HSURV

PRISE | BLISS | PRIMO | SHARP | SURGH

Abstracts 2020

HARVARD SUMMER
UNDERGRADUATE RESEARCH VILLAGE

2020 ABSTRACT BOOK

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LETTER FROM THE DIRECTOR

Dear Harvard Summer Undergraduate Research Village Fellows,

I am delighted to introduce this fifteenth volume of research abstracts from the 2020 Harvard College Summer Undergraduate Research Village, comprised of PRISE (Science and Engineering), BLISS (Social Sciences), PRIMO (Markets and Organizations, co-hosted by Harvard Business School), SHARP (Humanities and Arts), and SURGH (Global Health, co-hosted by the Harvard Global Health Institute). 2020 certainly marks a diversion from our customary Research Village summer. With the advent of the coronavirus pandemic, our community has been limited to remote participation, primarily through video links and electronic messaging. I admire every Fellow among our programs for pivoting and adjusting in so many aspects of their lives and who, even in such challenging circumstances, still could engage in formative research projects. And while the experience was not what any of us would have expected or otherwise would want, I very much appreciate and am grateful for the tireless efforts of our Program Assistant Fellows and Proctors who have stewarded a full schedule of engaging activities, albeit online, throughout the summer.

Our collection of abstracts here would not have been possible without the outstanding, determined work of the group of Research Village editors whose voluntary charge has been to collect, organize, and publish the works of all of the Fellows. I would like to thank this group especially for taking on the particularly complicated challenge to formally record the remote research projects of the Research Village community this summer.

To the Summer Undergraduate Research Village Fellows of 2020, I look forward to us all meeting in person someday soon. I very much wish you every success in your further intellectual growth and academic trajectory, especially considering the uncertain environmental landscape we have experienced this summer. I very much appreciate your enthusiasm and inclusiveness, and hope you have been able to develop personal and collegial relationships with your peers that extend beyond the Research Village going forward.

Sincerely,
Gregory A. Llacer
Director, Office of Undergraduate Research and Fellowships

LETTER FROM THE EDITORS

Dear HSURV Community,

The world's turned upside down. In other years, we would be savoring the last golden drops of summer while catching up over picnics on House lawns, roaming around scenic downtown Boston's streets, or biking along the glittering Charles River with the wind flying through our hair. In the evenings, we would dine with distinguished faculty speakers, sing karaoke in each other's common rooms, or curl up next to a bonfire to roast s'mores. In these last few weeks, we would hug and say tearful goodbyes.

But this summer, threatened by a historic pandemic, we remained apart, necessarily separated from each other in order to do our part in combating this virus. Further, the tragic loss of lives—those of George Floyd, Ahmaud Arbery, Breonna Taylor, and Elijah McClain, among many, many others due to police brutality and racial violence—called upon us to protest with outrage and to work together towards making meaningful change. In the midst of this fear, anger, uncertainty, and resolve, we built a research village together out of pixels, kindness, and community.

Indeed, while this summer has been an incredibly meaningful experience for us all, it is not lost on us that a lot of thoughtful dedication went into transforming an in-person research experience into an online one. And for that and more, we have many people to thank. To the faculty and mentors of our respective programs—thank you for supporting us so generously and for teaching us to think deeply, to be curious, to persist in the face of confounding results, and to pursue research questions with tenacity, care, and humility. Even from afar, you imparted important lessons to us about the world of research. To the program assistants and HSURV staff—thank you for finding different ways to introduce us to new friends, for making us laugh, for listening to us worry, and for welcoming us into the HSURV community with warmth and kindness, all while helping us cope with distance and different time zones. To our fellow students and friends—thank you for all the ways in which you built community and supported one another through the moment we are in. A special thank you to Trang Truong and Elizabeth Perten from URAF, who shared their support, time, and advice in helping us make the Abstract Book a reality. And last but not least, a heartfelt thank you to Greg Llacer, Chris Kabacinski, and the rest of the URAF staff for working tirelessly to create an intellectual and social community where we could learn, grow, and thrive. We will always remember and be grateful for your generosity and kindness during this moment in time.

Sincerely,
The 2020 Abstract Book Team

THOUGHTS OF THE ARTIST

Iris, Daffodil, and Tomorrow

A worldwide pandemic swallowed us whole. Our society has come to an abrupt halt, yet the underlying cries of struggling individuals escalate. Across the United States, masses rise in confrontation against racial injustice. Voices continue to push down the confining walls of gender. I wished to capture all of 2020's meaningful stories in a serene yet powerful way.

On the cover, two masked silhouettes face one another. One grips a blue iris representing hope and courage; the other holds a yellow daffodil symbolizing new beginnings. These silhouettes appear to be completely different in both identity and background, yet they are one.

During these trying times, we do not let go of the small bundle of hope for a better tomorrow. Some precautions implemented during the COVID-19 crisis may remain and become the 'new normal'. Victory in our fights for a more egalitarian society may require more patience. However, through unconditional unification, we will shed our shadows and bloom new beginnings.

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The interior graphics captures some of the many remarkable Harvard locations. As noticed, each of these attractions is pictured empty, underlining the changes that COVID-19 has thrust upon us. It sets the stage for a pleasant contrast with the following abstracts by showing that, even during this trying struggle, researchers are relentlessly hard at work.

The last page shows a packed Harvard Stadium, an image that is unimaginable at the moment, but a hope we all dream. The roaring cheers of the full stadium relayed from the picture also hold a celebratory meaning to all HSURV researchers and faculty who helped make this summer a success!

Ellen Choi
Cover Designer and Interior Graphics Artist

PROGRAM DESCRIPTIONS

PRISE: The Program for Research in Science and Engineering aims 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).

BLISS: The goal of this program is to Build Learning through Inquiry in the Social Sciences; we provide a formative and substantive social science research experience while also encouraging community, creativity, and multidisciplinary scholarship. A diverse cohort of BLISS Fellows works primarily on pre-designated research projects led by Harvard faculty, although in recent years, an independent project option has been added. In addition to conducting full-time research, BLISS Fellows participate in rich variety of programming, including social and academic activities.

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

SHARP: The Summer Humanities and Arts Research Program seeks to build community and stimulate creativity among a small cohort of Harvard undergraduate researchers in the humanities and arts. SHARP fellows work on research projects with Harvard-affiliated faculty, researchers, and senior library and museum staff. Fellows participate in rich weekly programming that includes both social and academic activities. To participate in SHARP, you must apply and be selected to work on one of the available SHARP research projects designed by the faculty/professional mentors or on an independent project you have personally designed.

SURGH: The Summer Undergraduate Research in Global Health 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 participate in rich evening programming including both social and academic activities.

Engineering & Applied Sciences

The Association Between Diet-Induced Health Risks and the Marketing of Processed Foods and Sugar-Sweetened Beverages

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Harvard T.H. Chan School of Public Health

Advisors: Sara Bleich, Caroline Dunn
Mentor: Jane Dei

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Worldwide increases in childhood obesity rates are striking. Rates in the United States are among the highest in the developed world, and children participating in the Supplemental Nutrition Assistance Program (SNAP) are at highest risk of obesity. Increasing availability and marketing of highly processed foods and sugar-sweetened beverages (SSB) in retail outlets may impact dietary patterns and subsequent health risk. The purpose of this research was to identify the association between the marketing of highly processed food items and/or SSBs which increase diet-induced health risks and the timing of benefit issuance in the Supplemental Nutrition Assistance Program (SNAP). Data extracted from a sample of SNAP-authorized food retailers (n=600) across six states with varying SNAP benefit issuance schedules was analyzed. The main outcomes of interest were the percent of SSBs (total SSB ads/total beverage ads) and the percent of processed foods (total highly or moderately processed foods/total food or beverage ads) in each circular. The relationship between state SNAP benefit issuance and marketing trends for SSBs and processed foods were evaluated using the difference-in-difference approach. Based on pilot data from 300 stores across 3 states, a subset of the overall sample, there was increased SSB and processed food marketing during SNAP issuance periods. The magnitude of these results was particularly magnified in stores located in census tracts with high SNAP participation. This form of predatory marketing may induce increased consumption of SSBs and processed food among SNAP participants, increasing adverse health risks for obesity and type 2 diabetes which are linked to excessive fat intake. Perpetuated systematic flaws and outdated or ineffective government policies are often the basis of health disparities. Through new policy, the common practice of food retailers promoting SSB and processed food intake for SNAP qualifiers through purposeful advertising timing should be prevented to reduce diet-induced health risks.

Structural and Impossibility Results for Obviously Strategyproof Mechanisms

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Mentor: Ravi Jagadeesan

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The field of mechanism design studies the construction of games, or *mechanisms*, in which some desired outcome results from the actions of the participants, or *agents*. It was traditionally assumed that agents act according to their own best interests to maximize their payoff in the mechanism. Under this assumption, the actions of agents should be predictable for mechanisms that are *strategy-proof*, that is, for mechanisms in which each agent has a strategy that maximizes their payoff, regardless of the other agents' strategies. However, following empirical evidence that participants of real-world strategy-proof mechanisms often play suboptimal strategies, a line of work has recently emerged studying simple mechanisms, which are robust to the illogical reasoning that results in suboptimal behavior. The most prominent notion of simplicity, *obvious strategy-proofness* (OSP), requires each agent to prefer all possible outcomes following each of their chosen actions to all possible outcomes following any deviating actions. While empirical evidence has supported using OSP to model human behavior, many open questions remain regarding the theoretical structure of OSP. We introduced a new formulation for OSP that reveals additional structure in OSP mechanisms. Using this formulation, we proved that no OSP implementation exists for multiple commonly used mechanisms for allocating goods among agents, including certain competitive equilibria, combinatorial auctions, and voting mechanisms. These results indicated that mechanism designers who prioritize simplicity must turn to alternative mechanisms. Furthermore, because the mechanisms we considered are all too complex to be OSP, their relative levels of complexity cannot be compared without more general notions of simplicity.

Adaptive Dynamics of Memory-1 Strategies

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Harvard Faculty of Arts and Sciences

Advisors: Christian Hilbe, Martin Nowak

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The evolution of cooperation is of much relevance to both biologists and economists. Sometimes called the third pillar of evolution (along with mutation and natural selection), cooperation is responsible for a vast array of important phenomena across human civilization and the rest of the biological world. Yet it is simultaneously a delicate structure capable of collapsing under pressure when its altruistic features are exploited. Here, we analyze a simple adaptive dynamics model of the evolution of cooperation which arises from the repeated Prisoner's Dilemma. Cooperativity in this model is a collection of four parameters, each representing the probability of a cooperative move in the next round of the Prisoner's Dilemma, given the outcome of the previous round. The differential equations governing the time-evolution of these parameters are not well understood. Computational tools are used to answer questions about monotonicity, stable and unstable fixed points, and limit points of trajectories satisfying the equations. A variety of findings were obtained. First, fixed points of the system were found and classified according to their stability. Second, a three-parameter subsystem of the four-parameter system was located: a subsystem in which individuals can no longer distinguish between themselves and others in their memory of the previous round. Third, an unexpected symmetry of the equations was discovered and proved. These results afford much progress in the understanding of evolution in this model, and suggest a further avenue of research. Specifically, the emergence of cooperation in a world in which individuals cannot distinguish between themselves and others has begun to be studied. This reveals cooperativity to be more robust than expected. Further research may well be able to make these observations precise and detailed.

Periodic Deployable Kirigami Pattern Structures

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Harvard John A. Paulson School of Engineering and Applied Sciences

Advisor: L. Mahadevan
Mentor: Gary P.T. Choi

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Strategically architected kirigami cuts can transform a plain sheet of material into a deployable structure composed of rotating tiles. Which cut patterns can be deployed in this manner, and what properties can deployable patterns achieve? This work uses wallpaper groups, which are 17 symmetry groups that characterize periodic tilings of the plane, to study the rotational and reflectional symmetry properties of deployable kirigami patterns. We show that at least one deployable cut structure can be found in each of the 17 wallpaper groups. Then, we design expansion cut methods for generating new associated patterns with greater size change from existing kirigami patterns. We analyze how deployment affects a pattern's symmetry and characterize the different wallpaper group changes that patterns can undergo. Finally, we discuss how representing patterns with their underlying lattices helps us understand the ways cut placement affects the topological and mechanical properties of the structure. Our results provide an approach for designing deployable kirigami-based metamaterial patterns with desired size change and symmetry properties.

Quasicrystalline Deployable Kirigami Pattern Structures

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Mentor: Gary P.T. Choi

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Deployable kirigami structures can exhibit exotic mechanical properties, such as a negative Poisson's ratio, desirable in fields like robotics and materials design. Existing research in this area has focused on deployable periodic patterns, in which a deployable unit cell can be translated as many times as needed to tile a given region. In this work, we extend deployable kirigami design methods to aperiodic patterns, which have no unit cell. Specifically, we propose several approaches for deploying quasicrystal patterns, which are aperiodic but still ordered. To model the deployment, we used a 2D rigid body physics engine to develop a kirigami simulation application. We discuss and analyze methods such as 1) adding thin rotating units between tiles to increase flexibility within the pattern, 2) removing tiles to increase negative space, and 3) deploying Hamiltonian cycles in the pattern for maximum size change. By extending kirigami pattern design beyond periodic patterns, the findings enrich our understanding of how kirigami cuts can be used for metamaterial design.

Analyzing Stereocilia Motion in a Computational Model of the Gerbil Cochlea

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When sound waves enter the mammalian ear canal, they are translated into mechanical vibrations by the middle ear before entering the fluid-filled cochlea, where they are converted into pressure waves. These waves deflect tiny rod-like protrusions (called stereocilia) on sensory hair cells along the cochlea's length, initiating signaling pathways to the brain. While classic theory accredits a stereocilium's deflection to a simple mechanical shear, recent experimental results have suggested more complex mechanisms. We hypothesize that this is related to the "W"-shaped arrangements of stereocilia on outer hair cells. To investigate these deflection mechanisms, the Puria Otobiomechanics Lab is developing a finite element model of the gerbil cochlea. This project operated in parallel with this model development study. MATLAB code was developed to process and analyze raw data obtained from the model, aiming to identify patterns that might improve understanding of stereocilia motion and transduction. The stereocilia's angle of deflection was illustrated graphically and plotted as a function of input stimulus frequency. Preliminary results—which are expected to change as the model changes—suggested that the angle of deflection was greater on the "legs" of the "W"-shaped stereocilia bundle than in the middle of the "W." This project forms a framework for illustrating and interpreting stereocilia deflection even as the model continues to be developed.

Non-monotonicity of Gene Regulation Functions

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Mentor: Rosa Martinez-Corral

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Until recently, gene regulation studies have been carried out under the assumption of equilibrium conditions. However, there is evidence that gene regulation involves energy expenditure, i.e. occurs away from thermodynamic equilibrium. Under non-equilibrium conditions, a gene's expression may have a non-monotonic dependence on transcription factor (TF) concentration. We explore non-monotonicity of the gene regulation function (GRF) analytically and numerically, assuming a model of two binding sites and two conformations with the expression strategy "average binding." Biologically, this describes two TFs binding to a gene and changing chromatin conformations, thereby modulating their binding affinities. Thus far, Python simulations exploring the parameter space have suggested that the degree of non-monotonicity is tied to the amount of energy expenditure. This can be quantified by the cycle ratio, the ratio of the product of forward transition rates to reverse transition rates around a cycle. The peak height of the GRF appeared to be maximized at higher values of the cycle ratio. However, the cycle ratio does not completely determine the behavior of the system, as parameter values in other parts of the graph may play a role. Overall, the analysis of non-monotonic behavior is helping unravel the interplay between energy expenditure and the context in which it occurs.

Preventing Catastrophic Forgetting with Memory Replay

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Boston Children's Hospital, Harvard Medical School, and The Center for Brains, Minds, and Machines

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Mentor: Mengmi Zhang

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A significant hurdle for machine learning algorithms is continual learning: the ability to learn from a continuous stream of data without forgetting. A common approach to enable continual learning is replay, wherein representations of previous training examples are shown to a model in order to prevent forgetting. These approaches are often inspired by hippocampal memory replay in humans, where experiences are replayed in wakeful and rest states to strengthen memories. Still, previous approaches suffer from large memory requirements and the inability of models to prioritize reading and writing certain experiences to memory. We propose a method that not only allows models to store compressed representations of experiences, but also grants models fine-grained control of what to write and read from memory. We observe promising results on a variety of datasets, including ImageNet and CoRE50.

Efficient Split Learning Over Non-Homogeneous Data

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Massachusetts Institute of Technology

Mentors: Ramesh Raskar, Praneeth Vepakomma

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Legal and ethical challenges surrounding raw data sharing in sectors such as healthcare have increased interest in private machine learning (ML). One privacy-preserving training method is *split learning*, wherein the communication between clients (data holders) and the server (model holder) is realized through network activations and gradients rather than raw data. Most of the work on private ML assumes homogeneity of distributed data sources, which in practice is rarely true. The models trained under this assumption on heterogeneous data systems either (i) fail to converge to an acceptable validation accuracy or (ii) unlearn insights from all but the most recent dataset, depending on the training procedure adopted. In our work, we propose a new training method that allows efficient joint learning over clients with non-homogeneous data sources in a split setting. Our procedure allows us to reach the performance of vanilla neural networks on benchmark datasets in a comparable amount of training time without sharing raw data. We further address issues with use of batch-dependent transformations such as *batch normalization* in split neural networks with non-i.i.d. data sources and suggest alternative normalization measures.

Enforcing Go Type Safety with Undervisors

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Advisor: James Mickens

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The growing reliance on data center computation raises an important question: how can we enforce the security and integrity of a program's execution when we don't control the physical machine? Cryptographic approaches such as fully homomorphic encryption are promising, but they are still magnitudes too slow for practical use. A more promising approach is trusted hardware. The Mickens group developed the notion of an "undervisor," a second pipeline that examines the state of application code running on the primary processor. This project focused on producing monitor code to be run on the second pipeline. The security policy of choice was type safety for Go, a high-level, managed language with strong, static typing. The central challenge was tracking objects over the lifetime of the program. Compiler techniques help the monitor determine the type and address of an object upon allocation, but they cannot determine when objects are destroyed or moved. To solve this challenge, we instrumented the Go runtime library to trigger monitor code on object deallocation or transfer, in order to track objects on the heap and stack respectively. Sensitive object accesses trigger compiler-emitted monitor code to check if the type matches what is stored in the monitor data. This work shows that enforcing security principles for a high-level managed language with an undervisor can be accomplished with a few lines of monitor code per object access. With undervisors and the accompanying software techniques, remote computation can be fast and secure under reasonable assumptions.

Using Deep Reinforcement Learning for Mechanism Design in Dynamic, Multi-Actor Worlds

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Harvard John A. Paulson School of Engineering and Applied Sciences

Advisor: David Parkes

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Relatively little is known about mechanism design in dynamic, multi-actor systems with decentralized information and rapidly changing situations in the environment. The goal of this study is to use deep reinforcement learning to train well-performing agents in Atari 2600 games to evaluate the effectiveness of various mechanisms in achieving different desirable outcomes. The study makes use of open infrastructures including the Arcade Learning Environment and OpenAI Gym, making modifications to the Atari 2600 platform and game emulator to introduce mechanisms, resource constraints, and noise into the Atari game Space Invaders. With the modified versions of the game, the study used deep reinforcement learning to train AI actors and examine the differences in rewards, resource consumption, and other metrics of these actors under different mechanisms and resource constraints. The results show an increase in performance of the AI actors under the introduction of an auction for the allocation of game resources, holding other factors constant. On top of that, results show that curriculum learning, where agents start out with a low stake, more frequent occurrence of mechanisms (e.g. auctions) and then gradually progress to a high stake, less frequent occurrence of mechanisms, holding the expected rate of allocation constant, is able to generate a boost in final performance under the same conditions compared to the alternative of constant rate training in most scenarios. The study demonstrates that introducing mechanisms for resource allocation is able to improve performances of AI actors under the game Space Invaders and that curriculum learning specifically is a promising training approach that could lead to better performance.

Learning Interpretable Time-series Summaries for Prediction from Intensive Care Data

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Advisor: Finale Doshi-Velez
Mentor: Sonali Parbhoo

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Machine learning models that use the dynamics of a patient's physiological time-series data have led to performance increases for several intensive care unit (ICU) risk stratification tasks. However, many of these time-series models and their learned representations are highly complex and therefore difficult for clinicians to interpret. Our work proposes a new optimization framework to learn summaries of clinical time-series that are both predictive and easily understood by humans. Specifically, our summaries consist of simple functions of physiological time-series data. We compare our learned summaries to static demographic and time-series data in the prediction of two ICU risk stratification tasks: in-hospital mortality and vasopressor onset. We hypothesize that our learned summaries, when combined with demographic and time-series data, achieve performance comparable to state-of-art models for both tasks. Because our learned summaries are easily understood by humans, clinicians can directly interpret how dynamics of a patient's physiological time-series affect the model's predictions for a given risk stratification task. Our architecture can be used to learn interpretable summaries of physiological time-series data that improve prediction for a variety of risk stratification tasks.

Sequential Consistency for Noria Using Shuffle Locks and STO

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Advisor: Eddie Kohler
Mentor: William Qian

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Noria, an implementation of the new partially-stateful streaming dataflow model that supports eviction and reconstruction of dataflow state on demand, has made dataflow viable for building long-lived, low-latency applications. However, it only guarantees eventual consistency, in which all accesses to a given data item eventually return the last updated value when the stream of updates stops. To guarantee stronger consistency, we need to extend Noria to support transactions. While locks are an essential building block of such an extension, traditional locks optimize for a single memory design and platform that adds to the cost of concurrency. In 2019, shuffle locks were introduced to optimize for non-uniform memory access as a way to mitigate the weaknesses of traditional locks. Building on recent research, they re-order the queue of threads waiting to acquire the lock in accordance with some pre-established policy that achieves an awareness of the underlying memory design. To minimize the added cost of transactions and achieve stronger consistency, we explore leveraging software transactional objects that track abstract operations on transactional data types, coupled with shuffle locks. Our implementation may demonstrate that the cost of augmenting Noria to provide sequential consistency is manageable.

Splicing Data from Multi-User Applications

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Advisor: James Mickens

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Many applications store sensitive user data in the cloud, but users typically have little control over how their data is used. New laws like Europe's General Data Protection Regulation (GDPR) give users the right to enumerate and delete personal data in the cloud. Unfortunately, the application developers lack the technical, systems-level mechanisms to enforce GDPR-style policies among a wide range of applications. This project investigates a new spreadsheet-inspired storage layer that natively supports the enumeration and deletion of user data. Spreadsheets are simpler than SQL databases but expressive enough to support interesting applications. However, even simple spreadsheet-style formulas have nontrivial deletion semantics due to data dependencies between the cells that provide inputs to and store outputs from formulas. Therefore, we define semantics that ensure, upon deletion, formulas evolve in a way that preserves the intended behavior of the application. We also ensure that deletion is efficient by introducing aggregation points (that keep track of all the values a user owns) and function decomposition (which caches the outputs of constituent sub-formulas). While spreadsheets do not include rich SQL queries such as SELECT FROM WHERE, we introduce new spreadsheet primitives such as LIST(), TUPLE() and TABLE() to allow developers to create higher-level data structures atop a traditional sheet. Finally, we show that our spreadsheet can act as a backend for a Twitter clone.

Multi-Agent Reinforcement Learning for Artisanal-Scale Mining Policy

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Harvard John A. Paulson School of Engineering and Applied Sciences

Advisor: David Parkes

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Artisanal-scale mining (ASM) is an essential livelihood for millions across the globe, yet its usually-informal practice contributes to unregulated deforestation, mercury contamination, and economic instability for miners. As in many environmental settings, short-term rewards do not incentivize long-term sustainability goals. Current real-world approaches to address these issues in ASM include evictions of miners and educational programs to introduce more sustainable mining practices; however, inconsistent implementation of these solutions, an absence of large-scale economic and environmental data, and setting-specific complexities make effective analysis difficult. To better understand agent incentives and behavior, these "tragedies of the commons" can be modeled as multi-agent sequential games. We modeled our agents using a Markov game for multi-agent reinforcement learning. In our model, mining agents compete for mining resources in a stylized grid world environment while the single government agent controls supervisory aspects of the environment, such as evictions of high-contaminating agents and subsidies for low-contaminating agents, without a physical presence in the grid world. Within the government actions, we also explored an "education" action that would change the mining agent's discount factor to reflect a learned, increased weighting for long-term future environmental costs. We trained agents using reinforcement learning algorithms such as deep Q learning and policy gradient methods in a modified OpenAI gym environment. Our results show that budgeted governmental action can effectively incentivize agents to contaminate less in this model.

Deep Learning to Predict Adverse Postoperative Outcomes after Cardiothoracic Surgery from Preoperative Chest Radiographs

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Advisor: Michael Lu
Mentor: Vineet Raghu

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Decisions whether to perform cardiothoracic surgery are guided by the Society of Thoracic Surgeons (STS) operative risk score. The STS score is time-consuming to compute ($>$60 inputs) and cannot be applied to 20% of cardiac surgeries. We hypothesized that a convolutional neural network (CNN) can use a preoperative chest X-ray image to identify patients at high-risk for five adverse postoperative outcomes: kidney failure, stroke, mechanical ventilation, prolonged length of stay ($>$14 days), and reoperation. Our dataset consists of 13,673 preoperative chest x-rays from Massachusetts General Hospital. The oldest 9,796 X-ray images were used for training the CNN (surgery prior to April 8, 2014) and the rest were used for testing (3,877 images). For each outcome, discriminative performance of the CNN model was compared to the STS risk score, using the area under the receiver operating characteristic curve (AUC). Results are provided for the test dataset, stratified based on whether surgical risk could (e.g. coronary artery bypass) or could not (e.g. tricuspid valve repair) be calculated using the STS risk score. The CNN model had a similar discriminative performance to the STS score when predicting kidney failure (CNN AUC 0.755 vs. STS 0.727, p=0.52), ventilator usage (0.732 vs. 0.734, p=0.95), and reoperation (0.527 vs. 0.645, p=0.44). However, the CNN model outperformed the STS model in predicting stroke (p=0.042), while STS better predicted prolonged stay (p=0.031). The CNN had similar performance across all outcomes in the 34% (1,332/3,877) of procedures where the STS risk score could not be applied. Ultimately, a CNN is able to predict adverse outcomes after cardiothoracic surgery with similar performance to the STS risk score, based on a preoperative chest X-ray image.

Undervisor: An Isolated Hardware Module That Can Enforce Run-Time Security Policies on Top-Half Instructions

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Harvard John A. Paulson School of Engineering and Applied Sciences

Advisor: James Mickens

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Rapid industry adoption of execution of code on remote machines (cloud computing) has brought to light security challenges associated with the lack of trust in privileged software. Intel's Software Guard Extensions (SGX) can prevent privileged code from accessing certain program state by sequestering a region of memory (an enclave) that only the program itself can access, but this restriction means that run-time security checks, such as enforcing control flow integrity (CFI), must run from within the enclave itself. This study aims to remove this restriction by adding an undervisor: a module that, on an isolated set of hardware resources, can examine the register state of a program running on the main processor, perform real-time security checks, and preempt malicious code execution. We created a software testbed for implementation of top-half processes along with associated monitor policies, and we implemented standard security policies running in the undervisor, including a shadow stack and forward-edge CFI. We found that enforcement of these security policies without having access to the top-half process memory is possible and easily expressible in the logic of the undervisor. Furthermore, we show that monitor policies can be automatically generated at compile time, which reduces software development overhead to the equivalent of current compiler-generated security checks. These results suggest that undervisors are a viable security technique for small binaries without a high density of monitored instructions. However, it remains to be seen what hardware designs or compromises must be made and how more complex (or more concurrently running) monitor policies will perform at scale, particularly with respect to their impact on the running time of top-half code.

Machine Learning Approach to Cancer Diagnosis

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PRISE Fellow

Brigham and Women's Hospital

Advisor: Faisal Mahmood
Mentor: Jana Lipková

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Applying machine learning to medical diagnoses is revolutionizing the field of computational pathology. This project used a previously developed, highly accurate, semi-supervised machine learning program called CLAM (Clustering-constrained Attention Multiple instance learning) that takes as input histology slides of biopsies or resections and outputs a cancer diagnosis, like renal cell carcinoma. This project examined how CLAM could be used with images from a bead microscope, a device which can be 3D printed for less than a dollar and attached to a smart phone camera. We preliminarily tested which cancers our process could diagnose effectively and will calculate its Area Under Curve (AUC) performance rating for various cancers. If it is shown that CLAM can be used effectively with a bead microscope, it could have large implications for communities that do not have access to expensive medical equipment (e.g. to make a histology slide) and that do not have a specialist to read the histology slides.

QuVis: A Quantum Circuit Visualization Tool for Novices

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QuVis is a novel educational platform for quantum circuit composition, exploration, and analysis for novices. The rapid growth of the quantum computing field surpasses the educational capacity of existing systems, which makes novices particularly in need of accessible tools. Often, novices struggle to understand a fundamental concept: how quantum gates affect circuit state probabilities over time. QuVis contributes two novel visualizations to develop this intuition. One visualization teaches users about the relationship between gates and single qubit probabilities. This feature integrates stacked bar charts into the traditional quantum circuit diagram to display the probability distribution of a single qubit after each gate application. The second visualization provides insight into the intermediate steps that contribute to the final state probability distribution. The combination of a radial bar chart and a time slider helps users see the probability distribution of the entire quantum circuit at a user-specified execution step. Based on preliminary user testing, our results showed that QuVis users created quantum circuits faster and found the platform more intuitive than a comparable tool.

Mechanism Design for the Optimal Allocation and Sharing of Limited Resources in Multiplayer Space Invaders

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Mechanism design is the design of an environment containing strategic players, or agents, to achieve certain desirable properties such as social welfare. In our research, we aimed to study whether introducing different mechanisms such as auctions into multiplayer Atari Space Invaders with a limited shared shot resource could improve the total reward through more efficient allocation of the resource. We began with a joint training setting where two players in the same Space Invaders game controlled by a single AI instance learned to maximize a shared reward. The two players shared a limited resource pool of shots, and one of the players was artificially handicapped to produce skill imbalance. We found that an auction mechanism where players must first bid for shots before firing attained significantly higher reward than a direct mechanism where players consume shots directly. Furthermore, we found that a mechanism artificially limiting the fire rate resulted in similar performance to the auction, indicating that the gains of the auction over the direct mechanism are mostly due to the fire rate limitation and not to the bidding component of the auction. We also experimented with mechanisms in a multi-game setting, where two agents in two separate single-player Space Invaders games were given independent action and observation spaces, but still shared a shot pool and aimed to maximize a shared reward. Our results suggest that there is no significant improvement with using the auction mechanism over the direct mechanism. Because in our multi-game setting the agents are not able to directly see each others' observations and actions, we expected it to be a more challenging learning environment. We are encouraged by the promising results from our joint training experiments and hope to expand our findings to designing mechanisms for settings containing both human and AI agents.

A Machine Learning Approach to Respiratory Viral Infection Diagnosis

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Accurate and efficient diagnosis of respiratory viral infections is crucial to effective treatment. Effective disease-specific treatment is essential, as many respiratory infections become comorbidities when paired with other respiratory diseases. Respiratory viruses often present high mutation rates, making classification methods that are generalizable across viruses and strains crucial. The goal of this study was to implement a machine learning approach to classify respiratory infection patients, which will culminate in efficient, generalizable diagnosis. Public microarray gene expression data from patients before and after influenza H3N2 virus, respiratory syncytial virus (RSV), and rhinovirus infections was obtained. Differential gene expression analysis was performed to identify dysregulated genes following infection compared to baseline. Pathway enrichment analysis was conducted to identify dysregulated pathways in each disease and across diseases. Using dysregulated gene expression data, random forest (RF), K-nearest neighbors (KNN), and support vector machine (SVM) classifiers were trained and tested. Important features for each model, while classifying disease, were extracted and compared to identify important genes across models. Pathway analysis was performed to identify pathways composed of these genes. Immune process, response/defense against virus, and type-I interferon response pathways were among those that were enriched across diseases. When classifying by disease, the models showed promising accuracy, ranging from 64% (RF) to 86% (SVM). When classifying disease status (infected/healthy), the models achieved similar accuracy (RF-75%, KNN-79%, SVM-75%). Immune process, response to cytokines, and cell communication pathways were among those that were important in classifying infected patients. Further analysis of machine learning models and enriched pathways are next steps in ascertaining the role of these diagnostic features in classifying respiratory infections. Approaches using artificial neural networks and stacking machine learning models, in which different models are used in succession to improve accuracy, will also be pursued. This may lead to an accurate, generalizable tool for diagnosing respiratory infections.

Fabricating an Auditory Aid Haptic Device with Dielectric Elastomer Actuators

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To those with hearing disabilities or who face language barriers, an instant translation device can be very beneficial. To induce direct translation and hearing through one's skin, dielectric elastomer actuators (DEAs) can be utilized. A DEA is a kind of artificial muscle that can be manipulated to vibrate with variation through voltage actuation. When a haptic device with several DEAs is created and worn, we are able to actuate differing patterns of vibrations to transmit a message. Much like Braille, language through vibrations has much potential. The major goal of this project is to precisely control the vibrations of each DEA which depend mostly on the elastomer composition, actuator geometry, and actuator voltage. Keeping the remaining two constant, the study was focused on the effects of the composition on the performance of the wearable haptic device. After creating a simulation of a DEA in COMSOL Multiphysics, several different elastomers were tested each with different Young's moduli and permittivity constants. Thus far, there have not been any concrete conclusions on DEA performance based on elastomer composition. However, with more trials and different compositions, we anticipate that a pattern should arise. The higher the force output and displacement of the vibrations from an elastomer, the larger the range of possible transmissions which makes the haptic device more versatile. After optimizing the performance of the actuation vibrations it is important to understand how the human somatosensory system will perceive the vibrations. A complete analysis will include the understanding of how subtle each signal can be to convey different messages as well as how distinct each message signal must be from one another. All of these steps combined are enough to make an effective hearing aid haptic device.

Analyzing Antiviral Mechanisms of Ionic Liquids and its Impact on Viral Infectivity Through Molecular Docking

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Months after the initial outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the world still faces the absence of an approved vaccine or targeted therapeutic to tackle its viral infectivity. Although there are ongoing clinical trials involving antivirals, the ultimate message this outbreak conveys is the need to not only turn towards drugs and treatments that have been previously developed, but even more so towards unconventional yet innovative approaches. This research aims to investigate the potential of ionic liquids (ILs) for viral inhibition. ILs are liquid state salts composed of cations and anions with melting points below 100°C that carry various roles in the biochemical field, ranging from enhancing drug delivery to applying their antimicrobial activity against viruses and bacteria, as previously demonstrated by the Mitragotri Lab. To analyze whether ILs impact rates of viral infectivity, molecular docking studies were performed on the model nonenveloped virus *Listeria virus p100*. Its major capsid protein, gp17, along with other protein homologies, were docked against anions of varied carbon chain lengths to model the interaction between proteins and ILs. The docking scores obtained thus far demonstrate a strong correlation between binding affinity and carbon chains: anions with longer carbon chains yielded higher docking scores, which translates into a stronger affinity between IL and the major capsid protein. These computational results agree with a previously published paper regarding the effect of ILs against viral infectivity of *p100*. The current findings implicate that ILs may affect viral infectivity through capsid protein interactions. This knowledge could open doors to the design of ILs as an antiviral agent to tackle pressing viral infections.

Identifying Mechanism of Anti-Viral Activity of Ionic Liquids Against Phi6 Envelope Proteins by Molecular Docking

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Ionic liquids (ILs), organic salts in liquid state, have recently been identified as promising pharmaceutical and anti-microbial agents. Many have negligible cytotoxicity to human cells and are easily transported, thus improving the delivery of small molecules and biologics. However, much remains unknown about the mechanism through which these ILs confer antiviral properties. In this study, we conducted a molecular docking analysis of eleven different anions on four envelope proteins (P3, P6, P10 and P13) of the virus Pseudomonas phage Phi6, with the structures of the proteins generated using protein-modeling programs. Phi6, an enveloped virus, represents a suitable surrogate for that class of viruses, including many disease-causing viruses such as SARS-Cov-2. To generate the most accurate representation of protein structure, two well-known programs, I-TASSER and MODWEB, were used to compare structure results, and the most accurate structures were selected based on homology alignment, sequence identity and C-scores for the docking experiments. Thus far, initial findings suggest that there may be an inverse relationship between the anion side-chain length and the affinity of the anion for the proteins, with the effect especially prominent for anions up to six carbons in length for proteins P3, P10 and P13. This study, paired with the findings in Gundolf *et al.,* potentially indicates a relationship between protein-anion affinity and infectivity of phage Phi6 that could also be representative of a general trend in viruses. Understanding IL mechanism of activity on viruses would prove vital in developing new and potent anti-viral drugs and increasing knowledge on how ILs display anti-viral properties.

Crossover in Aqueous Organic Redox Flow Batteries

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Aqueous organic redox flow batteries (AORFBs) have recently emerged as potential solutions to grid-scale storage of renewable energy. Decreased capacity and efficiency caused by crossover is derailing the commercialization of redox flow batteries (RFBs). Crossover mainly occurs via diffusion, migration and electro-osmotic drag. Crossover in all-vanadium batteries has been widely studied, but the effect of crossover in AORFBs is still mainly speculated. Data was obtained from various experiments in the literature. Cation-exchange membrane (CEM) and anion-exchange membrane (AEM) properties in all-vanadium, and methyl viologen (MV)/4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) chemistries, respectively, were used to model total crossover and crossover due to the individual processes. Membrane conductivity and membrane concentration of redox-active molecules (RAMs) were varied to determine the models' sensitivity to changes in experimental values. Crossovers of positive and negative species in the all-vanadium battery were dominated by electro-osmotic drag and migration, respectively. Electro-osmotic drag crossover was predominant for all species in the MV/TEMPO battery. The contribution of diffusional crossover to total crossover decreased with increase in applied current across chemistries. Membrane conductivity varied inversely with migration but had no effect on electro-osmotic drag and diffusion. Each process' contribution to crossover in AORFBs mainly depended on the membrane's properties and the battery's operating current. Both migration and electro-osmotic drag were current-dependent. Diffusional crossover was minimal due to the large size of organic molecules. Membrane concentration of RAMs affected all three processes, but conductivity had a greater effect on total crossover. Electro-osmotic drag was preeminent in AORFBs, since the counter-ions used in AORFBs such as K^+ and Cl^- have higher electro-osmotic drag coefficients than H^+. Understanding the individual contributions of each process to total crossover will hasten the production of fine-tuned membranes and subsequently the mass adoption of AORFBs as grid-scale energy storage options.

The Effect of Tympanic Membrane Perforation and Size on Hearing Loss and Sound Perception

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The internship was divided into two main parts: literature review and data organization. He conducted literature review to better understand how tympanic membrane perforation (TMP) size and location affects hearing in certain frequencies as well as how sound perception is impacted. For data analysis, he put experimental chinchilla hearing data that has been gathered over the past five years into an excel spreadsheet. He used HOLLIS to conduct his literature review. Through HOLLIS, he got access to multiple research papers in different peer-reviewed journals. To understand hearing loss from a neurological standpoint, he asked how hearing loss at certain frequencies could affect our perception depending on when the hearing loss occurs (e.g. childhood, teenage years, adulthood). Later, he investigated why certain frequencies might have a major impact on hearing and sound perception. The papers he has reviewed agree that as the TMP size increases, the hearing loss worsens. This is intuitive as a larger TMP would correlate with more conductive problems. Although there is controversy around how the location of TMP affects hearing, many of the papers suggest that the location of TMP does not significantly impact hearing quality. Another interesting finding was that conductive hearing loss, which is mostly associated with TMP, during infantry might onset sensorineural hearing loss in adult life due to neural adaptations during infantry. Last but not the least, the findings suggest that current tympanoplasties focus on treating low to mid frequencies and mostly ignore high frequencies. The findings suggest how serious of an issue hearing loss is, especially during childhood. The current surgical interventions have the shortcoming of addressing only a certain part of the frequency spectrum. This requires the development of new materials to be used as grafts, which is the work the team at Mass Eye & Ear is conducting.

Biophysical Modeling of Tough Adhesive Hydrogel Drug Delivery Systems in Tendon Healing

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Ruptures and repetitive strain injuries to tendon are often accompanied by tissue inflammation and degeneration. While current medications delivered orally or intravenously can be limited by drug denaturation or drug-induced toxicity, hydrogel-based biomaterials may offer advantages by increasing the drug bioavailability locally and allowing for sustained release. Previous studies have engineered an extended release system using a tough adhesive (TA) hydrogel system (synthesized by mixing ionically crosslinked alginate and covalently crosslinked polyacrylamide) with corticosteroid particles. Although the TA can provide extended drug release, a fundamental understanding of the release mechanisms and prediction of other release conditions remained limited. This study examined how drug dissolution and diffusion affect release kinetics under varying boundary and initial conditions using finite element analysis. We hypothesized that the drug release profile from the TA scaffold is largely determined by the diffusivity of corticosteroid in different materials. Diffusion-controlled release models in 2D and 3D governed by Fick's Law and convection were created using finite element analysis and validated with existing *in vitro* release curves. Furthermore, based on image segmentation from high frequency ultrasound images, 3D models were generated (3D Slicer) to take into account the effect of native tissue anatomy on drug release. These models enable the study of introducing a semi-permeable outer membrane that may direct unidirectional drug release into the tendon. While a higher concentration of the corticosteroid molecules diffused into the tendon even without the barrier, inhibiting drug release into the surroundings ultimately allowed for greater and more gradual delivery into the tendon. Current studies are screening potential outer membrane candidates from various elastomers and polyurethanes. Taken together, these models may provide a platform to study corticosteroid release from a TA-based drug delivery system and allow for quick examination of various conditions placed upon the drug depot.

Regulation and Marketing of a Novel Tympanic Membrane Graft

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The Remenschneider Lab at Mass. Eye and Ear is researching and developing an easily implantable synthetic tympanic membrane graft. This device is designed to simplify tympanoplasty surgeries in order to make them more accessible around the world. In order to explore the translation of this device, research was conducted on the regulatory and marketing processes of similar medical devices. In order to review the FDA regulation process, FDA regulatory documents were reviewed to maximize the efficiency of gaining approval allowing quicker access to the device. Additionally, both doctor and patient surveys were conducted to gain insight into the current market and priorities of patients and surgeons. Major findings include the need for simplified surgical procedures to maintain sterilization and decrease complications in third world countries and the patient desire for lower maintenance hearing devices. These findings correlate to an overall market for less invasive and lower cost procedures to benefit patients across the globe. The novel tympanic membrane graft developed by the Remenschneider Lab will benefit patients and doctors alike by filling an existing market hole. It will improve the overall health and hearing of individuals while decreasing procedure complications for doctors.

Data Set Compression

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Data compression is one of the fundamental problems in information theory. The theoretical lower bound for compression of a stream of data is well-understood and is given by Shannon's source coding theorem (1948), but the particular case of an unordered data source, also called a data set, has not been as thoroughly explored. With the growth of data science and statistical learning, data sets on the order of hundreds of gigabytes are stored and transmitted with increasing frequency. Existing methods for compressing an archive, such as ZIP, fail to leverage particular properties of data sets, despite their competitive performance on streams. We design and implement a lossless, universal compression scheme for data sets that exploits redundancy, inter-element dependencies, and the insignificance of the order of elements within the set. We draw inspiration from predictive coding methods for images, such as JPEG-LS, but extend the key prediction step to suit data sets. First, the data set is reordered to minimize the distance between adjacent elements. We then fit a predictor function to the reordered data and use it to generate a low-entropy representation in the form of sparse prediction errors and residuals. This representation can be efficiently compressed using classical methods such as Huffman and Golomb codes. Our scheme has been tested on real-world image and tabular data sets, including MNIST, CIFAR-10, and Adult, and often outperforms traditional, all-purpose compression schemes. Experiments show that even simple classes of predictor functions, such as linear and logistic regressions, can produce powerful compression. A tailored compression scheme for sets as opposed to streams allows for significant savings in storage space and transmission cost for servers and end users. Beyond machine learning, these benefits also extend to large-scale storage platforms used for cloud computing and databases.

Optimizing Aquatic Animal Tags for *P. macrocephalus*

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P. macrocephalus, commonly known as sperm whales, are an intelligent species with complex cultures and calls. The Cetacean Translation Initiative (CETI) strives to create a "lexicon" for the whales' language so we may better understand these leviathans and perhaps even respond. Gathering sufficient data for a lexicon requires a reliable system through which scientists can record the whales' behavior, environment, and calls. In this study, we strove to design a tag best suited for studying sperm whales. To achieve this, we carried out an extensive survey on existing tags for aquatic animals and vetted them in the context of sperm whales. Specifically, we analyzed the tags' robustness at extreme depths and temperatures, audio capacity and overall lifetime. With our analysis, we pinpointed where current tag technology is lacking: unreliable attachment, limited energy, limited memory, and poor retrieval methods. With these conclusions, we were able to design a hypothetical "perfect" tag, proposing various methods to address the shortcomings. These hypothetical tags would provide clearer, uninterrupted data that could span days, if not weeks, which would allow for gathering a wealth of data on whale calls and behavior that does not yet exist. In the future, we hope to begin prototyping these new mechanisms and to create an ideal tag.

Review of Irreversible Electroporation

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The safe removal or reduction of a malignant tumor is the goal of any cancer treatment. Recently, Irreversible Electroporation (IRE) has emerged as a new treatment modality that employs strong electric field pulses to create holes in cell membranes. IRE has shown promise for predictably and effectively creating permanent nanopores in cell membranes. This review examines the efficacy of High-Frequency Irreversible Electroporation (H-FIRE)–a variation of IRE with shorter pulses (1-25 μs) of voltage with alternating polarity–by evaluating recent *in-vivo* and *ex-vivo* studies. Furthermore, this review introduces and computationally assesses the potential efficacy of a non-electrode approach to IRE, namely, via electric field formation induced by x-rays around high-Z metallic nanoparticles. First, this review gathered papers on trials conducted using IRE treatments and compared these to H-FIRE studies; results relevant to efficacy include ablation success rate and ablation area. Modeling required researching the likely mechanisms of IRE and collecting data on the material properties of cells. Cell response to electric fields is then modeled in the context of a cluster high-Z nanoparticles (NP) irradiated with x-ray beams to form electric fields. This review found that H-FIRE treatments ablate marginally smaller areas when compared to IRE treatments of similar voltage and application time. However, many papers demonstrate that H-FIRE treatments cause less thermal damage, are less likely to stimulate nerves and muscles, and can be used safely at higher voltages than traditional IRE treatments. In summary, H-FIRE has shown promising success in many small trials involving animals and humans. It seems reasonable to suggest that more trials ought to be conducted in both animals and humans to further validate H-FIRE. Furthermore, many of the papers examined in this study gave focus to treating cancers in the liver or pancreas, so further research is needed on H-FIRE in other parts of the body.

Spacescrapers: Limitations of Solar Tower Construction on the Moon

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The Moon's south pole promises a potential lunar base nearly continuous energy supply on the "Peaks of Eternal Light." The "Peaks" are exposed to sunlight for up to 100% of the lunar cycle. However, the illuminated area is only a few square kilometers, limiting the available power. One way of increasing potential power output is to build high. This is not just an increase in area; illumination is more continuous as the tower rises above local topography. In our research, we explored the limits to how tall Moon-based solar towers could be. We focused on towers made of concrete, because transporting building materials to the Moon is very expensive, and it has been shown that concrete can be made out of lunar soil. We created mathematical models to describe the tower's structural limitations. We explored towers that become progressively thinner with height with different thinning rates. We found towers as tall as 1900 km could be self-supporting before crumbling under their own weight, even allowing a factor 4 safety margin. (The mass of the solar panels is small, compared to the concrete, in all cases.) Realistically, the tower will buckle before it reaches this height. Buckling occurs when a column suddenly "bows" under an applied load. At what height this happens depends on the base area of the tower, its thinning rate, and the thickness of the walls. A tower with a 500 m^2 base can be over 8 km in height. This increases exponentially with the base area. We are looking to improve the models to maximize height and minimize material, applying practical constraints, e.g. the mass of concrete needed and plausible construction times, to make the lunar tower proposal as feasible as possible. Future investigations of metal or carbon fiber truss structures would make for valuable comparisons of their feasibility.

Quantitative Electroencephalography for Prediction of Brain Injury Post-Cardiac Arrest

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Hypoxic-ischemic brain injury (HIBI) caused by oxygen deprivation during sudden cardiac arrest results in neurological impairments. Brain injury in this context is dynamic, and treatment is time-sensitive: early monitoring is necessary to capture changes in brain function which require rapid diagnosis and intervention. MRI scans, which are used to assess HIBI severity, evaluate a single moment in time and are often delayed due to patient instability, which can cause results to be unactionable. Conversely, electroencephalography (EEG) recording can be attained earlier and tracks changes in brain activity in real time. Burst suppression with "identical" bursts is an EEG pattern associated with irreversible HIBI and coma, which suggests the possibility of using EEG to identify patients at high risk for structural brain injury. This project investigates burst similarity as a predictor of structural brain injury during the first 72 hours post-cardiac arrest. Burst suppression was detected using EEG data from 111 cardiac arrest subjects. Burst similarity was tested as a predictor of structural brain injury severity using whole brain apparent diffusion coefficient (ADC), a quantitative MRI metric, at sequential 12-hour periods. The performance of dynamic time-warping (DTW), a novel similarity calculation method, was compared to the standard cross-correlation (XCORR) method in assessing burst similarity. 44 (40% of) subjects had burst suppression on EEG. Burst similarity measured using DTW, but not XCORR, was correlated with mean ADC volume in the first 36 hours post-cardiac arrest, with correlation coefficients (R) of -.69 (hours 1-12), -.54 (hours 12-24), and -.41 (hours 24-36). The correlation between burst similarity and structural brain injury indicates that burst similarity analysis can provide an early predictor of structural brain injury on MRI scans. This finding could improve HIBI severity prediction by supplementing neuroimaging with real-time brain function assessment, which could be particularly useful in low-resourced healthcare settings that lack MRI facilities.

Computational Simulation of a COVID-19 Passive Immunization Treatment via Machine Learning Antibody Design and DNA Origami Sequence Delivery

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The ongoing COVID-19 pandemic is an urgent global health crisis with no accepted treatment or vaccine. Passive immunization of infected patients through infusions of antibodies against the SARS-CoV-2 virus has shown promise in reducing severity of symptoms and viral load. However, the cost and difficulty inherent in mass-producing recombinant antibodies have hindered the deployment of this potential treatment. Taking advantage of the low costs and high yields of nucleic acid production, this research computationally explores the possibility of applying machine learning to develop a high-affinity antibody against SARS-CoV-2 and delivering the mRNA sequence for this antibody to B cells *in vivo*, where its subsequent expression can act as a passive immunization treatment. A machine learning model employing a variational auto-encoder was trained on a set of approximately 400 antibody sequences, including a set of 389 antibodies against SARS-CoV-2. The model was used to obtain an antibody sequence that effectively binds to the SARS-CoV-2 spike protein. In order to efficiently deliver this antibody mRNA sequence to B cells for expression, a DNA origami construct was employed due to the ease in self-assembly and programmable activities of such structures. A box-shaped DNA origami structure was constructed using caDNAno design software to encapsulate the mRNA payload, and was decorated with CD40L ligands to allow for specific binding and delivery to CD40 receptors on B cells. Molecular dynamics simulations validated the stability of this structure in physiological conditions, and further simulations will demonstrate origami binding to B cell receptors. This work comprises a computational proof-of-concept of a start-to-end system for antibody discovery and nucleic acid-based antibody sequence delivery to B cells, allowing for rapid and cost-effective passive immunization treatments for COVID-19.

Design of a Randomized Controlled Clinical Trial for a Novel Tympanostomy Tube

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Approximately 700,000 tympanostomy tube (TT) insertions are performed annually in the U.S. to treat chronic ear infections, making it one of the most common pediatric surgical procedures. However, TTs are associated with numerous complications, including premature extrusion from the eardrum, tube lumen obstruction, and otorrhea (persistent liquid drainage from the ear), which sometimes require revision procedures or drug administration. To address these complications, researchers from the Aizenberg group have developed novel fluid-selective and biocontamination-resistant liquid-infused TTs that potentially can reduce postoperative complications. The objective of this PRISE project was to design a clinical effectiveness trial to evaluate the clinical benefit of the novel TTs in humans. Following discussions with ENT surgeons, a randomized controlled clinical trial was designed to evaluate time to extrusion of the TTs from the eardrum and time to TT lumen's occlusion as the primary (composite) outcomes of the study. The patient sample size was estimated using StataMP software, based on an extensive literature review of clinical trials on existing, commonly-used commercial TTs. An analysis of the sensitivity of the sample size to the predicted performance improvement (or hazard ratio) and the survival probability of an exemplary control device was conducted under the same assumptions as for the nonparametric Mantel-Cox test. While specific figures are subject to clinician review and regulatory approval, a preliminary sample size calculation assuming a hazard ratio of 0.5, a censored control tube survival rate of 0.25, and a power of 0.8 shows around 60 patients (120 ears) may need to be recruited. If this study demonstrates the novel tube's efficacy in reducing early extrusions and occlusions, it may pave the way for this novel tube to become accepted by ENT surgeons for clinical use and save hundreds of millions of dollars from decreased TT revision procedures.

Integrating SLAM Support Within MAVBench

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With the rise of autonomous machines there has been increased interest in autonomous micro aerial vehicles (MAVs). One crucial algorithmic tool for MAVs is simultaneous localization and mapping (SLAM), which allows an MAV to build a map of its environment and maintain its location within that map. Prior work established MAVBench, a simulation framework that assists hardware and software designers of MAVs in benchmarking and simulating MAV applications. Currently, MAVBench lacks the capability to test how different SLAM algorithms affect performance and efficiency. This research project aims to provide 'plug-and-play' support, that is allowing users to plug in a SLAM algorithm of their choice, hence providing a research infrastructure to evaluate these frameworks in the context of the wider MAV system. As a first step, a popular SLAM algorithm, ORB-SLAM2, has been integrated into MAVBench, while previously ground truth data was used for localization. This integration involved creating a ROS node for ORB-SLAM2 to take in sensor data and output its pose estimate to the mapping node. Further work will test ORB-SLAM2's localization error compared to ground truth and generalize the methods used to integrate ORB-SLAM2 to allow for 'plug-and-play' support. Previous literature on SLAM indicates that different algorithms provide certain advantages depending on the application. For example, research has shown that algorithms using lines in addition to points as features provide better localization in low-textured environments, but add some computational complexity (Gomez-Ojeda et al., 2019). Similarly, particle filter approaches provide more flexibility to non-linear systems and can test different data associations, while sparse Kalman filter approaches can be implemented in constant time but are less flexible (Bailey and White, 2006). This all suggests that testing SLAM algorithms within MAVBench would allow users to find their optimal balance between performance and efficiency.

Dynamic Multi-Agent Sensor Coverage Algorithms for Target Tracking

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In systems with multiple robots, the optimal solution for a target tracking problem often requires a codependent controller for each robot. Such a target tracking control system utilizes various kinematic information of the robots in order to construct a means of seeking the target. With this information given, employing a constructed controller based on these values can allow the robots to converge on the target. In order to simulate such an environment, the Gazebo simulator was employed on Robot Operating System (ROS). Using Python scripts to write to the robots, their motion could be viewed in the Gazebo environments in response to various starting positions and control methods. In these situations, all tracking and target robots were modeled with kinematics of a two-wheeled robot. An efficient way to solve this problem is using the Fisher information matrix (FIM) to organize and synthesize trajectories for all of the robots comprising the multi-agent system. Using this in conjunction with a well-known efficient controller, such as the linear quadratic regulator (LQR), allows for a convenient means of tracking the target by a multi-agent robot system, although it is most efficient when the robots are spaced out. This study informs on ways multi-agent robotic systems can most effectively complete their tasks. Future paths of this research can be exploring alternative means of such control, particularly in the case within which the robots are close together, as well as several complex single-robot stabilization problems, particularly a track-following robot simultaneously stabilizing a pendulum.

Life Sciences

Metabolomics-Based Analysis of Female Genital Tract in a Cohort of Women at High Risk of HIV

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Advisor: Douglas Kwon
Mentor: Seth Bloom

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HIV remains an ongoing global health crisis, especially in sub-Saharan Africa where new infections disproportionately impact young women exposed through vaginal intercourse. In the majority of new infections, the female genital tract (FGT) is the primary site of HIV infection and initial viral replication. HIV infection risk is associated with sexually transmitted infections (STIs) including *Chlamydia trachomatis* infection and with non-STI FGT microbiota composition. The Kwon lab has observed that women with chlamydia infection have higher frequencies of cervical regulatory CD4+ T cells (Tregs) and lower frequencies of cervical T helper 17 (Th17) cells relative to STI-negative women. Existing literature also shows that in in vitro studies, chlamydia infection causes epithelial cells to upregulate the enzyme indoleamine 2,3-dioxygenase (IDO1), which catalyzes the rate-limiting step in catabolism of tryptophan to kynurenine, thereby inhibiting growth of C. trachomatis. Based on this and other studies, we hypothesize that chlamydia infection in the FGT will be associated with an elevated kynurenine-to-tryptophan ratio, providing a mechanistic explanation for chlamydia-associated elevation in mucosal Treg frequency and reduction in Th17 frequency. The Kwon lab has performed untargeted metabolomics on cervicovaginal lavage samples from 141 study participants with paired STI, microbiome, and T-cell data. After performing various data cleaning steps in R, we conducted basic data structure exploration. We then performed ordination and clustering methods to identify possible batch effects or evidence of sample contamination. We are now integrating other metadata to test for associations with metabolite levels. We will then assess the relationship between kynurenine and tryptophan. This will be paired with a more exploratory analysis that will provide a better understanding of the relationship between mucosal metabolism and the microbiological and immunological dynamics of the FGT. Our work has implications in development of methods to halt HIV transmission in women and in reproductive health more broadly.

Exploring the Structure of Two Insect Gustatory Receptors

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Insects respond to specific tastants in their environment using gustatory receptors (Grs). Grs are unique to insects and constitute a class of chemoreceptor proteins that function as non-selective cation channels. While a structure of a homologous Orco (odorant receptor co-receptor) has been determined, there is currently no known structure of a Gr. The Gr9 gene in *Bombyx mori* (BmGr9) and its ortholog, the Gr43a gene in *Drosophila melanogaster* (DmGr43a), encode ligand-gated ion channels that are activated by D-fructose. My project aims to identify the ligand binding pocket by testing the ligand specificity of BmGr9 and DmGr43a. To better understand the three-dimensional structures of BmGr9 and DmGr43a, I built homology models of the two receptors using Swiss Model, hhpred, MODELLER, and I-TASSER with the Orco structure as a template. I am currently analyzing these models to determine the best homology model for each BmGr9 and DmGr43a and conducting a literature search of mutagenesis experiments on other Grs and Ors. Mutagenesis experiments that resulted in a mutated receptor with altered sensitivity to either the original or a new ligand will help elucidate the location of the ligand binding pocket and specific residues that are important for binding ligand. Future studies will involve mutagenesis of the BmGr9 and DmGr43a binding pockets and functional assays to understand the effect of the mutations on their responses to D-fructose and other sugars. My research will aid in clarifying the function and structure of insect Grs and Ors. If the exact structure and mechanism of these receptors are identified, scientists will be able to design insect repellants or pesticides that will specifically inhibit insects and thus lessen harmful off-target effects.

Mg²⁺ Chelation Using Different Agents to Increase Primer Extension and Vesicles Stability

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The RNA World hypothesis suggests that current cells came from prebiotic cells that were merely RNA and simple membranes. And despite increasing evidence pointing to the existence of primordial RNA-based life forms, there remain multiple challenges in establishing such a system. The goal is to establish a living system that sustains solely depending on RNA and undergoes Darwinian evolution. One hurdle is achieving sufficient non-enzymatic RNA synthesis enough to support life while maintaining vesicle stability because the high concentration of Mg^{2+} required for effective primer extension (PE) causes vesicles disruption. We therefore proposed using chelating agents that form complexes with Mg^{2+}. These agents will make it more readily available for the PE reaction center at lower concentrations while ensuring the vesicles stability. We used two pieces of software. The first, SolEq, allowed us to study and titrate complex formation between Mg^{2+} and multiple candidates that we suspected had chelating functions based on their structures. The second, VMD, is a molecular dynamics software in tandem with crystal structures to simulate the binding of our Mg^{2+}-ligand complex to the PE reaction center. Then, multiple experiments were performed to empirically test the efficiency of these chelators in PE catalysis at both low and high Mg^{2+} concentrations. We used the association constant K_a to assess the affinity of a compound to chelate Mg^{2+}. Compounds that had high K_a values bound Mg^{2+} too tightly for it to react with the growing RNA strand, and vice versa. Multiple compounds were prebiotically plausible chelating agents, including amino acids and phosphate compounds family. These findings could be the key to solving the Mg^{2+} problem in the origins of life research, a step closer to an RNA-based life form.

Study of Reversibility of Protein-Free Strand Exchange Products Created During RecA Mediated Homologous Recombination

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Double-stranded DNA breaks in the chromosome must be repaired to ensure cell survival. In bacteria, the repair mechanism often follows the RecBCD pathway wherein double-stranded breaks are repaired through RecA mediated homologous recombination; one strand on each side of the break binds to a homologous region of a complementary strand from a damage-free chromosome, forming a heteroduplex product that facilitates the transfer of genetic information. Once the transfer is complete, ATP hydrolysis drives the unbinding of RecA from the heteroduplex, then the heteroduplex reverses and a repaired DNA is produced. However, if an incoming strand binds to a region of accidental homology in the damage-free chromosome and forms an incorrectly paired heteroduplex product, the product may not reverse, leading to unwanted permutations in the genomic code. In humans, these genomic rearrangements may lead to hereditary disorders like Bloom Syndrome and Werner Syndrome. We studied the reversal of the RecA-free heteroduplex products formed by accidental homology of bases (N) ranging from 82 to 420 nucleotides (nt). We studied this to understand if RecA mediated homologous recombination could result in these genomic rearrangements and found that reversibility of the heteroduplex is very high when N is around 80 nt but lower when N is greater than 160 nt. We used a biased random walk to model this reversal and found it varied strongly with their lengths. *In vivo*, most of these filaments are between ∼50 to ∼500 base pairs (bp), and we found that when a bias exists in favor of the extension of the heteroduplex, a 500 bp product could last ten thousand times longer than an 80 bp product, which is consistent with the results from previous *in vitro* experiments. Furthermore, our results show that in the absence of ATP hydrolysis, heteroduplex products with N > 75 remain strongly stabilized by their irreversible binding to RecA.

Exploring the Mechanism of Action of a Novel In-House Designed Drug CD 15-3

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The de novo folate synthesis pathway is an attractive target for the design of antimicrobials, as mammals lack this pathway and only derive folate from their diets. In an attempt to combat resistance against standard antimicrobials targeting the folate synthesis pathway in E.coli, compound CD 15-3 was designed to inhibit the activity of dihydrofolate reductase (DHFR), in both its wild-type and evolved mutant strains. The purpose of this study was to investigate potential off-target interactions of the drug CD 15-3. In the first phase of the study, molecular docking was employed to assess the binding of the small molecule to 7,8-dihydro-6-hydroxymethylpterin-pyrophosphokinase (HPPK), using the online docking service Swissdock. Structural analysis of the protein-small molecule complexes showed an abundance of interactions between CD 15-3 and residues TYR 53 and PHE 123 of HPPK. Afterwards, more precise docking using Maestro, a dedicated drug discovery software, rendered a binding mode of CD 15-3 in which the small molecule is "sandwiched" in between residues TYR 53 and PHE 123 of HPPK through pi-stacking interactions. A docking score of about -9.7 kcal/mol for the competitive binding in the pterin binding site of HPPK was obtained. Moreover, CD 15-3 appears to bind more favorably to HPPK, and not to DHFR, as it was previously assumed. Further, molecular dynamics (MD) and anisotropic network model (ANM) simulations would elucidate the binding interactions between the small molecule CD 15-3 and the flexible chain of the protein HPPK.

In Silico Development of Molecular Glues for Novel E3 Ligases

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Traditional small molecule design, which primarily focuses on inhibiting protein function, can only target about 15% of all proteins in the human body. However, small molecules that can redirect the activity of E3 ligases, part of the ubiquitin proteasome system, can theoretically "treat" all proteins by targeting them for degradation. Thus, our research involved the preliminary steps of small molecule design for E3 ligases using molecular glues, a molecule that interacts with both the E3 ligase and protein of interest favorably to promote ubiquitylation and degradation of the target protein. Our work first entailed building a comprehensive database of E3 ligases which identifies their binding pathway, degron recognizing sequence, protein structure, and native substrates. This database helped us select an optimal E3 ligase to use for immediate research purposes and will also assist in future projects that require a selection of E3 ligases to target based on these specific parameters. Based on the existing literature, we found that the E3 ligase GID4 (Glucose-Induced Degradation Protein 4) was an optimal E3 ligase for *in silico* development of ligands that may act as molecular glues. As GID4 intrinsically recognizes a proline N-Degron substrate, we utilized the molecular modeling software MOE to construct multiple molecular databases with a proline N-terminus and subsequent molecular adaptations towards the C-terminus. Next, specific molecules were chosen based on promising intermolecular interactions with GID4, interesting ligase-ligand surfaces for neosubstrate recruitment, and ease of synthesis once lab operations resume. Thus, the next phase of our research will be to synthesize the chosen molecules and test *in vitro* for strong interactions with GID4. If favorable interactions occur, Co-IP proteomics will be used to screen for the ability of these compounds to act as molecular glues and target traditionally "undruggable" proteins.

Renin as a Predictor of ARDS Severity (RAAS)

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Acute respiratory distress syndrome (ARDS) is a deadly form of organ failure in which the lungs become diffusely inflamed, leading to a lack of oxygen in the blood. Sepsis, a dangerous bodily response to widespread infection, is a leading cause of ARDS. Sepsis-induced ARDS is lethal, and few biomarkers that exist today are being used routinely in the clinical setting to accurately predict ARDS severity. The renin-angiotensin-aldosterone system (RAAS) is an important circulatory homeostatic mechanism, and in this system, renin is secreted in response to decreased tissue-perfusion and hypoxia. The goal in this pilot study was to investigate renin as a predictor of ARDS severity. The clinical data from ICU subjects in the BWH Registry of Critical Illness (RoCI) was interrogated using modern computational techniques to link renin and ARDS severity as a surrogate for mortality. The first step was to verify the data using newer computational tools like NumPy and Pandas, widely used data analysis libraries built for Python. A composite set of PaO2/FiO2 ratios, a measure of ARDS severity, was then determined for each patient at varying sets of times using the nonlinear imputation standardized in the literature. Statistical analyses included simple regression, correlation, categorical analysis, and multivariate lasso regression. This work is ongoing, with literature and analyses suggesting a potential relationship between increasing renin and worsening ARDS severity. Due to the small sample size and nature of a pilot study, it is anticipated that the results may not show any significant association of renin and ARDS severity.

Identifying Proteins Involved in Negamycin Biosynthesis

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Negamycin is a hydrazide-containing, peptide-based antibiotic that targets Gram-negative and Gram-positive bacteria by binding to ribosomal subunits and inducing miscoding. Moreover, its analogs are under active investigation for treating muscular dystrophy, so its biosynthetic pathway is valuable to understand. A SET nitrogen methyltransferase (NegN), oxygen methyltransferase (NegO), and ATP-grasp amide bond-forming enzyme (NegA) are three key proteins in the pathway that may be uniquely capable of modifying reactive hydrazine-containing intermediates. Data about these enzymes' superfamilies were gathered through the Interpro database, and proteins similar to NegN, NegO, and NegA were identified through the JGI-IMG and Uniprot databases. Sequence similarity networks, which classify subsets of closely related proteins, were created with EFI-EST. Having identified genes encoding proteins most similar to NegN, NegO, and NegA, their genomic context was then characterized through genome neighborhood analysis. In bacteria, genes with related functions are often co-localized in the genome, allowing functions and structures of new natural products to be predicted. Preliminary results suggest that genes encoding transcriptional regulators and nodulation proteins are encoded near the close relatives of NegO. The conserved genes more unique to the close relatives of NegN are ones associated with ATP-grasp family enzymes, whereas genes encoding Lysine 2,3 aminomutase and exporter proteins are commonly found within the genome neighborhoods of many nitrogen-transferases. Genes encoding M20 peptidases are more common in neighborhoods encoding close relatives of NegN, whereas exporter genes are often found near the entire superfamily. Moreover, through literature review and protein structure analysis, the predicted structure of NegA was found to be similar to that of Pgm1, a protein involved in the antibiotic pheganomycin's biosynthesis. Exceptions, such as truncated beta sheets that alter the active site environment, may be connected to NegA's unique biochemical capabilities. These results indicate that NegA, NegN, and NegO participate in a variety of biosynthetic pathways that share certain features but likely produce different products. Coupled with further bioinformatics and experimental work, other bacteria that produce valuable hydrazide-containing products may be identified.

Natural Killer Cell/T-Lymphocyte Interaction in Chronic Renal Transplant Rejection

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Transplant rejection remains a serious complication following renal transplantation, with roughly half of patients undergoing rejection within ten years. Transplant science has traditionally studied T-lymphocyte and donor antigen presenting cell (APC) interaction in part because this interaction has been clearly implicated in T-lymphocyte activation. T-lymphocytes in particular have been studied as mediators of rejection for their cytotoxic activity against donor cells. The role of NK cells in transplantation has not been extensively studied; however, the Chandraker Lab recently observed that CD226, an activator molecule, is upregulated on NK cells and that the inhibitory TIGIT (T Cell Immunoreceptor with Ig and ITIM domains) is downregulated following transplantation. Both NK and T cells express the various receptor and ligand molecules of the TIGIT/CD226 costimulatory axis, presenting new evidence that there is potential for direct interaction between these cell types. Through an extensive literature review, we have identified two additional receptor-ligand pairs, LFA-1/ICAM-1 and CD244/CD48, that may also play potential roles in the direct interactions of T and NK cells and may influence the TIGIT/CD226 costimulatory axis. Further studies will need to clarify whether NK cells influence the T-effector response (cytokine production, proliferation, and receptor regulation) towards the allograft. Assuming there is a correlation between NK presence and T cell behavior, additional research will need to confirm which ligand-receptor pairs facilitate these interactions and the extent to which NK cells are involved in renal transplant rejection.

Examining the Protein-Protein Interaction Mechanisms of Protocadherins

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Protocadherins are membrane proteins that play important roles in brain wiring and neuronal communications. Within the two largest groups of protocadherins, the δ-protocadherins and clustered protocadherins, individual proteins differ in their structures and protein-protein interaction mechanisms. Each clustered protocadherin only interacts with the same clustered protocadherin variant on the opposite cell membrane (homophilic *trans*-interaction), while some -protocadherins interact with different δ-protocadherin variants on the opposite cell membrane (heterophilic *trans*-interaction). The reason for this difference is not well understood. Multiple structures of protocadherins have been published to help to explain specific *trans*-interaction features. However, a comprehensive comparison between these *trans*-interfacing structures has not yet been done. We computationally analyzed the expression patterns of δ-protocadherins in brain tissues. We found that most δ-protocadherins that can interact heterophilically are expressed in different tissues, while δ-protocadherins that interact homophically are co-expressed in the same tissue. Our results suggest that the spatial arrangements of δ-protocadherins lead them to interact homophilically, even if they are capable of heterophilic interactions. We also collated all *trans*-interfacing protocadherin structures and are currently creating a comprehensive database that facilitates the comparative analysis of protocadherins' *trans*-interactions. The result of this analysis will help us predict the *trans*-interaction properties of unpublished structures and understand how certain residue mutations alter protocadherins' *trans*-interaction properties.

Ubiquitin Proteasome Pathway Responses in Coronavirus Infection

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The 26S proteasome is the primary site for protein degradation in eukaryotic cells. Impaired proteasome function can result in the accumulation of misfolded proteins, leading to several diseases. Additionally, the ubiquitin-proteasome pathway (UPP) is a component of innate immune responses to viral infection. Given the recent COVID-19 outbreak, our lab is investigating the interactions between the UPP and coronaviruses. The overall hypothesis is that reduced activity of the UPP increases cellular susceptibility to conditions that cause an accumulation of misfolded proteins (heat shock, proteasome inhibitors), including the unfolded protein response (UPR) and the heat shock response. A literature review is being performed to determine if UPP function is required and facilitates coronaviral productions including replication, assembly, and export. Several viruses elicit cellular stress responses, but it is not known whether coronaviruses activate such stress responses or if those stress responses are related (including causally) to inhibition of the UPP. Papers on the consequences of inhibiting the UPP on coronaviral productions and cellular responses, if any exist, are also being evaluated. Previous studies have shown that for some viruses, the UPP is necessary for replication; simultaneously, the UPP is also part of the host's defense mechanism that may recognize and eliminate viral components. A critical literature review is being performed to identify how viral entry, replication, and release are modulated by the proteasome and if these viruses alter the UPP. As part of my thesis, through a literature review, we hope to better understand if coronaviral proteins are degraded by the cell through the UPP and in the future, experimentally test if coronaviruses inhibit the UPP, and if activation of the UPP may be used therapeutically.

Standardized Benchmarking Data to Guide Quality Improvement in Congenital Heart Disease

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Congenital heart disease (CDH) is the 7th leading cause of death in children under 5 years of age. Few benchmarks exist to identify specific risk factors and to evaluate program performance in low- and middle-income countries. To address this gap, the International Quality Improvement Collaborative (IQIC) for Congenital Heart Disease at Boston Children's Hospital was launched to provide benchmarking data for congenital heart surgery in the developing world with the goal of guiding quality improvement efforts and reducing mortality for CHD. Today, there are currently 75 active sites in 28 countries enrolled with the IQIC. This project sought to use statistical analysis to examine the outcomes of surgeries performed between January to December 2019 of the participating sites and compared those to the outcomes of prior years, since 2010. The outcomes examined were in-hospital death, perfusion issues, surgical site infection, bacterial sepsis, any major infection, and 30-day mortality. Out of the 61 sites that participated in the collaborative within 2019, 46 sites had verified data. We tracked sites' individual progress from the annual benchmarking reports and identified strengths and opportunities for improvement. We compared each site to the rest of the collaborative to determine where programs stand in relation to their peers. Our main findings were that the proportion of cases in RACHS-1 risk categories 4 through 6 has increased slightly over time. The risk-adjusted in-hospital mortality generally decreased from 2010 through 2016; it increased slightly in 2019 relative to the previous three years. Additionally, the risk-adjusted major infection decreased from 2010 through 2015, with the exception of calendar year 2013; it has increased somewhat over the past two years. These standardized benchmarking data reports help to identify drivers of mortality and life-threatening complications, and guide the development of targeted quality improvement strategies.

Investigating the Role of the Complement System in Diabetic Kidney Disease

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Diabetic kidney disease (DKD) is a complication of diabetes characterized by progressive renal function decline leading to end-stage renal disease. There is limited understanding of mechanisms driving progressive diabetic kidney complications despite an urgency to improve health outcomes for patients. The Niewczas laboratory applies high-throughput technologies and advanced clinical epidemiology tools to search for potential determinants of diabetic kidney complications. The Niewczas laboratory aims to examine proteome-wide inflammation with a major focus on the Complement system and its role as a potential driver of progressive DKD. The role of Complement across diabetes types and chronic kidney stages remains to be established. I was specifically involved in the project evaluating the role of Complement in subjects with Type 1 diabetes (T1D) and early DKD. This is a case-control study of subjects nested within a prospective Joslin Kidney Study cohort of participants followed for 5-10 years. This project compares Complement proteome in baseline urine samples between subjects who developed renal function decline and those who remained with stable renal function. Multiple biostatistical and machine learning analyses are underway. I contributed to clinical data analyses and examined inter-relationships among Complement proteins (Spearman correlation matrices, hierarchical clustering) and some machine learning elements. Analyses employed several computational software: SAS, R, JMP PRO. I am a Joslin Kidney Study member approved by the Committee on Human Studies. Untargeted and targeted proteomic evaluations are ongoing. My contributions to targeted assays involved biobanking activities, assay protocol development, data integrity check, and analysis. Other activities included literature mining and interrogating data from publicly available databases of bulk and single cell transcriptomics. I became co-author of a poster presentation on this topic that will be presented December 2020 at the Society of Epidemiologic Research meeting. This comprehensive investigation suggests the important role Complement plays in DKD progression and its therapeutic potential.

Optimizing Infectious Disease Detection Through Identification of Unique DNA Signatures

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The COVID-19 pandemic has shown that a single infectious disease can, by taking millions of lives and infecting many more, drastically alter the way of life for millions of people. However, beyond COVID-19, infectious diseases of all sorts claim more than 17 million lives annually, with a vast majority being from underserved regions of the world. Hence, optimizing infectious disease detection could be a key strategy in the global health objective of curbing this number. This project aims to accomplish this goal by using computational tools to identify unique DNA signatures associated with 17 airborne infectious diseases, including COVID-19, influenza B, tuberculosis, and measles, among others. This was done through the collection of 18 base-pair n-grams (small fragments of DNA used commonly for bioinformatic analyses) from the genome sequence of each of these diseases using a computer code written in Python. Each n-gram was then compared against the n-grams of every other disease in the list of 17. The outcome was a short list of unique n-grams, which can hereon be considered DNA signatures, for each disease. Future directions include refining the lists of DNA signatures by removing signatures that create an internal hairpin loop or have other issues that make them impractical for disease detection. These DNA signatures can be utilized in the development of a disease testing chip in the form of a 24-well plate that contains all of these signatures and can evaluate saliva samples from patients to test for all of these diseases simultaneously. Deployment of such a device to clinics in underserved regions of the world could greatly optimize the detection of diseases that contribute to comorbidities among these populations, from COVID-19 to tuberculosis.

Pyroptosis as a Contributing Factor to the Hyperinflammatory Immune Response in Severe COVID-19 Patients

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COVID-19 cases number in the millions and continue to rise, yet few therapies are available. While the majority of cases are asymptomatic or mild, patients hospitalized for pneumonia exhibit cytokine release syndrome (CRS), an overactive immune response that could develop into fatal acute respiratory distress syndrome (ARDS). Pyroptosis, a fiery cell death in which innate immune cells release inflammatory signals through cell membrane pores, activates CRS. As the exact mechanisms behind CRS in COVID-19 remain unclear, it is proposed that SARS-CoV-2 viral proteins induce pyroptosis and thus hyperinflammation. In this study, a literature review of SARS-CoV-2 ORF3a, ORF8b, and E proteins, earlier seen in SARS-CoV-1 and MERS to have inflammatory potential, was conducted to predict potential mechanisms. SARS-CoV-2 protein structures were aligned with those of other coronaviruses through Uniprot; SARS-CoV-2 ORF3a mutations from the CoV-GLUE database and correlated to GISAID patient conditions were studied for effects on disease progression. Analysis of gene expression from the pyroptosis NOD-like receptor pathway in patients compared to healthy donors was performed using statistical language R on single-cell RNA sequencing (scRNA-seq) data from published studies using peripheral blood mononuclear cell and bronchoalveolar fluid (BALF). As SARS-CoV-2 ORF3a and E had high sequence identity with corresponding SARS-CoV-1 proteins, similar pathways of ion disequilibrium, mitochondrial dysfunction, or direct activation of inflammatory proteins were found to be possible mechanisms of pyroptosis in COVID-19. While scRNA-seq analysis did not conclusively support pyroptosis in patients, mitochondrial dysfunction and pyroptosis-associated genes *CASP1*, *NLRP3*, and *GSDMD* were found upregulated in patient BALF. These results suggested pyroptosis occurs in COVID-19 patients, but further analysis using cell staining and immunoblotting should confirm these results and elucidate pathways. If pyroptosis is seen, FDA-approved drug disulfiram, recently found to inhibit a major protein in pyroptosis, could benefit patients as an affordable targeted therapy.

Probabilistic Prediction of 3D RNA Motifs Given Covariational Constraints

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RNA transcripts that do not result in protein products are known as noncoding RNAs (ncRNAs). While some ncRNAs facilitate vital cellular processes, others have unknown functions, if any. One strong indicator of functionality is the presence of evolutionarily conserved structure, which many ncRNAs indeed exhibit. In fact, we can observe a phenomenon known as covariation, where pairs of structurally bound positions undergo accommodating mutations, resulting in particular patterns across an evolutionary alignment. Experimental methods for determining ncRNA structure prove difficult, raising the need for accurate computational methods. Although single sequence software for predicting secondary RNA structures are not very reliable, adding covariational information significantly improves performance. Still, these methods fall short of consistently detecting higher-level, tertiary features known as 3D motifs. Our approach is to construct a probabilistic model of RNA folding known as a stochastic context-free grammar (SCFG), which is a generalization of a hidden Markov model allowing transitions from single states (structural features) to arbitrarily spaced correlated states such as base pairs. The structure of a ncRNA sequence is then predicted by the most likely sequence of state-transitions emitting to that ncRNA, called a maximum probability parsing. We implemented a dynamic program determining the maximum probability parsing of a ncRNA sequence based on an SCFG targeting a 3D motif known as a GNRA tetraloop (four nucleotides beginning with guanine and ending with adenine between consecutive base pairs). In addition, we imposed informational constraints obtained by observing covariation. After training this prediction algorithm on a dataset of structurally predetermined ncRNAs, we expect the algorithm to consistently identify GNRA tetraloops with a low false positive rate. Modifying this targeted detection method to incorporate a library of other 3D motifs could provide a valuable set of tools for refining the current ability to predict tertiary structure in ncRNAs.

Cancer Immunotherapy: Refining Neoantigen Identification and Therapeutic Approaches

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The difficulty of conquering cancer treatment is associated with cancer cells' ability to escape immune response, as their genetic makeup differs from healthy host cells by merely a few somatic mutations. Only a very small fraction of these mutated peptides are presented on class I major histocompatibility complex (MHC-I), and an even smaller fraction of those are immunogenic. To fully harness the immune system's antitumor potential for a broader patient pool, we explore the failures and successes of neoantigen-targeted therapeutic approaches as well as the synergy of novel combination therapies. Groundbreaking innovations in *in silico* modeling have improved methods of identifying immunogenic target biomarkers and predicting clinical responses to treatment. Examples of such biomarkers are antigens that arise *de novo* from tumor genome mutations, termed neoantigens. We are working towards refining neoantigen identification techniques to make them more reliable for those with time-sensitive metastatic diseases. By administering these neoantigens through personalized vaccines or nanocarriers, we hope to see more homogeneously successful antitumor responses across diverse cancer types. This project aims to gain a more comprehensive picture of neoantigen-based immunotherapies by conducting a literature review surveying recent papers and review articles. Studies verified factors contributing to immunotherapy's clinical successes, such as treating tumors with high mutational load, preventing cancer immunoediting, and targeting multiple immunogenic neoantigens simultaneously. After returning to the physical laboratory, various methods will be tested to refine present-day neoantigen identification techniques, and real-time radioisotope imaging will verify the activation of systemic T cell responses. This information will better inform treatment options for cancers with high tumor mutational burden and promote the discovery of synergistic combination immunotherapies, ultimately helping to advance cancer treatment.

The Implications of Arborization Field 7 and Retinal Ganglion Cell Morphology in Prey Capture Behaviors of Larval Zebrafish

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Mentor: Mariela Petkova

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How neuronal circuits generate behavior remains to be fully understood. Limitations in technology make studying large neural networks in most vertebrates infeasible. One solution is to use a simpler vertebrate model: larval zebrafish. Zebrafish are highly visual animals whose small brains make it possible for image-based investigation of structures and connectivity using Electron Microscopy (EM). We focused on a subset of the neurons extending from the retina which transmit visual information from the eyes to the zebrafish brain. Visual information is received in the retina and transmitted through the optic nerve into 10 distinct retinorecipient areas, Arborization Fields 1-10. The optic nerve is composed of numerous Retinal Ganglion Cell (RGC) axons extending from the retina. Retinorecipient areas are places where visual information from the eyes is relayed to the brain and used to inform downstream behaviors. The disconnect exists in how this information is used after it leaves the retina and arborizes in the retinorecipient areas. This study's objective was to generate neuronal morphologies of the optic nerve and visualize the connections it makes after leaving the retina. This information was also used to improve automatic segmentation methods. In the future, these image stacks will be used to study connectivity patterns in the arborization fields, specifically Arborization Field 7 (AF-7). Previous studies implicate AF-7 in hunting behavior. Unpublished research from the Engert Lab shows that the neurons surrounding AF-7 are glycinergic or inhibitory, suggesting a tuning process that selects for prey. We plan to use the EM image stacks to verify if the RGC axons that travel to AF-7 synapse with glycinergic neurons. This information will inform future models of how the structure of neural networks in the brain relate to their function and produce a more accurate representation of how visual information drives decision-making.

Computational Profiling of Murine Testicular Structure Using Spatial Transcriptomic Data

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Advisor: Fei Chen
Mentor: Haiqi Chen

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Following the revolutionary development of single-cell RNA sequencing, techniques such as Slide-seq, a novel spatial transcriptomics method, add a new dimension of spatial resolution to sequencing information. Analyzing spatial gene expression patterns is crucial to better understand the molecular and spatial hallmarks of cell types and tissue architecture. In this study, we aim to analyze Slide-seq data derived from wild type and diabetic murine testes by measuring (1) cell-cell interaction between different cell types, (2) cellular neighborhood identification and visualization, and (3) cell type frequency by neighborhood. By comparing these metrics between the wild type and diabetic mice, we can investigate to what extent the biological structure of testes is disrupted in diabetic mice. In this analysis, we observed that the stereotypical structures of seminiferous tubules, the individual units within the testes, are mostly preserved in diabetic mice. Although we observed consistency in identifying neighborhoods of similar identities between the wild type and diabetic mice, we noticed more disorganization in the overall tissue structure of diabetic mice. Diabetes may perturb spermatogenesis by disrupting cell-cell interactions and neighborhood composition and, thus, lead to structural and molecular differences between wild type and diabetic cohorts. In addition to understanding the perturbations in diabetic mice, these analyses provide further insight into the spatial context and interactions between various cell types and regulatory pathways in healthy testes. On a broader scale, these data and observations are valuable in characterizing the testes under normal and diabetic conditions and create a single-cell resolution spatial transcriptomic atlas of mammalian spermatogenesis.

Novel Pro-Resolving Mediators and Their Actions During Infection: A Temporal and Single-Cell Analysis

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Acute inflammation is a protective mechanism that is evolved to eliminate pathogens and is characterized by the mobilization of phagocytes (neutrophils, monocytes and macrophages) from the bone marrow into the affected area. The resolution of inflammation is mediated through temporal regulation of a super-family of endogenous bioactive mediators known as specialized pro-resolving mediators (SPMs), discovered and functional characterized in my mentor's lab. SPMs are potent stereoselective agonists acting at sub-nanomolar quantities *in vivo* to limit neutrophil infiltration and promote microbial clearance. SPMs are produced in the bone marrow (BM) and phagocytes, yet, their functions within the BM are unknown at this time. The objective of this PRISE Fellowship is to establish the temporal regulation of SPMs within the BM and their function in phagocyte mobilization using single-cell mass cytometry (CyTOF). To this end, acute inflammation was induced using a well-established murine model of *E. Coli* peritonitis (10^5 C.F.U). Cells were collected from the BM and exudate at 0, 12 (inflammatory phase), and 72 hours (resolution phase) after infection and stained with 30 metal-labeled surface antibodies for CyTOF. The data was analyzed using t-distributed Stochastic Neighbor Embedding (t-SNE), a non-linear dimensionality reduction algorithm, to identify 15 main immune populations based on their surface expression using antibodies. T-SNE analysis of the exudate showed increased neutrophil infiltration (Ly6G$^+$CXCR4^{low}) and inflammatory monocytes (Ly6C^{high}) at 12 hrs compared to 0 and 72 hrs. At 72 hours in the resolution phase, we observed a declined in neutrophil population along with an increase in proliferation of F4/80 macrophages and reparative monocytes (Ly6C^{low}). These results provide fundamental new insights into the functions of SPMs and novel pro-resolving pathways in the regulation of phagocytes during infection.

Identifying Enhancer Candidates to Explain Imprinted Expression in Birk-Barel Syndrome

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Mentor: Daniel Loftus

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Enhancers, sequences of non-protein-coding DNA which stabilize the transcription complex, introduce two modulable variables for gene regulation towards cell differentiation: chromatin structure determines enhancer sequence accessibility, and transcription factors provide cell-specific contextual control. If disrupted, such complex systems produce disorders. Imprinting, preferential expression of one parental allele over the other, offers advantages for studying gene regulation-related disorders. For example, in the paternally imprinted (maternally active) Birk-Barel Syndrome, a disruptive mutation in the operational copy of the *Kcnk9* gene causes intellectual disability and hypotonia. While mutations causing Birk-Barel Syndrome are known, the regulation of *Kcnk9* is not. We hypothesize that parental alleles at this locus are expressed and silenced through enhancer activity. Elucidation of this enhancer mechanism through bioinformatics methods can open the door to therapeutic activation of the silenced and likely intact paternal allele, restoring *Kcnk9* expression in Birk-Barel Syndrome patients. From Hi-C datasets (chromatin interaction frequency), we saw strong interactions between *Kcnk9* and an upstream region of DNA. To determine candidate enhancer sequences, we looked at chromatin accessibility assays, namely ATAC sequencing, to ensure transcription factor access. Next, we looked at chromatin immunoprecipitation data for enhancer-associated histone markers, H3K27 acetylation and H3K4 monomethylation. Differential methylation at a binding site for CCCTC-binding factor (CTCF) protein, a regulator of chromatin structure, informed our model of gene regulation. MODEL: Maternal methylation at the locus prevents CTCF-binding and allows *Kcnk9* expression via long range chromatin interactions with an enhancer candidate. Absent methylation on the paternal allele allows CTCF-binding and competing chromatin structure, bypassing enhancer interactions necessary for *Kcnk9* expression. We plan to further *in vitro* test our enhancers of interest using a luciferase reporter enhancer construct assay. Within this gene expression model, reactivation of silenced paternal *Kcnk9* through targeted methylation emerges as a potential therapy for Birk-Barel Syndrome.

Effect of Estrogen on Differentially Expressed Genes Among SLE Patients

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Autoimmune diseases occur when the immune system fails to recognize and thus attacks the self, leading to tissue damage. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that predominantly affects young women between adolescence and menopause, which indicates that higher estrogen levels affect autoimmune diseases. Preliminary studies have shown that abnormal hyperactive T cells, which play an essential part in the immune system, are involved in lupus pathogenesis. The Moulton lab has recently uncovered new roles for a protein called serine arginine-rich splicing factor 1 (*SRSF1*) in normal function of T cells and shown that *SRSF1* levels are reduced in T cells from lupus patients. The goal of this study was to evaluate by comparative bioinformatics the relevance of these genes that we recognize as altered, upregulated, and downregulated, by *SRSF1*, in lupus utilizing publicly available gene array datasets. In this study, the NCBI Gene Expression Omnibus (GEO)2R database was used to identify and curate publicly available gene array datasets from 188 SLE patients and 29 healthy controls (women and men). Using Metascape, (GEO)2R, and xCell, we performed an enrichment analysis of the differentially expressed genes (DEGs) between SLE patients (women and men). After finding the DEGs through (GEO)2R, Metascape allowed us to check for genes involved in immune pathways relevant to SLE. There were 2298 DEGs between females and males with SLE. In the future, the RankCompV2 algorithm will be utilized to adjust for natural DEGs between males and females in healthy controls. Then, the DEGs will be checked against genes upregulated and downregulated by *SRSF1* to check for overlapping genes. Understanding which genes controlled by *SRSF1* are differentially expressed between female and male SLE patients will allow us to continue exploring the molecular mechanisms underlying aberrant T cells in the autoimmune disease lupus.

Effect of the Cohesin Complex from Surrounding Molecules

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Cohesin is a ring-shaped protein complex member of the genome-organizing SMC (Structural Maintenance of Chromosomes) family, which exists in many species, from bacteria to humans. Cohesin is made up of two SMC proteins, *SMC1* and *SMC3*, along with a 'kleisin' subunit, *SCC1/RAD21*. The most influential role of cohesin comes from its impact on chromosome segregation, where it provides the complex that connects two newly duplicated sister chromatids during the S-phase of replication until anaphase. This connection persists until the microtubules of the spindle correctly attach to the kinetochore at centromere regions of the chromosome and provide their unique "x-shape" in metaphase. In addition, cohesin also plays important roles in DNA repair, by favoring the recombination process of sister chromatids, and in gene expression regulation by impacting several aspects of transcription. The role of the cohesin complex involves the timely interactions of many proteins (TFs, chromatin remodeling factors...) and DNA (genes, promoters, enhancers...) in order to function properly. Alterations of cohesin subunits or related factors can cause a plethora of damages ranging from chromosome segregation and DNA repair defects to gene expression misregulation, which account for severe developmental syndromes. Because of the large amount of ambiguity that surrounds the cohesin complex and its many parts, this review will attempt to clarify our understanding of how cohesin regulates gene expression by looking at the local interactions of the cohesin complex from other molecules, as well as its larger impact on development in the frame of cohesinopathies.

Computational Approaches to Predict Regulators of Human Tfh Cell Development

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T follicular helper (Tfh) cell development has primarily been studied in mouse models over the last decade. However, little is understood about human Tfh cell development, and exhaustive genome-wide approaches have yet to be applied to the study of the differentiation of human Tfh cells. Tfh cells play a critical role in the induction of germinal centers and the generation of long-lived antibodies. Studies of natural immunity and vaccine design in the context of the COVID-19 pandemic have drawn renewed attention to the durability of the humoral immune response, which makes studying Tfh cells especially relevant. This study aims to identify novel regulators that control Tfh cell development. First, four stages of development were operationally defined for the study (naive, early pre-Tfh, late pre-Tfh, and germinal center Tfh). Then whole genome epigenetic and transcriptional profiling (ATAC-seq, whole genome bisulfite sequencing, genome-wide profiling of histone modifications, and RNA-seq) were used to predict putative enhancers. Next, enhancer clusters with possible super-enhancer function were obtained, and coordinately regulated genes in the vicinity of super enhancers were shortlisted as possible regulators of Tfh development for experimental validation. An improved understanding of the regulators of human Tfh cell development will provide new insights into the humoral immune response and the auto-immune diseases they play a role in, and it may also reveal novel targets for the therapeutic modulation of the immune response.

Accelerating the Search for New Microbes

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Recent technologies such as CRISPR-Cas9 have demonstrated the power of bacterial enzymes, but there are millions of other useful enzymes that remain undiscovered. Researchers have sampled countless environments to identify novel microbes, but few methods exist for comparing potential sampling sites. In this project, we devised a bioinformatics-based approach to identify novel organisms and assess their relative abundance in different environments. We compared bacterial 16S datasets from the Earth Microbiome Project with two databases: the Genome Taxonomy Database (GTDB) and Nucleotide from NCBI. For each dataset, organisms that NCBI identified as prokaryotes were plotted against how well they matched to known organisms in the GTDB. The resulting figures allowed easy comparison of the abundance of novel organisms in different environments. We found that the optimal environment for microbial discovery can vary based on the desired taxonomic level of novel organisms (e.g. phylum or species) and laboratory sequencing capacity. We also determined that as organisms increased in novelty, their abundance decreased, making it more difficult to characterize their DNA. This new approach allows researchers to select appropriate environments for microbial sequencing, speeding up the rate at which we discover novel bacterial enzymes and products.

Identifying Post-Transcriptional Regulation Patterns of Mitochondrial and Ribosomal Protein Gene Sets Triggering Chemoresistance in Quiescent (G0) Cancer Cells

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Cancer is most often characterized by rapid cell growth, but recent studies have uncovered tumorous subpopulations of quiescent (G_0) cancer cells that remain in a transient cell cycle-arrested state and therefore cannot be effectively targeted by chemotherapy or similar therapeutics. Thus, when these G_0 cells re-enter cell division upon cancer relapse, their chemoresistant phenotypes give rise to severe physiological consequences. Recent studies have uncovered that these cells' anomalous properties are largely due to patterns of differential gene expression at the post-transcriptional and post-translational levels, primarily regulated by small nucleolar RNAs (snoRNAs) and ribosomal maturation proteins, but very little is understood about the specific regulatory mechanisms that give rise to chemoresistance. In our study, we induce quiescence and chemoresistance in acute monocytic leukemia (AML) cells through serum-starvation (SS) and Cytarabine chemotherapy selection (AraCS), respectively, and we utilize these samples to gather transcriptome, translatome, proteome, and protein-binding data through RNA-seq, microarray, mass spectrometry, and ChIP-seq methods. Importantly, we confirm a strong positive correlation between protein expression patterns of quiescent SS cells and chemoresistant AraCS cells (R^2 = 0.68, $p < 0.0001$) versus wild-type (S+) cells. Through gene ontology (GO) and gene set enrichment analysis (GSEA), we find that the most altered gene expression patterns are among mitochondrial ribosomal proteins, with a significant number being upregulated (ES = 5.75, $p = 2.9 \times 10^{-9}$) or downregulated (ES = 8.4, $p = 1.5 \times 10^{-10}$) in SS and AraCS. Through ChIP-seq analysis of *DDX21*, a nucleolar RNA helicase vital for ribosome gene transcription and snoRNA binding, we find significant binding of the protein to the promoters of the mitochondrial genes in question. Further research is required to comprehensively understand the roles of these regulated mitochondrial proteins, including ATP's role in cell division and mitogen-associated protein kinase (MAPK) pathways, but we aim to eventually develop therapeutics to target the chemoresistance.

Identifying Signatures of Selection for Resistance to Malarial Invasion of Red Blood Cells

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Malaria is a widespread, global disease that is caused when protozoan parasites infect red blood cells. It is a particularly strong force of selection on humans, making population genetics an important tool for analysis of genes which have undergone malaria-driven selection. The objective of this study was to determine signatures of selection for malarial infection across East Asia and South Asia to identify polymorphisms and differences in genetic variation geographically. Target red blood cell genes were identified for analysis of parasite-host relationship, particularly genes linked to resistance to malaria invasion. Data were retrieved from the 1000 Genomes Project, a global sequencing project that identified genetic variants across 5 super populations. Malaria has characteristic effects on polymorphisms in genes impacting malarial resistance, and statistical tests can be used to identify candidate genes of malaria-driven selection. Various statistical tests were utilized, particularly F_{ST}, a measure of differences in allele frequency among populations which ranges from 0 (similar allele frequencies) to 1 (absolute differences), as well as a novel statistic which calculates total linkage disequilibrium (LD) values, a measure of divergent haplotypes, for variants in specific regions. Perl scripts were utilized to compute statistics when scanning whole-genome sequencing data. Several red blood cell genes were identified, particularly the glycophorin gene *GYPC* and the *CHST* family (carbohydrate sulfotransferase proteins) such as *CHST6*, which reported an F_{ST} value of 0.3 between European and East Asian populations, and the *UBA1* gene with an F_{ST} value of 0.3 among Europe and South Asia. Furthermore, *ABO* and *PDIA6* showed high LD values. This indicates that several red blood cell genes linked to malarial resistance appear as important targets. Other red blood cell genes such as the CHST family among Europe and East Asia need further investigation. Significant polymorphisms can then be tested experimentally, leading to candidate drug targets.

Understanding the Structure and Function of ZmaM: A Peptidase-Transporter Fusion Protein

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Bacteria produce organic molecules that have many different properties and implications in our daily lives. ZmaM is a peptidase-ATP binding cassette (ABC) transporter fusion protein found in bacteria producing Zwittermicin, a nonribosomal peptide with antimicrobial properties. ZmaM enables the production of zwittermicin through a prodrug resistance mechanism, in which an inactive precursor is exported by the ABC transporter and then cleaved by the peptidase domain to activate Zwittermicin. In this study, I aim to visualize the structural interaction between the peptidase and transporter parts of the protein and better understand the structural relationship of ZmaM to other proteins with similar architecture. I hypothesize that there is a novel interaction that occurs between the two domains of ZmaM and contributes to a mechanism of coupled function. I used homology modeling and residue conservation analysis to determine this potential interaction. I discovered many other proteins with a similar architecture in bacteria that have conserved features important for peptidase-ABC transporter fusion protein function. Additionally, I have delved into the literature behind these similar proteins to understand their respective roles. I used the aforementioned tools to identify residues important for substrate specificity in each of these proteins. My analysis deepens our understanding of ZmaM, how the two domains of the protein interact, as well as the role of these fusion proteins in nature. These insights will help us understand fusion proteins better as well as the pathway for the production of various antimicrobial peptides.

Identifying the Dominant Signal Sequence in the Peroxisomal Membrane Protein Pex14

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Peroxisomes are membrane-bound organelles that perform essential metabolic functions in eukaryotic cells. The absence of functional peroxisomes can result in a number of serious congenital disorders. Proper assembly of the peroxisome requires the effective targeting of key proteins to the peroxisomal membrane, but for many such proteins the underlying targeting mechanisms remain poorly understood. This project investigates the targeting of Pex14, a single-pass peroxisomal membrane protein essential to the peroxisome's import machinery, with a focus on the respective roles played by Pex14's N-terminal and transmembrane domain signal sequences. To this end, we have been analyzing a previously generated proximity-specific ribosome profiling dataset sent to us by Maya Schuldiner's lab. Proximity-specific ribosome profiling is a technique developed in Jonathan Weissman's lab that allows cell biologists to know with codon-level specificity which proteins are being translated at what subcellular locations. The raw output from this technique is a DNA library that has been generated from the sequencing of short mRNAs extracted from ribosomes that have visited a given subcellular location. In the case of the Schuldiner data, this location is the peroxisome. We are currently using the XPRESSyourself computational pipeline in collaboration with its developer Jordan Berg to analyze the raw DNA library provided by the Schuldiner lab. Our first goal has been to plot Pex14 reads from the Schuldiner dataset along the length of the Pex14 gene. If reads were to asymmetrically accumulate downstream of one of the signal sequences, that would help identify which of the two signals is dominant. Even with access to a computational pipeline, analyzing this raw DNA library is a rigorous process that has proved to exceed the scope of one summer. While this analysis has yet to yield any conclusions or figures, we are going to continue this work into the fall.

Culture Adaptation in Babesia Bigemina

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Babesia are apicomplexan parasites that are responsible for infecting cattle with bovine babesiosis (cattle-fever). Given its global distribution, bovine babesiosis can have devastating economic consequences, thereby making *Babesia* crucial to understand. An important tool in understanding the biology of parasites is our ability to propagate the organisms in a laboratory setting. However, current propagation methods are inadequate, which is why much of the *Babesia* genome is still uncharacterized. Previous literature on *Plasmodium*, another genus of apicomplexan, has suggested that understanding culture adaptation is key to the process of developing experimental models for such parasites. To investigate how *Babesia* parasites adapt to culture, a strain of *Babesia bigemina*, acquired from the JG-29 clonal line of Mexican isolates of *B. bigemina*, was cultured in 4% hematocrit in RPMI-1640 media. Genomic data from the unadapted (BIG600) and culture-adapted *B. bigemina* strains (BIGBULK) were then analyzed to detect single nucleotide polymorphism (SNP) variants that emerged. This was done to determine how *B. bigemina* adapted to culture and acquired mutations that allowed it to survive long-term culture conditions. Overall, fifteen mutated genes were identified as being of high interest, five of which belong to a protein family composed of sexual stage s48/45 antigens. Past research on culture adaptation in *Plasmodium falciparum* has shown a loss in the parasite's ability to sexually transform. Interestingly, sexual stage s48/45 antigens are surface proteins known to play an important role in fertilization in *Plasmodium*. This suggests that a loss in sexual reproduction may be a key mechanism by which *B. bigemina* (and potentially other /textitBabesia species) optimize their growth in the laboratory setting. These results also point to the possibility of comparable mechanisms of culture adaptation between *Plasmodium* and *Babesia*. Further studies to validate these mutations would need to be conducted on these fifteen identified genes.

Wall Teichoic Acids and Their Role in Biofilm Formation

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Mentor: Adnan Syed

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Staphylococcus aureus is a Gram-positive bacterium that is commonly found on our skin as part of our natural microbiota. However, the bacteria is also a successful pathogen in part due to its grouping into multicellular communities known as biofilms: resilient structures which provide protection to bacteria by guarding against host but also synthetic (i.e. antibiotics) clearance mechanisms. Although it is known that a subset of *S. aureus* cells have to undergo lysis in order for the biofilm to form, the genes that control this are still unknown. One candidate to control cell lysis are wall teichoic acids (WTAs): carbohydrate-based polymers covalently attached to the peptidoglycan molecules in the cell wall of many Gram-positive bacteria. These polymers are associated with tensile strength, rigidity, and proper shape of the cell wall and previous studies have found them to be integral in maintaining cell envelope integrity. *S. aureus* has two types of WTAs: L-WTA (made by *tarL*), which are longer and more predominant in the cell wall, and K-WTA (made by *tarK*), which are shorter and less predominant. Using luciferase reporters, I investigated how *tarK* and *tarL* expression levels change during biofilm formation. The reporter strains contain plasmids encoding the *tarK* or *tarL* promoter sequences driving expression of a Luciferase gene, therefore giving a direct readout of light intensity. These data suggested that during biofilm formation both *tarL* and *tarK* are downregulated. Further research is needed to reveal the mechanism by which these genes are controlled and that their downregulation leads to a decrease of WTAs. By further investigating the link between wall teichoic acid production and cell lysis, I hope to contribute to understanding how biofilms form and how they can be prevented.

Using Basal Gene Expression Profiles to Predict the Sensitivity of Cancer Cell Lines to Small Molecule Drugs

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One of the greatest challenges in cancer treatment is selecting the most effective drug to treat a given cancer cell line. Given the tremendous heterogeneity of cancer cell lines, there is a clear need to develop methods to predict how a tumor will respond to a drug based on its genetic composition. We used machine learning methods to predict drug sensitivity in 515 cell lines for 30 drugs based on basal mRNA expression. The model was trained on both cell-specific and drug-specific features. For cell-specific features, we used basal expression levels for approximately 1000 designated landmark genes. For drug-specific features, perturbation signatures were extracted from differential mRNA expression (before and after drug treatment) from public screening databases. A multivariate analysis was used to identify differentially expressed genes, and consensus expression signatures were then obtained using weighted averages based on signature similarity. A consensus signature aims to capture the essence of a drug's chemical activity across different cell lines. For target values for prediction, we used sensitivity scores representing cell viability after treatment. After classifying each cell and drug combination as either sensitive or insensitive, the model correctly predicted the class around 72% of the time. When used to directly predict actual sensitivity scores, the model achieved a Spearman correlation coefficient of approximately 0.5. This result demonstrates that a consensus signature for a drug based on a subset of cell lines can then allow for prediction of drug sensitivity for new cell lines. The combination of basal transcript levels and a signature indicative of a drug's effect across different experimental conditions is sufficient for relatively accurate sensitivity prediction. Further testing will seek to optimize the model by examining different possible architectures, using more robust methods for extracting drug consensus signatures, and incorporating more comprehensive information about each cell line.

The Role of ZFP467 in the Signaling Pathway by which PTH Regulates Osteocyte Expression

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Osteoporosis is a widespread chronic condition linked to aging and has many health and socio-economic consequences. PTH(1-34) (teriparatide) and PTHrP analog (Abaloparatide, ABL) are, together with sclerostin antibodies, FDA-approved anabolic therapy for osteoporosis. Daily injections of teriparatide (TPTD) increase bone formation rate (BFR) and bone mineral density (BMD) and decrease fracture risk. TPTD also increases bone resorption, resulting in a high turnover state, albeit with a positive bone balance that leads to increased BMD. However, the molecular and cellular mechanisms by which PTH affects BFR remain largely unknown. Identifying novel determinants of PTH provides greater understanding of these mechanisms and helps accelerate the development of novel osteoporosis treatments. The transcription factor zinc finger protein 467 (Zfp467) was recently shown to be repressed by PTH. Zfp467 is also an activator of the Sclerostin (Sost) gene, which codes for a protein essential for osteocyte function. Osteocytes, the most abundant cell in bone, are the target cells for PTH. They highly express the PTH receptor and the positive effect of PTH on BFR is largely tied to osteocyte effects. This study conducted a literature review investigating the effect PTH in osteocyte functions as well as the possible regulation of Zfp467 expression. This review was performed by search in a PubMed/MEDLINE database, an online scientific resource. The search terms used were "osteoporosis", "osteocytes", "parathyroid hormone" and "zinc finger protein 467". The literature search was performed July 15th, 2020 through on July 31, 2020. In total, 31 records were included in this review. In this process, in-depth insight was gained into the role of the novel axis PTH-osteocyte-Zfp467 in the regulation of skeletal homeostasis. This study is important for gaining insight from important literature into the mechanisms by which PTH regulates cells, and how they could possibly be applied to osteoporosis treatment.

Operation Outbreak Textbook Development

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In the current COVID-19 pandemic, societal reactions indicate a clear lack in public health and epidemiological knowledge worldwide. Targeted education initiatives designed to improve students' understanding of infectious diseases and control initiatives could therefore have strong long-term effects on their in-school interactions and in their adult life. The goal of the Operation Outbreak project is to develop an accessible resource on outbreak response accompanying an epidemic simulation in order to address these demonstrated needs. Through a thorough literature review of pertinent concepts related to epidemiology and public health, the team detailed subjects including vaccination, immune response determinants, and mathematical modeling of epidemics in a textbook format. The project employed science-writing with various pedagogical techniques to gear the text to a teenage audience. This work resulted in an accessible, scientifically accurate resource to be used in the fall 2020 semester within school systems in Florida, Illinois, and potentially additional states. The textbook covers several important topics, utilizing case studies about diseases like COVID-19, cholera, and malaria for an in-depth exploration of the field. The team believes that this has the potential to influence how students interact with each other and their studies in the districts that are reopening in person, and the team anticipates promising results pertaining to student learning and behavior. In the future, the Operation Outbreak resource and simulation will be rolled out on a national stage.

Using Computational and Data Mining Methods to Uncover the Regulation, Pharmacologic Susceptibilities, and Downstream Mechanisms of CTHRC1 in Tuberous Sclerosis and Cancer

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Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disease that affects 1 to 2 million people worldwide and leads to the growth of benign tumors throughout the body. Collagen Triple Helix Repeat Containing 1 (*CTHRC1*) is a secreted glycoprotein known to be overexpressed and correlated with proliferation, invasion, and metastasis in many cancers. Preliminary data has shown that *CTHRC1* is also dramatically overexpressed in TSC conditions and that *CTHRC1* knockdown reduces proliferation and colony formation potential in TSC cells. Computational and data mining tools were used to analyze publicly available datasets, such as The Cancer Genome Atlas, to understand the regulation, pharmacologic susceptibilities, and downstream mechanisms of *CTHRC1* in TSC and cancer. ChIP-seq, RNA-seq, mutation, survival, copy number alteration, and epigenetic data were analyzed, and bioinformatic methods developed by other researchers were applied. This study uncovered a complex picture for *CTHRC1*'s regulation, with expression being driven by the broader cell context and overall transcriptional regulator profile rather than one transcription factor or a small set of transcription factors. Results also suggest that inhibition of the ERK pathway may be particularly effective in killing or reducing the proliferation of high-*CTHRC1* cells. Additionally, a group of transcriptional regulators whose expression or activity may explain how *CTHRC1* produces its observed effects was identified. *CTHRC1* shows much promise as a therapeutic target in both TSC and cancer, and this project contributes to a more complete understanding of this not-well-studied protein. Key inferences and possibilities from this analysis will benefit from *in vitro* confirmation.

Simulating Contact Driven 4D Chromosome Folding

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X-inactivation presents a unique form of epigenetic control in which gene expression is silenced through heterochromatin condensation. Understanding the complex relationship between chromatin folding and gene expression is an active area of research. Modeling chromatin folding computationally is now achievable as a result of advances in chromosome conformation capture (HiC) methods, procuring empirical time-resolved 2D connectivity data. However, connectivity information alone does not show the complete view of the 3D organization of a chromosome. We sought to build a time-resolved 3D model of chromatin folding dynamics coherent with lower dimensional experimental data. Using a polymer chain structure in the Large Atomic/Molecular Massively Parallel Simulator (LAMMPS) molecular dynamics software package, we translated HiC chromosome conformation capture data into simulated bonds between regions of the chromosome that drive the majority of folding. We also analyzed the relative occurrences of contacts during the folding process through frequency and known sites of transcriptional activity, binning higher affinity areas with stronger bonds. Testing of this model across several initial conditions has shown improved accuracy compared to experimental results, suggesting that contact frequency is ample input to generate computationally representative models. Further testing is needed to assess empirical structure accuracy and applications across different chromosomes.

The Role of HCF1 in Hepatic Glucose Response

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Mentor: Dong Wook Choi

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Hepatic de novo lipogenesis (DNL) is the process by which the liver synthesizes fatty acids, and this process contributes to pathologies such as non-alcoholic fatty liver disease (NAFLD). The Danial lab has identified host cell factor-1 (HCF1) as a key molecular player in DNL in response to glucose stimulation. Carbohydrate response element binding protein (ChREBP) is a transcription factor that recruits HCF1 to the promoters of lipogenic genes, where HCF1 participates in their transcriptional activation. In order to characterize the spectrum of HCF1-regulated biological process relevant for hepatic glucose response beyond DNL, an integrative analysis of HCF1 ChIP-Seq and RNA-Seq was performed. The HCF1 ChIP-Seq in primary hepatocytes allowed identification of promoters occupied by HCF1 in response to glucose stimulation, while the RNA-Seq done in HCF1-depleted hepatocytes allowed identification of HCF1-regulated genes in the context of glucose metabolism. Preliminary results from gene set enrichment analysis (GSEA) of the ChIP-Seq data in both low and high glucose conditions show that genes related to mitochondrial or structural processes are significantly enriched in the low glucose condition, while genes related to catabolism or cellular localization are enriched in the high glucose condition. Upon further investigation into gene sets relevant to carbohydrate biosynthesis and homeostatic processes, several genes came to light as being highly enriched in one of the conditions and relevant for hepatic glucose response. Based on the final results of the RNA-Seq analysis, the genes that are direct targets of HCF1 will be indicated, and this integrative analysis will thus be able to provide information that will be useful for further hypothesis generation to explore the glucose response genes regulated by HCF1. Since the liver is crucial for glucose homeostasis, the insights delivered by these studies could be relevant for treatment or management of diseases such as diabetes and NAFLD.

Sequence Optimization of Ribozyme Ligases from an In Vitro Selection

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Mentor: Saurja Dasgupta

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The RNA world hypothesis proposes that early life was dependent on RNA molecules that performed the dual function of carrying genetic information and enzyme catalysis. To support an RNA-based biology, RNA enzymes, or ribozymes, must have played a central role in assembling complex RNA molecules from simpler monomeric or oligomeric building blocks. The Szostak lab recently identified ribozymes that catalyze ligation of RNA oligomers activated with prebiotically-plausible, 2-aminoimidazole groups using *in vitro* selection. From the millions of enzyme sequences identified from this selection, only a handful were experimentally characterized. By mining this sequence data, we aim to computationally identify genetic and structural features that are conserved both within and across various enzyme classes. Additionally, we are trying to elucidate the consensus secondary structures of each enzyme class using covariation analyses. While experimental secondary structure determination of >60 enzyme classes identified from *in vitro* selection is an extremely time and labor-intensive task, this can be potentially achieved by computation in a matter of days. With reliable secondary structure information, we can design shorter and thus prebiotically more accessible enzyme sequences (e.g., non-conserved base pairs can be deleted while preserving a stable base-paired stem). Predictions based on our computational analyses have already been verified experimentally and have resulted in the identification of shorter ribozymes. We are also interested in mapping the mutational pathways that resulted in the enrichment of catalytically active sequences from a random RNA library during multiple rounds of *in vitro* selection. Following the progress of selection at the sequence level will provide insights into how catalytic RNA sequences respond to selection pressure. Collectively, our computational analyses will help inform the next experimental steps toward the laboratory evolution of more efficient ligase ribozymes.

Proposing Molecular Mechanisms for Single-Cell Habituation

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While substantial data supports the crucial role of a nervous system in animal learning, much less is known about the learning capacity of aneural organisms, such as ciliates, and individual mammalian cells. Habituation, often termed "the simplest form of learning," is interesting due to its biological ubiquity and relatively unambiguous definition. A system habituates if its response strength dampens after repetitive stimulation, and, upon withholding stimulus, the response recovers spontaneously over time. Moreover, it has to show parametric features, including faster habituation to lower intensity or higher frequency stimulus. Finally, stimulus specificity is required to distinguish habituation from sensory adaptation or motor fatigue. The current research proposes plausible molecular mechanisms for habituation in single cells, which is a less explored topic given neuroscientists' predominant focus on associative forms of learning, such as conditioning. Inspired by preliminary literature search, ordinary differential equation models are constructed to describe chemical reaction or gene regulatory networks. Numerical integrations of these models then reveal distinct dynamic behaviors at randomly chosen parameter sets. Quantitative filters are designed and applied to select for habituating systems for further characterization. Supporting previous studies, timescale separation in various reactions along with feedforward/feedback motifs was crucial for maintaining a molecular memory. It's also found that a minimal number of nonlinear rate laws are necessary for producing the parametric features of habituation. Eventually, these findings may improve our understanding of how eukaryotic gene regulation can process temporal signals and allow cells to adapt behaviors to environmental changes.

Studying Morphological Differences between Excitatory and Inhibitory Neurons in the Larval Zebrafish

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Excitatory and inhibitory neurons play vital roles in the brain—excitatory neurons induce their target postsynaptic cells to produce signals, called action potentials, while inhibitory neurons suppress these signals. In neuroscience, form often informs function, and we seek to reveal certain morphological patterns that compose excitatory and inhibitory neuron functions in the larval zebrafish. We identify excitatory and inhibitory neurons using light microscopy by genetically labeling reporters for the expression of the neurotransmitters glutamate, for excitatory neurons, and GABA, for inhibitory neurons. To extract detailed three dimensional neuron morphologies in the larval zebrafish, we use a set of nanoscale resolution electron microscopy images of the entire brain. Using a Python-based tool called Neuroglancer, we have completed the initial reconstruction of over 150 excitatory and inhibitory neurons, allowing us to begin to categorize morphological differences. In the reconstructions of the neurons, we have begun to observe differences in features such as cell body shapes, branching patterns of axons and dendrites, and appearance and number of synapses. While we cannot confirm the qualitative patterns that have thus far been observed from these features—for example, excitatory neurons tend to exhibit a higher number of synapses and possess more globular-looking cell bodies—as the dataset continues to grow, we will conduct a variety of quantitative tests to verify some of the patterns and answer whether we can determine a cell's excitatory or inhibitory function from morphology.

Methodology Development for Model Zoology and Neural Taskonomy

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The comparison of biological brains and deep artificial neural networks is an increasingly popular method in the study of visual processing. The rapid proliferation of this method, while immensely fruitful, has left many foundational questions about its efficacy, accuracy, optimality and underlying theory unanswered. With new high resolution rodent neurophysiology data, it has now become possible to analyze the activation of individual neurons in biological brains with artificial neurons in artificial neural networks. The goal of my research project is to develop a more robust methodology for the comparison and analysis of biological visual cortex with deep neural networks and to apply it to the mouse brain data. First, PyTorch implementations of penalized regressions and dimensionality reduction methods were developed to enable faster analysis. Then, different cross-validation, regression, and dimensionality reduction methods were systematically compared on consistency, speed, and error. These methods were applied to compare regions of the mouse brain with neural network models built with different architectures or trained on different tasks. Preliminary results support partial least squares regression (PLSR) with a leave-one-out approach and data normalization as the most consistent method. PyTorch implementation of PLSR allowed much faster runtimes on large datasets. Although penalized regressions were faster and performed well in k-fold cross-validation, they were less suited for leave-one-out cross-validation. Thus far, deeper layers of larger neural network models have shown lower similarity to medial mouse brain regions than the final layers of smaller neural network models. Having more rigorously tested different submethods, I can now apply the faster, standardized method to a greater number of brain regions and neural network models, and potentially begin to use these models to better chart the representational geography of rodent visual cortex. Most importantly, I hope to show how different analytic methods may lead to different interpretations and create tests to determine the best method.

Developing a Novel Temperature-Modulated CRISPR-Cas12a Gene Editing System for iPSC Disease Modeling in X-linked Dystonia Parkinsonism

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The ability of induced pluripotent stem cells (iPSCs) to differentiate into various types of neurons has revolutionized the study of complex neurodegenerative diseases by providing robust *in vitro* models of diseases where previously obtaining disease-specific neurons was impossible. Our research focused on developing a novel iPSC model of X-linked dystonia parkinsonism (XDP), a rare neurodegenerative disease that almost exclusively affects males from the Panay Island in the Philippines. Previous research has shown that XDP is primarily associated with an insertion of a SINE-VNTR-Alu (SVA) retrotransposon in intron 32 of the *TATA-Box Associated Factor 1 (TAF1)* gene, a general transcription factor. To create our iPSC model, we planned to insert the SVA retrotransposon into a control iPSC line at the *TAF1* locus using a CRISPR-Cas12a-based gene editing system. However, because the recognition site for Cas12a remains unaffected in the initial process of inserting the SVA, Cas12a can potentially recut the DNA and reverse any editing or insertion that previously occurred. Thus, preventing recutting by Cas12a at its recognition site is necessary in order to allow efficient insertion of the SVA at the *TAF1* locus. We tested the temperature sensitivity and kinetics of CRISPR-Cas12a in iPSCs in order to develop an optimized temperature-modulated gene editing system using CRISPR-Cas12a that could be used to successfully insert the SVA retrotransposon into control iPSCs. Our research showed that the nuclease activity of Cas12a in iPSCs was significantly reduced at a lowered incubation temperature of 30°C, demonstrating that temperature modulation could be a successful strategy to prevent recutting of Cas12a. This optimized temperature-modulated CRISPR-Cas12a gene editing protocol can be applied to creating an iPSC model for XDP as well as other neurodegenerative diseases.

Prediction of Human Behavior from Electrocorticography Readings

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Over the past 100 years, the recording of electrical data through electroencephalograms (EEG) has been used to elucidate brain function. However, this method has low spatio-temporal resolution and significant noise, factors that prevent recording precise measurements. In more recent years, Electrocorticography (ECoG) has been used as a way to locate epileptogenic zones in patients with severe epilepsy. The placement of electrodes are on the cerebral cortex rather than the scalp as in the case of EEG measurements. This new arrangement in ECoG provides a unique opportunity for accessing electrical data from the brain at a high spatio-temporal resolution. With higher quality data, it is possible to better understand how behavior is related to the brain's neuronal circuits. In fact, ECoG data can even be used to predict behavior. Three patients with untreatable epilepsy underwent ECoG measurements and a recording of their activities was obtained for a total of 42 hours across all three patients. Common behaviors like sleeping, watching tv, and talking were labeled. The ECoG data was pre-processed to filter out artifacts. Predicting behavior then became a supervised learning problem in which voltage data across multiple electrodes was matched with different behaviors of interest. Initial results using linear classifiers show an ability to significantly predict behavior from ECoG data. More complex classifiers such as neural networks and machine learning models could produce higher performances, but this study is the first to show manually-labeled patient behavior can be predicted from ECoG recordings. Now complex behavior-related signals in the brain can be better understood, and these results also can be used to advance the development of brain-computer interfaces for treating patients with a wide range of disabilities.

Reconstructing Neural Circuitry for the Visually-Evoked Escape Behavior in an Intact Larval Zebrafish

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When an organism suspects predation, it responds by moving away. One of the main sensory modalities that drive this escape behavior is vision. Visually evoked escape behavior is innate to larval zebrafish, and current research with this model system has proposed both behavioral algorithms and underlying neural computations. However, the physical neural implementation of the proposed neural computations remains completely unknown. Here, we will use electron microscopy images of an intact larval zebrafish to visualize the structure of the neural circuit that is responsible for the escape behavior. In particular, we aim to follow the flow of visual information through the key anatomical regions involved in this behavior: the optic nerve, the optic tectum, and motor neurons (Mauthner cells). We begin by reconstructing the morphology and connectivity of the first neurons in the brain which are thought to receive escape-related visual sensory information. Specifically, we identify looming responsive neurons in the tectal neuropil which may indirectly receive information from the optic nerve arborization field 8. Thus far, tens of cells have been fully modeled in this vicinity. This work is a valuable starting point for quantitatively analyzing the circuit.

Creation of Ground Truth Data Towards Automatic Labeling of Synapses in Electron Microscopy Images of an Entire Larval Zebrafish Brain

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In the field of neuroscience, structure implies function. This crosstalk between nervous cells is carried out by synapses, the physical junction between neurons. The cell shape and placement of synapses determines the rules that govern the computations the nervous system can make. The new field of connectomics has expanded on this by analyzing not only shape, but circuity to explain function. This is especially important since synapse size and placement within a circuit defines the ways we "learn" and "adapt". Adapting is believed to be accomplished by modifying the strength of the connection between neurons by changing synapse size and number. To illustrate with examples, *Drosophila* can have polyadic synapses, forming multiple junctions between cells to strengthen signals. Mammals have spiny dendrites with boutons, allowing for synapses of varying sizes and strength. Little is known about the mechanisms that govern the zebrafish's nervous system; sizewise, it is comparable to small insects like *Drosophila*, but is a vertebrate like a mammal. Here, we use electron microscopy (EM) images to visualize the synapses between neurons in the zebrafish nervous system. We estimate that there are about 50 million synapses in the entire brain of the animal. Manually labeling each synapse is infeasible, but achievable with machine learning algorithms. The goal of this project is to manually create labeled "ground truth" images of a few thousand synapses to train such algorithms. Notably, these ground truth images will be used to develop initial hypotheses for the rules by which zebrafish physically arrange their nervous system as well as "learn" and "adapt" to their environment.

Investigating the Input Patterns of Projection-Defined NTS Neurons

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The nucleus of the solitary tract (NTS) is a brainstem hub for organizing internal sensory information. The NTS receives inputs from the vagus nerve, and then transmits signals broadly throughout the brain to generate behaviors, perceptions, and physiological responses. Previous work in the Liberles Lab discovered that NTS neurons can be organized into subgroups based on their projections to central targets. However, it remains unclear whether different subgroups perform specific functions in processing visceral inputs. To better understand the functions of projection-defined NTS populations, we used TRIO (Tracing the Relationship between Inputs and Outputs), a virus-based genetic strategy to analyze neuronal inputs. In TRIO experiments, we injected a retrograde adeno-associated virus encoding Cre recombinase into NTS projection targets, and revealed top-down inputs to NTS subgroups using rabies-mediated trans-synaptic circuit tracing. We showed that different projection-defined NTS subgroups receive direct and uniquely patterned long-range inputs in addition to feedforward inputs via local interneurons. The divergent input patterns of projection-defined NTS neurons suggest complementary physiological roles. Future behavioral and physiological studies will help define the functional roles of different NTS neuron types, providing a foundation for understanding strategies used by the brain to encode internal organ inputs.

Measuring Neurocognitive Impacts of Exposure to Early Life Adversity

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A growing body of literature suggests that early exposure to biological, environmental, and psychosocial adversity influences neural development and cognitive outcomes. The Bangladesh Early Adversity Neuroimaging Project employs imaging techniques and behavioral assessments to study the association between exposure to early life adversities and neurocognitive development in children in Bangladesh. Imaging techniques include functional near infrared spectroscopy (fNIRS), electroencephalograms (EEG), and magnetic resonance imaging (MRI). Behavioral measures include Mullen Scales of Early Learning and executive functioning tasks. The Mullen Scale assesses intellectual development and readiness for school in young children; the scale subcategories include Gross Motor, Visual Reception, Fine Motor, Expressive Language, and Receptive Language. This longitudinal study tests age cohorts of 6 months, 2 years, 3 years, and 5 years. Significantly, caregiving has been identified as an important protective factor against exposure to early life adversities. Our hypothesis posits that the relationship between early life adversity and neurocognitive development potentially attenuates in the presence of caregiving. Currently, our study investigates how perception of stress by caregivers mediates the association between socioeconomic status and neurocognitive development, as measured by the Mullen Scale. Data processing is done to standardize score outcomes in a cross-cultural context. When statistical analysis is completed, the study aims to identify demographic variables susceptible to caregiver mental status. By improving our understanding of neurodevelopment in children of Bangladesh, the study hopes to enrich the existing body of scholarship on the cognitive and neurological impacts of early life adversity. This work has implications for informing interventions that support neurocognitive development in children who live in low-resource environments.

The Impact of Exercise, Authoritative Parenting and Ties to Prosocial Organizations on Epigenetic Age

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Researchers have proposed that adversity can become biologically embedded through epigenetic mechanisms such as DNA methylation. This modification can alter gene expression without changing DNA sequences and is positively associated with early-life stressors that have long-term health outcomes. Importantly, DNA methylation has been harnessed as a tool to guide research through the epigenetic clock. Through epigenetic clocks, which predict an individual's biological age, researchers have harnessed DNA methylation as a biological marker that estimates positively or negatively accelerated epigenetic age. Individuals that have a positively accelerated epigenetic age express an epigenetic age that is older than the control. By contrast, individuals that have a negatively accelerated epigenetic age express an epigenetic age that is younger than the control. Numerous epidemiological studies have demonstrated a possible association between positively accelerated epigenetic age and mental disorders. However, fully understanding the impact of adverse events on the incidence of depression requires accounting for the effects of social protective factors on the epigenetic clock and how they might promote resilience to depression. Using data from the ALSPAC cohort, a longitudinal study with epigenetic data for 1,018 mother-infant pairs, we studied the impact of exercise, parental support, and ties to prosocial organizations as well-established protective factors for depression during development. This study used the Horvath and Hannum epigenetic clocks to estimate the individual's epigenetic age using peripheral blood at age 15-17. First, we identified the epigenetic clock that provided the closest approximation to chronological age. Second, we used generalized linear models to identify significant associations between exposure to the protective factors described above and epigenetic age, correcting for common covariates in epigenetic and epidemiological studies. Examining these social protective factors will not only further our understanding of the epigenetic vulnerability underlying depressive behaviors but will also help identify developmental periods for optimal early-life stress recovery.

Pathogenic Lawn Leaving as a Predictor of Immune System Neural Networks in C.elegans

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Caenorhabditis elegans, commonly referred to as *C.elegans*, are widely used in neuroscience research as a result of their simplified neural systems. However, much remains unknown as to which neural networks are primarily responsible for their characteristic immune response involving pathogenic bacterial lawn leaving behavior. Learning the neurons associated with immune behavior is crucial for more in depth knowledge of the immune systems of higher animals. As such, the long-term experimental goals are to further investigate these mechanisms, and identify the pertinent neurons and neural networks. The first objective was to obtain behavior and positional tracking data for many worms over long-term time courses while on bacterial lawn setups. To facilitate this, MATLAB scripts were developed and used in conjunction with traditional hands-on methods for improved efficiency of collection, to best maximize speed and accuracy. The next objective was to further investigate a previously compiled list of the top candidate neuropeptide receptors that are expressed in the neurons of interest through examination of the literature pertaining to each one. Thus far, key data has been collected pertaining to roaming and dwelling behavior over time, and it is expected that as more behavioral information is gained over time, a more complete picture of the effects of pathogenic behavior will be acquired. Analysis of the speeds over time have suggested both that dwelling behavior is more common than roaming, and that relative speeds increase off of the lawn as compared to on the lawn. Overall, learning which neurons are involved with the immune system behavioral responses will have larger implications for understanding other organisms' immune responses more effectively, including humans.

Investigating Emotion Regulation Processes in Preschool-Aged Children with Autism Spectrum Disorder (ASD)

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Emotion regulation, or the ability to regulate expression of emotion and behaviors, is important for the development of peer relationships and the well-being of children. Emotion dysregulation results in greater levels of depression and anxiety, impacts symptom severity of Autism Spectrum Disorder (ASD), and is most frequently associated with children diagnosed with ASD. The Process Model of Emotion is used to describe five domains of strategies used in emotion regulation. A coding system based on the Process Model was developed for this project and was used to measure emotion regulation processes in children with ASD and typically developing (TD) children. Coding was conducted by two coders who established reliability with the developer of the system by reaching 75% agreement with the master coder. Coders were blind to ASD status. To date, 71 files were coded (38 ASD, 33 TD) and at least 10% were double coded for reliability. Clinical and physiological correlates of emotion regulation were also explored. Parent-reported anxiety levels were assessed using the Behavior Assessment System, 2nd ed. (BASC-2). Resting electroencephalogram (EEG) data were also recorded. Frontal alpha power asymmetry between the left and right hemispheres was evaluated as a physiological correlate of emotion regulation behaviors. Because coding is still ongoing, results are not presented for comparisons between diagnostic groups. Preliminary results found the coding system to be effective in detecting individual variability among participants for four domains. At the conclusion of coding, differences in emotion regulation behavior between children with ASD and typically developing children will be examined.

Exogenous Oxytocin Administration at Birth Affects Neurobehavioral Development of Offspring in a Sexually-Dimorphic Fashion

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The neuropeptide oxytocin facilitates the delivery process by stimulating uterine contractions, and it is administered synthetically in hospitals to induce or augment labor. However, the long-ranging effects of exogenous oxytocin administration at birth on the neurobehavioral development of offspring are poorly understood. This experiment investigates whether oxytocin administration, or the administration of its synthetically-derived variant Pitocin in conjunction with the preservative chlorobutanol, to prairie vole mothers shortly prior to the birth event affects the neural circuitry of offspring and induces autistic-like behavior. In human mothers, labor is often induced as a result of stressful birth circumstances and underlying maternal health conditions such as obesity, making it difficult to establish a directional causal relationship between oxytocin exposure and variable health outcomes of offspring. By implementing an animal model, this study aims to establish causality by eliminating the confounding variable of maternal pre-existing pregnancy conditions. The five prairie vole treatment groups included offspring of mothers who had never been handled and who did not receive an injection; offspring of mothers who were administered the vehicle control solution of saline 12 hours prior to birth; offspring of mothers who were administered oxytocin in the vehicle solution 12 hours prior to birth; offspring of mothers who were administered Pitocin, akin to what human mothers are administered, in the vehicle solution 12 hours prior to birth; and offspring of mothers who were administered the preservative chlorobutanol in the vehicle solution 12 hours prior to birth. The prairie voles then underwent light/dark transition tests, play tests, and forced swim tests, and social behavioral analyses were performed to compare the behaviors of these 5 experimental groups. Our findings suggest that behavioral deficits in prairie vole offspring following exogenous oxytocin administration at birth exist and may be sexually dimorphic.

Identifying Molecular Pathways of Environmental Toxicants in Parkinson's Disease

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Parkinson's disease (PD) is the second-most common neurodegenerative disorder with a prevalence of 2-3% for individuals at least 65 years of age, second only to Alzheimer's disease. This condition is pathologically characterized by the progressive loss of dopaminergic (DA) neurons in the substantia nigra. There is an increasing amount of evidence supporting a significant contribution from both genetic and environmental factors, particularly toxicants such as agricultural pesticides, on the risk associated with developing PD. Previously performed drug screens have shown that several compounds leading to high levels of DA neuronal death *in vitro* also target NF-κB, a protein complex involved in a variety of cellular mechanisms, but notably in the regulation of genes for anti-apoptosis and neuroinflammation. Using DA neurons derived from PD-patient induced pluripotent stem cells (iPSCs), we aimed to elucidate the potential role of NF-κB through treatment with compounds known to inhibit this family of transcription factors. Following treatment of DA neurons with such compounds, live image analysis was used to evaluate and quantify the effects on DA neuronal survival. The results of this experiment will serve as an initial attempt in observing the role of NF-κB and will provide a preliminary validation for whether these compounds lead to DA neuronal death. Future efforts would seek to quantify changes in known molecular or genetic targets for each of these compounds. Finding evidence of changes in gene expression or in molecular pathways relevant to DA neurons from one or more of these compounds could begin to enable a better understanding of the role of NF-κB in neuronal death. Ultimately, an analysis of both the upstream and downstream targets for these compounds could potentially provide new information on the molecular mechanisms involved in PD and illuminate future routes for treatment exploration.

Neuropil Fraction in the Frontal Gyrus of Domesticated Silver Foxes

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Domestication applies selective pressures that lead to changes in animal behavior and phenotype. Previous work on domestication has characterized and extensively recorded the resulting changes in behavior and gene expression; however, the specific neural impacts of domestication remain unknown. This study uses tame, aggressive, and unselected fox strains from an ongoing experiment as a controlled model of domestication to study the changes in brain anatomy and connectivity that result directly from selective pressures for behavior. Neuroimaging data from earlier stages of this study used diffusion tensor imaging (DTI) that suggested greater white matter connectivity between regions of prefrontal cortex and subcortical regions in tame foxes as compared to aggressive foxes. To determine whether this difference is observable on a cellular level, the present study uses histology to estimate the amount of neuropil, an indirect measure of connectivity of a region, in the frontal gyrus of the prefrontal cortex. The fox brains have been sectioned at 40 μm thickness using a microtome, stained for Nissl ro reveal cell bodies, scanned at high magnification onto an online database, sorted without indication of behavioral strain, and converted into black-and-white binary images to quantify positive pixel staining in order to estimate the neuropil fraction (NF). Based on previous DTI findings, we hypothesized tame foxes would have a higher NF. Currently, the NF has been estimated from two foxes to be an average of 0.8355 and 0.7733, with ten more foxes in progress. This study provides further insight to ongoing studies of fox behavior and genetics, and may illuminate the pathways and circuits that have contributed to domestication in not only foxes but also potentially in other animals.

Calcium Signaling in Schizophrenia: The Role of CACNA1C in Synaptogenesis and Microglia-Mediated Pruning

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Schizophrenia is a crippling neuropsychiatric disorder whose cause—while speculated to be genetic—has remained elusive for centuries. However, recent studies suggest alterations in neuronal connectivity, potentially caused by decreased numbers of synapses, could underlie key schizophrenic symptoms. *CACNA1C*, a gene which encodes for a subunit of a neuronal calcium channel, is both commonly mutated in patients with schizophrenia and responsible for regulating a variety of processes important in synaptic growth. Although *CACNA1C* is widely recognized to be an important locus for schizophrenia research, there are currently few studies of *CACNA1C* that utilize human neurons to study how this gene impacts synapses. Therefore, this report uses extensive literature review to suggest that *CACNA1C* plays relevant roles in not only synaptic strength, but also destruction of synapses by microglia, the immune cells of the brain. To investigate this theory, human stem cells were mutated in the *CACNA1C* gene using CRISPR/Cas9 gene editing technology. These cells can be differentiated into both neurons and microglia using techniques pioneered by members of our lab. Cells without mutations will be compared to cells with mutations in a variety of assays, including electrophysiological analysis of neurons using microelectrode array plates, synaptic staining, intracellular calcium imaging, and time-lapse recording of microglia. Neurons and microglia will be grown and subsequently analyzed both individually and in co-culture through different combinations of wild-type and mutant neurons/microglia. We expect to observe less developed synapses in neurons and increased numbers of activated microglia in mutant cells compared to wild-type. We also expect to find increased synaptic pruning by mutant microglia in co-culture and significantly reduced numbers of synapses. This will not only further establish the role of *CACNA1C* in schizophrenia, but also illuminate relevant calcium channel biology and its importance to immune function in the brain.

Locating the Source of Perpetual Decision-Making in Larval Zebrafish as a Model for Other Species

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While underlying causes of certain behaviors in zebrafish may be well-understood, how these decisions become implemented in the brain are not nearly as well-understood. Prior research in this area reveals that random-dot motion with varying coherence levels of dot directionality shows a positive correlation with the amount of time larval zebrafish take to react in swimming with the directions of the dots. After watching performance under microscopic environments using brain-wide imaging, three neuronal clusters were found to carry out the implementation of the computations needed to make the decision of turning in a certain direction according to the directionality of the dots. An integrative circuit model, located in the hindbrain, indicating an evidence integrator in conjunction with a decision threshold was thus proposed as the underlying cause of these responses. In this study, we aim to verify this model by analyzing high-resolution electron microscopy images as a means of investigating the underlying structure of this nervous circuit structure on subsequent function. From the images, we extract both the morphologies and connections (synapses) between the cells. Using connectomics, we may expect to find intricate and particular details on how these neurons interact with one another. We expect that these findings can possibly then lead to uncovering the physical implementation of neural calculations such as integration and gating, which are general features of brain computation across species.

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

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Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that impacts communication and behavior. Symptoms of social communication impairment and repetitive behaviors typically appear within the first two years of life. The aim of the Infant Screening Project is to identify neural and behavioral risk markers in infants at familial and developmental risk for ASD. We will then observe whether these neural and behavioral risk markers predict later diagnoses of ASD or other neurodevelopmental outcomes. To investigate these questions, we compared gross motor development in three groups of infants: infants at low risk of developing ASD due to having no older siblings with autism and having passed a 12-month screener (Low-Risk Controls, or LRC), infants at familial risk for ASD due to having at least one older sibling with autism (High-Risk for Autism, or HRA), and infants at developmental risk for ASD based on early behavioral differences detected on a 12-month screening instrument (High-Risk Screeners, or HRS). Infants from each group were administered a set of behavioral and neural measures at ages 3, 12, 18, 24, and 36 months. Gross motor development data from behavioral assessments at 12, 18, and 24 months show that the HRS group had significantly slower gross motor development than both the HRA and LRC groups. However, there were no significant group differences in gross motor scores between the HRA and LRC groups. The lack of differences between the aforementioned groups further highlights the differences between the HRA and LRC groups. Future research should explore whether these gross motor delays are predictive of later developing ASD. Future research could also result in the utility of gross motor evaluation as a biomarker for ASD in children at familial and developmental risk.

The Effects of Perinatal Stress on the Mitochondrial Morphology and Development of Males and Females

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Autism spectrum disorders (ASD) are early-onset neurodevelopmental disorders characterized by deficits in social interaction that are more prevalent in males than females. Recent data reveal alterations in immune function and mitochondrial energy metabolism/morphology in patients with ASD. Alterations in mitochondrial function have been implicated in microglial dysfunction, and sex differences have been described in both immune and mitochondrial function, so exploring sex differences in microglial mitochondria may yield a better understanding of ASD. One potential difference between females and males early in life that could lead to brain sex differences underlying male vulnerability to ASD stems from differential exposure to sex hormones early in life; there is a critical period of brain differentiation surrounding birth in which only males are exposed to the gonadal sex hormone, testosterone, and its aromatized form, estradiol. Using this information, female, male, and masculinized female (that received the aromatized male sex hormone, estradiol) mice were immune challenged with lipopolysaccharide (LPS) or vehicle saline during the perinatal period. The social behavior of all mice was assessed for ASD-relevant alterations. Brain slices from the mice were collected and stained for mitochondria and microglia, and volumetric reconstruction was performed to determine mitochondrial morphological characteristics (i.e. length). Both males and masculinized females were significantly less social after the injection of LPS—an observation associated with ASD. LPS-challenged male and masculinized mice also exhibited shorter microglial mitochondria, while females were unchanged. These findings indicate that there is a correlation between microglial mitochondrial morphology and the male sex bias in ASD. They indicate that there likely is a connection between the presence of a surge in male sex hormones during development, microglia, and male susceptibility to neurodevelopmental disorders. This information may shed light on the relationship between the type of disorder—early vs late-onset—and one's vulnerability based on sex.

Identifying Molecular Mediators of Exercise-Induced Neuroprotection in Alzheimer's Disease

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Afflicting one in three seniors, Alzheimer's disease (AD) poses a significant public health concern with economic, social, and emotional costs that cannot be overstated. Adult hippocampal neurogenesis (AHN) describes the continued generation of new neurons from neural progenitor cells during adult life in the hippocampal dentate gyrus; it has been shown to decline with aging and the progression of AD pathology. Recent research has highlighted the importance of the neurogenic stem cell niche, which consists of astrocytes, microglia, and other cells in the local microenvironment, in AHN regulation. Exercise, particularly endurance exercise, is shown to improve cognition and importantly restore AHN, but the salient question of which underlying molecular mechanisms and secreted factors mediate exercise-induced neuroprotection remains to be answered. Successful identification of secreted factors that act as neurogenic mediators presents a promising therapeutic strategy to combat cognitive decline. We hypothesize that exercise increases the neurogenic potential of the hippocampal stem cell niche. Our study seeks to compare the adaptive response of the stem cell niche to exercise in transgenic murine models and to identify neurogenic mediators using a novel transcriptional approach. As exercise intervention, free-wheel running in mice was employed, followed by behavioral analyses for cognitive changes and image analysis of cellular proxies for the stem cell niche. Preliminary data support our initial hypothesis, and these insights are now informing concentrated efforts to locate differentially expressed genes or pathways that are induced by exercise in wild-type mice but are dysregulated in AD mice. Ultimately, these data taken together will help identify secreted factors that are expressed in the stem cell niche and that participate in the neurogenesis cascade, positioning them as attractive potential therapeutic drug targets for AHN stimulation and cognitive improvement.

Spinal Cord Injury: A Review of Pro-Regenerative Treatments

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Spinal cord injury (SCI) is a type of traumatic neurological injury that may result in the loss of sensory, motor, and autonomic functions. Traumatic SCI severs spinal cord axons, leading to a disruption in communication between the body and the brain. While functional recovery after SCI depends on the regeneration of injured axons and the sprouting of spared axons, axons in the central nervous system (CNS) do not readily regrow after CNS injuries such as SCI. A combination of cell-extrinsic and cell-intrinsic factors, which are currently being researched, underlies this lack of regeneration. One such factor is ionic zinc, which has previously been shown to contribute to cell death as well as suppress axon regeneration in animal injury models. Currently, there are no widely-used clinical SCI treatments that address the lack of regeneration. In order to understand how the field of SCI research is approaching this issue, we review the literature on axonal regrowth in the CNS. This involved studying the mechanisms behind axonal regrowth failure, regeneration, and sprouting with a focus on the corticospinal tract (CST), which is important for voluntary motor function in humans. Next, we explore the use of ionic zinc chelation to block zinc accumulation and promote axon regeneration after CNS injury. In addition, we discuss several other promising pro-regenerative treatments currently in development, specifically stem cells, biomaterials, and electronic spinal cord stimulation. In studying these pro-regenerative treatments, we considered both animal injury models, which are useful for understanding pathophysiology and potential therapeutic interventions, and clinical studies involving humans. The promising outcomes from these pro-regenerative treatments have exciting implications for improving functional recovery after clinical SCI.

Imaging of Glial Activation in ALS and PLS Patients

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Amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis (PLS) are two degenerative motor neuron diseases with unknown causes. ALS is characterized by the progressive deterioration of both upper and lower motor neurons and has a typical life expectancy of two to five years after diagnosis, while PLS is marked by only upper motor neuron degeneration and PLS patients can live decades beyond diagnosis. To better understand regional brain differences that may underlie pathological differences in ALS and PLS, we measured glial activation in the brain (inferred from [^{11}C]PBR28 uptake) using positron emission tomography (PET) and morphometry using magnetic resonance imaging (MRI). A total of 64 [^{11}C]PBR28 PET-MR data sets, including 43 with ALS and 21 with PLS, were available for comparison. Individual subject data were registered to the MNI brain template and subsequently, whole-brain voxelwise analysis was performed. Inspection of the regional difference maps between the two disease group data sets using Harvard-Oxford cortical and subcortical structural atlases was used to explore specific areas of the brain where the signal from ALS patients was significantly different than PLS patients at the group level. Next, a reverse transformation matrix was applied to the individual data sets to register the group activation maps back to individual subject space in order to quality control the group effects. Long term, this process will lead to a better understanding of the pathological differences between ALS and PLS.

Temporal Shift of Error Signal in Associative Learning

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Associative learning is primarily driven by midbrain dopamine neurons that deliver a sharp burst of activity in the presence of an unexpected reward. According to the temporal difference (TD) learning model, this dopamine transient is the mechanism by which reward information is associated with antecedent cues. The TD model predicts that this burst of dopamine initially coincides with the time of the reward delivery. Upon repeated pairing of the reward with a preceding cue, however, the burst of dopamine should occur earlier and earlier in time, eventually shifting to the time of the cue rather than the following reward. This temporal shift of dopamine is the mechanism by which reward learning is thought to occur, but it has not yet been confirmed *in vivo*. To address this unresolved question, we have recorded dopamine neuron activity in the ventral striatum (VS) using a genetically-encoded dopamine sensor while optogenetically activating dopamine neurons in the ventral tegmental area (VTA) as mice perform a Pavlovian conditioning task. With this approach, we can functionally isolate dopamine signals with the temporal specificity required to capture the potential activity shift that underlies learning. We have found preliminary evidence indicating a gradual shift of the dopamine transient across the interval from the time of the reward to the time of the cue, supporting the predictions of the TD model. Further work may focus on different variations of our conditioning paradigm, as well as potential modulations of other parameters described in the TD model. This analysis will allow us to characterize the potential backwards shift of phasic dopamine activity in accordance with computational learning models and to present direct evidence indicating that associative learning is driven by the temporal transfer of phasic dopamine.

The Fever Effect: Determining Behavioral Changes Induced by Fever in Autistic Mouse Models

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Autism spectrum disorder (ASD) is a disorder that impacts roughly 1 in 54 children in the United States every year. The symptoms of ASD are largely social in nature and organized into three broad categories: persistent deficits in social communication, restricted and repetitive patterns of behavior, and language impairment. The *fever effect* is a phenomenon observed in a subset of children with autism in which fever induces transient improvements across all behavioral categories. This phenomenon has the potential to reveal the underlying neural circuitry implicated in ASD. In order to further understand the fever effect, autism mouse models that mimic its characteristic behavioral changes must be identified. The goal of this study is to test Contactin Associated Protein-like 2 knockout (CNTNAP2-/-), Shank3B knockout, and heterozygous null 16p11.2dfl+ autism mouse models and determine if their change in behavior due to fever reflects the change in behavior in humans experiencing the fever effect. This study aims to use behavioral assays to assess the changes in social interactions, repetitive behaviors, and behavioral flexibility while mice are febrile. Initial observations from a social assay including an experimental CNTNAP2-/- febrile mouse and a wild-type non-febrile mouse revealed a statistically significant decrease in the total duration of sniffing and in bouts of sniffing in febrile experimental mice. Also, a significant increase in bouts of huddling in febrile experimental mice was shown. There was no significant difference in grooming behavior between febrile and non-febrile mice. The increase in bouts of huddling behavior indicates that fever has a significant impact on social behavior. If fever also causes a change in behavior in the assays measuring repetitive behavior and behavioral inflexibility, that may lead to the conclusion that CNTNAP2-/- is a viable autistic mouse model for the fever effect.

Neural Correlates of Foraging

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In the natural world, resources like food and water are often not uniformly distributed throughout an animal's environment but are instead clustered in rich areas called *patches*. For example, a deer may spend its day traveling between berry bushes. Crucially, the resources within a given patch are finite and because of this, animals must learn to leave patches under some optimal strategy to maximize their energy intake. We seek to discover the neural mechanisms underlying this decision-making process by studying mice foraging in a patchy environment in virtual reality. Mice run on a wheel to navigate through a 1D world, making decisions about when to leave rewarding patches, while we measure neural activity in the medial prefrontal cortex (mPFC), an area of the brain involved in decision making and evidence accumulation. Neurons in the mPFC elucidate a dynamic decision-making process in which spiking activity, correlated with patch leaving, builds up over time and is reset by reward reception. This encoding occurs both at the level of individual neurons and through coordinated population responses. This study will improve our understanding of the neural representations underlying economic decision-making in uncertain environments. In turn, this work may eventually feed into treatments to disorders in which such decision-making is compromised, such as addiction, schizophrenia, and bipolar disorder.

Ctip1 Function in Regulation of Callosal Projection Neuron (CPN) Axon Growth Cone-localized Molecular Machinery and Axon Guidance

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The transcription factor *Bcl11a/Ctip1* (*Ctip1*) has been recently discovered to have converging and likely connected biological importance in basic brain circuit development and human autism spectrum disorders (ASD). Deletion and mutations are monogenically causal in ASD/intellectual disability. Cerebral cortex deletion of *Ctip1* in mice causes the axons of callosal projection neurons (CPN) to project to nonspecific regions of the contralateral hemisphere rather than projecting to distinct clusters as they do in wild type mice. The Macklis lab has identified 50 transcripts that are differentially subcellularly localized in growth cones (GCs) upon *Ctip1* deletion; GCs are the sensing, growing tips of extending axons. The objective of this investigation was to identify candidates involved in the abnormal axonal projections in *Ctip1* null CPN. RNA sequencing analysis using Kallisto and sleuth programs was performed to verify transcripts that are differentially abundant in CPN GCs upon *Ctip1* deletion. A literature review was conducted on the transcripts, and factors such as well-established functions and localization of proteins were examined to select the most promising candidates. MATLAB and Fiji were explored as tools for image analysis once a candidate is selected, and microscopy was used to investigate the candidate's impact on axonal projections. Using literature research, the candidate list was carefully focused to six transcripts and one biological function (of others that will also be pursued): mitochondrial activity. This function was identified as a target for future research because six genes regulating mitochondrial activity are less abundant in the GCs and soma upon *Ctip1* deletion. Mitochondria are most highly concentrated in growing axons, and impaired mitochondrial division results in decreased axon length and GC activity. Mitochondrial dysfunction is also associated with 43% of ASD cases. More research on the relationship between *Ctip1*, mitochondria, and axon growth is necessary to clarify the role of mitochondria in cortical development.

Identifying Differences in Survival Outcomes for a Cohort of Glioblastoma Patients Based on Tumor Molecular Features

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Previous studies have shown that greater extent of resection (EOR) of glioblastoma (GBM) is correlated with longer overall survival. However, not all GBM are amenable to maximal resection depending on adjacent eloquent brain regions. In this study of 179 patients with glioblastoma (GBM) treated at Massachusetts General Hospital (MGH) between 2016-2020, we asked whether specific classes of molecular alterations are correlated with EOR and survival outcomes. Using targeted exome data from the Department of Pathology at MGH for 179 glioma specimens obtained between 2016 and 2020 at the time of initial resection, we identified 49 genes which were used as molecular markers. Data were then clustered into 11 distinct molecular groups based on gene function. Using these clustered data, survival analysis was performed on the cohort of 179 glioma patients. Analysis of survival data shows that GBM characterized by an increasing number of distinct molecular groups exhibited shorter overall survival (p = 0.061). Additionally, tumors with more somatic mutations showed shorter overall survival (p = 0.018). These data show that molecular features may be predictive of overall survival for this cohort of glioma patients. Our previous analysis of this data set suggested that tumors exhibiting a higher mutant allele fraction in TP53 tumor suppressor tend to have better survival outcomes than those with a lower mutant allele fraction, highlighting an impact of tumor heterogeneity or infiltration of normal brain parenchyma. Thus, in future studies we will explore whether specific classes of molecular features such as mutant allele fractions in the same set of 49 oncogenes can serve as predictive markers for surgical resectability of glioblastoma tumors and, ultimately, overall survival.

Developing Computational Models for an In Situ Multiplexed Single Molecule Protein Sequencing Technology

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In the past decade, advances in genomics and transcriptomics research have led to sensitive, high-throughput, and low-cost sequencing technologies of tens of thousands of DNA and RNA molecules at once. However, proteomics has lagged behind in terms of developing rapid sequencing and quantification methods for proteins. Although various technologies have been developed to better understand protein function, current methods such as mass spectrometry and Edman degradation are faced with the dilemma of gathering sequence information with single-molecule sensitivity while maintaining scalability to the entire proteome. In this study, we model an emerging nanopore technology for sequencing proteins, which involves stringing a peptide through an insulated membrane containing a nanometer-sized pore, located between two electrolyte-filled compartments. As the peptide is translocated across the nanopore, the modulation in ionic currents that results provides structural information regarding the amino acid functional groups. To probe the capabilities of nanopore sequencing, we harnessed the abilities of nanoscale molecular dynamics (NAMD), a software for high performance simulations of large biomolecular systems. NAMD allows us to view the dynamic "evolution" of the peptide-nanopore system, including biophysical and thermodynamic properties that play a major role in protein sequencing. By modifying peptide functional groups or controlling translocation time across the nanopore, we may further amplify amino acid discrimination by creating a greater distinction between their individual blockage currents. Further analysis and *in vitro* modeling of nanopore technology will advance the resolution of current protein identification methods, enabling comprehensive analysis of proteins throughout biological systems.

Profiling iPSC Technology Development in Neurodegenerative Motor Diseases

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Neurodegenerative motor diseases such as Parkinson's Disease(PD), Huntington's Disease(HD), and dystonias impair over 20 million lives globally, and no cure has been developed due to difficulties in uncovering their complex underlying molecular mechanisms. Induced pluripotent stem cell (iPSC) technology provides a crucial cellular model system for elucidating pathologically relevant mechanisms by enabling cells to be reprogrammed into a pluripotent state which can be differentiated into disease-specific neurons for robust *in vitro* modeling. However, the current lack of cross-disease iPSC reviews create a gap in understanding comparative applications and shortcomings in iPSC development across neurodegenerative diseases, such as limitations in validated differentiation methodology and genome stability. This project conducts a comprehensive literature review of the current landscape in iPSC differentiation methods comparatively between PD, HD, dystonias, as well as lesser known disease such as ataxias, myoclonus, Rett Syndrome, Tourette's, and others. All iPSC literature on PubMed pertaining to these diseases were recorded on a spreadsheet, which detailed causal genotypes, 2D vs. 3D culture processes, differentiation lineage, genome editing usage, model phenotypes, and clinically relevant findings derived from models. We summarized qualitative aspects of pathogenesis such as the affected neuronal cells and brain regions and observed effectiveness of using current differentiation methods. Cross-disease literature analysis pinpoints four major categories of experiments in the pipeline of iPSC modeling development: development of line, gene editing, *in vitro* modeling, and drug screening. Frequency analysis reveals trends including mitochondrial defects, phenotype mutations, and convergent gene mutations across neuronal cell types. iPSC trends are furthermore contextualized against progress in 3D modeling alternatives such as organoids. Future expansions include organizing tables and a schematic framework to trace iPSCs development for a manuscript publication. By synthesizing a cross-disease analysis of iPSC applications and shortcomings, this project aims to identify key research directions for *in vitro* motor neuron disorders.

The Use and Possible Functions of Non-Optimal and Wobble Codons in Cricket Genes

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The genetic code has 20 amino acids and 61 codons encoding it, leading to high codon redundancy (degeneracy), or synonymous codons. Evidence suggests that the synonymous codons for a specific amino acid often differ from each other in their relative frequency in genes and can vary with gene expression level, a phenomenon called codon usage bias. Non-optimal codons are those codons relatively rarely used in highly expressed genes, and wobble codons are codons that require wobble interactions with tRNAs at the third codon position. However, much remains unknown about the possible functions of these types of codons in mRNA translation. We conducted a literature review on this topic in order to summarize the current understanding of the biological functions of these codons. The literature reviewed suggests that many non-optimal and wobble codons potentially have key roles in slowing translation to control ribosome traffic and co-translational protein folding. Moreover, some data suggest they could even regulate preferential translation of mRNAs with certain functions, such as stress response. To further understand the role of non-optimal and wobble codons in translation, we are analyzing the gene ontology functions of highly expressed genes preferentially using these codons in the cricket species *Gryllus bimaculatus*. These genes were identified using relative synonymous codon usage (RSCU) values. If this analysis in crickets shows similar functions among the genes preferentially using non-optimal codons as well as among those using wobble codons, it may suggest these codons are consistently involved in regulating the translation of genes with specific biological roles. Otherwise, the analysis may show that they are involved in shaping translation for genes involved in a diverse array of functions. Either way, these findings will add valuable insights into the plausible functions of non-optimal and wobble codons in translation using a cricket model system.

Thoracic Adaptations for Ventilation in Human Swimmers during Aerobic Exercise

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Among primates, humans are uniquely adapted for sustained, aerobic activities such as running and swimming. Performance in such aerobic activities is largely limited by ventilatory capacity, but it remains unknown how the derived features of the human thorax, specifically the barrel-shaped chest, impact ventilatory capacity. One mechanism that could increase ventilatory capacity is an increase in movement of the thorax relative to the diaphragm during breathing. Previous studies have found that when breathing during aerobic activity, humans, as an endurance-adapted species, rely more on thoracic motion than other non-endurance adapted species. Our study aims to quantify thoracic motion during ventilation in three groups of individuals: runners, sedentary individuals, and swimmers. Because swimmers perform an endurance activity in a forced hypoxic environment and have been shown to exhibit increased ventilatory capacity, we expected swimmers to rely more heavily on thoracic motion during aerobic activity than other groups. Following analyses of thoracic movement relative to heart rate and mass-specific tidal volume measured during walking and running, results showed that thoracic motion is significantly increased in swimmers compared to runners and sedentary individuals. Additionally, there were no statistically significant differences in thoracic motion between runners and sedentary individuals. We conclude that increases in thoracic motion in swimmers compared to runners and sedentary individuals suggests that swimming exerts selective pressures on the thorax to increase ventilatory capacity that running, though an endurance activity, does not. These findings have evolutionary implications for the *Homo* genus, which originated 2 million years ago. In the same way modern human swimmers developed large chests to increase thoracic motion and ventilatory capacity to sustain aquatic aerobic exercise, *Homo* may have evolved barrel-shaped chests to increase thoracic motion and increase ventilatory capacity in response to selection for novel, endurance activities, such as endurance running.

Genome Mining of Opsins in Lepidoptera

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There is growing evidence that certain species of butterflies and moths (which make up the insect order Lepidoptera) can perceive and respond to near-infrared (nIR) signals. However, the molecular and genetic mechanisms that underlie this perception remain unknown. To investigate this, we mined Lepidoptera genomes for candidate nIR receptors. Specifically, we screened for opsins, a group of light-sensitive transmembrane proteins that are integral for vision, particularly long-wavelength opsins, as previous research has shown potential nIR sensing in this gene family. We first gathered a comprehensive dataset including all Lepidoptera genomes and transcriptomes available from NCBI, LepBase, and Ensembl databases. A bioinformatics pipeline was then developed to do comparative genomic screens using previously identified Lepidoptera opsin genes as reference queries. We extracted and aligned the resulting opsin sequences, and used the Multiple Sequence Alignment to reconstruct phylogenies of the Lepidoptera opsins. Selection tests were then run on the candidate genes from the phylogenetic analysis using a reference nIR gene. The novel candidate nIR receptor genes can later be functionally characterized in lab by *in vitro* and *in vivo* experiments. Finding functional nIR sensing genes could broaden our understanding of insect perception as well as further research in the applied field of optogenetics, which harnesses natural receptors as clinical tools to study brain function.

The Independent Impacts of Fat and Sugar Intake on Host-Microbial Interactions Involved in Metabolic Disease

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The prevalence of industrialized diets rich in fat and sugar, broadly termed the "Western" diet, is thought to be partially responsible for increased incidences of metabolic diseases such as obesity and type II diabetes in humans. Recent work on the microbiome has demonstrated the gut microbiota's role in mediating the effects of the "Western" diet on host physiology, including its causal effects on weight gain and inflammation. However, current interpretations of this diet have not investigated the independent effects of dietary fat versus sugar intake on gut microbial community structure or function. In this thesis, we compare the influences of high-fat, high-sugar (HFHS) diets, high-fat diets (HF), or high-sugar diets (HS) on gut microbial community structure. We first performed a meta-analysis on a curated set of mouse studies filtered using defined exclusion criteria. We then sourced the microbial sequence data from this list of studies and developed linear mixed-effects models to probe the relationships between fat versus sugar on host gut microbial structure. These structural signatures were assessed for any associations to metabolic disease states in humans. Initial findings from our literature review have demonstrated consistent patterns in enriched gut microbial taxa associated with either high-fat or high-sugar intake. These signatures from various HF, HS, and HFHS diets on gut microbial community composition have been linked with metabolic disease states, which include chronic inflammation and glucose insensitivity, across multiple studies. Through assessment of the independent impacts of fat versus sugar on the gut microbiota, we attain a clearer picture of the health consequences of a "Western" diet. These results will further our understanding of microbial contributions to metabolic illness and refine our ability to manipulate the gut microbiome for improved human health.

Increasing Network Size Leads to Shorter Evolutionary Repair Paths in Artificial Gene Regulatory Networks

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A gene regulatory network (GRN) is a self-interacting collection of molecular regulators that influences the expression of genes in an organism. GRNs control important processes in organisms, such as the cell cycle, metabolism, and signal transduction. While it is known that the interactions within GRNs are rewired during evolution, it is unknown whether these changes are adaptive. To explore this question, we used a computational GRN model, developed by Andreas Wagner, to study adaptive gene network rewiring. We began by generating two modular GRNs, that respond to environmental inputs, with no interactions between the two networks, allowing the networks to develop by mutating internal interactions. Then, we shut off the input to one of these networks, and allowed interactions between the two networks to form. We studied how these networks would evolve connections to turn the silenced network back on. As networks increased in size, the number of mutations required to repair fitness decreased, but the abundance of these mutations showed a complicated relationship with network size. There was a great degree of variance in the frequency of viable mutations between individual networks of the same size, allowing analysis into the wiring patterns of the GRNs that make a network difficult to repair. Both a case study approach and methods of statistical analysis have been adopted to bring light to experimental observations. Results from this experiment suggest that a study into the repeatability of rewiring pathways may provide insight into the mechanisms of network repair.

Developing an Auxiliary Education Initiative to Aid Infectious Disease Outbreak Response

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Recent infectious disease outbreaks have illuminated the world's inability to effectively respond to pathogenic public health emergencies. Approximately 14.1 million cases of COVID-19 have been confirmed worldwide, and nearly 600,000 deaths have been recorded to date (7-18-20). Alarmingly, there is evidence to indicate this may not be the last pandemic experience within the generation. Therefore, along with exploring signs of natural selection in pathogens and studying pathogens' genetic diversity to aid long-term intervention strategies, providing education on pandemics for students might provide the key to a quick and thorough response in future outbreaks. Operation Outbreak is an innovative platform for STEM education that teaches science, technology, public policy, mathematical modeling, and prevention topics in the realm of infectious diseases and outbreak preparedness. It culminates in an outbreak simulation in which students experience and respond to a virtual virus that spreads via a bluetooth enable app on their mobile phones. Information gathered on viral outbreak pathogen, governmental response, diagnostic, containment, and mathematical modeling initiatives, include data and documentation modified from the Center for Disease Control and World Health Organization protocol. Such data and documentation was compiled into a textbook format, designed to be accessible and engaging to a high school or college level audience. The education initiative also incorporates historical evidence and specific infectious disease outbreaks to complement and exemplify material covered within the established curriculum. Operation Outbreak will engage students in the public health issues affecting their communities, can enhance their STEM education through experiential learning, and will help provide students with critical tools to make more informed decisions about their health in times of an outbreak. Moreover, such an initiative has the potential to transform students into more confident public health leaders, allowing them to take an active role in keeping their communities safe.

Assessing the Impact of Genetic Variation on Phenological Timing in *Quercus rubra*

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An area of mounting concern in ecology is the impact of climate change on trees' productivity, physiology, and phenology. Urban trees are particularly vulnerable to rising temperatures due to a phenomenon called the Urban Heat Island (UHI) Effect, in which cities are hotter than surrounding suburban or rural areas due to emissions and albedo. Changing phenology, or the timing of seasonal growth, is a manifestation of climate change's advancement, though it remains unknown whether UHIs or genetic variation are primarily responsible. Our study aims to elucidate the relative impact of genetics and microclimate on phenological timing in *Quercus rubra* (red oak) trees, which are abundant across the eastern United States in both cities and forests. We documented phenological progress for red oaks in Harvard Forest throughout spring 2019. We collected and sequenced leaf samples from each tree to identify genetic differences between individuals, quantify genetic variation, and assess relatedness through kinship analyses. Sequencing data were regressed against phenological data to ascertain the degree to which variance in budburst timing is explained by genetic factors versus environmental response. Future steps include performing similar observation, collection, and analyses to characterize urban trees located in Cambridge, MA. Results are expected to reveal a high degree of relatedness between urban trees and those growing on the forested wetlands of Harvard Forest. Urban trees are frequently sourced from swamp ecosystems due to their favorability in poorly oxygenated and low drainage soils. Despite this predicted genetic similarity, the characteristically late budburst of swamp-grown trees and progressively earlier budburst of urban trees may suggest urban ecosystems are impacted by UHI and climate change more than previously realized. Quantifying the relative contributions of genetic and environmental variation to seasonal growth cycles can help more accurately forecast trees' response to projected climate change and inform future conservation methods.

Defining the Epidemiological and Spatial Distribution of STMN2 Depletion and Cryptic Exon Inclusion of ALS Patients

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TAR DNA Binding Protein, or *TARDBP*, is a gene that encodes for a splicing modifier called TDP-43. In Amyotrophic Lateral Sclerosis, a fatal neurodegenerative disease, many cases involve mislocalization of TDP-43 from the nucleus into the cytoplasm, causing the de-regulation of RNA transcripts, including the de-repression of a cryptic exon in the RNA of *Sthathmin 2 (STMN2)*. Inclusion of the cryptic exon leads to early polyadenylation of the *STMN2* RNA, causing a truncated RNA species and depletion of overall full length *STMN2* RNA and protein. Depletion of *STMN2* protein leads to motor neurons that have depleted axonal regeneration, suggesting that *STMN2* is the link between TDP-43 ALS pathology and neurodegeneration. We hypothesize that *STMN2* depletion is prevalent in most ALS cases and is caused by aberrant splicing of *STMN2*. Using RNA-seq data sets from patient brain and spinal cord tissues, we aim to define the prevalence of *STMN2* depletion and cryptic exon splicing in the CNS of ALS patients. We will focus on comparing the relative abundance of full-length and truncated *STMN2* transcripts, both between patients and non-neurological controls and between tissues of interest. Defining the relative abundance of *STMN2* depletion cryptic exon splicing will allow us to directly test our hypothesis. Currently, we have organized the metadata of about 300 patient samples to perform comparative expression analysis by ALS genetic subtype. We are awaiting the return of our samples from the bioinformatics core that perform sequence alignment of RNA-seq samples. Elucidating the prevalence of *STMN2* depletion and cryptic exon inclusion will help to define how much *STMN2* contributes to neurodegeneration in ALS at large and assist in nominating which ALS patient subtypes are amenable to exon-skipping therapies. Defining the spatial distribution of *STMN2* expression between ALS and control patients as well as within patients may help to elucidate the origins of the selective vulnerabilities of neuronal subpopulations.

Exploring the Role of HMGB1 in Cardiomyocyte Proliferation

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Compared to other tissues, the heart has extremely limited regenerative abilities that decrease with age. Lack of regeneration is explained partly by the low proliferative capacity of cardiomyocytes, which are the heart muscle cells within the ventricles. Previously, transcriptional profiling of the regenerating neonatal mouse heart demonstrated that the cardiomyocyte dedifferentiation process may allow regeneration from pre-existing cardiomyocytes. From these deep RNA sequencing experiments, a set of 37 transcriptional regulators as candidates for promoting regeneration was derived. In order to selectively induce the protein expression for each of the candidate genes, modified RNAs were designed to overexpress the proteins associated with each particular gene. Within the group of transcriptional regulators, the chromatin remodeling protein HMGB1 (High Mobility Group Box 1) was shown to significantly increase DNA synthesis upon transfection in neonatal cardiomyocytes. This indicated a potential increase in cardiomyocyte proliferative ability. Our current work aims to identify the HMGB1 mechanism of action in cardiomyocytes, as well as the affected downstream genetic pathways. To accomplish this, we will conduct structure-function analyses by selectively mutating HMGB1 protein domains. We plan to utilize RNA-sequencing and ATAC-sequencing to determine the changes in transcriptome and chromatin remodeling associated with full-length and mutated HMGB1 overexpression in neonatal cardiomyocytes. Altogether, this work will increase the understanding of key molecular pathways involved in cardiomyocyte proliferation.

Investigating the Role of Klf9 in the Division Pattern and Differentiation of Neural Stem Cells in the Adult Hippocampus

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Neurogenesis, or the production of neurons via neural stem cells, does not occur exclusively during development but has been shown to persist throughout adulthood in the dentate gyrus (DG) of the rodent hippocampus. The adult DG houses a neurogenic niche in which radial-glial like neural stem cells (RGLs) remain quiescent, symmetrically divide into more RGLs, or asymmetrically differentiate into astrocytes or neural progenitors, which give rise to neurons. Imbalances in RGL division patterns underlie many psychiatric and neurological diseases and merit further study. Klf9 is a transcription factor known to be important for DG granule cell maturation and is thought to play a critical role in maintaining quiescence of RGLs. This study investigates the potential regulatory mechanisms of Klf9 on DG RGL division and differentiation by characterizing DG adult born cell populations in Klf9 conditional knockout (f/f) versus wild-type (+/+) mice. Population analysis of hippocampal sections from Gli1-CreER^{T2} and Ascl1-CreER^{T2} mice revealed significantly higher proportions of RGLs in Klf9 f/f mice compared to wild type controls after 7 and 30 days of Cre-mediated lineage tracing. Further investigation through clonal analysis and examination of morphological differences in various cell-types is necessary to show that knocking out Klf9 results in increased symmetric division events. These findings are important because no transcription factor regulating adult hippocampal RGL expansion has been discovered to date. Further experiments, such as RNA sequencing, may yield better understanding of signaling pathways involved in RGL expansion or other genes potentially associated with Klf9's role in adult hippocampal neurogenesis.

Anatomic and Molecular Details of Corticospinal Neuron Development: Detailed Histological Characterization and Investigation of Growth Cone-Specific Transcriptomic Machinery

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One crucially important subtype of cortical projection neurons is corticospinal neurons (CSN). These neurons are centrally involved in many neurodegenerative and neurotraumatic conditions; degeneration of CSN ("upper motor neurons") in amyotrophic lateral sclerosis (ALS) causes spasticity and progressive loss of motor function, and damage to CSN axon projections in spinal cord injury (SCI) leads to loss of motor control below the lesion site. To identify potential future avenues to enhance regeneration, it is necessary to expand developmental knowledge. Extensive research in recent decades has generated first molecular insights into CSN development, but the exact mechanisms of CSN axonal guidance and maturation remain undiscovered. During development, axonal guidance and maturation of CSN likely follows a series of distinct and interleaved steps including axonal extension, grey matter innervation, and synapse formation, which are temporally staggered rostro-caudally along the spinal cord. The subcellular compartment executing these steps of axon guidance is the neuronal growth cone (GC), which is crucial for controlling axonal development and has been shown to contain compartment-specific molecular machinery distinct from its parent soma (Poulopoulos*, Murphy*, et al., 2019). In this project, we set out to deepen our understanding of CSN axonal development through two aims. 1) In a first set of experiments we aim to construct a detailed histological timeline of CSN development in mice using tissue clearing, 3D imaging, and a semi-automated analysis pipeline for processing to quantify CSN axon extension and grey matter innervation. 2) In a second set of experiments, we investigate GC-localized molecular machinery crucial for CSN axonal guidance during development using compartment-specific RNA sequencing. In-depth understanding of how CSN circuitry is generated during development will ultimately allow exploration of novel therapeutic approaches to enhance neural regeneration in conditions such as ALS or SCI.

Induced Pluripotent Stem Cell Modeling in Common and Uncommon Neurodegenerative Diseases

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Neurodegenerative diseases like Parkinson's Disease, Huntington's Disease, and Multiple System Atrophy are clinically characterized by symptoms of cognitive malfunction and muscle rigidity. However, the mechanisms behind their pathology remain elusive. Animal models and post mortem tissues have provided some insight into these mechanisms, but the recent development of induced pluripotent stem cells (iPSC) modeling has allowed us to more closely examine disease pathology and test novel treatments. iPSC models are created by transducing somatic cells with the transcription factors Oct4, Sox2, Klf4, and c-Myc. This allows cells to become pluripotent which is the ability to become, or differentiate, into any cells of the three germ layers. In the case of neurodegenerative diseases, research groups have been differentiating iPSCs into a variety of neurons which includes GABAergic, dopaminergic, and glutamatergic neurons. When the somatic cells are from patients with movement disorders, the differentiated neuron may show phenotypes that give insight into the underlying molecular mechanisms of disease. Recent developments include gene correction methods such as CRISPR-CAS9 and zinc finger nucleases that are able to excise a mutated gene in patient iPSC cells. In this review, we summarized iPSC-based neuronal models that depict movement disorders and organized them by neuronal subtypes. We also assessed the current drawbacks that arise from factors such as random genome integration and cell aging. Uncommon disorders such as Perry Syndrome, Frontotemporal Dementia and Parkinsonism linked to chromosome 17, and Wilson's Disease are also included as they underscore the broader limitations of 2D iPSC modeling. Lastly, we also discussed the current landscape for 3D modeling with organoids and its burgeoning potential.

Cerebral Organoid Fusions to Model Developing Projections in the Human Brain

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During development, axons of subtype-specific neurons form highly specific connections, and build functional circuitry between brain regions. Human pluripotent stem cells (hPSCs) can be differentiated into region-specific cerebral organoids. These cerebral organoids are three-dimensional aggregates of cells resembling some aspects of the developing embryonic human brain. Region-specific organoids can be fused into "assembloids" that can recapitulate simple aspects of axonal connectivity between brain regions, potentially allowing studies of human circuit development and neurodevelopmental disorders. We differentiated hPSCs into cerebral cortex-like and deeper brain thalamus-like organoids. We generated cortico-thalamic assembloids by placing cortex-like and thalamus-like organoids in close proximity in culture wells to activate spontaneous fusion. To map neuronal connectivity, we injected a fluorescent "retrograde" tracer into the thalamic side of the assembloid. This tracer is taken up by the neuron's axon tip at the injection site and retrogradely transported to the cell body, enabling us to label, isolate, and purify projection neurons that project from the cortical-like organoid to the thalamic-like organoid using fluorescence-activated cell sorting (FACS). Preliminary RNA sequencing data comparing FACS-purified neurons and whole cortical organoids demonstrate that retrogradely labeled neurons are cortical projection neurons, expressing high levels of cardinal cortical genes such as *EMX1*, *TBR1*, *FEZF2*, and *CTIP2*. These data demonstrate that retrograde labeling experiments in assembloids enable efficient isolation of mature circuit-forming neurons. Cerebral organoids offer a promising model to study specific simple aspects of the developing human brain. Several neurodevelopmental and neurodegenerative disorders exhibit connectivity defects. Preliminary data from cortico-thalamic-like assembloids show that retrograde labeling can isolate projection-forming neurons. However, these projection-forming neurons are likely heterogeneous, requiring single cell RNA sequencing to characterize the diversity and potentially shared characteristics of the isolated neurons. Fusion experiments offer a unique possibility to study *in vitro* molecular features that might contribute to human-specific disorders.

An Oncofetal Protein Network Maintains γ-Globin Expression in Fetal Erythroblasts

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The key oxygen transport protein, hemoglobin, undergoes a shift in composition after birth that is known as the fetal-to-adult hemoglobin switch. This process is clinically relevant because persistence of fetal hemoglobin has been shown to ameliorate sickle cell disease and thalassemia, the most common genetic disorders. BCL11A, the master regulator of this switch, is critically regulated by RNA-binding proteins which interact with *BCL11A* mRNA in order to repress its translation. Though BCL11A has been well characterized, less is known about the upstream factors responsible for its translational regulation. My project identifies and investigates potential RNA-binding proteins which repress BCL11A translation in order to maintain fetal hemoglobin expression in fetal erythroblasts. The first phase of the study leverages publicly available datasets to identify genes which are both upregulated in fetal erythroblasts and associated with the ribosome, where translation occurs. The second phase of the study develops a novel computational method to analyze the process of translational elongation using ribosome profiling data. Thus far, this approach has elaborated a list of candidate factors which are likely upstream regulators of BCL11A. The next step will be to draw a link between differential translation in fetal erythroblasts with the presence of these factors using experimental approaches. In sum, this project identifies novel genes regulating hemoglobin switching for functional follow-up and responds to existing limitations of translational analysis. The resulting findings expand our understanding of hemoglobin switching and more broadly translational regulation, while offering a suite of new tools relevant to future studies.

Characterizing Distal Epithelial Cell Types Present in Kidney Organoids

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As chronic kidney disease continues to increase in its global prevalence, stem cell derived kidney organoids offer possibilities as a human model system for studying development and disease with the potential for use in regenerative kidney therapies. Though existing organoids have been shown to contain a variety of renal cell types, the nature of the distal epithelial lineage cell types present remains poorly understood. By clarifying how these cells compare to the distal epithelial cell types of the mature kidney, organoids better representative of functional tissue may be generated. To this end, publicly available datasets from scRNA-seq experiments with healthy mature kidney samples were found and analyzed using the Seurat package in R. Cell types were identified using canonical markers, and differential expression testing was conducted on the three distal epithelial cell types: thick ascending limb (TAL), distal convoluted tubule (DCT), and connecting tubule (CNT). Having obtained transcriptional profiles for each, clustering analyses are now being done on fetal and organoid scRNA-seq datasets to identify distal epithelial cell populations present. These distal cell type clusters will then be compared to each other and to the TAL, DCT, and CNT cells of the mature kidney via differential expression testing. Knowing the genes which vary in expression the greatest between distal epithelial kidney cells of the organoid, fetus, and adult may provide insights into how well organoids presently relate to functional kidney and where changes in gene expression may allow for improvements in organoid maturity.

Determining Critical Signaling Pathways during Gastrulation through a Computational Evolutionary Comparative Approach

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The symmetry-breaking event of gastrulation is a crucial process that occurs during early mammalian embryonic development. Gastrulation has also been documented in other vertebrate organisms, further confirming its evolutionary importance. Despite its significance during embryonic development, the global cellular events and interactions that occur during gastrulation are still not completely understood. Therefore, there is a need to comprehensively understand and identify critical cellular interactions and developmental processes during gastrulation. To more thoroughly understand gastrulation and its critical signaling pathways, the goal of this project was to investigate evolutionarily conserved ligand-receptor interactions in Western Claw Toed frog (*Xenopus tropicalis*), zebrafish (*Danio rerio*), common mouse (*Mus musculus*), and human (*Homo sapiens*) embryos during gastrulation. Modification of single-cell RNA sequencing data (scRNA-seq) from these various species through RStudio prepared these data for analysis with Cell-Phone DataBase (CellPhoneDB), an extensive repository of human ligand-receptor pairs. Thus far, an analysis of mouse scRNA-seq data with CellPhoneDB has identified significant interactions in various cell types during gastrulation. In the future, this analysis will be repeated with scRNA-seq data from other species, revealing significant cellular interactions in the respective species. Conducting this CellPhoneDB analysis will be essential to confirm, challenge, or expand upon previous conclusions in the literature regarding essential cellular signaling during gastrulation. If these analyses reveal common cellular interactions among the various species, then those interactions may form integral parts of conserved molecular pathways during gastrulation. This analysis will, therefore, help address the ongoing challenge of studying the crucial mechanisms driving gastrulation and cellular specification on a single-cell, genome-wide, and whole-embryo level.

Gene Regulatory Network Analysis Reveals Transcription Factor Targets for Therapy of Aging Disorders

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Heterochronic parabiosis, a surgical process connecting the circulatory systems of young and old mice, is used to study the regulation of tissue aging and regeneration via protein factors found in blood. Several factors have been shown to improve central nervous system function and ameliorate the effects of aging in mice by increasing stem cell regeneration, but it is less well known which genes are differentially expressed in old mice to induce this "aging reversal" phenotype. We performed an *in silico* analysis of single cell RNA-sequencing (scRNA-seq) data from parabiosed mice to identify transcription factors (TFs) whose expression is significantly dysregulated between old mice and old-young parabiosed mice, which represent the reversed aging state. We employed single-cell regulatory network inference and clustering (SCENIC), a computational framework which identified gene regulatory networks (GRNs) from scRNA-seq data. Regulatory networks from old, old-old parabiosed (as a control), and old-young parabiosed mice were identified from scRNA-seq gene expression matrices spanning 31 cell types. Network activity was then scored by SCENIC as a function of gene expression levels in the networks. These scores formed the basis of comparison of transcription factors between old mice and parabiosed mice. The TFs identified thus far were verified against a set of TFs thought to be dysregulated with parabiosis via differential gene expression analysis. Preliminary results indicated that GRN analysis provides a robust platform for identifying TFs whose expression is significantly altered with parabiosis, and completion of this study will yield a comprehensive understanding of these TFs. In the future, these TFs can serve as therapeutic targets, as compounds can be administered to modulate the expression of these TFs and the genes they regulate in old mice to match the expression profiles identified in old-young parabiosed mice, potentially achieving the aging reversal phenotype.

Characterizing and Defining Cell Behaviors During Tendon and Enthesis Regeneration

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Tendon is a connective tissue that connects muscle and bone, and consists of an organized matrix of collagen fibers and other proteins. This structure can be permanently disrupted through an injury such that scar tissue interferes with the cellular organization and affects its function. Enthesis is the transitional tissue between tendon and bone, and it plays a role in transferring muscle force to bone. In mammals, tendon and enthesis morphology cannot be restored once injured. In this study we summarized critical physiological and cellular components known to contribute to both tendon and enthesis developmental and regenerative capabilities. We then used zebrafish to characterize tendon-to-bone healing in a highly regenerative model system. We utilized Edu and TUNEL assays to evaluate cell proliferation and death in injured zebrafish in time points ranging from 1-day post injury (dpi) to 5-weeks post injury (wpi). Preliminary results from the Edu assay indicate that the regenerative activity of tendon cells is most active in zebrafish 5 days post-injury as compared to the uninjured control, and that *scleraxis-a* (*scxa*) positive cells contribute to tendon regeneration post-injury through the popularization of the damaged tissue. To further understand the regenerative capability of zebrafish tendon and enthesis, we used transmission electron microscopy (TEM) to image collagen fibril diameter and morphology in injured and uninjured wild-type (WT) zebrafish tendon. The data suggests that the average collagen fibril diameter is not significantly different between injured and uninjured groups after 8 weeks, although the injured data set does appear to be skewed towards a smaller fibril diameter. Together, our findings further establish the zebrafish as a tendon and enthesis regeneration model. This may contribute to our understanding of cellular mechanisms that support tendon regeneration, which in turn may elucidate additional clinical research pathways for tendon repair in humans.

Transcriptomic Profiling to Investigate Systemic Influences on Stem Cells of the Skin
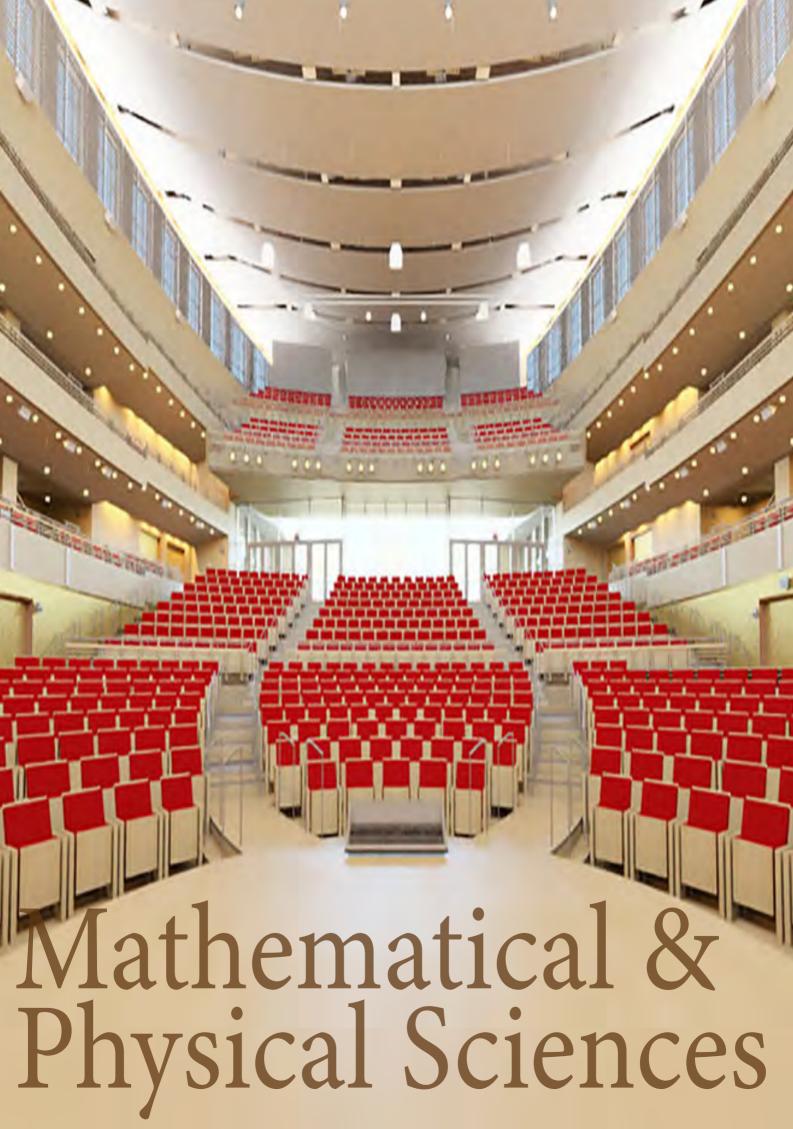
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The mammalian skin is a dynamic organ consisting of a diversity of cycling stem cell (SC) populations, including epidermal SCs, hair follicle SCs, and melanocyte SCs. These can be activated to proliferate and generate differentiated progeny of their lineage, which play important roles in tissue homeostasis, and much research has been conducted regarding how local signals and interactions in the skin initiate and coordinate processes like development and regeneration. However, these cells do not live in isolation; systemic cues, including those associated with conditions like stress and aging, also regulate SC activity. To elucidate the effects of systemic conditions at the cellular level, RNA sequencing was conducted in a variety of isolated SCs of the skin, both in controls and conditions of stress or aging. Gene expression profiles were compared to generate lists of differentially expressed genes which were then analyzed for enrichment of any biological pathways. In melanocyte SCs for example, genes like *Dct*, *Mitf*, *Sox10*, and *Tyrp1* were all found to be overexpressed in the aged condition compared to young controls; functionally, these genes are all involved in the pigment production pathway. Other dysregulated pathways in this condition included melanocyte differentiation and cell adhesion pathways. Similar analyses have also been conducted on melanocyte SCs in the stress condition compared to unstressed controls. Currently, epidermal and hair follicle SCs are being analyzed in both conditions, while future studies will investigate which pathways are universally dysregulated amongst all three SC populations in each condition. The identification of altered biological pathways associated with systemic conditions directly informs our understanding of development and regeneration, importantly yielding tentative explanations for the breakdown of these processes in stress and age. While further validation is needed, these results are essential in providing hypotheses regarding systemic influences on SCs of the skin.

Mathematical & Physical Sciences

Temporal Analysis of Products Reactor Simulations and Experimental Design

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It is important to understand the kinetics of catalytic reactions because 85-90% of all chemical products are made using catalytic processes. Temporal analysis of products (TAP) reactors are used to precisely study the chemical kinetics of heterogeneous gas-solid catalysis. TAP experiments are able to resolve kinetic information such as kinetic coefficients, activation energies, and pre-exponential factors for elementary steps of catalytic reactions. By running simulations of TAP experiments, catalytic reactions can be designed more efficiently, without the initial upfront costs required for real TAP experiments. These simulations are being performed using SimTAP, an in-house MATLAB software package. Kinetic information from five previously studied catalytic reactions are being used to design TAP experiments: ethylene oxidation over silver, methanol synthesis on copper, methane oxidation over palladium, methanol oxidation on gold, and carbon monoxide oxidation on platinum. Simulations for each reaction are being run at various temperatures, initial concentrations, catalyst dimensions, and inert diffusivities to determine which reactions can feasibly be analyzed using a TAP reactor and to direct future experimental design. Upon the completion of these simulations, we will have designed a set of experiments which will be implemented using the real TAP reactor. These reactions have not been well-studied in TAP reactors, so these experiments may reveal new kinetic information. In the future, simulations of TAP experiments could be useful in catalytic development, with simulations of catalytic reactions being utilized to create a database of kinetic information.

Solar and Continuous-Flow Chemistry: Limitations to Adoption by the Pharmaceutical Industry

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Solar photochemical and continuous-flow methods of chemical transformations present sustainable advantages over traditional thermal and batch processes. The efficient, mild, and waste-limiting nature of these methods may become crucial to the pharmaceutical industry, which often faces great material inefficiency and waste generation at laboratory and industrial stages of drug development. Recent literature has highlighted the implementation of solar and continuous-flow chemistry into various reaction settings; however, literature that characterizes limitations of these technologies as barriers to implementation in pharmaceutical processes is lacking. Through a survey of directly reported transformations, reviews of innovations in solar and continuous-flow technologies, and perspectives on their future utility, we account for limitations to these technologies that have barred their general adoption by the pharmaceutical industry. We find that optimization of reaction conditions and setup acts as the most significant practical barrier, with the production of complex drugs and advanced pharmaceutical intermediates (APIs) often not suited to these conditions. We further attribute the pharmaceutical industry's slow adoption of solar and continuous-flow methods to educational gaps. Ultimately, a rigorously multidisciplinary approach is necessary to address these limitations, with emphasis on collaboration between chemists and chemical engineers.

Investigation of "Inverted" Radical Ligand Field Character of Potential Photocatalysts via Density Functional Theory Calculations

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Chemical reactions that use photoactive compounds to effect redox transformations are becoming versatile tools in bond functionalization and formation. Among these compounds are metal-based coordination complexes that may rely on an "inverted" ligand field, wherein the ligand-centered orbitals lie lower in energy relative to the *d*-orbital manifold of the metal in the ground state, to achieve catalytic redox activity, with reactive radical character localized about the complexes' ligands. In addition to this ground state reactivity, certain metal complexes in the excited state may exhibit similar properties. To inform theoretical predictions of these complexes' reactivity, density functional theory (DFT) calculations may provide electronic and energetic properties of the complexes under study. Herein, we investigate the suspected radical character of various Cu(I)/(II)- and Ag(I)/(II)-centered complexes in both the ground and excited states. Currently, the Gaussian software is being used to run DFT calculations on these complexes, which can provide the quantitative energetic absorption spectra and qualitative molecular orbital pictures that characterize these complexes. Upon completion of these calculations, we may compare calculated absorption spectra to experimental spectra obtained for the actual complexes synthesized in lab, as well as determine whether the calculated orbital geometries match expectations for the synthesized complexes' reactivity in bond functionalization and formation. Our analyses may contribute to the rational design of future photocatalytic pathways.

Atmospheric Iodine Reactivity with Ozone

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Halogen species account for as much as 30% of lower stratospheric ozone loss. Counter to the trends of bromine and chlorine since the Montreal Protocol on Ozone Depleting Substances and its amendments were implemented, iodine emission to the atmosphere has increased and is expected to increase in the future as a consequence of anthropogenic activity. Due to the importance of the stratospheric ozone layer for life on Earth, it is important to understand evolving trends in the reactivity of iodine species with ozone. Using the Atmospheric and Environmental Research (AER) two-dimensional chemical-transport-aerosol model, we evaluated ozone depletion facilitated by iodine under several projections of the future composition of the atmosphere. To verify our results, we are currently replicating past studies by altering the kinetic constants in our model to match those on which older studies were based. These data indicate that iodine will remain hundreds of times more potent than chlorine in terms of ozone destruction in the lower stratosphere in perpetuity, without regard to the Earth's climate future. Additionally, we find that while the extent of ozone depletion by the sum total of all halogen species is expected to decrease as the climate evolves and anthropogenic halocarbon inventories decay, the extent of ozone depletion by iodine is expected to decrease less severely or even remain constant. Our findings suggest that greater attention should be placed on processes that have the potential to rapidly inject short-lived iodine species directly into the stratosphere such as boundary layer convective ventilation and explosive volcanism.

3D-QSAR Model of Chloramphenicol Analogues and Solvent Energy Analysis of Chloramphenicol Binding Site

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Chloramphenicol (CAM) is a natural product with broad spectrum antibiotic activity. Hundreds of analogues of CAM have been synthesized and tested for antibacterial activity, but none have proven more potent than CAM. As antibacterial resistance spreads, understanding the basis for the antibacterial activity of CAM and its analogues will aid in designing new antibiotics. 38 previously synthesized CAM analogues were docked in Molecular Operating Environment (MOE) using a crystal structure of CAM bound to its target, the ribosome, as a docking template. Molecular descriptors for a training subset of 28 CAM analogues were calculated with MOE, and a quantitative structure activity relationship (QSAR) model was developed via lasso regression. Additionally, an analysis of the energy of the solvent molecules was conducted in MOE using 3D-RISM, a DFT based computational model. The results of the QSAR model were inconclusive as testing the model on the test subset of 10 compounds yielded an R^2 of -1.66. Solvent analysis predicted that water molecules near the phenyl ring of CAM would yield approximately 5 kcal/mol gain in binding enthalpy when displaced. In contrast, water molecules near the dichloroacetyl tail were predicted to be tightly bound to the receptor. The results of this study demonstrate that the molecular descriptors calculated by MOE do not show good correlation between structure and activity of CAM analogues. Based on solvent analysis, we propose *ortho* or *meta* substituted CAM analogues, which are predicted to favorably displace water molecules and have strong binding affinity and antibacterial activity.

Contents and Components of Electronic Cigarettes for Cannabis

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Cartridges for electronic cigarettes are the fastest-growing segment of the cannabis market, but we don't know the impacts upon respiratory health that come from vaping cannabis extracts. The hazards from these electronic cigarettes are determined by the chemical species they emit, which derive from their contents and components. To learn about the contents of cannabis oils for vaping, I investigated the products sold by each cannabis dispensary in Massachusetts. I learned that cannabis oils for vaping are composed mostly of the active ingredient, tetrahydrocannabinol (THC, ~70-90%), along with some terpenes. I also produced statistics about prices, THC content, and major manufacturers of products for vaping cannabis. This market research also revealed that nearly 90% of the vaping products are packaged in cylindrical cartridges with 510-pitch threads that fit a standard electronic cigarette battery. A growing minority of these products are packaged in "pods," rectangular snap-in cartridges made by PAX, the parent company of Juul. Through deconstructing cartridges, imaging with X-ray tomography, and internet research, I have found that a common mechanism by which vaping cartridges aerosolize cannabis oils is a simple resistive heating coil wrapped in a cylindrical silica wick; an airstream is drawn through a central channel. The contents and components that I have determined are being used to understand the chemical processes that happen when people vape cannabis oils.

Porous Liquids: Water-Dispersible Metal-Organic Frameworks with Permanent Porosity and High Oxygen Solubility

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Porous liquids have recently begun to grow as a field of research due to their unique combination of properties, namely, fluidity and permanent porosity. A better understanding of this type of material and an increase in its gas solubility may lead to advancements in energy efficiency through processes such as gas separation as well as biomedical applications like imaging probes, drug delivery, and artificial blood substitutes. Specifically, metal-organic frameworks (MOFs) are of keen interest to develop into porous liquids for gas adsorption due to their high porosity and synthetic tunability. Here, we pursue the formation of a porous liquid by dispersing the MOF zeolitic imidazolate framework-8 (ZIF-8) in water through surface functionalization via post-synthetic modification. Based on existing literature, covalent functionalization via imidazole- or amine-based ligands as well as non-covalent functionalization via surfactants and polymers can potentially impart dispersibility of ZIF-8 in water using solvent-assisted linker exchange. Thus far, initial findings with nuclear magnetic resonance (NMR) spectroscopy have shown limited success with covalent functionalization via imidazole- or amine-based ligands, while the cetyltrimethylammonium bromide (CTAB) water system shows promising preliminary results. If ZIF-8 is successfully dispersed in water, we will proceed to the next phase of testing colloidal stability through dynamic light scattering (DLS) measurements, as well as measuring gas solubility.

Investigation of Water-Splitting Catalyst Materials for the Oxygen Evolution Reaction in Near-Neutral Media

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Mentor: Agnes Thorarinsdottir

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As the supply of fossil fuels diminishes and climate change intensifies, water splitting has emerged as a promising means of harnessing and storing renewable energy. The electrolysis of water can produce hydrogen for fuel cells and oxygen applicable to maritime operations. Given the abundance of saline water and wastewater worldwide, efficient water splitting in near-neutral electrolytes could significantly upscale electrolysis technologies. However, water sources can contain impurities including ions, salts, and bio-organisms, risking device corrosion. Additionally, the oxygen evolution reaction (OER) of hydrolysis is kinetically sluggish, involving four successive proton-coupled electron-transfer steps. To this end, electrocatalysts can accelerate the kinetics of OER. While benchmark noble-metal catalysts have traditionally been used, they confront scarcity, high costs, and limited electrolyte options. As such, earth-abundant catalysts were investigated as alternative materials for OER in near-neutral media. These electrocatalysts included metal-oxides and oxy-hydroxides derived from transition metals, nanoparticles and nanosheets, as well as doped, multi-metallic, and amorphous materials. The characteristics, merits, and drawbacks of each electrocatalyst were assessed. Specifically, the activity, stability, reaction media, and ease of processing were reviewed. Modifications that enlarge the electrochemical surface area of the electrode or increase the availability of active sites especially contribute to elevated OER activity. Optimizing catalysts to promote kinetic selectivity for oxygen production without oxidative side reactions is also necessary, which can be achieved through proton-conductive additives, dopants, and self-healing catalysts, all of which were studied. This literature search will guide the design of oxygen-evolving catalysts based on earth-abundant materials that possess high activity and stability in neutral water. The synthesized materials will be characterized using electrochemical and spectroscopic methods before and after OER to establish structure-function and structure-activity relationships. Exploration of new materials will broaden opportunities for active, cost-effective, and versatile oxygen-evolving catalysts to operate in seawater, wastewater, and other diverse media.

Using MagLev to Study the Properties of Thin Polymer Films

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Measuring the density of thin polymer films may help scientists understand why thin polymer films range exhibit different physical properties than the bulk polymers. Traditional techniques for measuring physical properties such as X-ray reflectivity (XRR) and ellipsometry are challenging to use on polymer thin samples, but Magnetic Levitation (MagLev) offers a simple and accurate alternative to measure the density of thin films of hydrophobic polymers (down to ∼10 nm in thickness). We chose to study poly(styrene) (PS) and poly(methyl methacrylate) (PMMA) as two model polymers for demonstrating the applicability of MagLev for measuring the density of thin polymer films. The polymer films were spin-coated on top of a sacrificial layer of the water-soluble polymer, poly (acrylic acid) (PAA), supported on a silicon wafer. We suspended the films in a paramagnetic solution and used the axial MagLev device to measure the density of the films. Our results demonstrate three major conclusions: (i) MagLev provides a simple route for the measurement of the density of thin films—particularly for films below 10 nm in thickness—which are difficult to measure directly otherwise, (ii) MagLev makes it possible to understand the effects of interfacial confinement on the properties of thin films, and (iii) MagLev can quantitatively characterize the isothermal crystallization process in thin films. This technique can potentially be used in the engineering of polymer films, such as organic electronics, membrane-based separations, and protective coatings.

Investigating the Liquid-State Porosity and Ionic Conductivity of a Hydrogen-Bonded Organic Framework

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Mentor: Adam Slavney

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Due to their structural tunability and high internal surface areas, porous organic polymers (POPs) have been researched extensively for use in applications such as gas separation and storage, ion conductivity, and catalysis. Hydrogen-bonded organic frameworks (HOFs) are an emerging class of POPs, which, owing to their weak and reversible hydrogen bonding, possess low melting points compared to other porous frameworks that often decompose prior to melting. The lower melting points of HOFs can provide access to liquids and liquid crystals with unique properties, including porosity; however, the structure of HOFs in the liquid state has not yet been elucidated. Herein, we investigate the liquid-state porosity, thermodynamic phase diagram, and potential electrolyte applications of a HOF composed of phenyl ether disulfonate and methyl guanidinium ions, $(MeG)_2(PEDS)$. The sulfonate and guanidinium ions are hydrogen-bonded in a quasihexagonal, bilayer structure in which porous cavities exist in the solid state. Upon melting, $(MeG)_2(PEDS)$ enters a liquid-crystalline state that retains spacing between the bilayers, as suggested by powder X-ray diffraction (PXRD) data; however, differential scanning calorimetry (DSC) and gas sorption measurements suggest collapse of framework pores upon melting. Gas permeability measurements and new synthetic approaches are needed to rationalize these findings. Lastly, $(MeG)_2(PEDS)$ stands as a promising candidate for Li-ion battery electrolytes due to its framework structure and low melting point, which could yield high transference numbers and continuous electrode-electrolyte interfaces for efficient ion conduction, a challenging task in current Li-ion batteries. A literature review of Li-polymer batteries reveals that electrolyte characteristics favoring single-ion conduction, such as fixed sulfonate moieties, are present in $(MeG)_2(PEDS)$. In the future, electrochemical impedance spectroscopy (EIS) will be used to measure the ionic conductivity of $(MeG)_2(PEDS)$ and assess its potential application in Li-ion batteries.

Semiclassical Analysis of the Quantum Tunneling Effect

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A single particle quantum system is described by a complex-valued function ψ such that $\int |\psi|^2 = 1$. Thus ψ is interpreted as a probability density. The evolution of the state ψ is described by a Hamiltonian, an operator that acts on ψ and is usually of the form $\hat{H} = -h^2 \frac{\partial^2}{\partial x^2} + V$. Here, V is some real-valued function that describes the potential environment of the particle, and h is Planck's constant. Quantum mechanics allows for states ψ with well-defined energy E, or eigenstates, that are nonzero in areas where $V > E$, which is strictly forbidden classically. In the case of a potential with several local minima, or wells, this means that an eigenstate that is localized in one well will still be appreciably nonzero in the other wells. This can give particles the appearance of spontaneously tunneling through potential barriers. We expound Helffer and Sjostrand's groundbreaking work on tunneling in the case of an arbitrary number of wells. Their work exposes the asymptotic behavior of the Hamiltonian on low-lying energy eigenstates for an arbitrary number of potential wells in the 'semiclassical limit' $h \to 0$. To derive these asymptotics one uses estimates of Agmon type, from which exponential decay information on eigenstates are derived. One can apply these estimates to get estimates on the resolvent of the Hamiltonian. The eigenstates of the total system are approximated by the eigenstates of the idealized isolated well problems. The leading behavior in h turns out to be the concatenation of the idealized problems, plus an interaction matrix which can be computed explicitly when the potential has some symmetry. Higher order terms decay exponentially in the Agmon metric and are therefore negligible.

The Mahler Measure of Pretzel Links

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Knots and links are embeddings of circles in three-dimensional space. In everyday life, we encounter them as chains and tangled ropes. But, knots and links play an important role in geometric topology. Three-manifolds can be built from link complements in the three-dimensional sphere by standard topological techniques. Many tools used to understand the geometry of links, such as the fundamental group of link complements and representations of braid groups, provide a bridge from the geometry of three-manifolds to algebra and number theory. One important link invariant that emerges from these tools is the Alexander polynomial. The task of measuring geometric complexity via links is thus related to the classical problem of understanding the roots of integer polynomials. The complexity of an integer polynomial is expressed by its Mahler measure, defined as the product of the absolute values of the polynomial's complex roots outside the unit circle normalized by its leading coefficient. It is a longstanding open problem whether or not the Mahler measure of a non-cyclotomic polynomial can be arbitrarily close to one. In this project, we applied the Seifert algorithm and linking form to connect properties of pretzel links to properties of their Alexander polynomials, such as their leading coefficients and Mahler measures. We derived explicit closed forms for the Alexander polynomials of a large class of pretzel links and found a relationship between the number of roots of the polynomial outside the unit circle and the signature of the symmetrized Seifert form. These results add to the methodology available for the census of three-manifolds and suggest new ways to apply the symmetrized Seifert form to the study of geometric and polynomial complexity.

Using Forcing Techniques to Investigate Kaplansky's Conjecture

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Kaplansky conjectured that every algebra norm on the Banach algebra C(X) of continuous complex-valued functions on a compact Hausdorff space X is topologically equivalent to the uniform norm. While the conjecture is algebraic, it is equivalent to the statement that every algebra homomorphism from C(X) to any algebra is continuous. Using this version, Dales and Esterle showed that Kaplansky's conjecture is consistently false by refuting it assuming the Continuum Hypothesis, the statement that every infinite set of real numbers is the same size as either the set of natural numbers or the set of real numbers. Woodin isolated a combinatorial condition on any counterexample to the conjecture, and using the set theoretic technique of forcing, Solovay constructed a model of set theory in which Woodin's condition fails. Thus, Kaplansky's conjecture is independent of the axioms of mathematics. Using forcing, we approached Kaplansky's conjecture, related independent statements, and the open question whether it is consistent for the Continuum Hypothesis to be false, Martin's Axiom to be true, and for there to exist discontinuous homomorphisms from C(X). As there are stronger forms of Martin's Axiom that imply that there are no discontinuous homomorphisms from C(X), this would shed light on whether Martin's Axiom already implies there are no discontinuous homomorphisms.

Rotation and Shear in Stacking of Van der Waals Materials

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Van der Waals materials have been of increasingly great interest as their 2D properties are expected to lead to new physics concepts and technology. However, before we learn how to accurately control the mechanical and electrical interaction of 2D materials we need to analyze many of its interactions. In this study we stacked layers of 2D material for the purpose of observing and further being able to predict their behavior. Stacking layers of such 2D materials leads to a lattice called a Moire figure. The average lattice constant is correlated with the relative rotation of the layers as well as their shear. After we extracted the lattice constant by converting the original data to a Fourier space, we could deduce the rotation angle. Since the resulting Moire figure varies locally, we automatized an algorithm that would analyze small regions of already captured images. Finally, this produced an overall view of how the layers have rotated due to their overlapping. To evaluate the contribution of the shear to the final figure, we had to analyze the lines of the lattice. By considering each repeating cell of the lattice to be topologically equivalent to a torus, we developed a mathematical model that allows us to define vortices and antivortices in an order parameter in this system. Our model claims that these antivortices, although hard to artificially produce, may exhibit unique electro-magnetic properties. By combining the computation of rotation angle and shear, our project aimed to make the analysis process more efficient for future processing of similar data and also allow for the study of bubbles, a topic of great potential for technology, which is yet unexplored.

The Role of Adaptive Ray Tracing in Analyzing Black Hole Structure

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The Event Horizon Telescope's (EHT) success in imaging black holes has opened up countless opportunities to expand upon our current understanding of general relativity. In order to make sense of the images captured by the EHT, researchers have developed simulations of black holes to test various models and parameters. In particular, these programs use a technique called ray tracing to simulate images of black holes, and these simulated images are then compared with real data to test theoretical predictions. Since black holes cause light to bend, a variety of optical phenomena arise in these images, some of which are only visible at very high resolutions. However, current ray-tracing techniques operate very slowly at these large resolutions, presenting an impediment to the EHT's simulation work. To remedy this issue, we developed a method of "adaptive ray tracing," by which pixel intensities of an image are computed on a selective basis, enabling ray tracing programs to dramatically increase the speed of image generation. We found that adaptive ray tracing consistently improves runtime by factors of 10+ while preserving accuracy. Using this technique, we then produced extremely high-resolution images of black holes, and we examined the theorized optical substructure that is present only on these fine scales, directly illuminating relativistic effects.

Detecting CDW Transitions in Cuprate Superconductors with Convolutional Neural Networks

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The mechanisms underlying high-temperature superconductivity in cuprate materials have not been fully elucidated. As cuprates are doped with oxygen atoms, they transition from an antiferromagnetic insulating state to a high-temperature superconducting state. This exotic transition is accompanied by the formation of a charge density wave (CDW), which is a periodic modulation in the conduction electron density. Currently, the linkage between the CDW and superconductivity is not well understood. When we apply atomic resolution imaging techniques to study cuprates, we face the challenge of disentangling the material's intrinsic electronic properties from its stochastic atomic-scale disorder. In $(Pb,Bi)_2(Sr,La)_2CuO_{6+\delta}$ (Bi-2201) imaged via scanning tunneling microscopy (STM), the electronic inhomogeneity, caused by local variations in doping, limits the precision of CDW wavevector measurements made with Fourier analysis techniques. This makes it difficult to quantify how the CDW evolves with doping. To overcome this limitation, we trained deep convolutional neural networks (CNNs) to differentiate between commensurate and incommensurate CDW instabilities in STM observables. We generated a training dataset of 120,000 pairs of simulated gap maps, which provide a spatial visualization of local variations in doping, and simulated charge maps, which contain the CDW structure. The simulated CDWs are locally correlated to a gap map by one of two existing wavevector-doping hypotheses. We diversified the training set with the same types of disorder prevalent in the experimental data. After training the CNN to 85% validation accuracy, we ran interpretability tests to verify that the CNN is robustly distinguishing between the two hypotheses. Moving forward, the CNNs will be used to make predictions about the doping-dependence of the CDW in experimental data. More broadly, our work lays the foundation for a machine learning approach to quantify intrinsic periodic order and correlations in disordered datasets.

X-ray Analysis of Panalytical Software

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X-ray diffraction (XRD) is a qualitative and quantitative method of analysis for determining the physical characteristics of a crystalline material. A material's diffraction pattern fingerprint is uniquely determined by analyzing the peak intensities of X-rays diffracted at various angles in a theta-two-theta scan. In a theta-two-theta scan, the off-axis lattice spacing orthogonal to the periodic thin film layer can be derived using peak intensity values and Bragg's law. The Python software developed this summer at the Harvard Faculty of Arts and Sciences aims to systemize the analysis of theta-two-theta scans from the Panalytical X-ray diffractometer. Each data file with the theta-two-theta scan data from the Panalytical software is uploaded onto Google Drive. Using the Google Drive API service, the data is downloaded onto a remote personal computer. Next, the software determines the thin film peaks using a pseudo-voigt smoothing function and a Gaussian curve fitting algorithm and calculates the off-axis lattice spacing using Bragg's law. The software plots the data in a formatted Jupyter notebook file which is uploaded back onto Google Drive. The user is able to interact with the data, zoom into segments of the theta-two-theta scan that are relevant to the research, and download MATLAB figure files.

Design and Development of a frame for a UHV, 9T, low-temperature 4-Probe Scanning Tunneling Microscope

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A multi-probe scanning tunneling microscope (STM) is a powerful tool that can take electrical transport measurements and resolve atomic-scale structures simultaneously. It allows us to understand novel behaviors of exotic materials by directly linking measurements of collective phenomena to the detailed local characterization of individual atoms, electrons, or spins. However, the STM is very sensitive to vibrations and thus requires a very controlled environment to produce accurate results. In this work, we have designed an outer frame, using T-slotted aluminum rails, to rigidly support several components of the STM system, including the UHV preparation chamber, the main operation UHV chamber, the cryostat, and heavy-ion pumps on vibration-isolating air-legs. We used the Autodesk Fusion 360 software to model the system setup, calculate the distribution of the weight, and ultimately design the optimal structure to support the system. In addition, a detailed simulation of the static stress from the structural load was performed on our designed Al frame to ensure the stability of the structure is within the safety range. Finally, we used our aluminum frame model to get formal quotes from several suppliers, comparing prices and structural stability offered.

Star-formation Efficiency and the Dark Matter Model: the Difficulty of Constraining the Dark Matter Particle Mass with JWST

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Advisors: Sownak Bose, Sandro Tacchella

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Galaxy formation occurs when large units of dark matter, known a halos, collapse under gravity. With the anticipated launch of the James Webb Space Telescope (JWST), it will be possible to observe the oldest galaxies in the Universe with unprecedented detail. The largest differences between the two leading theories of dark matter are most prominent in these old galaxies, and it is anticipated that observations will allow new insights into the composition of the Universe. In this project, we investigated the extent to which differences in the properties of dark matter particles are diluted by the uncertain parameters used to model galaxies. To investigate differences between the two models, we used a simulation of warm (WDM) and cold (CDM) dark matter particles, with stellar properties of the galaxies derived from the formation histories of individual halos. Simulations were run with two different values of a parameter, ε, which controls the efficiency of star formation in low mass halos for both WDM and CDM. We find that while WDM and CDM models show the expected variations in halo formation in the early Universe, the distinction between the high ε WDM and low ε CDM is less apparent. Studying the evolution of the cosmic stellar mass density (cSMD) shows that the high ε WDM and low ε CDM models evolve in time in a near-identical way. These results indicate that while JWST observations will be useful to establish new constraints and reduce uncertainties, they will not provide unambiguous answers concerning the nature of dark matter in the early Universe, contrary to previous claims in the literature. Our results show that WDM and CDM models can be made to resemble one another by simply changing the star-formation efficiency of low-mass halos, a parameter that is poorly constrained by present data.

Constraining The Nature of Dark Matter Interactions With Observations of The Early Universe

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Dark matter is five times more abundant than visible matter in the universe. Because we can observe only its gravitational influence, the exact nature of dark matter is still a mystery. Currently, there are many plausible models for representing the particle physics nature of it. However, the most prominent differences between individual models were in the very early universe, which is beyond the limit of our current observation capabilities. I used cosmological simulations of galaxy formation to compare two dark matter models: cold dark matter (CDM) and relativistically interacting (ETHOS), in the mentioned physically unobservable early universe to make predictions for upcoming James Webb Space Telescope (JWST) observations. The CDM model suggests dark matter particles have low velocities and are collisionless. ETHOS suggests dark matter particles are coupled with relativistic particles (particles traveling near the speed of light) and can scatter off one another. My analysis showed that compared to CDM, galaxies form later and there are fewer galaxies in ETHOS. Due to the delayed structure formation in ETHOS, galaxies in ETHOS have lower mass than their CDM counterparts in the same epoch. My simulations predict an absence of ETHOS galaxies more massive than 10^8, 10^9, 10^{10} solar masses when the universe was 470, 620, 900 million years old respectively, while such galaxies were present in the CDM simulation. Physically observing such galaxies at such epochs with JWST will provide strong constraints on the ETHOS model. Furthermore, JWST observations will enable us to calculate clustering statistics of the early universe galaxy population. Clustering analysis on my simulations showed clustering was weaker but had a steeper radial dependence in ETHOS compared to CDM. This suggests that galaxy clustering in the early universe could provide a potentially novel way to put new constraints on the nature of dark matter.

Phonon and Electron Models of Multilayered Two-Dimensional Crystals

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Solid properties such as total energy, density of states (DOS), and band structures (along high-symmetry points in the Brillouin zone) provide the crucial physics of crystals. In theoretical and computational practice, the use of density functional theory under a valence pseudopotential and approximated exchange-correlation functionals has become a standard method for determining the total energy for a solid due to its consistency with empirical measurements. However, consideration of density in an ideal lattice does not yet account for any introductions of vibrational energy into the crystal, including a nonzero temperature or even mechanical disturbance. In such cases, collective excitations due to the vibration of the ionic components in the crystal can be quantized into phonon quasiparticles. Not only do phonons interact with electrons and dramatically alter their structure (e.g. giving rise to low-temperature superconductivity), but they also have their own distinct band structure and DOS by frequency. We study the phononic properties of layered two-dimensional crystals (i.e. infinite periodicity in only two dimensions), computing their band structures and DOS corresponding to relaxed lattices. Analysis of these structures leads to a better understanding of the basic properties of two-dimensional solids and may be used to better interpret angle-dependent Raman spectroscopy, which in turn gives insight to the connection between crystal symmetries and magnetic order.

Investigation of the FeSe/SrTiO3 interface using Transmission Electron Microscopy and Electron Energy Loss Spectroscopy

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Monolayer iron selenide (FeSe) grown on a $SrTiO_3$ (STO) substrate is a high-temperature superconductor with a transition temperature T_c above 100 K. Multilayer FeSe on STO, however, has a significantly lower T_c of 8 K. What accounts for this difference? Characterizing the monolayer FeSe/STO interface is important to gain further understanding on the mechanism for the unexpected high-temperature superconductivity in this system. This study investigated the monolayer FeSe/STO interface structure using the atomic resolution imaging and characterization techniques of transmission electron microscopy (TEM) and electron energy loss spectroscopy (EELS). These techniques produced atomic resolution images of the interface which revealed that the STO substrate is terminated with a double TiO_2 layer interfacing the FeSe monolayer, as well as possible selenium diffusion into the top STO layers . These results corroborate previous studies predicting the existence of a double TiO_2 layer, and for the first time provide EELS evidence of selenium diffusion. By clearly depicting the interface structure, these results may provide insight into the mechanisms of this system's high-temperature superconductivity. Understanding these mechanisms can bring physicists a step closer to eventually engineering room-temperature superconductors.

XRD Data Processing and Analysis

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The research in the Mundy group is focused on synthesizing complex oxide thin films that have certain properties (e.g. strong spin frustration/exotic magnetic properties, superconductivity) and then probing these properties. After using the dual chamber reactive oxide molecular-beam epitaxy instrument to construct a film, its properties are examined. One of the tools used for characterizing the films is an x-ray diffractometer. The x-ray diffraction system allows us to determine atomic spacings and crystal structures for the films. There are some limitations with the data processing which we address with the project. We want to be able to read the data, smooth it, and find the peaks that are relevant to the film's analysis. The collected data is stored in an XRDML file and stores intensity along with angle data. With a group of undergraduate students, we have developed a script that assists with this data processing and analysis. We started by learning about crystal structure. We each researched smoothing functions (including gaussian, lorentzian, and pseudo-voigt functions, among others) for XRD data and tested various fits. The script uses a fit to smooth the data and isolate relevant film peaks. This software can be applied to various projects within the group and potentially to projects from other groups that collect XRD data.

A Survey of Rydberg Atom Pair States for Quantum Science Applications

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Quantum computers offer to revolutionize several fields, from materials research to artificial intelligence. One way to create a scalable, general purpose quantum computer involves an array of single atoms trapped using optical tweezers. We are working on an implementation using sodium and cesium atoms arranged in a plane. These atoms may then be excited to Rydberg states to implement logic gates, among other basic functionalities of a quantum computer. To create high-fidelity gates, however, it is necessary that the Rydberg states not only exhibit strong sodium-cesium interactions, but that sodium-sodium and cesium-cesium interactions are simultaneously minimized. We surveyed approximately 6,000 possible pairs of Rydberg states and evaluated each based on the interaction strength at several internuclear distances, and the ratio of sodium-cesium interaction strength to sodium-sodium and cesium-cesium interaction strengths, accounting for the fact that sodium-sodium and cesium-cesium interactions occur at a distance $\sqrt{2}$ times larger than sodium-cesium interactions. We write these quantities as $U(r)$, $\rho_1(r)$ and $\rho_2(r)$. When the internuclear and quantization axes are aligned, as in a one-dimensional array, we found that the states $|\text{Na}\rangle = 41^2\text{D}_{5/2}, m_j = 5/2, |\text{Cs}\rangle = 65^2\text{D}_{5/2}, m_j = 5/2$ and $|\text{Na}\rangle = 58^2\text{P}_{3/2}, m_j = 3/2, |\text{Cs}\rangle = 51^2\text{P}_{3/2}, m_j = 3/2$ to be optimal for two- and three-photon excitation schemes, respectively. The former achieved interaction strengths of 112 MHz at 2.95 ˉm, where $\rho_1 = 269$, $\rho_2 = 103$, while the latter achieved interaction strengths of 101 MHz at 3.87 ˉm, with $\rho_1 = 1036$, $\rho_2 = 2165$. In the case of a two-dimensional array with a normal magnetic field, we found the states $|\text{Na}\rangle = 45^2\text{D}_{5/2}, m_j = 5/2, |\text{Cs}\rangle = 40^2\text{D}_{5/2}, m_j = 5/2$ and $|\text{Na}\rangle = 58^2\text{P}_{3/2}, m_j = 3/2, |\text{Cs}\rangle = 51^2\text{P}_{3/2}, m_j = 3/2$ to be optimal for two- and three-photon excitation schemes. The former achieved interaction strengths of 109 MHz at 3.15 ˉm, where $\rho_1 = 38$ and $\rho_2 = 1475$, and the latter achieved optimal results at 3.85 ˉm, with an interaction strength of 278 MHz, $\rho_1 = \rho_2 = 37$. The survey work performed here forms the basis for potential implementation of Rydberg atom-based quantum computing schemes.

Angular Momentum Transfer in Disk Winds of High-Mass Protostar MWC 349A

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Winds rotating about the major axis of young stars are believed to carry angular momentum away from material in the star's accretion disk. Wind rotation is often difficult to observe due to the broad emission spectra of these systems that prohibit the detection of small velocity shifts caused by the winds. The unique hydrogen recombination line masers in the disk and winds of the bright radio source MWC 349A, however, allow spatial resolution of the motion. We analyze data of the hydrogen recombination line H26α and continuum emission at 345GHz obtained by the Atacama Large Millimeter/submillimeter Array (ALMA) in Chile. The observations were carried out on August 24, 2019 with 44 12-m antennas, and the resulting data were calibrated and delivered by the ALMA staff. The Python-based Common Astronomy Software Applications (CASA) program was used to image and analyze the data. The continuum image was made using data from two 1.87GHz-wide spectral windows, and H26α recombination line cubes were made using data from two spectral windows at a velocity resolution of 0.8 km/s and 0.2 km/s, respectively. At a resolution of 0.164″x0.018″, the images of the H26α emission exhibit clear evidence of a rotating structure surrounding the young star: the H26α data cube shows a redshifted region on one side of the center of the star and a blueshifted region on the other side, indicating a line-of-sight velocity gradient. Further image analysis is necessary to obtain velocity maps and rotation curves of the disk and wind present in the system, therefore providing insight into the angular momentum extraction mechanism.

Characterizing the Kinematics of Young Stars in the Radcliffe Wave

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Mentors: Gus Beane, Josh Speagle, Catherine Zucker

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We present the first evidence for the oscillation of the Radcliffe Wave, a 2.7-kiloparsec-long sinusoidal band of molecular clouds in our Galactic neighborhood. Molecular clouds are active sites of star formation, but large errors in traditional distance estimates have made it difficult to discern the 3D spatial distribution of these clouds in the Milky Way. However, with the second data release of the *Gaia* survey, which contains precise distance estimates for over one billion stars, the situation has dramatically improved. Besides enabling the discovery of the Radcliffe Wave itself, *Gaia* DR2 has provided an opportunity to study stellar kinematics in a subset of the wave. This is significant because, once the Radcliffe Wave's motion is known, it may provide important clues regarding the history and dynamics of star formation in the Milky Way, including the formation of the Sun. By incorporating new radial velocity measurements from *Gaia*, we computed 3D motions for thousands of young stars along the wave. We transformed the data to action-angle coordinates, which describe stars in terms of their oscillatory orbits and require fewer initial assumptions than do position-velocity coordinates. Our preliminary results indicate that the orbital phases of young stars associated with the Radcliffe Wave seem to vary significantly as a function of position, in a pattern consistent with a wave-like oscillation. This kind of oscillation is not seen in control fields consisting of older stars from *Gaia* and young stars in the Sco-Cen complex which lies outside the Radcliffe Wave. In the future, improved statistical modeling, in conjunction with better evaluation of uncertainties, should allow us to discriminate between a variety of hypotheses for the Radcliffe Wave's formation.

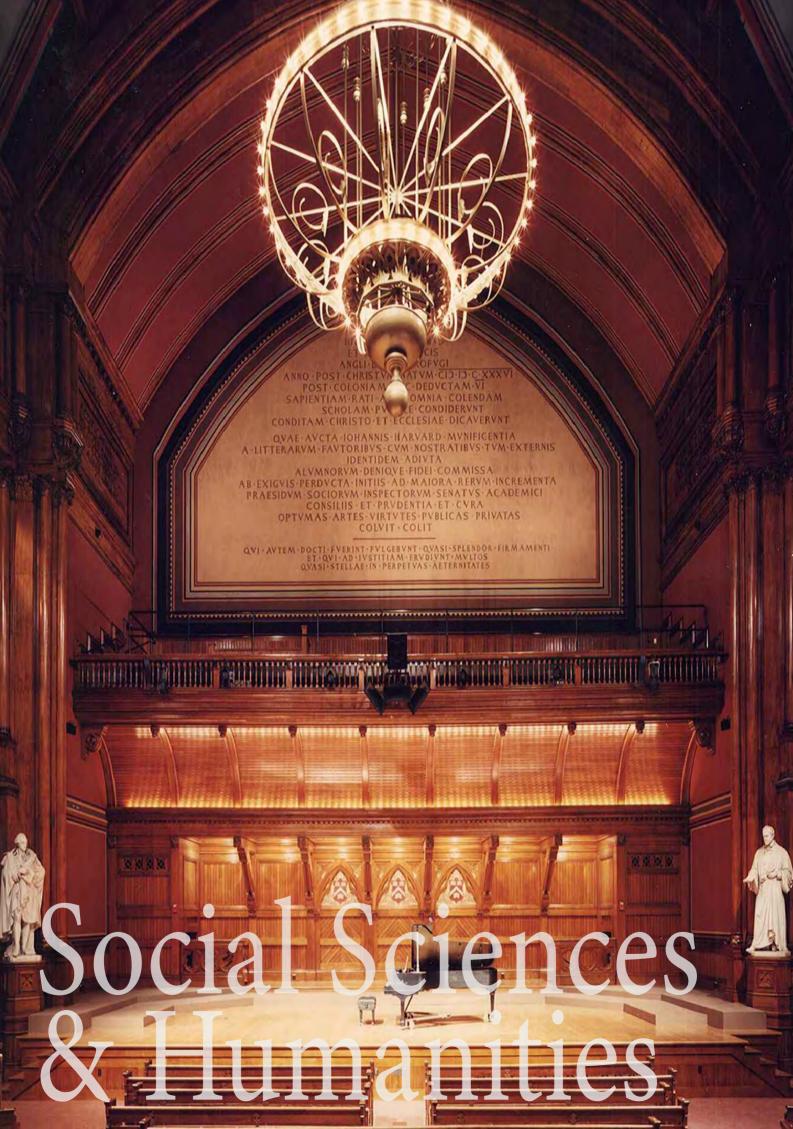# A Broad Search for Young Planets with TESS

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The analysis of young planets is essential to the understanding of planetary formation and evolution, as important signatures of these processes are often lost over time through processes such as stellar irradiation. A search of the sky for planets orbiting young field stars (less than 500 Myr old) was conducted using data from NASA's Transiting Exoplanet Survey Satellite (TESS), an all-sky survey mission designed to detect small decreases in the brightness of a star caused by the transit of a planet in front of it from Earth's perspective, rather than relying on young moving groups and clusters like past searches. The search method first eliminated non-main-sequence stars using stellar isochrones, then applied the Lomb-Scargle periodogram algorithm to look for rotational variation in the star's light curve, a sign of youth. Using the dominant period and basic gyrochronology formulae, age was estimated for each main-sequence star. A machine learning algorithm was trained to identify true rotational variables and was applied to the stars with an age estimate below 500 Myr. Finally, the machine-selected young stars were cross-matched with automatically-generated transit reports, and potential planet candidates were selected. Thus far, fifteen candidates of varying transit quality and rotational variability have been identified, and follow-up observations are being performed with the Tillinghast Reflector Echelle Spectrograph at the Whipple Observatory to ensure the youthfulness of the stars through the presence of lithium in absorption and calcium in emission. The properties of these young planet candidates are being compared with similar planets around older stars, and thereby helping to infer the properties of planets as a function of their age.

Social Sciences & Humanities

Diversity in Digital Space

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Advisors: Christina Linklater, Carol Oja

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In 1971, Renaissance and Black-American music scholar Professor Eileen Southern published *The Music of Black Americans*, a book that became foundational in the field of musicology. Professor Southern continued working in musicology and Afro-American studies, becoming the first tenured Black woman at Harvard University's Faculty of Arts and Sciences. To honor Professor Southern's work on *The Music of Black Americans*, as well as her work in musicology and Afro-American studies, an exhibition on her life in and out of academia was curated by students in a graduate course taught by Professor of Historical Musicology Carol Oja. The students created presentations based on archival information about Professor Southern and her work. The sources themselves ranged from letters written to and by Southern, interviews with people whose lives she influenced, and her written work. I worked on making sure that the sources were organized and reviewed them for accuracy, as well as the captions of video materials. Influential pieces of music were selected from *The Music of Black Americans* to highlight in the exhibition. This information served as a basis for in-person and digital exhibitions and provided a foundation in the effort to capture Professor Southern's life, work, and influence. This project is essential because of its goal to honor a figure in Harvard's history that greatly influenced musicology, ethnomusicology, and Afro-American studies, as well as paved the way for Black women who came after her. The work I did will ensure that the digital resource is accessible in both content and technology for all people looking to access the materials digitally and physically. I have also suggested some additional materials for the physical exhibition, such as specific video clips and pieces of music from *The Music of Black Americans*.

Co-Curricular Programming at the Harvard Art Museums

Kelsey Chen
History of Art and Architecture, Social Studies, 2022
SHARP Fellow

Harvard Art Museums

Advisors: David Odo, Jen Thum

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Historically, some of the most frequently organized and consistently attended co-curricular programming at the Harvard Art Museums include student guide tours and gallery talks. Though the museums have provided comprehensive and engaging programming meant to engage a broad spectrum of student experiences and audiences, the results of Student Museum Conference breakout sessions in 2018 and 2019 show that central concerns of students regarding co-curricular programming include accessibility, capacity to engage difficult histories, engagement with student-run campus organizations, involving students in curation and decision-making, as well as politically responsive programming. In order to provide recommendations regarding how better to develop co-curricular programming that is more engaging, inclusive, and accessible to students, we consulted DAPP reports, primary scholarship recording past student feedback from conference breakout sessions, and secondary scholarship analyzing museum programming performance; conducted interviews with Student Board members and Student Guides; and conducted a survey of current students. The results from this survey show that student respondents want to see responsive programming that engages with the current sociopolitical climate, programming which accommodates student schedules/timing, more self-reflective programming, more intellectually rigorous programming, and critical and interrogative programming rather than primarily expository or informative content. To better engage student audiences, co-curricular programming at the Harvard Art Museums should (1) Reconsider the definition of accessible programming to retain intellectual rigor while appealing to a variety of student experiences, (2) Implement creative technological solutions including asynchronized components of online programming, (3) Include students in decision-making processes, (4) Develop self-reflective programming which considers the specific history of Harvard's collections, (5) Strategically time programming to make use of regular student down-times, and (6) Identify opportunities for better liaising with student-led campus organizations. This project will come together as a report which presents and substantiates these recommendations to improve student engagement with co-curricular programming at the museums.

Family Programming at the Harvard Art Museums

Madi Fabber
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Harvard Art Museums

Advisor: Laura Muir

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The audiences of the museum world are expanding. As museums make the effort to welcome visitors of all different identities, museums must consciously create accessible programming that appeals to a broad audience. One of the most important types of accessible programming is family programming. Historically the Harvard Art Museums have offered family programs, but none of them have become permanent fixtures in the museums' operations. The goal of this research was to determine a series of recommendations for the museum to create engaging family programming that would become longstanding. This research was conducted by examining specific examples of engaging, family friendly programs at museums across the country as well as research into the Harvard Art Museums' previous family programming. The next step was interviewing museum staff to gather feedback on the museums' previous ventures as well as ideas for the future. Out of this research an activity book for children and families was created and sent out to a study group to test what kinds of engagement are most effective and to put the conclusions from the earlier research to the test. In order to create effective family programming the design of the program must be such that both the younger and older generations within a family unit can participate. Open ended questions and activities that allow families to think critically and be imaginative best engage the audience. Offering family programming that is thought-provoking, active, and activity-based is imperative in order for the museum space to appeal to a larger audience. By creating spaces in which families are welcomed and engaged the museum is not only able to welcome new visitors but also to convince them to keep coming back throughout their lifetimes.

Social Media Strategy for Harvard Art Museums

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Harvard Art Museums

Advisor: Jen Thum

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Museums' social media presence has become increasingly important during the COVID-19 pandemic, when institutions both nationally and across the globe have had to significantly limit visitors' physical access to their collections. Social media platforms provide a space not only for sharing artworks, but also for increasing public engagement and reaching new audiences. There are two components to my project at the Harvard Art Museums this summer. The first of these components included researching social media initiatives and strategies at various museums by closely monitoring their virtual presence and producing a research report with recommendations on strategic development of social media platforms. The second consisted of managing the Harvard Art Happens Instagram account, which included working collaboratively with student guides to transition the account for the summer months, creating a strategy for social media presence during the summer and beyond, doing research on works of art from the collections of the Harvard Art Museums, and generating content on the basis of this research, as well as trying out various ways of fostering audience engagement in the online space. This research report, combined with my work on the Harvard Art Happens account, will serve as a reference for both the Student Guides and museums staff, providing a foundation for sharing new and ongoing projects with broader audiences and making the collections of the Harvard Art Museums more accessible and engaging for the general public.

Illuminating the Commedia: A Vision of Dante's Cosmos

Madeleine Klebanoff O'Brien
Comparative Literature, 2022
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Houghton Library

Advisors: Kate Donovan, Kristine Greive

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Dante Alighieri's *Divina Commedia* articulates a definitive model of the medieval universe. Given the poem's emphasis on sight, relatively little scholarship has been devoted to visual representations of Dante's cosmos. In response to this deficit, my research situates Dante illustrations within the tradition of geocentric cosmography, emphasizing the didactic and devotional power of cosmographical 'maps'. It will culminate in the creation of my own map of the *Commedia*, accompanied by a written and illustrated commentary. I define a cosmography as any map that spans all three cosmic realms: elemental, ethereal, and empyreal. To create my Dantean cosmography, I turned to Houghton Library's rich store of Dante illustrations, devotional texts, pre-Copernican scientific treatises and Renaissance cosmographies. My own visual experimentation draws from this store of imagery, as well as from secondary sources and the text of the *Commedia*. Central to my work is the 3-sphere theory that sees Dante's universe as a hypersphere, both infinite and bounded. The 3-sphere forges an analogy between the 'extra' dimension of Dante's empyrean and that of relativistic space. While modern artists favor episodic illustrations of Dante's journey, only cosmographies maximize the transcendent capacity of the image. Theocentric cosmographies bridge the gap between the temporal and the eternal realms – between physics and metaphysics - allowing the viewer to approximate the unity of divine sight. Through 'illuminating' Dante's universe, I will voice the poem's cry for visualization and revive the cosmographical ambition.

Getting Started with Museum Data Guide

Marie Konopacki
Art, Film, and Visual Studies, 2021
SHARP Fellow

Harvard Art Museums

Advisor: Jeff Steward

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Over the past few years, new methods of arts research have emerged with the development of technology. To generate research opportunities, many museums have since digitized their collections, allowing the public to access their data. Although the data aims to be conducive to scholarly research, a major barrier remains: accessibility to researchers who do not have a technical background. Thus, in order to address the limitations that many art scholars face when trying to access information that requires coding, the Harvard Art Museums and I have created a guide. Informed through interviews with people who are familiar with the Harvard Art Museums' database and those who have never coded before, the guide intends to inform individuals with little or no technical background about how to get started with research in the Digital Humanities. Additionally, the guide demonstrates how the Museum's data can be utilized to solve unanswered research questions. Published on a website, the guide will be free and accessible to all, in order to break down the barriers in humanities research.

The Agents Behind the Game

Zachary Alerte
Statistics, 2021
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Harvard Business School

Advisor: Karim Lakhani
Mentor: Patrick Ferguson

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Across sports, fairly little is known about the role agents play in the lives of players. The goal of this research was to better understand how agents impact player behavior across sports with a specific focus on football (soccer). There are a number of phenomena that can be studied in this context including the principal-agent problem. This research was approached using both quantitative and qualitative methods. Data obtained on player movement from club to club was analyzed for trends. In addition, interviews were conducted with agents and players to gain a better understanding of the role of agents. Currently these interviews are being analyzed and could help provide insight into common challenges affecting agents and players. An analysis of quantitative data is still forthcoming but could prove insightful alongside interview data. If overarching conclusions can be reached on agents in sports then it might be plausible to extend some of those findings beyond the world of sports. Agents exist in a number of spaces including other talent industries as well as the spheres of real estate and home insurance.

Disease Outbreaks: Who Finds the Cure?

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Neuroscience, 2022
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Harvard Business School

Advisors: Joshua Krieger, Kyle Myers

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Often when viral outbreaks occur, there is a spike in scientific attention to the disease. However, following the initial containment, the attention fizzles away, resulting in missed opportunities for additional research and treatment breakthroughs. The first goal of this study is to understand what determines the extent and duration of research surges and which scientists move in and out of such research efforts. Second, we want to understand how these surges in publications influence society's ability to treat similar diseases in subsequent years. The first phase of the project was gathering data on the genetic relatedness of 200+ RNA viruses. The genetic sequence alignment tool BLAST was used to score how "similar" a particular virus is to previously studied viruses and outbreaks. From there, we mapped the viruses to all relevant academic publications via the Pubmed Medical Subject Heading (MeSH) classification system so that we can analyze the nature of the research surge by specific virus species and family. Next, we merged the set of distinct viruses to their historical outbreak events and their regional mortality tolls. The ongoing research now is identifying the number of scientific papers published for each outbreak as a proxy for scientific attention. With the mortality data on each outbreak and an understanding of the genetic similarity between outbreaks, the publication count may allow us to conclude whether a surge in attention results in a greater decrease in mortality for the disease in the following years. It could additionally yield insight on how our preparedness to deal with a disease is shaped by prior experience with similar viruses. The findings hold potential implications for the effective allocation of scientific attention and funding to speed treatment developments. Appropriately funding the productive surges in research following an outbreak could improve our future preparedness for treating similar diseases.

Building Purposeful Organizations

Rick Brown
Economics, 2022
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Advisor: Ranjay Gulati

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Why do organizations exist? While all firms deliver products or services, the most successful ones are equally focused on achieving a greater purpose, whether that be combating climate change or promoting diversity. The focus of this project was identifying the purposes of various organizations and deciding if they were truly purpose driven or simply engaging in purpose-washing (publicly announcing a purpose but failing to make this purpose a central part of the business). This process involved an extensive literature review of both companies selected based on media coverage of their purpose initiatives as well as traits of purpose-driven organizations in general. Companies examined included J. Front Retailing, Walmart, Theranos, and Method. Academic literature on purposeful organizations suggests that this type of company is becoming more prevalent both due to exceptional financial returns and increased employee interest in working for purpose-driven employers. It is difficult to distinguish between organizations that are purpose-driven and purpose-washing, but doing so will help companies to identify role models and emulate their traits. To that extent, this project will next examine how organizations turn purpose into visible results.

Filling in the Blanks: The Effect of Omissions on Inferences

Aspen Buck
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Harvard Business School

Advisors: Kate Barasz, Alison Wood Brooks, Ryan Buell, Leslie John, Michael Norton, Ting Zhang
Mentors: Hanne Collins, Emily Prinsloo

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Why do some people believe the #BlackLivesMatter movement implies other lives don't matter, so much so that a separate movement, #AllLivesMatter, has been created in opposition? In this research, we find that people's inferences depend on whether an omitted entity is in the same or a different reference set with the supported option. In a study, participants imagined that a friend had visited Greece and Italy in the same trip (same reference set) or in two separate trips (difference reference set). Next, the friend said she "liked Italy," omitting Greece from her statement. Participants inferred that their friend enjoyed Greece (vs. Italy) less when the friend visited Greece and Italy in the same trip (set) versus separate trips (no set). These results indicate that interpretations of omitted options might depend on whether an option is in a reference set with a complemented option or not.

Big Data at Work: Using Personal Data to Manage in the Age of Analytics

Ariana Chiu
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Harvard Business School

Advisors: Alexandra Feldberg, Barbara Kiviat

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In recent decades, the use of data in HR has exploded. For example, the field of "people analytics" has transformed from a niche discipline to full-fledged departments in many U.S. firms. Managers are using techniques drawn from this field to predict the behavior of employees, transform HR processes, and improve firm-wide performance. However, while new applications of data offer many solutions for companies, challenges have also emerged: even as 71% of companies view people analytics as a high priority in their organizations, only 8% report having usable data. Employee privacy is also a significant concern as workers in the U.S. have little say over the information their employers collect. Given the promises and perils of the recent explosion in data, this research focuses on select companies and explores how they turn to certain data in the first place, how they transform data into workable solutions, and how their utilization of data affects employee attitudes, performance, and treatment. We intend to use case study methodology to investigate how managers within companies are adapting to advancing technology and artificial intelligence while balancing transparency and employee rights. Our preliminary fieldwork suggests that HR departments are primarily concerned with reducing turnover, increasing employee engagement, and hiring strategically. These objectives are complicated by the evolving nature of work itself; as work becomes increasingly fast-paced and unpredictable employers must determine how much autonomy they can grant employees without sacrificing firm-wide strategy and culture. Findings will have implications for how companies can successfully introduce and integrate complex data practices into workplace procedures while prioritizing the well-being of employees.

China's Engagement with Africa and the Challenge of Democratic Ideology

Ben Chiu
Statistics, 2023
BLISS Fellow

Harvard Faculty of Arts and Sciences

Advisor: David Yang

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This project investigates the impact of Chinese construction projects from the Belt and Road Initiative (BRI) on local African political opinions on topics such as authoritarianism and democracy. The specific goal of this part of the project was to determine the location for a list of Chinese construction projects named by the Chinese Ministry of Commerce. This project explored various approaches towards locating the list of projects, generally using web scraping to find relevant information online. Additionally, since African locality names often have several different translations into Chinese characters, phonetic matching was used as well. The attempts at scraping the English internet were fairly ineffective – manual testing of automated results gave an abysmally low accuracy rate of approximately 15%. Tentatively, results for attempts using the Chinese internet appear more promising. Locating the list of projects will provide insight on the change in political attitudes in African communities located around any given project. If successful, this could provide important insights on potential influence-building by the Chinese government with the BRI.

Acquiring Knowledge from the Crowd: Evidence from Emerging Market Entrepreneurs

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Harvard Business School

Advisors: Geoffrey Jones, Tarun Khanna
Mentor: Nataliya Langburd Wright

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In the digital economy, the crowd has emerged as an important source of information as online platforms provide a cost-effective opportunity to source knowledge from a diverse audience. The use of the crowd amongst entrepreneurs stretches even before the digital revolution. We investigate the historical roots of crowdsourcing among entrepreneurs in a number of emerging markets, amalgamating research on crowdsourcing and open innovation with traditional sources of knowledge acquisition. We seek to determine the role of crowdsourcing in the innovation process, as well as identify contextual factors that predict the use of crowdsourcing. Pursuing these goals, we use a dataset of over 145 transcripts of interviews with prominent entrepreneurs and business leaders from emerging markets around the world. We make use of a methodology that combines inductive qualitative analysis of interview transcripts to derive how the crowd is used in the innovation process, as well as natural language processing and machine learning techniques to systematize the identification of the crowd and to understand predictors of the use of the crowd in knowledge acquisition. We hypothesize that there are historical precedents to entrepreneurs crowdsourcing in the digital age. We find that crowdsourcing may manifest in two forms: (1) an inductive approach in which the crowd informs the entrepreneur of both the problem and its solutions, as well as (2) a deductive approach in which the crowd informs the entrepreneur of solutions to an already known problem.

Assessing the Impact of Corporate Disclosures on Revenue Allocation to Stakeholders

Jay Garg
Economics, 2023
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Harvard Business School

Advisor: Ethan Rouen

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Since Milton Friedman first popularized the idea in a 1970 New York Times article, shareholder primacy has been the guiding mandate for public companies. Aggregate social welfare, he argued, is maximized when companies maximize their own profits over all else. However, as issues such as income inequality and climate change grow as global concerns, Friedman's dictate is being called into question. Many proposals to realign business with the desires of a broader set of stakeholders involve compulsory disclosures from businesses that allow stakeholders to hold management accountable for targets beyond profits, such as environmental mitigation and fair treatment of workers. In this research study, we look at voluntary corporate disclosures regarding revenue allocation to various stakeholders before and after the adoption of shareholder capitalism, which we represent as the publication of Friedman's article. Our research then examines the effect of disclosures on revenue allocation and how that effect changes over time. We use a difference-in-difference framework along with entropy rebalancing techniques to compare comparable firms that did and did not publicly disclose revenue allocation information immediately before and after said firms stopped reporting. Our results indicate that the effect of reporting on revenue allocation to stakeholders switched directions after the shift to shareholder capitalism: Before 1970, reporting was associated with higher outflows to non-shareholder stakeholders, like taxes or wages, but that effect became negative after 1970. One possible explanation is that disclosures motivate companies to behave in the way that they think investors expect. If society expects companies to maximize profit, disclosures will be used to increase shareholder value at the expense of other stakeholders. This research suggests that, if the goal is increasing revenue allocations to non-shareholder stakeholders, the best approach may be to keep disclosures voluntary, leaving managers the discretion to allocate revenues in a socially responsible way.

The Geography of New Technologies

William Hartog
Mathematics, 2021
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Harvard Business School

Advisor: Josh Lerner

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Through the utilization of language processing on text from earnings conference calls, newspapers, Burning Glass job descriptions and patents, a set of novel technologies was identified. This approach enabled the identification of 32 new technologies through correlation and clustering, as well as the visualization of the expansion of these technologies throughout American businesses and job markets. This visualization of the data yields three observations. First, as technologies grow, the size of the job pool related to this technology increases while the wage rate and education level required decreases. This development is natural thanks to the shift from PhD-holding employees to college- and high-school educated workers. Second, as technologies expand, the location of workers in the field across the country expands in turn from local hubs to a more spread out area. Finally, technologies tend to originate in university hubs and locations with high skilled workers, diffusing across the U.S. from the college towns where they develop. These results hold significance due to the goal of many areas in the U.S. to create employment, and these findings contribute to the understanding of the potential role new technologies play in that goal.

The Marketing of Bottled Water: Exploring Consumer Behavior

Audrey Jones
Psychology, 2022
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Harvard Business School

Advisor: Tomomichi Amano

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What causes consumers to change their purchasing habits? Our research approaches this question through the lens of the marketing of bottled water. Bottled water is a growing, multi-billion dollar industry despite the presence of a substitute that is readily accessible, more eco-friendly, and cost effective: tap water. Using Nielsen retail scanner data and local U.S. newspaper archives, we examined bottled water sales before and after almost 30 drinking water advisories (sudden tap water contamination events that require water to be boiled before drinking, otherwise known as water shocks) that each affected over 100,000 people in the U.S. during 2003-2017. Our hypothesis was that: 1) bottled water sales should "spike" around the week of the water shock, and 2) given the narrative that some people buy bottled water because of safety and health concerns, sales following the "spike" should see a sustained increase, especially because these water shocks could contribute to public perceptions that tap water is unsafe. We found that bottled water sales did indeed spike around the week of the water shock. However, unexpectedly, the majority of brands were unable to successfully retain customers for a significant period of time. This was true regardless of brands' messaging, dollars spent on advertising, consumer demographics, market region, and other factors, which we illustrate with graphical analysis and multivariate regression. This research suggests that consumers' behavior—and perhaps their habits and mindsets—may be remarkably difficult to change.

Judging a Charity by its Cover: Understanding the Factors that Influence Donor Decision-Making

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Cognitive Science/Neuroscience, 2021
PRIMO Fellow

Harvard Business School

Advisors: Kate Barasz, Alison Wood Brooks, Ryan Buell, Leslie John, Michael Norton, Ting Zhang
Mentors: Nicole Abi-Esber, Emily Prinsloo

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Understanding where people choose to donate money provides insights into prosocial behavior and decision-making. To measure this, in previous studies researchers have asked participants to choose between two charities. However, results were subsequently unclear due to confounding factors such as differences in popularity or credibility between the two. In the present study, to control for such factors, 34 charities were individually presented to participants via an MTurk survey, and participants were asked to rate the charities on their desirability to donate, trustworthiness, and familiarity. Results indicated that the charities varied across the three scales and that St. Jude's Research Hospital was the most trustworthy and desirable charity to donate to while Planned Parenthood was the most familiar. To obtain clearer results, future studies testing charity donor decision-making could consider comparing charities with liking ratings across the three scales.

Information Delays in Stock Market Bubbles

Jack Li
Applied Mathematics, 2022
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Advisors: Robin Greenwood, Andrei Shleifer

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We use text-based news data to study the revelation of information prior to the collapse of the dot-com bubble in the late 1990s. More specifically, we search for indications that market observers were concerned about overvaluation of the stock market prior to the actual correction. To quantify the divergence between bullish and bearish opinions, we perform lexicon-based sentiment analysis and find that that the difference in sentiment between articles that mention overvaluation (*overvalued* articles) and those that did not (*non-overvalued* articles) was maximized more than two quarters before the crash. Upon exploring the potential drivers behind sentiment, we observe that pre-cash sentiment for non-overvalued articles was significantly correlated with returns on technology stocks, while that for overvalued articles was not. Taken together, these findings suggest that overvaluation concerns had not only materialized quite early on, but were also fundamentally different from prevailing news.

How Top Indian Companies Present Themselves Online

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Harvard Business School

Advisors: Prithwiraj Choudhury, Tarun Khanna

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Discrimination can appear in different forms in the labor market, including how companies market themselves to future employees by offering a select image of themselves. To study how companies present themselves, we examined the top 100 companies in India's Nifty 500 stock index. Images from their recruiting and leadership pages were downloaded, and using a neural network, the extracted images were then categorized as North Indian, North Eastern Indian, South Indian, Caucasian, other Asian, and Black. Using regression analysis, the correlation between the faces presented on the websites and variables including company location, industry and type of entity, was performed. The findings suggest some correlation exists between the variables, including company headquarters and North Eastern Indian faces.

What is a B2B Company? A Multi-Method Approach to Identifying B2B Companies

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Harvard Business School

Advisor: Navid Mojir

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Firms that sell goods and services to other firms are broadly categorized as business-to-business (B2B). As it stands, the classification of a company as a B2B lacks standardization in marketing research. Moreover, many companies serve both end consumers and other businesses to varying degrees, which hints at a potential issue with the current literature that considers B2B status to be dichotomous. We have sought to develop an acceptable methodology of identifying B2Bs vs. their counterparts, business-to-consumer (B2C) firms. Combining information available from publicly released SEC 10-K reports, a Qualtrics survey on end-consumer brand awareness, and individual firm advertising spending, this study has developed a continuous measure for firms' B2B status. Further research into standardizing classification of B2B firms would improve the generalizability of studies of B2B markets.

The Cutter Incident and Trust in Public Institutions

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BLISS Fellow

Harvard Faculty of Arts and Sciences

Advisor: Melissa Dell

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Media plays a powerful role in shaping public opinion, but its effect on trust in public institutions, such as the government, is not well documented. In particular, local variation in news reporting and opinion pieces can lead to very different responses throughout the country for the same event. A particularly interesting event is the Cutter Incident in 1955, where hundreds of thousands of children were infected with polio disease due to government negligence and a fatal mistake in the vaccines themselves. We seek to analyze the various ways in which the Cutter Incident was reported throughout the country at the county level to better understand how editorial pieces influence Americans' trust in the government. As of today, we have merged the National Archives and the Library of Congress datasets to assign counties and other area-level characteristics to each local newspaper. Moreover, we have started on labelling and defining relationships between different sections of the newspapers, such as headlines, articles, and advertisements, to help the deep learning model understand the reading order of the newspapers. In our next step, we will apply sentiment analysis, where we will identify key words and phrases, that indicate whether the Cutter Incident and the government was cast in a negative or a positive light. After we identify the overall sentiment of each editorial piece, we will examine how the sentiment of each editorial piece ultimately influenced people's trust in the government. To concretely study changes in trust in the government, we will inspect both survey data that reports people's trust in the government and behaviors that are highly correlated with trust in the government, such as usage of vaccines.

Oren Rimon Or
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Advisor: Melissa Dell

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How does news coverage shape trust in public institutions? During the United States' early 1950s, the country experienced its largest polio epidemic wave. In what has become known as one of the worst historic pharmaceutical failures, the Cutter Laboratories distributed more than 100,000 lots of vaccines containing the live virus, leading to several death cases and numerous infected and paralyzed children. This paper studies how news coverage of the Cutter Incident impacted public trust in science and in public institutions. We scripted thousands of newspaper articles extracted from the National Archives, unlocking qualitative historical data and compiling quantitative data that was not available until now. We are in the process of building a model that recognizes the layout of newspapers and distinguishes between news and editorial content. In addition, we merged the National Archives data to the Library of Congress database in order to obtain the geographical location of each newspaper. Deploying deep learning (DL) and natural language processing (NLP) models on editorial and news content will allow us to analyze the attitude in different counties towards the Cutter Incident. By linking the sentiment analysis to measures of public trust, obtained from a series of surveys conducted by the Harvard School of Public Health, we will explore the possible influence of news coverage on the American people's trust in public institutions.

China's Engagement with Africa and the Challenge of Democratic Ideology

Richard Zhu
Applied Mathematics, 2022
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Harvard Faculty of Arts and Sciences

Advisor: David Yang

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China's rapidly increasing trade and investment in Africa has generated significant interest in China's role in the continent's political economy. As it displaces Africa's traditional Western partners, China offers African nations an alternative development model to Western democracies. Critically, African locals may see China's own rapid economic development under authoritarianism and challenge the conventional wisdom that democracy fosters growth and prosperity. Using data from China's Ministry of Commerce (MOFCOM) foreign investment database and local Afrobarometer polls across 36 countries, this project attempts to measure the role of Chinese economic engagement in shaping locals' political ideology regarding democracy. Keywords in MOFCOM-registered project names are used to assign investments into their respective infrastructure sectors and geographic locations. Significant heterogeneity in Chinese investment across Africa suggests that regressions could reveal key factors driving how locals respond to Chinese projects in their vicinity. Analyzing Chinese investment projects across sectors, locations, time, and other variables may provide insights into how locals view Chinese engagement. Indeed, as China seeks to expand its role in the future, certain investment projects may prove more integral than others in swaying local populations to support China's goal of developing long-term economic and political ties with Africa.

Pedagogical Resources for Intro Stats and Data Science Courses

Miroslav Bergam
Government, 2023
BLISS Fellow

Harvard Faculty of Arts and Sciences

Advisor: David Kane

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There is a dearth of open source online resources for data science to keep up with the field's current explosion in popularity. Preceptor David Kane along with a group of students spent this summer writing a high quality, open-source introductory data science and statistics textbook. The book is being tailored to Harvard's Government 50 course but will contribute to a larger community of open source educational tools. The book draws upon other open source materials but is unique in that it approaches the statistical concepts using a Bayesian framework rather than the typical frequentist approach used in most statistics classes. The book educates its readers on how to conduct and interpret Bayesian data analysis in the statistical programming language, R. It is also coded and written entirely in R. There were many steps to completing this book aside from writing and programming. To accompany the book, the team also spent the summer developing interactive tutorials and other pedagogical tools to be used in the class. Collaboration was also very important, as students served as "testers" for each other's chapters to ensure that there were no errors and that the flow of chapters was clear and smooth enough for students completely new to the subject. In addition to this, BLISS fellows served an organizational role in the creation of the book. They helped manage the GitHub repository for the project and educated other writers on how to use the version control program, in addition to creating informational guides on topics like coding an in-class tutorial in R.

Pedagogical Resources for Intro Stats and Data Science Courses

Evelyn Cai
Government, 2022
BLISS Fellow

Harvard Faculty of Arts and Sciences

Advisor: David Kane

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Data is more powerful than ever in the public sphere, as the movement towards publicizing data has resulted in a large amount of publicly available data. As such, students studying political science and government are increasingly encountering projects in which skills in data collection, analysis, and visualization are essential. These skills are not only vital in academia, in which most quantitative social sciences research requires an understanding of statistical methodology, but also in spaces such as nonprofits, federal agencies, and electoral campaigns. As such, our goal is to develop pedagogical resources to prepare students with limited statistical and technical background for these applications of data science. In doing so, we incorporated cutting-edge R tools in development and contributed to the open-source R community. Instead of providing a third-party subscription of data science tutorials to students, we focused on creating tutorials from scratch so that their content would match the content of the rewritten textbook. Moreover, we altered the datasets that are used as examples and tutorial questions to adapt the book to its purpose of teaching data science for government students. Current datasets include social science experiments, political surveys, and public goods data. Due to the real-world applicability of the data skills taught, we will also thoroughly discuss common pitfalls of data analysis. These issues, such as the dangers of hypothesis testing and the validity of analytical methods in mapping to the research question, have plagued the general academic social sciences community in the past few years. We hope to create tools that will not only empower students with technical skills, but also with the critical questions that will make them more conscientious academics, analysts, and people.

Measuring the Efficacy of Facebook Political Advertising

Corbin Duncan
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BLISS Fellow

Harvard Faculty of Arts and Sciences

Advisor: Horacio Larreguy

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Advertising on Facebook is increasingly one of the largest expenses for contemporary political campaigns. Some attribute election outcomes to the efficacy of political content on Facebook. Online advertising uniquely empowers advertisers to specify the viewership and frequency (saturation) of their content. We study the variation in efficacy of online advertising by content, saturation and viewership. Through a randomized online field experiment conducted in conjunction with an incumbent mayor's digital campaign, we study effects on vote-intention by four political advertisements at three levels of saturation. Facebook users were delivered treatments over two, week-long exposure periods and subsequently surveyed on their vote-intention. Treated users were randomized on the basis of age, gender and location. While effects on vote-intention varied strongly on content and on audience, they thus far do not appear to be a function of saturation. Total pooled effects of the campaign saw a 7.15pp increase in candidate vote-intention among treated subjects. Content-driven effects are demonstrable with one treatment recording a strong 12.8pp total increase in candidate vote-intention, compared to the weakest treatment with a 4.5pp increase, relative to the control group. Some effects were also demographic-driven with females 18-34 years of age recording strong effects across all treatments, while conversely some treatments recorded opposite effects among different genders of the same age group.

Restoring the Work of Italian Renaissance Political Theorist, Francesco Patrizi

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Advisor: James Hankins

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Niccolo Machiavelli is likely the most well-known Italian Renaissance political philosopher, known for his "ends justify the means" political outlook. In the current climate of extreme political polarity and uncertainty, this project looks back to the work of another Renaissance political theorist, Francesco Patrizi, in order to provide an alternative to the Machiavellian lens. Patrizi is a humanist and a proponent of virtue politics: put simply, the idea that a virtuous ruler paired with virtuous citizens can lead to prosperous commonwealths. However, his works have not been edited in modern times, so this project investigates, edits, and organizes Patrizi's works for modern day consumption. One portion of the project in particular focuses on his work "How to Found a Republic," which outlines techniques for said prosperous commonwealths, providing advice on topics ranging from governing and husbandry to medicine and warfare. The last time this work was translated was in a 1576 epitome called "A Moral Method of Civil Policy" by the English translator Richard Robinson. Thus, the project modernizes and sources Robinson's epitome so it can be read and studied for use today. This process of modernization is two-fold: it involves transcribing Robinson's archaic spelling and punctuation so that the work is legible and tracing classical references to their original sources for citation. The ultimate goal is to bring the work of Francesco Patrizi to light as well as to provide a "new" perspective on political philosophy for modern day political theorists and readers.

Social Movements, Media, and Shifts in Judicial Sentencing Behavior

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Advisor: Trung Nguyen

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The impact of social movements and media coverage of political events on the behavior of institutions remains unclear. Recent scholarship has explored the complex relationship between political ideology and the behavior of the judicial system, in particular focusing on racial and gender disparities in the criminal justice system. Such work has shown that the judicial characteristics such as gender and the politics of the appointment have differential relationships to the leniency of sentencing. In this project, we seek to identify possible links between event shocks including the #MeToo movement, the Black Lives Matter movement, and immigration protests on patterns of judicial decision making. We examine and analyze data on court case outcomes during key periods in the development of these social movements and expect to observe shifts in sentencing patterns by race and gender. The intensity and content of news and social media coverage combined with data on the impact of protests and real activities that occurred during these social movements offers the opportunity to quantify the variation in social sentiment or variation in treatment. We hypothesize that variation in judicial characteristics will generate heterogeneous treatment effects. If successful, this project can help elucidate the relationship between changes in social sentiment and shifts in judicial behavior.

Restoring a Great but Forgotten Work of Political Theory from the Italian Renaissance

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Advisor: James Hankins

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This project is based on the work of James Hankins, particularly his recent book on some of the most important political theorists of Renaissance Italy, *Virtue Politics: Soulcraft and Statecraft*. "Virtue politics" is the idea that politics should be based on, rather than separate from, questions of virtue and morality. There are several important thinkers who wrote on virtue politics, but Hankins argues that scholars ought to recognize Francesco Patrizi of Sienna, the author whose work is the focus of this project, as the main voice of Renaissance virtue politics. Unfortunately, neither of Patrizi's works has been translated from the original Latin into English. In 1576, the translator Richard Robinson wrote an epitome of Patrizi's *How to Found a Republic*, but there is no modern edition of this text. In order to bring Patrizi to a wide audience as soon as possible, this project has created a modern edition of the 1576 epitome of Patrizi's *How to Found a Republic*, complete with modernized spellings and punctuation, definitions of all words no longer in use, source notes, and additional commentary by James Hankins. Our team has used the edition of the epitome available on the database *Early English Books Online* as its source for the text. In the process of working on the text, our team met regularly with Professor Hankins to learn research and editorial skills. This work aims to bring a new perspective on virtue's place in politics, a topic that is certainly relevant to modern political thought.

Indian Philosophy Project

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The goal of this research project is to advance educational capabilities in the field of Indian Philosophy by conducting a literature review of pivotal works on the topic of caste in the pursuit of developing an educational module. While non-Western philosophy is often harmfully relegated to discourse as purely a novelty, classical Indian epistemology and political philosophy can bring valuable insights when put in conversation with European intellectual history. The research was conducted predominantly through a literature review that drew sources from three main areas: classical Vedic philosophy, colonial and early post-colonial political philosophy, and late twentieth/early twenty-first-century Indian ethics. The primary goal was to analyze the formation and change of caste as a political ideology through the course of Indian history. Additional research was also conducted on topics in the field of Nyaya and Mimamsa epistemology. Findings suggest that, while Caste was codified in Indian society from early Vedic times, its political rigidity did not play as large of a role as classical works in Indian socio-political theory, like the Law Book of Manu or the Arthashastra, may have made it seem. Rather, it was because of British orientalist ethnographic interest in Classical Vedic Texts that, in modern times, Caste is seen as the primary factor in the development of individual and cultural identity. Yet because of a dual post-colonial backlash and embrace of British sensibility, Caste remains simultaneously deeply ingrained and shunned in Indian society. This complex status quo can also suggest insight into the future of Dalit-Black solidarity and the broader influence of Indian Political Philosophy on diasporic identity. The educational modules developed through this review of Indian epistemic and ethical philosophy should improve the digital visibility of topics in this field. These discussions suggest further, unresearched areas of discourse on the topics of caste, class, and diaspora between European and Indian intellectual history.

Representations in the Brain

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The brain gives rise to the mind. How? Neuroscientists often argue that the brain "encodes" or "computes" mental processes. Computation and information are medium-independent; they depend on the brain's causal relations, but not its physical composition or organization. So, if the brain gives rise to the mind solely on the basis of its information processing abilities, then the relationship between brain and mind cannot depend on the properties of the brain as a physical substrate. I evaluate this claim by looking at how neuroscientists have argued that the fusiform face area (FFA) implements face perception. I argue that neuroscientists identified the role of the FFA in the mind based on both its information relations and also its physical organization. This suggests that scientists do not establish the relationship between brain and mind based on the brain's information processing abilities alone. I use my discussion of the FFA to criticize Nicholas Shea's recent account of mental representations, *Representation in Cognitive Science*.

Stereotypes about Physical Androgyny

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Advisor: Nicole Noll

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Theories of person perception posit that, in the absence of concrete evidence about an individual's internal and secondary attributes, we make assumptions about such traits based on what is immediately visible. Accordingly, perceived sex category and gender presentation serve as incredibly powerful organizers, shaping our perceptions of others in a matter of seconds. But what of individuals who violate our often binary expectations about gender? Specifically, what assumptions do we make about individuals who are physically androgynous? The present study aims to answer these questions by surveying people's beliefs about androgyny and androgynous people. Through open-ended questions about people's assumptions regarding androgynous individuals, ratings of faces' masculinity-femininity, and the classification of said faces as androgynous or not, we seek to get a better understanding of when people use the term androgynous, and what they mean by it. Initial results suggest that young adults have strong assumptions about the behaviors, interests, and worth of physically androgynous individuals. In addition, the ratings and classification of faces as androgynous, masculine, and/or feminine may suggest that the term "androgynous" itself is a label that is applied differently to certain demographics of people. Specifically, we may see that the term "androgynous" is more liberally applied to white people, and that it takes on more positive connotations when applied to cisgender white women than to men, women of color, and non-binary individuals. This trend has particularly pertinent implications when considered within the context of legal, medical, and societal discrimination, particularly against transgender and gender non-conforming people of color.

The Effects of Mindful Engagement on Effort in Cognitively Demanding Tasks

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Mentor: Peter Aungle

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Most people assume that cognitively demanding tasks are experienced as effortful and draining. Indeed, researchers contend that exerting effort draws upon a limited pool of resources, resulting in depletion effects that make it more difficult to sustain effort in demanding tasks for extended periods of time. In contrast to this perspective, we propose that approaching cognitively demanding tasks mindfully, where one attends to novelty in the task environment, can reduce one's subjective experience of effort. To test this hypothesis, participants will be randomly assigned to one of three conditions: mindful, mindless, or control. Then, participants will complete a cognitively demanding task, adding one or three to each digit in increasingly longer strings of digits. The participants must engage with the task for at least five minutes but are encouraged to challenge themselves and spend as long as they like. As participants complete the task, we will record data related to their performance and time spent on the task (i.e. on each question, each level of the task, and the task as a whole). Afterwards, participants will complete a post-task survey to assess their subjective experiences of effort and engagement. We anticipate that participants in the mindful condition will perform significantly better, report higher levels of engagement, experience the task as less effortful, and spend more time on the task than their counterparts in the mindless or control conditions. We also predict that the mindless and control conditions will not differ significantly from each other on any of these measures, suggesting that the default approach to cognitively demanding tasks may be mindless. If our hypotheses are correct, approaching any cognitively demanding task mindfully is likely to increase engagement and reduce depletion effects. Furthermore, the data would suggest our subjective experience of effort is something we can control.

Physical Androgyny Study

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When individuals do not conform to the gender binary, how are they perceived? This study seeks to answer this question by exploring assumptions about androgyny and perceptions of physically androgynous people. Formatted for an online study, the survey consists of around 30 questions which explore participants' assumptions about androgyny. It will be distributed to a study population recruited via the Harvard Psychology Department Study Pool. Results may suggest that individuals have positive, negative or neutral attitudes towards androgyny, and that this influences their evaluation of physically androgynous people. Survey responses may also show that knowledge of an individual's assigned sex results in varied beliefs about androgyny. Finally, results may illustrate societal assumptions in relation to androgyny, such as the belief that androgynous individuals are suited for some occupations over others, or that androgynous individuals are more likely to exhibit some physical characteristics over others. The implications are broad and may have wide-ranging effects in terms of public policy, employment, healthcare, and education.

Bringing Behavioral Science to Everyone

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Behavioral science research is vast and filled with useful knowledge, yet it remains mostly read and understood only by academics. Nearly everyone could benefit from the discoveries of our field, but many find it difficult to navigate through jargon-heavy articles and databases. We created an online platform to bridge this gap, called *The Game of Life Hacks*. We started by sending a survey to see what people are struggling with now, with the most common issues being productivity, physical and emotional well-being, finances, and relationships. We then found academic research articles relevant to these topics and "translated" them into a general tone that could be more broadly understood, regardless of the reader's background (as opposed to only accessible to psychologists). From the research, we created actionable tips, or "Life Hacks," that tell people how they can apply the research to improve their lives and meet their goals. Finally, we reached out to the experts: we helped professors and researchers create videos of themselves talking about their research and sharing helpful advice about how to apply it to people's lives. After launching, we will share this platform broadly, and encourage those who view it to do the same, utilizing social media platforms, email lists, and word-of-mouth. Our goal is to reach as many people as possible, so that more people can reap the benefits of behavioral science research.

Belief In and Source Memory for Emotional Fake News

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Mentor: Nadia Brashier

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Fake news undermines elections, harms health, and threatens the environment. Many misleading headlines include sensational details that incite emotional reactions. However, scientists know very little about how emotion impacts people's evaluations of news. This thesis tests whether emotional content distracts readers from the sources of information. Participants will view Facebook-style news posts, each including a headline, cover image, and source. Half of these posts will feature real headlines, and the other half will include fake headlines previously flagged by third-party fact checkers. Immediately after exposure, participants will see the headlines and images again without sources. They will rate the headlines' accuracy and indicate their willingness to share them with friends. Participants will also choose which media source published each headline. Emotional content, whether positive or negative, may distract participants from source details and make it more difficult to discern real from fake news; lower source memory scores may mediate the relationship between emotion and poor discernment. Lastly, participants may be more willing to share emotional content with friends. This research will reveal how emotion can lead to forgetfulness in a world where the news does not always tell the truth. The results could guide media policy and provide media consumers with the tools they need to avoid falling for misinformation.

Estimating Income Inequality

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Economic inequality has been increasing in recent years, with reports of the top 1% owning around 40% of all income in the U.S. How well do people understand the distribution of income? There have been conflicting reports on whether people overestimate or underestimate levels of inequality depending on whether participants are asked about wealth versus income, or depending on what levels of the income distributions the studies focus on, e.g. top 1% vs top 20%. In this study, we ask participants to estimate income distributions in their local counties. By eliciting estimates of income across the entire distribution at a more granular level, we can clarify where exactly on the distribution people are underestimating income and overestimating income. We hypothesize that people underestimate the income of the top, particularly of the top 1%, and overestimate the income of the bottom. We hope to reconcile findings that people seem to simultaneously overestimate and underestimate economic inequality in the U.S. by identifying specific regions on the income distribution where these distortions may occur.

Examining the Mental Health Effects of Covid-19 on Emerging Adults

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Mentor: Olivia Fitzpatrick

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The novel Coronavirus Disease (COVID-19) has led to a global health pandemic with adverse physical and psychological outcomes. Experts predict that COVID-19 and its resulting disruptions to daily life might impose especially negative consequences on the mental health of emerging adults. In an effort to address this public health concern, mental health professionals have been working to develop and disseminate remote mental health supports for emerging adults. Although these interventions might be beneficial, we have limited knowledge of which problems to focus on and which tools might be most helpful during this pandemic. One strategy for improving this understanding is directly asking the intended consumers of these tools, emerging adults, to report their top mental health problems and needs. 200 emerging adults (17-26 years old) completed a 5-10 minute survey measuring demographics, current living situation, anxiety and depression symptoms, and their open-ended top mental health problems and needs during COVID-19. These qualitative data were coded and clustered using a thematic, qualitative data coding procedure to identify and analyze common patterns. We hypothesize that emerging adults who report living in crowded, unsatisfactory living conditions and experiencing a loss of income will endorse greater levels of depression and anxiety. The main component of this study is qualitative and exploratory in nature, so we have not identified any additional a priori hypotheses. However, it is likely that we will identify a variety of mental health problems and needs through our thematic analysis procedures. These findings could offer data on the most prevalent mental health consequences of COVID-19 for emerging adults, as well as inform which mental health interventions, focusing on which problems, might be most effective for this population during this time.

Children's Acquisition of Negation: A Corpus Analysis

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Children learn to produce and understand the words for negation in English between the ages of one and three years. Despite the fact that negation is an important conceptual and linguistic milestone, this process is not well understood. Until recently, technological restraints have forced research in this area to focus on observations from just a few children, resulting in extremely limited data. Modern technology, however, has allowed the construction of the Child Language Data Exchange System (CHILDES), a large online database of child speech. Our research used computational methods to bring these data to bear on existing and under-supported claims in the child negation literature. These include, for example, the claims that English negators are learned in the order "no," then "not," then "n't," and that children go through a "pre-sentential" stage, during which "no" preceding a sentence negates the propositional meaning of the sentence (eg. "no the sun shining" to mean "the sun is not shining"). A fine-grained analysis of the CHILDES corpus of child speech revealed that, while the broad brushstrokes of many claims from the older, less data-rich literature hold up to scrutiny, they are missing the nuance that can only be provided by large data sets. We found that children do produce "no" before "not" and "n't," but those "no"s are due almost exclusively to single-word negation. When children's negation was filtered to only multi-word utterances, all three negators began to be produced at about the same age. Moreover, some claims, such as that of a pre-sentential negation stage, were completely unsupported by the data. These analyses imply that previous claims based on limited data must be re-evaluated now that a large, systematic collection of child language is available.

15-month-old Infants Incorporate False Beliefs in their Social Evaluations of Helpers

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Past work has found that infants prefer agents who help others over those who hinder others. In the present experiment, we ask: Do 15-month-old infants incorporate others' false beliefs in their social evaluations? First, infants watched a protagonist try to open one of two opaque boxes. Two helpers took turns opening the box, allowing the protagonist to grasp the toy inside. After the protagonist left, a pair of hands switched the position of the toys. Both helpers were present during the switch in the True Belief condition; they were absent in the False Belief condition. One helper directed the protagonist to the new location of its preferred toy while the other directed the protagonist to the original location of its preferred toy. We presented the infants with the two helpers and examined whether they preferred to look at one or the other. If infants incorporate mental states such as false beliefs in their evaluations, then infants should prefer looking at the helper who provides access to the original goal object in the True Belief condition; in the False Belief Condition, they should prefer looking at the helper who provides access to the original box. Finally, looking times were recorded offline to assess the infants' preference between the two helpers via preferential looking test. Infants (n = 41) looked at the helper who provided access to the original goal object 58% of the time in the True Belief condition, but only 42% of the time in the False Belief condition. These findings suggest that 15-month-old infants incorporate others' false beliefs in their social evaluations.

The Positive Effect of Rationalization on Cognition

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Rationalization, the act of changing your beliefs and desires to match your actions, is commonly seen as a mechanism that individuals unconsciously use to develop irrational beliefs or even justify abhorrent actions. However, rationalization may actually serve to improve the information we can access. This study seeks to explore whether rationalization can actually improve the transfer of information from our automatic processes, such as our habits and instincts, to our conscious processes: our beliefs and desires. To determine this, the present study will examine whether Amazon Mechanical Turk workers can better recall the grades a survey received after reading a review about that survey and a review about another survey. This design will demonstrate whether rationalization can impact individuals' ability to encode and recall their memories. If individuals' rationalizations actually improve their ability to accurately recall information, then this study will suggest that rationalization *does* improve the transfer of information from automatic to conscious processes.

Friend Watching, Reputation Changing: How Adolescent Risky Decisions Change under the Gaze of Peers

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Advisor: Leah Somerville
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Adolescence as a developmental period is characterized by significant behavioral, emotional, and cognitive changes. Hallmark behaviors include increased willingness to incur risks to obtain rewards. Previous studies have found that adolescents assimilate to their friends' perceived expectations in a manner that overemphasizes protecting friends from losses (Powers et al., 2018). In the current study, we examine the effect of this phenomenon by observing pairs of adolescents making individual choices that affect their own earnings and their friend's earnings, both alone and while their friend is watching. We compare this to observations in adult samples. Participants were presented with an economic decision-making task, with varying chances (10, 25, 50, 75, 90%) to earn money (between $5 and $100), for themselves and for their friend to test whether an individual's willingness to make risky choices is affected by the consequences that follow for their peers. We examine this in joint and competitive contexts, in which both peers get different earnings and when both peers get the same earnings. We aim to answer how accurate participants' assumptions about their own and their friend's risk preferences are and how strongly reputational motives, (i.e. choosing what your friend thinks you should choose), influence decisions. We hypothesize that adolescents' choices align with friends' expectations more often than adults' choices do. We further hypothesize that adolescents make poor predictions of their friends' risk preferences, whereas adults are more accurate. The implications of this study could provide insight into motives for adolescents in real-life risky decision-making circumstances when they are surrounded by peers.

Dynamic Micro Compliance Training

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Compliance and integrity training is a costly activity required of all corporations and employees. Training tends to be a generic and tedious process in which the employees watch a 30 minute or longer video and answer follow-up questions. This process leaves employees unengaged thus minimizing the efficacy of the training. Although online compliance training builds and reinforces legal knowledge, it does not raise awareness of corporate crime, which academic literature suggests is one of the main causes of corporate misconduct. To cultivate this awareness, this project seeks to design a micro dynamic way of training that best seizes the attention of employees and builds an intuitive understanding of risks that may arise in certain scenarios. Dynamic Micro-Training assigns each employee a tailored set of training questions every week based on their previous training performance in order to reinforce knowledge gaps, and employees are rewarded by receiving less frequent training. The training questions are customized for each company based on their work nature and culture, and the questions are designed to examine conceptual knowledge and apply it to real-life scenarios. Thus far, the training is still under conceptual development. Once the training platform is built the method itself and various distribution algorithms will be experimented upon.

From Having to Being: Self-Worth and the Current Crisis of American Society

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America faces increasing divisions around key social issues. People's sense of "worth" is organized around neoliberal values such as material prosperity and individualism, and around the American dream whose promises have failed to reach fruition for those who fail to achieve or abide by such definitions of worth. This chapter seeks to bring to light voices of those attempting to shift cultural perceptions of worthiness and inclusion, termed "agents of change." These individuals are working at the forefront of their industries, striving to shift cultural paradigms through narratives of hope and worth. Based on coded qualitative interviews conducted with over 140 such individuals across various industries, this chapter analyzes how change-makers use resources, tools, and platforms to promote diversity and inclusion, racial and social justice, sustainability and authenticity. Central to their efforts are narratives of hope and worth and their diffusion of such narratives through various channels, from grassroots organizing and community engagement to social policy and impact investing. This approach to cultural and social change proves central to combatting the scope and depth of the divisions and challenges faced by American society today and serve as a viable means of rethinking neoliberal conceptions of worth.

The Effects of Outreach and Advocacy on HIV and Opioid Epidemic Legislation and Education in MA

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Fenway Health

Advisor: Carrie Richgels

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Although HIV treatment and research has greatly improved over the past few decades, the number of people living with HIV (PLWH) has also increased. In the meantime, public interest in HIV has decreased overtime along with adequate HIV legislation. While there is greater public interest in the opioid crisis in terms of changing the pharmaceutical industry and providing people treatment, there is minimal interest in harm reduction efforts such as Supervised Consumption Sites. Thus, due to the lack of interest in harm reduction, public policy has failed to provide justice and compassion for people who inject drugs (PWID). In order to advocate for justice and dignity for PLWH and PWID in MA, the Getting to Zero (GtZ) Coalition works to push for greater legislative action and education to improve accessibility to treatment and decrease the stigma faced by PLWH and PWID. GtZ aims to revitalize HIV/AIDS advocacy in MA and eliminate HIV related stigma, AIDS related deaths, and new HIV diagnoses. In coordination with other organizations, GtZ creates a network of HIV advocates that increase awareness of new and existing treatments while also promoting greater accessibility to these resources. GtZ developed Activist Academy to educate community leaders across MA about HIV advocacy, legislation, and stigma. In order to drive forward the GtZ mission, Activist Academy advocates for several active bills in the MA legislature and engages supporting organizations and activists in these issues. Activist Academy is a driving force in educating and mobilizing advocates in MA. Overall, GtZ and Activist Academy use a network of advocates and supporting organizations to spread awareness regarding the current status of the HIV and opioid epidemics.

Poetry in America

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Poetry in America

Advisor: Elisa New

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For the general audience, poetry is an art form that is at come alluring and opaque. Many are interested in reading and learning about poetry, but are intimidated by poetry's structure and reputation as one of the "high arts." To address the shortage of poetry-related course materials available to the general public, Poetry in America is working with Chinese based podcast company Himalaya to develop a series of 6 pod-courses to launch on Himalaya's platform for both American and Chinese audiences. Reviewing content developed for Poetry in America's courses and TV series, I worked with a team of editors and producers to propose pod-course themes, and together we began developing episodes for the first 3 pod-courses: one on Black American poetry, one on female poets in America, and one on poetry of the natural world. I worked most closely on the content development stage of the pod-course on female poets in America, drawing from Poetry in America's materials on Anne Bradstreet, Mercy Otis Warren, Emily Dickinson, Edna St. Vincent Millay, Marianne Moore, and others. By combining lecture content with extracts from interviews with celebrities like Cynthia Nixon, our goal is to appeal to new audiences who might not otherwise be inclined to read poetry. Through the publication of these new pod-courses, we hope to open the door for more people to enjoy poetry outside of a university context and to help the general public better understand and appreciate poetry.

Abolitionist Women and Their Worlds: Course Development Research

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The Arthur and Elizabeth Schlesinger Library on the History of Women in America

Advisor: Tiya Miles

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Due to U.S. slavery's subjugating conditions and its fractured historical archives, learning about the institution, and the women involved in abolishing it, takes creativity. Limits in archival information are inevitable: many voices are missing, and the remaining perspectives are shaped by the social (dis)empowerment and other struggles of its writers, especially Black formerly enslaved women. To prepare for Professor Tiya Miles' spring 2021 class about abolitionist women, we assembled archival and artistic materials to depict the lives and legacies of seven women leaders. We created two sets of research: one set of 19th century archival evidence directly from and about the women, and another investigating representations of them in art up to the present. For the latter, we utilized Black feminist, literary, theatrical, and historical secondary sources to assess the legacies of three of the women: Harriet Tubman, Harriet Jacobs, and Harriet Beecher Stowe. These sources interpreted sculptures, poems, plays, films, and other art about Black womens' resistance to slavery. We discovered a pattern: art and narrative allow the imagining of interiority missing from the archives, and help portray longings for family and collective liberation that motivated and sustained much of our subjects' antislavery work. Key complications in the archival evidence (Jacobs' sexuality, Tubman's spirituality and disability) are often undertheorized in the art, flattening the figures into epic icons who are denied full, deep humanity. This project draws upon the lineage of Black feminist thought and practice, and suggests that knowledge of the abolitionist movement is gleaned from interior and communal processes. Our research process will illuminate comparisons between the seven women on our syllabus, and push students to theorize how these women's knowledge can be put into practice in current struggles.

Academic and Public Programming at the Harvard Museums of Science and Culture

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Harvard Museums of Science and Culture, Harvard Faculty of Arts and Sciences

Advisors: Reed Gochberg, Janis Sacco

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Since the founding of Harvard's Museum of Comparative Zoology, women workers and scientists have formed the backbone of the museum's day-to-day operations and research. Their contributions, however, have often been overlooked, particularly in the early history of the museum from 1870 to the 1920s. Even museum records fail to capture the stories of the women who for decades served as scientists, researchers, librarians, secretaries, and assistants, who discovered and donated new species, catalogued collections, mounted thousands of specimens, and designed public exhibitions. A forthcoming exhibit at the Harvard Museum of Natural History, led by Reed Gochberg, aims to uncover and honor the legacy of these pioneering women workers. This summer, we have created a timeline of 60 women workers at the museum, and have drawn on genealogical research, census records, and digitized archival materials to compile biographical profiles of 10 key figures in the museum's early history. The biographies of these women, taken alongside artifacts of their lives and work at the museum, tell broader histories of science, women's labor, and women's education in America. In addition to working with Dr. Gochberg on exhibit research, the project also includes working with Janis Sacco, Director of Exhibitions at the Harvard Museums of Science and Culture. Now that the Museums' doors are closed due to the COVID-19 pandemic, the HMSC has pivoted to producing educational and entertaining online content to reach a broad digital audience. In particular, a dedicated team has been working to develop the Extraordinary Things series, which highlights objects from across the Museums' collections and encourages online visitors to engage in thoughtful reflection and enriching activities related to these artifacts. Despite the restrictions imposed by the Museums' closure, the new online HMSC Connects! platform offers new opportunities for interdisciplinary collaboration and visitor outreach.

Analysis of NRA Archival Letters 1998-2016

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Harvard Faculty of Arts and Sciences

Advisor: Caroline Light
Mentor: Claire Boine

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For the last three decades, the National Rifle Association (NRA) has influenced American gun culture through identity-forming language that politically mobilizes its members. As recreational gun use has declined over the past two decades, there has been a steady rise in gun owners citing self-defense as their top reason for possessing a firearm. Recent research has not cross-studied the influence of the NRA's identity-forming language and the rise in gun ownership for self-defensive reasons. Our study seeks to understand the way in which group identity influences the gendered and racial implications of gun culture. We present a qualitative analysis of NRA editorial letters published from 1997-2016. These letters were submitted by readers of the following NRA magazines: *America's 1st Freedom*, *American Hunter*, and *American Rifleman*. Our study analyzes the word choice and themes of the archival letters to understand how the NRA uses identity formation to mobilize its members and shape the narrative of contemporary gun culture. We conducted a qualitative, content analysis with the Taguette program to create an archive of common language that reflects the perspectives of NRA members and gun owners. It seems likely that self-defense is a white supremacist patriarchal narrative that mobilizes its base on fear of racial minorities and the government. This social narrative may impact racial disparities in gun violence victims and self-defense legislation.

Abolitionist Women and Their Worlds

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African and African American Studies, Studies of Women, Gender, and Sexuality, 2022
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With 2019 marking 400 years since the first enslaved Africans were brought to the British colonies of what would become the United States and 2020 marking the centennial of the 19th Amendment, discussions on the history of abolition and women's suffrage are very prevalent today. During the 19th century, many women not only participated in both movements but also played key roles in their success. This research provides an archival and artistic analysis of seven women who were involved in abolitionist and suffrage work: Harriet Tubman, Harriet Jacobs, Harriet Beecher Stowe, Lucy Stone, Laura Smith Haviland, Angelina Grimke, and Sarah Grimke. A variety of primary sources, including newspapers, correspondences, oral histories, advertisements, narratives, photographs, plays, poetry, and maps, were used to compare, contrast, and deeply analyze these women's lives and accomplishments. The goal of this research was to reveal how these women's experiences, identities, surroundings, and families shaped their political visions and notions of abolition and suffrage as intertwined movements. Sexuality, intersectionality, social capital, and motherhood were important themes that impacted how these activists, especially Black female activists, became involved with these movements and how much they could accomplish. Through this research, differences relating to whose lives and legacies are preserved and who is represented in contemporary discussions on abolition and suffrage were also found. These findings lead to larger discussions on 19th century Black women's presence in the archive and public memory, along with how different life factors can lead to similar activist paths in social movements.

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Here's to tomorrow!

ACKNOWLEDGEMENTS

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