role in migratory and invasive behavior. The specific cytokines and molecular pathways involved in producing this effect have yet to be fully understood. This study aims to determine key products secreted by irradiated cells that promote the observed induced phenotype, which serves to identify potential adjuvant targets to enhance the efficacy of tumor therapy. In the initial stages of investigation, we analyzed the differential gene expression profiles of 16 irradiated human breast cancer cell lines to identify genes that encoded secreted proteins that were commonly induced by irradiation. Notable genes were screened for significant changes in expression ($|\log FC| > 1.0$) and possible epigenetic regulatory activity. *SCUBE2* and *CCL5* were identified as a prominent potential factors for further study. Subsequent experiments include conducting qPCR on irradiated human mammary tumor cells to confirm the induction of *SCUBE2* and *CCL5* and assessing the importance of these gene products upon the radiation-induced migratory phenotype. If significant induction is established, further testing of gene inhibition in conjunction with radiotherapy may provide promising approaches to improving cancer treatment. By extension, these studies also explore whether the secreted products induced by irradiation are also produced under other contexts of DNA damage such as genotoxic chemotherapies.

Electrode Design for EFX Crystallography to learn about Protein Structures

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Electric field-stimulated X-ray crystallography (EFX) is a recently developed method to better understand allostery in proteins. EFX deploys electric fields (EF) to induce conformational changes within crystals mounted upon capillaries and employs short X-ray pulses to create snapshots of resulting diffraction patterns. However, often crystal damage occurs during the process of bringing electrodes together to induce EF and in the gluing of crystals to capillaries. This research aims to improve upon electrode housing designs. Electrode housings must allow for precise positioning of electrodes, require limited setup, and allow for maximum views of crystals. Using OnShape software and a Formlabs-2 3D printer, the author is working on 1) updating the currently used top electrode design to better meet these specifications and 2) helping design another electrode housing approach known as the "pizza saver model" to make electrode positioning more precise. Designs were tested at the Advanced Photon Source synchrotron and improved based on resulting performance. I am concurrently attempting to introduce gel on capillary tips to provider a gentler alternative to gluing crystals. I have tested different methods of gel application, percentages of polyacrylamide gel, and humidity to determine the feasibility and optimization of smooth gel-layer polymerization on this surface. Gel polymerization atop a capillary was found to be possible. The ideal conditions for this process were also determined: steps involve transfering .1 microliters of 15% polyacrylamide gel that has been polymerizing for 15 minutes onto a capillary using a micropipette, and then using heat shrink tubing around the capillary to secure gel placement. Future work will focus on further improving 3D designs and test gel with crystals mounted on top. These data can help reduce crystal and data loss during EFX data collection.

Back to the Egg: Successful Generation of hEGs from hPGC-LCs

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Primordial germ cells (PGCs) are the group of cells within embryos fated to become egg or sperm cells. As the only cells that transfer genetic information between generations, they are crucial to studying the acquisition of heritable traits. While PGCs have been used to generate EGs, a germ cell-derived type of pluripotent stem cells, in mice, it is both logistically and ethically difficult to obtain human PGCs (hPGCs), and thus remains a controversial question whether hPGCs can be used to generate human embryonic germ cells (hEGs). We attempted to generate EGs from the human PGC cell culture model (hPGC-LCs) derived from human induced pluripotent stem cells (hiPSCs). The hPGC-LCs were generated from iPSCs over the course of two weeks using defined hPGC-LC medium. The batch was enriched for cells positive for the glycoprotein CD38, a hPGC-LC marker, using Fluorescence Activated Cell Sorting. hEGs were generated from hPGC-LCs, and their pluripotent status was established using immunohistochemical staining for the nuclear protein OCT4 and the membrane protein TRA-1-60. Further steps will include determination of the transcriptional profiles of hiPSCs, hPGC-LCs, and hEGs using RNA-sequencing. mRNA expression of marker genes for germline status and pluripotency will be compared between these cell types, and attempts will be made to identify marker genes that distinguish hEGs from hiPSCs.

Determining Changes in TET3 Protein Interactome by O-GlcNAcylation

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O-linked N-acetylglucosamine (O-GlcNAc) is a post-translational modification attached to serines or threonines by the enzyme O-GlcNAc transferase (OGT). O-GlcNAc plays a critical role in cellular signaling and metabolism and its dysregulation is implicated in a variety of diseases such as diabetes, cancer, and neurodegenerative disease. OGT associates tightly with TET3 of the ten-eleven translocation (TET) protein family, a DNA dioxygenase involved in epigenetic regulation through passive DNA demethylation. O-GlcNAcylation of TET3 by OGT could mediate its dioxygenase activity, protein binding partners, and cellular localization. Until recently, functional effects of increased TET3 O-GlcNAcylation could only be performed on a global level, rendering it difficult to determine whether observed phenotypes are a direct result of O-GlcNAcylation of TET3 or from indirect pathways. The development of a proximity-directed nanobody OGT system by our lab now allows for protein-specific O-GlcNAcylation. To determine the functional roles of TET3 O-GlcNAcylation, TET3 glycosites were identified and mapped using the proximity-directed nanobody OGT system and mass spectrometry. Validation of the glycosites through site-directed mutagenesis will allow us to probe changes in protein-protein and protein-glycan interactions using protein immunoprecipitation, diazirine O-GlcNAc crosslinking, and mass spectrometry. Due to the role of TET3 in epigenetic modifications, changes in TET3 protein binding partners mediated by O-GlcNAc would suggest broader implications in transcriptional regulation of genes and the progression and etiology of disease.

Exploring the Mechanism of MSP1 Substrate Detection in the Peroxisome of Saccharomyces cerevisiae, Using Modified PEX15

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The regulation of membrane protein biogenesis is essential for maintaining the identity and function of cell organelles. However, there is very little information about the maintenance of membrane protein biogenesis in peroxisomes. Peroxisomes are essential for normal cellular function as they oxidize fatty acids and degrade hydrogen peroxide. Msp1 is a conserved, integral membrane AAA (ATPase Associated with various cellular Activities) ATPase in Saccharomyces cerevisiae (a budding yeast model organism) known to remove mistargeted and misincorporated tail anchored (TA) membrane proteins from both peroxisomal and outer mitochondrial membranes in which it normally resides. However, it is not well understood how Msp1 detects peroxisomal substrates. We have set out to understand Msp1 substrate recognition by studying its only known peroxisomal substrate, the TA protein Pex15. Previous work from the Denic lab showed that Pex15, which is present in excess of one of its binding partners in the peroxisome membrane, is an Msp1 substrate. In preliminary experiments, we have developed Pex15-3L, a Pex15 transmembrane domain (TMD) mutant, that is recognized by Msp1 as a peroxisomal substrate even when expressed at its endogenous level. To define the mechanism of this novel example of Msp1 substrate recognition, I will test the role of a hydrophobic Pex15 sequence near the TMD that is known to be required for Msp1-dependent removal of mistargeted Pex15 from mitochondria. I will also test the hypothesis that Pex15-3L TMD mutations prevent proper membrane insertion. Successful completion of this project will provide new insight into how Msp1 recognizes its substrates and provide a better understanding of membrane protein quality control in peroxisomes at large.

Construction of Human Anti-PD1/scIL-12 Fusion Proteins for Use in Cancer Immunotherapy

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Cancer immunotherapy is a rapidly evolving field that uses a patient's immune system to attack tumor cells. Checkpoint inhibitors are a form of immunotherapy that block signaling between T cells and tumor cells by binding to receptors. The most well-known checkpoint inhibitor is PD-1, a molecule expressed on T cells that is critical for modulation of autoimmunity. Activation of the PD-1 pathway by its cognate ligand PD-L1 results in T cell suppression, giving PD-L1 expressing tumor cells the ability to evade the immune system. Native IL-12 is a heterodimeric cytokine that triggers the production of interferon gamma (IFN-y) and other stimulatory cytokines through the Th1 response. IL-12 has also been engineered to be expressed as a single chain fusion (scIL-12). We propose that by combining an anti-PD-1 antibody with scIL-12, we will be able to simultaneously inhibit T cell suppression and activate other elements of the immune system. In this work, two antibody constructs were designed utilizing our anti-PD-1 antibody with the scIL-12 fused to the C-terminus of either the heavy chain or light chain. We have demonstrated that the binding activity of both fusions to PD-1 are comparable to that of the FDA approved anti-PD-1 antibody pembrolizumab. To test biological activity, the fusion proteins will be incubated with anti-renal cell carcinoma (RCC) chimeric antigen receptor (CAR) T cells, allowing for *in vitro* analysis of the effects of PD-1 and IL-12. We expect the anti-PD-1 scIL-12 fusions to reverse and prevent exhaustion, induce T cell proliferation, increase cytokine production, and result in enhanced killing of RCC tumor cells. If this hypothesis proves correct, these fusions have the potential to be used both as a standalone drug and for development in novel CAR T cell factory therapies.

Identifying a Human Colon Cancer Cell Line with YAP-mediated Growth Suppression

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The Hippo pathway is a highly conserved signaling cascade that controls cell proliferation and organ size. Activation of an upstream phosphorylation kinase cascade in this pathway leads to the inhibition of the transcriptional coactivators YAP and TAZ. Many studies have established that inhibition of the Hippo pathway and consequent activation of YAP leads to increased cellular growth and survival in many organs, suggesting that YAP functions as an oncogene in many tissues. However, in the colon, we have shown that Hippo inhibition in organoid and mouse models of colorectal cancer leads to cellular growth suppression, indicating that YAP could act as a tumor suppressor. The goal of my project is to identify a human colon cancer cell line that has a YAP-induced growth suppressive phenotype as working with organoids and mice for mechanistic studies is more difficult than with 2D cell lines. Indeed, a recent study has shown that loss of LATS1/2 (large tumor suppressors 1 and 2), upstream negative regulators of YAP, in a mouse colon cancer cell line resulted in growth inhibition. To identify a more relevant human counterpart, we will activate YAP in a panel of human colon cancer cell lines using lentiviruses that will temporally knock out LATS1/2 via CRISPR/Cas9 or overexpress YAP upon doxycycline administration. We will then use proliferation assays to assess how YAP upregulation in these lines affect their growth and identify a cell line with arrested proliferation upon YAP activation. Using this line in future studies, we will dissect the underlying mechanism of YAP-mediated growth suppression and subsequently apply these findings to organoids and mice. Elucidating the inner workings of this regulatory network holds tremendous potential for uncovering novel therapeutic targets for combating colorectal cancer.

Determining Metal Selectivity Imparted by Variations in the Nramp Metal-Binding Site

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Transition metals such as iron, manganese, and zinc are important cofactors in several cellular processes. The natural resistance-associated macrophage protein (Nramp) family of transporters exists across the tree of life; these proteins typically transport divalent transition metals, such as Mn^{2+} or Fe^{2+}, into the cell. Structures of Nramp transporters and alignment of 6683 Nramp-family proteins revealed two conserved amino acid sequence motifs that form the metal-binding site. However, 45.5% of Nramp homologs contain different motifs in the metal-binding site; it is not known how these variations in the metal-binding site affects the Nramp selectivity for different metal substrates. The *Deinococcus radiodurans* Nramp (DraNramp) serves as our model bacterial Nramp homolog. By mutating the DraNramp metal-binding site to mimic the other binding site motif variants, I hypothesize that DraNramp selectivity for its substrates may change. To determine the metal substrate selectivity profile for these DraNramp metal-binding site motif variants, I am currently performing growth assays to compare the growth rates of cells expressing DraNramp binding motif variants grown in the presence of biologically toxic levels of a potential metal substrate. I am also performing in-cell metal uptake assays to determine Co^{2+} and Fe^{2+} transport, which can be determined by precipitating the metal with $(NH_4)_2S$ and measuring the darkness of the precipitate. Future studies will assay for the metal selectivity profile of full-length natural Nramp homologs containing analogous metal-binding motif variations. These results will show how different Nramp metal-binding motif variations impart different metal selectivity and contributes to understanding how nature selectively extracts both essential and toxic metals from the environment.

Understanding Atomistic Details of HemK-NTD Co-Translational Folding

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Proteins are an integral part of life, and their structures are indispensable to their ability to carry out functions. Protein misfolding can have detrimental consequences, including diseases such as Alzheimer's, Parkinson's, and cystic fibrosis. While *in vitro* folding experiments typically investigate the refolding of a full polypeptide chain, recent studies suggest that many proteins *in vivo* start folding as they are being synthesized on the ribosome, a mechanism known as cotranslational protein folding. However, we have yet to develop a detailed atomistic understanding of this process, and distinguish how it differs from *in vitro* refolding. We addressed these gaps in knowledge by studying the cotranslational folding of the N-terminal HemK domain (HemK-NTD) through a combination of atomistic Monte-Carlo simulations (including high temperature unfolding and replica) and fluorescence resonance energy transfer (FRET) experiments. These simulations showed that this protein is able to adopt a native-like structure at intermediate lengths, with folding kinetics comparable to those of the full length protein. This was different from some larger proteins which are prone to misfold in non-native kinetic traps, or energetically favored misfolded states; in these cases, co-translational folding appears to facilitate efficient folding. Although HemK-NTD maintained its topology as its length increased, it did undergo various structural rearrangements. These results shed light on a crucial mechanism by which proteins attain their functional structure in the cell, and which can result in disease when unsuccessful.

Characterizing Unexplained Ceftriaxone Antibiotic Resistance in *Neisseria gonorrhoeae*

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Neisseria gonorrhoeae, the Gram-negative bacterium that causes gonorrhea, has acquired resistance to every antibiotic class routinely used to treat it, including the current first-line antibiotic ceftriaxone. Like other third-generation cephalosporins, ceftriaxone inhibits the essential cell wall transpeptidase PBP2, resulting in bacterial cell death. Most ceftriaxone resistance is attributable to genetic variants of *penA*, the gene encoding PBP2. These *penA* variants, known as 'mosaic' *penA*, are interspecies mosaics in which part of the gene was acquired from commensal Neisseria species. In recent years, highly resistant strains lacking mosaic *penA* alleles have been identified, such as the clinical isolate GCGS1029. To identify the genetic basis of resistance in this isolate, we performed selective transformations in which we allowed the laboratory strain to recombine with and acquire variants from GCGS1029 genomic DNA. We then selected for recombinants that acquired resistance, as measured by an increased concentration of ceftriaxone required to prevent bacterial growth (the minimum inhibitory concentration; MIC). We found that recombinants with increased MIC acquired a single nucleotide change in the *penA* gene from the resistant donor GCGS1029. This *penA* A501V mutation increased the ceftriaxone MIC of the laboratory strain by 6-fold (from 0.002 µg/mL to 0.012 µg/mL), suggesting that it is a contributor to the increased ceftriaxone resistance observed in GCGS1029. However, the *penA* A501V mutation alone does not increase the MIC of the laboratory strain to the MIC observed in GCGS1029 (1 µg/mL): other genetic factors are clearly required for this level of resistance. Identifying the genetic basis of ceftriaxone resistance in strains without the canonical mosaic *penA* alleles will aid in the development of diagnostics and may guide novel therapeutic strategies.

Exploring the Potential of *NDUFAF2* in Parkinson's Disease Treatment

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Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting primarily the dopaminergic neurons of substantia nigra in the brain. A number of motor symptoms including muscle rigidity, tremors, and speech impairment often accompany the death of these neurons. Since PD takes both genetic and idiopathic forms, researchers have examined both genetic and environmental factors common among PD patients to better understand the disease and seek potential cures. Years ago, researchers noted a connection between impairment of mitochondrial complex I, and the symptoms and neuronal degeneration patterns in PD. More recently, we learned that the homozygous deletion of the *NDUFAF2* gene leads to such impairment. *NDUFAF2* is a complex I associated mitochondrial protein previously assumed to be an assembly factor. In its absence, the cell experiences widespread oxidative damage resembling that of neurodegeneration. Furthermore, comparing the effect of an *in vitro* transcription and translation-derived protein mix containing a *NDUFAF2* and *NDUFAF2* null mixture suggested that *NDUFAF2* could increase complex I activity in human liver mitochondria. This conclusion would be strengthened by assays performed using pure recombinant *NDUFAF2* protein. My project entails using bacterial cloning to find an ideal combination of vector, bacteria, and induction conditions to obtain recombinant *NDUFAF2*. A silent mutation in *NDUFAF2* will allow digestion with the restriction enzymes BamH1 and Xho1, and therefore ligation into the petsumo vector. We intend to use IPTG to induce the overexpression of the resulting plasmid after its transformation into *E. Coli* strain BL21.If this process is successful, we will then investigate its mechanism of activity in the mitochondria. If the protein is found to increase complex I activity, we will have grounds to explore its potential for treating or even preventing PD.

Investigating Neural and Behavioral Markers in Infants at High Risk for ASD and Language Delay

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Autism Spectrum Disorder (ASD), a neurodevelopmental disorder characterized by impairment in social communication and restricted, repetitive behaviors, affects roughly 1:58 children in the US. At the population level, children may be at higher risk for ASD if they fail an early screen for autism, or at familial risk if they have an older sibling with ASD (approximately 1:5 such infants develop autism). The aim of this study is to compare the high-risk screen group, the high familial risk group, and the low-risk typically developing group (i.e. negative screen and no familial risk) in order to identify neural and behavioral markers that differentiate the high-risk groups when compared to each other and to the low-risk group. In this ongoing longitudinal study, we collect electrophysiological (i.e. EEG and ERP) and behavioral data (e.g. Autism Diagnostic Observation Schedule and Mullen Scales of Early Learning) at 3-, 12-, 18-, 24-, and 36-months of age—by which time clinical diagnoses will be determined, if any—to identify the aforementioned markers. Preliminary results indicate that by 12 months, there are several endophenotypic measures, such as analyses of atypical lateralization, that may serve as useful risk markers. We expect that there will be potential in using these neural and behavioral risk markers to predict neurodevelopmental outcomes, which could lead to earlier detection and intervention of developmental delays or disorders.

The Role of Polydendrocytes and CS6-CSPG Clusters in Synaptic Plasticity

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Chondroitin sulfate proteoglycans (CSPGs) are macromolecules consisting of chondroitin sulfate (CS) chains, which are composed of repeated pairs of glucuronic acid and N-acetylgalactosamine, attached to core proteins. Sulfation at position 6 of CS elements (CS6) is thought to positively modulate synaptogenesis. According to extensive single-cell RNA sequencing data, polydendrocytes are the only class of glial cells that express the enzyme CS6-sulfotransferase responsible for 6-sulfation on CSPGs. Polydendrocytes are known to extend their processes onto synaptic targets, contributing to their function. CS6-CSPGs have been observed in the adult brain in the form of dandelion-shaped CS6 clusters, whose biological role is suspected to be involved dynamically in regulating synaptic plasticity. Preliminary data from the Berretta group suggests that polydendrocytes may be associated with CS6 clusters. Our study seeks to confirm the association between CS6 clusters and polydendrocytes, and potentially identify their shared contribution to synaptic plasticity. To test this hypothesis, a group of wild-type adult male mice were anesthetized and stimulated on the left facial whiskers. Two hours after stimulation, the mice were sacrificed by transcardial perfusion, and their brains were collected and sliced coronally. Using a combination of double immunofluorescence and quantitative microscopy, we quantified and classified polydendrocytes and CS6 clusters in the barrel cortex in both hemispheres. We observed that polydendrocyte processes are prominently co-localized within CS6 clusters. Additionally, our preliminary data showed that an increased total number of polydendrocytes in the right hemisphere was associated with an increased number of clusters. These results suggest that polydendrocytes may contribute to activity-dependent clustered plasticity. Insights from this study contribute new knowledge about the role of CSPGs in the brain. Ultimately, since CS6 clusters have been shown to be significantly reduced in the brains of people with major psychoses, understanding the biological function of such clusters will help investigate their implications in the pathophysiology of these disorders.

Modelling Biological Attention in Deep Neural Networks

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In computer science, "attention" is implemented as a set of weights used in training deep neural networks to achieve better performance. However, biological attention is a selection mechanism that helps the brain to allocate resources efficiently according to the task faced. This process involves competition between different stimuli, which is something absent from computer scientists' interpretation of "attention". In visual search, attention is dictated by bottom-up saliency of stimuli and top-down task-oriented regulation from the brain, with detailed mechanisms unknown. In this study, we aim to propose an attention mechanism in convolutional neural networks (CNN) for visual search tasks, which has a moderate effect in helping single class classification but provides significant improvements when distractors are present. We trained the Cifar-10 dataset on a simple CNN and extracted the distributions of activations from the highest convolutional layer as the network's "memory". We have tested various ways in which biological attention could be implemented, ranging from adjusting activation themselves and using fully connected layers to carry out classification, to shifting class conditional probabilities and using a Naïve Bayes classifier. Further representational similarity analysis (RSA) in CNN and collection of human reaction time data of performing the same visual search task will enable us to measure how comparable the proposed attention mechanism is compared to human attention. Ultimately, we hope to endorse this proposed mechanism as a viable explanation of how attention is implemented in our brain.

Investigating the Mechanisms of Adult Hippocampal Neurogenesis in the Pathology of Alzheimer's Disease

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Adult hippocampal neurogenesis (AHN) is the continued generation of new neurons during adult life from neural progenitor cells (NPCs) in the dentate gyrus of the hippocampus. These adult-born neurons are critical for learning and memory, and evidence shows that AHN is impaired prior to the onset of Alzheimer's disease (AD) pathology in AD mouse models and patients. Presenilin-1 (PS1) is a core protein in γ-secretase, which is the final enzyme complex that cleaves amyloid precursor protein (APP) to generate amyloid-β (Aβ), a molecular hallmark and hypothesized causative agent of AD. Recent research has indicated that PS1 regulates AHN; this presents a pharmaceutical conundrum, as AD drugs that act as PS1-specific inhibitors will not be effective if PS1 is also critical for AHN. Furthermore, it is not known if the role of PS1 in AHN is dependent on the larger γ-secretase complex. In this project, we investigate whether neurogenesis and gliogenesis of NPCs is altered by γ-secretase modulators (GSMs) or γ-secretase inhibitors (GSIs) in an AD mouse model (5xFAD mice). These 5xFAD mice harbor five familial AD (FAD)-linked mutations, including APP and PS1 transgenes, and experience impaired adult neurogenesis starting at two months old. 5xFAD and wild-type (B6SJL) mice were injected orally with GSM (SGSM-15606), GSI (DAPT), or with vehicle (PEG400) for 15 days. Then, the survival, proliferation, and neuronal/glial differentiation of NPCs were measured with BrdU immunostaining. Our preliminary results suggest that, in a small sample size, treatment with SGSM-15606 recovers NPC proliferation in 5xFAD mice. Understanding the processes that regulate AHN is important not only for considering the general mechanisms of neurodegenerative diseases, but also for the future implementation of amyloid-based therapeutics for AD.

Studying the Connectomics of Human Inhibitory Neurons

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Cortical processing in the brain is mostly comprised of two crucial, overarching classes of neurons. The glutamatergic excitatory neurons propagate action potentials over their relatively long axons and make up the majority of the neurons in the cortex. On the contrary, GABAergic inhibitory neurons make up only 20% of the cortical neurons but can profoundly attenuate the magnitude and frequency of excitatory neuronal firing . The inability to maintain a proper excitation to inhibition ratio, also known as the E/I balance, in the cortex has shown implications in various cognitive, neuropsychiatric, and neurodegenerative diseases. Connectomics, or the study of mapping neuronal connections, has shown implications in determining the underlying causes of many neurological disorders and diseases. For these illnesses of the nervous system, not only is there a lack of effective therapeutics, but also an absence of understanding the structural abnormality in the connections between neurons, or synapses, that occur. Due to this lack of information, neurological diseases have often been mischaracterized as mere abnormalities of behavior, thought, or pain and more importantly, inadequately treated. Using a proprietary volume annotation and segmentation tool (VAST), reconstruction of several inhibitory neurons has been conducted from a human electron microscope dataset. In particular, the role self-junctions onto the neuron itself will be investigated to elucidate a more detailed mechanism of inhibitory neurons in the cortex. Ultimately, obtaining a map of the different inhibitory neurons and its circuitry in the human cortex can help change our approaches to treatment of neurological diseases.

State-Dependent Olfactory Modulation in Larval Zebrafish

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There are a multitude of sensory processes that help acquire, process, and integrate sensory information in order to guide behavior. Animals can modulate their readiness to respond to these sensory cues to adapt to their changing environments and efficiently determine novel stimuli. Prior research on arousal in zebrafish larvae (Danio rerio) demonstrated that serotonergic neurons in the dorsal raphe (DR) perform state-dependent modulation of sensory responsiveness, specifically in the optomotor response (OMR). Since arousal is believed to increase the readiness to respond and stress the effectiveness of the response, serotonergic neurons in the DR may be highly interconnected with the HPI axis, homologous to the human hypothalamic-pituitary-adrenal (HPA) axis for cortisol release. While this state-dependent modulation was present in the OMR, it remains unclear how other sensory modalities are modulated during stress in larval zebrafish. Moreover, arousal and a low-stress state might be two ways of describing the same experience, as interactions between serotonin signaling and glucocorticoids (cortisol) have been observed. Here we plan to show that a stress experience, induced by strong tone, may induce a state-dependent modulation of olfaction during a continuous flow of odorant in head fixed zebrafish larvae. Since increased locomotion during arousal increases odorant availability at the olfactory epithelium in free-swimming fish, we would expect results indicating a change in behavioral and neuronal response to odorants after stress. These findings would suggest that there is a reduction in sensory gain or amplification processes for olfaction during arousal or a low-stress state in order to maintain a normal dynamic sensory range. Stress can be beneficial, but prolonged stress can be harmful. Therefore, understanding the underlying neural circuitry of stress and its effects on behavior and sensory modulation is an important field of research.

Help Us or Hurt Them? Neural Correlates of Learned Out-Group Harm

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Divisions between social groups—including cultural, racial, and political ones—very often produce intergroup conflict and harm. In particular, spite toward the out-group seems to drive decisions and policy preferences that reduce resources for the out-group without accruing any material benefit for a person's in-group. However, we still know relatively little about the neural mechanisms underlying out-group spite and decisions that cause intergroup harm in such settings. This project investigates behaviorally-revealed, latent preferences (as opposed to explicitly-stated preferences) for out-group harm in a reinforcement-learning paradigm. The study asks whether people differentially learn about the value of decisions that cause out-group harm compared to decisions with benign outcomes, and how these potential differences are instantiated in the brain. We used functional magnetic resonance imaging (fMRI) to assess neural activity while participants made a series of choices in a probabilistic decision-making task. To extract participants' latent preferences, we used a reinforcement-learning model to derive indices of participants' reward prediction error and choice valuations. These parameter estimates will be applied to the neuroimaging data to determine which brain regions drive participants' decisions to avoid or pursue out-group harm. We predict that the ventrolateral prefrontal cortex will modulate reward-prediction errors associated with rewards that do versus do-not-harm out-group members, such that harm-averse participants will exhibit reduced ventral striatal responses to rewards that harm the out-group. Improving scientific understanding of the neural correlates of latent preferences for out-group harm will help generate new avenues for research on the emergence, escalation, and hopefully attenuation of intergroup conflict.

Understanding Molecular and Cellular Differences in Corticogenesis in ADHD through Organoids

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Attention deficit hyperactivity disorder (ADHD) is a heterogeneous neurodevelopmental disorder with a devastating impact on the quality of life of millions of children, adolescents and adults. While ADHD is thought to be highly heritable, its etiology is largely unknown but likely to involve a combination of environmental factors and the contribution of multiple genetic defects. To understand the molecular underpinnings of ADHD, we hypothesize that 3D neuralized structures (organoids) derived from patient-specific induced pluripotent stem cells (iPSCs) can be used as a potential platform. In particular, the Prefrontal Cortex (PFC) is emerging to be of central relevance to the neural pathways of ADHD, as it connects extensively to sensory and motor cortices, as well as to the basal ganglia and cerebellum. These areas are intricately interconnected and modulated by a mesh of neurons that in ADHD display heavy deficits in dopaminergic and noradrenergic transmission. Thus, it is critical to understand the molecular influences modulating the PFC's function in order to develop novel medications for patients afflicted with the disorder. We have started to generate and characterize iPSC-derived cortical organoids from ADHD patients and healthy sibling controls to study the molecular and cellular differences in corticogenesis between diseased and control brains. Particularly, we propose that the root cause of the PFC's smaller structure involves a limited progenitor pool and impaired radial migration. To achieve these long-term goals, we have used our novel and non-viral reprogramming method to generate high quality control and ADHD-iPSC lines towards the optimization of in vitro region-specific organoid generation and consequently fusion organoid models. Our approach will facilitate examination of how disease risk is translated at the cellular and tissue levels through comparative studies of processes such as progenitor cell proliferation, migration and connectivity during development.

Lipid Dysregulation in Parkinson's Disease

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra, a midbrain structure integral to movement initiation. Research on PD, whose cause remains elusive, has largely revolved around proteins and genetics, and lipid storage has scarcely been examined. Based on preliminary data that suggest lipid droplets, organelles that sequester lipids, increase in PD dopaminergic neurons, we searched for similar trends in microglia, immune cells of the central nervous system. Eight healthy and eight PD human substantia nigral sections were double stained immunohistochemically for CD45 — a protein coating the microglial membrane — and with BODIPY — a fluorescent dye for lipids. Then the stained sections were imaged with confocal microscopy. The overlap of CD45 and BODIPY signals in each microglia image was computed to represent microglial lipid content. Microglia in the substantia nigra of PD patients had a 45.7 ± 29.4% increase in lipid droplets compared to healthy subjects, resembling the trend observed in dopaminergic neurons. This finding suggests that the cause of PD may not be based on proteins or neurons, challenging the long-standing protein-centered theories on PD that have not yet led to a cure despite multiple decades of research. Furthermore, this analysis of the human brain has implications for comprehensive novel therapies targeting lipids and glial cells that may outperform those available today.

Characterisation of Chloroquine-Evoked Scratching Behaviour in Mice

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Itch is a frequently debilitating feature of conditions such as atopic dermatitis and chronic kidney disease and a side effect of drugs such as opioids. Whilst the frequency of itching following administration of pruritic (itch-inducing) and anti-pruritic agents has been studied in detail, it is not clear whether the frequency of scratching is best correlated with the damage to the skin or pruritus (itchiness). Therefore, it was desirable to identify potential alternative metrics, starting with a proxy for scratching intensity. In this project, machine learning was used to generate mouse hindpaw trajectories from high-speed recordings taken of bouts of itching and these data were analysed to distinguish between different intensities of scratching. The antimalarial drug chloroquine phosphate is a non-histaminergic pruritic agent, and it will be investigated whether intradermal 1mM chloroquine phosphate solution injections into the nape of the neck in mice induce significantly different intensities of itching compared to 1μM or saline solutions. This project will lead to design of an automated system to classify itching by intensity in addition to frequency with the aim of generating more detailed information on the pruritic or anti-pruritic properties of different pharmaceutical agents in preclinical trials.

Localisation of Ciliary Neurotrophic Factor Protein Expression in the Mice Retina Post Optic Nerve Crush

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Ciliary neurotrophic factor (CNTF) is observed to have a neuroprotective, neuroregenerative and neuroinflammatory effect on the brain. CNTF is thought to be a key target that could be manipulated to promote neuroregeneration in devastating diseases such as Multiple Sclerosis, Alzheimer's or Parkinson's. In the mice eye, our experiments have shown that lens injury preconditioning improves axon regeneration and increases mRNA expression of CNTF. CNTF binds to CNTFR□ leading to heterotrimer dimerization to initiate downstream effects including JAK1/STAT3 activation. However, little is known about the protein expression of CNTF and its receptor in the retina and optic nerve in the context of lens injury preconditioning. Prior studies have shown that direct CNTF injection can't induce axon regeneration; however, AAV2-CNTF mediated injection shows extraordinary regeneration. Our project aims to characterise the protein expression of CNTF and its receptor in different cells in the retina of mice and to understand its effect on axon regeneration in optic crush model. We are using immunohistochemistry techniques to bind fluorescently tagged antibodies against CNTF and its receptor in the whole eye. We are also staining its downstream effectors including phosphorylated STAT3 in wild type mice. We will perform staining on the mice with and without optic nerve crush and with and without preconditioning lens injury to compare their effects. Once localised, these cells can be targeted in the future and manipulated to determine how CNTF works in the retina and give us an insight on whether CNTF is an appropriate target for future treatment.

Postnatal Stress and Cognitive Impairment in Mice

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Brain function is associated with critical periods of development when external stressors during early postnatal days have a lasting impact on behavior. Stress administered at early postnatal periods, such as P2-P9 (day 2 through 9), has been demonstrated to induce cognitive impairment and alterations in behavior of mice. The effect of stress given at later postnatal periods, such as P9-P16 (day 9 through 16), remains largely unexplored, although a previous study indicated that stress given at this period can cause depressive behavior later in life. The purpose of this study is to determine the effects of P9-P16 stress in comparison to those of P2- P9 stress on attention-related functions in adulthood. A fragmented maternal care model of early life stress was utilized, and attention was tested through a two-choice touchscreen visual attention task. Data acquired from maternal care pattern observations demonstrated that both P2-P9 and P9-P16 fragmented care (FC) models increased the number of interrupted dam-pup interactions in comparison to control care. The total duration of all interactions combined was similar, revealing less continuous maternal care under FC conditions. In comparison to P2-P9 FC, P9-P16 FC resulted in more continuous maternal care, implying that the potential cognitive impairment as a result of P9-P16 FC may be less severe. Exploring the P9-P16 period is expected to determine whether the timing of early life stress in mice impacts its effect on attention and behavior. This study will also serve as a launchpad for examining modulation of attention-related behavior though dopamine receptors, which are known to be altered in mice after P2-P9 early stress.

Rapid, Large-Scale Molecular Profiling of Individual Synapses

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How cells communicate in the brain at a chemical level remains a major unanswered question in neuroscience. Critical to this communication are synapses, the junctions between neurons. Though synapses are currently grouped in broad categories, such as neurotransmitter type, synapses likely have underappreciated molecular diversity in their mRNA and protein content. Despite the crucial role of synapses in brain function and disease pathology, the exact molecular makeup of individual synapses remains unknown. Synapses can be isolated from the rest of the neuron into membrane bound compartments, called synaptosomes, that form from the pre- and post-synaptic membranes. This study develops a new tool for high-throughput profiling of single synaptosomes by extending the single cell RNA sequencing technology, Drop-Seq. Synaptosomes were isolated from adult mice via dissection and homogenization. They were then spun in an ultracentrifuge to remove nuclei and cellular debris, and to separate synaptosomes from other material by density. Bulk RNA isolation and quantification confirmed high quality RNA was present. Immobilization on poly-lysine coated coverslips and immunofluorescence with synaptic markers revealed synaptosomes containing both pre- and post-synapse densities. Next, Drop-Seq was adapted for the isolated synaptosomes. Using microfluidics, single synaptosomes and DNA-barcoded beads are co-encapsulated into droplets. Synaptosomal mRNAs bind to the bead and are then reverse-transcribed to cDNA, PCR amplified, and sequenced: yielding the first RNA sequence library of single synapse content. To identify what transcripts are enriched in synapses relative to nuclei, Drop-Seq was also run on nuclei separated during the synaptosome isolation. To simultaneously analyze RNA and proteins, Drop-Seq was extended by conjugating DNA barcodes to antibodies using cross-linking, for use in future Drop-Seq experiments on synaptosomes. In parallel with synaptosomes, extracellular vesicles isolated and RNA and protein sequenced with Drop-Seq as a way to extend our method of sub-cellular profiling to another mechanism of cell communication.

Molecular and Spatial Profiling of the Single-Neuron Transcriptome using MERFISH Imaging

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Individual neurons communicate with each other through their processes (axons and dendrites), forming complex neural circuits that extend throughout our brains and nervous systems. Changes in the gene expression profile and in the mRNA spatial distribution within single neurons can disrupt these circuits, affecting the establishment of synapses, removing the neuron's ability to identify and separate its own processes, and causing long-term neurological disorders. In order to better understand the structural and functional diversity generated by single-neuron genetic codes, we use an image-based transcriptome profiling method developed in the Zhuang lab called multiplexed, error-robust fluorescence in situ hybridization (MERFISH) to map numerous mRNA species inside of single neurons and other brain cell types (astrocytes, oligodendrocytes, etc) in a cultured neuron system. MERFISH not only measures the absolute abundance of these transcripts but also crucially preserves the spatial contexts of RNAs in situ. By analyzing the differences in gene expression patterns in neighboring cells, distant neurons, and process bundles, we hope to gain further insight into how particular gene clusters affect the properties of single cells and the interactions between multiple cells in the brain.

Investigating Neuronal Circuit Processing Sensory Cues During Parenting Behavior

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Essential for survival and reproduction of species, parenting behavior is comprised of stereotyped motor patterns. The initiation of social behaviors, including parenting, is thought to depend on the individual's recognition of multimodal cues that identifies conspecific age, sex, and social role. Given the specificity of social interactions in many species and the rapid response to these sets of multimodal signals, a better understanding of how these cues are processed and the identification of pathways that initiate the corresponding behavior represent an important area of inquiry. Previous work in the Dulac Lab has characterized specific cell types in the Medial Pre-Optic Area (MPOA) as essential for the control of parenting in males and females. However, the neural mechanism and pathway which integrate and carry sensory information to the MPOA are not well-known. This study aims to identify the stimulus combinations which evoke most of the stereotyped motor sequences associated with parenting behavior, and the sensory regions in the brain that encode the cues necessary to initiate parenting behavior. We aim to present an adult parenting female mouse with a combination of pup cues (olfactory, auditory and somatosensory) and measure precisely the stereotyped parenting motor actions it evokes. To identify the stereotyped motor patterns, we use machine learning based tools (DeepLabCut) to identify body parts in video frames during parenting behavior. Subsequently, we use unsupervised clustering methods to identify stereotyped postures and motor actions during parenting behavior. To identify brain regions encoding the pup stimuli, we use cFos activity as a marker of neuronal activity. For this experiment we use TRAP2, a mouse model with an inducible Cre-recombinase in Fos-expressing neurons crossed with Ai9 mouse line which expresses a Cre-dependent fluorophore, to label cells across the brain active during parenting behavior. These findings should provide deeper insight into multisensory pathways governing parenting behavior in mice.

Characterizing the Repeated Evolution of Forest-Adapted Deer Mice Through an Analysis of Museum Specimens

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The deer mouse, *Peromyscus maniculatus*, is the most abundant small mammal in North America, and can be found in a wide array of diverse habitats. Of particular interest is the observation that some forest-dwelling populations show a number of morphological and behavioral differences that distinguish them from their nearby prairie-dwelling counterparts. The Hoekstra lab has illustrated that forest mice tend to possess longer tails, hindlegs, and whiskers, and that these features appear to have evolved independently in the populations studied. This project seeks to determine whether these differences, thought to be arboreal adaptations, are consistently observed in other parts of the species' range. There is only a limited understanding of the extent to which these adaptations are widespread. Further, little is known about how each of these putatively adaptive traits is associated with each other, and how consistently they are observed in forest-inhabiting mice. To investigate these questions and shed light on the predictability of evolution over periods of time, I have taken X-ray images and external measurements of 220 specimens from across the range of *P. maniculatus* using existing resources from museum collections. This stage has involved developing a reliable imaging method that will allow me to measure key traits from specimens of varying and often poor preservation quality. With this method now fine-tuned, I can use precise external and internal measurements from these images to conduct statistical analyses that relate these characters back to the habitat from which the mice came. The results of this work will allow quantification of how these traits associate with each other and with key habitat variables. In addition, the insights gleaned will help identify populations exhibiting classic forest-related adaptations, as well as those that deviate from the norm. Exploring these questions will advance our understanding of how convergent evolution operates across suites of traits and a variety of timescales.

A Study of 10,000 Generations of Experimental Evolution in Yeast and the Effect on Fitness and Ploidy

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It is difficult to study evolution over thousands of generations in organisms such as humans due to their long lifecycles and the length of time between generations. However, in microorganisms like yeast and bacteria, it is easier to study evolution experimentally due to shorter lifecycle times as well as easier and more efficient manipulability of evolutionary conditions. The Desai Lab has been evolving various lab and wild strains of yeast including both haploid and diploid populations in different environments based on temperature and richness of nutrient media for over 10,000 generations. Our project focuses on measuring the change in fitness of populations over generations through competitive fitness assays carried out for eight generation time-points, measuring growth rates of these evolved populations, measuring ploidy of the populations through Sytox staining, and whole-genome, whole-population sequencing, as well as making easily accessible freezer stocks of clones of populations for further studies. I carried out the ploidy stains and studied the evolution of ploidy. The impact of ploidy on adaptation has been poorly understood; typically, evolution experiments have evolved haploid and diploid populations separately rather than simultaneously. In preliminary ploidy stains, we observed deviations from the normal 1N (haploid) and 2N (diploid) strains, where the strains from the 11000 generations seem to have ploidies between 1N and 2N, above 2N or even below 1N. We will combine these ploidy results with our sequencing data to discern whether this is because of lost chromosomes, duplication of only a subset of chromosomes, or other reasons.

Size Scaling Effects on Ant Mimicry Effectiveness in *Salticus scenicus* and *Myrmyrachne formicaria*

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Protective mimicry, or predation avoidance by a palatable species through perceived similarity to an unpalatable model, is widely observed across the animal kingdom. However, it is often unknown whether predators avoid a specific unpalatable model or whether predators avoid all creatures sufficiently similar to the unpalatable model—an "archetype" of the model. Mimicry of ants by jumping spiders holds particular relevance to this question. Different ant species vary widely in shape and size, but only adults leave the hive, so individuals of a single species show a stable size and appearance to predators. Jumping spiders, in contrast, grow by molting and are active throughout their life cycle, so predators observe juveniles of the same species that are smaller than adults and their presumed ant models. As mimicry studies largely use adult mimics, it is unclear whether ant mimicry scales down to smaller mimics. In this study, I explored the potential effects of scaling on mimicry. Previous studies have shown that the jumping spider *Phidippus audax* will preferentially attack videos of non-mimetic jumping spiders over those of ants or adult *Mymyrachne formicaria*, an ant-mimicking jumping spider. Another non-mimetic jumping spider, *Salticus scenicus*, also preys upon jumping spiders and avoids ants, but is smaller than P. audax and hunts prey on the scale of juvenile *M. formicaria*. I exposed *S. scenicus* to scaled-down videos of ants, non-mimetic jumping spiders, and *M. formicaria*. As juvenile *M. formicaria* are evolved to resemble ants larger than (and therefore different from) *S. scenicus's* presumed ant avoidance models, a *S. scenicus* that avoids specific ants would likely attack a small *M. formicaria*. If *S. scenicus* avoids scaled-down *M. formicaria*, however, this would suggest that *S. scenicus* avoids all animals that resemble a generalized, archetypal ant recognized across size scales. I hypothesize that *S. scenicus* will avoid small *M. formicaria*.

Distinct Infant Vocalizations in *Peromyscus maniculatus*

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Peromyscus, commonly known as deer mice, live in a variety of ecological habitats across North America. *Peromyscus maniculatus*, the species used in this study, is the most common species within the genus. *Peromyscus* make ideal subjects because the genus has around 50 closely related species in it that often exhibit heritable differences in behavior. My study seeks an explanation for behavioral distinctions among species. Thus far, we have begun measuring and comparing the spectral and temporal features of infant vocalizations from four subspecies: P. m. *bairdii*, P. m. *nubiterrae*, P. m. *gambelii*, and P. m. *rubidus*. Infant vocalizations of each subspecies have been recorded starting on postnatal day three (P3) and ending on P15 with recordings taking place every other day. Each pup is isolated in a recording chamber for 10 minutes as their sonic and ultrasonic vocalizations are recorded. The features of these vocalizations will be analyzed to identify differences in vocal spectra among these subspecies. We hypothesize that the type of habitat of a subspecies is associated with how it vocalizes. If our hypothesis is supported, then the successful completion of the proposed project will demonstrate similarities in the vocalizations between P. m. *bairdii* and P. m. *gambelii* which live in fields and between P. m. *nubiterrae* and P. m. *rubidus* which live in forests. This study may highlight the impact of the environment on the evolution of behavior. Additionally, further investigation into why a behavior is more suitable in a certain environment over another could shed more light on behavioral divergence among species.

Software Analysis of *Peromyscus* Mice Infant Vocalizations

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Infant vocalizations serve a vital purpose in communicating survival needs between offspring and parent. Distress cries from young elicit powerful, immediate responses from parents in such a wide range of organisms that there is likely a shared neurochemical pathway mediating infant vocalization and parental response. Unlike vocal behavior in adults, infant vocalization is an innate behavior whose genetic basis is poorly understood. In this study we examine and quantify differences in infant vocalization in *Peromyscus* mice, a model organism for understanding natural genetic variation. Audio recordings of pup separation cries are collected every other day from three to 15 days after birth, which are then examined using signal processing software. Most software of this nature is geared towards the analysis of laboratory mouse (*Mus musculus*) vocalizations and does not adequately handle *Peromyscus*-specific features, such as a distinction between vocalizations in the sonic and ultrasonic frequency ranges. We created an application specifically for *Peromyscus* vocalization detection, analysis, and classification using machine learning on large audio files in a high-throughput manner. Though still in development, this audio pipeline has been used extensively on lab recordings and illustrates behavioral differences between species and through development. Preliminary results suggest that different *Peromyscus* species have markedly different vocalization features in infancy, particularly in the number of sonic vocalizations and the tendency to emit vocalizations in bouts before periods of silence. Further work will seek to discover genes involved through quantitative trait locus (QTL) mapping as well as parental response to vocalization through a videotaped behavioral assay. Given the ubiquity of infant distress vocalizations, insight into the genetic basis of the behavior may uncover commonalities in vocal processing pathways as well as the "meaning" behind infant vocalization types, including those in humans.

Axon Guidance Cues in the Visual System of Cephalopod *Doryteuthis pealeii*

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Cephalopods have an independently evolved, complex, camera-type eye and the largest nervous system of any invertebrate. Essential to building large, complex nervous systems is the process of axon pathfinding, where billions of neurons extend axons toward their target cells and form a precise network. While axon guidance molecules and mechanisms of axon pathfinding have been studied in vertebrates and *Drosophila*, very little is known about this process in cephalopods. During visual system development, photoreceptors in the cephalopod eye extend their axons to synapse on the outer nuclear layer of the optic lobe, where visual processing occurs. My goal is to better understand which guidance cues may be important during this process. Using the squid *Doryteuthis pealeii* as an embryological model, I am characterizing the spatiotemporal expression of 12 candidate genes during visual system development. These genes have been previously shown to play a role in axon pathfinding in vertebrates and *Drosophila* and include members of highly conserved families of axon guidance molecules: Semaphorins, Netrin, DCC, Slit, ROBO, Eph, and Ephrin. These proteins are the attractive and repulsive cues that guide axons as they grow towards their target cells and often work in pairs. The expression patterns of these genes will give insight into the function of these genes in cephalopods and the process by which retinal axons grow and synapse onto the optic lobe in *D. pealeii* to form this complex, camera-type eye.

Developmental Variation of the Crocodylian Palate throughout Ontogeny Using Geometric Morphometrics

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The crocodylian skull has been the subject of extensive study, particularly the evolution of modern morphologies and its variation across ecology and development. Crocodylian skull anatomy has been shown to converge among different ecomorphological groups but that the early development of the skull is largely conserved. While the cranium has received considerable attention recently, the palate of crocodiles has received little. Unlike other reptiles, crocodylians uniquely have a bony secondary palate, which has evolved independently to the mammalian bony palate. The bony palate is functionally important as it partitions the nasal and mouth cavities. This allows crocodiles to continue breathing while processing food in the mouth. Here we analyzed the ecological and developmental shape variation in the secondary bony palate of 11 species of modern crocodiles from late stage development into adulthood. These species fall into three broad ecological categories–blunt (brevirostrine), moderate (generalized), and slender-snouted (longirostrine). Shape was quantified using 2D geometric morphometrics (GMM), a method for mathematically quantifying variation in complex shapes. We placed 12 landmark and 12 semilandmark points on anatomically homologous locations on the palate and underside of the skull, and analyzed these using Procrustes superimposition and principal component analysis (PCA). The greatest axes of shape variation of the palate are the breadth and length of the snout and elongation of the suborbital fenestra. Initial findings indicate the presence of an embryonic region of morphospace, and that adult palate morphologies differ significantly among the three ecomorphs, each with unique developmental trajectories. This pattern is similar to the development of the cranium, which also shows an embryonic region; however, the shape of the palate has more ecomorphological differentiation at the embryonic stage. This suggests that palate shape may be less developmentally constrained and driven more by niche specialization than the cranium.

Neuropsychiatric Genetics of Psychosis in the Mexican Population

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Although Hispanics and Latinos make up almost 10% of the population worldwide, they represent only 1.3% of the DNA samples that have been analyzed as part of genome-wide association studies. Because different variants may be responsible for the same disease among different populations, this disparity means that precision medicine will be of less benefit to Hispanic and Latino individuals than to Europeans. The Neuropsychiatric Genetics of Psychosis in the Mexican Population (NeuroMex) Project aims to correct this imbalance by collecting genetic data from schizophrenia and bipolar patients, as well as healthy controls, from individuals of Mexican descent. A total of 8,000 DNA samples and accompanying phenotypic information will be collected across four sites in Mexico and genotyped at the Broad Institute. Throughout this summer, the NeuroMex team at the Harvard T.H. Chan School of Public Health and the Broad Institute has developed a study manual in Spanish and English. Additionally, quality control has been carried out on incoming data. Collaboration with investigators in Mexico has been essential to ensure adequate data collection and transfer samples from Mexico to the United States. When results are obtained, the study hopes to uncover genetic variants that are associated with psychosis in the Mexican population. By improving our understanding of psychosis in Mexico, the study hopes to add to the body of knowledge about psychiatric genetics in Latin America and increase the applicability of developing genomic medicine to Hispanics and Latinos.

Letter and Object Orientation: Using Reflections to Understand Representational Structures of Objects

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Orientation is an important aspect of object processing. How a given object is oriented may affect how we interact with it; the left or right position of a mug's handle, for example, influences the hand we might use to grasp it, and an animal running towards us might mean we need to run away. The aim of this work is to understand how orientation is represented within an object's overall representational structure and to understand if different classes of objects have different orientation representations. We study three object categories: (1) objects with a canonical upright orientation, like blenders, whose primary axis of elongation lies along an external vertical axis (2) objects without a canonical orientation, like combs, and (3) letters, which have both a canonical upright position and also a canonical left-right position. More specifically, we are interested in whether orientation is represented relative to an external frame or an object-centered frame. To understand the axes in an object's representational structure, we focus on processing of two types of mirror reflections: (1) object principal axis (OPA) reflections, or reflections across the object's principal (i.e., elongated) axis and (2) extrinsic vertical axis (EVA) reflections, or reflections across a vertical axis outside of the object's axes (i.e. the coordinate y-axis). Data from a 'same-different' task will be analyzed that compares reaction times to judge differences between EVA and OPA reflection. If data patterns suggest that OPA reflections are harder to tell apart, then this would suggest that objects are represented relative to an internal frame, and if EVA reflections are harder to tell apart, then this would suggest objects are represented relative to an external frame. By comparing the results from our three classes of objects, we will be able to understand how orientation influences the representational structure of objects more broadly.

Episodic Retrieval and Metacognition during Problem Solving

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In our daily lives, we draw on our past experiences, or episodic memories, to solve current problems. Previous research shows that brief training in recollecting details of past events helps people to generate relevant steps while solving personal problems. On the other hand, populations with episodic memory deficits (e.g., older adults, hippocampal lesion patients) produce fewer relevant steps when solving everyday problems than controls. The current project focuses on the metacognitive experience of relying on episodic memory during problem solving, a topic that remains relatively unexplored. In two experiments, participants learned four expert tips for plausible, yet rare, "worst case scenarios" (e.g., arrested overseas). Then participants recalled steps for old problems (retrieve condition) and came up with their own steps for new ones (generate condition). Participants also rated how prepared they felt for each scenario. In both experiments, participants provided more relevant steps and felt more prepared in the retrieve condition compared to the generate condition. A third experiment is currently underway, where participants initially learn irrelevant steps instead of useful tips. This study tests whether we have identified a metacognitive illusion, where feeling more prepared for a problem has no rational basis, or whether individuals only feel more prepared after learning high-quality information. Next, we will adapt this paradigm to the scanner to assess underlying neural correlates.

The Development and Neural Indices of Facial Emotion Processing in Early Childhood: A Study in fNIRS

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Elucidating the mechanisms underlying the recognition and processing of emotional expression is an essential area of research in developmental psychology. The Emotion Project is a longitudinal study at Boston Children's Hospital that aims to investigate the nature and neural architecture of emotion processing across the first 7 years of life. Our project uses functional near-infrared spectroscopy (fNIRS) to measure brain activity in response to passive viewing of female faces portraying happy, angry, and fearful expressions of varying intensities, where increased oxyhemoglobin (oxyHb) concentration and decreased deoxyhemoglobin (deoxyHb) concentration correspond to increased local brain activity. For our study, infants (at 5, 7, or 12 months of age, N=807) were recruited and participated in follow-up sessions taking place at 3, 5, and 7 years of age. In order to analyze video recordings of NIRS sessions, we are using SuperCoder to determine whether each block (face blocks as well as our control condition— 4-second periods of moving geometric shapes) should be included in analyses. Coders, blind to emotional condition, record when a child was oriented to the screen; blocks in which the child observed the stimuli for more than 60 of the time that the stimuli were presented will be included. By employing fNIRS, we will be able to illuminate regions of the infant and early childhood brain associated with happy, angry, and fear facial processing throughout the first several years of life. Further, we plan to investigate whether individual differences (as measured by assessing children's temperament, cognitive development, etc.) are associated with differential oxyHb responses to faces. This work has implications for children whose early development was impeded by limited access to the normative range of emotion and children whose basic emotion perception capacities have been impaired. Further, we hope that our results will provide insight into early precursors for the development of psychopathology.

Advance Planning Scope in Child Language Production

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Advance planning scope refers to how far in advance one plans out a sentence before speaking. While there is evidence that adults have a flexible planning scope—that is, they can switch between planning in advance and planning incrementally, before individual words—very little is known about how far in advance children plan. Through two different experiments, we investigate children's planning scope and how it compares to that of adults. The first experiment presented 25 5-year-olds with various pictures. The 5-year-olds were asked to name the pictures (e.g. apple, dog, spaceship), and their speech onset times were measured. The pictures and their names were varied on codability (a measure of name agreement, or how many possible names an object has) and frequency (a measure of how often children hear and produce those names in everyday life). In a parallel study run with adults, it was found that words of low codability or low frequency resulted in slower naming onset times, and we expect to see the same results in children. The second experiment involves showing 5-year-olds two objects (A and B) simultaneously. The participants are asked to construct a sentence in the format "the A is above the B." The effects found in the first experiment will be used in the second experiment to determine how far in advance children plan. For example, if children have slower naming onset times before a word with low codability and low frequency, such as "spaceship," then in a sentence such as "the A is above the spaceship," where they pause will give insight into where they are planning the word. If children show longer sentence onset times, it implies that they are planning the word in advance (before articulation), whereas if they plan incrementally, we should see no effect in sentence onset time.

The Impact of Birth Weight and Asthma on Behavioral Regulation in 14-Year-Old Children

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Among one of the most chronic health conditions in childhood, asthma has been designated a public health concern due to the increase in its prevalence among children and its effects on patients' quality of life. Of the perinatal factors associated with the risk of asthma, low birth weight has been linked to the development of decreased respiratory function, an increased risk of chronic respiratory symptoms and the development of asthma during childhood. While previous studies have shown a correlation between asthma and the prevalence of behavioral problems such as attention deficit hyperactivity disorder (ADHD) among children born at term, little is known about the relationship between the presence of asthma and behavioral development among preterm infants. This study investigates the impact of birth weight and asthma diagnosis on behavioral regulation utilizing the Behavioral Inhibition System and Behavioral Activation System (BIS-BAS) Questionnaire as well as the Vineland Adaptive Behavior Scales. We utilized data from a cohort of extremely low birth weight (ELBW) infants from the Neonatal Intensive Care Unit at Rainbow Babies and Children's Hospital in Cleveland, Ohio, and a matched control group of term-born peers. We compared BIS-BAS and Vineland scores between with birth weight group and by asthma diagnosis. Additionally, we ran regression models on the BIS-BAS domains (BAS- Drive, BAS- Fun Seeking and BAS- Reward Responsiveness). Preliminary analysis suggests that there is a significant association in the BIS-BAS domains with both ELBW and asthma. Additionally, the analysis showed that asthma may mediate the effects of ELBW on BAS- Fun Seeking and BAS-Total scores. We plan on conducting a deeper analysis of the meditative effects of asthma on BIS-BAS domain scores. Future results may have a broader implication in the underlying mechanisms of psychological disorders in ELBW children with chronic respiratory disease in terms of behavioral inhibition and activation systems.

Characterizing Training-Related Neuroplasticity in Developmental Prosopagnosia

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Studies have shown that humans demonstrate the capacity to recognize and discern faces as early as infancy. The ability to identify faces is crucial to several components of human interaction including but not limited to relationship development, emotion perception, threat detection, identity and demographic comprehension, and social intent. Prosopagnosia—often referred to as face-blindness disorder—is a neurological condition that affects one's ability to recognize familiar faces. This disorder renders individuals incapable of recollecting faces they have seen before, resulting in a compensatory reliance on distinctive characteristics such as hair, glasses, clothing, or voice to identify other people. Particular characteristics of prosopagnosia can be observed in autism spectrum disorders as well, which necessitates the unique study of a non-ASD participant pool in avoidance of confounding variables. In this experimental component of a larger study, we recruited 60 participants from 30 to 65 years old as an age-matched control group for the clinical iteration. Participants initially completed an eligibility-screening survey verifying their non-face-blindness followed by a series of computer-based behavioral tasks testing facial recognition, object recognition, and memory. The data collected will be used to provide a baseline metric to then pinpoint the mechanisms underlying face-blindness, analyze the discrepancies between normal recognizers with prosopagnosiacs, and potentially identify super-recognizers—those with an above average ability to recognize faces. This study was crucial to advancing our understanding of normal facial recognition and prosopagnosia by providing data from appropriate age-matched participants, as past literature did not account for aging and cognitive ability in selecting the control group.

An EEG Study Looking at Top-Down Processing in Adults

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In language comprehension, listeners can use information in a top-down manner to make predictions about the structures, sounds, and meanings of the words they are about to hear. This study asks what happens when those predictions are violated. We used EEG to record electrical signals that occur in response to syntactic category violations (e.g. when you hear a determiner where a preposition should be). We reasoned that stronger predictions about upcoming words would lead to faster and/or stronger detection of these violations. To test this, we manipulated the environment in which the violation occurred (high predictability vs. low predictability). We also compared what type of word was violated (i.e. determiners vs. prepositions) to see if word class influenced error detection. This study used a naturalistic listening paradigm, in which participants passively listened to sentences from a children's story with and without violations. In the EEG literature, error detection can be reflected in various neural responses, known as ERP effects. We predicted that we would see an early negative-going effect in the highly predictable environment, suggesting faster recognition of the error. We also predicted a later positive-going response in both conditions, reflecting an overall detection of the violation. Data collection is still ongoing, but at this time, there seems to be equal detection of the error in both high and low conditions. This error detection is not reflected in an early negative-going response but rather an earlier positive-going response (the P300 effect). The most novel finding, so far, is that there seems to be a difference in detecting violations that involve determiners being replaced compared to prepositions being replaced. We will further investigate this finding and determine what it can tell us about the predictions we make in real time and how they differ across word class.

The Neural Basis of Effects of Valanced Imagining on Memory

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People often use their episodic memories—memories of specific past experiences—to share stories and construct opinions. People also imagine events about the future frequently throughout their day. Future simulation and episodic memory exhibit a strong connection, such that future simulation works by recombining past episodic details of different memories, which then allows people to predict future experiences. This connection has been shown to affect reality monitoring, the process of knowing whether something was actually perceived or merely imagined. In a previous study, Devitt and Schacter (2018) examined whether positive or negative emotions in future thinking play a role in reality monitoring by having participants imagine a future scenario going well or poorly. Then they read a story of what hypothetically happened and were tested on their memory of valenced details in the story. Participants were shown to have an optimism bias for stories they imagined going well. They correctly recognized more true positive details, but also misidentified more false positive details when compared to negative details. In the current study, we examined the neural underpinnings of this optimism bias by adding fMRI analysis to the protocol of the aforementioned study. fMRI scans measured participants' brain activity by analyzing blood oxygenation levels during the imagination phase and during the subsequent recognition of story details phase. The first step was to train a classifier program to distinguish between positive and negative imaginations. Preliminary results have shown that positive and negative simulations can be identified based on activation in the ventromedial prefrontal cortex and anterior cingulate, which is consistent with previous research suggesting these areas play a role in positive simulations. This experiment lays the ground for future studies to examine patients suffering from affective disorders, which could lead to treatments targeting networks of brain regions found in this research.

Characterization of 16p11.2 Deletion and Duplication iPSC-Derived Neurons

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The 16p11.2 chromosomal segment has been associated with a number of neurodevelopmental disorders, notably autism spectrum disorders (ASD). A deletion (16p11.2del) or duplication (16p11.2dup) of this region is present in approximately 1% of ASD cases. Disruptions to this region yield dose-dependent symptoms, with 16p11.2del patients exhibiting motor and language delays, intellectual disability, attention-deficit hyperactivity disorder, pervasive developmental disorder, seizures, and macrocephaly. Alternatively, microcephaly and schizophrenia have been observed in 16p11.2dup patients. To understand the cellular mechanisms underlying these variable phenotypes, 16p11.2del and 16p11.2dup-derived induced pluripotent stem cells (iPSCs) were differentiated into neural progenitor cells (NPCs) and neurons for characterization. The soma size, dendrite length, and neurite branches of these neurons will be compared to controls via a Sholl Assay. To confirm the integrity of these cell lines as experimental models, the downregulation or upregulation of seven 16p11.2 genes- TAOK2, MAZ, KCTD13, MAPK3, ALDOA, SPN, SEZ6L2- will be confirmed in 16p11.2del and 16p11.2dup iPSCs, neural progenitor cells (NPCs), and neurons via RT-qPCR. Thus far, we have succeeded in validating the neuronal induction protocol and will continue with the differentiation of 16p11.2del/dup cell lines. Preliminary observations suggest that 16p11.2del/dup iPSCs and NPCs exhibit slower proliferation rates than controls. Quantification with a proliferation assay will substantiate these observations. The successful completion of the proposed project may inform us about the role of neuron morphology and proliferation in the macrocephaly and microcephaly phenotypes that accompany the 16p11.2 deletion and duplication, respectively.

Discovering Early Stem Cell Activation Mechanisms That Promote Long-Term Skeletal Muscle Regeneration

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Many tissues and organs have reserves of stem cells that can regenerate the tissue after injury. Satellite cells, or stem cells specific to skeletal muscle, are activated from their normally quiescent and non-dividing state to proliferate and differentiate into new muscle fibers to repair damage. However, the molecular regulators that promote activation from quiescence are not well characterized. Transcriptome profiling and protein analysis have revealed high expression of the transcription factor Fos in newly activated satellite cells. Fos expressing satellite cells begin dividing and differentiating more quickly than cells that do not express Fos, suggesting that Fos is critical for cell cycle entry and efficient muscle regeneration. Since Fos deletions in satellite cells have already been shown to cause short term delays in muscle repair, as assessed seven days post injury (dpi), we focused on a later time-point of fifty dpi to evaluate the long-term impact of Fos deletion on muscle regenerative potential. We used a Cre-loxP system to inactivate Fos in Pax7+ cells, generating FoscKO mice, and injured the tibialis anterior (TA) muscle of these animals with cardiotoxin (CTX) or freezing. While TA muscle fibers from uninjured control and FoscKO mice showed similar cross sectional areas, regenerated TA muscle fibers at fifty dpi appeared smaller in FoscKO mice when compared to age-matched controls. These differences suggest a potential long-term deficiency in muscle regeneration after deleting Fos in muscle satellite cells. Future work to evaluate Pax7+ staining, which specifically marks satellite cells in skeletal muscle, at fifty days after CTX or Freeze injury will reveal how Fos affects the return of satellite cells to quiescence after activation. Understanding the role of Fos in muscle repair will improve our understanding of myogenesis and satellite cell function, which can be useful for developing better regenerative therapies to enhance muscle regrowth and recovery.

CRISPR Targeted Recovery of Silenced Genetic Circuits in Human ESCs

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Type 1 diabetes is an autoimmune disease caused by an attack on the insulin producing beta cells in the pancreas. Millions of type 1 diabetics currently have to inject themselves with timed insulin doses to control their blood glucose. However, the development of stem cell derived beta cells which can be transplanted into diabetics and restore function has the potential to cure the disease. Currently preventing an immune reaction against the transplanted cells remains an obstacle to realising a regenerative cure for diabetes. To solve this, researchers have used CRISPR to knock out the beta-2-microglobulin (B2M) gene in human embryonic stem (hES) cells, which is required for the expression of cell recognition HLA proteins. Simultaneously, CRISPR has been used to knock in non-classical HLA molecules, and thus evade NK cell mediated lysis of HLA deficient cells. A problem encountered with this approach has been that expression of the transgenes has been silenced during the pancreatic differentiation protocol. We are attempting to recover the expression of the silenced transgenes by targeting a DNA demethylation domain to the promoter driving expression of the transgenes. This involved packaging lentiviral vectors expressing dead Cas9 fused to a DNA demethylation domain, followed by transduction of the previously gene-modified hES and delivery of the promoter specific gRNA. The expression of the transgenes will then be monitored during differentiation using a luciferase reporter assay. The aim of the project is to maintain the transgenes expression throughout the differentiation. The gene edits used to generate hypoimmunogenic beta cells for transplants could be transferred to other tissue types derived from stem cells. These 'universal cells' would be transplantable into any patient — representing a significant development in the field of regenerative medicine.

Exploring the Intersection Between Regeneration and Fibrosis in Axolotls Using *Thrombospondin-1* Mutants and Scar-Inducing Chemical Perturbations

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In the Western world alone, over 100 million patients per year suffer from fibrosis — the thickening and scarring of connective tissue — and its associated pain, discomfort, disability, and increased treatment-related costs. While humans and other mammals may exhibit fibrosis, regenerative organisms such as axolotls generally do not scar. Axolotls are a species of salamander that can regenerate full limbs as well as portions of organs, such as the brain and spinal cord, upon amputation or injury. As vertebrates, they are appealing animals to study in the context of advancing mammalian healing. While the major reason why human surgeries fail is because of scar tissue build-up, axolotls can undergo full amputations, more than once, without the formation of a single scar. To study how axolotls might antagonize fibrosis, we investigated the gene *thrombospondin-1 (tsp-1).* In cultured human dermal fibroblasts, we have evidence that TSP-1 inhibitors promote fibrotic phenotypes; however, studies of tsp-1 in regenerative organisms such as axolotls have been limited. We generated *tsp-1* mutant axolotls using transcription activator-like effector nucleases (TALENs). Upon validation of their *tsp-1* mutational status, forelimb amputations and subsequent blastema removals were performed on these mutants to characterize their regenerative capacities relative to wildtype axolotls. Preliminary results as of four weeks post-blastema removal indicate that, while *tsp-1* mutants retain the ability to regenerate, their rate of regeneration is significantly slower than their wild-type counterparts. This data suggests that tsp-1 plays a role in axolotl regeneration and possibly their capability to antagonize fibrosis. We also used discovery-based approaches to generate a model for fibrosis in axolotls by treating animals with bleomycin. The animals subject to these treatments also exhibited regenerative delays and defects that will be further characterized in the future. Continued investigation of healing in axolotls could lay the foundation for the development of improved treatments for injury in humans.

Developing Functional Immunoprotected hiPSC-β Cells for Type I Diabetes

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The large-scale production of insulin-secreting pancreatic β cells from human induced pluripotent stem cells (hiPSCs) has brought forth the potential of restoring glycemic control in individuals with diabetes via cell replacement therapy. Complications commonly associated with transplantation, including allogeneic responses, as well as the destruction of hiPSC-β cells as a result of autoreactive responses, remain fundamental challenges associated with type I diabetes (T1D). This led our group to the development of immune-modified hiPSC-β cell lines genetically engineered to evade immune attack. Target genes were selected using a mouse CRISPR-loss of function screening strategy and three mutant cell lines were generated based on T1D GWAS association using CRISPR-Cas9. Here we report the effect of the genetic modifications on hiPSC-β differentiation and methods of improving the function of the hiPSC-β. Purified β cells were subject to multiplex gene expression analysis to evaluate the relative expression of genes critical to the identity of the β cell. Upregulation in expression of genes involving β cell identity, maturation, and exocytosis, in comparison to the WT, was found in the Phx 1 KO line whereas the same genes were downregulated in the Phx 2 KO. Notably, there was no difference in relative expression between the WT and Phx 3 KO. To improve the function of the β cells, we developed media conditions that more closely emulate the in vivo environment of the β cell and quantified changes in insulin secretion after glucose-stimulated insulin secretion assays (GSIS). hiPSC-β cells exhibit increased insulin secretion in response to methylsuccinate, a precursor of a key substrate involved in the TCA cycle. This study presents efforts towards the generation of functional, immunoprotected β cells for long-term transplantation therapy eliminating the need for immunosuppression or encapsulation devices.

Using ChIP-Seq and CRISPaint to Provide Insights into Transcriptional Dysregulation in Acute Myeloid Leukemia (AML)

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Acute Myeloid Leukemia (AML) is a cancer of hematopoietic cells with annual incidence of 21,000 in the US, comprising up to 32% of all new leukemia cases. Various transcription factors (TFs) play a key role in the development and differentiation of hematopoietic stem cells into mature progeny and the pathogenesis of AML. Key TFs we have chosen to study are KMT2A, HOXA9, TLX1, and STAT5A. Understanding how these proteins interact with DNA and the binding sites of these DNA-associated proteins helps us to better understand how transcriptional dysregulation in hematopoietic cells leads to AML. Chromatin immunoprecipitation-sequencing (ChIP-seq) uses next generation sequencing analysis to measure the binding sites of TFs at the genomic level. However, many important TFs lack suitable antibodies to perform ChIP-seq experiments. To overcome this limitation, we have begun to undertake a CRISPR editing-based approach (known as CRISPaint) to endogenously tag the TFs with short epitope sequences for which ChIP-grade antibodies have already been developed. This approach will allow us to measure many new binding profiles for various TFs in leukemia cell lines and provide new insights into the transcriptional dysregulation in AML.

Mapping the Single-Cell Transcriptional and Epigenetic Landscape of Cardiomyocytes

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Heart failure is a global pandemic with more than half a million new diagnoses occurring in the United States every year. Systolic heart failure is characterized by cardiomyocyte death, often as a result of myocardial infarction. Only a small population ($\sim$1%) of adult mammalian cardiomyocytes are capable of regeneration, leading to inadequate replacement with mature, functioning cardiomyocytes. The composition of heart cell populations shifts from the majority of cardiomyocytes being mononucleated and diploid to binucleated/multinucleated and polyploid after birth. In this study, we aim to investigate the regulation of multinucleation of cardiomyocytes at the single-cell level. We are currently isolating cardiomyocyte populations based on nucleation through manual sorting and optimizing flow cytometry based methods. We plan to use single-cell RNA-seq and single-cell ATAC-seq to define the transcriptional and epigenetic landscapes of mononucleated, binucleated, and multinucleated cardiomyocytes. We anticipate differences in the upregulation and downregulation of gene expression between mononucleated, binucleated, and multinucleated cardiomyocytes that will provide insight into understanding cardiomyocyte proliferation.

Identifying Compounds that Affect the Survival of Dopaminergic Neurons

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic (DA) neurons from the substantia nigra of the midbrain. This loss of DA neurons results in severe motor deficits, including bradykinesia, resting tremor, and rigidity. The pathogenesis of PD and the associated degeneration of the DA neurons remains largely unknown. There are genetic variants such as GBA, *LRRK2*, and synuclein mutations, as well as several environmental toxins, such as pesticides, associated with increased risk of PD, suggesting that a combination of genetic and environmental factors interact to cause PD. To investigate gene-environment interactions relevant in PD, we first differentiated PD-patient derived induced pluripotent stem cells (iPSCs) into DA neurons using a previously established differentiation protocol. The iPSCs were CRISPR-modified to express a red fluorescent protein in DA neurons, allowing us to track and quantify the neurons. We then treated these DA neurons with compounds with known biological targets to model the effects of environmental toxicants and used live imaging analysis to assess and quantify the effects of these compounds on neuronal survival. The results from this experiment will elucidate whether these specific compounds have a direct protective or deleterious effect on the survival of DA neurons. Additionally, because we know the targets of these compounds, this study may reveal specific biological pathways involved in the protection or degeneration of DA neurons and thus help to identify potential new targets for PD treatment. Next steps in the project will involve investigation of downstream targets in these pathways to determine the precise mechanisms through which the compounds affect the survival of DA neurons.

Sox9 Expression Following Tendon Injury in the Mouse Model

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Tendons play key roles as structural and functional intermediaries in the musculoskeletal system. However, upon injury, mature tendon cells are replaced by structurally and mechanically inferior scar tissue, resulting in undesirable symptoms of tendinopathy. Much remains to be elucidated regarding the molecular mechanisms regulating the activity and presence of endogenous tendon cell populations under both homeostatic conditions and during healing, but previous data has implicated potentially key roles for the genes Sox9 and Axin2 in tendon healing. In this study, we utilize RT-qPCR to analyze expression of key tendon matrix and transcription factor genes and demonstrate that Sox9 is exclusively expressed in injured wild-type (WT) mice (textitMus musculus) tendon, with early upregulated transcripts at 4 days post-injury (DPI) and ending by 30DPI. To further explore the relationship between Sox9 and Axin2, we performed immunohistochemistry (IHC) on tendon sections taken from Axin2CreERt2; Rosa:LSLTdtom (abbreviated Axin2-TdTom) reporter mice, and analyzed colocalization of Tdtom and Sox9 expression. Preliminary results indicate Tdtom cells co-express Sox9 after injury, as measured at 30DPI. Together, our findings suggest that Axin2-lineage cells (Tdtom) turn on Sox9+ after injury and that the Sox9+/Axin2-Tdtom+ co-expressing cells comprise a subset of suspected proliferative tendon progenitor cells, which are necessary for tendon healing. As both Sox9 and Axin2 are involved in Wnt signaling, future research into these genetic relationships in the context of Sox9-expressing tendon cell activity, particularly following tendon injuries, holds great potential for new insights into the mechanisms regulating tendon healing, as well as possible avenues for novel therapeutic approaches.

Physical and Mathematical Sciences

Chemistry
Mathematics
Physics

A Flexible Low-Noise Compact Optical Transport System for Ultracold Molecular Chemistry

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The Ni Group is using ultracold atoms and molecules to explore the coldest chemical reactions in the world (~500nK). One of the crucial steps in these experiments is the transport of ultracold reagents from where they are made in a cooling chamber to the final chemistry chamber, which is about 30cm away. Both chambers have an ultra-high vacuum (UHV) inside and are connected by a tube.

The ultracold atoms and molecules are trapped in the focus of a laser beam, a mechanism called an optical dipole trap (ODT) or optical tweezer. We can move the focus of the ODT to transport reagents. In order to get accurate results, it is important that there is minimal heating and number loss throughout this process. Thus, the transport system needs to be low-noise (no jittering of its position), flexible (easily controlled moving trajectory), and compact (not occupying too much space).

The current setup involves a translation stage system to physically move the particles. However, this takes up significant space and has high building costs. It also has poor efficiency due to the vibration of the translation stage and changes in the focal powers of the lenses caused by the heat generated by the laser beams. My work this summer entailed the design and assembly of a temperature-correcting atomic dipole trap transport system. The optical set-up involves a focus tunable lens whose focal power can be controlled based on the current that is sent into it. As a result, monitoring both the current and temperature on the surface of the tunable lens and implementing it into an active temperature correction routine allows for stabilized control of the atom number and reduced wave-front error and beam aberrations. This set-up is also more robust, since it occupies less space and depends solely on the current being supplied to the tunable lens.

Probing Field Emission Electron Tunneling in Metal-Molecule-Metal Junctions

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The dimensions of electronic components are continuously shrinking such that these structures can now be on a scale of a few nanometers using individual molecules. At this scale, the motions of electrons are defined by the laws of quantum mechanics which involve electron tunneling, an effect that occurs when electrons are able to move through an energy barrier that they are not normally able to overcome. The motion of electrons through these molecules, when sufficiently understood, can allow for individual molecules to serve as electronic devices for data processing applications. Model systems composed of a self-assembled monolayer (SAM) of molecules were grown atop a gold electrode and a top contact of eutectic gallium indium alloy allowing for electrons to flow between the metal-molecule-metal junctions for conductance measurements to understand these electron tunneling mechanisms. We hypothesize that the potential at which the electron transitions from direct to field-emission tunneling is a result of the alignment between molecular orbital energies and the metal Fermi level. Measuring the critical points in conductance of SAM-forming compounds of varying sizes and polarities reveals the relationship between the structure of molecules and the transition energy between molecular energy levels which can be used to create individual molecules capable of data processing.

Kinetic Analysis of Catalyzed C-H Bond Amination

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Direct amination of inert C–H bonds in the absence of external oxidants and directing groups remains a highly desirable organic transformation due to the ubiquity of nitrogen-containing functionalities in common synthetic precursors, natural products, and pharmaceuticals. Herein, we report a trimeric iron complex that upon exposure to azide containing substrates, will catalyze intramolecular nitrene C–H insertion, forming pyrrolidine as the final product. In order to study the reaction mechanism, kinetics experiments were carried out using nuclear magnetic resonance (NMR) spectroscopy. Resting state of the catalyst is the trimer itself determined by NMR features observed during catalysis. A small, primary intermolecular kinetic isotope effect (KIE = 1.62) suggests the H-atom abstraction (HAA) step is the rate determining step (RDS) as well as a non-linear or asymmetric transition state. The reaction rate has first order dependence in both the catalyst and substrate concentrations, suggesting substrate binding before the HAA step. Activation parameters ($\Delta H\neq$, $\Delta S\neq$) of substrates with a range of C–H bond Bond Dissociation Energies (BDEs) are measured using Eyring analysis. Similar large, negative $\Delta S\neq$ (− 24 cal/mol·K) were observed in every case, implying a highly ordered transition state for the rate determining HAA. Enthalpic barrier ($\Delta H\neq$) shows shallow response to substrate C–H bond BDEs, potentially indicating an asymmetrically early transition state where C–H bond cleavage has not yet taken place.

Reaction Kinetics of Interactions Between Butenedial and Ammonium

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This project seeks to determine the factors affecting the kinetics of the reaction between butenedial and ammonium in the droplet and in the bulk to further understand its function as an atmospheric sink for butenedial. Additional studies of the products of this reaction are underway. This project involved synthesizing and purifying butenedial from acetic acid and 2,5-dimethoxy2,5-dihydrofuran, which resulted in a dark yellow oil with a nuclear magnetic resonance (NMR) spectrum distinguishable from the starting materials. The progress of the reaction between 2,5-dimethoxy2,5-dihydrofuran and acetic acid was monitored regularly by quantitative NMR (qNMR). Quantitative NMR refers to the use of NMR to determined the concentrations of chemical species in solution. The following reaction between butenedial and ammonium used ammonium sulfate to deliver ammonium ions. Using 1M diethylmalonic acid as an internal standard, the concentrations of butenedial, ammonium, and expected product 2-pyrrolidinone were measured over time to find the reaction rates. As the rate constant of glyoxal and ammonium depended more on pH than counter ion, examining reactions of ammonium with butenedial will focus on the salt ammonium sulfate and use sulfuric acid solutions to vary the pH of ammonium sulfate solutions between 1-5 pH. Further improvement and development of this project involves identifying the product of the reaction as 2-pyrrolidinone. At the time of this publication, this project was still in the process of determining ideal methods to accurately measure the reaction between butenedial and ammonium. Initial findings showed that the reaction between butenedial and ammonium can be measured with a qNMR assay. Studying the kinetics between butenedial and ammonium provides insight into reactions between ammonium and unsaturated dicarbonyls at atmospheric conditions and the atmospheric sink that ammonium provides to these compounds.

Design and Optimization of Harvard Ozone and Harvard Water Vapor Instruments

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Though much progress has been made over the past few decades in understanding the processes that control stratospheric ozone concentrations and in regulating the anthropogenic compounds responsible for the destruction of stratospheric ozone, the impacts of climate change on ozone column concentrations and its recovery are not well understood. Ozone is crucial for absorbing ultraviolet radiation before it reaches the Earth's surface. In humans, this radiation can lead to a range of adverse health effects including skin cancer. Therefore, understanding the causes of ozone depletion is a major concern. Through the Dynamics and Chemistry of the Summer Stratosphere (DCOTSS) mission, the Anderson Group, along with other research groups around the nation, plans to collect in situ measurements of chemical species with a high-altitude NASA aircraft to understand the impact of deep convective storm systems on the composition of the lower stratosphere. We are developing two of the twelve instruments that will be deployed in the March 2020 mission: Harvard Ozone (HOZ) and Harvard Water Vapor (HWV). HOZ measures ambient ozone concentrations through the absorption of 254 nm radiation by air that is fed into the instrument. The HOZ instrument is being developed from the ground up. We are specifically working on designing the mounting set up and optical configuration for the 254 nm radiation source. We are also analyzing collected data to determine the optimal photodiode detector and testing a new system for data acquisition and control. HWV measures water vapor mixing ratio in situ through two different mechanisms: diode laser direct absorption (HHH) and Lyman-α photo-fragment fluorescence (LyA). For the HWV instrument, we are working on optimizing its performance through calibrations of the HHH instrument as well as through thorough diagnosis and analysis of the fluorescent lamps use in the LyA instrument.

Metal-Organic Phase-Change Materials for Thermal Energy Storage and Management

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Although over 90% of global energy production and consumption generates heat, the development of materials for thermal energy storage has received little attention. Phase-change materials (PCMs) offer the ability to store heat in the energy of phase transitions, facilitating heat storage and transfer with minimal temperature change and no external energy input. Previous research has focused on solid-liquid PCMs, which carry challenges including leakage and phase separation, making them less practical when working with solid-state devices and electronics. Here, we investigate the design, synthesis, and analysis of solid-solid PCMs (ssPCMs), specifically organic-inorganic layered perovskites. These materials have divalent metal cations and halides that form 2D inorganic layers of corner-sharing $[MX_4]^{2-}$ octahedra, and bilayers of organic cations ($R\text{-}NH_3^+$) that are incorporated between the sheets to create the crystalline structure $(R\text{-}NH_3)_2MX_4$. Because the chains are constrained, the material itself remains solid even when the chains "melt," allowing for reversible solid-solid order-disorder transitions. We designed new perovskites with various functional groups to manipulate the thermodynamics and kinetics of these transitions. Synthesis began with simple alkylamines: octylamine, nonylamine, and decylamine. These ligands were then modified with hydroxyl addition or oxygen substitution to observe how additional inter and intra-chain interactions affect transition behavior. Consistent with previous literature, longer chains exhibited higher enthalpies and transition temperatures. Preliminary results also indicated that greater inter-chain H-bonding increased transition temperature, enthalpy, and entropy, while increasing intra-chain flexibility appeared to lower transition temperature through entropic effects. Ongoing experiments attempt to investigate the effects of modified chain lengths and the incorporation of both alcohol and ether functional groups on one ligand. Future research on ligand modifications will further connect structural and chemical features with their impact on the thermodynamic and kinetic properties of phase transitions, enabling improved tunability of ssPCMs and guiding the design of better thermal management technologies.

An Efficient Point-Counting Algorithm for Trinomial Superelliptic Curves

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Our paper is about the following question: given a fixed prime p and polynomial $f(x, y)$, how many pairs (x, y) are there such that $f(x, y)$ is a multiple of p? The difficulty and importance of computing the number of solutions to polynomial equations is well-known to mathematicians. For instance, Andrew Wiles awed mathematicians and sparked the public imagination when he proved Fermat's Last Theorem. Wiles settled this centuries-old conjecture by showing that the equation $a^n + b^n = c^n$ for $n > 2$, has no positive integral solutions. These ideas are prevalent in numerous subfields of mathematics, and also have important practical applications to other fields of science and engineering. Elliptic curve cryptography requires equations of the form $y^2 = x^3 + ax + b$ with special prescribed numbers of points. Moreover, much of computer security rests on our ability to find such equations with appropriate numbers of solutions; such polynomials can be used to make Goppa codes, which are among the best known error-correcting codes.

A polynomial equation in x and y defines a curve in the plane; solutions to such an equation are called points, which lie on the curve. In general, there are no simple methods to find the number of points. For special families of curves, however, we can do better. In particular, we employ the Hasse-Weil bounds in conjunction with efficient computation of the Hasse-Witt matrix modulo a prime to develop what we believe is the fastest known algorithm for computing the number of points on a trinomial superelliptic curve — a curve defined by the equation $y^a = mx^b + nx^c$. Our algorithm is also quite practical. For instance, while a brute-force algorithm that computes the number of solutions to the equation $y^4 = x^{11} + x^8$ modulo 10133 takes over six hours to run, our program computes the number of solutions to the same equation modulo 56481966994673551244454355 6507 in only 66.2 ms.

Finding Euler Characteristics of Hilbert Schemes using Colored Young Diagrams

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The Hilbert schemes of the singular space and of the orbifold are two structures that contain geometric data about group actions on a polynomial ring. Our goal is to understand this geometry by finding the Euler Characteristics of these spaces. The problem is equivalent to counting Young diagrams that are based on the group action. For the singular case, we count all zero generated Young diagrams that contain a certain number of 0 colored squares, and we prove a theorem greatly reducing the problem, sometimes into already solved cases. For the Hilbert scheme of the orbifold, we count all Young diagrams with a given coloring, and we develop a procedure to obtain the desired generating function, as well as closed form generating functions for special cases. We also explore the method of vertex operator algebras.

Riemann-Roch Theorem through Sheaf Cohomology with Applications to Elliptic Curves

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One of the most general ideas in higher mathematics is that the structure of abstract objects can be gleaned from functions defined on their subsets. This process can be generalized by defining sheaves, abstract objects endowed with properties similar to more concrete functions. The study of sheaves has become ubiquitous in modern algebraic geometry in particular because it provides an elegant framework for defining geometric objects and their properties. A beautiful central result of this field is the Riemann-Roch theorem, which lies at the intersection of algebraic geometry, differential geometry, and complex analysis. The earlier study of the subject that relied on analytic properties of manifolds does not generalize naturally to more dimensions and more general fields than the complex numbers; instead, this paper introduces the language of line bundles and sheaf cohomology with an emphasis on Serre duality. Based on these constructions, we will obtain a more general argument that applies to the setting of general fields. This step is necessary to employ the theorem in our study of elliptic curves and demonstrate that their abstract properties are equivalent to more concrete ones because we are often interested in more general, finite fields. Finally, we will generalize this method to demonstrate how abstract curves may be embedded into projective space of appropriate dimension by following a similar process.

The Okounkov-Vershik Approach to the Representation Theory of the Symmetric Group

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In this paper, I will present a description of the Okounkov-Vershik approach to the representation theory of the symmetric groups. In order to create a more natural description of the irreducible representations of the symmetric groups, we will use the properties of a Gelfand-Tsetlin algebra and a Gelfand-Tsetlin basis to decompose the irreducible representations of the nth symmetric group into a direct sum of one dimensional trivial representations. We can use the property that the Young basis (or Gelfand-Tsetlin basis) is an eigenbasis for the Gelfand-Tsetlin algebra. These eigenvalues allow us to define the spectrum, composed of the weights of each basis vector of every irreducible representation for a particular n, allowing us to define an equivalence relation by identifying vectors from the same representation. We get the action of the symmetric group on these spaces from the natural action of the Coxeter generators on these weights, as this set of weights is in bijection with the basis for the irreducible representations. We then can show that this spectrum is in bijection with the content vectors of Young Tableau with a similar equivalence relation, this one given by identifying Tableau with the same shape. This relation allows us to more easily calculate quantities associated with these representations, especially the dimensions of the irreducible representations and character relations.

Galois Groups of Plane Curves

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Given a polynomial with coefficients in a field K, we want to know if it is solvable by radicals, that is if its solutions can be expressed using only operations of addition, subtraction, multiplication, division, and extraction of roots of elements of K. Galois Theory assigns to each such polynomial a group — the Galois group; then the initial polynomial is solvable by radicals if and only if its Galois group is a solvable group, which is a property that is usually easier to study. Algebraic geometry is a branch of mathematics that studies the geometric properties of the zeros of polynomials. Our goal is to use Galois Theory to better understand the geometric properties of plane curves, a central object in algebraic geometry. Looking at a smooth complex plane curve C determined by the degree d homogeneous polynomial f, we are interested in finding its flexes — the points on the curve at which the tangent lines have an intersection multiplicity strictly greater than 2. It can be shown (using the Hessian determinant for example) that the number of these flexes, counting multiplicities, is 3d(d-2). A much more interesting problem is, however, determining if the coordinates of these flexes can be expressed in the coefficients of f. We approach this problem by looking at the field of rational functions in the coefficients of f and adjoining the coordinates of the flexes. The Galois group of this obtained field extension is solvable when it is possible to use the coordinates of f to express the flexes. However, this Galois group turns out to be the symmetric group, which is not solvable, implying that a general explicit solution for the coordinates of the flexes does not exist.

Representations of the Symmetric Group via Combinatorial Species

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The representation theory of the symmetric group has been very well-studied in the past century or so; in particular, the irreducible representations are completely known and classically described by the theory of Young symmetrizers and Young tableaux. We attempt to give yet another characterization of the irreducibles using the theory of combinatorial species.

Coulomb Drag in a Carbon Nanotube-Graphene Interface

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When two electrically conductive low-dimensional materials are separated by a dielectric layer, scattering occurs between charge carriers in the two materials. This phenomenon, known as Coulomb drag, has been known as a probe of electron-electron interactions for years, but recent advances in the nanofabrication of graphene-boron nitride heterostructures have unlocked new regimes of drag studies. The Dirac cone band structure of graphene facilitates a continuous tuning of carrier density between electrons and holes, and the position of the graphene Fermi energy allows investigation of drag in the Fermi liquid domain. We are studying Coulomb drag in a carbon nanotube-graphene interface, which differs from previous work due to the system's reduced dimensionality and variation in bandgap with nanotube type. Study begins with assembly of the nanodevices. Graphene and boron nitride are mechanically exfoliated on a silicon dioxide substrate and characterized via atomic force microscopy. Flakes are then assembled into Van der Waals heterostructures, and a carbon nanotube grown by chemical vapor deposition is integrated into the stack. The heterostructure is shaped into a Hall bar via reactive ion etching, and electrical contacts are established through electron-beam lithography and thermal evaporation. Measurements thus far have evidenced some unexpected results. These include the inaccuracy of a momentum drag description at the graphene charge neutrality point and a linear rather than quadratic dependence on temperature. Future work will investigate these effects further through the construction of devices with dual gate dependence, varying geometries, and greater variety of carbon nanotube bandgaps.

Development of Superconducting Materials

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Although high-temperature superconductors have been studied for over 30 years, their mechanisms remain poorly understood. More recently, flat band quantum systems have presented a path to better understanding the electron-electron interactions characteristic of high-temperature cuprate superconductors. However, flat band quantum materials are difficult, expensive, and timely to fabricate. An attractive classical analogue is provided by metamaterials, which are designed to exhibit unique properties due to their composite structure rather than the nature of their individual components. Specifically, phononic metamaterials can be produced relatively quickly and inexpensively, and their mechanisms are reasonably well-understood. By measuring both the amplitude and the phase shift of sound waves in the metamaterial, its behavior can be accurately visualized in both real and reciprocal spaces, which is not currently possible for quantum materials. Here, we present the design for a phononic metamaterial capable of realizing a gapped flat band. We have fabricated the metamaterial macroscopically and confirmed its ability to slow down and ultimately localize sound. Our results provide a clear pathway to fabricating an electronic material capable of localizing electrons via gapped flat bands, and have potential applications in furthering our understanding of quantum materials, specifically Mott Insulators.

Unsupervised Learning Topological Phases in an XY-Z2 Gauge Model

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An understanding of the mechanisms behind phase transitions is important to the study of condensed matter physics. Phase transitions can often be characterized within the Landau framework, in which a local order parameter will indicate that a symmetry in the Hamiltonian is broken and the system enters a new phase, making such phase transitions straightforward to identify. Exotic materials of recent interest, such as superconductors, do not obey this description. Their phases can instead be understood in terms of the presence or absence of topological defects. The success of supervised machine learning methods at constructing the phase diagrams for such systems has been demonstrated; however, these approaches require manual feature-engineering. The recent success of applying an unsupervised diffusion map to the 2D XY model and the Ising gauge theory shows the promise of unsupervised methods for learning topological phases. The goal of this project is to use this technique to learn the phase diagram of a 3D XY model coupled to an Ising gauge field. Integrating out the Ising degrees of freedom generates an effective theory that may be efficiently simulated. The diffusion map will be applied to samples generated from the effective model via Monte Carlo simulations, after which a local clustering algorithm will be applied to the resulting reduced feature space to finally classify the phases. If successful, this approach will represent another avenue for probing exotic systems with unknown phases that may one day lead to new and useful materials.

Stable Phase Coherent Narrow Linewidth Two-Laser System for Rydberg Molecule Excitation

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Chemical reactions depend probabilistically on the energy, orientation, type, and quantity of reactants interacting. Typically, scientists have studied chemical reactions on the macroscopic scale by grossly altering the characteristics of the reactants involved. Advances in ultracold molecules have provided the ability to study chemical reactions at ultracold temperatures (1μK), which decreases thermal averaging effects thereby revealing the effects of quantum mechanics on chemical reactions. The next step in developing these ultracold chemistry techniques is to increase our experimental control over the spatial orientation of the specific molecules we are investigating. We aim to achieve this through the creation of KRb-Rb* polyatomic Rydberg molecules which, due to their unique electronic structure and exceptionally large dipole moments, can be easily oriented and aligned in the lab frame using small, easily controllable electric fields. I have worked onDuring the summer, I have worked on my project is to creating the narrow linewidth, frequency stabilized, phase coherent two laser system necessary to generate KRb-Rb* Rydberg molecules. Rydberg molecules can only be created through the absorption of photons of specific wavelength. Therefore, keeping our lasers at the correct wavelength is of the utmost technical importance. More specifically, I will use an electromagnetically induced transparency (EIT) locking scheme in a Rb vapor cell to phase lock a 1014.6 nm laser to a stabilized 420 nm laser. Using this system, we hope to first observe the formation of KRb-Rb* polyatomic Rydberg molecules, measure their dipole moments, and then attempt to control their orientation.

On the Universal Relaxation Bound for Higher Dimensional Charged Black Holes and the Weak Gravity Conjecture

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The Weak Gravity Conjecture (WGC) roughly states that in any self-consistent theory of nature, gravity must be weaker than all other forces. In particular, for a U(1) gauge theory (a theory describing electromagnetism) coupled to gravity, the WGC implies the existence of a particle whose mass is smaller than its charge in natural units. A recent line of reasoning which aims to prove the WGC suggests and requires a connection between the Bekenstein–Hawking temperature of a black hole and the imaginary part of its fundamental quasinormal mode frequency, $\mathrm{Im}(\omega_0) \leq \pi T_{BH}$. It has been verified that this bound is satisfied for a near-extremal Reissner–Nordström black hole – a charged black hole whose electromagnetic charge is almost equal to its mass in natural units – as well as for a Kerr (rotating, uncharged) black hole in $D = 3+1$ spacetime dimensions. In our research, we investigated this connection for higher dimensional extremal and non-extremal Reissner–Nordström black holes as well as dilaton black holes. We found that for higher dimensional near-extremal Reissner–Nordström black holes, the bound can be proved analytically as in the $D = 3+1$ case, and we used a generalized version of the Bender–Wu technique to investigate the bound numerically in the general case.

Interface Superconductivity Between Underdoped and Overdoped $La_{2-x}Sr_xCuO_4$

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A superconductor is a material that, when cooled below a critical temperature T_c, drops to zero electrical resistance and expels magnetic flux. The lossless flow of current and the high, stable magnetic fields permitted by superconductor technology have led to advances in fields ranging from power transmission to medical imaging. However, the low T_c of superconductors—often below 20 K—has limited their commercial applicability. Previous work has demonstrated high-T_c superconductivity at interfaces between non-superconducting materials, such as between underdoped and overdoped $La_{2-x}Sr_xCuO_4$. Here, we examine the interface superconductivity between underdoped and overdoped $La_{2-x}Sr_xCuO_4$. We prepare heterostructures of $La_{2-x}Sr_xCuO_4$ with layer-by-layer growth using molecular beam epitaxy (MBE). We use x-ray diffraction (XRD) and atomic force microscopy (AFM) to assess the quality of the samples ex-situ. We then perform resistance measurements on the samples to observe the superconducting transition and determine whether the interface superconductivity between underdoped and overdoped $La_{2-x}Sr_xCuO_4$ occurs at significantly enhanced T_c. To investigate the possible mechanisms that give rise to superconductivity at the interface between underdoped and overdoped $La_{2-x}Sr_xCuO_4$, we use scanning tunneling microscopy/scanning tunneling spectroscopy (STM/STS) to assess the local topographic and electronic properties of the heterostructures. We also employ cross-sectional transmission electron microscopy (TEM) to characterize the structural properties of the interface and electron energy loss spectroscopy (EELS) to probe the Cu oxidation state throughout the sample. Analyzing and understanding the presence of high-T_c interface superconductivity in the $La_{2-x}Sr_xCuO_4$ family can serve to ease the restrictions placed superconductor technology by T_c.

Investigation of Lithium Morphology Effect on Lithium Metal Batteries and In-Situ Measurement of Solid-State Batteries

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Though there have been numerous advancements in the generation of renewable energy, the sources for renewable energy tend to be non-persistent, necessitating the use of an energy storage device. Li-ion batteries have been the standard with respect to mobile energy storage; however, the demand for energy is growing, and Li-ion batteries have been optimized to the degree that further improvements are difficult. Beyond-Li-ion batteries, such as lithium metal batteries and solid-state batteries, are thus important to the future of mobile energy storage. Li metal batteries are attractive due to Li metal's high specific capacity (3860 mAh/g) and low voltage with respect to the standard hydrogen electrode (-3.04 V). However, the application of Li metal batteries has been impeded by safety issues when using flammable liquid electrolyte, as well as a tendency to form Li dendrites that short-circuit the cell. We developed a method to coat any non-conductive substrate with copper and showed that this method can be used to create porous current collectors that minimize dendrite formation in lithium metal batteries. In particular, we investigated the relationship between Li metal morphology and cycling performance in our 3D copper cells. Solid-state batteries are considered to be the future generation of batteries due to the nonflammability of solid electrolytes and their potential to suppress lithium dendrite growth for the application of lithium metal anodes. However, some fundamental problems related to the Li metal battery remain unsolved due to a lack of sophisticated characterization techniques. We established an in situ test setup to measure changes in internal pressure of solid-state battery using a pressure sensor and off the shelf electrical components to better understand the mechanical conditions of the various battery components during cycling. The above studies will enable a better understanding of advanced, beyond-Li-ion batteries for their future applications.

Probing Dark Matter Substructures via Strong Gravitational Lensing

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In the Lambda-CDM standard model of cosmology, dark matter accounts for 27% of the mass-energy density in the universe. Nonetheless, the particle nature of dark matter remains mostly unknown. While dark matter does not interact via electromagnetism, it does interact gravitationally, so it can be detected using gravitational lensing. I am focused on strong galaxy-galaxy lensing, which is the lensing of the light from a background galaxy by the gravity of a foreground galaxy, producing multiple images and/or Einstein rings. According to current theories, dark matter forms halos around galaxies, and smaller clumps of dark matter within the halo form subhalos. When a subhalo appears to be close to the Einstein ring, its gravity is able to produce flux ratio anomalies and time-delays, which we can then detect using telescopes, allowing us to infer the presence of a subhalo. The subhalos detected so far are in the mass range of $10^7 - 10^{12} M_{\text{sun}}$, which is sufficiently small that predictions of various proposed theories of the particle nature of dark matter deviate from one another, allowing us to gain insight into how dark matter behaves. One of the challenges with this method is the uncertainty in the mass measurement of the subhalos, and to this end I have compiled a list of all the possible sources of uncertainty mentioned in the literature to better understand the limitations we face. Another challenge in constraining the properties of dark matter is the relatively small number of lensing systems that have been analyzed in search of subhalos. So far, I have identified lensing systems in 21 images from the BELLS survey and prepared over 380 pictures of strong gravitational lensing systems from the SLACS survey for future analysis, which will hopefully shed light on the many questions surrounding dark matter.

Combining Cold Buffer Gas Beam and Magneto-Optical Trap Techniques to Achieve a Fast and Dense Trap of Potassium Atoms

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The ability to generate ultracold gases of atoms or molecules provides unique opportunities to study quantum phenomena, ranging from simulating complex quantum systems to processing quantum information. In order to create and study such ultracold ensembles, the atoms or molecules must first undergo cooling and trapping stages. Two established experimental methods, the cryogenic buffer gas beam (CBGB) and the magneto-optical trap (MOT), are used in the Doyle lab. My project has been focusing on combining the two methods to develop a novel hybrid approach to cool and trap potassium atoms with a fast duty cycle. The project will improve the speed of the experiment by up to three orders of magnitude which would be of critical importance for future experiments. Moreover, we will focus on maximizing the density of the trapped atoms which would provide a novel mechanism for loading more sophisticated molecular traps.

We follow a multi-step method to laser cool the potassium atoms. Potassium (K) is initially produced by laser ablation of a solid metal target in the presence of cold helium gas at high density. This helium gas reduces the temperature of the K atoms to about one Kelvin. The cold atoms are then extracted into an atomic beam, and are cooled down even further using laser slowing techniques. The atoms are then trapped in a MOT which includes coils of wire producing a magnetic field. By carefully designing and positioning magnetic field and lasers, we are able to control the K atoms such that they are always pushed back towards the origin of the magnetic field. This provides an effective trapping force. A similar trick can be played by the laser light to ensure cooling. The MOT thereby provides simultaneous cooling and trapping forces.

Controlling Branched Flow in Random Scattering Media

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Branched flow is a wave phenomenon wherein intricate, stable branching patterns emerge from waves propagating over weak random scattering potentials. Branched flow exists in many disparate physical systems and on length scales ranging from nanometers to hundreds of kilometers. It has been shown that with sufficient manipulation of an incoming wavefront, wave propagation over a random potential can be restricted to just a single branch. This results in a stable path along which wave packets can be consistently transmitted through complicated random media. While previous researchers have used transmission data to comb through the Hilbert space for eigenstates characteristic of single-branch transmission, researchers at the Heller Group are working to reformulate this fine control in terms of complex phase and the evolution of the wavefront's manifold in phase space. They have employed the split operator method powered by a parallelized version of the fast fourier transform algorithm to quickly and accurately simulate wave evolution, and are working to recreate and refine methods for branch control. Due to the prevalence of the branched flow phenomenon, precise control of wave propagation in random media will have wide-spread implications in the fields of solid state physics, oceanography, and quantum transport.

A Search for Planets Orbiting the Star Vega

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Vega is one of the brightest stars in the sky, making it one of the most well studied. However, one question that has gone unanswered is whether or not this star hosts a planet. Previous attempts to answer this question through direct imaging surveys have ruled out objects as small as 6 Jupiter masses at wide separations, but objects orbiting closer to Vega are beyond the sensitivity of these observations. Radial velocities, however, may reveal the gravitational influence of a planet on the star, providing greater sensitivity to objects on close-in orbits. We have gathered spectra of Vega over the last decade using the Tillinghast Reflector Echelle Spectrograph from which we derive radial velocities and search for planets. In our analysis, we are unable to find sufficient evidence of a planet around Vega. However, by calculating the upper limits to the sensitivity of our data, we place new constraints on a possible object. We rule out planets as small as 2 Jupiter masses at .5 AU, and while our sensitivity falls off at wide separations, we still exclude companions more massive than 30 Jupiter masses at 6 AU. Combining our data with earlier studies, we extend this limit to 30 Jupiter masses for all separations around the star. We also find evidence of stellar activity in our data, and through further analysis, expect to document star spots on the surface of Vega. Relatively little is known about the formation of star spots on hot stars like Vega; the time spanned by our data provides a good opportunity to observe the evolution of these features and understand the mechanisms behind them.

Quasiparticle Interference in the Fractional Quantum Hall Regime of Graphene

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Traditional quantum mechanics classifies all elementary particles as fermions or bosons, which have exchange statistics of +1 or -1 or, equivalently, phase shifts of integer multiples of pi in the many-body wavefunction upon exchanging a pair of particles. In the fractional quantum hall regime (FQHE) where strong magnetic fields are applied to two dimensional systems of strongly interacting electrons, more general types of particles with quantum exchange statistics, called anyons, are expected to be found as quasiparticles. Anyon exchange statistics have more diverse phase shifts corresponding to the fractional resistivities of FQHE. Anyons are classified as abelian (commutative under exchange) and non-abelian (non-commutative under exchange). Non-abelian anyons also have non-degenerate ground states with significant energy gaps between those and the excited states, creating a discontinuous phase jump during particle exchanges as the wavefunction becomes a distinct combination of eigenstates. Previously, there have been attempts to measure exchange statistics for some abelian anyons in Gallium Arsenide, though results remain inconclusive. Graphene, a single atomic sheet of graphite, can provide more stable quasiparticles during exchanges owing to its large energy gaps in FQHE phases.

In this experiment, we investigate the exchange statistics of particles in the fractional quantum Hall regime of graphene. We created graphene heterostructures—vertical stacks of graphite, hexagonal boron nitride, and graphene—that maximize electron mobility and allow us to adjust the electron density using graphite gates. Currently, we are fabricating Fabry-Pérot interferometers to measure the phase shift interference.

Measuring fundamental, defining characteristics of unfamiliar quasiparticles is significant for the advancement of condensed matter physics and for its applications to topological quantum computation.

Causal Features of Black Hole Horizons

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General Relativity is the theory describing gravitation. It does so via the Einstein field equation which expresses how matter and energy influence the curvature of space-time — which is none other than the gravitational field itself — and vice versa. Mathematically we can generally view space-time as a 4-dimensional connected manifold M with a smooth Lorentzian metric, which intuitively means that it might exhibit curvature globally but it has to look flat locally, and that we have a notion, via the metric tensor, of how to compute space-time ”distances” between points in M. Furthermore M must be time-oriented, which means that at each point, we want to have a well-defined notion of the direction of time. Then the mathematical formalism of General Relativity will be differential geometry and topology, which can quantitatively express concepts such as curvature and relate them to the evolution of a physical system. In particular, solutions to the field equation for some physical systems are metrics that can exhibit singularities, which are roughly points of infinite curvature and are usually hidden behind an event horizon, i.e. a hyper-surface that causally separates a region around the singularity from the rest of space-time. This means that no causal signal (including light) can escape from the region given by the event horizon and its interior, thus its name, ”black hole.” Here I investigated the causal properties of these objects, which are reflected, for example, in the behavior of bodies on geodesics (straight lines in curved space) infalling towards the black hole. Additionally, a good way of studying the causal structure of black holes is through their conformal diagrams, which are compactifications of the space-time region of interest that nevertheless preserve causal relations between its points. Unfortunately the construction of such diagrams can be mathematically arduous.

Prospects for CNO Neutrino Detection in NEXT Detector

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Carbon-Nitrogen-Oxygen (CNO) neutrinos are generated within the solar core as a byproduct of the CNO cycle, one of the two fusion reactions that produce helium in the Sun. Whilst all other components of the solar neutrino spectrum have been measured experimentally, the CNO neutrino flux has not, primarily because they are low energy neutrinos, and current solar models predict that their flux is also relatively low. A precise measurement of the CNO neutrino flux is crucial for addressing the solar metallicity problem, which is that two distinct theoretical models for the metallic composition of the solar core currently exist. Though its primary purpose is to detect neutrinoless double beta decay, the NEXT neutrino detector (a high-pressure gaseous xenon time-projection chamber) may also be able to measure the CNO neutrino flux. The aim of this investigation is therefore to determine whether or not this is possible. To calculate the expected number of CNO neutrino events in NEXT, theoretical data for CNO neutrino flux from the standard solar model was used in conjunction with calculations regarding the neutrino survival probabilities, their cross sections and the number of targets in the detector. Including the entire energy spectrum of the CNO neutrinos and excluding backgrounds from within the detector and from other solar neutrinos, approximately 16 CNO neutrino events would be expected per year for a NEXT detector at the 1-ton scale. Similar calculations were carried out for the other components of the solar neutrino spectrum, and with these included, it seems that a measurement of the CNO neutrino flux will not be possible with the 1-ton NEXT detector, however additional analysis is underway using the simulation software GEANT-4. Further investigation is required to determine the required scale of a future model of NEXT that could successfully make this measurement.

Characterizing the External Magnetic Field of Jupiter

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Earth Sciences, 2020

Earth and Planetary Sciences Department
Bloxham Group
Advisor: Jeremy Bloxham

Understanding the physical origin of Jupiter's magnetic field provides important physical constraints on the internal structure of Jupiter, which offers insights into the evolution and formation of gas giants and the solar system. This work has important implications for assessing the habitability of exoplanets, and our own planet, in terms of magnetic shielding from solar radiation. However, Jupiter's magnetic field is complicated by the fact that it consists of both an internal field generated within the planet by the dynamo (flow of liquid metallic hydrogen), and an external field generated by electrical currents surrounding Jupiter. The NASA Juno Mission, in a 53-day polar orbit about Jupiter since 2016 is currently providing high resolution measurements of Jupiter's magnetic field. In addition to confirming the dipolar nature of the internal field (though revealing large non-dipolar fields in the northern hemisphere), this data has revealed the presence of an external field of previously unknown origin. In this study, we use new data from Juno to investigate the cause and location of this anomalous external field signal. An inversion of the full vector magnetic field was conducted to determine the location of this anomalous signal. The external component of the magnetic field was compared to the known electrical current systems in Jupiter's magnetosphere, such as the magnetodisc (a region of charged particles and plasma near the magnetic equatorial plane), using numerical modeling. Preliminary analysis suggests that this approach can be combined with other methods to constrain the physical parameters of the magnetodisc, and identify electrical current systems in planetary magnetospheres which were previously unexplained by theoretical models.

Micro-Lens Fabrication for Nitrogen Vacancy Center Study

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Physics and Mathematics, 2021

Center for Nanoscale Systems
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Advisor: Melissa Franklin

Nitrogen vacancy (NV) centers in diamond are exploited for their nanoscale magnetic spins that align with an external magnetic field to produce a measurable optical response via magnetic spin resonance. Given the nanometer scales of these NV centers and the corresponding observations, it is difficult to acquire high resolution and low noise measurements. The fabrication of efficient microlenses can increase photon count from NV centers, leading to magnetization measurements that are quicker, more precise, and more easily reproduced. In this study, various chemical and physical methods of nanostructure fabrication was explored to optimize the functionality of diamond lenses as optical waveguides for resonant fluorescent responses from NV centers. Traditional photolithography and etching tools were used to create diamond pillars from computer-aided designs before using thermal reflow techniques to melt them into hemispherical surfaces that functioned as lenses. After characterizing root mean squre roughness of the lens surfaces, the structures can be used in other research dealing with small scale optics, with potential commercial applications in high-resolution metrology, biological imaging, and quantum information science.

Functional Modifications of a Cryogenic Dipstick Setup for Electronic Measurement of Oxide Thin Films

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Research in the Mundy Group focuses on designing and fabricating oxide thin films and probing these novel materials for exotic properties, which include superconductivity and topological insulator states. Electrical transport measurements are arguably the most useful phenomenological characterization of such films for potential electronics application, so it is important that these measurements are efficient, accurate, and precise. Previously, samples were measured in a liquid helium dewar and dipstick setup, attached by four probe tips to a copper stage for quick resistance versus temperature feedback. Such setups, however, generally introduce substantial measurement noise from sources such as mechanical vibrations, temperature instabilities, and probe-to-sample contact noise. I will discuss the functional improvements I have made to the dipstick setup. These include an upgraded sample stage with improved mechanical stability, thermal contact, and electrical shielding, all under a new modular design to accommodate future functionalities. I will also discuss systematic experiments to identify the best method to minimize contact resistance between the probe tips and the sample, a long-standing challenge in oxide thin film measurements. The current solution involves the thermal evaporation of gold contacts which is time-consuming and expensive. To develop an alternative method that minimizes noise, I tested a number of silver paints under various controlled conditions and showed that the combination of ozone cleaning and EMS #12686-15 silver paint produces the least noisy data, comparable to gold, across multiple different samples with varying electronic behavior. Given these results, we will likely replace gold-contact deposition with the aforedescribed method, enabling us to make electrical measurements efficiently without loss of precision.

Social Sciences and Humanities

African and African American Studies
Art History
Economics
Government
Sociology
Philosophy
Studies of Women, Gender, and Sexuality

Visualizing the Emergence and Evolution of African and African American Studies at Harvard

Sydney Lewis
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African and African American Studies and History of Science, 2022

Graduate School of Design
Metalab
Advisors: Matthew Battles, Jeffrey Schnapp

Fall 2019 marks the semicentennial of the establishment of the African and African American Studies department at Harvard College. In the fifty years since, the department's curriculum, its methodologies, even its name, have changed in response to shifting socio-cultural forces, academic perspectives, and student interests. As the culmination of my research, I aim to construct an interactive, multimedia data visualization which will communicate side by side the process of curricular change at institutions of higher learning and the often abstract, complex forces which drive it. By tracking the emergence of certain terms, methodologies, and courses in the African and African American studies department using quantitative data, longitudinal shifts and patterns unfold. To comprehend the reasons for this evolution and begin to answer questions about what has informed Harvard's curriculum over time, preserved archival media were drawn upon, including newspaper articles, photos, books, course catalogues, statements, reports, and publications from before, during, and after the formation of the department. The existing conversation surrounding African and African American studies will be further enriched by soliciting the first-person testimony of alumni and faculty who contributed to this transformational time in Harvard's history. In using curricular evolution as a lens through which to view decades of struggle for equity, voice, and access, the visualization will present the curriculum as more than merely pedagogical and contribute to an understanding of the factors which drive curricular change. From African American studies in particular, given its interdisciplinary leanings and initial experimental nature, we stand to gain knowledge about how emergent fields form, evolve, and manifest in the curriculum at large. Taking these factors into account, my visualization will reflect upon Harvard's curriculum not as an incidental list of courses, but as a social phenomenon which responds to and reflects broader forces, values, and movements.

When Phoebe Met Phibba: The Imprint of Classical Antiquity on Black Culture in America

Serena Shah
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Classics and African and African American Studies, 2021

Classics Department
African and African American Studies Department
Advisors: Henry Louis Gates Jr., Paul Komsii, Michele Valerie Ronnick

This study originated with the pinpointing of a contemporary onomastic phenomenon that highlights the relationship between present-day black America and the ancient Roman world. Using the remarkably high frequency of classical first names (e.g. Julius, Marcus, Virgil, Evander, Lucretia, Octavia, Festus, Darius) among current African American populations as a point of inspiration, its goal is to trace the affinities of contemporary black culture to the world of ancient Rome. My research this summer, in particular, focuses on the use of classical slave names in the antebellum South. By concentrating on the records for the single plantation of South Carolina slaveowner James Henry Hammond, the case study attempts to craft a composite picture of what classical slave-naming practices might have looked like in the early nineteenth century Southern United States, and what the use of classical names would have meant for both master and slave. The cultural distortions that resulted from these unbalanced interactions form just one aspect of the broader project's focus, however, which encompasses the wider implications of classical antiquity on African American culture over the last three hundred years. I attempt to approach the discipline of black classicism from a historical-anthropological rather than literary lens, examining the ways in which classical culture has been passively received before being actively wielded by black figures throughout American history.

Academic and Public Programming at the Harvard Art Museums

Paul Tamburro
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Anthropology, 2021

Harvard Art Museums
Advisors: David Odo, Jennifer Thum

Roman sarcophagi often depict an Amazonomachy, or battle between Greeks and Amazons. These sarcophagi typically feature type-cast characters based on Greek prototypes and may feature one of several Amazon myths. However, despite extensive scholarship on Amazonomachies, the Harvard Art Museums' "Sarcophagus Sections with Men Fighting Amazons," which date to approximately 230 AD, have not been definitively linked to a specific myth. In order to better understand the development of the Amazonomachy genre and identify the myth represented on the Harvard sarcophagus, I surveyed secondary scholarship, consulted curatorial files, and evaluated pieces in other museums. The layout and arrangement of figures on Harvard's sarcophagus suggests that it was partially modeled on the fifth century BC shield of Athena Parthenos, which was created by the Greek sculptor Phidias. This lost artwork depicted the hero Theseus defending Athens from Amazons and was a symbol of Athenian prosperity during the Classical Period. The Harvard sarcophagus likely represents a later Roman adaptation of this politically charged myth, which reveals the ways in which Romans constructed political identities, integrated regional symbols, and interacted with broader economic systems through funerary art. This research also implies that further studies of sarcophagi may be useful to reconstructions of the Parthenon shield.

This information will be presented in both an interactive, half hour gallery talk and a larger tour that explores different historical perceptions of glory. Additionally, researchers are drafting a report for the 2019 Student Museum Conference that will discuss current issues in museums and serve as a resource for participating institutions.

Academic and Public Programming at the Harvard Art Museums

May Wang
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Comparative Literature, 2020

Harvard Art Museums
Advisors: David Odo, Jennifer Thum

The Harvard Art Museums is comprised of three constituent museums (the Fogg, Busch-Reisinger, and Arthur M. Sackler) that together exhibit works from the ancient world to the present and from the Americas, Europe, North Africa, the Mediterranean, and Asia. The Student Guide Program at the Museums offers tours that highlight themes across the three collections through the unique lens of an undergraduate. This tour, titled "The World from Within," unites research from Harvard's libraries and museum archives and highlights implicit and explicit depictions of self and character. Thomas Eakins' Miss Alice Kurtz (1903) portrait provides an unusually candid and anatomically detailed likeness of a young society woman at the turn of the century, as interpreted by an American artist trained in Europe and hospitals. The idealized landscape Awaiting Snow in Winter (1547), a Chinese hanging scroll executed by one of the Four Masters of Ming Dynasty painting, Wen Zhengming, alludes to the rich Chinese literati tradition that esteemed intellectual purity especially amidst political strife. Gustav Klimt's exuberant landscape Pear Tree (1903) evokes his role in modernizing Viennese art at the turn of the century as influenced by emergent theories of psychoanalysis and post-Impressionist art. The tours are just one facet of the Museums' Division of Academic and Public Programming, whose annual Undergraduate Student Museum Conference provides a platform for student voices especially in campus museums, often at the vanguard of museum planning. Students from fifteen universities converged to exchange experiences as students challenging the traditions of museum exhibitions, programming, and outreach at campus museums across the country.This summer's work will result in a report synthesizes the discussions about museum politics, identity, and representation from during that conference, as framed by the keynote speech of Fazal Sheikh, a photographer who has worked closely with displaced and marginalized communities around the world. The report will serve as a reference and guide to future museum development for participating staff and students.

Caravaggio's Calling: Dissimulation and Doubt

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History of Art and Architecture and English, 2022

Germanic Languages and Literatures Department
Advisor: Peter Burgard

Michelangelo Merisi da Caravaggio, commonly understood to be the preeminent Baroque painter, is the subject of extensive art historical scholarship. His major works consist largely of Counter-Reformation commissions, Catholic scenes imbued with intense drama and striking chiaroscuro. However, despite the apparently didactic nature of these works, close reading of Caravaggio's oeuvre reveals the pervasive presence of dissimulation and doubt. Many works—including The Calling of Saint Matthew, The Martyrdom of Saint Matthew, The Incredulity of Saint Thomas, The Beheading of Saint John the Baptist, the Capitoline John the Baptist, The Conversion on the Way to Damascus, The Entombment of Christ, both Supper at Emmaus paintings, and the Uffizi Sacrifice of Isaac—exhibit the themes of dissimulation and doubt both formally and thematically. These works frequently feature unorthodox portrayals of significant Catholic figures, near-heretical compositions, and deceptively obscure light sources. While many scholars have historically been content to accept facile interpretations of these elements—assuming rays of light to reliably represent divine illumination, for example, rather than asking where they come from and why Caravaggio chose not to make their sources easily legible—Caravaggio's oeuvre is far from straightforward or purely devotional. Beyond failing to reflect fully the religious zeal of the Counter-Reformation, he often subverts its objectives.

Implementing a Flexible Auction Model

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Economics, 2021

Harvard Business School
Advisor: Alexander MacKay

In this project, we implement a flexible auction model with weak data requirements in R. The model describes first-price auctions in which the lowest bidder wins. This framework is applicable to a wide variety of settings, and is particularly relevant to public procurement auctions. In this model, there is a distribution of private values, representing different cost realizations for each bidder, as well as a distribution of unobserved heterogeneity. The latter corresponds to factors the econometrician does not observe — these are assumed to be common to all bidders within one auction, and distributed across all observed auctions. The distributions of private values and unobserved heterogeneity are identified with only the winning bid and number of bids for each observed auction. The R package recovers estimates for both distributions given only the winning bid, number of bids, and (optional) user-specified controls. It does so through maximum likelihood estimation. The model specification imposes a flexible functional form on the distribution of private values (Weibull), and provides the user with a choice of functional forms for the distribution of unobserved heterogeneity (Weibull, Gamma, and log normal). The package also includes a data-generating function that outputs values for winning bids, number of bids, and (optionally) controls given user-specified distribution parameters for cost and unobserved heterogeneity. The goal of the package is to allow the user to recover estimates for these distributions in a simple and efficient way. At the end of the summer, we plan to apply this tool to auction datasets.

The Vietnam War and Trust in Public Institutions

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Economics, 2020

Economics Department
Advisor: Melissa Dell

The Vietnam War (November 1955-April 1975) is commonly referred to as the "first television war," owing to the large-scale news coverage of the conflict by United States media outlets after substantial deaths by US troops in the spring of 1965. US involvement in the war coincided with a period of dramatic decline in domestic trust in public institutions: while in 1964, 77 percent of Americans professed to "trust[ing] the government in Washington most or all of the time" the number had fallen to 34 percent following the war in 1976 (Pew Research Center). This pattern has persisted over time, with fewer than 50 percent of polled Americans responding that they trust the government in preceding years. This paper explores the relationship between the Vietnam war and decline in trust in government. It does so by examining whether and how local newspaper coverage concerning the Vietnam War influenced individuals' attitudes towards the government, including but not limited to spending on social welfare programs and redistribution. In order to quantify local sentiment, we apply Natural Language Processing (NLP) methods on Vietnam War editorials by 817 local newspapers to create a granular measure of the sentiment of their coverage. In order to address endogeneity concerns about local political attitudes driving media coverage slant, we use an instrumental variables strategy that relies on each local newspaper's ownership structure. We instrument newspaper sentiment by whether the conglomerate owning the newspaper has regulated holdings, such as television and radio stations. This strategy takes advantage of variation in the level of regulation of television and radio relative to that of newspapers, as the former were considerably more regulated than the latter. Since newspapers with regulated holdings require government approval for actions related to the management of all of their regulated holdings, we have reason to believe that local papers' coverage of the war might be more supportive of government actions. We investigate the immediate impacts of news coverage as well as the persistence of effects in following decades.

How Strategy Affects Returns in Private Equity Firms

Daniel Bodea
PRIMO Fellow
Computer Science and Statistics, 2021

Harvard Business School
Advisor: Paul Gompers

Private equity firms have long since been black boxes, incorporating secretive investment and thought practices, while maintaining spectacular returns. Those interested in studying venture capital firms have a similar dearth of information, while these venture firms post similarly exceptional results. Building off of Professor Gompers' private equity and venture capital surveys, I am working to identify interesting relationships between firm strategy and firm performance. I worked on gathering all performance data on those firms that responded to the survey through looking thorough the Pitchbook and Preqin databases. Then, marrying this private equity performance data with the initial survey responses of the firms, I will perform cluster and factor analysis to identify whether different groups achieve superior performance. Through investigating these groups, we can identify whether one of three possible firm type specializations identified by Professor Gompers (governance, operations, financial) does in fact alter performance. We hope to build on previous literature about beliefs on horse-jockey relationships in entrepreneurship and specialization and importance of management teams.

A Proposition to Enforce Truth-telling in Combinatorial Common Value Auctions

Aditya Dhar
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Advisor: Scott Kominers

A seller has multiple units of a good to sell to a group of bidders, and the sale takes place over multiple rounds in an auction. The good is costly to produce, and the bidders have a pure common value. Signals of that value are drawn from a commonly known prior distribution. The seller is unaware in regards to the bidders' profit beliefs and the signals received by the bidder, and evaluates each auction mechanism according to the lowest expected profit across all equilibria and prior information structures consistent with the signal profile distribution.

Within these generalized parameters, we note that traditional common value auctions suffer from bid shading, where agents are incentivized to under-report truthful values such that transfer payments of winning bidders decrease, thereby avoiding a 'winner's curse'. We then examine three common value auctions in a simplified multi-unit model: a standard Vickrey-Clarke-Groves Auction, a Uniform Price Auction, and the Discriminatory Auction, as well as a reserve price mechanism on the VCG auction. We find that the Nash equilibria of the VCG auction with reserve prices and the discriminator auction are strict improvements in regards to seller revenue when compared to standard UP or VCG auctions. We finally report useful properties of multi-round auctions by incorporating received signals into bidders' prior distributions.

Improving the Value of Health Care Delivery

Mariah Dimalaluan
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Biomedical Engineering, 2021

Harvard Business School
Advisors: Robert S. Kaplan, Mahek Shah

In the United States today, the health care industry amounts to 18% of the GDP, with costs increasing by about 3.9% yearly. Currently, the cost measurement standard is the fee-for-service approach, where costs and profits are based on the volume of procedures rather than the achieved outcomes. With the goal of increasing value and reducing costs for the patients, Professor Michael Porter and Professor Robert S. Kaplan sought to redefine healthcare through the application of the Value-Based Health Care (VBHC) System, a patient-focused system with an emphasis on fulfilling patient needs. Today's cost measurement methods, however, do not accurately measure the costs of each step of the care process, which deters health workers from understanding the inefficiencies in the current health system. As an alternative, Professor Kaplan created the Time-Driven Activity-Based Costing (TDABC) method, which allows a more accurate cost measurement of the care cycle.

In this case study, we implemented the VBHC and TDABC to Boston Children's Hospital's Cystic Fibrosis (CF) Center. Today, there are more than 30,000 individuals with CF in the United States alone. Due to the many treatment options available, the life expectancy of these individuals continues to rise and the lifetime cost to rise with it. Because of a greater need for an accurate cost measurement of CF, we created process maps that outlined the care process of CF patients, acquired the price of resources, collaborated with the health staff to ensure accuracy of the data, and applied the TDABC method to quantify the total expenses of a CF patient's care cycle. Thus, through this process, we aim to redesign CF care and optimize the CF treatment plan to maximize patient outcomes while reducing costs.

The Value Added of Being a Student Athlete

Peyton Dunham
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Economics, 2021

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Advisor: Paul Gompers

Collegiate student athletes are required to physically dedicate themselves to the sport they were recruited to play while also maintaining high grade point averages within rigorous academic programs. The experience of being a student athlete is believed to teach students important life skills and values through playing a sport, including leadership, discipline, teamwork and time management. This study looks at the impact of student athlete programs in instilling these values within students and the transferability of these skills into the professional sector. By leveraging the alumni databases of several secondary schools, we are able to collect data on the profile of student athletes including their name, sport, graduation year, major, and whether or not the received honors degrees. Using LinkedIn, we are able to uncover which professional field an athlete went into and their level of seniority in that field. Although this project is still in its early research stages, we intend to look at whether being a student athlete has any effect on a student's choice of major and/or the student's career attainment levels compared to the rest of their graduating class. The findings of this study will provide insight into the value-added of being a student athlete and highlight an environment where important professional skills can be learned through a unique team setting.

Investigating a Welfarist Role for Non-Welfarist Rules

Hannah Ellery
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Applied Mathematics, 2021

Harvard Business School
Advisor: Matthew Weinzierl

Economists rely on utilitarian welfare functions, which translate information about the world into welfare judgments, to analyze the benefits of public policy proposals. Making beneficial economic policy, however, can be difficult in an ever-changing world with limited access to information. To address this issue, we reconceptualize the calculation of welfare in economic policy decisions. This new model acknowledges that policymakers have limited information and seeks to use non-welfarist considerations, including norms and values, to provide information about the state of the world in order to fill these knowledge gaps. We first look to law to construct an analogy for this calculation. We review the wide literature on the philosophy of the use of precedent and the purpose of law. We also consider a model of legal precedent in which preceding cases serve as carriers of information that provide judges with more information about the world, which results in better decision making than natural reasoning alone. In this model, natural reasoning mirrors welfare calculation on pure and possibly limited facts, while precedent stands in for the norms and values introduced into the calculation of welfare. Next, aggregating a wide variety of studies from across time and continents, we turn to sociology to consider how the norms used in our welfare calculations may be created or changed. This will enable us to isolate norms and values that may carry important information about the world and thus allow us to improve the process of economic policymaking.

A Study of Sensitization to Violence

Jacqueline Feffer
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Harvard Business School
Advisors: Alison Wood Brooks, Francesca Gino, Leslie John, David Levari, Michael Norton, Ting Zhang

In a 1997 study, Fetherstonhaugh, Slovic, Johnson, and Friedrich found that participants rated lifesaving interventions as less valuable as the number of lives at risk increased. This phenomenon of psychophysical numbing illustrates the lack of sensitivity to violence and death that humans feel, especially due to its normalization by the media. In this research, I analyze possible ways to treat the desensitization, thus causing people to empathize more with victims of violence. In a literature review, I investigate various techniques that can be applied to enhancing empathy, such as symmetric conditioning, aversive therapy, meditation and implicit bias training. Furthermore, in order to determine which methods have the most impact on sensitization, it may be necessary to study how the brain is affected when the various techniques are applied. Future research will involve designing preliminary mTurk surveys to test these techniques, followed by more thorough lab experiments as well. This work shows promise for increasing empathy and interconnectedness amongst people.

Understanding Inequality to Address Inequity

Akari Furukawa
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Advisor: Ethan Rouen

Income inequality has been increasing at a rapid rate over the past few decades in the US. This growing gap between the “haves” and “have-nots” has captured the attention of regulators, business leaders, and the public. This shift has been made evident by the recent requirement that publicly traded firms disclose the “CEO Pay Ratio.” In the 1950s, the average ratio between the CEO and a median employee was about 20:1. In 2018, that ratio rose to about 172:1 for public companies. Though the ratio gives insight into various issues of inequality, like the fact that CEO’s compensation has risen at a faster rate than that of the average employee, it does little to address why inequality is a concern. There is ample evidence that many factors unrelated to individual ability and effort - such as race, gender, and power - influence compensation. This leads to the suggestion that when people rail against income inequality, what actually enrages them is income inequity, or that pay between groups is unfair and detached from the economics of compensation. Using the workplace as the unit of analysis, this research focuses on understanding how to differentiate inequality from inequity and how to mitigate the latter. We examine inequity from economic, political, and philosophical perspectives, and we discuss its possible causes, the challenges of identifying and measuring inequity, and the potential impact of addressing inequity.

Franchising, Asset-Light Business Models, and Activist Investing

Yinyu Ji
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Statistics, 2021

Harvard Business School
Advisor: Suraj Srinivasan

According to the Harvard Business Review, investors in today's digital age tend to prefer firms with fewer physical assets. In the restaurant industry, firms make important strategic decisions regarding their mix of company-owned and franchised units, with heavily franchised firms owning fewer physical assets. In particular, activist investors appear to favor heavily franchised models, as they believe that this improves return on capital. I investigate the validity of this belief and examine the correlation between franchising and firm outcomes by analyzing annual industry-specific metrics and valuation multiples of publicly traded restaurants from 2010 to 2018.

Reverse Termination Fees in Merger and Acquisition Agreements

Clara Li
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Computer Science, 2022

Harvard Business School
Advisor: Guhan Subramanian

Reverse Termination Fees (RTFs) are commonly used in merger and acquisition agreements to provide compensation for the target company if the acquirer reneges on the deal. There is a common assumption in academic and practitioner literature that the sizes of RTFs triggered by a failure to obtain antitrust approval are correlated with antitrust risk. We demonstrate that contract theory instead predicts that antitrust RTFs should be correlated with the costs of non-consummation for the target. To test this prediction, we examined 91 merger and acquisition agreements from the FactSet MergerMetrics database for deals announced between June 1, 2017 and June 1, 2019. We then coded all deals for antitrust risk, as measured by the issuance of a second request from the Department of Justice or Federal Trade Commission, common triggers of the RTF, as well as the structure of the fee. We found that the most common triggers were "Merger not Consummated by End Date," "Breach of Warranties or Covenants," and "Adverse Changes in Board Recommendation" on the part of the acquirer. The most common deal structure involved providing specific performance and other legal remedies to the target in addition to the fee. We also found no evidence that the issuance of a second request correlates with the size of the RTF as hypothesized. This paper contributes to the overall academic literature surrounding Reverse Termination Fees by providing an updated description of the most common usages and triggers, as well as rejecting the notion that the size of RTFs should be correlated with antitrust risk as is commonly misinterpreted in the field today.

The Vietnam War and Trust in Public Institutions

Nicholas Lore-Edwards
BLISS Fellow
Economics, 2021

Economics Departmnet
Advisor: Melissa Dell

During the 1960s and 1970s, the percent of Americans that trusted their public institutions steadily declined from a previously high average of about 70 percent to a low average of about 30 percent. This trust never fully recovered, indicating a lasting impact of this time period on US citizens. This paper studies the impact of pro-war and anti-war media coverage of the Vietnam War on Americans' trust in their public institutions. The analysis uses publication data from the Inter-university Consortium for Political and Social Research's United States Newspaper Panel and editorial content data from newspaperarchive.com. An instrumental variable strategy involving the regulation of national conglomerate holdings is used to isolate the effect of the war's media coverage on citizens' trust. The successful completion of this project might link the sentiment of a city's local newspaper to the shift in the local citizens' trust in public institutions. This study may also find similarities between the sentiments of papers owned by the same national news conglomerates. This may imply that national news conglomerates in the 60s and 70s had influence over the opinions of everyday Americans through the editorial section of their newspapers.

Using Synthetic Face Creation and Resume Audit to Discover Appearance Based Migration Frictions

Ethan Medlin
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Harvard Business School
Advisors: Prithwiraj Choudhury, Tarun Khanna

This project studies whether individual characteristics might prevent individuals from seeking employment in distant regions. Previous research has established the presence of informational, occupational, social, and physical barriers to migration. We attempt to discern frictions to migration based on individual characteristics and are designing a resume audit study to examine the effects of applying to jobs originating in different regions.

Effects of Winner Identity on Policy Choices and Economic and Social Outcomes

Carolina Ranfagni
PRIMO Fellow
Economics, 2022

Harvard Business School
Advisor: Vincent Pons

In democratic governments, people turn to the election polls to support the party or candidate whose promised outcomes and policies best align with their interests and who they believe can best deliver change. An individual's or their party's ability to stay in power depends to some extent on their ability to deliver on the promises they made during their campaign, regardless of how limited their ability to implement change is. In this project, we study the social and economic impact of electing a challenger instead of the incumbent. In other words, we want to measure the extent to which the identity of an elected official affects outcomes. To measure the impact of electing the challenger, we compile data on candidates and different social and economic indicators, like child mortality rate. Using data from Varieties of Democracy, the Inter-Parliamentary Union, and other academic sources, we collect data on election results, political parties and coalitions for elections in the past 200 years from all over the world. After identifying the head of state and the head of government, we use the information on regimes from different databases to determine if and to which extent elected officials are responsible for policy decisions. By assuming that the results of extremely close races are essentially random, a regression discontinuity design can measure the impact of electing the challenger. Finding evidence that the identity of the winner does not influence outcomes would suggest that it does not matter who you elect into power, along the lines of the sentiment that "it is all the same when it comes to politics." This result would discourage people from believing candidates that base their campaigns solely on promises of change.

Analyzing the Flow of Financial Patenting and Innovation

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Economics, 2021

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Lerner Lab
Advisors: Josh Lerner, Nick Short

Despite the breadth of literature on the growth and effects of manufacturing innovation, there is a paucity of research on the flow of financial innovation. The growing influence of technology in everyday life has led to an acceleration in both the rate and number of financial patents. To further investigate this trend, we employed a sophisticated machine learning approach to carefully select FinTech patents using keywords and US patent classes. After developing a comprehensive list of FinTech patents from 2000-2017, we were able to study the subjects of patent filings, the number of patent applications by year, and the nature of these patents following judicial decisions. The preliminary results suggest a sharp increase in the sheer number of financial patent filings throughout the past two decades. These findings may provide insight into what kinds of organizations are filing for patents as well as help contribute to the relatively new field of financial innovation.Despite the breadth of literature on the growth and effects of manufacturing innovation, there is a paucity of research on the flow of financial innovation. The growing influence of technology in everyday life has led to an acceleration in both the rate and number of financial patents. To further investigate this trend, we employed a sophisticated machine learning approach to carefully select FinTech patents using keywords and US patent classes. After developing a comprehensive list of FinTech patents from 2000-2017, we were able to study the subjects of patent filings, the number of patent applications by year, and the nature of these patents following judicial decisions. The preliminary results suggest a sharp increase in the sheer number of financial patent filings throughout the past two decades. These findings may provide insight into what kinds of organizations are filing for patents as well as help contribute to the relatively new field of financial innovation.

What Do Fans Want to See? Exploring the Uncertainty of Outcome Hypothesis in Professional Sport

Edward Richardson
PRIMO Fellow
Applied Mathematics, 2022

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In sports economics, a large body of research focuses on the effect of uncertainty about game outcomes on consumer demand. The notion that the uncertainty of a game's outcome has a positive effect on demand for a sporting event was first identified by Simon Rottenberg (1956), and his hypothesis has been extremely influential in the literature on the design of competitively balanced professional sports leagues. This study examines the validity of this uncertainty of outcome hypothesis (UOH) using data from two teams in the Australian Football League (AFL). Specifically, using panel home attendance data from season ticket holders, or members, of both clubs, we apply an instrumental variables regression model to study the effects of outcome uncertainty on member attendance, controlling for various individual and game characteristics. Because of bookmakers' high incentives to forecast outcomes of matches games as precisely as the available information permits, we derive our ex-ante measure of outcome uncertainty by averaging the reported betting odds taken from 12 different bookmakers. By running regression models for a member's decision to attend a certain match, we test the UOH by determining whether consumers react differently to high and low uncertainty matches using betting odds as a proxy for members' expectations about a game's outcome. Our preliminary results suggest the presence of heterogeneous treatment effects depending on different member characteristics, showing that some consumers react differently to expected uncertainty than others. These findings may suggest more accurate ways for professional sports franchises to anticipate consumer demand, which can have broad implications as leagues decide how to design more balanced contests and maximize revenues from the consumption of live sport.

Behavioral Economics and Decision Making

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Sometimes, we do things that are so basic, there does not seem to be an explanation. Whether it be in relationships, at work, or at school, there are some habits and mannerisms that simply cannot be explained because they seem so intuitive. Our research looks at how people make decisions. We explored how people make decisions in day to day life, including how they choose to shop for their family, discuss finances, donate to charities, and even interpret apologies. One of the more interesting projects our lab is working on examines how people seek advice: would they rather receive advice from someone with experience or expertise? We used a combination of online and in-person surveys to collect data and analyzed the transcriptions of conversations and audio recordings. So far, we have found that though people generally prefer some combination of the two, people normally seek advice from experienced people as they view their advice as more unique.

Be the Change! Harvard Square and its Setting

Jonathan Yuan
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Classics, 2022

History of Art and Architecture Department
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The closing and transfer of stores have created massive alterations to the appearance and business makeup of Harvard Square within the past decade, an issue representative of fast-paced development occurring around the globe. The aim of this research project was to understand the various dynamics and causes of this development and its implications on the local economy and lifestyle of those involved. Methods included categorizing current businesses and vacancies by attributes like type of business and GIS mapping that information, as well as interviewing government officials, business owners, and residents about development taking place in the area. Walking tours were also designed to celebrate the historical value of Harvard Square. Through analyzing archival records and interviews, It was found that the main causes of current development are the purchasing of land by wealthy property owners, rising leases, and pressures from the rise of online shopping. Approximately 10 of storefronts in the Square are vacant and the current business makeup is 68 local, a number expected to decrease as local businesses are targeted by rising property values. Property ownership is mainly controlled by six entities, including Harvard University itself, creating uncertainty due to the unchecked ability of these groups to determine the future of the Square through their leases and plans for construction. Though it may be difficult to compete financially with these wealthy owners, it is important to conduct discussions with them to reconcile their ideas of success with community concerns. Future work will be performed to test whether rezoning processes or administrative guidelines can be created to ensure that the Square does not completely leave behind its rich cultural and commercial history. If an equilibrium is struck, Harvard Square can provide an example to areas of the world struggling with gentrification of the successes that are possible when both economic and cultural complexity are working side by side.

Formalizing Land Titles in Cities of Developing Countries

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Urbanization is widely regarded as a stimulus to social development. Cities provide a platform for trade, enhanced connectivity, and the exchange of ideas. In developing countries, however, the economic efficiency of cities is often crippled by the ambiguity of property rights. Informal land titles reduce the owners' incentives for investment in the asset and hinder the proper execution of financial transactions such as exchanges of ownership and mortgages on the property, which have become increasingly important with the integration of developing countries into the global economy.

Our research seeks a new system for allocating land titles. Specifically, we propose a multi-stage mechanism that incentivizes residents to truthfully declare their property ownership and that of their neighbors. We establish the necessary conditions such as the existence of truth tellers and the constraints on the size of coalitions in order to guarantee a unique, desired Nash equilibrium of truthful reporting by all residents. Our results can provide urban planners in developing countries with key insights in future policy making, allowing them to formalize land titles for the citizens at minimal social costs.

Class in Race: A Multi-City Study on Chicago, Los Angeles, Atlanta, and New York

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Class and race powerfully motivate policy preferences, and growing income inequality within racial minority groups complicates the interaction of these two variables, potentially bringing racial and economic interests into conflict. Professor Jennifer Hochschild's class-in-group project navigates the relationship between class and race through a multi-city survey and four case studies, each on a salient issue in one major American metropolitan area. These are policing and stop-and-frisk in New York; housing, urban redevelopment, and gentrification in Atlanta; school choice in Los Angeles; and pension funds in Chicago. Each city presents a different angle on class-in-race interaction. New York offers the strongest race story, and Atlanta presents a clearer race-class conflict, whereas in Los Angeles and Chicago, the race and class contours lie below the surface.

In Chicago, decades of promised retirement pensions and benefits for public sector workers have left a funding crisis for politicians to solve (especially after the 2008 recession) that does not fall neatly along socioeconomic or racial lines. While Chicagoans rarely think the pension crisis has a race or class element, my analysis of interviews with community, political, and industry leaders revealed that the various potential funding solutions offered to solve the pension crisis implicate class and race more than the pensions themselves. For example, proposals that recommend taxing corporations, the financial sector, and the wealthy place the burden primarily on wealthy whites. Alternatively, raising revenue through flat fees, such as a garbage tax that charges the rich and impoverished equally ignores socioeconomic disparity, disadvantaging poor residents. Similarly, limiting spending on services such as policing and school funding to poor, often predominantly African American or Latinx neighborhoods, shields wealthy whites from the impact of the pension crisis while saddling poor communities and people of color with its repercussions.

The Private Interests of Public Officials: Financial Fraud and Legislator Voting Behavior in the US Congress

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The role of legislators' private interests in the public sphere, and the effects of such private interests on voting behavior raise important questions with significant and far-reaching implications. For example, past research has studied the effect of congressional actions in the years leading up to the 2008 financial crisis, with a particular focus on those decisions that deregulated financial markets - a deregulation that had significant consequences for the US economy. Continuing in this vein, we theorize that both personal experience with fraudulent stock holdings, as well as the presence of fraudulent constituent firms in one's congressional district/state, make legislators more likely to vote in favor of regulatory bills. We tested these expectations by examining congressional actions and voting behavior in the years between 1995 and 2019, focusing on bills pertaining to financial fraud and regulation. We measured personal experience with stock holdings through legislators' publicly disclosed personal financial assets via the Center for Responsive Politics. We determined the constituent firms engaging in fraudulent activities and the firms' respective congressional district locations via publicly available Accounting and Auditing Enforcement Releases (AAER) fraud data and company information available via Wharton Research Data Services (WRDS). Finally, we tracked legislator voting behavior on fraud-related bills via publicly available roll call information in government databases. In our analysis, we controlled for legislators' party and ideology, as well as total assets for each legislator, to obtain a relationship between our independent variables (personal asset holdings and fraudulent constituent firms) and our dependent variables (voting behavior).

Pre-Colonial Centralization, Chiefs, and Clientelism in Sub-Saharan Africa

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Applied Mathematics and Economics, 2022

Deparment of Government
Advisor: Horacio Larreguy

Recent studies show that regions of Africa with more pre-colonial centralization exhibit a contemporary advantage in the allocation of public goods. To explain this phenomenon, we tested a model in which electoral incumbents direct more transfers to jurisdictions where tribal leaders have a historic advantage in mobilizing voters. We focused on elections in 35 Sub-Saharan African countries from 1993 to the present. Using pre-colonial centralization measures for tribes in Murdock's Ethnographic Atlas, we determined the historic degree of centralization in our regions of study. Support for a given election's incumbent was measured using the fraction of votes for the incumbent and overall voter turnout, and ethnic affiliation with a candidate was primarly determined by geographic proximity. Other relevant measures, such as prevalence of corruption and vote-buying, were also obtained from the Afrobarometer data. Our primary dependent variable, public goods provision, was proxied by nighttime satellite imagery, which indicated the degree of rural electrification. Though data from 2014 onwards is still under analysis, preliminary regression results provide support for the incumbent transfer theory; these findings withstand robustness checks. For example, the model predicts that the association between pre-colonial centralization and public goods provision is stronger in areas with democratic elections—where the votes of co-ethnics and non-co-ethnics of the incumbent both must be garnered—than in areas with autocratic elections—where only co-ethnic votes are needed to win. These findings have significance in directing future investigation on the role of local leaders in African economic development.

Mind, Will, and Science

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It is rather unsurprising that philosophical questions often end up encroaching on the domain of science. Both subjects seek to describe reality at the most fundamental level, and both—though philosophy most conspicuously—require certain results of the other in order to justify its own conclusions. Nowhere is this truth more conspicuous than in philosophy of mind and the question of free will. The link between philosophy of mind and neuroscience is so tight that some have proposed reducing the former to "neurophilosophy," while the question of free will is considered by many to be contingent on the truth of determinism—a concept whose truth can only be gauged scientifically. In a series of essays, I will argue that each of these notions, though highly plausible, is ultimately false. Using arguments from Wittgenstein, Kripke, Aquinas, and others, I hope to establish that certain scientifically-motivated conclusions in each discipline are steeped in metaphysics, presupposing axioms that are implausible from both a philosophical and scientific standpoint. While neuroscience seems to reduce the mind to the brain, such an approach fails to account for the existence of objective meaning, posing a largely hidden threat to scientific reductionism. Similarly, though determinism seems prima facie incompatible with free will, this alleged incompatibility rests on dubious metaphysical claims, both mistaking the nature of the will and reading in an unnecessary account of causality. When the proper metaphysical stance is taken, such questions are revealed to be nearly independent of scientific results, a conclusion in stark contrast to our initial intuitions. To establish this, I will first analyze the relevant definitions of the mind and the will. I will then offer several arguments against the traditional accounts, arguing that they read an unnecessary metaphysics into scientific results. Finally, I will offer a positive account, outlining my own approach to the mind and the will and the relation of each to modern science.

Philosophical Study of the Phenomenon of Faith in the Visual Novel Umineko

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Umineko no Naku Koro ni (When the Seagulls Cry) is a 2-million-word Japanese fantasy visual novel that presents a framework for thinking about truth, metaethics and epistemology. It is an undiscussed work in academia because of its unique genre, language, and material, despite its literary and philosophical content. The purpose of the research was to extract and analyze issues of philosophical interest that arise from a close reading of the Umineko game text. Existing philosophical literature was studied on the nature of truth, the relation of belief to the will, the epistemic status of testimony, and philosophy of science, including the philosophy of Frege, Anscombe, Anselm, Augustine, Aquinas, van Inwagen, Feser, Healey, and Moran.

A series of essays will be produced that examines the phenomenon of faith in the motto proposed by Augustine and Anselm, "Believe that you may understand," as well as further essays discussing the relation of belief to the will and philosophy of science and teleological explanations of occurrences. Among other current findings, I defend the statement "Believe that you may understand" based on a relational understanding of testimony that necessitates belief in another for proper transmission of epistemic justification for knowledge. Furthermore, following the formal philosophical material developed in these essays, Umineko will be interpreted as a literary theodicy that incorporates many of the philosophical positions discussed. The results of this research may have implications for understanding the role of faith in knowledge, making sense of conflict that some perceive between faith and reason, as well as implications in the interpretation of science.

Executive Summary: Gender Bias in Women's Cases in El Salvador

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Since the late 1990s, women in El Salvador have been increasingly prosecuted for the "aggravated homicide" of their newborns. These women testified that their babies died either due to an obstetrical emergency or another birth complication. Yet, at every stage of the judicial process, the state aggressively pursued the mother's prosecution instead of pursuing the truth, beginning at the moment of the arrest and culminating in the moment of sentencing. We identified 71 of these cases and found overwhelming evidence of gender bias and discrimination present throughout the entirety of the legal proceedings. After examining these women's cases, gender bias was evident from the police, hospital personnel, judges, forensic specialists, prosecutors. In addition, there were several instances of professional incompetence from medical specialists and failures of the legal system to provide due process in these cases. This executive summary seeks to use the data on these women in order to shed light onto the injustices of this legal system, and to promote the careful and just application of the law in future investigations surrounding obstetrical emergencies that women experience. More so, it is the hope that by raising awareness of bias in the legal system, women and other disadvantaged groups will be able to benefit from justice and protection under the law.

Diversity and Discrimination in the Digital Age

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As both customers and employees become increasingly diverse, organizations must be vigilant about opportunities for discrimination. Failing to do so has costly consequences — many companies have recently faced public censure for incidents of race-based discrimination in customer interaction. This is further complicated by a growing reliance upon digital customer-employee and employee-employee interactions. Helping behaviors are a kind of organizational citizenship behavior that employees can direct towards customers, fellow employees, or the organization as a whole. We posit that the voluntary, discretionary nature of helping behaviors creates distinct pathways to discrimination as compared to competency-based decision-making behavior (*e.g.*, hiring). Through field studies and surveys, we analyzed potential mechanisms for race-based discrimination in the domain of helping behaviors. We found evidence that across both customer-employee and employee-employee contexts, differentials in helping behavior can be linked to the recipient's perceived foreignness. Usually not part of an employee's formal role requirements, the positive organizational effects of helping behaviors can range from improved customer perceptions of service to increased coworker cohesion. Understanding when discrimination is likely to occur and who is affected can therefore translate into organizational strategies for reducing discrimination and promoting positive helping behaviors.

Independent Analysis of Systematic Gender Discrimination in the El Salvador Judicial Process against Women Accused of the Aggravated Homicide of their Newborns

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I investigated the presence of gender bias in El Salvador during in the arrest, prosecution, and sentencing of women convicted of abortion in El Salvador, which the law treats as aggravated homicide. I also examined the social discourse surrounding reproductive health, family planning, and abortion. I coded two sources of data: (1) court documents from 36 cases of women charged with abortion and (2) 43 focus group interviews with El Salvadoran citizens. Using El Salvador as a case study, I clarified the process by which ideas of motherhood frame reproductive rights discourse and the restriction and criminalization of abortion. Ultimately, these findings suggest that after the criminalization of abortion in 1998, women, most of whom are low-income, of color, and reside in rural regions of El Salvador, have been punished for miscarriages. I hope that following the publication of these findings, the El Salvadoran government takes steps to address gender discrimination in its criminal justice system, where women have served years in prison for having experienced obstetrical emergencies out of their control.

Power, Politeness, and Profitability: Predicting Company Success and Financial Violations from CEOs' Politeness in Earnings Calls

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At the end of each quarter of the fiscal year, most publicly traded companies conduct earnings calls, in which CEOs discuss their company's finances with stock analysts. These calls provide a crucial inside look at how the company is performing for investors and analysts. While previous research has explored the relationship between the number of positive and negative words in these calls and stock returns, a gap in the literature exists in terms of analyzing other types of language in more depth. Using natural language processing (NLP) techniques, this analysis explores whether companies whose CEOs use more polite language are more profitable, less risky, and commit fewer financial violations. The current study examines 2000 earnings calls from nearly 500 companies to rate the politeness of the executives and stock analysts on the call. Proxies of politeness, such as gratitude and asking questions, are gathered for each call, and outcome measures including CEO compensation, stock returns, and financial violations are considered. Analysts are shown to be much more polite than executives, expressing significantly more gratitude and using many fewer negations. By employing NLP to demonstrate politeness and applying it in a new financial context, this research furthers the theory in organizational behavior. In the future, analysts and corporate accountability agencies may be able to use these results to predict companies' investment prospects as well as their potential to commit financial violations.

Going Back to Back-to-the-Land: A Humorous Study of Communal Living in the Late Counterculture

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Studies of Women, Gender, and Sexuality
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In an era of climate change, population expansion, rapid globalization, and—at the intersection of these trends—changing notions of community, the back-to-the-land movement and experiments in communality that took place during the 1960s and 1970s could be regarded by contemporary thinkers as critical early forays into alternative modes of living. However, this communal aspect of the 20th-century counterculture is generally treated with a certain amount of humorous disregard, such that what was, in fact, a period of groundbreaking experimentation is often treated instead as a vapid product of youthful idealism. This project—the construction of several sitcom episodes about a fictional commune in Northern California in 1967, based on the trajectory of a number of historical intentional communities around the country—constitutes an applied investigation into whether the humor with which the back-to-the-land movement is treated can be reappropriated as a venue for intellectual engagement as opposed to dismissal. While the immediate goal of the sitcom—as with any piece of comedy writing—is to elicit laughter from those who engage with it, the work more broadly seeks to explore humor as a lens for historical analysis and critique, as a mode of expression that can be used to negotiate a balance between purposeful commentary and satisfying entertainment. The sitcom seeks to play with various stereotypes and suppositions, subverting misconceptions and clichés about the back-to-the-land movement without shying away from critique of the movement itself. What emerges, ideally, is a work of intellectually engaging comedy that challenges both the inadequacies and vanities of the counterculture, but also the narrative complacency of its readers/viewers.

Executives and the Civil Rights Movement: How the Early Life Experiences of CEOs Affect Firm Diversity

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Diversity along racial and gender lines within organizations has been recognized by scholars as beneficial to the creation of new ideas and to innovation. Even so, many companies are struggling to create and sustain diverse work environments. We currently know very little about how the pre-career experiences of leaders in different areas affect the diversity of the teams they hire. In this study, we seek to expose the effect of the civil rights movement on the propensity for political and business leaders to have a diverse team. We do this by comparing the diversity of organizations in the south and similar organizations in the north before, during, and after the civil rights movement. The key difference between these environments is the proximity to explicit and outward acts of racism. We build on status theory and stigma management to better understand why leaders with apparent pro-diversity backgrounds, evidenced by their involvement in the civil rights movement, hire minorities at a higher rate than those leaders that don't publicly speak out about their involvement in such movements. We also build on the mechanisms by which the past experience of organizational leaders can trickle down to affect the hiring decisions of more junior employees by expanding on executive influence theory. Our theories and findings will highlight the importance executive boards should put on looking into the personal histories of the individuals they are selecting from to become a CEO if their desired outcome is not only an operationally efficient company but, a diverse one as well.

The Reemergence of Independent Bookstores and Radical Innovation Adoption in Senior Executive Teams

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Following the entrance of Amazon.com in 1995, brick-and-mortar independent bookstores saw a significant decline in their numbers, plummeting 43 percent in the United States between 1995 and 2000. However, since 2009, independent bookstores have experienced a resurgence in their popularity. Between 2009 and 2017, the American Booksellers Association reported a 41 percent growth in the number of independent booksellers, from 1,651 stores to 2,320. This study explores how independent actors in a mature industry (i.e., an industry that has surpassed its early emergence and growth phases) collectively respond to a technological discontinuity—a breakthrough innovation that not only advances the technology that characterizes the industry but also generates new markets. To explore this idea, this project utilizes data from over 200 ethnographic interviews; focus groups with bookstore owners, publishers, and authors; in-depth field observations of bookstore activities and industry conferences; and over 1,000 newspaper and trade publications articles mentioning independent bookselling in some fashion. The study finds that independent bookstores have managed to survive and even thrive in spite of Amazon and other online retailers based on three dimensions: community, curation, and convening. They connect with the local community through movements like localism; curate inventory that allows them to provide a more personal and specialized customer experience; and promote their stores as intellectual centers for convening customers with like-minded interests. In my role, I am conducting literature reviews, designing data categorization frameworks, and developing processes for data management and data coding. I am also supplementing the study's existing qualitative research with quantitative analysis, including market research on the retail industry. I am comparing net and operating income, as well as EBITDA, across the supply chain for independent and large bookstores from 1995 to 2018. In addition, I am conducting a comparison analysis of independent and chain hardware stores. Together, my work explores how incumbent actors in a mature industry—and throughout a supply chain—respond to radical innovation challenges.

Complicating the Experience of Women in Engineering: How the Intersection of Gender with Race/Ethnicity, Social Class, and Pre-College Experiences Influence Women's Experiences and Integration in Engineering

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Drawing on 10 in-depth interviews with a demographically diverse sample of woman-identifying engineering undergraduates at an elite university, I focused on their gendered experiences in the engineering school and the strategies they adopt to successfully integrate themselves into the engineering community. Given the multiple social group memberships to which students belong, I examined the ways in which gender intersects with race/ethnicity, social class, and pre-college experiences to uniquely influence each respondent's experience as a woman in engineering and how these diverse experiences shaped the extent to which they successfully integrated themselves into the school of engineering. I measure "successful integration" into the school of engineering by the level and content of their engagement with majority-male faculty and peer friendship and study networks, as well as their involvement in engineering-based extracurricular activities on and off campus[MOU1] . Drawing on scholarship on intersectionality, cultural reproduction in education, and higher education, the findings will extend previous research on the experiences of women in male-dominated fields. More specifically, the findings of this research will expand on our understanding of the heterogeneity of women's experiences in engineering.

The Effects of Periodic Coordination Meetings on Innovation Outcomes

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In designing effective meetings in organizations, there is a trade-off between each member specializing in their tasks and closely integrating their work with others. To promote collaboration, iterative coordination involves regularly scheduled stand-up meetings to discuss progress towards larger company-wide goals. Collaborating with people in different departments may focus everyone's efforts on serving the company's mission and thus better address the needs of their customers. However, these frequent meetings may take valuable time and attention away from each team member's ability to focus on their specialized area, thereby limiting their novel contributions to an initiative. Indeed, a field experiment conducted at a Hackathon found that teams that experienced regular check-in meetings produced applications that better met market needs but were less advanced than those of teams that did not experience such meetings. To further support and expand on these findings, we are conducting a laboratory experiment to examine the effects of check-in meetings on how well teams of three people collaborate and brainstorm innovative product ideas. We hypothesize that stand-up meetings will increase the usefulness yet decrease the novelty of product ideas that teams brainstorm. This research may help organizations design meetings that better address their innovation goals of novelty and usefulness.

Assessing the Role of Diversity and Networking on the Impact of HIV Advocacy in Massachusetts

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As antiretroviral treatments and treatment availability consistently improve, more tools and resources become available to prevent, treat and maintain HIV. As a result, the number of people living with HIV (PLWH) is steadily increasing. Despite the steadily increasing number of PLWH, the public interest in HIV has remained stagnant and public policy surrounding the treatment of PLWH has remained unaccommodating. Persisting stigma and discrimination surrounding HIV status make it difficult for PLWH to not become an immediately tokenized exception.

In response to the absence of change surrounding society's treatment of HIV, the Getting to Zero Coalition (GtZ) of Massachusetts formed to re-energize and transform the HIV agenda in Massachusetts, and to further support the 90-90-90 goals outlined by UNAIDs. As a part of its mission, GtZ looks to shift the HIV agenda in Massachusetts by revolutionizing the existing network of HIV advocates and building a more diverse, intergenerational network of individuals both living with and without HIV. To push that networking goal, GtZ launched the Activist Academy Fellowship. The fellowship looks to educate community leaders across Massachusetts in advocacy, community mobilization, and community education via assigning them to one of six projects pre-selected by GtZ that actively deal with current HIV-related bills in the Massachusetts legislature.

By implementing the Activist Academy Fellowship, and capitalizing on a cohort of individuals diverse by race, gender, sexual orientation, age and HIV status, we predict that we will more positively influence public concern around HIV, and subsequently, positively engage the public on ongoing contemporary issues in HIV. Overall, we hope that the Academy will improve the HIV advocacy network in Massachusetts, and further empower the goals of the GtZ coalition.

Implicit Gender Stereotyping in Judgments of Fame: 30 Years Later

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In 1995, Banaji and Greenwald (B&G) showed implicit male-favoring gender-fame stereotyping by revealing a bias in implicit memory using signal-detection analysis. Over the past thirty years, social change has brought many more women into public life, including the categories used by B&G, such as music, art, politics, and sports. This research poses a simple question to which the answer is unknown: Has sufficient social change occurred since the years 1990-1993 (when B&G's data were collected) that women and men will equally be assigned the quality of fame given equal familiarity in memory? In Experiment 1, participants are first familiarized with a list of non-famous names. Between 24 and 48 hours later, the participants are shown a new list of names that contains some of the previously seen names as well as new famous and non-famous names that have not been presented before and asked to make a simple judgment: Is this person famous or not famous? B&G showed that the statistical component called the criterion (β) to measure the cognitive threshold for judging fame was set higher for female names than it was for male names. If gender parity in the world has reached new levels, this experiment should show lower or no gender bias. If on the other hand, the same level of false fame bias is obtained today as by G&B, we would conclude that progress on gender parity has not been sufficient to have translated into individual decisions about granting the quality of fame equally to equally undeserving men and women. We view this approach as a way to measure change in society as it is reflected in the implicit biases that individual minds carry without awareness.

Course Development in Poetry in America

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The American public education system currently operates under a significant teacher shortage. This shortage is a particular impediment for schools in rural areas and schools with large concentrations of low-income students, which have greater difficulty attracting and retaining highly educated teachers. As a result, accessible online education is an essential tool for both students and teachers, particularly in more specialized subjects that teachers may not be qualified to teach without supplementation from outside sources.

Poetry in America's Fall 2019 course "Poetry in America: The City from Whitman to Hip Hop" will be piloted to over 500 high schoolers in predominantly Title I schools. The course provides a comprehensive introduction to poetic analysis through the lens of American urbanism, and spans works from Walt Whitman's "Song of Myself" to the music of Nas and Kendrick Lamar. It integrates classroom-based activities, online readings, and video lectures to support a wide range of learning styles; the course also includes teacher-specific materials to facilitate instructors' positions as resources for students.

The goal of "The City" is to provide an engaging, flexible, and accessible space for both students and teachers to encounter the poetic discipline, which can seem needlessly complex and impractical to those unfamiliar with it. Opening the door for low-resourced institutions to overcome those barriers is an essential step forward for the American educational system.

Just Posturing: An Exploration of Nonverbal Displays and Gender Affinity

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Psychology Department
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Particular body postures, like manspreading, are associated with specific genders. Existing studies provide support for the notion that an agent adopting such postures can influence how an onlooker perceives their gender. Less studied is whether such postures affect gender perceptions of the agent themselves. This research asks how adopted body postures influence self-perceptions of gender, as well as gender frames used to parse and interact with the surrounding environment. Using a between-participants experimental design, undergraduate participants are instructed to adopt either a masculine or feminine body posture. A series of questions evaluate participants' gender primes, their mapping of gender onto gender-neutral figures, and their consequent affinity toward same- and differently-gendered figures. Findings will have implications for purposive posturing as an adaptive strategy to undermine entrenched gender role ideology and gender relations.

The Science of Conversations

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Although conversations are an integral part of everyday life, the elements that make for an enjoyable conversation and a strong first impression have not been explored adequately in social psychology. Recent research on the enjoyment of conversations has suggested that when two people have a conversation, a liking gap emerges. On average, people believe that they liked their conversation partner more than their partner liked them, and that they enjoyed the conversation more than their partner did. The gaps persist in three-person conversations, and on average, people also mistakenly believe that they were the least liked person in the conversation. Using the questionnaire data collected from all participants after hundreds of two- and three-person conversations, we now pivot to see what else we can learn about conversations. How does the deepness and the humor of the conversation affect how much people enjoy a conversation? How much does a participant's rating of their own and others' authenticity affect how much they enjoyed the conversation, and how much they believe their conversation partners enjoyed the conversation? We ask these questions of both dyadic and triadic conversations to understand whether the factors that contribute to an enjoyable conversation and strong first impression differ when talking to one person and when talking to two. The ultimate goal of this research is to gain insight into factors that contribute to people's satisfaction with social interactions.

Strategic Ignorance: What Lies Behind This Moral Quirk?

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Strategic ignorance is the act of avoiding information with motivated reasoning. The classic paradigm of strategic ignorance involves participants choosing not to reveal how other players will be affected by their choice in order to justify picking the option that gives themselves more money. One school of thought regarding why this happens is that participants want to avoid dissonance that might arise in decision-making. Another view, one which believe to be more accurate, is that participants avoid revealing how other players will be affected in order to preserve their reputations as "fair" people. To answer the question as to which explanation prevails, we added a manipulation to the paradigm. We added a scenario in which participants would make a decision that only affected themselves: they would decide whether or not to complete a "fun" or "boring" task in exchange for a random and unknown monetary value, again having the opportunity to reveal the values beforehand. The first view (that people ignore information primarily to avoid dissonance) would predict that participants would forego the information in this scenario as often as in the condition similar to the original study (where the money goes to the other player) because it would still create dissonance if one revealed that they had to complete the "boring" task to receive more money. Our explanation, however, would predict the opposite: participants would reveal the information much more in the scenario that affects only them because their reputation would not be affected by seeing the monetary values. Initial findings indicate that our prediction is correct: strategic ignorance arises primarily when the hidden payoffs affect another person, and not when they affect the participants themselves. This and similar research can help us better understand how different moral quirks — such as strategic ignorance — arise in situations of decision-making in the real world.

The Effects of Age on the Content-Specific Relationship Between Episodic Remembering and Episodic Imagining

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Psychology, 2022

Psychology Department
Schacter Memory Lab
Advisors: Daniel Schacter, Preston Thakral

Several studies indicate that our ability to recollect past events (*i.e.*, episodic memory) and our ability to imagine novel future events (*i.e.*, episodic simulation) overlap with respect to their cognitive and neural processes. Specifically, according to the constructive episodic simulation hypothesis (Schacter & Addis, 2007a, 2007b), episodic memory allows access to episodic details (*e.g.*, who, what, when, where information) and the recombination of those details into novel future events. A recent study conducted by Thakral et al. (2018) demonstrated that the content of specific episodic memories (*e.g.*, people and locations) is sampled when imagining future episodes. The purpose of the current study is to extend the findings of Thakral et al. (2018) by determining whether such a content-specific relationship across episodic memory and simulation is observed in older adults. Specifically, the current study seeks to examine whether the decline in episodic memory and simulation ability observed in older adults is due, in part, to a reduction in content-specific access from memory. Both younger adults and older adults are being recruited to participate in this study. Participants initially recall episodic memories that each contain two episodic details, a personally familiar location and person. Participants subsequently imagine novel future events, comprising recombined details taken from different memories. For each remembered and imagined episode, participants rate the vividness of each detail in the event. Preliminary findings in younger adults indicate that the vividness of the remembered detail co-varies with the vividness of the simulated detail. However, preliminary findings in older adults show that they have a weaker relationship between the vividness of specific details across memories and simulations. These findings suggest that the decline in episodic processing observed in older adults reflects, in part, a lack of access to specific detail information during episodic memory and simulation.

Long 19th Amendment Suffrage Portal Database

Ciara Hervás
SHARP Fellow
History and Literature and Studies of Women, Gender, and Sexuality, 2021

Schlesinger Library
Advisor: Rachel Guberman

Professor Durba Mitra's class, "Solidarity: Transnational Women's Rights from Suffrage to NGOs," takes an intersectional approach to the study of women's and sexual rights, beginning in the late nineteenth century and working up to the present day. I am working with Professor Mitra to develop the syllabus for the class, which will be completed by the end of the summer. I am researching archival materials at the Schlesinger Library and determining which ones will be helpful for the course, as well as searching for secondary source material throughout the Harvard library system. The course will utilize primary source materials from collections such as the Chinese American Women's Oral History Archive, the papers of the Boston Women's Health Book Collective, the papers of Charlotte Bunch, the papers of Pauli Murray, the Feminist Ephemera collection, and the papers of Catharine MacKinnon. Secondary source materials include, but are not limited to, bibliographies on Black women's transnationalism, United States-based women of color organizations working on issues related to war, women's and sexual rights in the context of indigenous histories in the United States, and suffrage for women of color inside the United States and transnational suffrage organizations outside the US The course aims to explore the diverse international connections between individual feminists and women's and LGBTQ rights organizations, and the ways that trends in the United States influenced rights around the globe. Studying these relationships and the interactions, scholarship, and events that they produced gives us a more accurate historical record of the feminist and LGBTQ movements as a whole, and broadens our understanding of the ways that these movements created lasting cultural change in the United States and abroad.

Solidarity: Transnational Women's Rights from Suffrage to NGOs

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History and Literature, 2021

Studies of Women, Gender, and Sexuality
Advisor: Durba Mitra

Professor Durba Mitra's class, "Solidarity: Transnational Women's Rights from Suffrage to NGOs," takes an intersectional approach to the study of women's and sexual rights, beginning in the late nineteenth century and working up to the present day. I am working with Professor Mitra to develop the syllabus for the class, which will be completed by the end of the summer. I am researching archival materials at the Schlesinger Library and determining which ones will be helpful for the course, as well as searching for secondary source material throughout the Harvard library system. The course will utilize primary source materials from collections such as the Chinese American Women's Oral History Archive, the papers of the Boston Women's Health Book Collective, the papers of Charlotte Bunch, the papers of Pauli Murray, the Feminist Ephemera collection, and the papers of Catharine MacKinnon. Secondary source materials include, but are not limited to, bibliographies on Black women's transnationalism, United States-based women of color organizations working on issues related to war, women's and sexual rights in the context of indigenous histories in the United States, and suffrage for women of color inside the United States and transnational suffrage organizations outside the US The course aims to explore the diverse international connections between individual feminists and women's and LGBTQ rights organizations, and the ways that trends in the United States influenced rights around the globe. Studying these relationships and the interactions, scholarship, and events that they produced gives us a more accurate historical record of the feminist and LGBTQ movements as a whole, and broadens our understanding of the ways that these movements created lasting cultural change in the United States and abroad.

Do Self-Defense Laws Protect or Harm Women?: Race, Class and Gender in the Legal System and its Effects on Female Incarceration

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Sociology, 2021

Studies of Women, Gender, and Sexuality
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Historical and anecdotal evidence suggest that women who use guns and other forms of self-defense against their largest statistical threat—their own male partners/exes—are more likely than men to be held criminally liable. We want to determine how many women incarcerated for violent offenses were actually trying to defend themselves. By qualitatively analyzing two databases, we observe why and how race, class, and gender intersect and affect the legal system. By investigating qualitative data from 426 female perpetrated homicide cases, where suspect and victim were strangers, collected by the NVDRS (National Violent Death Reporting System), a national database, we have discovered that approximately less than 5 qualify as legitimate self-defense cases. This suggests that female gun use is primarily offensive rather than defensive, disproving the message expressed by gun-supporters that the "good woman with a gun" is the optimal solution to gender and sexual violence. We further investigate whether the law protects the few cases that involve self-defensive claims made by women. By collecting and coding legal documentations of female perpetrated homicide cases with the TCJC (Texas Criminal Justice Coalition) in Texas, a state with one of the top ten highest female incarceration rates and a strong Stand Your Ground law, we aim to identify self-defense cases and determine which result in the defendant's incarceration and which in acquittal. We expect results to show that women are more likely to be charged than men and pose the question of whether all threats, including home intrusions or burglary must always demand a lethal response. By shedding light onto the multidimensional intersectionality of violence, our research aims to create a legal and publicly accessible database of cases that speaks more to disadvantaged women in the legal system.

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