EARLY CAREER RESEARCHER SYMPOISUM

Thursday, April 15 – Friday, April 16, 2021

HOSTED BY NSF-Simons Center for Multiscale Cell Fate Research UC Irvine

MORE DETAILS COMING SOON ON cellfate.uci.edu/2021-ecrs

*Organized by UCI CMCF ECRS Committee: **Axel Almet, Trini Nguyen and Raul Ramos***

Thursday, 04/15/2021

08:50 - 09:00 **OPENING REMARKS**

09:00 - 10:00 **SCIENCE COMMUNICATION WORKSHOP WITH PAKINAM AMER**

10:00 - 10:20 **REMY VU, UC IRVINE**
IOA team members: Remy Vu, Johnny Le (UC Irvine)
Characterize aging-induced metabolite alterations in wounds and the subsequent effects on immune cell fate

10:20 - 10:40 **XIAOJIE WANG, UC IRVINE**
Skin niche talks alter resident stem cell fate

10:40 - 11:00 **VASYL ALBA, NORTHWESTERN UNIVERSITY**
Dimensionality-Reduction in the Drosophila Wing as Revealed by Landmark-Free Measurements of Phenotype

11:00 - 11:20 **TESSA MORRIS, UC IRVINE**
IOA team members: Avraham Moriel (Weizmann Institute, Israel), Tessa Morris, Richard Tran (UC Irvine)
Cardiac Cells Under Mechanical Stimulation: A combined Mathematical, Computational and Experimental Approach

11:20 - 11:40 **KRISHNA SHRINIVAS, HARVARD UNIVERSITY**
Dewdrops on the genome: Regulation and organization of nuclear condensates by RNA activity

11:40 - 12:00 **HONGLEI REN, UC IRVINE**
Genomic correlation reveals chromatin region specificity of DNA methylation maintenance kinetics

12:00 - 12:20 **LORENZO SCIPIONI, UC IRVINE**
Multidimensional Microscopy for real-time physiological profiling in living cells

12:20 - 12:30 **BREAK AND POSTER LIGHTNING TALKS (SELECT ABSTRACTS FROM POSTERS. 2 MINUTES)**

12:30 - 01:30 **POSTER SESSION 1**

Friday, 04/16/2021

09:00 - 09:20 **SOHYEON PARK, UC IRVINE**
IOA team members: Samuel Morabito (UC Irvine), Sohyeon Park
Data Driven Mathematical Modeling of Single-Cell Gene Regulatory Dynamics in Alzheimer's Disease

09:20 - 09:40 **AUSTIN LEFEBVRE, UC IRVINE**
Heterogeneous mitochondrial morphological, motile, and metabolic fates in breast cancer subtypes

09:40 - 10:00 **IRINA TOLKOVA, HARVARD UNIVERSITY**
Acoustic Source Separation for Avian Biodiversity Monitoring

10:00 - 10:20 **HECTOR BANOS, GEORGIA TECH**
A substitution model for tRNA microevolution in the presence of transcription-associated mutagenesis

10:20 - 10:40 **JUNHAO GU, UC IRVINE**
IOA team members: Michael Caldwell (UC Irvine), Junhao Gu
Identifying Gene Network Motifs Within Stochastically Transitioning Melanocyte Subclusters

10:40 - 11:00 **FEDERICO BOCCI, UC IRVINE**
Characterizing intermediate states during the Epithelial-Mesenchymal Transition with scRNA-seq data

11:00 - 12:00 **PANEL: CAREERS DEVELOPMENT ADVICE**
Dr. Zixuan Cang
Postdoctoral Scholar, Department of Mathematics, UC Irvine
Dr. Lara Clemens
Postdoctoral Fellow at DILIsym Services, a Simulations Plus Company
Dr. Daniel Haensel
Postdoctoral Scholar, Department of Dermatology, Stanford University
Dr. Gemechis Degaga
Sr. Scientist, Computational Discovery at Champions Oncology, Inc.

12:00 - 12:10 **BREAK AND POSTER LIGHTNING TALKS (SELECT ABSTRACTS FROM POSTERS. 2 MINUTES)**

12:10 - 01:10 **POSTER SESSION 2**

TALK ABSTRACTS

JOHNNY LE AND REMY VU, UC IRVINE

Characterize aging-induced metabolite alterations in wounds and the subsequent effects on immune cell fate

Aging-dependent alterations in the wound healing metabolic environment are poorly understood even though released metabolites can serve as signals or modify physicochemical properties of the surrounding tissues to alter cell fates. Monocytes are recruited to skin early and express inflammatory cytokines and mobilize more immune cells to the wound. Although the predominant energy source of inflammatory macrophages is glycolysis, the tricarboxylic acid cycle can be reprogrammed to produce signaling molecules for inflammatory macrophage activation in the form of fatty acids. Once inflammation subsides, macrophages take on more anti-inflammatory characteristics, which rely on oxidative phosphorylation and fatty acid oxidation. From single-cell RNA-sequencing (scRNA-seq) datasets of young (8-week-old) and aged (88-week-old) mice, we found lower oxidative phosphorylation, higher hypoxia and glycolysis in inflammatory macrophages compared to anti-inflammatory macrophages. We also observed a higher frequency of inflammatory macrophages and more hypoxic macrophages in aged compared to young wounds suggesting differential metabolomes between the wound environments. From preliminary mass spectrometry data designed to optimize metabolite collection and detection, wound-induced metabolites detected in anterior and posterior dorsal wounds shared common metabolomes and differentiate from unwounded dorsal skin. In future experiments, we aim to 1) characterize metabolites present in inner versus outer wounds, 2) identify metabolites contributing to the delayed wound healing phenotype observed in aged skin, and 3) measure metabolic flux using stable isotope tracing. Our metabolomics study will also pave the way for future directions targeting cell fate changes and metabolic reprogramming, genetically or pharmaceutically, to improve wound healing.

XIAOJIE WANG, UC IRVINE

Skin niche talks alter resident stem cell fate

Resident stem cell fate is closely coordinated with tissue niche cells. In the skin, hair follicle stem cells can be activated by mesenchymal dermal papilla cells at the individual hair level or by signals from neighboring other cell types. Excessive hairs in the hairy nevi suggest that regeneration of hair follicle stem cells happens in the presence of senescent melanocytes. Hair follicles regenerate in a cyclic manner, progressing through anagen for growth; catagen for regression; and telogen for resting. Persistent anagen phenotype in Tyr-Nras^{Q61K} and Tyr–Cre ^{ERT2}; Braf ^{V600E} mouse models is a prototype of human congenital and acquired hairy nevi, respectively that rely on the constitutive expression of an Nras or Braf mutant under a tyrosinase promoter. The hyper-pigmented melanocytes enter a cellular senescent state after hyper proliferation stage. We identified Spp1 as a novel senescent associated secretory phenotype (SASP) factor using whole transcriptome profiling, followed by validation via functional assays. The fate of hair follicle stem cells in the skin can be changed from quiescence to regeneration by nearby senescent melanocytes.

VASYLE ALBE, NORTHWESTERN UNIVERSITY

Dimensionality-Reduction in the Drosophila Wing as Revealed by Landmark-Free Measurements of Phenotype

Organismal phenotypes emerge from a complex set of genotypic interactions. While technological advances in sequencing provide a quantitative description of an organism's genotype, characterization of an organism's phys- ical phenotype lags far behind. Here, we relate genotype to the complex and multi-dimensional phenotype of an anatomical structure using the Drosophila wing as a model system. We develop a mathematical approach that enables a robust description of biologically salient phenotypic variation. Analysing natural phenotypic variation, and variation generated by weak perturbations in genetic and environmental conditions during development, we observe a highly constrained set of wing phenotypes. In a striking example of dimensionality reduction, the nature of varieties produced by the Drosophila developmental program is constrained to a single integrated mode of variation in the wing. Our strategy demonstrates the emergent simplicity manifest in the genotype-to-phenotype map in the Drosophila wing and may represent a general approach for interrogating a variety of genotype-pheno- type relationships.

AVRAHAM MORIEL, TESSA MORRIS AND RICHARD TRAN, UC IRVINE

Cardiac Cells Under Mechanical Stimulation: A combined Mathematical, Computational and Experimental Approach

The heart is a dynamic mechanical environment, and both cardiomyocytes and fibroblasts play an important role in myocardium function. Both the mechanics and cell composition of the myocardium changes in pathology. The interplay between the cell phenotype and mechanical stimulation needs to be considered to understand the biophysical cell interactions in healthy and diseased myocardium. The design is challenged by the different response of fibroblasts and cardiomyocytes to the cyclic stretching. Indeed, in isolation the fibroblasts orient perpendicular to cyclic strain, while the cardiomyocytes will generally align parallel. This is in contradiction to the cellular architecture in a healthy heart. In this work, we hypothesized that the dominant cell type dictates the overall tissue organization in the heart through cell-cell interactions. To test this, the cardiomyocytes and fibroblasts were co-cultured at different ratios in a cyclic stretcher that mimics the myocardial environment of the heart. The intercellular junctions were disrupted with peptides and antibodies to see the effects of cell-cell interactions on organization. We developed an image analysis pipeline to automatically measure cell type specific organization relative to the stretch direction under different co-culture and drug treatment conditions. The results from this study will provide insight on how to mimic the dynamic mechanical environment of the heart in engineered tissue, as well as provide valuable information about the cardiac remodeling response in the diseased heart.

KRISHNA SHRINIVAS, HARVARD UNIVERSITY

Dewdrops on the genome: Regulation and organization of nuclear condensates by RNA activity

Precise, regulated, and robust expression of genes is fundamental to development, cell-type specificity, and physiology. Regulation of biological processes such as transcription often incorporate mechanisms that spatially localize the relevant biochemical cascades and temporally modulate initiation and termination of underlying pathways, often through feedback control. Recent evidence suggests that the key transcriptional proteins phase separate to form dynamic membraneless assemblies, known as condensates, at specific genomic loci - similar to dewdrops on a leaf. How these dynamic condensates are regulated dynamically and organized spatially remain largely unknown.

We leverage approaches from non-equilibrium statistical physics, complex coacervates, and biochemistry to propose a model in which active RNA synthesis regulates condensates. We find that low amounts of RNA synthesis promote condensate formation and higher amounts, such as from high levels of gene expression, can dissolve condensates - thus providing a dual feedback mechanism. Predictions that connect perturbations of key dynamic parameters underlying transcription and RNA diffusion to variations in condensate size and lifetime are verified by experiments in vivo. We then extend our model to study how spatial patterns of gene organization lead to long-range information transfer between sites of RNA synthesis and transcriptional condensates. This model provides a unified framework to explain diverse puzzles pertaining to nuclear condensate morphologies that have been documented for over a century. Together, our model ties in RNA activity, both from coding and non-coding loci, as a regulator of gene expression and nuclear condensates.

HONGLEI REN, UC IRVINE

Genomic correlation reveals chromatin region specificity of DNA methylation maintenance kinetics

New experimental techniques enable the measurement of epigenetic marks in the context of DNA replication, shedding new light on how the epigenetic landscape is maintained in cells across the cell cycle. We combined statistical inference and mathematical modeling to analyze replication-associated bisulfite sequencing measurements of DNA methylation in embryonic stem cells. In this study, we found that the maintenance kinetics of DNA methylation shows region specificity, suggesting different mechanisms of methylation maintenance in different genomic regions. We further showed that the kinetic patterns observed can be partially, but not fully, explained by a 1D diffusion model of enzymes processing along with DNA.

LORENZO SCIPIONI, UC IRVINE

Multidimensional Microscopy for real-time physiological profiling in living cells

Fluorescence Lifetime Imaging Microscopy (FLIM) and spectral imaging are two broadly applied methods for increasing dimensionality in microscopy. However, their combination is typically inefficient and slow in terms of acquisition and processing. By integrating technological and computational advances, we built a robust and unbiased Spectral FLIM (S-FLIM) system to extract detailed and precise information about the photophysics of fluorescent specimens at optical resolution, named Phasor S-FLIM. Phasor S-FLIM allows for the simultaneous acquisition and analysis of multiple environment-sensitive fluorescent probes that can report on key physiological parameters of interest in living cells, such as chromatin compaction, mitochondrial membrane potential, lipid droplets composition and membrane fluidity at the same time. We show that our approach is capable of characterizing physiological heterogeneity in 2D cultures as well as in 3D tumor spheroids.

SAMUEL MORABITO AND SOHYEON PARK, UC IRVINE

Data Driven Mathematical Modeling of Single-Cell Gene Regulatory Dynamics in Alzheimer's Disease

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder that causes systemic changes in the gene expression landscape of the brain, some of which are associated with hallmark pathologies such as Amyloid Beta (Aβ) plaques and neurofibrillary tangles of tau. While tissue-scale sequencing studies have characterized various aspects of the genome, epigenome, and transcriptome in AD, many of the biological systems involved in disease progression are still poorly understood with respect to gene dysregulation in specific cell-types and cell-states. Recent developments in single-cell sequencing provide an opportunity for strengthening our understanding of the molecular alterations brought on by disease at unprecedented resolution, and have proven to clarify novel biological phenomena in many systems including AD. **Here we propose to study gene regulatory dynamics in**

AD using a network-based mathematical modelling approach informed by epigenomic and transcriptomic single-cell measurements in the human AD brain. We aim to use single-nucleus ATAC-seq (snATAC-seq) and single-nucleus RNA-seq (snRNA-seq) data from multiple studies to construct a consensus cell atlas of the AD brain to identify gene-linked cis-regulatory elements (gl- CREs) with respect to specific cell-types and cell-states and construct regulatory networks of transcription factors (TFs) and their down-stream targets. We consider different models such as a system of ODEs, linear models, and neural networks to perform **in silico gene perturbation experiments**, allowing us to understand how TFs contribute to the gene expression changes throughout AD progression.

AUSTIN LEFEBVRE, UC IRVINE

Heterogeneous mitochondrial morphological, motile, and metabolic fates in breast cancer subtypes

Mitochondria are the powerhouses of the cell, but the difficulty of segmenting, tracking, and analyzing individual mitochondria has led to a bottleneck in discovering important biological insights about these complex organelles. Here, we introduce Mitometer, an automated software for unbiased segmentation and tracking of mitochondria in live cell 2D and 3D fluorescence time-lapse images. We multiplex Mitometer with FLIM of NADH to assess metabolic changes between 5 breast cancer cell lines of varying invasiveness: 3 triple-negative (TNBC), 2 receptor-positive (ER/PR+), and one normal breast epithelial cell line. Additionally, we run a comprehensive 2D and 3D analysis of mitochondria in a large panel of the aforementioned cell lines, alongside two TNBC patient-derived xenograft models (HCI-010, HCI-002), and normal breast epithelial cells from reduction mammoplasties of 5 different individuals. We show large variations in many mitochondrial parameters and show the ability to predict whether a mitochondrion belongs to an ER/PR+ cancer cell or a TNBC cell. Mitometer, and these results will further the understanding of mitochondria as drivers of complex diseases.

IRINA TOLKOVA, HARVARD UNIVERSITY

Acoustic Source Separation for Avian Biodiversity Monitoring

Passive acoustic monitoring (PAM) is emerging as a relatively low-cost, non-invasive methodology for automated species-level population surveys. However, PAM systems are limited by the complexity of natural soundscapes; particularly by high occurrences of noise and simultaneous vocalizations. We propose addressing this difficulty by utilizing a first-order ambisonic microphone to perform source localization and separation prior to the classification pipeline. We describe the foundations and implementation of two algorithms -- MUSIC and CAIM -- for source separation with an acoustic vector-sensor. We then experimentally evaluate and compare these approaches, with a focus on avian vocalizations in terrestrial environments.

HECTOR BANOS, GEORGIA TECH

A substitution model for tRNA microevolution in the presence of transcription-associated mutagenesis

Modeling the evolution of genes subject to strong selection poses many challenges, and is even more difficult when such genes are subject to increased mutagenesis such as transcription-associated mutagenesis (TAM). One class of such genes is the tRNAs. In an effort to uncover the main forces governing the evolution of genes subject to and influenced by TAM, we present a model that describes their microevolution by examining their allelic variation in a population. Continuous Markov substitution models form the basis for our model. We use the model to successfully describe most of the allelic variation at tRNA genes in the model system *C. elegans*, and show that TAM dominates tRNA microevolution.

MICHAEL CALDWELL AND JUNHAO GU, UC IRVINE

Identifying Gene Network Motifs Within Stochastically Transitioning Melanocyte Subclusters

The inherent stochastic behavior of gene expression, and the lack of information on kinetic parameters make gene regulatory network inference a long-standing challenge. On one hand, purely theory-driven analytical methods of solving gene expression dynamics shed lights on interpretation of single cell RNA-seq data, however, they are still mostly limited to single gene dynamics or over-simplified two-gene interactions. On the other hand, data-driven network inference approaches have gained much popularity in the recent years thanks to state-of-the-art machine learning algorithms and the efficient single cell RNA seq technologies, and many of the data-driven approaches rely on common statistical analysis of co-expression data as feature inputs, which often overlook the potential multimodality and stochastic fluctuations. In Read Lab, we propose to use the bivariate co-expression distribution as the "fingerprint" of gene interactions, by cataloging these "fingerprints" from simulated data of theory-driven models, and comparing with single cell RNA-seq data from experiment. This provides another mean of data analysis and feature selection that potentially helps in narrowing down the choice of ground truth network topology. In this project, we applied out analysis pipeline to models with more detailed phenomena. We also applied this pipeline to melanocytes' single cell RNA-seq data to learn more about their regulatory networks.

FEDERICO BOCCI, UC IRVINE

Characterizing intermediate states during the Epithelial-Mesenchymal Transition with scRNA-seq data

The Epithelial-Mesenchymal Transition (EMT) is a major driver of cancer progression. During EMT, epithelial cells partially or completely lose cell-cell adhesion and apicobasal polarity while gaining motile and invasive traits, thus enabling migration from primary tumor and seeding of metastasis in anatomically distant sites. EMT is often characterized by intermediate cellular states with mixed epithelial and mesenchymal traits. These hybrid epithelial/mesenchymal (E/M) phenotypes are associated with stem-like traits and poor prognosis across several cancers. Yet, identifying and characterizing these intermediate states currently remains challenging.

Here, we analyze several single cell RNA sequencing (scRNA-seq) datasets from different cancer types to investigate common and specific features of intermediate E/M states. First, we integrate QuanTC - a tool for trajectory reconstruction from scRNA-seq data - with expression of known epithelial and mesenchymal gene signatures to identify intermediate states along EMT. Moreover, we use scEpath to quantify the plasticity of a regulatory network of epithelial and mesenchymal genes. Remarkably, this analysis suggests that many transitions are characterized by co-activation of epithelial and mesenchymal genes, and even mesenchymal states still exhibit a strong epithelial signature. Furthermore, we use Cellchat to quantify signaling between cells in different EMT states, showing that a partial or complete EMT triggers the activation of several cell-cell communication pathways.

Overall, our analysis highlights many distinctive features of intermediate states along EMT and suggests that many measures of stemness typically applied in developmental and physiological contexts, such as total number of genes expressed, might not be easily applied to the context of cancer.

POSTER ABSTRACTS

JOEL DOKMEGANG, NORTHWESTERN UNIVERSITY

Quantification of cell behaviors and computational modelling show that cell directional behaviors drive zebrafish pectoral fin morphogenesis

Understanding the mechanisms by which the zebrafish pectoral fin develops is expected to produce insights on how vertebrate limbs grow from a 2D cell layer to a 3D structure. Two mechanisms have been proposed to drive limb morphogenesis in tetrapods: a growth-based morphogenesis with a higher proliferation rate at the distal tip of the limb bud than at the proximal side, and directed cell behaviors that include elongation, division and migration in a nonrandom manner. Based on quantitative experimental biological data at the level of individual cells in the whole developing organ, we test the conditions for the dynamics of pectoral fin early morphogenesis. We found that during the development of the zebrafish pectoral fin, cells have a preferential elongation axis that gradually aligns along the proximodistal axis (PD) of the organ. Based on these quantitative observations, we build a center-based cell model enhanced with a polarity term and cell proliferation to simulate fin growth. Our simulations resulted in 3D fins similar in shape to the observed ones, suggesting that the existence of a preferential axis of cell polarization is essential to drive fin morphogenesis in zebrafish, as observed in the development of limbs in the mouse, but distal tip-based expansion is not.

GAOTIAN ZHANG, NORTHWESTERN UNIVERSITY

The genetic architectures of gene expression variation in wild C. elegans

KRISTIN JOHNSON, NORTHWESTERN UNIVERSITY

Quantitative analysis of transcriptome dynamics during developmental state transitions

During embryonic development, cell potency becomes increasingly restricted, progressing from a pluripotent state to different lineage restricted states. The pluripotent cells of Xenopus blastula-stage embryos are well suited to studying cell state transitions during the developmental decision-making process. This process spans just hours, revealing dynamics at high temporal resolution. Here we use transcriptomics to interrogate the way pluripotent cells transit to four different lineage restricted states; neural progenitors, epidermis, endoderm and mesoderm. We find that the transition from pluripotency to a neural progenitor state is unidimensional, whereas the trajectory to achieving an epidermal or mesendoderm state is more complex. Our results provide independent support for, and novel insights into, the neural default model. Additionally, our data suggests that ectodermal cells share a trajectory until stage 10.5 when cells that will become epidermal are redirected away from neural progenitors with the onset of Bone Morphogenetic Protein (BMP) signaling. By contrast, cells progressing towards a mesendoderm lineage diverge right away with the onset of activin signaling. Interestingly, the divergence between neural and epidermal cells cannot be expedited with the early activation of BMP signaling. Rather, early BMP activates both the BMP and activin signaling pathways simultaneously. This underscores the importance of precise BMP timing in epidermal lineage adoption.

SASHA SHIRMAN, NORTHWESTERN UNIVERSITY

Physical constraints on cuticle stretch within C. elegans triggers larval-stage transitions

For the nematode Caenorhabditis elegans, as with all organisms, regulation of growth during development is essential to establish organism size and ensure proper organismal development. C. elegans development is characterized by four larval stages and an adult stage. Transitions from one stage to the next consist of a molt period during which the nematode sheds its flexible external cuticle layer. Previous studies demonstrated that C. elegans growth rate can be described by a 'Sizer' model in which larval-stage transitions occur at characteristic animal sizes. This sizer model requires that animals are capable of sensing and communicating size information when making developmental decisions.To investigate size dynamics surrounding molt events, we collect high throughput population measurements of animal length and width over developmental time. We observe differences between animal length and width during larval-stage transitions. To explain these differences, we propose a 'Stretcher' mechanism for growth control whereby C. elegans senses body size through physical constraints on cuticle stretch and triggers larval-stage transitions when the cuticle reaches its maximum capacity for stretch.

MORGAN DRAGAN, UC IRVINE

Transcriptional mechanisms of epidermal barrier maintenance

Skin is the body's very first line of defense against the harsh environment. While severe skin barrier dysfunction can lead to premature death, minor barrier defects are linked with skin diseases such as atopic dermatitis and psoriasis. The cellular and molecular mechanisms that regulate barrier function and its links with whole-body physiology remain to be fully understood. Ovol1 and Ovol2 encode homologous transcriptional repressors present in the skin that regulate epithelial differentiation and cell adhesion in development. Alone, Ovol1 loss causes growth arrest of embryonic epidermal cells. In adulthood, Ovol2 confers directionality to migrating epidermal cells during wound repair, and loss of Ovol1 causes a susceptibility to inflammation. However, the function and potential redundancy between Ovol1 and Ovol2 in adult skin homeostasis and inflammation is unknown. We generated mice with both Ovol1 and Ovol2 inducibly deleted from epidermal cells in adulthood and found the mice to develop skin barrier defects. Subsequently, they develop elongated toenails and lower bodyweight. Using ChIP-seq we found that epithelial Ovol1 and Ovol2 directly binds to the promoters of genes involved in controlling proliferation/differentiation (e.g. Id1) and genes involved in cytoskeletal structure, adhesion and metabolism (e.g. Zeb1, Ccdc88a, Flot2, and Faah). Metabolic cage analysis shows that these mice eat more and are metabolically more active than their control littermates. Current experiments focus on testing Ovol1/2 repression and function of key molecular targets. Our goal is to elucidate the mechanism by which Ovol1/2 regulate skin barrier function and how cutaneous defects are linked to alterations in whole-body physiology and metabolism.

ERIC JOHNSON, NORTHWESTERN UNIVERSITY

EMBEDR: Distinguishing Signal from Noise in Single-Cell Omics Data with a Statistical Approach to Dimensionality Reduction

Single-cell "omics" measurements produce data sets that are often high-dimensional, and therefore subject to the "curse of dimensionality". As a result, Dimensionality Reduction (DR) algorithms are necessary for data visualization, and ideally can be used for quantitative analysis. However, the lack of a principled methodology for separating signal from noise in DR algorithm output has limited the confident application of these methods in unsupervised analyses of single-cell data, greatly hampering researchers' ability to make data-driven discoveries. In this work, we present a general framework for uncertainty estimation called EMBEDR, which directly facilitates the confident quantitative analysis of noisy, high-dimensional data like single-cell omics data sets. EMBEDR employs a sample-wise, data-driven, and statistical approach to assess the quality of DR outputs in order to separate biological signal from noise in dimensionally-reduced representations of data. Applying

EMBEDR to published scRNA-seq data reveals where representations of the data are faithfully capturing the high-dimensional structures in the original data, and where they are more consistent with noise. EMBEDR produces an easily interpreted p-value for each sample in a data set, facilitating the comparison of different DR methods and the optimization of their hyperparameters. Most compellingly, EMBEDR allows for the analysis of single-cell data at a single-cell resolution, allowing for DR methods to be constructed in a cell-wise optimal manner. Applying such a technique to real data results in a biologically interpretable view of the data with no user supervision. In this work, we demonstrate the utility of EMBEDR in the context of several data sets and DR algorithms, illustrating its robustness and flexibility as well as its potential use in making rigorous, quantitative analyses of single-cell omics data. EMBEDR is available as a Python package for immediate use.

WING TAT LEUNG, UC IRVINE

Multiscale modeling of solid tumor growth

There is much evidence that growth patterns of solid tumors may be described using physical principles. However, most mathematical models are phenomenological since the parameters used at the tissue scale represent the combined effects of heterogeneities and processes, such as cell-cell, cell-ECM interactions, that are not directly obtained from cell or molecular scale measurements. This makes it difficult to identify the key contributors to the emergent behavior, which ultimately limits the predictiveness of the model. New multiscale models are needed that are capable of integrating data at the molecular and cellular levels and predicting emergent behavior at the tissue scales. Here, we develop such a model by exploiting the framework of dynamic density functional theory (DDFT) from statistical physics for bridging the cell and tissue level scales. In particular, we connect an agent-based model to a cell-level continuum model for the cell densities and momentum using DDFT. The cell densities are oscillatory that reflect the probability of finding cells at precise locations, which arise from cell-cell correlations. We then coarse grain the continuum model by identifying slowly varying components of the cell densities—the average density and the amplitude of the oscillating modes—and deriving equations for them. The resulting density-amplitude equations are further coarse grained to the tissue level using asymptotic theory. The resulting tissue-scale model resembles classical tumor growth models where the tumor is treated as an elastic material. Model parameters are linked directly to measurable quantities at the cell scale. We present numerical results that confirm our analysis and we investigate the role of mechanical feedback on tumor growth.

LIANNA FUNG, UC IRVINE

Multiple morphogens and rapid elongation promote segmental patterning during development