Workshop on Dynamics, Randomness, and Control in Molecular and Cellular Networks

November 12-14, 2019

Tuesday, November 12

Time	Speaker	Title/Abstract
8:30 - 9:20am	Breakfast	
9:20 - 9:30am	Welcome	
9:30 - 10:20am	Intro Talk: Andrew Murray	**Title:** Looking for a place for theory **Abstract:** Mathematics and physics have universal, simplifying truths. Biology does not; it's a mass of complicated details and almost every rule we can enunciate has clear exceptions. Can we bring order to this mess by finding ways to produce descriptions that are sufficiently abstract to make them tractable for mathematics while retaining enough detail to make predictions that biologists can test. I will discuss two problems. The first addresses whether cells need complicated regulatory mechanisms to maintain a constant average composition and comes to the conclusion that they do not, leading to the suggestion that the primary function of these regulatory circuits is to change the composition of cells when they are exposed to different environments. The second is an example of purpose in biology: the ability of a group of genetically identical cells in the same environment to exhibit to two different, heritable phenotypes as a way of maximizing their reproduction and survival in an uncertain future.
10:20 - 10:50am	Coffee break	
10:50 - 11:20am	Joe Howard	**Title**: Branching in Neuronal Dendrites: From Molecules to Morphology **Abstract:** Dendrites are fine processes of nerve cells that form branched arbors. These arbors, which are often of staggering complexity, serve as each neuron's antenna, receiving input and integrating signals from tens to tens of thousands of other neurons. The morphology of a dendrite, together with its contacts with other neurons, determines the connectivity of the neuron and is therefore the physical substrate for information processing in the brain. The goal of our research is to elucidate the rules underlying dendritic branching morphogenesis. What determines the number of branches, and their density? How are the lengths of branches regulated? What sets the overall size of the dendritic arbor, and the speed at which it grows? How do molecular lesions perturb dendritic structure? We are using the highly branched Drosophila Class IV dendritic arborization cells as a model system because of the ease of imaging and the availability of

		genetic tools in flies. The arbors of these mechanoreceptors reach diameters of about 500 μm after five days, at which time they contain more than 1000 branches. Yet, the individual dendritic tips, whose diameters are only 0.25 μm, grow and shrink at rates of a few microns per minute, which is roughly 100 times faster than the long-term growth of the arbor. We are combing high-resolution imaging of neutrons in living larvae, agent-based and mean-field models, and genetic analysis to determine how the dynamics of individual dendritic tips specifies the overall morphology of the dendritic arbor.
11:25 - 11:55pm	Olga Dudko	**Title:** On the Border of Order: Chromosomal Organization in Space and Time **Abstract**: Many processes in biology, from antibody production to tissue differentiation, share a common fundamental step — establishing physical contact between distant genomic segments. A key outstanding question is then: How do genomic segments that are strung out over millions of base pairs along the DNA find each other in the crowded cell on a remarkably short timescale? This question, fundamental to biology, can be recognized as the physics problem of the first-passage time. I will show how concepts from statistical physics help reveal the physical principles by which cells solve this first-passage problem with astonishing efficiency. I will illustrate these ideas in the context of adaptive immunity – the system that enables the individual to respond to a great variety of pathogens through a diverse repertoire of antibodies.
12:00 - 2:35pm	Lunch	
2:35 - 3:05pm	Antonis Papachristodoulou	**Title:** Signal Sequestration as a Feedback Mechanism in Biocontroller Design **Abstract:** This talk will introduce a new design framework for implementing negative feedback control in Synthetic Biology. Central to this feedback architecture is sequestration of existing fluxes (reactions) in the process to be controlled. The signal sequestration mechanism appears in many natural biological systems and can often be easier-to-realise than other sequestration and comparison motifs necessary for feedback design. As a case study, feedback in two-component signalling systems is considered where a second response regulator is introduced to compete with the natural response regulator thus sequestering kinase activity. Our feedback architecture was implemented in vivo on the Taz-OmpR system with the experimental results supporting our theoretical analyses. Finally, a recently developed experimental platform that can be used to understand dynamics of such processes in real time will be presented.
3:10 - 3:40pm	Sharad Ramanathan	**Title:** Discovering and controlling key nodes in simple biological networks
3:45 - 4:30pm	Coffee break and	

	group photo	
4:30 - 5:30pm	Panel	Domitilla del Veccio, Olga Dudko, Pieter Rein ten Wolde, David Anderson and Joe Howard
5:30 - 6:30pm	Reception	

Wednesday, November 13

Time	Speaker	Title/Abstract
8:30 - 9:00am	Breakfast	
9:00 - 9:30am	Krešimir Josić	**Title:** Mathematical Modeling for the Rational Design of Synthetic Microbial Consortia **Abstract:** Synthetic microbial consortia have a number of advantages over isogenic system as biochemical and regulatory tasks can be divided between the strains. However, the complexity of these systems makes it difficult to engineer them from scratch. Coordinating gene expression is particularly challenging in spatially extended consortia because the range of signaling molecules is limited by diffusion. I will discuss two examples where mathematical modeling and analysis allowed us to understand experimentally observed dynamics in such system, and use such modeling to control their behavior: First, I will show how modeling predicts that spatio-temporal coordination of gene expression can be achieved even when the spatial extent of a consortium is much greater than the diffusion distance of the signaling molecules. Experiments confirmed these observations, and the need for an intrinsic positive feedback loop that amplifies and propagates intercellular signals. In a second example, we built a three-strain consortium that pulses in response to an external signal. We also developed a computational model which predicts the system's behavior at different strain ratios, and can be used to control its dynamics. Our work thus shows that mathematical modeling can be used to rationally and predictably tune complex synthetic biological systems allowing us to engineer biology more rapidly.
9:35 - 10:05am	Johan Paulsson	
10:10 - 10:40am	Coffee break	
10:40 - 11:10am	Pieter Rien ten Wolde	**Title:** Optimal cellular information transmission **Abstract:** Experiments in recent years have vividly demonstrated that living cells can measure chemical concentrations with remarkable accuracy. Importantly, these concentrations often vary on the timescale of the response of the system. In this talk, I will discuss the optimal

		design of cell sensing systems. I will show that not only receptors and readout molecules fundamentally limit the accuracy of sensing, but also time and power; each of these resources imposes a fundamental sensing limit, which cannot be enhanced by raising another resource. This observation leads to a novel design principle for the optimal allocation of cellular resources in systems that need to detect time-varying signals. This prediction is tested for the chemotaxis system of the bacterium E. coli.
11:15 - 11:45am	Massimiliano Esposito	**Title:** Thermodynamics of open chemical reaction networks **Abstract:** Open chemical reaction networks (CRNs) play a central role in biology, in particular for metabolism. I will show how open CRNs can be seen as thermodynamic machines transducing energy and information far from-equilibrium. More specifically, the following questions will be addressed: What is minimal chemical work needed to bring a CNR into a given nonequilibrium state? [1] What is a thermodynamically meaningful notion of information in a CRN? [1] How does the topology of a CRN affects its thermodynamics? [2] How can one coarse grained the description of a CNR without altering its thermodynamics? [3]. How can one account for fluctuations [4-5] and spatial inhomogeneities? [6]. [1] R. Rao and M. Esposito, "Nonequilibrium Thermodynamics of Chemical Reaction Networks: Wisdom from Stochastic Thermodynamics", Phys. Rev. X 6, 041064 (2016) [2] M. Polettini and M. Esposito, "Irreversible thermodynamics of open chemical networks I: Emergent cycles and broken conservation laws", J. Chem. Phys. 141, 024117 (2014). [3] A. Wachtel, R. Rao and M. Esposito, "Thermodynamically Consistent Coarse Graining of Biocatalysts beyond Michaelis-Menten", New J. Phys. 20, 042002 (2018). [4] M. Polettini, A. Wachtel and M. Esposito, "Dissipation in noisy chemical networks: The role of deficiency", J. Chem. Phys. 143, 184103 (2015). [5] R. Rao and M. Esposito, "Conservation Laws and Work Fluctuation Relations in Chemical Reaction Networks", J. Chem. Phys. 149, 245101 (2018). [6] G. Falasco, R. Rao, M. Esposito, "Information Thermodynamics of Turing Patterns", Phys. Rev. Lett. 121, 108301 (2018).
11:50 - 2:00pm	Lunch	
2:00 - 2:30pm	David Anderson	**Title:** Network structure and dynamics for biochemical reaction networks **Abstract:** Models of cellular processes are often represented with networks that describe the interactions between the constituent molecules. The mathematical study of how dynamical properties of a system relate to graphical properties of its associated network often goes by the name "reaction network theory". In this expository talk, I will connect some of the classical results of reaction network theory, including the Deficiency Zero Theorem and its analog in the stochastic setting, with some current results. Topics will include: (i) a characterization of when a stochastic model will admit a time-dependent distribution that is a product of Poissons, (ii) the

		prevalence of deficiency zero in binary reaction networks, and (possibly) (iii) designing reaction networks that admit a particular (marginal) stationary distribution.
2:35 - 3:05pm	Domitilla del Vecchio	**Title:** Loads in biological circuits: How to engineer modular systems? **Abstract:** Engineering biology has tremendous potential to impact applications, from energy and environment, to health. As the sophistication of engineered biological circuits increases, the ability to predict system behavior from composing subsystems becomes more limited. In fact, while a system's component may be well characterized in isolation, its salient properties often change in surprising ways once it interacts with other systems. This context-dependence of biological circuits makes it difficult to perform rational design and leads to lengthy, combinatorial, design procedures where each component is re-designed ad hoc when other parts are added to a system. In this talk, I will describe some causes of context-dependence, focusing on problems of resource loading and will introduce design-oriented mathematical models that account for it. I will then propose a general engineering framework, grounded on control theoretic concepts, that can serve as a basis for creating devices that are "insulated" from context and can thus be modularly composed. This framework supports rational and modular design of sophisticated genetic circuits and can serve for engineering biological circuits that are more reliable and predictable.
3:05 - 3:35pm	Tom Kurtz	**Title:** Modeling controlled Markov chains **Abstract:** Methods of specifying continuous time Markov chains will be reviewed and then extended to controlled processes. Martingale arguments show that the controlled process can be characterized by a controlled analog of the master equation. Long run average optimal control problems will be introduced indicating how the solution is given by the solution of a linear programming problem, in general infinite dimensional, analogous to the approach of Manne for finite state Markov control problems. Drawing heavily on a recent paper of Aoki, Lillacci, Gupta Baumschlager, Schweingruber, and Khammash, the possibility of implementing the optimal control in a chemical network will be explored.
3:45 - 4:30pm	Coffee Break	
4:30 - 5:30pm	**Colloquium:** Heather Harrington	**Title:** Algebra, Geometry and Topology of ERK Enzyme Kinetics **Abstract:** In this talk I will analyse ERK time course data by developing mathematical models of enzyme kinetics. I will present how we can use differential algebra and geometry for model identifiability and topological data analysis to study these the wild type dynamics of ERK and ERK mutants. This work is joint with Lewis Marsh, Emilie Dufresne, Helen Byrne and Stanislav Shvartsman.

Thursday November 14

Time	Speaker	Title/Abstract
8:30 - 9:00am	Breakfast	
9:00 - 9:30am	Jorg Stelling	**Title:** Analysis of Cell-to-Cell Variability with Dynamic Non-Linear Mixed Effects Models **Abstract:** A key step for understanding heterogeneity in cell populations is to disentangle sources of cell-to-cell and intra-cellular variability. While single-cell time-lapse data provide potential means for this, the corresponding analysis with dynamic models is a challenging open problem. Most of the existing inference methods address only single-gene expression or neglect correlations between processes that underlie heterogeneous cell behaviors. The talk will focus on a simple, flexible, and scalable method for estimating cell-specific and population-average model parameters to characterize sources and effects of cell-to-cell variability. The framework relies on non-linear mixed effects models (NLMEs) consisting of a dynamic mechanistic ODE model for an individual cell and a statistical model describing the distribution of parameters between cells in a population. NLMEs account for multiple sources of uncertainty such as between-cell variability due to differences in parameters and initial conditions, within-cell variability, and (potentially complex) measurement noise. We demonstrate our framework's accuracy and performance compared to state-of-the-art methods from pharmacokinetics with a published model and dataset. An application to endocytosis in yeast demonstrates that one can develop dynamic models of realistic size for the analysis of single-cell data. Combined with sensitivity analysis for identifying which biological sub-processes quantitatively and dynamically contribute to cell-to-cell variability, this application shows that shifting the focus from single reactions or parameters to nuanced and time-dependent contributions of sub-processes helps biological interpretation. In perspective, generality and simplicity of the approach can help addressing open problems in analyzing single-cell dynamics such as the principled identification of cell sub-populations based on molecular differences rather than differences in observables or the untangling of contributions of correlated biological processes along cell lineages to observed cellular heterogeneity and effects on population dynamics.
9:35 - 10:05am	Samuel Kou	**Title:** Statistical inference of dynamic systems via constrained Gaussian processes **Abstract:** Parameter estimation of nonlinear dynamical system models using noisy and sparse experimental data is a vital task in many fields, yet current methods are still limited, especially with

		correct characterization of estimation uncertainty. We proposed a fast Bayesian inference method to estimate the ODE parameters with real data from biological/physical experiments via constrained Gaussian process. Our method involves Gaussian Process regression that is explicitly conditioned on the functional manifold that describes the ODE system. Using this constrained Gaussian process regression, we completely avoid the numerical solver and thus achieve dramatic saving in computational time. Our method is distinct from other existing approaches due to our clean construction within the Bayesian framework. We demonstrate the speed and statistical accuracy of our approach using three realistic examples.
10:10 - 10:40am	Coffee break	
10:40 - 11:10am	John Fricks	**Title**: Renewal-reward processes arising from switching diffusion systems with applications to cellular transport. **Abstract:** Many intracellular processes involve the interaction of Brownian forces with chemical kinetics to drive motion within the cell. Switching diffusion systems have been an important modeling paradigm for this phenomena, often approached from a master equation perspective. In this talk, I will discuss recent work with Veronica Ciocanel, Peter Kramer, and Scott McKinley to view these models from a renewal-reward perspective including several examples in cellular transport.
11:15 - 11:45am	Lea Popovic	**Title**: Spatial effects in stochastic dynamics of intracellular networks **Abstract**: To address intracellular heterogeneity, molecular crowding, and other spatial features affecting intracellular reactions several modeling and simulation frameworks have already been developed. Modelling intracellular reactions as inherently stochastic introduces coupling of reaction and diffusion dynamics that can result in complex stochastic systems. To obtain efficient simulation schemes a modeling reduction is often needed, and a careful choice of the mesoscopic scale is required. In this talk we start with a detailed spatial stochastic model for intracellular reactions and molecular diffusion in terms of a measure valued Markov process (a Markov process on spatial distribution/counts of different species types). We then explore possible ways to reduce this exact model that rely on the multi-scale nature of intracellular reactions and molecular amounts. Interesting new models of stochastic spatial dynamics arise (combining PDEs and jump-Markov processes) which retain all the relevant stochastic features of the spatial dynamics. We use our rigorous approximation results to decrease the simulation time and simplify statistical calculations on a simplified example of self-regulation of gene expression.
11:50 - 2:00pm	Lunch	

2:00 - 3:00pm	Eduardo Sontag	**Title:** Dynamical responses, transient behaviors, and signatures of biological network motifs **Abstract:** A central concern of systems and synthetic biology is that of identifying, and understanding the roles of, signal transduction pathways and feedback loops, whether in natural systems or as an aid in engineering networks that exhibit a desired behavior. This talk will discuss how certain types of network qualitative information can be gleaned from "dynamic phenotypes", a term that we take as encompassing transient characteristics of temporal responses, particularly when using richer classes of probing signals than step inputs. Examples of dynamic phenotypes include fold-change detection (scale invariance), non-monotonic responses, and induced subharmonic oscillations. We will present theorems that relate different behaviors to circuit motifs, and touch upon biological applications at multiple scales, including enzymatic mechanisms, chemosensing, the generation of certain stress responses, and the kinetic recognition of self vs non-self by the immune system.
3:00 - 3:30pm	Coffee break	
3:30 - 4:30pm	Concluding Discussion	