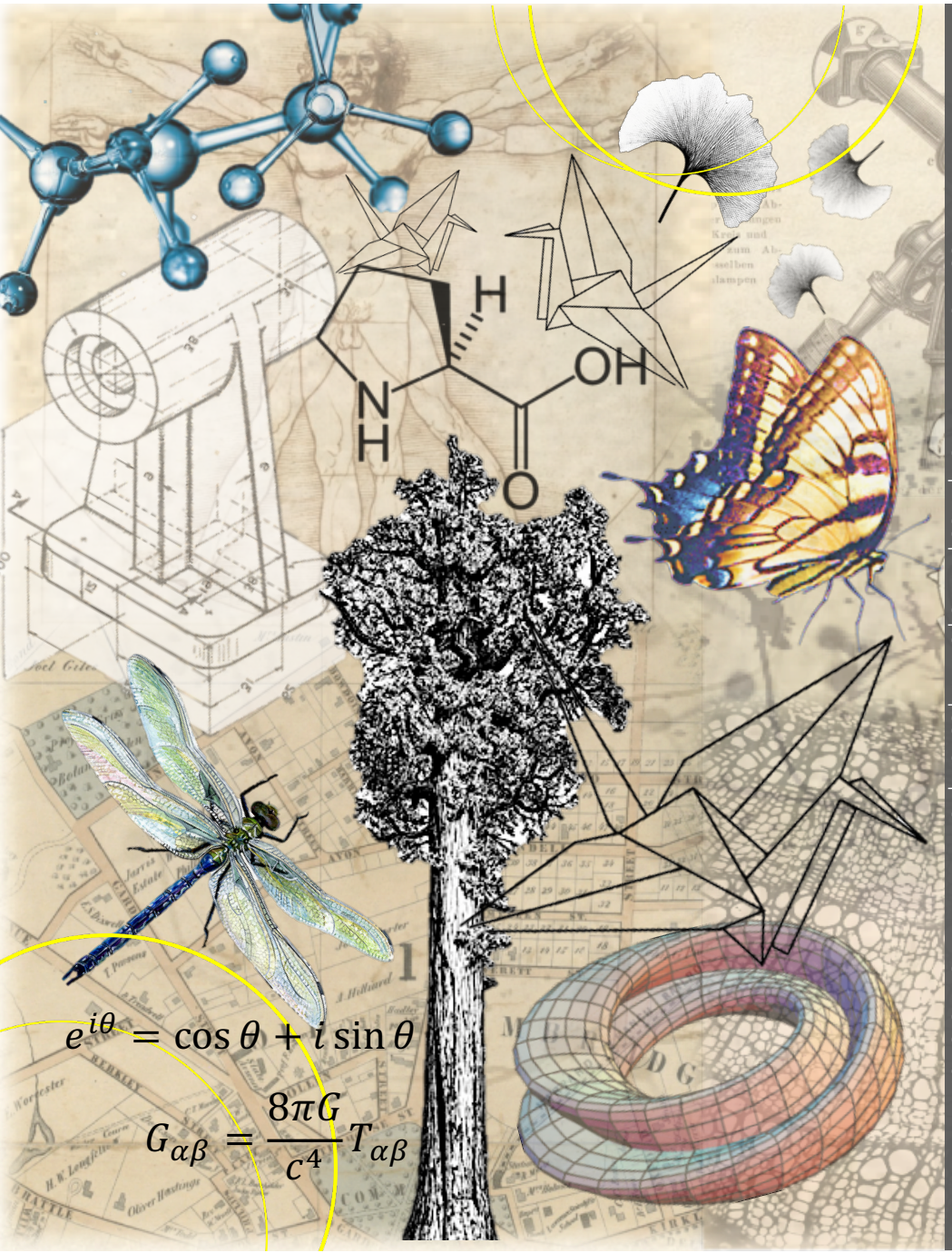

HARVARD COLLEGE

PRISE | BLISS | PRIMO | SHARP | SURGH | PCER

ABSTRACTS 2017

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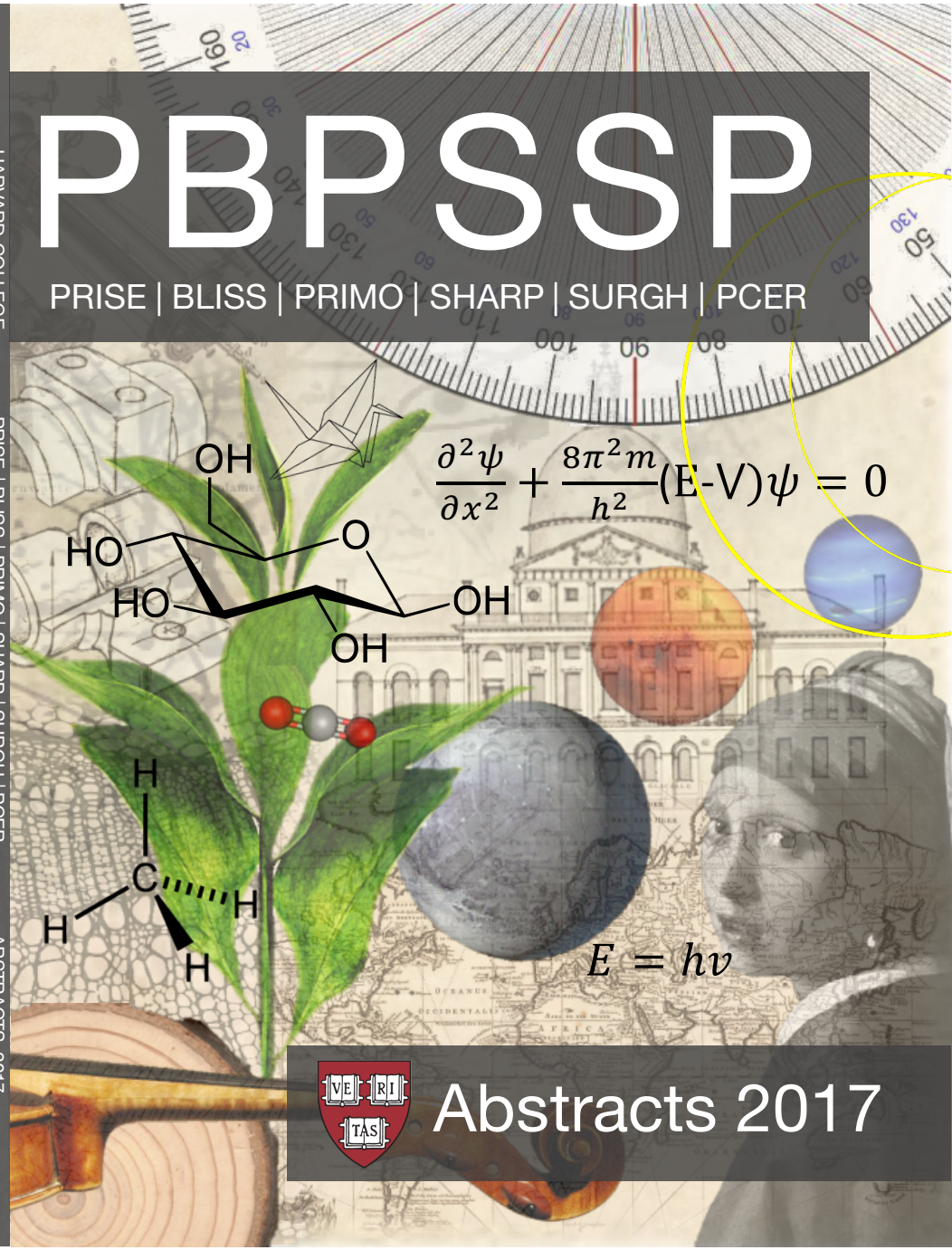

Abstracts 2017

Harvard Summer Undergraduate Research Village

ABSTRACT BOOK 2017

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Summer Undergraduate Research in Global Health (surgh)

Office of Undergraduate Research and Fellowships
Harvard University

The Editorial Board

Contents

Letter from the Director

Dear HSURV Community,

On behalf of Rakesh Khurana, the Danoff Dean of Harvard College, and Jay Harris, the Dean of Undergraduate Education, I am writing with pleasure to introduce the 2017 Abstract Book of the Harvard College Summer Undergraduate Research Village community. The Village is comprised of PRISE (the Program for Research in Science and Engineering), BLISS (the Behavioral Laboratory in Social Sciences), PRIMO (the Program for Research in Markets and Organizations), SHARP (the Summer Humanities and Arts Research Program), SURGH (Summer Undergraduate Research in Global Health), and our latest affiliated program, PCER (the Program in Community-Engaged Research), which is celebrating its inaugural summer.

From the beginning of PRISE in the summer of 2006 and the subsequent evolution of the Summer Undergraduate Research Village, I have been gratified by the continuing development of interdisciplinary opportunities that provide formative and substantive exposure to research under the auspices of faculty and subject experts across the university. As members of our residential community will attest, this experience is fortified by a compelling, meaningful social engagement in which these six programs together are inextricably linked with enthusiasm, inclusivity, and deeply-felt kindheartedness.

The abstracts included herein speak for themselves: impressive in their considerable interdisciplinary range, the projects are a testimony to the fellows' diligent effort and compelling sense of purpose. With gratitude to our faculty hosts, the abstracts further underscore the truly inspiring research happening across the Harvard universe.

I wish each of the fellows in PRISE, BLISS, PRIMO, SHARP, SURGH, and PCER satisfying accomplishments in your academic endeavors going forward and hope your curiosity continues to be piqued through further prospects to conduct research on topics that fascinate you. I suspect the important relationships you have cultivated over the summer will parlay into long-term friendships that positively influence you during your time at Harvard and beyond. Thank you for sharing your summer with me!

Yours truly,

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

Letter from the Editors

Dear HSURV Community,

As the summer draws to a close, we commemorate the incredible research conducted by all of the fellows in this community with this collection of abstracts. HSURV is a unique experience, allowing motivated and driven student researchers to spend ten weeks living and learning together. We will cherish our memories of discussing research, wandering Boston, watching whales on the open sea, and cheering on our peers at the packed coffeehouses.

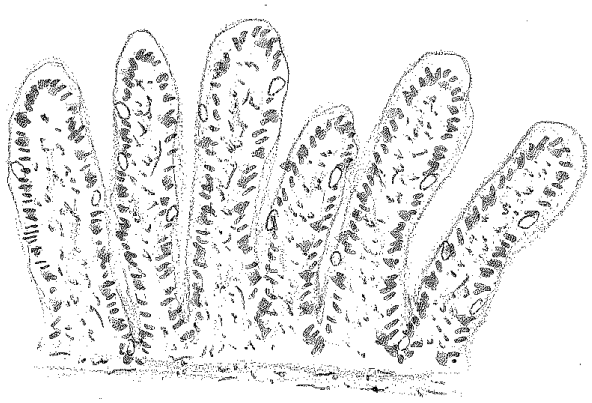
The research we conducted this summer showcases talents beyond mundane acts of pipetting and reading; even more, our research was diverse, collaborative, and multidisciplinary. Small or great, preliminary or groundbreaking, we are pushing the frontiers of human understanding. It has been a privilege and a pleasure reading about the hard work of those in this community. We are incredibly grateful to our dedicated fellows and peer editors, without whom this book would not have been possible.

This summer was the result of the hard work of numerous groups and individuals. Thank you to the proctors, PAs, and PBPSSP and Leverett House summer staff: you have made this a summer filled with fun and have turned Leverett House into our home. To our PIs, advisors, and mentors: we are beyond grateful for both the knowledge you have shared and the general wisdom you have imparted to us. And most of all, thank you to Greg Llacer and the entire URAF team: this village would not exist without your enthusiasm, experience, and expertise, which drive these programs forward.

And now, we invite you to explore our work this summer—happy reading!

Sincerely,

The 2017 HSURV Abstract Book Editorial Board



Behavioral Laboratory in the Social Sciences (BLISS)

Assessing Ethics Education at Harvard University

Ikeoluwa Adeyemi-Idowu — Harvard College
Sociology — Class of 2019

Danielle Allen
Edmond J. Safra Center for Ethics

Mentors
Jess Miner, Edmond J. Safra Center for Ethics
Michael Blauw, Edmond J. Safra Center for Ethics

Researchers at the Edmond J. Safra Center have begun a holistic assessment of ethics education across the Harvard University's thirteen schools. As part of a National Ethics Project to examine ethics instruction across the United States, our team is aiming to determine how and where Harvard teaches ethics. To do so we have created an archive of course descriptions, student/faculty surveys, and syllabi determined to provide information about ethics instruction. After assembling a weighted three-tier system of 82 key terms, the team was able to identify courses that fit within the broad limits of our methodological framework. Analysis of the archive utilized the methods of the Humanities and Liberal Arts Assessment Lab (HULA), which involved coding a variety of excerpts to track learning pathways and human development. As this qualitative data analysis continues, the team aims to discover emergent patterns across the body of ethics instruction at Harvard. The results of this assessment will provide crucial information to give the university a clearer image of what and how it is teaching in the realm of ethics and whether Harvard is being true to its mission to educate the citizens and citizen-leaders of our society.

The Role of Empathic Learning in Harm Aversion

Stephanie Campbell — Harvard College
Computer Science — Class of 2019
Mind, Brain, Behavior

Mina Cikara
Harvard Intergroup Neuroscience Laboratory

Mentors
Fiery Cushman, Department of Psychology
Indrajeet Patil, Department of Psychology

Empathy is a strong contributor to the remarkable human aversion to inflicting harm. Although extant work has investigated how *present* empathic responses prevent harmful actions, little work has focused on how our *past* empathic experiences help us *learn* to assign negative values to harmful actions.

Our approach is to understand this process of learning moral values by drawing on formal computational models. We use the two distinct systems known to guide choice behavior: the habitual internalized "model-free" system, and the goal-directed planning "model-based" system.

We modeled our empathic learning experiment on a previous two-step reinforcement learning task that identifies which of the two decision-making systems has greater control in making non-social choices. This task can dissociate model-based and model-free strategies based on different predictions these strategies make on how second-stage rewards affect subsequent first-stage choices. We investigate the computational architecture for moral decision-making by introducing empathy-inducing stimuli—morphed images of faces expressing varying degrees of pain.

Thus, the questions of interest are: as people explicitly reason the consequences of their behavior on the welfare of others, how will they choose actions that will minimize harmful outcomes? Does empathy have a greater impact on decision-making by

using a goal-directed planning system or by triggering an automatic and internalized dislike for actions that cause harm?

Assessing Ethics Education at Harvard University

Valerie Elefante — Harvard College
Social Studies — Class of 2019

Danielle Allen
Edmond J. Safra Center for Ethics

Mentors
Jess Miner, Edmond J. Safra Center for Ethics
Michael Blauw, Edmond J. Safra Center for Ethics

As part of the National Ethics Project, a comprehensive examination of ethics instruction at universities across the country, researchers at the Edmond J. Safra Center of Harvard University are seeking to answer this question: how and where does Harvard teach ethics? Our team assembled an archive of course descriptions, syllabi, and faculty/student surveys considered to be evidence of ethics education. Using a weighted three-tier system of 82 key terms designed to capture relevant courses across the 13 schools of the university, the team was able to identify those that fell within the boundaries of our methodological framework. Qualitative data analysis of the artifacts utilizing the methods of the Humanities and Liberal Arts Assessment Lab (HULA) revealed the short term cognitive capacities and long term human development that ethics courses intend to promote. Based on a review of relevant literature, variances in empathy and open-mindedness in students are among the developments the Harvard researchers aimed to make explicit. More broadly, we are continuing our analysis in order to uncover gaps and trends within the entire landscape of ethics instruction at Harvard, and eventually perfect generalizable methodologies that can be applied to various other universities. The results of this study will assist faculty and administrators in strengthening ethics curricula in order to better educate and prepare future leaders for the world.

The Great American Schism: Examining the Political and Cultural Divides between Elites and Non-Elites

Enya Huang — Harvard College
Sociology and Chemistry — Class of 2019

John Donahue
Harvard Kennedy School

Contemporary conversations around American politics suggests a divide between more privileged Americans and their counterparts. Social movements such as Occupy Wall Street emphasize "the one percent" and "the ninety-nine percent" to highlight the supposed difference between elites' and the general public's interests, and the 2016 presidential election underscored tensions particularly between liberal elites and other Americans.

The Young American Elites Project analyzed the political views and cultural affinities of American elites and American non-elites to see how they differ and change over time. Using relevant results from the General Social Survey as measures of ideology, we employed the possession of a four-year college degree by the respondent, respondent's father, or respondent's mother as the marker of elite status.

Based on this analysis, there is an ideological divide between American elites and non-elites that seems to have, on the aggregate level, stayed constant. For example, in the past two decades, elites and non-elites alike decreasingly believe that immigration to America should be reduced. Other noteworthy findings include, as of 2006, elites trusting white people significantly more than non-elites do, with both elites and non-elites trusting whites significantly more than people of their own races.

The ideological divide between American elites and non-elites seems to have stayed constant, with, among other changes, both groups showing increased pessimism about the future and decreased trust in their fellow citizens over time. This lack of faith manifested itself in the 2016 election and will likely continue to affect American politics.

The Politics of Genomic Science

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Sociology — Class of 2020

Jennifer Hochschild
Harvard Kennedy School

As one of the most up-and-coming fields in the scientific world, it is likely that genomic science will soon make its way into the political sphere; yet, up to this point, discourse on the subject has remained minimal. To better understand where the public currently stands on issues surrounding genomics, we collected survey data from the Roper Center for Public Opinion Research. We first examined what people think are the main causal factors of human traits, characteristics, and actions such as crime, sexual orientation, health problems, obesity, and intelligence. Based on preliminary data, people are not convinced that genomics plays a significant role in much else besides certain chronic diseases, though the belief that it plays a role in sexual orientation has increased in recent years. Interestingly enough, there does not seem to be a clear divide among varying demographics; liberals may be slightly more apt to believe genetics cause various traits or actions than conservatives, but the variation is not significant. We also collected data on the moral perceptions of genetic engineering, gene therapy, cloning, and other similar practices. When confronted with these moral questions, the majority of the public stood against such practices, except when the practices could help prevent the transmission of certain genetic diseases. Aside from morality, religion, fear of government, and employer regulations and restrictions played a significant role in the public's stance on these issues. Thus, our research gives us insight into how genomics could enter the realm of politics and how public opinion could shape the future of genomics.

Applications of the Method of Direct Estimation for Causal Inference

Charles Liu — Harvard College
Computer Science — Class of 2018

Dustin Tingley
Department of Government

As datasets grow increasingly rich in the number of variables observed, methods for causal inference that can successfully handle all of the potential covariates and confounders gain importance. One such method is the Method of Direct Estimation (MDE), a newly developed method by Ratkovic and Tingley (2017) which uses non-parametric model fitting and sparse Bayesian regression to estimate the causal effects of treatment variables. MDE improves on existing methods for causal inference because it can model linear and nonlinear effects and because it can identify heterogeneity in treatment effects for different subgroups. First, I used MDE to reanalyze two datasets that have previously only been studied using standard ordinary least squares methods for causal inference. The first dataset was analyzed to show whether a legislator's position on a Congressional committee has a causal effect on the amount of federal funds their constituents get. The second dataset studied whether the degree of segregation in cities influences the amount of money spent on public goods. Then, I explored the application of MDE in the causal mediation analysis setting by running Monte Carlo simulations.

The Effect of Education on Political Participation: Evidence From Malawi, Mozambique, Kenya, and Tanzania

Will MacPhee — Harvard College
Applied Mathematics — Class of 2019

Horacio Larreguy
Department of Government

The often-held assumption that education has a positive effect on political participation has been supported by research conducted in developed democracies, but recent studies in several African countries, such as, Nigeria, Senegal, and Zimbabwe, show mixed evidence. This project aims to perform similar analyses for Kenya, Malawi, Mozambique, and Tanzania.

The project emphasizes causal inference by making use of instrumental variables and difference-in-differences strategies. Using census and opinion data

from the Afrobarometer surveys in the above countries, we use the impacts of large-scale school reforms to instrument individuals' education levels and ultimately to estimate the causal effect of education on political participation.

A key phase of the process is evaluating the first stage of the instrumental variable regression, in order to assess whether a school reform sufficiently impacted the difference in education levels between more-and-less-initially-educated districts in the country. The focus on this difference suggests that school reforms were aimed at equalizing education access across the districts within each country. So far, a study of Mozambique was found to have an insufficient first stage, preventing causal inference. However, first stages in Malawi and Kenya have been found to be strong. In Malawi, there seemed to be no relationship between education and political participation in general, which was anticipated. The analysis of the effects of education in Kenya and Tanzania are forthcoming.

The hope is to use these studies to contribute to the current literature on this topic that suggests nonlinear variation in the effect of education by regime type. Our research will help assess whether improving education leads to political—and ultimately economic—development.

How We Learn Analogy: Making Relations Relevant

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Harvard College
Class of 2019

Susan Carey
Department of Psychology

Mentor
Ivan Kroupin, Harvard Laboratory for Developmental Studies

When we say the mitochondria is the powerhouse of the cell, we compare mitochondria to powerhouses because they serve similar purposes, even though they do not look alike. This is relational reasoning: the ability to match based on analogy. Adults are very good at reasoning with relations. But children under the age of five struggle with relational reasoning. When making comparisons, children tend to match based on object physical appearance (i.e. color, shape). They would not initially see that mitochondria can be compared to powerhouses on the basis of function. Current research questions whether this focus on object appearance rather than relations indicates that children are incapable of making these relational comparisons. Alternatively, it may be that children are capable of making relational comparisons but have a tendency to make comparisons based on object appearance. If children are capable of relational reasoning, certain matching games designed to draw attention away from the appearance of objects should encourage matching based on relations. This is being shown in ongoing studies. Several such games have significantly increased relational reasoning performance among 3 to 5 year-old children. The results indicate that children *can* reason with relations–they just have to move past a focus on object appearance before reaching the underlying structural similarities. These results have implications for how we think about the development of relational reasoning: the cornerstone of analogy, poetic metaphor, and creative scientific discovery.

Catherine the Great's Town Plan Project, 1770-1820: Exploring the Geospatial Relationships Connecting the Russian Empire

Sierra Nota
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Harvard College
Class of 2019

Kelly O'Neill
Department of History

As a part of Catherine the Great's 18th provincial reforms, state urban planners were charged with mapping 391 individual towns comprising the entirety of the Russian Empire. These maps depict each town's current state as well as a plan for reconfiguration and repurposing the town to adapt a modern system of roads, town grids, centralized squares and industries that were previously uncommon throughout the empire. Despite the vast wealth of information on the first large-scale urban planning initiative to ever take place in the Russian Empire that these plans provide, the majority of them have sat untouched in the national archives of Moscow since the mid 19th century. Therefore, deciphering their contents is of great interest. In order to do this, the legends of the plans have been transcribed and categorized within a relational database. Their individual features, such as rivers, churches, bridges, government buildings, and fortresses have been both tallied and geospatially referenced, so that the plans may eventually be georectified. After this, their extracted features can be compared to modern maps

of the same region. This provides the most comprehensive lens yet through which to examine the transformation of both the natural and man-made landscape of modern Russia over the past two hundred years. An examination this information, when compared with already established databases on economic yield, transportation times and routes, and centers of government administration, will reveal for the first time the long term economic and political successes and failures of this relatively unexamined urban planning initiative.

Optimal Interpersonal Styles in Negotiation

Vanessa Ruales — Harvard College
Government and Psychology — Class of 2020

Julia Minson
Harvard Kennedy School

Mentor
Mike Yeomans, Department of Economics

This summer, I worked at the Harvard Decision Science Lab, an experimental laboratory that systematically studies human decision-making. A principal study I worked on sought to answer the following question: how does interpersonal style affect negotiations? In other words, is it better to be warm and friendly or tough and firm when negotiating? Much of the literature suggests that having a warm interpersonal style will lead to the most successful results for the negotiator when negotiating a distribution of resources (for example, the price of a single transaction); however, our previous lab studies suggested that toughness yields better outcomes. To see if this would work in the field, we sent 'nice' or 'tough' emails (formulated through a previous study using a natural language processing algorithm to identify 'warm' styles) to 900 qualified iPhone sellers on Craigslist from 14 of the largest cities in America. In this current study, sellers were presented with one of three types of nice or tough messages and were offered 80 percent of their asking price. When a seller responded, we recorded the length of time they took to respond and whether they accepted the offer or not as a measure of a successful outcome. Although the data is still being analyzed, a preliminary study showed that overall, toughness and niceness are equally effective. However, warm buyers are significantly more likely to receive counter-offers. Based on these results, we conclude that, contrary to the popular literature, having a firm interpersonal style leads to the best outcomes.

The First Generation of Independent African Leaders and the Making of the African Nation-State

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Emmanuel Akyeampong
Department of History

The modern economic and political climate in sub-Saharan Africa leads people to question why the constituent nations have not had sufficient political, economic, or social development after fifty years of independence. Was there any vision, set of policies, ideology, or any aspiration toward which the leaders of these countries, especially the first generation of leaders, were hoping to lead their countries? If there was, what happened to those visions and why, after fifty years, have things seemingly not worked out? Through a close look at government and scholarly documents from five West African and East African countries in the 1960s, 1970s, and 1980s, one realizes that the first generation of African Leaders was exceptionally visionary and thought to reshape, not only their countries after the tragic system of colonialism, but also the world political economy by, for example, their political position of non-alignment in an era of cold war, and trying to introduce a unique economic ideology (besides capitalism or communism) named African Socialism. However, as it turns out, not only was the world geopolitics of that time, especially the cold war situation, too oppressive for these newly born countries, but also attempts from Bretton Woods institutions to help these new economies sometimes proved rather toxic to the rise of the countries. Development economics did not deliver prosperity, and structural adjustment from the 1980s brought more chaos than help. This study reclaims the history of the exceptionality of the first generation of independent African leaders while calling for the rethinking of African challenges in that period of its history and to the re-conscientization of all Africanists, in today's attempts to bring stability, peace, and development in Sub-Saharan Africa.

Feminisms & Pornography

Jordan Villegas — Harvard College
Anthropology — Class of 2020
Studies of Women, Gender, and Sexuality

Jane Kamensky
Department of History

Mentors
Amanda Strauss, Schlesinger Library
Mark Vassar, Schlesinger Library

Despite the historical and contemporary influence of the feminist "sex wars" of the 1970s and 1980s—a polarized period of grassroots demonstration and academic debate on the politics of sex and sexuality, including sadomasochism, prostitution, lesbian sexual practices, and, most significantly, pornography—few comprehensive histories have been written on the subject. Utilizing the manuscript, audiovisual, and periodical collections of The Arthur and Elizabeth Schlesinger Library on the History of Women in America, a "sex wars" research guide was composed, surveying relevant primary source documents within the collections of anti-pornography feminists including Susan Brownmiller, Florence Rush, Robin Morgan, Barbara Deming, Shere Hite, Catherine MacKinnon, and Andrea Dworkin; anti-censorship feminists Betty Friedan and Ellen Willis; and photographers of the second-wave feminist movement Freda Leinwand and Lane Bettye. Organizational records of Coyote, Women Against Pornography, and Boston Women's Health Book Collective and feminist publications *Outrageous Women* and *Ms. Magazine* were also used. Periodicals including *Off Our Backs*, *On Our Backs*, *Heresies*, *Eidos Magazine*, *Playboy*, and *Hustler* were also referenced to frame personal and organizational records within their cultural context. Additionally, the archival holdings of feminist pornographers Gloria Leonard and Candida Royalle, including recently acquired, unprocessed manuscripts and audiovisual materials, were reviewed and described in preparation for student researchers in a seminar on feminisms and pornography to be taught in the 2017 fall semester. A preliminary close reading of a sample of Royalle's extensive run of diaries (1964-2015) was carried out to evaluate the documents' potential research value. The analysis of these archival materials will lay important groundwork for further scholarship on the relatively under-examined era of the American feminist movement.

Class-In-Race: Political and Ideological Tensions Within American Race/Ethnic Groups

Bruno Villegas McCubbin — Harvard College
Social Studies — Class of 2019
Romance Languages and Literatures

Jennifer Hochschild
Department of Government

Mentors
Chris Chaky, Department of Government
Libby Dimenstein, Department of Government

Much political science literature has focused on dynamics between racial groups in metropolitan areas and their effects on policy. However, less research has noted tensions within racial groups. We examine how increasing levels of income inequality have created distinctions in voting patterns, ideologies, and public perception on key issues within races. Moreover, we demonstrate the importance of class and income, rather than shared race, in shaping personal identities and policy stances. To address these intra-racial tensions, we tackle four issues in four metropolitan areas: school reform in Los Angeles; pension reform in Chicago; policing in New York; and housing in Atlanta. In addition to using newspaper articles, scholarly papers, and legislation for research, we interview around forty people per city to glean first-person perspectives on intra-racial tensions and class dynamics. Preliminary data suggest that, in Los Angeles school reform, middle-class district employees are more critical of charter schools than lower-income communities that benefit from charters, but there still may be communities suffering extreme poverty that remain systemically excluded. Our research hints that in New York, most frisking occurs in the lowest-income African-American communities. Furthermore, Atlanta appears to point towards tension between business-oriented minority representatives and their working-class constituents. Taxation policies trying to fund the pension system in Chicago show wealthier individuals against progressive taxation and working-class individuals against regressive taxation. We expect this research will allow us to note more class-based voting, particularly in these local and regional policy settings, alongside studying how political representatives attempt to appeal to those nuances.

Self-Regulation in Youth Psychotherapy

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John Weisz
Department of Psychology

Mentors
Melissa Wei, Department of Psychology
Katherine Corteselli, Department of Psychology

Although there are several empirically-supported psychotherapies for children and adolescents who have mental health problems, relatively little is known about how these therapies work—that is, what processes account for their beneficial effects. One hypothesis is that psychotherapies teach self-regulation strategies that allow young people to consciously influence their thoughts, behaviors, and emotions. For instance, cognitive therapies often teach ways to challenge negative beliefs, and behavioral therapies often teach ways to overcome fears or avoid misbehavior. We are performing a meta-analysis to evaluate the effect of psychotherapies on self-regulation. We are including randomized controlled trials of psychotherapies for young people that measured both clinical symptoms (i.e. severity of anxiety) and self-regulation (i.e. frequency of challenging negative beliefs). We are using the data from these trials to answer two main questions: 1) How effective are psychotherapies at improving self-regulation and 2) Are changes in self-regulation associated with changes in clinical symptoms? Understanding the specific reasons why therapies work may help psychologists to create new therapies and optimize existing ones. If teaching certain self-regulation strategies helps to reduce clinical symptoms, new therapies might prioritize teaching the strategies that have been most effective in past research. Furthermore, identifying the most valuable self-regulation strategies in existing therapies may help psychologists make these therapies shorter and more cost-effective.

Method of Direct Estimation for Causal Inference

Daniel Alpert — Harvard College
Statistics — Class of 2018

Dustin Tingley
Department of Government

The Method of Direct Estimation (MDE) is a machine learning model developed by Harvard professor Dustin Tingley and Princeton professor Marc Ratkovic. MDE estimates the causal effect of a treatment, and unlike ordinary least squares regression, two-step least squares regression (for instrumental variables), or mediation analysis, it is able to consider many variables (on the order of millions) that are both linear and nonlinear. MDE incorporates both variable selection techniques and a Bayesian sparse regression model that allows for causal estimates. As this Method is new to the statistics world, and especially the applied statistics realm, this summer my goal was both to test out the model and to help facilitate better use for others.

I analyzed various data sets to better understand the contexts where MDE is useful and to find limitations in the Method and its R package. For example, I explored the causal effect of oil prices on democracy using out of region natural disasters as an instrument. MDE outperforms classic techniques especially when data sets have a very large number of variables and when these variables are potentially nonlinear. I built a web application with a simple user interface that allows users to learn about and run MDE both to analyze data and to get acquainted with the method. Through the application, users can upload data and compare MDE to more classical methods by viewing diagnostic information. I also helped develop visualizations for the outputs of the method.

There is No Place Like Home: Theory and Evidence on Decentralization and Politician Preferences

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Class of 2019

Michael Kremer
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Ryan Sheely
Harvard Kennedy School

Past research has demonstrated that politicians in a wide range of countries, particularly in the developing world, tend to favor their home region when allocating public resources. To better understand the welfare implications of this phenomenon, we construct a simple model of public good distribution by politicians who exhibit home favoritism. The model suggests that if home favoritism is sufficiently great, decentralizing the allocation of public goods may lead to higher social welfare and less corruption. Various forms of centralization that limit the potential for favoritism in the targeting of public goods may perform well in the absence of corruption, but when levels of both home favoritism and corruption are high, decentralization can increase welfare and decrease corruption relative to these constitutional structures as well. Lastly, the model suggests possible welfare advantages to matching the boundaries of political jurisdictions to the boundaries of geographic or ethnic identity areas. These results point to the mitigation of welfare loss from home favoritism as a possible additional factor to consider in the ongoing debates over decentralization in parts of the developing world.

Harvard College-Mindich Program in Community-Engaged Research (PCER)

Violence Against Transgender and Nonbinary Individuals

Sally Chen — Harvard College
History and Literature — Class of 2019
Studies of Women, Gender, and Sexuality

Caroline Light
Studies of Women, Gender, and Sexuality

This project focused on the disproportionate violence that transgender and nonbinary people face in the U.S. and the difficulties in generating accurate data on their experience of violence. Our research team sought to partner with groups dedicated to transgender advocacy, such as Fenway Health and TransGriot, to ensure the relevance of our work to community action. The framing of inquiries and interpretation of results were all in collaboration with our community partners, who mainly track this violence through media and news sources.

We collaborated with experts from the Harvard School of Public Health to code information from the National Violent Death Reporting System (NVDRS), a database which details every violent death in participating states in the U.S., for both quantitative and qualitative analysis. In the NVDRS, we searched for silences regarding transgender and gender nonconforming people that arise when law enforcement, medical examiners, and coroners are not familiar with the nuances of nonbinary identities and experiences. Officials may not recognize when someone is transgender or will use incorrect language or pronouns in the victim narrative, which generates inaccurate records of transgender and nonbinary people in the NVDRS. Researchers examined geographic and chronological trends in language used by officials when identifying and discussing these populations. Additionally, researchers tracked trends in circumstances that led to homicide and suicide, such as gender-based harassment and assault.

Preliminary results suggest a significant underreporting of transgender deaths both in the NVDRS and in estimates by media outlets and nonprofits. Future directions include generating a recommendation to the CDC to improve the efficacy of the NVDRS and contributing our findings to other organizations tracking violence against transgender and nonbinary people.

Research on Intersectional Violence

Julia Wiener — Harvard College
Studies of Women, Gender, and Sexuality — Class of 2019

Caroline Light
Studies of Women, Gender, and Sexuality

The United States has a significant gun violence problem and the prevalence of guns makes domestic violence, suicide, legal intervention, and other forms of violence even more fatal. There are many factors that place vulnerable populations at risk of violence and isolating one type of oppression (racial, economic, gender) obscures many people with multiple identities and the various complexities of a violent incident. This project looked at these intersecting facets of violence and identity with a focus on community action and raising awareness.

Research questions were rooted in collaboration with partners involved in violence prevention, response, and awareness and their interpretation of social issues and data. Community partners included Violence in Boston, a grassroots organization that addresses the prevalence of violence and related trauma in underserved communities in Boston, and Sodina, an organization that humanizes lethal violence nation-wide through memorialization of individual deaths. In addition to collaborating with community organizations about broad understandings of intersectional violence and gun use, we examined laws related to and efforts to help domestic violence survivors who became criminalized for defending

themselves or their children against their abusive partners.

Rather than aim for a traditional academic publication, this project's goals were to collaborate with partners on their projects and share knowledge throughout the process in the pilot summer of PCER. This collaboration allowed both sides to bring their respective knowledges to the project: our humanist knowledge and academic background and our partners' personal histories with violence and on-the-ground work experience. In the future, I hope to focus on the aspects of our work that involved incarcerated domestic violence survivors, a population disproportionately affected by issues of class, race, and gun use.

Program for Research in Markets and Organizations (PRIMO)

Risk in Preferences, Compensation Design, and Strategy

Alan Castro — Harvard College
Psychology — Class of 2018

Susanna Gallani
Harvard Business School

Mentor
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Executive compensation packages vary in their levels of risk depending on the sensitivity of the compensation amount to the price of the underlying stock. The price of the underlying stock, in turn, is influenced by CEOs' strategic decisions. While equity-based incentives have long been used to align shareholder and agent interests, the literature lacks consensus as to their influence on the riskiness of CEOs' strategy. According to prospect theory, decisions are highly influenced by personal risk preferences, but the compensation literature has not fully explored this relationship. In this study, we will use a laboratory experiment to analyze the moderating effect of a compensation package's riskiness on the relation between individual risk preferences and the riskiness of agents' decisions. Participants will complete a financial risk preferences questionnaire and be randomly assigned to one of four compensation groups varying in payoff sensitivity to performance. In each of five consecutive rounds, participants will select one of three games with random probabilities and known levels of risk. Participants will learn the outcome before making subsequent selections. They will then be randomly assigned to a different compensation plan and play five more rounds with similar modalities. Ultimately, we will examine how compensation risk moderates the influence of personal risk preferences on the riskiness of decisions. If the data corroborate our prediction that compensation riskiness moderates the relationship between risk preferences and strategy riskiness, this study will contribute empirical evidence of how incorporating behavioral measures into compensation design can better align shareholder and manager interests.

The Role of Agile on Innovation

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Agile software development characterizes a product management methodology that is marked by emphasis on rapid iteration, among other features. Agile often manifests itself in the form of stand-ups, or regular team meetings during which members report current progress and delineate tasks to accomplish prior to subsequent stand-ups. Though now commonly adopted by large technological corporations such as Google, Microsoft, and Twitter among others, the potentially hindering effect of Agile's routinely iterative methods on innovation has largely been underexplored.

In this research project, we gathered and analyzed qualitative and quantitative data to better understand the relationship between Agile and productivity and innovation in software development. In a field experiment which took the form of a Google-sponsored hackathon, we collected data from the participating teams, half of which comprised the treatment group and half of which served as the control group. Treatment consisted of a proxy for Agile methodology, executed by Google mentors who routinely conducted stand-ups with their teams while the control groups received generic check-ins at scheduled intervals throughout the event. Using the qualitative data collected by the mentors as

well as tracking each team's activity through online GitHub repositories, we hope to determine whether Agile methodology is as effective in accomplishing its goals as it's largely accepted to be, which may help contextualize the way corporations approach the organizational processes of software development.

Examining the Role of the NIH in Financing Biopharmaceutical Innovation

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The National Institutes of Health (NIH) are the world's largest funder of biomedical research with nearly $32.3 billion spent in 2016. NIH grants reach more than 300,000 individual researches across 2,500 institutions and are often catalytic to major medical and biopharmaceutical innovations. Many have argued that because research is a public good, in the absence of additional funding, certain types of biomedical research would decline to a point below what is socially optimal, a so-called "market failure." Thus, public institutions such as the NIH play an important role in addressing these shortcomings.

This summer, we investigated how NIH funding is allocated. We explored the amount and share of funding provided by the NIH across disease groups and stages of research to understand if grants appear to address private market failures. We used data from the Institute for Health Metrics and Evaluation to calculate disease burden, which can be used as a proxy for market size. In addition, we collected NIH funding data, broken up by disease categories from *Research, Condition, and Disease Categorization Reports* and the *Cortellis Competitive Intelligence Clinical Trials Database* to understand the NIH's role in financing new drugs. With these data sources, we explored two particular situations in which one might expect private market failures to occur: funding for basic science (which leads to the enhancement of public knowledge, but not necessarily large financial gains) and funding for the development of drugs for rare diseases with small patient populations.

Strategy and Innovation in the Direct-To-Consumer Genetic Testing Industry

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In nascent markets, the most fundamental questions—who the customers are, what the optimal business model might be, and what the rules are, for example—are left open-ended. Businesses in these markets must therefore innovate and interact in the face of these uncertainties, and in the process, the businesses have the opportunity to shape and define their industries, rather than the other way around. Perhaps the most notable of such cases are those of Airbnb and Uber: each of these enterprises in essence created a new market where there was none before; instead of having to fend off entrenched incumbents, they had to define from scratch what their products and who their customers would be while fending off pressure from regulators who were equally unfamiliar with the market landscape.

Our project focuses on the direct-to-consumer personal genetic testing industry. Out of the five original major players in this market, three have either opted to exit entirely or been bought out and shut down, unable to outlast the regulatory winter. We thus seek to understand the various factors at play in the successes and failures of these firms, focusing especially on the key strategies and processes each company employed in attempting to overcome business and regulatory uncertainty. Our analysis relies mainly on the qualitative analysis and synthesis of interviews with industry executives and the quantitative analysis of such market metrics as media attention and subscriber data. Our research can be widely generalized to many up-and-coming fields and could guide managers of future startups in navigating uncertainty in their business sectors.

What Skills Are Needed to Equip the Next Generation of Leaders?

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What skills are needed to equip the next generation of leaders? This is a question often debated in the fields of educational, developmental, and organizational Psychology. We developed a business leadership program for underprivileged youth at the Harvard Business School. First, a comprehensive framework and curriculum were modeled through consulting leaders in the fields of Business, Psychology, Law, and Medicine. The program integrates research from each of these fields by distilling best practices in each of these fields. To validate the impact of the program, a 300+ item analytical assessment was created by compiling together various psychometric tools to measure educational impact. These research efforts demonstrated a need for leaders to develop capabilities in order to lead the self and lead others effectively. While leadership research tends to focus on hard or technical skills, we found that a variety of character traits are crucial. These include resilience, optimism, gratitude, self-regulation, and critical thinking. Not only are these skills essential for leadership of others, but also for the improvement of individuals' overall well-being and the equipment of students to contribute successfully to the workforce. Further applications include exploring methodologies of teaching the curriculum and modifying the program to suit individual needs.

Spinoff Transactions Driven by Hedge Fund Activism

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Hedge fund driven shareholder activism is presently one of the most important yet controversial developments in the US business world. Shareholder activists are those who believe that a company's management is doing an inadequate job, and who attempt to gain control of the company and replace management for the good of the shareholders. In the last few years, hedge fund managers such as Bill Ackman (Pershing Square), Carl Icahn (Icahn Enterprises), and Daniel Loeb (Third Point) have become a powerful force in US corporate governance. However, the long-term effects of hedge fund activism are controversial. It has been long debated whether hedge funds obtain private gains through activism at the expense of long-term firm value or if activists can better discipline management to bring long-term company growth.

In this project, we look specifically into hedge fund-driven spinoff transactions over the past ten years. Corporate restructurings through spinoffs have long been a key tool for management to unlock shareholder value. We use both qualitative and quantitative methods to analyze how successful active hedge fund campaigns have been in pushing for spinoffs that provided enhanced strategic focus and more discipline in the allocation of capital. We also aim to shed light on whether hedge fund activism creates long-term value for companies.

Understanding Patent Troll Behavior Through Examination of NPE Personnel

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Non-practicing entities (NPEs)—those who own patents yet do not utilize them to produce future innovation—have had a significant impact on innovators. Rather than practice their patents, NPEs focus on generating licensing fees to which innovators and manufacturers are often prey. NPEs typically receive rights to such patents through either patenting their own ideas or purchasing patents from other inventors. To illustrate, opportunistic NPEs—which critics have labeled as "patent trolls"—amass patents through purchasing large patent portfolios and submit vague patent applications in attempts to secure rights to promising ideas in the near future. Each year, NPEs file excessive lawsuits against innovators. NPEs' disregard for the quality of patents being litigated can be explained by how the present legal system holds defendants responsible for legal fees regardless of NPEs' substantiation of claim. In taking a lawsuit to court, both the NPE and defendant

incur legal fees; however, the defendant's cost is compounded by the lawsuit's duration, which effectively diverts attention from innovation—a significant factor not applicable to NPEs.

In an effort to reduce patent trolling, we seek to first gain a better understanding of those who are behind it: NPE personnel. Through conducting an in-depth examination of their personnel, we hope to gain key insights into how they operate, and ultimately, provide explanation for patent trolls' behavior—a crucial step towards reducing the total amount of patent trolling.

The Value of Health Care Delivery

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As drug and procedure prices rise in America, the contemporary politics of healthcare have not effectively dealt with its accounting and financial system. Currently in American healthcare, the pay-per-service model does little to evaluate a competitive market price for treatment of disease. A competitive healthcare market cannot exist without accurately accounting for the costs of a care cycle and measurable outcomes. Traditionally, providers saw healthcare costs as fixed, but Kaplan's Time Driven Activity Based Costing Method (TDABC), changed that. TDABC involves creating detailed maps that outline the process and time of a care cycle with the cost associated per time unit. Our research spanned hospitals around the world, with my focus at the Massachusetts General Hospital Opioid Bridge Clinic. This revolutionary clinic overdose emergency department alternative functions as a commonly under-insured business model but produces sustainable results. My work has been to build the process maps and perform cost analysis, and collect data from these providers like this and accurately show costs for the care cycle. This accounting data, accompanied with the healthcare outcome standards, set The International Consortium for Health Outcomes Measurement (ICHOM) to provide a competitive and effective service in the healthcare industry. Our research can provide influential data to competitive and fair healthcare policy and systems.

Data Driven Personnel Economics

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With half of Americans having left their jobs due to issues with direct management sometime during their careers, data driven research into managerial economics has become increasingly important. General productivity-enhancing effects of supervisors have been explored in prior literature, but a limited amount of work has been done to pinpoint the determinants of good matches between workers and their supervisors. In order to address the question of matching—differences which are specific to a particular worker and boss rather than the general quality of a supervisor—as well as to investigate boss effects on employee progression within organizations, the study analyzes short-run productivity data of sales-level employees of a large commercial bank matched to different supervisors in the organization.

This project is based on an extremely rich dataset collected during a 5 year period and supplied by the bank. The data contain millions of records, but importantly include information on demographics, education, internal evaluations and performance measures such as salaries, wages, and commissions. During the research, we utilized libraries in the Python programming language (Pandas, SciPy, Matplotlib, scikit-learn) to perform data manipulation, management and exploratory analysis, as well as applied standard statistical tools in order to derive insights from the data. In particular, we are in the process of using machine learning tools to determine which sets of predictors determine extraordinary match quality between bosses and workers. Preliminary results are still in progress, as considerable effort was expended cleaning and manipulating data, but the match effects appear significant. The potential findings are important in increasing employee productivity during their progression within organizations and furthering research in managerial economics.

Strategyproofness in Educational Mechanisms: From Course Allocation to Affirmative Action

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The role of market designers is to examine failures in the processes by which individuals interact with marketplaces and attempt to re-engineer those marketplaces to achieve certain design goals. When designing markets that need to be fair to all participants regardless of their level of information, economists often focus on creating strategyproof mechanisms, where the dominant strategy for any individual is to be truthful about their preferences over courses/schools and there is no incentive to manipulate and game the system by submitting false preferences.

This summer, I focused on the extent to which mechanisms are non-strategyproof by investigating the potential strategic incentives for optimizing an individual's course allocation given any general welfare function under a newly proposed multiple-draw random serial dictatorship mechanism to lottery for classes in the economics department. Separately, I also sought to understand how varying the size of minority reserves in school districts with affirmative action policies impacts the expected loss of strategyproofness in the mechanism by which students are assigned schools. Using Python simulations to model these markets, we studied the expected welfare increases for a lying individual and the structure of manipulative strategies that consistently led to those welfare improvements. In the future, we hope to analytically and empirically study the effects of non-strategyproof mechanisms in larger markets with real data to understand the likelihood and real-world impact of these manipulations given different preference distributions.

Organizational Structure in Private Equity and Venture Capital

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Understanding the determinants and consequences of organizational structure within private equity firms has been a topic of interest to economists. These private investment organizations are responsible for billions of dollars in a single investment, yet there has been little systematic work deciphering organizational structure inside the black box of these firms. Having gathered a database of over 700 private equity funds, we would like to explore the structure of the full organization, in terms of concentration of decision making and economics distribution, and its relation to specific actions of PE funds.

Our premise is that a firm with an organizational structure that allows a direct line of communication from bottom to senior management is more efficient in decision-making and market-timing. In order to make results comparable across PE firms, I first identified a methodology that determines how hierarchical a firm is based on its organizational structure through both literature search and quantitative analysis of our database. The next step is to expand and code data to reflect breadth (number of people reporting to top level management) and depth (number of reporting layers) of the hierarchy within these firms. We then need to examine whether PE firms with flatter organizational structure are better at marketing timing. To capture market-timing, we focus on the timing of the Initial Public Offering, one of the major forms of exit for a PE firm, and assess whether the IPO takes place in a hot issue market, represented by high IPO volume in terms of number of issuers, or in a cold issue market. Future research will focus on substituting IPO information with data on Mergers & Acquisitions, the other major form of exit, to create a holistic view of how firms with different organizational structure respond to market-timing.

VC and PE: Funding Equality

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A common argument is that the main reason that there were many fewer females involved in important decision-making within a company was because fewer female were well-educated compared to men. Today, the education factor is clearly not the reason. However, there is still a very limited number of women entrepreneurs in any industry.

In fact, according to Professor Paul Gomper's study, fewer than 10 percent of start-ups in the tech sector are owned by women, even though recent studies show that women business owners had fewer failures than men. Potential explanations for this disparity include a lack of female mentorship to female founders and female founders receiving less external capital from angel investors or venture capitalists. IFC (a member of the World Bank Group) reports that female-owned small and medium-sized enterprises face a financing gap of $285 billion. A McKinsey Global Institute report found that minimizing the gender gap in labor force participation can add $12 trillion to global GDP by 2025. Our research relates to equality of funding. We plan to do some qualitative interviews with VCs in addition to raw data collection and analysis on existing available dataset.

Moral Discrimination

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Title VII of the Civil Rights Act of 1964 prohibits discrimination in the terms and conditions of employment based on the protected categories or characteristics of race, color, religion, sex, or national origin. The Bona Fide Occupational Qualification provision of Title VII provides an exception for cases in which religion, sex, or national origin is reasonably necessary to the normal operation of that particular business. Thus, some forms of discrimination are actually deemed lawful, causing a blurry line between permissible and impermissible forms of discrimination. For instance, Chinese restaurants are able to hire waiters of Chinese origin to maintain the authenticity of the business. However, in 2007, a hot dog shop was sued and deemed unlawful for trying to hire only White waiters. Evidently, in some contexts, racial discrimination in the hiring of waiters is permissible. It is unclear if these distinctions are influenced by existing stereotypes about what kinds of people typically hold a certain job position. Do people tend to find discriminating against certain races or genders more permissible than discriminating against others, even when the contexts are similar? Do people think that a hospital hiring only female nurses is more permissible, both by the law and their own morals, than a hospital hiring only male nurses? These are the questions that I will be exploring through experiments, testing whether people's general determinations of morality and legality are biased through a preference for behaving congruently with stereotypes.

The Value of Return Migrants and Attracting Human Capital in Nascent Markets

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To study the value of hiring workers with foreign experiences, particularly return migrants, we cleaned and analyzed an employee-wide data set of a large and prominent non-profit in a developing country. Return migrants are those individuals who grew up in the relevant developing country, studied abroad or worked abroad and then returned to the developing country for work. We wanted to see if hiring these workers would increase the firm's knowledge and access to resources and, therefore, its productivity. Relatedly, we also investigated problems of re-integration return migrants faced and how

firms in developing countries with thin labor markets attracted the requisite talent. First, we looked at the Hindu and Muslim return migrant response to exogenous political shocks specific to Hindus or Muslims, such as political coups or religion specific riots. Next, many different algorithms and methods, such as a Google Maps Application Program Interface, which looks up an educational institution on Google Maps and returns the country location, and a frequency gram analysis, were utilized to find the country in which the employee completed their high school or college education. This country location was used to identify return migrants. Since the religion of the employee was not present in the data set, the religion (Hindu or Muslim) of employees had to be inferred from their name. Finally, we studied the history of the developing country in depth to identify political shocks. Although not yet completed, this study's results could have important implications on how to attract human capital to firms in nascent markets.

Gender & Responsiveness to Competitive Incentives

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Within behavioral economics, existing literature on gender and competition has shown that men are more likely to enter competitions than women. However, studies have not shown that men are more likely to maximize utility from these entry decisions. This project adds to current findings by exploring how men and women react to the costs and benefits of competition. The hypothesis that men enter competitions to maximize utility was tested by running a controlled experiment of subjects on Amazon Mechanical Turk. Subjects were asked to solve captchas for several timed rounds. In the first round, subjects chose between a piece-rate and competitive payment scheme. Under the piece-rate payment scheme, subjects would be paid \$0.02 per captcha. Under the competitive payment scheme, subjects were matched with a random, anonymous opponent. If they solved more captchas than their opponent, they were paid \$0.06/captcha; otherwise, they earned nothing. In subsequent rounds, subjects were given an endowment of \$3 and presented with the payment scheme decision and an added incentive: either the subject or the opponent would receive an assured bonus or penalty if they chose the competition. Thus, decision patterns measured how reactive subjects' competitive preferences were to the costs and benefits of competition. Preliminary results indicate that women are more responsive than are men to situational cues in competitive environments. This suggests that women are more likely to change their competition decisions based on increased costs or benefits. These results could shed light on how women's choices to compete in the job market may be driven more by strategy than fear.

Suggested Tipping in Restaurants

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While I participated in a variety of projects related to consumer behavior for the NERD Lab this summer, I also had the opportunity to develop a research idea and start a project. This involved designing the study, preparing the IRB, running the study, analyzing the data, etc.

I specifically examined how suggested tipping amounts impact tipping behavior. I manipulated suggested tipping amounts and examined how much customers actually tip at the end of a check. Previous literature has shown that providing tip recommendations does not influence how much customers tip, but it decreases overall variability. In this study, we had four conditions for suggested tip amounts: a control condition (i.e., no tip recommendation), a 15-20% tip recommendation, a 20-30% tip recommendation, and a 30-50% tip recommendation. Participants were recruited through the online platform Amazon Mechanical Turk (N = 792, 47.4% male, Median(age) = 34.9 years, σ = 11.2) and were asked to complete a five-minute study in exchange for monetary compensation. I observed a significant effect on increasing the suggested tip amount on the actual amount participants gave through an ANOVA ($F(3, 789) = 30.912$, $p < .001$). Thus, these results suggest that companies can in fact alter the way customers tip their employees through suggesting their amounts.

Companies can test this further to see if there is a threshold where suggest tipping amounts are too high and have no effect. Future studies can include varying the price to see if this impact exists for higher prices or just the $20 bill that we provided.

Procurement in Academia

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Academic institutions have struggled in recent years to streamline procurement methods. Procurement divisions are unique in higher education because their responsibilities range from bulk purchasing to supplier contract renewal. The structure of procurement divisions is highly variable, from highly centralized core-decision making divisions to decentralized models. Because each of these procurement divisions also vary greatly in size and structure, there can be many variables that distinguish the most successful procurement systems.

For this study, I make use of interviews of different Boston-area universities to analyze the consequences of key differences in procurement structure and the niche each procurement division provides at its institution. The responsibilities and budget each procurement is responsible for per school is analyzed, with similar sized institutions being cross-compared. In addition to interviewing seven different institutions, I also interviewed various hospitals and local coffee shops to better understand procurement systems in the private sector. Doing so enables a comparison between public and private sectors and the consequences of limiting supplier competition. I observed various procedures, such as cost comparison and contract sharing, that institutions can implement for similar issues found in the private sector, as well as unique results that each solution can obtain. Ultimately, this research may prove useful to uncovering new avenues to improve the operational efficiency for each institution.

Leaders and Institutions That Cultivate Courage in Society

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This project is an exploration of leaders and institutions across various industries that not only act courageously, but also inspire valor and courage among others in society. Before this summer, the project has already accumulated over 20 different narratives about leaders ranging from US Labor Secretary Francis Perkins, who passed the Social Security Act in 1935, to relatively lesser-known local heroes like Father Vien Ngyuen, a Catholic priest who led the reconstruction of a community in New Orleans devastated by Hurricane Katrina. This summer, we are focusing on additional inspiring life stories. We began by exploring the history of Susan B. Anthony, a leading American suffragist in the late nineteenth century, who devoted over half a century to women's rights movements. We are also compiling an account on Dr. Paul Farmer, an American anthropologist and physician who founded Partners in Health, a social justice and health organization. Farmer is known for his humanitarian efforts to provide high quality healthcare to rural parts of the developing world, particularly in Haiti, for the last three decades. In looking at courageous leaders, we are trying to better understand what tools leaders use to drive social movements in society. On the institutional side, we are exploring the strategies the Marine Corps uses to encourage courageous action amongst its troops. We have found that the Marine Corps, in particular, inculcates a strong sense of Marine culture and courageous action, traits that stay with Marines for the rest of their lives. We wish to understand the implication of this strong, unique culture on Marine lives.

Program for Research in Science and Engineering (PRISE)

Astronomy and Astrophysics

Active Optics Subsystems Tests for the Giant Magellan Telescope

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The Giant Magellan Telescope (GMT) aims to be the first of a new class of Extremely Large Telescopes and will employ seven 8.4 m primary mirror segments and seven 1 m secondary mirror segments to achieve the diffraction limit of a 25.4 m aperture. In order to maintain image quality, an active optics system is employed to sense and control mirror position and curvature. The active optics system design consists of four moving probes that analyze a sliver of incoming light by passing it through optics leading to visible and infrared cameras. We present the initial results of five projects designed to test the accuracy and feasibility of various components of the GMT active optics system. 1) We employed an infrared camera to confirm that the lab's cleanroom curtains are opaque at infrared wavelengths to a 0.1% confidence and therefore are a suitable for testing the active optics system. 2) We tested four types of proximity sensors by simulating crashes to determine the best system for avoiding collisions between moving probes. 3) To optimize active optics speed, we characterized the latency (delay time) in three cameras by observing controlled light pulses. 4) We observed a calibrated test-optic to determine if an optical rotation stage rotates to our prescribed 0.4° level of accuracy. 5) We observed a light source with a camera at several different rotations to determine if a visible wavelength camera is equally precise at any orientation. The results of these experiments will allow the GMT team to proceed in constructing the active optics system with confidence in the safety and accuracy of various key subcomponents.

Searching for Stellar Surface Activity in Solar Spectra

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The radial velocity (RV) method of exoplanet detection exploits Doppler shifts in stellar spectra induced by gravitational interactions with orbiting planets. Noise due to star surface magnetic activity, which exceeds 1 m/s, presents a barrier to the detection of earth-like exoplanets, which demands RV precision of under 10 cm/s. The sun, as the only star whose surface we can resolve, provides a unique test case for reducing this activity threshold. We analyze our own sun as a star by correlating measurements of disk-integrated solar spectra, performed with a small solar telescope and the HARPS-N spectrograph, with magnetic activity indicators extracted from high-resolution Solar Dynamics Observatory (SDO) images of the sun's surface. In order to apply these findings to the exoplanet search, however, proxies for magnetic activity must be found directly from spectral measurements. The relative abundance and magnetic sensitivity of iron line absorption features make these lines a suitable target for correlating spectral shifts and distortions with surface activity.

HARPS-N measurements of Fe I lines between 450-680 nm were fit with various parameters to reflect changes in the line core, wings, and overall asymmetry. Correlating these fit parameters with SDO-derived activity indicators reveals sets of lines that

appear to respond either thermally or magnetically to surface activity. These correlations improve our understanding of the atomic and solar physics mechanisms behind line-shape distortions, and may aid in recovering surface activity directly from stellar spectra. Such spectroscopically derived activity indicators would reduce RV-measurement noise, advancing the search for earth-like exoplanets.

Biomedical Engineering and Science

A Strategy for Engineering Temperature-Inducible Proteins Applied to dCas9

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Across all domains of life, organisms have evolved temperature sensing mechanisms to survive in dynamic environments. In recent years engineers have sought to adapt these natural temperature sensors to design cells which can respond to a temperature input. This can be used to facilitate gene expression studies or allow engineered microbes to respond to temperature changes in the body, like fever. While some systems exist that can modulate the expression of a single gene in response to temperature, better tools are needed for to allow arbitrary proteins to be toggled on and off with temperature for faster, more customizable design of temperature-responsive cells.

This study aims to extend the toolbox of temperature responsive systems by engineering catalytically dead Cas9 (dCas9), the gene-editing protein of the CRISPR system, to programmably repress target genes in response to temperature. To achieve this, we designed a library of dCas9 fusions with domains collected from natural temperature sensitive proteins. We aim to screen this library with fluorescence-activated cell sorting for temperature inducible variants, which can be further characterized. We hope a temperature responsive dCas9 could have applications in tight regulation of gene therapy and that this strategy could be applied to other proteins, facilitating the use of temperature as a signalling modality.

Overcoming Die Swell to Decrease Hyaluronic Acid Nanofiber Diameter Variability

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Die swell is the tendency for a viscoelastic material to swell to a size greater than the die diameter it was extruded from. It poses an array of problems for polymer processing, including increasing the variability of Hyaluronic Acid (HA) nanofiber diameter. To overcome the issue of die swell of Hyaluronic Acid, my research focused on finding optimal die geometry, in terms of shape, length, and aspect ratio, and applying these conditions to the Parker Lab's *immersive Rotary Jet Spinning (iRJS)* technology used to spin HA and other viscoelastic fluids at high speeds (5-15k RPM). By applying optimal conditions—in particular, orifices of a relatively large ~2 mm diameter—to the *iRJS* system, we thought we could reduce die swell of HA and decrease variability of HA nanofiber diameter. To test this hypothesis, I first quantified die swell of HA in a controlled system, using a range of needles of varying properties including material, die diameter, length, and shape. Following this, I performed high speed camera analysis of die swell of jets extruded from varying orifice diameters, as well as scanning electron microscopy of fibers spun from these dies. Results demonstrated that fiber size is not a function of orifice diameter, due to an increase in die swell with decrease in orifice size. Thus, a larger orifice diameter would decrease die swell and enable a greater consistency of fiber diameter.

Optimization of an Enzyme-Linked Immunosorbent Assay for the Detection of Cis P-Tau

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Mentor
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Alzheimer's disease (AD) is now the sixth leading cause of death in the United States and third leading cause of death for older people. Treatments currently being developed could halt or slow the progression of AD; however, most patients are not diagnosed until extensive atrophy and loss of cognitive function have already occurred. A key to solving this problem may lie in the tau protein. Elevated levels of hyperphosphorylated tau are one of the earliest signs of many neurodegenerative diseases and the progression of degeneration and cognitive decline closely follow the spread of phospho-tau pathology. Recent studies have suggested that phospho-tau monomers in the *cis* conformation may be the source of tau toxicity. The purpose of this study was to develop and optimize an assay that can detect cis p-tau in human cerebrospinal fluid. An enzyme-linked immunosorbent assay (ELISA) was chosen for its ability to detect proteins in their native conformation. Various antibodies and setups were tested to find an optimized system which maximized tau signal while minimizing background signal and cross reactions. The sandwich ELISA setup was chosen, as the use of 2 antibodies to detect the protein made the assay far more specific for *cis* p-tau. Additional studies will be needed to further decrease the background signal and detect extremely low concentrations of tau more easily and accurately. If optimized, this assay could serve as an invaluable tool in assessing and diagnosing tau-associated neurodegenerative disorders at earlier stages when preventative treatments may be effective.

Combination Therapy of an Oncolytic Herpes Simplex Virus and a DNA-PKcs Inhibitor in Glioblastoma Cells

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Glioblastoma, one of the most common types of brain cancer, is a condition with no current treatment. Like most cancer cells, glioblastoma cells divide very rapidly, and their DNA replication is very error-prone. If the errors in DNA replication accumulate as unrepaired DNA damage, the glioblastoma cells will die. One particular detrimental form of DNA damage is a double-stranded break (DSB), in which both strands of DNA are broken, and the DNA fragmented in two. A DSB is usually repaired through one of two pathways: the homologous recombination (HR) pathway, and the non-homologous end joining (NHEJ) pathway. Cancer cells can survive DSBs by relying on these pathways. Two potential methods of blocking these pathways selectively in cancer cells are the use of oncolytic herpes simplex viruses (oHSVs) and the use of DNA-PKcs inhibitors. oHSVs block the HR pathway, and DNA-PKcs inhibitors block the NHEJ pathway. When either of these therapies is used alone, the cancer cells can survive by activating the other pathway. This project hypothesizes that blocking both pathways by using the two therapies in tandem leads to an accumulation of DSBs and, eventually, the death of the cancer cell. To measure cancer cell viability, glioblastoma cells were treated with different combinations of oHSVs and DNA-PKcs inhibitors, and assessed for viability with MTS assays. To measure the changes in response of the virus and the inhibitor, dose-response analyses were performed. Finally, to analyze synergy of the therapies, the combinations were assessed with the Chou-Talalay method.

CRISPR Cas9 Depletion of Abundant Human Background for Sequencing Infectious Pathogens

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A crucial effort in infectious disease treatment and prevention is establishing effective diagnostics and genetic surveillance of pathogens. While there exist many ways to selectively diagnose known pathogens, there are relatively limited ways to characterize unknown infections.

Because viral DNA is present in a patient's genome in small quantities, sequencing a whole-blood sample with Next Generation Sequencing would not provide substantial information about the pathogen, as most reads represent background information from the host's genome. Obtaining a higher viral sequencing yield requires the depletion this background while preserving the pathogenic sequence.

This can be accomplished using CRISPR-Cas9, a promising development that can target and cut specific genomic sites. By designing guides targeting sequences in conserved regions of the human genome, we can degrade regions known to be nonviral, in order to increase viral concentration and consequently, viral reads.

We constructed sequencing libraries containing Enterovirus spiked into common bacterial sequencing contaminants *Ralstonia insidiosa*, *Cupriavidus metallidurans*, and human plasma. We designed sgRNA sequences targeting the bacterial/human regions for Cas9 to degrade and increase Enterovirus reads. To determine optimal depletion conditions, we tested a range of Cas9 and sgRNA concentrations. Sequencing results can communicate the efficiency of each sgRNA sequence. To control for amplification differences between guides, the sgRNA oligo pool was also sequenced.

Preliminary results suggest that after Cas9 incubation, sample concentrations were undetectable; we confirmed presence of DNA after qPCR amplification. This could potentially imply successful depletion, though this will be clearer after sequencing. Preliminary sgRNA sequencing results suggest guides of approximately 50% GC content displayed highest amplification.

This depletion approach can lead to earlier diagnosis of unidentified pathogens and effective genomic surveillance, allowing for targeted and effective treatment. Consequently, this harbors great potential in preventing viral outbreaks around the world.

Protein Corona Pattern Recognition for Novel Coronary Artery Disease Diagnosis

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When nanoparticles (NPs) come in contact with biological fluids (plasma), the attract plasma proteins to their surfaces, forming protein coronas (PCs). The PCs adsorbed on the NPs give them a completely different biological identity, altering charge, size, affinity, and aggregation state. The composition of the PCs depend on both the properties of the nanoparticle and the condition of the biological fluid. Since pathological conditions change the plasma proteome, they will also alter the PC composition. In this work, disease-specific PCs were used as proteomic biomarkers and as a diagnosis tool. A sensor array nano-system of six different nanoparticles was developed to analyze the PC composition differences for coronary artery disease (CAD) using statistical analyses such as Partial Least Square Regression and Principal Component Analysis. The developed system successfully detected CAD in plasma of affected patients, presenting a valuable alternative to the current invasive method of CAD detection. This promising result also opens doors for the usage of disease-specific PCs as a diagnosis tool for many more conditions that are difficult to detect.

Hydrogels as Agents for Delivery of Ultra-high Concentrations of Antibiotics in Burn Wounds

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There is a critical unmet need to improve treatment of severe face and extremity battlefield burns, particularly when definitive treatment is delayed. While intravenous and oral delivery of antibiotics and traditional wound dressings are simple to use, attaining targeted and controlled release of drugs as well as minimizing infections become very difficult in severe cases. Oftentimes, efficacy of antibiotic treatment intravenously competes with the deleterious side effects and toxicity of high drug concentrations. In this study, we developed Alginate-$CaSO_4$ hydrogels as high-concentration antibiotic delivery vehicles to be incorporated in a revolutionary new Platform Wound Device (PWD), a sterile transparent enclosure that can be applied immediately after burn injury to provide a protective dressing. Common burn-treatment antibiotics such as Minocycline, Gentamycin and Vancomycin, were incorporated at 10X, 100X, and 1000X their respective EC50 in the hydrogels and their release profiles studied over a course of five days using Liquid Chromatography Mass Spectroscopy (LCMS.) Rheology studies were also done to observe the visco-elastic and flow properties of the hydrogels. Lastly, Differential Scanning Calorimetry (DSC) was employed to study the long-term stability of the hydrogels at low and high storage temperatures. Preliminary results suggest alginate hydrogels with $CaSO_4$ concentrations between 0.5 and 0.8% exhibit desirable physical properties like viscoelasticity, flowability and temperature stability when made with Carboxymethylcellulose additives. These engineered hydrogels followed a zero-order antibiotic release, where about 80 - 100 μg/ml of the antibiotics is released in the first 24 hours and remains fairly constant for four days. With the aforementioned formulations, Ca-alginate hydrogels were able to effectively and safely deliver antibiotics at doses significantly higher than those administered orally or intravenously.

Optimized Production of Antimicrobial Peptides Using *E. coli* Curli Nanofibers

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Antimicrobial peptides, or AMPs, provide a promising alternative to traditional antibiotics, as their mode of action does not foster antibiotic resistance. However, chemical synthesis of industrially relevant molecules is often accompanied by various environmental hazards. Biological synthesis, on the other hand, does not produce any toxic byproducts, nor does it require expensive starting materials. Furthermore, both naturally occurring and synthetically designed antimicrobial peptides can be expressed relatively easily in microorganisms.

Our project focuses on using curli fibers, the main proteinaceous component in *E. coli* biofilms, as the platform on which to biologically synthesize antimicrobial peptides. The secretion and self-aggregation mechanisms of the curli fibers are well documented, as is the potential for fusing functional proteins to the curli fiber monomers while retaining both the curli fibers' aggregative properties and the protein fusion's function and structure. In anticipation of potential obstacles, which include inducing toxicity in the host cell and limiting functionality of the fused AMP, we will be using a library approach to screen a wide variety of antimicrobial peptides. In addition, we aim to scale up production of the curli-AMP fusion to industrially competitive standards through a combination of pathway, systems, and process optimization. Our findings will inform the manufacture of not only other antimicrobial peptides fused to curli fibers, but also a variety of other functional proteins as the optimized production pathway is applicable to any curli fusion.

A 3D Printed Bioreactor for Inexpensive Bioproduction Optimization

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Controlling the biological production that results from the transcription and translation of recombinant DNA enables researchers to synthesize substances that would otherwise be difficult to obtain. Widely-available methods exist that provide sufficient production for most small-scale research applications. Specifically, shaker flask cell culture techniques create a suitable environment for cell proliferation by agitating cells suspended in media in a flask However, shaker flasks cannot maintain the optimal environment for bioproduction. Well-resourced labs can access expensive tools that can produce higher yields through better environmental control. However, to support the advance of synthetic biology, it is increasingly important to provide access to low-cost, high-efficiency methods for effective bioproduction. This access will allow researchers to obtain sufficient quantities of bioproduced substances to explore their applications.

To help fulfill this need, I am working on a 3D printed bioreactor which will provide a cheap way for researchers to cultivate bacteria in ideal conditions for bioproduction. By maintaining an empirically determined ideal environment for bioproduction (controlling temperature, pH, media composition, etc.) cells will produce the desired substance more effectively that those cells would in a shaker flask.

Oxygen concentration in the culture is a known limiting factor in bioproduction. DO concentration is driven by the mixing induced by fluid flow within the bioreactor as well as the method of aeration. We predict that by increasing agitation in the culture without inducing shear on the cells, we can achieve more efficient bioproduction. By measuring DO in the culture chambers while iterating through different dimensions for the structural components that impact agitation (including culture chamber diameter, baffle dimension, impeller size and RPM), we can enable more efficient cell culture for bioproduction.

Carbohydrate Intake and Its Effects on HbA1c in a Population Sample of Patients With Insulin-Dependent Diabetes

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In a survey study, our group has observed excellent glycemic control in a self-selected cohort of patients with insulin-dependent diabetes mellitus (IDDM) following a very-low carbohydrate diet (< 50 g/day). The efficacy of such diets for IDDM is poorly understood, but benefits are physiologically plausible because limiting carbohydrate decreases postprandial blood glucose excursions, and thus insulin requirements. This analysis aimed to determine the effect of carbohydrate intake on glycemic control in IDDM in a population-based dataset. NHANES surveys from 1999-2014 were analyzed by ANOVA to determine if there were significant differences in HbA1c between Low (n = 24, < 26% kcal/day), Moderate (n = 416, 26-45% kcal/day), and High (n = 675, > 45% kcal/day) carbohydrate intake in IDDM. Multiple linear regression evaluated the effect of carbohydrate intake on HbA1c. Carbohydrate was the primary predictor with typical confounders as covariates. Mean HbA1c for Low, Moderate, and High intake were 7.904% ± 1.615, 8.236% ± 1.866, and 8.381% ± 2.000 respectively. ANOVA reported an F-statistic of 1.209 (p = 0.299). The significant predictors in the model were absolute carbohydrate ($t = 2.42, p = 0.02$), age ($t = -5.82, p \leq 0.001$), BMI ($t = -2.91, p = 0.004$), total cholesterol ($t = 8.92, p \leq 0.001$), and fiber ($t = -2.18, p = 0.02$). Multiple R^2 was 0.1485. Each gram of carbohydrate was associated with a 0.002% increase in HbA1c. Significantly lower HbA1c was not found in the Low intake group as predicted, but carbohydrate did positively correlate with HbA1c. The study had limitations in sample size, single day dietary info, and wide carbohydrate ranges. The significant predictors reiterate the multifactorial nature of diabetes control. Further studies may be warranted to reconcile the findings in our self-selected cohort and this analysis.

Programming Commensalistic Gut Bacteria to Be Living Diagnostics of Inflammatory Bowel Disease

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Inflammatory bowel disease is a chronic condition that can cause severe abdominal pain, diarrhea, and other disabling complications. Currently, the primary method of diagnosis is by invasive colonoscopy. This study aims to develop a noninvasive diagnostic: a strain of commensalistic *E.coli* engineered to safely live in the gut and report the presence of inflammatory markers. These bacteria detect signals through a genetic circuit composed of two primary elements: a trigger and a memory. The trigger consists of an inflammation-activated promoter that upregulates a downstream gene and the memory element is activated by the protein produced by the trigger to upregulate a reporter gene, in this case lacZ.

To construct the trigger elements, nine inflammation-sensitive promoters were identified from a literature review. DNA synthesis techniques and Golden Gate Assembly were used to create a library containing the promoters and 11 different ribosome binding sites to vary sensitivity. The library was transformed into the probiotic strain, *E. coli Nissle 1917*, and integrated into the bacterial genome using Tn7 integration. The remaining promoters, napF and torCAD, were individually cloned. These latter two promoter variants are activated by two molecular inflammation signals, nitrate and TMAO respectively, and will be tested *in vitro* in high concentrations of each to confirm that each promoter responds to their respective signal.

Further steps include orally gavaging these *E. coli Nissle 1917* strains into mouse models for *in vivo* testing. A mouse cohort will be fed dextran sulfate sodium to induce gut inflammation, and the *E. coli* in their fecal matter will be plated and sequenced to validate the function the genetic circuits.

The Role of Mechanotransduction in Cancer Stem Cell Behavior: Cell Encapsulation in Tunable Hydrogels

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Tumor microenvironments (TME) play key roles in promoting tumor progression. Specifically, physical properties of TME such as extracellular matrix (ECM) density, cross-linking density, and stiffness affect tumor growth and malignancy. However, little has been known whether and how these physical properties can influence the cancer stem cell population. Cancer stem cells (CSCs), a tumor initiating population among heterogeneous cancer cells, cause poor clinical outcomes due to therapy resistance. Therefore, understanding which physicochemical cues from CSCs niches aid in maintaining CSC population is essential for combating cancer. Thus, we aim to investigate how physical properties influence CSC behavior by utilizing collagen-alginate interpenetrating network (IPN) based 3D scaffolds. This summer, we focused on optimizing our material systems and characterizing CSC population among malignant breast cancer cell, MDA-MB231. First, we aimed to mimic the physical properties of mammary TME as compared to normal mammary tissue. To achieve the stiffnesses (<500 Pa for normal mammary tissue vs. ~5 kPa for mammary tumor) of our collagen-alginate IPN, we altered concentration of alginate and calcium concentration. To change the crosslinking types of alginate from ionic to covalent crosslinking, we used click alginate, which can form covalent crosslinks via tetrazine-norbornene chemistry. In addition, we characterized CSC population from cancer cells based on their surface markers (CD44+/CD24-/CD133+/ESP+/Nanog+) via flow cytometry, immunofluorescence, and image analysis. Then, we isolated CSCs based on the their markers and incorporate them into the 3D scaffolds with varying stiffness and a type of crosslinking, and analyze for the behavioral changes. In the future, we hope to further elucidate the role of physical cues in regulating CSC behavior so that we can develop new therapeutics to target not just the cancer cells but also their microenvironment.

Chemistry and Biochemistry

Development of New Drug and Chemical Linking Strategies for Antibody Drug Conjugates (ADCs)

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Delivery of drug molecules to desired targets is of utmost importance for maximizing efficacy and minimizing off-target toxicity. Currently, cancer patients receive chemotherapy that affects both malicious and healthy cells, leading to universal damage throughout the body. Antibody drug-conjugates (ADCs), composed of an antibody linked to a drug molecule with a chemical chain, have the potential to deliver cytotoxic drugs specifically to cancer cells that express unique receptors recognized by the antibody. This targeted drug therapy can minimize the undesired and harmful side effects of currently available cytotoxic chemotherapies. In the early stages of this project, novel drug compounds with previously unexplored DNA cleavage functional groups were synthesized. The novel compounds were then tested for efficacy on cellular lysates of bacterial DNA. This process entailed optimizing visualization of DNA cleavage bands in gel electrophoresis before optimizing the comparison of efficacy. Preliminary results suggest current compound candidates are cleaving DNA as predicted. Once the potency and effectiveness of the candidate compounds are optimized, the compound candidates will be tested with cell kill assays in tissue culture and mass spectrometry analysis. Potent drug candidates will be attached to an antibody via chemical methods developed by the group. Future success of this project will create new ADC combinations that could potentially be further explored in animal and clinical studies. This project contributes to medicinal chemistry and drug therapy through the introduction of new linking methods for ADC development, potentially leading to new ADC drug treatments for cancer patients.

Efficient Syntheses of Methyltransferase Inhibitors: A Concise, Gram-Scale Synthesis of Sinefungin

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Methyltransferases are a large class of enzymes that methylate their target substrates. While this process, in general, is crucial for genetic regulation in cells, anomalous methylation is linked to many life-threatening conditions including cancer, obesity, and diabetes. For this reason, methyltransferase inhibitors are promising candidates in drug discovery research. Sinefungin is a naturally occurring, pan-selective, competitive methyltransferase inhibitor. Without any inherent selectivity, sinefungin is not a good drug candidate on its own, but when modified, it can lead to selective methyltransferase inhibitors that target only the enzyme of interest without disrupting essential cellular processes. However, current synthetic routes to sinefungin require more than twenty steps, generate only milligram quantities of material, and are not readily amenable to analogue synthesis. My project aims to synthesize sinefungin on a gram-scale large enough to perform synthetic modifications and subsequently test the viability and efficacy of the novel sinefungin analogues as selective methyltransferase inhibitors. Using techniques developed in the Shair Lab on related methyltransferase inhibitor syntheses, my project utilizes robust synthetic organic chemistry methods to synthesize sinefungin from affordable, commercially available starting materials. Upon completion, we expect our strategy to shorten previously published synthetic routes by up to eight steps. Our synthesis is cost-conscious, time-conscious, and will accelerate the rate of discovery of drugs that target methyltransferases.

Synthesis of N3′-P5′-linked Phosphoramidate Oligonucleotides

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The RNA World hypothesis is integral to the question of the origin of life. It postulates that on a primitive Earth, RNA—or a chemically similar precursor—acted as the predominant information carrier and catalyst in protocells. Primordial RNA molecules would have initially replicated in a world without polymerases, but non-enzymatic replication of arbitrary RNA sequences remains challenging. A close chemical analog of RNA, N3′→P5′ phosphoramidate DNA (NP DNA), can be copied more efficiently, and this alternative genetic polymer might allow for the development of model protocells in the laboratory.

To this end, we are developing a novel synthetic strategy for NP DNA oligonucleotides. Traditionally, phosphoramidite chemistry has been used for the synthesis of DNA and RNA oligonucleotides on solid supports. However, the corresponding pathway for NP DNA, which utilizes an amine-exchange coupling reaction, has yielded mixed results. Instead, we are developing an alternative coupling chemistry for solid phase synthesis of phosphoramidate oligonucleotides. This synthesis cycle will make use of a new set of reactive monomers, which will be polymerized to yield NP DNA oligonucleotides of arbitrary sequence on an automated chemical synthesizer. Thus far, I have focused on synthesis of the protected adenosine and thymidine monomers from the corresponding 3′-amino-2′,3′-dideoxynucleosides. I have also been optimizing flash chromatography purification conditions to maximize the yield of activated monomers.

Bacterial Outer Membrane Synthesis and Antibiotic Combination Therapy

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Gram-negative bacteria have an outer membrane (OM) that makes them impermeable to many small molecule antibiotics. We are interested in studying this membrane to identify novel antibiotic targets. The OM contains an asymmetric lipid bilayer with molecules of lipopolysaccharide (LPS) on the outer leaflet and phospholipids on the inner leaflet. LPS is transported to the OM by the LptBFGCADE protein complex. LptBFG is an ATPase that provides the energy for the transport of LPS to the OM. I overexpressed, isolated, and purified proteins using state-of-the-art affinity purification technology. Then, I tested the activities of these proteins by measuring the rate of ATP hydrolysis *in vitro*. I also purified LptB mutants for X-ray crystallography, a tool we used to visualize the structure of the protein variants.

Furthermore, I investigated antibiotic combination therapy for the treatment of pathogenic gram-negative infections. Many antibiotics are highly toxic, and combining multiple antibiotics can lower the dose required to fight infection. I investigated the mechanism of action of a particular case of antibiotic synergy, in which the effect of two antibiotics combined is more than the sum of their separate effects. I did *in vivo* studies using antibiotics for humans as well as several derivatives I synthesized. These studies tested the scope of this synergy in several species of bacteria, including *Escherichia coli*, *Acinetobacter baumannii*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, which constitute a significant portion of hospital acquired infections.

Modular Synthesis of a Non-Cleavable PEG Linker for Protein- Drug Conjugation via HaloTagTM Covalent Linking

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As the field of Chemical Biology continues to expand and develop new molecular machinery, customized linkers are becoming more prevalent. One common use of linkers is in the process of antibody drug conjugation (ADC). In an ADC system, linkers are used to connect an antibody to a specific drug of interest to increase the efficacy of the drug. The study of ADC systems has led to the creation of both cleavable and non-cleavable linkers that are utilized according to the project's needs. In this study, we are developing building blocks for the modular synthesis of a non-cleavable linker in order to link a drug of interest to a protein of interest. This is similar to ADC; however, we deviate from the standard linking of an antibody to a drug. Instead, we are developing the linker such that it can link a drug to a desired protein via HaloTagTM covalent linking.

Developing Biocompatible Polymer Electrodes to Grow Plants in the Dark

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Within the chloroplasts of plants, photosynthesis uses sunlight and water to create oxygen and energy-storing molecules (e.g. ATP, NADH). These energy-storing molecules power the Calvin Cycle to transform atmospheric carbon dioxide to glucose and more plant material. Despite the abundance of sunlight and water in the environment, photosynthesis is a very inefficient process, only capturing < 1% of available solar energy. Integrating high-efficiency photovoltaic-derived electricity with the Calvin Cycle and bypassing a plant's dependence on sunlight could increase energy efficiency and represent a new paradigm to increase global food production for an ever-growing population.

This project works to develop biocompatible polymer electrodes that facilitate NADH and ATP production inside cyanobacteria: a free-living, functional analog for chloroplasts. Synthetic dyes can act as biocompatible electrocatalysts for the regeneration of NADH, or membrane-associated quinones, which both drive the biological production of ATP in cyanobacteria. Creating electrodes with polymerized dye molecules that pass through the cell membrane of immobilized cyanobacteria could facilitate significant NADH production by mimicking natural transmembrane proteins and providing a direct conduit between the electrode and the cyanobacterium. To do this, I have fabricated electrodes based on polymerized lipophilic dyes. The design of this polymer incorporates hydrophobic stability in the cyanobacterium phospholipid membrane, and redox potentials to promote catalytic interactions with ATP-generating proteins. These polymer-cyanobacteria electrodes have been characterized with a suite of electrochemical and spectroscopic techniques, and push the field towards growing plants at higher efficiency or even in the dark.

Discovery and Characterization of Histone O-GlcNAcylation sites

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Epigenetics is the study of the mechanisms by which gene expression is affected by factors other than the genetic code. Often these changes in expression are mediated by post-translational modification (PTM) of histone proteins. Histones form complexes known as nucleosomes, which DNA wraps around. The degree of compaction of the nucleosome affects the accessibility of DNA, and therefore its ability to be transcribed. The compaction status of nucleosomes is changed by PTMs on histones. Many of these modifications are well characterized, but a recently discovered modification by a carbohydrate, N-Acetylglucosamine (GlcNAc), is less understood.

Currently, there is disagreement about which specific sites on histone proteins are being modified with GlcNAc. Furthermore, for many of the modified sites, the consequence of the modification is not known. To elucidate the modification sites and their effects on epigenetics, a fusion protein GlcNAcylation tool is being developed whereby a nanobody, which can recognize specific proteins, is conjugated to O-GlcNAc transferase (OGT), the enzyme responsible for attachment of GlcNAc to proteins. Using this tool, specific proteins such as histones, can be targeted for GlcNAcylation to selectively increase glycosite occupancy on the protein of interest. This tool, in theory, can be utilized to more effectively detect GlcNAcylation sites, which are more likely to contain the sugar modification after exposure to the nanobody-OGT construct. Importantly, the tool can also be used to cause specific proteins to be GlcNAcylated, meaning the larger consequences of the modification of specific proteins with GlcNAc can be tested with regard to processes such as the cell cycle.

Autotitration as a Project-Based Learning Opportunity

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Based on the current desire for automation and increased use of technology within the classroom, our teaching team synthesized chemistry, programming and electronics to develop a project-based learning opportunity for undergraduate chemistry students at Harvard University. The students developed an automatic titration machine that obtains pH data from the titration and computes relevant values based on the generated curve. A series of pumps transport acid and/or base into a beaker while a pH meter automatically stores the data. The titration curve is analyzed to determine the equivalence points and subsequently the concentration and Ka(s) of the unknown solution. The students programmed on a Raspberry Pi computer with the coding language Python to develop the protocol for the experiment. The teaching fellows gave the students an unknown acid, which they had to analyze with their developed protocol and programs. The learning application of this exercise was to create a project that integrates several important educational concepts with the familiar lab experiment of titration.

Biosynthesis of L-Alanosine by *Streptomyces alanosinicus*

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Nitrogen-nitrogen (N–N) bonds in organic molecules comprise less than 0.1% of known natural products. However, this linkage is featured disproportionately in pharmaceutical drugs. With approximately 10% of FDA approved chemotherapeutics containing a N–N bond, it is believed that the N–N bond may be a privileged moiety in drug design. L-alanosine is one such molecule that has been investigated as a therapeutic for late-stage pancreatic cancer in phase II clinical trials. As part of a larger effort to fully characterize the biosynthesis of L-alanosine by the bacteria *Streptomyces alanosinicus*, this project focuses on characterizing a pair of enzymes, AlaA and AlaB, within the putative L-alanosine biosynthetic gene cluster. With reference to previous studies, it is hypothesized that the PLP-dependent AlaA and NADH-dependent AlaB consume the metabolites O-phospho-L-serine and L-glutamic acid to form α-ketoglutarate and L-2,3-diaminopropionic acid (L-DAP) via N-(1-amino-1-carboxyl-2-ethyl)-glutamic acid as an intermediate. The generation of L-DAP is proposed to be the initial step in the biosynthesis of L-alanosine. The characterization of AlaAB would confirm our hypothesis and allow for the in-vitro chemoenzymatic reconstitution of radioactively labelled L-DAP for the elucidation of subsequent biosynthetic steps. So far, only few instances of N–N bond formation by enzymes have ever been confirmed within the field; in particular, the enzymatic catalysis of the N-nitroso N–N bond featured in L-alanosine has never been documented. Thus, demonstrating the biosynthetic mechanism of the formation of L-alanosine could prove to be incredibly useful for drug development in the future.

Computer Science

Simple Proof of Sparse, Sign-Consistent JL

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In many modern algorithms, which process high-dimensional data, it is beneficial to pre-process the data through a dimensionality reduction scheme preserving the data's geometry. Dimensionality reduction schemes have been applied in streaming algorithms, numerical linear algebra, and graph sparsification. One of the main results that drives dimensionality reduction schemes is the Johnson-Lindenstrauss lemma, which proves the existence of a Euclidean-norm-preserving probability distribution over linear maps into a low-dimensional space.

Dimensionality reduction schemes also have relevance outside of algorithms; for example, in neuroscience. In convergent pathways in the brain, information stored in a massive number of neurons is compressed into a small number of neurons, and nonetheless the ability to perform the relevant computations is preserved. A plausible minimum requirement is that convergent pathways preserve the similarity structure of neuronal representations at the source area, which gives rise to dimensionality reduction schemes as a model for neural information compression. The biological limitations of neurons impose two main constraints on the underlying dimensionality reduction scheme: *sparsity*, since a neuron is only connected to a small number of postsynaptic neurons, and *sign-consistency*, since a neuron is usually purely excitatory or inhibitory.

In the context of these constraints, Allen-Zhu, Gelashvili, Micali, and Shavit constructed and analyzed a modified Johnson-Lindenstrauss distribution restricted to sparse, sign-consistent matrices. However, their analysis requires a complicated combinatorial graph-based argument. We present a simple, combinatorics-free analysis that yields the same dimension and sparsity guarantees as the original analysis. Our proof also yields dimension/sparsity trade-offs, which were not previously known.

Securing Smartphone Apps Using Hardware-Only Isolation Primitives

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Smartphones are the primary computational device for many individuals, and frequently execute programs that manipulate sensitive data. To help safeguard this data against attackers, modern devices can support both a general-purpose rich execution environment (REE) and a security-crucial trusted execution environment (TEE). Device manufacturers often rely on a combination of hardware-assisted virtualization and software-based virtual machine monitors (VMMs) to isolate these EEs. For example, a number of processors restrict EE access to a subset of CPU registers and tag secure data. Nonetheless, a VMM is generally trusted to manage context switches and possible interactions between EEs. Any vulnerabilities in the VMM could compromise EE isolation.

We propose that a more secure model of EE isolation can be provided by expanding native hardware virtualization support throughout the device. Here we describe TEE-BONE, a system in which all EE isolation mechanisms and policies are implemented in the device's hardware. During an attested boot process, TEE-BONE uses a read-only firmware policy to divide the virtualizable hardware into static REE and TEE partitions, where each EE has direct and exclusive access to its partitions. TEE-BONE prohibits simultaneous execution of EEs, provides no mechanisms for inter-EE communication, and requires human-hardware interaction to switch between EEs. By placing these restrictions on the system and shifting the burden of virtualization to the hardware, we eliminate the need for complex VMM management of system resources. Such prevention of inter-EE subversion at the software level improves the underlying security of trusted applications, thereby encouraging further software development in high-security fields such as government and finance.

A Metric for Interpretability in ML Models

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In recent years, machine learning (ML) systems have pervaded innumerable domains like medicine, law, and government. These systems use cutting-edge computation techniques to learn from data and simulate phenomena, often outperforming humans. While these models are held to a high standard of predictive accuracy, there does not exist an equivalent standard for interpretability, defined as a model's ability to explain its decisions to humans unambiguously. In tasks where human lives are at stake, such as medical diagnoses or bail decisions, it becomes even more important for models to be interpretable, so that humans can detect biases and shortcomings. A complex model can be simplified to local 'explanations,' which have the same framework as logical formulas. The interpretability of the model depends on the complexity of its explanations. The goal of this work is to derive a metric for interpretability by providing humans with explanations of varying levels of complexity. Through this work, we aim to investigate what makes an explanation easier to interpret. In a series of human trials, we provided participants with inputs to a hypothetical recommendation model and an explanation. We then asked the participants to verify if the recommendation makes sense with the explanation. By varying the complexities of the explanations and collecting data on the performance of our subjects, we can see which features of a model heavily affect its interpretability. This metric will allow us to differentiate interpretable models from more arcane ones, ultimately fostering more trust and oversight of ML systems.

Automated Scholarly Editor: Generating a Provisional Critical Edition of a Text Using a New Edit-Distance Metric for Documents

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Scholarly editing is an academic activity that attempts to provide comparisons of various versions of a text to gain a better understanding and appreciation of the text and also to serve as the foundation for further analysis of the text. The traditional practice of scholarly editing is however, painstaking and demanding, since it requires textual scholars to examine the extant editions of the literary text at the hand through a very careful manual comparison, report both the nuances between the surviving copies and some important annotations that would help the readers understand the document's editing history or the writer's unique writing style and then assemble a critical edition.

To address this problem, we are designing a system that will automatically generate a provisional scholarly edition of a text by measuring the textual differences and similarities of multiple editions of the same text with a new minimum edit-distance function for documents. Edit-distance metrics measure the minimum number of operations—such as insertion, deletion and substitution—needed to transform one string to another, thereby giving a sense of how dissimilar two strings are.

We have investigated the theoretical nature of this string-to-string matching problem and experimented with some standard edit-distance metrics (such as Levenshtein edit-distance metric) and longest common substring algorithms, resulting in our development of new efficient algorithms to detect similar passages between two texts—in particular, finding the longest common substring with a certain number of mismatches determined by the user.

Once we complete our design of the automated system, we plan to test it on large documents, such as the *Synoptic Gospels* and variants of *Don Quixote*. We believe that the automaticity of this process will enable a more efficient method for developing and revising scholarly editions. Our system will also mitigate the need for the exhaustiveness and definitiveness of any particular version, while giving users an opportunity to scan through all the extant editions of a given document at once.

Developmental Biology

Understanding Role of Immune Cells During Xenoengraftment in Adult Immune Compromised Zebrafish

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The zebrafish has emerged as a promising tool for cell transplantation studies, yet approaches to engraft human cancers into adult fish have been limited by the availability of immune deficient zebrafish models. Previously, we have developed compound mutant zebrafish deficient in prkdc (protein kinase, DNA-activated, catalytic polypeptide) and interleukin-2 receptor gamma a (il2rga). These fish were generated in the Casper-background and are severely immune compromised; lacking acquired immunity and a subset of NK cells. Remarkably, these immunocompromised fish are viable as adults and allow engraftment of a subset of mouse and human cancers, including melanoma, rhabdomyosarcoma, Ewings sarcoma, and fibrosarcoma. However, the specific role of each immune cell type in the process of tumor engraftment or rejection remained unclear.

By utilizing the nitroreductase-mediated cell/tissue ablation technology, we aim to generate a complete array of immune lineage-specific ablation transgenic lines, thus providing a comprehensive view of the differential behavior of each immune cell subtype following engraftment or tumor rejection. A total of five transgenic lines, each depleting either T-, B-, NK-lysin cells, macrophages or neutrophils, will be made. Each transgenic line will be tagged with a different fluorescent protein and generated in the Casper background, facilitating live, real-time visualization of immune cell behavior at a single cell resolution. My work will define which cell types modulate engraftment of human cancers into the zebrafish, providing new insights and models for preclinical drug validation studies using patient-derived xenografts in the future.

Earth and Planetary Sciences

Microscopic Paleomagnetism

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Metallic rocks are able to record earth's magnetic field at the time of formation, and paleomagnetism is the study of these fields. Usually macroscopic rocks or structures are used in this type of analysis, but some specialized and precise measurements require microscopic scales.

A diamond magnetic microscope can make measurements of magnetic fields on microscopic scales, and a new diamond magnetic microscope is currently being built in order to improve upon the current prototype. The electric current sources, translation stages, and microscope body structures need to be tested as they arrive and then assembled. As new parts come in, they can be attached to the prototype to test their efficacy and testing so far suggests that the new microscope will surpass the current model. If this device is accurately constructed, the ability to make more precise magnetic field measurements of small magnetic particles such as dusty olivines in meteorites will be possible. The next step for this device would be the characterization of fine magnetic fields in zircons and carbonaceous chondrites, which would lead us to understand the early history of the Earth and the birth of the solar system.

Economics

Maximizing Profit With Parking Fees: Returns to Restricting Entry in Auctions

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A profit-maximizing auctioneer may face a tradeoff between attracting bidders and implementing favorable auction rules. A classical result, due to Bulow and Klemperer (1996), establishes that the auctioneer always prefers a market with more bidders in a setting where bidder entry is exogenous. However, real-life auctions, such as charity auctions, often charge an admission fee, thereby deliberately excluding potential bidders. To explain this discrepancy, we investigate whether Bulow-Klemperer-type results extend to auctions with endogenous entry. In our setting, potential bidders learn their values only after a costly entry. For example, a charity art auction reveals the artwork on-site, which potential art collectors can only examine after investing time and energy to attend the auction and possibly paying a parking fee to the auctioneer. Our main result is that Bulow-Klemperer often breaks down in such settings, and the auctioneer would rather charge admission fees than run a thicker market. We assess the degree of the breakdown by establishing conditions and bounds on the tradeoff. We show sufficient conditions under which the auctioneer prefers an auction with N potential bidders and admission fees to a second-price auction with $N + 1$ potential bidders and no fee. We also illustrate that Bulow-Klemperer may significantly break down, in the sense that the auctioneer may even want to set a prohibitively high admission fee.

Embracing Uber Driver Heterogeneity

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In the design of ride-hailing algorithms (like those employed by Uber and Lyft) it is desirable that matches made are incentive aligned on the driver side, meaning that it is always in the driver's best interest to accept the match at the offered price. However, most models of ride-hailing markets ignore driver heterogeneity. Some drivers prefer to drive in the city, others along the coast, and algorithms that ignore such idiosyncratic preferences cannot truly be incentive aligned. As a result, learning driver preferences is of importance to the platform, but simply asking drivers to report their preferences can lead to drivers "gaming" the system to get more profitable rides. Thus, we study the design of a mechanism to elicit true driver preferences. We model a static, steady-state market where drivers have identical monetary incentives but idiosyncratic preferences over locations. In this context, we will investigate overweighting less popular preferences and linking preference reports together to encourage truthful reporting. Our work has the potential to align incentives and thus improve social welfare through better matching.

Engineering and Applied Sciences

Incorporating Mechanical Interactions Into the Cellular Potts Model

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The Cellular Potts Model is a lattice-based computational approach to modeling cellular interactions. It has been widely used to model systems on both the tissue and cellular level, but its lattice-based perspective has made it difficult to incorporate mechanical interactions that are important in many biological processes. Recently, the Reference Map Technique has been developed, which allows large-strain solid mechanics to be simulated using a fixed regular lattice, via a special reference map field that tracks material deformation. In this project, I seek to couple the Cellular Potts Model with the Reference Map Technique to understand the mechanical behavior of multicellular clusters attached to a deformable substrate. This hybrid model allows the Cellular Potts Model to account for the complex mechanical interplay between the substrate and the cells. To do so, I augment the Hamiltonian energy function in the Cellular Potts Model that governs cellular growth and movement to include coupling terms to the Reference Map Technique. I hope that this hybrid model can serve as a generalizable computational framework for future studies of mechanical interactions between cells.

Instrumentation for Magnetic Resonance Force Microscopy

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Magnetic Resonance Imaging (MRI) has revolutionized medical imaging through non-invasive, three-dimensional mapping of tissues. However, the spatial resolution of MRI is limited to approximately one micron because of pickup coil design and magnetic gradient generation. By replacing the pickup coils of MRI with a resonant mechanical cantilever, Magnetic Resonance Force Microscopy (MRFM) has extended the advantages of MRI to nanometer resolution with potential for further improvement to true atomic scales. Applications include single-copy mapping of proteins and nanostructures and characterization of magnetic nanoparticles.

To enable development of novel MRFM technologies and push the technique towards commercialization, a new microscope was developed. Compared to legacy instruments, cost was reduced, ease of assembly and operation improved, and the ability to independently control temperatures of the sample and probe, critical for biological samples, added. Systems and mechanical design of the instrument have been completed and fabrication is in progress.

Chacterizing Voltage on Minerva; An Integrated Circuit Enabling Low-Power, Highly-Accurate Deep Neural Network Accelerators

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Deep neural networks (DNNs) are an increasingly popular method for machine learning (ML). Inspired by the brain's ability to compute and communicate, deep neural networks artificially implement what is analogous to the neurons and synapses of the brain. The neural network takes an input vector and outputs a corresponding output vector. A large dataset of input/output examples are used to train the network - that is, the network learns some complex function for data fitting, allowing it to classify information with a high degree of accuracy.

DNNs have a wide range of applications but the complex and expensive computation presents difficulties for the implementation of DNNs, particularly on devices with limited power and computation capabilities - such as mobiles and other IoT (web enabled) devices. Specialized hardware for DNNs makes it possible to overcome these limitations.

There are a number of existing devices that implement DNN techniques; however they usually offload computation to backend servers. Solutions that fully implement DNNs in hardware can improve latency, autonomy, power consumption, and security for a number of applications.

The Brooks and Wei labs have developed Minerva, a chip which enables low-power, highly accurate, deep neural network accelerators.

I have been focusing on characterizing the chip in order to demonstrate how Minerva is competitive with some of the best DNN ASIC (application-specific integrated circuit) accelerators built to date. For example, in order to minimize power consumption on the chip, we can characterize the voltage requirement across a number of clock frequencies, optimizing the frequency-accuracy tradeoff. At lower clock frequencies there tend to be less errors accumulated on the datapath and memory registers of the chip resulting in better accuracy.

Minerva has been shown to be capable of making highly accurate predictions across a number of ML datasets and doing so on very low power, making it an ideal solution for implementing DNNs on power constrained devices such as mobile.

Actuated Tail for Harvard Ambulatory MicroRobot

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At the Harvard Microrobotics Lab, the Harvard Ambulatory MicroRobot (HAMR) specializes in high speeds, quick turns, and general maneuverability. This 4.5 cm long, 1.5 gram, 4-legged robot can move faster than 10 body lengths per second and can climb inclines as steep as 55 degrees. To assist the robot in climbing and traveling at high speeds, I am designing an actuated tail to support the robot and enable greater maneuverability. Multiple design iterations have shown numerous possibilities for the tail design.

A direct drive tail uses a piezoelectric actuator with a 15 mm extension that produces a calculated 120 mN of force. A second design changes the position of the actuator to shift the center of mass forward on the robot so it does not tip over backwards while climbing steep inclines. The actuator is linked to the tail through a flexible wire, and the tail rotation is allowed by a polyimide flexure to link the tail to the chassis. These different tail design iterations will allow for development of a tail that best supports the robot in climbing and mobility.

After successful completion of the tail, the analysis of HAMR's gait, through looking at body angle, voltage, and phasing, will provide data for how a tail can increase speed and inclined climbing capabilities in exploration of new terrain. In the future, HAMR could be used for search and rescue missions or could explore places too dangerous or inaccessible to humans.

Advanced Signal Processing for the Enhancement of Millimeter-Wave Imaging Technology

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Crowded, high trafficked areas pose safety and security risks for citizens and institutions due to the lack of visibility and inability to efficiently screen for threats. Millimeter-Wave (MMW) imaging is a non-ionizing, cost-effective method of obtaining information about concealed threats and can be deployed as mid-size stationary sensors in diverse locations. The ability of our MMW device to mitigate risk and increase screening efficiency is a result of its real-time, video-rate capabilities. Successful implementation of the MMW device requires precise engineering design and novel and efficient signal processing to reconstruct informative images from electrical signals.

This research explored signal processing in multistatic MMW imaging to quantify range and field-of-view capability. Cost and performance measurements incorporated quantitative and qualitative indicators. Dependent variables tested included spectral windowing, spatial domain sampling, and spectral domain normalization. To efficiently and reproducibly evaluate parameter choices, a multi-objective optimization algorithm was constructed to evaluate multiple cost functions, including image noise and accuracy. A pairwise rating algorithm was used to incorporate human visual perception. These algorithms more effectively determined the impact of signal processing decisions.

Positive outcomes of this research include the identification of "Pareto frontiers" of local optimal solutions of MMW signal processing decisions based on objective measurements. Global improvements occurred after applying customized spectral windows adjusted according to the frequency and subject range.

Improving image quality by advanced signal processing provides security agents with a more effective assessment of the existence of concealed threats. This project is in line with missions of defense and security organizations. Further research will include refining quantitative and qualitative assessment metrics to ensure their reliability in a diverse set of environments and expanding the toolbox of signal processing considerations.

Genetics

Investigating the Molecular Basis for Infertility Associated with Abnormality in a Novel Candidate Gene, SYCP2

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Infertility is one of the most common diseases for people of reproductive age, affecting 10-15% of couples. The etiology for 20% of these cases is unexplained, hindering precise treatments for these couples. Identifying genes that cause such cases of infertility may lead to more appropriate and effective interventions. To identify genes that cause unexplained infertility, we studied DGAP230, a subject with oligospermia (low sperm count) and a balanced translocation. We hypothesized that a gene critical for fertility may be disrupted or dysregulated at the translocation breakpoints. We identified a candidate gene, *SYCP2*, which showed exclusive dysregulation within the topological associating domain (TAD) of one of the breakpoints. This gene encodes synaptonemal complex protein 2, a meiotic protein that may impact spermatogenesis, resulting in DGAP230's phenotype. A circularized chromosome chromatin capture (4C) assay revealed several regions of differential genomic interactions within the *SYCP2* promoter, thus indicating a potential mechanism for *SYCP2*'s dysregulation. We next designed a functional assay to determine the effect of various *SYCP2* mutations identified in the larger population on the protein's ability to properly form the synaptonemal complex. DGAP230 and other subjects with balanced chromosomal aberrations with distinct phenotypes have highlighted a need to predict candidate genes dysregulated by rearrangement breakpoints. This project has led to the development of an optimized pipeline for clinical geneticists to use when interpreting cases of balanced chromosomal aberrations. The pipeline relies on the Human Phenotype Ontology of the patient as well as an examination of the overlap of the breakpoint and other genomic elements, such as enhancers, DNase I hypersensitive sites and regions of physical chromatin interactions.

Functional Motif Discovery in Massively Parallel Reporter Assay of Untranslated Regions

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Integrative Biology

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While recent advancements in sequencing technology have led to the discovery of disease and trait associated loci, functional follow-up of these loci remains a challenge, especially in noncoding regions. To address the limitations of traditional low-throughput functional methods, we adapt the Massively Parallel Reporter Assay (MPRA) and Polysomal Profiling to assess the biological activity of untranslated variants in the human genome. We deployed MPRA for its capabilities of examining thousands of sequences and polysomal profiling to explore mRNA-ribosome interaction during translation. We find that regulatory activity reported by MPRA is strongly correlated with known regulatory mechanisms, and functional variants are associated with important physiological processes. Polysomal

profiling indicated that in our experimental conditions, the untranslated region segments had little effect on translation. In order to characterize key motifs that affect expression, we applied support vector machines with gapped k-mer features for motif discovery and analysis. Curiously, variants with high uridine concentration were enriched for both stabilization and destabilization of the mRNA, while variants with contiguous stretches of uridine were enriched for destabilization only. This unbiased approach provides functional analysis of thousands of variants and putative causal alleles, and can be coupled with computational tools for de novo prediction of regulatory activity in the untranslated regions of the genome.

Mathematics

Perfect State Transfer, Equitable Partitions, and Cycles With Potential

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Inspired by problems in quantum computational theory, the mathematical theory of perfect and near-perfect state transfer addresses questions regarding the transfer of information through quantum computational networks evolving through time. Specifically, these problems address the question of when a graph G with adjacency matrix A satisfies the condition that $|\langle u| e^{iTA} |v\rangle| = 1$ for some vertices u and v and some time T, or where there exists some sequence $\{t_j\}$ of times such that $|\langle u| e^{it_jA} |v\rangle|$ converges to 1. My research this summer has focused on a variant of this problem. Specifically, it has explored the extent to which the introduction of potentials in a given system of particles can induce state transfer. To this end, the theory of equitable partitions is elaborated upon in order to relate the spectra of graphs to certain properties of weighted self-loops in graphs.

Linearization: A Cheap Tactic to Make Weak Proofs Stronger

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Enumerative Algebraic Geometry studies sets of shapes that satisfy certain requirements. Often, the property studied is cardinality, or number. For example, questions that might be asked are: In 3-space, how many lines meet four random lines?; and In a plane, how many circles lie tangent to three random circles? Other times, the set we want to understand naturally has some geometry itself and we consider different features. Central to this pursuit are the concepts of parameter space, and linearization. The main idea is that you can find a space (a geometric object) such that points of that space are naturally identified with shapes having a certain property. Every plane conic is the set of solutions to a unique equation $ax^2 + bxy + cy^2 + dx + ey + f = 0$ (up to scalar), so the parameter space of plane conics is a six-dimensional vector space. In this case, nonzero vectors that are scalar multiples of each other are treated equally. Linearization is the somewhat silly insight that linear problems are easy to solve, and everything else is hard. For example, linearization theory posits that it is difficult to determine whether the vanishing locus of a polynomial in 3 variables, such as $x^3 + y^3 + z^3 = 0$ contains a line, but it is easy to determine whether it contains a specific line, such as $x - y = z = 0$. Linearization combines nicely with the idea of parameter space. In solving the above problem of lines on a surface we can switch from solving a hard problem at every point in the space of cubic surfaces to solving an easy problem at every point in the space of lines.

3263 More Conics Than You Ever Cared to See

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Some equations are simpler than others. Consider, for example, the graph of $x^2 + 3xy + y^2 = 0$ and the graph of $x^2 + 3xy + y^2 = 1$. The first example factors, and its graph is simply a pair of lines, while the second equation does not factor, and its graph is a hyperbola. Fascinatingly, however, the only difference between these two equations is the constant term. As we shrink the constant term, we get a sequence of hyperbolas that converge to just a pair of lines, which are much easier to understand. This is an example of *specialization*, where we take a complicated equation and deform it into something we understand a lot better. By doing exactly this form of specialization—converging hyperbolas into pairs of lines—we analyze how many *plane conics* (degree two polynomials in two variables) are tangent to other plane conics. Using specialization, we can easily check that there are infinitely many plane conics tangent to a given plane conic—and even infinitely many tangent to four different plane conics! However, given five conics, we expect there to only be finitely many. Using specialization techniques, we will demonstrate that there are 3264 such tangent conics. Through this process, we will see just how much we can stretch out plane conics into objects we understand much better.

Lines on Hypersurfaces and Other Enumerative Problems

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Much recent research in the field of algebraic geometry has been motivated by classical problems. For instance, it is a theorem of Cayley from 1849 that there are precisely 27 lines contained in a smooth cubic surface in $\mathbb{P}^3$, three-dimensional projective space. One can ask more generally for the number of lines on a hypersurface of degree d in n-dimensional projective space $\mathbb{P}^n$; there may be finitely many lines, infinite families of lines, or no lines at all. The theory of Chern classes, important to differential geometry and algebraic topology, as well as algebraic geometry, gives a sufficiently general and powerful framework for answering this question. Computations with Chern classes can be automated and carried out by computers, giving researchers the power to deduce, for example, that there are exactly 2891396386327556 25 lines on a general degree-15 hypersurface in $\mathbb{P}^9$.

One must be careful with how these questions are phrased: the word "general" in the preceding sentence has precise meaning. There are indeed degree-15 hypersurfaces in nine dimensions with fewer lines than the above 18-digit number. When one discards a small ("codimension-one") subset of such surfaces, the statement becomes true. Enumerative computations such as the line-counting mentioned have spurred an incredible volume of work in modern and classical algebraic geometry, allowing for the development of abstract techniques that ultimately give concrete, numerical answers.

Molecular and Cellular Biology

Design of a New Cancer Model System to Map the Travel Histories of Tumor-Infiltrating Cells

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Recent research has revealed an increasingly complex cellular network surrounding the immune response to tumors. Existing strategies are unable to capture transient cellular interactions within the tumor microenvironment, nor track the fates of tumor-infiltrating cells over large regions in both space and time. In this project, we sought to develop a new cancer model system that maps the travel histories of tumor-infiltrating cells across the body of an organism. To do this, we transduced cell lines including B16 melanoma and KPC pancreatic cancer to express a membrane-bound variant of sortase A. Sortase A is a transpeptidase derived from Gram-positive bacteria that attaches surface proteins onto the bacterial cell wall by creating a covalent bond between a 5-amino acid sequence motif (LPXTG in *Staphylococcus aureus*) and an oligoglycine linked molecule. For our desired *in vivo* application, we generated a new sortase variant by combining multiple mutations to yield an enzyme that was both calcium-independent and highly active. In mice inoculated with sortase

transduced cancer cells, tumor-infiltrating cell populations are labeled when an LPXTG-fused probe (e.g., HA-LPETG or AlexaFluor647-LPETG) is injected intravenously. This model system enables us to map the migration patterns of tumor-infiltrating immune cells over time *in vivo*, allowing for the investigation of many important questions about the role of different lymphocyte populations in cancer. More broadly, this cell-labeling technology has the potential to capture transient cellular interactions and migration histories in a wide range of settings.

Genome-Editing Using Zinc-Finger Proteins

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Our laboratory focuses on developing genome-editing technologies, including Zinc-Finger Proteins, TAL Effectors, and CRISPR systems. We have significant experience in developing both targeted nucleases and other effector protein fusions to insert, delete, modify, or modulate the expression of genetic material in multiple organisms and cell types. Through the development of these technologies, we seek to improve the safety and specificity of genome-editing techniques, including delivery to different cell types and detection of modifications. This project seeks to further that broader goal by investigating the genome-modifying capabilities of Zinc-Finger Proteins. In the past, we have modified Zinc Fingers to create designer genetic mutations with high efficiencies in zebrafish, plants, or human somatic and pluripotent stem cells. Here, we demonstrate that Zinc Fingers remain a useful technology for genome modification and highlight their capabilities in DNA targeting. The experiments conducted in this project make an important addition to the formidable suite of tools available to researchers in the field. Continual improvement of these technologies is essential for both basic scientific research as well as efforts to bring genome-editing technologies to the clinic.

Self-Management Skills in Adults with Celiac Disease

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The only treatment for celiac disease (CD), a gastrointestinal autoimmune disease, is lifelong adherence to a gluten-free diet (GFD). Celiac patients are faced with a complex set of skills to master in order to manage their dietary intervention and overall health. In this study, we sought to assess patients' acquisition of relevant self-management skills following diagnosis, and to explore the potential role of demographic factors in the rate of skill acquisition. Adults with CD completed an anonymous survey during an outpatient clinic visit for follow-up of celiac disease. Survey items included demographic information and questions assessing the rate at which various skills relating to maintenance of the GFD were mastered, as well as questions assessing patients' quality of life. 137 patients (79% female) returned a completed a survey. Participants reported shorter periods of time necessary to acquire relevant self-management skills for themselves as compared to their estimates for an average person with CD. Survey responses indicated that as skills progressed in perceived difficulty, necessary time for acquisition increased. Skills involving the assessment of basic food safety for people on a strict GFD were associated with the least amount of time, while learning how to explain CD and the GFD to others required longer reported amounts of time. Assessing risk of gluten exposure at restaurants and during travel required the longest amounts of time to master. There is a clear spectrum of skills relating to management of CD and its requisite GFD. Demographic factors that I am currently analyzing may also influence the rate of learning these skills. Awareness of this continuum of self-management skills will aid physicians and dietitians in providing targeted education and resources to patients in order to facilitate maintenance of their chronic disease, and therefore, improve quality of life.

Investigating the Role of Lymphocyte Activation Gene 3 in Transplant Outcomes

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The continued shortage of organs, combined with the adverse health effects of harsh immunosuppression regimes and ultimate graft rejection/failure, underscores the importance of transplant research. Understanding the mechanisms of organ tolerance and rejection is imperative to the promotion of systemic tolerance. This study focuses on Lymphocyte Activation Gene-3 (LAG-3), a cell-surface receptor and soluble protein involved in the inhibition of memory T-cells and promotion of T-regulatory cell immune suppression. We have shown that LAG-3 is necessary for recipient dendritic cells to inhibit generation of allograft-specific T-cell memory. Using allogeneic mouse strains as allograft donors and recipients, DBA/2 (H-2d) cardiac or skin allografts were transplanted without immunosuppression into wild type C57BL/6 (H-2b) controls and LAG-$3^{-/-}$ C57BL/6 knockout mice. Cardiac and skin allografts in WT recipients exhibited a slower rejection time by 2-4 days than LAG-3 KO recipients. Interestingly, a greater number of IFN-γ secreting memory T cells were observed among LAG-3 KO T cells between 1 and 5 weeks after heart and skin transplant rejection than among WT recipients. LAG-3+ dendritic cells from wild type C57BL/6 mice were adoptively transferred into LAG-$3^{-/-}$ C57BL/6 knockout mice. After one week, DBA/2 skin allografts were performed. Following complete rejection, the mice were sacrificed and splenic T cells were isolated, and IFN-γ secreting memory T cells were assessed by ELISPOT. Adoptive transfer of LAG-3+ dendritic cells reduced T-cell memory cell reactivity to that of wild-type recipients. Our research suggests that LAG-3+ dendritic cells are important for controlling T-cell memory generation.

Effects of *Let-7* on Synapse Morphology and Plasticity

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There is a critical gap in the understanding of precisely how synaptic activity leads to the spatial and/or temporal translation of specific mRNAs. MicroRNAs (miRNAs) are a likely candidate to be playing a role in this process. We investigated the role of a specific miRNA, *let-7*, in regulating the morphology of the synapse in response to synaptic activity in *Drosophila melanogaster*. The expression level of the miRNA gene *let-7* is known to change in the *Drosophila* central nervous system, a presynaptic region, as a result of artificially stimulated neuron activity. We are building upon this research and examining *let-7* expression in the postsynaptic region to determine if it also responds to activity on the other side of the synapse. First, we extracted miRNA from flies that had undergone spaced synapse stimulation to promote synapse growth and compared changes in the expression level of several individual miRNAs measured through a Nanostring assay. We then performed qPCR to further quantify the difference in expression level of certain miRNAs, including *let-7*, between the flies with induced synapse growth and control flies. Lastly, in order to further understand the function of *let-7*, we looked for morphological differences in the synapse for *let-7* loss-of-function mutants in both normal conditions and after the spaced synaptic stimulation. These results will lead to a greater understanding of the part miRNA plays in synapse formation and support a model in which miRNA plays a crucial role in regulating activity-dependent synaptogenesis.

Characterizing the Role of idsE *in vivo* in Populations of *Proteus mirabilis*

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Proteus mirabilis is a familiar Gram-negative bacterium to the human body: commonly found as part of the microbial community in the gastrointestinal tract and a leading cause of urinary tract infections in patients requiring prolonged catheter intubation. Noted for its robust cooperative swarming behavior, it utilizes self versus nonself recognition through its *ids* operon to determine these swarm patterns. For successful self-recognition and subsequent swarming of two populations, the IdsE protein of one cell is hypothesized to bind with the IdsD physically transferred from another cell if they are genetically identical; a physical boundary will form if the populations are not. Little is known about the specific interactions and signaling that IdsE participates in to regulate swarming.

For this project, we wanted to characterize the role of IdsE *in vivo* and observe how different mutations in the IdsE protein can affect swarming. By employing a general mutagenic PCR screen to identify restricted swarmers, we are able to sequence and map specific mutations that play a role in this changed behavior onto the predicted membrane topology of IdsE. It will also eventually allow us to determine the effects of these mutations as natively expressed through placing them on the chromosome; this can elucidate any changes in gene expression that *P. mirabilis* is able to make when self-recognition is impaired. Studying IdsE will allow for a better understanding of how self-recognition and social motility influence bacterial fitness across strains and population-level swarming behavior.

Characterization of VPS37A and TMEM41B in Mammalian Autophagy

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In autophagy, specialized vesicles called autophagosomes build around potentially toxic structures such as damaged organelles and protein aggregates. When autophagosomes fuse with lysosomes, this cargo is degraded. Autophagy-related (Atg) proteins mediate the mechanisms of this process. Hereditary and sporadic mutations in Atgs have been implicated in diseases ranging from cancer to Crohn's; however, the disease targets of autophagy are not well understood. This lack of understanding stems from our incomplete knowledge of how known Atg proteins function and the potential existence of uncharacterized protein factors essential for autophagy. As a result, defining the role of these Atgs is the first step towards understanding mechanistic defects that lead to disease.

Through a CRISPR-based genome-wide screen, the Denic lab has identified a list of potentially novel autophagy-related proteins, among them Transmembrane Protein 41B (TMEM41B) and Vacuolar Protein Sorting 37A (VPS37A). My primary goal this summer was to define the role of TMEM41B and VPS37A in autophagy by analyzing their gene deletion phenotypes using microscopy, as well as by genetically screening for genes that have synthetic genetic interactions with TMEM41B$^{-/-}$. Intriguingly, this work has identified that TMEM41B functions in an intermediate stage in autophagy: enclosing cargo. Conversely, VPS37A functions at a late stage, interrupting cargo delivery to the lysosome. My future work will focus on narrowing these stages further and uncovering the molecular function of TMEM41B outside of autophagy.

A Shotgun Approach to Creating ORF Libraries for Bacterial Perturbation

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Currently the scientific community lacks an efficient way to develop open reading frame (ORF) libraries, leaving existing libraries scattered and incomplete. We aim to develop a fast, robust, and cheap method for generating ORF libraries for all species of bacteria, allowing for quicker characterization of various infectious bacteria. We designed a plasmid that selects for in-frame ORFs at an ampicillin concentration of 50 μg/mL by including a sequence coding for β-lactamase directly downstream of the ORF insert site. This allows for the ribosome to continue translating β-lactamase immediately after translating the ORF. The β-lactamase protein is only translated correctly if the upstream ORF is in-frame and contains a stop codon, allowing only bacteria with plasmids containing a full, in-frame ORF to survive in the presence of ampicillin. Using the ORF for red fluorescent protein (RFP), we have shown that the plasmid successfully selects for the in-frame RFP ORF over the out-of-frame ORF. Through mutagenesis, we removed the stop and start codon from the ORF and observed that transformed colonies were no longer resistant to ampicillin, suggesting that the plasmid also selects against ORFs missing a start or stop codon.

Using NEBNext dsDNA fragmentase, we designed a protocol that shears *E. coli* genomic DNA to ORF-sized lengths. In future experiments, we will test the plasmid with the sheared gDNA and sequence plasmids of colonies that grow on ampicillin plates. Since the *E. coli* ORF library has been well mapped, we will compare the sequences we have found to these ORFs to determine if the plasmid successfully selects for the majority of ORFs within *E. coli* gDNA. The goal of this research is to eventually construct an ORF library for *M. tuberculosis* to use for genetic perturbation.

Role of Noncoding RNA in Chemo-Resistant Cancer Cells

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Cancer cells have the ability to enter a quiescent stage, G0, where the cells lay dormant to survive chemotherapy. This causes the patient to experience cancer recurrence as the G0 cancer cells enter their normal cell cycle after the treatment. Recently, in the study of chemo-resistant G0 cancer cells, there is a growing interest in noncoding RNA, transcribed RNA which do not encode known proteins. Some noncoding RNA strands turn out to interact with other RNA or protein molecules, but many of these interactions have yet to be studied.

This project aims to study the role of an interaction between a long noncoding RNA (lncRNA) and a protein in causing a cancer cell to enter G0. The lncRNA and protein are known to bind with each other and are found to be overexpressed in G0 cancer cells. To find all the different proteins that bind to the lncRNA, a specific tag was attached to the lncRNA through a series of digestions, ligations, and *E. coli* transformations. Sequencing results showed that the ligation between the tag and lncRNA was successful. This product will be transfected into cancer cells to check that the tag does not interfere with the cancer cells' capability to enter G0. Finally, using the tag, the lncRNA will be precipitated with all the proteins bound to it. Further steps include mutating the lncRNAs binding site for the protein to see if the lack of an lncRNA-protein interaction can stop chemo-resistance by preventing cancer cells from entering G0 and possibly reduce cancer recurrence.

Requirements for NK Cell Activation Using a Skin Transplantation Model

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Natural Killer (NK) cells, an innate lymphoid cell type, act as part of the body's critical first line of defense against pathogens. NK cells were originally described by their ability to kill tumor cells in culture. However, the optimal signals necessary to recruit and activate NK cells to block against early phases of malignant transformations *in vivo* is unknown. Our laboratory previously developed a mouse model to test the signals required for activating NK cells by using a NK cell-specific activating ligand, m157, which is a surface protein expressed by mouse cytomegalovirus recognized only by an activating receptor on NK cells called Ly49H. Surprisingly, the lab discovered that skin expressing m157 and lacking MHC Class I (β2m knockout, which identifies the cell as self and inhibits NK activation) remain intact in presence of massive NK infiltration into the skin suggesting NK tolerance.

For our current project, we are using a skin transplantation model in mice to further understand the requirements for overcoming NK cell tolerance and induce their activation. After grafting skin from $m157^{tg}$, $\beta 2m^{-/-}$ mice onto wild-type mice, we introduce additional activating cytokines to NK cells *in vivo* in order to determine whether a NK-cell dependent rejection phenotype will develop. We will then use flow cytometry and immunofluorescence histology analysis to compare these mice with a negative control population in order the determine the changes in NK cell biology that led to their full activation against the target *in vivo*.

Metabolic Reprogramming of FoxP3 Deficient Regulatory T cells

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Regulatory T cells (Tregs) are a subset of T lymphocytes whose roles are to downregulate the intensity of an immune response, and maintain immunological tolerance. Their suppressive function is mediated by different mechanisms including cell-cell contact and production of soluble anti-inflammatory cytokines. Dysfunctional Tregs in humans induces a fatal autoimmune disease called Immune dysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome. An analogous condition, scurfy, can be seen in FoxP3-deficient mice.

The metabolism of Tregs is characterized by high fatty acid oxidation and low glycolysis, whilst the converse is true of effector T cells (Teffs). FoxP3 is pivotal for the suppressive capacities of Tregs, but its loss of function does not prevent Treg cell differentiation but only alters their phenotype, including their metabolism, towards proinflammatory effector-like T cells. This appears to be due to loss of suppression of pro-glycolytic upstream signals, such as mTORC1+2, normally carried out by FoxP3. The hypothesis of the lab is that metabolic reprogramming of FoxP3-deficient Tregs to decrease glycolytic levels may restore their suppressive capacities.

I studied mouse models to test this hypothesis using suppression assays to examine the functionality of Tregs. Suppression assays involve using flow cytometry to detect proliferative stains of Teffs in the presence of Tregs. I conducted suppression assays following pre-treatment of FoxP3-deficient Tregs with a glycolytic inhibitor, 2-deoxyglucose, and an inhibitor of oxidative phosphorylation, rotenone. Both pre-treatments acted to increase fatty acid usage as a source of energy and it was found to partially rescue Treg suppressive function. This suggests that decreasing levels of glycolysis could provide a therapeutic method of controlling IPEX syndrome.

The Kinetics of Dynamic BH3 Profiling: Measuring Cancer Cell Sensitivity to Apoptosis

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Despite the widespread availability of cancer chemotherapies, many malignancies eventually only partially respond, relapse, or become resistant to drug treatment. With the dilemma of trying new therapies while limiting cytotoxicity, it is important to be able to identify the best chemotherapy drugs prior to patient delivery. To address this need, our lab has developed BH3 profiling as a biomarker for detecting cell sensitivity to mitochondrial-mediated apoptosis, or priming. Pro-apoptotic peptides trigger mitochondrial outer membrane permeabilization (MOMP), causing a release of cytochrome c that in turn activates protein-cleaving caspases. Since cell death follows shortly, our assay considers MOMP as cell commitment to apoptosis. Loss of cytochrome c levels serves as a proxy for MOMP and is thus an indication of a cell's proximity to its apoptotic threshold. In dynamic BH3 profiling, we are able to measure how effective single or combinatorial drug treatments are in shifting cancer cells towards their apoptotic threshold, a phenomenon we call delta priming.

While our assay provides a powerful means to perform chemical screens, little is known about the kinetics of delta priming. We have an incomplete understanding of tumor priming behavior after drug treatment, and specifically, how delta priming changes as a function of time of drug exposure. To address these unknowns, our project focuses on performing dynamic BH3 profiles on pancreatic cancer cells that have been exposed to different chemotherapy reagents for variable incubation periods. Successful completion of this project will yield critical information on the kinetics of delta priming, including at what point we may reach a saturation period where prolonged exposure to drug no longer yields an effect on delta priming. The ability to determine the earliest point of appreciable delta priming expands the utility of our assay and provides a clear clinical impact by enabling quicker feedback on drug efficacy.

Testing Drug Therapies for Tauopathy in a Transgenic *Drosophila* Model

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Accumulation of Tau protein, often due to hyperphosphorylation, leads to neurodegenerative diseases called tauopathies, which can be present in Alzheimer's and Parkinson's diseases. As a result, there is a need for drugs that inhibit tau accumulation, preventing or lessening the effects of these disorders. To model tauopathy in the fruit fly, *Drosophila*, transgenic wild-type human tau (hTau) and patho-genic R406W mutant human tau (hTau-R406W) were expressed using the GAL4/UAS system. Gal4 driver lines included the pan-neuronal Elav-Gal4 driver, the notum-specific Eq-Gal4, eye-specific GMR-Gal4 and pan-neuronal Elav-GeneSwitch driver, which requires the drug mifepristone to activate expression and can therefore be used to turn on hTau expression in adult flies, bypassing any developmental defects. Flies expressing hTau display several robust phenotypes that can be used to determine the severity of the tauopathy including decreased lifespan, rough eyes, increased activity, and a decreased number of short bristles on the notum. In addition, four lines of Elav-hTau flies showed strong expression of both total and phospho-hTau on western blots, confirming hTau expression. Using these phenotypes, we are screening a library of drugs that reduced hTau levels, phosphorylation, or both when used on a mammalian tauopathy cell line model *in vitro*. Drugs have been administered to our *Drosophila* models by adding to food, and their ability to modify hTau phenotypes will be assessed. A positive result in an *in vivo* model will be an important step in assessing the potential for these drugs to serve as therapies for tauopathy-related disorders.

Decoding the Noncoding Genome: A Method to Systematically Identify Gene Regulatory Elements

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Noncoding genomic elements regulate gene expression to affect phenotypes and disease states. However, the functional relationships between target genes and most noncoding elements remain unknown. Historically, geneticists lacked systematic approaches to characterize these relationships. Our lab recently developed a high-throughput approach using clustered regularly interspaced short palindromic repeat interference (CRISPRi) to characterize the regulatory functions of noncoding elements. In this experiment, we used fluorescent tags to sort cells into bins based on expression of a gene-of-interest, and subsequently sequenced the guides in each bin to infer their effects on gene expression.

Determining the true effects of each sgRNA on gene expression from aggregated bin frequencies was a further challenge. We developed a framework for reconstructing individual fluorescence distributions for each sgRNA using recursive maximum-likelihood estimation. This approach yielded a more accurate quantification of the mean signal, as well as a method for quantifying variance. We analyzed the resulting framework parameters with a windowing approach against negative controls to identify regulatory elements for particular genes, including ones that affected either mean or variance. We then optimized the locations and widths of sort bins by testing simulated datasets to determine high-power binning strategies. As proof-of-concept for a method of evaluating the contact model of enhancer-promoter function, we assessed comparisons for the GATA1 gene locus to identify putative enhancers. This framework will be used to determine the relationships between additional gene loci and their noncoding neighborhoods to better interpret the contributions of noncoding genetic elements to human disease.

Identification and Characterization of an *Rrf-1* Mutation and Its Impacts on RNA Interference Sensitivity in *Caenorhabditis elegans*

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RNA interference (RNAi) is a biological pathway that allows for targeted down regulation via sequence complementarity. It has enormous applicability in various fields, including functional genomics and therapeutics. My work attempts to further elucidate pathway mechanisms, specifically that of *rrf-1*, an RNA-dependent RNA polymerase (RdRP) critical for amplification of primary small interfering RNA (siRNA) into secondary siRNA. A particular point mutation in *rrf-1*, called the 11.2 mutation, has been found to result in an unusually high resistance to RNAi, much stronger than deletion of the gene. This summer, I worked to understand how alteration of a single nucleotide produces such a strong phenotype and to contribute information to the field's understanding of the mechanism of *rrf-1* in the amplification step. There are three main aims of this project: 1. determine whether expressing a wild-type copy of *rrf-1* will restore RNAi sensitivity in the 11.2 strain, 2. determine whether expression of *rrf-1* and/or a neighboring gene is affected by the 11.2 mutation, and 3. determine whether 11.2 *rrf-1* protein interacts with a co-expressed RdRP to create the strong RNAi resistant phenotype.

The Effects of Bariatric Surgery on Bone

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About 7% of US adults have morbid obesity (BMI $\geq$ 40kg/m^2), and prevalence is expected to increase. Morbid obesity is associated with a number of comorbidities that have significant effects on mortality such as diabetes mellitus and cardiovascular disease. Bariatric surgery is a popular treatment option for weight loss and for improving obesity-related comorbidities. However, one of the most common bariatric surgeries, Roux-en-Y Gastric Bypass (RYGB), has been shown to cause negative effects on skeletal health. To date, we have found

that bone mineral density (BMD) declines by 10% at the hip during the first 2 years after RYGB. Bone metabolism remains highly disordered throughout this time, and it is likely that BMD may decline further in subsequent years. While the mechanism of bone loss is unclear, we have seen changes in bone turnover markers as early as 10 days after surgery. Our current project involves examination of long-term bone outcomes in a 5-year longitudinal cohort of RYGB patients. Our preliminary data indicates that bone loss may indeed continue for at least 5 years after RYGB. In addition, we are now recruiting RYGB patients 10 years after surgery to determine whether RYGB causes long lasting detriment to bone density and microarchitecture. Lastly, we are launching a new pilot study to investigate the efficacy of anti-resorptive medications prior to surgery, in an attempt to mitigate the unintended consequence of bone loss after RYGB. Through these various studies, we hope to characterize the changes in bone that are occurring after bariatric surgery in order to provide effective treatment for bone loss.

Evaluating the Role of the *C. elegans* MAPK Pathway in Chromatin Organization During Embryogenesis

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Epigenetic modifications, such as dimethylation of lysine 9 on histone 3 (H3K9me2), are necessary for inducing regions of the *C. elegans* genome from transcriptionally active euchromatin to become inactive heterochromatin. This process allows the cells in the embryo to progress from a pluripotent to a differentiated stage of development. Previous studies have shown that mitogen-activated protein kinase (MAPK) becomes active in *C. elegans* oocytes during fertilization, implicating MAPK as a possible timer for inducing heterochromatin formation at the onset of gastrulation. Furthermore, several proteins in the MAPK pathway interact weakly with MET-2, the methyltransferase responsible for H3K9me2, through association with proteins in the *C. elegans* synMuv pathway. Given the temporal activation of MAPK and the modest involvement of MAPK proteins in chromatin condensation, this project seeks to determine if the MAPK pathway acts as a timer of H3K9me2 as the embryo progresses from early to late stages of development. To this end, mutant strains and RNA interference (RNAi) were used to suppress the expression of several proteins in the MAPK pathway. Embryos at early and late stages of embryogenesis were then stained for H3K9me2 in wild type and MAPK-deficient worms using immunofluorescence microscopy. Preliminary findings show that embryonic H3K9me2 signals in wild type worms and two MAPK-deficient strains, *pmk-1* and *mek-1*, are extremely similar through all stages of embryogenesis.These results suggest that the MAPK pathway is not implicated in the timing of H3K9me2 in *C. elegans* embryos. However, future research will test both positive and negative protein regulators of the MAPK pathway for involvement in H3K9me2 timing. Unveiling the mechanisms of chromatin condensation in model organisms such as *C. elegans* can help elucidate how early differentiation takes place in more complex organisms such as humans.

CC-885 Mediated GSPT1 Degradation in Murine Cells

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CC-885 is a novel thalidomide analogue shown in cell lines and patient samples to be active against leukemia, although the mechanism of action is unclear. CC-885 modulates cereblon, a substrate receptor protein that is part of the CRL4-CRBN E3 ubiquitin ligase complex. CC-885 causes cereblon to target GSPT1, a translation termination factor, for ubiquitination and proteasomal degradation, which has been shown in previous literature to lead to decreased cellular proliferation in tumor cells. A murine model is necessary to study the effects of the drug, but mice are insensitive to CC-885 due to amino acid differences between mouse and human cereblon at critical binding sites. In this project, humanized constructs of mCrbn were cloned, introduced into retroviral vectors, and transduced into Ba/F3 murine leukemia cells in order to induce drug sensitivity. The cells were treated with a range of doses of CC-885, lysed, and Western blots were conducted to examine relative levels of GSPT1 degradation, which was used

as an indicator of drug sensitivity. Initial results demonstrate that the alteration V380E successfully induced drug sensitivity in the Ba/F3 cell line, while E149D and I391V appeared to have little to no effect. Through the introduction of various combinations of human amino acids at crucial sites in the cereblon sequence, successful completion of this project will contribute to the creation of the optimal drug-sensitive murine cell model. The murine cell model would be useful in future experiments to better characterize the mechanism of action of CC-885.

Identification of Factors for Peroxisomal Membrane Protein Turnover

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Cells maintain protein homeostasis by ensuring that polypeptides are properly synthesized, folded, trafficked, and degraded. Defects in a cell's ability to sense or respond to abnormalities, such as elevated protein misfolding and aggregation, may cause diseases ranging from cystic fibrosis to cancer. Degradation of misfolded or damaged proteins at the endoplasmic reticulum (ER) and mitochondria proceeds via the ER-associated degradation (ERAD) and mitochondria-associated degradation (MAD) pathways, respectively. Much less is known about protein degradation at other organelles, including peroxisomes, whose major role is lipid metabolism. We hypothesized that there exists an analogous peroxisome-associated degradation (PRAD) pathway that dislocates peroxisomal proteins into the cytosol and targets them for destruction by the proteasome. We investigated in *Saccharomyces cerevisiae* the degradation of Inp2, a peroxisomal membrane protein. Previous work has suggested that Inp2 must be degraded for proper peroxisome inheritance during mitosis. Disrupting the proteasome by deleting the Pre9 subunit or treating with the proteasome inhibitor MG132 both partially stabilized Inp2 levels, while deleting vacuolar genes (*ATG1*, *YPT7*, and *PEP4*) did not. These data suggest that the ubiquitin-proteasome system is involved and argue against the possibility of Inp2 degradation by vacuolar proteases. Next, we tested peroxisomal candidate genes that mirror the function of quality control genes in ERAD and MAD (*PEX1*, *PEX2*, *PEX4*, *PEX5*, *PEX10*, *PEX12*, and *MSP1*), but none showed any effect on Inp2 when knocked out. Future work will include an unbiased fluorescence-based genetic screen to uncover Inp2 degradation factors.

Genetic Causes of Central Precocious Puberty: Mutations Within the Imprinted Genes MKRN3 and DLK1

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Central precocious puberty (CPP) is a condition in which individuals prematurely develop puberty. CPP is characterized by the development of secondary sexual characteristics, in girls and boys as early as 8 and 9 years of age respectively. Although studies show that CPP is determined largely by genetic factors, the specific genetic determinants of CPP are to a great extent unclear.

The onset of puberty in humans is due to the secretion of gonadotropin-releasing hormones (GnRH), which stimulate pituitary gonadotropin, LH and FSH, to activate gonadal function. Studies in Dr. Kaiser's lab have recently shown an association between mutations in the makorin RING finger protein 3, *MKRN3*, and individuals with CPP. As a result, these individuals exhibit secretion of GnRH earlier and puberty is initiated sooner. Provided that *MKRN3* was a maternally imprinted gene, the affected individuals inherited the mutation from their fathers. This further suggested that the loss-of function of *MKRN3* mutation had a causative relationship with CPP.

Although *MKRN3* is now known to be the most common cause of CPP, literature indicates that the mutation accounts for about 40% of familial cases. Recently, a deletion in Exon 1 of (*DLK1*), encoding Delta-like 1 Homolog was identified in one CPP family from the original study that identified *MKRN3*. We are utilizing polymerase chain reaction (PCR) amplification followed by Sanger sequencing to screen for mutations in *DLK1* and *MKRN3* in patients with CPP. Results from the PCR amplification have demonstrated perfect segregation of the *DLK1*

deletion with the phenotype and have also confirmed the *MKRN3* variants. Consequently, *DLK1* shows potential in being a likely cause of CPP as a loss-of-function mutation. This research on *MKRN3* and *DLK1* provides insight into both the extensive genetic role of imprinted genes in CPP and their contribution to regulating pubertal development.

Computational and Structural Investigation of Conformational Changes in Nramp Family Proteins

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Transition metals, such as iron and manganese, are vital to living systems; abnormal iron uptake in humans increases susceptibility to infectious and neurodegenerative diseases. To maintain metal ion homeostasis, cells use transmembrane proteins to transport divalent metals across cellular membranes. One such class of transport proteins is the Natural resistance-associated macrophage protein (Nramp) family transporters. One mammal Nramp homolog is present in the small intestine, where it facilitates dietary iron absorption; another mammalian homolog enhances host immune response by extracting essential metals from pathogens.

To transport divalent metals, the Nramp family generally features a "rocking bundle" alternating access mechanism. In this mechanism, the binding site for the substrate is at a fixed point. The protein scaffold remains relatively stationary in the cell membrane while the four-helix bundle rocks relative to the scaffold, alternating the protein between extracellular-facing (outward) and intracellular-facing (inward) conformations. However, morphs of other rocking bundle transport proteins in the Leucine Transporter (LeuT) family indicate that the helices in the scaffold still exhibit significant conformational changes. To help elucidate these conformational changes, I have computed the difference distance matrices (DDM) for several rocking bundle proteins, an objective method of providing insight into conformation and movement of protein regions as the protein alternates between inward and outward conformations. In addition to computational methods, I have also prepared two mutant Nramps in an effort to crystallize and eventually obtain novel structures.

Using a multiple sequence alignment and coevolution methods of a large set of Nramp family protein sequences, we hope to further investigate the structure of proteins in the Nramp family. Ultimately, in doing so, we hope to identify critical features and functions of the protein that may lead to more insight into the implications the transporters have in biological systems and disease.

Inferring HIV-1C Transmission Networks in Botswana Using Next-Generation Sequencing of Near Full-Length Viral Genome

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HIV prevention strategies and combined intervention packages are increasingly important to controlling the HIV/AIDS epidemic, and to the reduction of HIV incidence. Better understanding of HIV transmission dynamics, could help to gauge the effects of current interventions and determine the most efficient prevention interventions for the future. Monitoring the emergence of drug resistance mutations in circulating viral lineages has a direct clinical implication. We are conducting a phylogenetic cluster analysis of HIV-1 subtype C, analyzing the near full-length HIV genomes isolated from patients sampled within the Botswana Combination Prevention Project (BCPP).

In our research, we amplify a near full-length fragment (~8 kb) of the HIV-1 genome through RT-PCR (viral RNA) or PCR (proviral DNA). This first round product is verified for specificity through a control second-round PCR, before being used as a template in next-generation sequencing (NGS) at the Biopolymer core facility. The raw sequencing data are analyzed by running quality control metrics, selecting the HIV-1 subtype C reads, and assembling the Illumina short reads into consensus sequences for each patient sample (FASTA files) and generating minor variants files. We are currently optimizing the methodology for long-range HIV genome amplification to achieve maximum cost-effectiveness.

The generated viral sequences are used for analysis of HIV transmission dynamics and identification of minor mutations associated with drug resistance. Specifically, we infer viral phylogeny by Maximum Likelihood and estimate strength of clustering by bootstrap and pairwise genetic distances to better understand the magnitude and patterns of HIV transmission networks across Botswana communities. We also analyze drug resistance mutations in viral sequences to monitor the ongoing scaling-up of the anti-retroviral treatment (ART) program in Botswana.

Neuroscience

The Effects of a Glycosylated Variant of Microglial SIRP Alpha on Early Development

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Microglia, the immune cells of the brain, are integral components of the central nervous system. They communicate with several other brain cell types to regulate neural circuit refinement. Importantly, microglia characteristically engulf material, known as phagocytosis. Microglia have been shown to phagocytose cells, myelin, and even synapses, actively shaping the structure and function of neural circuits. Dysregulated microglial phagocytosis can lead to impaired neural communication, compromising brain development and function and contributing to neurodevelopmental and psychiatric diseases.

We have been investigating the role of signal-regulatory protein alpha (SIRPα), a membrane protein enriched in microglia during early postnatal ages, in regulating microglial phagocytosis. Our preliminary data show that when SIRPα is knocked out in the whole animal, microglial engulfment of neural inputs is increased. Interestingly, microglia express a variant of SIRPα that contains a glycosylation modification that is most prominently expressed at early postnatal stages when microglia are highly phagocytic. To determine if glycosylation is important for regulating microglia phagocytosis, we generated a viral construct in which the glycosylation sites in SIRPα are mutated so that they are all removed. Using an *in vitro* microglial phagocytosis assay, we will test the effects of SIRPα glycosylation on microglial phagocytosis by comparing microglia expressing mutated SIRPα to wild type SIRPα. Afterwards, we will delete each of the glycosylation sites in separate constructs to determine how localized removal of these glycosylation sites will affect SIRPα function. This will give us insight into SIRPα function and how it could be interacting with other molecules to influence phagocytosis.

Exploring Pathogenic Cascades of Alzheimers Disease Using 3D Human Neural Cell Culture Models

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Alzheimer's disease (AD) is the most common form of dementia. The pathologic hallmarks of AD include amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs). Current AD mouse models develop Aβ plaques but do not progress to the later stage including Aβ-driven NFTs and robust neurodegeneration. Our work focuses on understanding pathogenic cascades using the 3D culture model of AD.

Previously, we identified 790 differentially regulated genes in AD 3D cultures by whole RNA sequencing analyses ($n = 4$ for control and $n = 3$ for AD; $FDR < 0.05$, $|\log FC| > 1.0$). To further understand the pathogenic cascade, we took RNA sequencing data from our 3D models and compared it with previously published human AD brain microarray data. Our analysis centered on documenting where genes overlapped in expression in the same direction across samples. Using Ingenuity Pathway Analysis (IPA, Qiagen), we identified multiple cellular pathways and upstream regulators that are altered both in our 3D AD culture model and human AD brain samples. We plan to test if chemical/genetic manipulations of these pathways can modulate pathogenic cascades.

Our work also includes continued development of new AD cell lines based on selected mutations,

which can specifically alter the ratio of pathogenic Aβ species. We are constructing multiple lentiviral vectors that can deliver these mutations into human neural stem cells. These would provide valuable information regarding AD pathogenic cascades, triggered by different Aβ species.

Our study will assist both in understanding the mechanism behind AD and finding viable treatments for AD patients.

Visual Learning in Non-Human Primates

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What do we recognize when we look at an image, for example, this abstract book? Rather than an insignificant mental snapshot of a rectangle, corners, lengths, and angles superimposed on our lenses, our visual system is able to untangle these into meaningful objects. This occurs via a process known as invariant object recognition, the extraction of individual features independent of background illumination and orientation. While our knowledge of this peripheral processing of an image is substantial, our understanding of higher level visual cortex processing is still nascent.

The use of rodents in the study of visual learning is becoming increasingly popular, as more studies demonstrate their ability to discriminate between objects. Their neuroanatomy also has many parallels with the human cortex; in humans the ventral "What" stream is responsible for determining the presence of object features in an image, and the rodents' cortical regions "LM, LI and LL" are thought to play a similar role.

This project aims to create a functional and anatomical map of visual learning in rats. To do this, rats are trained to discriminate between two visual objects in exchange for liquid rewards using high throughput behavioral training rigs until they have mastered this behavior. After training, rats will have a head implant attached for imaging sessions, and a cranial window through which it is possible to image the brain's neurons underneath. This will allow us to establish which neurons are active when learning.This information can aid our creation of the visual map as well as inform our understanding of visual recognition in non-human primates.

3-D Reconstruction of Mammalian Brain Clock Connectome

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The mammalian sleep-wake cycle is regulated by two biological mechanisms. The first component is homeostatic sleep drive, in which sleep pressure builds up as the need for sleep increases over a period of wakefulness. The second component regulates circadian rhythms, which are processes that oscillate about every 24 hours independent of the need for sleep. In most mammals, these cycles are regulated and maintained by the suprachiasmatic nucleus (SCN), which acts as the body's central circadian pacemaker and is located within the hypothalamus.

The SCN displays unique network properties that allow the body to entrain to environmental time cues including light exposure while maintaining a near 24-hour sleep-wake cycle in the absence of these cues. A subset of neurons that contain vasoactive intestinal polypeptide (VIP) are the primary drivers of this circadian rhythm. To visualize the connections among these neurons that facilitate communication and synchronization, serial electron microscopy enables the resolution of individual neurons and synapses in a 3-D block of tissue. The images are processed using software developed by Daniel Berger to reconstruct entire volumes of brain tissue and create digitized wiring diagrams, which provide three-dimensional datasets that allow for structural analysis of the tissue. Describing the structure of the clock would provide a groundwork for understanding how it keeps time, which could eventually be applied to understanding debilitating circadian rhythm disorders that can result in conditions such as insomnia and incapacitating excessive daytime sleepiness. Shift workers, the visually impaired, and frequent travelers are especially susceptible to these disorders.

Characterizing the Morphology and Interactions of Microglia in the Developing Cerebellum

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During developmental and adult learning, neural circuitry is refined by synapse addition and elimination, leading to altered connectivity in synaptic networks. The result of this synapse rearrangement is a functional network containing memory traces that generate and influence behaviors. Of recent interest in the ways synaptic connections are altered is a class of non-neuronal cells known as microglia. These cells are commonly referred to as the resident immune cells of the central nervous system because they take care of debris from damaged neurons and other cells in the brain. Furthermore, because microglia are present in the brain during development, and because deletion of microglia-related genes is associated with neurodevelopmental cognitive disorders, researchers suspect that these cells play an important role in maintaining and pruning synapses.

This project aims to characterize microglia in the context of morphology and cell-cell interactions in the developing mouse cerebellum. Microglia were identified in serial electron microscope (EM) data from postnatal day 7 mouse cerebellum, and traced using VAST, a computational tool developed in the lab. My preliminary reconstructions show extensive branching and at least one instance of phagocytic encapsulation of a dying neuron, consistent with what is known about the cells ramified structure and immune function. Visual inspection also revealed that processes can be tendril-like, weaving through extracellular space, or sheath-like, encapsulating neuronal processes. A better understanding of microglial characteristics and their role in synapse reorganization may provide insight into how the normal brain matures and what is disrupted in disease.

Whole-Brain Activity Mapping of Early Onset Schizophrenia in Zebrafish

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Schizophrenia is a chronic neurological disorder afflicting about one percent of the population. It is characterized by degeneration of thinking, motor and emotional processes. While its symptoms such as hallucinations and behavioral regression are widely recognized, its causes are not well understood. Although schizophrenia has been diagnosed in children, early onset schizophrenia has received little attention in research literature. Furthermore, recent epidemiological and genetic studies have revealed a bidirectional link between epilepsy and schizophrenia. Epilepsy, a disorder defined by recurrent seizures, also affects one percent of the population. By examining the genetic overlap between the two diseases, we hope to better understand phenotypic abnormalities in both disorders.

In this study we used CRISPR/Cas technology to create genetic knockouts of genes associated with either or both diseases in zebrafish. We focused on examining genes implicated in early onset schizophrenia (EOS): atp1a3, pdxdc1, ntan1; nrxn3; ptprg, kcnq3, and in epilepsy: pcdh19. Some of the genes involved in EOS are also associated with epilepsy, such as atp1a3 and ntan1. In order to localize the neural circuits involved in generating schizophrenic behavior, we are currently examining the neural activity of these knockout zebrafish through phosphorylated extracellular-regulated kinase (pERK) brain imaging, a technique that documents the full brain activity of the zebra fish at the moment of fixation. In addition, we will conduct behavioral tests, to examine the difference in their response compared to wild type fish. Our goal is to shed light in the biological pathways and mechanisms involved in these diseases, so that we can identify suitable treatments to target these mechanisms.

Social Dominance Influences Competitive Foraging in Mice

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Social interactions play a key role in both human and animal behavior, and are commonly involved in neurocognitive disorders such as schizophrenia and autism. Despite the importance of interactive social behavior and its dysfunction, its single-neuronal basis and causal underpinnings are not well understood. One significant instance of social interaction dynamics between individuals is competitive foraging within groups of animals. In this study, we sought to elucidate the dynamics of competitive foraging behavior within groups of mice and investigate its neural underpinnings. Specifically, we observed the influences of social dominance hierarchies in groups of familiar mice performing a competitive food foraging task. Preliminary data indicates that social dominance influences the order in which mice access food, and this influence changes depending on the abundance of food. Next, we will use single-unit electrode recording to monitor neural activity in the anterior cingulate cortex, a center for processing information involved in competition, while the task is underway in order to link differences in behavior and socialization to different patterns of neural activity. Finally, we will observe differences in behavior and ACC activity between wild-type mice and Shank3 genetic knockouts during the task; Shank3 knockouts serve as a loose model of Autism Spectrum Disorder in mice, and allow us to investigate the effect of ASD symptoms on competitive foraging.

This research will give insight into the social and neurobiological mechanics of competition and success, allowing us to better understand the basics of group competitive behavior and how it differs from competition between two animals. Our hope is to open the door for further studies into competition in large and complex groups, the patterns of brain activity associated with such behaviors, and the effect of disease on competitive outcomes.

Effects of Maternal Immune Activation on Mouse Cortical Development

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Autism Spectrum Disorder (ASD) is a series of developmental disorders that affects approximately 1 percent of the world's population. Patients with ASD often exhibit difficulties in social behavior, challenges with communication, and a tendency of repetitive behaviors. The underlying causes of ASD are not well understood. Among various genetic and environmental risk factors, maternal immune activation (MIA) during pregnancy has been reported to increase the ASD risks in offspring. Mouse models are often used to mimic and better understand the phenotype exhibited by humans with ASD through introducing alterations of the mouse genome or systematic treatment by a bio-active reagent.

To investigate the mechanisms by which MIA contributes to ASD, we utilized polyinosinic:polycytidylic acid (polyI:C), a synthetic mimic for viral double-stranded RNA (dsRNA), which has been shown to cause cortical malformations during mouse development. We administered intraperitoneal injections of polyI:C or a saline control to pregnant mice during different gestational ages, which are critical periods of neural development of the embryos. The brains of the newly born pups were collected, cryopreserved, sectioned, and immunostained for cortical lamination markers, Satb2 and Tbr1. The images will be captured by a fluorescent microscope and the fluorescent stain-positive cells will be quantified by ImageJ. In the case of successful experiments, both the number and spatial distribution of Satb2- or Tbr1-positive neurons in the somatosensory cortex should show a significant difference between the groups treated with saline and polyI:C at different gestational ages. Based on the cortical phenotypes of the MIA mouse model, we will further examine the cerebrospinal fluid (CSF) composition and explore dysregulated signaling pathways responsible for the cortical phenotypes. These experiments may help us to better understand the cause and to discover novel therapeutic targets of ASD.

Proteasomal Modulation of AD-associated Tau Toxicity

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The deleterious neurodegenerative pathology associated with Alzheimer's disease (AD) is correlated with elevated levels of neurofibrillary tangles composed of tau protein and senile plaques constituted by beta-amyloid peptide. Examining the role of the proteasome in the context of the cellular antioxidant response pathway may elucidate molecular pathways underlying Alzheimer's onset and progression.

In *Drosophila* models of tau-induced Alzheimer's disease, flies display adult-onset progressive neurodegeneration, early death, and accumulation of abnormal tau, consistent with human Alzheimer's pathology. Using the UAS/GAL4 system, human tau (τ-WT28) was expressed ectopically in *Drosophila* to deduce gene function and molecular underpinnings of AD. Since the *Drosophila* eye reporter is highly susceptible to cytotoxic stress, even minute damage results in several-fold amplification and disruption of the lattice, resulting in a rough eye phenotype. Using the GMR driver, a fly expressing tau with a mild rough eye phenotype was crossed with proteasomal modifier lines to screen for effects of those modifiers on modulating tau toxicity; observed suppression or enhancement of the corresponding rough eye phenotype suggests molecular interactions between tau and the modifiers.

The rough eye phenotype was enhanced in all proteasomal activity-suppressing modifiers, implicating the proteasome in ameliorating neurotoxic effects of abnormal tau accumulation. No differences between male and female rough eye phenotypes were observed. Future experiments will examine whether proteasomal activators are able to rescue severe rough eye phenotypes. One protein in particular, DmPI31, activates the proteasome *in vivo* and is a molecular target for upregulation that may elucidate pathways related to Alzheimer's and other tauopathies.

Biological and Computational Investigations of the Effect of Transcranial Random Noise Stimulation on Numerosity

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Transcranial electrical stimulation (tES) is a type of noninvasive brain stimulation that seeks to modulate cognitive function by applying a weak electrical charge to the scalp. There are three principle types of tES: transcranial direct current stimulation (tDCS), transcranial alternating stimulation (tACS), and transcranial random noise stimulation (tRNS). For tRNS, the random noise refers to the application of alternating currents of random frequencies. This increases the signal to noise ratio in the brain through a process known as stochastic resonance. Ultimately, this allows subjects to increase cortical excitability and up-regulate neuronal firing. Although research into tRNS's effects on mathematical cognition are preliminary, it appears to be able to increase subjects' performance on a variety of tasks ranging from tests of numerosity to arithmetic.

This summer I have begun engaging in both biological and computational testing of tRNS's effect on judgements of numerosity. Biologically, this entails performing tRNS on parietal regions of human subjects and testing for an effect in performance on a number discrimination task. Computationally, I am working on developing an artificial neural network to mimic the assumed reaction of biological neural networks to tRNS. This must be one that accurately identifies numbers and becomes more accurate following the injection of medium amounts of random noise into the system.

Molecular Mechanisms of Circadian Clocks: Structural Analysis of the Mammalian Nuclear PER Complex

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Circadian clocks are endogenous cellular oscillators that drive daily rhythmic cycles of metabolism, physiology and behaviour. In mammals, this involves executive control via a feedback loop present in most tissues, in which Period proteins (PERs), acting in a large nuclear PER complex (NuPER), repress Clock-Bmal1, the transcription factor that drives their expression.

The macromolecular composition of the mammalian NuPER complex is poorly understood. Our ultimate aim, therefore, is to resolve its structure using cryo-transmission electron tomography to obtain a three-dimensional model at atomic resolution. However, such analysis requires a sample with a high concentration of the NuPER complex, whose compositional and conformational heterogeneity can also be resolved. Thus, we assessed sample quality and concentration from mice liver extracts, with the core component of the NuPER complex tagged with FLAG and HA epitopes. These were subsequently purified by FLAG and HA co-immunoprecipitation, and then quantitatively analysed by size-exclusion chromatography coupled to multi-angle light scattering (SEC-MALS). This revealed a macromolecular complex of diameter 46.41 ± 2.14 nm and molecular mass 1.56 ± 0.18 MDa, which is consistent with previous results. The presence of this 1.6 MDa complex was also confirmed by Western blots and NuPAGE monitoring of the SEC-MALS elution fractions.

Obtaining a high-resolution structure of the mammalian NuPER complex will significantly advance the field of chronobiology, allowing us to elucidate the specific molecular interactions between its constituent proteins. This will enable further investigation into the fundamental mechanisms governing circadian control.

Degradation of Perineuronal Nets Leads to Increased Plasticity and Higher Learning

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Critical periods are times in early life during which plasticity, the ability of the brain to reorganize neural networks based on experiences, is especially high. As critical periods close, mechanisms in the brain such as perineuronal nets (PNNs) put a brake on plasticity. PNNs are structures which solidify around neurons with age, thus limiting plasticity. The Hensch lab is researching the ability to increase plasticity in adult mice, effectively re-inducing critical periods, by degrading PNNs inthe medial prefrontal cortex with the enzyme Chondrotinase-ABC (ChABC).

The lab is using a 4-choice odor-based foraging paradigm. Mice are injected with ChABC or penicillinase (control), and three days later have their learning tested by searching for treats correlated to certain odors. Learning is quantified by number oftrials to reach criterion, in both discrimination and reversal tasks. After testing is complete, mice are sacrificed and their brain slices are stained with WFA to highlight PNNs and DAPI to highlight nuclei, in order to observe the extent of PNN degradation.

The lab has found that mice with degraded PNNs learn at a much faster rate, in both discrimination and reversal. These adult mice exhibit the same learning capabilities as juvenile mice still in their critical periods.

With such results, degradation of PNNs continue to appear as a promising method to re-induce critical periods plasticity in adults, and more specifically, increase learning capabilities. Additional research should explore if there are other affects to short-term PNN degradation, such as increased oxidative stress on neurons.

Partial Reconstruction of the Corticofugal Feedback Pathway From Visual Cortex to Thalamus

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The lateral geniculate nucleus (LGN) is a brain center located in the thalamus which is primarily known as a relay center for sensory visual information from the retina to primary visual cortex. However, the majority of synaptic inputs to the LGN actually comprise a modulatory feedback pathway from visual cortex to thalamus, called the corticofugal pathway. In order to partially reconstruct the connectome, or wiring diagram, of this feedback corticofugal pathway, we used serial section electron microscopy, a technique in which biological tissue is perfused, cut into thin sections, imaged, and digitally reconstructed. Small-bouton axonal inputs to the distal dendrites of thalamocortical cells (TCs) were examined and traced through the network to identify their postsynaptic partners. Preliminary findings raise the possibility that corticofugal axons might target TCs with less specificity than retinofugal axons from the forward pathway do. If this result is confirmed, this could suggest a more globalized and less specific modulatory function for the feedback pathway as compared to the forward pathway to LGN.

Identifying Genes Involved in Axon Regeneration Through a Forward Genetic Screen

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Unlike many neurons in the Peripheral Nervous System (PNS), neurons in the central nervous system (CNS) have very limited regeneration following axonal damage. After a CNS neurons axon is cut or crushed, Wallerian degeneration of the axon and neuronal death typically occur. There is a general consensus among scientists that both extrinsic (i.e. environmental) and intrinsic (i.e. cellular) factors play a role in this limited regeneration. Our research attempts to shed light on the intrinsic factors by identifying potential transcription-factor (TF) coding genes that are involved in inhibiting axon regeneration.

We hope to accomplish this goal through a forward genetic screen. We are using an in-vivo CRISPR procedure to knock-out various TF genes in the retinal ganglion cells (RGCs) of a mouse model and then measuring the relative degree of axon regeneration post-damage. The greater the axonal regeneration, the more likely the knocked-down gene is involved in inhibiting regeneration.

While we have not yet identified a silver bullet, preliminary results reveal that certain transcription factors are more involved in axon regeneration than others. We expect that, after testing all TF-coding genes, we will be able to compile a list of potential genes/TFs that are integral to regeneration and warrant further study.

Understanding the intrinsic factors underlying axon regeneration is integral to finding a way to restore CNS neuron regeneration. This, in turn, has countless medical applications, such as repairing nervous system damage in paraplegics. Our results will greatly contribute to future neuroregeneration research.

Image Registration for *in vivo* Voltage Imaging in Awake Behaving Mice

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Motion artifacts are a challenge for *in vivo* voltage imaging of neurons. These artifacts, resulting in part from heartbeats, breathing, and ambulation, make it difficult to extract and analyze accurate voltage traces of the cell membranes in an imaged movie. Thus, motion correction or image registration is critical for the success and utility of *in vivo* voltage imaging in behaving animals, most commonly mice. This

study introduces an image registration algorithm for imaged movies that corrects for motion in the x-y plane using the normalized cross correlation matrix of each frame compared to a reference frame. To increase efficacy, the algorithm restricts attention specifically to user-identified regions of interest that closely circumscribe the visible cell bodies. In addition, using the third and fourth central moments, or skewness and kurtosis, of pixel intensities in each frame, the algorithm is able to identify and eliminate most defocused frames caused by unwanted motion in the z direction. This method improves upon the motion correction algorithms, such as TurboReg and moco, that have been used for *in vivo* calcium imaging data by accounting for the lower signal-to-noise ratio (SNR) and the narrower spike patterns seen when employing voltage imaging. The algorithm's accuracy has allowed for improved collection of *in vivo* voltage traces from walking mice that allows for better analysis of spiking patterns and subthreshold levels.

The Effects of Substance P Blockade on Dry Eye Disease

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Dry eye disease (DED) is a multifactorial disorder of the ocular surface system affecting more than 10 million individuals in the U.S. alone. While the pathogenesis of DED is not fully understood, it is hypothesized that inflammation plays a prominent role in the development and progression of DED.

In normal corneas, resident populations of bone marrow-derived immature CD11b+ antigen presenting cells (APCs) are present. While immature APCs express low levels of cell surface protein MHC-II, inflammation induces APC maturation via increased expression of MHC-II and costimulatory molecules. One such substance implicated in inflammation is substance P, a neuropeptide that has been shown at increased expression levels in the early induction phase of DED.

In one experiment, substance P receptor antagonists were applied to dry eyes induced mice. Corneal fluorescein staining (CFS) and whole-mount immunofluorescence corneal staining for CD11b and MHC-II were performed. Images from the immunofluorescence corneal staining were taken using a confocal microscope, and the number of corneal CD11b+ and MHC-II+ cells were counted and compared. Flow cytometry was used as a secondary method to confirm the number of CD11b+ and MHC-II+ cells.

DED is associated with increased CD11b+ cell number and MHC-II expression levels, and preliminary results show that treatment with substance P antagonists actually decreased corneal fluorescein staining, CD11b+ cell numbers, and MHC-II expression levels. As CFS is used as a clinical measurement of dry eye severity, the results suggest that suppressed APC activation may be the mechanism by which substance P blockade reduces DED severity. Further study of substance P is needed to more fully characterize its role in DED pathogenesis, of which an understanding is necessary for the development of novel therapies that more effectively treat the inflammatory changes and clinical signs accompanying DED.

Organismic and Evolutionary Biology

Quantitative Analysis of Epigenetic Modifications in Immune Cells Following Exposure to *Mycobacterium bovis* in Humans

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Mycobacteria and humans have co-evolved beginning over 100,000 years ago. However, in the past century, a greater emphasis on hygiene reduced the bacteria's ability to sufficiently mature the immune system. This supports the "Hygiene Hypothesis" that widespread increases in autoimmune diseases and allergies in humans today are from decreased symbiotic relationships with bacteria. Global efforts are being made to successfully reintroduce mycobacteria to the human microbiome as a defense against autoimmune disorders such as type 1 diabetes mellitus (T1D). Current clinical trials have produced vast arrays of data highlighting the epigenetic changes

in T1D humans following the administration of the Bacillus Calmette-Guérin (BCG) vaccine, which introduces *Mycobacterium bovis* back into the human body.

In an effort to elucidate the mechanism by which the BCG vaccine acts on the human immune system, I have examined the epigenetic changes resulting from these immunized T1D patients using statistical software such as R's Bioconductor package and specialized BioIT tools such as Qiagen's Ingenuity Pathway Analysis (IPA). In this analysis of T1D subject data, I have observed significant epigenetic changes within various genes spanning the entire genome, including several known clusters directly involved in T1D metabolism. By examining a gene set of over 21,000 genes, including ~450,000 sites of DNA methylation, I have observed the epigenetic effects of the BCG vaccine in two cell types—CD4 T-cells and monocytes—in both *in vivo* and *in vitro* experimental settings. Preliminary results show significant methylation differences among patients in genes directly involved in glucose metabolism, specifically in pathways such as glycolysis, the Krebs cycle, and the pentose phosphate shunt. The epigenetic shifts may provide evidence for the efficacy of the BCG vaccine as a novel, widely available, and inexpensive treatment for T1D patients.

Monogamy and the Evolution of Cooperative Burrowing in a Deer Mouse

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Cooperation is an evolutionary puzzle, given that competition for resources favors selfish actions. Yet cooperative construction of a shared shelter is widespread among animal taxa. In rodents such as naked mole rats, high genetic relatedness drives cooperation. However, motives for cooperative burrowing between unrelated individuals, as observed in the oldfield mouse (*Peromyscus polionotus*), remain unclear. Among burrowing species in the genus, only the oldfield mouse is genetically and socially monogamous, with both parents caring for offspring. Past studies of joint burrow construction between pairs of mice show that cooperation is highest in male-female pairs, suggesting the shared effort provides a reproductive benefit. However, the relationship between mating system and burrowing has not been formally examined.

My aim this summer is to determine whether male burrowing behavior changes with reproductive investment. Comparisons of individual trials show that males spend more time burrowing than females, and significant differences in burrow size between individual and paired trials only arose if one of the partners was male. To investigate the male-dominant asymmetry in burrowing behavior, I am conducting burrowing assays of mated male-female pairs. Using photo and video data, I will record burrow morphology and division of labor between males and females and compare these results to those of familiar but unbred male-female pairs. Increased male burrowing output in the presence of a mate would suggest that male effort is motivated by offspring investment, while the opposite would suggest that male burrowing proficiency may be more important for initially securing a mate. Ultimately, this study could shed light on the adaptive value of cooperative behavior in a monogamous mammalian system.

Investigating Neoblast Niche Markers in the Acoel *Hofstenia Miamia*

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Scientists have long sought to understand the molecular mechanisms underlying regeneration, the ability to repair wounds and to replace missing tissue. Recently, the acoel *Hofstenia miamia* was established as a novel model system for studying whole-body regeneration. Acoels are potentially the earliest bilaterian metazoans, and so identifying and comparing their regenerative mechanisms to those of later-branching groups may provide valuable insight into understanding regeneration from an evolutionary perspective. *Hofstenia* has a population of pluripotent adult stem cells called neoblasts that are both necessary and sufficient for regeneration. Throughout other model organisms, stem cells have been found to be maintained by the niche—a microenvironment in which the stem cell resides and receives fate-determining extrinsic signals. In this

project, we sought to identify and test the function of niche factors in *Hofstenia miamia*. We first conducted a literature search to identify niche genes in other model organisms of which there were homologs within *Hofstenia*. With the understanding that niche cells themselves are not stem cells, we conducted fluorescent *in situ* hybridization experiments to visualize the expression patterns of potential niche factors and to compare them to that of a known neoblast marker. Finally, we performed RNAi knockdown experiments to test the function of these candidate niche genes by examining if the knockdown of these genes impacted regeneration in amputated animals. Through these experiments, we hope to begin exploring the stem cell niche of *Hofstenia* and to eventually be able to compare it to that of evolutionarily distant species so that we may better understand the extent to which regenerative mechanisms are conserved across species.

Effects of Water Status on Phloem Loading and Leaf Turgor in *Quercus rubra*

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The photosynthetic performance of trees is closely linked with soil water availability. Because drought is predicted to increase with rising atmospheric CO_2, studies of the interaction between the xylem, the water transport pathway, and phloem, the carbon transport pathway, will shed light on how global climate change may impact forest productivity.

This study explored how changes in water status relate to the loading of sugars into the phloem of *Quercus rubra*, a major species in New England deciduous forests. It also investigated how soluble carbon compounds influence leaf turgor over the course of the day and the season. Leaves of five mature *Q. rubra* trees in the Harvard Forest were analyzed at four points over the growing season. During each seasonal time point, measurements and analyses were done over a 24-hour period to determine net photosynthesis, water potential, osmolality, and metabolite profile of the leaves.

Preliminary results showed that photosynthesis and osmolality increase as stomata open during the day. Based on the first two seasonal time points, midday osmolality and photosynthesis also increased over the summer. These findings suggest that there may be diurnal and seasonal trends of rising sugar concentrations in leaves, perhaps to help maintain turgor in times of water stress.

Further work will explore how phloem-loading is affected by diurnal and seasonal changes in plant water status. These findings will help us better understand how *Q. rubra* responds to changing water levels.

Integrative Pathophysiologic Associations of Cerebral Autoregulation, Vasoreactivity, and Neurovascular Coupling in Post-Concussion Adolescents, Young Athletes, and Adults

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The incidence of concussion is high among young adults, and recovery is often prolonged. Thus, understanding pathophysiologic changes underlying post-concussion symptom burden is important to devise effective treatments that can minimize its long-term sequelae. An impairment in cerebrovascular function may be among the culprits: prior data suggest that cerebral autoregulation (vascular ability to buffer against changing perfusion pressure) may be impaired; our group demonstrated that an impairment in vasoreactivity (vascular ability to respond to changes in blood gases) are strongly associated with post-concussive headaches and cognitive difficulties; and our preliminary data suggest that neurovascular coupling (vascular ability to alter regional blood flow to meet neurometabolic demand) may be directly associated with post-concussion cognitive difficulties.

Given these data, our study aims to evaluate the integrative relationships between autoregulation, vasoreactivity, and neurovascular coupling in relation to concussion. We recruited twenty-four young adult individuals diagnosed with a sports-related concussion within one year of their injury (six symptom-free, assessed using Post-Concussion Symptom Scale, and seven controls). We measured cerebral blood flow velocity in the middle cerebral artery (transcranial Doppler), end-tidal CO_2, and arterial blood pressure during a number of physiologic maneuvers designed to engage autoregulation, vasoreactivity, and neurovascular coupling responses in the subjects. Our interim results indicate

impaired autoregulation and a relationship between neurovascular coupling and cognitive symptom burden. These data have the potential to reveal important relationships between cerebrovascular pathophysiology and post-concussion burden, and may provide potential prognostic biomarkers for recovery interventions and treatments.

Microbiome-Level Effects on Atrazine Resistance in *Nasonia vitripennis*

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Pesticides are widely used in agriculture for pest management; however, non-target organisms are at risk of health conditions ranging from cancer to reproductive disease that are associated with pesticide exposure. Resistance to these chemicals may be due, in part, to the bacteria that live inside an organism, composing its microbiome. These bacteria can metabolize compounds into more or less toxic secondary metabolites. Despite their prevalent use and potential risks, exact mechanisms of pesticide detoxification within organisms remain largely unstudied.

Here we are investigating how the second most applied pesticide in the U.S., atrazine, affects the Hymenopteran model organism, *Nasonia vitripennis*–a laboratory model for insect pollinators. Previous studies, which involved rearing successive generations of Nasonia, found that wasps with a history of exposure can survive at higher rates than naive wasps. Because bacteria are responsible for chemical detoxification in many organisms, these differing survival rates may be due to their microbiome. Subsequent work has confirmed that bacterial strains isolated from the exposed wasps can metabolize atrazine *in vitro*. However, it is has yet to be verified if these bacteria are indeed responsible for the degradation of atrazine demonstrated *in vivo*.

We are testing whether the isolated bacteria are responsible for atrazine degradation in *N. vitripennis*. To test this, we fed atrazine-degrading bacteria to the wasps and compared their resulting survival rates. Detoxification of atrazine will also be confirmed and quantified using high performance liquid chromatography.

Results from these studies can help elucidate mechanisms of atrazine detoxification in living organisms and provide insight into pesticide resistance in target agricultural pests. Additionally, studies are imperative to understanding and protecting living organisms exposed to pesticides, from insects to consumers.

Detecting Pathogens in Cases of Encephalitis

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The cause of encephalitis, a sometimes life-threatening infection of the central nervous system, is often difficult to establish in a clinically relevant time frame. Moreover, traditional serological techniques are biased, meaning they require knowledge of the pathogen. Metagenomic sequencing (MGS), coupled with verification by reverse transcription quantitative polymerase chain reaction (RT-qPCR), is a new, robust technique for unbiased screening of pathogens causing encephalitis and other infections. Recently, MGS and RT-qPCR have been used for diagnosis and surveillance during the outbreaks of Ebola, Lassa virus, and Zika virus.

In an effort to apply this technique to an emerging virus, we have designed and optimized an RT-qPCR assay to validate Powassan virus (POWV) RNA in clinical samples. POWV is a tick-borne pathogen that causes encephalitis and is comprised of two distinct lineages in the Northeast and Midwest, spread by *Ixodes scapularis* and *Ixodes cookei*, respectively. In *I. scapularis*, POWV shares a vector with Lyme disease, and it is suspected that POWV coinfection with Lyme disease, in addition to POWV infection in cases of encephalitis of unknown etiology, is currently underappreciated. Briefly, we used synthetic DNA (gBlocks® gene fragments, IDT) of a conserved region of the POWV genome to test different primer designs and reagent conditions. We aimed to maximize efficiency and specificity of the assay while maintaining a strong correlation among serial dilutions of the gBlocks® to be used as standards. We then tested the optimal assay conditions using RNA in-vitro transcribed from the gBlocks® to more closely mirror a clinical sample.

Our assay can reliably detect POWV RNA concentrations as low as 10 copies per microliter four weeks faster than serological methods used by the Centers for Disease Control. This allows for time-sensitive, pathogen-specific clinical management and the continued, cost-effective surveillance and studies of POWV.

Sexual Dimorphism as a Metric for Early Speciation in *Anolis sagrei*

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Since the age of Darwin it has been known that habitat plays a major role in speciation. Speciation can occur when a single species is divided into two populations occupying different niches which are then subject to different selection pressure.The early divergence of one species into two can be signaled by observable morphological and behavioral differences between populations. One such difference is degree of sexual dimorphism, or the suite of characteristics known to differ between male and female sexes. The lizard species *Anolis sagrei* is commonly found across the islands of the Greater Antilles and is known for its rapid diversification and large degree of sexual dimorphism. This makes the species a prime candidate for the study of both morphological and behavioral differences between sexes, as well as the differing degrees to which this sexual dimorphism plays out across different habitats.

In order to precisely quantify sexual dimorphism, a set of diverse, sexually dimorphic performance-based and morphological traits of *A. sagrei* were measured. This was done using two different populations from two different habitats, forest coppice and beach scrub. Measurements including cling capacity, sprint speed, jump distance, bite force, and physical dimensions of lizards were compiled using principle component analysis to provide a complete view of sexual dimorphism. Preliminary results suggest that the performance data of males and females correlates with morphological data and previously observed sex- and habitat-specific behavior, and successful completion of this project could support the view of sexual dimorphism as a mechanism for niche expansion and evolutionary change in *A. sagrei*.

Physics and Biophysics

Designing a Self-Shielding Solenoid System With Low Field Region for the Lepton CPT Experiment

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According to the Standard Model, the charge, parity, and time reversal (CPT) symmetry is an exact fundamental symmetry of physical laws. If we reverse electric charge, invert the space coordinates and reverse time derivatives for all particles simultaneously, the new universe obtained will behave exactly like the original.

One implication of this CPT invariance is that the electron and positron have the same magnetic moments (but with opposite signs). The magnetic moment is a constant that relates the magnetic field applied and the torque it causes on a particle.

The most precise measurement of the electron magnetic moment was done by the Gabrielse Group in 2008. An array of electric fields and a uniform magnetic field was applied on the particle, restricting it to a small space called the Penning trap. Analyzing the motion of the particle inside this trap led to the measurement. The same principle can be used for the positron.

It is essential that the magnetic field be homogenous in space and time for an accurate measurement. External magnetic field sources (eg. subway) can disturb this uniformity. We use superconducting solenoids to produce the magnetic field. Flux conservation in the solenoids and Faraday's Law can be used to show that certain configurations of these solenoids provide self-shielding to the trap from external fields.

To this end, we calculate the self-shielding factor over the volume of the trap under changes in pressure, external fields, and system dimensions. A superconducting quantum interference device (SQUID) is proposed to be placed within the magnet bore above the trap. Based on superconducting

loops containing Josephson junctions, it can measure sensitive magnetic fields. However, there is a critical field below which materials exhibit superconductivity. We are involved in the design of a solenoid system with a high shielding factor and a low field region (<2000 gauss) to place the SQUID.

A STIRAP Laser System for the Ultracold Ground-State Molecular Assembly of NaCs

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Ultracold ($\sim$ 1μK) assembly of ground-state molecules would open up many exciting new possibilities for research in fundamental physics and chemistry. Examples include the study of chemical reaction dynamics in the quantum regime and the construction of complex systems for many-body quantum physics, alongside various applications in quantum computing.

Using the techniques of atomic, molecular and optical physics to work towards the ground-state assembly of NaCs molecules, the Ni group has recently demonstrated quantum motional control of constituent atoms. Two optical tweezers containing Na and Cs will be merged to create a weakly bound NaCs molecule. The final step in the production of ultracold ground-state NaCs is to coherently drive a transition from the weakly bound state to the molecular ground state, utilizing a scheme known as stimulated Raman adiabatic passage (STIRAP).

This project aims to construct a laser system to drive this STIRAP transition. The system includes two external cavity diode lasers, which are tunable and have a narrow linewidth. After initial construction the lasers will be completed by locking to a high-finesse reference cavity, which provides the necessary frequency stability.

Exhibiting Proximity-Induced Spin-Orbit Coupling in Monolayer Graphene with the Anomalous Hall Effect

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Majorana fermions may be the building blocks of future fault-tolerant quantum computers. They are predicted to emerge as quasiparticle excitations, or emergent particle-like phenomena, at the edges of 2D topological superconductors. Graphene, a one-atom-thin semiconducting carbon lattice, exhibits conducting edge states in the presence of spin-orbit coupling, or the magnetic interaction between electron spin and momentum. The proximity effect between a conventional superconductor and graphene's edge states theoretically produces Majorana bound states at the junction. While graphene is an ideal high-mobility 2D electron system, it ordinarily exhibits negligible spin-orbit coupling. I aim to enhance spin-orbit interaction by coupling graphene to a ferromagnetic yttrium iron garnet (YIG) film, in ultimate pursuit of topological superconductivity. I will probe proximity-induced ferromagnetism in graphene by demonstrating the anomalous Hall effect (AHE), a manifestation of the Hall effect that results from spin-orbit coupling. I first exfoliate and deposit graphene and boron nitride (BN) on SiO_2 substrates, using atomic force microscopy to identify clean, homogenous flakes. Graphene flakes are transferred to YIG using a dry-transfer process, capped with BN to improve transport, and topped with a metal gate and HfO_2 dielectric to tune carrier density. I use a combination of electron-beam lithography, reactive-ion etching, and thermal metal deposition to define device boundaries and write gold contacts. After completing device fabrication, I will measure the gate voltage and external magnetic field dependencies of graphene's transverse and longitudinal resistivity at 4K. A magnetization-dependent contribution to the transverse resistance would signify the AHE, allowing me to preliminarily characterize a possible host system for Majorana bound states.

Improving Two-Legged Walking Gait With Centroidal Dynamics Approach

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Designing efficient walking algorithms for bipedal robots navigating uneven or unpredictable terrain is a difficult and important problem in robotic locomotion. In the past few years, several researchers have explored approaches that reason about centroidal dynamics. These approaches design walking behaviors by optimizing the linear momentum and angular momentum about the robot's Center-of-Mass (COM) by controlling external forces and torques applied at the robot's contact points.

For my summer research, I investigated an approach to robot walking control design that marries ideas from physics-based reactive locomotion strategies with trajectory optimization for aperiodic locomotion. The first part of my summer project was to implement this approach to centroidal dynamics on a model of a two-legged ostrich-like robot, named Cassie. I translated the mathematical model into code, tested the algorithm on the simulated model of Cassie using the Drake simulation toolbox, and evaluated how this method compared to previous walking gaits. The second part is to marry this centroidal dynamics approach with trajectory optimization algorithms that our lab has created. These algorithms will enable the robot to not just step forward blindly, but plan beforehand, which is necessary for walking on uneven surfaces. This two-sided solution should enable both reactive and predictive movement across uneven and unpredictable terrain.

Preparation and Characterization of Atomically Flat, Singly Terminated $SrTiO_3$ Substrates Using a Deionized Water and HCl Acid Etch and Anneal Under O_2

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We report a reproducible procedure to prepare atomically flat, singly terminated (001) surfaces of Nb-doped $SrTiO_3$. $SrTiO_3$ is a widely-used substrate for growth of thin films by molecular beam epitaxy (MBE), and high quality growth is dependent upon the substrate surface that can be terminated by either SrO or TiO_2. Procedures for preparing Ti-terminated surfaces usually incorporate etching and subsequent annealing under O_2. We compare a one-step etch of only hot deionized water to a two-step etch of hot deionized water and HCl acid, and we compare various anneal temperatures under O_2. Etching the $SrTiO_3$ samples in 90°C deionized water followed by HCl and subsequent annealing at 1000°C in O_2 resulted in the best quality surfaces. Atomic force microscopy (AFM) and reflection high energy electron diffraction (RHEED) were used to analyze surface topography. Of the 12 samples prepared with this procedure, AFM measurements showed atomically flat terraces of $\sim$ 400 pm step heights, suggesting single termination, with a typical roughness of less than 100 pm. RHEED showed 1×1 and $\sqrt{13} \times \sqrt{13}$ surface reconstructions, stable at least up to 800°C. This procedure has demonstrated consistent results, and it can be applied to preparing $SrTiO_3$ substrates for applications such as MBE growth of FeSe. This would enable further investigation of the 1 unit cell $FeSe/SrTiO_3$ heterostructure in how it increases the superconducting transition temperature of FeSe.

Mapping of the Odorant Response Space of the Nematode Worm *Caenorhabditis elegans*

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Olfaction presents difficulties not seen in vision or hearing, as the input space is not defined by one convenient axis (i.e., spatial or temporal frequency), and attempts to create such an odour space have as yet not been completely successful. We use the nematode worm *Caenorhabditis elegans* as a model for olfaction, studying how it parses this high dimensional odour space and how it responds behaviorally.

A genetically modified strain of *C. elegans* was used whose ciliated neurons, which includes all of those

thought to transduce chemosensory information, expressed GCaMP. This protein fluoresces in a calcium concentration dependent manner, and as calcium is a direct indicator of activity in the neurons of *C. elegans*, light intensity serves as a proxy measurement of activity. Odours were then presented to the worm using a microfluidics environment which permits repeatable application of set amounts of odour. In this setup the neuronal response was recorded.

Initial trials show activation of putative receptor neurons with each application of odorant. Areas of interest are the extension of the experiments to many more chemicals to attempt to map the odorant response space of the worm. In addition, the variation of the neuronal response with odorant concentration, which for the specific cases studied in previous literature is thought to be highly adapting and can even change from attractive to repulsive at different concentrations, could provide a rich vein of future analysis. Beyond *C. elegans* this will potentially provide a useful case study in neuronal processing for future application within neuroscience.

Angular Dependence in Junction Tunneling of Thin Film BSCCO

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High temperature superconductors are particularly interesting to scientists and engineers both because of their comparatively accessible superconducting states and their demonstration of a quantum mechanical phenomenon at temperatures governed primarily by classical mechanics. One such superconductor is the cuprate $Bi_2Sr_2CaCu_2O_{8+x}$(BSCCO). BSCCO has a lattice structure, with planes of copper oxide alternating with oxides of the alkaline metals. This structure makes superconductivity possible in thin flakes that contain a small number of periods of different oxide planes, but most superconductivity happens in the CuO_2layers.

Our experiment will test how the supercurrent travels between planes by measuring the junction resistance in crystals that have been split and rotated before being put back together. By pressing flakes between a silicon wafer and a sticky polymer, we can introduce forces larger than those holding the intermittent layers together, causing flakes to exfoliate when pulled from both sides. Rotating the substrate and returning the top portion of the flake creates an arbitrary rotation angle between adjacent planes in the lattice. Then using a stencil mask and gold evaporation to create contacts on each part of the exfoliated flake, we can pass a current between the layers and quantify the junction resistance; this is measured as the sample is cooled from room temperature to far below the superconducting transition. Repeating this in devices at various rotation angles (0, 45, and 90 degrees) aims to give better understanding about tunneling between layers, which can hint at the mechanism behind the crystal's ability to superconduct.

Imaging Electron Flow in Graphene

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Graphene is a two-dimensional allotrope of carbon with novel electronic properties arising from a unique band-structure. It is a zero-gap semiconductor, meaning that its valence and conduction bands intersect at points in momentum-space, termed Dirac points. At these points, on account of the linear relation between energy and momentum, charge-carriers in graphene can be modeled as massless fermionic quasiparticles described by the (2+1) dimensional Dirac equation. Thus, the conventional model of electron behavior in metals, Fermi liquid theory, theoretically breaks down around the Dirac points in graphene. Recent studies have found that, in this regime, strong Coulombic interactions make the electron flow hydrodynamic in nature.

The goal of this study was to fabricate a monolayer graphene device, and to image electron flow in that device using scanning gate microscopy. We are still in the fabrication stage, which involves encasing graphene with hexagonal boron nitride substrates (to enhance electron mobility), and evaporating gold electrical contacts onto this hetero-structure (to facilitate electrical conduction). By varying the temperature of our graphene sample, we seek to probe the regime where the predictions of Fermi-liquid theory and Dirac-liquid theory diverge.

A Characterization of the 2D Ising Model Phase Transition With Deep Learning

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Phase transitions, transitions between two phases of matter arising from broken symmetries, are present in physical systems such as cell membranes, atomic nuclei, and the early universe. These transitions are often analyzed with a statistical technique called the renormalization group, the repeated coarse-graining of a system to extract its salient features. Neural networks, such as Restricted Boltzmann Machines (RBMs), have also been used to analyze phase transitions. In an RBM, a dataset of visible elements, each represented as a string of binary data, is inputted, and the neural network performs unsupervised learning to relate the visible elements to a smaller string of hidden bits. Recently, an exact mapping was created between the renormalization group and an RBM. Using this exact mapping, the current research created an RBM to characterize the phase transition in the 2D Ising Model, a model of ferromagnetic matter that loses its magnetic properties past a critical temperature. More specifically, physical quantities such as the heat capacity and magnetic susceptibility were determined for the 2D Ising Model at temperatures close to the critical temperature. With the method developed by the current research, RBMs could be used to explore the properties of other phase transitions and the renormalization group.

Validity of the Adiabatic Born-Oppenheimer Approximation in the Tight-Binding Model of Graphene

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The adiabatic Born-Oppenheimer (ABO) approximation is widely used in molecular and atomic physics to simplify quantum mechanical calculations. In a molecular system that possesses nuclei with time-dependent coordinates, the electronic wavefunction can be computed in the ABO approximation by solving the time-independent Schrödinger equation at several time points for a Hamiltonian that is purely a function of the nuclear coordinates. We aim to show that this approach breaks down when calculating the time evolution of the electronic wavefunction of a finite sheet of graphene in the presence of thermal lattice vibrations.

We initially simulate a finite graphene sheet with thermal lattice vibrations, assigning nuclear coordinates that oscillate along normal modes. The Hamiltonian operator is then constructed explicitly as a sparse matrix using the nearest neighbor tight-binding approximation: the only nonzero terms in the matrix are the diagonal terms and the (i, j)-th elements for which atoms i and j are immediately adjacent in the graphene lattice. We then explore the dynamics of the graphene electronic wavefunction in the ABO approximation by explicitly solving the time-independent Schrödinger equation for multiple time points, considering only the n-th eigenstate of the Hamiltonian at each time point. Additionally, we calculate the system's true time-evolved wavefunction by approximating a solution to the time-dependent Schrödinger equation, taking the n-th ABO eigenstate at $t = 0$ as the initial condition. We then determine the probability that the ABO state predicts the true time-evolved state as a function of time; low probability indicates breakdown of the ABO approximation. Data acquisition from multiple simulated trials is currently in progress.

Realization of a Quantum Simulator With Boron-11 Nuclear Spins

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The computational resources required for numerical simulation of quantum mechanical systems rises exponentially with number of particles. Quantum analog simulators, where a well-controlled quantum system simulates the dynamics of another, promise a solution to such computational barriers. While research interest in quantum simulators has risen in recent years, an easily scalable, room-temperature quantum simulator remains elusive. We are trying to realize such a quantum simulator using strongly interacting nuclear spins on a diamond surface.

Our approach uses Boron-11 nuclear spins in hexagonal Boron Nitride deposited on a diamond surface to build such a quantum simulator. The ^{11}B nuclei can be manipulated using NV centers embedded in the diamond. The Hartmann-Hahn polarization transfer scheme offers a promising technique to initialize, read and control qubit using NV centers. The challenge in this project is to convert the spin-$\frac{3}{2}$ ^{11}B-nuclei into effective spin-$\frac{1}{2}$ qubits. This requires engineering of suitable quantum control over spin-$\frac{3}{2}$ that resembles standard gate operations on effective qubits. Furthermore, since the nuclear interaction between the nuclei impedes effective control of the spins, we need to develop methods to suppress interactions and isolate the nuclear spins. My project this summer is to theoretically engineer quantum control on spin-$\frac{3}{2}$ systems, understand the nature of interactions between ^{11}B nuclei and engineer techniques to isolate the nuclear spins, all towards the larger goal of realizing a scalable, room-temperature quantum simulator.

Characterizing the Gold-Mediated Exfoliation of Transition Metal Dichalcogenides for the Efficient Nanofabrication of Van Der Waals Heterostructures

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Mechanical exfoliation has become a typical method for obtaining monolayers from bulk transition metal dichalcogenides (TMDCs) for use in the nanofabrication of Van der Waals heterostructures. This method, however, is highly inefficient because of its low yield of monolayers. In this study we characterize the comparative efficiency of an alternative technique, the recently introduced gold-mediated exfoliation method for obtaining large monolayers. After mechanically exfoliating TMDC, gold is evaporated onto the TMDC's surface. A lattice mismatch between gold and the TMDC causes the topmost TMDC layer to adhere more strongly to the gold than to the rest of the TMDC. Thermal resistant tape is used to peel off the gold along with the topmost TMDC layer attached to it, and these are thermally released onto a silicon dioxide chip. The gold is etched off, leaving large area monolayers of TMDC on the silicon dioxide chip. We expand this method to the exfoliation of boron nitride, another frequent component of Van der Waals heterostructures, determining the most effective metal interfaces for this purpose. Large area monolayers of TMDC and Boron Nitride are invaluable for more efficient nanofabrication and the ability to scale the production of the devices made through this process.

Quantum Diffusion in the Strong Tunneling Regime

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We investigate the behavior of a quantum mechanical wavepacket on a lattice which has noisy energy fluctuations. A simple implication of quantum mechanics is that such a lattice with no noise and equal energy at each point (an ordered lattice) allows the wavepacket to spread at a constant velocity (an example is an electron traveling unimpeded in a clean metal). If instead the lattice points have different energies (disorder) the width of the wavepacket will remain constant over time for sufficiently strong disorder, a phenomenon known as Anderson localization. The disordered lattice model is relevant for understanding electron localization in a crystal with impurities. More recently it has been found that letting the energies fluctuate randomly in time will lead to a compromise between the two; the wavepacket diffuses, i.e. its width grows as the square root of time. We investigate the diffusion constant for this phenomenon under different regimes of three parameters: the strength of the noise, the correlation time of the noise, and the strength of tunneling between lattice points. A general solution for weak tunneling is known, and we extend this to stronger tunneling using the solution to the classical Landau-Zener problem on two-state quantum systems. These results may have implications in the study of ion diffusion in molecular crystals, probe particles in a photonic lattice, and Bose-Einstein condensates, to name a few.

Development of Precision Atom Translation in the Erbium Microscope

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The Greiner Lab studies various quantum mechanical interactions and effects present in ultracold gases, most recently in Erbium gas, which has very strong dipole-dipole interactions. The atomic gas is cooled down, slowing the atoms; two counterpropagating laser beams generate a set of optical well potentials, which serve to trap the Erbium atoms in an optical lattice. The Erbium lab is still in the construction phase of the experimental apparatus required to slow, trap and image the atoms. This project attacks one technical challenge, aiming to accurately and reliably transport atoms from one holding chamber to another. The required precision of the position of the atoms proves challenging: the atoms must be accurately moved to within tens of nanometers of the targeted area, since only well-positioned atoms can be accurately focused and imaged. Preliminary results match predictions from modeling and theory: an interferometer provides enough signal contrast (with an SNR of approximately 64) to accurately locate glass surfaces with ~4% reflection. The accurate location of glass surfaces in the system, such as the surface of the imaging lens, dictates the desired final position of the Erbium atomic lattice. In further work, the lab will seek to integrate this component of the setup into the larger experimental system.

Magneto-Optical Trapping of CaF With High Density

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Quantum computing—the use of quantum mechanical properties of a system to manipulate information—represents an exciting and growing area of research. However, most of what we know about quantum computers today is essentially theoretical, and the few practical developments are based on the interactions between single atoms, whose manipulation presents many challenges and limitations.

Polar molecules, thanks to their more complex structure, are an excellent candidate for the development of systems that can allow quantum computing. The first step in creating such a system is to cool down the molecules to very low temperatures (starting from the micro-Kelvin regime). In fact, since molecules in a solid are too stable and require very high interaction energies, and molecules in room temperature gases move too fast to be controlled, quantum computing requires very slow molecules, hence low temperatures (since temperature is a measure of the speeds of the molecules).

In John Doyle's group we work on magneto-optical trapping of CaF (calcium monofluoride) to achieve such a goal. Magneto-optical trapping (MOT) is based on the Zeeman effect—the splitting of degenerate energy states due to the application of a magnetic field—so that photon scattering can be efficiently used to restrict the motion of the molecules to a small volume. This promising technique has recently allowed us to cool about a hundred thousand CaF molecules to around 340 μK and further improvements could yield important applications in quantum computing.

Moir Superlattices in Stacks of Two-Dimensional Transition Metal Dichalcogenides

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The emergence of Van der Waals (VdW) heterostructures of two-dimensional or atomically thin materials has enabled novel electronic structures for charge carriers and light to interact with. In particular, the close spatial proximity between the crystal lattices creates new stable states that are governed by the separate electronic structures of the layers, and electrical interactions between electrons and holes in these layers. This project is interested in a stack of two transition metal dichalcogenides (TMDC) molybdenum diselenide ($MoSe_2$) and tungsten diselenide (WSe_2), which are two-dimensional direct bandgap semiconductors. The TMDC 2H phase of both $MoSe_2$ and WSe_2 have hexagonal crystal lattices. The dry transfer method used to make these stacks is imperfect, and without tunneling electron

microscopy (TEM) or other optical techniques it is difficult to stack these lattices commensurately. Even small rotation angles between $MoSe_2$ and WSe_2 creates a Moir superlattice that splits states that should be degenerate in commensurate stacks. However, the inability to sensitively (sub 1 degree) manipulate the rotation angle between the TMDCs makes it extremely difficult to study this splitting. This project seeks to fabricate a device to sensitively and reproducibly manipulate this angle.

Psychology

Overconservation in Grey Parrots (*Psittacus erithacus*)

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Inferential reasoning tasks are common in comparative studies of animal cognition. Piagetian liquid conservation, for instance, requires subjects to infer that a quantity of liquid remains unchanged even if its appearance changes or it is transferred to a differently-shaped container. A study by Pepperberg et al. indicated that grey parrots can solve conservation tasks by inference when the transfer is shown or when the parrot has previously observed visible transfers. In a related overconservation task, in which liquid quantities are not the same but appear to be, Suda and Call found that great apes sometimes used inference, but often relied heavily on perceptual cues in order to make their decision, leading to incorrect choices.

To learn more about parrots' abilities and to examine whether they display the same patterns of behavior as great apes, an overconservation task is being conducted with four grey parrots. The parrots are being tested in preliminary trials, in which different amounts of juice are poured into clear or opaque cups, either in the cup directly adjacent or across from it, so that the quantity on the left is poured in the cup on the right. Opaque destination cups prevent the birds from making simple visual comparisons. Birds are expected to pick the greater amount, as this means they could drink more juice, which they consider to be a treat. In the future, one destination cup will have a fake bottom so the amounts look the same. This will test whether the parrots are basing their choice on perceptual cues or inference.

Effects of Parental Socioeconomic Status on the Profile of Borderline Personality Disorder

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Borderline personality disorder (BPD) is a mental illness characterized by the inability to appropriately manage emotions, which frequently results in impulsive, dangerous behaviors and unstable relationships. BPD is present in 1-3% of the general population, and approximately 10% of patients who receive the diagnosis commit suicide. Further, costs associated with treatment and care present a major burden the healthcare system. While several studies have assessed the role of socioeconomic status (SES) as a risk factor for a BPD diagnosis, little research exists on the effect of SES on the various sectors and traits of the disorder, and how SES shapes the overall BPD profile. A total of 368 subjects—132 with BPD, 134 without BPD, and 102 with major depressive disorder—were administered 4 detailed interviews to assess demographic information, psychopathology, and treatment history; further, subjects' nuclear family members were interviewed over phone to obtain diagnostic assessments and family history. Using various statistical analyses on the IBM SPSS software, I will investigate the effects of parental SES on four core sectors of BPD—affective/emotional, interpersonal, behavioral/social, and cognitive—as well as a host of common traits of the disorder. Based off of prior research and the lack of treatment options available to lower SES groups, I predict SES to be negatively associated with impulsive and harmful behaviors, cognitive distortions, and extreme fears of abandonment. Further, I predict SES to be positively correlated with distorted sense of self, demandingness/entitlement, and anxiety. Assessing the differences in BPD symptoms and phenotypes across different SES groups will better inform future treatment directions and early interventions, particularly for populations of lower SES where treatment is currently lacking.

Understanding the Primary Visual Cortex (V1): Altered Resting State Functional Connectivity in the Congenitally Blind

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A single chair can be viewed from a thousand different angles and still be recognized as the same chair. The human visual processing system is complex and hardwired into the brain as a visual hierarchy, spanning from the eyes to the dorsal and ventral visual streams. The primary visual cortex (V1) is a well-understood hub for visual processing in healthy, sighted humans. What is far less understood is the function of V1 in the blind brain. The roles ascribed to the blind V1, deprived of its typical input, range from maintaining topographic mapping to functions remote from its original role, including language and memory. Beyond examinations of altered V1 connectivity to isolated brain regions, the relative connectivity of V1 to different regions of interest (ROIs) remains unquantified, and the role of V1 in the blind remains elusive. In this study, resting state functional magnetic resonance imaging scans are acquired from 12 congenitally blind subjects and 14 sighted control subjects. Signal decomposition analyses will be used to decompose the activity of V1. Decomposition with enable the connectivity of V1 to many ROIs across the brain to be quantified in a single dataset, to examine the total extent of plasticity in the connectivity fingerprint of this region. Blind V1 connectivity may be consistent with well-supported concepts of neuroplasticity and change of regional function. This study represents a small, quantitatively-driven piece of a larger puzzle to understand the role of V1 in the blind brain.

Examining Galvanic Skin Responses to Angry, Happy, and Fearful Faces to Explore the Development of Emotion Processing in the First Year of Life

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The ability to distinguish amongst emotional expressions and respond appropriately is crucial to human survival. At 7 months of age, infants look longer at fearful faces compared to faces with other expressions. However, infants likely do not process the meaning of the expression or show a physiological response until later in development. While undergoing a study on emotion processing of fearful, angry, and happy expressions, galvanic skin response (GSR) data were collected as a proxy for activity in the sympathetic nervous system and physiological arousal. Infant visits were conducted at 5, 7, or 12 months of age, with a total of 66 participants showing acceptable GSRs. Given that the fear bias typically develops at 7 months, it was predicted that 5- and 7-month-old infants would not show GSRs to any of the facial expressions. Since a physiological response to fearful stimuli may develop later, we hypothesized that, in contrast to the younger infants, 12-month-olds would display GSRs to fearful faces. To analyze these data, I will first look at the average number of GSRs to each emotional expression in the three age groups. Next, I will conduct an ANOVA to examine the interaction effects of age group and emotional expression on average number of GSRs. If our hypothesis is correct, then there will be a significant interaction effect. Post-hoc tests will reveal that 12-month-olds show a significantly larger number of GSRs to fearful faces compared to the other age groups. Future work will focus on whether this GSR response correlates with behavioral responses to fear.

Statistics

On Generalization and Capacity Control in Deep Networks

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Computer Science

Tomaso Poggio
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Mentor
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In recent years convolutional neural networks (CNNs) have experienced significant success on tasks such as object detection, but the reasons for this success are not fully understood. In particular, recent work has revealed that CNNs have the ability to learn random labels attached to image datasets such as MNIST, images of handwritten digits, and CIFAR-10, images of everyday objects. Nevertheless, on such datasets CNNs avoid "overfitting" and achieve low out-of-sample error when trained on true labels. Moreover, when the number of weights of a CNN that fits its training data perfectly is increased, the out-of-sample error can further decrease, in contrast to the behavior predicted by classical theory. Recent explanations proposed for this behavior include norm-based capacity control via Rademacher averages, algorithmic robustness arguments, and arguments based on the "flatness" of local minima found by gradient descent. In this work we strengthen Rademacher complexity-based bounds on neural network classes and provide an upper bound on the Rademacher complexity of function classes in terms of an algorithmic robustness parameter.

Modeling Severe Beijing Winter Haze Events Under Climate Change

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Daniel Jacob
School of Engineering and Applied Sciences

Mentor
Lu Shen, Department of Earth and Planetary Sciences

Accumulation of atmospheric particulate matter (PM2.5) in Beijing is responsible for economic slowdowns, extensive costs to health care systems, and a decrease in life expectancy; this accumulation is more likely under certain meteorological conditions. We study these conditions in the present and project their future changes under climate change at the end of the century.

We develop a statistical model using extreme value theory (EVT) capable of modeling exceedances of PM2.5 concentrations over public health thresholds, and use it to estimate changes in severe pollution episodes from 2009-2100. We perform a principal component analysis (PCA) on meteorological data, such as lower and mid-tropospheric winds, temperature instabilities in the atmosphere, and relative humidity, and identify leading areas of weather variance; this allows us to reduce the dimensionality of the problem and better optimize our model.

We then apply the two leading PCA components, accounting for 89% of meteorological variance, as covariates in a nonstationary Point Process (PP) model of PM2.5 concentration using the principles of EVT, allowing us to predict the probability of an extreme pollution event occurring under given weather conditions. We apply the resulting EVT model to projections of meteorological data from an ensemble of CMIP5 models reflecting a moderate climate change scenario (RCP4.5). The results of our analysis reveal issues with modeling relative humidity, an important predictor of PM2.5, and suggest a need for further study.

Stem Cell and Regenerative Biology

Cardiomyocyte Cell Cycle Dynamics With Multiple Stable Isotope Pulse Labeling and Clonal Analysis

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Richard Lee
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Mentor
Ana Vujic, Harvard Stem Cell Institute

After years of controversy, the frequency of new heart cell formation has been convincingly demonstrated to be around 1% per year in both mice and humans. However, many questions remain regarding new heart cell formation in mammals. Do some cardiomyocytes divide more than others? Do daughter cardiomyocytes stay together after mitosis? To address these questions, I will use dual

pulse-chase administration of stable isotopes 15N-thymidine and 13C-thymidine for two sequential pulse time periods in mice. I will image the cardiomyocytes that have enriched one or both of these stables isotopes into their nuclei using quantitative multi-isotope mass spectrometry (MIMS), and this allows me to determine when a given cardiomyocyte passed through the cell cycle, or if that cardiomyocyte passed through the cell cycle more than once. In addition, by using a fluorescent rainbow reporter system, the Myh6CreERRainbow mouse, I am able to test whether cardiomyocytes that divided during one or both stable isotope pulses localize with a clonal pattern. To provide the background of substantial cardiomyocyte cell cycle activity, I will induce a myocardial infarction in these mice, which has been shown to significantly increase cardiomyocyte cell cycle activity near the infarction area. This work will further the understanding of cardiomyocyte dynamics during the mammalian response to cardiac injury.

A Developmental Role for *Kazald1* in Axolotl Salamanders

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Jessica Whited
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Mentor
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Almost 10 million people worldwide suffer from limb loss and its devastating effects. While humans lack regenerative capabilities, axolotl salamanders can regenerate complex tissue structures, such as limbs. They provide an ideal model for studying limb regeneration, as the process occurs in a relatively short time frame and many of the structures in the axolotl limb mirror human counterparts.

The Whited lab has identified a gene significant in the limb regeneration process: kazal-type serine protease inhibitor (*kazald1*). *Kazald1* is highly upregulated in the blastema, a structure made of progenitor cells that forms shortly after amputation and will eventually give rise to the regenerated limb. However, it is not expressed in limb buds, intact limbs, or late-stage regenerating limbs. Investigating *kazald1* during the later stages of limb development is important, as experiments in the Whited Lab have demonstrated that misexpression of the gene during regeneration leads to severe limb defects.

While *kazald1*'s role in a regenerative context has been examined, the gene's role, if any, in initial limb development is still unknown. In mice, the orthologous *kazald1* plays a part in bone development and regeneration (Shibata et al.), and may have a similar function in axolotls. By performing in situ hybridizations on full-body tissue sections at multiple early developmental stages, we can visualize expression of the *kazald1* RNA transcript. Elucidating differences between the developmental and regenerative functions of a gene such as *kazald1* may open the door to triggering regenerative responses in usually non-regenerative organisms.

Evaluating Complementary and Alternative Medicines for the Treatment of Major Depressive Disorder in Human iPSC-derived Neurons

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Major depressive disorder (MDD) is a common mental disorder, affecting 10-15% of the population worldwide. Current research suggests that a dysregulation of neurogenesis plays a role in the pathophysiology of disease. Patients with MDD have decreased hippocampal volume due to abnormalities in the endocrine response to stress, thus indicating a need for disease-modifying therapeutics that address neuronal loss. Complementary alternative medicines (CAM), such as docosahexaenoic acid (DHA) and S-adenosyl methionine (SAMe), serve as promising candidates for targeting stress-induced neuronal loss. CAM demonstrate some success in clinical trials as adjunct treatments for MDD, yet their antidepressant mechanisms remain unclear and appropriate treatment doses are not well established.

Rodent studies suggest that CAM impact neurodevelopment and potentially protect neurons from oxidative stress. To examine these findings in the context of human disease, we studied the cellular response to both compounds in induced pluripotent stem cell (iPSC)-derived neural progenitor cells (NPCs) and neurons. Through a series of cellular assays, we confirm the effectiveness of CAM treatment on increasing the viability of NPCs. In

immature, one-week differentiated neurons, treatment with DHA and SAMe significantly improves cell survivability, suggesting that CAM may confer pro-resiliency. From reporter assays, we find DHA increases Wnt signaling, an essential pathway that regulates cell proliferation and cell fate. Using L1000 gene expression profiling and qPCR analysis we identified genes related to adult neurogenesis and oxidative stress regulated by CAM. Finally, we begin to characterize the mechanisms of CAM treatment in human-relevant *in vitro* disease models with implications for clinical research and treatment efficacy response.

Circulating Mediators Contribute to Cardiac Remodeling in Pressure Overload

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Mentor
Inbal Rachmin, Department of Stem Cell and Regenerative Biology

Hypertrophic cardiac remodeling is known to contribute significantly to ventricular dysfunction in various heart diseases including cardiomyopathy, hypertension, and ischemia-reperfusion. Despite important advances in our understanding of the pathophysiology and the availability of effective treatment strategies, the mechanisms through which hypertension eventually leads to heart failure remain unclear. It has long been assumed that the heart changes with hypertension due to the direct pressure overload on the cardiomyocytes. My project explores the concept that circulating blood factors play a role in the response of the heart muscle in a pressure overload model.

Parabiosis, the surgical joining of mice, allows for the study of circulating factors since the two mice share a common circulation. With a parabiosis model, we can separate the direct pressure effects of a transverse aortic constriction (TAC) operation from hormonal effects involved in cardiac remodeling, as we can study the mouse without pressure overload. A parabiosis or sham parabiosis operation will be performed; after circulation is joined, a TAC or sham operation will be performed. The TAC will induce pressure overload in the counterpart operated on, and the pairs will be monitored. Heart weight to tibia length ratio and cardiac hypertrophy and fibrosis markers are significantly increased in both the TAC and non-operated counterparts compared to the sham and their non-operated counterparts. Preliminary data indicate that a substantial component of the pressure overload response is mediated by circulating factors. The findings of this project have the potential to impact our understanding of how circulation factors contribute to pathological cardiac hypertrophy and offer potential targets for the treatment of heart failure.

Signalling Pathway Interactions in Basal Cell Carcinoma

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Mentor
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Basal cell carcinoma (BCC) is the most common form of skin cancer in humans. Like other cancers, BCC is caused by loss of regulation of signalling pathways that govern cell growth and proliferation. Mutations in the Hedgehog pathway have been shown to be the main drivers of BCC. However, it has been observed in a BCC mouse model that tumours are reduced in the absence of the transcription factor Yap. Yap is the key effector of the Hippo pathway, which has vital roles in tissue development and regeneration. RNA sequencing data has identified changes in expression of a number of JNK pathway genes in Yap knockout tumours. It is therefore clear that BCC carcinogenesis is dependent on complex interactions between multiple signalling pathways.

This project aims to clarify the nature of the interactions between these pathways, using inducible Yap knockout cell lines and BCC mouse models. Activity of different pathway components in wild-type and Yap knockout cells will be measured using Western blots for active phosphorylated forms of proteins and RT-qPCR to quantify mRNA levels. Immunofluorescence and immunohistochemistry will be used to monitor subcellular localisation of Yap (which translocates to the nucleus when activated) and JNK pathway activation.

A more complete understanding of the network of pathways activated in carcinogenesis will assist in identification of therapeutic targets. Because many of these pathways are also implicated in the response of tissue to injury, this work may also have applications in regenerative medicine.

Defining Small Molecules That Improve Muscle Transplantation

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Mentor
Dr. Sahar Tavakoli, Department of Stem Cell and Regenerative Biology

Cell transplantation is a potential therapy for local myopathies, or muscle disorders. However, transplantation is currently limited by low engraftment frequency and the poor survival of donor myocytes, or muscle cells. The pre-transplantation treatment of donor myocytes and muscle progenitors with effective small molecules could increase cell longevity and the frequency of successful transplantations, making transplantation of muscle a functional therapy. To identify these small molecules, bioactive compounds were screened using muscle cells differentiated from zebrafish (Danio rerio) embryonic stem cells. The condensed developmental timeframe of zebrafish allows for the rapid generation of muscle cells. In contrast to human muscle cells, which take 35-40 days to generate, zebrafish myocytes can be generated in 2-3 days. Muscle cells marked with a fluorescent reporter protein were treated *in vitro* with the candidate compounds and transplanted into translucent zebrafish. The host fish were then sacrificed a week after transplantation and imaged to measure the number and patch size of engrafted cells. Effective compounds were defined as those that increased the number or patch size of engrafted cells in comparison to cells treated with dimethyl sulfoxide, a control compound. Two classes of compounds have been identified as putatively effective: fatty acids and anthranilic acid derivatives. Future work would identify these compounds' molecular mechanism of actions, and identify if combination therapies further increase engraftment frequency.

Decellularization of Embryonic Organ (AGM) in Mice for Hematopoietic Stem Cell Formation

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Hematopoietic stem cells (HSCs), cells capable of differentiating into different components of blood including erythrocytes, leukocytes, and platelets, have great potential in developing new therapies to treat patients with leukemia, lymphoma, and a wide array of other blood disorders. During normal embryonic development, the first definitive, or transplantable-into-the-adult, hematopoietic stem cells emerge in a region of the embryo known as the aorta-gonad-mesonephros (AGM). Endothelial cells in the AGM can differentiate under specific hormonal and organizational conditions to generate definitive HSCs. To test the hypothesis that hematopoietic stem cells can be created *in vitro* by mimicking the microenvironment of the endothelial-to-HSC transition, an AGM scaffold was created from a mouse embryo using decellularization: a process in which all cellular material was removed, leaving behind only the acellular components of the organ. Next, DAPI staining and collagen staining was performed to test the quality of the decellularization process developed. Preliminary results showed that the majority of cellular components were absent yet the collagen was found intact. With this decellularization technique, we will be able to study the surface and interior properties of the organ. A deeper understanding of the regulatory mechanisms performed by the extrinsic cells in the AGM on HSC formation would allow us to develop personalized stem cell therapies to treat blood disorders such as leukemia and bone marrow failures.

Investigating the Mechanism of the ALS-associated Gene Mutation in C9orf72

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Amyotrophic lateral sclerosis (ALS) is an incurable and fatal disease caused by the progressive degeneration of motor neurons in the brain and spinal cord. Advances in technology have allowed us to better understand the genetic basis of ALS, and it was discovered that a repeat expansion in the noncoding region of C9orf72 is a major genetic cause of both frontotemporal dementia (FTD) and ALS.

Currently, there are several hypotheses on how the C9orf72 mutation is linked to ALS. Our hypothesis focused on the loss of function model, proposed by previous researchers who found a 50% reduction in mRNA levels of C9orf72 in C9-mutant ALS patients. The loss of function model suggests that the haploinsufficiency produced by the decrease in C9orf72 expression is the major cause of disease onset and development. This project sought to test the validity of this hypothesis and further explore the role of C9orf72 in the neuromuscular system by studying the physiological consequences of reduced C9orf72 expression in a mouse model over time. To accomplish this, we characterized the behavioral phenotype of mutant C9orf72 mice as well as identified the effect of reduced C9orf72 levels on the neuromuscular system, focusing on the degeneration of motor neurons and the neuromuscular junction.

Preliminary results in a cohort of older mice found neuromuscular junctions of smaller area as well as a behavioral phenotype characterized by shorter lifespan and significant motor defects. Completion of the project will allow us to understand the developmental timeline of these defects and the association between internal abnormalities and manifestations of these abnormalities in external behavioral differences. These results will provide insight into the endogenous role of C9orf72 and ultimately provide an avenue for further study of the mechanism of the C9orf72 mutation.

Therapeutic Efficacy of Engineered Stem Cells

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Glioblastoma multiforme (GBM) is the most malignant form of brain cancer and accounts for approximately 50% of all brain tumors. A universal goal of cancer treatment is to target cancer cells without affecting the surrounding normal cells. A lack of high selectivity for cancer cells in current treatment options has pushed for research advancements in stem cell-based therapies because many stem cells possess intrinsic tumor-tropic and anti-tumor properties. Stem cell-based therapy has shown promise in treating cancers like GBM. Our laboratory has previously shown that adult stem cells can be engineered to secrete therapeutic proteins that are specifically targeting cancer cells followed by local stem cell transplantation, thereby achieving high local concentrations of anticancer agents. However, a drawback in this approach can be autocrine-toxicity of expressed therapeutic molecules towards engineered stem cells. In this project, we aim to modify stem cells with CRISPR in order to increase their efficacy to a broad spectrum of cancer. Inherently linked to this project, we will incorporate fluorescent and bioluminescent markers in both tumor cells and stem cells and assess the fate and therapeutic efficacy of engineered stem cells *in vitro* and *in vivo*.

The Role of Mkrn3 in the Control and Mechanism of Puberty Initiation

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MKRN3, encoding the makorin ring finger protein 3, is a chromosome 15 gene whose mutations have been implicated in the appearance of human central precocious puberty in several families. *MKRN3*

follows a maternal imprinting inheritance pattern in which the allele from the mother is silenced and expression is dependent on the paternal allele. The Kaiser Laboratory is investigating the role and function of *MKRN3* as a regulator of puberty onset, and a major player within the endocrine hypothalamic-pituitary-gonadal axis. We hypothesize that *MKRN3* is an inhibitor of GnRH (gonadotropin-releasing hormone), whose release triggers puberty onset; *MKRN3* deficiency removes its inhibition, leading to early reactivation of the puberty initiation pathway. We characterize this process by following pubertal phenotypes with an *in vivo* model of transgenic knockout mice that lack either one or both *Mkrn3* alleles. We perform PCR on ear tissue samples to identify the genotypes ($Mkrn3^{+/-}$, $Mkrn3^{-/+}$, $Mkrn3^{+/+}$, $Mkrn3^{-/-}$) of mice born to $Mkrn3^{+/-}$ parents that inherited the mutation from their fathers. The timing of markers of puberty onset—the preputial separation in males, and the vaginal opening and the first estrus in females—is analyzed. RT-qPCR assays are performed to measure the amount of *Mkrn3* mRNA that is present in RNA extracted from the cortex of these mice once they reach adulthood. These readings confirm the genotype results obtained by PCR and in the case of heterozygote mice, allow us to trace if their single *Mkrn3* allele is maternal ($Mkrn3^{+/-}$) or paternal ($Mkrn3^{-/+}$) in origin. We will also extract mRNA from the arcuate nucleus and preoptic areas of the hypothalamus to look for expression of other regulators of puberty, such as kisspeptin and neurokinin. Elucidating *Mkrn3*'s niche within the pathways regulating GnRH will contribute to understanding the networks that control puberty initiation and lead to new treatments for disorders related to puberty and reproduction.

Summer Humanities and Arts Research Program (SHARP)

Origins of Psychedelic Drugs in America

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History and Literature — Class of 2020
Studies of Women, Gender, and Sexuality

Emilie Hardman
Houghton Library

Mentor
Heather Cole, Houghton Library

Media and writing about psychedelic drugs tends to focus on LSD and mushrooms in the late sixties, when the drugs were used by long-haired hippies in the Haight, Woodstock, or Vietnam War protests. But psychedelic drugs have a history in America a decade and a half before the hippies ever got their hands on them. This project seeks to explain that, despite popular associations between psychedelic drugs, hippies, and political activism, the inherent political and religious quality ascribed to these substances originate in the high-brow, well-funded, predominantly white and male institutions and people that assigned this quality to them.

By working with materials in the Ludlow Santo Domingo (LSD) Library in Houghton Library and reading original works from Aldous Huxley, R. Gordon Wasson, Timothy Leary, Richard Alpert, I looked at the origins of the psychedelic movement and the work, both in science and advertising, that led to the rise of psychedelic drugs in America. By using primary source material from Leary's crusade to popularize LSD, like newsletters from his International Federation for Internal Freedom and his Psychedelic Review, as well as using Leary's writing from 1960 all the way to 1980 to understand the trajectory of his strategy to promote LSD and the figures who initially inspired his understanding of LSD, I have sought to understand the true origins of psychedelic drug use in America.

By starting with how and when psychedelic drugs were brought to America, the adoption of the drugs in well-funded research facilities and elite creative circles, and how the drug became popularized, I hope to illuminate the exclusive origins of the drug and the ways in which powerful, white men actually constructed the legacy of the drug.

Student Engagement at the Harvard Art Museums

Richard Dunn — Harvard College
Classics — Class of 2019

David Odo
Harvard Art Museums

Correna Cohen
Harvard Art Museums

The Harvard Art Museums have been seeking to increase engagement with the broader community, through enabling undergraduates at Harvard to bring people they serve into the museum, including elementary and secondary school students of Cambridge and Boston, among others. My goal was to establish an infrastructure to facilitate, increase, and maximize the quality of organized community visits to the Museums. To do this, it was first necessary to understand why Harvard undergraduates had not been bringing people they worked with from the community into the Museums. I consulted a variety of students, to determine their motivations, and museum employees, to evaluate the success of past approaches. After conducting this outreach, I developed a series of recommendations for how to improve community engagement, including: the creation of customized programming for various types of student groups; personalized contact and relationship-building with representatives from student organizations; and the creation of new publicity measures and social media campaigns, among other proposals. Upon successful completion of the project, I will have submitted a major report detailing all my findings and recommendations, and will have

started to implement these recommendations, with the creation of a database of customized programming that student guides at the museum can use to maximize the benefit of community visits. More broadly, my work considers an increasingly important theme for art museums—how to maintain and cultivate a rich level of engagement with students and other young people in the 21st century. My research has shown that amidst this backdrop, personal relationships and tailored approaches will be key to cultivating student interest.

The Abstract Moon

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Eugene Wang
Department of History of Art and Architecture

"Humans are so very ugly," responded Liu Guosong when asked why he never painted people. Liu (1932-) is a Taiwan-based abstractionist and influential figure of Chinese modernist art who has lived through some profound suffering and achievement of the twentieth century. Early in his life, he lost his father in the Sino-Japanese War. Three decades later, impressed by the Apollo space missions, he created a series of about 300 "Space Paintings". Among those is *Which is Earth?*, depicting in rough brushstrokes the moon as viewed from Earth's horizon, or Earth as viewed from the moon.

I am helping to write an essay film—a documentary-like pursuit of ideas—taking Liu's life and work as starting ground. I work alongside poems, photographs, video clips, music, and historical accounts, considering their interactions within a cinematic whole. I follow the events and figures surrounding him and trace through their points of convergence to develop a global narrative.

Poet W. H. Auden, whose life had unwittingly intersected Liu's in wartime Wuhan, also reacted to Apollo, although negatively, in his poem "Moon Landing". Whereas Auden's experience with war convinced him of the moral role an artist must play in society, Liu turned away to face nature and abstraction. The ambiguity between the terrestrial and lunar landscapes in *Which is Earth?* will provide visual ground in the film for Liu's non-anthropocentric cosmic vision. This project will bring Chinese modernist painting into the context of the 20th century world, sustained along the arc of one human life.

Museums in the 21st Century: Lessons and Models for Digital Asset Sharing

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Ed Rodley
Peabody Essex Museum

Mentor
Austen Barron Bailly, Peabody Essex Museum

While the Internet has allowed museums to have global reach, a perception of exclusivity is still attached to them. A key strategy in demolishing this perception is the promiscuous spread of their digital assets. In May 2014, the Peabody Essex Museum (PEM) held its first Wikipedia edit-a-thon, during which museum assets were used to create and enrich dozens of articles. The research I conducted provided PEM with statistics and lessons learned from the edit-a-thon, as well as logistical advice and an informational framework for future efforts focused on the digital spread of institutional assets.

By gathering and analyzing pageview statistics, I prepared an analytical report on the May 2014 edit-a-thon. My results showed that an effective strategy for the spread of digital content within Wikipedia is prioritization of creation of new articles, as their impact on accessibility to a museum's collections is easily measurable. Results also showed that adding images to Wikimedia Commons is a low-cost investment with long-term benefits. I later created an informational model for primary and secondary research to be gathered in a detailed and effective manner for both internal and external use, aimed at organizing research around women artists of curatorial interest in PEMs collection. This informational model has grown to become a generalizable and valuable resource for any GLAM (Galleries, Libraries, Archives and Museums) institution with internal repositories of unique resources, and interest and staff to make these accessible. This research supports the view of digital asset sharing as a valuable strategy allowing museums to deliver on their missions to educate, stimulate, and enrich people's lives.

A Closer Look at the Troubled Life of W.H. Ireland

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Class of 2018

Emilie Hardman
Houghton Library

Heather Cole
Houghton Library

In 1794, William Henry Ireland, then 19, discovered a collection of documents bearing the rare signatures of William Shakespeare. Over the course of eighteen months, the young man presented these documents to his father, Samuel Ireland, who in turn began to present the cache to the public on a wild ride to literary notoriety. However, only two years from that first "discovery," the scheme ultimately collapsed in the face of scathing criticism. He would go on to author novels, poems, and histories in an attempt to recover his reputation, but in the end, he died without the esteem he always wanted.

Ireland's tumultuous story makes it difficult to ascertain if he was more of an impoverished rogue than a genuine penman. My project seeks to unpack this mystery in the form of a fictional biography that offers a plausible narrative that a destitute and sickly Ireland presents as amends for his troubled past. In order to build a strong historical foundation for my creative piece, I spent the summer studying materials in the Hyde Collection at the Houghton Library. This involved perusing Ireland's forgeries and reading many of the hand-written notes that accompany each of these documents. For background research, I read secondary materials on the subject and also explored other documents of 18th century forgery. In all, the goal of my creative piece is to explore the different ways in which Ireland's story reflects a period in the history of literature when the canon was yet to be consolidated and the notion of the author was yet to be solidified.

Building a Network: New England Women Artists at the Peabody Essex Museum

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Class of 2017

Austen Barron Bailly
Peabody Essex Museum

Mentor
Sarah Chasse, Peabody Essex Museum

Recent gifts to the Peabody Essex Museum (PEM) have expanded the American painting collection with more than a dozen female artists working professionally in New England; this development warranted an updated effort to advance a robust catalogue of PEM's American female painters. These talented women forged careers as artists and teachers but remain little known. My project seeks to constellate these women's lives, art, influences, as well as contemporary and retrospective reception. Amassing and organizing bibliographic and biographic information on these artists will inform the forthcoming total reinstallation and reinterpretation of the American art galleries at PEM. Externally, I will be collaborating with the SHARP-PEM Fellow for Integrative Media Delfina Martinez Pandiani to orchestrate the information sharing required to host a PEM Wikipedia Edit-a-thon. In addition to determining which of these artists merit the Wikipedia criteria for entries, I will prepare each artist file with documents ready to reference for a Wikipedia biography as well as code documents to alert Wikipedia editors of the document's relevant information. The method of data collection cultivated for these projects will lend itself for further internal PEM use for collection research and development. The expected outcome of new or enhanced Wikipedia pages for these understudied artists by Wikipedia editors will broaden the local and international public knowledge of these women artists and support future academic study.

Socialist Aesthetic Debates in German Exile Journals

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Anne Shreffler
Department of Music

Following Hitler's rise to power, the persecution of the German political left resulted in the silencing of leftist political discussion and the exile of huge numbers of German socialists and communists. As a result of this, Newspapers and Journals published by these intellectuals in exile became the most valuable source of uncensored German writings during the 1930s. These years were also a period of upheaval for Socialist art as more Russian and German intellectuals voiced their opinions following the Soviet institution of Socialist Realism. This study seeks to investigate how such aesthetic debates were addressed in these exile journals. Using indexes such as RIPM and the Deutsche Natioanale Bibliothek Exilepresse Digital database, articles addressing key terms in the debate were found and analysed in relation to their political context. The study found that even within the German exile community, there was a spectrum of aesthetic views. For example, highly Soviet sympathetic journals, such as Internationale Literatur based in Moscow, repeatedly printed statements from significant Soviet figures such as Bukharin and Zdhanov, promoting Realist notions to the German exiles in Moscow. Whereas, in Paris, the German editorial policy of the Pariser Tageszeitung was more even-handed with regard to reporting on Soviet policy and aesthetic debates. These journals are a historical recourse rarely used for such aesthetic analysis. Since debate within Nazi Germany itself was suppressed, they were the primary medium for aesthetic debate and are thus key in understanding the development of socialist influenced trends in modern art.

Digital Humanities at metaLAB

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Computer Science

Matthew Battles
metaLAB at Harvard

Mentors
Sarah Newman, metaLAB at Harvard
Jessica Yurkofsky, metaLAB at Harvard

metaLAB at Harvard is a knowledge design lab, led by Professor Jeffrey Schnapp, that explores the intersections of art, technology, and the humanities, with components of teaching, scholarship, art and design, and other forms of creative research. My summer work at metaLAB has focused on two projects. The primary project is Curricle: a new platform for Harvard course selection that merges the ability to register for current courses with the opportunity to explore the evolution of the Harvard curriculum over time. My focus has been historical research, including analysis of previous, printed course catalogs from the archives. I have surveyed course selections of famous alumna (T.S. Elliot and Gertrude Stein) to generate "micro-narratives" for integration into the platform. I have also proposed data specific data visualization ideas, and worked with metaLAB's team of designers to further enrich these ideas for implementation. My other focus at metaLAB has been participation in the early stages of an initiative to explore the intersection of Artificial Intelligence (AI) and Art. For AI + Art, I have curated content for a new website, AI Compass, and helped facilitate an interactive workshop at the Berkman Klein Center for Internet & Society. Alongside supporting research within the broader AI + Art initiative, I have also been developing my own creative project, Color Rx, which explores concepts of color, perception, and human-machine interaction. Color Rx is an interactive art installation that uses a computer algorithm to assess a viewer's subjective inputs and "prescribe" a color in response. Drawing on historical information from the Forbes Pigment Collection, the project explores the line between belief and truth, and contends, critically and playfully, with the implications of our growing reliance on automated black box systems. Color Rx will debut in a one day exhibit in the Lightbox Gallery at Harvard Art Museums on Friday, August 11th, after which time I will migrate it to a website for continued access and iteration.

Educational Television Series at Poetry in America

Christian Vazquez
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Elisa New
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Mentor
Leah Reis-Dennis, Department of English

This summer I worked with Poetry in America, a multi-platform digital project that aims to show poetry's relevance and accessibility to a wide audience through conversations with poetry enthusiasts from all walks of life.

My work focused on conveying the goals and values of Poetry in America through engaging, visual storytelling. I served as a production assistant, videographer and editor, engaged with idea translation from inspiration to realization and the many conversations in between. I sifted through archival footage, offered feedback on edits and re-cut extraneous footage to be made available for a diverse audience. The work allowed me to engage with the discussion of poetry outside of a traditional academic context in a format that is greatly instructive given my interest in filmmaking.

One component program I contributed to, the Harvard Arts and Humanities Public Partnerships Initiative (HAHPPI), aims to facilitate the creation and dissemination of high-quality work in the digital humanities by students, alumni and professionals. HAHPPI works to delineate and expand the types of inquiry that humanists are typically trained in through their studies; in the process, new productive outputs are validated and pathways to master traditional forms of inquiry are augmented. With the Bok Center for Teaching and Learning as a central hub, HAHPPI explicates the professional development of the next generation of humanists: How can we prepare today's Harvard humanists for contribution to wider cultural conversations? How can we nurture the link between academic discourse and the creative process?

Lesbian, Gay, Bisexual, Transgender, and Queer History

Patric Verrone
Psychology
Harvard College
Class of 2018

Michael Bronski
Studies in Women, Gender, and Sexuality

The advent of the Gay Liberation Movement in 1969 led to the genesis of lesbian, gay, bisexual, transgender, and queer (LGBTQ) studies. In the early 1990s, Queer Theory emerged out of feminist and LGBTQ scholarship as its own branch of post-structuralist critical theory. This project seeks to compile one-hundred seminal essays that survey the existing scholarship on LGBTQ history. While this field of study has historically focused on Anglo-American history and the West, this collection will broaden the canon and include contributions from across the globe. The process of acquisition includes finding and reading hundreds of essays, making an initial cut, and organizing them into a bibliographic record. The essays gathered for this collection will be organized into four volumes: Theories of New Understanding, a survey of influential works on Queer Theory; the Pre-Modern Period extending from ancient times to 1500 AD; the Modern Period from 1500-1900; and Contemporary writing of the twentieth and twenty-first century. Each published volume will include introductions written by Professor in the Practice in Activism and Media Michael Bronski and published by Bloomsbury Publishing. In creating this anthology, we hope to unite disparate oeuvres of scholarship on LGBTQ history across the world and represent works that have yet to enter the Western LGBTQ canon. We seek to balance, broaden, and complicate the older, Western-centered canon by placing traditionally-cited works in conversation with newer, more global scholarship.

The Necessity of Public Intellectuals

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Philosophy and Government — Class of 2020

Eric Beerbohm
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Mentor
Jacob Roundtree, Department of Government

In modern democracy, we face complex, long-term problems that require action and accountability. The automation of human jobs, global warming, and economic forces that foster inequality and immobility are examples of public problems which demand preemptive action before we suffer their consequences. Democracy is intrinsically flawed at dealing with these kinds of problems. For one, citizens are cognitively overburdened with their daily lives and often cannot fully educate themselves about political problems and public policy. Moreover, citizens who do not recognize the existence and implications of long-term problems cannot hold their representatives accountable for acting on them. Past thinkers, recognizing this issue, have called for improved public communication, more rigorous truth-telling journalism, and even epistocratic alternatives to modern democracy.

This political theory project seeks to argue for the general necessity of public intellectuals as the solution to the public's current inability to identify, offer solutions for, and make decisions about these long-term problems. I define public intellectuals as experts who accessibly and innovatively frame public problems and their implications for the public. John Dewey and Walter Lippmann, for instance, are paradigmatic examples. In particular, I stress that these ideal public intellectuals must be separate from formal political authority. Given effective public intellectuals in public discourse, I argue democracy can preserve its procedural virtues – namely, equal political liberty – and arrive at better instrumental and epistemic outcomes through addressing long-term problems.

Currently, this argument is taking the form of a paper. Eventually, I hope to develop a political theory of effective public intellectuals in response to the challenges they face in seeking to inspire and advance public deliberation and opinion.

Delaying Tough Problems: Democracy, Citizenship and Spectacle

Henry Scott — Harvard College
History — Class of 2018

Jacob Roundtree
Department of Government

How equipped are democracies at solving long-term problems, whose negative effects will only manifest at some relatively distant point in the future? An example of such a problem is the climate change crisis. Drawing on the work of Guy Debord, Jacques Lacan, and Herbert Marcuse, I construct a model of the citizen in modern democracy. The model highlights those behavioral biases that agents tend to acquire when socialized within the structures of a late-capitalist system. Agents socialized in such environments have a low tolerance for the uncertainty and ambiguity one experiences when cognitively processing complex problems and have a strong preference for immediately satisfying comforts. Such agents avoid cognizing complex information about long-term problems and will be hostile to internalizing the short-term costs of the policies designed to avoid long-term problems. This tendency should cause citizens to pressure elected representatives to avoid tackling complex, long-term problems and instead to focus on providing the public with immediately beneficial services at the expense of the political community's long-term interests. In another paper, I investigate how the increasing domination of the public sphere by the sharing of images and short-form discourses has helped reinforce the anti-cognitive bias and the immediate gratification bias of bourgeois social subjects, while crowding out those forms of open-ended and rigorous deliberation about shared conditions of life that could potentially help correct for these biases.

Gravity: a Research-Writing Poetry Project

Tawanda Mulalu
Philosophy and Physics
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Class of 2020

Heather Cole Cole
Houghton Library

Emilie Hardman
Houghton Library

'Gravity' is a research-writing project that will attempt to resolve, in the unique language of verse, the mystery of the fourth fundamental force of the universe, gravitation. The project investigates primary source materials in the Houghton, Harvard's rare book and manuscripts library, concerning the history and physics of gravity. This information is used as raw material for the crafting of several poems. Such primary sources include first edition copies of the original translation of English physicist Sir Isaac Newton's 'Philosophiae Naturalis Principia Mathematica' and a general audience popularization of Newton's ideas by French philosopher and author, Voltaire, titled 'The Elements of Sir Isaac Newton's Philosophy.' Secondary source materials, such as Thomas S. Kuhn's 'The Structure of Scientific Revolutions' and Kurt Hübner's 'Critique of Scientific Reason,' are used to contextualize the reasoning and development of scientific ideas such as the theory of gravity over time. Poems included in this project include 'Descartes' Vortex', an exploration of the Descartes' own debunked theory of gravity in a modern context and 'The Tides,' a meditation on the journey of black slaves across time and space, with references to scientific determinism and materialism and how the the gravity of the moon carried slave ships from the African continent to North America.

Summer Undergraduate Research in Global Health (SURGH)

Developing HIV-1C Transmission Networks in Botswana Through Long Range Genotyping Methods

Olatunde Badejo — Harvard College
Molecular and Cellular Biology — Class of 2018
History and Science

Max Essex
T. H. Chan School of Public Health

Mentor
Melissa Zahralban-Steele, T. H. Chan School of Public Health

The HIV epidemic is a continuing global health problem with more than 35 million people currently living with the disease worldwide. About 70 percent of all HIV-infected individuals reside in Sub-Saharan Africa. South African countries have been particularly hard hit by the HIV-1C epidemic. Botswana is one such country that has struggled to control the spread of HIV-1C, and about a quarter of all adults are infected with the disease.

Recent research has pointed to the efficacy of Treatment as Prevention (TasP) methods as a possible solution to the crisis. These methods treat HIV-infected individuals with antiretroviral therapy (ART) to lower HIV transmission rates. The Botswana Combination Prevention Project (BCPP) is a collaborative study that seeks to demonstrate the efficacy of TasP on a community level. In this pair-matched randomized trial of 30 communities in Botswana, one village in each pair receives the current standard of treatment, while the other receives the combination prevention package. As part of this study, the Essex lab performs HIV genotyping and analyzes viral sequences. Specifically, an innovative long-range HIV genotyping protocol utilizes polymerase chain reaction (PCR) to amplify a near full-length HIV-1C genome. This method is crucial because it allows for the amplification and sequencing of proviral DNA, as samples from virally suppressed subjects would not contain enough viral RNA for conventional methods. Next generation sequencing (NGS) and analyses are then used to generate a consensus sequence for each participant. These sequences are then used for phylogenetic inference and retrieving the structure of the HIV-1C transmission network. This network is utilized to map transmission patterns within the BCPP communities in the hopes of demonstrating, through phylogenetic linkages and clusters, that the TasP methods used in the combination prevention package reduce rates of HIV transmission, and prevent new HIV transmissions. The results of this study will help guide large-scale HIV intervention strategies, and inform continuing efforts to reduce the burden of the disease.

Mental Health and Early Childhood Development Among Youth in Post-Genocide Rwanda

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Theresa Betancourt
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Mentor
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Youth around the world face situations of compounded adversity, in which conditions of poverty, conflict, and infectious disease align to influence the development and mental health of children. The Research Program on Children and Global Adversity at the Harvard T.H. Chan School of Public Health works to understand how children develop and cope in situations of adversity.The lab also applies research findings to create evidence-based psychosocial interventions for these children. Using mixed methods research, one project this lab examines surrounds children and families living in post-genocide Rwanda.

Rwanda has faced a history of internal conflict, leaving thousands of vulnerable families and

strained relations within the country after the 1994 genocide. Forty-nine percent of the rural population in Rwanda live below the national poverty line, and conditions of compounded adversity have left families vulnerable to trauma and poor child development outcomes such as undernutrition and neonatal mortality. My work in the lab is focused on an Early Childhood Development (ECD) evidence-based psychosocial intervention called *Sugira Muryango*, or "Strong Families Thriving Children." This home-based intervention targets the poorest, most vulnerable families in Rwanda through a combined government public works program and family strengthening curriculum. The curriculum is delivered to individual families by community-based lay workers and addresses topics of communication, nutrition, responsive parenting and alternatives to violence. The intervention hopes to positively impact outcomes of early childhood development, parental involvement in the family, and intimate partner violence, working towards creating safer, healthier homes.

Investigating the Function of FtsH and Identifying FtsH Substrates in Mycobacterium Smegmatis

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Tuberculosis remains one of the world's deadliest infectious diseases. *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis, is so virulent partially because it is extremely adept at tolerating stress. Further understanding the importance and function of conserved genes in mycobacteria is required to expand our knowledge of how *M. tuberculosis* tolerates stress. FtsH is a membrane-bound, ATP-dependent protease that has been shown by transposon insertion sequencing (Tn-seq) studies to be important for *M. tuberculosis* virulence. To elucidate the biological functions of this protease, we are characterizing strains of *M. smegmatis*, a non-virulent, fast-growing relative of *M. tuberculosis*, that lack FtsH and identifying FtsH substrates. To help understand the role of FtsH in stress response of mycobacteria, we can compare the sensitivity to oxidative stress between wild type *M. smegmatis* and FtsH gene knockout strain. By mutating the proteolytic activity of FtsH, we can create a protease trap to identify interacting partners of this protein. By testing the importance of FtsH in stress response and identifying interacting partners of FtsH, we can better understand the biological functions and importance of FtsH in *M. tuberculosis*. This could lead us to better understanding the mechanisms of virulence of this mycobacterium.

Structural Barriers to Treatment as Prevention in the Greater Boston Area: A Qualitative Needs Assessment

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Bisola Ojikutu
Harvard Medical School

Mentor
Wanda Allen, Harvard University Center for AIDS Research

In recent years, epidemiologic evidence has clearly indicated a treatment as prevention approach to ending the HIV/AIDS epidemic. Viral suppression through consistent antiretroviral therapy (ART) has been shown to substantially lower the risk of transmission among serodiscordant, heterosexual couples. These advances led to FDA approval of emtricitabine/tenofovir (Truvada) as pre-exposure prophylaxis (PrEP), now the gold standard of HIV prevention for at-risk individuals. However, a significant proportion of US primary care providers (PCPs) are unaware of or uncomfortable prescribing PrEP, which continues to be a significant barrier to HIV prevention. Given a substantial body of evidence for treatment as prevention, we are in the process of conducting a needs assessment of treatment as prevention efforts in Boston's underserved communities. We have selected a purposive sample of individuals who provide HIV testing in community health centers (CHCs) and non-clinical sites for qualitative interviews. The survey is conducted in two sections: the first is provided to the site directly in writing, in order to examine facility protocols and its patient population, while the second assesses individual providers' HIV screening and prevention practices through a qualitative interview. Questions were specifically designed to target providers' practices around linkage and PrEP with structural barriers to accessing care, such as income, institutional resources, lack of knowledge, stigma, medical mistrust, and racial discrimination. Though the survey is

ongoing, exploratory interviews suggested needs for increased engagement between CHCs and communities around PrEP, greater HIV/AIDS funding specified to injection drug use, and greater resources for PCP education on PrEP.

Investigating the Genotype to Phenotype Relationships in G6PD Deficiency

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Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most prevalent enzymopathies, affecting over 400 million people worldwide. G6PD deficiency can clinically manifest in acute episodes of oxidant induced hemolytic crisis. Studying the relationship between the G6PD deficiency genotype and disease phenotype is made challenging by the high number of polymorphisms (160 have been identified to date) and the variability genetic background among individuals with G6PD deficiency. These challenges have prompted us to develop a genetically tractable *in vitro* experimental system for studying G6PD deficiency. Applying shRNA knockdown and CRISPR gene editing to EJ immortalized red blood cells (RBCs), we have begun generating different types of G6PD deficient RBCs with the same genetic background. Subsequent phenotypic assays of red blood cell susceptibility to oxidative insult have allowed us to begin deciphering the relationship between the G6PD genotype, G6PD levels in the RBCs and susceptibility to oxidative hemolysis. We hypothesize that the extent to which a given G6PD deficiency allele affects the level of G6PD activity will directly correlate with the susceptibility of the red cell to hemolytic crisis. Developing a genetically tractable experimental system for G6PD deficiency will allow us to directly compare different G6PD variants with the same genetic background and elucidate the relationship between the G6PD deficient genotype and the disease phenotype. Looking forward, this system has to potential to provide an invaluable foundation for forward genetic and small molecule screens for modulators of oxidative hemolysis that could be developed to protect G6PD deficient individuals from hemolytic episodes.

Developing Integrated Platforms for Surgical Training

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John Brownstein
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Mentor
Gajen Sunthara, Boston Children's Hospital

Uncommon surgeries present difficult situations for academic health systems such as Boston Children's Hospital. Although the best care may come from an experienced surgeon who has performed the operation before, the hospital has a responsibility to train the next generation of clinical providers to handle such cases. Prior training for the surgeons who are learning a particular procedure is limited because the opportunities to attend similar cases are limited. Only a few inexperienced surgeons can be in the OR at a given time and get a surgeon's point of view for the procedure. Furthermore, it is difficult to teach surgeons at smaller partner hospitals.

The inspiration for our project was a rare surgery that was only being performed twice a year in Boston. The desire was to teach this rare operation to surgeons in other pediatric health systems, but there were many difficulties in communicating the specific surgical strategies and techniques. The project strived to improve the interface for surgeons training on new surgeries by better connecting surgeons to the context of the operating room. By capturing more precise surgical points of view and the ability to incorporate radiology scans and other diagnostic DICOM images, the platform may be able to help surgeons better prepare for these cases in training and lead to improved clinical care. On the research side, eventual goals would be to incorporate augmented or mixed reality technologies as a better view of the operating room.

A Needs Assessment of HIV Testing and Counseling Sites in Boston

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Bisola Ojikutu
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Mentor
Wanda Allen, Harvard Center for AIDS Research

In 2014 there were 180 new HIV diagnoses reported in Boston. While this number reflects a decrease in new diagnoses in the past decade, there are still consistent disparities in infection for certain populations. Men who have sex with men, people who inject drugs, and latinx and black residents experienced a disproportionate rate of positive diagnoses in Boston.

This project focuses on the creation of a needs-assessment for different HIV testing and counseling sites to determine factors that contribute to these disparities. The data for the assessment will be collected through interviews with providers of HIV testing and counseling services. The interview questions were informed by meetings with community stakeholders who shared their perspectives on the Boston epidemic. Through these preliminary interviews it was determined that two focuses of the needs-assessment would be protocol providers have with Pre-Exposure Prophylaxis (PrEP) and their protocol for linkage to care when a client tests positive.

Currently, interviews are in the process of being conducted. It is expected that providers are not engaging clients enough with information about PrEP based off of the limited knowledge various populations have of the drug and low enrollment in drug assistance programs.

When this needs assessment is complete, it can help provide local HIV-focused organizations with data about PrEP and linkage protocols which can inform future initiatives that can improve prescription rates and general education in different clinics and communities. Additionally, this assessment can provide insight into various barriers that clients may face when accessing treatment or PrEP.

Antibody Transfer Across the Placenta

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Molecular and Cellular Biology — Class of 2019

Galit Alter
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Madeleine F. Jennewein, Ragon Institute

The placenta, a temporal organ that only exists during pregnancy, is often overlooked, but is crucial to the health of the growing fetus. The placenta not only delivers nutrients to the fetus, but it is also crucial to the development of the infant's immune system as it transfers antibodies from mother to child. However, the mechanism by which antibodies cross the placenta is not completely understood; the goal of this project was to better understand this process and identify the receptor transiting the antibodies. This was done by staining placenta tissue samples for the three cell types that form the barrier between the mother and fetus: trophoblasts on the maternal side, fetal endothelium, and Hofbauer cells in between. Fluorescence microscopy was used to determine which tissue sections allowed for the easiest visualization of all three cell types. Following this, twelve different stain sets were done on slides from the sections that allowed for the best visualization to see what antibody receptors were present. Particular focus was on the antibodies found in the fetal endothelium because certain antibodies such as cytotoxic antibodies are getting across the placenta in larger quantities. Since cytotoxicity is linked to antibody glycosylation and receptor binding is dependent upon glycans, it was expected either to find specific receptors on the trophoblasts that could transfer highly functional antibodies or to find such receptors on the fetal endothelium. Ultimately, reaching a better understanding of antibody transfer across the placenta is crucial for delivering vaccines to mothers that protect the neonate.

Investigating Mutation in DHODH: Fitness Costs of Resistance to Novel Antimalarial Compounds

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Malaria is a globally important vector-borne disease caused by parasites of the genus *Plasmodium*. Drug resistance is a primary obstacle that prevents malaria control; however, while genetic diversity in parasite populations may lead to emergence of drug resistance through mutation, such mutations often result in a fitness cost, or diminished ability of the parasite to survive and reproduce in the absence of drug. Dihydroorotate dehydrogenase (DHODH) is a potential target for future antimalarials, as the enzyme is critical in the parasitic biosynthesis of pyrimidine. *In vitro* resistance to antimalarials is typically conferred by mutations in *dhodh*; it was hypothesized that *dhodh* mutations would be associated with a fitness cost. This study involved assessment of the relative fitness of *Plasmodium falciparum*, the most widespread and deadly species of malaria, using competition assays. Drug resistant strains were cocultured with wildtype strains; we then extracted genomic DNA from mixed culture and amplified the *dhodh* locus before submitting it for Sanger sequencing in order to assess change in allele abundance, at points of mutation, over time. Further, dose-response drug assays were run to explore changes in mixed culture resistance to DHODH inhibitors, indicative of change in relative strain abundance. To measure the abundance of single-nucleotide mutations quantitatively, high-resolution melting was implemented. Initial results suggest that the described methodology is sufficient in determining culture composition and potential fitness costs of resistance. Preliminarily, we have not detected a significant change in fitness cost to be associated with resistance to DHODH-inhibiting compounds. This study is essential in understanding *P. falciparum* fitness and assessing threats associated with mutant strains.

Implementing and Evaluating an Early Childhood Development Intervention in Rwanda

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The political environment in Rwanda strongly supports early childhood development (ECD) interventions that aim to stimulate young children and enrich their home environments. Sugira Muryango is an ECD intervention based on the Family Strengthening Intervention (FSI) model that was previously used to help HIV/AIDS-affected families in Rwanda build effective communication and parenting skills.

The Sugira Muryango intervention is a clustered randomized controlled trial that consists of 12 in-home modules delivered by community based lay workers in rural Rwanda. The modules focus on strengthening family relationships and improving parenting skills by teaching caregivers about the importance of communication, nutrition, hygiene, and early stimulation. This study targets beneficiaries of the Vision 2020 Umurenge Program (VUP), a social protection program that administers cash-for-work benefits to individuals living in poverty. In order to measure the effects of Sugira Muryango, caregivers will undergo qualitative and quantitative assessments. Data on the intervention itself, including lay worker evaluations and cost benefit analysis, will also be collected. These data will teach us about the impact of an ECD intervention in Rwanda and help guide policy related to family strengthening.

My work focuses on finding the best practices for fidelity monitoring and supervision of lay workers. Treatment fidelity refers to the strategies used to ensure the intervention is delivered consistently to all subjects, which is important for determining intervention efficacy. I have been researching how other interventions have monitored their fidelity and supervised their lay workers, enabling me to recommend and formulate methods for our own intervention.

The Combination of Potent Broadly Neutralizing Antibodies (bNAbs) PGT121 and PGDM1400 Reduce Viremia in SHIV-infected Monkeys.

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HIV remains a major global pandemic; currently, an estimated 37.6 million people are infected worldwide. Yet, to date, there is neither a cure nor an effective vaccine for the disease. Large research efforts have resulted in the development of antiretroviral therapy (ART), a combination of drugs that confers inhibition of HIV viral replication but not absolute elimination of viremia. This is due to the formation of latent viral reservoirs that form as early as acute infection. These viral reservoirs can reactivate after ART treatment is discontinued, causing viremia to rebound. Current therapeutic strategies have not eliminated these viral reservoirs. To keep viremia at innocuous levels, HIV infected patients have to undergo ART their entire life. Adherence to an ART regimen poses financial and social challenges, particularly in the developing world. As such, the administration of ART is effective but, due to high compliance and cost challenges, calls for novel effective HIV therapeutic and prevention strategies.

In the quest to develop novel vaccine and therapeutic strategies, we are exploring different combinations of HIV-specific monoclonal antibodies (mAbs), in particular the extremely potent, broadly neutralizing antibodies (bNAbs) PGT121 and PGDM1400. After administration of these bNAbs to Simian-Human Immuno Deficiency Virus (SHIV)-infected rhesus monkeys, a significant decrease of plasma viremia is observed by monitoring the viral load through quantitative RT-PCR. We have also observed a decline of the latent viral reservoir, although we have not yet seen complete elimination. Combination treatments with reservoir activators are ongoing. The potency demonstrated by these bNAbs suggests that highly efficacious HIV cure strategies are viable and strongly calls for clinical trials of these strategies in human subjects.

Elucidating the Role(s) of the *Shigella flexneri* IpaH Effector Proteins in Bacterial Innate Immune Evasion

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Shigella, a bacterial pathogen, is the causative agent of bacillary dysentery, an infection that kills over one million people each year. *Shigella* pathogenesis is dependent on its syringe-like type III secretion system (T3SS), which it uses to deliver proteins, referred to as effectors, directly from the bacteria into the cytosol of human host cells. *Shigella* contain a large virulence plasmid that encodes T3SS and almost all its effectors. However, genes encoding IpaH effectors are present on both the *Shigella* chromosome and virulence plasmid. The IpaH effectors are novel E3 ubiquitin ligases (NELs) that target host cell proteins for ubiquitination and degradation. The targets of the chromosomal IpaH proteins are unknown; however, published data suggest that one or more of the chromosomal IpaH proteins act to regulate host innate immune responses. This project aims to identify potential host cell targets by testing IpaH effectors' ability to interact with candidate human proteins involved innate immune responses using the yeast two-hybrid assay. In addition, this project will generate and test whether strains lacking IpaH effectors are involved in enabling *Shigella* to promote macrophage death and to prevent epithelial cell death. Together, these studies should identify proteins involved in human innate immune response that are targeted for degradation by IpaH effectors. In the long term, this project has the potential to contribute to our knowledge of the pathogenesis strategies of *Shigella* and other Gram-negative bacterial infections that cause diarrheal diseases and could potentially lead to new implications for therapeutic development and global health outcomes.

Understanding Patient Experience Through Twitter

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Patients regularly use social media to give feedback on their healthcare experience. For hospitals and public health officials, social media is an attractive datastream to learn about patient experience because of its wide usage and live-time availability, especially in comparison to traditional survey methods. This project aims to use machine learning and statistical methods to collect and analyze data from the popular microblogging service Twitter to understand patient-perceived quality of care.

While previous research has demonstrated the usefulness of Twitter for hospital-directed tweets, the focus of this project was on characterizing broad interstate trends over a four-year span (2013 to 2017) for tweets discussing *any* healthcare experience. 334,508 tweets pertaining to patient experience were isolated and labeled with a sentiment score using natural language processing. These tweets were categorized into content topic(s) using a machine learning classifier.

The tweet data was analyzed through the dimensions of time, topic, and location. The analysis revealed that tweet sentiment consistently grew more positive over the four-year span. The growth was driven by an increase in fraction of positive tweets rather than an increase in the degree of degree of positivity. Some topics were associated with positive sentient, such as "Medical Care", while other topics were associated with negative sentiment, such as "Pain". Geographically, states differed in average sentiment and distribution of topics.

Patient feedback expressed in social media highlights broad trends not readily apparent in survey data. Analyzing this data is an important step toward improving quality of care.

Modeling HIV/AIDS in Botswana

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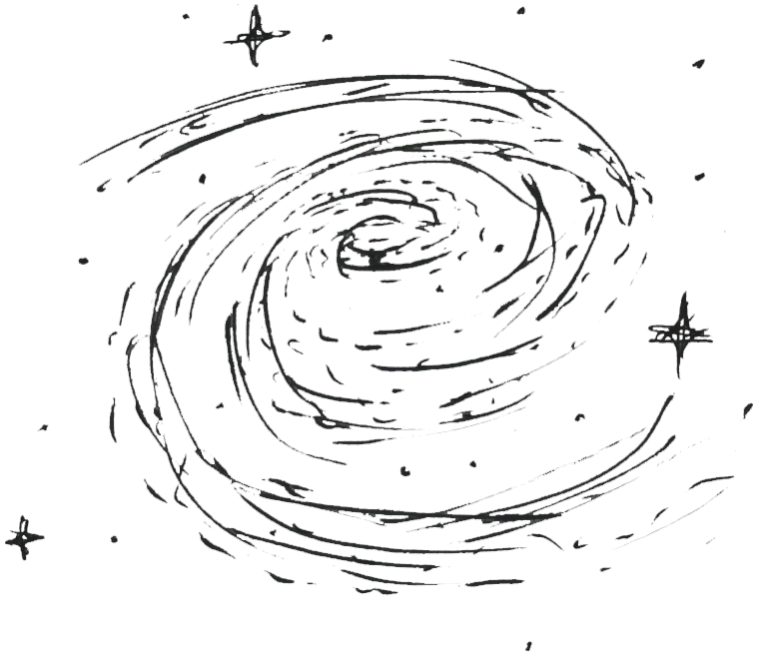
With an HIV prevalence of 22.2%, Botswana has the third highest rate of HIV in the world. Showing strong commitment to an effective response against HIV/AIDS, Botswana was the first country in sub-Saharan Africa to provide universal free antiretroviral treatment to people living with HIV. Understanding the transmission network of HIV in Botswana is important to assess the ongoing efforts of HIV prevention interventions, much of which relies on antiretroviral therapy that lowers the chance of transmission. In general, prevention and treatment efforts span circumcision, microbicide, condoms, pre-exposure prophylaxis (PrEP), and test-and-treat methods. By using an agent-based modeling methodology, simulations can be run in the HIV Calibrated Dynamic Model (HIV-CDM). Inclusion of behavioral, demographic and biological parameters allows the model to more closely approximate the epidemic. Furthermore, outputs from the model allow for programming visuals. Graphically visualizing the sexual transmission network in which HIV transmission occurs can provide a greater understanding of the interactions that occur between various subpopulations that include heterosexuals, men who have sex with men (MSM), and commercial sex workers. Preliminary results show how effective prevention efforts in Botswana have been at controlling and possibly reducing the spread of HIV. If our analysis demonstrates that prevention and treatment policies enacted in Botswana have been effective at averting incident cases of HIV, these results may inform the implementation of similar policies in the region.



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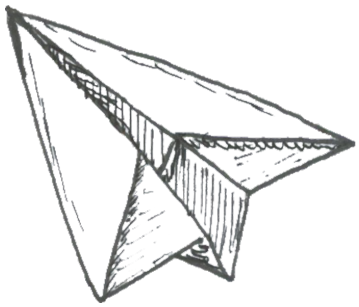

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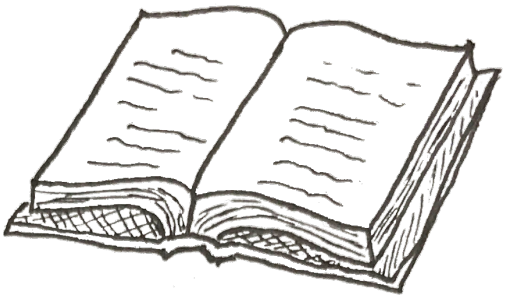

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