PRISE
BLISS
PRIMO
SHARP

ABSTRACT BOOK

2013

ABSTRACTS

2013

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Letter from the Director

Harvard's Summer Undergraduate Research Village 2013 has been an outstanding collaboration of College scholars across the full spectrum of academic disciplines conducting formative and substantive research projects with Harvard faculty in the Faculty of Arts and Sciences, virtually all the other Schools in the Harvard universe, the teaching hospitals, and affiliated research enterprises across the Boston area. Along with the Program for Research in Science and Engineering (PRISE, now in its 8th year), the Behavioral Laboratory in the Social Sciences (BLISS, year 3), and the Program for Research in Markets and Organizations (PRIMO, co-hosted by the Harvard Business School, year 3), we have added the pilot SHARP: the Summer Humanities and Arts Research Program.

I continue to be gratified and amazed by the consistently high degrees of enthusiasm, inclusivity, creativity, and energy in the Research Village residents of Mather House—the mind-boggling, diverse calendar of fellow-initiated activities is a testimony of the great effort and works in building community among these talented young investigators.

The contents of this abstract book reflect the inspiring intellectual projects the 175 fellows have taken on this summer. Although ten weeks pass in what seems like the blink of an eye, the impressive array of research experience herein described tells the terrific story of an amazing group of students who clearly have had a productive and fun summer. To each of you PRISE, BLISS, PRIMO, and SHARP fellows, I wish the best of success going forward, and hope that the relationships you have built over these ten weeks last long into the future.

Yours truly,

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

Letter from the Editors

Dear PBPS Fellows,

It is not often that one has the opportunity to spend a summer with individuals of such diverse backgrounds, talents, and interests as those of the PBPS community. This summer, PRISE, BLISS, PRIMO and SHARP Fellows have had the opportunity to listen, gain professional advice, and be inspired by a wide array of faculty through our Faculty Chat and Distinguished Speaker series. Fellows did so while exchanging knowledge with each other through weekly journal clubs, discussions, and tutorials. Outside of the academic sphere, students had the opportunity to lead a multitude of activities ranging from coffeehouses, visits all over Boston, all while conducting rigorous yet exciting research. In our opinion, what is truly exceptional about the PBPS community is not just the environment that flourishes with curiosity and knowledge, but the genuine desire of members to share common interests, learn from each other, and teach each other so that we can grow both as researchers and individuals. Many a time, research traveled past our labs and out of our lab notebooks as we spent countless dinners at Dudley Dining Hall talking about lab failures and successes, or spent some late evenings in the Mather JCR exchanging ideas for future experimentation. We hope to commemorate this summer of excitement, bonding, and growth in this abstract book as a means to remember the pioneering steps in our professional and academic journeys. Whether you are a biologist, a philosopher, or economist, we hope that you enjoy diversifying your current research knowledge by exposing yourself to material from different fields represented in our publication. As we become alumni of the Harvard Summer Undergraduate Research Village, we go as witnesses of the power of community, curiosity, communication, and collaboration within the research setting and beyond.

All our best,

Elissa Lin '15 and Gabriela Ruiz-Colón '16
Editors-in-Chief

The PRISE 2013 Abstract Book Editorial and Distribution Staff:
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BLISS

Julia Bruce
Sociology
Currier 2015

Evaluating a Social-Emotional Elementary School Intervention

Stephanie Jones
Prevention Science and Practice
Harvard Graduate School of Education

As elementary school educators increasingly focus on academics, less time in school is spent on improving children's social, emotional, and behavioral skills. However, studies have shown that social-emotional skills and executive function abilities, which include self-control, working memory, mental flexibility, and focus, may be taught and strengthened in children. Research indicates that well-designed programs targeting these skills promote children's academic success and healthy development. Professor Stephanie Jones's research team has developed a curriculum supplement that promotes social-emotional learning and executive function skills called SECURe (Social, Emotional, and Cognitive Understanding and Regulation in education). SECURe includes lessons and activities for teachers to utilize throughout the school day. It is designed to give children the tools to become more engaged students and more cooperative peers.

This summer I helped evaluate the effects of the SECURe program, which has been implemented in several elementary schools in Arizona and New York and serves primarily low-income children. I entered, cleaned and conducted preliminarily analysis on data collected from hundreds of students, teachers, and parents participating in the SECURe program. Additionally, I helped to write an IRB application and create a direct child assessment for an upcoming research trip to a New York elementary school. Next steps include continuing to study the outcomes of the children in SECURe, and expanding the program into additional schools, grades, and out-of-school settings.

Tuyet Cam
Social and Cognitive Neuroscience
Eliot 2014

The Effects of Co-experience and Mental Access

Bethany Burum and Daniel Gilbert
Harvard College

What happens when we share experiences with other people? Co-experience, defined as believing another person is having the same experience at exactly the same time, pervades our daily lives, from watching TV together to riding thrilling rollercoasters. In an earlier co-experience study, Burum and Gilbert showed that sharing an experience with another person could enhance the emotions we feel during the experience. In this research, we are interested in investigating whether co-experiencing an event can also lead people to feel a stronger mental connection with another person. When we co-experience, do we believe others have access to our private thoughts? If so, does this change our beliefs and feelings about our experiences?

To study the effects of co-experience on perceived mental connection, we designed an experiment in which participants believed they were trying to tap the rhythm of common songs so that another participant could guess them. The participant was always assigned as the "tapper" and the confederate was always assigned as the "guesser." In the solo condition, the confederate would leave the room while the participant tapped the songs for a recording. In the co-experience condition, the participant would tap the songs in real time with the confederate in the room. Results demonstrated that participants who tapped the songs in real time believed that the guesser was more likely to guess the songs correctly. Currently, we are demonstrating that this phenomenon is due to participants feeling a greater sense of mental connection with the other person.

Seung Jae (Sean) Cha
Applied Mathematics - Statistics
Dunster 2015

The Olympic Game: A Study of Corruption in Different Cultures

Kobi Gal
Harvard Decision Science Laboratory
Harvard School of Engineering and Applied Sciences

Corruption, defined as preferential treatment following a bribe, has been an important policy concern in many countries. Prior research efforts have attempted to emulate and model such behaviors of corruption; however, this has proven to be quite difficult in the confinements of the laboratory because it requires study participants to be primed for "corruption." This cross-cultural behavioral study allows human subjects in a group of four to engage in an online board game with limited transparency and separation of powers to study how corruption affects individuals and aggregate performance. This study has clear open-ended rules with no hints of priming for corruption.

One player is randomly chosen to be the "auctioneer," representing the government official. The other three players are "bidders," representing private interests. Each bidder is allotted an amount of online chips, which he or she can use with the help of the auctioneer to reach a goal on the game board for a high monetary prize. In addition, the players are given time to communicate with each other and to send chips to one another.

The preliminary results indicate that instances of corruption are more prevalent in the U.S. than in Israel (41% vs. 31%). In addition, in games where corruption plays a role, the auctioneer ends up with a much higher monetary reward in the United States but not in Israel. It was also observed that the auctioneer is much more likely to approach the bidders about possible bribery in the U.S., whereas bidders are more likely to approach auctioneers in Israel.

Marina Chen
Economics
Kirkland 2015

How Do We Respond to Cheating Over Time?

Julia Lee
Harvard Decision Science Laboratory

Does cheating elicit a physiological response (i.e. sweating, changes in heart rate)? Does it get easier over time? We hypothesized that physiological arousal, as measured by skin conductance response, is associated with more cheating and that repeated cheating leads to a decrease in physiological arousal—potentially because people become desensitized with their own cheating over time. In our experiment, "Predict the Future," participants were told that they would be compensated based on whether or not their prediction of a coin toss was correct. They were asked to complete five rounds of the coin toss (which was done on an online coin-toss generator), and with each correct forecast, they would be able to keep a dollar bill from an envelop containing five, one dollar bills that was placed in front of them in their own private cubicle. Unbeknownst to the participants, the coin-toss website stores a log of each participant's coin toss outcome. While participants might think they have gotten away with a few extra dollars, their true responses are recorded, allowing us to figure out who cheated and who did not.

Mark Daley
Government
Adams 2016

The History of Petitioning in America

Dan Carpenter
Harvard College

The First Amendment of the United States Constitution affords citizens the right "to petition the Government for a redress of grievances." Prior to the advent of public opinion polling and modern communication technologies, millions of citizens relied on petitions to communicate their opinions, desires, and protests to legislators. Petitioning was also a principal mechanism that legislators of years past used to gauge public opinion in their constituencies and around the country. The practice of petitioning, although less prevalent in recent decades, persists even today, specifically with the use of electronic petitions.

Professor Carpenter's principal research goals include creating an archive of petitions submitted to legislatures throughout history. To this end, I created a database of anti-slavery petitions sent to Representative John Quincy Adams, a staunch supporter of this crucial First Amendment right. I also performed exploratory research at the Massachusetts State Archives in an effort to gauge the prevalence of petitioning on the subjects of women's suffrage and Native American rights.

An additional component of Professor Carpenter's research aims to comprehend the manner that petition authors collected the signatures in these historical documents. In order to understand the methods used to compile signatures, we have begun a project analyzing two New York City anti-slavery petitions that include street addresses in the signatory lists. We will use GIS methods to show how citizens circulated these petitions, and we will analyze the sequence of the signatures to determine if these "petitions" are, in fact, an aggregate of smaller petitioning efforts.

Vicente de la Torre
Economics, Psychology secondary
Winthrop 2015

Pinpointing the Development of Fairness in Humans Through a Study in Inequity Aversion

Felix Warneken and Katherine Mcauliffe
Laboratory for Developmental Studies
Harvard College

Where does morality come from? One thing we know for certain is that we move forward in time, as does our nature. By studying the development of morality as it has assembled itself over time we may eventually have enough insight to make an educated guess into the origin. This question is the reason why I have personally taken an interest in Professor Warneken's research this summer of 2013, and after speaking with him and others in the lab I have found that they have similar reasons as well. So that is the big picture, the forest, but we must accept our limitations and dedicate our efforts toward a single tree. That single tree this summer has been Dr. Katherine Mcauliffe's (a post-doctoral fellow in the lab) experiment on inequity aversion. We make our way to Boston Common and set up our apparatus—on one side sits the recipient and on the other the actor who has control of a green lever and a red lever. Our subjects are children 4-9 years old. The experimenter will distribute different distributions of skittles to the actor and the recipient. The actor then has to make the decision to accept (green lever) or reject (red lever) the distribution. We have found that up to age eight, children value fairness and reject uneven distributions, while older subjects, including adults, are more rational and exclusively pull the green lever. With each pull of the lever we come closer to the peek into the origin.

Chiemeka Ezie
Psychology
Currier 2015

The Neurodevelopment of Anxiety

Leah Somerville
Psychology/Center for Brain Science
Harvard College

Affective psychologists have proposed the existence of two different forms of anxious emotion: phasic anxiety, a transient anxious experience, usually cued by a specific stimulus; and tonic anxiety, a period of worry that lasts longer and may not be connected to a specific stimulus. Recent research has suggested that these different forms are mediated by different regions of the brain. Our present study modifies a procedure from some of the aforementioned research suggesting the existence of the two types of anxiety in adults and uses a population of children, adolescents, and young adults. In our task, subjects are presented with picture stimuli as we manipulate two variables: the emotional valence of the pictures (positive, negative, or neutral) and whether the subjects know when the picture will appear (as marked by a clock counting down) or cannot tell when the picture will appear (the clock ticks to random positions). We monitor the subjects' responses to stimuli using functional magnetic resonance imaging and skin conductance response recording. We hypothesize that, as in previous research, the conditions with the random clock are more likely to create a tonic anxious response

than those with the countdown clock, and that the negative pictures will produce higher responses of anxiety than the neutral or positive pictures. The present study has the potential to increase the understanding of the divisions of anxiety by identifying developmental changes in the circuits regulating them. In addition, the present study may establish a population for a longitudinal study of anxiety disorders.

Sebastian Gomez
History and Literature; Latin America Field
Leverett 2014

Neighborhoods and Schools: Navigating Choice in Boston/Cambridge Public Schools

Natasha K. Warikoo
Harvard Graduate School of Education

For many children in the United States, the town or residence they live in often dictates their school choice. In small suburban towns there may be only one elementary school from which parents can choose to send their kids. Some school districts may have several elementary schools that ultimately feed into one larger high school. Urban school districts are often more complex, having a wide array of schools at the elementary, middle and high school levels. In these districts, neighborhood dynamics and location affect where children attend school.

This pilot study looked at the way immigrant parents conducted searches regarding neighborhoods and schools. During interviews, parents were asked what the guiding force behind their school selection was. Parents were asked to explain how they choose the school their children attended and whether they actively sought to live in areas of Massachusetts known for their "good" schools. This pilot study sheds light on area of school choice that, as of late, has only begun to be examined. Our focus on Latino and Asian parents was an attempt to study how different immigrant ethnic groups navigate similar school choices. The study took into consideration issues of economic status and education to see how these socio-economic differences affected where parents sent their children. Ultimately, this study aimed to understand the dynamics of school choice among immigrants and how different groups navigate school choice systems to guarantee the best education for their child.

Our preliminary findings show that immigrant parents rely on similar grape vine networks as those of their White and African-American counterparts. However, immigrants parents interviewed thus far cite this grape vine knowledge as second to many other deciding factors when choosing schools. Instead, many parents base their school choice on visits to schools or meetings with the administration conducted before enrollment. Parents with economic means often tried to find better schools by moving to towns known for their good school districts. Interviews ultimately indicate that many parents aim to find the best schools in their own district instead of trying to move to a new town. This was often achieved either by moving closer to a zoned school, known for its better quality, or using the in-district choice system to guarantee a better school for their child.

Michael Gribben
Applied Mathematics
Mather 2015

Inter-group Relations in the Middle East

Ryan Enos and Dustin Tingley
Harvard College

This summer I have had the pleasure of working on two political science projects with faculty at the Government Department.

The first, with Professor Ryan Enos, was a study of group relations in Israel, specifically those between Secular and Ultra-Orthodox Jews. This situation is useful for study as it is an example of a strong cultural divide that has led to various homogenous and separate communities, but is not based upon ethnic factors. Professor Enos hopes to use the results from this study to see whether the findings of studies that he and others have done on racial groups in the US are universal to societies with these types of divides. Secular and Ultra-Orthodox Israelis were asked to take part in co-operative games with members of different groups, and were also given a survey on divisive issues in Israel and their opinion of different groups. This data will be used alongside their geographical location to assess factors that affect negative relations between these groups.

The second project, with Professor Dustin Tingley, involved collecting a large dataset from Twitter of Arabic-speaking political tweeters from Middle-Eastern countries. We collected their history of tweets and list of followers to recreate the networks of Twitter users. We will use information about how often people with different political ideologies retweet and follow each other to analyse how often people in these areas of the world interact with people who hold differing political beliefs.

Victor A. Mata
Economics
Quincy 2014
Monica J. Wilson
Anthropology
Pforzheimer 2014

Parent-Teacher Communication Study

Todd Rogers
Center for Public Leadership
Harvard Kennedy School

We are assisting with the extension of a study conducted in the Boston Public Schools Summer Review Program last summer by Todd Rogers and Matt Kraft. The study objective is to determine what kind of enhanced communication from teachers to parents increases student performance and completion of the program the most. Although the study produced promising results last summer, this year we hope to further explore the mechanisms behind increased summer school completion rates. We are responsible for the data collection, survey administration, and parent communication portion of the study at the BPS Summer Review Program.

The study involves assigning consenting parents and students into three categories: a control group, a positive message group, and a needs-improvement group. Each week, we collect both a positive and a needs-improvement sentence for every student written by their teachers. These sentences allow teachers to indi-

cate something the student is doing well—a positive sentence—and something they can improve upon-- a needs improvement sentence. Depending on which category the student is sorted into, we call the parents with the appropriate message that the teachers wrote. We gave all the students in the study a survey halfway through the program asking about their communication with their parents regarding summer school. We hope this will shed light on the mechanisms behind any possible increase in student performance or attendance.

Eleanor Parker
Human Evolutionary Biology
Eliot 2015

Biology and Executive Function

Susan Carey
Department of Psychology
Harvard College

Young children tend to operate on a strictly movement- or agency-based theory of what it means to be alive, often identifying the sun as a living thing. It is not until around age six that they supplant these initial concepts with a vitalist theory that takes into account the systems and cycles supporting life. We hypothesize that variation in age of developing this first biological theory of life stems from individual variation in executive function (EF), a suite of abilities that includes working memory, inhibition, and setshifting. Children with higher EF might arrive at a vitalist theory sooner as they are better able to inhibit their prior agency-based responses. Our work replicates and extends a study conducted by Zaitchik, Iqbal, and Carey (in press) that found such a correlation between EF and biological reasoning.

Each of the 6-year-olds in our sample of 70 participated in a biological interview (including sections devoted to animism, death, and body parts) and a subsequent executive function battery. In addition to the inhibition- and setshifting-focused tasks of the original study, we included working memory and verbal fluency measures for more comprehensive EF analysis. Further, we expanded the repertoire of control tasks beyond verbal IQ to include tests of nonverbal IQ and factual knowledge. We anticipate that vitalist understanding will correlate with executive function independently of age, factual knowledge, verbal IQ, or nonverbal IQ. We also expect an isolated correlation between nonverbal IQ and our biological measure, considering the importance of analogical reasoning in conceptual change.

Ryan Romain
Psychology
Eliot 2014

Gender Stereotypes in Child Custody Decisions

Mahzarin Banaji
Harvard College

While it is often women who are thought of as the disadvantaged gender according to gender stereotypes, in some situations men are also discriminated against merely because they are men. For example, men are often at a disadvantage in child custody cases, as 82.2% of custodial parents are mothers (Grall, 2009). Such asymmetry may be the result of judges (and all people in fact) having a bias that women are better parents than men. This bias may be inaccurate and may lead to children being placed in the custody of unfit mothers when they would be better with their fathers. The present research aims to explore whether one's implicit bias associating women with good parenting predicts a tendency to award custody to mothers over fathers—even if the father is the more fit parent. Participants will be presented with a vignette depicting a child custody case, and their implicit associations regarding the relationship between gender and being a good parent will be assessed with an Implicit Association Test (IAT). Participants will then be asked to render a judgment on the custody case, and the correlation between one's decision and IAT score will be assessed. The researchers hypothesize that individuals who have an IAT score indicative of a stronger implicit association between women and being a good parent will be more likely to award the mother custody when asked to render a judgment about the vignette.

Kendra Rosario
Neurobiology
Eliot 2014

The impact of sleep and spindle activity on memory processing

Erin Wamsley
Center for Sleep and Cognition
Beth Israel Deaconess Medical Center

In the past, both sleep after learning and sleep spindle activity are strongly linked to one another and to memory task performance. For the first time, we plan to demonstrate that theta frequency waves, REM sleep, as well as sleep spindles positively correlate with performance on a spatial navigation task across a night of sleep. We presented two groups of participants with the 3-D video game task; the sleep group initially did the maze in the evening, while the wake group is first exposed in the morning. Nine hours later, both groups retested. We expect, first, that the sleep group, monitored by EEG, EMG, and EOG in the lab, will improve while the wake subjects will improve significantly less or even perform more poorly than during the initial testing. Secondly, we hypothesize that task improvement in sleepers will be directly correlated with the amount time in of stage two sleep, which is characterized by sleep spindles and K-complexes. In addition, because past studies show REM sleep and theta frequency waves are associated with emotional memory processing, given the realistic and somewhat morbid imagery of this edition of the first-person spatial navigation task, we expect low density polysomnography to show larger amounts of these sleep phases in participants that improve most. These predictions suggest that memory consolidation depends heavily on the duration and quantity of polysomnographic qualities during the sleep.

Natalie Smith
Sociology and Visual and Environmental Studies
Lowell 2015

The Quest for Equality and Respect: Dealing with Stigmatization in the United States, Brazil, and Israel

Michéle Lamont
Department of Sociology and
African and African-American Studies
Robert I. Goldman
Department of European Studies
Harvard College

How is social difference conceptualized differently in different societies, upon what basis do groups draw boundaries between themselves and others, and in what ways do individuals respond to the exclusion and inequalities which often arise from such social divisions?

The 'Responses to Stigmatization Project' utilizes the qualitative analysis of in-depth interviews with middle and working class African-Americans, Afro-Brazilians, and Arab-Palestinian citizens of Israel to consider how different collective narratives and sociopolitical histories have shaped responses to stigmatization within these three national contexts.

This summer, Professor Lamont and her collaborators in Israel and Brazil have been engaged in constructing a cross-national comparison between each case study to illuminate dimensions of the social and cultural boundary drawing, which might have otherwise remained unexposed. While the comparison of Brazil's color hierarchy and national narrative of the 'racial democracy' has traditionally been the subject of comparative sociologies to the United States Black-White racial essentialism and narrative of the American Dream, the addition of the Israeli case – which explores ethnoreligious status as the basis of exclusion and Zionism as the central collective narrative – highlights new dimensions of the boundary configurations found in each.

In focusing upon the stigmatized individuals' everyday responses to the assaults on worth and discrimination, this study provides insights into the politics of recognition and the production of social resilience.

Ren Jie Teoh
English and Government
Quincy 2016

Investing Rape Culture in the Media

Dara Kay Cohen

There has been considerable scholarly research performed on the biases in news coverage of rape and other forms of sexual violence. Many believe that these biases constitute evidence of a "culture of rape" that promulgates the view that rape is not a real crime and that its victims are responsible for their own violation.

The primary empirical aspect of the project will be the creation of a micro level dataset of global news coverage of rape and sexual violence. For each of approximately 2,500 newspapers in 108 countries since 2000, the dataset will measure (1) whether that newspaper published a story about rape on a given day, and (2) the extent to which the tone and content of that story (or stories) offers evidence of rape culture as it is commonly understood in the academic literature and by experts. A similar dataset will be created for social media, using geo-referenced data on approximately 10% of all Tweets posted by users worldwide since 2011. Machine-learning software will be used to automate coding. The data will be used to conduct further analysis on correlation between the incidence of rape culture in the news of a given country and the legal and social status of it women.

My role in the project has mainly been to review existing scholarly literature for new methods, information or techniques we can absorb into the project. I have also conducted a small pilot study to test the feasibility of the project on a limited selection of newspapers.

Ava Zhang
Psychology
Eliot 2016

Social Similarity: How We Represent and Categorize Others

Jason Mitchell
Social Cognitive and Affective Neuroscience Lab
Harvard College

Human beings spend a great deal of time thinking about other human beings, this much is certain. But how do we represent and categorize others? Do we think about them primarily in terms of their demographic characteristics, or their personality traits, or their relationships to ourselves? Many models have received empirical support, but their relative contributions and neural substrates require further investigation.

In the present study, we seek to better understand what makes one individual seem similar to another. Subjects first rate 40 people that they know personally on a variety of metrics, such as age, race, openness, neuroticism, competence, and degree of authority. After an optimization algorithm selects the 20 most disparate individuals, subjects are asked to make comparisons from within that subset: "Is Ursula or Humphrey more similar to Geraldine?" Analysis of this data will allow us to identify the qualities that best predict perceptions of similarity. We will also be able to test the strength of different personality models by assessing how well they correlate with holistic judgments of similarity.

The next phase of this project will combine the above behavioral task with functional magnetic resonance imaging. Subjects will imagine 20 people in a variety of situations: "Myrtle is sitting at a bar"; we can thus collect data on the patterns of brain activation that appear when subjects think about given individuals. Using a multi-voxel pattern analysis, we will compare the ratings from the behavioral study with neural data to produce a mapping of where different types of social information are represented in the brain.

PRIMO

Cristina Cornejo
Economics
Winthrop 2015

How Language Creates Unearned Status Gain In Global Business

Tsedal Neeley
Harvard Business School

The literature primarily treats status as a static concept, emphasizing the experience of possessing high or low rankings. Recently, a few scholars have begun to recognize and explore the dynamic nature of status in organizations. Joining this emerging area of study, my research focused on developing theory on unearned status gain and related responses. An unearned status gain occurs when an organization takes action that results in certain people receiving a status boost without additional effort. Drawing from qualitative data from American subsidiaries of an Asian multinational corporation that recently issued an English language mandate, we examined how native speakers reacted to their unearned status gain in the company. Preliminary results suggest that an organization can activate dormant status characteristics that objectively advantage workers. We find that those who experience unearned status gain will often exhibit ambivalence towards their counterparts who are nonnative speakers (earners), have concerns around the durability of their new advantage, and be uncomfortable about gaining advantages without effort in a meritocratic culture. These findings suggest that unearned status gains may lead to conflicted employees within the workplace, and highlight the uncomfortable nature of such changes in status. What seems at first like a positive development in a person's career, may actually serve as a reminder of the volatility of their position, especially in dynamic global environments.

Zaki Djemal
Social Studies
Adams 2015

Decision Making and Behavioral Economics

Francesca Gino, Michael Norton, Leslie John, Ryan Buell
Harvard Business School

My research this summer has focused on decision-making and behavioral economics. More specifically, I have been looking at how extrinsic incentives affect prosocial behavior. This inquiry encompasses the 'crowding out' and 'crowding in' of volunteering, rituals and their prospects for building strong habits and value formations, signaling and status attribution, online disclosure habits, and why and when people cheat. I have designed and carried out experiments in the lab and field and compiled extensive literature reviews. I am now in the process of writing up my findings. I am co-authoring a paper arguing that the crowding out of prosocial behavior by extrinsic motivations can be mitigated by a set of interaction terms found in the area of volunteering. These include the repetition of a prosocial act, the presence of real life social interactions, and the emphasis on giving time versus donating money.

Annie Garofalo
Neurobiology, Economics secondary
Currier 2015

Decision Making Under Uncertainty

Uma Karmarkar, Marketing
Harvard Business School

Online consumer reviews have changed the way products and services are evaluated. What was once only possible through in person conversation can now be accomplished via the Internet, changing the channels through which consumers process such information. There are currently many websites, such as Yelp.com, that act as platforms where consumers can share experiences about product quality, rating and commenting on products from household appliances to bus services. Such online consumer review websites improve the information available about product quality, with an impact that is larger for products of relatively unknown quality (Luca 2011). In other words, consumer reviews decrease uncertainty in individuals who wish to use some service or purchase some appliance. Previous work largely examined how such reviews influence retailers; however, there is still much to be explored from the consumer's perspective and how consumers are processing information through reviews as opposed to normal social channels. My research uses restaurant reviews to try and better understand how consumers use reviews to approach new service experiences. I'm specifically looking at how a reviewer's profile picture affects other consumers' integration of information in the review in order to determine how individuals interpret consumer feedback online.

Cybele Greenberg
Applied Math
Pforzheimer 2016

Understanding the Changing Expectations of Young Professionals

Boris Groysberg
Harvard Business School

This longitudinal qualitative study explores the changing expectations of recently graduated Harvard College seniors as they transition into becoming young professionals. The complete project includes three rounds of interviews, each a year apart. This report analyzes the second round of interviews—which took place in 2012—by transforming the qualitative interview transcripts into quantitative data that can be compared over time. It shows how one extra year of experience in the 'real world' significantly affects the participants' experiences and perceptions. Some of the most salient categories included the participants' professed greatest strengths in the professional world, their greatest weaknesses, their greatest challenges, and the three most important things they had learned about themselves in that single year since the first round of interviews. Because the answers to all of these questions were self-reported, it was also possible to dissect the style, tone, and context of the participants' responses, an element that added a complex layer of

meta-analysis. Going forward, the plan is to review the third round of interviews to discover if the patterns we see between the first and second rounds of interviews are also applicable in the long-term.

Joseph Hall
Economics
Currier 2016

The Impact of Transparency in Food Service

Operations Francesca Gino, Michael Norton, Leslie John
Harvard Business School

A group of researchers in the Organizational Behavior and Marketing fields at Harvard Business School are dedicated to exploring human behavioral and psychological effects and their real-world applications. One such application setting is the world of consumer satisfaction: if customers feel happy, they will return to your business. Many food service companies try to enhance customer satisfaction by opening up their operations to transparency. For example, Subway is very popular in part because they make all the sandwiches directly in front of the customers. We investigated the effects of this type of "operational transparency" with a variety of methods. We ran experiments on Amazon's MTurk service and in the Harvard Business School CLER lab, showing subjects videos of ordering and receiving a sandwich with varying degrees of operational transparency. We also ran a 2-week study in Annenberg dining hall, whereby i-pads were placed in the servery and kitchen, allowing video conferencing between chefs and students. These i-pads could be off, one-way, or 2-way, allowing us to isolate the effects of consumer-side or employee-side transparency, as well as their combined effects. Further analysis and experiments are needed, but our findings seem to be building a strong case for the value of operational transparency in food service, where managers can enhance not only consumer experiences but those of employees as well.

Elena Helgiu
Psychology
Eliot 2014

How can we influence others to do the right thing?

Max Bazerman, Francesca Gino, Leslie John, and Mike Norton
GiNorton Laboratory

Have you noticed that the fruit and vegetables are always near the entrance of a grocery store? This is an example of a nudge, an inconspicuous intervention that steers our behavior toward the ethical, healthy, or financially optimal choice. In theory, nudges act as a lending hand, helping our "should" self overcome our "want" self. However, it still remains unclear whether nudges can backfire, resulting in worse outcomes than without the nudge. One of the projects I worked on this summer looked at whether awareness of a nudge causes people to engage in the opposite behavior that the nudge intended. In a study done on Amazon MTurk, participants were asked to indicate their satisfaction with a default 401(k) plan that saves at a suboptimal rate over an opt-in program that does not restrict savings rate. The results indicated that even though participants were aware of the nudge and its intentions to increase enrollment in a savings plan, they approved of its use in the workplace. In addition to this study, I also contributed on ongoing projects interventions that look at whether multiple nudges can interact to inspire a creative solution to a moral dilemma. Although the results of this study have not yet been gathered, I coded responses to 4 ethical dilemmas, rating them on creativity, effectiveness in solving the problem and adherence to the rules, and extent to which ethics played a role in the decision. The preliminary results support the hypothesis that two nudges may be better than one.

Courtney Hooton
Psychology
Mather 2016

The Cost of Greed

Eugene Soltes,
Department of Accounting and Management
Harvard Business School

This summer, I was fortunate to be under the tutelage of Professor Eugene Soltes and assigned to explore the corporate finance world. We were interested in examining the psychology behind corporate deviance. Specifically, why do top tier executives compromise their integrity and professionalism for financial gain, especially in situations where they stand to lose far more than they would gain from these dishonest transactions?

My research was specifically focused on the firm Berkshire Hathaway run by international businessman, Warren Buffett. Berkshire Hathaway is one of the most successful investment firms in the world. What has made this firm so successful is its unprecedented reputation. This reputation is not only reflective of an honest company, but of the personal character of Warren Buffett. Therefore, it was such a surprise when Warren Buffet's star employee, David Sokol, was involved in a scandal that forced his entire company to be investigated by the SEC. David Sokol was a man who came from humble beginnings in Omaha, Nebraska, yet became a powerful player in the investment world. He became such an asset that it was widely believed he would be the replacement to Warren Buffet. Professor Soltes's research begs the question of why someone like Sokol, who seemed to have it all, would give up billions of dollars for just a few million.

Katherine Coley Mentzinger
Chemistry
Dunster 2014

Marketing: Decision Making and Behavioral Economics

Francesca Gino, Michael Norton, and Leslie John
Harvard Business School

We are constantly making decisions. Whether they are inconsequential or life changing, we struggle to make considered and reasonable choices. But we are buffeted by the whims of human nature that can alter our decisions and lead us astray. We might find ourselves unintentionally conforming to social norms, incorporating irrelevant data, or even violating our own ethical principles when we make choices. The Gi-Norton lab examines decision-making and how it is driven by morality, pro-social intentions, heuristics, creativity, and external manipulation. The lab's research findings can

help individuals reach optimal decisions that enhance their well-being and can help organizations increase employee satisfaction and customer appeal.

This summer I explored various environments in which consumers make choices. In the food services industry, I looked at financial decision-making, in particular how ordering behavior and satisfaction are affected by different methods of splitting a check. I also looked at how a restaurant's operational design drives consumer choices when I helped with a field experiment conducted in Annenberg. My group considered situations in which consumers could see the chef, in which the chef could see consumers, and in which consumers and the chef could see each other. I shifted my focus to print media, designing a survey to evaluate how paying every month as opposed to every year for a magazine subscription affects satisfaction and subscription renewal. Finally, I assisted with a study that asked participants to imagine themselves in various ethical dilemmas. I evaluated the respondents' creativity and morality.

Fran (Shi Hyun) Lee
Economics
Eliot 2015

Characterizing Frontier and Emerging Markets

Eric Werker and Aldo Musacchio
Harvard Business School

In this paper, we characterize each frontier and emerging economy into four distinct markets. These markets have different characteristics, give businesses different incentives, require different approaches by a regulator, and lead to different firm strategies. In order to characterize these markets, we first define frontier markets based on criteria pertaining to weaker institutions and low factor prices.

We categorize the Four Markets into a 2x2 matrix based on two axes: the amount of rent existing within the market (high-rent or competitive) and the degree of focus on exports (export-oriented or domestic-focused). This classification results in the Four Markets: Rentiers, Powerbrokers, Workhorses, and Magicians.

Rentiers operate in the high-rent, export-oriented market. A typical example is a natural resource exporter, who makes a bargain with the state to extract and sell a sovereign resource in exchange for a payment structure. Powerbrokers operate in the high-rent, domestic-focused market. They are typically monopolists or oligopolists, either because of a natural scale effect, or because of sovereign-granted rights. Workhorses operate in the competitive, domestic-focused market. They are small retailers or local producers who compete based on costs or differentiation. Lastly, Magicians operate in the competitive, export-oriented market. Magicians are typically manufacturers or service exporters who generate economic activity without using sovereign resources or crowding out business activity.

Foreign investors in emerging economies can utilize this Four-Market Analysis to examine business opportunities and make better-informed decisions. Governments can also benefit from recognizing the differences between these four distinct markets when making policy decisions.

Chisom Okpala
Economics and African Studies
Lowell 2015

Unpacking Great Leadership

Ranjay Gulati
Harvard Business School
Organizational Behavior Unit

The overarching vision of this project is creating a comprehensive online leadership training website to reach a global audience. Professor Gulati whose area of expertise is in the fields of leadership, strategy and organizational issues is looking to examine leadership lessons in diverse fields, and in extraordinary stories of everyday leaders around the world.

This project has two parts. In the first part, we explore some of the fundamental theories of leadership and translate them for a younger audience. The goal here is to make the decades worth of leadership research in business schools relevant to high school and college students. We first assessed the vast domains of leadership and found social entrepreneurship, organizations and athletics to be very rich with powerful leadership lessons. For instance, what leadership lessons are to be derived from Matt Flannery's strategic and innovative mobilization of lenders and borrowers through Kiva? How did Steve Jobs emphasis on excellence motivate his employees to relentlessly strive for a culture of innovation? We've been conducting extensive research to find illustrations, stories, and videos that effectively communicate key principles of leadership to our audience. In the second part of this project, we explore some of the leading psychometric tools available to assess an individual's leadership potential and provide practical online training activities and exercises that teach leadership skills.

While our proximate audience is the youth, it is our strong conviction that by making our website easily accessible to a younger audience, it is ultimately appealing to older demographics, as one's capacity for leadership is never static no matter one's age. There are always opportunities to improve one's ability to lead and make a difference in the world. This website will provide the leadership training that can greatly facilitate our vision of a world in which everyone makes an impact.

Alydaar Rangwala
Applied Mathematics
Currier 2015

Impact Investing in Emerging Markets

Shawn Cole, Tarun Khanna, Eric Weker
Harvard Business School

The world is facing growing social problems, and government funding and charitable donations are proving to be insufficient to address these issues. Impact investing is a new alternative for utilizing large-scale private and commercial capital for social good. Impact investments are investments in which both financial returns and social benefit are considered. Current impact investors range from philanthropic organizations to commercial institutions to high net worth individuals, investing across a variety of business sectors and geographic locations. This research investigated the differing characteristics of impact investors versus traditional commercial

investors. Using two large datasets of venture capital and private equity deals, known impact investors were evaluated on a variety of metrics such as deal size, GDP of target countries, number of firms per deal, and date of investment among others. Initial results indicate that impact investors significantly differ from commercial investors in deal size, GDP of target countries, and geographic location of investments. These results fill an academic gap in the impact investing literature and may better identify characteristics needed by prospective impact investors. It also serves to provide evidence of the viability of impact investing as an emerging asset class.

Ana Sofia Guerra Rodriguez
Chemistry
Adams 2015

Women and Work Around the Globe

Kathleen McGinn

Gendered beliefs and practices affect the economic outcomes of individuals, families, organizations and communities. Most of the existing research on gender, social construction and enactment of roles, interactions and practices focuses on social processes rather than economic outcomes. As a result, my research with Professor McGinn explores the effects of gendered beliefs and practices on economic outcomes. I have participated in 5 different projects that study these effects across multiple industries and countries, using various methodologies. Studies within families, organizations, and communities of employed and self-employed women in developing countries and across countries are carried out through the analysis of census data between 1981 and 1991 in 17,000 villages in the Indian state of Gujarat, ISSP data covering over 100 countries, and data collected by surveying employers in the top 10 companies in Mexico. A study on leadership development and high potential women in developed countries was conducted by interviewing the senior leaders of major investment banks in Toronto, New York, and Chicago to study their life decisions and career development. Lastly, we are developing a project to study the payoff of investing in women through African government-run programs. Thus, we will be looking into the effects of cash payments on the welfare of the household and the children.

Bilguun Ulammandakh
Government, Economics secondary
Lowell 2014

Mobile-based Agricultural Extension in India: Impact and Pricing

Shawn Cole
Harvard Business School

Across firms and farms, there is tremendous heterogeneity in productivity around the world. My group's research seeks to explore the role of management decisions in explaining this variation; and in particular the possibility that timely, relevant, high-quality advice can dramatically improve productivity decisions. The research consists of two individual projects. The first is a mobile-based agricultural extension service, called Awaaj Otalo, which has been shown to dramatically improve agricultural decision-making by rural farmers. The second project provides customized financial and business consulting to micro- and small-enterprises in India.

Astronomy and Astrophysics

Ruby Almanza
Neurobiology and Astrophysics
Leverett 2016

Building Atmospheric Models for Exoplanets Orbiting Main-Sequence Stars

Dimitar Sasselov
Harvard Smithsonian Center for Astrophysics

Late in the 20th Century, scientists began to detect and confirm the existence of planets outside of our solar system. By March 7th of 2009, NASA had launched the Kepler telescope to explore the possibility of Earth-like planets outside of our solar system. Today there are ~2300 Kepler Objects of Interest, and astrophysicists are currently working on determining which of these Earth-like planets host Earth-like life. However, instruments capable of detecting bio-signatures from afar do not yet exist, presenting the need for research contributing to their development.

Our contribution to this effort involves building atmospheric models for Earth-like planets discovered by Kepler. These models enable us to produce synthetic spectra merging the information we gather from Earth's atmospheric bio-signatures with the information we can gather from Kepler. While most models focus on planets which exist within the habitable zones of their corresponding stars, we aim to create models for planets that orbit just outside of the outer limit of their star's habitable zone. The purpose is to show that shifts in atmospheres, such as excessive greenhouse gases which warm the planet enough to sustain liquid water, have a drastic effect on the habitability of a planet. Consequently, these variables have to be taken into account when building instruments to determine the probability of life outside of our solar system.

Zoey Bergstrom
Astrophysics and Physics
Cabot 2015

NH3 as Probe of Early Phase Massive Star Formation in IRDCs

Qizhou Zhang
Harvard-Smithsonian Center for Astrophysics

Infrared Dark Clouds (IRDCs) are clouds of dust and gas that lie on the near side of the Milky Way's galactic disk. IRDCs appear as infrared extinction features against the Galactic background. Such regions are potential sites of early high-mass star formation because their mass and density are similar to those of dense molecular clouds known to form massive stars, but their temperature is much lower.

Using ammonia as a probe, I determine the physical properties of 13 IRDCs using data obtained with the Green Bank Telescope (GBT). To map these characteristics, I fit Gaussian curves to the main and satellite hyperfine components of the ammonia spectral features at each relevant velocity, and obtained the optical depth of the line. By comparing optical depth of the NH3 inversion transition (J, K)=(1,1), and (2,2), I derived the temperature of the gas. I also produced maps of moment 0 (integrated flux), moment 1 (velocity flow), and moment 2 (linewidth) for each cloud, and calculated their column density and thermal sound speed.

In order to determine the presence of protostars, I looked for bright infrared sources within the dark clouds using data obtained from the Herschel Space Telescope, and confirmed their location within the clouds based on increased column density and optical depth in those regions. Upon comparing the ammonia data to the infrared bright spots, I was able to establish or refute the presence of protostars in each of the IRDCs and draw conclusions about the physical conditions of high-mass star formation.

Michelle Cone
Physics
Currier 2015

Designing a User-interactive Animation of Star Positions to Teach Celestial Navigation Principles

John Huth
Department of Physics
Harvard College

People have long used the stars for navigation, although this practice has been less common with the advent of technology such as Global Positioning Systems. Celestial navigation still serves an important purpose for those who do not have access to such technologies. With a basic knowledge of the positions of stars and their motion, one can use them as a compass, orientating himself or herself based on position relative to stars. The position of stars can also help to fix one's location on the Earth, using the position of a star at a given time and the angle to that star from the location. My work was to create an animation for the movement of the stars throughout the day using basic principles of celestial navigation.

My animation uses a latitude and longitude entered by the user to generate lines of constant azimuth and altitude on a map of the Earth. Altitude and azimuth are spherical coordinates used to locate the position of a star relative to one's position on the ground. The angle along the horizontal is the azimuth while the angle along the vertical is the altitude. My animation also changes the positions of the stars based on the time zone and the time of year relative to the Spring Equinox since the longitude of the stars changes throughout the day and year. This animation will help others become familiar with the positions of stars so that they can use celestial navigation principles on their own.

Kewei Li
Undeclared
Pforzheimer 2016

Changes in Stellar Color due to Atmospheric Water Vapor Variations

Christopher Stubbs
Department of Physics and Department of Astronomy
Harvard College

Stellar color is defined as the ratio of two (calibrated) fluxes at different wavelengths. We used data from the PS1 telescope in Hawaii (currently the only functioning part of the Panoramic Survey Telescope and Rapid Response System, or Pan-STARRS) to look for changes in diagrams of stellar color against stellar color (color-color diagrams). If there are deviations from the standard stellar locus on color-color diagrams, we hope to characterize the deviations as a function of median stellar color. PS1 observes in 5 bands: g, r, i, z and y. The g and r bands should be insensitive to water vapor, while i, z and y bands might show some changes in response to water vapor. Data from stacked images were used to build a catalogue of stars by first identifying objects representing stars, and then using stellar locus regression to calibrate the stellar colors. We tracked changes in stellar color of these catalogue stars using unstacked nightly exposures. Color-color diagrams (mostly with the abscissa as g-r color) were made with airmass corrected observations. This procedure was tested on high quality medium deep field data from PS1 and seems to work well. Now we are trying to apply it to new data from the north celestial pole to eliminate any effects due to airmass. However, high quality stacked images are currently unavailable for the north celestial pole, and I'm trying to find some workarounds to build the catalogue of stars.

Aaron Markowitz
Physics and Mathematics
Pforzheimer 2016

Measuring the CMB Dipole at 11 GHz—For Cheap!

John Kovac
Department of Astronomy and Department of Physics
Harvard-Smithsonian Center for Astrophysics

The Cosmic Microwave Background radiation (CMB) is a nearly isotropic thermal radiation left unchanged from about 300,000 years after the Big Bang. This primordial radiation is a useful probe of the early universe, and CMB research is highly relevant for constraining cosmological models of inflation. Though mostly uniform, the CMB displays some anisotropies, the most noticeable of which is the dipole, a pan-sky Doppler shift resulting from the velocity of our planet with respect to the surface of last scattering (equivalently, the rest velocity of the Big Bang). The dipole temperature is a few mK on a CMB temperature of 2.7K.

This project modifies a telescope designed by Harvard's Astronomy 191 course, increasing its sensitivity by a factor of 100, enough to measure the CMB dipole. As a secondary goal, the resulting full-sky map near 11GHz would test the model for spinning dust contributions to foreground emission at low frequencies. The telescope's design allows replication of the experiment within the budget of similar laboratory research courses. We use a low-noise block (LNB) receiver and a bandpass filter to amplify radiation at 10.7GHz, and rotate at constant angular velocity and elevation to provide coverage of the entire visible sky over 24 hours. Before modifications, satellite interference, ground-based interference, data collection, and data processing introduced significant errors into the initial full-sky maps. With current modifications, the telescope can collect data continuously for over 24 hours and under proper weather conditions should return a positive detection of the dipole.

Cyndia Yu
Physics
Winthrop 2016

Development and Characterization of Vacuum Windows for the Keck Array and BICEP3

John Kovac
Department of Astronomy and Department of Physics
Harvard-Smithsonian Center for Astrophysics

The current cosmological model posits a period of inflation, or exponential growth of the Universe in the first 10^{-35} seconds. This model resolves the flatness and horizon problems and explains the origins of structure, but remains unconfirmed. Inflation predicts B-mode polarization with vanishing divergence arising from gravitational waves in addition to the curl-less E-mode polarization of scalar density perturbations. Detection of B-modes in the polarization of the cosmic microwave background (CMB) would thus provide a critical test of the inflationary model. Furthermore, constraints on the ratio of tensor to scalar spectra amplitudes r provide information regarding the energy scales of inflation.

The Keck Array is a CMB polarimeter in search of B-mode polarization. The detectors in the focal plane are cooled to 250mK via a pulse tube cryostat, necessitating a vacuum vessel in order to maintain the desired temperature. Thus, vacuum windows are a crucial part of this vessel in allowing vacuum to be held while allowing maximum transmission at microwave frequencies. Windows are constructed with aluminum frames, Stycast 2850 epoxy, and HD30, a nitrogen-expanded high density polyethylene foam. We optimized the construction of these windows in the development of improved methods for maintaining transmissive area during in situ degassing and increasing epoxy-foam adhesion. Mechanical testing for bowing and creep as well as optical testing of scattering, absorption, and reflection are critical to the characterization of window performance.

BICEP3 is a further upgraded polarimeter set to deploy in 2015. Its windows are approximately four times the area of Keck windows and must be given special anti-reflective coating. We further pursue the development of these methods and characterization of their mechanical and optical properties.

Chemistry & Biochemistry

James Bothwick
Chemistry and Physics
Quincy 2015

Polymerization of ADP Bound RecA on dsDNA

Mara Prentiss
Department of Physics
Harvard College

RecA is a protein found in prokaryotes that plays a central role in Homologous Recombination, an essential process in meiosis and DNA repair. During recombination, RecA binds a single-stranded DNA in site 1 and forms a nucleoprotein filament. This filament searches for a homologous double-stranded DNA strand. Once found, strand exchange occurs, with the homologous strand of the dsDNA and the ssDNA exchanging Watson Crick pairing. In the absence of external force, RecA bound to ADP will not directly polymerize on dsDNA. We demonstrate that by pulling on the 3' and 5' ends of one dsDNA strand, RecA bound to ADP can directly polymerize on dsDNA. RecA polymerizes on dsDNA in a piecewise linear rate that is a function of the force, change in force, and number of nucleation sites. When the force applied is decreased, RecA unbinds from dsDNA. RecA can unbind in a controlled manner without destroying the nucleation sites if the force remains above 52 pN. With only ADP present in my experiments, no ATP hydrolysis can occur. During strand exchange ATP hydrolysis is essential in the unbinding of DNA from Site 1 on RecA, but it is unclear whether energy released from or the structural changes caused by ATP hydrolysis is more important. Since ADP bound RecA unbinds in a controlled manner from dsDNA when the pulling force is decreased, the energy released from ATP hydrolysis is likely more important than the structural changes caused by ATP hydrolysis when RecA unbinds from DNA during strand exchange.

Perry Choi
Neurobiology
Lowell 2015

Development of Peptide Macrocycle Catalyst for Transesterification Reactions

Eric N. Jacobsen
Department of Chemistry and Chemical Biology
Harvard College

Research efforts in synthesis of peptide catalysts are few and remain modest in efficacy. Concerning transesterification catalysis, the majority of efforts thus far have attempted to mimic catalytic themes in biological systems, namely proteases. For example, many of these catalysts utilize histidine residues, which often function to control the pH environment for optimal catalysis. Nevertheless, these approaches are heavily dictated by random generation of amino acid sequences.

The current project seeks to utilize fundamental chemical knowledge to reduce the role of randomness and develop a library of effective peptide catalysts by design. We use computational modeling to design optimal macrocyclic peptide catalysts for the given reaction based on geometry in a given solvent. Specifically, modeling helps find catalysts that most often orient aspartate and/or glutamate residues in the ideal position for catalysis.

After synthesis and purification, these catalysts are subjected to high throughput screening in different conditions with a variety of ester substrates. If our computational modeling proves effective, 1) we expect to see a hit within several hundred catalysts (as opposed to several thousand for random screening), 2) this will be the first example of successful computation-based catalyst design of peptide macrocycle catalysts, and 3) this will validate the program and advocate implementation of similar programs to facilitate catalyst design for other reactions.

Emma Dowd
Chemistry and Physics
Eliot 2015

Voltage Imaging of Zebrafish in Hypoxia

Adam Cohen
Department of Chemistry and Chemical Biology
Harvard College

Most vertebrates require constant exposure to oxygen for survival. Tissues can only survive a lack of oxygen for a short period of time; they must be reintroduced to a normoxic environment to prevent permanent damage. However, the restoration of blood flow to viable ischemic cells, rather than returning them to normal function, can cause oxidative stress and thus exacerbate tissue damage, known as ischemia-reperfusion injury. A rare exception to the anoxia sensitivity of vertebrates can be found in the developing zebrafish. Embryonic zebrafish enter a state of "suspended animation" in anoxia, ceasing observable cellular function. Surprisingly, upon reintroduction to normoxia, they continue with normal development and are able to reach sexually mature adulthood.

We study the voltage and calcium dynamics in zebrafish under conditions of hypoxia using a genetically encoded fluorescent reporter of membrane voltage derived from the protein Archaerhodopsin 3 (Arch) in parallel with a calcium indicator (GCaMP) derived from GFP. We place live zebrafish expressing Arch and GCaMP under cardiac and ubiquitous promoters in hypoxia at different embryonic stages and image them using a custom-built spinning disk confocal microscope. From the fluorescence levels we quantify fluctuations in membrane voltage and calcium concentration. Data collected from fish surviving anoxia will help us understand how they are resistant to ischemia-reperfusion injury, and fish that die upon reintroduction to oxygen will allow us to model ischemia-reperfusion injury in vertebrates; both will contribute to a better understanding of how ischemia-reperfusion injury occurs and how to prevent it.

Ian Dunn
Chemistry and Physics
Leverett 2014

A Quantum Chemical Approach to the Thermodynamics of Metabolism

Alan Aspuru-Guzik
Department of Chemistry and Chemical Biology
Harvard College

Metabolic engineers want to know the thermodynamic properties that drive metabolic reactions such as those involved in renewable fuel and food production. The Gibbs reaction free energy (ΔG^0_r) is one such thermodynamic property that characterizes the 5400 known metabolic reactions. Existing methods for finding ΔG^0_r include experimental measurement which is prohibitively expensive, and the semi-empirical group contribution method which is insufficiently robust to accurately handle all metabolic reactions. Therefore we have developed a first-principles computational technique that relies on basic quantum chemistry and statistical mechanics to calculate ΔG^0_r.

To calculate ΔG^0_r we subtract the Gibbs formation energies of the reactants from those of the products. To find the formation energies we model the metabolites as individual solute molecules surrounded by several explicit water molecules, surrounded by an implicit water model using the Conductor-like Screening Model (COSMO). After generating several geometric conformations of this system, we use density functional theory to minimize the energy of each conformation and then calculate the normal modes of the system. We then use all of this data in conjunction with formulas from molecular thermodynamics to determine ΔG^0_r.

Comparing our results to existing experimental results we find that our estimates have an error of 5 kcal/mol and in some cases as little as 1 kcal/mol. Therefore we are approaching the 2-3 kcal/mol accuracy of the group contribution method. Our goal of ~1 kcal/mol error could open doors for improved metabolic engineering, synthetic pathway design, and discovery of thermodynamic principles governing natural metabolic pathways. Looking ahead we will continue to refine our techniques, and we will also examine reactions with larger molecules including sugars and cofactors.

Lukas Gemar
Bioengineering
Winthrop 2015

Engineering Arch

Adam Cohen
Department of Chemistry and Chemical Biology
Harvard College

The main project of my lab is to develop robust optical methods for probing voltage changes in living tissue. Specifically, the lab works with a fluorescent rhodopsin protein known as Arch. Arch fluorescence is proportional to the voltage across the membrane in which the protein is located. Most commonly, Arch is localized to the cell membrane where it can provide information about membrane potential. This is useful in examining electrical activity in cardiac cells or neurons.

Ultimately, I want to pattern neurons into circuits and optically detect their electrical activity. The main problem with this endeavor is that the Arch fluorescence is very dim, making it difficult to detect quick action potentials over many neurons with high temporal resolution. There is a tradeoff between resolution in the time domain and the signal-to-noise ratio. In order to get a good enough signal to make the patterning experiment possible, I need a brighter mutant of Arch that still preserves the protein's voltage-sensitive qualities. There are two specific amino acid residues that are involved in the Arch chromophore, and mutating these residues has produced some versions of the protein that are brighter and more voltage-sensitive.

This summer I have worked to develop a high-throughput method for screening mutants of Arch. There are many parameters about the protein that I would like to optimize–speed and sensitivity as well as membrane trafficking–but none of these matter if the protein is not bright. Therefore, the first step in the process is to determine which versions are brightest so that I can perform a more thorough characterization of the protein's qualities.

Carew Giberson-Chen
Undeclared
Leverett 2016

Determining the Structure of LptD to Better Understand Gram-negative Outer Membrane Biogenesis

Dan Kahne
Department of Chemistry and Chemical Biology
Harvard College

Gram-negative bacteria are difficult to target with antibiotics because the presence of highly compacted lipopolysaccharide (LPS) in the outer leaflet of the outer membrane greatly enhances the impermeability of the outer membrane to small hydrophobic molecules. LPS is translocated from the periplasmic leaflet of the inner membrane to the outer leaflet of the outer membrane by a seven-protein "Lpt" complex, and it is hoped that a greater understanding of this "Lpt" transport mechanism will lead to innovations in antibiotic development.

We focus specifically on the protein LptD, the barrel component of a plug-and-barrel complex in the outer membrane that inserts LPS into the outer membrane. Ultimately, through x-ray crystallography, we hope to attain the structure of the n-terminal domain of LptD (n-LptD), which we hypothesize to directly interact with LPS, in hopes of better understanding the mechanism through which LptD operates. Previous attempts to define the structure of n-LptD have failed because the protein tends to degrade more quickly than crystals can form. However, the successful crystallization of LptA and LptC, with which n-LptD shares critical similarities, suggests that successful crystallization of n-LptD is possible as well. Still in the early stages of this project, we have developed five different n-LptD constructs with varying degrees of c-terminal sequence truncations and are investigating the stability of these new constructs in hopes of identifying one or more that will remain sufficiently stable over a long enough timeframe to allow formation of the crystals necessary for a successful determination of structure through x-ray crystallography.

Jen Guidera
Chemistry
Adams 2015

Building a Small Molecule Catalyst for the [2,3]-Wittig Rearrangement

Eric N. Jacobsen
Harvard College

In a chemical transformation, given starting materials can often react in many ways, leading to the formation of multiple products. An important challenge in organic chemistry is figuring out how to favor the formation of just one of many possible products. The key to favoring just one product is lowering the highest energy point along the pathway to that product, a point known as the 'transition state'. A small molecule catalyst can lower the transition state energy by interacting favorably with the starting material at this high-energy point through interactions such as hydrogen bonds.

The goal of my project is to build a small molecule catalyst for the [2,3]-Wittig rearrangement. The Wittig rearrangement is a chemical reaction that is useful in the synthesis of certain complex molecules that could have therapeutic properties. What are the challenges of building a small molecule catalyst for the Wittig rearrangement? At this stage of the project, one challenge is figuring out what functional groups, i.e. what groups of atoms with special reactive properties, will interact favorably with starting material in the transition state of the pathway to desired products. Ultimately, a small molecule catalyst for the Wittig rearrangement would be useful in the synthesis of certain molecules, and would also teach us about the Wittig rearrangement itself, particularly where charge is distributed in the transition state.

Daniel J. Kramer
Chemical and Physical Biology
Leverett 2015

Whole Blood and Leukocyte Separation by Aqueous Multiphase Systems of Polymers

George M. Whitesides
Department of Chemistry and Chemical Biology
Harvard College

Aqueous Multiphase Systems (MuPS) allow for the stable separation of immiscible polymers sorted by density. Entropic losses from phase separation are compensated for by the enthalpic gains from molecular interactions between molecules of mutual phases. This could not be achieved between different polymers, here Ficoll and Dextran, due to variations in molecular weight. Phases are distinct, making the density uniform in each. This produces sharp density changes at each interface, steps which can be calibrated as small as 0.001 g•cm^{-3}, while layer composition and properties are maintained. These characteristics make MuPS valuable in point-of-care and clinical diagnostics using biological samples, such as human blood. In addition, MuPS provides a physiologically relevant environment by controlling for pH and isotonicity, allowing separated components to maintain morphological viability for extraction and future study in research settings. This is especially pertinent to human leukocytes—white blood cells (WBCs)—whose current means of separation subject cells to non-physiological conditions that alter cellular functionality, and require using secondary systems of separation and further washing steps. The densities of MuPS were highly tuned to that of blood components, enabling isolation and separation of WBCs, from whole human blood, into mononuclear cells (MNCs) and polymorphonuclear cells (PMNs). In the next stage of this work, polymorphonuclear neutrophils—key players in innate immunity and wound healing—will be further isolated by adding lumican from the extracellular matrix (ECM) to the MuPS system. Lumican specifically binds neutrophils' β2 integrin receptors, causing them to move toward the bottom phase, thus serving as a model for neutrophil migration and cellular adhesion.

Dylan Neel
Neurobiology
Mather 2015

Evaluation of small molecule modulators of the Max network

Angela Koehler
Broad Institute of MIT and Harvard

Aberrant expression of the transcription factor Myc leads to a host of cellular consequences: uncontrolled cell proliferation and growth, genomic instability, failure to initiate apoptosis, and immortalization of cultured cells. Recent efforts to develop probes for Myc-dependent transcription have focused on modulating the formation of the Myc/Max heterodimer. Over 20,000 compounds were screened for binding to Max using a small molecule microarray (SMM). 19 SMM positives showed dose-responsive inhibition in a Myc reporter assay. Two compounds, BRD-1677 and BRD-3496, were prioritized for follow-up assays based on potency and initial purity of the screening stocks. Protocols were developed for the expression of Myc and Max, using transformed Rosetta (BL21) bacteria. Pull-down assays were run using both bacterial purified proteins and whole-cell lysates. Our preliminary data suggest that the compounds do not directly affect the formation of the Myc-Max heterodimer, or the Max-Max homodimer. Growth curve analysis also revealed that the proliferation of a Burkitt's lymphoma cell line (Namalwa) was not sensitive to treatment with the compounds. Ongoing experiments using surface plasmon resonance and immunoprecipitation are focused on determining whether the compounds affect formation of the Max-Max and Mad-Max dimers, since small molecule stabilizers of these complexes have been previously shown to decrease Myc-dependent transcription. Differential scanning fluorimetry will also be done to confirm that the test compounds bind directly to Max.

Jonathan Marks
Chemical and Physical Biology
Mather 2015

Mechanistic Studies of a Novel Oxidative Coupling in the Lomaiviticin and Actinorhodin Biosyntheses

Emily P. Balskus
Department of Chemistry and Chemical Biology
Harvard College

The biosynthesis of the highly-functionalized polyketide natural products lomaiviticin and actinorhodin proceeds via a novel oxida-

tive C-C bond forming dimerization. Lomaiviticin, which contains a rare diazo functional group, is a potent antitumor antibiotic known for its unique cytoxicity profile and genotoxic effects. Actinorhodin is a natural benzoisochromanequinone antibiotic with an unknown mechanism of action that is known for its unique litmus-like properties, fluorescing bright blue in alkaline and red in acid. While the chemical syntheses of the lomaiviticin aglycone and the actinorhodin monomer have been reported, little is understood about the enzymatic mechanism that catalyzes the selective and sterically-hindered coupling of the putative dihydroquinone prelomaiviticin and preactinorhodin monomers.

We approached the study of the dimerization of lomaiviticin and actinorhodin using both computational and experimental methods. After aligning the sequences of both putative dimerization enzymes, Lom19 and Act4, with known structures, we used a threading algorithm to generate 3D homology models of both enzymes, optimizing them with molecular dynamics using a conjugate gradient algorithm. We modeled an induced fit ligand docking of the putative monomers along with the NADP+ cofactor and identified key catalytic residues for further mutagenesis activity screens. Experimentally, we have successfully cloned, overexpressed, and purified both Lom19 and Act4 using Ni2+ affinity, anion exchange, and gel filtration chromatography, obtaining multiple milligrams of relatively pure protein to be used in enzyme assays. We are currently studying the biochemical properties of both proteins, characterizing their oligomeric state and NAD(P)(H) binding affinities with spectroscoptic and size exclusion assays. Future work includes developing a synthetic route to the preactinorhodin monomer for use in enzyme assays and performing activity assays coupled with a mutagenesis screen to substantiate the results of our computational predictions.

Jenny Shih
Human Developmental and Regenerative Biology
Quincy 2015

Probing the Interaction of hOGG1 Repair Enzyme with DNA

Gregory Verdine
Department of Chemistry and Chemical Biology
Department of Stem Cell and Regenerative Biology

In the human body, oxidation of the DNA base guanine to 8-oxoguanine (oxoG) has been linked to the onset of various diseases such as cancer and atherosclerosis. The human repair enzyme 8-oxoguanine DNA glycosylase I (hOGG1) corrects oxoG through base excision repair by extruding and cleaving the lesion. While the base-flipping extrusion of oxoG is known, hOGG1's mechanism to identify oxoG from guanine remains a mystery since the bases differ by only two atoms and show no significant structural alternations in DNA. Here, we present a crystal structure showing intra-helical guanine base interacting with hOGG1. We utilized a disulfide crosslinking technique and a newly synthesized tether (X8) to capture the hOGG1-DNA interrogation complex. Crosslinking of hOGG1 residue Y207C with guanine base modification yielded 2.35 Å crystals, revealing an intra-helical DNA-protein complex. A comparison of the guanine intra-helical complex with an oxoG intra-helical complex showed unique conformational differences between the DNA. The crystal structure suggests that the greater stability of oxoG complex over guanine allows hOGG1 to discriminate between the two chemically similar bases. Continued structural analysis will quantify the energetic differences between oxoG and guanine to further reveal the mystery behind hOGG1's specific search mechanism.

Stephanie Threatt
Chemistry
Eliot 2014

Novel Method for Utilization of [18F] fluorodeoxyglucose as Synthon in PET Imaging

Jacob Hooker
Massachusetts General Hospital

Currently, the technology and funding necessary to generate radiolabeled molecules makes these compounds very inaccessible outside the field of radiochemistry. One radiolabeled molecule which has been made very accessible through an automated, inexpensive synthesis process is [18F]fluorodeoxyglucose (18FDG). 18FDG is a fluorine derivative of glucose that is commonly used for PET medical imaging. Because of its widespread availability, 18FDG is a potentially attractive synthon (building block) for making other fluorine-18 labeled molecules, specifically for radiolabeling proteins with fluorine-18. Methods for radiolabeling molecules using 18FDG currently exist, and they have notably increased the ability to radiolabel molecules with fluorine-18; however, these current methods require multistep syntheses and harsh conditions that often cause proteins to denature and result in low radiochemical yields. Additionally, these methods often produce low specific activity and less conclusive PET data because the large excess of glucose that accompanies 18FDG when it is produced is never broken down.

My project aims to develop a procedure for radiolabeling molecules using 18FDG that is simple, rapid and accessible to individuals outside the field of radiochemistry. This method involves the production of the fluorine-18 labeled synthon 2-[18F]fluoromalondialdehyde (18FMDA) by oxidizing 18FDG and the excess glucose. Additionally, I intend to verify the reactivity of 18FMDA by identifying the conditions necessary to conjugate this synthon to a specific amino acid. Once 18FMDA has been stably conjugated to an amino acid, a purification method will be used to isolate the fluorine-18 labeled amino acid or protein for use in PET medical imaging.

Computer Science

Marcus Comiter
Computer Science and Statistics
Eliot 2014

Numerical Techniques and Applications of Machine Learning through a Sparse Coding Framework

H.T. Kung
Harvard School of Engineering and Applied Sciences

Sparse coding is a machine learning technique that offers novel ways of approaching many open problems in computer science. Through training an over-complete dictionary of atoms, signals can be transformed from their normal representation to sparse representations that correspond to combinations of the learned dictionary atoms. Beyond these compression benefits, sparse coding transforms the data into a feature domain which is more amenable for solving complex problems. As such, in my research with the lab, we have been working on two areas related to sparse coding. First, we have been working to develop novel numerical techniques to increase the speed of the algorithms that underpin the sparse coding framework. As with many machine learning techniques, speed is an important factor, especially when working with large datasets. Advancements in these algorithms allow the research community to more easily utilize these frameworks. Second, we have been applying sparse coding to several complex, open problems. Specifically, we have been developing techniques to apply sparse coding to discovering and classifying malware. Malware is a malicious type of software that poses significant threats to all computer users. As malware authors build increasingly more complex viruses to attack computers, it is very important to continue evolving the tools used to fight these viruses. Our approach towards this problem hopes to improve the state of the art in terms of classification accuracy, robustness to code obfuscation, and overall efficiency.

Nicholas Longenbaugh
Computer Science and Linguistics
Cabot 2014

Modeling Complexity in Language

Stuart Shieber
Harvard School of Engineering and Applied Sciences

Models of natural language have existed since at least the work of the ancient Vedic grammarian Panini, circa 400BCE. Our (slightly more recent) work has focused on a particular grammatical model from formal language theory, the Tree Adjoining Grammar (TAG). We have explored a novel technique combining this formalism with the data in bilingual dictionaries to inform automatic translation from English to Japanese, as well as investigated using TAGs to handle various linguistics phenomena such as ambiguous quantifier scope and the distribution of anaphora. Underlying this and all related research is the assumption that natural language is "complex" enough to warrant description by a formalism with the computational power accorded by TAGs, i.e., that natural language is non-context-free. While this assumption is rather uncontroversial, to date only two languages have been proved to exhibit non-context-freeness in the weak generative sense. We propose the addition of a third language, Romanian, to this list. In particular, we argue that the combination of Romanian's obligatory and extremely unconstrained multiple wh-extraction with its robust case system allows us to construct sentences whose structure is reminiscent of the "cross-serial dependencies" exploited in the classic treatment of Swiss-German. It follows that if we intersect the image of entire stringset of Romanian under a suitable homomorphism with the appropriate regular language, we arrive at the language L = {a^n b^m x^n y^m : n, m > 0}, which may be shown by a simple pumping lemma argument to be non-context free. The stringset of Romanian is thus non-context-free, increasing the tally of such languages to three and lending credence to the view that language modeling should look to formalisms more powerful than context free grammars.

Jackson Steinkamp
Computer Science
Eliot 2015

Using 3D Vision to Assist a Surgical Robot

Robert Howe
Harvard Biorobotics Lab
Harvard School of Engineering and Applied Sciences

The use of robots in a variety of surgical procedures has become a standard part of operating room practice. The RAVEN II surgical robot has been developed to be a low-cost, open-source platform for research in surgical robotics. Surgeons use teleoperation devices to remotely guide the robot's end effectors, and can receive force feedback via haptically rendered environments. Within the last decade, RGB-D cameras, which use IR emitters and sensors to evaluate the depth of each pixel in a frame, have become commonplace and affordable. These depth cameras allow for the development of software applications which parse three-dimensional scenes in real-time, identifying and tracking objects as they move and rotate in 3D space.Vision and robotics are an undeniably useful pair. Vision anchors the robot in the world, allowing the robot to know where it is in relation to other objects, and to use this information to execute tasks more effectively. This summer, my research focuses on developing a robust system for scene parsing, using depth cameras and the Point Cloud Library (PCL) software to parse the RAVEN's workspace in order to track the robot and other objects in its path. With a robust vision system for scene parsing and object tracking in place, the RAVEN can be guided to perform automated tasks, such as needle passing or obstacle avoidance, in real time. I have implemented an early version of the scene parser and tool tracker, which is capable of tracking all objects in the depth camera's field of view, and am currently working on automating simple tasks.

Jasmine Yan
Computer Science
Eliot 2016

A Neurobiologically-Inspired Dynamic Computational Model for Visual Recognition in Videos

Gabriel Kreiman
Department of Neurology and Ophthalmology
Boston Children's Hospital
Harvard Medical School

Visual object recognition is an effortless task for humans, but a difficult one for computers. Human brains have evolved to recognize objects selectively, quickly, and robustly, motivating the study of the neuronal circuitry behind this process. Furthermore, it has been shown that humans exploit temporal and spatial information in object recognition. If there is an unperturbed object on a table, humans would expect the object to remain there. Therefore, we aim to improve object recognition in computers by accounting for temporal and spatial contiguity.

We are working with HMAX (Hierarchical Model and X), a feedforward model for the ventral visual stream (the "what" stream), which is associated with object recognition and form representation. HMAX has two main features: invariance with preserved selectivity, and learning. Objects are classified by support vector machines (SVM). In this study, we process frames from dynamic video sequences. We modify the SVM to be multi-class, and work to include prior probabilities that depend on spatial and temporal context. Object recognition has great implications for many fields, from medicine to the military. Although no algorithms have yet surpassed the human brain's performance, it is very likely that computer vision will someday surpass and enhance human vision.

Earth & Planetary Science

Alex Morgan
Earth and Planetary Sciences and Environmental Engineering
Lowell 2014

Biogeochemical Reconstruction of Paleoenviornment at the Cambrian Explosion

David Johnston
Harvard College

My research focuses on the disappearance of the Ediacara biota from the fossil record before the Cambrian Explosion, 542 million years ago. There are three suggested hypotheses explaining this: 1) a mass extinction event driven by environmental conditions, 2) a gradual and natural competitive replacement of Ediacara biota by Cambrian animals, and 3) the elimination of unique preservational settings that are necessary for biota to be preserved in the fossil record.

With a National Geographic funded research team, I traveled to one of the few sections throughout the world that preserves the Ediacaran-Cambrian transition without a break in sedimentation. For two weeks at the Nama Basin in southern Namibia, Africa we collected samples that record the disappearance of the biota and emergence of Cambrian life.

I am currently performing geochemical analyses on the collected Namibian rocks using a multi-proxy approach to reconstruct redox sensitive metal budgets and biologically active major element cycles (carbon, sulfur, and iron cycles) to decipher the paleoenvironmental coincident with the biological transition. My research methodologies include iron speciation chemistry, the carbonate associated sulfate method, small vial dissolutions, and the chromium-reducible sulfur method. Once the samples are processed, I can run them through the mass spectrometer, which will allow me to analyze the isotopic and concentration data obtained. I will compare my results with those of rocks collected in June Lake, Canada that record the same transition, to provide a more holistic summary of what occurred on Earth at this time.

Engineering & Bioengineering

Johnathan Budd
Electrical Engineering
Winthrop 2015

Warrior Web Development

Professor Conor Walsh
Biodesign Lab Wyss Institute

The goal of the warrior web project is to reduce injury in soldiers during long marches carrying heavy loads. In order to address this problem the Biodesign Lab is developing a soft exosuit. Worn like a pair of pants this wearable robot applies force to the legs during walking to reduce fatigue over long distances and thus reduce injury. There is also a huge potential for medical applications for this technology, assisting patients during rehabilitation and those with muscular disorders.

My work has focused primarily on designing new sensors for the suit. In order for the suit to be as useful as possible it must be incredibly lightweight, so commercially available parts often are not ideal for our purposes. Working with a soft exosuit also poses a unique set of challenges because it must interface with a moving human body. The suit is constantly moving and changing shape with the body so the sensors must be accurate in a variety of conditions. The sensor I developed works not as a stand alone sensor but rather as a part of the suit that serves multiple functions. In essence I took what was once a structural part of the suit and designed a sensor that can perform the same structural function while sensing the force being applied to aid in walking, without adding any weight. The result is a force sensor that is lighter, smaller and more robust than commercially available products, allowing our suit to provide a greater reduction in the cost of walking.

Ishan Chatterjee
Engineering
Adams 2016

Development of a Robust, Low-profile Tension Sensor for Webbing

Conor Walsh
Harvard School of Engineering and Applied Sciences
Wyss Institute for Biologically Inspired Engineering

Webbing is a strong, lightweight, and flexible material that experiences low extension. For these reasons, it is commonly used as an ergonomic interface for high-load uses, for instance, as seatbelts or as straps for tote bags, suitcases, and backpacks. More recently, webbing has found an application in wearable robotics, a field that aims to assist or enhance human movement with devices worn on the body. One such device, the Warrior Web suit being developed at the Harvard Biodesign Lab, aims to decrease the body's energy consumption during long or burdened walks. This goal is realized in a soft "exo-suit" design that pulls up at the heel, actuating the ankle, and communicating the reaction force to a network of webbing anchored to the hips and legs. A low-profile tension sensor for webbing can provide information regarding the forces throughout the suit. In particular, an accurate measurement of force delivered at the ankle can be integrated into the suit's control scheme to precisely time actuation with gait cadence or to determine ankle position.

A webbing load cell will use conventional strain gauges to obtain a load measurement based on the deflection of the cell. Measuring force on webbing is complicated by the elastic hysteresis of the material; therefore, designs must transfer force to a low-deflection elastic material. The final prototype must be less than 50 g and operate over a 20 to 400 N range with 5 N resolution and less than 5% hysteresis.

Zarmeena Dawood
Biomedical Engineering
Adams 2015

The Role of the Extracellular Matrix and LRP5 in Breast Cancer Progression

Donald Ingber
Department of Vascular Biology
Boston Children's Hospital

Tumor angiogenesis, the growth of a network of blood vessels that supply the cancerous tumor with nutrients and oxygen, is a requirement for tumor progression and metastasis. The mechanical properties of tissue microenvironment play a critical role in angiogenesis. In a previous study we have shown that when a brain tumor becomes compacted (since it grows very rapidly in confined spaces), this compaction induces the tumor cells to secrete growth factors such as VEGF, which attracts blood vessels to the tumor, providing it with a supply of nutrients and oxygen for further tumor growth (Am. J. Pathol. 2013, in press).

Here we hypothesize that this phenomenon could also be applicable to breast cancer and that if rapidly growing mammary tumors become compacted then this may induce tumor angiogenesis and progression. We found that tumor cells are compacted and collagen expression increases during breast cancer progression in our C3(1)/Tg transgenic mouse model in which breast cancer is spontaneously progressed. Cell compaction increases collagen and VEGF expression in E0771 breast cancer cells and VEGFR2 expression in endothelial cells in vitro when analyzed using a microcontact printing system. We also found that Wnt co-receptor LRP5 induces tumor angiogenesis. LRP5 expression increases during breast cancer progression in which tumors are compacted. Tumor angiogenesis and progression are repressed in LRP5 knockout mice when analyzed using a mouse orthotopic breast cancer model and a modified matrigel plug assay. Importantly, LRP5 expression is altered in cultured E0771 cells and endothelial cells in a cell compaction dependent manner, suggesting that cell compaction controls tumor angiogenesis and breast cancer progression through LRP5 signaling. We are currently testing whether cell compaction controls breast cancer progression in vivo by manipulating collagen crosslinking to reduce compaction and examine the effects on breast cancer growth and tumor angiogenesis.

Raja Ghawi
Biomedical Sciences and Engineering
Kirkland 2015

Use of Collagen Mimetic Peptide to Modify Decellularized Rat Lungs

Harald Ott
Harvard Medical School
Harvard Stem Cell Institute
Massachusetts General Hospital

With the new developments in tissue engineering and biomaterials, scaffold design, modification and optimization offer great hope for tissue engineering and regeneration. Currently, chemical cross-linking is the major method used to modify scaffolds, attaching beneficial peptides to a matrix to improve cellular adhesion, growth or phenotypic display. Chemical cross-linking, however, changes the mechanical and biological properties of the material it is used with, which limits its clinical applications. This summer, I tested collagen mimetic peptides (CMPs) which can, through stereoselective triple-helical hybridization, integrate themselves into collagen based matrices and scaffolds. I hypothesize that two different conjugates of CMP, namely CMP-RGD and CMP-QK (QK is a short peptide sequence with similar structure to VEGF) can benefit the adhesion and growth of endothelial cells on decellularized, collagen-based rat (and thus, potentially human) lung matrices.

Michael Hoffer-Hawlik
Biomedical Engineering
Dunster 2015

Single-Cell Nucleosome Mapping Using Droplet-Based Microfluidics

David Weitz
Harvard School of Engineering and Applied Sciences

Microfluidic systems offer scientists a way to process, analysis, and sort cells on an individual level. By compartmentalizing single cells with various proteins, reagents, and ligands, these microfluidic devices allow for reactions that normally occur in bulk processing to be carried out in a pico to nano scale environment. The microfluidic system is based on monodisperse aqueous droplets transported by inert carrier oil within the channels of the PDMS-based microfluidic device. These droplets can further be manipulated and controlled, using technology such as electrocoalescence and picoinjection. Our lab uses droplet microfluidic systems for a variety of applications including DNA sequencing, drug screening, and diagnostics.

My work aims to create a diagnostic tool that researchers and physicians can utilize to sequence and analyze the genomic material confined in the nucleosomes for a limited number of cells, between 100-1,000, using droplet microfluidic techniques. The mapping of a cell's nucleosomes offers valuable data and information concerning the epigenetic modulations of gene and protein expression within the cell. The process occurs as follows: yeast cells are first run with a lysis buffer containing MNase in an oil phase. The droplets harboring individual cells are then merged with droplets containing DNA barcode, which allows for the unique cellular identification of genomic material after DNA amplification. Once merged, these combined droplets are injected with ligation buffer, allowing the bar codes to bind to the mononucleosomes. Through this technique, nucleosome mapping, once limited to bulk processing, can be performed on a restricted number of available cells.

Jillian Lee
Engineering Sciences
Adams 2015

Mechanical Properties & Release Kinetics of Electrically Conductive Hydrogels

Sujata Bhatia
Harvard School of Engineering and Applied Sciences

Many modes of drug administration can harm parts of the body other than the targeted area. Poloxamer hydrogels could provide a way for targeted and sustained drug release while minimizing the detrimental systemic effects of toxic drugs. This gel can also be used as a scaffold for neural tissue regeneration because it can create an environment appropriate for the desired tissue. One can impregnate the gel with carbon nanobrushes, which renders the gel electrically conductive, which is conducive to the growth of tissues designed to transmit electrical signals. The thermo-reversible gel, which is liquid at refrigerated temperatures and transitions to a gel around 15°C, can be injected into the body around a tumor or even between vertebrae to form a drug depot or tissue engineering scaffold.

The amount and type of drug in the gel along with carbon nanobrush content determine the drug release profile, gelation temperature and how the gel responds to stress and strain. Developing a mathematical model to describe how these factors will affect the gel's properties may be useful for future work in implementation of the gel. 5-Fluorouracil, a hydrophilic anti-cancer drug and Indomethacin, a hydrophobic anti-inflammatory drug are used as model drugs to show how drug hydropathicity alters release kinetics. Recent work has shown enhanced success in cancer treatment using the sequential administration of two distinct drugs over simultaneous exposure. Demonstrating the sequential release of two drugs loaded within a gel depot may later prove useful for the development of a gel system to more effectively and safely treat cancer.

Kathy Lin
Chemical and Physical Biology
Mather 2014

Getting to the Other Side

Joanna Aizenberg
Harvard School of Engineering and Applied Sciences

Many medications need to be administered continuously through oral or intravenous therapy. These methods can often be inconvenient and uncomfortable, which has led researchers to investigate implantable devices that can release drugs gradually. One promising approach is releasing drugs from highly ordered porous nanostructures. Their highly ordered nature makes them easily tunable and thus allows an accurate and predictable design of periodicities and porosities at the nanoscale. Our lab is particularly interested in the inverse opal structure, which consists of a series of spherical cavities (50 nm – 1 μm in diameter) stacked similar to how oranges are stacked in a grocery store with each cavity opening up to each of its neighbors. This structure is ideal to work with because it can be made quickly and easily without the need of expensive equipment via evaporative self-assembly. In addition, it can be constructed with

silicon, which is biocompatible. I will be building membranes of inverse opals and determining the diffusion constant of aqueous solutions through the membrane, using the dye rhodamine B as a probe. I will start by using a solution of rhodamine B in water so that I can use UV-Vis spectroscopy to detect when the dye moves from the structure to the bulk solution. I will then determine how the size of the opals and their ellipticity affect the diffusion rate of rhodamine. Finally, I will try to combine multiple layers of inverse opals, where each layer has a defined pore size different from the next layer, to achieve staggered diffusion rates. These experiments will elucidate whether inverse opals release liquids on a timescale that would be useful for bio-devices and tell us how tunable such a device might be.

Valentina Lyau
Engineering Sciences
Lowell 2015

3D Printing of Functional Materials

Jennifer Lewis
Harvard School of Engineering and Applied Sciences

Developed decades ago for rapid prototyping, 3D printing has been receiving increasingly more attention lately as a disruptive manufacturing technique. 3D printing is an additive process in which layers of material are built up successively to create complex physical forms. Our group focuses on design and creation of functional inks for 3D printing and using these inks to create functional devices.

Specifically, our group focuses on filamentary printing, in which a custom ink is extruded from a nozzle that is mounted to a high-precision computer-controlled stage. These inks have an engineered rheological response – they are both shear-thinning and possess a defined yield stress. These characteristics allow ink to readily flow through the nozzle upon application of pressure and re-solidify upon deposition. To date, novel complex forms with myriad ink formulations have been realized using this approach.

This technology can readily pattern many length scales ranging from a micron to a meter with high speed and precision. Building upon this, my work, in particular, has been focused on the printing of biologically-relevant geometries - bifurcating networks that resemble microvasculatures. However, due to the sensitive nature of our work, I am not at liberty to divulge additional details at this time.

Ronit Malka
Engineering Sciences
Lowell 2015

Design of Microscale Flexure Hinges for Endurance Life

Robert Wood
Wyss Institute for Biologically Inspired Engineering

Flexure hinges, or living hinges, are often preferred over standard rigid hinges because of their efficiency and ease of production. These hinges have become increasingly relevant for robotics, especially in microscale or soft design applications. However, a major barrier in using flexible hinges is their highly variable fatigue failure profile, which is very sensitive to off-axis loading, hinge dimensions, and design features, among other factors. This summer I characterized the design of microscale polymer flexure hinges, particularly for straight-edged hinges used in the RoboBee. By adding certain design features and altering hinge dimensions slightly to reduce the stress repetitively imposed in the hinge, the RoboBee hinges now last for a couple million cycles rather than a few hundred thousand cycles, extending the bee's flying time dramatically.

Tiana Raphel
Biomedical Engineering
Currier 2016

Characterization and Optimization of Alginate Microspheres

Sujata Bhatia
Harvard School of Engineering and Applied Sciences

As bioengineers evolve in their approach to medical innovation, they trend toward specialized, biocompatible and elegant forms of treatment. In this manner, damage and disruption are minimized.

An innovation that aligns with this evolving approach is the use of alginate microspheres for treatment. Alginate microspheres, made from alginate found in seaweed, are biocompatible. Furthermore, they are adaptable and possess the potential to be utilized in widely varied applications throughout the human body. Possible areas of application include drug release, embolization, contraceptives and space filling.

This project investigated the properties of alginate microspheres so that they may be adapted to effectively treat illness. More specifically, this project examined how changing the concentrations of alginate and calcium chloride affected the formation of the microspheres, how the microspheres reacted with phosphate buffered saline, a fluid commonly used to mimic the blood stream, and finally, yeast encapsulation, to further study the levels of biocompatibility that the alginate microspheres could offer in delivering drugs and cells to desired areas.

Information gathered from this work demonstrates that alginate microspheres are highly adaptable and can be made with characteristics to fit needs in many parts of the body. By changing parameters such as alginate concentration and calcium chloride concentration, this project was able to optimize the size and sphericity of the microspheres. The biocompatibility of these alginate microspheres is also an asset in treating illness. A simple, yet effective, and adaptable body-friendly treatment, through the honing of alginate microspheres, could be a reality in the near future.

Elizabeth Strong
Mechanical Engineering
Cabot 2015

Designing Dynamic Materials for Controlled Micoscale Mechanical Stimulation of Live Cells

Joanna Aizenberg
Wyss Institute for Biologically Inspired Engineering

Cells cultured in current, state-of-the-art conditions have significantly different gene expression than in vivo cells. This is likely due in part to the lack of mechanical strain to which in vivo cells are normally exposed. This motivated a project to develop a novel dynamic cell culture surface using a recently developed material called Hydrogel-Actuated Integrated Responsive System (HAIRS) to create a system that can exert forces up to 20 mN on cells grown on its surface.

Research has shown that the physical characteristics of the substrate on which cells grown play important roles in both stem cell differentiation and cell growth. For example, mesenchymal stem cells grown on materials with low, intermediate, and high stiffnesses differentiate into brain, muscle, and bone precursor cells, respectively. Another phenomena associated with cell-substrate interaction is contact guidance, which is how cells detect and grown in specific directions in response to anisotropic microenvironments.

We hypothesized that cells would align themselves on our HAIRS surfaces in a manner that maximized the surface area in contact with the regions that promote cell growth. I produced a simulation based on this hypothesis and then developed an image analysis algorithm to compare the experimental results taken from microscope images to the model. This work will be continued in the coming months and it will be analyzed once more images have been processed.

Mathematics & Statistics

Gita Bhattacharya
Applied Mathematics
Cabot 2016

Mathematically Modeling Gene Expression in the Inner-Ear

Zheng-Yi Chen
The Massachusetts Eye and Ear Infirmary
John Hall
Harvard Department of Mathematics

Development of inner-ear hair cells, the neurons responsible for converting sound waves into electrical impulses, depends on the orchestrated expression of various genes. The Notch signaling pathway is involved in creating the mosaic of sensory hair cells and supporting cells in the cochlea. Microarray and in situ hybridization data of the developing mouse utricle reveal that Notch and its downstream effector, Hes1, which has been shown to repress hair cell formation by inhibiting Atoh1, are highly expressed in cells destined to be supporting cells. In contrast, Delta and Atoh1 are highly expressed in hair cell precursors. However, no quantitative threshold of Hes1 has been determined above which a meaningful amount of hair cell regeneration is no longer possible due to Atoh1 inhibition. To find such a threshold, a system of ordinary differential equations was developed to model the change over time of Notch and Delta expression in both hair cells and supporting cells, as well as Atoh1 and Hes1 expression in order to analyze how different parameter values affect equilibrium solutions and their stabilities. Numerical solutions to the system using "biologically normal" parameters match experimental results for gene expression in the normal inner-ear. The model is most sensitive to changes in the ratio of Delta to Notch activity, Atoh1 degradation rate, and rate of Notch and Delta activation. Future experimentation should focus on using drugs to biologically mimic the mathematically-produced parameters values presented here. At these parameters, the system has the potential to keep Hes1 at a low enough stable equilibrium value such that regeneration of inner-ear hair cells is possible in mammals.

Meena Boppana
Mathematics
Lowell 2016

A Voronoi Game

Michael Mitzenmacher
Professor of Computer Science
Harvard School of Engineering and Applied Sciences

Our research problem concerns a game on a Voronoi diagram. Given a finite number of nodes, the Voronoi diagram is a decomposition of the plane into regions based on which node a point is closest to. At the start of the game, all n players are randomly assigned two points on the torus. Players simultaneously choose one of their two points and the Voronoi region with each of these n points as nodes is drawn. Each player's objective is to maximize the area of the Voronoi region corresponding to his or her point.

In this project, we sought to analyze whether Nash equilibria exist as the number of players n approaches infinity. If so, with what probability do they exist and can we classify the situations in which they do?

By computationally simulating this game thousands of times, we found the following results. Nash equilibria exist most, but not all, of the time. We conjecture that the probability of a Nash equilibrium goes to 1 as n approaches infinity. Moreover, in the majority of cases, at least two Nash equilibria exist, which rules out standard monovariant approaches for proving the existence of Nash equilibria.

This game has applications in both economics and computer science. In economics, the nodes may represent businesses that each want to maximize the number of customers closest to them. The problem is relevant in computer science in distributing a load across servers in geometric space.

Daniel Cooney
Mathematics
Leverett 2014

Tournament Dynamics

Martin Nowak
Department of Mathematics and Department of Organismic and Evolutionary Biology
Harvard College

A tournament is a mathematical structure designed to describe an election with n candidates. More precisely, a tournament is a binary relation that specifies which of two candidates would win if pitted against one another in a pairwise election. If there is a candidate that beats each other candidate in a pairwise vote, then we call such a candidate the Condorcet winner of the tournament. When a tournament does not have a Condorcet winner, it is unclear which of the candidates will actually win the n-candidate election. This has led to the development of various solution concepts which seek to define sets of candidates that are more capable of winning the election. Many of these solution concepts have unclear motivation, but do select sets of strategies with interesting properties.

For this project, we seek to determine how a tournament is actually played out. We reinterpret a tournament to be a competition in an infinite population in which there are n possible strategies with which an individual can play. At an individual time-step, individuals are paired up, and, if the paired individuals have different strategies, the individual whose strategy loses in a pairwise competition dies, and the winning individual reproduces. As a consequence, the proportion of each strategy in the population should serve as a reflection of the likelihood for an individual with the strategy to win a tournament. We define the tournament dynamic set to be the set of strategies that survive in the long-run population. The goal of our project is to fully characterize the tournament dynamics set and to determine how this set relates to the sets associated with traditional solution concepts.

Theresa Gebert
Statistics
Currier 2015

Social Decision Making

Christine Looser
Harvard Business School

Humans are an incredibly social species. A wide range of human thinking and behavior is devoted to seeking, developing, and understanding social relationships. But how well do we really understand the people around us? This summer I have been studying, designing, and running experiments that quantitatively examine how people perceive the value of certain experiences for themselves in contrast to how they think other people value the same experiences.

My initial focus was on previously collected data, which showed that people believe they themselves strongly value mental attributes over physical ones, but do not believe other people value mental attributes quite as much. Using the data collected from a ranking survey I had run on over 200 individuals online, I also examined how our perception of self-identity changes when asked to consider our own self-identities versus others'. For example, people were asked to rate how fundamental their ability to make others laugh was to their sense of self, as opposed to how fundamental this same trait might be for the average person.

So far, my results seem to show, again, that there are significant differences between what people value and and what people think others value. For example, we tend to rank the ability to do math higher for ourselves than for other people. This work has theoretical implications for how we understand ourselves, but also practical implications for how institutions can motivate individuals to work and how our society allocates resources to mental health institutions.

Zoë K. Hitzig
Mathematics and Philosophy
Quincy 2015

Memoryless Language Learning on Graphs

Martin Nowak
Department of Mathematics
Department of Organismic and Evolutionary Biology
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The emergence of language–a complex communication system with infinite expressibility– marked a turning point in human evolution. And yet language remains largely mysterious: how do infants learn to form sentences without being explicitly taught the rules of grammar? Noam Chomsky's theory of Universal Grammar posits that the ability to learn language is wired into the brain: that the brain is equipped with an algorithm that generates the rules of grammar based on input sentences. In our model, we attempt to gain insight into the nature of this algorithm by examining a lower limit–a completely memoryless language learning process .

We explore this memoryless algorithm on graphs. Graphs reflect the important fact that language learning happens among socially and physically heterogenous peers. Each individual is placed at a vertex and vertices are connected by edges that define interactions. We focus on the time it takes until an entire population speaks one language or uses one language trait. Specifically, we explore the dynamics of this peer learning process on simple graphs like the star and the cycle, as well as on complex networks such as small-world networks, scale-free networks and Erd Øos-R Ønyi random graphs. These processes are examined through simulations and direct analysis (when possible). Our results are applicable to a wide range of linguistic phenomena, from the evolution of certain words or phrase structures, to acquisition of new phonemes and rules of grammar.

Anthony Liu
Mathematics
Eliot 2014

Statistical Methods for Detecting Damage in Structures

Luke Bornn
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Harvard College

The rapid expansion of computational capabilities in recent years has greatly increased our ability to apply statistical techniques to a wide variety of problems. One particular area of application is Structural Health Monitoring (SHM), a field concerned with the development of better methodologies for the identification of damage in bridges, planes, buildings, and other engineered systems. Improvements in SHM technology promise great life-safety and economic benefits by allowing engineers to accurately diagnose and monitor the condition of everyday structures.

At the heart of most SHM methods is a common template: first, the characteristics of a healthy structure are determined, and then damage is identified whenever the structure's behavior deviates from that of the known healthy state. However, damage isn't the only source of changes in structural characteristics, and so this naive form of SHM is not accurate enough for real applications. The key to more robust methods for SHM lie in developing successful approaches to dealing with sources of variation in structural behavior unrelated to the condition of the structure, categorized in the literature as environmental and operational variation (EOV). Developing SHM methods robust to EOV was the focus of our research this summer.

In particular, we focused on two projects: first, we explored the possibility of adapting a method developed for the physiological monitoring of hospital patients to the context of SHM; second, we worked on new methods for increasing the accuracy of computer models of structural behavior.

Alex Lombardi
Mathematics
Currier 2016

The Asymptotic Behavior of the Fourier Coefficients of Fast-Growing Automorphic Forms

Wilfried Schmid
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The special linear group $SL_2(R)$ acts naturally on the upper half-plane H; each matrix acts as a linear fractional transformation. In this context, given Γ, a subgroup of $SL_2(R)$ satisfying certain con-

ditions, an automorphic form is a meromorphic function f on H that satisfies a functional equation which 'respects' the action of Γ on H. Automorphic forms, which are of interest to mathematicians because of their extremely powerful symmetry, arise naturally in disciplines such as number theory and mathematical physics.

As a result of the symmetry conditions imposed, an automorphic form may be expressed as a convergent Fourier series about certain points called "cusps" of Γ. We may then ask: given some f, how do its Fourier coefficients grow in the long run? A precise answer tells us a lot about the behavior of f near the real line. It also allows us to classify the behavior of the formal Fourier series as a hyperfunction on the real line (despite the fact that f itself is not defined there).

This question has been studied in detail in cases where f is a modular form. In these cases, the slow growth of f makes the question very difficult to answer. I investigate cases in which f has a finite-order pole at infinity, which makes its Fourier coefficients easier to approximate. I first establish weak bounds in a general setting, and then provide much more accurate estimates in the particular case of $f = 1/\Delta$, where Δ is the modular discriminant.

John T. Sheridan
Mathematics
Winthrop 2014

Schubert Calculus

Joseph Daniel Harris
Department of Mathematics
Harvard College

Algebraic Geometry is a branch of mathematics that studies geometric objects arising as the zero-locus of collections of polynomials (these objects are varieties). Think of a single-variable quadratic polynomial, $x^2 +3x+2$. This factors as (x+1)(x+2), and we then say that the equation $x^2 +3x+2 = 0$ has real solutions (or "zeroes") x = –1 and x = –2. If we now swap our polynomial for another having two variables instead of one, we can get infinitely many real solutions. For example, $x^2 + y2 – 1 = 0$ has solutions (x, y) = (cos ⍰, sin ⍰) for all ⍰ in the range [0,2π). Plotting these solutions in the Cartesian plane yields a circle of radius 1 centered at the origin - our first interesting example of a variety.

In the examples above, we had polynomials whose degree was only 2, and which either had one or two variables. In general, we can take polynomials of ar- bitrary positive (integral) degree, with any number of variables. Visualizing the varieties produced from such polynomials becomes virtually impossible, but there are other tools we can then use to detect their local and global structure. For a particular variety, known as the Grassmannian, one such tool is Schubert Calculus. The Grassmannian is a parameter space for vector subspaces - i.e. given a vector space V, the Grassmannian G(k, V) is the set of all subspaces of V having dimension k. This can be exhibited as a variety, and Schubert Calculus refers to the manipulation of subvarieties of the Grassmannian to answer enumerative questions about vector subspaces. My research involves using Schubert Calculus to build an algebraic tool known as the Chow ring to help answer more questions about the Grassmannian.

Siddarth Viswanathan
Statistics
Winthrop 2014

Utilizing Gaussian Graphical Model and RandomForest Algorithms for Patient Survival Prediction and Analysis

John Quackenbush
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Harvard School of Public Health

To further develop and implement improved cancer therapies it is critical for hospitals to understand which measurable clinical factors play the largest role in impacting patient survival. The Cancer Genome Atlas project has analyzed messenger RNA expression and microRNA expression along with 29 clinical variables including tumor stage, survival status, and cancer sub stage for thousands of patients; we use this data to gain insight into the connection between gene expression data and clinical data and also to identify clinical factors best predicting patient survival. Ovarian cancer is the fifth-leading cause of cancer death among women in the United States, thus understanding which variables are strong predictors of patient survival could sharpen future analyses thereby enabling more accurate treatment planning and markedly reducing Ovarian cancer deaths. In this paper we are analyze 18 clinical datasets with combined clinical data for over 5000 patients and 29 clinical variables. To rank variable importance we use the RandomForest machine learning algorithm. To find variable relationships we implement Gaussian Graphical Models (GGMs). Combining the results from both algorithms can offer insight about how patient treatment truly impacts patient survival, offering hospitals and doctors better recommendations about the most effective methods to treat Ovarian cancer.

Tom Silver
Mathematics and Computer Science
Mather 2016

A Novel Method of Imputation using Optimally-Derived Mutual Information

Pardis Sabeti
Department of Systems Biology
Harvard College

While the explosion of datasets in fields as diverse as genomics, global heath, and the social sciences has created new opportunities in a wide range of experimental research, missing data threatens the integrity of quantitative analyses. Numerous methods of dealing with missing data are available, but none are sufficiently unbiased, general, and accurate to use universally. Here we suggest two interrelated new methods to address this issue. The first is a method for estimating mutual information using "optimal" two-dimensional histograms or kernel density estimations (KDE); second, a method for imputation through weighting one-conditional probabilities by mutual information. A histogram or KDE is optimal if it is estimated to minimize the mean integrated square error with respect to the underlying distribution. This method of imputation is attractive because it is nonparametric, efficient, and accurate. Computer simulations demonstrate the viability of both novel methods and analysis using information theory and statistics provides mathematical justi-

fication for the imputation method.

Ved Topkar
Chemical and Physical Biology
Eliot 2016

Genome-Scale Epigenetic Analysis Reveals Quantitatively Definable Trends in Promoter Landscapes

Jeremy Gunawardena
Department of Systems Biology
Harvard Medical School

After the completion of the Human Genome project in the early 2000s, it became clear that the DNA base pairs that make up the genetic code of an organism do not tell the whole story of biology. The mechanisms of gene expression — especially epigenetics — also play a key role in cellular and organismic function. In order to better understand the vast world of DNA modifications (including transcription factor binding profiles, histone modification profiles, nucleosome position profiles, and DNA methylation profiles) the Encyclopedia of DNA Elements (ENCODE) project was started in 2007 to use new genome-wide epigenetic data collection technologies such as ChIP-seq, RNA-seq, and RRBS, to create a database of all DNA modifications across a number of cell types.

As this database has been populated over the past 6 years, a number of studies have begun referencing this data to apply their localized findings across the genome, epigenome, transcriptome, and proteome. However, few have analyzed this database in its entirety to try to uncover its emergent properties.

Here, we report an initial analysis of the ENCODE dataset, with particular attention having being paid to the epigenetic landscape of gene promoters. The RefSeq gene annotation database was used to find all promoters in the genome, including pseudogenes and computationally predicted genes. We found all sites of transcription factor binding at promoters for 149 transcription factor binding profiles, and scored each promoter's intersection profile with a list of integer counts. Then, an unsupervised "Complete" clustering algorithm utilizing a simple Euclidean distance metric was run to find objective clusters in the results. This yielded 8 categories of promoters, each of which seem to have some biological significance. Future studies will refine the promoter scoring techniques, will incorporate even more epigenetic data, and will look at a higher-resolution picture of promoter landscapes through a a process of promoter 'binning'.

Microbiology & Immunology

Nicole West Bassoff
Undeclared
Adams 2016

Evaluating Therapeutic EGFR-Targeted Nanobody Conjugates for Use in a Variety of Cancer Types

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Molecular Neurotherapy and Imaging Laboratory
Massachusetts General Hospital

The Epidermal Growth Factor Receptor (EGFR) is one of four members of the ErbB family of receptor tyrosine kinases. Overexpression or activating mutations of EGFR have been implicated in many different cancer types. The EGFR antagonist Cetuximab has been developed clinically to block EGFR signaling in EGFR-dependent cancers; however, due to a variety of factors, many cancer types develop resistance to Cetuximab. Especially in highly malignant and deadly cancer types like glioblastoma multiforme (GBM), there is need for the development of more effective therapies targeting EGFR.

Our lab has developed EGFR-specific nanobodies (ENb) conjugated to proapoptotic tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). We have shown that ENb-TRAIL is capable of simultaneously targeting the extracellular domain of EGFR to block signaling as well as the extracellular domain of the TRAIL receptors, called Death Receptor 4 and 5 (DR4/5), to stimulate apoptosis. We are interested in the efficacy of ENb-TRAIL in a variety of Cetuximab-resistant cancer types.

In this project, we compared DR4, DR5, and EGFR expression levels across six different Cetuximab-resistant brain, lung, and colon cancer lines. We performed immunoprecipitation of DR4, DR5, and EGFR in ENb-TRAIL treated cell lines to further investigate the mechanism of ENb-TRAIL binding to receptors. At the same time, we have used modified cancer lines overexpressing EGFR or constitutively active EGFR-VIII mutant to evaluate the efficacy of EGFR inhibitor PF299804 in vitro. Finally, we did a pilot experiment to assess the in vivo delivery of ENb-TRAIL via human mesenchymal stem cells (hMSCs) in a GBM mouse model.

Jenifer Brown
Chemistry
Leverett 2015

Selection of scFvs for Co-crystallization of Nramp Membrane Proteins Using Phage Display

Rachelle Gaudet
Department of Molecular and Chemical Biology
Harvard College

Crystal structures of proteins reveal valuable information about their structural, chemical, and functional properties. Of the over 70,000 solved protein crystal structures, less than 1,000 of these are of membrane proteins, despite their high importance. Due to their high hydrophobic content, membrane proteins are notoriously difficult to crystallize. Their hydrophobicity leads to insolubility and a lack of crystal-forming polar contacts. One method to overcome these challenges uses protein-specific antibody fragments called single-chain variable fragments (scFvs) as chaperones to enhance a membrane protein's proclivity to crystallize. Using scFvs produced and selected from a phage display library as co-crystallization chaperones, our goal is to determine the crystal structure of an NRAMP membrane protein.

NRAMPs (natural resistance-associated macrophage proteins) are conserved in eukaryotes and bacteria, and transport divalent metal ions (including Mn2+ and Fe2+) across the plasma membrane using a proton gradient. Humans possess two NRAMP homologs: NRAMP1 is involved in the antimicrobial immune response via a proposed metal withdrawal defense mechanism, while NRAMP2 is responsible for dietary iron and manganese uptake.

We will employ the Tomlinson I & J phagemid libraries to select for and produce scFvs that recognize 4 NRAMP species. From these libraries we can propagate bacteriophages (i.e. viruses) that display scFvs on their coat proteins. We will then incubate the scFv-displaying phage with NRAMP to select the most tightly binding scFvs. After isolating these scFvs, we will crystallize the NRAMP-scFv complex, obtain high-resolution diffraction, and determine the NRAMP crystal structure. This will provide a wealth of knowledge about the molecular mechanism of divalent metal transport and homeostasis.

Kevin Bu
Chemical and Physical Biology
Winthrop 2015

Investigating Choline Metabolism in Gut Microbes

Emily P. Balskus
Harvard College

The study of enzymes involved in biosynthetic pathways can yield a better understanding of the transformations and natural products that link microbial metabolism and human health. Glycyl radical enzymes are of particular interest because they catalyze challenging chemical transformations and because many enzymes in this superfamily have yet to be characterized. One such glycyl radical enzyme, CutC, catalyzes the conversion of choline into trimethylamine and acetaldehyde. Misregulation of this pathway by microbes in the human gut is associated with diseases such as fatty liver disease and atherosclerosis.

Wild type isolates of CutC have been unsuitable for structural characterization via X-ray crystallography due to their instability in solution. In Desulfovibrio alaskensis, it is hypothesized that CutC is localized in microcompartments, stabilizing environments absent from our heterologous expression system. Based on homology modeling with other glycyl radical enzymes, it is hypothesized that CutC possesses a sequence of 52 amino acid residues that causes it to aggregate in vitro. By removing portions of this region, we hope to generate CutC variants that remain active but are more

stable in solution. We also examine a CutC homolog purified from a gut-commensal E. coli strain because this homolog exhibits an additional 300 amino acid domain that may contribute to increased stability. Initial purification and activity assays of truncated CutC variants indicate that the removal of the 52 amino acid region leads to greater stability without loss of catalytic activity. These results suggest that our truncated CutC variants are more suitable candidates for crystallization.

Jordan Alexander Canedy
Applied Mathematics
Pforzheimer 2016

A Novel Screen for Targeting Drug Resistance in Plasmodium falciparum

Dyann Wirth
Broad Institute of MIT and Harvard
Harvard School of Public Health

Managing the development of resistance through drug combinations is key to prolonging the effectiveness of new antimalarial therapies. Typical combination therapies pair drugs that are each effective as monotherapies and employ differing targets in order to avoid the possibility of cross-resistance. However, pairing drugs that target independent sites presents the opportunity for the parasite to individually develop resistance to each compound, rendering the combination ineffective

We proposed to develop new kinds of antimalarial combination therapies where the changes giving rise to resistance become the target for the second drug, a drug that may not be active against the wild type parasite. This approach has distinct advantages over combinations that attack different targets; first and foremost, it incorporates built-in protection for the partner drug from development of resistance. When resistant mutants to the first drug occur then, and only then, does the second drug act, greatly diminishing the population subject to selection.

We screened the Malaria Box, an open-access assemblage of 400 diverse chemical compounds provided by the Medicines for Malaria Venture, against a panel of mutant, drug-resistant P. falciparum parasites to determine the half maximal concentration (EC50s) in order to identify compounds with differential activity between mutant and wild type parasites. In vitro drug sensitivities were determined through the SYBR Green assay method, and EC50s were then calculated using a nonlinear-least squares regression curve fit in GraphPad® Prism 6.

While previous screening efforts included limited probing of drug resistant parasite lines, these experiments represent a completely novel and far more comprehensive approach in the study of resistant organisms and their unique susceptibilities.

Jessica Izhakoff
Organismic Evolutionary Biology
Mather 2015

Is Food Allergy an Infectious Disease?

Dale Umetsu
Boston Children's Hospital
Harvard Medical School

The microbiome, especially the microbiota in the gastrointestinal system, has an enormous impact on the human body's immunological functions, including the development of helper and suppressor lymphocytes, and the development of many lymphoid structures. The establishment, therefore, of specific populations of gut microbiota in early life appears to regulate and possibly cause the development of a number of immunological diseases, including allergy, asthma and food allergy. Most food allergies in children develop in the first or second year of life, which is consistent with the dramatic changes that occur in the composition of the gut microbiome in early childhood, associated with different environmental exposures including the method of delivery, antibiotic use and breastfeeding.

For this project, we are studying the change in the gut microbiota and comparing composition of the gut microbiota in children who do and do not have food allergies. In addition, since food allergy in children often resolves, or develops with greater exposures to foods, children who crossover between those two categories will also be studied. Currently, we are collecting stool samples from infants (children younger than one year of age), and at various time points over the ensuing 3 years of their lives. Our goal is to follow the evolution of the gut microbiota in these children, and identify bacterial strains or populations associated with the presence or absence of food allergies. To move beyond associations and examine possible cause, we plan to later transplant the identified microbiota into germ free mice and determine if they influence the development of food allergy. My role in this project has been to compile patient data regarding early childhood environmental exposures in order to analyze the patient stool samples at each time point. In addition, I have led the development of an electronic data capture program, which allows more accurate data collection and easier analysis of the data.

Bianca Mulaney
Economics
Quincy 2016

Combinatorial Effect of Zaragozic Acid and Antibiotics on Staphylococcus aureus

Roberto Kolter
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Harvard Medical School

Biofilms are bacterial aggregates that form on surfaces, held together by an extracellular matrix of exopolysaccharides, proteins, and nucleic acids. Because biofilms can grow on almost any surface, they have a tremendous impact on humans and the environment. Of particular concern, bacteria within a biofilm become more resistant to antibiotics, making them hard to control in clinical settings.

The Kolter Lab recently discovered certain non-lethal compounds capable of inhibiting biofilm formation in numerous bacteria, including the pathogen Staphylococcus aureus. One such compound, zaragozic acid, inhibits production of membrane lipid microdomains that harbor proteins important in biofilm formation and virulence. Although zaragozic acid was shown to inhibit biofilm formation in S. aureus, the bacteria themselves did not die – to kill the bacteria, an antibiotic would need to be introduced.

Here, we examine the effect of combinatorial treatments of zaragozic acid and various antibiotics with the goal of eventually identifying combinations that can more effectively treat and eliminate biofilm-related infections. We have found that combining zaragozic acid with the protein synthesis inhibitor gentamicin both interferes with biofilm formation in S. aureus and kills the bacteria using a lower concentration of antibiotic than that required when applied alone.

Interestingly, the potentiating effect of zaragozic acid on antibiotic activity is not observed universally – antibiotics that target cell wall synthesis become less potent in the presence of zaragozic acid. This indicates that the effect of zaragozic acid on antibiotic activity is complex. We are currently conducting experiments to better understand the effect of these molecules on cell physiology.

May Yang
Chemical and Physical Biology
Pforzheimer 2015

Investigating Satellite dsRNAs in Trichomonas Vaginalis

Max Nibert
Department of Microbiology and Immunobiology
Harvard Medical School

Trichomoniasis, caused by the protozoan parasite Trichomonas vaginalis, is the most common non-viral sexually transmitted infection. Trichomoniasis can have devastating consequences including increased risks of pregnancy complications, HIV infection, and cancer due to HPV. A dsRNA virus in the Totiviridae family, Trichomonas vaginalis virus or TVV, infects most T. vaginalis isolates, with up to four different TVV strains co-infecting a single clonal isolate of T. vaginalis. Studies have shown that TVV may affect the expression of some T. vaginalis virulence factors and that TVV itself causes a proinflammatory response in humans. The effect of TVV on T. vaginalis and the human host is further complicated by the presence of satellite dsRNA in some strains. Satellite nucleic acids are genomes that rely on a helper virus for replication and encapsulation, but are not derived from the viral genome. The TVV satellites are categorized into three groups (S1, S1´A, and S1´B) and any combination of these satellites, from none to all three, can be found in TVV-infected T. vaginalis.

These complex parasitic relations in T. vaginalis raise many interesting questions and this summer, I am working toward better understanding the satellites' role in this system. I am cloning the satellites from various T. vaginalis strains and sequencing them to form a foundation for future studies. Furthermore, I am beginning to identify interactions between the satellites and TVV strains, specifically if each type of satellite associates with a particular TVV strain, by noting which TVV and satellite strains appear together in isolates.

Molecular & Cellular Biology

Stephen Albro
Molecular and Cellular Biology
Pforzheimer 2016

Why Does Dynein Walk Like it's Drunk?

Andres Leschziner
Department of Molecular and Cellular Biology
Harvard College

This summer, I am working with a graduate student in Andres Leschziner's lab on cytoplasmic dynein, a motor protein that walks on microtubules. Dynein performs a variety of functions in both mitosis and interphase of the cell cycle, including anchoring and positioning microtubules and carrying cellular cargo. Unlike the cell's other motor proteins, kinesin and myosin, dynein "walks" with irregular step size and frequency. My research attempts to ascertain how and why dynein walks so irregularly. We have created a library of three mutants that increase dynein's affinity for microtubules. Because of this, the high-affinity mutants walk longer distances on the microtubule before falling off; that is, they have longer "run lengths." In comparison, wild-type dynein appears to have a suboptimal run length. We hypothesize that dynein's affinity for microtubules has evolved to produce a more liberal and irregular stepping behavior, enabling dynein to step over and around obstacles on microtubules inside living cells. To test this, I am using total internal fluorescence microscopy (TIRF) to assay the motility of wild-type dynein along with its three mutant counterparts, each one with and without obstacles. We are using immobile kinesin proteins, which also bind to microtubules, as obstacles. If our hypothesis is correct, the increased affinity of the mutants for the microtubules will decrease their ability to step around obstacles, and the dyneins will fall off the microtubules, rendering much shorter total "run lengths."

Alice Berenson
Molecular and Cellular Biology
Mather 2016

Component Dynamics and Interactions in the Type VII Secretion System of Bacillus subtilis

Briana Burton
Harvard College

Protein secretion is essential for pathogenicity in many bacteria. The recently discovered Type VII Secretion System (T7SS) exports virulence factors from Mycobacterium tuberculosis and Staphylococcus aureus, among others. While its structure and composition are largely unknown, a recently described T7SS found in Bacillus subtilis is made up of the seven proteins coded by the yuk operon. Preliminary analysis predicts that two of these proteins, YukBA and YueB, are multipass membrane proteins. Since they are required for secretion, we hypothesize that YukBA and YueB comprise the translocation channel of the secretion apparatus and thus interact in vivo. The goal of this work is to test whether these proteins interact within the functional secretion apparatus and to determine which other system components help establish or maintain this interaction. To do this, I first monitored the dynamics of YukBA and YueB, each tagged with green fluorescent protein (GFP), within the membrane using Total Internal Reflection Fluorescence (TIRF). Next, I will examine these proteins in the context of various yuk operon gene deletions. To further assess in vivo interaction between these two proteins, I will employ Fluorescent Resonance Energy Transfer TIRF (FRET-TIRF) by co-expressing YukBA and YueB components fused with fluorescent proteins recently optimized for FRET, Clover and mRuby2, respectively. Results of these microscopy analyses will inform about exactly which protein interactions are required for secretion in the T7SS. Knowledge about the T7SS could improve our ability to impede secretion of infectious agents, thus potentially contributing to new vaccines against human pathogens.

Aaron Cheng
Chemical and Physical Biology
Quincy 2015

Understanding the Role of BCL11a in the Hemoglobin Switch

Stuart Orkin
Department of Hematology
Boston Children's Hospital

β-hemoglobinopathies, or deleterious mutations in the β-globin gene, continue to be a leading cause of blood disorders such as sickle-cell disease and β-thalassemia. Patients with these rare disorders are unable to produce functional red blood cells and must undergo frequent transfusions in order to replenish their bodies' supply of oxygen-carriers. These treatments often cause further potentially fatal complications such as iron overload. A potential way to treat sickle-cell disease and β-thalassemia is to trigger the expression of fetal (γ-) hemoglobin, which has been shown to effectively diminish the effects of dysfunctional β-hemoglobin.

BCL11a is a major protein involved in the switch from gamma to beta hemoglobin, which occurs at around six months of age in humans. We have been studying potential methods of interfering with BCL11a in order to prevent the down-regulation of gamma hemoglobin. One of the properties we are studying is SUMOylation of BCL11a, by specifically mutating the SUMOylation sites on BCL11a and observing changes in protein function in vitro. Another approach is to conduct drug screens with clinically-approved small molecules to isolate drugs that can induce the expression of gamma hemoglobin. By coupling Luciferase with γ-globin and Renilla with β-hemoglobin, we have been able to use fluorescence assays to isolate nineteen chemicals that seem to induce γ-globin. We are in the process of conducting toxicity tests and dose response assays to further isolate potential compounds.

With our results, we hope to ultimately contribute to the understanding and treatment of β-hemoglobinopathies.

William Clerx
Molecular and Cellular Biology
Cabot 2014

Erratic Light Exposure and Entrainment of Circadian Cellular Oscillators: Effects on Neuroendocrine Rhythms in College Undergraduates

Charles A. Czeisler
Brigham and Women's Hospital
Harvard Medical School

Circadian clocks are essential components of living organisms, from single-celled bacteria to humans. Environmental stimuli, termed zeitgebers, can alter circadian clock phase and amplitude. Zeitgebers synchronize internal (biological) and external (environmental) rhythms. The most powerful zeitgeber is typically light, and studies in chronobiology have primarily involved chronic, stable light/dark schedules in controlled conditions. While informative, imposed stable schedules are not ecologically relevant, particularly for humans with irregular day-to-day schedules. Consequently, we are studying the effects of irregular light exposure patterns on human circadian rhythms in college undergraduates—a population with naturally irregular light exposure. We analyzed sleep/wake data from prior studies of Harvard undergraduates, statistically describing regularity of sleep duration and timing, and effects of class load. These findings demonstrate large inter-individual variability in sleep regularity. Motivated by this work, we are launching a project in Fall 2013 to study undergraduates in the campus setting through sleep diaries, actigraphy, and urine collection for analysis of cortisol and melatonin (two reliable neuroendocrine outputs of the circadian clock). The collected data will allow us to test the hypotheses that irregular light exposure in young adults is associated with (1) increased nocturnal and decreased early morning light, and increased daily duration of light; (2) lower peak value, later peak timing, and shorter duration of nocturnal melatonin secretion; and (3) elevated minimum and later nocturnal rise of cortisol. As circadian disruption and hormonal changes are closely tied to metabolic and behavioral disorders, these findings will have important implications for individuals and broader policies shaping the social construction of sleep schedules.

Charles Du
Chemistry
Eliot 2015

Identifying Putative Families of Rare Driver Mutations Using Mutation Hotspots in Consensus Alignments

Matthew Meyerson
Broad Institute of MIT and Harvard

Many efforts in cancer genomics are focused on differentiating "driver" mutations, which play a role in oncogenesis, from "passenger" mutations, which co-occur randomly. Driver mutations will tend to occur in biochemically significant regions of a protein. This leads to a nonrandom distribution of mutations across the length of driver genes, a phenomenon exploitable in cancer gene discovery efforts. My work is aimed at discovering rare driver mutations that only have several occurrences in a data set, and therefore evaded standard significance testing.

The core of my strategy lay in aligning related proteins and aggregating their mutation counts to amplify statistical signal. First, a metric of "related" must be established. I started with groupings defined in the Pfam database, and computed pairwise protein alignment scores. Using these scores as an inverse distance metric, I used clustering analysis to form groups of genes. For each group, I mapped mutations onto a consensus sequence, and tested for nonrandom distribution. Initial validation has been promising; my algorithm reproduced known mutation hotspots in RAS and RTK family proteins. Moreover, performing the same analysis on olfactory receptors gave a relatively uniform mutation distribution with no significant hotspots. Current directions involve applying this analysis to gene families (as annotated by Pfam) with at least one previously identified cancer gene.

Richard Ebright
Chemical and Physical Biology
Cabot 2014

Correlating β-catenin Upregulation in Tumors with Selective Sensitivity to Navitoclax

Stuart L. Schreiber
Broad Institute of MIT and Harvard

Personalized cancer treatments have all but eliminated a handful of cancers, most notably the successful treatment of CML by imatinib. However, few cancer patients can be effectively treated with current drugs. As such, there is a strong need for the identification of drugs that selectively target specific tumors.

Recently, the Schreiber lab conducted a large-scale screen, connecting cancer cell genetics and small molecule sensitivity. One correlation found from this screen was a connection between cancers driven by mutations in the oncogene CTNNB1 (CTNNB1^{mut}) and sensitivity to the small molecule navitoclax, which inhibits anti-apoptotic BCL2 proteins. Mutations in CTNNB1 result in accumulation of the CTNNB1 protein product, β-catenin. Last summer, I showed that cancer cells with higher levels of β-catenin are selectively sensitive to navitoclax. Moreover, I showed that increasing cancer cell levels of β-catenin led to increased sensitivity to navitoclax, suggesting a causal relationship.

I now seek to understand why cancers with high levels of β-catenin are sensitive to navitoclax. I have identified a number of genes that are frequently upregulated in CTNNB1^{mut} cancers and that connect β-catenin to the BCL2 proteins that navitoclax targets. My initial studies suggest that high levels of β-catenin activate the tumor suppressor p53, upregulating apoptotic proteins and potentiating cancer cells for death. As such, only small doses of navitoclax would be necessary to selectively kill the cancer cells, leaving other cells unharmed.

A better understanding of the connection between high levels of β-catenin and sensitivity to navitoclax will allow for the development of additional drugs that selectively target CTNNB1^{mut} cancers, as well as the design of successful combination therapies for CTNNB1^{mut} tumors.

Fayola Fears
Organismic and Evolutionary Biology
Cabot 2014

Prkar1a and Adaptive Sperm Morphology in Peromyscus Mice

Hopi Hoekstra
Harvard College

Female mating strategies can have a large influence on the evolution of post-copulatory reproductive traits as the level of sperm competition affects the intensity of sexual selection. Peromyscus polionotus and P. maniculatus are sister-species, but P. polionotus is strictly monogamous, as confirmed by behavioral and genetic data, while P. maniculatus females often mate with multiple males within a reproductive cycle and frequently carry multiple-paternity litters in the wild. P. polionotus experiences virtually no sperm competition because sperm from only one male is present in the female reproductive tract, while P. maniculatus experiences high sperm competition because sperm from any one male must compete with sperm from up to several other males in order to be successful. In such a competitive context, male reproductive success is associated with sperm motility. Previous research has indicated that sperm midpiece length is positively correlated with sperm swimming velocity, and that P. maniculatus sperm have longer midpieces than P. polionotus sperm. Quantitative trait loci mapping in second-generation hybrids of the species indicate that the gene Prkar1a is associated with sperm midpiece length. Sequencing of Prkar1a cDNA in the two species and assessment of gene expression together suggest that the differences in phenotype may be due to differences in the regulation of Prkar1a. Thus, the goal of the study is to sequence the regulatory region of Prkar1a in diverse wild-caught mice from P. polionotus and P. maniculatus to determine if there is a signature of selection or evidence of a causal mutation.

Jack Huang
Undeclared
Eliot 2016

Good Bugs Gone Bad: Exploring the Diversity of the Pathogenicity Island in Enterococcus faecalis

Michael Gilmore
Harvard Medical School
Massachusetts Eye and Ear Infirmary

Enterococci have long lived as commensal microbes in the gut of humans and animals, but recently have also emerged as leading causes of multidrug resistant hospital-acquired infection, with ~70% caused by Enterococcus faecalis. Key virulence factors in E. faecalis have been found to cluster on a pathogenicity island (PAI), previously characterized as a 150 kilobase sequence in strain MMH594. In previous studies, we examined the genetic variability of the PAI by probing a set of E. faecalis strains for genes of the MMH594 prototype PAI, and found evidence for modular accretion of functionally related genes. In this study, we aimed to capture the diversity of the PAI using whole-genome sequencing of over 100 strains, representing the breadth of E. faecalis. Our results highlight the diversity of the PAI – we expanded its gene repertoire from 129 open-reading frames to over 300, confirmed the modular structure and identified at least seven new putative blocks of genes, adding to the six functional modules identified previously. Interestingly, we identified numerous mobile element associated genes within the modules that may play a role in their horizontal transfer. To confirm this, we compared PAI sequence relatedness to the core genome phylogeny of E. faecalis. Although PAI modular structure is usually conserved among closely related strains, we also observed substantial variation in PAI sequence between clonal isolates, suggesting a key role of horizontal transfer in PAI evolution. These results shed light on the parallel evolution of the PAI in E. faecalis and our understanding of its pathogenicity.

Yvette Leung
Chemical and Physical Biology
Mather 2014

Identification of Telomere Length Regulators in Plasmodium falciparum

Manoj Duraisingh
Department of Immunology and Infectious Diseases
Harvard School of Public Health

Malaria is a mosquito-borne disease which is responsible for nearly 700,000 deaths worldwide each year. While malaria can be caused by several members of the Plasmodium family of parasites, infection by Plasmodium falciparum (P. falciparum) is the most deadly. P. falciparum invades red blood cells and evades the immune system by expressing different variants of protein antigens on the red blood cell surface. Antigen switching is controlled by differential expression of subtelomeric virulence genes, which in turn are regulated by epigenetic factors including histone modifications. Histone modifications by proteins such as histone deacetylases play a role in regulating telomere length in many organisms. However, the mechanism by which virulence genes are regulated in P. falciparum remains unknown, though one potential mechanism involves changes in telomere length mediated by histone deacetylases. In this study, I investigate how expression of the previously uncharacterized histone deacetylase PfHda2 impacts telomere length and screen for candidate genes which regulate telomere length in P. falciparum.

Elissa Lin
Chemistry
Cabot 2015

Understanding Molecular Pathways between AMPK and TOR in Longevity

William Mair
Department of Genetics and Complex Diseases
Harvard School of Public Health

Aging is a universal trait that induces greater risk for a number of human pathologies, yet little is known about the biological reasons for our natural molecular deterioration. By studying the cellular and molecular processes involved in aging, it may be possible to find therapeutic strategies that reduce the threshold of risk for multiple age-onset disorders. Dietary restriction (DR), the reduction of food intake without malnutrition, is known to slow aging and protect against disease. Two central mediators of DR are

AMP-activated protein kinase (AMPK) and Target of Rapamycin (TOR), which are antagonistically regulated by low food intake, being activated or suppressed respectively. AMPK and TOR also have opposing effects on longevity; activating AMPK promotes healthy aging while in contrast, suppressing TOR increases lifespan. However, although AMPK and TOR are known to regulate each other in vivo, whether they work together to regulate aging is unknown. To address this question, I tested the prevailing paradigm that AMPK increases lifespan via suppression of TOR. S6K is a major downstream effector of TOR and thus S6K null represents down-regulation of TOR activity. I therefore examined the lifespan of AMPK activated worms in an S6K null background and found that AMPK extends lifespan independently of S6K. In contrast, lifespan extension via inhibition of S6K requires AMPK. These data therefore suggest that AMPK acts down rather than up-stream of TOR in longevity, contrary to the prevailing yet untested paradigm, and highlight AMPK as a promising target for drugs regulating longevity in humans.

Brooke McLain
Molecular and Cellular Biology
Eliot 2016

The Effects of Varying Diets on the aak C. elegans Mutant

Alexander Soukas
Center for Human Genetic Research
Massachusetts General Hospital

Using an aak C. elegans mutant strain containing a GFP reporter at the myosin gene and a RFP reporter at the aak gene as identified by Dr. Lienfeng Wu, the lipid droplet size and number at the L4 to gravid stages were identified using a high power microscope after varying the diets of worms. In the first diet experiment, various E. coli bacterial strains obtained from the K12 strain were used along with Comamonus bacteria, C. elegan's natural diet source. During this screen the bacteria HT115 strain was found to decrease the size of lipid droplets while increasing the number of lipid droplets as well. The other strains that were tested seemed to be very similar to the standard OP50 bacterial lawn used on NGM plates. Strangely enough, glucose has no real effect on the RFP expression. This could be in part due to the fact that glucose is toxic to C. elegans or the fact that this mutation does not allow the dietary system to absorb glucose. The next portion of the experiment will be to test varying metabolites in the citric cycle and glycogenesis cycle along with two anti-diabetic drugs: metformin and phenformin.

Nick Moore
Molecular and Cellular Biology
Eliot 2014

Scanning Bacterial Genomes by Systematic Codon Substitution

Roy Kishony
Department of Systems Biology
Harvard Medical School

The genomes of Escherichia coli and other bacteria have been sequenced for some time. Yet we are still unable to predict what parts of that sequence are mutable without changing an organism's ability to survive and reproduce relative to wild type, defined as fitness. The fitness effects of synonymous and nonsynonymous mutations vary enormously. One approach to understanding this variation is to generate the full set of single codon mutations in a subset of genes and calculate the fitness of each mutant. Using new technologies for genome engineering and sequencing, the Kishony lab has substituted every codon in the essential E. coli gene infA and measured the fitness of each mutant. I aim to do the same for several other essential genes that have never been systematically mutated in this way. In making genome scanning high-throughput, I will demonstrate the extent to which nonsynonymous and synonymous codon substitutions affect fitness, potentially supporting hypotheses of codon usage bias. I will then extend this method of genome scanning to a continuous region of the E. coli genome, in order to probe other noncoding mutations that affect fitness.

Arvind Narayanan
Undeclared
Adams 2016

Investigating the Disaggregation of Tail-Anchored Proteins

Vladimir Denic
Department of Molecular and Cellular Biology
Harvard College

The Guided Entry of Tail-anchored proteins (GET) pathway targets proteins with a single C-terminal transmembrane domain (TA proteins) to the ER. Under sugar starvation and occasionally in the absence of any stress, TA proteins reversibly accumulate in cytosolic aggregates. These aggregates result in a heat shock response, indicating a loss of protein homeostasis. Get3 and Sgt2, components of the GET pathway, localize to these aggregates, along with Hsp104, a protein disaggregase. However, it is not clear to what extent and in what combinations these components can reverse or prevent aggregation of TA proteins. To characterize the mechanism of disaggregation, we use an in vitro system to observe TA protein aggregation and disaggregation in the presence or absence of factors that localize to the aggregates in vivo. In doing so, we hope to better understand a mechanism that the cell has to address toxic membrane protein aggregation.

Qaren Quartey
Molecular and Cellular Biology
Mather 2015

Preparation and Purification of Müllerian Inhibiting Substance for Treatment of Ovarian Cancer

Patricia Donahoe
Pediatric Surgical Laboratories
Massachusetts General Hospital

The severity of ovarian cancer is evident in its fatal effects on thousands of women in North America. Presently, the chemotherapeutic agents in use for treatment of ovarian cancer are ineffective in their impact on cancer stems cells, tumor-initiating cells capable of metastasis and unlimited self-renewal (Wei et al, 2010).

This stem cell/progenitor population has been shown to be resistant to chemotherapeutic drugs such as doxorubicin, cisplatin, and pac litaxel(2010). Previous research has indicated that Müllerian Inhibiting Substance (MIS) may have a role in addressing this characteristic drug resistance.

Known for causing regression of the Fallopian tube and ovaries, MIS also shows efficacy as a tumor suppressor, which motivated genetic modifications to increase the production of recombinant c-terminal MIS. Combining modification of an endogenous cleavage site to a more consensus Kex/Furin site with a human serum albumin sequence resulted in higher expression of MIS, along with increased yield of the active c-terminus (Pépin et al, 2013). To optimize the preparation and purification of MIS, the impact of media supplemented with insulin, transferrin, and selenium (ITS), with non-essential amino acids (NEAA), and a gradation in percentage of female fetal bovine serum (FFBS) was evaluated. Although addition of FFBS increases MIS production, the presence of increased amounts of proteins complicates the purification process. To address this, MIS production levels in Chinese hamster ovary (CHO) cells grown in serum free media such as D-MEM, CHO-V and CHO Freestyle were assessed. Preliminary results suggest that supplementing serum free media with ITS is by far the most beneficial, followed by serum free DMEM media and media supplemented with NEAA. These changes now make it feasible to scale MIS for use in clinical trials.

Martin Reindl
Molecular and Cellular Biology
Pforzheimer 2015

Characterization of Amino Acids Involved in SecY-YidC Interaction in Escherichia Coli Using a Random Mutagenesis Approach

Marcia Goldberg
Massachusetts General Hospital

About 50% of currently approved drugs target membrane proteins (Overington et al., 2006), yet the biogenesis of these proteins is still incompletely understood. In Escherichia coli the majority of membrane proteins is introduced to the lipid bi-layer via the lateral gate of the bacterial translocon SecY (Du Plessis et al., 2011). A subset of membrane proteins utilizes YidC, a highly conserved protein that associates with SecY, for efficient insertion in this context (Gray et al., 2011). While the structure of SecY has been resolved and its contact interface with YidC has been mapped (Sachelaru et al., 2013), the structure of YidC, its contacts with SecY, and the mechanisms of SecY-YidC interaction are still poorly understood. We investigate the molecular basis of the interaction of YidC with SecY by identifying amino acids required for this interaction. Preliminary data shows seven amino acid changes in YidC that affect the SecY-YidC interaction. Several mutation groupings show promise as being required for YidC-SecY contact. Currently ongoing research aims to verify and expand initial data in order to create a mutant strain useful for studying the mechanism of SecY-YidC interaction and the role of this interaction in the transfer of nascent membrane proteins from the SecY translocon into the membrane bi-layer.

Katherine Selwa
Molecular and Cellular Biology
Leverett 2016

Regulation of Retrotransposon Content of Extracellular Vesicles in Medulloblastoma

Scott Pomeroy
Boston Children's Hospital

Forty percent of the human genome is comprised of the remnants of ancient viruses. While most of these are inactive relics from our evolutionary history, a small portion are actively jumping retrotransposons. The most common retrotransposon is the Long Intersperesed Element-1 (LINE-1). LINE-1s are actively able to reverse transcribe the RNA intermediate and insert the cDNA elsewhere in the genome. LINE-1s are mainly active in neural progenitor cells during development, with a proposed role in increasing neural diversity. A Wnt-regulated complex comprised of HDAC1 and Sox2 usually represses LINE-1 activity, but demethylation events and changes in this pathway can lead to their activation outside of development. Random reinsertion can wreak havoc in the genome, and a high proportion of active LINE-1s are present in certain neuronal cancers. LINE-1s are especially active in medulloblastoma, the most common malignant brain tumor in children, and can be exported from the cell by extracellular vesicles (EVs) that have long been thought to carry cellular waste. EVs have been investigated for use in cancer diagnostics, but recently evidence has appeared to indicate that EVs can transmit certain cancer states from cell to cell, thereby playing a role in immune response and tumor niche development. Genome sequencing data obtained by our lab has shown mutations in epigenetic regulators in medulloblastoma patients that might play a role in LINE-1 maintenance, reinsertion and export. I investigated the effect of the presence of these regulators on the levels of LINE-1s in the EVs.

Nina Shevzov-Zebrun
Human Evolutionary Biology
Pforzheimer 2016

Examining the Role of miRNA in Activity-Mediated Plasticity in the Drosophila Neuromuscular Junction

David Van Vactor
Department of Cell Biology
Harvard Medical School

The Drosophila neuromuscular junction (NMJ), which features glutamate receptors and conserved synaptic effector proteins, serves as an excellent model for examining mechanisms of synapse development and axon guidance in higher vertebrate species. By helping to regulate translation, microRNAs (miRs) have been shown to play a role in synapse development, allowing the nervous system to adapt to changes in the environment. We crossed flies containing the channelrhodopsin (light-sensitive channel protein) gene with OK371-Gal4 flies to drive channelrhodopsin solely in motor neurons. We then exposed half of the resulting larvae to retinoic acid (RA) to activate channelrhodopsin in those experimental animals. All larvae (+RA and –RA) were then exposed to blue light until the late third instar stage. Immunohistochemical methods were used to

stain dissected larval pelts—different antibodies bound to and thus highlighted the motor neuron cell surfaces and post-synaptic areas. Imaging of the stained NMJs revealed an overall increase in bouton number in +RA animals consistent with other increased neuronal activity models. Nanostring miR profiling technology revealed that levels of certain miRs in the two groups varied, suggesting that those miRs are involved in gene regulation that leads to morphological change in response to stimulus. Further experimentation using RNAi and other technologies could help identify targets of these miRs, ultimately playing a role in therapy development for mental illnesses such as schizophrenia that have been linked to certain miRs.

David Shin
Molecular and Cellular Biology
Dunster 2014

Examining the Inhibitory Role of SIRT3 in the Src/FAK Pathway and Metastatic Breast Cancer

Marcia Haigis
Department of Cell Biology
Paul F. Glenn Laboratories for the Biological Mechanisms of Aging
Harvard Medical School

SIRT3, a mammalian homologue to the yeast longevity protein Sir2, is a NAD+-dependent protein deacetylase localized to the mitochondria. Studies have shown that SIRT3 is involved in the regulation of a number of different metabolic processes, including oxidative metabolism and the mitochondrial antioxidant system. The misregulation of SIRT3 has been implicated in a variety of different diseases, and it is therefore of great importance to study SIRT3 with respect to the regulation of cellular pathways linked to disease.

Recent evidence has shown that SIRT3 may be linked to metastasis through its role in reducing levels of mitochondrial reactive oxygen species (ROS). ROS, which is known to oxidize and thereby fully activate different protein tyrosine kinase proteins, has been linked to the upregulation of the Src/FAK pathway via activation of the tyrosine kinase c-Src. Importantly, the activated Src-FAK complex is involved in the stimulation of cell motility, thereby having important relevance to metastasis. As an important source of ROS is the mitochondria, we aim to study whether SIRT3, which is involved in the modulation of mitochondrial ROS levels, is involved in the regulation of the Src/FAK pathway. More specifically, we hope to confirm that SIRT3 is associated with the inhibition of Src/FAK signaling and collective cell migration via the modulation of ROS and determine the mechanism by which SIRT3 is involved in Src/FAK signaling and the metastasis of breast cancer to the bone.

David Su
Chemical and Physical Biology
Cabot 2014

Escherichia coli Chromosome Organization: In Vivo Analysis Using Super-resolution Fluorescence Microscopy

Xiaowei Zhuang
Harvard College

Escherichia coli contain a single circular 4.6 Mb chromosome that replicates bidirectionally from a specific origin. When extended, the DNA chromosome can reach more than 1 mm in length. However, the chromosome resides in a region called the nucleoid, which is less than 1 μm in diameter. As a result, it must be linearly condensed more than 1,000-fold to fit inside the nucleoid, while also preventing entanglements with replicating sister chromosomes. Even though recent evidence shows that the bacterial chromosome is compacted into negatively supercoiled domains with the help of neighboring proteins, the condensing mechanism underlying its organization is poorly understood. Molecular experiments and simulations have estimated these supercoiled domains to be ~10 kb in length. However, the diffraction-limited optical resolution of standard fluorescence microscopy leaves these domains too small to be observed in detail.

I aim to identify structural characteristics of the topological microdomains on the bacterial chromosome at a sub-diffraction-limit scale. My approach is to analyze the differences between the genomic and physical distances of a distribution of DNA locus pairs within a chromosomal macrodomain using localization-based super-resolution microscopy. To model these chromosome clusters, I will image a distribution of clones, each with a different pair of chromosome loci fluorescently labeled using a fluorescent repressor-operator system (FROS). Due to the sheer number of E. coli clones generated and the time required for image preparation, I have also engineered a microfluidics chip that will serve as a high-throughput imaging platform that will speed up the super-resolution imaging process by several orders of magnitude. Using these methods, I hope to characterize the static and dynamic organization of DNA folding within the bacterial chromosome.

Sora Tannenbaum
Molecular and Cellular Biology
Dunster 2015

Epigenetic Regulation in the Mouse Brain and Social Dominance

Catherine Dulac
Harvard College

A current hypothesis suggests that epigenetic modifications to chromatin—the material of which chromosomes are composed—perform a significant role in neuroplasticity and intellectual ability. In people with impaired intellectual ability, genetic mutations have been found in regions that code for enzymes affecting the chromosomal regulation of gene expression. However, a full understanding of how chromatin modifications affect complex behaviors has yet to be reached. Epigenetic variation may help explain variation in complex behavior of vertebrates, including mice. Inbred strains of laboratory mice, which are produced to eliminate genetic variation

between individuals, still exhibit marked differences in behavioral phenotype . This difference despite genetic homogeneity implicates epigenetic regulation as a potential cause of behavioral variation. One particular form of phenotypic behavioral variation in mice is in social dominance interactions between males. When non-sibling males are placed in an environment with a limiting resource, they compete to establish a social hierarchy consisting of dominant and subordinate members. The goal of our research is identify the potential role of epigenetic gene regulation in producing dominant-subordinate phenotypic variation. We address two questions. First, is there a difference in epigenetic modification in specific brain regions (e.g. hypothalamus, prefrontal cortex, or amygdala) in dominant and subordinate mice? Second, if there are such differences, do they play a casual role in this behavioral variation?

Paul Wei
Chemical and Physical Biology
Quincy 2015

Regulation of Cardiac Exercise Phenotypes by microRNA-222

Anthony Rosenzweig
Cardiovascular Institute
Beth Israel Deaconess Medical Center

Heart disease is the leading cause of death in developed countries and also one of the most expensive, surpassing $100 billion every year in healthcare costs and lost productivity in the United States alone. Numerous clinical studies have shown that exercise plays a significant role in preventing or mitigating the detrimental effects of heart disease, but little is known about the molecular pathways that underlie these effects. One of the ways through which gene expression in the heart is regulated is through micro-RNAs (miRs), short strands of RNA that bind to and downregulate the expression of its target genes. A comprehensive screen of miR expression in the hearts of exercised mice found sixteen miRs to be differentially expressed, among which miR-222 was confirmed to be the most robustly upregulated in two separate mice exercise models. Using markers of cellular proliferation and measurements of cell size, we have determined that miR-222 is necessary and sufficient for cardiomyocyte hyperplasia (proliferation) as well as hypertrophy in vitro and in vivo, corresponding to the phenotype observed in the hearts of exercised mice. We hypothesize that miR-222 also has a cardiac protective role, in addition to its regenerative abilities, by reducing the levels of apoptosis in the heart. However, we did not find a robust protective effect of miR-222 overexpression in vitro in primary neonatal rat cardiomyocytes, after the cells overexpressing miR-222 were subjected to several forms of stress. We are still in the process of assessing whether transgenic mice overexpressing miR-222 may have improved cardiac function or decreased levels of apoptosis following surgical models cardiac diseases and heart failure.

Michael Pei-hong Wu
Molecular and Cellular Biology
Kirkland 2014

Characterizing the Effects of Cancer-associated Fibroblasts and Collagen on the Spatial Distribution and Activation State of Tumor-infiltrating T Cells

Shannon Turley
Department of Cancer Immunology and AIDS
Dana Farber Cancer Institute

The immune system not only guards against foreign pathogens, but can also act as a defense against cancer. Although cancer cells are immunologically "self," many express aberrant cell surface antigens that enable immune cells to recognize and target them for destruction. Therefore, for a tumor to survive and grow, it must successfully evade the immune system. How this tumor-immune escape occurs remains one of the central questions in the field of cancer immunotherapy.

The microenvironment that develops around a growing tumor is immunosuppressive, and therefore is a major contributor to this immune escape. Within the tumor microenvironment, cancer-associated fibroblasts (CAFs) are important regulators of infiltrating T cells. CAFs produce much of the collagen inside and surrounding solid tumors, and are a major part of the tumor stroma. Our preliminary data shows that tumor-infiltrating lymphocytes are frequently found in direct contact with CAFs and the collagen produced by CAFs. However, the consequences of these interactions remain unknown. My project aims to study the interactions between CAFs, collagen, and lymphocytes and their effects on the activity of tumor-infiltrating T cells in mouse tumor models. Through image analysis, we have enumerated the CD8+ T cells making contacts with CAFs and collagen fibers and found that treating mice with an anti-fibrotic drug increases the amount of T cell infiltration into tumors. Future work will investigate the effects of CAF-T cell interactions on T cell activation states.

Zijian Wu
Molecular and Cellular Biology
Currier 2014

Quantifying the Roles of miR-29b and MCL-1 on Heterogeneous Drug Sensitivity

Joan Brugge
Department of Cell Biology
Harvard Medical School

While chemotherapeutic drugs that induce the death of replicating cells have shown efficacy in many types of cancer, their therapeutic efficacy is limited by their lack of specificity. As cancer research advanced, pathways overactive in cancer have been identified and more specific inhibitors have been developed. Even so, resistance to cell death occurs due to a variety of genetic and non-genetic mechanisms. One non-genetic mechanism that leads to drug resistance may involve stochastic differences in protein expression. It is known that resistance can also arise when alternate survival pathways are upregulated in the cell following inhibitor treatment

of one pathway. Previously, we found that a potent combination of BCL-2, EGFR, and P13K-alpha inhibitors induced cell death in only 10% of immortalized, non-transformed MCF-10A human mammary epithelial cells. These inhibitors were expected to potently induce apoptosis by neutralizing the BCL-2 family of proteins directly via BCL-2 inhibition or indirectly via Akt inhibition through the EGFR and PI3K pathways. However, associated with the resistance to this inhibitor cocktail was an unexpected drop in miR-29b levels in the population. Because miR-29b negatively regulates expression of the anti-apoptotic protein MCL-1, the resistance to these inhibitors may be due to maintenance or increase of MCL-1 levels via miR-29b reduction. This project aims to determine the inhibitor combination and dosage that maximizes the difference between MCL-1 degradation and anti-apoptotic miR-29b down regulation by separating and individually quantifying the kinetics and inhibitor dose responsiveness of Akt-dependent MCL-1 stabilization and miR-29b dependent MCL-1 degradation upon inhibitor treatment.

David Zhang
Applied Mathematics
Mather 2015

NAD+ Precursor as Therapeutic for Tumorigenesis

David Sinclair
Department of Genetics
Harvard Medical School

The hypoxia-inducible factors (HIFs) are transcription factors essential to changes in the cellular environment (oxygen, nutrients, and metabolites), conferring the cells the ability to change their metabolism and adapt to new environments, thus acting as important players in tumor initiation and tumor progression. Previous work in our lab has shown that under normal conditions, increases in nicotinamide adenine dinucleotide (NAD+), a common cofactor necessary for the activity of many enzymes, destabilizes hypoxia-inducible factor 1-alpha (HIF-1α) and allows cells to function and grow normally. Thus, we hypothesize that increasing NAD+ levels in cells derived from cancers by treating them with an NAD+ precursor, nicotinamide mononucleotide (NMN), will revert the metabolic changes characteristic of cancer cells and decrease their tumorigenic potential. To test our hypothesis, we study the proliferative potential of several cancer cell lines, in particular HeLa (cervical cancer), A549 (lung cancer), and HCT116 (colon cancer) in the presence and absence of NMN. By measuring the growth curves of these cell lines every day over the course of a week, we can test if treatment of NMN has a decreasing effect on the growth rate. If in fact NMN treatment does attenuate the proliferation of these cancer cells, measuring the survival rate (using trypan blue) will allow us to untangle whether NMN changes proliferation by making the cells more similar to non-transformed cells, or if instead NMN induces cell death. Non-cancerous fibroblasts will also be treated with NMN as well to test whether the effect is specific to cancer cells or rather is a non-specific effect. If the hypothesis holds true, the result could lead to an exciting and new strategy to treat cancer in patients.

Neuroscience and Psychology

Katherine Clements
Neurobiology
Leverett 2014

Spatial Memory Development in Infants

Charles A. Nelson
Boston Children's Hospital

Declarative memory, a cognitive function that allows us to remember facts and autobiographical events, is fundamental to our everyday life. This function emerges both before and after birth. Interestingly, the areas of the medial temporal lobe that subserve this function mature in a similar manner. For example, while the parahippocampal cortex is thought to be mature at birth, the hippocampal formation exhibits structural maturation postnatally. Few studies, however, have addressed how specific changes in brain structure and function might underlie the emergence of declarative memory processes.

In this study, we aim to determine the link between brain functional maturation and development of spatial memory, a fundamental component of declarative memory. To establish this connection, we used both electrophysiological and behavioral measures of two spatial memory abilities: egocentric spatial memory (locations coded in relation to the body) subserved by the parahippocampal cortex and allocentric spatial memory (locations coded in relation to the surrounding environment) subserved by the hippocampal formation.

This study provides the first electrophysiological and behavioral evaluation of developing spatial memory abilities. Given the abnormalities observed in the MTL structures and declarative memory processes in several neurodevelopmental disorders, it is particularly important to understand the normal development of this function and the brain structures that underlie it.

Wendy Melissa Coronado
Neurobiology
Mather 2014

Stria terminalis in First Episode Schizophrenia

Martha Shenton
Brigham and Women's Hospital

Schizophrenia has been described as a debilitating disorder, not simply defined by psychotic symptoms. Affective arousal impairment in the form of negative and positive symptom changes, sometimes comparable to mood disorders and depression at initial diagnosis, is linked to limbic and hypothalamus functional deficits. The stria terminalis fibers connect the hypothalamus with the amgydala, an important component of the brain's limbic circuitry. Given previous studies implicating other limbic structure changes and psychiatric measure changes, the stria terminalismay also show changes to white matter integrity, asymmetry, and the possibility of sex differences. Using diffusion tensor imaging, it will be possible observe alterations to this fiber tract, and provide further insight into early changes in the brain to schizophrenia.

As the nervous system ages cognitive functions such as memory decline, reflexes and mobility deteriorate, and the brain becomes more susceptible to disease. However, little is known about the molecular causes of these alterations. To begin to uncover these molecules, we have focused our analysis on the mammalian retina. The retina is an ideal system to undertake such studies as it is composed of identifiable populations of neurons whose circuitry underlies the first stages in visual processing. In addition, an aged retina recapitulates many changes observed in an aged brain, including alterations in neuron connectivity. Our studies have shown that photoreceptors, the light sensing neurons in the retina, are especially vulnerable to age-related changes. With age, the connections between these neurons rewire and become mislocalized, which may contribute to decreased visual function in the elderly. To uncover the molecules responsible for these processes, we are undertaking a series of studies using both microarrays and RNA-seq to compare the gene expression profiles of photoreceptors from young and old mice. In addition to elucidating the underpinnings of neuronal aging, these studies may identify pathways that could potentially aid in preventing or reversing neuronal miswiring with age.

Alden Green
Psychology
Quincy 2015

Relationship between legal codes and ethical conceptions

Yuval Feldman

The impact laws, rules, and standards have on people's behavior is determined in large part by a variety of subtle factors that many do not consider when they write these rules in the first place. Factors such as ambiguity, specificity, personal appeal, examples, and even graphics can all have an effect on how people respond to regulations; specifically, to what level they act in implicitly corrupt ways. Our research this summer spanned several projects, unified by the common theme of better understanding how instructions influenced both people's ethical perceptions, and their subsequent behavior.

One project dealt with the impact of purposefully ambiguous language. Subjects were asked to answer a series of questions, and were given various incentives, such as cash or an appeal to ego, to get questions right. Subjects were allowed to choose how many hard and easy questions they were answered, and told to choose a "reasonable mix" of the two. We then studied how time restrictions, incentivizing selfish behavior, and a requirement of justification affected subjects' implicit corruption, measured by how many more easy questions they answered.

Other projects included an examination of the effects of specific instructions on subjects' performance in a task requiring them to edit a document, the relationship between ethical instructions and performance in a test of a creativity, and the effect various aspects of corporate codes (such as personal appeal and harshness) had on the level of ethical compliance of employees.

Alexandra Haber
Neurobiology
Kirkland 2014

Neural Correlates of "Set" Expertise

George Alvarez
Vision Lab
Harvard College

Visual perception is a complex process that consolidates information at multiple levels. The brain detects lines, combines them into shapes, and then processes those shapes and their spatial relationships in higher visual areas like the fusiform face area, a region selective for faces, and the lateral occipital complex, a region that responds to objects. An important form of visual processing performed by the human brain is complex pattern recognition - we solve puzzles and parse information rapidly and abstractly, and we often improve dramatically in these tasks with practice (reading is a good example). An interesting manifestation of this ability is the popular card game Set, which requires rapid recognition of groups of three cards where each of their four characteristics (color, number, shape, and shading) is either all the same or all different across the three cards. Applying this rule, faster players find more "sets" more quickly and thereby win the game, and the speed of these Set experts can be quite impressive - they can recognize the rule-based groupings of cards at a speed that would not seem to allow sequential perception of each relevant feature. These experts seem to have formed a more holistic representation of the "set" concept, possibly by adapting a higher visual brain area to form an intermediate percept or by training it to integrate all the visual features extremely quickly. It is unknown where in the brain this rapid computation or holistic processing occurs, but fMRI may help determine the answer. Here we have expert Set players undergo fMRI while viewing "sets" and "nonsets," as well as single-card displays, to try to pinpoint the neural locus of their perceptual expertise. Identifying such an integration area may lead to further insight into complex and abstract visual processing in the human brain.

Vivian Hua
Neurobiology
Leverett 2016

Observation and Quantification of the Maternal Behavior of Mice in a Semi-natural Enclosure

Catherine Dulac
Harvard College

Maternal action plays an important role not only in the growth of infants, but also in their physiological and psychological developments into adulthood. The maternal behavior of mice have been studied extensively in laboratory settings, and although these studies have revealed basic mammalian behaviors, the full repertoire of their maternal characteristics is likely more diverse and has not been fully explored, especially in the context of a natural environment.

In this two-part project, we aimed to observe and quantify the maternal behavior of mice in a semi-natural environment. Firstly, we sought to archive a full collection of maternal behaviors in a large enclosure, which represents an enriched, semi-natural environment. Our round-the-clock observation of four female C57BL/6 mice allowed us to document a rich repertoire of behaviors, which will be useful for future behavioral studies involving animals with social behavioral deficits.

Secondly, we sought to establish a semi-automated quantification of maternal behaviors. To this end, we established an experimental system that not only allowed the precise measurement of the amount of time each adult mouse spent exhibiting specific behaviors, but also enabled long-term computer-assisted automatic trakcing of up to three individual mice.

These results, taken together, form an important basis for future studies, in which we hope to compare and contrast the maternal behaviors of genetic knockouts against wildtype mice, parturient females against nulliparous females, or related mice against unrelated mice—thereby further elucidating the environmental factors and neural circuits that regulate the maternal behavior of mice in a social colony.

Riley Kessler
Neurobiology
Currier 2014

Identifying Cell Surface Receptors in the Vagus Nerve

Stephen Liberles
Harvard Medical School

The vagus nerve is critical for monitoring a variety of physiological states in the body to coordinate autonomic, immune, endocrine and behavioral responses. For example, vagal afferents detect trachea and lung irritation to regulate the cough reflex, monitor changes in blood pressure and pH to regulate respiration and heart rate, and respond to gastric distention and intestinal nutrient perfusion to regulate feeding behavior. Named for its "wandering" trajectory, the vagus nerve travels from the brain through the thoracic and abdominal cavities innervating many visceral tissues. The majority of vagal fibers are sensory afferents and have their cell bodies located in the nodose ganglion, just outside the base of the skull.

Currently, little is known about the specific repertoire of sensory mechanisms residing in vagal afferents or the diversity of vagal cell types transmitting signals from the periphery to the brain. Defining the cell-surface receptors expressed by vagal afferents can enhance our understanding of their receptive fields. Additionally, the Liberles Lab is utilizing receptor expression as a foundation to query the functional and anatomical organization of the vagus nerve. To complement these efforts, I have selected candidate cell-surface receptors and cloned them from nodose cDNA to confirm their expression in vagal afferents. Ultimately, I will use RNA in situ hybridization to examine the expression patterns of these genes within the nodose ganglion. This will help build a molecular framework to better understand vagal sensory neurons and supports ongoing studies aimed at dissecting the diverse physiological roles of vagal afferent neurons.

Austin W. Lee
Undeclared
Dunster 2016

Optimizing a Robust Screen to Assess Activation of BDNF-TrkB Signaling Pathways

Lee Rubin
Harvard Stem Cell Institute

Huntington's disease (HD) is a debilitating, neurodegenerative disorder that affects 1 in every 10,000 people. An autosomal, dominant disorder, HD is genetically inherited and results from an expansion in the CAG triplicate on the Huntingtin (HTT) gene, that codes for the Huntingtin protein (htt). There is currently no cure for HD or available treatment to slow its progression.

A significant area of interest is the impact mutated htt has on the brain-derived neurotrophic factor (BDNF) - tyrosine kinase receptor (TrkB) signaling pathway. The BDNF-TrkB phosphorylation cascade is a crucial cellular process that plays a fundamental role in neuronal survival, plasticity and morphogenesis. It has been reported in mouse models and in human postmortem brains that the htt mutation reduces the level of BDNF in the striatum, the area preferentially damaged in HD. The dysfunction of the BDNF-TrkB signaling leads to faulty neuronal processing and phenotypic attributes associated with HD, such as chorea. Therefore, identifying therapeutic molecules that restore complete activation to the BDNF-TrkB phosphorylation cascade is of interest. In preparation for a prospective screen, this summer I worked on optimizing a robust protocol that would quantify BDNF-TrkB signaling activation. Through rat hippocampus neuron cultures, plate treatments, antibody staining and image analysis, I delineated a set of parameters for time trial length, positive control identity and concentration, chemical conditioning and protein readout that best indicated pathway activation. These criteria will likely serve as guidelines for assessing future screens.

Chloe Li
Neurobiology
Winthrop 2016

Investigating the Misregulation of Genes in Visual Cortex of MeCP2 Knockout Mice Using Quantitative Real-time Polymerase Chain Reaction

Michela Fagiolini
Boston Children's Hospital
FM Kirby Neurobiology Center

Rett syndrome (RTT) is a neurodevelopmental disorder caused by loss-of-function mutations in the X-linked gene methyl-CpG-binding protein 2 (MeCP2), which codes for a transcriptional modulator. Typically, RTT afflicts girls and produces neurological symptoms such as regression or loss of language, motor skills, and cognitive skills following a period of outwardly normal development. Mouse models lacking Mecp2 recapitulate RTT symptoms. In Mecp2-null mice, defective synaptic circuitry, abnormal dendrite morphology, and altered excitation-inhibition balance are typical. The Fagiolini lab recently demonstrated that, in Mecp2-null mice, regression in cortical visual function occurred with the appearance of the RTT phenotype. Importantly, hyperconnectivity of parvalbumin-positive (PV) interneurons to excitatory neurons and silencing of visual cortical synaptic circuitry precedes regression in visual acuity. Transcriptome analysis at three critical stages in visual cortex development, postnatal days 15 (P15), 30, and 60, revealed progressive misregulation of gene expression. By P60 there were approximately 600 misregulated genes, an increase of a factor of 10 from the number misregulated at P30.

Using the GeneCards database, we selected 60 candidate genes based on their relevance to RTT, related neurological disorders, and circuit function. Using quantitative polymerase chain reaction, we are evaluating the expression profile of these 60 genes in visual cortex homogenate of WT and KO littermates at P15, P30, and P60. Fluorescence activated cell sorted (FACs) PV cells will then be analyzed. Results of these experiments will serve as a first step in elucidating the gene expression dynamics in the circuitopathy of RTT

Andrew O'Rourke
Biomedical Engineering
Currier 2016

Investigating Invariant Object Recognition

David Cox
Molecular and Cellular Biology
School of Engineering and Applied Science
Harvard College

The best machine known to man capable of visually recognizing objects is the human brain. It follows that the best way to design an artificial visual system would be to study the brain and discover how it performs such sophisticated object recognition. This summer at the Cox Lab, I have been involved in performing research using rats that helps us uncover the inner workings of mechanisms in the brain that result in our amazing ability to recognize faces and other objects. Using rats to study vision was not accepted in the scientific community until Dr. David Cox and other scientists proved that rats do in fact have sophisticated visual systems (Zoccolan et al. 2009). The hope is that this reverse engineering of the rat brain will aid computer scientists in their efforts to forward engineer computer visual systems to be more accurate. With well-trained rats, we can learn a lot about how particular cells in the region of the brain thought to be involved in object recognition react in different visual situations through experiments involving two-photon imagining, optogenetics, and electrophysiology. In particular, the Cox Lab is interested in invariance, which refers to the ability of both rat and human brains to recognize novel images. If the rat brain's mechanism for doing so was better understood, we could more easily find a way to give computers that same ability.

Youkyung Sophie Roh
Neurobiology
Mather 2014

Enhancement of Poststroke Recovery Through Promotion of Plasticity in Lynx1-KO Mice

Takao Hensch and Larry Benowitz
Boston Children's Hospital

Although stroke is ranked as the third leading cause of death worldwide, most patients in fact do not die from their first incidence of stroke. They survive, but on a heavy price. In the United States alone, stroke forces 7 million survivors to live with varying degrees of motor and cognitive impairments.

Fortunately, these varying levels of burden of stroke also imply that there is a varying degree of recoverability. Indeed, stroke patients experience partial spontaneous recovery during a short window of time following the event, suggesting that the damages to neuronal networks due to hypoxia can be undone during this critical period, albeit limitedly, as neurons rewire together and new synapses are formed, providing alternate pathways that compensate for lost tissues.

Our research thus strives to go beyond the currently available forms of stroke treatment, such as anticoagulants and rehabilitation, and enhance the recovery process by extending the critical period. We focus on Lynx1 protein, recently identified as a promising target of study in the visual and motor learning system. A naturally-occurring prototoxin, Lynx1 modulates signaling by inhibiting nicotinic acetylcholine receptors (nAChR). While acting as a protective agent against nicotine, epilepsy, and neuronal deaths, Lynx1 also serves as a brake to synaptic plasticity; Lynx1-KO mice have been demonstrated to exhibit a longer delay before the closure of the critical period.

We plan to examine whether the use of Lynx1-KOs or cholinesterase inhibitors (i.e. physostigmine and Donepezil) has an effect in promoting recovery after ischemic stroke by prolonging the critical period. We plan to focus on motor impairments, and have identified and developed behavioral tests that are sensitive enough to quantify the fine details of motor functions, including the skilled forelimb-reaching task, cylinder test, and a modified water T-maze test. The use of FDA-approved drugs imply that, should current research on animal models seem promising, they will be easily applied to human clinical trials in the near future.

Aida Octavia Rocci Ruiz
Psychology
Kirkland 2014

Understanding Co-experience

Daniel Gilbert
Harvard College

When people want to enjoy an experience, they do it in company. Humans are social creatures and as such we have a special sensibility to what we do with others. My thesis investigates the effect of co-experience, the mere belief that we are having the same experience as someone else at the same time has. One salient question about co-experience is whether it affects how we feel during the experience. Another is how it impacts our connection to the other person having the experience.

Previous studies by Burum and Gilbert suggest that when two people share an experience, they rate the experience as more intense than if they were experiencing it alone. However, we do not know what happens when people do not share all aspects of the experience, what we call partial co-experience. Because people have an epistemic need to have similar knowledge of the world as the people around them, I hypothesized that when two people are sharing a slightly different experience, they expect the other person to have a different opinion, and thus rate the experience as less intense and do not feel as connected. My first thesis study found an interaction with sex, and the predicted pattern of affect in males, and of connected in females. The follow-up study focuses on females, and tries to understand better how affect is influenced by increasing levels of co-experience.

Vera Say
Neurobiology
Eliot 2014

Neural Correlates of Visual LTM

George A. Alvarez
Vision Sciences Laboratory
Harvard College

A vital component of human experience, long-term memory (LTM) facilitates the cultivation of a collective conscience, enables the formation of meaningful, reciprocal relationships, and gives rise to nostalgia. The improper functioning of visual LTM can irreparably hinder the lives of individuals with serious memory disorders or aging brains. Although researchers have qualitatively demonstrated that subjects discern subtle object variations after encoding thousands of stimuli into LTM, the fidelity with which subjects store object representations has not been quantified. Using the CIE lab color space, a continuous report metric that consists of an optimized color wheel, this research project examines memory for subtle color differences as a proxy for quantifying feature detail in LTM representations.

While the hierarchical processing theory of visual perception posits that upstream areas along the visual processing stream store more abstracted representations of object features, researchers have yet to address how the encoding locus of a memory is related to the level of detail stored for a specific object feature. To investigate the neural correlates of visual LTM fidelity through fMRI, this project characterizes presented stimuli as those that subsequently elicit high-fidelity memory, low-fidelity memory, or are completely forgotten. By examining brain activity during encoding under each of these conditions in V4, an area implicated in color representation, and VO1, an upstream fusiform gyrus area that contains higher-level color representations, this project seeks to identify correlations between the localization and fidelity of visual memory traces. This research investigates how patterns of activity during encoding ultimately impact our ability to retrieve stimuli details long after presentation.

Marc Shi

Neurobiology
Adams 2014

Using Phase-Amplitude Coupling to Isolate Biomarkers of ASDs in Infant EEG

Charles Nelson
Labs of Cognitive Neuroscience
Boston Children's Hospital

Autism Spectrum Disorders (ASDs) are characterized by repetitive behaviors and deficits in social communication and interaction that persist from childhood. Currently, there are no biological diagnoses for ASDs, and diagnoses are made either clinically or behaviorally with tools such as the Autism Diagnostic Observation Schedule (ADOS). Previous research has shown that the baseline electrical activity in the brain, as measured through electroencephalography (EEG), differs between those at high and low risk for autism before diagnosis. Furthermore, recent findings have shown that the level of coupling between the phase of low-frequency and the amplitude of high-frequency oscillatory activity in the brain can be used to distinguish adolescents with and without confirmed autism diagnoses. However, there is not currently any research examines whether phase-amplitude coupling may also be atypical in infants at high risk for autism or who go on to develop an autism diagnosis. As differing frequencies of oscillatory activity have been associated with a variety of cognitive functions, examining this activity in children that go on to develop ASDs may shed light on the mechanisms driving the disorder. Furthermore, by analyzing the phase-amplitude coupling between the low and high frequency bands in infant baseline EEG, we hope to be able to isolate predictive markers of autism that appear before diagnoses are typically made, allowing for earlier diagnosis and intervention.

Taehwan Shin
Neurobiology
Currier 2015

Evaluation of Candidate Ligands on Amyloid Precursor Protein Processing Using Human Induced Pluripotent Stem Cells

Dennis Selkoe
Department of Neurology
Brigham and Women's Hospital
Harvard Medical School

The Amyloid Precursor Protein (APP) is initially processed by α- or β- secretase to generate APPsα or APPsβ. Further cleavage by γ-secretase results in Aβ, which has been implicated in Alzhiemer's Disease. To study the normal function and processing of APP, we have investigated the effect of candidate ligands on APP processing in numerous cell lines and found Reelin, Lingo-1, and Pancortin have the most robust effects. However, their role in human neurons, as well as their underlying molecular mechanisms, remains unclear. Here we have used neuronal precursor cells (NPC) and neurons derived from human induced pluripotent stem cells (hiPSC) and overexpressed or knocked down of interest to observe the effects on APP processing.

Using AMAXA nucleofection, I was able to overexpress Pancortin, Reelin, and Lingo-1 in NPCs. For Pancortin, we found an isoform specific reduction on APP processing, as we did in other cell lines. Lingo-1 overexpression lowered APPsβ levels as expected from results in other cell lines, but unexpectedly produced no changes in APPsα.

We have also developed a protocol to knockdown specific gene targets using lentiviral transduction. To optimize conditions, we used shRNA constructs for APP and confirmed knockdown by qPCR and ELISA. We obtained almost complete knockdown of APP in NPCs and 50% knockdown in neurons. Multiple shRNA constructs have now been validated, including the top candidate ligands and their signaling pathways, to further investigate potential mechanisms involved. Understanding of the role of these ligands could open up novel drug targets for the currently untreatable disease.

Advik Shreekumar
Undeclared
Leverett 2016

In Vivo Antimicrobial Activity of the Amyloid-β Peptide

Rudolph Tanzi
Department of Neurology
Massachusetts General Hospital

The amyloid β (Aβ) peptide is canonically cast as the central molecule responsible for pathology in Alzheimer's disease (AD) for its role in synapse loss and brain inflammation. However, little consideration has been given to the natural role of Aβ in the body. Recent research has revealed that Aβ has potent antimicrobial activity resembling that of LL-37, a naturally occurring human antimicrobial peptide. We are investigating this property in vivo using two mice models: nontransgenic (NonTg) controls and 5xFAD diseased mice. 5xFAD mice carry five separate human Alzheimer's mutations and aggressively produce Aβ from an early age. We induce encephalitis in both groups via a hippocampal injection of Salmonella typhi, and track the progression of the infections using a combination of clinical scores, physical testing, change in mass, and change in body temperature. Preliminary results show that 5xFAD mice outlast NonTg peers and maintain a higher standard of health, indicating that Aβ may confer a protective effect.

These findings suggest that AD therapeutics should shift away from suppressing overall Aβ production and toward modulating its expression levels. Aβ is secreted as the result of a variable processing event that can produce short peptides of 38-43 amino acids, with increased levels of Aβ42 associated with AD. Rebalancing the expression ratio to favor Aβ40 and other products may strike a more favorable balance between combating AD pathology and maintaining a healthy immune response.

Nina Sokolovic
Neurobiology
Adams 2014

Socioeconomic Status and the Development of Executive Function

Margaret Sheridan
Boston Children's Hospital
Harvard Medical School

Childhood socioeconomic status (SES) is an important determinant of cognitive performance throughout life. In particular, research has shown that children from low SES backgrounds perform poorer on executive function tasks, a factor which may be involved in the inter-generational cycle of poverty. There are at least two different explanations for this finding: first, that these differences are a product of how SES background impacts motivation to perform in research settings, or second, that these differences are associated with neural correlates in the pre-frontal cortex, the region of the brain associated with executive function skills such as inhibition and working memory.

My project at the Sheridan Lab has been to investigate these potential explanations. At the Children's Hospital Primary Care Clinic, I have been collecting SES data from parents while running a randomized control trial, asking children to complete executive function tasks for which they are told either that they will earn a sticker regardless of their performance, or that they will be able to earn a $10 toy if they perform exceptionally well. My preliminary findings suggest that incentives and parental income interact significantly to affect performance. Specifically, children from low SES backgrounds perform poorer when given incentives, whereas the opposite effect is observed in high SES groups. Additionally, I have also been collecting structural MRI data from children to determine whether SES predicts brain volume in regions of the pre-frontal cortex. The ultimate goal of this work will be to better understand how and why childhood SES affects cognitive performance.

Viet Dinh Tran
Neurobiology
Winthrop 2016

Determining Neurotoxicity of Long Amyloid Betas

Michael Wolfe
Department of Neurology
Brigham and Women's Hospital

Studies on Alzheimer's disease have failed to address the role of long amyloid betas (Aβs) in AD brains. These longer forms of Aβ are not only precursors to the secreted 42/40 Aβ forms, but can also remain untrimmed by γ-secretase and held in the membrane. This study aims to investigate whether these long Aβ's are neurotoxic and capable of inducing any pathological changes to tau, a central protein in microtubule integrity. Gene constructs for C-terminally truncated Amyloid-Beta Protein Precursors (APP) modified to produce Aβ 45, 46, 48, and 49 will be used to express these proteins in N2A cells. The gene expression will be controlled using the Tet-on system, in which the addition of doxycycline induces the cells to express said genes. Cells will be treated with γ-secretase inhibitors to ensure the long Aβs are not processed into shorter forms, which would keep the proteins in the cell membrane. The cytotoxicity of the cells will be measured by examining LDH release at set intervals. It is hoped that the experiment will reveal any neurotoxic effects long Aβ possess, which might be higher due to their proximity to the cell membrane. If further tests of long Aβ in N2A cells reveal neurotoxicity, then tests will move on to human blastoma cells, which provide a better representation. If long Aβ's are indeed neurotoxic, the progression of AD will be better understood since levels of Aβ plaques in AD brains do not correlate well with disease progression while levels of long Aβ's do.

Jennifer Tu
Neurobiology
Lowell 2016

Modeling the Astrogliosis of Alzheimer's Disease with Human Stem Cells

Tracy Young-Pearse
Brigham and Women's Hospital
Harvard Medical School

Alzheimer's disease (AD) is the world's leading cause of dementia, but the mechanisms underlying its pathogenesis remain unclear. To characterize AD-relevant phenotypes at the cellular level, we have generated neuronal cultures from familial Alzheimer's disease (fAD) patient-derived human induced pluripotent stem cells (hiPSCs). Although fAD constitutes less than 1% of clinical cases, its genetic basis is the most clinically relevant platform on which researchers hope to determine mechanisms and devise therapies for all forms of AD.

Our previous studies had established an in vitro system showing that the London fAD amyloid precursor protein (APP) mutation (V717I) leads to pathological increases in amyloid beta 42/40 and Tau expression in forebrain neurons. Here, we adapted this system to determine whether and how astrogliosis, the reaction of astrocytes to CNS injury or neurodegeneration, contributes to AD. We observed an increase in glial fibrillary acidic protein (GFAP), an established marker for activated astrocytes, showing higher astrogliosis in fAD neuronal cultures compared with healthy controls. However, we observed no change in a general marker of astrocyte fate, S100 calcium binding protein B (S100B), suggesting that phenotypic changes, rather than cell proliferation, underlie astrogliosis.

It is surprising but exciting that our system can model astrogliosis, since this aspect of AD can appear several decades after onset of the disease. We plan to further investigate whether the cell autonomous effect of fAD is due to neuronal or astrocytic changes. In addition to elucidating the mechanisms of astrogliosis, a process highly related to plaque pathogenesis, neuritic dystrophy, and cognitive decline, these studies may identify pathways to target the symptoms of Alzheimer's disease.

Octavio Viramontes
Neurobiology
Quincy 2015

Characterizing Sensitization of TRPV1

Clifford Woolf, M.D., Ph.D.
Director of the F.M. Kirby Neurobiology Center,
Children's Hospital Boston
Professor of Neurobiology, Harvard Medical School

Temperature sensing ability in animals and humans is necessary and essential to their survival. The transient receptor potential (TRP) ion channel family is important for sensing temperature. TRPV1 is a heat-activated TRP channel that is located chiefly in sensory neurons triggered by temperatures higher than 42 °C, cap-

saicin, acidic pH, and other endogenous agonists. Sensitization of the TRPV1 receptor is considered an important molecular mechanism for inflammatory sensitization. Studies in knockout mice of TRPV1 show decreased inflammation and thermal hyperalgesia. Also, local pharmacological activation of TRPV1 through saturation of capsaicin concentrations results in analgesia. We introduce sensitizers and antagonists to the TRPV1 receptor to better understand the molecular pathways involved in its sensitization. Using Ca2+ imaging techniques on both a traditional microscope and in a high-throughput imaging system, we looked at the different characteristics of sensitization of TRPV1 in the dorsal root ganglion (DRG) cells.

We first looked at the dose response sensitization of a sensicocktail to understand the kinetics of activation and sensitization of TRPV1. This was done via a high-throughput imaging system Hamamatsu FDSS7000EX. The main result is that capsaicin sensitization is best seen at sub-maximal agonism. At lower concentrations of capsaicin-based activation, we see stronger, activation. Therefore, it's less about the sensitizer, and more about capsaicin. We began a systematic microscope-based interrogation of various sensitizing compounds to acquire results with increased resolution and information. Moreover, we were particularly interested in wortmannin, a potential sensitizer to our channel.

Michelle Wang
Neurobiology and Women and Gender Studies
Quincy 2014

Long-term Consequences of Social Defeat in Hyper-aggressive Bully Flies

Edward Kravitz
Harvard Medical School

Animal behavior is greatly influenced by both genetics and experience. In "bully" Drosophila melanogaster bred over 35-40 generations for hyper-aggressive behavior, researchers have found that social interactions such as defeat in male-male fights seem to trigger a learning and memory mechanism. However, the persistence of the effects of experience-based memory mechanisms of social defeat in fighting behavior in Drosophila is not yet known. Normally, bully flies have a competitive advantage of winning about 80% when fought against wild-type Canton S flies. After experiencing social defeat, in a second fight fought 30 minutes later against Canton S, bully flies lose this competitive advantage. In the proposed study, we ask if the learning mechanism associated with social defeat, the "loser mentality," is a permanent effect by running second fight experiments at different time intervals. We demonstrate that the loser mentality is indeed an experience-based phenotype by showing that bully flies do in fact "forget" their loser mentality and return to their hyper-aggressive state 24 hours after their defeat. We also tracked the behaviors exhibited in the first and second fights to study what experiences build a loser mentality and how those experiences change a loser's second fight fighting strategy, respectively. We found that loser flies that experienced more mid to high intensity interactions, such as lunging and boxing, won significantly more second fights. We also found that in comparison to winners that win their second fight, losers than win their second fight have significantly less encounters in their second fight.

Nivanthika Wimalasena
Chemical and Physical Biology
Winthrop 2014

The Potential Neuroprotectivity of GW8510 in Response to Cellular Stress

Stuart Schreiber and Rakesh Karmacharya
Broad Institute of MIT and Harvard

Parkinson's disease (PD) is primarily characterized by significant dopaminergic cell death in the substantia nigra that leads to cognitive and motor decline1. The Cdk (cyclin-dependent kinase) 2/5 inhibitor known as GW8510 (GW) was chosen out of a set of compounds that were computationally screened for a gene expression profile opposing a PD expression profile compiled from the literature. Existing literature2 and preliminary work has shown that this compound is neuroprotective in response to cellular stress in cultured neuronal rat cells and a dopaminergic rat cell line. In the proposed research I will examine whether this effect is seen in human neuronal and neural progenitor cells (NPCs). To do this, I will probe the types of cellular stress for which this compound is protective using several sets of toxins that 1) selectively induce mechanistically distinct types of cell death, 2) cause disease phenotypes of various neurodegenerative disorders, 3) cause organelle-specific stress, or 4) cause excitotoxicity. Ultimately, I will attempt to discover whether any observed neuroprotection conferred by GW is cell type-specific and whether it is contingent on the type of stress applied. These studies will enable a better understanding of the specificity and scope of the protection conferred by GW and may provide insight into the mechanism of action of the compound.

Linda Buwei Xu
Neurobiology
Eliot 2016

Tracing synaptic connectivity in the mouse thalamus

Jeff Lichtman
Department of Molecular and Cellular Biology
Harvard College

Despite the rapid advancement of neuroscience research in recent decades, the link between structure and function in the brain remains elusive, largely due to the unique complexity and plasticity of neural circuits. However, with the development of high-resolution automated electron microscope imaging, it has become possible to construct extensive maps of neural connectivity in the brain. In the Lichtman Lab, work is being done specifically on the mouse thalamus to trace the thalamic synaptic connectivity between the retina and the cerebral cortex.

As this will be the first map to study the synaptic connectivity of such a large number of cells within a single area of the central nervous system, it is doubtless that this project will reveal a wealth of information about the organization and connectivity of cells in the brain. Furthermore, not only will this project trace the connectivity of one class of neurons to another, but it will also further explore how neurons of a single class distribute their synapses among different post-synaptic targets. The manual tracing results produced in this project will also be used to train automated tracing programs to distinguish membranes and synapses, thus facilitating the transition from manual tracing to automated tracing and making the brain-mapping process more efficient. Our hope is that creating

these structural maps of neural circuits will be the first step in elucidating the links between structural organization and pathological function in the brain.

Connie Zhong
Neurobiology
Adams 2014

Characterizing the Role of Cholinergic and GABAergic Neurons in C. elegans Gait Control

Yun Zhang
Harvard College

The ability for an animal to sample the environment during forward locomotion is critical for its survival. In the nematode Caenorhabditis elegans, such behavior can be mediated by its head deflections. During foraging, the tip of the animal's head moves side-to-side in a sinusoidal motion, which may provide sensory information to guide the direction in which the animal proceeds. Thus, gait control for head deflection is important for optimal sensorimotor response.

Previous studies have postulated that excitatory cholinergic SMD motor neurons and inhibitory GABAergic RME motor neurons play an important role in modulating foraging behavior. Worms with ablated RME neurons display exaggerated head bends, suggesting that RME neurons limit the amplitude of head bending, while worms with defective SMD signaling display stiff head movement, suggesting that SMD neurons positively regulate head deflection. Despite these observations, the exact interactions between cholinergic and GABAergic neurons in gait control is still unclear.

To investigate the relationship between these two types of neurons, we are examining their calcium activity during head bending and their relevant receptors. Intracellular calcium imaging has suggested that SMD neurons depolarize muscles on one side of the head, while RME neurons hyperpolarize antagonistic muscles on the contralateral side to generate optimal gait. We hypothesize that SMD activity drives RME activity to promote head bending and that reciprocally, RME neurons inhibit SMD activity to restrain head bending. By performing genetic rescue experiments and behavioral assays, we hope to elucidate the neuronal mechanism underlying C. elegans gait control during foraging.

Organismic & Evolutionary Biology

Emily Alana Burke
Organismic and Evolutionary Biology
Lowell 2014

Phylogeography of Bdellouridae: Genetic diversity and population structure of commensal flatworms

Gonzalo Giribet
Museum of Comparative Zoology
Harvard College

Bdellouridae is a family of marine planarians (Platyhelminthes, Triclada, Maricola). I will be working within the family Bdellouridae on the species Bdelloura candida and Bdelloura propinqua. These species live ectocommensally on the book gills and appendages of the Atlantic horseshoe crab, Limulus polyphemus, feeding on food debris. Bdellouridae are excellent organisms for phylogeographic research for several reasons. Bdellouridae have little capacity for dispersal and cannot survive independently. Without a larval stage, the marine triclads develop directly from egg capsules attached to the book gills of L. polyphemus and are often restricted to living on their original host. Geologic events have also had a major influence on the speciation of marine triclads. Bdellouridae have been appearing in scientific journals since their discovery in the mid-1800s, but are generally understudied. My research on the phylogeography of Bdellouridae involves analyzing their genetic diversity, population structure, and geographic distribution. There are many questions that can be addressed by this research: How is the genetic diversity of Bdellouridae structured? Is there an isolation by distance pattern in the phylogeography of B. candida? Does symbiont phylogeography closely mirror host geography, or will it be more restricted (perhaps relating to the life cycle of the organism?) Can genetic diversity be related to latitude or geological breaks (e.g. between the gulf and the east coast)? Are there cryptic species in these symbionts (a common phenomenon in similar systems), and if so, how are those cryptic species distributed in space and time? Studies of genetic variation and geographic differentiation have been conducted on Limulus but not on most members of Maricolan flatworms.

Josh Fries
Organismic and Evolutionary Biology
Mather 2014

Adaptive Radiation of Vollenhovia on Vanuatu

Naomi Pierce and Christian Rabeling
Department of Evolutionary Biology
Museum of Comparative Zoology

Adaptive radiation is the process of one group of organisms spreading out and undergoing speciation to become a multitude of distinct and separate species. This phenomenon is especially prevalent when a group is introduced to a new island that has not been colonized to its capacity. Doctor Christian Rabeling and Doctor Ed Wilson traveled to Vanuatu and collected more than ten thousand ants, and the idea that some ants could be used for a study in adaptive radiation was born.

The genus Vollenhovia is mostly concentrated in Southeast Asia, Australia and the Pacific Islands. The group is well represented on Vanuatu, both in number of species and number of organisms collected. After an extensive process of sorting through the ants, labeling, counting and databasing, the ants of Vanuatu from two separate trips are documented and preserved. We are analyzing the members of the genus Vollenhovia not only from the collecting done on Vanuatu, but also from the collections of other scientists on the nearby islands Australia, Papua New Guinea, New Caledonia, Philippines and Fiji. We are extracting the DNA from a representative over 100 collection sites and sequencing multiple genes to create a basic phylogeny of the Vollenhovia. From there, we can compare the relatedness of Vanuatu organisms to the outside groups. If the Vollenhovia on Vanuatu are more closely related to each other than on other islands, it is likely that they descended from a single colonizing event on the island, and proliferated through adaptive radiation

Physics & Biophysics

Mark J. Arildsen
Undeclared
Currier 2016

The Effect of Addition of Charge on the Electrorheological Behavior of Silica Particles in Oil

David A. Weitz
Harvard School of Engineering and Applied Sciences

Electrorheological fluids (ER fluids) are dispersions of particles in non-aqueous solvent that exhibit changes in properties such as viscosity upon application of an electric field. These fluids see applications in everything from car brakes and shock absorbers to flow control in microfluidics. After looking at a variety of candidate fluids, we decided to explore a system of 1μm diameter silanized silica particles in canola oil or silicone oil. These solvents were able to disperse the silica particles well, and they exhibited a strong ER effect.

The mechanism behind the ER effect is the formation of aggregated chains of particles along the field lines that impede flow. Microfluidic devices with various electrode configurations were fabricated to allow the examination of this structure across microscopic channels. The fluids were dyed with Nile Red, a fluorescent dye, and viewed by confocal microscopy. The images captured by this method allowed for particle tracking and quantitative examination of chain structure.

The variation in the ER effect due to the addition of aerosol-OT (AOT), a surfactant that adds charge to the system, was also examined. Various concentrations of AOT were added to the canola oil system. (Silicone oil and AOT did not mix.) Conductivity measurements were taken to quantify the amount of charge added, and to determine the extent to which the particles were charged. The comparative strength of the ER effect was also observed directly by confocal microscopy.

Aftab Chitalwala
Physics and Mathematics
Lowell 2016

Homogenous bubble nucleation in Si3N4 pores

Jene Golovchenko
Department of Physics
Harvard College

Despite its ubiquity in nature and industry, there is a surprising lack of understanding of homogenous nucleation in metastable liquids. Homogenous nucleation refers to the formation of new phases (e.g. vapour bubbles in water) in the bulk of a liquid rather than at an interface with another phase (typically surfaces of containers). The difficulty of reaching sufficiently high temperatures without provoking bubble nucleation at surfaces and the random location of these events create hurdles to experimentally investigating this phenomenon.

My experiments are setup using a pore (⊠1 μm in diameter) in a thin membrane of Si3N4 which separates reservoirs of an ionic fluid (3M NaCl solution). When a voltage is applied across the membrane, impedance to the resulting ion current develops over the pore. This leads to localised Joule heating that creates a small volume of superheated solution centred at the pore. At relatively high voltages (⊠10 V), short-lived, high-impedance disturbances are observed in the current-voltage trace, which appear to be bubbles when imaged.

My short-term aim is to develop a spatial and temporal profile of the temperature during a voltage pulse, while remaining below the threshold for bubble nucleation. I use Fourier optics to predict the results of optical lensing due to temperature-dependent refractive index changes within the solution and quantitatively compare them to experimental diffraction patterns captured using high-speed cameras. This should yield information about the characteristic size and temperature of the heating, and serve as a first-step towards performing similar analyses on the bubble nucleation process.

Casey Fleeter
Physics
Leverett 2015

Powering Penning-Ioffe Traps for Antihydrogen Atoms

Gerald Gabrielse
Department of Physics
Harvard College

Cold, ground-state antihydrogen atoms are produced within a Penning trap which itself is contained in an Ioffe trap. Future observations of these antihydrogen atoms through laser spectroscopy will ultimately test CPT and Lorentz invariance and possible differences in the gravitational force on antimatter and matter. The rig includes many BiasDACS and UberElvis devices, voltage output machines and high voltage amplifiers respectively, which routinely need to be repaired and calibrated to ensure proper output. The devices were thoroughly calibrated after data acquisition of each output channels' functionality, while broken channels were repaired via the internal circuit board.

Tudor Giurgica-Tiron
Physics
Pforzheimer 2016

Quantum Scattering of a Bose-Einstein Condensate off a Charged Nanotube

Lene Hau
Department of Physics
Harvard School of Engineering and Applied Sciences

The advancement of cold atoms technologies are allowing for fast and efficient creation and manipulation of Bose-Einstein condensates (BECs), a state of matter reached at temperatures of the order of nano-Kelvins in which the wavefunctions of bosons overlap such that they are in the same coherent quantum state. This allows for the study of quantum effects at macro scales (in our case, tens

of microns). In the Hau Lab, newly-developed methods allow for condensation of Rubidium atoms into BECs that can be directed towards different custom targets. One such experiment involves launching a BEC cloud into an electrically charged nanotube. The purpose of my project is to theoretically analyze the BEC-electric field interaction and to predict the outcomes of lab measurements, both analytically and numerically.

This experiment is particularly interesting due to the special effective potential obtained. In the approximation of the infinite linear charge, the electric field behaves as 1/r. However, the linear polarizability of the neutral atoms makes the effective potential 'felt' by the atoms in the BEC behave as an attractive 1/r2 law, which, due to scale invariance, poses significant mathematical difficulties. Just like in the case of a classical particle, we regain the fall to the center of particles in states of low angular momentum and the scattering of high angular momentum states. To test my theoretical predictions, I developed a 2D wavefunction simulator for the Schrödinger equation (and its non-linear extension for BECs, the Gross-Pitaevskii equation) in Mathematica using the Crank-Nicolson method for diffusion-like partial differential equations.

Ian Ochs
Physics
Eliot 2015

Novel Mechanism for the Crossing of Fitness Valleys in Higher Species

Michael Desai
Department of Organismic and Evolutionary Biology
Harvard College

To keep things simple, many models of evolution assume that the fitness effects of different genetic mutations are independent. Often, this assumption is safe, as the vast majority of phenotypic traits do not interact. However, there are certain situations where the interaction of epistatic effects cannot be ignored. For instance, mutations in the binding sites of a ligand and receptor will necessarily interfere, as will mutations at different sites in the core structural domain of a protein.

Such epistatic effects can create a fitness valley, so named because mutations that are individually deleterious combine to create a beneficial effect. Even if the end benefit is large, such valleys can be hard to cross, given the rarity of multiple-mutation events. Previous work has shown that larger populations can cross such valleys in a process known as stochastic tunneling, where a drifting single-mutant produces beneficial multiple-mutants without ever itself comprising a large portion of the overall population. Thus a large population will offer more opportunities to tunnel, and more quickly find the optimal genotype.

Our current research shows that even though the speed of fitness valley crossing does increase monotonically with population size, the probability that the fitness valley will be crossed in the presence of other beneficial mutations varies nonmonotonically with population size. Using both simulations and analysis, we show that the increased importance of neutral genetic drift in small populations increases the probability of fitness valley crossing, providing a possible mechanism for the evolution of complex traits in species, such as higher animals, that exist in smaller numbers in the wild.

Derek Robins
Physics and Astrophysics
Eliot 2014

Ground Loops: Detection and Elimination

Gerald Gabrielse
Department of Physics
Harvard College

Ground loops can be one of the most difficult types of electromagnetic interference to isolate and eliminate in experimental set ups that involve many different electronic components. Grounds loops can originate from accidental shorts between devices or equipment and flawed ground system design. A range of undesirable effects can result from ground loops including unwanted voltage fluctuations, data measurement errors, equipment damage, and electrical safety hazards. Ground loops can be found in a wide variety of electrical equipment including audio, video, medical, and scientific measuring instruments.

In ultra high precision physics experiments, measurements of the moments of electrons, protons, hydrogen and their antiparticles require highly sensitive electronics and minimal background noise, one source of which can be ground loops. Identifying and eliminating ground loops can be a time consuming, iterative, trial and error process that can often result in experiment interruptions.

Accordingly, a method was developed to identify and eliminate ground loops in physics experiments with minimal intervention using the commercially available LoopSlooth ground loop detector. This device allows easier troubleshooting of ground loops by inductively injecting a test current into a system ground through an instrument power cord and then detecting this test current elsewhere in the system if a loop exists. Once a ground loop is found, it can be eliminated by: removing an accidental short to ground, using devices such as an isolation transformer or optical isolator, or overhauling the ground system design.

Michael Sayegh
Physics
Adams 2015

Observing restructuring of the bacterial flagellar rotary motor in vivo

Howard Berg
Department of Physics and Molecular and Cellular Biology
Harvard College

Escherichia Coli swims by rotating corkscrew-shaped flagella attached to rotary motors. When all the motors rotate counterclockwise, the bacterium runs. When one or more motors rotate clockwise the bacterium tumbles. When a gradient of attractant or repellent is encountered, the frequency of tumbling changes. In this way the cell performs a random walk with drift up or down the gradient of attractant or repellent, respectively. Changes in levels of attractant or repellent translate to changes in the levels of an intracellular signaling molecule called CheY-P, which binds the motor and induces switching of the direction of rotation of the motor. Since CheY-P binds cooperatively to the motor, the range of the motor response to the signaling molecule is narrow. However, due to cell-to-cell variation, the background value of CheY-P is often outside the range of motor response. The motor resolves this problem by changing the number of its constituents. In other words, the motor

restructures itself on the fly to respond to the background level of CheY-P concentration. Thus it remains sensitive to small changes of attractant or repellent even if the background concentration occurs initially outside its range of response. Our project consists of probing for this kind of adaptation in a motor protein called FliN. We obtained bacterial strains with fluorescently labeled FliN, and we observe changes in motor fluorescence in vivo while changing the concentration of attractant. Thus, we observe live remodeling of the complex flagellar rotary motor.

Olivier Simon
Physics
Currier 2016

Toward a More Accurate Measurement of the Electron's Magnetic Dipole Moment

Gerald Gabrielse
Department of Physics
Harvard College

Just like the Earth rotating on itself possesses a north-south magnetic dipole, a single electron, exhibiting a quantum mechanical property called spin, acts like a tiny bar magnet. The electron's magnetism is expressed by the quantity g/2. An experimental measurement of g/2 and a comparison with its theoretical value allows for the most stringent test of quantum electrodynamics, a cornerstone of modern physics describing the way light and matter interact through photons. It also provides the most precise method for determining the fine structure constant α characterizing the strength of electromagnetic interactions. The measurement of g/2 is carried out by confining a single electron in an electromagnetic trap. The trap and the electron together artificially replicate the energetic structure of a weakly bond atom. Microwave excitation and spectroscopy are used to determine the separations between the energy levels of the artificial atom which can then be related to g/2. In 2008, members of the Gabrielse Laboratory measured g/2 with an accuracy never reached before of 0.28 parts per trillion and α at 0.37 parts per billion. We are now aiming to refine this measurement even more. The experiment must be conducted at extremely low temperatures of the order of 0.1 K. Thus, constant refrigeration of the system by liquid helium is necessary. My task is to prevent the vibrations coming from the helium liquefying system from disturbing the highly sensitive confinement cavity holding the electron.

Brian Zhang
Physics
Eliot 2015

Pseudomagnetic Fields in Graphene via Thermal Strain Engineering

Amir Yacoby
Department of Physics
Harvard College

In 2004, two professors at the University of Manchester used Scotch tape to isolate a single layer of carbon atoms from graphite. For their work, Geim and Novoselov were awarded the 2010 Nobel Physics Prize, and the resulting material, called graphene, has seen a surge in scientific interest for its amazing physical properties. My project involved studying the effects of strain on the electrical properties of graphene. Previous theoretical work has shown that when graphene is stretched in a particular way, its electrons behave as if they are traveling through an extremely strong magnetic field. Such "pseudomagnetic fields" should have noticeable effects on graphene's conductivity, leading to detection of the so-called quantum Hall effect without an actual magnet.

In the first part of my internship, I learned the experimental techniques for fabricating and measuring graphene devices. This included training in the techniques of electron beam lithography, thermal evaporation, cryogenics, and of course, Geim and Novoselov's original Scotch tape method. By measuring such a graphene device in the presence of an electromagnet at 4 Kelvin, I was able to successfully observe the quantum Hall effect. For the second half of my internship, I performed computer simulations using COMSOL Multiphysics to design device geometries with observable strain. Future work would involve combining these two parts – synthesizing and measuring actual devices in the laboratory.

Stem Cell & Regenerative Biology

Kwan-Keat Ang
Human Developmental and Regenerative Biology
Pforzheimer 2015

Towards targeted cellular differentiation as a therapy for acute myeloid leukemia

David Scadden
Harvard Stem Cell Institute
Massachusetts General Hospital

Patients afflicted by acute promyelocytic leukemia (APML) have seen drastically improved survival rates with the advent of all-trans retinoic acid (ATRA), a drug that induces the differentiation of immature progenitors. However, differentiation therapies still remain elusive for acute myeloid leukemia (AML), a deadly disease for which no effective therapy exists. AML results in the overpopulation of immature, cancerous myeloid precursors in the bone marrow thus hindering the production of normal and healthy blood. We hypothesize that inducing terminal differentiation of leukemic immature progenitors will limit their indefinite proliferation and greatly improve the survival rates for patients with AML. Therefore, we are currently working towards creating novel cell-permeable DNA-targeting proteins that are capable of modulating transcription and enabling AML differentiation. While preliminary data is promising, further experimentation must be conducted to evaluate the DNA binding affinity and sequence specificity of these proteins. To achieve this goal we will generate and use recombinant versions of the proteins to fully characterize their DNA binding properties.

Ryan Chow
Human Developmental and Regenerative Biology
Pforzheimer 2016

The Role of Submucosal Glands in Airway Repair and Maintenance

Jayaraj Rajagopal
Harvard Stem Cell Institute
Massachusetts General Hospital

While the surface epithelium of the airway has been extensively characterized, the role of the underlying submucosal glands (SMGs) largely remains unascertained. It has long been established that SMGs span the entire length of the human trachea, whereas in mice, SMGs have only been found at the proximal end. However, upon inspection of tracheas from two-year-old mice, we saw SMGs extending along the entire trachea, and similarly observed an expansion of SMGs following chronic sulfur dioxide inhalation, suggesting that the formation of airway SMGs may in fact be an immunological response to injury. Though previous research has provided preliminary evidence of a surface epithelium-contributing stem cell population in the SMGs, stringent lineage tracing experiments of the SMGs following airway injury have yet to be performed. To that end, we have identified SOX9 as a robust marker of SMGs, and have generated a SOX9/CreER mouse line in order to elucidate the role of SMGs in airway repair. As for uncovering the transcriptional program responsible for SMG formation, we have further identified several markers for the various cell types in the SMGs. Notably, the expression profiles of the basal and luminal cells of the SMGs suggest that new SMGs develop from the surface epithelium, as opposed to migration of preexisting SMGs.

Rainjade Chung
Human Developmental and Regenerative Biology
Kirkland 2014

Identification of Molecular Targets of Metformin

Chad Cowan
Harvard Stem Cell Institute

Diabetes mellitus type 2 is characterized by high blood glucose levels and insulin resistance and deficiency. Metformin is the most commonly used antidiabetic medication used to treat type 2 diabetes (Zhou 2001). The mechanistic pathway of metformin involves activation of AMP-activated protein kinase (AMPK), but the direct molecular targets of metformin remain unknown (Hundal 2000). The discovery of metformin's molecular targets could lead to the development of more effective and robust drugs that could potentially improve the quality of life for people living with type 2 diabetes. Genome wide association studies in humans and RNAi screening in C.elegans have identified ACAD10, SLC22A, PRKAA1, and PRKAA2 as candidate targets of metformin action. I will confirm the involvement of these genes in the metformin response pathway by knocking them out and measuring metformin response.

Angela Frankel
Human Developmental and Regenerative Biology
Quincy 2014

Elucidating the Role of Ltbp3 in Second Heart Field Maintenance and Specification

Caroline Burns, Geoffrey Burns
Stem Cell and Regenerative Biology
Cardiovascular Research Center
Massachusetts General Hospital

Each year, roughly 36,000 children are born with a congenital heart defect in the United States. The prevalence of these disorders necessitates further research into the underlying mechanisms that cause such heart defects to arise. Recent studies have identified a late-differentiating subset of heart stem cell progenitors responsible for the formation of cardiac structures known to be malformed in several distinct classes of congenital heart defects. The gene ltbp3 (latent TGFb-binding protein 3) has been identified as a potential regulator of this distinct population of cells, known as the second heart field (SHF). Morpholino-directed knockdown studies have provided initial indication that ltbp3 is necessary for SHF cell maintenance.

My research this summer, and leading into this upcoming aca-

demic year, involves characterizing the role of ltbp3 with regards to SHF progenitors, testing the hypothesis that ltbp3 is required for SHF specification and cell maintenance. My work has included developing 2 distinct lines of ltbp3-mutant fish, performing in-situ hybridizations for a variety of heart-specific and SHF-specific genes in homozygous mutant fish, as well as developing a line of transgenic fish capable of expressing photoconvertible fluorescent protein in the heart for future lineage tracing experimentation. Eventual results of these studies will indicate the role of this gene in cardiogenesis, as well as in the development of congenital heart defects.

Tejinder S. Gill
Human Developmental and Regenerative Biology
Winthrop 2015

Examine the effect of HOX overexpression on hematopoietic stem cells and progenitors during development

Leonard Zon
Boston Children's Hospital
Harvard Stem Cell Institute

Hematopoietic stem cells (HSCs) maintain blood homeostasis throughout the life span of a host. Strategies to expand HSC numbers ex vivo have widespread clinical applications. Homeobox (Hox) genes are one of the most potent stimulators of HSC expansion. Specifically, Hox genes A9 and B4 are especially relevant in the production and maintenance of myeloid and erythroid progenitors during development. The overexpression of these genes may result in an effect on hematopoietic development, and may lead to further details on their roles in hematopoiesis.

Bridget Gosis
Human Developmental and Regenerative Biology
Currier 2015

The Importance of the Common PPARγ2 Polymorphism (Pro12Ala) in Adipogenesis and Maintenance of Mature Fat

Chad Cowan
Department of Stem Cell and Regenerative Biology
Harvard College

The transcription factor peroxisome proliferator activated receptor gamma isoform 2, or PPARγ2, acts as a nuclear receptor, is highly specific to adipose tissue, and has long been known as a crucial component of adipogenesis. By forming a heterodimer with retinoid X receptors (RXRs), PPARγ2 acts as a master regulator of genes important for fat differentiation along with lipid and glucose metabolism. Association studies have shown that a Pro12Ala substitution in the PPPARG2 gene is associated with a decreased predisposition for type 2 diabetes.

Using the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) genome-editing system, we aim to model this polymorphism in adipocytes in vitro by first introducing this specific mutation in human embryonic stem cells. The CRISPR system utilizes a Cas protein, guided by a specific guide RNA, to create a double-stranded break in a DNA molecule at a region of interest; in this case, the PPARG2 gene. The gene is then subsequently knocked-out, or is mutated to the Pro12Ala version of the gene.

From there, we differentiate these mutant hES lines to mesenchymal progenitor cells (MPC), which we subsequently differentiate into adipocytes via overexpression of the Pro12Ala PPARγ2 dox-inducible viral vector. This will allow us to study the role of the Pro12Ala mutation in adipogenesis. Moreover, by turning off this viral expression at the end of adipogensis, we are also able to examine the role of the Pro12Ala substitution in the maintenance of mature fat, due to the endogenous mutation we have made via the CRISPR system.

Preston Hedrick
Human Developmental and Regenerative Biology
Cabot 2016

Harnessing the Power of Co-Inhibitory Molecules: Protecting Stem Cell-Derived Non-Autologous Transplants from Immune Rejection

Chad Cowan
Department of Stem Cell and Regenerative Biology
Harvard Stem Cell Institute

Stem cell biology constitutes a highly promising field in terms of its applications for cell replacement therapy; however, we have yet to overcome the immune rejection that non-autologous transplanted cells face. One possible approach to overcoming this immune barrier is to mimic part of the tolerance system employed at the fetal-maternal interface during pregnancy. Previous studies show that members of the B7 family of co-inhibitory molecules are expressed at the fetal-maternal interface and thus may help the semi-allogeneic fetus evade a maternal immune response. Utilizing the same mechanism of up-regulating B7 family molecules, we hope to protect stem cell-derived cells from rejection by their host's immune system. Using qPCR we first screened JEG-3, a choriocarcinoma cell line, which is resistant to T cell-mediated lysis, for expression of B7 family molecules. We have confirmed expression of 5 out of the 6 family members we screened. Subsequently, we knocked out selected members of the B7 family using the Crispr technology and we will perform a T cell proliferation assay to identify the main inhibitory molecules. We expect to see an increased T cell activation due to a loss of inhibitory signals. Next, we will use lentiviral gene transfer of these same molecules into stem cells and again assess their immunogenicity in a T cell proliferation assay. We hypothesize that, with the addition of B7 family members, stem cells and their derivatives will be better equipped at evading an immune response from the host and show better engraftment.

Daniel Henderson
Human Developmental and Regenerative Biology
Eliot 2015

Kevin Eggan
Department of Stem Cell and Regenerative Biology
Harvard College

Amyotrophic Lateral Sclerosis, also known as ALS or Lou Gehrig's Disease, is a disease of nervous and muscular systems characterized by rapid and sudden death of motor neurons, ultimately resulting in major muscular atrophy and paralysis. Research down on

familial ALS has shown that a small percentage of ALS cases can be attributed to distinct genotypic variants of genes such as SOD1 and TDP43. Familial cases of ALS, however, represent only a minority (<10%) of ALS patients worldwide, and most instances of sporadic ALS (which account for more than 90% of ALS cases) have no known or certain root cause. Without a thorough understanding of the cause, clinicians are unable to deliver accurate ALS diagnoses until long after a patient's condition has significantly deteriorated, precluding the possibility of the patient receiving beneficial treatment when ALS symptoms have yet to completely manifest. Analysis of deep sequencing data taken from a group of ALS and control patients has lead to the identification of a moderate-sized set of genes that are differentially regulated in ALS patients relative to control populations. Eventually, surveying expression levels of these genes in patients who may or may not be suffering from ALS could be used as a powerful diagnostic tool by clinicians. This could potentially allow for earlier identification of ALS with less ambiguity than other methods which rely upon macroscopic symptoms for diagnosis.

Shakkaura Kemet
Human Developmental and Regenerative Biology
Winthrop 2015

The Role of TIF 1 Gamma in Erythrocyte Differentiation

Leonard Zon
Boston Children's Hospital
Harvard Stem Cell Institute

Sickle cell anemia and thalassemia are devastating disorders that are linked to the accurate production of globins. The globin locus has been studied as a model for transcriptional regulation and distinct globins are expressed at unique developmental periods. One of the phases in transcription, transcription elongation, has been found to be an important rate-limiting step in regulation of developmental genes. Zebrafish moonshine embryos mutant for Transcriptional Intermediary Factor 1 gamma (tif1γ) fail to develop erythrocytes and thus have a bloodless phenotype. The Zon lab found that TIF1γ is essential for transcription elongation of blood-relevant genes, including globin. Biochemical and genetic data support a mechanism by which TIF1γ recruits positive transcription elongation factor b (p-TEFb) to RNA polymerase II (Pol II) to facilitate transcription elongation. We are currently undertaking a chemical suppressor screen in which the ability of compounds to suppress the moonshine bloodless phenotype is tested by in situ hybridization for ß globin expression. One of the identified chemicals, Clofibrate, is a peroxisome proliferator-activated receptor alpha (PPARα) agonist. PPARα may recruit p-TEFb to Pol II in place of Tif1γ in moonshine embryos. We are testing other chemicals of the fibrate class to see whether fibrates in general are able to suppress the bloodless moonshine phenotype. Moreover, we are overexpressing PPARα in moonshine embryos as a first step to determine whether Clofibrate acts through PPARα. Chemical hits from the screen might enable us to better understand transcriptional elongation in erythroid differentiation and may have clinical applications for the treatment of anemias.

Kameron Kooshesh
Human Developmental and Regenerative Biology
Eliot 2016

Pioneer Transcription Factors and their Role in Binding all Chromatin Contexts

Richard Sherwood
Department of Genetics
Harvard Medical School
Brigham and Women's Hospital

Recently characterized 'pioneer' transcription factors shape the chromatin landscape by opening up closed chromatin to allow more transcription factors to bind; understanding how these factors function could improve our ability to manipulate stem cell fate. While pioneers sometimes open chromatin at their motifs, a significant contingent remains unbound, calling into question whether the current characterization of pioneers is truly the complete picture. We hypothesized that there are DNA sequences close to pioneer motifs correlated and anti-correlated with binding. By analyzing DNase-seq data, we identified specific sequences that are correlated with pioneer binding, the strongest of which are known to bind members of the Klf/Sp pioneer family, and sequences that are anti-correlated with pioneer binding, the strongest of which are previously uncharacterized AAACA sequences. To test whether binding-associated sites attract pioneers and cooperative factors more strongly than binding-disassociated sites, we constructed a library of "phrases", or a combination of Klf/Sp and AAACA sites separately juxtaposed with pioneer motifs. Then, we randomly seeded the genome in both open and closed chromatin contexts with these phrases using PhiC31 pseudo-integrase and Tol2 transposon. Thus far we have seen from preliminary ChIP-qPCR data that with randomly inserted Klf/Sp binding-correlated sequences present, pioneers bind much more frequently across the genome than without the Klf/Sp sequences or with the AAACA sequences. Deep sequencing DNA with a library of phrases randomly inserted will allow us to assess whether the pioneers can open closed chromatin, or whether pioneers are dominantly controlled by chromatin contexts regardless of the strength of their binding domains.

Alice Huai-Yu Li
Human Developmental and Regenerative Biology
Winthrop 2014

Studying the Effect of Satellite Cell Depletion in the Mouse Model of Duchenne Muscular Dystrophy

Amy Wagers
Department of Stem Cell and Regenerative Biology
Harvard College

Duchenne muscular dystrophy (DMD) is the most severe and common form of muscular dystrophy. The muscles of DMD patients are highly susceptible to contraction-induced damage because they lack dystrophin, which links the actin cytoskeleton of the mus-

cle fiber to the extracellular matrix. While DMD histology shows the replacement of muscle with non-contractile fibrotic and adipose tissue, injured muscles of wild type individuals show regenerated fibers due to the activation of unipotent muscle stem cells (satellite cells). These are critical to the "satellite cell exhaustion" model for DMD pathogenesis, which posits that the constant contraction-induced damage from lack of dystrophin constantly stimulates satellite cell activation, leading to continuous rounds of muscle degeneration and regeneration that ultimately exhaust the satellite cell pool. Previous unpublished data from the Wagers lab has shown that when satellite cells are depleted in the muscles of wild type mice, the satellite cell pool is not replenished in the absence of acute muscle injury. However, if the satellite cell pool were restored in satellite cell depleted dystrophic mice, this would suggest that dystrophic pathology could cause multiple rounds of satellite cell activation and would support the satellite cell exhaustion model. In February 2013, I began injecting tamoxifen and diptheria toxin into Pax7-CreER::Rosa26-iDTR mdx mice, in which cells expressing the Pax7 satellite cell marker are specifically depleted. In August 2013 I will assess muscle pathology using cross-sectional histology on diaphragm with Hematoxylin & Eosin (H&E) staining and quantify the number of satellite cells in these mice via fluorescence-activated cell sorting (FACS) and manual counting of satellite cells on Pax7-stained single fibers and longitudinal TA sections. A clearer understanding of the pathogenesis of DMD will enable new therapies for this debilitating disease.

Ryan Lindeborg
Human Developmental and Regenerative Biology
Eliot 2016

Identifying Molecular Controls over the Development of Corticostriatal Projection Neurons

Jeffrey Macklis
Department of Stem Cell and Regenerative Biology
Harvard Stem Cell Institute

Intratelencephalic corticostriatal projection neurons (CStrPNi) are a unique subset of neurons that extend their axons from layer V of the cortex to the ipsilateral and contralateral striatum and contralateral cortex. Previous studies suggest that this population of neurons is clinically significant in Huntington's disease, Parkinson's disease, and cerebral palsy, and is involved in cognitive, emotional, and motor functions in the brain. Despite their importance, CStrPNi have only been studied deeply with respect to their electrophysiological properties, and their molecular profile is largely unknown. This study sought to define these molecular controls and functionally characterize them within a developing mouse brain.

To elucidate the molecular identity of these neurons, in-utero electroporation gain-of-function constructs were cloned for candidate genes that were selected after analysis of microarray data. These constructs will be used to assess phenotypic effects of overexpression of certain genes and whether mutant phenotypes may be rescued. Protein and mRNA expression profiles will continue to be analyzed via immunocytochemistry and in-situ hybridization assays, respectively. Results will inform hypotheses regarding in which stages and in what ways candidate genes impact development, whether it be during fate specification, axon guidance, or maturation and pruning. Understanding the molecular profile of CStrPNi holds great importance and relevance for future study of the developing mammalian brain, as specific genes could be used as markers to verify CStrPNi identity or be applied to generate CStrPNi populations via in vitro direct differentiation and transplantation or endogenous precursor differentiation.

Kevin Parker
Human Developmental and Regenerative Biology
Leverett 2016

Characterizing the Effects of Epigenetic Drugs on the Renal Progenitor Cell Population in Adult Zebrafish

Robert Handin
Department of Hematology
Brigham and Women's Hospital
Harvard Stem Cell Institute

Nephron progenitor cells capable of kidney regeneration have previously been identified in the adult zebrafish kidney. Furthermore, initial data suggests that certain epigenetic drugs, such as histone deacetylase (HDAC) inhibitors, may increase the number of these renal progenitor cells. We have identified three target drugs, SAHA, WT-161, and Merck 60, and are working to quantify the effect they have on not only the renal progenitor cell population, but also the kidney as a whole. These drugs are injected intraperitoneally into the adult zebrafish, and the kidneys are harvested at various time points after injection for analysis. As the drugs are injected into transgenic zebrafish with markers of the progenitor cells driving fluorescent reporters, we are able to quantify the effects of the drugs through flow cytometry. In addition to confocal imaging of the whole kidney, stains for BrdU, apoptosis, and senescence are completed on tissue sections of the harvested kidneys, allowing us to visually observe the effects of the drugs. Lastly, RT-PCR is used to observe the effects the HDAC inhibitors have on gene expression in the renal cells. Future plans include embryo screens to further characterize the phenotypic effects of these HDAC inhibitors, as well as comparing the effects these drugs have in juvenile and elderly zebrafish.

Gabriela D. Ruiz-Colón
Human Developmental and Regenerative Biology
Quincy 2016

Localization of CITED4 in Neonatal Cardiomyocytes

Anthony Rosenzweig
Cardiovascular Institute
Beth Israel Deaconess Medical Center
Harvard Stem Cell Institute

Cardiac hypertrophy occurs as a result of hemodynamic stress causing the heart to increase its mass. When hypertrophy occurs in response to disease states such as aortic valve disease or hypertension, it can lead to heart failure, a condition defined as pathologic hypertrophy. However, hypertrophy can also result from endurance training and is actually protective from multiple forms of cardiovascular disease. This case, known as physiologic hypertrophy, represents a model for the development of therapies for the nearly one

million Americans that die each year from heart attacks. Recent studies in exercised mice have demonstrated increased markers of proliferation as well as cardiac protection from models of hypertension-induced heart failure. RNA profiling demonstrated up-regulation of the transcriptional co-activator CITED4 in these hearts (Boström et. al). While preliminary experiments suggest that CITED4 may be located in the cytoplasm of cardiomyocytes, the co-activator has not been precisely localized. Using a synthetic modified mRNA method, originally designed for generation of induced pluripotent stem cells (Mandal and Rossi), these modified mRNAs serve as a substitute for viral transfection and is more applicable for cell-based therapeutic applications. Modified mRNA technology allows for the penetration of virtually any protein in many types of cells; thus, using this modified mRNA, the expression of CITED4 in vitro, and ultimately in vivo, is possible. Using the vector pORFin in tandem with a GFP molecule as a reporter gene, transfected cardiomyocytes can be tested using different assays to confirm biological function.

Hannah Rasmussen
Human Developmental and Regenerative Biology
Adams 2016

Oncostatin-M: A Novel Drug Target for Bone Marrow Transplant Therapies

David Scadden
Harvard Stem Cell Institute
Massachusetts General Hospital

Research in the Scadden lab focuses on the hematopoietic niche, a bone marrow (BM) microenvironment in which the hematopoietic stem cell (HSC) resides. The precursors to all differentiated blood cells, HSCs are indispensable to patients undergoing chemotherapy and radiation therapy—treatments that kill BM cells. In current BM transplantations, administration of a drug known as G-CSF (granulocyte colony stimulating factor) mobilizes HSCs into the peripheral blood, so that simple blood collection obtains the cells. While this process improves upon traditional bone-drilling procedures, problems include inadequate HSC mobilization, and inefficient HSC homing/engraftment after transplant. Studying the players involved in mobilizing and retaining HSCs could reveal novel drug targets for improved therapies.

While the niche's complex interactions are not completely understood, its various components contribute immensely to making the microenvironment hospitable for HSCs. Of particular interest to my lab is the macrophage, a phagocytic immune cell. Recent studies indicate that macrophages secrete a soluble factor(s) which supports HSC retention. Earlier this year our lab identified this factor in vitro as Oncostatin-M (OSM), a protein cytokine which binds to osteoblasts—niche cells lining the endosteal surface. This summer, we began confirming these findings in vivo. By treating macrophage-depleted mice with OSM and subsequently measuring HSC mobilization and SDF-1 (a protein associated with niche support) levels, we hope to ascertain whether OSM treatment reduces HSC mobilization in the absence of a macrophage population. This would lay the foundation for further studies to validate OSM as a drug target within the HSC niche.

Marissa Suchyta
Human Developmental and Regenerative Biology
Pforzheimer 2014

Identification of initiating factors of axolotl limb regeneration

Doug Melton
Harvard Stem Cell Institute

The aim of this project was to identify a factor in the axolotl wound epidermis that initiates limb regeneration. The broad purpose of the research is to gain a greater insight into the axolotl regenerative process in hopes of utilizing a similar mechanism to further mammalian regenerative capacity. The first step of this project was to determine molecular markers of cellular dedifferentiation during limb regeneration. The researcher identified, through RT-PCR and qPCR, three genes that are upregulated in the early stages of regeneration. Next, the researcher established an in vitro regeneration assay to manipulate the regenerative process ex vivo. This system was then utilized to determine potential secreted wound epidermis factors initiating regeneration. The researcher also performed RNAseq of wound epidermis compared to normal limb epidermis to further identify factors initiating the regenerative process.

Caitlin Ballotta
English

SHARP

Adams 2014

Zinesters as Authors: An "Alternative" Reading

Dan Hazen, Rebecca Wingfield, Katherine Leach, Gregory Eow
Collection Development, Harvard College Library
Enlivening Zines Project with Widener Library

What does it mean to be an author? Who merits the designation, to your sensibilities? Certainly, the novelist, the playwright, and the journalist—those writers whose works we encounter through mainstream channels—spring to mind. But what of the blogger who, with the click of a button, sends his or her thoughts into the void? What of the student who produces page after page of analysis or reflection throughout the semester? My summer project has called me to revise my previous conception of authorship.

In the past weeks, I have been working with the Library's newly-acquired collection of zines—that is, small-print, self-published, often handmade, "alternative" publications that are produced without regard for profit and that focus on any theme of the author's choosing (whether travel, music, sexuality, or bicycling). Reading through countless photocopied-and-stapled sheets, I have found that zinesters (zine authors) are everywhere present in their texts: highly conscious of their roles as writers, publishers, and literary critics, they give rare insight into the creative process and develop standards for evaluating their own and others' works. I feel, then, that zinesters are members of an intellectual community who dedicate themselves to experimenting with new modes of self-expression. By creating a simulated online course that identifies similarities and differences between the zinester and the author of mainstream publications, moreover, I hope to demonstrate how zines might be used by future researchers—to convey that zines are cultural artifacts that can (and perhaps should) be read as academic texts.

Joshua Blecher-Cohen
Philosophy and Classics
Cabot 2016

Bridging the Divide: A Novel Approach to Integrating Theory and Practice in Humanities

Sean Kelly
Department of Philosophy
Harvard College

Run in conjunction with the Harvard Department of Philosophy, the "Philosophy, Education, and Community Action" project (PECA) contained multiple constituent programs. These included a philosophy of education seminar and the development of philosophy education curricula for K-12 students, resulting in trial programs run at both the elementary (at the Peabody Essex Museum in Salem, MA) and high school (at Harvard University) levels over the course of the summer. This project exists as another component of the overarching program, researching the structure of humanities curricula with a focus on integrating practical methods into humanities education. Specifically, this investigation examines a model for post-secondary humanities courses which includes fieldwork components in addition to traditional classroom-based study. Based on an analysis of previously implemented syllabi in a range of humanities disciplines and the field-based philosophy education programs developed and run by the PECA project, this report proposes a novel structure for fieldwork-based humanities courses.

Nora Garry
Women and Gender Studies
Eliot 2014

The Trope of Celebrity in Zines

Dan Hazen, Rebecca Wingfield, Katherine Leach, Gregory Eow
Collection Development, Harvard College Library
Enlivening Zines Project with Widener Library

We document and make sense of our existences contemporaneously; researchers attempt the same endeavor in hindsight. Remnants of lives are parsed together, subjected to analysis, generalization, and publication in the name of enlightenment. That which we leave behind, it is supposed, says something about our specific cultural period. In truth, it says more about the collection and conservation capabilities of institutions of knowledge. With the recent acquisition of 20,000 zines, then, Widener Library preserves these radical relics of the '80s and '90s for future academic study. Enabled thus, scholars will access the same material as former subscribers to these self-published, small-distribution periodicals, which range in subject from punk rock and DIY to third-wave feminism and queer erotica, and in format from comics and cut-and-paste collages to poetry and parody.

My work this summer foreshadows that of future researchers, to the extent that I carried out analysis for the purposes of publication. I investigated specifically the trope of celebrity in zines, as well as the function facilitated by the form that, though alternative, mimics and undermines the mainstream media. Iconographic and factual manipulation of celebrities join with their repetition and casual discussion to promote humor and subversion, but also to convey the worldview of zinesters as catalogued in their writing. My final findings and selections from the collection are presented in a web-comic that displays and pays homage to the zine genre.

Ian MacGillivray
Philosophy
Leverett 2015

Sean Kelly
Department of Philosophy
Harvard College

I am working this summer on research regarding philosophy as a component of grade school (K-12) education. To obtain a theoretical foundation for this project, I participated, along with the other SHARP interns in my project and certain members of the Harvard Philosophy Department, in a seminar on the philosophy of education lead by Professor Kelly. We read a number of texts from several different philosophical periods, including selections from Plato,

Locke, Rousseau, Kierkegaard, and other authors. Our discussions of these texts were aimed primarily at attempting to answer the question "What is an education for?" in addition to exploring other related topics.

We have also worked on planning two programs designed to get students doing philosophy: one geared toward elementary school students, and another toward students in high school. The latter consists of running two Ethics Bowls for local teenagers. These Bowls begin with informal philosophical discussions of ethical prompts, texts, and thought experiments and then progress to structured debates. The elementary school program, on the other hand, will be taking place at the Peabody-Essex Museum (PEM) in Salem, MA. In conjunction with PEM's existing summer programs, each intern has designed, and will be running, an activity aimed at getting students engaged with various philosophical issues. The activity that I have planned uses rule changes in games as a method of starting discussion about the issue of essential as opposed to accidental change. Through these programs and activities, we hope to instill in students improved critical thinking skills and intellectually rigorous patterns of thought.

Nathan Otey
Philosophy
Pforzheimer 2015

SHARPening Young Minds: an Enquiry

Sean Kelly
Department of Philosophy
Harvard College

I worked on a variety of projects with the overall goal of developing and implementing different philosophy-based critical thinking and learning programs for kids at both the high school and elementary levels. My group has read extensively in the Western tradition, analyzing and contrasting different theories in the philosophy of education. Our research has also included consultations with developmental psychologists, elementary teachers who are piloting philosophy programs, and a panel of school administrators. Many competing perspectives have emerged, but one common thread is that developing the art of discourse--actively listening to others, critically examining competing claims, and formulating and expressing one's own opinions in response to an ongoing academic conversation--is central to any meaningful education generally, and to a philosophical education in particular.

As such, we have focused our "field research" not on a particular philosophical problem, writer, or tradition; but rather on initiating and sustaining an engaging philosophy-based dialogue between students in which they naturally build these vital critical thinking skills. To this end, we have held Ethics Bowls with high schoolers introducing them to thought experiments, philosophical texts, broad ethical frameworks, and structured team dialogues on current ethical issues. We have also conducted classes on arts-related philosophical questions with elementary school students at the Peabody-Essex Museum in Salem, MA. Finally, we have worked on developing curricula and lesson plans for the Open Minds program to implement in schools in the Boston area, although we hope to have a broader impact by making these more widely available.

Sara Price
History and Science
Adams 2016

Critically Thinking Children: Philosophy Education for a New Generation

Sean Kelly
Department of Philosophy
Harvard College

My project commenced with a review of theories on the philosophy of education in order to best determine how philosophy can be used to enhance education. Philosophical thinking is a critical tool for cultivating students' academic and interpersonal understanding. Teenagers in particular are reaching a point of development at which they must rationally and independently engage with moral issues in order to make informed decisions. Perplexingly, though, they view philosophy as the work of ancient Greek men discussing abstract ideas rather than a thoughtful approach to their problem solving. In order to counter such attitudes, our team planned and conducted a thought experiment seminar for the on-campus Crimson Summer Academy as well as two Ethics Bowls for local high school students. Through these events, we introduced teenagers to philosophy as a rewarding field of study in college while ultimately encouraging them to pursue informed inquiry in life's everyday quandaries.

We are also extending this inquiry to a younger set of children by creating curricula for use in elementary schools. We have developed several hour-long lesson plans which present basic concepts of philosophy through tangible connections to art, architecture, and music. Pilot versions of these activities are currently being conducted in conjunction with the Arts Adventure Camp at Peabody Essex Museum in Salem, MA. It is our hope that our outreach efforts will prompt students young and old to discover the beauty of philosophy as they begin to think more clearly and critically about the world surrounding them.

Levi Roth
Philosophy
Kirkland 2014

Philosophy, Education, and Community Action

Sean Kelly
Department of Philosophy
Harvard College

This summer, I worked with Professor Sean Kelly in a reading group focused on the topic "What is an education for?" We read and discussed several important texts in the history of philosophy, from the classical - Plato and Aristotle - through the early modern - Locke and Rousseau - to the contemporary - John Dewey and Hubert Dreyfus. I have found that many of these works emphasize education as a form of character development. Aristotle, for example, is concerned mainly with the refinement of virtue, while Dewey treats education as a kind of societal homeostasis. One thing missing from this picture is the importance of education as a means of skill-development. To me, it seems implausible that the only reason to teach people algebra or chemistry is to pass down moral virtue or a piece of cultural heritage. So, I am working on a paper which argues that the actual skills taught in the classroom are in themselves a valuable part of an education.

Our reading group has a purpose beyond philosophical investigation. We are also working with Open Minds, a nonprofit dedicated to teaching philosophy to K-12 students. We are devel-

oping two projects in particular. One is a series of "Ethics Bowls," debates which teach high school students to recognize and critically assess moral arguments. The second is an arts-based program for elementary and middle-school students at the Peabody Essex Museum, with a goal of teaching young students to discuss with others why they believe what they believe.

Colton Valentine
Undeclared
Lowell 2016

Development and Implementation of Pre-Texts Assessment Protocol

Doris Sommer
Department of Romance Languages and Literatures
Harvard College

Conventional language and literature programs for elementary through high school students focus on a "bottom up" approach: teachers begin with grammar and vocabulary lessons that leave students bored and disengaged. Little to no time remains for the creative and critical skills at the pinnacle of Bloom's taxonomy. Pre-Texts, an arts-based literacy program developed by Professor Doris Sommer, seeks to address these pedagogical inadequacies by using classic literature as an excuse for making art. The methodology strives to promote literacy and higher-order thinking skills, along with creativity and civic virtues. While Pre-Texts is a highly popular and successful program, having been implemented widely in Boston and in international sites such as El Salvador and Zimbabwe, the program lacks instruments to assess its effect on student learning.

To address this deficiency, we developed a two-pronged assessment protocol: a written pre-post test focused on student analysis of a complex text combined with interviews and classroom observations. We then implemented these evaluations at the Talented and Gifted (TAG) program during their five-week middle and high school summer curriculum, which employed Pre-Texts for English Language Learners. While students demonstrated increased confidence in class and seemed closely involved in the text, the mean test score decreased from a 39% to a 26% with p value: < .02. This trend was preserved across genders and classrooms, though a lack of student motivation during post-testing, among other factors, may have undermined the findings. Future assessments will involve a control group at a longer Pre-Texts program and consider an incentivizing process.

Victoria Zhuang
Literature
Pforzheimer 2015

Mapping the Progress of African Art

Suzanne Blier
History of Art and Architecture
Harvard College

The African diaspora and slave trade, major historical events occupying the middle centuries of the last millennium, profoundly disrupted the distribution of African peoples in the world. In part as product of these events, artists inheriting this cultural legacy have produced an array of important works that influenced global art and culture.

This summer, seeking to lay the grounds for research into the link between modern historical events and the production of African art, I worked for Professor Suzanne Blier on a project that seeks to map all African artists dating from the time of the diaspora.

Compiling the requisite information required us to exhaustively transfer and standardize biographical data on each artist, from an online database, then organize the data and edit for accuracy. Ultimately, the data we compiled was arranged into a spreadsheet of over 15,500 African and African-American artists. Then with the assistance of GIS specialists at Harvard we geocoded all the artists to find the latitudes and longitudes of their locations when alive, giving them a position in time and space relative to other artists.

The final product, when this geocoded data has been uploaded to a Harvard-based website called WorldMap, will be an interactive online map that visualizes the spread of the artists, over their various decades, throughout the world. By tracking the locations and dates of these artists, we can also begin trying to identify trends that may yield insight into the relation between complex political-historical events, and the work of these artists.

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