Rosenfeld Science Scholars Symposium

Yale

Kline Geology Laboratory

Lecture Hall 123

September 6, 2017

5:00 -7:00 PM

Schedule of presentations

5:00	Dr. Sandy Chang *Associate Dean of Science and QR Education*	Welcoming remarks
5:00-5:15	Emma Garcia *Dept. of Chemistry*	Development of an orthogonal tRNA synthetase for site-specific β-amino acid incorporation *in vivo*
5:15-5:30	Peter Wang *Dept. of MBB*	Expansion of the chemical probing toolkit for RNA conformation analysis
5:30-5:45	Luis Fernando Machado Poletti Valle *Dept. of Physics*	Simulated Groups of Galaxies as Probes of Cosmological Parameters
5:45-6:00	Cindy Yang *Dept. of Cell Biology*	Reprogramming hematopoietic progenitors into insulin-producing beta-like cells
6:00-6:15	Gabrielle Roberts *Dept. of Applied Physics*	Building Tools to Simulate and Represent the Evolution of Quantum Superconducting Circuits

Poster presentations

Charlotte Brannon *Depts. of MCDB and Physics*	Collective migration of *Escherichia coli* in semi-solid agar
Carl Mansson *Dept. of Chemistry and Cell Biology*	Super Resolution Imaging of Acidic Organelles
Geeta Rao *Dept. of Psychiatry*	Pupillary diameter as a biomarker for stress responsiveness in male and female mice
Stephen Wang *Dept. of MCDB*	Studying PROTAC-induced Degradation of p38 MAPK
Dylan Young *Dept. of Physics*	Optimal Quantum Error Correction for Binomial Codes in a Bosonic Mode

Development of an Orthogonal tRNA Synthetase for Site- Specific β-Amino Acid Incorporation *in Vivo*

Emma Garcia[1,2], Wesley Robertson[3] and Alana Schepartz[2,3]

[1]Rosenfeld Science Scholar, Yale College, New Haven, CT 06520
[2]Department of Chemistry
[3]Department of Molecular, Cellular, and Developmental Biology
Yale University, New Haven, CT 06520

It has been known for decades that protein synthesis involves the incorporation of the ~20 canonical α-amino acids into polypeptides, the sequence of which is encoded by the mRNA. However, if this system can be modified to incorporate monomers other than α-amino acids into a polymer, then novel sequence controlled macromolecules can be synthesized, with extensive potential applications in materials science, industry, and medicine. Mutant ribosomes have been previously developed to be able to incorporate β-amino acids *in vivo*, but due to the lack of an orthogonal tRNA – synthetase pair, it is currently impossible to exploit the full potential of this ribosome to incorporate β-amino acids in a site-specific manner. To solve this problem, the PylRS/Pyl-tRNA pair was used as a starting point in efforts to develop a synthetase to incorporate β- amino acids, with Pyl-tRNA recognizing the open UAG stop codon. Libraries of mutant synthetases, with selected mutations informed by Statistical Coupling Analysis (SCA) to the active site, were used as the starting point for a series of positive and negative selections paired with next generation sequencing in order to develop a list of potential β-amino acid specific synthetases. These mutants are currently being tested for their ability to incorporate β- amino acids through Chloramphenicol Acetyl Transferase (CAT) screening assays and mass spectrometry. An active tRNA synthetase would allow for site specific incorporation of β-amino acids into full length proteins *in vivo*.

Expansion of the chemical probing toolkit for RNA conformation analysis

Yuk Pung (Peter) Wang[1,2], Alec N. Sexton[2] and Matthew D. Simon[2]

[1] Rosenfeld Science Scholar, Yale College, New Haven, CT 06520
[2] Department of Molecular Biophysics and Biochemistry
Yale University, New Haven, CT 06520

Long noncoding RNAs (lncRNAs) carry out diverse and critical roles in cells, but deciphering their functions is challenging due to their complexity and heterogeneity. *Xist* is a lncRNA known to be responsible for dosage compensation between the sexes via X-inactivation, but its mechanism has remained elusive. Chemical probing, with recent adaptations to next-generation sequencing techniques, has allowed high-throughput and quantitative analyses of RNA base-pairing with single-nucleotide resolution, providing structural insights into the function of RNAs, including lncRNAs. However, most current techniques rely on SHAPE reagents, which are only reactive to the sugar backbone, and dimethyl sulfate (DMS), which modifies the Watson-Crick face of adenine and cytosine but not guanine or uracil. To remedy this shortcoming and improve current *Xist* models, we developed two carbodiimide reagents that are reactive to guanine and uracil for sequencing-based probing. CMC usage has not been extended to sequencing-based assays, while EDC is a new reagent for RNA probing. Chemical adducts formation from reactions with RNA agrees with the predictions for both carbodiimides. We subsequently used these reagents to probe one region of *Xist.* By comparing the results with DMS reactivity, we found support for some previous conformation models, but also found discrepancies that led us to refine the models. Overall, insights from CMC and EDC led to a new improved conformation model of a section of *Xist*, opening the door for broader use of these reagents to improve insight into RNA through chemical probing.

Simulated Groups of Galaxies as Probes of Cosmological Parameters

Luis Fernando Machado Poletti Valle[1, 2] and Daisuke Nagai[2, 3]

[1]Rosenfeld Science Scholar, Yale College, New Haven, CT 06520
[2]Department of Physics and [3]Astronomy
Yale University, New Haven, CT 06520

Current state-of-the-art Astrophysics and Cosmology focuses on answering one fundamental question: what exactly is the Universe made of? Under the current understanding, about 5% of the Universe is made of “normal matter”, which comprises everything we can observe, from people and buildings to stars and galaxies. The remaining 95% is divided into “dark energy” and “dark matter”, both of which cannot be directly observed, and need instead to be inferred from their interactions with normal matter. As a result, studying dark matter and dark energy depends on how we model their interactions with normal matter (also called “baryonic matter”). In a nutshell, observing normal matter sheds light onto our current models of the Universe. Due to this connection between normal matter and dark matter/energy, current cosmological simulations focus on modelling several phenomena regarding normal matter, which carry unique information regarding the structure of varied observed astronomical objects. In particular, my summer project focused on studying groups of galaxies, which are excellent probes of phenomena involving baryonic matter. This project aimed at comparing a new set of simulations of galaxy groups to a recent state-of-the-art observation of a galaxy group. As a result, this comparison seeks to analyze the impact of baryonic physics on several observed features in such galaxy groups, ultimately allowing for a more precise inference from observations of normal matter to properties of the large scale structure of our Universe.

Reprogramming Hematopoietic Progenitors into Insulin-producing Beta-like Cells

Cindy Yang[1,2] and Shangqin Guo[2]

[1]Rosenfeld Science Scholar, Yale College, New Haven, CT 06520
[2]Department of Cell Biology & Yale Stem Cell Center, New Haven, CT 06520

Cell fate can be altered, or reprogrammed, by defined transcription factors. For example, pluripotency related transcription factors Oct4, Sox2, Klf4, and cMyc, also known as the Yamanaka factors, can reprogram differentiated cell types into pluripotent stem cells. Guo lab has previously identified a fast-cycling subset of hematopoietic progenitors that display extraordinarily high reprogramming efficiency to pluripotency. While we are investigating the molecular basis of the epigenetic plasticity associated with these hematopoietic progenitors, we are attempting to harness this plasticity and reprogram them directly into other cell types of clinical relevance. We chose insulin-producing pancreatic beta cells as our target cell type due to their therapeutic possibility for diabetes.

Pancreatic endocrine transcription factors Pdx1, Ngn3, and MafA (PNM factors) are key regulators in beta cell development and can convert pancreatic alpha cells, intestinal crypt cells and antral stomach cells into insulin-producing cells. We wanted to test whether the PNM factors can convert the highly plastic hematopoietic progenitors into insulin-producing cells. Thus far, we have succeeded in cultivating hematopoietic progenitors in medium used to maintain beta cells in vitro and observed extensive cell survival and proliferation, a prerequisite for further cell fate manipulation. We then tested whether primary mouse hematopoietic progenitors engineered to express the PNM and Yamanaka factors can be induced toward a beta cell fate. Preliminary results suggest a slight activation of insulin gene expression. Further studies will be performed to improve and enhance this activation.

Building Tools to Simulate and Represent the Evolution of Quantum Superconducting Circuits

Gabrielle Roberts[1, 2], Steven Touzard[2] and Michel Devoret[2]

[1]Rosenfeld Science Scholar, Yale College, New Haven, CT 06520
[2]Department of Applied Physics, Yale University, New Haven, CT 06520

Quantum superconducting circuits have strong potential as quantum bits. However, these experiments are hard to optimally design. We built a group of functions that can be used to simulate the evolution of these complicated experiments based on given experimental parameters, as well as represent the output data. Our functions were modeled off Qutip, a pre-existing Python package. We used the theoretical formalism from quantum optics in our code.

Our functions can be used to create a matrix representation of any arbitrary quantum state or operator. It is then straightforward to build up common states and Hamiltonians, as well as plot useful distributions like the Wigner function. Our code implements two time evolution schemes: a Monte Carlo solver and a master equation solver. Both can take into account system defects, energy dissipation, and other forms of unwanted interaction with the environment.

Unfortunately, the simulations still run too slowly to be truly useful. As a next step, we hope to implement different algorithms in the time evolution functions to increase their efficiency. We also hope to use to use the group of functions we have developed to simulate one of Qlab's recent proposals to encode, protect, and manipulate information in a quantum harmonic oscillator using Schrodinger Cat states, thus creating a stable logical quantum bit that could be used to perform universal quantum computations.

Collective migration of *Escherichia coli* in semi-solid agar

Charlotte Brannon[1,2], Setsu Kato[2] and Thierry Emonet[2,3]

[1]Rosenfeld Science Scholar, Yale College, New Haven, CT 06520
[2]Department of Molecular, Cellular, and Developmental Biology
[3]Department of Physics
Yale University, New Haven, CT, 06520

Bacteria should be considered for how they move both individually and collectively. Individually, even a clonal population of *E. coli* exhibits significant variation in a swimming phenotype called *tumble bias* (the probability that a cell will abruptly change its swimming direction in a given time). Collectively, even though cells swim with different tumble biases, they somehow manage to do so in a coordinated manner. That is, in a nutrient-rich environment, they travel together in sharp, well-defined bands. This phenomenon is both impressive and baffling. How can cells that individually swim in such different ways—some tumbling frequently, some barely at all—manage to move together in a cohesive group? The Emonet lab has addressed this question by studying *E. coli* in liquid media environments. They find that when cells swim together in liquid media, they spatially sort themselves based on tumble bias and local nutrient signal, which allows them to move collectively in bands. To extend these findings, I examined *E. coli* swimming behavior in semi-solid agar media. Agar has a rigid, three-dimensional structure that cells must navigate, and which may affect the sorting and selection of tumbling phenotypes. My preliminary results suggested that the tumble bias distribution of a cell population varies based on the nutrient concentration of the agar media, and which band is being examined. These findings further suggest that the mechanism by which cells maintain both individual diversity and collective behavior is carefully managed, and perhaps able to sustain across different environmental conditions.

Super Resolution Imaging of Acidic Organelles

Carl Mansson[1], Alexander Thompson[2], Aarushi Gupta[2], Alanna Schepartz[2], Derek Toomre[3]

[1]Rosenfeld Science Scholar, Yale College, New Haven, CT 06520
[2]Department of Chemistry and [3]Cell Biology, Yale University, New Haven, CT 06520

We present a two-component method for imaging lysosomes at a super-resolved scale. The system is based on a transcyclooctene bound tertiary amine (lyso-TCO) and a far red-shifted silicon rhodamine dye featuring a tetrazine moiety (SiR-Tz). We show that lyso-TCO selectively localizes in the lysosome and subsequently assembles with SiR-Tz by a “click” reaction. This strategy has enabled long-term live-cell super-resolution imaging videos of lysosomes by STED microscopy. We also discuss a novel approach to SMS imaging of acidic organelles, which relies on structural modifications to manipulate zwitterionic equilibria of a similar silicon rhodamine dye.

Pupillary diameter as a biomarker for stress responsiveness in male and female mice

Manasa G Rao[1,2], Alfred P Kaye[2] and Alex Kwan[2]

[1]Rosenfeld Science Scholar, Yale College, New Haven, CT 06520
[2]Department of Psychiatry Yale University, New Haven, CT 06520

The diameter of the pupil has been used in behavioral neuroscience as a non-invasive measure of physiological arousal. In humans, disease states such as PTSD correlate with increased pupillary reactivity to stress as measured by infrared pupillometry, making pupil dilations a possible biomarker for the disorder. However, it is unknown how these pupillary changes might relate to changes in neural circuits that underlie psychological disorders like PTSD. In rodents, the diameter of the pupil correlates with global brain states and even with the activity of individual neurons across the brain. In this study, we compare both spontaneous and evoked fluctuations in pupillary diameter in a mouse model of acute traumatic stress. By measuring pupillary fluctuations prior to the induction of stress, we can determine how prior variability in arousal states relates to stress response. Finally, we consider sex as a source of biological variability in stress responsiveness.

Studying PROTAC-induced Degradation of p38 MAPK Isoforms

Stephen Wang[1,2], Blake Smith[2], Saul-Jaime Figueroa[2], Jing Wang[3] and Craig Crews[2,4]

[1]Rosenfeld Science Scholar, Yale College, New Haven, CT 06520
[2]Department of Molecular, Cellular, and Developmental Biology
Yale University, New Haven, CT 06520
[3]Arvinas LLC, 5 Science Park, New Haven, CT 06520
[4]Departments of Chemistry and Pharmacology, Yale University, New Haven, CT 06520

Proteolysis Targeting Chimeras (PROTACs) are heterobifunctional small-molecule compounds that recruit E3 ubiquitin ligases to target proteins for ubiquitination and their subsequent proteasome-mediated degradation. PROTACs have shown promise as a potential alternative therapeutic option for various cancers. Recently, the biophysical understanding of PROTAC function has shifted as new evidence suggests the formation of a trimeric complex of target:PROTAC:ligase playing an important role in PROTAC degradation capacity and efficiency. In this study, we observed two different isoforms of the p38 mitogen-activated protein kinase (MAPK13 and MAPK14) that were differentially degraded by two PROTACs with identical warheads but different E3 ligases. We sought to explore the validity of the trimer model as an explanation for the observed ligase selectivity. Based on molecular dynamic simulations and modeling data, we generated a small library of mammalian expression vectors containing mutagenized MAPK proteins that carried mutations affecting steric interactions near the binding pocket, secondary structure formation throughout the protein, and protein-protein interactions at the trimer interface. We additionally generated mutants that examined lysine selectivity as a metric of degradation efficiency. Mutating specific residues in MAPK14 that were important for secondary structure formation, protein-protein interactions, and steric clashing of PROTAC near the kinase binding pocket demonstrated that key residues can engender degradation regardless of the E3 ligase used. Additionally, reducing the number of lysine residues available for ubiquitination in MAPK13 seems to decrease PROTAC degradation capacity. Knowledge from this work will be able to inform the design of potent PROTACs, including those that can possibly degrade undruggable proteins immune to traditional small-molecule inhibitors.

Optimal Quantum Error Correction for Binomial Codes in a Bosonic Mode

Dylan Young[1,2], Liang Jiang[2], Kyungjoo Noh[2] and Victor A. Albert[2]

[1]Rosenfeld Science Scholar, Yale College and [2]Yale Quantum Institute, Dept. of Applied Physics, Yale University, New Haven, CT 06520

The search for a practical quantum computer has been a focus of applied quantum physicists and quantum information theorists for the past couple decades. Due to a high sensitivity to errors from the environment, current quantum computers can only faithfully run algorithms that complete within a short time period, known as the coherence time of the system. Rather than attempting to decrease the error rate of the system, this research focuses on increasing the system's coherence time using quantum error correction. In essence, this works by encoding a two-dimensional (qubit) subpsace within a higher-dimensional Hilbert space, allowing the system to experience errors, and then extracting the maximum possible information out of the larger space.

At the Yale Quantum Institute (YQI), researchers are primarily interested in encoding quantum information using microwave photons in a cavity, a system known as a bosonic mode. In particular, this research studies a specific class of encodings within the bosonic mode Hilbert space known as binomial codes, with the goal of minimizing the uncorrectable error rate over all encoding and decoding schemes. Numerically, we noticed that the ideal encoding scheme for certain error rates ($\gamma \sim 0.1$) and given average photon number $\bar{n}$ seems to satisfy a relationship $S \sim 2N$, where S and N are parameters of a binomial code. We are still working on an analytical description of this phenomenon, but we have managed to work out analytics for the channel in the limiting condition $\gamma\bar{n} \ll 1$, which seems to exhibit a similar qualitative relationship.

Morton and Maggie Rosenfeld, J.D.

Mort and Maggie Rosenfeld, born and raised in St. Louis and Chicago, respectively, have lived in Los Angeles for 45 years. Mort holds an undergraduate degree from Princeton and a JD from the University of Michigan Law School. He practiced law for more than 42 years in Los Angeles, the last 26 of which at a small business law firm which he founded. He retired three years ago and is presently writing novels. Maggie is a graduate of the University of Michigan and UCLA Law School. She practiced at a well-known Los Angeles law firm for 18 years before turning to part time practice for a period of time before assuming her current position as the head of business operations for a private elementary school where she previously served as the Chair of its Board of Trustees.

The Rosenfeld's are the parents of two sons who are Yale graduates. Andrew earned both a BA and MA in Economics as a member of the Class of 2004. Daniel received a BS and MS in Chemistry in 2007. Daniel spent each of his summers at Yale doing research, which, following discussion with Yale science administrators, inspired the funding for Rosenfeld Science Scholars originally known as Yale Science Scholars. The Yale College Dean’s Office would like to thank the Rosenfelds for their generous support of Yale undergraduate STEM research.

Acknowledgments

In addition to the Rosenfelds, we wish to thank the following individuals for their contributions to the 2017 Rosenfeld Science Scholars' Program:

Peter Salovey, President, Yale University

Benjamin Polak, Provost, Yale University

Marvin Chun, Dean of Yale College

Sandy Chang, Associate Dean, Science and QR Education, Yale College

Alexia Belperron, Director of STEM Fellowships, Yale College

Douglas Kankel, Dept. of MCDB, Rosenfeld Selection Committee

Patrick Vaccaro, Dept. of Chemistry, Rosenfeld Selection Committee

Donalee Slater, Yale College Science & QR

Sarah DelVecchio, Yale College Science & QR