Saturday 11/17

**Effects of Stochasticity on Circadian Rhythms**

**Chaitra Agrahar**[1], Michael J Rust[2]
[1]University of Illinois at Chicago, [2]University of Chicago

Circadian rhythms, cell cycles, segmentation, etc. are a few examples of biological phenomena where rhythmicity is of import. Many different biological circuits can be constructed that give rise to stable limit cycle oscillations deterministically. There have been several studies focusing on the topologies or the optimization of interaction strengths in circuits that give rise to limit cycles over a broad range of frequencies or at constant amplitudes. However, the fact that a cell is subjected to internal and external noise has not been accounted for very well. In this study, we hope to understand whether the response of a circuit to stochasticity is a factor in determining which topology efficiently achieves a certain biological function at a certain system size, and if the parameters are optimized to achieve a robust response from the circuit. We do this by studying different network motifs, like the repressilator, or the Goodwin Oscillator.

Friday 11/16

**Single-cell Quantification of Gene Expression Reveals Mechanisms of Transcriptional Regulation in Developmental Genes**

**Rachael Bakker**, William Finnegan, Ritika Giri, Madhav Mani and Richard Carthew
Northwestern University

During development, cells gain unique identities by modulating gene expression in response to extracellular signals. A fundamental mechanism for controlling gene expression is at the level of transcription. Transcription itself is a stochastic process in which a gene's promoter switches between discrete states of differing transcriptional activity. This results in periods of mRNA production known as transcriptional bursts, followed by periods of no transcription. From this model, it follows that there are two quantitative parameters involved in the mechanism of transcription: the number of mRNAs produced per transcriptional burst, known as burst size, and the time between bursts, or burst frequency. When a gene is transcriptionally upregulated or downregulated by an upstream signaling event, which of these parameters is being regulated? Using *Drosophila* imaginal discs as a model system for animal tissue patterning, we measured levels of nascent and mature mRNAs via smFISH for genes responsive to the *Drosophila* homologs of TGFb and Wnt signaling. These signals form gradients across the tissue that allow us to make inferences about how the dynamics of transcription change along the gradient. Our results show that burst frequency correlates with changes in transcript number across signaling gradients in the genes observed. Conversely, burst size does not correlate well with transcript number. This is consistent with a model of transcriptional regulation in which burst frequency, rather than size, is the primary mechanism by which mRNA number is modulated in this context. Our results shed light on the mechanism of transcriptional responses downstream of conserved signaling pathways in developing animal tissues, and add to a body of evidence quantifying transcriptional responses to signaling changes in different contexts.

Saturday 11/17

**Comparing Fluorescent Staining versus Digital Staining as a Method for Living Cell Discovery**

**J. Coleman**
IL Science + Technology Park

Improve the study of *in vivo* cell biology by using non-invasive holographic tomographic microscopy to analyze the data of cell types, organelles, and dynamic processes such as cell division, cell morphology in biochemical assays for drug discovery screening, and cell death. Specifically, the use of fluorescent staining versus digital staining as a method for cell discovery will be compared. A live cell is transparent and offers no contrast for imaging in classical optical microscopy. Hence, chemical markers are used to provide contrast between cells and their subsystems. Traditional fluorescence microscopy is invasive, marker-dependent, and has limited end points. An intense high power laser is required to excite an exogenous fluorescent marker added to live cells, which is incompatible with normal physiological conditions and causes bleaching, phototoxicity, and limits observation time. On the other hand, digital staining used in non-invasive 3D live cell imaging involves no bleaching, no phototoxicity, and is marker free. A low intensity laser is used to scan a cell sample at the rate of 1.5 second per 3D image. Digital staining allows you to observe and identify cells based on their refractive index (an inherent natural property) for quantitative analysis via a color code to generate a 3D reconstruction of a cell. Various live cell samples will be studied using fluorescence staining and digital staining to compare and contrast the effectiveness of fluorescence microscopy versus holotomographic microscopy.

Friday 11/16

**High chemical affinity increases the robustness of biochemical oscillations**

**Clara del Junco,** Suriyanarayanan Vaikuntanathan
The University of Chicago

Biochemical oscillations are ubiquitous in biology and allow organisms to properly time their biological functions. In this poster presentation I will discuss minimal Markov state models of non-equilibrium biochemical networks that support oscillations. Using a perturbation theory, we obtain analytical expressions for the coherence and period of oscillations in the networks. These quantities are expected to depend on the detailed makeup and arrangement of transition rates in the Markov state model. However, our analytical calculations reveal that many of these details - specifically, the location and arrangement of the transition rates - become irrelevant to the coherence and period of oscillations in the limit where a high chemical affinity (i.e. ATP hydrolysis) drives the system out of equilibrium. This allows the coherence and period of oscillations to be robustly maintained and tuned. Our results also confirm the postulated bound on the coherence of biochemical oscillations set by the chemical affinity of the network (Phys. Rev. E 95, 062409). While recent work has established that increasing energy consumption improves the coherence of oscillations, our findings suggest that it plays the additional role of making the coherence and the average period of oscillations robust to changes that can result from the noisy environment of the cell.

Friday 11/16

**Shape Dependent Motility During the Establishment of Tissue Structure**

**John Devany**[1], Daniel M Sussman[2], M Lisa Manning[2], Margaret L Gardel[1]
[1] The University of Chicago; [2]Syracuse University

Mature epithelial tissues have distinct cellular architecture, which is maintained despite externally applied forces, wounding, and cell division or death. Here we investigate how a model tissue develops and maintains cellular structure by quantifying single cell dynamics and cell shape in newly formed MDCK monolayers. Over time cells in the monolayer become increasingly hexagonal and arrest at a final structure resembling a mature epithelium. Throughout this process we observe glassy dynamics controlled by cell shape, as predicted by vertex models. Varying substrate stiffness causes monolayers to form and evolve with different cell density, but a similar relationship between cell shape and dynamics. This suggests the changes in cell density often observed in tissue development may not directly impact cell motility. We find that inhibiting regulators of the actin cytoskeleton cause monolayers to arrest with elongated cell shapes. Interestingly, across a diverse set of conditions we find a relationship between the final cell shapes and velocity correlation length which we explore in vertex models by including cell alignment coupling. Our results demonstrate that multicellular coordination of motility affects the regulation of cell shape and determination of final tissue structure.

Friday 11/16

**Optimal Drift Time for Crossing Fitness Valleys**

**Mario E. Di Salvo**, Kimberly Reynolds, and Milo M. Lin
UT Southwestern

Epistasis dramatically alters the fitness landscape creating peaks and valleys. Natural selection drives populations of individuals towards peaks by acquiring beneficial mutations. But how evolution might cross fitness valleys remains an unresolved problem. It is shown here that, depending on the mutation rate and the number of epistatic mutations, there is an optimal time-scale for which the selection pressure should be switched off that maximizes the probability of crossing a fitness valley. If the environmental conditions underlying the selection pressure are modulated on this time-scale, adaptation rates can be accelerated by many orders of magnitude as compared with continuous selection pressure. In an in vitro experiment involving RNA ribozymes and error prone PCR, we test the theoretical framework by looking for the existence of the optimal environmental fluctuation that can speed up the escape from local fitness maxima. The model can be used to design optimal selection protocols that accelerate or retard rates of evolutionary dynamics for protein engineering.

Friday 11/16

**Cross-tissue protein expression in the Genotype-Tissue Expression (GTEx) collection**

**Marian S. Fernando**, Meritxell Oliva, Caroline Linke, Fan Wu, Andrew Skol, and Barbara E. Stranger
University of Chicago

Due to the dynamic nature, the proteome is a vital element in the causal network that links genetic risk factors to clinical endpoints. As part of the enhancing Genotype-Tissue Expression consortium (eGTEx), we aim to determine the cross-tissue protein expression variability and the effect of genetic variation on protein expression in humans. We employ Microwestern Arrays to quantify the relative protein abundances of transcription factor and cell signaling genes in samples from GTEx. The project is in two phases. Dimensions of many tissues but few individuals are tested in Phase I. Dimensions of many individuals but few tissues are tested in phase II.

In Phase I on average, cross tissue ranks based on protein levels are not highly correlated with ranks derived from transcript levels. However, tissue specificity shown at a protein level may be more indicative of the contribution of a gene to a phenotype of interest than transcript level patterns. We observe both positive and negative correlations of inter-individual mRNA and protein levels within tissues and highlight examples of GTEx expression quantitative trait loci (eQTLs) that are consistent at the protein level suggesting pQTLs. Currently, we are quantifying the same 353 proteins within and between 12 GTEx tissues (N=216 per tissue) to better characterize the protein expression landscape, assess the genetic basis of protein expression variation within and between tissues, and build protein-mRNA regulatory networks.

Friday 11/16

**Patterning of the *Drosophila* compound eye**

**Kevin D Gallagher**, Madhav Mani, and Richard W Carthew
Northwestern University

Diffusing chemical signals and local intercellular communication cannot encode geometry and, therefore, cannot plausibly account for spatially extended patterns. Instead, such patterns must emerge dynamically during development. Our research takes aim at the following fundamental questions: How do patterns of gene expression and morphology synchronously emerge? What are the feedback mechanics that guide and correct the emergence of physical form? We use the compound eye of *Drosophila melanogaster* as an experimental system to address these questions. This sensory organ transitions from a disorganized epithelium into a patterned array of photoreceptors during late larval life. Patterning is initiated by a mechanical wave called the morphogenetic furrow (MF) that moves across the developing eye disc over the course of two days. In its wake, periodic clusters of cells begin to differentiate into photoreceptors and proceed through a stereotyped cascade of changes to their morphology and topology. Each of these clusters of cells will become the units, or ommatidia, of the compound eye. We created a technique to *ex vivo* culture the developing eye for up to 16 hours that allows us to monitor both morphology and gene regulation in real time through fluorescence-based reporters. Our technique has revealed surprising patterns of cellular flow through the MF. Rather than acting like a simple compression wave moving through the tissue, as naively hypothesized, the MF differentially captures and retains cells selected to become photoreceptors, displacing them further anteriorly relative to non-selected cells. Photoreceptor capture and retention appears to be the mechanism by which the MF controls the spacing of photoreceptor clusters, which emerge as a hexagonal lattice on the posterior side of the MF. We are currently working to understand how gradients and anisotropies in mechanical stress along the interfaces of cells are driving these cellular flows through the MF.

Friday 11/16, Saturday 11/17

**Stochastic gene expression destabilizes ordered patterns**

**Ritika Giri**[1], Dimitrios Papadopoulos[2,3], Diana Posadas[1], Hemanth Potluri[1], Pavel Tomancek[2], Madhav Mani[1] and Richard W Carthew[1]
[1]Northwestern University, [2]Max Planck Institute of Cell Biology and Genetics,[3]University of Edinburgh

Stochasticity is a universal feature of molecular interactions. In living organisms, this property renders cell fate decisions probabilistic rather than deterministic. A classic model to study noise driven self-organization via mutual cell competition is sensory patterning in *Drosophila.* Indeed, sensory patterning relies upon gene expression noise to initiate the self-organizing process of mutual competition. Paradoxically, sensory organs are often arranged in highly-ordered assemblies as a means to predictably map environmental stimuli to neural circuitry. While the emergence of order from disorder is a hallmark of development, how is pattern formation rendered immune to the underlying stochasticity of gene expression? I explore this by measuring stochastic noise in the expression of sensory-fate determinant transcription factor Sens. I do this by employing allele specific two-color expression measurements of Sens, a cell fate regulator gene, in the fruit fly. BAC recombineering was used to create genomic constructs of Sens fused in frame to sfGFP or mCherry, and these completely replaced the endogenous *sens* gene (deleted by null mutations). I then correlated red-green fluorescence levels in thousands of individual wing disc cells using quantitative microscopy. Previous studies have shown that protein fluctuations in dissociated cells behave like simple Poisson-like processes with a constant Fano factor. In contrast, Sens Fano factor displayed a complex relationship to protein abundance, with a peak in cells containing < 300 molecules and constant Fano floor thereafter. Post-transcriptional regulation of Sens mRNA by a microRNA acted to decrease the Fano 'floor' uniformly, whereas transcriptional perturbations only affected the amplitude of the Fano peak. Together with simulations, these data allowed us to conceptually frame Sens noise as coming from two distinct sources 1) transcriptional bursting kinetics and 2) RNA/protein birth-death processes. Infrequent transcription burst produce a Fano peak which decays as promoter switching becomes faster. The size of transcription bursts determines Fano peak amplitude. Further, Sens noise during development translates into pattern disorder in adults. Curiously larger Fano peaks correlate with ectopic sensory cells but higher Fano floors do not. We also find that stochastic noise can drive pattern disorder independently of Sens abundance. Our results suggest that stochastic noise in gene expression is an evolutionarily constrained parameter optimized to initiate self-organization without disrupting ordered patterns. This allows accurate fate resolution without requiring the production of large numbers of molecules.

Friday 11/16

**Temporal precision of molecular events with regulation and feedback**

**Shivam Gupta**, Sean Fancher, Hendrik Korswagen, Andrew Mugler
Purdue University

Cellular events such as cell migration, division, and cell differentiation rely on precise timing. Molecular events inside cells are highlystochastic, and yet cells trigger events with high timing precision. We explore the effect of gene regulatory networks on first passage timing precision. We devise a method to find the global regulation function between the regulator and target gene which optimizes the timing precision. This method can be applied to a range of networks involving two genes such as regulation by an external species combined with autoregulatory feedback on the target gene itself. We confirm that feedback alone is not helpful in increasing timing precision. However, if a regulator is present then the combination of feedback and regulation is more beneficial than regulation alone. Specifically, higher timing precision is achieved by positive feedback when the regulator is high and negative feedback when the regulator is low. Our results are relevant to experimental gene regulatory systems where high timing precision is crucial, such as neuroblast migration during *Caenorhabditis elegans* development.

Friday 11/16, Saturday 11/17

**Tuned polymerization of the transcription factor Yan limits off-DNA sequestration to confer context-specific repression**

**C Matthew Hope**, Jemma L Webber, Sherzod Tokamov, Ilaria Rebay
The University of Chicago

During development, transcriptional complexes at enhancers regulate gene expression in complex spatiotemporal patterns. To achieve robust expression without spurious activation, the affinity and specificity of transcription factor-DNA interactions must be precisely balanced. Protein-protein interactions among transcription factors are also critical, yet how their affinities impact enhancer output is not understood. The Drosophila transcription factor Yan provides a well-suited model to address this, as its function depends on the coordinated activities of two independent and essential domains: the DNA-binding ETS domain and the self-associating SAM domain. To explore how protein-protein affinity influences Yan function, we engineered mutants that increase SAM affinity over four orders of magnitude. This produced a dramatic subcellular redistribution of Yan into punctate structures, reduced repressive output and compromised survival. Cell-type specification and genetic interactions defects suggest distinct requirements for polymerization in different regulatory decisions. We conclude that tuned protein-protein interactions enable the dynamic spectrum of complexes required for proper regulation.

Saturday 11/17

**Interphase chromatin as a self-returning random walk**

**Kai Huang**, Vadim Backman and Igal Szleifer
Northwestern University

We introduce a self-returning random walk to describe the structure of interphase chromatin. Based on a simple folding algorithm, our de novo model unifies the high contact frequency discovered by genomic techniques, and the high structural heterogeneity revealed by imaging techniques, which two chromatin properties we theoretically prove to be irreconcilable within a fractal polymer framework. Our model provides a holistic view of chromatin folding, in which the topologically associated domains are liquid-tree-like structures, linked and isolated by stretched out, transcriptionally active DNA to form a secondary structure of chromatin that further folds into a “3D forest” under confinement. The model pivots a wide array of experimental observations and suggests the existence of a universal chromatin folding principle. Based on a global folding parameter, the model reveals a unique structure-function relation of chromatin, which is abnormal from a polymer point of view but explains some experimental observations of how chromatin responses to stress.

Saturday 11/17

**The Self-tuned Sensitivity of Circadian Clocks**

**Kabir B Husain[1]**, Weerapat Pittayankachit[1,2], Amir Bitran[2], Ofer Kimchi[2], Mirna Kramar[2], Amanda Parker[2], Ching-Hao Wang[2], Gopal Pattanayak[1], Michael J Rust [1], Arvind Murugan1[,2],
[1]University of Chicago, [2]Cargese Biophysics Summer School

Living organisms make unreliable observations of their environment while also making unreliable internal predictions of what their environment should be. The theory of Kalman filtering suggests that predictions should be updated by measurements using a time-varying environmental sensitivity that reflects the estimated unreliability of these quantities. We show that the circadian clock in S. elongatus can naturally show such self-tuned environmental sensitivity by analyzing the feedback coupling between clock and metabolism quantified in recent experiments. The metabolic coupling detects mismatch between clock predictions and environmental light conditions and can temporarily raise the clock's sensitivity to light changes, allowing faster entrainment in case of mismatch. We also analyze analogous behavior in recent experiments on switching between slow and fast osmotic stress response pathways in yeast. In both cases, Kalman-like strategies allow an organism to naturally switch from states of low to high sensitivity under stress. Our work suggests experiments that probe the history-dependence of environmental sensitivity in biophysical sensing mechanisms.

Friday 11/16

**Diet-Dependent Fat Body Transcriptome Analysis Reveals the Proteasome as a Molecular Link Between Circadian Rhythms Clocks, Longevity, and Dietary Restriction**

**Dae-Sung Hwangbo[1]**, Yong-Jae Kwon[1], Marta Iwanaszko[1], Peng Jiang[1], Alan L. Hutchison[2], Aaron R. Dinner, Rosemary I Braun, and Ravi Allada
[1] Northwestern University, [2]The University of Chicago

Circadian clocks may mediate lifespan extension by caloric or dietary restriction (DR). We find that the core clock transcription factor Clock is crucial for a robust longevity and fecundity response to DR in Drosophila. To identify clock controlled mediators, we performed RNA-sequencing from abdominal fat bodies across the 24 h day after just 5 days under control or DR diets. In contrast to more chronic DR regimens, we did not detect any significant changes in the rhythmic expression of core clock genes. Yet we discovered that DR induced de novo rhythmicity or increased expression of rhythmic clock output genes. Network analysis revealed that DR increased network connectivity in one module comprised of genes encoding proteasome subunits. Adult fat body specific RNAi knockdown demonstrated that proteasome subunits contribute to DR-mediated lifespan extension. Thus, clock control of output links DR-mediated changes in rhythmic transcription to lifespan extension.

Saturday 11/17

**Stochastic Modeling of Transforming Growth Factor-β2 Receptor Formation**

**Michelle Ingle**, Bobby Madamanchi, David Umulis
Purdue University

Transforming growth factor (TGF) β2 is a small secreted signaling protein vital in cell growth and development. It signals through a tetrameric complex made up of two TGF-β type I and two type II receptors (TβRI and TβRII, respectively). The TGF-β2 pathway relies on a nonsignaling coreceptor called betaglycan in order to form the tetrameric receptor. While it is known that betaglycan is essential to promote signaling, the mechanism of its action is not yet understood. We developed mechanistic stochastic models of betaglycan and TGF-β2 signaling and tested alternative hypotheses for betaglycan's role in the regulation of signaling. Our early results suggest that betaglycan must function to alter reaction kinetics to confer the measured boost in complex formation and it cannot function as stronger source of available ligand to receptors. This model of the TGF-β2 pathway will enable researchers to better understand the mechanics of this pathway and its critical role in cell development.

Friday 11/16

**Extraction of Quantum Timescales in Photosynthetic Proteins**

**Shawn Irgen-Gioro**, Karthik Gururangan, Elad Harel
Northwestern University

The amount a time quantum states maintain coherence dictates the timescale quantum effects play a significant role. Electronic coherence frequency and lifetime are observed from both Light Harvesting Complex II (LH2) and the Fenna-Matthews-Olson (FMO) complex and occur at the same timescale (<100 fs) as energy transport. A systematic methodology to extract coherences is developed using multidimensional spectroscopy and global analysis, leading to the observation of two distinct timescales of population dynamics and coherences. The same procedure in BChla reveals no electronic coherences as expected, supporting the validity of our methodology. In LH2, global analysis of population dynamics reveals that energy transfer between states at the energy level difference equal to the coherence energy occurs at a similar timescale (~74 fs). This result suggests that quantum effects may play a role in photosynthetic systems at a <100 fs timescale.

Friday 11/16

**Neuronal identity and neuron-specific gene cycling between PDF and DN1 neurons in the *Drosophila* brain**

**Marta Iwanaszko**, Elzbieta Kula-Eversole, Ravi Allada, Rosemary Braun.
Northwestern University

Approximately 150 neurons of the 200,000 neurons in the *Drosophila* brain comprise the fly's circadian neural network. Two main types of cells, PDF and DN1, have diverse functions in guiding fly circadian activity and behavior. PDF (or “morning”) cells control the morning peak of activity and are important in short photoperiods. DN1 cells, part of group called “evening” cells, control the evening peak of activity as well as the morning peak, and enhance morning arousal. DN1 cells feed back to morning and evening cells and promote sleep. It has been shown recently that temperature and sleep regulate activity of DN1 neurons. Using a variety of computational methods, we analyzed cycling patterns of gene expression in RNA-seq data from both DN1 and PDF neurons under different diet and temperature conditions. While the core clock genes retain their phase of oscillations in both cell types and under all conditions, we observe clock-regulated genes with a strong phase difference between the neuron types. We introduced perturbation in form of combinations of temperature and dietary conditions. Summer and winter photoperiods are characterized by different temperatures and access to nutrition. We investigated behavior and gene expression data of flies entrained in 25$^{o}$C (High temperature) and 18$^{o}$C (Low temperature), under high/low calorie regimens (15%/5% of yeast extract), and collected periodograms (frequencies of fly movement in time-series data) of flies entrained in light-dark (LD) conditions to analyze changes in their general behavior and compare respective conditions in view of number and type of cycling genes. Our analysis shows that differentially expressed genes in PDF cells are more responsive to the temperature changes than dietary changes. In case of DN1 response to temperature and diet is more similar. High number of cycling genes is shared between PDF and DN1 cells, and among these genes we observe more than 50% of genes to cycle with phases shifted by more than 2 hr. Differential expression analysis shows that temperature impacts gene cycling profiles more strongly than diet in these neurons. Analysis of gene rhythmicity, differential cycling and functional clustering provides insights into these neurons’ distinctive functions and their response to environmental perturbations.

Friday 11/16, Saturday 11/17

**Analyzing Cell Fate Decisions through the Lens of Dynamics**

**Ashika Jayanthy***, **Simon Freedman***, Kristin Johnson*, Carole LaBonne, Madhav Mani
Northwestern University

As an embryo develops from a fertilized egg to a complex anatomy, its cells progress from a pluripotent state toward different lineage restricted fates. While the start and end points of this process have been well studied, much less is understood about the dynamics of developmental decision making. The pluripotent animal cap cells of early *Xenopus* embryos are an ideal system to study these dynamics. When removed from the embryo these cells can be instructed to form any embryonic cell type and achieve lineage restriction on a time scale of hours. Absent other instructions, autocrine BMP signaling directs cells to an epidermal state. By contrast, inhibiting this BMP signaling by exposure to the BMP antagonist Noggin directs these cells to a neural progenitor state. We will analyze gene expression data (obtained via RNA-seq) during multiple timepoints along this fate decision, and use it develop a predictive mathematical model of trajectories through cell-fate landscapes. We will also use this data to identify specific changes in genetic regulation that guide these cells toward their specific lineage restrictions. Our work will aid in determining the necessary molecular pathways to lineage restriction in pluripotent cells, and more broadly, how cell fate landscapes change over the course of development.

Friday 11/16, Saturday 11/17

**Inflationary Embryology**

**Ojan Khatib Damavandi**, David K. Lubensky
University of Michigan

Tissue growth is fundamental to biology and is noisy. Noise has important implications for morphogenesis and tissue integrity, yet a basic theoretical description of noisy tissue growth has been lacking. Growth nonuniformity leads to a build-up of mechanical stresses, and many tissues respond to stress by modulating their growth. Then, how does the interplay between noise and stress feedback affect tissue growth, and what can we predict about the statistical properties of experimentally accessible quantities? We model the tissue as a continuum, elastic sheet undergoing exponential growth with mechanical feedback and find that the density-density correlations show power-law scaling in space. In anisotropic growth, the standard deviation in clone sizes is comparable to the mean, in contrast to the isotropic case where relative variations in clone size vanish at long times. The high variability in clone statistics observed in anisotropic growth is due to the presence of two soft growth modes, which generate no stress. Our work analyzes the simplest model of noisy growth of elastic tissues. It thus both introduces a new class of nonequilibrium growth models and represents a first step towards understanding specific biological contexts.

Friday 11/16

**Regulation of Motions of Myosin Motors in the Actin Cortex**

**Wonyeong Jung**, S.M. Ali Tabei, Taeyoon Kim
Purdue University

Active transport driven by molecular motors in the cytoskeleton plays an important role in various cellular processes. It has been hypothesized that motions of myosin motors in the cortex are determined by the architecture of the cortex. However, the effects of dynamic, force-dependent behaviors of cytoskeletal components on myosin motors remain elusive despite their potential importance. In this study, we employed an agent-based computational model to study motions of myosin in the cell cortex. The model accounts for possible governing factors, including force-dependent walking of motors and the turnover of cross-linkers and F-actin. We found that motions of motors can be suppressed due to three reasons. Motors can slow down significantly either by local force generation or global force transmission between motors. It is also possible F-actin aggregation prevents motors from consistently walking. However, F-actin turnover can recover motor motility in all three cases by inducing force relaxation on motors and cross-linkers. Our results shed light on how myosin motions are regulated by many factors in vivo.

Friday 11/16

**Regulation of Pulsed Contraction of Actomyosin Networks**

**Jing Li**, Qilin Yu, Michael P. Murrell, Taeyoon Kim
Purdue University

Actomyosin contractility regulates various biological processes including cell migration and cytokinesis. Cell cortex underlying a membrane, which is a representative actomyosin network in eukaryote cells, exhibits dynamic contractile behaviors. Interestingly, the cell cortex shows reversible aggregation of actin and myosin called pulsatile contraction in diverse cellular phenomena, commonly associated with the spatiotemporal expression of a Rho GTPase: RhoA. While contractile behaviors of actomyosin machinery have been studied extensively in several in vitro experiments and computational studies, none of them successfully reproduced pulsed contraction observed in vivo. In this study, we employed an agent-based computational model based on Brownian dynamics to identify critical factors facilitating the pulsatile contraction of actomyosin networks. We reproduced the pulsed contraction only with the mechanical and dynamic behaviors of cytoskeletal components. We found that clusters with physiologically relevant size and duration can appear in the presence of both F-actin turnover and angle-dependent F-actin severing resulting from buckling induced by motor activities. We concluded that the strong pulsatile contraction of actomyosin networks only occurs when there is subtle balance between force generation from motors, global force relaxation via actin turnover, and local force relaxation via angle-dependent actin severing. Our study sheds light on the underestimated significance of F-actin dynamics for the pulsed contraction during various physiological processes.

Friday 11/16, Saturday 11/17

**Pre-Knowledge Based Lasso for Gaussian Graphical Models**

**Keren Li**
Northwestern University

Structure learning in graphical models has drawn considerable attention in many fields, such as computational biology, protein networks, and social network analysis. In such fields there often exists annotated database for interactions between nodes, which is useful but often incomplete or error-prone. The real data collected however frequently faces the curse of small sample size and high imensionality, lacking the power to infer the complete graph structure in a blind way. How to combine the real data and existing knowledge for discovery of graph structures becomes a challenging problem. We propose a pre-knowledge based lasso for the Gaussian graphical model, using the known partial structure to configure initial weights of regularization parameter for a pathwise regression. Simulation studies show that it outperforms original lasso in terms of either true positive rates or true negative rates for $p > n$ case. This method can be implemented to other lasso-family members, such as SCAD, elastic net and adaptive lasso, etc.

Friday 11/16, Saturday 11/17

**Comparing structures and dynamics of *in silico* molecular clocks**

**Sungsoo Lim** and Karna Gowda
University of Illinois at Urbana-Champaign

In nature, evolution produces a diversity of forms with equivalent functions – there are numerous examples of different molecular and regulatory structures which behave as biological clocks that regulate basic functions. This project uses genetic algorithms to generate a collection of ordinary differential equations (ODEs) that model molecular clocks. We compare these ODEs in terms of their structures and dynamics in order to characterize the dimensionality of evolved structures that perform equivalent functions.

Saturday 11/17

**Three-dimensional growing finite element model of BMP gradient formation during epiboly of the early zebrafish embryo**

**Linlin Li**, Xu Wang, Tzu-Ching Wu, Adrian Buganza Tepole, David Umulis
Purdue University

Bone Morphogenetic Proteins (BMPs) play a primary role in dorsal-ventral (DV) patterning of the early zebrafish embryo. BMP signaling is regulated by a complex network of intra- and extracellular modulators, and processes on cell membranes. Despite the advances in understanding each modulator and its likely function, the overall picture of how those modulators work systematically to generate the BMP gradient as a robust system is still not clear. Here we use mathematical modeling as a tool to elucidate mechanisms of BMP regulation that drives pattern formation. We developed a three-dimensional finite-element model to simulate BMP patterning and growth during epiboly. Updated Lagrangian formulation are applied to model the cell moving and domain growth during epiboly and track the stress free state throughout the deformation. The growing mesh allows for remising to handle extreme deformations. Quantitative whole mount RNA scope data of BMP2b and phosphorylated-SMAD data are collected and analyzed to precisely to test the hypotheses of gradient formation mechanism in our model. We found that the growth model results in consistent spatially and temporally with early zebrafish embryo DV patterning. The three dimensional model supports a source-sink mechanism for pattern formation around the margin in early development, however the role of feedback during later stages of gastrulation are still being deciphered.

Friday 11/16

**A wavelet-based exploratory statistical analysis of hydrophobic content in homologous pairs of proteins in mesophile and thermophile bacteria.**

**Jack Linehan**, Jesus Pando
DePaul University

This study consists of a wavelet-based exploratory statistical analysis of the hydrophobic content of homologous pairs of proteins in two types of bacteria, mesophile and thermophile. The hydrophobic effect is a temperature dependent process and is one of the major driving forces behind protein folding. It is possible that hydrophobic information is encoded into the proteins in each pair in a way that reflects both their homologous function and different evolutionary lineages. Hydrophobicity signals are generated for each protein by assigning a hydrophobic value from three different scales to each amino acid in the polypeptide. The signals are then passed through the Wavelet Packet Transform resulting in a multiresolution analysis of the hydrophobic content of the proteins. A control set of data is established by bootstrapping the hydrophobicity signals, which maintains the frequency of each amino acid while removing its position dependence. Spectrum analysis shows that the variance per width in hydrophobic content is similar between the proteins in a homologous pair at certain frequencies. This result occurs ten times more often in the biological sequences than in the bootstrapped control data and may show that the localized fluctuation in the hydrophobicity signals reflects the homologous function of the pair.

Friday 11/16, Saturday 11/17

**Growth Control of *Drosophila* Wings**

**Andrew Liu,** Richard Carthew
Northwestern University

One fundamental aspect of developmental biology is growth control – how growth rate and final organ size is determined. The *Drosophila* wing imaginal disc is a well-established model system, where growth is spatially homogenous and exponential during the second and early third instars. Previous research suggested that, in the wing pouch, the gradient of Dachsous (Ds) and Four-Jointed (Fj) within the Fat signaling pathway may regulate growth. Specifically, it is the juxtaposition of high and low Ds/Fj in neighboring cells that drives proliferation. Therefore, a young, small disc with a steep gradient will continue to proliferate while an older, large disc with a shallow gradient will not proliferate further. My first aim is to quantify and manipulate the global gradients of Ds and Fj using temperature, nutrition, and gender differences. Furthermore, *ex vivo* live-imaging of wing disc explants has been successfully implemented to support growth similar to *in vivo* conditions. I seek to combine live imaging with microfluidic devices to manipulate local gradients and assay the changes in growth control.

Saturday 11/17

**Correlated amino acid fluctuations regulating adhesion uropathogenic Escherichia coli (UPEC) fimbrial protein FimH**

**Jenny Liu**, Kerim Dansuk, Luis Amaral, Sinan Keten
Northwestern University

Uropathogenic Escherichia coli causes urinary tract infections and has a fimbrial adhesion protein, FimH, which can bind strongly to mannose on urothelial cell surfaces, limiting clearance during urination. Although the binding site has been an active area of research, no drugs currently target the native allosteric site that controls the switch between strong and weak adhesion. The switch from weak to strong affinity for mannose is activated by mechanical separation of the two domains of FimH. The mannose-binding lectin domain has small changes in structure, as well as changes in dynamics. In literature, regulation has been described alternatively as both structural and dynamical allostery. Using molecular dynamics simulations, we study mannose-binding, focusing on correlated fast dynamics, which are ns-ps timescale motions, on the order of sidechain rotamer angle fluctuations. In other allosteric proteins, correlated fast dynamics have been shown to enable information transfer between the allosteric and functional sites. These correlations have previously been captured using information transfer models on networks, but there is no consensus for selecting dynamics features. We use multilayer networks to capture many methods that describe fast dynamics. Multilayer networks capture qualitatively different types of connections – e.g. different types of transportation (bike, bus, train) in a city– without favoring one type of connection or ignoring differences through averaging. In these networks, nodes are residues, and in each layer, edges are weighted by a different method, e.g. contact frequency (short-range) and electrostatic interaction energy (long-range). Analysis relevant to FimH allostery will focus on network properties related to information transfer, community organization of residues with similar connectivity patterns, and network topology. In addition to understanding correlated fast dynamics for FimH, this framework could also be used to study homologous adhesion proteins and other allosteric proteins.

Saturday 11/17

**Quantitating the in vivo relationship between Notch signaling and the protein Olfactin in the developing olfactory system**

**Joseph N. Lombardo**, Brogan L. Casper-Strauss, Ankur Saxena
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Development of the vertebrate olfactory system is mediated by a complex set of biological processes spanning multiple tissues and cell types. In zebrafish, the olfactory epithelium (OE) contains two main types of olfactory sensory neurons—ciliated (cOSNs) and microvillous (mOSNs)—which project axons to the olfactory bulb (OB). A previous protein trapping screen yielded a transgenic zebrafish line with a currently unidentified protein, which we have named Olfactin, fused to a Citrine fluorophore. Expression of this fluorescent fusion protein, Olfactin-Citrine (Olf-C), occurs in the OE and OB at the earliest stages of their formation, and therefore, we hypothesize that Olf-C may play a critical role in olfactory development. Through in vivo confocal microscopy and the quantitative measurement of fluorescence intensities that directly represent Olf-C protein concentrations, we obtain linearly-scaled readouts of Olf-C levels in the developing olfactory system with high spatiotemporal resolution. We can use these readouts to investigate which signaling pathways modulate Olf-C protein levels and subcellular localization. Notch signaling is a highly conserved pathway known to play critical roles in cell fate and differentiation in multiple tissues. Based on the expression pattern of Notch receptors in the olfactory system, we blocked Notch signaling in vivo with the ɣ-secretase inhibitor DAPT from 24 to 31 hours post-fertilization (hpf), a significant timeframe for OSN differentiation, and imaged embryos from 36 to 48 hpf. We found that inhibition of Notch signaling increased the average level of Olf-C protein per cell in the OE while not affecting the overall number of Olf-C+ cells. Further quantitation revealed that the distribution of Olf-C concentrations was differentially affected in cOSNs and non-cOSN cells. To validate these results, we induced overexpression of Notch signaling via the heat shock transgenic zebrafish line hsp70:NICD at 22 hpf and imaged embryos from 33 to 48 hpf. Preliminary data suggest that increased Notch signaling initially reduced Olf-C in the cOSNs, consistent with the previous effects of Notch signaling inhibition. However, by 48 hpf, Olf-C levels in cOSNs of heat-shocked transgenic embryos had surpassed that of their control siblings, perhaps suggesting the presence of a dynamic reequilibration system in the developing olfactory system. Future investigation will clarify the modulatory effects of Notch signaling on Olf-C protein levels and localization in OSNs, in addition to directly investigating Olfactin's roles in olfactory development.

Friday 11/16

**Kinetic inversion of repressors and activators in gene expression regulation.**

**Zhiyue Lu**, Chudong Wu, Aaron Dinner
The University of Chicago

In gene expression regulation, repressors and activators compete to bind with the gene's regulatory element, and the chance of activators binding with the regulatory element dictates the activation level of the gene. In a thermal equilibrium regime, this chance of binding is well determined by the concentrations of activators and repressors as well as their binding free energies to the regulatory element -- a high concentration of repressor will result in a low chance of activator binding. However, inspired by the experimental observations of cooperativity between activators and repressors, we propose a non-equilibrium dynamics model to describe the gene regulatory dynamics when the concentration of the repressor changes rapidly over time. We demonstrate a minimal Markov model where a rapidly changing level of repressor significantly increases the level of activation beyond predicted by equilibrium theory and effectively enhance the activator. Our model introduced an internal degree of freedom of the regulatory element, and its kinetic barrier allows the system to harnesses the chemical work done by the rapidly changing concentration of the repressor and use it to boost the level of gene activation beyond the equilibrium prediction.

Friday 11/16

**Simulating the role of BMP heterodimer signaling in embryonic patterning**

**Aasakiran Madamanchi**[1], M. Shahriar Karim[2], David M. Umulis[1]
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In developing tissues the interpretation of morphogen gradients provides cells with positional information and determines cell fate specification. Bone morphogenetic protein (BMP) signaling gradient directs patterning and dorsoventral axis formation during early embryogenesis. Published experimental evidence indicates that dorsoventral patterning during zebrafish embryogenesis requires signaling of the BMP2-7 ligand heterodimer through a hetero-tetrameric receptor complex comprising of one BmpR1 and one Acvr1 type I receptor and two type II receptors. However the evolutionary basis for the requirement of this specific combination of ligand and receptor tetramer during embryogenesis remains unclear.

To explore this question, we developed a stochastic model of BMP ligand binding and receptor tetramerization.. Our model of BMP ligand binding and receptor tetramerization was informed by published reports of binding kinetics of BMP ligand-receptor interactions in cell-free systems. Our stochastic model was deployed in simple one-dimensional models of the BMP morphogen gradient to assess the intrinsic noise and information transduction properties of different ligand-receptor tetramer complexes.

Unexpectedly we observe that the BMP2-7:BmpR1:Acvr1:RII:RII complex, the active ligand-receptor tetramer complex during zebrafish embryogenesis, has greater noise at steady state than other BMP ligand-receptor tetramer complexes across a broad range of ligand levels. However, spectral analysis indicates that at steady state, BMP2-7:BmpR1:Acvr1:RII:RII has less contribution of low-frequency oscillation than other ligand-receptor tetramer complexes. Consequently, the BMP2-7:BmpR1:Acvr1:RII:RII complex reaches steady state after changes in ligand levels more quickly than other BMP ligand-receptor tetramer complexes. Further, despite greater noise as measured by coefficient of variation, the BMP2-7:BmpR1:Acvr1:RII:RII complex offers greater temporal fidelity than other BMP ligand-receptor tetramer complexes. Our study suggests that there is an information-theoretic advantage for signaling through BMP2-7:BmpR1:Acvr1:RII:RII which may provide the evolutionary basis for its role during embryogenesis. Further our work suggests that established metrics of noise and information.

Friday 11/16, Saturday 11/17

**Correlative Microscopy enables a High Content Cryo Workflow**

**Joel Mancuso**[1], Vimal Gangadharan[1], Jeff Marshman[1], Kirk Czymmek[1], Patrick Mitchell[2], Gong Her Wu[2], Wah Chiu[2]
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Cryo Microscopy is becoming the technique of choice for high-resolution data acquisition from functionally relevant biomolecules. One struggle has been to investigate the structure of biomolecules relative to its biological context instead of collecting data from isolated proteins or protein complexes. To circumvent the problem, groups have incorporated focused ion beam scanning electron microscopes (FIBSEM) to thin vitrified cells prior to cryo TEM tomography imaging and analysis. Although insightful, demonstrated workflows do not target specific regions of interest and therefore generate low yields of useful data. We have demonstrated higher specificity and throughput can be achieved using Cryo CLEM approach starting with Airyscan technology on a laser scanning light microscope equipped with a cryo stage. The high Signal to Noise ratio (SNR) and superresolution capabilities of Airyscan enables us to target specific subcellular regions within cells using fluorescent tags that serve as a map to easily identify the same structures on the SEM. Combining this workflow with a unique detection system in the FIBSEM to detect unstained structures in vitrified cells allows us to generate lamella creation with high precision.

Friday 11/16, Saturday 11/17

**Coupled Differentiation and Grain Boundary Formation in the Zebrafish Cone Mosaic**

**Hayden S. Nunley**, David K. Lubensky, Mikiko Nagashima, Pamela A. Raymond, Kamirah Demouchet, Alcides Lorenzo Gonzalez
University of Michigan

In zebrafish retinae, cone photoreceptor cells self-organize by subtype into a crystalline lattice called the cone mosaic. This two-dimensional lattice lies on the surface of the retinal hemisphere. As the lattice grows from the rim, topological defects, called Y-junctions, must be inserted to maintain constant cell spacing. Y-junctions form grain boundaries, similar to those in physical crystals on curved surfaces. By tracking UV cone motion, we rule out Y-junction motion after initial mosaic formation as a mechanism for grain boundary formation. We then demonstrate that a mechanical model of cone mosaic development naturally generates grain boundaries during initial mosaic formation.

Friday 11/16

**TimeCycle: Topology Inspired MEthod for the Detection and Direct Comparison of Cycling Transcripts Across Conditions**

**Elan Ness-Cohn**, Ravi Allada, and Rosemary Braun
Northwestern University

As modern medicine continues to improve and rates of age-related diseases continue to rise, understanding the aging process becomes of paramount importance to human health. Early age-related characterization studies reported dietary restriction as a robust anti-aging intervention that spans the biological hierarchy. Recently, findings in the field of Circadian Biology implicate the circadian clock as a central player in these increased longevity phenotypes. The circadian clock coordinates the cyclic expression of ~40% of genes across all tissues, and is entrained by environmental signals, Zeitgebers, such as light, temperature, and food. Nonetheless, the cause and effect relationship between the clock and dietary restriction-mediated longevity are largely unknown. At the core of elucidating these mechanisms is the ability to detect and compare rhythmicity across conditions in time-course gene expression data. To date, no method has adequately addressed the problem of identifying differentially cycling genes across conditions.

We present a topology-based rhythm detection method for gene-expression data designed to identify cycling transcripts and compare their degree of rhythmicity across experimental conditions. For a given time-series, the method reconstructs the state space using time-delay embedding, a data transformation technique for dynamic systems. Takens' theorem6 proves that the dynamics of a rhythmic signal will exhibit circular patterns in the embedded space. The degree of circularity of the embedding is calculated as a persistence score using persistent homology, an algebraic method for discerning the topological features of data. By comparing the persistence scores across conditions, the method assesses whether the embedded topological structures differs significantly between phenotypes, thereby quantifying differences in gene expression rhythms.

Saturday 11/17

**Temporal Pattern Recognition through Molecular Computation**

Jackson O'Brien and Arvind Murugan
The University of Chicago

Living cells communicate information about physiological conditions by producing signaling molecules in a specific timed manner. This phenomenon stands in contrast to the typical paradigm where information is transmitted via structurally specific interactions (e.g. the lock and key model). Consequently, signaling through time dynamics via shared components raises natural questions about how such interactions can effect only the intended response. Here, we demonstrate design principles for circuits with temporal specificity, that is, molecular circuits that respond to specific temporal patterns in a molecular concentration. We restrict ourselves to pulsatile patterns in a molecular concentration characterized by three fundamental temporal features - time period, duty fraction and number of pulses and develop circuits that respond to each one of these features while being insensitive to the others. We demonstrate our design principles using abstract Chemical Reaction Networks and with explicit simulations of DNA strand displacement reactions. In this way, our work develops building blocks for temporal pattern recognition through molecular computation.

Saturday 11/17

**Competitive Tuning of Ca2+/Calmodulin-activated proteins provides a homeostatic effect in synaptic plasticity**

**Matthew Pharris**, Neal Patel, Christopher Rust, & Tamara L. Kinzer-Ursem
Purdue University

Synaptic plasticity depends on NMDA receptor-mediated calcium ion (Ca2+) flux. Intracellular Ca2+binds to the Ca2+-sensor calmodulin (CaM), which modulates downstream effector proteins including kinases, phosphatases, and ion channels, whose differential activation leads to either potentiation or depression of synaptic strength. The activation of individual downstream CaM binding proteins (CBPs) is in-part a function of the frequency of Ca2+ flux, such that each CBP is preferentially "tuned" to different Ca2+ input signals. Tuning of CBP activation may depend on a variety of mechanisms such as feedback loops and spatial effects. Here, we will explore an additional mechanism called "competitive tuning" in which competition among CBPs for binding to Ca2+/CaM is sufficient to recreate in silico the observed in vivo Ca2+ frequency-dependence of several CBPs. For this, we use detailed computational simulations executed in the deterministic solver Mathematica, as well as the particle-based and spatial-stochastic engine MCell.

Friday 11/16, Saturday 11/17

**Tuning Evolution Towards Generalists Through Resonant Environmental Cycling**

**Vedant Sachdeva**[1], Kabir Husain[1], Shenshen Wang[2]
[1]The University of Chicago, [2]University of California - Los Angeles

Some evolutionary systems are naturally tuned towards population strategies that address a common aspect of environments seen in its history. These strategies, termed to be 'generalist' strategies, can be hard to evolve because they may be entropically disfavored or lower fitness than strategies specialized to the current fitness landscape. We demonstrate that time-dependent evolutionary protocols, such as environmental cycling or chirps, can tune evolutions towards 'generalist' strategies in spite of entropic or fitness costs, even in cases where time-independent evolutionary protocols fail. We further demonstrate that the utility of these time-dependent protocols is dependent on the ruggedness of the landscapes, the size of the common part of the environment, and the timescale of cycling, enabling prediction of when time-dependent strategies are needed.

Friday 11/16

**Sampling of Amyloid Beta-42 Dimer Ensemble by A Novel Approach with Conformational Symmetry**

**Levent Sari** and Milo M. Lin
UT Southwestern Medical Center

Small amyloid beta oligomers are known to play key roles in the pathology of Alzheimer's disease (AD). However, the atomic resolution structure of any oligomeric form has resisted experimental efforts, and therefore no oligomeric structure has ever been resolved even at the dimer level. On the other side, computational samplings in atomic resolution face two well-known challenges; (i) inaccessibly large conformational space and (ii) kinetic trapping in local energy minima. We have established a novel general approach to constrain multi-protein simulations to sampling the conformational symmetric subspace in which all copies of the protein adopt the same conformation, and have showed [*] exponential speed-up of conformational sampling. To escape from local minima, we have integrated it with metadynamics. Here, the combined method is applied on Aβ42 dimer ensemble, and is shown to produce convergent sampling overcoming both computational challenges effectively. Simulations demonstrate that the dimer ensemble is populated by monomeric single and double hairpins, with a preference of dimeric face to face packing where intermolecular hydrophobic sidechain interactions stabilize the dimer unit. We have identified 3 main groups of dimer conformations; (1) dimers with compactly folded monomers with no beta structure, (2) conformations with separated monomeric hairpins, (3) compact dimers having monomeric hairpins stabilized by intermolecular side-chain interactions.

Friday 11/16, Saturday 11/17

**Large-scale investigation of the reasons why potentially important genes are ignored**

**Thomas Stoeger**, Martin Gerlach, Richard I. Morimoto, Luıs A. Nunes Amaral
Northwestern University

Biomedical research has been previously reported to primarily focus on a minority of all known genes. Here, we demonstrate that these differences in attention can be explained, to a large extent, exclusively from a small set of identifiable chemical, physical, and biological properties of genes. Together with knowledge about homologous genes from model organisms, these features allow us to accurately predict the number of publications on individual human genes, the year of their first report, the levels of funding awarded by the National Institutes of Health (NIH), and the development of drugs against disease-associated genes. By explicitly identifying the reasons for gene-specific bias and performing a meta-analysis of existing computational and experimental knowledge bases, we describe gene-specific strategies for the identification of important but hitherto ignored genes that can open novel directions for future investigation.

Saturday 11/17

**Interpreting morphogen gradients in cochlea development**

**Matthew J. Thompson,** Alexandra Fister, Donna M. Fekete, Vidhya Munnamalai, David M. Umulis
Purdue University

Quantitative, systems-level characterization of cochlea development is needed to gain further significant insight into how the functionally necessary spatial organization arises in this intricately patterned sensory organ. The organ of Corti contains a single row of inner hair cells, three rows of outer hair cells, and supporting cells arranged with a positional accuracy less than one cell diameter. This pattern emerges from a homogeneous field of prosensory epithelium. Major morphogenetic pathways active during the critical period for cell specification in the organ of Corti have been identified, including Bmp, Wnt, Notch, Fgf, and Shh. Preliminary data quantitatively addressing gradient interpretation within the prosensory epithelium of pSmad, an indicator of Bmp4 activity, and Sox2, a downstream integrated output of the combined network, will be presented.

Friday 11/16, Saturday 11/17

**In vivo dynamic equilibration of multicellular motion during olfactory neurogenesis**

**Vijay Warrier[1]**, Céline Cluzeau[1], Bi-Chang Chen2, Dani Bergey[1], Eric Betzig[3], Ankur Saxena[1]
[1]University of Illinois, [2]Academia Sinica, [3]HHMI Janelia Research Campus

Olfactory neurogenesis is a fascinating research context because it involves the contributions of multiple stem cell populations (the neural crest and ectodermal placode) to sensory neurons that retain regenerative capacity into maturity. To understand the relationships between these populations, we need to characterize complex four dimensional phenotypes in vivo. We take advantage of the zebrafish embryonic model system and new imaging technologies to accurately track cranial neural crest and ectodermal placode-derived stem cell migration in vivo for hundreds of cells during olfactory organ patterning. These data have allowed us to identify, at a system-wide level, patterns of multicellular relationships between individual progenitor cells and cell lineages that form olfactory sensory neurons. We have focused on the posterior-to-anterior ingression of neural crest cells into the olfactory epithelium by considering displacement time series of both types of cells and analyzing these data with methods derived from econometrics, namely volatility analysis and cointegration. Our analyses demonstrate that cranial neural crest cells migrating into the olfactory epithelium segregate, based on behavioral characteristics, into two distinct, previously unidentified subtypes that we have termed ‘trend’ and ‘dispersed’ lineages. Furthermore, we show that neural crest and placodal progenitor migration and intercalation are coordinated by at least two novel types of collective behavior. The first is a dynamic stochastic equilibration of the average mean separation between and within sets of placode and neural crest lineages, i.e. the lineages behave as if they are ‘elastically’ tethered. The second behavior, ‘spatiotemporal exclusion’, involves a striking lack of trajectory overlap between dispersed neural crest lineages and placodal lineages. Together, our results reveal a highly dynamic interplay between different progenitor cell types during the formation of the olfactory system and demonstrate how unbiased statistical methods from econometrics have utility in the characterization of complex developmental patterns.

Friday 11/16, Saturday 11/17

**Decoding functional and cellular heterogeneity in solid tumors using single-cell and single-nucleus RNA-seq**

**Bingqing Xie**[1], Susan Olalekan[1], Olga V Volpert[2], Natalia Maltsev[1], and Oni Basu[1]
[1] The University of Chicago, [2]University of Texas

Understanding structural, functional and cellular heterogeneity present within solid tumors is necessary to advance current cancer therapies. Although bulk RNA-Seq is informative, it fails to identify respective contributions from individual cell-types, and their complex interplay in cancer progression. The goal of this study is to use two high-throughput, droplet-based, single-cell/ single-nucleus mRNA sequencing techniques, Drop-Seq (Cell, '15) and DroNc-Seq (Nature Methods, '17), to profile human cancer tumors and correlate them with their unique genetic/ molecular signatures. To this end, we analyze Glioblastoma (GBM) and ovarian cancer (OvCa) tumor samples. The GBM samples are obtained from a patient derived xenograft mouse model and analyzed using DroNc-seq. Primary and metastatic ovarian cancer samples are resected from patients, graded by pathology, and profiled using Drop-seq. Using unsupervised learning techniques, we identify constituent cell-types, including cancer, stromal, and immune cell compartments, and investigate their function from their individual gene expression profiles.

Friday 11/16, Saturday 11/17

**Modeling Cell Polarization in Fission Yeast**

**Bin Xu**
University of Notre Dame

Regulation of polarized cell growth is essential for many cellular processes, including spatial coordination of cell morphology changes during growth and division. We present a mathematical model of the core mechanism responsible for the regulation of polarized growth dynamics by the small GTPase Cdc42. The model is based on the competition of growth zones of Cdc42 localized at the cell tips for a common substrate that diffuses in the cytosol. We analyze the bifurcations in this model as the cell length increases. We find that a stable oscillation and a stable steady state can coexist, which is consistent with the experimental finding that only 50% of bipolar cells oscillate.

Saturday 11/17

**Reverse-Engineering Calcium Signaling in a Developing Organ**

Jeremiah J. Zartman
University of Notre Dame

Organ development depends on a complex cellular signal transduction network for cells to sense and integrate information from a diverse range of chemical and mechanical cues. Signals are transduced to regulate cell processes through key integrators such as calcium ions. However, how calcium signaling contributes to organogenesis at a systems level is poorly understood. Very few tools exist to study cell signaling at millimeter length scales. Here, we present collaborative efforts to advance organ-level experimentation and quantitative analysis methods. We developed a fluidic device called the Regulated Epithelial Microenvironment Chip to modulate multiple stimuli acting on micro-organs. As a specific demonstration, we are using advanced genetic tools available in a fruit fly-based model of organ growth, the larval wing imaginal disc, to quantitatively study the regulation and function of calcium signaling dynamics occurring during organ growth in vivo. The system also enables live imaging of cell signaling responses. This approach enabled us to decouple the contributions of biochemical signaling and mechanical loading to calcium signaling dynamics. We discovered that mechanical stimulation of intercellular calcium waves (ICWs) depended upon the pre-loaded organ state, rather than the magnitude or duration of mechanical loading. Intercellular calcium signaling relies on calcium induced calcium release and propagation through gap junctions. These results provide evidence for a “Mechanical Stress Decay” hypothesis of calcium signaling. This hypothesis states that stimulated intercellular calcium transients provide a readout of organ size and contribute to the regulation of growth, cell mechanics and cell differentiation as the organ grows. These studies help identify strategies for spatiotemporally encoding information through calcium signaling within the multicellular context. Ultimately, advances in calcium signaling engineering can lead to novel approaches to detect a broad range of stimuli in cell-based biosensors, target cancer, and accelerate tissue regeneration.