Science, Technology and Research Scholars
STARS

Annual STARS II Research Symposium

Yale

Rosenfeld Hall
109 Grove St., Room 101
April 27, 2016

Annual STARS II Research Symposium
Wednesday, April 27th, 2016

5:00 p.m. **Opening Remarks and Presentation of Certificates**
Dean Carl Hashimoto & Sara Katrancha

Speakers

5:15 p.m. **Optimizing the Constrained Conformal Bootstrap**
Jason Parisi
Department of Physics

5:30 p.m. **Constructing an Automated Networks-Based Algorithm for Determining Germline Immunoglobulin Heavy Chain V Segments**
Hanah Otis
Departments of Pathology and Immunobiology-YSM

5:45 p.m. **Role of Location and Passage Time on Endothelial Cell Characteristics**
Olga Wroblewski
Departments of Anesthesiology-YSM and Biomedical Engineering

6:00 p.m. **Dinner & Poster Presentations**

Optimizing the Constrained Conformal Bootstrap

Jason Parisi[1,2] and David Poland[2,3]

[1]Science, Technology, and Research Scholar, Yale College, New Haven, CT 06520
[2]Department of Physics, Yale University, New Haven, CT 06520
[3]School of Natural Sciences, Institute for Advanced Study, Princeton, NJ 08540

Conformal field theories (CFTs) are quantum field theories (QFTs) that describe systems with additional symmetry properties than most standard QFTs. We use a range of numerical and analytic numerical bootstrap techniques to explore solved and unsolved CFTs. Using the Taylor expansion of the sum rule, $\partial_z^m \, \partial_{\bar{z}}^n \sum_{\{\Delta,l\}} p_{\Delta,l} \, F_{\Delta,l} = 0$, obtained from the conformal bootstrap (Gliozzi's method), we demonstrate the validity of Gliozzi's method by reproducing results for already solved models - the 2D Ising Model and the 4D free scalar theory - and finding the local CFT data. Gliozzi's method is also applied to an unsolved theory: the 3D Ising Model. This information is used to systematically optimize many of the uncertainties in Gliozzi's method. We then analytically derive new bounds on the convergence of the operator product expansion, and apply standard error propagation techniques to place bounds on local CFT data. Through this study, we were able to optimize Gliozzi's method, and better understand errors in CFT data in unsolved theories.

Constructing an Automated Networks-Based Algorithm for Determining Germline Immunoglobulin Heavy Chain V Segments

Hannah Otis[1], Daniel Gadala-Maria[2], Steven H. Kleinstein[3]

[1]Science, Technology, and Research Scholar, Yale College, New Haven, CT 06520
[2]Interdepartmental Program in Computational Biology and Bioinformatics, Yale University School of Medicine, Yale University, New Haven CT 06520
[3]Interdepartmental Program in Computational Biology and Bioinformatics, Department of Pathology and Department of Immunobiology, Yale University School of Medicine, Yale University, New Haven CT 06520

Understanding an individual's germline immunoglobulin genotype is key to analyzing adaptive immunity. Variation in the germline genotype is associated with differences in disease susceptibility, as well as responses to vaccination and infection. Current methods that attempt to identify V(D)J allele genotypes from high-throughput repertoire sequencing data are ineffective at finding distant alleles, as well as alleles that are present at a low frequency in the B cell repertoire. This project attempts to overcome these limitations with an automated networks-based method for determining the set of germline immunoglobulin heavy chain V allelic segments carried by an individual. Using repertoire sequencing data from the blood sample of a healthy individual, we create two different mathematical networks for each gene: the distance network and the clonal network. In these networks, (1) each node represents a unique V segment and (2) edges represent sequence similarity on the distance network and clonal relationships on the clonal network. Our approach then determines whether each node represents an allele sequence by examining the isotypes, diversity of junction sequences, characteristics of connected components in the clonal network, and the number of unique sequences in the data set with the given V sequence. The method identifies 82 alleles in the current data set, all of which (1) are perfect matches to alleles in the IMGT reference database, (2) have been found by the previously developed TIgGER method, or (3) have been manually validated by examining plots of frequency of mutation at that nucleotide by number of overall sequence mutations—a portion of TIgGER's analytical process. Twenty-one of these alleles are expressed by less than 100 sequences, with some represented by as few as five unique sequence reads each. In some genes, one allele was less than 1% the size of another allele. Four predicted alleles had no match in the IMGT reference database. These results suggest that alleles can be present at very low frequencies, with significant differences in frequencies even within a given gene. It also suggests a networks-based method for finding them.

Role of Location and Passage Time on Endothelial Cell Characteristics

Olga M. Wroblewski[1,2], Angela Liu[2], Ashley L. Gard[2], Amogh Sivarapatna[2], Laura E. Niklason[2]

[1]Science, Technology, and Research Scholar, Yale College, New Haven CT. 06520.
[2]Department of Anesthesiology, Yale School of Medicine, and Department of Biomedical Engineering, Yale University, New Have CT. 06520.

Endothelial cells (ECs) are important in lung tissue engineering because they line the interior surface of all blood and lymphatic vessels. The endothelial cell phenotype varies greatly not only between lymphatic and blood vessels but in different segments of the organ's vascular loop. In addition, cell phenotype is known to change drastically *in vitro*, as cells are expanded to higher passage numbers. A crucial component of cell selection for tissue engineering is the original phenotype and phenotypic stability of the cell line. To determine the EC-phenotype of cells lines available in the laboratory, human pulmonary microvascular endothelial cells (HPMECs) and endothelial colony forming cells (ECFCs) were tested for hematopoietic and lymphatic cell markers via PCR and immunostaining. To investigate phenotype change over time, four different passages of rat pulmonary arterial endothelial cells (PAECs) and rat pulmonary venous endothelial cells (PVECs) underwent phase-contrast imaging and growth analysis. PCR and immunostaining analysis for lymphatic and hematopoietic cell markers were also conducted. Results showed that both HPMECs and ECFS display endothelial cell markers, but HPMECs show large upregulation of lymphatic markers while ECFCs show large up regulation of hematopoietic markers. Phase-contrasting imaging of PAECS and PVECs suggest that PVECs begin to differentiate into other cell types as early as passage 8, while PAECs maintain phenotype for much higher passages. These results can be used to determine which cell lines are most suitable for bioreactor seeding.

Coincident Muon Analysis Between the DM-Ice17 and IceCube Detectors

Nikita S. Dutta[1], Reina H. Maruyama[2]

[1]Science, Technology, and Research Scholar, Yale College, New Haven, CT 06520
[2]Wright Laboratory, Department of Physics, Yale University, New Haven, CT 06520

DM-Ice17 is a direct detection dark matter experiment with two detectors located within the volume of the IceCube Neutrino Observatory at the South Pole. Muons, negatively charged particles produced in the upper atmosphere, are a source of significant background for both experiments. We report the use of muons coincident between DM-Ice17 and IceCube to verify muon identification in DM-Ice17 and provide a novel calibration technique for IceCube. Such events are unique within the IceCube data sample because they are known to pass through each 2.3×10^{-12} km^3 DM-Ice17 crystal volume within IceCube's 1 km^3 total volume. Different muon track reconstruction techniques were explored to optimize resolution by minimizing distance from DM-Ice17 and maximizing accuracy in angles of approach. Reconstructions were performed both on data and simulation. Results indicate a strong improvement in the reconstruction accuracy of low-energy events with the addition of DM-Ice17 information.

Establishing a Wnt/β–Catenin and p63 Signaling Axis during Epidermal Fate Specification

Bertie Geng,[1] Christina S. Kim, Stephen Le Breton, Amanda Farrell, Samantha Lin[2] and Valerie Horsley[2]

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

Epidermal precursor cells derived from human embryonic stem cells (hESCs) have great therapeutic potential for replacing damaged epidermal tissue in patients with skin specific diseases or severe traumas. The p63 transcription factor plays a fundamental role in the transition of epithelial precursor cells towards an epidermal fate. However, the molecular mechanisms that control p63 expression during epidermal fate commitment have yet to be elucidated. Using RNA sequencing we show that the transcription of genes in the Wnt/β-catenin pathway were upregulated as hESCs entered an epidermal fate. In support of this data, previous studies showed that Wnt/β-catenin signaling regulates p63 expression during midfacial ectoderm development. Collectively these studies led us to hypothesize that Wnt/β-catenin signaling functions upstream of p63 to direct epidermal fate specification. To test this hypothesis, we examined the relationship between the Wnt/β-catenin signaling axis and p63 expression in a timecourse of hESCs undergoing epidermal fate commitment. We confirmed our ability to cue hESCs towards an epidermal fate by measuring decreases in the protein and transcript levels of two pluripotency markers, Oct4 and Nanog. Importantly, we also observed an increase p63 expression in differentiated cells compared to hESCs. To establish a relationship between p63 expression and the Wnt/β-catenin signaling pathway, hESCs were transduced with a fluorescent GFP lentiviral Wnt reporter. Immunostaining revealed that a proporation of cells co-expressed GFP and p63. Furthermore, we show that transcript levels for Wnt/β-catenin target genes and p63 isoforms are upregulated during fate specification. Altogether, these studies demonstrate a correlation between an increase in the activity of the Wnt/β-catenin pathway and p63 expression that could potentially be therapeutically harnessed to enhance the specification of hESCs towards an epidermal fate.

Characterization of the Role of HIF-1 in the Regulation of the CXCL12-CXCR4 Ligand-Receptor Axis in the Migration of Bone Marrow Stem Cells to Endometrial Lesions

Reine Ibala[1], Ramana Mamillapalli[2], Kevin Lindsay-Rivera[2], Hugh S. Taylor[2]

[1]Science, Technology, and Research Scholar, Yale College, New Haven, CT 06520
[2]Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale School of Medicine, New Haven, CT 06520

Endometriosis is a disease characterized by the presence of endometrial cells outside of the endometrium. The disorder has been linked to severe pain, infertility, and an increased risk of ovarian cancer. During endometriosis, endometrial lesions develop ectopically, continuing to grow, bleed, and shed during the menstrual cycle. However, without an exit route, the waste material remains trapped within the body, causing adhesions that can bind, scar, and irritate surrounding tissue and organs. Bone marrow stem cells (BMSCs) have been found to travel to the endometrial lesions and contribute to their maintenance and proliferation. However, the mechanism by which these BMSCs migrate throughout the body remains unknown. Our study focused on characterizing potential modulators of the CXCL12-CXCR4 ligand-receptor axis, which is responsible for homing BMSCs to the lesion sites. Regulators that were targeted for this investigation were estradiol (E2), progesterone (P4), and hypoxia inducible factor 1 (HIF-1). While both increased levels of E2 and P4 were found to increase expression of CXCR4 at similar levels, only E2 was found to have a significant impact on the expression of CXCL12. We hypothesize that HIF-1 will increase levels of CXCL12 expressed in human endometrial stromal cells (hESC) due to its documented role in causing differential expression of CXCL12 and involvement in promoting the development of endometrial lesions through its upregulation of proangiogenic factors. However, due to HIF-1's vulnerability to degradation in normoxic conditions, varying concentrations of cobalt chloride were used to attempt to preserve HIF-1 for analysis. Preliminary data remains inconclusive regarding the effect of cobalt (II) chloride on HIF-1a expression. On the other hand, a change of approximately two-fold was observed in CXCL12 expression following increased $CoCl_2$ concentration treatments. Further studies will be conducted to analyze the presence of HIF-1 with increased expression of CXCL12, including optimizing western blot analyses to quantitate HIF-1a and potential mutagenesis knockout and upregulation assays to further elucidate HIF-1a's role in CXCL12-CXCR4 modulation.

High-throughput semi-3D morphometric imaging of macrofossils: a test case using Northeastern Pacific patellogastropods

Sara S. Kahanamoku[1], Pincelli M. Hull[2], Seth Finnegan[3], Leanne E. Elder[2], Allison Y. Hsiang[2], David R. Lindberg[3], Kaylea Nelson[4]

[1]Science, Technology, and Research Scholar, Yale College, New Haven, CT 06520
[2]Department of Geology and Geophysics, Yale University, New Haven, CT 06511
[3]Department of Integrative Biology and Museum of Paleontology, University of California, Berkeley, CA 94720-4780
[4]Center for Research Computing, Yale University, New Haven, CT 06511

Measuring size and shape in species assemblages using traditional methods is time- and labor-intensive, and results in a reduction in information quality. For example, single exemplar measurements are used to represent species' average states, but necessarily ignore intraspecific variation in time and space. Here we showcase a novel method, macroscopic high-throughput imaging, that allows for automated collection of morphometric data from entire assemblages. It is useful for community- or assemblage-level projects, as a single image can contain hundreds of individuals, and our automated image processing software (AutoMorph) drastically reduces processing time while concurrently digitizing each specimen. We apply this method to examine individual variation in an understudied group, Patellogastropoda (true limpets), across a latitudinal gradient (namely, the Northeastern Pacific). The transect studied, which ranges from Alaska to Baja, California, showcases large amounts of environmental variation and encompasses a number of faunal breaks. As such, it is a perfect test of the ability of morphometric imaging to capture ecological trends at high resolution.

Dual-site pontine and thalamic neurostimulation to restore consciousness during and after seizure

Adam Kundishora[2], Abhijeet Gummadavelli[4], Chanthia Ma[1], Mengran Liu[2], Cian McCafferty[2], William Biche [2], Maria Gilardi[2], Eric Musonza[2], Nicholas D. Schiff[5], Jon T. Willie[6], Robert E. Gross[6], Jason Gerrard[4], and Hal Blumenfeld[2,3,4]

[1]Science, Technology, and Research Scholar, Yale College, New Haven, CT 06520
Departments of [2]Neurology, [3]Neuroscience, [4]Neurosurgery, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06520, USA
[5]Department of Neurology, Weill-Cornell Medical College, New York, NY 10021, USA
[6]Department of Neurological Surgery, Emory School of Medicine, Atlanta, GA 30322, USA

Impaired consciousness during and after seizures from medically and surgically refractory epilepsy has a dramatic impact on morbidity, mortality, and overall quality of life. The ability to improve consciousness would be highly beneficial to patients. We have developed a partial limbic seizure rodent model which mimics the human electrophysiological and behavioral characteristics associated with the loss of consciousness in temporal lobe epilepsy. Additionally, we have shown EEG and fMRI suppression of multiple arousal structures including the brainstem cholinergic and thalamic nuclei. Herein, we investigate the effects of single-site pontine nucleus oralis (PnO) or central lateral intralaminar thalamic (CL) deep brain stimulation (DBS) as well as dual-site CL + PnO DBS on cortical arousal and behavior in our animal model. Electrodes were placed sterotactically and localization was confirmed via histologic staining. Seizures were induced with a brief 2 second hippocampal stimulation at 60 Hz. Stimulation of the bilateral intralaminar thalamic CL at 100 Hz and PnO at 50 Hz was then applied at varying current intensities during the ensuing seizure for up to 120 seconds while we synchronously recorded electrophysiology and behavior. We found that dual-site stimulation during seizures reduced cortical slow waves by greater than 85% while simultaneously eliciting robust behavioral arousal as measured by spontaneous exploratory behavior (n=6). This effect resembled that seen with stimulation during physiological sleep (n=6) and under anesthesia (n=6). In contrast, stimulation of just CL or PnO alone was insufficient to produce reliable cortical desynchronization and behavioral improvement during seizures (n=12). We postulate that necessary dual, rather than single-site, stimulation provides further support for the network inhibition hypothesis, which itself describes how widespread subcortical inhibition during limbic seizure results in loss of consciousness. These data also suggest a novel therapeutic approach to improving consciousness during and after seizures. Finally, pairing this with responsive neurostimulation algorithms may lead to rapid implementation of a therapy for preventing impaired consciousness during and after seizures. Studying this model with expanded behavioral tasks will help to illuminate the degree of cognitive recovery in the ictal and postictal periods. Finally, other states of decreased consciousness may similarly benefit from multi-site stimulation.

Interneuron and Immune Dysfunction in Tourette Syndrome

Cristal Suarez[1], Jessica Lennington[2, 3], Flora Vaccarino[2, 3, 4, 5]

[1]Science, Technology, and Research Scholar, Yale College, New Haven, CT 06520
[2]Child Study Center, Yale University School of Medicine, New Haven, CT 06520
[3]Program in Neurodevelopment and Regeneration, Yale University School of Medicine, New Haven, CT 06520
[4]Yale Kavli Institute for Neuroscience, Yale University School of Medicine, New Haven, CT 06520
[5]Department of Neurobiology, Yale University School of Medicine, New Haven, CT 06520

Tourette syndrome (TS) is characterized by childhood onset of chronic motor and vocal tics, and is diagnosed in approximately 1% of children. Previous studies have focused on the role of the basal ganglia in the pathogenesis of TS, and have identified reductions in various interneuron populations as well as the up-regulation of immune-related genes in this region. To clarify whether there is global genetic predisposition to interneuron and immune dysfunction in TS, we sought to determine whether interneuron population disruptions and immune changes occur only in the basal ganglia or extend to either additional or all regions of the brain in TS. The densities of the following cell populations were analyzed: parvalbumin (PV)+ interneurons; nitric oxide synthase (NOS)+ interneurons; and ionized calcium binding adaptor protein-1 (IBA-1) labeled microglia. These populations were evaluated in postmortem cortical tissue from individuals with TS and normal controls using unbiased stereological techniques, in both Brodmann area (BA) 6, a brain region previously implicated in TS basal ganglia motor circuitry, and BA17, a region not presently implicated. To determine whether microglia show a greater immune-response activated phenotype in TS, microglia cell bodies and processes were traced using unbiased 2D neuron mapping to evaluate mean soma area and process length. Our findings revealed a trend toward a decrease in PV+ interneurons and IBA-1 labeled microglia in the BA6 region of the TS brain, and a moderate significant decrease in NOS+ interneurons in the BA6 and 17 regions. These results may implicate disrupted cortical interneuron signaling and immune response in the pathophysiology of TS.

Expression of P/Q Type Calcium Channel Cav2.1 in the Developing Olfactory Bulb

Mahbuba A. Tusty[1,2], Austin W. Jaspers[2], Frank Zufall[4] , Charles A. Greer[2,3]

[1]Science, Technology, and Research Scholar, Yale College, New Haven, CT 06520
[2]Departments of Neurosurgery and [3]Neuroscience, Yale University School of Medicine, New Haven CT, USA
[4]Department of Physiology, University of Saarland School of Medicine, Hombur/Saar, Germany

Voltage-gated Ca^{2+} channels are a primary mediator of depolarization induced Ca^{2+} entry into neurons. Ca^{2+} entry leads to local elevations of intracellular Ca^{2+} which, among other possible functions, initiates the cascade leading to fusion of synaptic vesicles with the presynaptic membrane to release neurotransmitters. One such voltage-gated calcium channel, the P/Q type Cav2.1, has been implicated in hippocampal and neocortical dynamics of synaptic vesicle release. Less, however, is known about Cav2.1 in the olfactory system and how it is involved in modulating the organization of the system or odor processing. To begin probing the molecular mechanisms that may regulate synaptic transmission in the olfactory system, we have explored the expression of Cav2.1 developmentally using confocal and electron microscopy in the olfactory bulb of C57BL/6 mice. Cav2.1 was expressed most robustly in selective individual glomeruli beginning at postnatal day (PND) 10, with similar selective expression seen at PND 20 and in the adult. Double labeling with antibodies to olfactory marker protein and vesicular glutamate 2 protein, as well as electron microscopy, confirmed that localization was specific to the axons and terminals of olfactory sensory neuron axons. The selective expression in only a small subset of glomeruli was reminiscent of the specificity seen with individual odorant receptors. The data are consistent with Cav2.1 playing a role in the synaptic dynamics of olfactory sensory neuron terminals. Moreover, the selective expression in only a few glomeruli suggests that Cav2.1 is associated with a small subset of odorant receptors and may be differentially modulating odor processing.

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