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IP1

Counterintuitive Optimization for Airplanes and Medicines: How to Improve Patient Outcomes Using Mathematics

Improving an outcome by even 5% can make a big difference. For example, finding a treatment regimen that increases median patient survival time by 5% means extra time with loved ones for patients. It can also mean the difference between clinical trial success and failure for a therapy. In the past, trial and error was used to find treatment regimens that yield better patient outcomes. Now we have mechanistic mathematical models of disease-therapy dynamics, sometimes called quantitative systems pharmacology (QSP) models, that can help. Optimal control applied to QSP models can compute regimens that are predicted to achieve the best outcomes; these regimens can then be tested experimentally and clinically. Optimal control can be especially helpful when there are many possible different combinations to consider, or when optimal regimens are counterintuitive. I will share our framework for modeling and analysis applied to various models built by my group, including a QSP model of melanoma-immune dynamics. We used RNA-Seq data for model building, sensitivity and identifiability analysis for understanding the model, and optimal control for optimizing combination regimens. I will make the case that counterintuitive solutions can be best in the real world, for both airplanes and treatment regimens, and that we may be missing out on substantial patient benefit when we dont calculate optimal regimens for our QSP models.

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IP2

Nonreciprocity in Cell Locomotion

Cellular motility is mechanically constrained by the surrounding environment. Over the last two decades, research into the hydrodynamics of swimming cellssuch as bacteria, plankton, and spermhas expanded significantly, bridging multiscale mechanics from intracellular force regulation to flexible body dynamics and transport in external flows. Due to the nature of hydrodynamic equations at the cellular scale, nonreciprocal deformation is essential to generate net propulsion, a principle known as the Scallop Theorem. In this talk, we provide an overview of several mathematical frameworks aimed at elucidating the nature of nonreciprocity in cell locomotion, ranging from fluid equations and noncommutative gauge field theory to dynamical metamaterials such as odd elasticity, nonequilibrium statistical mechanics, and coupled oscillator models.

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IP3

Parkinsonian Oscillations Episode 2: Motor Rescue

The basal ganglia comprise a collection of deep brain neuronal populations involved in a variety of motor and cognitive functions. In Parkinsons disease, the death of certain cells leads to a variety of alterations in neuronal dynamics that likely contribute to the debilitating motor effects that emerge. Yet within this general framework, many fundamental details remain uncertain. In this talk, I will discuss work using mathematical and computational approaches to address some of the central remaining mysteries. In particular, I will focus on which forms of altered dynamics may be most relevant to parkinsonian motor symptoms, how these dynamics may originate, and how these factors relate to some exciting possibilities for long-term motor improvements, or persistent motor rescue, based on much shorter-term interventions.

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IP4

From Small-noisy to Big-biased Data: Modeling, Learning and Inference Across Scales Under Uncertainty During Pandemic Crisis

Accurate inference and prediction from noisy and biased data remain critical challenges. This is particularly true during crises like the COVID-19 pandemic when such analyses form the basis for real-world decisions. In this talk, I will share lessons learned from studying the spread of SARS-CoV-2 across different biological scales using diverse data sources. First, I will describe our work on understanding the rate of SARS-CoV-2 spread at the earliest stage of the outbreak in Wuhan, China in late 2019 and early 2020. Using two inference methods on multiple datasets, we reached to the conclusion that the virus was spreading much faster than initially estimated, and that social distancing efforts would be necessary to contain its spread, contrary to conclusions from most other studies and prevailing public opinions at that time. Next I will describe our efforts in using within-host infection data to characterize heterogeneity in transmission potential and to help policy makers to design frequent antigen testing in supporting return-to-school or work strategies in the US. Finally, I will highlight our work on using transformer-based deep learning models to analyze large but biased genomic surveillance data to better forecast trajectories of emerging variants. Together, these studies emphasize the importance of selecting appropriate models for datasets at hand, enabling reliable insights from imperfect data for real-world decision-making.

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IP5

Mathematics of Self-Organisation Across Scales

How does the linear DNA encode reproducible three-dimensional organ morphologies, and how can the same developmental programme operate reliably across embryos that differ in size and speed? I present two developmental systems that achieve scale invariance by distinct mechanisms. In the vertebrate neural tube, morphogen gradients coupled to an evolutionarily conserved regulatory network enable precise patterning and coordinated developmental timing despite differences in embryo size and speed. In the lung, fluidstructure interactions establish and maintain an energy-efficient fractal organisation across species of vastly different sizes. Together, these examples show that biological systems employ diverse physical and regulatory mechanisms to ensure scale- and speed-invariant outcomes. Identifying the underlying principles poses a fundamental mathematical challenge and is reshaping our

quantitative understanding of development.

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IP6

Topology for Multiscale Biology

Many processes in the life sciences are inherently multiscale and dynamic. Spatial structures and patterns vary across levels of organisation, from molecular to multicellular to multi-organism. With more sophisticated mechanistic models and data available, quantitative tools are needed to study their evolution in space and time. Topological data analysis (TDA) provides a multi-scale summary of data. We review persistent homology and then highlight applications of single parameter persistent homology and multiparameter persistence to proteins, cancer and spatial transcriptomics. Time permitting, we present in-progress work for quantifying spatio-temporal trajectories, which builds on work by Kim and Memoli, Bubenick, Vipond and Lesnick, Bender and Gfvert.

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SP1

SIAG/Life Sciences Early Career Prize Lecture: Understanding Self-organization in the Cell Cytoskeleton with Simulation-based Inference

The cells ability to generate large-scale organization from smaller-scale ingredients is both beautiful and fundamental for sustaining life. In the cytoskeleton (a structural mesh of filaments, motors, cross linkers, and accessory proteins), self-organization drives basic functions like cell division and movement, and results from a dynamic interplay of biochemical and mechanical feedbacks on the molecular scale. As many of the key players are conserved across cell types, an important question is how the same set of feedbacks can give rise to different phenotypes in different contexts. In this talk, I will reveal potential sources of diversity through a combination of data analysis, mathematical modeling, and simulation-based inference. Focusing on an activator/inhibitor system coupling the Rho GTPase RhoA and filamentous actin, I will show data from three different cell types which demonstrate diverse patterns of RhoA activity. Based on the hypothesis that pattern formation is tuned by F-actin stochasticity and heterogeneity, I will introduce a mathematical model coupling RhoA activity to discrete F-actin filament kinetics, then employ neural network-based methods to infer model parameters directly from experimental data. Parameter inference reveals how RhoA activity patterns are tuned by F-actin assembly, and guides follow-up experimental measurements which confirm model predictions.

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JP1

Joint Plenary Speaker with 2026 SIAM Annual Meeting: When More Isnt Better: A Lesson from Rethinking Scale in Single-cell Foundation Models

The success of transformer-based foundation models on natural language and images has motivated their use in single-cell transcriptomics. In this talk, we will assess how pre-training dataset size and diversity affect the performance of single-cell foundation models. Using a corpus of 22.2 million cells, we pre-trained 400 models and evaluated over 6,400 experiments. Our results show that current methods tend to plateau in performance with pre-training datasets that are only a fraction of the size, challenging the assumption that ever-larger datasets are required for optimal generalization. This will lead us to the second half of the talk where we evaluate training data composition on model performance. Focusing on human hematopoiesis, we train and analyze deep generative models with a variety of training datasets, including cells from adult and developing tissues, disease states, and perturbation atlases. Here, we observe that (1) deep generative models generalize poorly to unseen cell types and (2) addition of malignant or perturbed cells to healthy corpora does not consistently improve modeling of novel states. These findings highlight the nuanced roles of dataset size and heterogeneity, suggesting that strategic curation, rather than indiscriminate scaling, is key for optimizing single-cell foundation models.

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CP1

A Multiscale Model for T Cell Exhaustion in the Tumor Microenvironment

T cell exhaustion (TCE), characterized by progressive loss of effector function and epigenetic reprogramming, is a major barrier to effective immunotherapy of solid tumors. However, the nonlinear interplay between T cell activation and exhaustion within the tumor microenvironment (TME) is poorly quantified. To address this, we developed a hybrid multiscale modeling framework coupling an agent-based model (ABM) with ordinary differential equations (ODEs). The ABM captures spatiotemporal cellular interactions and tumor infiltration. Intracellular ODEs incorporate cues from each T cells local neighborhood in the TME, including oxygen and nutrient availability, utilizing nonlinear Hill-type kinetics to model T cell activation and exhaustion as continuous state variables. This hybrid approach simulates exhaustion as a continuous, nonlinear process spanning from early to terminal exhaustion states as the active T cell response is downregulated via cancer cell interactions. Preliminary computational results demonstrate that the model captures nonlinear tumor-immune interactions driving TCE dynamics. The framework is calibrated using time-series flow cytometry data from CD8+ T cells and pancreatic cancer cells co-cultured under hypoxic conditions to identify the critical temporal windows of exhaustion onset and progression. This approach provides quantitative and mechanistic insights into TCE dynamics in the TME, serving as a foundation for modelling therapeutic interventions.

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CP1

Targeting KV10.1 Channels in Breast Cancer: Ion Channel Genetics in In Silico Electrophysiological Mechanisms and Drug Discovery

Ion channel genetics is increasingly recognized in cancer biology, with the voltage gated potassium channel KV10.1 (Eag1) playing a critical oncogenic role in breast cancer. Its overexpression promotes motility, proliferation, apoptosis resistance, and epithelial to mesenchymal transition (EMT), while influencing immune interactions in the tumor microenvironment. This study applies computational modeling and molecular docking to investigate KV10.1s impact on membrane potential and cancer cell behavior. Structural predictions were cross validated with experimental data, focusing on identifying inhibitors and simulating their effects. Models revealed altered gating kinetics and increased conductance in cancer cells, producing hyperpolarized states (25 mV) that enhance excitability and metastasis. KV10.1 disruption favored proliferation and migration, while docking identified tricyclic antidepressants as potent inhibitors. At nanomolar concentrations, these restored resting membrane potential, reversed cancer associated changes, and potentially impaired EMT and oncogenic signaling. Findings highlight KV10.1 as a promising therapeutic target. Selective inhibition may reduce metastatic potential and enhance immune recognition, offering a novel strategy in breast cancer management. By integrating computational and experimental insights, this work underscores the broader role of ion channel genetics in precision oncology and calls for further validation in clinical studies.

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CP1

An Random Differential Equation Model to Recover Sensitivity to Treatment in Cancerous Tumors Under Cyclical Therapy

Resistance to treatment, which comes from the heterogeneity of cell types within tumors, is a leading cause of poor treatment outcomes in cancer patients. Previous mathematical work modeling cancer over time has neither emphasized the relationship between cell heterogeneity and treatment resistance nor depicted heterogeneity with sufficient nuance. To respond to the need to depict a wide range of resistance levels, we develop a random differential equation model of tumor growth. In the inverse problem, we aim to recover the sensitivity to treatment as a probability mass function. This allows us to observe what proportions of cells exist at different sensitivity levels. After validating the method with synthetic data and murine cell lines, we expand the model to depict cyclical treatment. This basis allows us to generate a cohort of virtual patients and assess whether there is one single treatment schedule that is optimal for different initial sensitivity levels.

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CP1

Optimizing Adoptive Cell Therapy Injection Schedules for Melanoma Using a Reinforcement Learning Approach

Adoptive cell therapy is the transfer of T cells (T) specific for the melanoma cells (C) as immunotherapy. To improve T cell functionality, dendritic cell (DC) vaccine was administered. To prevent the binding between melanoma cells and T cells, anti-PD-L1 antibodies (Ab) were injected, which enhances the efficacy of adoptively transferred T cells in combination with DC. Using pre-clinical murine data from untreated, T-treated, (T + DC)-treated, and (T + DC + Ab)-treated injection groups, an ordinary differential equation (ODE) model was developed to capture the interaction dynamics. These model parameters were fitted to average mouse data. To determine the schedule with minimal T cell injections that also minimizes the tumor burden, we employed a model-based reinforcement learning (RL) framework. Here, we fixed the DC and Ab injection schedules and the total T dose. At each decision time point, the RL agent selected whether to administer a T dose, subject to a hard constraint on the total number of T injections and treatment holidays. A tabular Q-learning algorithm was used to learn an optimal policy. After training, the learned policy was used to generate the optimized T injection schedule. We found that 3 to 4 minimal T injection doses resulted in a reduction in the tumor burden by over 60% when compared to the experimental T injection schedule.

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CP1

Integrating Egf-Receptor Interactions into Tumor Growth Frameworks to Quantify Tumor Initiation Thresholds

The binding of epidermal growth factor (EGF) to its receptor activates downstream signaling pathways promoting cell survival and proliferation. In cancer, mutations amplify these interactions by increasing EGFR copy number or enabling constitutive receptor activation. In this work, we investigate how aberrant EGFREGF signaling drives tumorigenesis by extending cancer models to incorporate explicit receptor-ligand dynamics. We first refine a previous 3D multiscale model by introducing explicit receptor domains and coarse-grained Brownian dynamics simulations of EGF-EGFR interactions at receptor clusters. We then derive a continuous population model that structures cells, for the first time, according to the number of active receptors. Using moment reduction, we obtain a reduced population-dynamics model in which the tumor growth rate depends on the mean number of activated receptors. The reduced model enables analytical characteri-

zation of tumor growth conditions linking extracellular ligand availability, receptor-ligand binding, and intracellular signaling. Our results show that elevated receptor numbers lower the EGF threshold required for tumor initiation. They also predict that increased EGF-EGFR affinity enhances tumorigenic potential when ligand and receptor concentrations are low. The models can be integrated with pharmacokinetic and pharmacodynamic models of kinase inhibitors and patient-specific data to support the development of personalized therapeutic strategies.

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CP1

The Potential Utility of In-Silico Approach in Identifying Phytochemicals Against Various Targets for the Management of Lung Cancer

Research on novel treatment approaches is crucial for lung cancer, because it is one of the most common and fatal cancer in the world. The potential advantages of using in silico methods to find phytochemicals for lung cancer treatment have been summarized in this review. This also highlighted the various computational tools such as ADMET profiling, network pharmacology, molecular docking, and machine learning algorithms involved in identification of potential phyto-constituents for lung cancer therapy. Key molecular targets that were assessed against a range of phytochemicals that shown multi-target binding and promising pharmacokinetic properties included EGFR, KRAS, ALK, and PD-L1. Prominent compounds such as quercetin, curcumin, and luteolin showed notable interactions with carcinogenic pathways, tumor microenvironment modulators, and apoptosis inducers. Mechanistic understanding, high-throughput screening, and economical drug development were made possible by this computational approach. This review demonstrates the potential utility of in silico techniques to bridge the gap between precision oncology and traditional medicine, as well as the intriguing function of phytochemicals as supplemental medicines in lung cancer therapy.

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CP2

A Physics-Based Model Reveals Mechanisms of Epigenetic Memory

Cell identity relies on epigenetic marks like H3K9me3 and H3K27me3. Cell division dilutes these marks, making pattern restoration a key biophysical challenge. We introduce the LEAP (Looping, Enzyme And Phase-condensate) model, a Markov chain framework of epigenetic memory. The rate of adding a mark is: $Q(x_i = 0 \to x_i = 1) = \sum_j k_m P_L(i,j) P_E(j)$. LEAP relies on three principles: 1. Looping: Contact probabilities decay as an inverse power-law. 2. Enzyme localization: Methyltransferases preferentially bind their own product. 3. Condensates: Enzymes form high-density condensates around methylated regions. These mechanisms enable the robust maintenance of epigenetic domains over hundreds of divisions. To overcome the costs of genome-wide evaluations, we developed a coarse-grained approximation. We validate simulations against genome-scale CUTRUN data from human fibroblasts and endothelial cells, recapitulating megabase-scale topological patterns. Finally, we use this framework to conceptualize epigenetic drift and reprogramming therapies.

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CP2

Bayesian Inference of Gene Regulatory Networks at Stochastic Steady State

Gene Regulatory Networks (GRNs) form the regulatory backbone that coordinates gene expression. The architecture of GRNs shapes their function and constraints the biochemical pathways through which information flows. Inferring the structure of regulatory interactions is thus essential for understanding biological systems, and designing targeted therapies. Despite substantial progress in GRN inference, most approaches – from statistical methods to deep learning – do not take into account fundamental biochemical processes that drive regulatory dynamics. To address this shortcoming, here we present a novel Bayesian inference approach based on using the Chemical Langevin Equation (CLE) as a model of gene expression dynamics at stochastic equilibrium. Interactions in GRNs are sparse, and we thus use a regularized horseshoe prior enabling selective shrinkage of unsupported interactions while identifying strong regulatory edges. We evaluate our method using synthetic gene expression data, allowing for benchmarking against a known ground truth. Our approach allows us to infer kinetic parameters, identify network structure, and infer regulatory cycles without the need to observe transient dynamics. This Bayesian alternative to current methods thus provides both biological interpretability and structural identifiability in GRN inference.

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CP2

Embedding Kernels for Sequence-Function Relationships

A central challenge in biology is understanding how variation in biological sequences (DNA, RNA, and protein) impacts function. Although high-throughput experiments are now capable of measuring these sequence-function relationships at a massive scale, novel computational techniques for inference and interpretation are still needed. We address these problems using Gaussian process regression, a Bayesian method that imposes a Gaussian prior on sequence-function relationships via a kernel encoding how sequence similarity relates to covariance in measured functionality. Here, we explore kernels in which the covariance depends on the distance between sequences in an embedding space, making these kernels expressive yet interpretable. Embedding features can either be (i) precomputed, for example, from evolutionary sequences or large language models, or (ii) learned from experimental data via a factor analysis kernel. We describe the mathematical relationship between our embedding kernels and existing kernels for discrete sequence space as well as classical kernels for continuous spaces. Our embedding kernels improve predictive performance across various high-throughput sequence-function datasets, including protein datasets ranging from short motifs to full-length proteins. The inferred embeddings also capture known and novel features of the sequences underlying functionality. Overall, these models provide new tools to understand and predict sequence-function relationships.

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CP2

Sprint-Ms: A High-Throughput Platform for Identifying Protein-Protein Interactions Using Pooled Ip-Ms and Sparse Signal Recovery

This talk will present SPRINT-MS (SParse Reconstruction of INTeractions by Mass Spectrometry), an integrated experimental and computational platform to accelerate the discovery of protein-protein interactions (PPIs). PPIs, which govern critical cellular and physiological processes such as development and disease, form extensive networks that vary across time, conditions, and cell types, creating a complex, high-dimensionality problem. Thus, there is a pressing need for universally applicable tools capable of mapping and quantifying PPI networks and their context-dependent dynamics with high efficiency. SPRINT-MS builds on compressed sensing and uses an algorithmically optimized antibody (or lysate) pooling scheme, immunopurification-mass spectrometry (IP-MS), and a novel sparse signal reconstruction algorithm to enable pooled PPI capture experiments. This approach increases throughput by an order of magnitude, while reducing sample input requirements. This talk will both discuss the mathematical methods underlying the platform and demonstrate that SPRINT-MS, applied to 30 bait proteins of interest via either antibody or lysate pooling, is comparable to standard individual IP-MS experiments in the identification of PPIs and recapitulation of known interactions.

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CP3

Correlated Variability in Recurrent Networks of Competing Inhibitory Subtypes

Cortical circuits contain diverse inhibitory interneuron populations whose mutual interactions shape network dynamics and information processing. While recent theoretical work has characterized how correlated trial-to-trial variability emerges across segregated excitatory subnetworks, less is understood about the structure of shared variability among competing inhibitory subtypes. In Layer 2/3 of the cortex, vasoactive intestinal peptide-expressing (VIP) and somatostatin-expressing (SST) interneurons form a mutually inhibitory motif, while in Layer 1, subtypes of neuron-derived neurotrophic factor-expressing (NDNF) interneurons engage in analogous competitive interactions. Using mean field circuit models and pathway expansion techniques, we investigate how the connectivity structure between these inhibitory populations shapes their pairwise covariability. We identify the circuit regimes under which mutual inhibition enhances or suppresses shared variability. Our results reveal how the balance between within-subtype recurrence and cross-subtype inhibition governs the correlation structure in these circuits, offering predictions for how interneuron diversity contributes to the statistical features of cortical population activity. This work extends the theoretical framework linking connectivity motifs to correlated variability beyond excitatory assemblies, providing insight into the functional role of inhibitory subnetwork organization across cortical layers.

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CP3

Wearable-Based Circadian Rhythm Modeling: Applications to Phase Prediction and Infection Detection

As consumer-grade wearable technology has become more prevalent in recent years, large-scale longitudinal datasets of free-living physiology and behavior have been made available for researchers. Using wearable activity/steps and heart rate data, we adapt and validate mathematical models to accurately estimate circadian phase (dim light melatonin onset, or DLMO) across populations. We evaluate the performance of limit cycle oscillator models in real-world scenarios (where ground-truth circadian timing is difficult to obtain at scale), including home-based cohorts of later-life adults and wearable-based lighting interventions for reducing cancer-related fatigue. Beyond phase prediction, we leverage similar modeling frameworks to quantify rhythm robustness and disruption over time. Circadian rhythms display disruption during acute illness, and we demonstrate systematic shifts in physiological features (e.g., circadian phase, phase uncertainty, and resting heart rate) extracted from wearable devices during influenza and other respiratory infection events. These results have implications for model- and wearable-based early detection of infections. Overall, these results illustrate how mechanistic circadian modeling paired with wearables can generate

interpretable biomarkers of internal time and health state, with potential to support personalized interventions and early detection in real-world settings.

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CP3

Magnitude-Constrained Optimal Chaotic Desynchronization of Neural Populations

We calculate magnitude-constrained optimal stimuli for desynchronizing a population of neurons by maximizing the Lyapunov exponent for the phase difference between pairs of neurons while simultaneously minimizing the energy which is used. This theoretical result informs the way optimal inputs can be designed for deep brain stimulation in cases where there is a biological or electronic constraint on the amount of current that can be applied. By exploring a range of parameter values, we characterize how the constraint magnitude affects the Lyapunov exponent and energy usage. Finally, we demonstrate the efficacy of this approach by considering a computational model for a population of neurons with repeated event-triggered optimal inputs.

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CP3

Data-Driven Heterogeneous Network Assembly in the Parkinsonian Basal Ganglia

The substantia nigra pars reticulata (SNr) is the output nucleus of the rodent basal ganglia that integrates multiple inhibitory inputs and exhibits neural firing heterogeneity. Through extending a previous conductance-based model, we develop a data-driven framework for constructing heterogeneous neural networks directly from experimental recordings. Rather than independently sampling parameters, our tuning algorithm assembles the best fitting neural networks by selecting units across various simulated network parameter regimes that best fit individual experimental recordings. This approach allows for preservation of heterogeneity found in intrinsic cell parameters and network interactions. We find that networks tuned to reproduce experimental slice firing rate and variability distributions can be further modified to capture in vivo recordings in healthy data by amplifying background noise and increasing recurrent connectivity. Then, we demonstrate how combinatorial parameter sweeps of disease inspired parameter changes best capture experimentally observed Parkinsonian firing statistics. Decision-tree analysis reveal a hierarchy of disease-associated parameter changes to reproduce experimental data. This work demonstrates how data-informed heterogeneous network assembly can identify dominant control patterns in high-dimensional conductance-based neural networks and provides a framework for mechanism inference for Parkinsonian SNr dynamics.

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CP3

Mixed-Mode Dynamics and Transitions in a Biophysical Neural Oscillator Model

Mixed-mode bursting oscillations (MMBOs) combine bursting dynamics and mixed-mode oscillations (MMOs), with the latter characterized by alternating large-amplitude oscillations and small-amplitude oscillations. While there has been a growing interest in studying MMOs with three timescales, the analysis of MMBOs has largely been confined to two-timescale systems, and the mechanisms governing transitions between these regimes remain even less understood. In this work, we use geometric singular perturbation theory to investigate the organization and mechanisms of MM(B)Os in a biophysical model of cortical theta neuronal oscillators with three distinct timescales. We examine how variations in relative timescales shape the underlying mechanisms and transitions between different dynamical regimes. We show that MMO and MMBO dynamics are organized along isolated bifurcation branches in parameter space, known as isolas. During transitions between MMOs and MMBOs, small-amplitude oscillations can arise through distinct mechanisms, including delayed Hopf bifurcation, canard mechanism, and saddle-focus effects. Our results highlight the central role of timescale structure in shaping MMO and MMBO dynamics and organizing the transitions between them.

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CP4

Modeling, Analysis, and Simulation of Stochastic Dengue Dynamics with Random Transmission Rates

Dengue is endemic in Colombia and other tropical regions, with transmission driven by interactions between human hosts and the mosquito vector Aedes aegypti and influenced by environmental variability. We propose a structured stochastic SIRSI model incorporating random perturbations in transmission rates to represent environmental uncertainty. The stochastic dynamics are analyzed, and numerical simulations are performed using the Euler-Maruyama method. Model parameters are obtained from the literature, calibrated estimates, and epidemiological data from Colombias Public Health Surveillance System (SIVIGILA) for 20142024. To complement the stochastic approach, a Seasonal Autoregressive Integrated Moving Average (SARIMA) model is used to capture seasonal patterns and generate short-term forecasts. The results show that stochastic modeling improves the representation of observed variability and provides a flexible framework for analyzing and predicting Dengue dynamics under un-

certainty.

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CP4

A Novel Mathematical Model of Oropouche Virus Transmission Dynamics

Oropouche virus (OROV) is a vector-borne arbovirus that has caused more than 500,000 infections across South America, Central America, and the Caribbean. Its primary vector, the midge species *Culicoides paraensis*, acquires the virus from wild reservoir hosts and transmits it to humans during blood feeding. As outbreaks within the Amazon basin continue to occur and confirmed cases steadily increase, a proper understanding of the interplay between climatic variables, vector behavior, and OROV transmission is needed to develop effective public health interventions. In this work, we develop a novel mathematical model of Oropouche virus spread in Amazonas, Brazil using ordinary differential equations (ODEs). First, we derive the basic reproductive number at baseline to assess the potential for disease persistence. We then incorporate seasonal forcing and fit the model to weekly incidence data from the 2023-2024 outbreak using least squares optimization. With our model structure, quantitative results show that the seasonal variation in OROV transmission is best explained (in the sense of minimum l^2 error) by an exponentially decaying pulse applied to midge recruitment, which captures the incidence data with a relative l^2 error of 11.94%. This approach outperforms precipitation-based and other functions intended to model general seasonality or the right-skewed incidence curve.

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CP4

Quantifying Reinfection-Driven COVID-19 Transmission with Physics-Informed Neural Networks

The evolution of SARS-CoV-2 underscores the significance of immune escape and reinfection in the spread of epidemics. This study proposes a two-strain compartmental model of the Omicron and Delta variants of SARS-CoV-2, combining it with the Physics-Informed Neural Network (PINN) method to estimate time-dependent epidemiological parameters using daily epidemiological and variant-specific COVID-19 data from the State of Tennessee. The model captures the dynamics of primary transmission among susceptible individuals and secondary transmission resulting from the reinfection of recovered individuals with the other variant, thereby providing a mechanistic understanding of partial cross-immunity. The PINN integrates the nonlinear equations of the dynamics into the learning process using automatic differentiation, thus satisfying the equations with the observed infection and recovery data. Time normalization, scaling of the system states, and log parameterization are used to improve the stability of the optimization process and maintain the positivity of the estimated epidemiological parameters. Immune escape effects are quantified across reinfection scenarios, ranging from no reinfection to bidirectional reinfection, to assess their impact on epidemic sustainability. The trained PINN enables 30-day forecasts of multi-strain dynamics, variant dominance, and resurgence risk, demonstrating a principled framework for learning non-stationary epidemic systems from real-world data.

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CP4

Attention to Heterogeneous Information Sources Affects Epidemic Outcomes

During an epidemic, disease transmission and human behavior are closely related: high infection levels trigger risk awareness and preventive behaviors, which suppress the transmission of disease. While these coupled dynamics have been heavily investigated, less has been done to explore how different ways to establish the awareness of disease affect infection levels. This study presents a mathematical model of two interacting groups to investigate how epidemic outcomes are affected by the choice of information source, i.e., one's own group and/or the other group. We demonstrate that for different physical contact patterns the system can undergo a bifurcation from a uniform endemic equilibrium to a non-uniform endemic equilibrium, resulting in a persistent infection level difference between groups that is driven by each group's choice of information source. Our results reveal strategies to minimize infection: 1) a group with low infection level benefits by prioritizing information from a group with high infection level thereby overestimating risk and 2) a group with high infection level benefits by accessing information only about its own infection level thereby avoiding underestimation of risk. These results emphasize the need to promote awareness of disease levels in addition to observation of anti-epidemic measures. We highlight conditions under which strategies that benefit one group may conflict with strategies that minimize the total infection level of both groups.

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CP5

Parameter Sensitivity and Synchronization Dynamics in Beta Cells: Insights from Genetic Algorithms and Neural Networks

Beta cells in the pancreas play a crucial role in regulating blood glucose by secreting insulin. They are electrically coupled via gap junctions, and disruptions in this coupling can impair coordinated insulin release and contribute to diabetes. Beyond gap junction integrity, parameters governing gap junction connectivity and cellular excitability, which influence bursting activity and synchronization, are essential for beta cell function. To systematically explore

this complex parameter space, we employed genetic algorithms on a beta cell network model. Candidate parameter sets were identified that produce two distinct behaviors: complete synchronization under control conditions and total desynchronization when a specific cell is silenced via chloride current activation. We generated six candidate sets meeting our objective. Comprehensive statistical analyses further revealed how fluctuations in these parameters modulate network synchronization and highlighted the factors exerting the greatest influence. In parallel, we implemented a neural network classifier to distinguish candidate sets that exhibit both full synchronization and complete desynchronization. This enabled us to confirm that silencing a specific cell yields typical switch cell behavior, thereby providing new insights into beta cell regulation. Ultimately, our findings underscore robust relationships between parameter variations and network dynamics, enhancing our understanding of beta cell functionality.

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CP5

A Real-Time Digital Twin for Biological Oscillators: Phase-Tracking Via Reduced-Order Hybrid Maps

We present a hybrid learn-and-lock digital twin for real-time tracking and synthesis of oscillatory biological signals. Offline, the model learns a parametrized family of waveforms by extracting frequency, baseline, amplitude, and a PCA shape basis so that the full trace can be generated from a single phase variable. Online, a PLL-inspired synchronization mechanism locks the latent phase to measurements, suppressing drift under model mismatch, parameter variation, and noise while keeping computational cost low. We demonstrate the approach on the HodgkinHuxley neuronal model and the cardiac-like FitzHughNagumo model. We also validate the performance on real-time ECG and EEG data. Across these examples, the twin achieves accurate timing and waveform reconstruction with minimal online computation, providing a practical pathway to low-latency digital twins for monitoring, forecasting, and closed-loop control.

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CP5

Automated Ensemble-Based Bifurcation Analysis (ABBA)

We present an ensemble bifurcation analysis framework integrating Latin Hypercube Sampling (LHS) with MATCONT-based numerical continuation to construct ensemble bifurcation landscapes for nonlinear ODE models. Rather than analyzing codim-1 bifurcations (saddle-node (SN), Transcritical (TC), Pitch-fork (PF), Hopf-bifurcations (HB)) for a single parameter set, we generate parameter ensembles and perform continuation on each, transforming bifurcation diagrams (BDs) into statistical objects. This shifts inference from trajectory fitting to dynamical-structure fitting, identifying parameter regions that realize specific dynamical phenotypes. The approach reveals that a single biological network can support multiple mechanistic routes to similar behaviorsfor example, transitions via SN, PF, or SNTC (SNTC), and oscillations via supercritical or subcritical HB, each with distinct hysteresis and robustness properties. Applied to a dual phosphorylationdephosphorylation 2D model, the framework captures ultrasensitivity, bistability, and biphasic responses and uncovers hidden SNTC and PF structures, demonstrating the power of ensemble-based dynamical analysis.

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CP5

Stability and Robustness of a Generalized Pump-Leak Model for Epithelial Vesicles

Classical pumpleak equations (PLEs) model epithelial ion and volume regulation at the level of a single compartment, but many epithelial functions arise from interactions between a cell and an enclosed lumen. We develop a two-compartment pumpleak model consisting of an intracellular compartment coupled to a luminal compartment across the apical membrane, with both compartments connected to an infinite extracellular bath via the basolateral membrane and a paracellular pathway. Extending five-dimensional single-cell PLEs, we formulate a ten-dimensional system and derive analytical steady states for both passive transport and Na?/K?-ATPasedriven active transport. We analyze parameter dependence, local stability, and robustness across physiological regimes. Focusing on closed epithelial systems with steady luminal volume, we find a strong asymmetry between apical and basolateral membrane potentials and identify conditions under which apical pump placement and limited potassium recycling lead to luminal volume expansion. This framework provides a tractable foundation for studying epithelial transport and dysfunction.

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CP5

A General Framework for Data-Driven Model Identification of Bursting Neurons

Data-driven model identification strategies forgo physics-based representations in favor of dynamical models that capture the important features of time series data. While many such approaches have been developed in recent years, they often struggle to find adequate representations for the highly nonlinear behavior of bursting neurons which alternate between rhythmic firing and quiescence. Here, we consider a data-driven model identification strategy tailored to conductance-based bursting neurons. Starting with a linearized representation for states evolving on a slow manifold near a fixed point associated with the quiescent regime, a diffeomorphism relating the slow manifold to a set of

carefully chosen coordinates can persist far beyond the linear regime allowing for the inference of the fully nonlinear dynamics from time series data. Numerical illustrations are provided for elliptic, parabolic, and square wave bursters. For each, the proposed model identification strategy preserves the topology of the bifurcations that mediate the transition between spiking and quiescence, ultimately providing a more accurate representation than other commonly used model identification strategies.

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CP5

Fast-Slow Analysis of a Model For the Stimulation of Enzymatic Activity by a Competitive Inhibitor

Competitive inhibitors can paradoxically stimulate an enzymatic reaction at low to moderate doses. Competitive inhibition occurs when an inhibitor binds to an enzymes active site and blocks its substrate. We recently proposed a detailed but straightforward mass action model for competitive inhibition of phosphoglycerate kinase 1 (PGK1) by Terazosin (TZ). The full PGK1 model has two substrates and two products that bind and release in either order, known as a random bi-bi mechanism. This model predicts an increased reaction rate at low or moderate TZ doses, suggesting stimulation is an intrinsic feature of competitive inhibition in enzymes with two products. This mechanism may aid development of novel therapies, since enzyme activators are rarer and harder to design than inhibitors. Here we propose a three time scale reduction of the model and show the resulting rate equation retains three essential attributes of competitive inhibitor stimulation: a biphasic dose response, dependence on relative product dissociation rates from binary and ternary complexes, and the parameter region permitting stimulation. The rate equation is a rational function, monod in each substrate but quadratic in the denominator in inhibitor dose. We derive analytical expressions for peak activation and optimal dosing and compute the parameter subset allowing stimulation, illuminating how a competitive inhibitor can enhance enzyme activity.

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CP6

Birds Are the Opposite of Trees

I'll present some thoughts on different mathematical representations in spatial ecology. If we think of spatial ecology in terms of trying to understand how the movement and interactions of organisms shape ecological patterns, the choice of mathematical representation of movement becomes central. The choice of model formalism diffusion/advection, dispersal kernels, movements across networked habitats, metapopulation approaches, etc. influences the phenomena we can capture and the questions we can ask, but should also be "true" to the organism is some sense. Ill reflect on how the fidelity of these representations to specific organismal movement shapes the insights we can draw.

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CP6

Modeling Honey Bee Colony Stability under Increasing Thermal Variability

Temperature plays a critical role in honey bee colony survival, particularly under increasingly variable environmental conditions. In this study, we investigate how temperature fluctuations influence colony dynamics. We develop a novel mathematical modeling framework that integrates a neural-network-based approach to characterize the nonlinear relationship between thermal variability and honey bee population change rates. Results reveal nonlinear threshold behavior in mortality responses under specific patterns of thermal variability, with both fluctuation magnitude and temporal structure significantly affecting colony stability. These findings provide a flexible, data-driven framework for understanding how environmental variability shapes honey bee population dynamics under climate change.

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CP6

Nonlinear Population Dynamics of Communication Strategies in Intergroup Competition

Competition among honeybee colonies for shared food resources provides a natural framework for studying how communication strategies shape long-term outcomes in resource-limited environments. Recruitment-based signaling coordinates foraging effort, yet high communication intensity can generate diminishing returns under crowding and limited resource availability. This trade-off motivates a mathematical investigation of communication strategy evolution under intergroup competition. We develop a nondimensional nonlinear ODE model describing interacting colonies competing for shared resources. The system captures how relative recruitment intensity and environmental feedback determine effective growth of committed foragers. By coupling ecological return dynamics with replicator-type strategic adaptation, the framework allows communication strategies to evolve in response to competitive pressure. We analyze equilibrium states and their local stability to characterize parameter regimes leading to dominance of one colony versus stable coexistence. Using time-averaged colony return as the payoff functional, we further examine how communication rates influence commitment dynamics and long-run performance. Stability analysis identifies evolutionarily stable communication strategies within the competitive environment, providing a tractable applied dynamical systems perspective on collective behavior under resource competition.

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CP6

Predicting Hawaiian Leafhopper Population Responses to Climate Change Using Short-Term Experiments

The endemic Hawaiian leafhoppers (Hemiptera: Cicadelli-

dae: Nesophrosyne) comprise over 200 species distributed across the archipelago, making them sensitive indicators of the health of a broad range of ecosystems. Understanding how temperature shifts influence leafhopper populations will enable land managers to anticipate potential biodiversity loss resulting from climate change. As efforts to conserve Hawai'is biodiversity continue, there is a need for conservation tools that translate short-term fitness experiments into long-term predictions of population vulnerability to temperature change. Here, we developed an age-structured population model to quantify how temperature conditions influence the dynamics of leafhopper generations. We estimated model parameters using n fitness assays with a tractable laboratory leafhopper population (Macrosteles quadrilineatus) reared for one month under moderate to severe predicted climate change scenarios. Based on historical and projected temperature data from the National Oceanic and Atmospheric Administration, we determined the projected temperature changes over the island of Maui and then applied our model to predict the resulting population shifts. As a result, we created geographic maps that highlight vulnerable areas, giving land managers tools to inform conservation and policy decisions and enabling early interventions to reduce biodiversity loss.

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CP6

Competition for Space: Species Zonation Promotes Coexistence in the Rocky Intertidal

Food web models have historically focused on trophic (consumptive) interactions, disregarding the role of non-trophic (non-consumptive) interactions that are known to provide a foundation for community persistence. Key interaction types are defined with a multiplex network, in which each link type represents a different class of species interaction. We integrate the multiplex network into the ODE based Allometric Trophic Network (ATN) model which describes biomass changes over time and uses allometric scaling for parameterization. Applying this framework to the well-studied, biodiverse Chilean rocky intertidal, we focus on non-trophic interactions that modify the quantity of space available, such as competition for space and facilitative multi-species stacking. Empirically-derived competition networks based on species zonation are compared to simulated random competition networks. Across model structures, the presence of ecological refugia for sessile consumers is a key mechanism supporting species coexistence. The enhanced persistence is notable at higher trophic levels, where realistic network structures facilitate more favorable biomass distributions. This research demonstrates how the interplay of competitive and facilitative interactions affects food web dynamics and provides a novel modeling framework to study the dynamics of multiplex networks.

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CP6

Quantifying Diffusive Dispersal of Mosquitoes

Using a diffusive agent-based model, we design a computational method, called Recapture of Diffusive Agents Particle Swarm Optimization (RDA-PSO), that estimates the diffusion coefficient associated with mosquito dispersal. With input from mark-release-recapture field experiments, our computational method offers a simple and reliable approach to quantify insect dispersal, overcoming several experimental limitations, such as low recapture rates and uneven capture site distribution.

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CP7

A Spatial Understanding of Coral Dynamics with

Bistability

Modeling coral ecosystems in a theoretical framework typically focuses on tradeoffs between coral, algae, and grazing fish populations, highlighting its bistable dynamics; however, spatial understanding of this system is often suppressed. Analysis of models with spatial features is crucial, as degraded, patchy reef systems become more common, and the size, clustering, or overall connectivity of these patches play a key role in the persistence and the emergent dynamics. More broadly, the implications of spatial heterogeneity and connectivity in systems with alternative stable states are complex and underexplored. In this work, we explore the long term dynamics, through both numerical and mathematical analysis, of a spatial model of a coral ecosystem, extended to multiple reef patches. Our results explore the mixed-blessing that connectivity can have on coral metacommunities.

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CP7

Spatial Asymmetry Alters Stability and Extinction Thresholds in PredatorPrey Metapopulations

Dispersal asymmetry is a pervasive feature of advective environments such as ocean currents and wind-driven transport. In spatially structured predatorprey metacommunities, prey and predators may experience different degrees of directional transport, generating connectivity mismatches that modify trophic coupling across patches. We develop a mechanistic metacommunity model parameterized by species-specific connectivity matrices describing directional fluxes among local populations. Dispersal distance, linked to larval duration, determines spatial reach, while asymmetry mismatch alters the effective strength of trophic interactions. Using dynamical systems analysis combined with numerical simulations, we examine how dispersal asymmetry and mismatch influence spatial population structure, qualitative regimes, and extinction risk. Small mismatches promote sustained oscillations with relatively homogeneous mean densities, whereas larger mismatches weaken trophic coupling and produce spatially heterogeneous but stable equilibria. Dispersal distance further modulates extinction risk by controlling the depth and duration of population minima. These results show that spatial asymmetry reshapes stability and extinction thresholds in trophic metapopulations.

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CP7

Surprising Spread Patterns in Plant Hoppers, Predicted by Principled Models

A principled model for the transition of agents of a plant hopping species between hosts is presented. A multi-scale analysis of the model shows under which circumstances macroscopic breaks in symmetry, such as drift and anisotropy, can arise, even if the microscopic agent movement to and from hosts is fully uniform and isotropic. Moreover, the important role of edge ecosystems for the species movement is established: it is shown (i) how the movement of agents (such as spotted lanternfly) within vineyards can be strongly affected by tall hosts (such as trees or poles) outside of the vineyard, and (ii) how transportation routes (such as roads or train tracks) can affect the emergent spread patterns.

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CP7

Incorporating Thermal Physiology Into a Dynamic Food Web Model

Predicting how intertidal species will respond to environmental change has motivated extensive research in quantifying their thermal physiological responses via thermal performance curves (TPCs). How these responses scale up from individuals to populations to ultimately affect community abundances is largely unknown. The Allometric Trophic Network (ATN) is a food web model that describes abundance dynamics using ordinary differential equations (ODEs) given the predator-prey interactions (edges) between each species (nodes) in the community network. I introduce thermal dependencies inspired by TPCs, which measure how a physiological metric changes with temperature, into food web model parameters. By applying curve similarity metrics between the model TPCs and change in steady states across simulated temperatures, I assess (1) the role of diversity in thermal response sensitivity and affinity across species in promoting overall food web persistence, and (2) how important individual thermal performance is in determining their realized abundance performance given the interaction network. This approach seeks to disentangle the ecological and physiological drivers of species composition in complex communities.

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CP7

Mathematical Modeling of a Coral-Symbiont System to Assess Heat-Induced Bleaching

Coral reefs are a vital part of marine ecosystems across the planet, providing shelter and food to sea creatures and protecting coastlines from storms and floods. However, reefs are threatened by coral bleaching, which can be caused by a number of factors, including long-term heat stress. Bleaching results from symbiotic algae leaving the coral, and may eventually result in host death. While coral can recover from some of these bleaching events, this process may take months or years. As these events occur more frequently, it is essential that we study coral growth and heat-induced bleaching dynamics. To do so, we construct a dynamic compartmental model consisting of four nonlinear ordinary differential equations to track changes in coral

host, symbiont, nutrient, and nutrient reserve populations. We calibrate the model using experimental data of ambient and elevated temperatures. We then simulate various scenarios with altered temperatures for coral with varying symbiont reliances and nutrient capacities, and assess the resulting level of bleaching and/or death. That is, we use the model to explore the behavior of different corals under heat stress.

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CP8

Learning Novel Types of Method and Theory for Eeg-Based Ai

Understanding human decision-making through EEG signals remains a fundamental challenge due to the complex, high-dimensional nature of neural activity. In this study, we explore novel EEG-based AI theory and methods that integrate directional deep learning, geometrical modelling, and probabilistic inference to capture cognitive states during multi-class choices. A simulation environment was designed to consider multiple decision scenarios, enabling us to refine methods and discover patterns beyond traditional deep learning. Directional deep learning is particularly suited for identifying circular and angular patterns in EEG microstates, allowing more precise detection of hesitation, uncertainty, and choice-related brain activity. Using the DEAP dataset, which includes EEG recordings of 32 participants responding to music videos, along with binary arousal and valence labels, we performed directional analysis of brain waves and geometric modelling of mouse trajectories to infer cognitive states and choice probabilities. Our study demonstrates that combining simulation-based learning, geometrical analysis, probabilistic inference, and directional deep learning improves prediction and interpretability of cognitive states compared to conventional models. This approach provides new insights into brain behaviour dynamics and extensions for advanced AI applications in neuroscience and life sciences.

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CP8

Image Segmentation for Automatic Data Acquisition of Aiptasia

As temperatures rise, photosymbiotic marine species are presented with unique challenges. Exaiptasia diaphana (aiptasia) is a highly adaptable model organism for studying these challenges. Current methods to measure the size of aiptasia are destructive or require laborious manual counting. In this work, we aim to automate the acquisition of biological data using deep learning methods for image segmentation. A 2-month acclimatization trial to assess physiological response of aiptasia to temperature stress was completed. Using population-level experimental images, we build and test machine learning algorithms. We compare our measurements of size via image segmentation to destructive biomarkers to create a new non-destructive gold standard for aiptasia sizing. We bridge computational image analysis with marine biology to enable scalable, non-destructive measurements of coral analogs.

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CP8

Functional Identifiability for Universal Differential Equations

Differential equations are widely used to model real-world phenomena. Typically, deriving predictions from these models requires first estimating unknown parameter values from data. In many settings, however, not only parameters but also functional components are unknown. Examples include the rate of protein production as a function of transcription factor concentration, and the rate of infection as a function of the number of infected individuals. Recently, universal differential equations (UDEs) have been introduced as a framework for recovering such unknown func-

tions from data. A UDE augments a differential equation with a neural network representing the unknown function. The model can then be fit using standard parameter estimation procedures, after which the learned function can be recovered by interrogating the neural network. In this work, we study identifiability, our ability to recover true system properties, for UDEs. While identifiability for parameter estimation is well established, identifiability of unknown functions is not. We present new tools for assessing functional identifiability, determining when such functions can be recovered from data. We consider both structural identifiability (whether model structure prevents function recovery) and practical identifiability (whether available data are sufficient to estimate the functions). Finally, we draw comparisons with parametric identifiability and examine how the presence of unknown functions influences it.

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CP8

Data-Driven Classification of the Dynamics of Thoracic Aortic Morphology

Thoracic aortic dissection (a tear in the wall of the body's largest artery) creates a false lumen that can lead to rupture, organ malperfusion, or progressive dilation. Thoracic endovascular aortic repair (TEVAR) attempts to redirect flow and induce favorable remodeling, yet no standardized clinical classification system exists to stratify patient trajectories post-intervention. We developed an unsupervised framework to discover morphological dynamics directly from imaging data. Anatomic features (normalized aortic surface area and normalized fluctuation in integrated Gaussian curvature) were extracted from longitudinal CT angiography to define a low-dimensional state-space tracking structural evolution. Using a variation of Sparse Identification of Nonlinear Dynamics (EM-SINDy) that incorporates the Expectation-Maximization algorithm, we inferred ordinary differential equations governing feature dynamics without requiring predefined clinical labels. This data-driven approach identified four distinct remodeling classes, each characterized by unique flow fields and attractors that capture the temporal behavior of post-repair aortic structure. This method provides a principled route to cohort discovery when clinical ground truth is unavailable. The resulting framework offers interpretable models of aortic remodeling, establishing a foundation for clinical stratification in the absence of established outcome categories.

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CP8

Dynamic Modeling of Abdominal Aortic Aneurysms

Abdominal aortic aneurysm carries rupture risk, and endovascular repair alters sac morphology in ways not captured by size alone. We developed a noise-aware framework modeling aortic remodeling in a low-dimensional state space defined by normalized sac surface area and normalized fluctuation in integrated Gaussian curvature. Using Sparse Identification of Nonlinear Dynamics (SINDy), we inferred ordinary differential equations governing feature evolution for regressing and stable sac cohorts, then embedded these dynamics in a Bayesian decision framework enabling static (coordinate-based) and dynamic (derivative-based) classifiers. Across 75 patients and 220 CT scans from two international cohorts, learned models yielded class-specific flow fields and fixed points: regressing sacs converged toward a low-size/low-shape attractor, while stable sacs maintained near-constant size with elevated shape fluctuation. The dynamic classifier confidently separated 87% of patients at one year post-repair versus only 1% with static methods, showing that rates of change become informative before static distributions diverge. We further extend this framework with expectation-maximization for unsupervised cohort identification, relaxing the need for predefined clinical labels. These results provide a principled route from interpretable geometric features to individualized, probabilistic remodeling forecasts and offer guidance for surveillance design.

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CP8

Object-Aware Deep Learning for Robust Colony Counting in Densely Clustered Images

Colony counting is a common task in microbiological experiments. In most laboratories, it is still performed manually, which is time-consuming and vulnerable to human error. Although automated image analysis methods based on semantic segmentation have shown promising results, they often require large amounts of human-annotated data and struggle to separate densely clustered colonies. Moreover, conventional pixel-level metrics such as Dice or IoU do not necessarily reflect counting accuracy, leading to evaluation mismatch in practical applications. In this work, we develop a deep learning pipeline for robust colony segmen-

tation and counting on agar plate images. Our approach leverages synthetic image pretraining and transfer learning to address limited annotated real data and employs a UNet-based architecture for segmentation refinement. To better align model performance with biological objectives, we use an object-level evaluation framework that directly measures instance consistency and counting error. Experimental results demonstrate improved counting accuracy and enhanced generalization from synthetic to real data compared to pixel-level baselines on as few as 10 labeled images. This framework provides a scalable and reproducible solution for high-throughput microbial colony quantification and highlights the importance of object-level evaluation in biological image analysis.

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CP9

Diffusion-Driven Growth Dynamics with Moving Interfaces: A Stefan-Type Model for Biological Transport

Transport-limited growth processes arise in many biological and life-science-related systems, where evolving interfaces are governed by diffusive transport in the surrounding medium. In this work, we present a mathematical study of diffusion-driven growth with a moving boundary, formulated as a Stefan-type free-boundary problem. The model couples a parabolic diffusion equation in the bulk phase with an interfacial evolution law linking the growth rate to local diffusive fluxes. By exploiting a separation of spatial scales and assuming laminar transport conditions, the governing equations are reduced to a simplified formulation that preserves the essential biological transport mechanisms while allowing analytical insight. Asymptotic solutions are derived in diffusion-dominated regimes, yielding explicit scaling laws for the temporal evolution of the interface. These analytical predictions are supported by numerical simulations of the full coupled system, showing strong agreement across a range of parameter values. The proposed framework provides a flexible mathematical tool for understanding diffusion-driven growth and deposition phenomena relevant to biological transport, tissue growth, and life-science-related material processes, and can be extended to incorporate additional transport effects and nonlinear mechanisms.

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CP9

A Numerical Analysis of a Stabilized Hyperbolic Equation Modelling Bio-Polymerization

This talk discusses a stabilization method for first order hyperbolic differential equations applied to DNA transcription modeling. It is known that the usual unstabilized finite element method contains spurious oscillations for non-smooth solutions. To stabilize the finite element method the authors consider adding to the first order hyperbolic differential system a Vreman stabilization term in space. Numerical analysis of the stabilized finite element algorithms and computations describing a few biological settings will be presented.

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CP9

An Optimal Control Approach to Nonlinear Wave Speed Selection in Reaction-Diffusion Equations

Travelling wave solutions of reactiondiffusion equations are widely used to model the spatial spread of populations and other phenomena in biology and physics. In this work, we reinterpret the classical variational principle approach through an optimal control formulation, in order to obtain a lower bound on the invasion speed of travelling wave solutions in systems of nonlinear partial differential equations (PDEs). We begin by analysing single-species models, governed by a scalar PDE with a density-dependent diffusion term and a nonlinear reaction term. We show that for any admissible test function, maximising with respect to the parameter of interest yields a bound on the travelling wave speed. Extending this approach, we then consider multi-species systems of reaction-diffusion equations and reframed as Pontryagin-type optimality systems, we derive analogous bounds on the travelling wave speed using a variational framework under weak coupling. We apply this framework to several examples, including the porous-Fisher equation, and examine when nonlinear selection mechanisms dominate over the classical linear marginal stability criterion, using numerical simulations to confirm the accuracy of the predicted wave speeds across a range of illustrative examples.

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CP9

Reaction-Diffusion Modeling of Cross-Feeding in Iron-Acquisition of Two Bacteria Strains.

Iron acquisition is essential for microbial survival, biofilm formation, and pathogenicity. Many bacteria use

siderophores, such as pyoverdines produced by fluorescent pseudomonads, to chelate iron under limiting conditions, and studies show that siderophore production and cross-feeding confer a fitness advantage over species that lack these abilities. This phenomenon has been experimentally studied in species such as rhizosphere bacterium Pseudomonas protegens Pf-5 and Pseudomonas aeruginosa PAO1 using chemostat and batch culture systems. However, most previous studies do not account for spatial heterogeneity. In contrast to well-mixed, homogeneous environments, bacterial populations typically grow in spatially structured communities such as colonies. In this study, we address this gap by extending a previously developed ordinary differential equation model of iron chelation and cross-feeding into a reaction-diffusion model for two related species in two-dimensional space. This approach leads to a highly non-linear system of partial differential equations. To solve it numerically, we use a finite difference method with semi-implicit discretization in both space and time. Our findings indicate that siderophore production and cross-feeding confers a significant growth advantage even in spatially structured environments. This modeling approach provides a quantitative framework for understanding complex microbial interactions in heterogeneous environments.

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CP9

Bioconvective Pattern Formation Influenced by Domain Changes

Bioconvection is the pattern formation from the collective swimming of microorganisms against gravity. Initially, microorganisms swim toward the fluid surface, where they accumulate into a dense layer whose mass density eventually exceeds the threshold of what the fluid can support. This triggers a RayleighTaylor instability initially characterized by finger-like structures which plummet to the bottom layer. Due to the inherent drive to vertically swim, the microorganisms begin to swim toward the surface again thereby producing vortex patterns with alternating regions of high and low concentration. In this talk, I will present our mathematical and computational overview of modeling the incompressible NavierStokes equations coupled with a transport equation for microorganism movement. Building on our previous results, we aim quantify the role of domain geometry in shaping vortex patterns over long simulation times (t = 2400 s). To this end, we examine rectangular, trapezoidal, and right-triangular domains and systematically change the length and height but fix the volume and aspect ratio (the ratio of length and average height). This allows us to isolate geometric effects on vortex size, number, and spatial patterns, where we find that extreme aspect ratios producing more vortices and near-unity aspect ratios producing fewer, larger vortices. These results highlight how geometric constraints fundamentally shape pattern formation in bioconvective flows.

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CP9

Traveling-Wave Solutions in Nutrient-Limited Biofilm Growth on Agar

Biofilm expansion on agar substrates is driven by nutrient diffusion from the underlying medium and biomass production within the growing colony. We study a continuum model in which nutrient diffuses in the agar, is transported, and consumed in the biofilm, and regulates biomass growth. The biofilmair interface advances as a moving boundary whose normal velocity is determined by the biomass production. We analyze the regime in which expansion is limited by nutrient transport and establish the existence of traveling-wave solutions describing steady front propagation. Asymptotic analysis reveals scaling laws for front speed and interface structure, capturing the multiscale coupling between diffusion in the substrate and growth within the biofilm. We further incorporate anisotropic growth mechanisms and examine their impact on colony morphology. Numerical simulations based on a level-set formulation validate the analytical predictions and illustrate how anisotropy modifies expansion dynamics. These results provide a mathematical framework for transport-limited biofilm spreading and suggest experimentally testable signatures of anisotropic growth.

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CP10

A Level-Set Model of Neuronal Growth Morphodynamics

Neurons are commonly characterized by electrical activity; however, an equally important property is their continuous change of shape, particularly the complex patterns formed by dendrites and axons. These growth processes are governed by interacting internal and external signaling pathways [Graham, *Mathematical modelling and numerical simulation of the morphological development of neurons*]. We present a spatially resolved model of ten reactiondiffusionconvection PDEs describing signaling dynamics that determine morphology. The neuron and extracellular space form a domain divided into intracellular (tubulin, MAP-2 free/phosphorylated/bound, calcium) and extracellular (Slit-like inhibitor) regions separated by a moving boundary [Flores-Pretell, *A Brief Proposal for a 2D Neuronal Morphodynamic Model of Growth Cone Motility*]. Complex neuronal shape changes, such as elongation, branching, and retraction, are simulated using a Level-Set formulation in which the interface velocity is computed from the solution fields and evolved with three signed distance functions [Frolkovic, Logashenko, and Wehner, *Flux-based level-set method for two-phase flows on unstructured grids*]. The equations are discretized by a vertex-centered finite volume scheme with implicit Euler time stepping and geometric multigrid in ug4 [Vogel, *UG4: A novel flexible software system for simulating PDE based models on high performance computers*].

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CP10

Cell-Cell Viscosity in Active Network Models of Cell Monolayers

Multicellular assemblies collectively exhibit physical intelligence through the development and maintenance of complex morphologies at the tissue scale without centralized control. During morphogenetic events, cellular aggregates must navigate the anatomical morphospace by coordinating individual cell actions. In confluent cell assemblies, cellular behavior is physically mediated through shared junctions. Active network models (ANMs), which operate over these connections, have proven an effective approach to multicellular modeling. We present a generalized ANM that represents confluent cell monolayers as networks of mechanically coupled computing agents. In particular, we explore the implementation and impact of cell-cell viscous interactions on collective migration, a feature often overlooked in cell network models. We validate our bottom-up simulations with experimental data on endothelial monolayers. We probe both the experimental and digital systems and quantify the responses to assess the accuracy and robustness of our viscosity model. Our results suggest that endothelial cells exhibit shear-thinning cell-cell viscous interactions, wherein the strength of the viscous coupling between neighboring cells decreases with shear rate.

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CP10

Simulating Podocyte Wall Shear Stress Considering Anatomical Features of the Slit Diaphragm

The kidney is an organ that modulates the composition of the blood by excreting metabolic waste and reabsorbing essential material back into circulation. This filtration process is facilitated by the glomerulus, a cluster of capillaries that function as a multilayer ultrafilter composed of size restrictive cell junctions and extracellular barriers. Of these filter layers are specialized junctions between podocytes called the slit diaphragm. The uncertainty in the architecture of the slit diaphragm has driven recent imaging studies that have challenged the classic zipper interpretation of the slit structure. Direct measurement of the filtering capabilities of alternative slit diaphragm structures is difficult due to the nanoscale components of the filter, leading to boundary value problems of varying complexity that reflect current morphology parameters. ANSYS Fluent, a computational fluid dynamics (CFD) software package, is used to analyze the effect of cell morphology on flow dynamics under known physiological conditions. Of interest is the wall shear stress (WSS) generated on the slit fibers and the surface of adjacent podocytes. The WSS calculated for each proposed structure dictates the detachment forces on the podocytes cells, which vary considerably between spacings parameters obtained from previous imaging studies. This provides relevant shear forces estimates for a pathophysiological mechanism for glomerular dysfunction.

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CP10

Unfitted Finite Element Modelling of Surface-Bulk Viscous Flows in Animal Cells

This talk presents a novel unfitted finite element framework to model coupled surface-bulk viscous flows in animal cells, focusing on the interaction between the active actomyosin cortex and the viscous cytoplasm. The cortex generates contractile forces through molecular motors, driving cell shape changes and inducing intracellular flows. To simulate this complex system, we combine the trace finite element method for the surface flows with the aggregated finite element method for the bulk flows, enabling sharp-interface modelling on fixed grids without the need for remeshing. The model incorporates mechanochemical feedback via the surface transport of a molecular species that regulates active tension. This leads to a mixed-dimensional PDE system solved in a fixed Cartesian grid using level-set-based surface tracking. Numerical experiments confirm the method's accuracy and stability, capturing phenomena such as self-organized pattern formation, curvature-driven relaxation, and cell cleavage. We also present an application of the framework to the study of the embryo viability of abnormally stiff mouse oocytes. The framework offers a robust and extendable tool for exploring increasingly complex morphogenetic processes in animal cells.

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CP10

Closed Loop Solute Transport in Blood Vessels and Organs

Hypoplastic left heart syndrome (HLHS) is a congenital heart disease that accounts for 2-3% of congenital heart diseases in the United States and 40% of all neonatal cardiac deaths. HLHS causes oxygenated blood to mix with deoxygenated blood, resulting in death. This raises a critical need to accurately model the transport of oxygen in blood vessels and organs throughout the human body to improve outcomes in patients with HLHS. Previously, numerical reduced models have been created to solve for blood flow and concentration of one solute. These models reduce the dimensions of the vessels and organs to improve computational efficiency. This work extends the models from open network of blood vessels to closed loops and includes organs. Appropriate transmissibility conditions at each vessel junction and organ bed are constructed, that are based on balance laws. The class of interior penalty discontinuous Galerkin methods is used for the discretization of the models.

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CP10

Accelerating Regularized Stokeslet Simulations Utilizing Linearly Implicit Rosenbrock-Wanner Time Integrator

Using the test problem of a flexible, undulating filament in a viscous fluid, we explore the computational performance of different time integrators in regularized Stokeslet simulations. While explicit integrators are commonly used, stability considerations require prohibitively small time steps. Although fully implicit methods do not have such restrictions, they require the solution of nonlinear equations at each time step. To address these difficulties, we have considered the Rosenbrock-Wanner (ROW) method, a linearly implicit time integrator. Using the ROW method, we observed approximately ten to a hundred times speedup in computational time over explicit methods. To understand this success, we analyze how various model parameters, such as stiffness constants or filament diameter, contribute to the numerical stiffness of the system and, in turn, affect simulation runtimes as they vary. We will discuss these successes, as well as challenges and directions of further improvements.

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CP11

Operator Inference of Therapy-Conditioned Immune Dynamics from Longitudinal Immunoprofiling Data

Longitudinal immunoprofiling studies generate high-dimensional immune trajectories, yet their dynamical structure is rarely quantified. We develop an operator-based framework that infers low-dimensional immune dynamics from time-resolved cell count data and characterizes therapy-specific behavior through eigenvalue spectra and dominant immune modes. Using retrospective single- and multi-treatment arm immunotherapy studies, we construct reduced immune state vectors comprising aggregated T cell, B cell, NK, and myeloid compartments. Sparse regression is used to infer candidate linear operators, followed by eigenvalue and eigenvector analysis to identify dominant immune modes and spectral stability structure. In single-arm cohorts with responders and non-responders, we test whether a cohort-level operator captures persistent stability differences associated with outcome. In multi-arm studies with heterogeneous time-to-progression, we examine whether combination therapies induce distinct eigenstructures reflecting therapy-conditioned immune remodeling. Ongoing analysis focuses on comparing modal alignment, spectral stability, and operator geometry in association with progression timing. This work tests the hypothesis that immune stability structureencoded in operator eigenvalues and modesacts as a quantitative mechanistic biomarker of therapeutic response, reframing retrospective endpoint immunomonitoring as a problem in dynamical systems identification.

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CP11

Inside the Wavering Mind of an NK Cell: Mathematical Modeling of NK Cell Activation

The paradigm of NK cell activation is the Missing-Self Hypothesis; NK cells kill cells that lack MHC. When considering a single interaction between an NK cell and a target cell, the Missing-Self Hypothesis offers a plausible explanation for NK cell activation. However, an NK cells interaction with a target cell is not an isolated event. Experimental studies have shown that NK cells in an MHC-deficient environment, fail to lyse cells lacking MHC. Curiously, a study by the Yokoyama lab (Wash U) found that when 10% of cells in a well-mixed environment lacked MHC, the NK cells failed to lyse most of the cells. Our hypothesis is that target cell recognition is less about the balance of the presence or absence of markers, and more so about detecting outliers in an environment. We developed mathematical models of how NK cells assess and learn from their environment under static and dynamic MHC suppression. Our results suggest NK cells may be vulnerable to slow growing danger which makes detecting outliers challenging. We are collaborating with the Weis lab (Huntsman Cancer Institute) to experimentally test our model predictions.

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CP11

Data-Adaptive Estimation of Glucose Derivatives with Uncertainty Quantification

During an oral glucose tolerance test (OGTT), the derivative of an individuals glucose profile is required in several established dynamic models of metabolic health, including models of beta-cell function and tissue-specific insulin sensitivity. However, as sampling during OGTT is often noisy, sparse, and non-uniform, accurate and precise estimation of glucose derivatives from glucose concentrations are challenging. Moreover, derivative estimates are often taken to be error-free when utilized in models of metabolic health despite the presence of sampling and modeling errors. To overcome these challenges and provide principled uncertainty quantification, this work proposes a data-adaptive method to estimate glucose derivatives based on variably scaled kernels (VSKs). By constructing kernels informed directly by the OGTT data, this method can adapt automatically across a variety of sampling sched-

ules and glycemic responses. Additionally, by interpreting VSKs as Gaussian covariances, uncertainty in the derivative estimates can be quantified and propagated through to estimated indices of metabolic health.

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CP11

Optimizing Hiv Germline-Targeting and Sequential Immunization Regimens Via Multiscale Dynamic Modeling

Developing an effective HIV vaccine remains a major challenge due to the viruss extensive genetic diversity, rapid mutation, and ability to evade immune responses. Germline-targeting (GT) vaccine strategies offer a promising approach by activating rare broadly neutralizing antibody (bnAb) precursor B cells and guiding their maturation through sequential immunization with rationally designed immunogens. However, identifying optimal vaccination parameters, such as dose, timing, and delivery platform, to reliably induce desired immune responses remains challenging. To address this need, we developed a multiscale mechanistic mathematical model of the humoral immune response to vaccination. The model integrates immunogen kinetics, B-cell evolution, germinal center dynamics, and antibody production to predict immune outcomes across diverse GT and sequential immunization scenarios. This framework enables systematic in silico evaluation of vaccination regimens, including homologous versus heterologous immunogen sequences, fractionated versus bolus dosing, and alternative booster schedules, to identify strategies that maximize the potency, breadth, and durability of vaccine-induced antibody responses.

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CP11

Computational Modeling Reveals Mechanisms Determining Efficacy of Sirolimus Treatment in Sars-CoV-2 Patients

Early SARS-CoV-2 infection arises from nonlinear and often antagonistic interactions among immune cells, cytokines, and intracellular signaling pathways. We developed a mechanistic agent-based model (ABM) of early lung infection integrating pneumocytes, macrophages, natural killer (NK) cells, type-I interferon (IFN) signaling, and the mTORC1 inhibitor sirolimus. To enable large-scale analysis, we trained a Deep Gaussian Process (DGP) emulator on ABM simulation data and generated a virtual patient population spanning physiologically plausible regimes. We performed global sensitivity analyses via Morris and functional ANOVA and identified regime-dependent drivers of infection outcomes at 48 hours post-infection. When IFN-mediated viral inhibition spans a broad range, viral replication kinetics dominate system behavior and sirolimus markedly reduces viral load and inflammation despite immunosuppressive effects. In contrast, when IFN inhibition is highly effective, IFN secretion rate becomes the primary determinant of viral load, and the impact of sirolimus is attenuated. The model further predicts context-dependent roles for macrophage polarization, reconciling conflicting experimental observations. Overall, this work demonstrates how machine-learning surrogates coupled to mechanistic models enable scalable, uncertainty-aware inference in complex immunological systems and provide a principled AI-driven approach to studying heterogeneous therapeutic responses.

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CP12

GapTrim: Resolving Assembly Gaps in Plant Genomes Using Hybrid Deep Learning Architecture

Crop improvement programs rely on whole genome sequences to identify genetic markers linked with desirable traits such as yield, disease resistance, and climate adaptability. However, current sequencing technologies produce draft genome assemblies with gaps where nucleotide bases are unknown. These gaps create uncertainty in identifying better genetic variants. Existing computational tools like Sealer fill only approximately half of the available gaps. Deep learning offers new possibilities for handling complex patterns where this problem can be modeled via character-level sequencing. A Long-Short Term Memory model has recently been applied here and works better than existing computational tools; however, its performance also leaves scope for improvement that we address. We develop GapTrim, a Transformer architecture integrated with a Convolutional Neural Network for capturing long-range and short-range dependencies, respectively. We test GapTrim on 150 gaps arising in a soybean whole genome sequence, and compare its performance with Sealer and the LSTM-based GapPredict model. We divide the gaps into two sets; Set-1 that contains gaps mostly filled by Sealer; and Set-2 that contains gaps where Sealer completely fails. In Set-1, the average correctness obtained by various models is as follows: Sealer 95.3%, GapPredict 93.6%, and our GapTrim 97.7%. In Set-2, the same numbers are as follows: Sealar 0%, GapPredict 88.3%, and our GapTrim 97.1%.

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CP12

Mathematical Analysis of Nuclear Position Problems in Fly Cells

Nuclear placement and shape are tightly linked to intracellular transport, yet quantitative principles connecting geometry to transport efficiency remain incomplete. We develop and analyze two diffusion-based models for fly

muscle cells in which nuclei are modeled as small elliptical inclusions. In an absorption setting, uniformly produced signal is removed at nuclear boundaries, leading to an MFPT Poisson problem with Neumann conditions on the cell membrane and Dirichlet conditions on nuclei. A matched-asymptotic expansion for e?0 yields a two-term approximation for the MFPT and nuclear uptake fluxes; the correction term reveals how ellipse orientation and aspect ratio enter through dipole and quadrupole moments coupled to the Neumann Greens function. In a production setting, nuclei act as localized sources for a screened diffusion equation. We validate the theory using finite element computations on a disk with elliptical exclusions and on realistic cell geometries extracted from imaging data, aided by high-order boundary-integral evaluation of Greens functions using chunKIE. We then pose constrained optimization problems to identify nuclear configurations that minimize MFPT or improve distribution, and we compare optimized arrangements with experimental nuclear data to assess which geometric features are most predictive of transport performance.

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CP12

A Network of Local and Global Recycling of Ribosomes During Simultaneous Mrna Translation

Gene expression is a crucial cellular process and analysing mRNA translation has become an integral area of study for biologists. Due to the depletion of tRNAs or other physiological stresses, it has been observed that ribosomes become stalled. Several experimental studies demonstrate the circular nature of the mRNA that could lead to interactions between the sites, forming a mechanism of rescuing stalled ribosomes to make them available for local translation. The studies have considered mRNAs competing for the global pool of ribosomes, but they do not incorporate the local recycling provided by the closed-loop structure. We develop a system of nonlinear ordinary differential equations modelling this scenario and prove that the solutions of the system converge to a steady-state using tools from contraction theory and Robust Lyapunov Functions. Next, we analyse that the effect of local recycling of ribosomes in the mRNA may be both positive and negative for the pool density. In the special case where ribosomes from the last site are only available for local translation, there is a decrease in the pool density. If there are rescue systems upstream and downstream of the mRNA, we are able to demonstrate that the rescue of upstream ribosomes can increase the protein production from this mRNA.

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CP12

Antisense Transcription Regulation of the Myosin Heavy Chain Locus

A key marker of heart disease progression is the shift in the ratio between the expression of myosin heavy chain 6 (Myh6) and myosin heavy chain 7 (Myh7). Healthy adult hearts exhibit a higher expression of Myh6, while adult hearts in heart failure exhibit a higher expression of Myh7. These two genes are adjacent on chromosome 13 and a long non-coding RNA, Mhrt, is located in antisense to Myh7. That is, Mhrt is transcribed from the opposite DNA strand but in an overlapping interval. First, we explore the implications of the antisense transcriptional interference between Myh7 and Mhrt using a stochastic process formulation tracking the locations of the RNA polymerases in the overlap. Next, we investigate the regulation of transcription of Myh6 through the interaction of Mhrt with the ATP-dependent chromatin remodeler, BRG1, using a system of non-linear ODEs. Finally, we combine the two mechanisms to create a comprehensive model for the gene regulatory network. Each of the individual mechanisms exhibits a monotone dependence on the BRG1 concentration. However, when coupled, the system can undergo a pair of fold bifurcations and exhibit hysteresis. This suggests that in response to cellular stress, the rise in BRG1 may lead to a switch in transcriptional program that is difficult to reverse.

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CP13

What Can Hormone Data Really Tell Us About Stress Regulation? An Identifiability Perspective

This study investigates the dynamics of molecular components of the hypothalamic-pituitary-adrenal (HPA) axis. Specifically, we ask whether parameter fitting of an ordinary differential equation-based mechanistic model of the HPA axis to realistic hormone measurements can be used to infer certain aspects of stress regulation with confidence. Previous studies have focused on parameter estimation performance and do not analyze the structural and practical identifiability properties of the underlying HPA model. To address this gap, we applied a sequence of methods for analyzing both structural and practical identifiability analysis, as well as a method for quantification of prediction uncertainty, which in tandem constitute a protocol for dynamic model calibration, to learn which state variables and parameters of the HPA axis model are identifiable under multiple data availability scenarios. These results emphasize the importance of collecting data on key biomarkers for stress response and pave the way towards a more quantitative measurement of stress-related dysregulation.

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CP13

The Minimum Inhibitory Dose (mid): A Dynamic Analogue to the Minimum Inhibitory Concentration (mic) for Periodically Driven Antibiotic Treatments

Rising antimicrobial resistance is a global crisis which makes crucial the need for dosing strategies that maximize bacterial eradication while minimizing unnecessary drug exposure. Standard indices of antibiotic efficacy, such as the minimum inhibitory concentration (MIC) or the time spent above MIC ($\%T_{>MIC}$), are static snapshots that often fail to capture the underlying time-varying dynamics of periodic dosing. To address this gap, we introduce the

minimum inhibitory dose (MID), a dynamic MIC analogue defined as a threshold dose size, above which bacterial populations show net negative growth from one dose to the next. We use Floquet theory on a coupled bacterial-growth and antibiotic pharmacokinetic/pharmacodynamic (PK/PD) model to calculate the MID in terms of the dose schedule and PK/PD properties. We show how this MID framework recapitulates recommendations from distinct antibiotic classes: minimizing the MID normalized by dose period simultaneously recovers frequent dosing as optimal for time-dependent antibiotics (e.g. ampicillin) and infrequent dosing for concentration-dependent antibiotics (e.g. rifampin). Finally, we apply this framework to N. gonorrhoeae treated with ceftriaxone, showing how analysis via the MID predicts historical dose size adjustments due to shifts in MIC and fitness costs. Together, our results position the MID as a unifying, mechanism aware metric to guide future rational antibiotic dosing strategies.

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CP13

Amortized Bayesian Experimental Design for Quantitative Systems Pharmacology Models of Cancer Immunotherapy

Quantitative systems pharmacology (QSP) models of cancer immunotherapy involve dozens of uncertain parameters, yet calibration data are sparse. Determining which measurements to collect and when is critical, particularly in pancreatic cancer (PDAC) where tumor biopsies carry significant patient burden. Bayesian experimental design addresses this via expected information gain (EIG), but computing EIG requires repeated posterior inference: MCMC must run to convergence for every candidate dataset under every candidate design, making the approach intractable for high-dimensional QSP models. Each design also defines a different observation space, seemingly requiring separate inference per design. We address both bottlenecks through joint amortization: using simulation-based inference, we train a single neural density estimator that takes observed data and experimental design as inputs and returns an approximate posterior at negligible marginal cost. Once trained on forward simulations, the network enables rapid EIG evaluation across thousands of designs without retraining. We apply this to a QSP model of tumor-immune dynamics and checkpoint inhibitor therapy in PDAC, where the design space consists of measurement timepoints and sampling compartments (tumor biopsy vs. blood). We use EIG to identify minimal measurement sets achieving target parameter identifiability and quantify the information tradeoff between invasive and non-invasive sampling.

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CP13

Treatment Strategies of Alzheimer's Disease - a Study Based on Cognitive Decline

Alzheimer's disease (AD) is a multifactorial neurological disorder that represents a global health concern. In this work, we introduce the amyloid cascade system in the ordinary differential equations (ODEs) framework designed to replicate the core pathophysiological dynamics of Alzheimer's disease, incorporating the fact that neuron degradation affects amyloid beta ($A\beta$) production. We perform a rigorous sensitivity analysis to quantify the impact of the model parameters on the disease trajectory and identify the predictive measure for prophylaxis. We calibrate the model using the least squares method for parameter estimation based on Mini-Mental State Examination (MMSE) score data across different age groups. Our study highlights the most sensitive factors, emphasizing their central role in disease progression. This work simulates the effects of anti-amyloid beta therapies (Lecanemab and donanemab) and emerging treatments (Blarcamesine and BIIB080). In silico treatment strategies validate the results of clinical trial simulations, reducing $A\beta$ and p-tau levels and significantly affecting cognitive decline. Our study demonstrates that strategies that enhance the clearance of $A\beta$ and p-tau are promising for significantly delaying neurodegeneration and cognitive decline, more than any monotherapy. These findings pinpoint the key pathological drivers, providing a strategic roadmap for advancing combination therapies to alter the disease course.

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CP13

Generation of Model-Based Virtual Patient Cohorts with Neural Networks

Virtual patient generation for in-silico clinical trials retools experimental or clinical datasets to inform model parameterizations that can then be leveraged to explore new treatment protocols. Here we propose a new method of virtual patient generation that uses bootstrapping and neural networks to construct a population with the desired level of variability. We explore our framework with the addition of noise and denoising techniques, benchmark it against the standard Markov Chain Monte Carlo method, and apply it to a case-study of oncolytic viral therapy. Our results suggest that the new framework provides a scalable, computationally efficient method for virtual patient generation and the exploration of virtual clinical trials.

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CP14

Periodicity, Stability, and Synchronization of Solutions for a Family of Delayed Population Model of Nicholson Type on Time Scales

This work investigates the periodicity, stability, and synchronization of solutions for a family of delayed population

models of Nicholson type formulated within the framework of coupled dynamic equations on time scales. By employing the coincidence degree theory, we establish novel criteria ensuring the existence of periodic solutions for systems with multiple discrete and distributed delays. The proposed model generalizes and unifies several well-known population models, including Nicholsons blowflies, Mackey-Glass, and Lasota-Wazewska equations, thereby bridging continuous, discrete, and hybrid dynamics within a common analytical framework. Furthermore, we derive sufficient conditions that guarantee the asymptotic stability and exponential synchronization among coupled systems. These results extend existing theories on delayed biological networks by incorporating hybrid effects and nonautonomous perturbations that naturally arise in life science applications. Numerical simulations and illustrative examples demonstrate the effectiveness of the proposed criteria, providing insights into the dynamic behavior of complex delayed population interactions.

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CP14

A Review on Innovations in Hydroxyapatite: Advancing Sustainable and Multifunctional Dental Implants

The increasing relevance of biomaterials in medical curements and the care of aging populations has led to significant advancements in modification of these materials. Hydroxyapatite (HAp), a biocompatible ceramic that mimics the composition of bone mineral, stands out for its remarkable abilities. Its stability in body fluids and ability to integrate with bone without causing toxicity or inflammation made it a prime candidate, particularly in odontology and orthopedics. Dental implants are enhanced by coatings of calcium phosphate-based materials like HAp. This enhances osseointegration, ensuring a strong bond and longevity of the implant. HAp may be synthesized both synthetically and from natural sources like mammalian bones, marine shells, and plants, each offering unique trace elements that improve its bioactivity. Hence, this abstract aims to explore the synthesis, properties, and biomedical applications of hydroxyapatite (HAp), with a special emphasis on its role in improving the performance and durability of dental implants.

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CP14

Kinetic Limit of Balanced Networks

The theory of 'Balanced Neural Networks' is a very popular explanation for the high degree of variability and stochasticity in the brain's activity. We determine equations for the hydrodynamic limit of a balanced all-to-all network of $2n$ neurons for asymptotically large n. The neurons are divided into two classes (excitatory and inhibitory). Each excitatory neuron excites every other neuron, and each inhibitory neuron inhibits all of the other neurons. The model is of a stochastic hybrid nature, such that the synaptic response of each neuron is governed by an ordinary differential equation. The effect of neuron j on neuron k is dictated by a spiking Poisson Process, with intensity given by a sigmoidal function of the synaptic potentiation of neuron j. The interactions are scaled by $O(n^{-1/2})$, which is much stronger than the $O(n^{-1})$ scaling of classical interacting particle systems. We demonstrate that, under suitable conditions, the system does not blow up as $n \to \infty$ because the network activity is balanced between excitatory and inhibitory inputs. The limiting population dynamics is proved to be Gaussian: with the mean determined by the balanced between excitation and inhibition, and the variance determined by the Central Limit Theorem for inhomogeneous Poisson Processes. The limiting equations can thus be expressed as autonomous Ordinary Differential Equation for the population variance, coupled to an algebraic constraint for the mean-activity.

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CP14

Statistical Properties of Steady States and Regime Transitions in a Stochastic Population Model with Behavioral Fear

Predatorprey systems are a research area of interdisciplinary importance that extends beyond the boundaries of population biology. In recent years, studies in ecology and evolutionary biology have suggested that prey populations in predatorprey systems are influenced not only by contact-based predation but also by fear effects resulting from the presence of a predator. We propose a model for a prey population under the Allee effect, where fear functions through different mechanisms. We construct a stochastic representation of the model within a Langevin formalism that incorporates both additive and multiplicative white noises, as well as their correlation. By deriving the corresponding FokkerPlanck equation, we analytically obtain the steady-state solution and validate the results with numerical simulations. We investigate the phase regime shifts described by the model using phenomenological bifurcation analysis and a three-dimensional representation of the distribution. We also calculate the mean first passage time (MFPT) to analyze the temporal dynamics of the system. In this study, we also perform mean, variance, and skewness analyses of the steady-state distribution and conduct a Fisher information analysis. Our model demonstrates that the fear effect is not simply a stress factor, but a structural parameter that reorganizes stochastic regime transitions and population dynamics.

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CP14

Optogenetic Stimulation of Echolocating Bats Sequences Spatial Orienting Behaviors

Navigating dynamic environments requires sequencing orienting behaviors via incoming sensory information. For example, when traversing a crowd, we orient around moving people and objects to avoid crashing. The superior colliculus (SC) is a midbrain structure that integrates sensory information to drive orienting behaviors. In humans, the SC drives spatial attention by eye, head, and torso motion, and in echolocating bats by sonar calls, ear, and head motion. In bats, these can be precisely quantified to model sequential control of orienting behaviors. Yet though the SC is evolutionarily conserved and spatially topographic, prior SC stimulation studies have restrained mammals to only one movement type. Thus, how the SC coordinates multiple movements are unknown. We virally controlled excitatory SC neuronal activity in echolocating bats via optogenetics using a subdermal wireless microLED. We put stationary, unrestrained bats in an open enclosure, with ear, head, and body kinematics plus vocalizations recorded before and during stimulation. Stimulation duty cycle, frequency, and duration varied across trials. As the injection location differed across each bat, we hypothesized stimulation parameters, and the location and spread of the virus, predicts movement direction, magnitude, and kinematics. We find evidence that the SC sequences spatiotemporally-precise ear, then head rotations in bats, giving clues to how the SC drives sensorimotor integration and spatial attention.

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CP14

Is This A Game? Frequency-Dependence Can Emulate Or Hide Frequency-Independent Selection in Evolving Populations

Replicator equations for evolving populations capture the dynamics of frequencies of sub-populations (fractions of each type comprising the total population) as functions of their adaptive fitness, often equated to exponential growth rate. But for co-evolving populations, the whole is different from the sum of its parts: measure the growth rates of two genotypes of cells in mono-culture, then measure again in a co-culture; deviations may appear due to interactions among the distinct cell types, which may be quantified in a game-theoretic framework by frequency-dependent fitness. Yet we show that, for certain values of interaction parameters, the effects of frequency-dependence can disappear: the population behaves as if there are no interactions, but the effective selection coefficient (quantifying relative fitness) is possibly distinct from the underlying intrinsic value. We highlight four illustrative cases for two genotypes: maintenance, in which effective selection matches intrinsic selection; mirroring, in which interactions reverse the expectation of which genotype dominates the population; masking, in which interactions cancel underlying fitness differences to produce effectively neutral evolution; and mimicry, in which no intrinsic fitness difference still manifests as one dominant genotype due to interactions. We further explore these emulation classes in the presence of both mutation and noise.

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MS1

Modeling Cardiac Electro-Fluid-Mechanics

This presentation will describe work to build comprehensive computational models of the heart that account for interactions between electrophysiology, mechanics, and fluid dynamics. Cardiac mechanics, fluid dynamics, and fluid-structure interaction (FSI) are simulated using the immersed finite element-difference method, an extension of the immersed boundary method for FSI models that include elastic bodies described using nonlinear continuum mechanics. The anatomical model is based on computed tomography images of a healthy human subject. The mechanics of the myocardium, the aortic and pulmonary valve leaflets, and the mitral and tricuspid valve apparatuses are described using nonlinear constitutive models calibrated with tensile tests of human tissue specimens. Mechanical loading is provided by reduced-order models of both the circulation and pericardial tethering. Muscle contraction timing is governed by a whole-heart monodomain electrophysiology model that includes the atrial and ventricular myocardium, as well as major components of the specialized cardiac conduction system, including the sinoatrial node, Bachmanns (interatrial) bundle, the atrioventricular node, and the His-Purkinje network. The presentation will provide an overview of the major physiological aspects of the model and will highlight key physiological outputs, including demonstrations of its ability to provide acute predictions of the hearts response to perturbations in driving or loading conditions.

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MS1

Heart-Rate Variability and Turbulence Onset in the Equine Aorta

Horses routinely operate at the edge of mammalian cardiovascular performance. In horse racing, aortic flow reaches Reynolds numbers where laminar assumptions can fail, yet the onset and structure of turbulence in strongly pulsatile, curved vessels remain poorly understood. I will present 3D simulations of pulsatile flow through the equine aorta as a model for extreme work. I will show how waveform shape and vessel curvature shift the transition to turbulence, with a focus on secondary vortices and intermittent, deceleration-driven turbulence. I will then introduce heart-rate variability (HRV), treating beat-to-beat variability as a controlled perturbation to the inflow. These comparisons identify regimes where variability disrupts coherent structures and delays transition, versus regimes where it amplifies fluctuations and triggers earlier turbulence.

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MS1

A Domain Decomposition Method for Solution of a Pde-Constrained Generalized Nash Equilibrium Model of Biofilm Community Metabolism

In this talk we propose a domain-decomposition-based method for the solution of a PDE-coupled generalized Nash equilibrium problem. Our motivation is a problem for a multispecies biofilm community. Microbes are able to deploy different strategies in response to, and depending upon, local environmental conditions. In the setting of a microbial community, this property induces a Nash equilibrium problem because access to environmental resources is bounded. If microbes are also distributed in space, then those resources are subject to transport limitations (encoded in a PDE) and so microbial strategies at one location influence resources and, hence, microbial strategies, at another. The domain decomposition method we propose here uses overlapping subdomains, and this feature is important in the numerical solution of the PDEs. We illustrate this in particular for a 1D problem, where the resulting ODE is stiff, but the proposed method is shown to overcome this difficulty. An example consisting of a model with two microbial species biofilm with 33 externally transported chemical concentrations is also presented.

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MS1

AdvectionDiffusion with Flow in Moving Cell Domains: Immersed-Boundary Models of Actin-Driven Migration

We will present continuum models and numerical methods that couple advectiondiffusion of cytoskeletal components with viscous fluid flow on moving cell domains. The core framework describes actin network dynamics by advectiondiffusionreaction equations over a deforming domain, coupled to Stokes flow through an immersed boundary formulation that captures fluidstructure interaction between cytosol, actin network, and membrane. The analysis and simulation of this coupled system show how actin network depolymerization and contractility produce biphasic dependencies of cell speed and mechanical power output on key kinetic and mechanical parameters. Our simulations in two dimensions are based on an implicit immersed boundary scheme with advectiondiffusion on a moving interface, which resolves evolving cell shape, intracellular flow, and actin redistribution and reveals how actin dynamics organize polarization, elongation, and spreading.

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MS2

Physics-Informed Random Features Model for Solving Partial Differential Equations

Partial differential equations (PDEs) are central to modeling complex phenomena across physics, engineering, and finance. Data-driven methods for solving PDEs have gained as flexible alternatives to classical numerical schemes, but training neural networks remains computationally challenging. In the talk, we present a random features-based method for solving PDEs. The method retains strong approximation power, and connects to kernel method and neural networks-based method. We will focus on the approximation error of our proposed method. Numerical experiments indicate competitive accuracy with significantly reduced computational complexity.

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MS2

Pde-Ode Models for Collective Dynamics in Go-Or-Grow Populations.

Spatial constraints can determine whether invasive cell populations persist or go extinct. In particular, many reaction-diffusion models exhibit a critical domain size: below a threshold habitat size, populations cannot sustain nontrivial steady states. We investigate this phenomenon in go-or-grow models, which describe cell populations whose individuals either migrate or proliferate but not simultaneously, and which are widely used in modeling glioma invasion. Focusing on steady states in bounded domains with hostile boundaries, we extend classical critical domain results to settings with nonlinear phenotype

switching and general uniformly elliptic diffusion. The hybrid PDE-ODE structure introduces a degeneracy in the non-diffusing compartment, leading naturally to Young-measure-valued steady states. We show that domain size alone determines persistence or extinction, revealing how phenotype switching and spatial structure reshape classical threshold behavior.

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MS2

Collective Behavior in Social Mobilization: Multilayer OnlineOffline Dynamics on Networks

The prevalence of social media has strengthened the influence of online activity on offline behavior, from daily decisions to large-scale collective movements. At the same time, empirical studies show that offline events can also drive online engagement, suggesting a bidirectional feedback between online and offline social activities. These real-world phenomena call for new mathematical modeling frameworks to capture and better understand coupled onlineoffline dynamics. We propose frameworks for modeling participation dynamics on coupled online and offline layers, where agents interact through online networks. The model captures agent-based microscopic dynamics and enables analysis of the resulting macroscopic behavior. Using tools such as mean-field approximations and the reproductive number, we study population-level collective behavior and characterize conditions leading to outbursts, providing mathematical models that capture mechanisms by which large-scale online and offline social mobilization can trigger one another.

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MS3

Dynamics of Discrete Multi-State Models with Nonexpanding Global Transition Function and Applications to Iron Homeostasis

Discrete dynamical systems with categorical-valued components have been successfully applied to biological networks. While Boolean models are common, multi-state models offer greater resolution. However, they introduce what we call discontinuities, meaning that variables can change by more than one unit in a single time step. To address this, we apply an additional rule that preserves fixed points, though this constraint may introduce new cyclic attractors. This presentation examines how enforcing one-step dynamics affects the state space of multi-state network models. We analyze synchronous, sequential, and block-sequential update schedules and establish conditions under which no new cyclic attractors arise when the additional rule is applied. This work was motivated by modeling intracellular iron homeostasis, which will be used in the presentation to illustrate various aspects of such networks.

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MS3

Homeostasis Patterns and Mode Interactions

Homeostasis is a regulatory mechanism that keeps a specific variable close to a set value as other variables fluctuate. The notion of homeostasis can be rigorously formulated when the model of interest is represented as an input-output network, with distinguished input and output nodes, and the dynamics of the network determines the corresponding input-output function of the system. In this context, homeostasis can be defined as an 'infinitesimal' notion, namely, the derivative of the input-output function is zero at an isolated point. Combining this approach with graph-theoretic ideas from combinatorial matrix theory provides a systematic framework for calculating homeostasis points in models and classifying the different homeostasis types in input-output networks.In this work, we develop this theory by introducing the notion of a homeostasis mode interaction, defined as two homeostasis types are triggered simultaneously. Specifically, our work provides a direct method to determine whether an input-output network exhibits a bifurcation or homeostasis at a mode interaction, depending on the pattern relationship between the two triggered homeostasis types.

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MS3

Period Homeostasis Near a Hopf Bifurcation

Homeostasis is a biological phenomenon in which a function of the state of the system remains approximately constant as an input varies. Recently, a mathematical theory of homeostasis was developed based on methods from singularity theory. In this theory, the state is a steady state, and the function is often a coordinate of the steady state. The weaker requirement that a function of the state remains approximately constant is replaced by the requirement that the derivative of the function with respect to the input parameter vanishes at an isolated point. This notion of a zero derivative has the name (steady-state) infinites-

imal homeostasis. Homeostasis can also apply to many oscillatory biological processes. For example, the period of circadian rhythms remains approximately constant as parameters such as ambient temperature and gene expression levels vary. In this talk, we develop a notion of infinitesimal period homeostasis to describe such phenomena. Utilizing the symmetry of Hopf normal form, our main result is that singularity theory can be used to find infinitesimal period homeostasis. The result is illustrated using a simple model of the mammalian circadian clock.

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MS3

Mathematical Tools for Understanding Homeostasis in Biological Networks

Homeostasis occurs in a biological or biochemical system when an output quantity remains approximately constant as input parameters vary over a range. In classical homeostasis, one asks what structural features of a regulatory network allow a system to adjust its internal variables along a one-parameter family of steady states so that a variable of interest (such as core body temperature or metabolite concentration) remains nearly constant despite changes in an external parameter (such as environmental temperature or external osmotic conditions). When a physiological system depends on sustained oscillations of a rhythmic subsystem, such as breathing or cardiovascular circulation, one may consider a one-parameter family of limit cycles and the regulated quantity may be the cycle-averaged value of some variables rather than their instantaneous or steady-state values. In this talk, we present new approaches to the study of homeostasis in network systems. These include combinatorial matrix methods for identifying structural motifs that support steady-state homeostasis, which have led to the development of an automated classification algorithm in Python, as well as variational tools for analyzing homeostatic regulation in oscillatory dynamics.

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MS4

Modern Equation Learning in the Life Sciences

The creation and inference of mathematical models is central to modern scientific discovery in the life sciences. As more realism is demanded of models, however, the conventional framework of biology-guided model proposal, discretization, parameter estimation, and model refinement becomes unwieldy, expensive, and computationally daunting. In this talk, I will provide an overview of the classes of equation discovery methods presented in the minisymposium. I will also describe an overview of the Weak form Sparse Identification of Nonlinear Dynamics (WSINDy) method, as well as how it compares to other modern methods. I will demonstrate some of the performance properties via applications to problems in structured population modeling, cell migration, and mathematical epidemiology.

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MS4

Ddmo - A Python Package for Data-Driven Parametric Modeling

Interpretable data-driven methods have proven viable for deriving complex vector fields directly from experimental data. Their inherent differential formulation, however, make them vulnerable to noise, which can compromise the sparsity of the inferred models. In order to promote sparsity, a weak formulation can be employed. Then, finding the optimal set of basis functions is a necessary prerequisite, yet a challenging task to determine in advance. We present the release version of the Data-Driven Model Optimizer ddmo, a symbolic regression tool which provides fine-grained control over the admissible space of candidate terms. Its core contribution lies in the systematic optimization of the library of functions, implemented through two complementary engines: a standard SINDy-based differential formulation and a weak-form variant. Its modular structure further enables the optimization of test functions within the weak formulation. An overview of the software capabilities is provided, alongside with a case study illustrating the reconstruction of effective kinetics from experimental reactor data.

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MS4

Fokker-Planck-Inverse Reinforcement Learning: A Physics-Constrained Approach to Markov Decision Process Models of Cell Dynamics

Inverse Reinforcement Learning (IRL) is a compelling technique for revealing the rationale underlying the behavior of autonomous agents. IRL seeks to estimate the unknown reward function of a Markov decision process (MDP) from observed agent trajectories. However, IRL needs a transition function, and most algorithms assume it is known or can be estimated in advance from data. It therefore becomes even more challenging when such transition dynamics is not known a-priori, since it enters the estimation of the policy in addition to determining the system's evolution. When the dynamics of these agents in the state-action space is described by stochastic differential equations (SDE) in Itô calculus, these transitions can be inferred from the mean-field theory described by the Fokker-Planck (FP) equation. We conjecture there exists an isomorphism between the time-discrete FP and MDP that extends beyond the minimization of free energy (in FP) and maximization of the reward (in MDP). We identify specific manifestations of this isomorphism and use them to create a novel physics-aware IRL algorithm, FP-IRL, which can simultaneously infer the transition and reward functions using only observed trajectories. We employ variational system identification to infer the potential function in FP, which consequently allows the evaluation of reward, transition, and policy by leveraging the conjecture.We demonstrate the effectiveness of FP-IRL by applying it to a synthetic benchmark and a biological problem of cancer cell dynamics, where the transition function is inaccessible.

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MS4

Highlighting and Overcoming Challenges Associated With Data-driven Modeling for Agent-based Models

Agent-based models (ABMs) are a bottom-up framework capable of capturing the complex nature of biological systems. Despite wide interest in the use of ABMs to interpret biological data, their data-driven usage remains a significant challenge due to their lack of closed-form equations and heavy computational requirements. This talk will highlight the challenges associated with data-driven modeling (e.g., parameter estimation and uncertainty quantification) for ABMS, and how the use of neural networks as ABM surrogate models can overcome some of these limitations. We will apply the methodologies to case studies in population growth, epidemiology, and wound healing. Our results suggest that surrogate modeling offers a robust framework for data-driven ABM modeling, which presents an exciting opportunity for the future application of equation learning methodologies.

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MS5

Exploring the Topological Shape of Plant Data

Shape and structure play a fundamental role across all plants at all observable levels. Cells and tissues arrange into elaborate motifs to form sophisticated leaves and root patterns, which in turn are arranged into complex canopies and architectures. From micro- to macro-scale data, it is possible to observe diverse shape changes through interaction, development, and evolution. Measuring and modeling these diverse morphological dynamics from data is key to expand our insights and predict biological outcomes. But shape is often too complex to be comprehensively quantified, as traditional methods are limited to homologous points shared across samples or to just measuring 2D contours. In this talk, we will showcase how Topological Data Analysis (TDA) offers novel frameworks to comprehensively quantify the structure of cell patterns, and to assess the structure of genomic data. The first case study focuses on a large collection of microscopy images of nodule, leaf, and sepal cell patterns. We adapt ideas of geospatial persistent homology to measure the overall patterns made by these plant cells, and to determine the location of specific infected or giant cells with respect to the rest of cell types. The second case study focuses on RNAseq data related to different rice varieties responding to various bacterial infections. We adapt ideas from Mapper to determine an overall genomic structure of genes responding differentially to different bacterial infection types.

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MS5

Geometric and Topological Approaches to Proteus Mirabilis Swarm Characterization

Proteus mirabilis, a bacterium found in the intestines of many animals, is a leading cause of urinary tract infections in humans. Upon engagement and growth on surfaces, individual cells engage in programmed developmental changes that contribute to drastic alterations in the morphology and spatial configuration of the population as a whole. Formal characterization of the topology and geometry of the bacterial swarm at both local and colony levels is key to assessing experimental results and understanding swarm behaviors. In this talk, we present methods for the multi-scale analysis of images of *P. mirabilis* swarming. We will begin with an evaluation of the strengths and weaknesses of traditional topological data analysis when used to understand how overall swarm structure is affected by cell-cell contact. Then, we will present methods designed to capture local interactions through the construction of a network of cell-cell contact and for tying these interactions back to larger-scale phenomena, again paying attention to the information gained and lost in the process. Our talk will conclude with a discussion of the interleaving of both sets of meth-

ods and their results in order to construct an informative, multi-resolution analysis of the ways that micro-scale cell interactions contribute to meso-scale swarm structure.

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MS5

A Curvature-Based Method to Recover Manifold Structure and Clusters in High-Dimensional Data

High-dimensional point clouds often have low-dimensional manifold structure, and we can analyze that structure using methods based on ideas from differential geometry and topology. Many of these algorithms begin with a nearest-neighbor graph as input. However, nearest-neighbor graphs often result in an inaccurate representation of the underlying manifold because of spurious shortcut edges that bridge distance neighborhoods of the manifold. In this talk, Ill introduce ORC-ManL, a new algorithm to prune shortcut edges from nearest-neighbor graphs using a criterion based on Ollivier-Ricci curvature and estimated metric distortion. Well show that our method significantly improves the performance of many downstream geometric data analysis tasks. As an application, we look at single-cell RNA sequencing data sets, where we have measures of the gene expression levels of thousands of genes in thousands of individual cells, producing a large high-dimensional point cloud. We demonstrate that ORC-ManL improves clustering and manifold learning of single-cell RNA sequencing data.

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MS5

Topological Data Analysis of Zebrafish Skin Patterns

Zebrafish are known for their pigment patterns which arise from the interactions between different types of pigment cells. We show interest in developing a mathematical framework, using topological data analysis, to quantify certain properties of such skin patterns. Using different filtration types in persistent homology, we categorize these patterns based on their topological persistence, identifying robust features such as the counts and widths of stripes, breaks, and bridges. This allows us to identify abnormalities in skin pattern development, which may indicate health or genetic issues in the fish, offering potential applications in biological research, genetics, and developmental biology.

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MS6

Accuracy Vs. Understanding: Interpretable Decoding of Social Context in the Amygdala

The amygdala responds to a large variety of socially and emotionally salient environmental and interoceptive stimuli. The context in which these stimuli occur determines their social and emotional significance. In previous studies we found that context, such as the presence of a social partner, induces persistent brain states that can be recovered from the spontaneous, inter-trial firing rate of neurons. Indeed, the spontaneous firing rates of neurons in the amygdala are different during blocks of gentle grooming touches delivered by a trusted social partner, and during blocks of non-social airflow stimuli delivered by a computer-controlled air valve. Here, we examine the local field potentials (LFPs) recorded during periods of spontaneous activity to determine whether information about context can be extracted from these signals. We found that context-dependent information is present in the LFP during periods of spontaneous activity, as both classical and modern machine learning methods (SVM and CNN) can reliably decode social context from spectrograms of spontaneous LFPs. Unfortunately, while modern machine learning techniques like deep learning can accurately classify and decode neuronal data, even the simplest deep neural networks can be opaque. This lack of biological interpretability limits the scope and usefulness of deep neural networks for tasks like identifying neural correlates and generating testable hypotheses for future experiments. To address this challenge, we develop two novel shallow neural networks implementing data-driven time-frequency matched filters and compare them with the previously validated deep CNN model. In the context of our experimental data, we show that these shallow matched filter classifiers can be competitive with deeper networks while offering more accessible insights into the underlying neural dynamics.

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MS6

Timescale Localization and Signal Propagation in

Large-Scale Cortical Networks

The brain operates at multiple speeds: sensory areas respond rapidly in tens of milliseconds, while higher-order areas integrate information over hundreds of milliseconds or longer. In this talk, we present a data-driven multi-areal dynamical model of the marmoset cortex that reproduces this hierarchy and clarifies how strong local integration can coexist with reliable long-range communication. The model is constrained by electrocorticography (ECoG) recordings and a quantitative, directed anatomical connectome. Our model identifies an important feature: a macroscopic gradient of recurrent excitation that increases from sensory to higher-order areas, consistent with experimentally measured spine counts. This gradient yields a spectrum of time constants matching the observed timescale hierarchy. Furthermore, our model demonstrates that the cortex operates near a critical point (on the edge of instability), optimizing both local integration and reliable global signal propagation. The near-criticality also accounts for the observation that functional connectivity patterns become increasingly decoupled from anatomical connectivity in higher-order cortical regions. Our results illustrate how integrating empirical data with modeling can uncover general principles of biological networks.

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MS6

Data-informed Modeling of Biological Systems And an Example From Visual Neuroscience

This talk is an introduction to the minisymposium on data-driven and data-informed modeling of biological systems, whose aim is to gather together researchers using data driven and data informed methods in biological modeling on a range of scales and to identify both unifying principles and problem-specific strategies. After a discussion of general issues, I will describe an example from a collaboration on modeling the primate primary visual cortex.

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MS6

Reproducing C. Elegans Premotor Neural Dynamics with a Biology-Based Network Model

C. elegans produce many behaviors, such as foraging, by switching between forward and reversal states with turns ending reversals. While experimentalists have identified subsets of neurons that drive forward and reversal states, these premotor neurons are highly integrated into a larger network whose collective dynamics govern behaviors. Analyzing collective network dynamics presents a major challenge in C. elegans and other biological networks where a subsystem of interest is embedded in a complex larger system. In this talk, I will discuss a driven dynamical systems model of relevant subnetworks within the C. elegans neural network and strategies for extracting relevant subnetworks for such models as well as dimension reduction of resulting models for analysis.

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MS7

Mechanical Forces Modulate Dwell Time Fluctuations to Optimize T-cell Activation

Mechanical forces have been shown to play an indispensable role in immune response. However, how their effects manifest to decide the speed and accuracy of T-cell activation remains a matter of ongoing research. It has been argued that the formation of catch-bonds with the non-self antigens and slip-bonds with the self ones leads to an improved T-cell response. On the contrary, we show that the catch-bond model may not be conclusive in describing the T-cell accuracy in certain cases. In particular, we show that mechanical forces alter the TCR-pMHC bond dwell time distribution beyond the simple exponential fit. We derive an analytically tractable theory to exactly evaluate the speed and accuracy of T-cell response under any generic TCR-pMHC bond dwell time distribution. By incorporating the non-Markovian bond dwell time distributions from experiments, we see that the fluctuations play a crucial role in modulating the T-cell response. Interestingly, we find that T-cells may lead to poor accuracy despite catch bond formation when the intrinsic fluctuations in the dwell times are relatively higher. The study opens up a new avenue to understand the T-cell response under mechanical forces through the modulation of bond-dwell time fluctuations.

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MS7

First Passage Times to T Cell Activation

Effective detection of foreign antigens by the adaptive immune system relies on T cell activation by antigen-presenting cells (APCs) within lymph nodes. Searcher T cells may encounter cognate APCs that trigger activation, non-cognate APCs that do not, or exit the lymph node before productive binding occurs. We develop a stochastic model in which T cellAPC interactions proceed through sequential recognition steps represented by a multistage Markov process, with activation occurring only upon reaching a terminal cognate APC state. This dynamics is coupled to spatial diffusion and lymph node exit, leading to a system of partial differential equations. Using first-passage time theory, we compute activation probabilities and mean activation times in the presence of abundant non-cognate APCs, and show how kinetic proofreading via stochastic resetting enhances specificity.

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MS7

Advances in Numerical Computation and Asymptotic Analysis for Cellular Signaling Problems

In this talk I will discuss recent advances in singular perturbation analysis for a class of cellular signaling problems. Cellular activity is modulated by noisy signaling dynamics at small localized surface receptors. One classic variant of these problems is the classic Berg-Purcell problem which seeks the steady state flux into a three dimensional cell with a number of localized reactive sites. Another is the mean first passage time (MFPT) problem which seeks the expected time for a diffusing molecule to reach one of many reaction sites either located internally or embedded on a manifold. In each of these cases, we show how to develop asymptotic expansions for these key quantities for general 3D domains. These expansions are developed in terms of the regular part of a Greens function which we develop a numerical routine to obtain. We demonstrate these new results for a variety of different signaling problems on a range of 3D domains.

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MS7

Intermittent Diffusion Enables Fast Dna Target Finding

Facilitated diffusion enables regulatory proteins to locate short, specific binding sequences within a much larger DNA substrate by alternating between slow one-dimensional motion along DNA and fast three-dimensional excursions through the cytosol. We analyze a stochastic switching model for this intermittent search and show how it can markedly shorten target-finding times relative to models without switching. In many experimentally relevant regimes, timing is dictated by extreme events, particularly the minimum first-passage time to the target among many independent proteins. Through short-time asymptotic expansions of the first-passage distribution, we identify distinct regimes for these extreme statistics and quantify how the fastest target-finding time depends on protein copy number and on switching rates. Incorporating extreme first-passage behavior can also reconcile discrepancies between observed binding times and predictions from earlier models.

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MS9

Integrating Poroelastic Simulations and Machine Learning for Mechanical Parameter Identification of Porcine Lungs

Accurate and rapid characterization of lung mechanics remains a major challenge in the management of respiratory disease. Physics-informed poroelastic finite-element (FE) models can capture detailed tissue-airflow interactions, but their substantial computational expense precludes real-time clinical deployment. Conversely, lumped-parameter compartment models are routinely used at the bedside for fast assessment of disease severity, yet they provide limited mechanistic insight and no spatial resolution. In this work, using porcine-specific data, we combine multi-fidelity poroelastic FE simulation data with machine learning approaches to enable fast, uncertainty-aware estimation of respiratory system compliance (C_{rs}) and resistance (R_{rs}).

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MS9

BrainACTL: Adaptive Temporal Brain Connectivity Learning for Functional Link Prediction and Age Estimation

Functional Magnetic Resonance Imaging (fMRI) captures dynamic patterns of brain functional connectivity, where regions transiently synchronize and desynchronize even at rest, reflecting evolving neural states linked to behavior and neuropsychiatric disorders. Modeling these dynamics requires temporal connectivity representations, yet conventional graph neural networks (GNNs) struggle with long-range temporal dependencies in dynamic fMRI data. We propose BrainATCL, an unsupervised, non-parametric framework for adaptive temporal brain connectivity learning for functional link prediction and age estimation. BrainATCL dynamically adjusts the temporal lookback window based on newly added edges and encodes graph sequences using a GINEMamba2 backbone to learn spatiotemporal representations. To improve biological interpretability, we incorporate structure- and function-informed edge attributes, including hemispheric identity and subnetwork membership. Experiments on rs-fMRI data from 1,000 Human Connectome Project participants demonstrate superior performance and strong generalization, including cross-session prediction.

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MS9

Blood Viscosity Prediction Via Physics-Informed Neural Networks (Blood-Pinns) with ParticleContinuum Integration

Accurate prediction of blood viscosity is essential for understanding hemodynamics and disease-related alterations in red blood cell (RBC) mechanics. However, traditional computational approaches, such as full-scale particle-based or continuum simulations, are often time-consuming and computationally intensive, limiting their applicability for large-scale or patient-specific studies. To address these challenges, we propose BloodyPINN, a hybrid physics-informed neural network (PINN) framework that integrates dissipative particle dynamics (DPD) data with continuation-based learning for efficient and interpretable blood viscosity prediction. The framework embeds governing fluid dynamic and rheological equations directly into the loss function, ensuring physical consistency while significantly reducing the need for extensive simulation data. By training on DPD-generated datasets across varying hematocrits, pressure gradients, and pathological cell deformabilities, BloodyPINN learns multiscale relationships between cellular mechanics and macroscopic flow behavior. Validation against DPD and experimental benchmarks confirms that BloodyPINN reproduces shear-dependent viscosity trends with high fidelity while achieving a substantial reduction in computational cost. This study establishes a reproducible and extensible AI-enhanced hemorheology framework for rapid and physics-consistent prediction of blood viscosity under both physiological and pathological conditions.

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MS10

From Molecules to Networks: Multiscale Modeling of Rho GTPase Signaling

Rho-family GTPases are key signaling molecules, regulating diverse processes including cell polarity, cytoskeletal organization, and morphogenesis. Through nonlinear interaction networks, these molecules produce a wide variety of dynamic and spatial behaviors, including spatial segregation, oscillations, and stable complex patterning. Here, we present a network-centered dynamical systems framework for understanding Rho protein dynamics, demonstrating how network structure constrains and organizes emergent behaviors of mathematical models. Choices made at each level, from the structure of the regulatory interaction network to model formulation and parameter regimes, constrain which dynamics are possible. Using deterministic models grounded in biological observations, we analyze how feedback loops, competition, and symmetry-breaking mechanisms embedded in the network structure generate transitions between dynamical regimes. This approach demonstrates how network structure defines the space of admissible behaviors and provides a mathematical framework for linking signaling systems to emergent cellular phenotypes.

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MS10

Abstracting Gene Regulatory Logic: How 'teams' Reveal Design Principles Driving Cancer Metastasis

Cancer metastasis is governed by complex gene regulatory networks (GRNs) that coordinate transitions between epithelial, hybrid epithelial-mesenchymal (hybrid E/M), and mesenchymal cellular states. While network topology encodes functional logic, extracting interpretable design principles from high-dimensional regulatory interactions remains a central challenge. Here, we introduce teams groups of genes that act coherently as functional units as a framework for abstracting regulatory logic. A key insight is that team membership is not apparent from direct interactions alone; teams often emerge from indirect regulatory relationships, revealing that the functional organization of a GRN is encoded at a higher order than pairwise connectivity. Using Boolean network modeling, we define quantitative metrics team strength and team impurity that capture the robustness of coordinated gene activity and demonstrate that team structure predicts attractor repertoire, phenotypic plasticity, and stability of hybrid E/M states across EMT networks. Applying this framework to cancer-relevant GRNs, we reveal recurrent architectural motifs whose team organization correlates with metastatic aggressiveness and resistance to state transitions, offering a tractable route to identifying design principles driving phenotypic plasticity in cancer metastasis.

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MS10

The Estrogen Advantage: A Hormonal Key to Blood Pressure Control?

Hypertension is a global health challenge: it affects one billion people worldwide and is estimated to account for $> 60\%$ of all cases or types of cardiovascular disease. Premenopausal women have lower blood pressure and hypertension prevalence compared to age-matched men, but that female protection is lost after menopause, the onset of which marks the beginning of a rapid decline in estrogen levels. The precise mechanisms by which estrogen protects premenopausal women from hypertension have yet to be elucidated. What is known is that estrogen has a

plethora of interactions with other hormone systems as well as physiological processes known or hypothesized to impact the regulation of blood pressure. Thus, an objective of this study is to identify the primary contributors to the estrogen-mediated cardiovascular protection. To accomplish that goal, we develop a blood pressure regulation model that incorporates the effects of estrogen on the renin-angiotensin system, the reactivity of renal sympathetic nervous activity, vascular tone, and renal epithelial transport. Model simulations suggest that estrogen's vasodilatory effect, especially on the afferent arterioles, is the largest cause of premenopausal women's lower blood pressure and resistance to developing hypertension. Furthermore, the model predicts that angiotensin receptor blockers are more effective than angiotensin converting enzyme inhibitors in treating hypertensive women throughout their lifespan, even as estrogen levels decline.

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MS10

Multi-Omics Methodological Framework to Redefine Disease Endotypes and Therapeutic Determinants in Dermatology

Quantitative experimental technologies in life sciences have advanced at an unprecedented pace. Multi-omics profiling, organoid systems, and in vivo live-imaging now generate vast amounts of high-resolution data, positioning data as a central pillar of modern science. However, in medical research, complex disease mechanisms are often inferred from limited patient samples, and substantial challenges remain in addressing inter-individual variability and selecting optimal therapeutic strategies. In this talk, I will introduce a novel framework that integrates structure-based mathematical modeling with high-dimensional, unstructured biological and clinical data to systematically understand disease mechanisms. Using dermatological diseases as a primary example, we present an integrative and multidisciplinary approach, a multi-omics methodological framework, designed to bridge fundamental disease biology with clinically actionable insights. This framework enables the identification of disease endotypes, elucidation of mechanistic heterogeneity, and prediction of therapeutic determinants, ultimately contributing to precision medicine through a quantitative and mechanistic understanding of human disease.

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MS11

Developing Virtual Patients for Advancing Clinical Trial Design Via Biology-Based Modeling.

We present a framework for generating virtual patient populations of triple-negative breast cancer with explainable and tunable heterogeneity to conduct in silico trials for neoadjuvant therapy. Clinical trials in oncology are limited by small patient cohorts, which fail to capture the heterogeneity of tumor characteristics observed in the population. Addressing the need for patient-specific treatment optimization, our group has previously developed a biology-based mathematical model, which captures the spatiotemporal changes in tumor cell number due to cell movement, cell proliferation, and treatment-induced death, to predict response to treatment. We now use this model to generate virtual patient populations and conduct in silico clinical trials to systematically evaluate many treatment regimens. Using serial MRI data from 44 patients in the I-SPY2 trial, we estimate model parameters (growth rate, chemotherapy efficacy) via the Levenberg-Marquardt method, and approximate tumor anatomy (cell density, perfusion) via spherical harmonics. We then estimate multivariate distributions of the parameters and anatomy from which we sample to generate virtual patients distinct from the original population; the distributions can be scaled to tune the population heterogeneity. Finally, we demonstrate that the framework can generate a virtual population that can recapitulate the treatment response observed in the I-SPY2 trial.

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MS12

Mathematical Modeling of Bone Remodeling After Surgical Menopause

Osteoporosis is a skeletal pathology characterized by decreased bone mass and structural deterioration resulting from an imbalance in bone metabolic processes. Estrogen deficiency in postmenopausal women leads to an increased risk of osteoporosis, while women who have undergone complete oophorectomies display an even higher risk due to the sudden decrease in estrogen. Some evidence indicates that bone loss slows in the period beyond 15 years after surgery; however, there is substantial uncertainty in clinical data. To explore the effects of surgically induced menopausal transition, here we propose a mathematical model for the bone cell dynamical responses to sudden estrogen deficiency, which extends an existing model for osteoporosis due to aging and natural menopause. Using data on key effects observed in female mice and humans after bilateral oophorectomy, this new model considers the role of osteocytes embedded within the mineralized bone matrix in regulating bone remodeling, which results in net

bone loss after surgical menopause. The model parameter values in natural and surgical menopause were estimated from aggregated human clinical data from existing longitudinal studies. The new model effectively captures the previously unmodeled increase in bone loss during the first 15 years post-surgical menopause and the rebound in bone mineral density in the long-term. With this model, effects of treatments on targeting osteocyte dynamics could be explored in the future.

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MS12

Integration of Estrogen into Cell Signaling Models of Valve Interstitial Cells

A decade following the mandate from the National Institutes of Health (NIH) to incorporate Sex As a Biological Variable (SABV) in the design, analysis, and reporting of preclinical research, biomedical research has entered a new era of understanding health processes across different populations. This SABV initiative has uncovered numerous effects of biological sex and sex hormones that had previously been overlooked, including the adverse effects of commonly-prescribed beta blockers on women following a heart attack. The latest NIH initiative seeks to reduce the use of animals in preclinical research to prioritize New Approach Methodologies (NAMs), including the use of computational models to simulate complex biological systems, disease pathways, and drug interactions. While an admirable goal, computational scientists modeling disease pathways are often confined to sub-optimal literature values from related cell types and typically do not have access to sex-dependent kinetic parameters. The challenge, then, is to embrace the potential of computational platforms to serve as NAMs while remembering that we have only had a decade of work that has forced the consideration of SABV. Our joint experimental-computational work developing kinetic models of disease-relevant pathways in valve interstitial cells elucidates previously unknown contributions of biological sex and 17β-estradiol on TGFβ, TNFα, IFNα, and IFNγ pathways.

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MS12

Mathematical Modeling to Inform Automated Insulin Delivery for Women With Type 1 Diabetes: A Model-based Digital Twin Approach Addressing Menstrual Cycle-related Metabolic Variability.

Women undergo hormonal changes across the lifespan that impact multiple systems including the metabolic, immune, and endocrine system. Insulin sensitivity has been observed to fluctuate across the menstrual cycle; in type 1 diabetes (T1D), this may result in suboptimal glycemic control and increased exposure to hyperglycemia following ovulation, if insulin therapy is not modified accordingly. Mathematical models have been increasingly used to formalize metabolic processes, estimate key metabolic parameters, and inform T1D therapy. These models are at the core of digital technologies for treatment personalization and adaptation to time-varying insulin requirements. Model-based digital twinning techniques have shown promising results, enabling a detailed digital representation of individuals physiology to inform highly-personalized advisory systems and support optimal lifestyle and treatment decisions. For T1D management, digital twins have been successfully used to guide insulin dosing under multiple therapy regimens. In this talk, I will review the existing literature on mathematical model-based developments related to glucose metabolism and glycemic control in women with T1D, and I will present recent developments on the use of model-based digital twins to inform insulin therapy adaptation across the menstrual cycle in women with T1D.

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MS12

Modeling Progesterone Dynamics and Its Impact on Recovery Following Mild Traumatic Brain In-

jury in Women

Mild traumatic brain injury (mTBI), or concussion, is a complex injury with significant short- and long-term health impacts. Recent research suggests sex-based differences in recovery and outcomes following mTBI. Females injured during the follicular phase of the menstrual cycle tend to have outcomes similar to males and females using hormonal birth control, whereas females injured during the luteal phase often experience worse outcomes and longer recovery. One hypothesis is that progesterone has neuroprotective effects that reduce neuroinflammation and neuronal cell death, but mTBI may disrupt progesterone synthesis for the remainder of the cycle, causing a sharp decline during the luteal phase when levels are normally high. In contrast, progesterone levels are already low during the follicular phase and in males, so a comparable drop does not occur. Females using hormonal birth control continue receiving synthetic progesterone after injury, which may lessen neuroinflammatory effects associated with progesterone loss. In this work we develop a mechanistic model of post-injury progesterone dynamics and examine how changes in progesterone levels may influence the duration and severity of neuroinflammation. The model is adapted from established kinetic models of intracranial and serum S100B, a widely studied biomarker of mTBI.

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MS13

Modeling the Impact of Human Behavior on Sars-CoV-2 Transmission Dynamics

The COVID-19 pandemic has not only profoundly impacted global health and socioeconomic systems, but has also significantly impacted human behavior toward adherence or lack thereof to public health interventions and mitigation measures implemented in communities around the world. However, a relatively small number of epidemiological models have attempted to assess the impact of human behavior on the dynamics of SARS-CoV-2 transmission. In this talk, several behavior-incorporated models will be used to assess the impact of incorporating human behavior into epidemiological models. I will also discuss immunological perspectives on human behavior and disease dynamics.

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MS14

Bridging Transmission Pathways in Mechanistic Epidemic Models

Infectious diseases remain a major global health challenge, shaped by environmental variability that influences transmission. Seasonal variation can strongly influence host susceptibility, pathogen viability, and vector abundance, altering both transmission intensity and outbreak timing. Moreover, environmentally persistent pathogens introduce indirect transmission through contaminated reservoirs, linking host dynamics to environmental processes. To address these challenges, we present a unified framework for analyzing direct, vector-borne, and environmentally mediated transmission models under seasonal variation. Using stochastic formulations and branching process approximations, we examine seasonal probabilities of disease extinction and how phase shifts between transmission pathways and environmental drivers influence epidemic trajectories. We further examine epidemiological outcome measures in constant versus seasonal systems and investigate how synchrony and asynchrony between direct and indirect transmission shape persistence patterns. These results highlight how mechanistic models help improve our understanding of extinction probabilities and outbreak timing across transmission pathways.

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MS14

Modeling the Hazard Function with Non-linear Systems in Dynamical Survival Analysis

Hazard functions play a central role in survival analysis, offering insight into the underlying risk dynamics of time-to-event data, with broad applications in medicine, epidemiology, and related fields. First-order ordinary differential equation (ODE) formulations of the hazard function have been explored as extensions beyond classical parametric models. However, such approaches typically produce monotonic hazard patterns, limiting their ability to represent oscillatory behavior, nonlinear damping, or coupled growthdecay dynamics. We propose a new statistical framework for modeling and simulating hazard functions governed by higher-order ODEs, allowing risk to depend on both its current level, its rate of change, and time. This class of models captures complex time-dependent risk behaviors relevant to survival analysis and reliability studies. We develop a simulation procedure by reformulating the higher-order ODE as a system of nonlinear first-order equations solved numerically, with failure times generated via cumulative hazard inversion. Likelihood-based inference under right censoring is also developed, and moment generating function analysis is used to characterize tail behavior. The proposed framework is evaluated through simulation studies and illustrated using real-world survival data, where oscillatory hazard dynamics capture temporal risk patterns beyond standard monotone models.

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MS14

Title: Synchronization of Disease Dynamics Between Groups Via Social Coupling

The spread of infectious disease is strongly influenced by social dynamics. In addition to infection risk, individuals vaccination decisions depend on prevailing social behavior: high infection levels and widespread vaccination can increase vaccine uptake, which in turn suppresses infection. This feedback can generate sustained oscillations in disease prevalence and vaccination behavior. In this talk, we study two such populations undergoing the same behavioral–epidemiological limit cycle and introduce weak coupling between them through social influence. We show that coupling leads to synchronization of disease dynamics between the two groups. Depending on behavioral payoff sensitivity, the synchronized state may be either in-phase or out-of-phase. Moreover, we find that lower payoff sensitivity enhances the rate of synchronization.

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MS14

Title: The Role of Patch Dynamics and Additional Food in Biological Control.

Mathematical models are widely used to study biological control, and this talk presents modeling frameworks motivated by challenges in pest management. The focus is on a two-patch predatorprey model inspired by agricultural practices such as the STRIPS program, which promotes integrating prairie strips within crop fields. By dividing the landscape into a prairie-strip patch and a crop-field patch, we examine how predator movement and generalized competition influence system dynamics. Our analysis shows that complete pest extinction in both patches is globally asymptotically stable under different predator movement mechanisms. We observe that introducing a patchy environment, along with generalized competition among predators, enhances overall pest control and supports the effectiveness of spatially structured agricultural practices.

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MS15

Multiscale Mathematical Models of Fibrinolysis: Mechanisms, Insights, and Open Questions

Understanding mechanisms driving fibrinolysis, the enzymatic degradation of the fibrin mesh that stabilizes blood clots, is critical for improved stroke treatment. The structure of the fibrin mesh, the biochemical environment, and the inherent and applied tension acting in and on the fibrin all contribute to how easily the clot degrades. We present several mathematical models that are currently being used in conjunction with laboratory experimentation to uncover the mechanisms regulating fibrinolysis. Results from these multiscale, stochastic models suggest that: forced unbinding of enzymes from fibrin can speed up degradation; and thinner fibers require a higher percentage of the fibrin in their cross-section to be degraded before the fiber cleaves in two, compared to thicker fibers. In honor of Aaron Fogelsons milestone birthday, we will commemorate the spirit of collaboration and curiosity that he fosters by ending with open questions that encourage group-meeting-style discussion.

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MS15

A Model of Gastric Mucosal PH Regulation: Extracting Relevant Information from Mechanistic Models Using Sensitivity Analysis

Epithelial cells making up the lining of the mammalian stomach are responsible for maintaining a healthy pH adjacent to the stomach wall. In most situations they effectively do so, even in the face of an enormous electrodiffusive potential driving transport of acid from the interior of the stomach to the wall. Mathematical modeling has indicated that a relatively simple secretion control mechanism of ion exchange within the epithelium may explain this maintenance, even as parameters vary. However, questions remain regarding the nature of the control that specific parameters exert over the wall pH of a healthy stomach. Techniques from sensitivity analysis can address these questions and elucidate the role of individual parameters. In this work, our analysis uncovers a control parameter which governs the tightness of control' that the secretion mechanism exerts on wall pH, which we use as a surrogate for gastric health. Finally, we show how uncertainty in this unidentifiable parameter can be reduced using expert information about higher moments, and speculate about the physiological advantage conferred by this control mechanism.

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MS15

Platelet Plug Microstructure and Flow Modulate Fibrin Gelation Dynamics: Insights From Computational Simulations

During thrombus formation, the architecture of the growing platelet aggregate is heterogeneous, with areas of dense and loosely packed platelets. The surface of activated platelets facilitate biochemical reactions that comprise the coagulation cascade, ultimately resulting in the formation of a fibrin network which stabilizes the thrombus. How platelet-plug microstructure and flow jointly govern the onset and development of fibrin is not completely understood. Here, we present a novel 2D computational framework that integrates a pre-adhered, discrete platelet aggregate, a reduced coagulation model on discrete platelet surfaces, and a fibrin polymerization model. Our results suggest that early fibrin gelation dynamics are influenced by both flow and intraplatelet architecture, which each affect transport within the aggregate. By treating platelets as discrete surfaces rather than a continuum, we find that chemical accumulation and transport within the pre-formed platelet aggregate determines the location of the initial fibrin gel. Our simulations show that a dense clot results in a fibrin gel that initializes on the outer edge of the platelet aggregate, which coincides with thrombin trapped within the platelet plug. However, the looser platelet plug results in an initial fibrin gel by the injury zone. These findings suggest a hypothesis as to why clot contraction occurs later in time and our framework can provide a basis for studies of plateletcoagulation interactions under flow.

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MS15

Development of Platelet Aggregates at High Shear Rate Driven by Von Willebrand Factor

Platelet aggregates develop pathologically in partially occluded blood vessels due to an increase in the local wall shear rate. The polymer von Willebrand Factor (vWF) is essential for rapid initial attachment of platelets to the wall and each other. It is currently unclear how the chemical and mechanical properties of vWF allow for stable aggregate growth. Thus, we have developed a spatially averaged model that tracks the development of a platelet aggregate in flow as a system of ODEs. We utilize first principle arguments from disciplines such as fluid dynamics and protein kinetics to determine how platelet attachment contributes to aggregate growth. We also utilize tools from probability theory to determine the likelihood of platelet detachment due to the drag force imparted on crosslinking bonds. We find that at high shear rate, inclusion of platelet-vWF-platelet crosslinking stabilizes the aggregate not only by increasing the total number of crosslinks, but also by allowing platelets to attach without a prior activating signal. Furthermore, we show that the polymeric structure of vWF allows for more stable aggregation compared to the monomer case. These results have implications for aggregation in stenotic regions as well as in disease states such as von Willebrands Disease.

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MS16

Learning Drift and Noise from Observing Stochastic Dynamics with Complex Noise Structures

Stochastic differential equations (SDEs) are a ubiquitous modeling framework that appear in physics, biology, engineering, social science, and finance. Due to the availability of large-scale data sets, there is growing interest in learning mechanistic models from observations with stochastic noise. In this work, we present a unified nonparametric learning framework to infer both the drift and diffusion terms in systems of SDEs with a relatively general noise structure. Many classical inference methods assume that the SDE noise is both non-singular and independent of the state of the system. Our main contribution in this work is to extend these methods to the case of singular state-dependent noise structures, which appear frequently in models inspired from second-order equations in classical physics. We provide a unifying algorithm for constructing estimators given trajectory data and demonstrate the effectiveness of our methods via a number of examples from physics and biology. As the developed framework is most naturally applicable to systems possessing a high degree of dimensionality reduction (i.e. symmetry), we also apply it to the high dimensional models studied in collective dynamics and show that it is able to accurately infer the low dimensional interaction kernel from trajectory data.

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MS16

Parameter Estimation in An Agent-Based Model of Zebrafish Through Pair Correlation Functions

Complex systems in biology are those in which the interactions among individual agents give rise to diverse group dynamics. To better understand the factors driving these dynamics, we estimate parameters of the mathematical models that simulate such systems. In particular, we build on an existing model of pattern formation in zebrafish skin and apply the Approximate Approximate Bayesian Computation (AABC) method to estimate the model parameters. We use pair-correlation functions of two distinct cell types in the zebrafish skin as summary statistics in the AABC method. Our results highlight which zebrafish mutants, summary statistics, and developmental time points provide the most informative insights into the mechanisms behind pattern formation. We also discuss our analysis to determine the hyperparameter values in the AABC method that yield the most reliable parameter estimates.

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MS17

Dynamical Breathing: Neuromodulation and Sensorimotor Integration in the Respiratory Network

Understanding the network mechanisms that enable the adaptive control of breathing requires simultaneously monitoring the activities of neuronal populations across the brainstem. To tackle this challenge, we use high-density multi-electrode arrays in the in situ perfused preparation of rats to enable large-scale recordings of respiratory neuronal activities. Here, we consider two datasets that challenge the view of the respiratory network as a mutually-inhibitory central pattern generator (CPG) network. In the first case, we developed a Hopfield model with fast- and slow-synapses constrained by respiratory neuronal firing patterns of the pre-Btzinger complex. Surprisingly, this model could explain the experimentally observed network activity evoked by systemic administration of 5HT1a- or -opioid receptor agonists. In the second case, we investigate the population activity of the pontine respiratory group (PRG), an area necessary for the expression of physiologic breathing pattern. At baseline, PRG population activity was tonic, consistent with its role as a source of tonic drive in CPG models. However, during the carotid body-dependent arterial chemoreflex, PRG ensembles became transiently oscillatory or encoded the duration of the tachypneic phase of the reflex. Taken together, we propose that model classes beyond the CPG be considered to explain the network mechanisms underlying the generation and control of breathing.

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MS17

Feedback Regulation of Physiological Limit Cycle Systems Via Averaging

Rhythmic physiological processes such as breathing may be modeled as nonlinear dynamical systems exhibiting limit cycle oscillations (LCOs). These LCOs help maintain homeostasis by regulating dynamical variables such as blood oxygen levels. We investigate homeostatic regulation within a control-theoretic framework as a tracking/disturbance-rejection problem. Specifically, we view the hypoxia-driven respiratory control model proposed by Diekman et al (2017, 2023) as a closed-loop control system with a limit cycle module (the central pattern generation circuit) embedded in the control loop. We interpret the perturbation of the system due to an increase of metabolic demand as a disturbance to be rejected, and the mean blood oxygen level (the objective of homeostasis) as a reference signal to be tracked. In order to apply existing tracking/disturbance-rejection methods to this system, we introduce an averaging method applied to the limit cycle / CPG subsystem. Initial results suggest that some combination of output regulation theory, differential geometry-based feedback design, and limit-cycle stabilization techniques may be used to specify control schemes improving robustness of the respiratory oscillator, for example by broadening the range of metabolic demands for which the breathing rhythm can be sustained.

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MS17

Data-Driven Modeling of Closed-Loop Respiratory Control

In a clinical setting, breathing pathologies are diagnosed and studied via pulmonary function tests (PFTs), with the most ubiquitous of those being spirometry. Broadly, the major pathologies are considered to be restrictive or obstructive, representing different mechanical problems in the lung. We examine an existing model of respiration that incorporates essential lung biomechanics, oxygen chemosensation, and metabolism in a closed-loop control circuit. We aim to use spirometry and other clinical data to improve and extend this closed-loop model. We also look to ground the model in anatomical elements, such as airway resistance and nonlinear lung biomechanics, in order to more accurately simulate and study mechanical problems in the lungs. In this talk, we will identify the essential characteristics of a spirogram and what these represent in the lungs; then, we will proceed to spirograms produced from clinical data to observe the typical curve; finally, we will discuss the work to bridge the gaps between the expected spirogram and the simulated one, and the benefits of establishing this data-driven link to clinical PFTs.

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MS17

Using a Computational Model of COVID-19induced Changes in Breathing to Inform Clinical Care

Silent hypoxemia is a puzzling phenomenon in which patients who have contracted COVID-19 exhibit very low oxygen saturation ($SO_2 < 80\%$) but do not experience discomfort in breathing. The mechanism by which this blunted response to hypoxia occurs is unknown. We have previously shown that a computational model of the respiratory neural network, the 7DO2 model [Diekman et al., 2017, J. Neurophysiol] can be used to test hypotheses focused on changes in chemosensory inputs to the breathing central pattern generator (CPG). We hypothesize that altered chemosensory function at the level of the carotid bodies and/or the *nucleus tractus solitarii* are responsible for the blunted response to hypoxia. In this presentation, we discuss the use of our model to explore this hypothesis by altering the properties of the gain function representing oxygen sensing inputs to the CPG. We then vary other parameters in the model and show that oxygen carrying capacity is the most salient factor for producing silent hypoxemia. We call for clinicians to measure hematocrit and metabolic markers as a clinical index of altered physiology in response to COVID-19 and other infections.

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MS18

Weak-form Methods in Statistical Modeling

We discuss how weak-form methods, originally developed in the context of differential equations and finite element analysis, can offer a powerful and flexible framework for statistical modeling that extends classical regression techniques. Weak-form formulations replace pointwise estimation objectives with integral-based functionals, providing

enhanced noise robustness, numerical stability, and theoretical insights. For example, while traditional linear regression minimizes the squared residual norm directly, the weak-form methods instead project the residual onto a test function space, seeking β such that $\langle y - X\beta, \psi \rangle = 0$ for all test functions ψ in an appropriate function space. We examine how the weak-form perspective unifies several important statistical concepts, from smoothing to regularization.

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MS18

Identifiability and Physics-Informed Learning of Spatially Varying Stochastic Dynamics from Static Snapshots

Single-molecule localization microscopy such as smFISH provides high-resolution snapshots of particle positions in fixed cells, where temporal dynamics are irretrievably lost. In this talk, we will present a framework to investigate the inverse problem of inferring spatially heterogeneous diffusion coefficients $D(x)$, birth rates $B(x)$, and boundary permeabilities κ from steady-state particle densities. By analyzing the ambiguity operators associated with the underlying stochastic differential equations (SDEs), we establish rigorous criteria for structural identifiability. We demonstrate that while standard "Fickian" diffusion models exhibit an intrinsic gauge freedom rendering them structurally non-identifiable, models based on It calculus combined with specific source topologies possess unique, recoverable solutions. In particular, we prove identifiability in two extended regimes: (1) multiple point sources with shared intensity ($N \geq 2$), where redundant flux jump conditions over-determine the system, and (2) a downstream species whose source term is the observed precursor density, providing a distributed constraint that breaks the degeneracy. These results provide a theoretical foundation for the application of modern machine learning methods to single-molecule biology.

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MS18

Weak Form Learning for Mean-Field Partial Differential Equations: An Application to Insect Movement

Insect populations subject to epidemic infection, predation, and anisotropic environmental conditions may exhibit preferential movement patterns. Given the virtually random nature of the exogenous factors driving these patterns over short timescales, individual insect trajectories often resemble overdamped stochastic processes. Consequently, data-driven modeling approaches designed to learn effective mean-field governing equations from observed insect populations serve as ideal tools for understanding and predicting such behavior. In this talk, we will summarize recent work extending existing weak-form equation learning techniques to learn effective partial differential equation models for lepidopteran larval population movement directly from sparse experimental data. We demonstrate the utility of the method on an experimental dataset obtained in simulated agricultural conditions.

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MS18

From Static Patterns to Dynamical Systems, One Shot Learning Fro M Collective Behaviors

We develop a learning framework to perform system identification for understanding the observation data of a single snapshot of collective dynamics. Such learning problem can become highly ill-conditioned, and our proposed learning framework is able to handle such ill-conditioning with proper regularization tools. These tools include the incorporation of the empirical distribution of static patterns. We investigate special scenarios of such data, including steady states and scenarios of relative patterns remaining fixed. We provide extensive examples to show the efficiency and effectiveness of our learning.

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MS19

Persistent Homology of Functional Connectivity Predicts Fatigue in Prolonged Wakefulness

We applied topological data analysis on functional connectivity matrices extracted from fMRI data collected across extended wakefulness. Persistent diagrams were computed and compared using the Wasserstein distance. Infradian patterns are observed in the connectivity of the salience and emotion network regions as well as the connectivity between the left and right hemispheres. Total persistence in the frontolimbic region predicted psychomotor vigilance, and the Wasserstein distance between persistence diagrams of the same region in consecutive fMRI sessions predicted subjective fatigue.

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MS19

Ai-Driven Topological Data Analysis of Intracranial EEG in Epilepsy

Epilepsy affects more than 50 million people worldwide and is characterized by recurrent seizures, which reflect time-evolving electrophysiological changes with substantial heterogeneity. Yet most seizure detection approaches rely on signal features and population-level models that do not capture this variability. Topological Data Analysis (TDA) offers a complementary framework for studying such complex systems. Persistent homology (PH) yields scale-invariant descriptors of network structure. We applied PH intracranial electroencephalography (iEEG) signal coupling to classify seizure periods and presented these methods in an integrated platform that enables reproducible TDA workflows alongside machine learning tools targeted for clinician use. We then leveraged large language models (LLMs) for TDA-based seizure classification, marking the first use of TDA for input to multimodal generative AI and highlighting opportunities to integrate semantic reasoning with topology. Further, because PH assumes independent time windows and monotonic filtrations, we apply zigzag PH to model how iEEG changes over time during a seizure. In parallel, we developed an LLM-based patient matching approach that encodes clinical phenotype from discharge summaries and integrates this similarity with zigzag topological descriptors, improving context-aware seizure detection. Together, this work illustrates an AI-driven paradigm for TDA in epilepsy.

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MS20

Geometry of Neural Population Dynamics in Recurrent Networks: Why Linear Theory Fits Nonlinear Data

Recent advances in large-scale neuronal recordings have revealed multi-dimensional structures of population activity beyond traditional averaged descriptions. Understanding how these structures emerge from circuit connectivity is fundamental to comprehending brain function and dysfunction in neurological diseases. The covariance eigenvalue distribution, or spectrum, has been proposed as a robust measure to characterize neural population geometry beyond simple dimensionality (Hu Sompolinsky, 2022). This spectrum can be analytically derived in random recurrent networks and has shown accurate matching to experimental data across brain areas and species, serving as a computational biomarker linking population activity patterns with network connections. However, a theoretical gap exists: the neural network model used to derive the spectrum consisted of minimal, linear neurons. Here we close this gap by studying the covariance spectrum in nonlinear networks and broader dynamical regimes, including chaos. Surprisingly, we find that the spectrum can be precisely understood using equations analogous to linear theory, but with an effective connection strength parameter capturing both synaptic weights and neuronal nonlinearity. This parameter provides unified interpretation for how dimension and spectrum evolve across dynamical regimes and reveals broad near-critical states without fine-tuning. These results offer mechanistic insights into how recurrent synaptic interactions shape collective neural dynamics and provide tools for identifying neural dynamic states.

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MS20

Reconstructing Actin Dynamics of the Leading Edge from Observational Data

Mesenchymal cell migration starts with the protrusion of the cell's leading edge, enabled by the branching growth of the actin network. Two crucial molecular players in protrusion are actin filaments and the Arp2/3 protein complex, the branching agent. Traditionally, protrusion models are intuited from several perturbative experiments. Recent multiplex microscopy imaging data promise to drastically change this paradigm by providing measurements of naturally fluctuating densities of key proteins at the leading edge of unperturbed cells. We report the first attempt to reconstruct the mechanistic protrusion model from such data. We analyze fluctuations of F-actin and Arp2/3 densities and cell edge velocity using phase space and regression analysis to reconstruct linearized stochastic actin-Arp2/3-velocity coupled dynamics. We then build a

nonlinear partial differential equation model of these dynamics based on previous knowledge of this system and parsimony. The resulting model recovers the rates of reactions and mechanical and transport processes in the lamellipodium from a single non-perturbative experiment. The model posits that the only essential nonlinearities in the lamellipodial dynamics stem from the retrograde flow of F-actin. The model suggests that the protrusion is dominated by a damped oscillatory cycle resulting from a combination of positive feedback from Arp2/3 to protrusion velocity and negative feedback from F-actin to the velocity.

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MS20

Generative Learning for Parameter Landscape Beyond Low-dimensionality

Parameter landscapes of biological dynamical systems are notoriously hard to interpret: they are high-dimensional, expensive to probe by simulation, and structured by bifurcations that partition behavior into sharply different regimes. As a result, local optimization or low-dimensional sweeps often miss large portions of the viable set and obscure how robustness emerges from parameter interactions. I present a score-based diffusion (generative) framework that learns the geometry of *viable parameter manifolds* and the organizing *codimension-1 bifurcation skeleton* directly from data, enabling fast exploration beyond low dimensionality. We begin with randomly sampled parameters, simulate the model, and summarize long-term behavior by a small set of indices. Conditioning on target index values, the diffusion model generates new parameters concentrated on the corresponding viable manifold. To learn bifurcation skeletons, we condition on features of invariant sets (equilibria and limit cycles), including spectral and geometric descriptors, to recover the loci where qualitative dynamics change. Results span three systems. For the Lorenz ODE, we reconstruct viable manifolds and the bifurcation skeleton in a 3D parameter space; away from the skeleton, manifolds are highly regular and form parallel, level-setlike sheets across index values. For the Izhikevich neuron model, viable manifolds for diverse spiking patterns reveal local compensation geometry, suggesting a quantitative route to heterostasis: multiple parameters co-vary to preserve function. The diffusion model also learns intrinsic manifold dimension, exposing the effective rank of the parameter-to-index map. Finally, for dsODE (our ODE theory for spiking neural networks), we identify firing-rate viable manifolds in a 12D parameter space that align with EI balance while uncovering previously hidden dependencies; the learned bifurcation skeleton organizes steady activity, gamma/beta oscillations, and multistability. Overall, generative learning provides a principled, scalable lens for mapping mechanism and robustness in complex biological models.

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MS20

Theory and Algorithms for Constructing AI-Based Dynamic Virtual Cells

Artificial Intelligence Virtual Cell (AIVC) is increasingly emerging as a frontier in the interdisciplinary integration of biology and artificial intelligence. Its core vision is to construct digital twins capable of simulating and predicting the dynamic evolution of cellular states, thereby providing computational support for experimental design and mechanistic analysis. We have explored a unified modeling framework that integrates generative artificial intelligence methods and dynamical systems theory. By combining mathematical theories such as Optimal Transport, Schrdinger Bridge, and differential geometry with generative AI techniques like Flow Matching and diffusion models, this framework effectively infers continuous dynamic processes of complex state transitionssuch as cell proliferation, apoptosis, differentiation, migration, and interactionsfrom static, heterogeneous single-cell omics temporal snapshots. Compared to black-box methods, this approach not only exhibits strong generative and generalization capabilities but also offers improved mechanistic interpretability. It enables the generation of cell state data across temporal scales and spatial structures, providing a promising direction for constructing dynamic virtual cell models with interpretability, predictive power, and the ability to integrate biological priors.

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MS21

Branching Under First-Passage Resetting

Many biological replication processes, from cell division to viral lysis, are triggered when an internal stochastic variable crosses a threshold. In this talk, we introduce Branching under First-Passage Resetting, a general framework in which replication events arise endogenously from first-passage dynamics rather than from externally imposed lifetime clocks. We will show that the resulting population dynamics obey an exact renewal equation linking single-trajectory first-passage statistics to the population growth rate. This connection allows us to derive a universal criterion for when stochastic fluctuations actually enhance growth. Furthermore, our framework exposes a fundamental yielddelay tradeoff: because offspring yield is often a function of the first-passage time, longer waiting times increase the yield but delay subsequent replication. Finally, we will demonstrate how our framework allows us to analytically address this optimization problem, ultimately providing a unified probabilistic framework for threshold-driven replication processes.

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MS21

Dynamic Redundancy and Mortality in Stochastic Search

Search processes are a fundamental part of natural and artificial systems. In such settings, the number of searchers

is rarely constant: new agents may be recruited while others can abandon the search. Despite the ubiquity of these dynamics, their combined influence on search efficiency remains unexplored. We will discuss a general framework for stochastic search in which independent agents progressively join and leave the process, a mechanism we term dynamic redundancy and mortality (DRM). Under minimal assumptions on the underlying search dynamics, this framework yields exact first-passage time statistics. It further reveals surprising connections to stochastic resetting, including a regime in which the resetting mean first-passage time emerges as a universal lower bound for DRM, as well as regimes in which DRM search is faster. We illustrate our results through a detailed analysis of one-dimensional Brownian DRM search.

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MS21

Extreme Survival Trajectories for Populations of Identical Random Walkers

A collection of identical and independent first passage times is considered. The problem of finding the slowest out of N such events to occur is called an extreme survivor. Increasing the number of walkers N is equivalent to conditioning on a larger first passage time to reach the boundary. We present a qualitative description of the pathway taken by an extreme survivor by conditioning on $t' < \tau_{\max}^N$ for some fixed $t' > 0$.

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MS21

Extreme First Passage Times with Fast Immigration

Many scientific questions can be framed as asking for a first passage time (FPT), which generically describes the time it takes a random 'searcher' to find a 'target.' The important timescale in a variety of biophysical systems is the time it takes the fastest searcher(s) to find a target out of many searchers. Previous work on such fastest FPTs assumes that all searchers are initially present in the domain, which makes the problem amenable to extreme value theory. In this paper, we consider an alternative model in which searchers progressively enter the domain at some 'immigration' rate, which may be constant, time inhomogeneous, or proportional to the population size. In the fast immigration rate limit, we determine the probability distribution and moments of the k-th fastest FPT. Our rigorous theory applies to many models of stochastic motion, including random walks on discrete networks and diffusion on continuous state spaces. Mathematically, our analysis involves studying the extrema of an infinite sequence of random variables which are both not independent and not identically distributed. Our results constitute a rare instance in which extreme value statistics can be determined exactly for strongly correlated random variables.

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MS22

Adaptive Exponential Integrate-and-Fire Models of the Lateral Superior Olive Exhibit Differences by Firing Type in Sensitivity to Level and Time Difference Cues for Sound Localization

The principal neurons of the lateral superior olive (LSOPNs) compare excitatory inputs driven by the ipsilateral ear and inhibitory inputs driven by the contralateral ear. This gives them intrinsic sensitivity to interaural level and time difference (ILD and ITD) cues used for sound localization. Rate-based ILD encoding and timing-based ITD encoding may benefit from functionally specialized LSOPN populations. Indeed, LSOPNs show two distinct firing types to depolarizing current steps: onset- and multi-spiking. We designed data-driven adaptive exponential integrate-and-fire models with excitatory and inhibitory (E-I) synaptic inputs to test the advantages for encoding of ILDs and ITDs across firing types. We simulated ILDs with E-I event rate differences and ITDs with relative E-I event time shifts. For temporally paired E-I events (analogous to E-I time-locking to discrete click-like transients in natural sounds), all models had some level of sensitivity to both ILDs and ITDs. However, for decorrelated E-I event times (akin to weaker E-I time-locking expected for higher rates of transients and presynaptic jitter), the onset model was mainly ITD-sensitive, whereas the multi-spiking model was mainly ILD-sensitive, but its ITD sensitivity was improved by smaller time constants (tau). We propose that all LSOPNs may encode ILDs and ITDs, but cellular properties like firing type and tau may adjust their cue-sensitivity for robust azimuth encoding over a wide range of stimuli.

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MS22

Computational Modeling to Assess the Functional Roles of the Nuclei of the Trapezoid Body in the Auditory Brainstem

Accurate sound localization depends on precise temporal processing in the auditory brainstem. Besides the sound localization principal nuclei (LSO MSO), the process is tuned by neural inhibition from the medial (MNTB), lateral (LNTB), and ventral (VNTB) nuclei of the trapezoid body. The distinct computational roles of these nuclei remain incompletely understood. We developed a biophysically grounded spiking neuronal network model that encodes auditory nerve firing activity from sound waves and simulates neuronal responses along the afferent auditory pathway. The framework is highly configurable and supports multiple levels of biological detail and flexible synaptic dynamics. This modular design enables systematic probing of nucleus-specific mechanisms underly-

ing binaural processing. Simulations reveal that MNTB provides fast inhibition that sharpens spatial sensitivity and acuity, while LNTB plays a similar role through ipsilateral inhibitory control. VNTB delivers feedforward inhibition that narrows temporal integration windows, enabling higher temporal resolution for sequential encoding of binaural cues. These predictions were tested using in vivo extracellular recordings combined with optogenetic manipulation, showing strong agreement with model simulations across a wide range of test conditions. This modeling framework provides a quantitative and flexible tool for linking cellular mechanism to circuit-level dynamics and system-level auditory processing.

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MS22

The Dynamic Mechanisms Underlying Selective Responses to Time-Varying Inputs

While the properties of intrinsic oscillators subject to periodic input signals are well understood, much less is known about the factors that determine the response precision of excitable units when activated by subthreshold periodic forcing and stochastic noise. One motivation for considering this issue comes from the behavior of medial superior olive (MSO) neurons in the mammalian brain stem, which achieve sound localization by producing spikes at temporally precise phases relative to the periodic sensory signals that drive them, despite jitter in the arrival times of these signals and cycle skipping. To account for this response precision, we introduce the notion of a dynamic threshold curve (DTC), which estimates at each time the effective likelihood that noise will subsequently induce a spike. The DTC summarizes, in a single curve, a representation of the response precision of an excitable model, as we demonstrate by showing that the distribution of spike times produced in this setting is well captured by the first passage time of a simple, Gaussian stochastic process to the distance from the deterministic, forced trajectory to the DTC. We analyze how the properties of an excitable neuron model and its periodic forcing shape the DTC and how the peaks, troughs, and slope of the DTC determine when, and with what precision, model spikes will occur. This work establishes the DTC as a useful tool to explain what properties give rise to the response precision of auditory neurons, as we illustrate in a well-established auditory neuron model.

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MS22

Impacts of Heminode Disruption on Auditory Processing of Noisy Sound Stimuli

Hidden hearing loss (HHL) is an auditory neuropathy characterized by altered auditory nerve responses despite normal hearing thresholds. Recent studies suggest that permanent disruptions to heminode positions in spiral ganglion neuron (SGN) fibers contribute to these deficits, but the interaction between such disruptions and noisy backgrounds remains unexplored. This study uses computational modeling to investigate how noise interacts with peripheral disorders and how deficits propagate to sound localization circuits. We analyzed phase locking of SGN fiber responses to sound stimuli and modeled subsequent effects on interaural time difference (ITD) sensitivity in the medial superior olive (MSO). We found that near-tone-frequency noise disrupted SGN phase locking through cycle-to-cycle variability in spike phases, consistently across tone frequencies. Mild heminode disruption produced frequency-dependent degradation in SGN phase locking, with effects observed only at higher frequencies tested, without reducing overall firing rates. The effects of noise and heminode disruption were additive, with combined exposure leading to reduced ITD sensitivity and large temporal fluctuations at the MSO. Severe heminode disruption, which additionally reduced firing rates, produced profound localization deficits across all frequencies tested. Thus, our model results suggest that noisy environments exacerbate auditory deficits from peripheral disorders implicated in HHL and could impair speech intelligibility by degrading localization.

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MS23

Machine-learning Integration of Clot Growth and Thrombin Generation Simulations Into PK-PD Anticoagulant Models

Clot growth simulations under flow require substantial computational resources, which limits their integration into patient-specific pharmacokineticpharmacodynamic (PKPD) models. In addition, these models often depend on parameters that are not directly measurable in clinical settings. We address these limitations by linking

in vivo computational fluid dynamics (CFD) simulations of clot growth under flow with in vitro thrombin generation (TG) assays through regression-based machine learning (ML). The ML models learn the mapping between the inputs and outputs of both frameworks, enabling direct parameterization of clot growth dynamics using clinically measured TG parameters. We then incorporate the trained ML surrogate into a PKPD model to quantify the effect of anticoagulants, as reflected by drug-induced modulation of TG metrics. This integration allows simulation of patient-specific therapeutic windows for nonvitamin K antagonist oral anticoagulants (NOACs). Because the surrogate model has low computational cost, it supports efficient optimization to identify individualized dosing strategies. As a proof of concept, this work demonstrates that ML can embed high-fidelity, computationally intensive clot growth simulations into clinically tractable PKPD frameworks, enabling rapid and mechanistically informed patient-specific treatment decisions.

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MS23

Data-Driven Modeling of Heart Valve Biomechanics Using Transformer-Based Neural Operators

Fast and accurate estimation of mechanical responses in heart valve leaflets under varying transvalvular pressure loads and material parameters is essential for patient-specific cardiovascular assessment and clinical decision-making. While the finite element method offers high fidelity, its computational cost limits practical use in rapid, multi-query scenarios. We propose a transformer-based neural operator that directly processes complex 3D valve geometries and accommodates variable boundary conditions, jointly predicting displacement, strain, and stress fields in real time. The architecture leverages attention mechanisms to capture long-range spatial dependencies inherent in leaflet deformation, enabling accurate generalization to unseen loading conditions and material parameters. We demonstrate strong performance on both in-distribution and out-of-distribution tasks, achieving real-time inference while maintaining accuracy comparable to finite element simulations. Our approach enables efficient exploration of high-dimensional parameter spaces previously intractable with traditional computational methods.

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MS23

Efficient Modeling of Bio-Molecular Kinetics with Random Features

Metastable states and the conformational transitions in between them are key to understanding dynamical behaviour and function of large-scale molecular systems. By combining basic dimensionality reduction techniques with a state-of-the art approximation of the Koopman operator associated to molecular dynamics simulations (MD), we show that these states and transitions can be analyzed very efficiently based on MD simulation data. To construct the Koopman approximation, we employ a kernel-based method and solve the associated matrix equations using random Fourier features, leading to accurate solutions while maintaining low computational effort. On a benchmark set of fast-folding proteins, we demonstrate that key properties such as transition timescales, free energies, secondary structure elements and hydrogen bonding patterns can be computed with remarkable robustness across hyperparameter regimes.

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MS24

Quantitative Systems Pharmacology Model of B-Cell Dynamics for B-Cell Targeting Therapies.

B cell targeting therapies represent a promising strategy for autoimmune diseases driven by pathogenic immunoglobulin production. We have developed a quantitative systems pharmacology (QSP) model to mechanistically describe B cell dynamics across developmental and functional compartments. The model integrates B cell maturation and differentiation processes, interactions between multiple B cell subpopulations (nave B cells, memory B cells, plasma blasts and plasma cells), as well as T follicular helper cell-dependent germinal center reactions and immunoglobulin production processes. By capturing B cell and immunoglobulin dynamics, the model enables implementation of different mechanisms of action (MoA) for B-cell targeting therapies. Preliminary virtual populations for healthy individuals and patients with rheumatoid arthritis or systemic lupus erythematosus were generated using published clinical data from several B-cell targeting therapies including anti-CD20, anti-CXCR5, anti-APRIL and anti-APRIL/BAFF. Simulated B cell subset and immunoglobulin profiles provide a quantitative framework to assess therapeutic efficacy to explore and optimize dosing regimens for B cell targeting therapies.

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MS24

Making Math into Medicine: Math Application to and Impact on the Pharmaceutical Industry

A broad range of health-care industries are applying Mathematical and Data Sciences, informing decisions by generating data and transforming them into information and human knowledge. The data are increasingly across disparate domains, scales of time and space, and sources. As the complexity and quantity of available data continue to expand, using them will require an expanded collection of capabilities along with advances in analyses to ascertain trustworthiness of the resulting model-based conclusions. A brief overview will be provided for applications

from healthcare sectors such as pharmaceutical, biomedical equipment (instrumentation and prostheses), and digital health. Therapeutic and prophylactic examples will show how quantitative approaches are driven by the underlying scientific questions. The examples will illustrate how these approaches reveal, enable, and inform cross-disciplinary collaboration on assumptions, experimental design, and scientific strategy. The presentation will touch on a broad range of fields impacting healthcare such as differential and partial differential equations, visualization, pattern recognition ML/AI, network inference, probability, (stochastic) optimization, numerical analysis and simulation, discrete mathematics, control theory, dynamical systems, inverse problems, image processing, natural language processing, and topology.

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MS24

Mathematical Modeling As a Common Language: Seamless Integration from Basic Biological Principles to Clinical Practice and Drug Development

This panel discussion will explore how mathematical models can serve as a common language bridging basic science, clinical medicine, and drug development. Together with the panelists, we will examine strategies to dissolve disciplinary boundaries through quantitative thinking. We will discuss how mathematical frameworks not only transcend specialized domains but also facilitate the translation of fundamental discoveries into actionable, real-world decisions. Special emphasis will be placed on identifying optimal levels of abstraction that balance mechanistic fidelity with practical relevance to both clinical and translational settings. The discussion will also address key technical challenges, including how complex mechanistic models can be synergistically integrated with modern AI and data-driven approaches to generate reliable and interpretable predictions. Furthermore, we will consider the structural and institutional conditions required to establish mathematical modeling as a standard component of societal implementation, including academiaindustry collaboration and the development of next-generation quantitative scientists. Through this dialogue, we aim to articulate a vision in which mathematical sciences truly bridge foundational research and the frontlines of medicine and drug development.

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MS25

GBM-FORECAST: Predicting recurrence in glioblastoma using serial white blood cell counts

Glioblastoma is an aggressive cancer with poor progression-free survival. Rapid recurrence detection is critical to enhance the benefits of secondary treatment. White blood cell (WBC) counts and WBC-derived markers are known recurrence biomarkers, but prior work has treated them as static, single risk assessments, often using data far from recurrence. However, WBC counts are not static and are measured throughout follow-up. In this work, we consider whether longitudinal WBC data contain predictive signal and their potential as dynamic recurrence risk biomarkers. Training random survival forest models to predict recurrence, we found low prediction error (mean integrated Brier score of 0.05 ± 0.03) and moderate ability to distinguish early and late recurring patients (integrated dynamic AUC of 0.65 ± 0.14), supporting the presence of informative signal in the data. Moving to model application, we calculated a near-term, recurrence risk score, the GBM-FORECAST score. Despite the absence of imposed temporal structure, we observed quantitative cross-patient risk score patterns: an initial increase, followed by a decline, and subsequent increase in score through the end of follow-up. These transition points coincide with the shift from chemoradiotherapy to maintenance chemotherapy and the onset of increasing recurrence rate. While the origin of these patterns requires further study, they suggest a connection between counts, treatments, and disease dynamics.

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MS25

Personalization of Medical Digital Twins

A medical digital twin (MDT) is a virtual representation of disease which is updated in real-time. Measurements (such as that of heart rate, blood pressure, cell count, etc) are collected from the patient and are used to construct models which form the foundation of MDTs. Medical Digital Twins are useful as they may be simulated forward in time to predict disease outcomes. For example, there is current interest in the use of MDTs to predict an optimal chemotherapy schedule for Acute Myeloid Leukemia (AML) patients. We develop novel methods to recover and personalize parameters of models relevant to MDTs. In doing so, selected model parameters are decomposed into a common and personalized component. The common component represents a commonality between patients and is estimated once, while the personalized component is patient-specific and may be updated with new measurement data. We then formulate and solve a minimization problem to recover the components. Afterwards, the methods are applied to synthetic data from known dynamical models such as logistic growth with interventions and Lotka-Volterra. We also apply our personalization method to a model that has been parameterized with patient data from AML (Acute Myeloid Leukemia).

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MS25

Toward Development and Deployment of MRI-guided Digital Twins for Neoadjuvant Therapy of Triple Negative Breast Cancer

We have established practical cancer digital twins to address the unmet need of patient-specific treatment tailoring for triple-negative breast cancer (TNBC). The core of the digital twin is a biology-based mathematical model calibrated to early monitoring MRI scans to predict patient-specific response to neoadjuvant chemotherapy (NAC) (AUC=0.82; n=105). We used each patients digital twin to theoretically optimize outcome by identifying optimal A/C-T schedule from 128 clinically-feasible options. The personalized optimization yielded a significant improvement in complete response rate of 20.95-24.76%. Retrospective validation was conducted by virtually treating the twins with AC-T schedules from historical trials and obtaining identical observations on outcomes: bi-weekly A/C-T outperforms tri-weekly A/C-T, and weekly/bi-weekly T outperforms tri-weekly T. More recently, we designed an interactive interface for clinicians to conveniently review digital twin outputs, including summary of predicted patient-specific responses to three treatment options (i.e., default, escalation, de-escalation) and the visualization of predicted tumor dynamics. Efforts on structured interviews to collect clinician feedback on the interface design and output utility in decision-making are ongoing. This multi-year project has been making fundamental progress to enable clinically practical implementation and validation of digital twins for personalizing breast cancer care.

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MS25

Schedule Optimization for Treatment of Acute Myeloid Leukemia with Venetoclax/Azacitidine using Digital Twin Models

Acute myeloid leukemia (AML) is a complex and multifaceted hematological malignancy with a low 5-year survival rate. Current treatment protocols for AML tend to depend on standard protocols with dependence on clinician judgment and discretion, in particular with the timing and dosage of treatments. The development of medical digital twins has the potential to improve AML treatment by simulating treatment programs in silico, allowing the design of patient-specific treatment schedules that are optimal for both halting disease progression and reducing treatment toxicity. We have developed a computational framework for AML treatment schedule optimization. It is built on previously developed digital twin models of AML coupled with a multiobjective optimization method and uncertainty quantification. The treatment schedules are designed to be Pareto-optimal with regards to both disease progression (as represented by blast percentage) and treatment toxicity (as represented by neutrophil count). Using the VenEx clinical trial data (NCT04267081), we tested our framework by identifying the Pareto frontier of optimal treatment schedules for specific treatment cycles. To evaluate the optimized treatment schedules, we compared these schedules with the actual treatment schedules. Our results suggest that patients with actual treatment durations that are more similar to the optimized schedules have more favorable survival.

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MS26

Systems Immunology at the Maternal-Fetal Interface

Systems biology and mathematical modeling are uniquely positioned to study normal and pathological functions of the immune system across time and space. Here, we use a combination of multiplexed experimental measurements with computational modeling (mechanistic modeling, statistical learning) to study immunity at the fetal-maternal interface. Newborns are vulnerable to infections, and receptor-mediated transfer of maternal IgG antibodies passively immunizes neonates against pathogens previously encountered by the mother. To identify maternal and placental regulators of IgG transfer, we used a multi-pronged systems biology approach. We quantified placental Fc gamma receptor (FcγR) expression in

paraffin-embedded tissue using multiplex immunofluorescence histology (mIFH). A mechanistic model of placental IgG transfer, informed by single-cell RNA sequencing and mIFH, revealed key drivers and was validated with in vitro experiments using human umbilical vein endothelial cells. To identify immunization windows of opportunity to maximize IgG transfer, we integrated a model of vaccine-induced B cell activation and antibody production into the mechanistic model. The model indicated the second trimester is optimal to maximize vaccine-induced IgG transport to newborns. We conclude that integrated mathematical modeling and experimental measurements of human samples can guide precision prenatal immunization by tuning vaccine timing, dosage, and adjuvant.

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MS26

Multiscale Model of Uterine Adaptation During Pregnancy

The uterus grows and remodels to support the fetus during pregnancy, remaining relaxed to avoid premature contractions and preterm birth (PTB), which affects 10% of births worldwide. Mechanics and hormones drive uterine growth, remodeling, and contraction. Here, we develop a multiscale model (MM) of the pregnant mouse uterus by coupling a tissue-level finite element model (FEM) with an intracellular signaling network model (SNM) to understand mechanical and hormonal interactions over 19 days of a mouse pregnancy. We compare our MM predictions to a previous FEM investigating the mechanics of uterine growth and remodeling. While the MM overpredicted growth in early gestation compared to known uterine weight changes, it correctly predicted the increase between gestation days (d)6-14. These growth predictions resulted in lower elastic stretch between d0-8 but agreed between d10-15 compared to our previous FEM. The MM predicted Cauchy stresses were significantly higher after d11 compared to our previous FEM. Our accurate growth predictions demonstrate the feasibility of our MM model to simulate hormonal and mechanical interactions that drive uterine adaptations. Here, the initial decrease in elastic stretch resulted from tissue growth due to increasing hormone levels in early pregnancy. Future work will include further calibration, expanding the SNM, and a more accurate uterine geometry in the FEM, ultimately using the MM as a tool for understanding the mechanisms driving PTB.

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MS27

Heterogeneity in Epidemic Dynamics: Modeling Disease Spread in Complex Populations

Understanding how population heterogeneity shapes epidemic dynamics is essential for accurate disease forecasting and effective intervention design. In this talk, I will explore how environmental, demographic, behavioral, and mobility-driven heterogeneity shapes patterns of disease transmission within complex populations. Using both mathematical and data-driven modeling frameworks, we show that heterogeneity can significantly alter outbreak size, timing, and persistence compared to homogeneous assumptions, often amplifying both local and systemic risks. These findings highlight the need to incorporate population-level complexity into epidemic models to improve prediction accuracy and inform targeted public health strategies.

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MS27

Modeling Reveals Azd5582-Reactivated Cells Differ from Productively Infected Cells

AZD5582 (AZD) is a SMAC mimetic that reverses latency by activating the non-canonical NF-?B pathway and can trigger 3-4 logs transient viremia in ART-suppressed macaques. Yet, the reductions in the latent reservoir have been modest. Detailed analysis of the mechanisms is difficult to study due to low amplitude and fluctuating viral load signals. We compiled longitudinal measurements from published ART-suppressed, SIV-infected rhesus macaques treated with AZD alongside other interventions, e.g., SIV Env-specific monoclonal antibodies, the IL-15 superagonist N-803, and/or anti-CD8a depleting Ab MT807R1 (n=29). We fit an ensemble of mechanistic viral-dynamics models to plasma SIV RNA and SIV CA-DNA using a nonlinear mixed effect modeling framework. The model ensemble recapitulated AZD5582-associated reactivation patterns in plasma SIV-RNA and SIV DNA. Across best-fit models, AZD-reactivated cells exhibited reduced virion output and lower death rate by 32 - 89%. Mechanistic modeling explains the limited reservoir reduction despite robust AZD-mediated latency reversal: reactivated cells behave differently from fully productively infected cells and pass through a temporary refractory state. The modeling framework provides a quantitative basis for optimizing AZD-based combinations and other drugs that target the non-canonical NF-?B pathway (e.g., Ciapavir) in future macaque and clinical studies.

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MS27

Resolving Gradient Pathology in Physics-Informed Epidemiological Models

Physics-informed neural networks (PINNs) are increasingly used in mathematical epidemiology. However, training these hybrid networks is often unstable due to competing optimization objectives. The gradient vectors derived from the data loss and the physical residual often point in conflicting directions, leading to slow convergence or optimization deadlock. While existing methods attempt to resolve this by balancing gradient magnitudes or projecting conflicting vectors, we propose a novel method, conflict-gated gradient scaling (CGGS), ensuring stable and efficient training. This method utilizes the cosine similarity between the data and physics gradients to dynamically modulate the penalty weight. Unlike standard annealing schemes that only normalize scales, CGGS acts as a geometric gate: it suppresses the physical constraint when directional conflict is high, allowing the optimizer to prioritize data fidelity, and restores the constraint when gradients align. We prove that this gating mechanism preserves the standard $O(1/T)$ convergence rate for smooth

non-convex objectives, a guarantee that fails under fixed-weight or magnitude-balanced training when gradients conflict. We demonstrate that this mechanism autonomously induces a curriculum learning effect, improving parameter estimation in stiff epidemiological systems compared to magnitude-based baselines. Our empirical results show improved peak recovery and convergence over magnitude-based methods.

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MS28

Seasonal Epidemic Dynamics of Rotavirus-Norovirus Co-Infection with Deterministic and Stochastic Extensions

Rotavirus and norovirus are principal viral agents of acute gastroenteritis and are primarily transmitted through close contact. Although each virus can independently sustain outbreaks, simultaneous infection is associated with more severe outcomes, particularly in pediatric populations. To investigate these interactions, we develop a continuous-time deterministic SIR co-infection model to analyze the prevalence of rotavirus and norovirus and to assess how seasonal variation in transmission influences epidemic dynamics and co-infection burden. We conduct equilibrium analysis and numerical simulations to characterize the behavior of the individual diseases and their co-circulation. Both basic and seasonal reproduction numbers are derived, and sensitivity analyses are performed to identify key parameters driving infection dynamics. Seasonal transmission is modeled using sinusoidal forcing motivated by observed winter peaks of both viruses in temperate regions. We further explore how changes in the amplitude, timing, and alignment of seasonal transmission peaks affect long-term dynamics. Our published results show that transmission rates strongly influence infection prevalence and outbreak magnitude. Increasing seasonal amplitude significantly alters both basic and periodic reproduction numbers and drives pronounced seasonal epidemic patterns. Moreover, shifts in the relative timing of rotavirus and norovirus peaks substantially affect co-infection outcomes. When seasonal peaks align, higher maximum and cumulative co-infection levels are observed, whereas misalignment leads to reduced and more variable co-infection burdens. These findings demonstrate that seasonal forcing not only governs outbreak timing and intensity but also plays a critical role in shaping co-infection dynamics. This modeling framework provides insight into how interacting pathogens respond to seasonal variability and highlights mechanisms underlying pediatric co-infection burden. Future work will extend this framework to incorporate vaccination effects, alternative seasonal forcing structures, and stochastic formulations, such as continuous-time Markov chain models, to capture random fluctuations in transmission and better reflect the variability observed in real populations.

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MS28

Bifurcations in Prey-Predator Systems with Additional Food

The concept of additional food suggests that providing predators with supplementary resources can improve their ability to regulate pest populations. In this study, we analyze a predator-prey model that incorporates both additional food supplementation and intraspecific competition among predators. We focus on the systems bifurcation structure and identify parameter regimes in which the interior equilibrium undergoes a higher-codimension Bogdanov-Takens bifurcation. We derive analytical conditions for the critical parameter values and show that the equilibrium corresponds to a higher-codimension cusp singularity. These results offer insight into how additional food and predator competition together influence complex population dynamics and have potential implications for sustainable pest management strategies.

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MS28

Improving *Wolbachia*-Based Control Programs in Urban Settings: Insights from Spatial Modeling

Arboviral diseases remain a major public health concern, particularly in tropical and subtropical regions where mosquito populations thrive. One promising strategy to curb transmission is the release of *Aedes aegypti* mosquitoes infected with *Wolbachia*, a bacterium that reduces their ability to spread viruses. However, past large-scale releases have not always been successful, especially in complex urban settings, where restricted access to certain areas often leads to infection establishment failures and wasted resources. To address this, we developed a partial differential equation model that simulates how *Wolbachia*-infected mosquitoes are established in different urban environments. We also explored strategies to improve their success under constraints on release size and the efficacy level of insecticide used for pre-release interventions. Our findings suggest that targeted releases are most effective in areas with limited mosquito movement without additional insecticide use. In higher-dispersal areas, reducing at least 35% of wild mosquitoes before release significantly improves establishment within nine months. Additionally, distributing releases over 2–5 weekly batches enhances success more than a single large release, even without other interventions. These findings offer practical insights for designing cost-effective and efficient Wolbachia-based mosquito control programs, reducing the burden of mosquito-borne diseases on vulnerable communities.

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MS29

Mechanisms of Thrombin Inhibition by Protein S and the Tfpia-FV-Short-Protein S Complex

Blood coagulation is critical for an effective clotting response. Protein S (PS) is an important anticoagulant implicated in pathological bleeding and thrombosis. PS binds with two other coagulation proteinsTFPIα and factor V shortto form the protein S complex (PSC), which enhances anticoagulant function by incompletely understood means. To investigate, we extend an experimentally validated mathematical model of blood coagulation and platelet deposition under flow by adding new proteins, including PSC, and their reactions. We find that PSC accumulates on platelets far more than expected, and that de-

termining the affinity for PSC binding with fXa is necessary to understand PSC's anticoagulant properties. We show that deficiencies in PSC can rescue thrombin production in several bleeding disorders, including severe hemophilia A.

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MS29

The Gift That Keeps on Giving: A Mechanistic Model of Flow-Mediated Coagulation and Its Lasting Impact

This talk celebrates Aaron Fogelsons contributions to blood coagulation and the lasting influence of his mechanistic mathematical model of flow- and surface-mediated coagulation and platelet deposition, developed more than two decades ago. The model was the first to explicitly couple flow with coagulation reactions in plasma and on platelet and subendothelial surfaces, revealing how transport and surfaces jointly regulate thrombin generation. The model uncovered novel system behaviors, including sharp TF dependent threshold behavior of thrombin, flow-dependent regulation, and the dominant role of platelet deposition in attenuating subendothelial reaction activity. Over time, this modeling framework evolved alongside newly discovered biological mechanisms, incorporating endothelial cell reactions, feedback through factor?XI, initiation of venous thrombosis, and disease specific perturbations. These extensions illustrated how careful mechanistic modeling can guide experimental investigation. I will discuss how these studies demonstrate that models capturing biological mechanism and context can generate meaningful hypotheses, deepen our understanding of coagulation, and provide insights that continue to inform the field. Applications of this model will be further highlighted in subsequent talks in this session.

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MS29

Modeling the Role of Platelet-Released Polyphosphates in Tissue-Factor-Initiated Coagulation under Flow

Activated platelets release polyphosphate (polyP), a linear polymer of inorganic phosphate residues. Experiments performed under no-flow conditions show that polyP alters the kinetics of tissue factor (TF) pathway reactions, accelerating FXI activation by thrombin and FV activation by FXa and thrombin, and may impact inhibition by tissue factor pathway inhibitor α (TFPIα). How polyP influences this pathway in conjunction with platelet deposition under flow remains understudied. We extended a previously validated mathematical model of platelet deposition and coagulation under flow to examine polyP-mediated effects following a small vascular injury during intravascular clotting. Simulations varied TF surface density, wall shear rate, and plasma TFPIα concentration. PolyP shifts the threshold TF density for a thrombin burst to lower TF densities. For TF densities above this threshold, polyP shortens the lag time to thrombin generation. Although no explicit effect of polyP on TFPIα function was included in the model, thrombin generation was much less sensitive to TFPIα concentration with polyP, in a TF-dependent manner. Relative contributions of accelerations of FV and FXI activations depend on incompletely known enhancements by polyP. The experimentally observed influence of polyP on TFPIα function may arise indirectly from accelerated FV and FXI activation, with the dominant effect from accelerated conversion of FV to FVa by thrombin.

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MS29

Computationally Driven Discovery in Coagulation

Mathematical models grounded in biophysical mechanisms and validated against experimental data can serve as engines for hypothesis generation and discovery. By systematically varying inputs and analyzing outputs, models generate synthetic datasets that reveal non-intuitive relationships and identify candidate modifiers of system behavioreven when experimental observations are sparse or incomplete. In this talk, I will illustrate these principles through flow-mediated coagulation modelinga field to which Aaron has made pioneering contributions. I will

show how computational perturbation of clotting factors and inhibitors identified key modifiers of thrombin generation and bleeding severity in hemophilia. These predictions guided targeted experiments that confirmed the model's hypotheses, exemplifying Aaron's vision of mathematical models as drivers of discovery that transform mechanistic understanding into predictive insight and uncover previously unrecognized regulators of disease phenotypes.

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MS30

Understanding Developmental Changes in Human Sleep: A Mathematical Modeling Approach

Sleep behavior undergoes substantial reorganization during early childhood, as many children shift from a daily nap and nighttime sleep to a single consolidated nocturnal episode. This developmental change is gradual and heterogeneous, with considerable variability in both timing and patterning. In this talk, we introduce a neurophysiologically based mathematical model of the sleep-wake network that couples arousal circuitry with circadian and homeostatic processes. Using longitudinal and cross-sectional sleep data from preschool-aged children, we calibrate the model to capture representative dynamics of habitual nappers and children who have transitioned to consolidated nighttime sleep. We then explore how gradual changes in key model parameters lead to transitions from biphasic to monophasic sleep. Through bifurcation analysis and numerical simulation, we characterize distinct transition pathways, such as abrupt versus gradual nap loss. These results provide a mechanistic framework for understanding individual differences in nap cessation and suggest how environmental factors, such as light exposure and schedule constraints, may modulate the stability and timing of developmental sleep transitions.

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MS30

Infraslow Rhythms in NREM-REM Sleep Cycling

During sleep, the mammalian brain alternates between two major brain states, rapid eye movement (REM) and non-REM (NREM) sleep. Recent work has shown that the electroencephalogram (EEG) during NREM sleep in both humans and mice shows a pronounced infraslow (50 s) modulation in the s (10-15 Hz) power range. This infraslow s power (ISP) rhythm is strongly reflected in the firing activity of brainstem REM sleep-regulatory areas such as the dorsomedial medulla (dmM) and the periaqueductal gray (PAG) areas. Importantly, transitions from NREM to REM sleep and spontaneous awakenings are synchronized with the ISP rhythm, suggesting that the rhythm plays a crucial role in shaping NREM-REM sleep cycles and overall sleep architecture. Recent recordings of brainstem neural activity have identified subpopulations of REM sleep-activated and -inhibited neurons with opposing infraslow oscillatory activity suggesting mutually inhibitory interactions. We have developed a mathematical model of REM sleep regulatory circuits in the brainstem to analyze how infraslow rhythmic dynamics and slow ultradian processes that promote REM sleep combine to govern NREM-REM sleep cycling and the temporal architecture of sleep.

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MS30

Infraslow Oscillations and the Dynamics of Noradrenaline

Wake, rapid eye movement (REM) sleep, and non-REM (NREM) sleep are characterized by differential release of neuromodulators such as noradrenaline (NE). The noradrenergic locus coeruleus (LC) promotes wakefulness and exhibits state-dependent changes in neuronal activity and NE release. Recent experimental advancements have described the LC-NE system with high temporal resolution and refined our understanding of how LC activity changes with behavioral state. Specifically, LC activity and NE release are highest during wakefulness, but they vary with attention and activity level. In NREM sleep, LC activity is phasic and drives infraslow extracellular oscillations in NE. During REM sleep, LC activity ceases, and extracellular NE decays slowly until the offset of REM sleep. In previous work, we developed a firing rate model formalism that describes both firing rate and associated neurotransmitter release. In current work, we refine this formalism to develop a data-driven model of LC-NE dynamics.

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MS30

From Blackboard to Bedside: Translating Mathematical Sleep Models into Samsung Galaxy Watch

Mathematical models of sleep regulation, rooted in dynamical systems theory, have long explained how homeostatic sleep pressure and circadian rhythms shape human sleepwake patterns. However, translating these mechanistic models from controlled laboratory settings into real-world, large-scale applications remains a major challenge. In this talk, I present how physiologically grounded sleep models were integrated with wearable sensor data to power sleep analytics in the Samsung Galaxy Watch. By combining dynamical modeling with machine learning, we infer latent biological statessuch as sleep pressure and circadian phasefrom noisy, free-living data. This work illustrates how mathematical theory can move beyond the blackboard to become an engine for scalable digital health innovation.

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MS31

Intrinsic Cellular Organization Shapes Rhythmogenesis and Modulatory Responses in Respiratory Networks

The preBtzinger complex (pBC) in the mammalian brainstem generates inspiratory rhythm. Experimental studies have identified two intrinsic biophysical mechanisms, a persistent sodium current (I_{NaP}) and a calcium-activated non-selective cation current (I_{CAN}), as important contributors to rhythm and pattern generation. Although I_{CAN} modulation is known to have differential effects on different intrinsic firing phenotypes in the pBC, including intrinsic bursting pacemaker neurons and silent followers, its network-level consequences in heterogeneous populations remain poorly understood. Here, using a computational model of a synaptically coupled excitatory pBC network, we show that I_{CAN} can exert fundamentally different effects on network amplitude and synchrony depending on how it is expressed across intrinsic phenotypes. In networks with uniformly distributed intrinsic properties, population activity amplitude shows minimal sensitivity to I_{CAN} modulation. In contrast, when intrinsic properties are organized into distinct rhythogenic and pattern-forming subpopulations, the same modulation yields pronounced changes in network dynamics, despite comparable overall parameter ranges. Thus, the network-level effects of I_{CAN} depend critically on the structural organization of intrinsic cellular properties across the population. By combining large-scale simulations with dynamical systems analysis, we uncover the mechanisms underlying this differential modulation. Together, our findings highlight the organization of intrinsic cellular properties as a key determinant of circuit robustness and flexibility in generation and modulation of respiratory rhythms.

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MS31

Adaptation Via Integral Control in Engineered Biomolecular Networks

Achieving robustness to environmental perturbations remains a major challenge for synthetic genetic circuits. While integral controllers have been widely adopted in many engineering domains, it has been challenging to realize them inside living cells because molecule dilution resulting from cell growth causes integrator leakiness. In this talk, I will introduce biomolecular circuit architectures that can achieve quasi-integral control, wherein the effect of dilution is mitigated by virtue of time scale separation. I will illustrate how regular and singular perturbation theory can be applied to prove asymptotic adaptation to constant and slowly changing disturbances. I will then provide experimental results showing the performance of these controllers in bacterial and mammalian cells. I will finish the talk highlighting open questions still remaining regarding global stability properties of these control architectures.

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MS31

From Spike Shape to Burst(lets): Activity-Dependent Control of Respiratory Rhythm and Pattern Generation

A central question in respiratory neuroscience is how neurons in the preBtzinger complex generate and control the rhythmic patterns underlying breathing. Recent work has shown that a neuron's ability to exhibit intrinsic bursting can be altered through modulation of its spike shape [Phillips et al., PNAS, 2024], yet the underlying mathematical mechanisms remain largely unexplored. In this study, we use mathematical modeling to show that: (1) tuning specific spike shape features regulates intrinsic bursting by altering the bifurcation structure of a neuronal model, and (2) time-dependent changes in spike shape, driven by ongoing neural activity, interact with the gating dynamics of the persistent sodium current (I_{NaP}) to enable activity-dependent transitions between tonic spiking and bursting. In an isolated neuron, this mechanism produces ramping burst patterns, where slow tonic spiking gradually accelerates into a burst. Such patterns are typically attributed to emergent network properties rather than intrinsic cellular dynamics. Surprisingly, when this mechanism is introduced into a network model, spike shape dynamics gate the transition from low- to high-amplitude network oscillations, analogous to burstlets and bursts. Our findings provide an alternative mechanistic framework explaining how activity-dependent spike shape dynamics can contribute to the emergence of ramping patterns and burstlet/burst dy-

namics at both cellular and network levels.

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MS31

Modeling and Analyzing Pedunculopontine Neurons and the Impact of Their Projections on Respiratory Patterning

We developed a conductance-based model of pedunculopontine nucleus (PPN) neurons in the motor brainstem that receive basal ganglia input and project to the medullary respiratory centers. We leverage patch-clamp data to ensure our PPN model, consisting of a system of nonlinear ODEs, reproduces the diverse activity patterns observed experimentally in response to various forcing signals applied within this nucleus, including post-inhibitory rebound and facilitation, transient low-threshold activity and low gamma-band oscillations. Using a multiple-timescale framework, we leverage bifurcation analysis to analyze how distinct ionic gating mechanisms and intracellular calcium concentrations shape these transient dynamics. Finally, we examine how these intrinsic firing properties may influence respiratory rhythms.

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MS32

Weak-form Upscaling of Agent-Based Models

Agent-based models (ABMs) are a flexible framework for simulating complex biological systems that are often difficult or impossible to model with traditional methods. However, their computational cost and inherent stochasticity limit their utility for inference. Classic compartmental models like the Susceptible-Infected-Recovered (SIR) model are deterministic and analytically tractable, but they rely on significant simplifying assumptions. We employ weak-form sparse identification of nonlinear dynamics (WSINDy), a data-driven algorithm for model selection, in order to infer deterministic mean-field ordinary differential equations (ODEs) from SIR-type ABMs with multiple levels of population mixing and distributed infectivity. We study convergence of the ABM processes to the learned equations, contrasting it with the classical SIR dynamics, and characterizing the deviations arising as a result of multi-scale interactions and heterogeneous transmission rates. The results demonstrate that WSINDy is able to recover deterministic mean-field equations from stochastic simulations that differ from the traditional mean field limits of interacting particle systems. This work demonstrates the usefulness of WSINDy for coarse-graining ABMs in order to find interpretable and computationally efficient lower-order models of complex biological systems.

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MS32

Integrating Weak Form Equation Learning Within a Bayesian Hierarchical Framework for Species Distribution Modeling

The Douglas-fir tussock moth is an ecologically harmful and thus economically significant native defoliator to the western United States and parts of southern British Columbia. Modeling their evolving species distribution can help inform forestry management in order to limit the scope and impact of their defoliating outbreaks. The forestry service has curated data documenting their boom and bust outbreak cycles which shows population peaks every seven to ten years, often corresponding to significant defoliation. We look to incorporate weak form equation learning into the Bayesian hierarchical framework in order to create a spatiotemporal model for these population dynamics. This would allow us to create a flexible species distribution model which can account for sources of uncertainty and noise common in ecological processes while incorporating outside knowledge. The ultimate goal of this modeling approach is to facilitate efficient model learning and parameter inference, as well as robust prediction and control of insect outbreaks under climate change.

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MS32

Weak Sindy for Identification and Parameterization of Transport Models for Interstitial Fluid Flows in Solid Cancers

Interstitial fluid flow is integral to the study of solid tumors, characterizing transport phenomena including advection and diffusion, and perfusion in vivo. Historically, blood perfusion was measured by fitting compartmental ODE models to dynamic contrast-enhancement data, obtained from MRI. However, as dynamic MRI is inherently noisy, and as transport is more accurately described as a PDE, we utilized Weak SINDy for PDEs, developed by Messenger and Bortz, to directly quantify interstitial fluid flow in aggressive brain tumors. As both cancer and thera-

peutic cells utilize chemotaxis and mechanotaxis as mechanisms for invasion and transport, this methodology allows us to study these phenomena non-invasively, in vivo. Additionally, weak SINDy is computationally efficient, accurate, and robust to the noise inherent to dynamic MRI. We validate our measurements against hydrogel microfluidics, histological perfusion measurements in vivo, and tumor invasion predictions in a mouse model of brain cancer. We also apply this framework to patient-specific fluid flows in a clinical trial of CAR-T therapy for aggressive brain cancer, demonstrating that fluid flow quantification reveals physiological mechanisms underlying individual patient responses to CAR-T treatment.

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MS33

Model discovery across parameter space for biological systems

Agent-based models (ABMs) are a powerful means of understanding self-organizing biological systems, but they are computationally intensive and often not analytically tractable. Here, we draw on methods from equation learning (EQL) to derive continuum models from ABM data. We are particularly interested in multi-experiment EQL, which allows to learn models that generalize across parameter space. We demonstrate these methods by learning continuum models from a noisy birthdeath mean-field model and from an on-lattice agent-based model of birth, death, and migration with spatial structure, often used to investigate cell biology experiments. We find that the methods proposed can be effective in recovering parameters from agent-based simulations.

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MS33

Data-Driven Extensions to An Ensemble Kalman Filter-Based Algorithm for Personalizing Agent-Based Models

A key challenge in applying computational models in biomedicine is the process of dynamically calibrating these models to individual patients using data collected over time. This calibration is vital for improving model-based predictions and enabling personalized medicine. Biomedical models are often complex, incorporating multiple scales of biology and both stochastic and spatially heterogeneous elements. Agent-based models (ABMs), which simulate autonomous agents such as cells, are commonly used to capture how local interactions affect system-level behavior. However, no standard personalization methods exist for these models. The main challenge is bridging the gap between measurable macrostates (e.g., blood pressure, heart rate) and the detailed microstate data (e.g., cellular processes) needed to run the model. In this talk, we will discuss algorithms that we are developing to address this issue broadly. We build on prior work in which we formulated an algorithm that applies the ensemble Kalman filter, a classic data assimilation technique, at the macrostate level. We link the Kalman update at the macrostate to corresponding updates at the microstate level, ensuring that the resulting microstates are compatible with the desired macrostates and consistent with the models dynamics. This approach improves the personalization of complex biomedical models and enhances model-based forecasts for individual patients.

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MS33

Multi-Objective Bayesian Inference in a Stochastic Agent-Based Model of Zebrafish Pattern Formation Via Topological Data Analysis

In many biological settings, agent-based models provide a natural framework for capturing stochasticity and individual-level interactions amongst large number of cells. However, inferring the parameters in such models poses significant challenges that limit the predictive power of these models. We demonstrate that combining topological data analysis with approximate approximate Bayesian computation is a computationally feasible approach to addressing these challenges. In our study, we focus on an existing agent-based model of pattern formation in zebrafish skin, and we show how to estimate parameters and perform identifiability analysis in this complex, stochastic model. In particular, we show how to use multi-objective inference to combine multiple biologically meaningful summaries of model output to be able to accurately determine parameter values.

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MS33

Integrating Topological Data Analysis and Mathematical Modeling to Characterize Murine Tumor Growth and Angiogenesis

In 2019, Hormuth II et al. developed and validated a family of coupled PDEs that use non-invasive imaging data of C6 gliomas to forecast the spatial-temporal evolution of murine tumor and blood volume. While such models capture key biophysical processes, accurate prediction typically requires careful parameter calibration to faithfully reproduce experimental observations. Topological data analysis (TDA) offers a framework to support this calibration by characterizing shape in spatial data. Persistent homology, the most prominent method in TDA, quantifies topological features such as connected components and loops across multiple scales (see e.g., [Edelsbrunner, Harer, 2010]). In angiogenesis research, TDA has recently been used to summarize vascular network morphology based on experimental data in Stolz et al. (2022), while McDonald et al. (2025) and Nardini et al. (2021) applied TDA for model selection and parameter stratification exclusively, however, relying on simulated data. In this talk, I present novel ongoing work of bridging reactiondiffusion models of tumor growth and angiogenesis to experimental data with TDA. By providing explicit and interpretable summaries of spatial morphology, TDA facilitates parameter selection and tuning. Preliminary results demonstrate the potential of this approach, as extracted topological features successfully distinguish necrotic from non-necrotic murine tumor samples [Stolz et al., 2025].

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MS34

Predictive Biology in Crops: Bridging the Genotype to Phenotype (G2P) Gap

A central challenge in modern agriculture is accurately predicting complex phenotypes from high-dimensional genomic data. As global climates become increasingly volatile, bridging the "genotype-to-phenotype" (G2P) gap has transitioned from a theoretical pursuit to a critical need in biology. This research explores the integration of foundational research in the model legume Medicago truncatula with predictive frameworks to decode crop performance mechanisms. As a pivotal "nodal" system, M. truncatula offers sophisticated resources, including PacBio-based genome assemblies (Mt5.0), extensive Tnt1 retrotransposon-tagged and Fast Neutron Bombardment mutant collections, and multi-omics atlases like the Medicago Gene Expression Atlas and the Small Secreted Peptide Database. Leveraging these, we identify core regulatory nodes through targeted mutant phenotyping to transition from descriptive "omics" to integrative systems biology. This approach combines transcriptomic, proteomic, and metabolic profiles with environmental variables to create multi-scale models where the environment is a primary input rather than mere "noise." We examine how characterizing signaling cascades and nutrient flux provides training data for machine learning and mechanistic models to forecast field-scale outcomes in crops like alfalfa. Ultimately, integrating experimental validation with computational synthesis enables a "design-to-spec" approach to engineer resilient, high-yielding genotypes.

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MS34

ResGene: A 2D and Tensor Image based Residual Network Approach for Genomic Prediction

For crop improvement, breeders grow multiple plant varieties and observe their physical traits (phenotypes), then correlate these with genetic data (genotypes) to select superior varieties. This process is time-consuming. Genomic prediction (GP) accelerates this by predicting phenotypic values using genotypic data. Generally, GP has relied on statistical methods with recent machine learning (ML) and deep learning (DL) models. However, no single method consistently outperforms others on diverse datasets. Thus, this performance, which is typically measured by a Pearson Correlation Coefficient (PCC), requires improvement that we address here. When applying DL models in GP, the genotypes are usually fed as a sequence of characters to the 1D-Convolution Neural Network (CNN). We propose a novel DL method that recast genotypes into 2D and 3D/tensor images, and feed them into a 2D-CNN. The use of 2D-images for case-control (classification) task in bio-informatics exists; however, we are the first to apply in GP (regression). The use of 3D/tensor image is new. To avoid the vanishing gradient problem, we use a ResNet-based model, termed ResGene. We test ResGene on three crop species (soybean, rice, and sorghum) across ten phenotypic traits, comparing against seven widely used models. ResGene beats all with PCC gains from 14.51% to 41.51%, achieving best performance on 8 out of 10 traits, with an average rank of 1.3. In comparison, the second-best and the third-best models achieve the best performance on 0 and 1 out of 10 traits with average ranks of 3.4 and 3.9, respectively.

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MS34

IndoBlightCast: A Pan India Forecasting Model on Potato Late Blight Appearance and Its Management

A late blight forecasting model "INDO-BLIGHTCAST" has been developed using meteorological data and late blight appearance dates at four locations in the Indo-Gangetic plains (Jalandhar, Punjab; Modipuram, UP; Pantnagar, Uttarakhand and Kalyani, West Bengal). The model involves computation of physiological days (P-days) and mean relative humidity (RH) of the night, accrued over seven consecutive days. Late blight was predicted to appear within 15 days if moving cumulative effective temperature (P-days) and RH exceeded 52.5 and 525, respectively for seven consecutive days. The developed model was also tested against independent data sets at three locations in the plains (Faizabad, UP; Patna, Bihar and Jorhat, Assam), two in plateau region (Hassan, Karnataka and Dharwad, Karnataka) and three in the hills (Shimla, HP, Shillong, Meghalaya and Ootacamund, Tamil Nadu). Statistical comparisons of observed and predicted dates of late blight appearance showed that the mean absolute error was 10.48, while the residual mean square error was only 13.17 indicating that the errors were quite low. The Willmott D index was 0.84 which is quite close to unity thus indicating high accuracy of model predictions and its applicability across regions and seasons. Receiver operating characteristic analysis also confirmed the superiority of this combination (accuracy of 73.6%, AUC of 0.725) to predict late blight appearance as well as its non-appearance in unfavourable years.

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MS34

Scalable Feature Extraction and AI/ML for AgriTech Innovation

Clustering emerges as a promising approach, aiding in organizing and categorizing plant genomic sequences to uncover patterns and functional elements. However, the large-scale and high-dimensional nature of data in plant genomics complicates the clustering process and reduces accuracy. Additionally, the time-consuming nature of alignment-based approaches present obstacles to real-time analysis. This necessitates the development of efficient dimensionality reduction methods such as feature selection, scalable feature extraction methods and AI/ML techniques using Big Data frameworks with GPU accelerated codes on high performance computing to enhance computational efficiency and model efficacy. The session will focus on the Novel scalable feature selection, scalable alignment-free feature extraction, and fuzzy clustering algorithms to address plant genomics challenges. These cutting-edge technologies address key challenges in the agriculture sector by developing a pipeline of technologies for crop improvement in less time. AgriHub : A Centre of Excellence in AI/ML Deep Learning at IIT Indore India is a platform to identify the need of such technologies by collaborating with stakeholders in industry, academia, government and catalyze the development of emerging technologies for sustainable crop development.

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MS35

Modelling Cellular Resource Accumulation Using Queueing Theory

The proper management of resources whose arrival and consumption are subject to environmental randomness is a process intrinsic to the correct functioning of cells. Examples of this include axonal transport and cytoneme-based morphogenesis. Under the assumption of in-target consumption, accumulation of resources can be modeled as a queuing process, with a finite number of servers, whose arrival distribution is determined by a first-passage process. In this talk we will present the modelling rationale of cellular resource accumulation with queueing theory, and we will introduce results relating the spatial configuration of 1D search processes with the convergence to a steady-state distribution of the queue length. Finally, we will present results on the effects of including stochastic resetting in the search process on the convergence of the number of resources in the original model.

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MS35

Resource Accumulation by Ideal Collectives in Stochastic Environments

How should collectives allocate foragers between exploration and exploitation when environmental conditions fluctuate unpredictably? We address this question for environments following a two-state Markov process. We derive scaling laws for optimal allocation as a function of group size, showing that optimal exploration effort scales logarithmically with collective size when the environment is unfavorable. We also show that decentralized strategies with heterogeneous risk tolerances can match centralized optimal performance. These results provide a mathematical framework for collective foraging under uncertainty.

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MS35

A Lightning Solver for the Solution of Planar Diffusion Equations with Applications to Chemical Signaling

Diffusive signals to surface receptors provide cues for cellular decision making, for example how to mobilize. In this talk we will describe the advancement of both asymptotic and numerical methodologies to describe and interpret these signals. A particular focus of these new methods is to describe the full time dependent fluxes over surface receptors. This talk will describe a rapid, accurate and easy to implement numerical solution of the planar heat equation based on a lightning solver, a recent development in the numerical solution of linear PDEs which expresses solutions using sums of polynomials and rational functions, or more generally as sums of fundamental solutions. This method has demonstrated an ability to accurately represent solutions of PDEs with solution singularities. The method solves elliptic PDEs by forming series solutions whose coefficients are determined by an overdetermined linear system at a collocation grid. Our approach utilizes the Laplace transform to obtain a modified Helmholtz equation, solve it via the lightning method, and then numerical inversion of the Laplace transform to yield a solution to the diffusion problem. Our validation of the method against existing results and multiple challenging test problems, shows the method is robust across a wide range of time ranges and geometric configurations.

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MS35

Gated First-Passage Processes

For two molecules to react they first have to meet. Yet, reaction times are rarely on par with the first-passage times that govern such molecular encounters. A prime reason for this discrepancy is stochastic transitions between reactive and nonreactive molecular states, which results in effective gating of product formation and altered reaction kinetics. To better understand this phenomenon we developed a unifying approach to gated reactions on networks. Beyond reaction kinetics, the first-passage time is a quantity of considerable interest in many areas, e.g., time series analysis, sensor detection, and single-molecule chemistry. However, in realistic scenarios, various forms of gating prevent first-passage times from being directly accessible. The crucial challenge is then to infer the first-passage time statistics from gated observations, i.e., from the actual times at which events are detected. We provided a universal, model free, scheme which solves this long-standing inference challenge.

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MS36

Modeling the Impact of Ocular Hemodynamics and Venous Collapsibility on Retinal Tissue Oxygenation

Glaucoma is a leading cause of irreversible vision loss worldwide. Beyond elevated intraocular pressure (IOP), impairments in retinal blood flow and oxygenation contribute to disease progression. In this study, a theoretical model of the retinal vasculature is expanded to allow for venous collapsibility. The model also accounts for mechanistic flow regulation and oxygen transport to predict retinal blood flow and tissue oxygenation as intraluminal pressure, oxygen demand, and IOP vary. Venules are represented as Starling resistors, allowing collapse when external pressure exceeds intraluminal pressure. At baseline IOP, blood flow exhibits an autoregulatory plateau. With elevated IOP and venous collapsibility, this plateau shifts to higher pressures, indicating reduced autoregulatory capacity under physiological conditions. Venous resistance correspondingly increases with IOP. The model further predicts a diminished increase in blood flow in response to elevated oxygen demand when collapsibility is present. These findings suggest that venous collapsibility may contribute to hemodynamic dysfunction observed in glaucoma and provide a framework for comparison with sector-specific clinical data.

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MS36

Quantifying Retinal Hemodynamic Risk under Stochastic Intraocular Pressure and Blood Pressure

Blood pressure (BP) and intraocular pressure (IOP) exhibit physiological fluctuations, yet the hemodynamic consequences of variability are not well-studied. We introduce a stochastic modeling framework that represents BP

and IOP as stochastic processes and quantifies the effects of their variability on retinal hemodynamics. In this preliminary study, BP and IOP were modeled as mean-reverting stochastic processes with physiologically motivated reversion rates and variability levels. Different variability regimes were simulated using normative mean BP and IOP. Stochastic BP and IOP inputs produced beat-to-beat hemodynamic fluctuations throughout the retinal circulation. Monte Carlo analysis demonstrated pronounced, scenario-dependent differences in per-cycle venous vulnerability despite identical mean BP and IOP levels, with the highest risk observed under high IOP variability. The proposed SDE framework is designed to serve as the forward simulator within an amortized Bayesian inference pipeline, enabling patient-specific estimation of variability parameters from sparse clinical measurements. The resulting features can extend the recently developed digital twin for ocular hemodynamics framework from static, mean-value hemodynamic profiling to variability-aware profiling where patients with potentially identical mean IOP and BP, but distinct variability signatures can be differentiated and clustered according to their individualized risk of hemodynamic compromise.

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MS36

Ocular Deformation due to Intraocular Pressure and Contact Lens Wear

Myopia is one of the most common ocular disorders in the world impacting approximately 28% of the global population. Soft and rigid contact lenses are used to treat myopia, however one in three users will stop wearing contact lenses due to discomfort. It has been shown that, when placed on the eye, both the lens and the ocular surface deform. The goal of this project is to develop a mathematical model to predict the deformation of the ocular surface due to contact lens wear, where the shapes of both the eye and the lens are emergent properties of the model. In this presentation, we will discuss how we model the ocular tissue first as a linear elastic material and then as a poro-elastic material. We present the governing equations and the numerical method we implement to approximate them. We present results of tissue displacements and stresses with and without the presence of a contact lens. Additionally, for the poro-elastic model, we present an in silico experiment in which we evaluate the displacement of the ocular tissue when using a time-dependent intraocular pressure. We will end by discussing future model extensions to achieve the long-term goal of studying the effectiveness of contact lens treatments for myopia.

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MS37

Designing Programmable Molecules with Discrete Generative Models

In this talk, we present generative algorithms for designing functional biologics directly from sequence. We began with protein language models that de novo design peptides targeting undruggable disease proteins, with experimental validation in neurodegeneration, pediatric cancer, and viral infection. To move beyond binding alone, we have developed discrete diffusion and flow-based models that generate peptides, proteins, mRNAs, and isoform-specific modulators under explicit, controllable objectives. Most recently, we have pioneered Schrdinger bridge models that learn biologically meaningful trajectories, that not only model biological states but also the trajectories connecting them, from protein folding to cell-state transitions, establishing a unified and programmable framework for molecular design grounded in physics and context-aware dynamics.

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MS37

Knowledge Graph-Driven Ai in Life Sciences: Case Studies in Kinase-Substrate Association Prediction and Veteran Suicide Risk Assessment

The data revolution in life sciences, from system biology to population health, offers new opportunities but also major integration challenges. Traditional artificial intelligence (AI) methods often treat data as independent features, limiting their ability to capture the relational structure of biological and clinical data. This talk presents a unifying framework based on knowledge graphs (KGs), semantic networks of entities and relationships, to support accurate and interpretable AI across life science domains. We demonstrate this framework through two case studies at different biological scales. At the system level, we present KSMoFinder, a model built on the Protein Knowledge Network (ProKN) to predict kinasesubstrate relationships. By learning from biological context such as pathways, functions, and molecular interactions, KSMoFinder achieves high accuracy while producing biologically explainable predictions. At the population health level, we show how a patient-centric Social Determinants of Health (SDoH) knowledge graph integrates clinical and social factors to uncover multifactorial health risks. Applying graph-based learning to this interconnected data not only outperforms standard, non-graph approaches but also provides powerful, interpretable explanations rooted in the network struc-

ture. Together, these studies illustrate a KG-driven AI framework that bridges basic research and clinical application to accelerate discovery and address complex health challenges.

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MS37

Machine Learning for Image Based Reconstruction of Patient Cardiac Blood Flow

Characterizing cardiac flow patterns offers unique insights into patient cardiac function and is essential for understanding the initiation and progression of cardiac diseases. Computational fluid dynamics (CFD) simulations can investigate detailed intraventricular flow patterns arising from the dynamic motion of the beating heart. To be clinically useful, such a framework must achieve reasonable turnaround times, reproduce available patient measurements such as pressures and flow imaging, and provide additional spatiotemporally resolved flow information that is not directly accessible in routine clinical practice. We present a machine learningassisted CFD framework for efficient simulation of patient-specific cardiac flow. Deep learning (DL)based approaches are developed for automated cardiac segmentation and reconstruction of dynamic meshes directly from medical imaging data. The resulting moving-domain flow problem is solved using the Arbitrary LagrangianEulerian formulation to accommodate large cardiac deformations. All four cardiac valves are modeled as immersed surfaces using penalty-based resistance terms incorporated into the incompressible NavierStokes equations. We demonstrate its application in both a healthy subject and a pediatric patient with congenital heart disease. We also discuss emerging DL methods in our lab aimed at directly inferring high-resolution cardiac flow fields from medical images.

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MS38

Mechanistic Modelling of Tumor-Immune Dynamics to Identify Therapeutic Targets under Data-Sparse Conditions

Triple-negative breast cancer (TNBC) refers to a type of breast cancer that has none of the three most-common breast cancer receptors (estrogen, progesterone, and HER2). Because it lacks these receptors, it is a disease with limited options for treatment and significant mortality. The tumor microenvironment (TME) plays a vital role in the disease, and is an active area of therapeutic research. Mechanistic mathematical models can be used to describe the complex biological interactions within a TME and can be analyzed to understand disease dynamics and search for therapeutic targets. We developed a mechanistic mathematical model to describe key dynamics of the TNBC TME, based on literature and expert input. Our model is a system of ordinary differential equations that represents dynamics of M2 macrophages, cancer-associated fibroblasts, TNBC cells, cytotoxic T lymphocytes, and regulatory T cells. We simulated TME dynamics over the course of a typical treatment period. We performed a global sensitivity analysis to determine parameters that are most influential on tumor size. Pathways containing these highly-influential parameters represent potential therapeutic targets. We plan to add treatments to our model to mathematically calculate combination drug regimens that maximize treatment efficacy while minimizing side effects. Our approach, using mathematical modeling and analysis to find potential therapeutic targets and optimize regimens, can also be applied to other diseases.

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MS38

Mechanistic Modeling of Igf1 Receptor Inhibition in Thyroid Eye Disease

In this talk, I present a case study showing how mechanistic mathematical modeling can integrate diverse data to generate insight into disease dynamics at the site of action, where direct measurements are often challenging. We focus on thyroid eye disease (TED), where dysregulated IGF-1R pathway activity in orbital muscle and fat drives inflammation and tissue swelling. A major challenge with modeling this disease is the significant difficulty of collecting measurements from these tissues outside of a surgical environment. As a result, clinical studies typically rely on alternative, observable readouts such as proptosis (a measure of eye swelling) and circulating blood IGF-1 ligand measurements to assess efficacy. I will describe a mechanistic model that links these clinically styled measurements with published non-clinical data on systemic IGF-1 kinetics in a single quantitative framework. Using this model, we infer otherwise unobservable tissue-level IGF-1/IGF-1R dynamics, quantify how those dynamics are affected by IGF-1R-targeting monoclonal antibody therapies (one already approved and others in late-stage development), and translate inferred site-of-action behavior into clinically meaningful predictions. This case study illustrates how mechanistic models can integrate limited clinical measurements with alternative data sources to infer unobserved biology and produce decision-relevant qualitative and quantitative insight beyond the data.

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MS38

Mechanistic Modeling of ADCs and a Shared-Pool Framework for Cell-Contact-Mediated Immunotherapies

This talk will first provide a brief overview of the use of mechanistic antibodydrug conjugate (ADC) models across preclinical and clinical development, and highlight recently published work from our group on mechanistic bystander ADC models. Next, we will introduce a novel modeling framework for crossbridge formation at cellcell interfaces, such as immunological synapses between cancer and immune cells. Most existing models focus only on receptor dynamics while neglecting cell dynamics, effectively assuming that all receptors are available for crossbridge formation. This can lead to overestimation of crossbridge formation, since only receptors located within active cell-cell synapses are available for crossbridge formation. To address this limitation, we propose an integrated frame-

work that jointly captures cell and receptor dynamics while maintaining computational tractability through the pooling of repeated reactions across free cells and cells in contact. This approach is broadly applicable to models capturing cell-contact-mediated mechanisms, including T-cell engagers (TCEs) and immune checkpoint blockade therapies. We will demonstrate the methodology using a 1+1 TCE case study and present calibration results against experimental data.

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MS39

Dynamics of Clonal Evolution in the Hematopoietic System and Associated Malignancies

The presentation will focus on stochastic models of evolutionary processes in spatially structured tumor cell populations. It will explore how spatial structure alters evolutionary dynamics compared to models assuming well-mixed cell populations, and will demonstrate this with specific examples that are based on data from hematologic malignancies and solid tumors. Cell evolution in both expanding populations (growing tumors) and cell populations at steady state (pre-malignant evolution or tumor evolution during temporary stasis) will be considered. Emphasis will be placed on evolutionary processes that drive disease progression and resistance evolution to therapies.

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MS39

Quantifying Fitness in Clonal Haematopoiesis: LogisticMoran Modeling of Evolutionary Dynamics and Therapy Response

Clonal haematopoiesis (CH) is an age-associated evolutionary process in which hematopoietic stem cells (HSCs) acquire somatic mutations that may alter self-renewal and competitive fitness. Although sequencing studies have identified recurrent CH drivers, most inference frameworks assume exponential growth and constant selection, neglecting homeostatic constraints and the possibility that selection changes with age or inflammatory stress. We develop a unified LogisticMoran modeling framework that couples deterministic logistic growth (constrained HSC pool) with stochastic Moran dynamics. Using longitudinal VAF trajectories from the Bolton et al. CH cohort and our breast cancer cohort, we show logistic models systematically improve fits over exponential growth and, as a result, reduce bias in inferred fitness. We infer time-dependent selection s(t), supported by mechanistic evidence that TET2-mutant HSPCs exhibit epigenetic silencing of AP-1 factors (FOS/JUN) and a weaker gene-expression response to inflammation, consistent with context-dependent fitness. Finally, Moran simulations show that therapy-induced contraction of the HSC pool amplifies stochastic drift, increasing variability in clonal trajectories and enabling modestly advantageous clones to expand through ecological opportunity. Together, LogisticMoran modeling provides a mathematically rigorous framework for CH fitness inference and therapy-aware risk prediction.

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MS39

Stochastic Models and Time Series Data for Leukemia Evolution

Acute myeloid leukemia (AML) exhibits profound heterogeneity in treatment response, driven by stochastic fluctuations in leukemic cell populations and their microenvironmental interactions, which are manifested in gene expression profiles. To capture these dynamics, we develop a mathematical modeling framework grounded in Langevin equations to represent intracellular and population-level sources of noise influencing leukemic proliferation, differentiation, and treatment susceptibility. This stochasticity is modeled as trajectories in a state-space that links bulk and single cell gene expression dynamics over time to observable clinical markers such as blast counts and measurable residual disease. The corresponding FokkerPlanck equation is used to characterize the evolution of probability density functions over clinically relevant state variables, enabling quantitative predictions of disease trajectories and therapeutic outcomes. By integrating patient-specific data with these stochastic dynamical systems models, we quantify uncertainty in treatment response and infer individualized parameters describing leukemic persistence and relapse risk from properties of state-space dynamics and trajectories. Collectively, this work establishes a clinically actionable stochastic modeling platform for AML, linking biophysical mechanisms to patient-level decision-making and offering novel insights into the probabilistic nature of disease progression and treatment resistance.

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MS40

Predicting Conduction Velocity from Cardiac Ionic Models Using Machine Learning

Conduction velocity (CV) measures the rate at which electrical signals responsible for initiating contraction propagate across cardiac tissue. Despite its physiological importance in determining cardiac wavelength and susceptibility to arrhythmias, the mechanisms governing CV at the cellular and tissue levels remain poorly understood. Currently, there is no existing framework that can reliably predict CV from single-cell properties alone. This work aims to use interpretable machine-learning approaches to predict CV from cardiac ionic models. Various features were extracted from the phase space of a single action potential produced from the Fenton-Karma and Beeler-Reuter models, including parameters capturing the overall shape and other characteristics of the graph. Several machine learning models were utilized, including nonlinear and ensemble methods, to examine patterns in the data. We discuss our findings and insights into the cellular dynamics that drive CV.

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MS40

Discovering Minimal Stimulation Patterns for Reentry in Excitable Media via Reinforcement Learning

Excitable media, such as cardiac tissue, can transition from transient activity to self-sustaining reentrant rhythms. General principles governing reentry initiation across varied geometries remain incompletely understood. We propose a deep reinforcement learning (RL) framework to discover minimal stimulation strategies that induce reentrant dynamics. An RL agent interacts with a cellular automaton model of excitable media, selecting spatiotemporal stimulation protocols to maximize sustained activity while minimizing the number of applied stimuli. The learned policies produce surprisingly minimal stimulus sequences that induce reentry, often through mechanisms distinct from classical S1-S2 protocols. Simulations in ionic models and experiments with in vitro cardiac monolayers indicate that some learned strategies generalize beyond the training system. These results suggest that reinforcement learning can serve as a computational tool for probing mechanisms of reentry initiation in nonlinear excitable systems.

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MS40

Sinoatrial Node Network Structure Emerges from Adaptive Gap Junction Plasticity

The sinoatrial node (SAN) is the primary pacemaker of the heart. Recent studies have shown that the SAN has a complex network structure, composed of heterogeneous cells with varying intrinsic calcium release characteristics and thus oscillatory rates. The SAN network structure, with a neuronal-like distribution of connections implies a more complex developmental process compared to working myocardium. However, the process by which this structure is created and maintained is not currently well defined. Here, we expand on our previous work by modeling SAN activity in an adaptive network, where nodes have variable conductances governed by a calcium feedback model with a set calcium target, while edges are plastic. For edge plasticity, we use a neuronal derived spike-timing dependent plasticity model. Moreover, the network prunes its connections stochastically: low connection weight increases the probability of the edge being removed. We find that, starting with a random distribution of inherent cellular calcium targets, cells self-organize into activity clusters showing a power law distribution in edge weights. Further, the activity shows an inherently variable activation rate. Finally, the network remodels in the presence of nervous stimulation, leading to the emergence of two distinct activation patterns resembling the inferior or superior SAN. These results suggest activity-dependent plasticity may explain the developmental origins of SAN's complex network topology.

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MS40

The Effect of Intercell Ephaptic Coupling on the Scale Length of Spiral Wave Turbulence in the Heart

A phenomenon called discordant alternans, the out-of-phase alternation of action potential durations as electrical waves travel through cardiac tissue, is thought to be a precursor for the development of spiral waves, which in turn may lead to dangerous rapid rhythms in the heart. However, when computer models are constructed to model this phenomenon, wave propagation speeds consistent with those seen in the heart lead to discordant alternans having scale lengths much longer than those observed in the heart. Previously, we showed that an improved model of intercell connectivity called ephaptic coupling can solve this problem. The next step is to show that discordant alternans, so generated, will indeed lead to persistent spiral wave turbulence with similar scale lengths. To accomplish this, we created a new spatially two-dimensional model. So that the model will exhibit ephaptic coupling in both directions, we employed a staggered arrangement of cardiac cells, which also more realistically models how cells are organized in the real heart. We find that the spiral waves with the correct spatial scale length can indeed be initiated in this model. We also find, however, that the spiral waves exhibit a "tunneling" behavior that will require further scrutiny.

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MS41

How Vaccines Shape B Cell Evolution : a Modelling and Phylogenetics Approach

Optimizing existing vaccination programs and designing new ones for emerging health challenges requires understanding how the immune system evolves upon exposure to vaccines. Of the immune cells that respond, B cells are an important class of immune cells, known to produce antibodies. These mount response through the extrafollicular (EF) and germinal center (GC) pathways. Longitudinal studies have shown that B cell populations evolve with each vaccine dose, changing the breadth of the repertoire in the process. Although the mechanisms of these two pathways are known individually, how these work together to generate response in case of different vaccination strategies and whether that leaves a signature in the evolutionary history of B cell clonal families has not yet been well studied. In this study, we use a bitstring model consisting of the two pathways to simulate the evolution of B cell response in a two-dose vaccine regimen in homologous and heterologous vaccination systems, and subsequently, examine the phylogenetic trees of simulated clonal families using various tree metrics. We looked at differences in the overall B cell response in case of the two vaccination systems and also explored the effect of time gap between doses in both vaccination systems and antigenic distance

between doses in the heterologous system on B cells phylogenies. Our results show higher percentage of EF response post the booster dose in case of homologous vaccination while similar amounts of GC response was produced after both doses in case of heterologous response. Booster dose responses in the two vaccination systems showed distinct patterns of B cell evolution reflected in the trends of the tree metrics over time, with a more robust response observed in the heterologous setting. Varying the time gap between doses and antigenic distance also had an effect on the evolutionary signatures of B cells.

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MS41

How human behavior shapes epidemic dynamics

Human behavior plays an integral role in the spread of infectious diseases, a reality that the world observed during the COVID-19 pandemic. Human behavior has long been incorporated into disease models, but recent efforts have sought to improve upon past methods and models, formulating behavior mechanisms to better understand human behaviors influence on disease outcomes. One promising mechanism is the behavior-transmission feedback loop, which captures how changes in human behavior drive changes in the amount of infections, which in turn drives changes in human behavior. A simple mechanism when considered in the framework of a deterministic compartmental model, this tool has strong fitting and forecasting capabilities and provides important insights into how adaptation of behavioral responses impacts disease prevention and control in the context of single- or multi-disease outbreaks.

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MS42

Neural Operator Identification of Mechanobiological Drivers of Thoracic Aortic Aneurysm Using Local Dilatation and Distensibility

Thoracic aortic aneurysms (TAAs) stem from mechanobiological disruptions in the aortic wall and can lead to dissection or rupture, yet current surgical criteria based on aneurysm size and growth fail to predict disease trajectory and patient risk. Recent evidence suggests that degradation of elastic fibers and impaired cell-matrix interactions critically weaken aortic mechanics, underscoring the need to quantify factors driving mechanical vulnerability. We developed an integrated computational framework that trains neural operators to identify TAA contributors using synthetic datasets spanning varying elastic fiber integrity and cellular mechanosensing insults. A finite element model of aortic growth and remodeling generates spatial maps of local geometry (dilatation) and mechanics (distensibility) under multiple insult combinations. We compare multiple operator architectures and different input representations to establish robust subject-specific prediction standards. We show that these models accurately recover heterogeneous insult distributions from combined dilatation and distensibility maps. Prediction errors using dilatation alone, analogous to current clinical guidelines, are significantly higher than those using both metrics, highlighting the value of localized measurements of aortic dilatation and distensibility for identifying underlying disease drivers and advancing mechanism- based treatment strategies for TAAs.

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MS42

Multi-Fidelity Deep Learning for Estimation of Infarcted Myocardium From Strain Imaging

Chronic myocardial infarction is a major contributor to heart failure, yet current gold-standard assessment relies on late gadoliniumenhanced cardiac MRI, which is invasive, time-consuming, and difficult to scale. Here, a completely non-invasive methodology is developed to identify the location and extent of infarcted regions in the left ventricle via a deep learning model using only cardiac strains as inputs. In this framework, circumferential, radial, and longitudinal strains on American Heart Association bullseye maps are represented as multichannel images that feed a UNet-based encoderdecoder architecture. A hierarchical composite network couples this low-fidelity UNet, trained on a large library of finite-element rodent heart simulations with randomized infarct size, stiffness, and location, to two high-fidelity convolutional correction networks that adapt predictions to sparse human LGE-CMRderived labels via a generalized linearnonlinear regression scheme. The resulting model achieves accurate infarct segmentation on limited human data and demonstrates how simulation-informed, multi-fidelity scientific machine learning can enable non-invasive, data-efficient cardiac risk stratification, with potential impact on broader biomedical applications where human data is scarce.

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MS42

Structure-Preserving Neural Surrogate for Long-Time Molecular Dynamics

All living organisms are composed of complex biomolecules, which are abundant within their cells. Understanding how these molecules evolve over time, with respect to

their structural changes and interactions both within the molecule and with their environment, is essential to determining how they function within biological systems. With the advent of machine learning, numerous approaches have been developed to predict static molecular structures, yet effectively capturing the long-term dynamics remains a challenge. While numerous machine learning approaches help accelerate the dynamics, they preserve macroscopic observables through imposed constraints. In this work, we use a structure-preserving neural surrogate to learn and predict the dynamics of molecular systems of increasing complexity with the long-term goal of faithfully capturing biomolecular dynamics over extended timescales.

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MS43

Keeping Clocks in Sync: from Intracellular Oscillations to Intercellular Rhythms

The circadian rhythm is generated by intracellular molecular oscillators that must remain synchronized to produce coherent rhythms at larger scales. In cyanobacteria, the clock emerges from ordered phosphorylation and dephosphorylation cycles of the protein KaiC. In multicellular organisms, including insects and mammals, oscillations arise from transcription-translation feedback loops that drive rhythmic gene expression. Despite their mechanistic differences, both systems face a common constraint: microscopic oscillations must remain coordinated, both among molecules within a cell and among cells within a tissue, to sustain organism-level rhythmicity. This coordination is challenged by growth, turnover, and measurement limitations. For example, in a growing cyanobacterium, KaiC must be continually synthesized to maintain concentration, yet newly-produced KaiC is unphosphorylated. If average phosphorylation state encodes circadian phase, how is temporal information preserved under continual dilution and replacement? In multicellular systems, single-cell transcriptomics can provide insights into gene expression, but is destructive; one cannot observe the same cells over time. To what extent can cellular synchrony and phase structure be inferred from static 'snapshots' of the population at different times? In this talk, I will present our recent work using mechanistic ODE models and deep learning–based inference to address these questions. We show how growth and molecular turnover can be accommodated without loss of phase coherence, and we develop methods to reconstruct cell-level synchrony from snapshot data. Together, these approaches provide a quantitative framework linking microscopic molecular oscillations to macroscopic rhythmic behavior.

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MS43

Inferring Mechanisms of Circadian Regulation of Cardiac Dynamics from ECG Recordings

Key properties of cardiovascular function exhibit circadian (24-hour) rhythms, including heart rate, blood pressure, and electrocardiogram (ECG) waveforms. The biophysical mechanisms underlying these daily rhythms are not fully understood. In this talk, we use neural posterior estimation to link mechanistic models of cardiac dynamics to ECG recordings. By comparing the model parameter distributions inferred from ECGs recorded at different times of day, we gain insight into which aspects of cardiac electrophysiology are being regulated by the circadian clock.

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MS43

Modeling the Interaction Between the Human Circadian Clock and the C-Myc Oncogene

Cancer can disrupt human circadian rhythms and overexpression of the oncogene MYC completely destroys rhythms. It has been shown that MYC acts as a transcription factor, (dis)regulating key clock genes BMAL1 and REV-ERBα. Recently, we showed that MYC expression has a circadian rhythm in the U2OS human cancer cell line. Using these and other experimental results, we extended an ODE model of Leloup & Goldbeter (2003) to incorporate interactions between MYC and the mammalian clock. Here, we present our analyses of the mechanisms by which MYC can suppress oscillations. We learn that, for example, the clock can tolerate higher levels of MYC if it is oscillating in the expected phase.

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MS43

Time-of-Day Matters: Circadian Control of Cardiac Dynamics and Proarrhythmic Risk

Circadian clocks regulate cardiovascular physiology, including cardiac electrophysiology, arrhythmia susceptibil-

ity, and drug metabolism. Epidemiological studies show that sudden cardiac death and malignant ventricular arrhythmias occur more frequently in the morning, indicating that endogenous circadian timing modulates cardiac electrical stability. However, the mechanistic links between molecular clocks, tissue-scale arrhythmogenesis, and drug safety remain unclear. We develop mechanistic electrophysiological models incorporating experimentally observed circadian variation in ionic currents, particularly L-type calcium conductance, to study multiscale effects on cardiac excitability. Bifurcation analysis shows that circadian modulation organizes early afterdepolarization dynamics through a codimension-2 TakensBogdanov structure, while spatial simulations reveal time-of-day dependent spiral-wave breakup associated with ventricular fibrillation. We then investigate chronopharmacology using computational safety assessment frameworks inspired by the Comprehensive in vitro Proarrhythmia Assay (CiPA). Simulations of multiple drugs demonstrate strong dosing-time dependence: a high-risk drug taken at an optimal circadian phase may be safer than a nominally low-risk drug at an unfavorable phase. These results link circadian timing, nonlinear cardiac dynamics, and drug safety, highlighting chronobiology as a missing dimension in arrhythmia modeling and computational pharmacology.

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MS44

Batched Global Bandits with Covariates: Exploiting Shared Structure for Coordinated Decisions

This talk studies batched global bandit problems with covariates, where multiple actions are selected in groups and rewards are observed with delay. The model allows decisions across arms and batches to be statistically coupled through shared structure in the reward functions, enabling information pooling without centralized optimization. I will present algorithms that exploit this structure to coordinate exploration and exploitation at the batch level. Theoretical results characterize learning efficiency and scaling behavior as functions of batch size, dimension, and the strength of shared structure, highlighting regimes in which batching accelerates learning and reduces cumulative regret. Simulation studies illustrate how coordinated decision rules emerge from structural coupling and how batch design affects performance.

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MS44

How Do Animal Collectives Solve the Best-of-N Problem In Complex Decision Landscapes

In collective decision-making, the best-of-N problem (BNP) is a type of task where a group of agents is required to integrate information about the attributes of N discrete options and commit to the best one. Despite the importance of capturing the complexity of situations encountered in the real world, BNPs remains poorly understood beyond simple, low-complexity cases involving only a few options that differ in a single attribute. Here, we study collective decision-making in animal groups, who are known to solve BNPs across a wide range of problem complexities. Using cockroach groups as an example, we develop mean-field and agent-based models to characterize how groups process single- and multi-attribute information as N scales. Our models incorporate inter-individual and individual-environment interactions, where the probability of a cockroach leaving a shelter decreases with crowdedness and increases with brightness. Our results reveal a counter-intuitive prediction: decision time is non-monotonic in N, initially decreasing as the number of options grows. We use dynamical systems theory to explain the underlying mechanisms by showing how the properties of local interactions result in qualitatively distinct decision-making dynamics at different levels of problem complexities. These findings provide novel insights into how collective decision-making mechanisms scale with problem complexity, with applications to artificial systems like swarms of robots and virtual agents.

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MS44

Social Foraging Across Species: Theoretical and Experimental Reflections

Social foraging is a ubiquitous behavior, crucial for survival of animal groups faced by environmental uncertainty. In this this talk, I will present theoretical advances in our understanding of social foraging behaviors focusing on mechanistic models that implement "microscopic" social interactions giving rise to distinct "macroscopic" foraging patterns. Moreover, I will give examples of experimental data we are using aiming to test and modify these social foraging models.

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MS44

Data-Driven Modeling of Collective Communication and Food Distribution in Honeybee Colonies

How do thousands of honeybees coordinate who feeds whom, and when? It is known that they use a process called trophallaxis to distribute resources in a hive, yet the communication mechanism facilitating this remains poorly understood. We find that bees use scenting - wing-flapping that pushes pheromones directionally - to assemble functional aggregations around fed donor bees that carry food. This behavior demonstrates extended classical stigmergy, where individuals communicate by perceiving and manipulating the physical fields of chemical concentration and airflow rather than relying on static environmental information. Guided by these observations, we build an agent-based model that couples scenting with trophallaxis to probe aggregation dynamics and distribution efficiency across conditions. Our model confirms directional scenting as an effective mechanism for coordinating resource exchange in this simulated population, and allows us to further vary behavioral parameters such as pheromone thresholds and scenting probability. These findings offer a new

framework for understanding distributed communication and resource allocation in social insects.

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MS45

: Is Natural Hovering Extremum Seeking Natures Simple and Optimal Solution for Flapping Flight Physics?

The new theory and concept of Natural Hovering Extremum Seeking (NH-ES) made it possible to characterize hovering flight physics as universal, simple, model-free, real-time, computationally basic and sensory basic feedback mechanism. Such mechanism only requires the natural oscillations of the wing, already inherited in the system, to function. Such characterization sparked worldwide scientific attention and has been hypothesized as biologically plausible given the limited computational abilities of flapping insects and how NH-ES matched biological data. But how optimal NH-ES? In order to validate the NH-ES characterization from optimal control theory perspective, we developed a mathematically rigorous, nonsmooth, optimal control solver using tools from the generalized derivatives theory, particularly the Lexicographic differentiation, to judge if NH-ES is plausibly nature's simple solution for real-time optimal hovering.

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MS45

Natural Hovering Extremum Seeking: A New Paradigm for Understanding and Mimicking Flapping Flight by Insects and Hummingbirds

Understanding the physics of the hovering phenomenon in flapping insects and hummingbirds is a challenging task due to the multi-body, multiple-timescale, non-autonomous body dynamics and complex aerodynamics involved in this phenomenon. In this work, we introduce a paradigm shifting concept called Natural Hovering Extremum Seeking (NH-ES), which succeeded in characterizing hovering flight physics as a universal, simple, model-free, real-time, computationally-basic and sensory-based feedback mechanism. Such mechanism only requires the natural oscillations of the wing, already inherited in the system, to function. Such characterization sparked worldwide scientific attention and has been hypothesized as biologically plausible given the limited computational abilities of flapping insects and how NH-ES matched biological data. We also present preliminary experimental results and evidence that NH-ES settles the decades-long stability/instability debate about stability of hovering including pitching dynamics.

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MS45

Universal Real-Time Extremum Seeking Mechanism for Lift Variation in Soaring Birds Optimized Flight

Our work reveal a universal, very simple extremum seeking natural feedback law that governs, adapt, and generate in real-time, optimized lift variations for successful energy gain flight in presence of wind shear. The introduced law, which is computationally minimal and needs only sensory information of the wind (i.e., model-free) is able to characterize and replicate dynamic soaring strategy of windward climb in real-time, for a variety of soaring birds species, namely wandering albatross, black-browed albatross, grey-headed albatross and giant petrel. We confirm the effectiveness of this new simple, real-time law by successful comparisons with sophisticated non-real-time optimal control solver and reported biological data in literature.

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MS45

Parametric Sensitivities of a Nonsmooth Wilson-Cowan Neural Mass Model

Wilson-Cowan type neural mass models follow the dynamics of excitatory and inhibitory neural populations. The firing rate function, which determines the proportion of neurons receiving at least threshold excitation in a given population, has been commonly modeled using either a smooth sigmoid function or nonsmooth/discontinuous sigmoid-like functions (such as ramp or Heaviside functions). In the latter case, the system is nondifferentiable and thus mathematical analyses requiring derivative information cannot be carried out using standard theory. This indicates a need for nonsmooth theory and tools from generalized derivatives, such as lexicographic derivative theory. In this talk, we present the results of a stability analysis of a nonsmooth Wilson-Cowan model that characterizes the long-term behavior of the system. We also perform a sensitivity analysis by calculating lexicographic directional derivatives to analyze the influence the model parameters have on the dynamics of the system. We then compare the results of our nonsmooth analyses to that of a smooth Wilson-Cowan model and uncover discrepancies that indicate the choice in firing rate significantly alters the behavior of the model. Our findings allow us to conclude which parameters the model is most sensitive to, indicating the importance these

values have to the biological accuracy of the model.

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MS46

Data-Driven Discovery of Biological Models with Unobserved Dynamical States Using Degeneracy-Robust Algorithms

Complex multi-component biological systems are often only partially observable despite rapid advancements in experimental measurement techniques. Discovering predictive nonlinear dynamical models and their parameters directly from noisy experimental observations with unobserved dynamical variables is essential for understanding such systems. A key challenge introduced by unobserved dynamical states is model degeneracy, where multiple structurally distinct models match observed variables. By combining concepts from dynamical systems, optimization, and differential algebra, we show that for finite-degree polynomial ordinary differential equations, equivalent models lie on a continuous surface in parameter space. I will give examples of these degeneracies on models for biological oscillators, ecology, and chaotic systems. By understanding the space of these model degeneracies, we can develop a robust model selection algorithm for data with unobserved dynamical variables and gain insights into how available data constrain mechanistic insight. I will demonstrate the algorithm on experimental data of glycolytic oscillations in yeast.

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MS46

Assessing Practical Identifiability for Biological Systems Using Weak-form Parameter Inference

Compartmental modeling of epidemiological systems provides insights into biological and behavioral interactions that cannot be observed directly. Accurate and robust parameter estimation is critical to applying such models as decision-making tools for public health interventions. A common approach to parameter estimation is nonlinear least squares using a forward solver. However, as model size and noise in data increase, these methods become computationally expensive to maintain accuracy in parameter estimates. In this work, we establish a weak-form based method of parameter estimation for systems with unobserved variables by generating weak-form input-output equations using differential algebra techniques. We show that practical identifiability of the weak-form system can be assessed more quickly in comparison to output error based parameter estimation using criteria informed by the additive error in observed variables. Finally, we demonstrate that using a weak-form based method to estimate transmission rates is computationally efficient and robust to noise.

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MS46

Simulation and Inference Methods for Non-Markovian Stochastic Processes

Stochastic models of biochemical reaction networks are widely used to capture intrinsic noise in cellular systems. The typical formulation of these models are based on Markov processes for which there is extensive research on efficient simulation and inference. However, there are biological processes, such as gene transcription and translation, that introduce history dependent dynamics requiring non-Markovian processes to accurately capture the stochastic dynamics of the system. This greater realism comes with additional computational challenges for simulation and parameter inference. We develop efficient stochastic simulation algorithms for well-mixed non-Markovian stochastic biochemical reaction networks with delays that depend on system state and time. Our methods generalize the next reaction method and τ-leaping method to support arbitrary inter-event time distributions while preserving computational scalability. We also introduce a coupling scheme to generate exact non-Markovian sample paths that are positively correlated to an approximate non-Markovian τ-leaping sample path. This enables substantial computational gains for Bayesian inference of model parameters though multifidelity simulation-based inference schemes. We demonstrate the effectiveness of our approach on a gene regulation model with delayed auto-inhibition, showing substantial gains in both simulation accuracy and inference efficiency of two orders of magnitude. These results extend the practical applicability of non-Markovian models in systems biology and beyond.

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MS47

Autocatalysis and Boundary Stability in Biochemical Reaction Networks

Recent work has established autocatalysis as a primary driver for complex dynamical behaviors in biochemical reaction systems, including bistability, oscillations, chaos, and robustness. In this talk, we explore the specific role of autocatalysis in establishing the stability and instability of boundary steady states. Determining the stability of these states is crucial, as it identifies the thresholds for species extinction and survivalthe tipping point between metabolic processes thriving or shutting down. To quantify these dynamics, we employ the next-generation matrix method, which has only recently been adapted to biochemical reaction networks, to characterize previously incomputable

thresholds for the stability of boundary steady states. We focus on pathways with bifunctional enzymes as a model system.

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MS47

Stationary Distributions of Stochastic Reaction Networks with Autocatalytic Reactions

We present a theoretical study of a class of autocatalytic reaction networks that exhibit discreteness-induced transitions, including the well-known TogashiKaneko model. For this family of stochastic reaction systems, we establish positive recurrence, finiteness of all moments, and geometric ergodicity. For specific parameter regimes, we derive closed-form expressions for the stationary distribution.

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MS47

Fragility in a TogashiKaneko Stochastic Model with Mutations

In this talk, we explore the sensitivity of a prototypical stochastic autocatalytic reaction network model that is known to exhibit dramatic switching behavior. The original model is called the TogashiKaneko model, and we consider a variant of it that allows for additional mutations. We establish a rigorous stochastic averaging principle that describes slow dynamics in terms of certain ergodic means of fast variables. For the two species model, we demonstrate a sensitivity of the model to even slight departures from symmetry in the autocatalytic reactions. We call this high sensitivity property fragility. Our preliminary explorations for models with more than two species point to a wealth of open questions for future research. Fragility appears to be an understudied phenomenon, which is likely to affect the formulation and interpretation of autocatalytic models across a spectrum of applications in the life sciences. Based on joint work with Y. Fu, H-W. Kang, W. Khudabukhsh, L. Popovic, G. Rempala.

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MS48

Mechanosensitive Reversal Control in Myxobacteria

Adjusting motility patterns according to environmental cues is important for bacterial survival. *Myxococcus xanthus*, a bacterium moving on surfaces by gliding and twitching mechanisms, modulates the reversal frequency of its front-back polarity in response to mechanical cues like substrate stiffness and cell-cell contact. In this study, we propose that *M. xanthus*s gliding machinery senses environmental mechanical cues during force generation and modulates cell reversal accordingly. To examine our hypothesis, we expand an existing mathematical model for periodic polarity reversal in *M. xanthus*, incorporating the experimental data on the intracellular dynamics of the gliding machinery and the interaction between the gliding machinery and a key polarity regulator. The model successfully reproduces the dependence of cell reversal frequency on substrate stiffness observed in *M. xanthus* gliding. We further propose reversal control networks between the gliding and twitching motility machineries to explain the opposite reversal responses observed in wild-type *M. xanthus* cells that possess both motility mechanisms. These results provide testable predictions for future experimental investigations. In conclusion, our model suggests that the gliding machinery in *M. xanthus* can function as a mechanosensor, which transduces mechanical cues into a cell reversal signal.

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MS48

Mult-Iscale Data-Driven Model of Early Epithelial Cell Clustering and Collective Motion

During wound healing, distinct large cells emerge at the wound edge and interact with surrounding regular-sized cells, promoting cell clustering and coordinated movement. Although large cells are fewer in number, they have long been thought to act as leaders that guide the movement of smaller cells and accelerate wound closure. However, recent experimental data suggest that regular-sized cells can also influence the direction and organization of collective movement. Experimental observations further showed that mixed clusters of large and regular-sized cells, before forming a coherent tissue sheet, may exhibit rotational motion. To examine how mechanisms that determine cell polarity affect collective dynamics, we developed a novel multiscale computational model that incorporates actomyosin dynamics and cell-cell and cellsubstrate adhesion. Using this framework, we studied the rotation of cell doublets and the initiation of collective cellular motion in clusters containing one large cell and several regular-sized cells. Under the assumption that the cell's polarity is oriented away from regions of high myosin concentration, model simulations demonstrate both persistent rotation and cessation of motion in cell doublets. In mixed clusters containing a large cell and several regular-sized cells, distinct behaviors are observed-depending on how myosin redistributes itself within the large cell-including sustained translation or rotation. The model integrates subcellular dynamics with multicellular motion and offers insight into the combined effects of cellsubstrate and cellcell interactions on collective epithelial migration, a process essential for wound healing.

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MS48

A Systematic Computational Framework for Practical Identifiability Analysis in Mathematical Models Arising from Biology

Practical identifiability is a fundamental challenge in the data-driven modeling of biological systems, as many model parameters cannot be directly measured and must be estimated from experimental data. I introduce a novel mathematical framework for practical identifiability analysis in dynamic models. Starting from a rigorous mathematical definition, it is proved that practical identifiability is equivalent to the invertibility of the Fisher Information Matrix (FIM). The relationship between practical identifiability and coordinate identifiability is further established, intro-

ducing an efficient metric that simplifies and accelerates identifiability assessment compared to traditional profile likelihood methods. To address non-identifiable parameters, new regularization terms are incorporated,enabling uncertainty quantification and improving model reliability. To support experimental design, an optimal data collection algorithm that ensures all model parameters are practically identifiable is proposed. Applications to biological models demonstrate the effectiveness and computational efficiency of the proposed framework in uncovering critical biological processes and identifying key observable variables.

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MS48

Geometric, Topological, and Algebraic Invariants in Single-Cell Biology

Single-cell technologies, including single-cell RNA sequencing and spatial transcriptomics, generate high-dimensional, heterogeneous, multiscale, and noisy data that encode complex biological processes such as differentiation, signaling, and disease progression. A central challenge is to extract robust, interpretable, and transferable features from these data. To address these challenges, we develop mathematical AI paradigms that embed deep mathematical invariant structures of single-cell biology into neural networks. By incorporating invariants from algebraic topology, differential geometry, geometric topology, and commutative algebra, we substantially enhance the robustness, interpretability, and predictive power of AI models for single-cell analysis. I will also briefly discuss our invariant-embedded mathematical AI frameworks for applications in drug discovery, viral evolution, protein engineering, and biomedical imaging.

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MS49

When Data Meets Dynamics: AI for Systems Medicine

In complex biological systems, the most important dynamics are often the ones we cannot directly measure. AIAristotle is a principled framework for discovering missing terms or unknown interactions in mechanistic models by leveraging indirect observations. Rather than relying purely on data-driven prediction, the method infers the mathematical structure of unobserved dynamics from the data that are available, embedding physical and biological constraints into the learning process. Building on this idea, we introduce compartment-model-informed neural networks (cMINNs), which integrate classical compartmental ODE models with physics-informed learning to uncover hidden mechanisms in systems medicine. As an application, we study tumor response under multiple dosing regimens and use cMINNs to infer latent resistance dynamics and time-varying cell death rates that are not directly observable. This approach enables interpretable discovery of biologically meaningful interactions, providing mechanistic insight into treatment resistance while preserving the predictive power of modern AI.

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MS49

Practical Indistinguishability in a Gene Regulatory Network Inference Problem

Current automated model discovery algorithms have been widely applied to biological data sets, but often require high-frequency temporal sampling of the system, relatively low noise, and the explicit measurement of most, if not all, relevant state variables. Biological data from experimental studies often deviate from at least one of these characteristics. To explore inference outside this data regime, we attempted an inference problem based on infrequently sampled, noisy gene expression data collected over the course of development in the nematode Pristionchus pacificus. This nematode can form one of two distinct mouthform phenotypes during development, depending on specific environmental conditions and its genetic background, but the structure of the regulatory network underlying this developmental decision is currently unknown. To learn more about the underlying mechanism, we fit approximately 14,000 gene regulatory network model variants to gene expression data across three experimental conditions. We then used machine learning approaches to find model sets, or collections of models with shared regulatory features that best fit the data, for each experimental condition. In the intersection of the three model sets, there exists a regulatory network model that explains the data across all three conditions, uncovering a new possible regulatory network that may control the developmental decision. This study acts as a generalized sensitivity analysis across model structures, illuminating what we can honestly infer about biological systems from limited experimental measurements.

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MS49

Learning Heterogeneous Dynamics in Structured Populations with Weak-Form Methods

Structured population models are a standard tool for describing how individuals distribute and evolve across physiological traits such as size, age, or cell state. In practice, however, these dynamics are rarely homogeneous: growth, division, and mortality vary across individuals and over latent subpopulations, and the governing PDE terms are often only partially known. This talk presents a weak-form, data-driven framework for discovering heterogeneous structured population dynamics directly from measurements. We first introduce WSINDy (Weak-form Sparse Identification of Nonlinear Dynamics) as a principled approach for learning PDE population models from aggregate density observations. By recasting candidate PDE operators in the weak formulation, WSINDy reduces sensitivity to noise and avoids the need for explicit differentiation, enabling reliable identification of transport and source terms. In an attempt to bridge scales, we then extend this method to make use of individual-level trajectories where we infer distributions of growth rates (and related heterogeneous parameters) that are consistent with the learned population-level dynamics, thereby linking mechanistic PDE structure to variability at the level of individuals.

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MS49

Learning Equations of Oscillatory Biochemical Systems Using Neural Networks

Data-driven model identification techniques have transformed how scientists infer models of dynamical systems from data. Interpretable (white-box) machine learning methods like Sparse Identification of Dynamical Systems (SINDy) or Symbolic Regression (SR) can generate symbolic differential equations that describe system dynamics. Especially SINDy has been successfully applied to synthetic data across diverse fields, including biology. However, SINDy, SR and similar methods are still not often used to successfully identify interpretable models directly from experimental datasets. Beyond data limitations like resolution, noise, and dimensionality, effective model discovery often requires understanding underlying phase space structures, which significantly impact results. Key information, such as nullcline forms and fixed-point positions, can be crucial for model identification. Previously, we showed that this hidden information can be uncovered by varying an offset in oscillatory data while applying SINDy. Although promising, this approach remains constrained by SINDys requirement for a term library.To overcome these limitations, we propose a new method called CLINE (Computational Learning and Identification of Nullclines) that uses a simple feed-forward neural network, trained on time series data, to directly reveal nullcline structures. Integrating this neural network insight with symbolic methods such as SINDy or SR allows us to leverage strengths of Deep Learning while producing interpretable models in differential equation form.This enhances model discovery from time series data as we show applying CLINE in combination with SR to learn the underlying equations describing the Belousov-Zhabotinsky equation directly from experimental data without any prior knowledge.

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MS50

Assessing Biological Fidelity in Dimensionality Reduction: Scrna-Seq, Cytof, and Cite-Seq

Modern biological datasets require dimensionality reduction (DR) to enable meaningful analysis and visualization of high-dimensional measurements. Despite the availability of numerous DR methods, their ability to preserve biologically relevant structures remains inadequately characterized. Our previous benchmarking study systematically evaluated 16 DR algorithms across scRNA-seq, CyTOF, and CITE-seq platforms, focusing on metrics that assess pairwise distance preservation and local neighborhood retention. While these metrics effectively capture local geometric properties, they fail to evaluate preservation of global biological progression patternsessential for interpreting cell differentiation, disease progression, and developmental lineages. This lecture will present a comprehensive research program addressing this critical gap in DR evaluation for biological applications. We introduce mathematical frameworks for quantifying trajectory preservation, including metrics such as Hausdorff distance and dynamic time warping, to assess how DR algorithms maintain biological paths through high-dimensional space. Through systematic evaluation across diverse datasetsincluding glioblastoma progression, pancreatic differentiation, immune cell characterization, and atherosclerotic tissue architecturewe demonstrate that DR method selection profoundly impacts biological interpretation.

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MS50

Positive Affect and Sleep Quality As Predictors of Pain Onset in Pediatric Sickle Cell Patients

Sickle cell disease (SCD) is an inherited blood disorder affecting millions worldwide, most of whom are of African descent. Individuals with SCD produce abnormally shaped red blood cells with shortened lifespans that can obstruct blood vessels, leading to recurrent severe pain episodes. Managing pain remains a major challenge in improving quality of life for pediatric patients. Valrie et al. (2021) reported associations between sleep quality and next-day pain, as well as between positive affect (PA) and pain. Positive affect, measured through self-reported diary scales, reflects the level of positive emotional states experienced by a child. Motivated by these findings, we developed a mathematical modeling framework to investigate pain dynamics in pediatric SCD, focusing on sleep quality and PA as predictors of pain. Using longitudinal diary data, we construct dynamical models that capture day-to-day pain changes while accounting for age- and medication-related differences in children and adolescents. We first evaluate PA or sleep quality separately as pain modulators, then extend the model to include both simultaneously, allowing us to examine their joint and potentially offsetting effects. This flexible framework can incorporate additional affective, behavioral, and physiological variables, clarifying how interacting factors shape pain over time and supporting more individualized intervention strategies.

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MS50

Multi-Scale Computational Modeling of Tumor Vasculature: Integrating Anatomical and Functional Dce-Mri Data for Sarcoma Treatment Monitoring.

Understanding spatial drug distribution within tumors is essential for predicting chemotherapy response in sarcoma. We introduce a framework integrating vessel segmentation, topological data analysis (TDA), and perfusion-based clustering to characterize tumor heterogeneity using DCE-MRI at pre-treatment, mid-treatment, and pre-surgical timepoints. First, we construct a dual-scale vascular model for undifferentiated pleomorphic sarcoma. Automated dual-vesselness filtering segments vessels and tracks them across contrast phases to quantify enhancement kinetics and radius. Branching analysis classifies vessels into large arteries (early enhancing, larger radius), tumor-associated arteries (later-appearing, smaller radius) and large veins, establishing structural understanding of tumor blood supply. Second, we cluster tumor voxels by wash-in and wash-out kinetics to identify spatially and functionally distinct subregions. Longitudinal analysis across timepoints reveals dynamic patterns in therapeutic response. Third, we apply TDA to wash-in rate maps, capturing topological features such as connected components and loops that characterize spatial organization of drug uptake. Integrating macroscale vascular architecture, micro-scale perfusion and topological analysis, our framework moves beyond conventional imaging toward spatially resolved tumor characterization, providing quantitative tools for tracking vascular evolution through treatment to inform personalized therapy.

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MS51

Strong-Inference Model Selection for Host-Pathogen Dynamics: Lessons from Klebsiella Pneumoniae

Severe Klebsiella pneumoniae infection progresses from localized pneumonia to bacteremia through nonlinear interactions among bacterial growth, immune activation, tissue damage, and heme-driven inflammation. Prior mathematical models have captured pieces of this process but typically embed a single mechanistic assumption, limiting their ability to discriminate among competing biological hypotheses. To address this, we developed a strong-inference modeling framework consisting of a full seven-state mechanistic model and four hypothesis-driven variants representing alternative drivers of systemic spread: iron acquisition, epithelial damage amplification, LPS-mediated vascular disruption, and blood-borne toxicityinduced vascular leakage. Each variant is fit to murine time-series data for bacterial burden, hemopexin, and immune activity using a robust log-space optimization pipeline. Model behavior is evaluated using AICc/BIC, global sensitivity analysis via Latin Hypercube Sampling and PRCC, and steady-state bifurcation and stability analysis. This framework enables systematic comparison of competing biological mechanisms, quantifies how uncertainty propagates through the system, and provides a principled basis for identifying the pathways most likely to underlie progression to bacteremia as additional data and model refinements become available.

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MS51

MCS in Drug Development

The ISoP MCS SIG has sought to accelerate the translation of existing and emerging mathematical and computation methodologies into drug discovery and development, supporting the use of model-informed drug development (MIDD). This has been realized through activities including fostering academic and industry collaboration, engagement with regulatory frameworks, and supporting communication of novel methodologies to the community. Background on the SIG and work to support these goals will be provided, as a means to frame discussion and set up case studies of MCS in drug development and how different modeling approaches and techniques (e.g., PBPK, popPK, QSP, AI/ML, SA/UQ) all contribute to more efficient, effective development of medicine for patients.

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MS51

Unleashing the Power of Mathematical Modeling to Inform Drug Discovery and Development

This minisymposium speaker will be able to submit their abstract if the proposal is accepted, due to constraints from their employer.

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MS51

Tailored Identifiability Analysis Approaches for Model Reduction with Applications to Fibrin Polymerization

In the early stages of wound healing, fibrin polymerization plays an essential role in clot formation and retraction. Sialic acid is known to impact fibrin polymerization kinetics, but the exact mechanisms are not well understood.

We consider techniques for data driven and computational modeling of the polymerization of fibrinogen into fibrin matrix as mediated by thrombin, which can be represented as a system of ordinary differential equations with reaction rates as parameters. We build upon existing studies by introducing randomization to local sensitivity-based parameter identifiability analysis, facilitating greater exploration throughout parameter space. Our approach generates several model realizations that are screened for the quality of curve fits to data for fibrin matrix concentration and then used to determine consistently unidentifiable parameters as candidates for removal. Among the candidate reduced models, the most accurate one is selected and used to estimate and compare influential parameter values from data corresponding to three experimental designs with different levels of sialic acid. We employ statistical significance tests on the estimated values of influential parameters across designs, and results are interpreted to inform the mechanisms that may be impacted by sialic acid concentration on fibrinogen.

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MS52

Characterizing Tumor Growth Dynamics During Colorectal Cancer Evolution

Understanding the dynamics of tumor growth during the early stages of cancer development is crucial for establishing effective detection strategies. As cells accumulate driver mutations, populations that harbor these mutations start to grow abnormally, with cells with more drivers typically exhibiting more aggressive behavior and faster growth. The progression of cell behavior in colorectal cancer coincides with the progression from healthy tissue to early and advanced benign tumors (adenomas) and finally to cancer. We propose a multi-type stochastic branching process model that tracks the sizes of individual colorectal adenomas to study local dynamics in early cancer evolution. Using a semi-deterministic approach, we compute the distributions of waiting times for early and advanced adenomas, as well as the sizes of adenomas present at any given age. We use data collected from electronic health records for colonoscopies to fit the parameters of our model in order to understand the effects of those parameters on tumor growth.

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MS52

Measuring Growth Dynamics of Barrett's Esophagus with Stochastic Models and Epigenetic Clocks

Esophageal adenocarcinoma (EAC) remains a highly lethal malignancy with poor long-term survival when diagnosed late, making early detection and prevention strategies essential. EAC develops from the precursor Barretts esophagus (BE) and a clearer understanding of BE origins and tissue maintenance is needed to define the drivers of progression to EAC. In this talk, we present DNA methylation data from 90 multi-region esophageal tissue samples from 17 BE patients. We first inferred BE tissue age (i.e., dwell time) for each sample using our previously developed BE epigenetic clock model and found that BE ages collectively indicate spatial age and diversity gradients in the esophagus; younger crypts were located distally near the gastroesophageal junction (GEJ) and have more heterogeneous tissue ages than proximal regions. To explain these patterns, we built a minimal agent-based model incorporating birth and death events and fit this model to our data. To reproduce a spatial age gradient, we found that close fits to the data required the assumption that young crypts regenerate from the GEJ. In this model framework, birth and death gradients together form a source region of new BE continually developing near the GEJ, while less growth occurs proximally in BE. These findings represent a first step in inferring ongoing BE growth dynamics, also providing a minimal model that can serve as a candidate tool for identifying mechanisms of BE to EAC progression in future datasets.

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MS52

From Tumorigenesis Timelines to Cancer Risk: Data-driven Stochastic Models of Tumor Evolution

Cancer arises through the stochastic accumulation of somatic alterations in self-renewing tissues, yet the timing of driver events, their tissue-specific ordering, and the origin

of large differences in mutation burden between normal and cancer cells remain poorly understood. This talk presents three stochastic modeling approaches calibrated from epidemiologic and sequencing data. First, a continuous-time evolutionary model incorporating tissue-specific stem cell population sizes, division rates, carrying-capacity constraints, and heterogeneous driver fitness effects is introduced. Parameters are inferred through large-scale simulations combined with Gaussian-processbased calibration. Despite lacking closed-form solutions, the model reproduces cancer incidence patterns across multiple organs and inherited syndromes, suggesting early initiation followed by prolonged clonal expansion. Second, a simplified formulation with closed-form expressions for age-dependent accumulation of endogenous somatic mutations in normal tissues shows that endogenous processes explain most variation in cancer risk across tissue types. Finally, a related model comparing normal and cancer individuals reveals a consistent multi-fold increase in mutation burden and enables quantitative testing of mechanistic hypotheses. Together, these approaches provide a unified quantitative framework for cancer evolution, risk, and prevention.

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MS52

Quantification of the Effect of Early-Stage Cancer on Cell-Free Dna Levels in Plasma

Cell-free DNA (cfDNA) is a promising biomarker for cancer detection. However, cfDNA dynamics in the presence of cancer are still poorly understood. Leveraging a rich dataset of cfDNA in healthy individuals and early-stage cancer patients, we find a multiplicative increase in cfDNA concentration in the presence of cancer. This increase is cancer type-specific, ranging from a 1.3-fold increase in lung cancer, to a 12-fold increase in liver cancer, and does not originate from tumor, but from healthy tissue. Employing an additional dataset reporting the tissue of origin of cfDNA, we observe a significant increase in the correlation between cfDNA originating from leukocytes and from non-leukocyte sources in cancer patients. Introducing a mathematical model for cfDNA dynamics, we find that the observed correlation can be explained by a saturation mechanism in cfDNA clearance. Saturation in clearance implies that smaller increases in cfDNA shedding from healthy tissue due to cancer may lead to the larger observed multiplicative increases in cfDNA levels.

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MS53

Deep Echo State Networks Improve Cardiac Voltage Time Series Prediction

Many real-world time series, including cardiac action potential dynamics, can exhibit complex dynamics, which makes reliable forecasting a difficult task. Although recent machine-learning methods have shown encouraging results, learning these dynamics accurately remains challenging. Echo state networks (ESNs), a class of recurrent neural networks with randomly connected internal units and trained output layers only, have been proposed as an effective solution for multi-step-ahead prediction. ESNs can model complex temporal behavior while keeping training costs low, which makes them computationally efficient. Deep echo state networks extend the standard ESN by stacking multiple reservoir layers, allowing different layers to capture distinct features of the underlying dynamics. For this talk, we evaluated the performance of deep ESNs across several network configurations, including a novel hybrid model that incorporates a knowledge-based component. The models were tested on two complex datasets, including a Mackey-Glass time series that describes white blood cell population density and a dataset of complex experimental zebrafish cardiac voltage recordings. Our results indicate that, for certain architectures, deep ESNs substantially outperform standard ESNs, and the proposed deep hybrid architecture is particularly effective for the cardiac dataset.

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MS53

Alternate Pacing and Chaos in Cardiac Tissue

We investigate the period-doubling bifurcation to alternans in heart tissue. We examine the impact of strategically perturbing an underlying dominant frequency, which we define as alternate pacing, to better understand how small, carefully calculated deviations from the underlying pacing rate impact electrical response. We will share our experimental results in hearts excised from an adult bullfrog (Rana catesbeiana) and discuss the impact of temperature on the bifurcation to alternans. Furthermore, we will show how this experiment lead to an in-depth investigation of alternate pacing in the logistic map. We will also discuss how the complete investigation of alternate pacing helps illuminate the usefulness of the systems noise. We believe the noise can also led to a methodical technique to explore chaos. More specifically, by computing the power spectrum from the noise that is present during chaos, we will share how this can give insight into the underlying dynamics of the system.

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MS53

Observability Analysis and Data Assimilation Strategies for a Cardiac Action Potential Model

To improve our understanding of cardiac dynamics, various researchers have characterized the ability of data assimilation (DA) algorithms to reconstruct quantities that are difficult to measure, yet are thought to contribute to arrhythmia formation. Observability, which is a control-theoretic property that indicates whether a given set of measurements is sufficient for uniquely identifying a past system state, is related to DA but less commonly examined in cardiac research. In the present study, we computed modal observability values for a two-variable action potential (AP) model, then compared observability with DA performance. We numerically linearized a nondimensional FitzHugh-Nagumo (FHN) model that was modified by other researchers to produce cardiac-like AP behav-

ior. We found, for the range of cycle lengths (CLs) examined, that membrane potential was the more informative choice of measured variable, in the sense of maximizing observability, for shorter CLs, whereas measuring the refractory variable yielded stronger observability for longer CLs. Next, we tested the ability of a Kalman filter (KF) and an unscented KF (UKF) to reconstruct one FHN variable from measurements of the other, where all measurements were simulated with the linearized model. Measurements yielding stronger observability corresponded with lower KF estimation errors, as expected. For the UKF, measurements yielding stronger observability led to more accurate estimates of the unmeasured variable.

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MS53

Learning Cardiac Action Potential Equations in the Presence of Unobserved Variables

Sparse Identification of Nonlinear Dynamics (SINDy) is an interpretable machine-learning method that can be used to fit a set of differential equations to data given a library of terms that may appear in these equations, and as such, it is a potentially useful tool for constructing new cardiac electrophysiology models. In this presentation, we explore the feasibility of using modified SINDy to fit simple cardiac models when certain variables cannot be measured experimentally. This use case reflects the reality of real-world cardiac experiments, where often only voltage (and perhaps intracellular calcium) can be observed directly, while gating variables remain unobservable. In this proof-of-concept work, the FitzHugh-Nagumo (FHN) model and a few variants are used to generate test datasets in which the voltage variable is considered observable and the recovery variable is considered unobservable. Several modifications of SINDy for partially observed systems are considered, including Latent ODE (L-ODE) methods, in which multi-dimensional systems of first-order ODEs are converted to a single higher-order ODE; time-delay embedding based on Takens' theorem; and deep-learning methods such as deep delay autoencoders and SINDy-SHRED. After comparing the feasibility and effectiveness of these methods on FHN variants, preliminary results applying the same methodologies to real-world data will be discussed.

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MS54

Oncolytic Virus Therapy: Overview and the promise of picornaviruses

Many viruses have been tested as possible treatments for cancer, with the central challenge of finding ones that do not damage the host directly without being cleared too fast by the immune system, and that engage the immune system to attack the cancer after the virus has been cleared without causing autoimmune damage to the patient. After presenting an overview of how mathematical models have been used to address these questions and to think about combination approaches with chemotherapy and immunotherapy, this talk will introduce mathematical models we have been developing to harness the power of picornaviruses. This large family includes many enteroviruses, which in turn include rhinovirus, the most common cause of the common cold. In particular, we are collaborating with a laboratory to model how prior exposure to a virus such as the enterovirus Coxsackievirus A21 might affect efficacy through existing immunity. This provides the key background for our main focus on rhinoviruses, which have the benefit of being widespread, extraordinarily diverse, relatively avirulent, and modifiable to attack melanoma. We present models of how to assess and overcome the complex challenges created by the wide range of pre-existing immunity.

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MS54

The Role of the Immune Response in Oncolytic Virus Treatment

Oncolytic viruses present a promising path for cancer treatment due to their selectivity in infecting and lysing tumor cells and their ability to stimulate the immune response. While the immune response can help eliminate the tumor, it also acts to clear the virus and often limits the effectiveness of oncolytic virus therapy. We use data from experiments using oncolytic viruses to develop mathematical models that incorporate various components of the immune response. We find that moderate immune responses that help prolong, but not eradicate, the viral infection are best for eliminating the tumor.

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MS54

Effect of Virus-Specific Immune Responses on Oncolytic Viral

One of the main challenges in oncolytic virus therapy is delivering the virus to the tumor site. A major obstacle is that virus-specific immune responses may clear the virus and prevent the spread of infection within the tumor. Here, we consider two types of virus-specific immune responses: (1) an antibody (Ab) response that blocks the attachment of a free virus to a cell; and (2) a cytotoxic T cell (CTL) response that kills infected cancer cells. We use mathematical modeling to assess the impact of each of these virus-specific immune responses on treatment outcomes. Our results show that the activation of an immune response can have three different types of effects on treatment outcomes: 1- It renders the therapy relatively ineffective. 2- It has no effect on the treatment outcome. 3- It enhances the result of the therapy. The third outcome occurs only

when a CTL response is activated. We derive parameter constraints under which each scenario is observable. We show how the presence of a virus-specific immune response affects the optimal treatment outcome and how this effect depends on viral virulence.

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MS54

Effect of Increased Cell Death Relative to Division Rates on Mutant Burden in Expanding Populations: Implications for Using Viruses to Reduce Drug Resistant Mutants in Tumors

Expanding cell populations, such as bacterial and tumor colonies, continuously accumulate mutations as they grow. In the context of cancer therapy, oncolytic viruses are being explored as agents that selectively infect and kill tumor cells. Even if such viruses do not completely eradicate a tumor, increasing the death rate of cancer cells relative to their division rate may alter the burden of drug-resistant mutants and potentially improve subsequent treatment outcomes. This motivates a fundamental question: how does mutational burden depend on cell turnover, defined as the ratio of birth to death rates, in expanding populations? Despite its importance, the dependence of mutant burden on turnover remains poorly understood. Elucidating this relationship is crucial for predicting how populations adapt to changing environments, including during evolutionary rescue and resistance evolution. Previous theory suggested that higher turnover increases mutant abundance at a given population size, since more cell divisions are required to reach that size. Using well-mixed and spatial stochastic models, we find the relationship is more nuanced. For advantageous mutants, higher turnover does increase mutant numbers. For disadvantageous mutants, however, mutant abundance can actually decrease with turnover or exhibit non-monotonic behavior, with these somewhat counterintuitive patterns being more pronounced in spatially expanding populations. We derive explicit analytical boundaries separating different regimes and quantify the contribution of stochastic jackpot events to mutant burden. In spatial models, we show that the interplay between two timescales is critical: the time to reach the target population size versus the time for wild-type cells to erode disadvantageous mutant clusters. Our results reveal how basic demographic parameters influence the ability of cell populations to overcome selective barriers during growth, with implications for understanding both evolution in natural settings and disease progression.

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MS56

Inviscid Vortex Sheet Models for Bioinspired FluidStructure Interaction

Thin plates and membranes are finding considerable interest as lightweight and efficient lifting surfaces. It is very expensive computationally to stably and accurately compute fluid flows around macroscopic deforming bodies due to the fine vortex structures created on the body surface. As viscosity goes to zero, the boundary layer becomes a layer of vorticity of zero thicknessa vortex sheet. The vortex sheet separates from sharp edges evolves with the body as a coupled system. We discuss two applications of vortex sheet methods. The first is 2D and 3D membrane flutter in fluid flows. Thin membranes occur in the deforming wings of bats and engineered vehicles, though we focus on the basic dynamics of the fluid-structure interaction. The second application is falling plates in a fluid, whose dynamics are relevant to falling leaves and gliding wings. We simulate their motions byincorporating leading-edge shedding in a robust way for the first time.

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MS56

Optimizing Metachronal Paddling at Low Reynolds Number with Reinforcement Learning

Metachronal paddling is a swimming strategy in which an organism oscillates sets of adjacent limbs with a constant phase lag, propagating a metachronal wave through its limbs and propelling it forward. This limb coordination strategy is utilized by swimmers across a wide range of Reynolds numbers, which suggests that this metachronal rhythm was selected for its optimality of swimming performance. In this study, we apply reinforcement learning to a swimmer at zero Reynolds number and investigate whether the learning algorithm selects this metachronal rhythm, or if other coordination patterns emerge. We design the swimmer agent with an elongated body and pairs of straight, inflexible paddles placed along the body for various fixed paddle spacings. Based on paddle spacing, the swimmer agent learns qualitatively different coordination patterns. At tight spacings, a back-to-front metachronal wave-like stroke emerges which resembles the commonly observed biological rhythm, but at wide spacings, different limb coordinations are selected. Across all resulting strokes, the fastest stroke is dependent on the number of paddles; however, the most efficient stroke is a back-to-front wave-like stroke regardless of the number of paddles.

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MS56

Effects of Mechanosensory Feedback and Environment Interactions on the Locomotion of Lampreys with Spinal Injuries

Spinal cord injuries in many vertebrates, including mammals, often result in permanent loss of locomotor function. Other vertebrates, such as lampreys, can partially or wholly recover locomotor functions following severe spinal injuries. The exact mechanism of recovery is not well understood. One hypothesis is that function may be recovered through amplified proprioceptive (body-sensing) feedback. Lampreys serve as model organisms for such vertebrate neurophysiology and swimming studies. In this work, we implement a multiscale, integrative, computational model of an anguilliform (eel-like) swimmer fully coupled to a viscous, incompressible fluid in an immersed boundary framework and examine the effects of mechanosensory input on swimming performance and injury recovery. We discuss our results showing that some types of amplified feedback can restore functional swimming. We also consider the effect of the external environment on recovery strategies.

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MS56

Emergent Metachronal Paddling and Swimming in a 3-dimensional Fluid-Structure Interaction Model of a Gossamer Worm

Metachrony is often found throughout nature in many locomotory and fluid transport systems. Gossamer worms, also known tomopterids, are a soft-bodied, pelagic polychaete that employ metachronal paddling, with flexible parabodia on both sides of their body that navigate the midwater ecosystem which they inhabit. In the following study, we introduce a three-dimensional, computational, fluidstructure interaction model of a tomopterid, using a stadium (i.e. a rectangle with two half circles) with flexible parapodia appendages. The motion of the flexible parapodia will emerge from the interplay of passive body elasticity, active tension, and hydro-dynamic forces, and metachrony will result from differences in phase between the parapodia. The body is freely swimming as a result motion of the parapodia and the metachronal waves formed on both sides of the body. The model is used to explore how variations in phase across the body affect the resulting swimming performance and stability.

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MS57

Ephaptic Propagation of Subthreshold Neural Signals

Experiments in hippocampal slices shows that slow amplitude oscillatory waves can propagate across tissue even when synaptic transmission is blocked, including propagation through a complete transection. These waves travel at 0.1 m/s, maintain their frequency, generate extracellular fields ¡1 mV/mm, andunlike spikescan interfere constructively or destructively, demonstrating true wave behavior at very low amplitudes. To investigate the mechanisms that permit such analog, nonsynaptic transmission, we developed a self-consistent ephaptic-coupling model in NEURON/Python. A 2-D sheet of reduced CA1 pyramidal neurons (50 cells, 33 compartments each) was embedded in an infinite volume conductor and solved implicitly using a Jacobian-free NewtonKrylov method. Each compartment had leakage, NaP, and potassium channels. Propagation was initiated by subthreshold current injection at one end of the array, and the extracellular field was computed from the sources and sinks at each compartment assuming a homogeneous volume conductor. The results show that the model supports low-amplitude propagation and that subthreshold waves can transition to self-sustained ephaptic propagation at speeds around 0.15 m/s. Since many brain rhythms such as theta, sharp waves, ripples, and other low-amplitude signals propagate at similar speeds and are crucial for encoding and memory, these findings suggest that significant neural processing may occur below threshold through ephaptic mechanisms.

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MS57

Mathematical Modeling of Ephaptic Coupling Effects in Axon Bundles

Experimental and theoretical studies have shown that ephaptic coupling leads to the synchronisation and slowing down of spikes propagating along the axons within peripheral nerve bundles. However, the main focus thus far has been on a small number of identical axons, whereas realistic peripheral nerve bundles contain numerous axons with different diameters. We present a computationally efficient spike propagation model, which captures the essential features of propagating spikes and their ephaptic interaction, and facilitates the theoretical investigation of spike volleys in large, heterogeneous fibre bundles. We first lay out the theoretical basis to describe how the spike in an active axon changes the membrane potential of a passive axon. These insights are then incorporated into the spike propagation model, which is calibrated with a biophysically realistic model based on HodgkinHuxley dynamics. The fully calibrated model is then applied to peripheral fiber bundles with a large number of axons and different types of axon

diameter distributions. One key insight is that the heterogeneity of the axonal diameters has a dispersive effect, and that a higher level of heterogeneity requires stronger ephaptic coupling to achieve full synchronization between spikes. We further demonstrate that in sufficiently large white matter fiber bundles in the brain, contrary to the findings in peripheral nerves, ephaptic coupling increases the velocity of spikes.

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MS57

Intercalated Disc Nanostructure Governs Ephaptic Coupling-Mediated Regulation of Local Ionic Currents and Concentrations and Cardiac Conduction

The intercalated disc (ID) is a structurally heterogeneous junctional complex essential for cardiac conduction. Perturbed ID structures are found in arrhythmia patients, yet most computational models use oversimplified geometries with uniform ion channel distributions. We developed a physiologically realistic finite element framework incorporating spatially heterogeneous gap junctions, multiple ion channels (NaV1.5, Kir2.1, CaV1.2, NKA), and dynamic cleft ionic concentrations. We generated 384 ID configurations and simulated tissue-level conduction across multiple coupling regimes. Using multilayer perceptron neural networks for sensitivity analysis, we quantified how geometric and nanostructural factors influence cleft dynamics and conduction. Gap junctional coupling, cleft geometry, and nanostructure heterogeneity dominantly determine sodium current synchronization and conduction velocity. Ionic fluxes critically alter local currents: sodium depletion drives compensatory calcium influx, significantly increasing ID calcium current. Concentrated ion channel or gap junction clusters slow conduction, while tissue-scale ID heterogeneities cause conduction block or spatially varying velocities, suggesting a re-entry mechanism. Membrane separation exhibits context-dependent effects depending on coupling strength. These findings establish a quantitative framework linking nanoscale ID structure and heterogeneity to tissue-scale conduction.

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MS57

A Novel Paired Cardiomyocyte Model to Dissect Individual Contributions of Gap Junctional and Ephaptic Coupling

Background: Cardiac electrical conduction is mediated primarily by gap junctional coupling (GJC) and ephaptic coupling (EpC). A fundamental question is whether GJC and EpC operate independently or interdependently. To address this, we developed a paired-myocyte model to investigate their interplay. Methods: A single patch-clamp configuration was used to record whole-cell sodium current (INa) in isolated end-to-end paired mouse myocytes. Based on the EpC hypothesis, widening the sodium channel (Nav)rich perinexus within the intercalated disc, where EpC is proposed to occur, should increase perinexal INa and thereby increase whole-cell INa in paired myocytes. Results: We first validated the feasibility of this model by demonstrating comparable INa densities between single and paired myocytes at 25-mM sodium. A distinctive INa trace in paired myocytes can reflect Nav activation in the unpatched myocyte. Using this trace, we confirmed that EpC alone is insufficient to support electrical conduction when GJC was compromised, even if widening the perinexus alone indeed increased INa. Further, increasing sodium from 25 to 35 mM restored the blocked electrical conduction, consistent with enhanced EpC. Conclusion: Using this model, we demonstrate that EpC is dependent on GJC under low extracellular sodium and identify extracellular sodium level as a critical determinant of conduction when GJC is impaired. These findings can advance our mechanistic understanding of cardiac conduction

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MS58

Quantifying Exploration-Exploitation in Collective Problem Solving Using Information Theory

Decentralized collectives, from animal groups to human problem-solving networks, must both explore new regions of a solution space and integrate distributed knowledge to find optimal solutions. While certain structural features such as small-world topology are associated with ef-

ficient performance, the causal information dynamics underlying these effects remain unclear. In this talk, I will present results from an agent-based model of combinatorial search, the Potions Task, and introduce an information-theoretic framework that quantifies explorationexploitation in networks through measures of redundancy and synergy in agents discoveries. I show that high-performing systems regulate information overlapbalancing local redundancy with long-range synergy. However, synergy robustly predicts performance across network structures and can override structural advantages, revealing a potentially general principle governing decentralized collective problem-solving.

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MS58

Nonlinear Affective Cascades in Decision Dynamics

Individual emotional states fluctuate continuously, pulled toward personal baselines while remaining sensitive to external events. We formalize this using DynAffect-C, an empirically grounded affective update rule capturing two forces: a pull back toward an individual's emotional baseline, and the tendency of external inputs to linger rather than dissipate instantly. Embedding this rule in a coupled network model where agents decide whether to express their internal state to neighbors, whose expressed states then feed back as external input yields clear conditions for collective cascades. Cascades emerge when social coupling and signal persistence jointly amplify transient shocks faster than baseline regulation can absorb them, causing local perturbations to propagate system-wide a dynamically richer analog to emotion contagion. Nonlinear baseline attraction generates tipping points and path dependence: identical shocks produce either rapid group-wide transitions or negligible drift depending on the group's starting state. Unlike standard contagion models, DynAffect-C's parameters are estimable from individual behavioral data, grounding collective predictions empirically. This yields testable hypotheses about how individual differences in baseline regulation versus signal persistence shape expression decisions, cascade initiation, and the stabilityresponsiveness tradeoff in collective affective decision-making.

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MS59

Open Mathematical Problems in Manifold Learning for Single-Cell Data

Single-cell transcriptomics provides unprecedented resolution into high-dimensional biological manifolds. Dimensionality reduction techniques, notably t-SNE and UMAP, have become the standard for visualizing these structures. However, while these algorithms are widely used as investigative tools, their mathematical foundations, particularly regarding global structure preservation and topological stability, remain poorly understood. In this talk, I will highlight these specific open problems and discuss the challenges of providing a rigorous mathematical interpretation of the resulting low-dimensional embeddings.

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MS59

Stochastic Optimization of the Race Between Pathogens and Clinicians with Birth Death Fitness

Our talk presents data-driven stochastic optimization strategies for the evolutionary race between a pathogenic cell population and a clinician. In this system, the clinician seeks to eliminate the adversarial cell population through optimally changing their environment and fitness, while conversely, the cells make optimal decisions to adapt and survive. In addition to its applications in translational medicine, our work generalizes to businesses and institutions to optimize their adaptability and resilience to environmental stress. This is joint work with Linh Huynh.

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MS59

A Proximal Trust-Region Method for Nonsmooth Optimization with Random Models

Many practical applications require the optimization of uncertain or noisy systems that involve constraints and nonsmooth regularization to enforce desired properties like sparsity. These stochastic optimization problems necessitate the development of rigorous and scalable probabilistic methods for nonsmooth optimization. In this talk, we discuss the ProxSTORM algorithm for minimizing the sum of a possibly nonconvex Lipschitz-smooth function that can only be evaluated stochastically, and a nonsmooth, deterministic, convex function. We demonstrate that ProxSTORM is convergent with probability one under mild assumptions and that it yields competitive expected complexity bounds for achieving a prescribed stopping tolerance. We illustrate ProxSTORM's performance on two examples from machine learning and structural design.

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MS59

Random Matrix Limit Theorems in the Six Vertex Model

I will discuss various limiting objects which appear in the six-vertex model with fixed boundary conditions as the size of the model approaches infinity.

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MS60

Astrocytic Resource Diffusion Stabilizes Persistent Activity in Neural Fields

We introduce a coupled astrocyte-neural field model in which synaptic efficacy is regulated by depletion and recovery of a conserved resource pool that is recycled and

spatially redistributed through diffusively coupled astrocytes. The model supports spatially localized stationary bump solutions representing persistent activity patterns used in theories of parametric working memory. In a canonical ring architecture, we obtain explicit bump profiles and self-consistency conditions for bump width and amplitude. Linearizing the neural field while carefully accounting for perturbations at bump boundaries, we analyze the resulting spectral problem governing stability. Our analysis, supported by numerical simulations and complementary low-dimensional Fourier truncations, shows that astrocyte-mediated diffusion stabilizes bumps against translational perturbations: sufficiently strong diffusion suppresses drift instabilities and enlarges the parameter regime in which stationary bumps persist. More broadly, the analysis provides a tractable framework for studying coupled localnonlocal dynamics arising from resource-mediated feedback in neural field models.

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MS60

Transport Phenomena of Active Rods in Long Confined Channels

Many types of microswimmers, such as elongated motile bacteria and bimetallic particles, exhibit complex dynamics when subjected to background flow in confined environments like microchannels. These microswimmers deviate from streamlines and tend to accumulate along boundaries, with a preference for regions of high curvature and at corners. An individual trajectory typically alternates between intervals of upstream swimming near channel walls and downstream motion in the bulk fluid. This talk focuses on elucidating the extrusion dynamics of a dilute suspension of active microswimmers in long microchannels using mathematical modeling. We begin with an individual-based model of active rod in three-dimensional cylindrical microchannels. By considering various channel cross-sections, we identify potential geometric controls on the upstream swimming of active rods. Furthermore, three-dimensional Monte Carlo simulations show that the concentration profile of active rods along the major axis of the channel effectively evolves according to a one-dimensional advection-diffusion process.

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MS60

Spatiotemporal Patterns of Particle Size Distributions

Phase transitions in biological systems can generate spatiotemporally varying patterns of particle-size distributions. We present a spatially resolved population balance model framework for the evolution of particle size distributions in biological systems that couples nucleation, growth, and aggregation and transport. The experimental motivation is pattern formation of a class of pigments in plants called anthocyanins.

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MS61

Stochastic Evolutionary Models in Fragmented Populations as Autocatalytic Reaction Networks

Autocatalytic reactions can be dominated by stochastic variation when a reactant is at low count, and switching dynamics or extinction can occur in such systems. In this talk, we demonstrate our analysis on an evolutionary model in fragmented populations. Although this model is not directly understood as a system involving autocatalytic reactions, it can be described using a (bio)chemical reaction network with autocatalysis, and the theoretical tool developed in this work has potential broad applications to singularly perturbed continuous time Markov chains and autocatalytic systems. When the population is fragmented, individuals mainly evolve within each deme via reproduction or death events, and demes are connected through occasional migration events. We use a small parameter ε capturing the time scale separation between fast reproduction and death and slow migration. Wodarz and Komarova (2025) proposed a coarse-grained approach to study mutant fixation for this system with certain symmetry in rate parameters. In this work, we give a rigorous formulation of this coarse-graining for generic parameter values through singular perturbation analysis, and this allows us to characterize mutant fixation in fragmented populations as ε goes to zero.

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MS61

Efficient Enumeration of Autocatalytic Subsystems in Large Chemical Reaction Networks

Unstable cores are the origin of dynamic instability in chemical reaction networks (CRNs). Among those, the ones of positive-feedback type also comprise the elementary structures that characterize the emergence of autocatalysis, i.e., autocatalytic cores. They are represented as square submatrices of the stoichiometric matrix whose columns can be rearranged as irreducible negative-diagonal matrices (Child-Selection or CS matrices) in Metzler form (nonnegative off-diagonal entries). We show that irreducible Metzler CS matrices are represented as strongly-biconnected subgraphs - *Fluffles* - in the bipartite Knig representation of a CRN. *Fluffles* can be efficiently enumerated via suitable superpositions of elementary circuits using an equivalence relationship that is defined via the reactant-to-reaction edges. Autocatalytic *Fluffles*, and in particular autocatalytic cores, are detected via spectral properties of their corresponding CS matrix or by solving an ILP. The resulting algorithm is able to enumerate all autocatalytic CS matrices with irreducible Metzler part, and our implementation determines complete sets of autocatalytic cores for genome-scale metabolic models of various species.

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MS61

Using Delay-Differential Equation to Analyze Autocatalytic Systems

For a biological system to grow and expand, mass must be transferred from environment to the system and be assimilated into its reaction network. Here, I characterize biomass transferring process for a large class of exponential-growing systems including linear and nonlinear dynamics. By tracking biomass along reaction pathways, we can characterize the asymptotic growth trend of an n-dimensional ordinary differential equation (ODE) by reformulating it as a one-dimensional delay differential equation (DDE). The kernel function of this DDE represents the amplification and transferring delay of biomass, and summarizes the autocatalysis dynamics of the system. The DDE formulation allows us to compare reaction networks with various topologies and complexities, and provides a rigorous scheme for estimating system growth rate under dimensional reductionFor a biological system to grow and expand, mass must be transferred from environment to the system and be assimilated into its reaction network. Here, I characterize biomass transferring process for a large class of exponential-growing systems including linear and nonlinear dynamics. By tracking biomass along reaction pathways, we can characterize the asymptotic growth trend of an n-dimensional ordinary differential equation (ODE) by reformulating it as a one-dimensional delay differential equation (DDE). The kernel function of this DDE represents the amplification and transferring delay of biomass, and summarizes the autocatalysis dynamics of the system. The DDE formulation allows us to compare reaction networks with various topologies and complexities, and provides a rigorous scheme for estimating system growth rate under dimensional reduction.

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MS62

Mode Switching in Organisms for Solving Explore-Versus-Exploit Problems

Trade-offs between costly information-gathering movements (explore) and leveraging acquired information to achieve task goals (exploit) are central to decision-making, yet remain underexplored in sensorimotor control. We use the weakly electric fish Eigenmannia virescens as a model organism performing station-keeping inside a refuge with both vision and electrosense. Reduced sensory salience is known to elicit burst-like ancillary movements associated with active sensing, consistent with the increased demands for information gathering. However, distinguishing exploratory from exploitative movements remains unresolved. Here, using extended (600s) trials across varied conditions, we show that velocity-threshold classification is inadequate and develop improved criteria to disambiguate explore versus exploit behaviors. Specifically, we categorize high-speed bursts as either exploration of the environment or exploitation of learned spatial preferences by incorporating additional temporal contextspost-burst settling behavior, and refuge-relative position dynamics. We further quantify whole-body kinematics with DeepLabCut to compute changes in body curvature and tail-beating patterns, supporting a robust behavioral classification. Our results refine mode-switching models in active sensing and yield generalizable insights for sensorimotor control. This work was supported by NIH: R01NS147767

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MS62

Inference of Crosstalk Induced by CellCell Communication in the Era of Single-Cell Transcriptomics

Regulatory pathways in cells hardly function alone. During cell-cell communication, pathways activated by different ligand-receptor pairs may have crosstalk with each other. Understanding how pathways crosstalk is critical to uncover how signal transduction is regulated to serve various functionalities. In this talk, we explore how to dissect such crosstalk using single-cell and spatial omics data. We begin with SigXTalk, a computational method that quantifies the activation of pathways and identifies crosstalk with a specialized hypergraph learning approach that uncovers higher-order regulation in cells. Analysis of disease data shows SigXTalks capability in identifying crucial signals, targets, regulatory networks, and cell-cell communication patterns that distinguish different disease conditions. Applications to the data with multiple time points reveals SigXTalks capability in tracking the evolution of crosstalk pathways over time. We then extend the concept of crosstalk to spatial transcriptomics data. We develop SpaXTalk, to study the spatial heterogeneity of crosstalk by measuring the activation of cell-cell communication signals and its downstream pathways at the individual-cell level. Together, these studies show how computational tools and multi-omics data can decode the crosstalk in-

duced by cell-cell communication signals at different resolutions and in different biological scenarios.

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MS62

Data-Driven Spatiotemporal Modeling Reveals Personalized Trajectories of Cortical Atrophy in Alzheimer's disease

Alzheimer's disease (AD) is characterized by the progressive spread of pathology across brain networks, yet forecasting this cascade at the individual level remains challenging. We present a personalized graph-based dynamical model that captures the spatiotemporal evolution of cortical atrophy from longitudinal MRI and PET data. The approach constructs individualized brain graphs and learns the dynamics driving regional neurodegeneration. Applied to 1,891 participants from the Alzheimer's Disease Neuroimaging Initiative, the model accurately predicts key AD biomarkers – including amyloid-beta, tau, neurodegeneration, and cognition – outperforming clinical and neuroimaging benchmarks. Patient-specific parameters reveal distinct progression subtypes and anticipate future cognitive decline more effectively than standard biomarkers. Sensitivity analysis highlights regional drivers of disease spread, reproducing known temporolimbic and frontal vulnerability patterns. This network-based digital twin framework offers a quantitative, personalized paradigm for AD trajectory prediction, with implications for patient stratification, clinical trial design, and targeted therapeutic development.

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MS62

Reconstructing Data-Driven Biophysical Virtual-Cell Models for Cell State Transition Dynamics

Cells are building blocks of life. The success of AlphaFold and large-language models such as ChatGPT and Gemini have inspired explosive interest on building virtual whole-cell models, but the results are typically not better than baseline models using simple regression. These results raise a serious question whether the problem has been formulated properly. Meanwhile, dynamical systems theories are the natural language widely used in mathematical and systems biology for modeling cellular processes. Over the years my lab has been developing theoretical and computational approaches for integrating high-throughput single cell data into constructing data-driven mechanistic biophysics-based whole-cell models. We notice that it only takes a few minutes on a desktop to reconstruct a biophysical whole-cell model from scRNAseq data. Even without any prior knowledge as input, the model reveals detailed regulatory programs, and simulated trajectories even show cell cycle arrest at various cell cycle checkpoints. In this talk I will introduce the framework we developed, then focus on recent developments.

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MS63

Scalable Agent-Based Modeling with the Memilio Framework

Agent-based models (ABMs) are well suited for studying infectious disease dynamics at the individual level, particularly for assessing the effects of non-pharmaceutical interventions (NPIs) in heterogeneous populations. However, their widespread application to high-resolution, large-scale scenarios is often limited by substantial computational demands. We present a highly scalable agent-based modeling framework for pandemic simulation at city and regional scales, enabling detailed representation of individual behavior, contact structures, and a comprehensive range of NPIs, including detailed testing strategies, contact reductions, and isolation strategies. The model is designed to support high spatial and temporal resolution while maintaining computational efficiency. To address scalability challenges, we employ a hybrid parallelization strategy using OpenMP and MPI, allowing efficient execution on modern high-performance computing architectures. This approach enables simulations with large agent populations and extensive scenario exploration. We demonstrate the capabilities of the framework through two case studies, one for Brunswick with approximate 370k individuals and one for the city of Munich with 1.5m individuals. We illustrate how the model can be used to analyze the epidemiological impact of different NPI strategies at the local level and combined with a waste-water dynamics model. Our results highlight the potential of scalable ABMs as decision-support tools for infectious disease modeling and public health planning.

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MS63

EpiHiper: Recent Advances in Large-Scale, Networked, Computational Epidemiology

EpiHiper: a state-of-the-art, high performance computational modeling framework for epidemic science. The EpiHiper modeling framework supports custom disease models, and can simulate epidemics over dynamic, large-scale networks while supporting modulation of the epidemic evolution through a set of user-programmable interventions. The nodes and edges of the social-contact network have customizable sets of static and dynamic attributes which

allow the user to specify intervention target sets at a very fine-grained level; these also permit the network to be updated in response to non-pharmaceutical interventions, such as school closures. The execution of interventions is governed by trigger conditions, which are Boolean expressions formed using any of EpiHiper's primitives (e.g. the current time, transmissibility) and user-defined sets (e.g. people with work activities). Rich expressiveness, extensibility, and high-performance computing responsiveness were central design goals to ensure that the framework could effectively target realistic scenarios at the scale and detail required to support the large computational designs needed by state and federal public health policymakers in their efforts to plan and respond in the event of epidemics. The modeling framework has been used to support the CDC Scenario Modeling Hub for COVID-19 response.

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MS63

Using Person Trajectories in Order to Quantify Exposure-Based Health Impacts

Most infectious disease models focus on the pathogen and its transmission characteristics. Our approach, informed by transport planning and agent-based modeling experience, centers on individual agents, their movement patterns, and behavior. We present a large-scale agent-based epidemiological model tracking both communicable and non-communicable diseases, specifically heat-related health problems and influenza, unified through a common dose-response framework. The model requires three inputs: population data with demographics and residential information; facilities data with geolocated activity locations; and event files capturing agents' timestamped activities, enabling daily activity plan construction. For non-communicable diseases like heat-related health problems, the focus is each agent's activity plan, including outdoor and indoor exposure. Agents accumulate heat dose during activities, feeding into the dose-response model to calculate heat stroke probabilities and similar outcomes. Health outcomes are not binary; initial results are probability-based, followed by a disease progression model determining hospital admission and long-term consequences. For influenza, requiring human-to-human transmission, our contact model will exploit event files to overlay agents activities to determine when and how long agents meet. Each contact triggers an infection model using dose-response methodology to compute infection probability based on exposure characteristics.

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MS64

A Systems Approach to StudyResponse to Immunotherapyin HER2+ Breast Cancer

HER2+ breast cancer is an aggressive form of cancer with poor outcomes. These tumors are immune infiltrated, suggesting patients may benefit from immunotherapy. However, treatment combining the HER2 monoclonal antibody trastuzumab and the PD-1 inhibitor pembrolizumab in HER2+ breast cancer, lead to just a 15% response rate in patients with PDL1+ tumors. This low response rate may be due to a highly immune-suppressive niche, containing myeloid derived suppressor cells (MDSCs), T regulatory cells (Tregs), and tumor-associated macrophages. Understanding the interactions between immune subtypes, and their interactions with HER2+ breast cancer cells, may be instrumental to improving response to immunotherapies. To address this goal, we developed an agent-based model (ABM) to study tumor-immune interactions. The model includes tumor cells, MDSCs, T cells (CD4+, CD8+, and Tregs), macrophages, and NK cells. The ABM is initialized using digitized multiplex immunohistochemistry (mIHC) slides of untreated spontaneous lung metastases from a HER2+ murine model. Modeling in silico tumors treated with dual checkpoint inhibition (anti-PD-1 and anti-CTLA) reveals how properties of MDSCs and CD8+ T cells and their interactions with cancer cells determine response to treatment. By uncovering the dynamics and immune interactions that shape treatment outcomes, our model offers a pathway to tailor immunotherapy strategies to improve patient outcomes in advanced HER2+ breast cancer.

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MS64

Therapeutic Target Identification and Optimization of Therapeutic Regimens for a Quantitative Systems Pharmacology (QSP) Melanoma Model Based on RNA-Sequencing Data

Despite advances in the treatment of melanoma in the last 15 years, there are still patients who do not respond to therapy. Understanding tumor-immune dynamics in melanoma is critical for the development of new therapies and for improving response rates to current therapies. We used mathematical methods to identify the most-promising pathways to target, and optimize regimens for therapies that target these pathways. We obtained primary tumor samples, and diseased and healthy lymph nodes, from canine melanoma patients; we obtained normal tissue samples from healthy canine controls. We built an initial tumor-immune dynamics model based on literature and included 15 different immune cell types. We reduced this model by applying immune cell deconvolution to bulk RNA sequencing data, which identified four key immune cells: M1 and M2 macrophages, CD8+ T cells, and regulatory T cells. Comparison of differentially-expressed genes with the KEGG melanoma whole-genome background informed which pathways to include in our model. We performed global sensitivity analysis (eFAST and Sobol methods) to rank the most-influential parameters representing pathways with high therapeutic potential. We then used identifiability analysis to ensure that the most-influential parameters could be estimated from data. We incorporated three therapies related to these pathways and used optimal control to determine their optimal combinations, with a goal of minimizing the total tumor mass.

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MS64

Focused Ultrasound and Immunotherapy in Brain Cancer

Patients with brain tumors such as glioblastoma multiforme (GBM) typically have a deficient anti-tumor immune response. Recent experimental work shows that focused ultrasound (FUS) can modulate the tumor microenvironment by altering the bloodbrain barrier permeability, triggering inflammatory signaling, and shifting immune-cell populations. Immunotherapies such as check-point inhibitors have also shown promise in treating GBM, and FUS can be used to enhance the delivery of these drugs. However, the effectiveness of these therapies requires accurate timing and spatial targeting - hence the need for predictive mathematical models. In this talk I will describe some modeling approaches and the accompanying challenges. For example, acoustic propagation unfolds over microseconds and requires high-fidelity wave models in heterogeneous skull and brain tissues. Drug transport, clearance, and cellular responses evolve over minutes to hours. I will present one modeling framework that couples acoustic fields, drug kinetics, and FUS-induced biological responses, and discuss how patient-specific anatomy and variability shape both the focusing of ultrasound and the potential therapeutic effects.

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MS64

Mathematical Models for Guiding Adoptive Cell Immunotherapies in Bladder Cancer

Adoptive cell therapy is a personalized immunotherapy approach that uses patients own T cells that are expanded ex vivo and reinfused back to the cancer patient. The specificity of bladder cancer allows for intravesical delivery of drugs and T cells directly to the tumor, thus reducing the systemic toxicities and side effects. I will discuss different mathematical models: micropharmacology agent-based model, continuous ODEs with a virtual cohort, and machine learning predictors, that were driven by demographic, histology, and longitudinal ultrasound data, and used to address questions in adoptive cell therapy with tumor infiltrating lymphocytes (ACT-TIL) in bladder tumors. In particular, our results include patient stratification for the ACT-TIL that take into account the capacity to successfully expand TILS, the role of tumor immune and metabolic landscapes in treatment efficacy, and optimization of multi-treatment scheduling with the goal to maximize bladder tumor response to adoptive immunotherapy.

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MS65

A Mechanistic Population Viral Kinetic and Epidemiological Model to Evaluate the Risk of Herpetic Infections in Patients Receiving Imlygic Treatment and Their Caregivers

IMLYGIC (T-VEC) is an oncolytic virus approved for the treatment of melanoma. T-VEC is a live attenuated HSV-1 virus administered by injecting into tumor. Although designed to replicate selectively in tumor cells, T-VEC infections in patients are a clinical safety concern. T-VEC treatment may also reactivate latent HSV in patients; and put healthcare providers (HCPs) and close contacts at risk for viral infections. Clinical trials to quantify infection risk associated with IMLYGIC treatment are challenging due to the low incidence rate of infections, and short overall survival times of melanoma patients. Here, we develop a mechanistic model for the infection and spread of T-VEC and HSV viruses in patients treated with IMLYGIC, and their close contacts/HCPs. We use a viral dynamics framework to describe the time-course of infections in patients. The reactivation of latent HSV due to T-VEC dosing is modeled as a stochastic process. Infection spread among HCPs is captured using an HSV epidemiological model. The prevalence of infections among patients is validated using IMLYGIC clinical and post-marketing data, and HSV infection studies in literature. The model confirms the expected low infection rate in patients and healthcare providers and is supported by the limited observations from clinical trial data.

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Extending a Platelet Life-Cycle Quantitative Systems Pharmacology Model to Predict Platelet Recovery After Immunosuppressive Therapy in Aplastic Anemia

Objectives: Aplastic anemia (AA) involves T cellmediated suppression of hematopoietic stem cells (HSCs), leading to pancytopenia. Although immunosuppressive therapy (IST; anti thymocyte globulin and cyclosporine A) can restore hematopoiesis, some patients are ineligible or refractory. We developed a quantitative systems pharmacology (QSP) model linking IST driven T cell suppression

to HSC dynamics and platelet recovery to support future immunomodulatory drug development. Methods: We extended a published QSP model of the platelet life-cycle by adding (1) IST PK/PD and T cell suppression, (2) T celldependent HSC inhibition, and (3) HSC turnover coupled to platelet production. A virtual patient population (Vpop) was generated to match clinical HSC data; model performance was evaluated using platelet trajectories and externally validated against independent datasets. Results: The Vpop reproduced baseline HSC levels, platelet counts, and thrombopoietin concentrations in AA, capturing key components underlying thrombocytopenia. Simulated platelet time courses after IST agreed with clinical observations and were consistent across external datasets including different disese severities. Sensitivity analyses identified baseline platelet count and thrombopoietin as key determinants of recovery. Conclusion: This AA QSP model quantitatively connects IST pharmacology, T cellmediated HSC regulation, and platelet recovery, supporting evaluation of immunomodulatory strategies.

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MS65

Model-Informed Development of Oral GLP-1 Therapies for Weight Management

GLP-1based therapies have transformed the treatment landscape for obesity and related cardiometabolic diseases. With the emergence of oral small-molecule GLP-1 receptor agonists, the field is entering a new phase in which formulation, dose escalation, treatment duration, tolerability, adherence, and long-term effectiveness all become important considerations for development strategy. This presentation will discuss how model-informed drug development can support decision-making for oral GLP-1 and next-generation weight-management therapies. Population pharmacokinetic and pharmacodynamic modeling, exposure-response analysis, and clinical trial simulation provide quantitative tools to characterize variability across participants, evaluate dose and titration strategies, and integrate efficacy, safety, and tolerability into development decisions. Using the evolving oral GLP-1 therapeutic landscape as a motivating example, the talk will highlight key quantitative challenges in obesity drug development, including delayed and time-varying body-weight response, gastrointestinal tolerability, treatment discontinuation, adherence, baseline body weight, treatment duration, and heterogeneity in longitudinal response. Publicly available clinical data from the field will be used to illustrate how pharmacometric thinking can help translate emerging evidence into practical questions around regimen optimization, trial design, and decision-making. As obesity treatment advances beyond injectable GLP-1 monotherapy toward oral agents, combination regimens, and multi-target therapies, model-informed approaches will remain essential for integrating biological understanding, clinical pharmacology, and longitudinal outcome data into actionable development and regulatory decisions.

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MS65

Mathematical Modeling of Management of Postoperative Bleeding in Cardiac Surgery

Excessive postoperative bleeding is a common complication in cardiac surgery. A major contributing factor is reduced coagulation capabilities due to the dilution and depletion of necessary coagulation proteins and platelets. Fresh Frozen Plasma (FFP), the conventional treatment, is limited by immune and transfusion related risks. Prothrombin Complex Concentrate (PCC), supplementation of select coagulation proteins, has emerged as an alternative but as off-label usage. Recent studies demonstrate its efficacy, but further mechanistic understanding is needed to establish standards for routine surgical care. We extended our previously developed ODE-based mathematical model of flow-mediated coagulation to simulate post-surgery patients treated with FFP or PCC. A virtual population was created to explore variabilities in treatment outcomes, and its relationship with patient profiles. The model was able to capture efficacy trends shown in clinical trials. Simulation results suggest that low platelet levels reduce patient responses to FFP and low fVIII levels reduce patient responses to PCC. Our results provide insights into the mechanisms of both treatments and assistance for the development of clinical guidelines and optimized coagulation management in cardiac surgery.

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Host-Parasite Dynamics: Bistability and Backward Bifurcation in Two Immune Response Models

Motivated by the dichotomy between acute and chronic phases of Chagas disease, we analyze two within-host immune response models. Both models couple identical parasite dynamics with distinct mechanisms for CD8? T-cell proliferation. While both exhibit bistability and hysteresis, the model incorporating homeostatic immune maintenance additionally permits backward bifurcation, enabling endemic persistence even when the basic reproduction number R0 ¡ 1

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MS66

Stochastic Modeling of Stromal-Induced Resis-

tance

Cancer-associated fibroblasts (CAFs), a major component of the tumor stroma, are widely recognized for their role in promoting therapeutic resistance through microenvironmental remodeling. To investigate this phenomenon, we developed a stochastic population-dynamics model to characterize the coupled dynamics between tumor cells and CAF populations under dabrafenib treatment. By integrating experimental data with statistical inference, we compared multiple mechanistic hypotheses and evaluated their consistency with the observed drug response. This study provides a quantitative and computational framework for analyzing microenvironment-mediated regulation of therapeutic response and offers a theoretical basis for the design of subsequent mechanism-validation experiments.

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MS66

Mechanistic Models of Curative Cancer Therapy

We present a novel mechanistic mathematical framework for modeling combination cancer therapy that represents both cell-to-cell and patient-to-patient heterogeneity in treatment response as continuous probability distributions. The model is applied to simulate curative combination therapies for large B-cell lymphoma (LBCL). Stochastic clinical trial simulations reproduce progression-free survival and longitudinal ctDNA dynamics observed under standard therapy, and accurately predict the success or failure of nine randomized first-line combination trials using efficacy distributions inferred from relapsed/refractory LBCL. We further show how the framework enables quantitative prediction of treatment outcomes in molecular lymphoma subtypes. These results demonstrate that this stochastic simulation approach can be used inform the rational design of combination regimens with curative intent.

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MS66

Exploiting Drug-induced Resistance and Addiction for Adaptive Cancer Therapy

More than 95% of pediatric cases of Anaplastic Large Cell Lymphoma (ALCL) are ALK-positive. ALK inhibitors (ALKi) have been recently tested in relapsed/refractory patients, but continuous treatment almost invariably selects for resistance. We experimentally characterize the evolution of resistance to different ALKis (Crizotinib, Alectinib, Brigatinib) in an ALCL patient-derived cell line over six months in culture. Classical dose response models (e.g. Hill function) are nonlinear, however we observed the emergence of non-monotonic dose response curves, where ALKi resistant cells exhibit a marked decrease in their growth rate in the absence of drug. This phenomenon, known as drug-addiction (or dependence) suggests that the adaptive response mechanism for resistance comes at a fitness cost to proliferation in the absence of drug. We hypothesize that intermittent dosing (rather than continuous therapy) is a viable resistance management strategy, in order to capitalize on the collapse of drug-dependent cells during treatment holidays. Analysis of a parsimonious dose response mathematical model calibrated with experimental data suggest that a period of continuous dosing followed by intermittent dosing can extend ALCL remission nearly twice as long as continuous dosing. These findings demonstrate that drug-addiction emerges in pediatric ALK+ ALCL, and that such addiction could be exploited. Interestingly, a recent clinical report showed that intermittent Loratinib prolonged tumor control in a 2-year-old patient. Extending the analysis to dynamic, adaptive dosing indicates that optimal dosing depends on whether cells undergo drug- addiction or resistance without drug- addiction.

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MS67

From Microdomain Noise to Whole-Cell Order: Emergence, Averaging, and Failure of Whole-Cell Models

In this presentation, I would like to address the problem of using whole-cell models to study cardiac malfunction related to intracellular calcium cycling in cardiomyocytes, such as in AF. The computational burden of simulating how calcium really works at the subcellular level, with thousands of stochastically coupled release units and micrometric spatial resolution makes the simulation of whole-organ behavior using subcellular models numerically impossible. Proper whole-cell organ models require an understanding of the relationship between the stochastic nature of calcium release and the need for a deterministic whole-cell model to scale up to the whole organ or even tissue. More specifically, understanding when the average behavior of calcium release units can be properly translated into whole-cell dynamics is crucial. To address this problem, we have developed a Scalable Aggregate Calcium Release Unit (SA-CaRU) model for human ventricular myocytes that integrates a recently developed Markov Chain (MC)-based description of LCCs, replacing classical Hodgkin–Huxley gates. Our single-SA-CaRU system captures, within a unified framework, key features of microscale and macroscale Ca^{2+} cycling and allows, for the first time, systematic exploration of variability in SR Ca^{2+} release as a function of effective microdomain size and coupling. By analyzing how the behavior of the SA-CaRU evolves as the number of constituent channels increases, we can directly assess the relationship between stochastic microdomain activity and deterministic whole-cell behavior and track if there is a robust relation between both. We will show that, for normal, healthy behavior, we have found very good agreement between subcellular and whole-cell models... but this agreement fails upon changes in the channels, typically associated with changes in phosphorylation, opening the necessity of new avenues of research on this topic.

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MS67

Web-PDE-LLM: A Multi-Agent Framework for Real-Time Cardiac PDEs Solving via LLM-Driven WebGL Computing

Solving Partial Differential Equations (PDEs) for cardiac electrophysiology, such as the Fenton-Karma 3V model, in real time, traditionally requires high-performance computing clusters. Current SOTA approaches like CodePDE and OpInf-LLM have demonstrated the potential of Large Language Models (LLMs) in coding simulations. However, they often struggle with execution speed and seamless user interactivity due to their reliance on Python. We present Web-PDE-LLM, a multi-agent framework designed to bridge the gap between natural language intent and high-performance browser-based simulations. By leveraging LLMs to automate the generation of complex WebGL code, our framework achieves high numerical precision and a significantly reduced error rate. This facilitates seamless, real-time interactivity directly within the browser, allowing users to generate simulations from PDE specifications without requiring specialized expertise in WebGL.

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MS67

Foundation Models for Multimodal Cardiac Modeling

Foundation models are increasingly used in applications such as chatbots, software coding assistance, and healthcare research. These models are highly generalizable to several diverse tasks due to pre-training on large datasets, in contrast to traditional supervised models that are optimized for specific labeled tasks and often require retraining or new data to transfer to different tasks. This talk will cover recent developments in foundation models for cardiac applications. We will focus on models trained on multimodal cardiac datasets, including ECG, cardiac echo, clinical notes, and EHR data. Studies from our lab include foundation models for predicting atrial and ventricular myopathy, optimizing ChatGPT to improve prediction of ventricular tachycardia, and generating diagnosis text reports from ECG signals. The talk will conclude with a discussion of the role of foundation models in understanding arrhythmias and improving treatment outcomes.

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MS68

From Animal Models to Human Field Studies: Mathematical Modeling of a 13C-Sucrose Breath Test to Assess Intestinal Dysfunction

Stable isotope breath tests offer new opportunities to better understand gastrointestinal function in health and disease. The 13C-sucrose breath test (13C-SBT) has been proposed to estimate sucrase-isomaltase enzyme activity and is a promising test for intestinal mucosal damage caused by gut dysfunction or chemotherapy. Unlike intestinal biopsies, breath tests are noninvasive and can be performed and analyzed in low-resource settings. However, it is often not clear how to isolate information about a gastrointestinal or metabolic process of interest from a breath test curve (serial measurements of 13CO2 concentrations), and it is generally unknown how well summary statistics from empirical curve fitting correlate with underlying biological rates. We developed a mathematical framework to make mechanistic inference about the metabolic rates underlying a 13C-SBT curve, determining identifiable parameter combinations and characteristics of the breath curve associated with different metabolic processes, and developing a model-based diagnostic for distinguishing between those with and without gut dysfunction. We applied our model to analyze multiple populations: healthy adults in a high-income country with induced sucrase-isomaltase inhibition, rats with chemotherapy-induced mucosal damage, and adults and children in low-income countries who are at high risk of environmental enteric dysfunction. Our work develops a better understanding of how the underlying biological processes impact different aspects of 13C breath test curves, enhancing the clinical and research potential of these 13C breath tests for gut dysfunction.

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MS68

Uncovering the Mechanisms of Shiv Dynamics in Rhesus Macaques Undergoing Immune Therapy

Understanding the mechanisms underlying post-therapy control of simianhuman immunodeficiency virus (SHIV) is critical for the development of functional cure strategies. In this study, we develop viral kinetic models and validate them using viral load data from four cohorts of SHIV-infected nonhuman primates: untreated controls, animals receiving HuAd5 SIV Gag/Tat vaccination, animals treated with antibody therapy, and animals receiving combination therapy. Each model is fitted to longitudinal viral load measurements to quantify how different interventions alter viral dynamics. Using bifurcation analysis and numerical simulations, we identify parameter regimes in which therapy drives viral loads below the limit of detection. Furthermore, we characterize the conditions that enable sustained viral control after cessation or waning of immune-based interventions.

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MS68

Modeling the Latent Reservoir

Combination antiretroviral therapy controls human immunodeficiency virus-1 (HIV) but cannot eradicate latent proviruses in immune cells, which reactivate upon treatment interruption. Anti-latency therapies like shock-and-kill are being developed but are yet to succeed due to the complexity of latency mechanisms. This review discusses

recent advances in understanding HIV latency via mathematical modeling, covering key regulatory factors and models to predict latency reversal, highlighting gaps to guide future therapeutic approaches.

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MS68

Mechanisms of Synergy and Resistance: Modeling Dynamic Pd-L1 Regulation in Combination Immunotherapy

The efficacy of Immune Checkpoint Inhibitors (ICIs) is frequently limited by adaptive immune resistance via the PD-1/PD-L1 pathway. While pairing ICIs with potent immunostimulants (such as NHS-muIL12) offers a strategy to overcome this, foundational mathematical models often struggle to capture complex preclinical behaviors, specifically non-monotonic tumor responses. In this talk, we introduce a refined deterministic model that addresses this limitation by incorporating PD-L1 expression as a fully dynamic variable rather than a static parameter. We demonstrate that this model, using a single parameter set, successfully reproduces experimental data across six distinct treatment arms, including monotherapies and combinations. This framework provides a robust mechanistic explanation for dose-dependent treatment failure driven by adaptive PD-L1 upregulation, while also elucidating the drivers of therapeutic synergy. We will present the systematic development of the model and simulation results.

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MS69

Computational Fluid Dynamics Model for Assessing Surgical Strategies for Liver Shunt Closure in Dogs

The creation of 1-dimensional computational fluid dynamics (1D-CFD) models with physiologically realistic geometries enables scientists to non-invasively track patient-specific hemodynamics and gain insight into various cardiovascular diseases. This study aims to create a framework for canines with an extrahepatic portosystemic shunt (EHPSS). An EHPSS is a common congenital malformation in various small dog breeds. It is characterized by an anomalous vessel that bypasses the liver, directing unfiltered portal blood from the intestinal tract to the systemic circulation. This anomaly causes toxin accumulation in the systemic circulation, resulting in hepatic encephalopathy and premature death. EHPSSs are treated by surgically implanting a constrictor device that encircles the offending shunt to occlude the vessel gradually. Computational simulation of hemodynamics in dogs with two common shunt configurations and dogs with a normal configuration will allow us to identify differences in waveforms and perfusion between these groups. Furthermore, simulating the placement of a constrictor device in dogs with shunts will allow us to predict and study surgical outcomes before the procedure. By simulating incomplete shunt occlusion, we will gain insight into the severity of post-surgery residual shunting, which is a possible complication of the occlusion procedure. This may be a valuable tool for determining when a second surgery is needed in cases where shunt closure is unsuccessful.

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MS69

Applications and Modeling in FluidStructure Interaction: A Practical Guide and Examples

Mathematical and computational modeling play an important role in understanding the mechanics of life in low Reynolds number flows. The method of regularized Stokesles (MRS) is a popular approach for solving fluid-structure interaction problems in this regime. In this talk, I present the development of an introductory guide to MRS designed to mentor undergraduate research students or researchers new to this field, along with results from student projects. This framework can be adapted to support high-impact undergraduate research at any level.

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MS69

Flow Through Jellyfish Oral Arms: Transport and Mixing in Complex Morphologies

Rising ocean temperatures have contributed to increasing populations of Cassiopea sp. (upside-down jellyfish), a benthic species that actively pumps fluid into the water column while resting inverted on the seafloor. Through periodic bell contractions, Cassiopea generate vertical jets that drive nutrient transport, feeding, and waste removal. Extending into this flow are highly branched oral arms whose complex morphology plays a central hydrodynamic role, yet most previous models neglect these structures or treat them as solid appendages. We present a fluidstructure interaction model that explicitly incorporates a deformable bell and rigid porous oral arms. Using an Immersed Boundary Finite Element framework coupled with the incompressible NavierStokes equations, the bell dynamics generate pulsatile flow while the oral arms are represented as a porous medium introducing distributed resistance. Complementary simulations in ANSYS Fluent examine sensitivity to permeability, pulsation frequency, and Reynolds number. Our preliminary results demonstrate that modeling the oral arms as porous structures significantly alters jet formation, vortex dynamics, and mixing patterns. This work highlights the importance of resolving morphological complexity in biologically driven flow models and provides new insight into the hydrodynamic impact of expanding Cassiopea populations in warming coastal ecosystems.

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MS69

Simulating Extrusome Ejection Through the Collapse of a Capsule

Extrusomes are extrusive organelles found in a variety of organisms, including cnidarians, dinoflagellates, and protists. These organelles typically contain a fluid-filled capsule that houses a structure, such as a coiled tubule or barb, which is rapidly ejected toward a target. Although the ejection mechanisms and morphology vary widely, a common feature is the rapid acceleration of the ejected structure through a fluid. We develop an idealized model to simulate the collapse of an extrusome capsule, which enables the ejection of a barb or other internal structure. Specifically, we used the immersed boundary method in 2D to numerically simulate the collapse of a simplified capsule, modeled as the two sides of an elliptical shell with a flat plate along the bottom. Biophysical parameters, such as Reynolds number, barb stiffness, and capsule opening gap size are varied. Results demonstrate that decreasing the capsule opening gap size leads to increased firing velocity and shorter ejection times. Simulations with higher values of Reynolds number generally result in faster target contact, even at longer initial distances, and stiffer barbs hit their targets sooner. Overall, these findings provide a foundational understanding of the biomechanics and fluid dynamics of extrusome ejection with potential applications to microscale drug delivery.

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MS70

Searching for Molecular Mechanisms That Determine the Period of Circadian Rhythms

Circadian rhythms are endogenous biological rhythms that exist in most organisms enabling them to align physiological processes with daily environmental fluctuations such as light-dark cycles. Previously, it was demonstrated that a time-delayed transcriptional-translational negative feedback loop (NFL) generates autonomous circadian oscillations in eukaryotic systems. However, the mechanism determining the period of circadian rhythms remains elusive, which is one of the few remaining gaps in knowledge in the circadian field. In other words, it is not clear whether there exists rate-limiting steps that control the period of circadian rhythms. In this work, we explore potential mechanisms regulating the period of circadian rhythms.

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MS70

Phase Separation and Feedback: How Biomolecular Condensates Control Gene Expressions

Intrinsically disordered proteins (IDPs) allow proteins to undergo spontaneous phase separation (PS) in living cells to form biomolecular condensates. As a result, cytoplasm will de-mix into two phases: one enriched with the protein and another depleted with the protein, which will modulate corresponding biochemical reaction rates. It has been hypothesized that biomolecular condensates accelerate gene expression since many transcriptional activator (TA) proteins are enriched with IDPs. However, previous experimental measurements reported contradictory results. Motivated by this, this study investigates roles of PS in modulating gene expression through measurements in *E. coli* and mathematical modeling. First, synthetic TA proteins are created by fusing *E. coli*s native TA with a variety of IDPs and red fluorescent protein (RFP) so that 1) the TA will undergo PS, and 2) the TAs concentration can be approximated by RFPs fluorescent intensity. At the same time, green fluorescent protein (GFP) gene is placed under the control of TA so that we can quantify the TA-IDPs strength by measuring the GFP fluorescent intensity. On the other hand, a coarse-grained gene expression model is developed to describe dynamics of gene expression in the presence of PS. To estimate unknown parameters of the model, single-cell fluorescent microscopy is employed to measure both RFP and GFP. Based on the model, we will discuss implications of PS in kinetics and stochasticity of gene expression.

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MS70

Distributed Delay Constructively Impacts the Dynamics of Genetic Regulatory Networks

Delay is an inherent feature of genetic regulatory networks. It represents the time required for the assembly of functional regulator proteins. The protein production process is complex, as it includes transcription, translocation, translation, folding, and oligomerization. Because these steps are noisy, the resulting delay associated with protein production is distributed (random). My collaborators and I have shown that distributed delay can significantly impact the dynamics of genetic regulatory networks in construc-

tive ways. It can accelerate signaling in feed-forward architectures, denoise biochemical oscillators, and stabilize metasta

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MS70

Using Network Architecture to Achieve Multistationarity in Conjunctive Networks

The capacity of biological systems to support multiple stable steady states is often attributed to complex nonlinear dynamics. However, while multistability is easily achieved using complex components, here we demonstrate that it can emerge solely from the architecture of simple building blocks. We propose conjunctive networks systems of differential equations governed by AND gates as a minimalist framework for achieving any desired number of stable steady states. We show that the number of equilibria is analytically predictable from the wiring diagram's topology rather than through precise parameter tuning. Since AND gates are modular components already successfully engineered in synthetic biology, our results provide a scalable, modular approach to designing networks with arbitrary phenotypic complexity from the bottom up.

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MS71

Inference on Biological Dynamics with Memory

Biological systems are fundamentally dynamical. Cells grow and divide, respond to stress, and integrate information over time. Yet the mathematical tools we often use in dynamical systems theory come up short when applied to living systems, which are intrinsically stochastic, history-dependent (non-Markovian), and observed only through noisy, indirect measurements.To make sense of such systems, we often turn to Bayesian inference, which provides a principled framework for learning mechanisms from stochastic data. However, traditional Bayesian methods rely on analytical likelihoods, which are rarely available for realistic biological processes especially when memory, such as cell-division history and molecular inheritance, plays a central role. In this talk, I show how neural networks can approximate such likelihoods directly from simulations, extending Bayesian inference to otherwise intractable models. As a case study, we examine protein production across dividing cells, where standard inference procedures fail to account for the timing of divisions and inheritance of molecules. By explicitly accounting for cell-division history, our approach reveals that gene activation events (such as glc3 in yeast expression observed in flow cytometry) are rarer and more transient than nave analyses suggest. Later, we will discuss other problems we tackle with neural network-assisted Bayesian inference.

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MS71

Bayesian methods and Hamiltonian Monte Carlo for the analysis of spectroscopic data from living cells

Fluorescence correlation spectroscopy (FCS) is a specialized experimental technique that probes molecules in real time within their native environment. Nowadays, FCS experiments are used across molecular biology and biochemistry to investigate biomolecules in-cellulo and gain direct insights into the dynamics within living cells. However, the analysis of in-cellulo FCS data remains an open challenge due to the stochastic motion of the biomolecules, nonlinear response of the measuring devices, detection noise, and the large volume of measurements acquired during a typical experiment session. In this work, I present a novel data-analysis methodology that addresses these limitations. The proposed approach leverages Bayesian statistical models to extract information from raw FCS data and Markov chain Monte Carlo sampling (MCMC) for the characterization of the arising posterior distributions that propagate uncertainty due to stochastic motion and noise. To maintain efficiency and ensure scalability to large data volumes, we develop a specialized MCMC sampler by means of Hamiltonian Monte Carlo and investigate its stability in the parameter regime of diffusion coefficients and time-scales appropriate for live-cell conditions. Numerical simulations indicate that our method can successfully analyze FCS data acquired under realistic conditions and carry over to the analysis of data from living cells.

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MS72

On the Shannon Capacity of Biological Signal Transduction

We consider a multistate extension of the Poisson-type channel, originally introduced by Kabanov, in which the channel is a continuous-time Markov chain with transition rates modulated by a Markovian input signal. Biological examples include systems that transmit information by inducing conformational changes in proteins through varying intensities of light, voltage, or concentration of signaling molecules. We focus on the case in which the channel is fully observable, i.e., the output is the channel state, and derive upper and lower bounds for the Shannon capacity under stationarity. The structural information of the channel is encoded through the invariant measure of an associated Markov chain, and we numerically illustrate how the underlying graphical structure affects the channel's communication capability.

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MS72

Optimizing Energy Costs in the Evolution of Noise

Regulation by MicroRNAs

Many of the physical processes in a cell consume energy, but we are only beginning to understand how these costs have influenced the course of evolution. Biology is strewn with counter-intuitively complex mechanisms whose evolutionary predecessors must have consumed significant energy resources without any clear fitness benefit. So how do such mechanisms evolve in the first place, and how strong is the guiding hand of thermodynamic optimization? My talk explores these issues through one specific example: gene regulation in higher organisms (including humans) by microRNAs. These small RNA molecules (only 22 nucleotides long) are versatile tools for controlling the expression of genes into proteins, interfering with the messenger RNAs that are an intermediate step in the expression process. They provide a way of reducing noise in protein population levels, which helps stabilize cells from making sudden random changes in their state. Because a single microRNA type can interfere with the expression of hundreds of genes, this regulation can impose a substantial cost on the cell, since it is forced to compensate by increased messenger RNA transcription. We argue that mRNA systems are a potential instance of thermodynamic optimization: the chemical parameters have been fine-tuned by natural selection to achieve noise control in the most energy-efficient manner. Along the way, we provide insights into one peculiar feature: why we need such short RNA molecules to get the job done, i.e. why the "micro" in microRNA.

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MS72

Spin Glass Informed Algorithms to Infer Associative Memories from fMRI Data

Classical Hopfield networks have long been used as associative-memory models of brain dynamics, in which stored memories appear as attractor states of a recurrent neural system. Recent work has generalized this framework through Dense Associative Memory (DAM) models, also known as modern Hopfield networks, which allow continuous neural states and substantially larger storage capacity than the classical binary pairwise model. In this talk, we study the inverse problem for such models: given time-series observations of neural activity, can one infer the underlying memory patterns or attractor structure? We propose a maximum-likelihood estimator for the DAM inverse problem and derive an optimization procedure for estimating the model parameters from observed dynamics. We then apply the method to fMRI time-series data to investigate whether the inferred attractor structure captures meaningful features of large-scale brain activity.

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MS73

Dictionary-Based Estimation of Parameters for Models of Gas Transport Across Cell Membranes

Gas transport across cell membrane is a very important process in biochemistry which is essential for many crucial tasks, including cell respiration pH regulation in the cell. In the late 1990's, the suggestion that gasses are transported via preferred gas channels embedded into the cell membrane challenged the century old Overton's theory that gases pass through the lipid cell membrane by diffusing across the concentration gradient. Since experimental evidence alone does not provide enough evidence to favor one of the proposed mechanisms, mathematical models have been introduced to provide a context for the interpretation of laboratory measurement.In this talk we propose an algorithm based on dictionary learning for estimating cell membrane permeability. Computed examples illustrate that the novel approach, which can be applied when the properties of the membrane do not change in the course of the data collection process, is computationally much more efficient than particle filter.

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MS73

Parameter Identifiability in a Pde Model of Blood Flow Using Emulation and Dimension Reduction

Biophysical models have immense potential in providing new tools for the diagnosis and management of disease. This includes cardiovascular monitoring. However, cardiovascular simulations typically require numerous parameters and suffer from limited data. This leads to issues in parameter identifiability, which renders parameters uninterpretable. Assessing identifiability is difficult due to expensive forward solves from the model. Here, we overcome this limitation by using dimension reduction and emulation to expedite computation. We use polynomial chaos expansions (PCEs) on the principal components of a blood flow PDE model to provide a succinct platform for forward model solutions. We use this framework to assess model sensitivity, and follow with a formal identifiability analysis using the profile-likelihood. We show how experimental design choice drastically changes identifiability in the context of blood flow monitoring.

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MS73

Statistical Calibration of Coupled Multi-Output Ode Models with Discrepancy: Applications to Dy-

namical Models in Physiology

Coupled systems of multi-output ordinary differential equations (ODEs) are widely used to model complex physiological processes. In these applications, ODE model parameters must be calibrated to field data to enable prediction and parameter inference. In practice, the governing ODEs are an imperfect approximation to the true biological system, leading to non-negligible model discrepancy that must be incorporated to avoid biased parameter estimates. However, it is well known that highly flexible discrepancy models can confound discrepancy and parameters, leading to poor identifiability. As a result, practitioners often must impose problem-specific prior constraints to adequately regularize the discrepancy, which can be challenging and cumbersome. Alternatively, recent work has shown that constraining the discrepancy prior to be orthogonal to the forward-model gradient can improve calibration in single-output computer models. Building on this idea, we propose a novel calibration framework for coupled, multi-output ODE systems that enforces automatic, model-structural constraints on the discrepancy, improving identifiability without requiring application-specific discrepancy priors. Forward-model gradients are computed via sensitivity equations, solved jointly with the ODE system as a coupled initial value problem. Posterior inference is performed using an adaptive Metropolis-within-Gibbs sampler tailored to the resulting constrained posterior. We demonstrate the approach on a challenging calibration problem for a nonlinear cardiovascular model.

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MS73

An Introduction to Uncertainty Quantification in Mathematical Biology

Uncertainty is inherent in biological systems, arising from measurement error, parameter variability, structural model limitations, and stochasticity. This introductory talk provides an overview of uncertainty quantification (UQ) in mathematical biology, emphasizing both its conceptual foundations and practical implementation and establishing a unifying framework for the minisymposium. I distinguish between forward problems, in which parameter uncertainty is propagated through a model to assess predictive variability; inverse problems, in which data are used to infer uncertain parameters or model structure; and optimization under uncertainty, where decision-making must account for variability in system dynamics. Key definitions and methodological frameworks, including probabilistic representations of uncertainty, sensitivity analysis, and parameter inference, are introduced. Brief case studies illustrate how UQ enhances modeling and prediction in complex biological systems, including examples from my own work applying UQ methods to ecological models. I conclude by highlighting current methodological challenges and opportunities for advancing UQ in mathematical biology.

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MS74

Modeling Motor Regulation of Microtubule Length at Both Ends

Microtubules are dynamic biopolymers whose lengths are continuously regulated by the concerted actions of polymerization, depolymerization, and motor-protein activity. While numerous mathematical models have explored the regulation of filament length, most have been formulated in the context of growth and shrinking at a single tip of a microtubule, effectively ignoring the mechanistic description of complex phenomena such as treadmilling. Here, we develop a multiscale model for microtubule length regulation that explicitly couples the kinetics of two classes of kinesin molecular motors to filament dynamics at both microtubule tips. Motor densities along the filament are modeled using one-dimensional parabolic partial differential equations. The microtubule length evolves dynamically through a shrinkage term that depends on motor density, which closes the system. In the adiabatic regime, where motor kinetics are fast relative to length dynamics, we derive a reduced model amenable to analytic study and identify simple parameter relationships distinguishing growth, catastrophe, and treadmilling behavior. Numerical simulations of the full system reveal qualitatively distinct dynamical regimes and demonstrate how bidirectional motor transport modulates filament length distributions. We parameterize our model with both in vivo and in vitro data and thus lay the foundation for developing mathematical models yielding a better understanding of cytoskeleton dynamics in living cells.

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MS74

From Molecular Interactions to Collective BehaviorsMultiscale Modeling of Microtubule and Microtubule-Associated-Protein Dynamics

Microtubules (MTs) are energy-utilizing cytoskeletal polymers essential for cell growth, division, and intracellular transport. Many of these functions rely on regulation of microtubule dynamics by microtubule-associated-proteins (MAPs) a diverse group of proteins interacting with the tubulin dimers of MTs. First, I will talk about quantitative characterization nonequilibrium steady states (NESS) in dynamical systems of microtubules. Using agent-based simulations parameterized by experimentally grounded kinetics, we identify multiple, distinct steady statesGTP-cap, polymer-flux, polymer-mass, and length-distribution steady states and derive predictive relationships linking the time to reach these states to control parameters such as free tubulin concentration. Remarkably, we find that both transient and steady-state fluctuations of polymer-mass temporal dynamics exhibit an affine invariance across concentrations, enabling robust prediction of system-level properties from minimal data. Next Ill discuss a phase-field reaction-diffusion model to biophysically characterize MAP-driven biomolecular condensation on the MT lattice, specifically to understand how MT surface heterogeneity modulates condensate nucleation and localization. Altogether, I will present a multiscale theoretical and computational framework for understanding the nonequilibrium dynamics of MTs and MAPs spanning molecular interactions, mesoscale phase separation, and system-level collec-

tive behaviors.

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MS74

Plant Cortical Microtubules: Curvature Sensing by Elastic Curves on Smooth Surfaces

The self-organization of microtubules (MTs) along the inner surface (cortex) of the plant cell membrane is an essential element in the development of plant cells. MTs are dynamic polymers found within many cell types, serving roles in vital cellular processes. Within plants, the organization of MTs into ordered patterns is necessary for directional cell growth. The key questions are: what gives rise to the ordering and orientation of MT patterns? Mathematical and computational modelling has proven successful in providing insights: the process is distilled into a system of interacting curves on a 2D surface. There has been recent interest in the role of cell geometry in this process. Our recent work revisited a common assumption, that MT shapes are described by geodesics. More realistically, MTs are relatively rigid filaments and should seek to minimizing bending. A model of MTs as elastic curves on cylindrical cells has shown that the curvature influence on MTs should orient MTs in directions opposite to what is biologically favourable. Building on this, I present our ongoing work in generalizing this model to general smooth surfaces. This work indicates that there must be additional processes involved to overcome geometric influences. The identity of these processes is the subject of active debates, with many hypotheses being proposed. Lastly, I present the current state of the field and the ongoing effort to overcome the associated modelling challenges.

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MS74

A New Description for MT Dynamics Parameters: Deriving MT Rescue and Catastrophe Frequencies For a Theoretical Description of MT Dynamics That Includes Growth, Shortening, And Paused States

Microtubules (MTs) are protein polymers found in all eukaryotic cells. They are crucial for many cellular processes including cell movement, cell differentiation, and cell division. In performing these functions, they go through a process called dynamic instability whereby MT go through random periods of relatively slow polymerization (growth), followed by very fast depolymerization, an event referred to as a catastrophe. After a catastrophe, MTs can be rescued and the process repeats itself. Here we focus on developing and analyzing a continuous model for dynamic instability to also account for a paused state, an extension to the classical two state MT model of just growth and shortening. Newer ABMs have looked at how parameters describing MT dynamics, namely the rescue frequency and catastrophe frequency, can change according to phase transitions between growth, shortening and paused states (like MTs that switch from growth to shortening, or growth to paused, then shortening, etc). Here, we explore how both the rescue and catastrophe frequency parameters can be derived from our new modeling framework that includes MT pause, and compare these values to the results of the ABM and to those found in experiment.

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MS75

Scalable Filtering Algorithms for Applications in Single Molecule Screening

Experiments probing *single-molecule Frster resonance energy transfer (smFRET)* are used in molecular biology and biochemistry to study the interactions and conformational dynamics of individual biomolecules. Measurements take the form of time series data that are challenging to analyze because of noise and photophysical artifacts such as fluorophore blinking, background, and cross-talk. For this reason, the analysis of smFRET data requires advanced statistical techniques such as *factorial hidden Markov models (fHMM).* In particular, a fHMM allows for noise and stochastic transitions over time and, to isolate artifacts, also allows for independent representation of the conformational and photophysical states of the biomolecules and their fluorophores. Nevertheless, existing algorithms for the evaluation of fHMM rely on successive *matrix-vector operations* with high computational complexity that render them impractical for the analysis of large datasets such as those obtained in a typical smFRET experiment. In this work, we introduce *tensor-based operations* to reduce the computational complexity of fHMM and obtain efficient algorithms for smFRET data analysis. Our approach provides the computational foundation for the development of fully Bayesian analysis workflows of experimental data and large scale single-molecule screening.

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MS75

Beyond Binary Prediction: Interpretable Machine Learning for Patient-Level Risk Stratification in Opioid Care

Machine learning has shown strong potential for predicting opioid-related outcomes using electronic health record data, with prior research applying a range of approaches, including tree-based and deep learning models. Much of this work has focused on binary overdose prediction, with comparatively less emphasis on how model outputs can be translated into clinically actionable risk assessments. To address this gap, we develop a machine learning framework that estimates patient-level probabilities of experiencing an adverse opioid event (AOE) following opioid therapy initiation. We leverage these model-predicted probabilities to construct ordered risk tiers, enabling structured stratification of patient risk. Data analysis across these risk tiers serves as a second analytic layer that complements model-level feature importance by examining how clinical factors manifest across progressively higher-risk levels. This stratified analysis provides additional insight into associations between clinical features and AOEs that may not be captured by model-level summaries alone. Overall, this work builds on prior opioid-related research by connecting

patient-level outcome prediction with interpretable, tier-based characterization of risk, supporting more informed and actionable decision-making in real-world clinical settings.

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MS75

Deep Learning for Multivariate Functional Data Clustering: A Novel Method with An Application to Intraoperative Icu Risk Phenotyping

Clustering multivariate functional data is challenging due to high dimensionality, heterogeneous temporal dynamics, and complex cross-variable dependence. Existing methods typically rely on predefined basis expansions (e.g., splines, Fourier, FPCA) followed by clustering, requiring substantial domain knowledge and limiting flexibility. We propose DeepMFDC, an end-to-end deep learning framework that jointly learns functional representations and cluster structure directly from discretized trajectories. DeepMFDC introduces an Adaptive Learnable Basis layer that models variable-specific basis functions using small neural networks and estimates basis coefficients via differentiable numerical integration. The resulting representations are refined through an encoderdecoder architecture with coupled contrastive objectives: a global semantic branch enforcing subject-level consistency across variables and a local clustering branch promoting cluster-wise agreement while reducing variable-specific noise. Simulation studies demonstrate improved clustering accuracy over established functional data clustering methods under noisy, correlated, and temporally overlapping settings. Applied to intraoperative monitoring data from 10,000 non-cardiac surgeries, DeepMFDC identifies four clinically meaningful phenotypes associated with postoperative ICU admission, delirium, and hospital length of stay.

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MS76

Metaverse Demystified: Lessons Learned from Using PatchSim for Pandemic and Epidemic Response Support

Metapopulation models allow for a networked representation of population interactions in aggregate and serve as a valuable intermediate between ODE and agent-based models. Multiple approaches exist based on the aggregation dimension, such as agegroups, geography, and risk classes. In this talk, we will describe how such techniques can be used to aid real-time pandemic and epidemic response, using the open-source simulation engine PatchSim. We will also show how real-world and modeled datasets can be used to guide the underlying network construction process.

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MS77

Modeling Ctdna Dynamics: Tracking Progression and Response in Hpv-Related Solid Tumors

Real-time assessment of treatment response in HPV-associated solid tumors, specifically anal squamous cell carcinoma (ASCC) remains challenging. Traditional tumor volume measurements require serial imaging that is costly, time-intensive, and delays clinical decision-making. Circulating tumor DNA (ctDNA) offers a more accessible, real-time alternative biomarker–yet its predictive value for guiding treatment adaptation remains undefined. We developed a mechanistic mathematical model of tumor volume-ctDNA dynamics parameterized using longitudinal data from 32 HPV-associated ASCC patients receiving pembrolizumab immunotherapy every 3 weeks and fit the model. ctDNA demonstrated strong positive correlation with tumor burden and predicted clinical response status within 4 weeks of treatment initiation. Critically, ctDNA kinetics preceded volume changes in multiple patients, providing early signal for response assessment before imaging confirmation. The mathematical model robustly captured heterogeneous patient dynamics. ctDNA functions as a leading indicator biomarker enabling early identification of treatment response in HPV-associated ASCC. Our quantitative framework translates this biomarker into actionable clinical predictions for real-time treatment decisions, which enhances precision oncology with accessible blood-based monitoring–particularly impactful for underserved populations with limited imaging access.

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MS77

Linking cfDNA Clearance to Fragment Length with Mechanistic Models

Liquid biopsy studies consistently report both elevated circulating cell-free DNA (cfDNA) concentrations and shortened fragment lengths in cancer. These features are often attributed to tumor-specific processes, despite tumor-derived cfDNA frequently constituting less than 1% of the total. Here, we consider an alternative explanation: Saturation of cfDNA clearance, which prolongs cfDNA circulation time, increases exposure to plasma nucleases and is expected to produce similar fragmentomic signatures independent of tumor burden. By combining a mechanistic model of cfDNA fragmentation with analyses of two independent cancer patient cohorts, and publicly available clearance-perturbation experiments, we find that elevated cfDNA levels are accompanied by a characteristic leftward shift in fragment length distributions consistent with impaired hepatic clearance. This fragmentation signature tracks total cfDNA concentration but is independent of circulating tumor DNA (ctDNA) fraction, is reproducible under experimentally reduced clearance, and is independently

prognostic of patient survival. Together, these results identify saturating clearance as a central determinant of cfDNA abundance and fragment length, rather than ctDNA content alone.

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MS77

Coupled Sde-Ode Modeling of Tumor-Immune Dynamics to Infer Biomarker Release

Tumorimmune interactions are central to cancer progression and treatment response, driving cell death through immune-mediated killing and resource-limited competition. In early-stage disease or following effective therapy, tumor populations are often small and difficult to observe directly. Disease monitoring therefore relies on biomarkers such as circulating tumor DNA (ctDNA), which provide noisy, concentration-dependent proxies for tumor burden. Existing approaches lack mechanistically grounded frameworks to infer tumor size from these signals near detection thresholds. We present a coupled deterministicstochastic framework linking tumorimmune dynamics to biomarker release. Tumor and immune interactions are modeled using a two-prey, one-predator LotkaVolterra system capturing competition between tumor subpopulations under shared resource constraints. Biomarker production is described by stochastic differential equations driven by tumor cell death arising from immune-mediated apoptosis and intra-tumor competitioninduced necrosis. To reflect concentration-dependent measurement variability, we incorporate both square-root (CIR-type) and multiplicative (geometric-type) noise, representing count-limited fluctuations near the detection limit and proportional variability at higher concentrations, respectively. Within this framework, we derive analytical expressions for biomarker trajectories and first-passage statistics, including mean detection times. Our results suggest how tumor heterogeneity, immune pressure, and stochastic variance structure jointly shape biomarker emergence and detectability, providing a mathematically tractable and biologically interpretable foundation for inferring tumor burden from noisy biomarker signals.

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MS78

Modeling Immune Dynamics in Liver Transplantation: Challenges and Insights

Liver transplantation is a life-saving intervention for patients with end-stage liver disease, however improvement of long-term outcomes remains a formidable challenge, with 10-year survival rates averaging just 65% nationally. A key determinant of long-term survival is the delicate balance of immunosuppression; under-dosing leads to allograft rejection and over-dosing leaves patients vulnerable to life-threatening infections, both of which contribute to significant morbidity and mortality. Current immunosuppressive medication management strategies are limited in their ability to effectively balance these risks. We used mathematical modeling to characterize the long-term recipient immune response dynamics after liver transplantation and identify mechanisms key to maintaining an optimal immunosuppression state. Our model is a system of 6 ordinary differential equations (ODEs) representing critical interactions between the transplanted liver, immune cell populations, and cytokine IL-2. In this presentation, I will discuss the selection of immune interactions to include, translation to a system of ODE equations, parameterization using literature, and sensitivity analysis. I will conclude with the mechanisms most influential on the health of the transplanted liver and implications for clinical management.

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MS78

Integrated Systems Pharmacology Modeling of Severe Asthma and the IL-33/ST2 Pathway

Asthma is a chronic disease of the airway characterized by the involvement of multiple pathways and cytokines directing the proliferation, survival and effector function of immune cell populations and their interaction with airway mucosa. Drug development targeting asthma for diverse patient populations and etiologies remains an important goal due to unmet medical need. Predicting the effects of novel therapies requires a quantitative modeling approach integrating diverse data sources across multiple therapeutic targets. To facilitate this quantitative understanding and support drug development, we developed a quantitative systems pharmacology model examining the interplay between crucial inflammatory pathways characterized by the effects of cytokines like IL-4, IL-5, IL-13, TSLP and IL-33 in moderate - severe asthma. Our approach combines dynamical systems modeling with critical

clinical endpoints including fraction of exhaled nitric oxide (FeNO) and forced expiratory volume in 1 second (FEV1). Using a virtual population approach, the model captures several relevant biomarkers at baseline and the response to multiple approved therapies. We use this population to predict the effect of anti-IL33 therapy on clinical biomarkers and utilize sensitivity analyses to explore the impact of the relative effect of anti-IL-33 upon type 2 cytokines and other pathways. The developed model will be useful for further model-driven asthma therapy development in the severe asthma population.

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MS78

Mechanistic Insights by Combining QSP and ML: An Inflammatory Bowel Disease Case Study

Objective: QSP models can reveal disease mechanisms and treatment effects, but their complexity limits interpretation. We present a framework using machine learning (ML) on QSP simulation outputs to extract mechanistic insight. As a case study, virtual population simulations from an Inflammatory Bowel Disease (IBD) QSP model were analyzed to identify factors determining responder vs non-responder. Methods: A previously developed virtual population was used to simulate responses to anti-p40 and anti-TL1A therapies. Thirty-nine model variables served as ML input features. Several classifiers were trained to differentiate responders, defined as virtual patients with predicted endoscopic scores of 01. Performance was evaluated using multiple metrics including ROC-AUC and RMSE, and feature importance was assessed for the best-performing model. Results: Random Forest achieved the highest ROC-AUC and the lowest RMSE. Shared key predictors included tissue neutrophils, CRP, epithelial damage, IL-6, IL-8, and TNFa. TL1A and Th1 differentiated anti-p40 responders, whereas IL-12, IL-17, and GM-CSF were most relevant for anti-TL1A, indicating overlapping yet distinct immune drivers. Conclusion: Integrating QSP with ML enables identification of mechanistic determinants of treatment response not easily captured from QSP outputs alone. Applying this approach to model parameters and QSP platforms may support identification of sensitive pathways and virtual population refinement.

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MS78

QSP Models in Inflammation and Immunology: Introduction and Case Studies

Quantitative Systems Pharmacology (QSP) models address unique challenges in inflammation and immunology (I&I) by integrating mechanistic biology with quantitative prediction of therapeutic outcomes. In I&I, understanding feedback loops and compensatory mechanisms is often critical to predicting therapeutic success and safety — considerations that QSP is well-suited to capture. This presentation introduces QSP methods through two case studies. First, in atopic dermatitis, we showcase models that identify optimal combinations of drug targets, inform patient stratification, and assess target product profile characteristics. Second, in systemic lupus erythematosus (SLE), QSP modeling assesses the repurposing potential of B cell targeted therapeutics from oncology. Specifically, we systematically compare molecular and clinical responses to T cell engagers and CAR-T cell therapy by remixing QSP models from oncology with trial data in SLE, working towards predicting clinical endpoints via mechanistic biology. Together, these examples illustrate how QSP facilitates safe and effective I&I therapy development by capturing biological compensatory mechanisms and informing rational therapeutic strategies.

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MS79

Analyzing Sensitivity of Inflammatory May Determine Optimal Treatment Protocols - Using a Whole-Body Sepsis and Inflammatory Model

Sepsis remains a major clinical challenge characterized by dysregulated host inflammatory responses that can lead to multi-organ dysfunction and high mortality. A critical barrier to optimizing therapeutic strategies is understanding how individual sensitivity to inflammatory processes shapes disease trajectories and treatment outcomes. In this work, we employ a whole-body sepsis and systemic inflammation model to analyze the impact of inflammatory sensitivity on disease progression and the efficacy of intervention protocols. Building on the whole-body BioGears mathematical sepsis model, which integrates pathogen dynamics with cardiovascular, immune, and physiologic feedback systems, we perform a comprehensive sensitivity analysis of key determinants of inflammatory responsiveness, including cytokine activation rates, immune regulatory feedback, and endothelial dysfunction mechanisms. Our results reveal that variations in inflammatory sensitivity produce distinct virtual patient phenotypes, ranging from effective infection resolution with minor physiologic disruption to hyperinflammatory or immunosuppressed states that predispose to persistent bacteremia and tissue damage. These phenotypes modulate the timing and magnitude of responses to antimicrobial therapy, fluid resuscitation, and immunomodulatory interventions, indicating that uniform treatment protocols may be suboptimal across the spectrum of host responses. Notably, heightened sensitivity to pro-inflammatory signaling necessitates early modulation to prevent excessive tissue damage, whereas reduced sensitivity may benefit from aggressive pathogen control to avert persistent infection. By linking mechanistic sensitivity analysis with simulated treatment outcomes, this study underscores the importance of individualized inflammatory profiling in designing optimal sepsis management strategies. The modeling framework supports hypothesis generation for clinical studies and highlights opportunities to tailor interventions based on host inflammatory sensitivity.

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MS79

Comparing Important Factors in Autoimmune Hair Loss and Hormonal Hair Loss Through Parameter Estimation and Uncertainty Analysis

Hair loss commonly occurs due to a hormonal imbalance, as in the condition androgenetic alopecia (AGA), or due to an autoimmune response against the cells that produce hair, as in the condition alopecia areata (AA). These disorders disrupt the cycling of hair follicles through phases of growth and rest. Through parameter estimation, we calibrate a mathematical model for the human hair cycle with experimental data for the lengths of hair growth and rest from control subjects and subjects with AGA. We also connect a mathematical model for AA with information from the literature about approximate durations for the hair cycle phases. Subsequently, we perform uncertainty quantification and sensitivity analysis for the cases of control, AGA and AA. Comparing the results between the control and AGA subject groups as well as among the control, AGA and AA cases helps to see differences in factors with high impact in autoimmune hair loss versus hormonal hair loss, which is important for therapeutic options.

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MS79

Mathematical Modelling of Retinal Immune Cells During Inflammation

Inflammation alters both the behaviour and spatial distribution of retinal microglia, the primary immune cells of the eye. In experimental studies, mice were administered lipopolysaccharide (LPS), and microglial cell densities were quantified over 48 hours within each retinal layer. Notably, total microglial density remained approximately conserved while substantial redistribution occurred between layers. To explain this phenomenon, we developed ODE model describing inter-layer microglia migration during inflammation. A pharmacokinetic (PK) subsystem was first parameterized to capture LPS dynamics and was subsequently coupled to an immune cell subsystem in which their migration rates depend on LPS concentration. The resulting system provides a quantitative description of ocular inflammation and expands the small number of computational models of neuroimmune dynamics. Reparameterization enables predictions of microglia redistribution across varying LPS dosages, host species, and routes of administration, demonstrating robustness to differences in experimental design. Classical analyses, including sensitivity analysis and parameter sweeps, are used to identify the biggest drivers of microglia redistribution.

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MS79

A Mechanistic Model of Inflammation in Invasive Pulmonary Aspergillosis: Linking Heme, Complement (C5a), and Tissue Injury

Invasive pulmonary aspergillosis (IPA) is a life-threatening fungal infection in which Aspergillus germinates and develops hyphae that invade lung tissue and, in severe cases, penetrate blood vessel walls, leading to hemorrhage. Clinical and experimental evidence has linked iron availability, heme toxicity, and complement activation to IPA severity, yet the mechanistic pathways connecting these processesand how they differ across host immune statesremain poorly understood. Notably, immunocompetent hosts often control infection rapidly, whereas neutropenic hosts can experience progressive infection due to impaired fungal clearance in which fungal growth, state transitions, and related parameters become critical determinants of outcome. We propose a mechanistic hypothesis that bleeding-associated heme release can over-activate the complement system, amplifying inflammation and accelerating tissue damage, thereby worsening pathology and promoting further bleeding. To investigate this, we develop an ordinary differential equation model that couples fungal dynamics to innate immune responses through complement-mediated signaling and leukocyte movement. The model captures interactions among complement activity (including the C5a axis), recruitment and turnover of neutrophils and monocytes, and heme and damage accumulation, enabling systematic comparison of infection trajectories under immunocompetent versus neutropenic conditions. Using this framework, we explore how variations in iron/heme-associated processes and complement activation shape key quantities of interest such as peak fungal burden, peak complement activity, and cumulative tissue damage. The model provides a quantitative platform to interrogate competing mechanisms underlying host-dependent outcomes in IPA and to evaluate whether targeting complement overactivation can reduce immunopathology while preserving effective fungal clearance.

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MS80

Estimating the in Vivo Potency of Ganciclovir in the Treatment of Cytomegalovirus in Hematopoietic Cell Transplant Recipients Using Intrahost

Mathematical Modeling.

Randomized trials demonstrating the effectiveness of cytomegalovirus (CMV) treatment after hematopoietic cell transplantation (HCT) with the antiviral drug ganciclovir were performed several years before the advent of clinical CMV DNA testing with PCR. Thus, only limited quantitative viral load data describing the natural history of untreated CMV viremia exists. Previously, to overcome this limitation, we performed CMV DNA viral load testing on frozen serum samples from the first, placebo-controlled, randomized trial evaluating early treatment of CMV infection with ganciclovir (Goodrich et al. NEJM 1991, Duke et al. JCI 2021). Using this data, we developed a deterministic, ordinary differential equation (ODE), mathematical model that included an explicit, dynamic immune response the reproduced the viral dynamics of untreated CMV viremia after HCT (Duke et al. Viruses 2021). In this study, we have expanded the data set to include the participants from the clinical trial who received ganciclovir treatment and extended the model to include an antiviral treatment parameter to estimate treatment potency.

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MS80

Mathematics of Sterile Insect Technology to Control Malaria Mosquitoes

In the absence of an effective and safe vaccine for use in humans, malaria control efforts are focused on the widespread use of chemical insecticides (in the form of larvicides, indoor residual spraying and insecticide-treated bednets) to control the immature and adult mosquito population and the treatment of those with symptoms using artemisinin-based therapy. Unfortunately, the widespread use of these insecticides and therapies has resulted in the evolution of vector and parasite resistance to the insecticides and drugs, respectively. This, coupled with the concerted global effort to eradicate malaria by 2030, necessitate the use of other control strategies, notably biological controls. The sterile insect technology (SIT) is one such strategies being widely considered (aimed at reducing the abundance of adult female mosquitoes). The talk will assess, via modeling, the population-level impact of SIT in combatting malaria mosquitoes in an endemic area. This study, which uses relevant data from malaria-endemic areas in sub-Saharan Africa, shows that the release of sterile male mosquitoes may either lead to eventual extinction or increase the long-term average adult mosquito density.

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MS80

Estimating Incidence of Hiv-1: Using Biomarkers Data to Estimate Sweden's Unaids Goal

In 2021, the Joint United Nations Programme on HIV and AIDS (UNAIDS) upgraded their original 90-90-90 targets set in 2014 to 95-95-95. These targets state that by 2025: (1) 95% of all people living with HIV (PLHIV) should be diagnosed; (2) 95% of all diagnosed PLHIV should be on antiretroviral therapy (ART); and (3) 95% of those on ART should be virally suppressed. While calculating the latter two numbers can be achieved using patient data, determining the first number is a non-trivial task due to several factors such as group differences in risk awareness, unknown times since infection when diagnosed (TI), systematic variation in TI among transmission modes and over calendar years, rate of disease progression, and influx of PLHIV from abroad. To estimate this first number, we expanded previous work on our multiple biomarker model to directly estimate the TI of a diagnosed PLHIV and subsequently estimate the HIV incidence and the number of undiagnosed PLHIV per year. We estimated the yearly HIV incidence and fraction of undiagnosed PLHIV in Sweden between 2003 and 2022, using biomarker data available in InfCare-HIV, a national quality registry and research database of all diagnosed PLHIV since 2003 plus incomplete sampling going back to 1979. Our work suggests that by 2022, 96% of all PLHIV in Sweden will have been diagnosed, of which 99% are on ART, with 98% being virally suppressed.

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MS80

Optimal Treatment of Prolonged Sars-CoV-2 Infection

The viral kinetics of documented SARS-CoV-2 infections exhibit a high degree of interindividual variability. We identified 6 distinct viral shedding patterns, which differed according to peak viral load, duration, expansion rate, and clearance rate, by clustering data from 768 infections in the National Basketball Association cohort. Omicron variant infections in previously vaccinated individuals generally led to lower cumulative shedding levels of SARS-CoV-2 than other scenarios. We then developed a mechanistic mathematical model that recapitulated 1,510 observed viral trajectories, including viral rebound and cases of reinfection. Lower peak viral loads were explained by a more rapid and sustained transition of susceptible cells to a refractory state during infection as well as by an earlier and more potent late, cytolytic immune response. Our results suggest that viral elimination occurs more rapidly during Omicron infection, following vaccination, and following reinfection due to enhanced innate and acquired immune responses. Because viral load has been linked with COVID-19 severity and transmission risk, our model provides a framework for understanding the wide range of observed SARS-CoV-2 infection outcomes.

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MS81

Multiscale Model of Red Blood Cell Clogging in Microfluidic Devices

Microfluidic devices that sort cells by their deformability hold significant promise for medical applications including low-cost diagnostics. However, clogging in these microfluidic systems may cause them to change behavior over time, potentially limiting their reliability. Here, we propose a coarse-grained theoretical model to capture the aging of microfluidic devices under different conditions including constant flow and constant pressure. We compare the predictions of the coarse-grained model to those of stochastic simulations and previous studies. Lastly, we apply the

model to experimental data on the clogging of sickle red blood cells in a microfluidic cell-sorter and discuss its wider applicability.

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MS81

How Molecular Motors in Flagella Respond to Fluid Rheology

Many different microswimmers propel themselves using flagella, which are thin, threadlike filaments which beat in a periodic wavelike motion. The shape of the flagellar waveform emerges from the surrounding fluid interactions, which depends on the fluid rheology; from passive mechanical properties, like extensional and bending forces; and from active motor forces. It is thought that the mechanical feedback on the molecular dynein motor proteins in the flagella is responsible for the spatiotemporal coordination among motors. However, the means of mechanochemical feedback are not well understood, since the motor forces cannot be measured directly. We develop a computational model using experimental data of flagella in different types of fluids to extract information about how motor forces change in response to external forces and different fluid rheologies.

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MS81

Immersogeometric Fluid-Structure Interaction Modeling of the Human Mitral Valve and Its Repair

is essential for personalizing and optimizing patient outcomes. Mitral valve (MV) transcatheter edge-to-edge repair (TEER) is a minimally invasive procedure for treating MV regurgitation (MR), which clips MV leaflets with a device such as the MitraClip and prevents leakage. The assessment of the condition of a mitral valve primarily depends on in-vivo measurements, but given the number of possible configurations and the complexity, it is highly unlikely that MV TEER optimization will be achieved by clinical trials alone. Consequently, a predictive approach to treatment selection that accounts for patient-specific variations in MV shape and deformation is critical to guide disease management and treatment and to ensure the benefit of the repair. To have a better understanding of the cardiovascular condition and the guidance of treatment selection for each patient, we develop a computational fluid-structure interaction model based on immersogeometric analysis that can account for complex interactions between a patient-specific MV and blood flow in the left heart, along with accurately modeling patient-specific MV behaviors. A penalty coupling method imposes a clip-equivalent force that constrains displacements and rotations of the MV leaflets, which allows physiological deformations and movements of the clipped MV by interacting with the blood flow. Then we investigate post-operative hemodynamics such as transvalvular velocity or left atrial and ventricular pressure based on different clip configurations. Furthermore, the developed computational model examines how the hemodynamic changes of TEER influence the MV functions, such as a significant reduction of the MV effective orifice area. This study will allow us to gain a better understanding of how pre- and post-operative MV condition, geometry, mechanical behaviors, and flow affect the post-TEER functional state, and it will eventually help clinicians develop precise MR treatment guidance for patient-specific stratification, which is essential for personalizing and optimizing patient outcomes.

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MS81

Computational Biofluid Dynamics for Precision Medicine: Optimizing Devices, Personalizing Interventions, and Pioneering Nanorobotic Delivery

Advancing precision medicine and ensuring patient safety requires a mechanistic understanding of how biological fluid dynamics govern the efficacy of medical devices and therapeutic interventions in patient-specific physiological environments. This presentation details a cohesive research program focused on developing predictive computational digital twinshigh-fidelity, validated biofluid modelsto deliver deep, personalized insight. We explore the critical role of computational fluid dynamics (CFD) in replicating and optimizing clinical scenarios across diverse organ systems. Case studies will demonstrate the breadth of this approach: (1) Fluid-structure interaction (FSI) simulations of bioprosthetic aortic valves to assess patient-specific hemodynamics and device-tissue compatibility; (2) Full 3D CFD models of dynamic gastric motility, crucial for predicting drug dissolution rates and nutrient absorption under varied digestive conditions; and (3) Coupled CFDDEM models of dry powder inhalers, evaluating particle flow and regional drug deposition in complex pulmonary geometries for regulatory assessment. Finally, we introduce ongoing work combining microscale biofluidic CFD with nanorobotics to model the active navigation and targeted release of therapeutic agents, charting a path toward truly intelligent, autonomous drug delivery systems.

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MS82

Robustness of Optimal Control Policies for Stochastic Boolean Models

Markov Decision Processes (MDPs) offer a powerful frame-

work for modeling and controlling complex biological systems. However, the reliability of these models often hinges on the accuracy of their underlying parameters. In this talk, we focus on MDPs derived from Stochastic Boolean Networks equipped with control actions, specifically examining how parameter fluctuations influence optimal control policies. We present a detailed sensitivity analysis across two distinct biological models: T-cell Large Granular Lymphocyte (LGL): We quantify how propensity parameters impact policy effectiveness and establish specific thresholds that guarantee performance. The Boolean Repressilator: We investigate how changes in propensity parameters affect critical dynamic properties, including time to absorption and mixing time. Additionally, we address the practical impact of simulation noise on policy optimality. Our results provide a roadmap for ensuring that computational control strategies remain effective in the face of the inherent stochasticity and uncertainty of biological data.

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MS82

Recovery of Synchronization after Beta Cell Loss

Networks of gap-junctionally coupled excitable cells often synchronize electrical signals, such as beta cells in pancreatic islets synchronize electrical bursting for pulsatile secretion. Disruptions in synchronization can signal disfunction and pathology. We consider the question, how sensitive to disruption is such a network to a single cell? How does the heterogeneity of the cells and the coupling strength impact this sensitivity? We show cases of networks where a single cell, switch cell, disrupts the synchronized network and apply optimization to produce open neighborhoods in high-dimensional parameter space where such cases are found. We can then train basic neural networks to identify whether a cell in a given a network is a switch cell based on model parameters rather than on testing a Synchronization Index. In line with the feedback theme of the minisymposium we further hypothesize that feedback to enhance coupling or to modify cell excitability can recover synchronization after the loss of a switch cell.

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MS82

Multiscale Modeling in Microbial Consortia: Spatial Heterogeneity and Collective Dynamics

Multiscale interactions shape the structure and function of microbial consortia, where processes ranging from intracellular metabolism to population-level transport collectively determine community behavior. This talk presents mathematical and computational models that connect single-cell dynamics, spatial heterogeneity, and emergent collective effects in structured environments. We develop continuum and agent-based frameworks to capture growth, resource exchange, and mechanical interactions, and use analysis and simulation to identify how diffusion limitations, local crowding, and metabolic coupling drive pattern formation, coexistence, and functional stability. The results highlight how spatial structure modulates cooperation and competition and demonstrate how multiscale modeling can guide the design and control of synthetic and natural microbial communities. As time permits we will discuss universal features present here and in other biological systems.

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MS83

SHEPHERD: Stochastic Evolutionary Control of Therapeutic Resistance in Heterogeneous Populations

Therapeutic resistance emerges from stochastic evolutionary dynamics in heterogeneous populations, posing a central challenge in cancer and infectious disease treatment. We introduce the SHEPHERD protocol (Stochastic Heterogeneityinformed Evolutionary Policy Hampering the Expansion of Resistance to Drugs), which integrates WrightFisher population genetics with Markov decision processes (MDPs) to compute optimal drug policies that minimize long-term population fitness, thereby reducing resistance. SHEPHERD couples a diffusion approximation of WrightFisher dynamics with a simplex-to-hypercube coordinate transformation, followed by a lattice discretization that enables numerically tractable policy optimization. On synthetic multi-drug fitness landscapes with 3, 4, and 8 genotypes, SHEPHERD maintains substantially lower mean fitness than any constant or periodic two-drug regimen. Sensitivity analyses reveal convergence at moderate resolution in genotype-frequency space, but a strong dependence on the drug-update interval, underscoring the importance of rapid feedback for maintaining control. Our study establishes a foundation for applying MDP-based optimization to stochastic evolutionary dynamics, highlighting the opportunities and challenges of steering evolution through drug sequencing.

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MS83

On the Fitness Landscapes in the NK Model

The NK model, introduced by Kauffman, Levin, and Weinberger, is a stochastic process used to describe the fitness landscape of certain species with N genetic loci, each interacting with K others. It is expected to capture rugged land-

scapes in some evolutionary systems and has been instrumental in studying evolutionary dynamics through adaptive walks. Earlier literature has been focused on the case K being a fixed positive integer and used tools from Ergodic and Markov theory. In this talk, I will present some new results concerning the fitness landscape in the NK model under the regime that K/N is proportional. These include the explicit formulas for the free energy and maximum fitness, overlap gap properties, and multiple peak structure of the level set near the maximum fitness, and the existence of evolutionary paths of nearly maximum fitness. Along the way, I will discuss the implications of our results in relation to evolution dynamics and explain how spin glass theory is of great use in our study. Based on a joint work with S. Tang.

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MS83

Optimal Ecosystem Management Under Rapid Environmental Change

Climate change is accelerating environmental shifts at unprecedented rates, creating novel challenges for ecosystem management. Traditional approaches focus on critical parameter thresholds that trigger regime shifts (bifurcation-induced tipping), but ecosystems may tip simply because they cannot adapt quickly enough (a phenomenon called rate-induced tipping or R-tipping). Despite growing recognition of R-tipping, optimal management strategies for systems facing this risk remain unexplored. We use Markov Decision Processes to investigate how R-tipping risk alters optimal harvesting and conservation policies in a bistable population model. By varying the rate of environmental change, stochasticity levels, and intervention costs, we examine key management questions: When should managers intervene versus accept collapse? How do optimal strategies differ between slow and rapid environmental change? Are rapid, decisive interventions more effective than gradual approaches?

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MS83

Evolutionary Optimization of Influenza Vaccines

Seasonal influenza viruses undergo rapid genetic and antigenic evolution driven by the challenge of its human host immune system. The biannual selection of vaccine strains, performed several months before vaccine distribution, can therefore be viewed as an optimization problem under uncertainty of a co-evolving system: how can we track, predict, and ideally counteract adaptive viral change in a heterogeneous and co-evolving host population? In this talk, I present a framework that integrates large-scale, time-resolved sequence data with phenotypic and epidemiological information to infer ongoing, time-dependent selection and to quantify inferred vaccine protection. By analyzing observed evolutionary dynamics and predicted variant trajectories through information-theoretic measures, we retrospectively analyze vaccine strain choices as an optimization problem on a coupled virusimmune landscape. This approach enables the inference of selection pressures directly from viral phylogenies and provides principled criteria for evaluating and comparing candidate vaccine viruses. More broadly, this perspective illustrates how evolutionary inference and probabilistic modeling can inform rational vaccine selection in rapidly adapting pathogens, and offers a quantitative framework for assessing predictability and control in viral populations.

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MS84

Spin Glass Active Inference for Optimal Decision-Making in Stochastic Switching Systems

Motivated by the biological challenge of designing optimal treatment schedules in which clinicians alternate between collaterally sensitive drugs while cancer cells exploit phenotypic switching to cultivate resilience, this talk develops an operations research framework grounded in spin glass theory to characterize optimal decision-making under uncertainty. Spin glass models, as paradigmatic systems of disorder and frustration, capture randomly competing interactions that generate intricate energy landscapes with numerous metastable states, providing a mathematically rich foundation for analyzing adaptive strategic behavior in complex stochastic environments.

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MS84

The Value of Simple Models for Characterizing Complex Uncertainty

Modeling complex biological systems requires inference from indirectly observed, noisy, and partially constrained data. In estimating both inventories and projections of cropland carbon and greenhouse gas balance, uncertainty arises from inputs, parameter identifiability, model structure, future climate, and variability in management. Using a simple and modular process-based biogeochemistry model, we represent these uncertainties explicitly and propagate them through nonlinear dynamics using an ensemble framework. The ensemble serves as a computational experiment that tracks how alternative inputs, parameter draws, and structural choices influence predicted stocks and fluxes across space and time. Sensitivity analysis decomposes contributions from different sources, while calibration, validation, and parameter constraint through informative priors and meta-analysis redistribute and bound uncertainty. The modular structure of the model separates parametric from structural uncertainty, allowing us to evaluate how alternative process representations affect predictive variance. Simple, transparent models are especially valuable for making complex uncertainty interpretable and for clarifying the limits of inference in high-dimensional biological systems.

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MS84

Mapping the North American Terrestrial Carbon Cycle: A Process-Based Reanalysis Using State Data Assimilation (sda)

Accurately assessing ecosystem carbon (C) budgets is essential for management and mitigating climate change. State data assimilation (SDA) harmonizes observations with models while reducing uncertainty. In this study, we employed a hybrid SDA framework combining process-based terrestrial biosphere modeling, hierarchical Bayesian inference, and machine learning (ML) to integrate bottom-up and remotely-sensed data (SoilGrids, MODIS, Landsat, and SMAP). This approach constrained major C and water stocks across 8,000 pre-selected 1km locations in North America. ML was used to correct systematic errors in the SIPNET process model and interpolate data onto a 1km grid, making it computationally feasible to generate annual ensemble maps. Uncertainties for each variable were reduced compared to observations or models alone, with a significant reduction in uncertainty for soil organic carbon (SOC). Spatiotemporal analysis revealed a slight decrease in aboveground biomass (AGB) in the western US, leaf area loss in the boreal, and greening in the Alaskan tundra. Validation against GEDI, ICESat-2, FIA, and ISCN data confirmed accurate C pool estimates. Our ML-debiasing algorithm further improved AGB and SOC accuracy. This continental SDA framework facilitates global C monitoring, reporting, and verification (MRV) by providing precise C-cycle estimates and spatiotemporal uncertainties.

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MS85

Astral Architecture Can Enhance Mechanical Strength of Cytoskeletal Networks by Modulating Percolation Thresholds

A repeated pattern in cytoskeletal architecture is the aster, in which a number of F-actin filaments emerge star-shaped from a central node. Aster-based structures occur in cytoplasmic actin, the early stages of the cytokinetic ring in yeast, and in the context of biomimetic materials engineering. In this work, we use computational simulation to show that there is an optimal number of filaments per aster that maximizes rigidity, even at a fixed density of F-actin. This nonlinear dependence holds for both the shear and extensional moduli. At physiological parameters, the maximum corresponds approximately to the same filaments-per-aster observed in recent super-resolution images of cortical F-actin. Furthermore, we find that increasing filaments-per-aster leads to dramatic increases in the sample-to-sample variability in network rigidity. We explain both effects using percolation theory, wherein the probability that a given network is productively connected exhibits a sharp dependence on parameters. The dependence of network rigidity on this nanoscale architectural feature may suggest a mechanism by which cells tune the physical properties of their actin networks locally and rapidly (since no new F-actin must be assembled) and may inform efforts to create adaptive synthetic metamaterials inspired by actin networks.

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MS85

Force Generation and Contraction of the Actin Cytoskeleton

Cells need mechanical forces for their biological functions, such as migration and cytokinesis. The actin cytoskeleton contracts and generates most of the cellular forces via interactions between cytoskeletal components, such as actin filament, myosin, and cross-linkers. Myosin II is known to play the most important role in force generation and contraction. Myosin II self-assembles into filaments with various structures depending on myosin II isoforms, such as skeletal muscle, smooth muscle, or non-muscle myosin II, and other conditions such as pH and ionic concentration. In addition, for identical myosin isoforms, functionally distinct motors are present in cells, such as myosin IIA vs myosin IIB in vertebrate cells and NMY-1 vs NMY-2 in C. elegans. It has remained elusive how contraction and force generation in actomyosin structures are regulated by these various properties of myosin II filaments. In this study, we used an agent-based model to investigate how the properties of myosin II filaments determine the extent and efficiency of force generation and the rate of network contraction, depending on the number, spatial distribution, and architecture of myosin II filaments. Our study provides key insights into understanding the roles of myosin II filaments in actomyosin contractility.

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MS85

Modeling Resource Competition of Actin-Propelled Beads

The actin cytoskeleton—complex self-organized assemblies of actin protein filaments and auxiliary proteins—dynamically rearranges during the cell cycle, forming networks harnessed by the cell for mechanical support and processes like motility. Multiple actin networks coexist simultaneously in the cell, competing for common limited resources: actin monomers and actin-binding proteins. However, how networks coexist in the competitive cellular environment is still poorly understood. Recently, our collaborators used a reconstituted system composed of actin-propelled beads in closed microwells to demonstrate the importance of protein turnover for resource distribution between networks (Guerin et al. 2025, Curr. Biol.). Interestingly, they observed that when many networks compete simultaneously, a selection process occurs which favors assembly of strong networks over weak ones. To understand the mechanisms underlying actin network competition, we approach this system from a biophysical modeling perspective, using ODEs to interrogate the underlying protein turnover dynamics. Our model reproduces key experimental results and demonstrates that monomer recycling becomes the limiting rate in competition between equal networks. Importantly, we find that selection is a consequence of the autocatalytic nature of actin network assembly, allowing for a "winner-takes-all scenario between unequal strength networks with important consequences for actin network coexistence in cells.

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MS86

Consistency of Feature Attribution in Deep Learning Architectures for Multi-Omics

Machine and deep learning have grown in popularity and use in biological research over the last decade but still present challenges in interpretability of the fitted model. The development and use of metrics to determine features driving predictions and increase model interpretability continues to be an open area of research. We investigate the use of Shapley Additive Explanations (SHAP) on a multi-view deep learning model applied to multi-omics data for the purposes of identifying biomolecules of interest. Rankings of features via these attribution methods are compared across various architectures to evaluate consistency of the method. We perform multiple computational experiments to assess the robustness of SHAP and investigate modeling approaches and diagnostics to increase and measure the reliability of the identification of important features. Accuracy of a random-forest model fit on subsets of features selected as being most influential as well as clustering quality using only these features are used as a measure of effectiveness of the attribution method. Our findings indicate that the rankings of features resulting from SHAP are sensitive to the choice of architecture as well as different random initializations of weights, suggesting caution when using attribution methods on multi-view deep learning models applied to multi-omics data. We present an alternative, simple method to assess the robustness of identification of important biomolecules.

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MS86

Machine Learning Applications on Antimicrobial Resistance and Healthcare-Associated Infections

Antimicrobial resistance (AMR) reduces the efficacy of life-saving antibiotics in patients infected with resistant bacteria, leading to worse outcomes and mortality. Advances in technologies and electronic medical records are generating an ever-increasing amount of data regarding AMR. The large number of exposures and outcomes poses challenges for classic epidemiologic analytic methods, which can be overcome with machine learning methods. Here, we introduce two applications of machine learning in AMR: identifying context-specific environmental and genotypic drivers of AMR and predicting infections with multidrug-resistant organisms (MDROs) using electronic health records. To identify environmental and genotypic drivers of AMR, we apply chain graph models to a multi-layer data structure that includes genomic data on resistance, environmental exposures, and antimicrobial susceptibility testing in the form of minimum inhibitory concentrations. The structure and parameters of chain graphs were learned using a penalized maximum likelihood method. Chain graph models generated insights into the complex epidemiology of AMR by characterizing context-specific resistant drivers and facilitating causal discovery. In hospitals, infections with MDROs are rare events. To predict MDRO infections from available electronic record features, we combined up-sampling techniques, penalized feature selection, and a gradient boosting classifier to identify patients at risk.

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MS86

Geospatial Deep Learning for Fine-Scale Indoor Radon Exposure with Uncertainty Quantification

Indoor radon accounts for an estimated 37% of population-level exposure to ionizing radiation in the United States, yet publicly available metrics are typically reported at coarse spatial scales that obscure substantial local variability and limit epidemiologic utility. To support complex health data integration and analysis, we developed a high-resolution, uncertainty-aware machine learning framework to estimate indoor radon concentrations across Utah. A total of 19,497 residential measurements collected between 2006 and 2016 were integrated with environmental and housing covariates and analyzed using a geospatial neural network that captures spatial dependence and nonlinear effects. Predictions were generated on a uniform H3 hexagonal grid at 0.73 km^2 resolution (level 8). Household-

level out-of-sample performance showed moderate correlation with observed concentrations (Pearson r = 0.44), reflecting considerable household-specific variability. Predictive uncertainty was well calibrated: 24.3% of held-out observations exceeded the predicted 75th-percentile threshold, close to the nominal 25%. Spatial maps of predicted concentrations and exceedance probabilities above 4 pCi/L revealed pronounced fine-scale heterogeneity not evident in conventional summaries. These findings demonstrate how an uncertainty-aware machine learning framework can integrate complex environmental and health-related data to enable fine-scale, decision-relevant exposure assessment.

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MS86

Multimodal Large Language Models for Clinical Decision Making

The rapid advancement of Artificial Intelligence (AI), particularly Multimodal Large Language Models (MLLMs), presents a transformative opportunity for healthcare. This talk explores the intersection of MLLMs and clinical decision-making, demonstrating how AI can evolve from a passive predictor to an active partner in patient care. First, I will introduce PULSE, a framework that teaches LLMs to interpret electrocardiographic (ECG) images using an ECGInstruct dataset. Next, I will discuss SepsisLab, which rethinks sepsis prediction by incorporating uncertainty quantification and active sensing to recommend specific lab tests that resolve missing data. Finally, I will present a CardioAI System for monitoring cancer treatment-induced cardiotoxicity, integrating EHRs, wearables, and voice interaction for continuous risk detection. These works demonstrate how AI augments physician decision-making rather than replacing it. More details can be found at https://www.pingzhang.net/

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MS87

Hybrid Simulation of Epidemics: Spatially Integrated Agent-Based and ODE Models

Compartmental ODE models provide efficient, population-level descriptions of infectious disease dynamics but typically average out heterogeneity, mobility structure, and localized outbreaks. Conversely, agent-based models (ABMs) can represent individual behavior, contact processes, and spatial structure in detail, yet become computationally demanding at scale. Motivated by policy-relevant epidemic simulation settings that require both realism and scalability, we present a spatially coupled hybrid ABMODE framework that partitions the domain into regions modeled either discretely (ABM) or continuously (ODE), while allowing bidirectional population exchange across the interface. This framework is first tested in a proof-of-concept toy model, exhibiting runtime speedups as the ODE-modeled fraction grows and reproducing pure ABM/ODE dynamics under homogeneous mobility, while revealing pronounced interface effects under heterogeneous mobility. We then apply the approach to a data-driven COVID-19 case study of highly connected regions in Germany, incorporating mobility, weather, and policy data. Relative to a full ABM, the hybrid model preserves key epidemic trajectories while achieving substantial runtime reductions for a population of several million individuals. We discuss model allocation strategies and robustness across scenarios.

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MS87

Beyond Common Random Numbers for Noise-Free Comparison of Stochastic Simulations

Random numbers are at the heart of every agent-based model (ABM) of health and disease. By representing individuals in a synthetic population, agent-based models enable detailed analysis of intervention impact and parameter sensitivity. Yet agent-based modeling has a fundamental signal-to-noise problem, in which small changes between simulations cannot be reliably differentiated from stochastic noise resulting from misaligned random number realizations. We formalize this problem through the lens of structural causal models and show that standard PRNG practices can yield causally incoherent paired counterfactual comparisons even when the mechanistic specification is otherwise sound. This formalization leads to methodology that eliminates noise due to misaligned random numbers. Our solution enables meaningful individual-level analysis between ABM scenarios because all differences are driven by mechanistic effects rather than random number noise. We demonstrate the benefits of our approach on three disparate examples. Results consistently show reductions in the number of simulations required to achieve a given standard error with levels exceeding 10-fold for some applications.

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MS87

Bridging from Detailed Networked Models to Patch Models - Thoughts and Illustrations.

Meta-populations, capturing aggregated dynamics offer computational advantages vis-a-vis networked agent-based models (ABMs). In contrast, high-resolution ABMs provide means to capture contagion dynamics at the level of individuals. At the cost of more complex calibration and computational complexity, ABMs are highly expressive and usually support direct translation of policy-driven interventions into existing model parameters and model structure. Patch-type, aggregated models, on the other hand, often require a translation layer to map interventions to their model representations, sometimes with the addition of compartments. In this talk we illustrate some of the interplay between the EpiHiper ABM and the patch models PatchSim with examples including early phase dynamics such as the introduction of novel diseases (e.g., COVID-19).

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MS87

Linking Time-Series, Patch, and Agent-Based Models of Measles in Laser, with Applications to Measles Transmission in Nigeria

Disease modeling requires researchers to choose between simple cohort-based models and computationally intensive agent-based simulations, each with distinct advantages. We present a measles transmission model implemented in the Python-based LASER framework, which bridges this gap by enabling flexible model specification through a unified interface. This approach allows researchers to build and compare both modeling paradigms using consistent syntax and design patterns. We demonstrate the framework's capabilities through a case study of measles transmission dynamics in Nigeria, presenting the model architecture and key applications.

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MS88

Predicting Treatment Outcomes from Adaptive Therapy - A New Mathematical Biomarker

Adaptive therapy is an evolution-based treatment paradigm in metastatic cancer, which dynamically adjusts treatment to control, rather than minimize, tumor burden. Promising clinical results in prostate cancer indicate the potential of adaptive treatment protocols to delay relapse, but demonstrate broad heterogeneity in patient response. There is a significant unmet clinical need for a biomarker to predict patient-specific progression under adaptive therapy, enabling the personalization of treatment protocols. Modeling the dynamics of drug-sensitive and -resistant tumor populations, we predict the expected benefit of adaptive therapy and extend this to a trio of mathematical biomarkers that can predict the time to progression and mean daily dose under a range of clinically realistic treatment protocols. These predictions are made following an initial standardized treatment cycle and enable the personalization of subsequent treatment. We apply our mathematical biomarkers to two distinct patient cohorts from trials of metastatic prostate cancer. Our mathematical framework accurately identifies patients with the greatest delay to progression, or reduction in mean daily dose, enabled by adaptive therapy. We demonstrate that the most favorable strategy varies among patients and present a possible framework for stratifying patients into distinct treatment arms, allowing for a personalized and mathematically-informed approach to treatment scheduling.

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MS88

Radiotherapy Dose-Finding to Balance Efficacy-Toxicity and Toxicity-Toxicity Trade-Offs in Head and Neck Cancer

Ionizing radiation is an effective localized therapeutic strategy that is used to treat approximately 50% of all cancer patients and 75% of head and neck cancer (HNC) patients. However, off-target effects in the radiation field vicinity of the head-and-neck region may induce toxicities that exacerbate patient symptoms, including dysphagia (necessitating interventions such as insertion of a feeding tube), oral pain, and nausea and vomiting. Such symptoms can be measured using patient-reported outcomes (PROs). Motivated by a published dataset of longitudinal PROs in HNC patients treated with RT, we developed a mathematical model to capture both on-target tumor response and off-target toxicities. The classical linear-quadratic dose-response model was employed to describe tumor response to RT with exponential growth. To model off-target toxicities, we introduce a novel concept of radiation exposure analogous to drug exposure. We then employed an inhomogeneous continuous-time Markov chain model with radiation exposure as a time-varying covariate to describe PRO dynamics. As a proof-of-concept, we leveraged the developed mathematical model to explore various efficacy-toxicity and toxicity-toxicity trade-offs with respect to dose, RT plan (sparing versus non-sparing), and concurrent chemotherapy. While efficacy-toxicity trade-offs were sensitive to dose and concurrent chemotherapy, toxicity-toxicity trade-offs were more sensitive to RT plan. Furthermore, we derived minimum efficacious dose (MED) and maximum tolerable dose (MTD) for various scenarios of tumor response and toxicity endpoints and evaluated viability of RT. Overall, this model offers adaptable, data-informed treatment decisions by integrating both tumor control and quality of life considerations into a singular model. We envision that future iterations of the model developed here will aid clinicians in dose-finding and selecting a RT plan that will optimize trade-offs between target efficacy and toxicity endpoints.

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MS88

Ensemble forecasting of glioblastoma growth from sparse longitudinal MRI biomarkers

Glioblastoma progression and treatment response are monitored through longitudinal MRI, providing sparse imaging biomarkers of tumor burden. However, limited time points and inter-patient variability make traditional parameter estimation ill-posed. We present an uncertainty-aware ensemble forecasting framework based on a simple reaction-diffusion tumor growth model. Rather than fitting individual parameters, we systematically sample biologically plausible ranges to generate ensembles of tumor evolution trajectories consistent with observed MRI measurements. We evaluate how sparse imaging data constrain forecast distributions and assess agreement with observed volumetric and spatial tumor changes. Our results demonstrate how low-complexity mechanistic models can generate realistic ranges of short-term outcomes while explicitly characterizing uncertainty and identifiability limitations. This work illustrates the role of ensemble modeling in biomarker-driven prediction under severe data sparsity.

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MS88

Mechanistic Modeling of cfDNA Fragmentome Dynamics Predicts Progression to Immunotherapy

Plasma cell-free DNA (cfDNA) shows promise as a predictive biomarker of treatment resistance in cancer patients. However, the mechanisms governing its production, fragmentation, elimination, and their relationships with tumor burden and disease progression, remain poorly understood. We developed a mechanistic model jointly describing the dynamics of short (75–¡ 580 bp) and long (= 580–1650 bp) cfDNA fragments alongside tumor kinetics in 112 advanced cancer patients receiving immune checkpoint inhibition, using a population modeling approach, to specify inter-individual variability in cfDNA kinetic parameters. The model captured complex longitudinal cfDNA patterns, including early treatment-associated spikes. Analysis revealed substantial inter-patient variability and demonstrated a 7.4-fold higher shedding rate for short versus long fragments. A model-derived parameter estimated at 6 weeks of treatment — reflecting increased release or reduced elimination of short fragments — was significantly associated with progression-free survival (PFS, HR=1.6, 95% CI: $1.2 - 2.2, p = 0.001$). Incorporating this parameter to baseline clinical variables significantly improved PFS prediction (C-index: from 0.78 [95% CI: 0.73-0.89] to 0.80 [95% CI: 0.74-0.90], $p < 0.0001$). This framework provides quantitative insights into cfDNA biology and offers a non-invasive approach for early prediction of treatment resistance, with implications for adaptive therapeutic strategies from longitudinal liquid biopsy.

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MS89

A Data-Driven Mathematical Model of inflammation During Ischemic Stroke

Neuroinflammation immediately follows the onset of ischemic stroke. During this process, microglial cells are activated in and recruited to the tissue surrounding the irreversibly injured infarct core, referred to as the penumbra. Microglial cells can be activated into two distinct phenotypes; however, the dynamics between the detrimental M1 phenotype and beneficial M2 phenotype are not fully understood. Using phenotype-specific cell count data obtained from experimental studies on MCAO mice, we employ sparsity-promoting system identification techniques based on the SINDy algorithm combined with Bayesian uncertainty quantification to generate a continuous-time

predictive model of the M1 and M2 microglial cell dynamics. The resulting data-driven model includes constant and linear terms but does not include nonlinear interactions between the cells. Results emphasize an initial M2 dominance followed by a takeover of M1 cells, captures potential long-term dynamics of microglial cells, and suggests a persistent inflammatory response.

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MS89

Mathematical Modeling to Capture Exacerbation Dynamics in Disease Progression of COPD

Chronic obstructive pulmonary disease (COPD) is a chronic condition caused by damage to the lungs, which leads to inflammation and other problems that obstruct airflow. The repeated and progressive activation of immune cells plays a pivotal role in the pathogenesis of COPD [1]. A COPD exacerbation is an acute worsening of respiratory symptoms that may last for days or weeks, often triggered by a viral or bacterial infection or exposure to pollutants, which can leave behind permanent lung damage and accelerate disease progression [2]. Decreasing exacerbations is a key goal of therapeutics, but predicting exacerbation frequency and severity is difficult due to their heterogeneous and random nature. In this work, we have developed a semi-mechanistic model of pathogen-immune interactions in COPD using random perturbations to simulate exacerbations in disease progression. Through model simulations and sensitivity analysis, we explore sources of variability in exacerbation rates and identify key mechanisms that drive exacerbation frequency and severity. References: [1] Ni, L., & Dong, C. (2018). Roles of Myeloid and Lymphoid Cells in the Pathogenesis of Chronic Obstructive Pulmonary Disease. Frontiers in immunology, 9, 1431. https://doi.org/10.3389/fimmu.2018.01431 [2] Wedzicha, J. A., & Seemungal, T. A. (2007). COPD exacerbations: defining their cause and prevention. Lancet (London, England), 370(9589), 786–796. https://doi.org/10.1016/S0140-6736(07)61382-8

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MS90

Modeling Feedback Between Vascular Adhesion, Inflammation, and Pain in Sickle Cell Disease

Sickle cell disease (SCD) is a family of inherited blood disorders caused by a mutation in the hemoglobin subunit (HBB) gene, affecting more than 100,000 people in the United States and millions of people worldwide. A hallmark complication of SCD is vaso-occlusive crises (VOCs), which arises from a cascade of sickle red blood cells, white blood cells, and platelets that adhere to the vascular wall, leading to obstruction, severe pain, and both acute and chronic complications. Emerging evidence suggests that disrupted sleep exacerbates pain in SCD patients, possibly through pro-inflammatory pathways. We present an ordinary differential equation (ODE) model that investigates the dynamic relationship between inflammation, pain, and sleep in patients with SCD. The model consists of four compartments representing pro-inflammation, anti-inflammation, pain, and adhesion, with sleep treated as an external input. Feedback mechanisms allow pain to disrupt sleep, poor sleep to upregulate inflammation, and elevated inflammation to amplify pain. Model simulations explore the relative impact of interventions that target increased sleep quality or reduced pro-inflammatory pathways on the severity and frequency of pain crises. The overall goal of this work is to identify interventions that could mitigate the impact of key feedback loops and reduce pain burden in patients with SCD.

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MS90

Mathematical Models of Systemic Infection Responses

This study evaluates mathematical models describing whole-body responses to different types of infection, including the healthy response, aseptic infection, and septic infection. Septic infection can be defined as an infection of the blood in which the pathogen remains elevated and causes extensive damage to the internal organs, affecting millions of individuals each year. In contrast, aseptic infection also causes extensive organ damage but ultimately results in depletion of the pathogen. By analyzing and comparing computational models, we aim to improve understanding of how these infection types differ and how they may be more effectively identified and treated, potentially refining current medical perspectives of sepsis. Simulations are produced using MATLAB and Matcont to illustrate the dynamics in the levels of pathogen, organ damage, inflammatory cytokines (including TNF-alpha, IL-6, and IL-8), and anti-inflammatory cytokines (including IL-10) experienced throughout the body during these different infection responses. Additionally, bifurcation analysis is used to identify the initial conditions that lead to more severe responses within the body, such as the persistently elevated pathogen levels characteristic of sepsis.

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MS90

Risk Assessment in Topologically Connected Dynamical Systems With Applications to Neurodegenerative Diseases

Risk is an intrinsic part of our daily lives. It governs the choices we make, what possibilities we forgo, and what opportunities we may set forth to pursue. While visible risk can be managed and contended with, invisible risk, however, is particularly insidious in form and in function. As the brain ages, it undergoes changes; one example is the onset of low-grade chronic inflammation as our immune system becomes less effective. Disruptions to brain equilibrium can shift the biological and neurological mechanisms that give rise to neurodegenerative diseases like Alzheimer's Disease (AD). We understand that what brain areas are affected by AD, and in what order, can tell us something about the severity of AD and its associated health risks. In this talk, I will discuss a novel framework to assess risk in network dynamical systems that makes use of a recent advance in topological data analysis. I am working to apply my framework to the study of the shape of first passage times to AD pathology and to understanding the associated health factors, like inflammation, as risk indicators on the road to developing AD.

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MS90

Linking diet to Alzheimer's Disease: New opportunities in interdisciplinary mathematical and computational AD research

Alzheimer's disease (AD) is a significant global health concern. With no reliable pharmaceutical treatments on the horizon, the best path forward is preventative. Dietary patterns are related to one third of AD risk factors and have long been thought to influence the onset or the progression of AD. Dietary intake patterns are related to three important mechanisms of AD: inflammation, oxidative stress and insulin resistance. These mechanisms are upregulated in the AD brain and tied to both diet and the protein pathology, aggregated amyloid-beta and tau, that are the hallmarks AD. At the same time, current AD therapeutics centered around the amyloid hypothesis are not faring well, leading the National Institutes of Health to call for the development of new approach methodologies (NAMs), such as mathematical, computational and AI models, in human AD research. This talk introduces the audience to an open, novel and interdisciplinary research question: can we predict the implications of diet on AD? The current view of AD biomarker pathology and our understanding of diet, AD risk and AD biomarkers will be briefly reviewed. Following this, we will present a class of state-of-the-art mathematical models for AD biomarker research alongside open questions that highlight new modeling opportunities for the influence of diet in AD. Mathematics and computing are poised to provide NAMs for interdisciplinary human AD research.

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MS91

Optimal Treatment Schedules in Circadian Medicine

A growing body of evidence suggests that the timing of treatment relative to a persons circadian clock can profoundly affect treatment outcomes. With limited data on dosing around the clock, coupled with minimal controls for inter-individual variability in the real world, solid insights into when the optimal timing is and how much timing actually matters for medicine can be hard to come by. Yet with computational techniques and mathematical modeling, we can begin to build an intuition for the conditions under which timing should and should not play an important role, as well as how factors such as pharmacokinetics, target availability, and therapeutic window may interact with endogenous rhythms in the body and even even predict optimal treatment schedule. We will present case studies of our modeling framework applied in antihypertensive drugs and chemotherapy treatment for glioblastoma.

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MS91

All Models Are Wrong, But Some Are More Consistent With The Data

The late English statistician George Box famously wrote that "all models are wrong, but some are useful.' This talk addresses Box's philosophy in the context of mathematical medicine, where complex disease processes like cancer present particular challenges to mathematical modelers. On the one hand, it is natural to try to capture what is known about the relevant biology, but on the other, data limitations often lead to unobservable parameters and initial conditions. Furthermore, there is often no obvious correspondence between imaging and other diagnosit data and the state variables and rate constants of interest in the mathematical model. In such cases, data assimilation

cannot be performed when the modeling objective involves patient-specific predictions. I will make the case that the most useful models in such situations are the simplest ones. I will describe how these issues arise in an effort to model the progression of malignant brain tumors and efforts to devise a clinically useful prediction tool for patient counseling.

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MT1

Interpretable Machine Learning and Deep Learning for Biological Modeling

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MT1

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MT2

Practical tools for Model calibration with SimBiology

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MT3

Practical tools for Model Calibration with SimBiology

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MT4

Structure-based Modeling of Biochemical Reaction Networks using BioNetGen

See session abstract.

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MT4

Structure-based Modeling of Biochemical Reaction Networks using BioNetGen

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Structure-based Modeling of Biochemical Reaction Networks using BioNetGen

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MP1

Teacher Leadership for Modeling and Data Science in Rural Communities

This poster describes the NSF Noycefunded Data Science in Rural Utah with Mathematical Modeling (DRUMM) program, which prepares teacher leaders to integrate modeling and data science into secondary mathematics and science classrooms. The program combines graduate coursework, summer institutes, and classroom-based action research centered on locally relevant socio-ecological issues. Participants develop modeling lessons, analyze real data sets, and build professional learning communities that extend into rural districts. We share curriculum examples, teacher reflections, and emerging outcomes demonstrating increased teacher confidence, student engagement, and cross-disciplinary collaboration. DRUMM illustrates how sustained partnerships among universities, schools, and communities can expand access to meaningful quantitative learning opportunities in rural settings.

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MP1

Computational Modeling Labs for First-Year Life Science Students Using Colab and Python

We developed a sequence of fifteen computational labs for a new first-year life science calculus course grounded in a *Modeling Life* approach. After evaluating several platforms, we selected Google Colab and Python to provide accessible, browser-based computation, supplemented with selected labs in Excel and NetLogo. The labs scaffold students computational skillsfrom defining variables and visualizing models to Eulers method, derivatives, symbolic computation, equilibrium analysis, stability, competition models, bifurcations, and agent-based ecological simulations. Biological contexts such as predatorprey dynamics, disease spread, protein synthesis, and population growth anchor each activity. These labs build computational fluency while deepening conceptual understanding of calculus and dynamical systems, preparing life science students to use modeling and simulation in their disciplines.

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MP1

Extensions of the Romeo and Juliet Model with Further Mathematical and Biological Applications

The Romeo and Juliet model is repeatedly used in the Modeling Life approach to teaching Dynamics to biology undergraduates. It is effective because it is memorable to the students. This model also serves as a simplified gateway to understanding more complicated biological models. The model can be extended to exhibit more complex oscillations, such as quasiharmonic, quasiperiodic, and chaotic motion, to help students understand other routes to chaos seen in biological systems. The mathematical concept of Fast Fourier Transforms and Power Spectrum Analysis can also be introduced to aid in distinguishing quasiperiodic and chaotic motion graphically.

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MP1

A Water Transfer Experiment Linking Physical Systems and Mathematical Models

This poster presents a hands-on laboratory activity that introduces students to modeling water transfer processes across physical systems. Using simple experimental setups, students collect data on flow and transport, develop mathematical models to describe observed behavior, and test model predictions against measurements. The lesson connects concepts from biology, environmental science, and differential equations while emphasizing data analysis, parameter estimation, and model validation. Adaptable for undergraduate courses and secondary classrooms, the activity provides an accessible entry point to interdisciplinary modeling grounded in real-world environmental phenomena.

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MP2

Rethinking Fibrin Branching: A Combined Mathematical and Experimental Approach

The coagulation cascade generates a three-dimensional (3D) fibrin gel that seals wounds and prevents the loss of blood. While much experimental and modeling work has been done to understand the gelation process, there has been no direct visualization of fibrin polymerization with the spatial and temporal resolution necessary to characterize fibrin branching. Using SimView light sheet microscopy, we captured the first videos of fibrin fibers forming junctions and gelling. Surprisingly, we found that branching occurs due to the moving and binding of mature fibers, not through the splitting of fibers or through the lateral association of small fibrin oligomers (protofibrils). In this poster we present a 3D agent-based model of rod-like fibers that diffuse and stick together. Model results of relative frequency of different branch types and distribution of fiber angles after binding match well with the experimental results, confirming the bind-and-stick branching mechanism. Together, these results represent a paradigm shift in our understanding of how fibrin branches and gels.

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MP2

Quantifying Thrombus Failure and Embolization at High Shear Rates

Blood clotting is a complex phenomenon that involves the interplay between biochemistry and fluid dynamics. Exposure to tissue factor and collagen leads to the activation of platelets, which are in a high-affinity state that promotes adhesion to the subendothelium and cohesion with neighboring platelets. At sufficiently high shear rates, von Willebrand factor can elongate and bind with unactivated platelets, providing another pathway for thrombus formation. Embolization of these clots can pose serious health risks, such as myocardial infarction or ischemic stroke; however, the strain and failure stress of thrombi formed under varying conditions remains poorly quantified. In this work, we present a detailed mechanics model of clot formation that captures the viscoelastic stresses from the interplatelet bonds at high shear rates. We introduce metrics to quantify clot failure criteria. We further extend this model to incorporate fluid-structure interaction using the immersed boundary method, addressing how clot forma-

tion and adhesion to structures occurs.

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MP2

Continuum and Discrete Modeling of Binding-Site Distribution-Mediated Reactions on Lipid Surface

Surface-dependent reactions play a central role in biological systems such as blood coagulation, yet how the spatial distribution of surface binding sites influences reaction efficiency is not well understood. We study how surface organization of binding sites affects generation of reaction products. We consider a simplified coagulation reaction system with surface dependency and positive feedback using two modeling approaches: a PDE model and a particle-based model. In the PDE framework, we develop a two-dimensional bulk-surface reaction-diffusion model with binding sites arranged in patches along a reactive boundary. Fixing the total number of binding sites and varying the patch number, the PDE model predicts that increasing the number of patches monotonically enhances reaction efficiency. In the particle-based framework, we perform simulations in both quasi-2D and three-dimensional settings. Varying the number and size of surface patches reveals a non-monotonic dependence of reaction efficiency on patch number: efficiency initially increases but decreases when patches become overly fragmented. This discrepancy arises from continuum assumptions that permit fractional binding, whereas reactions at small spatial scales require a discrete representation. Our results suggest that moderately sized, high-density surface patches optimize reaction efficiency and highlight the importance of discrete modeling when the spatial scale of interest approaches the single-molecule level.

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MP2

A Discrete Platelet-Bonding Model for Simulating Platelet Adhesion Via Von Willebrand Factor

Hemostasis is the healthy clotting response to a blood vessel injury. A major component of clotting is platelet aggregation, which includes platelet-platelet and platelet-wall binding interactions. A continuum model of platelet aggregation represents both platelets and the plasma flow as a continuum, lacking single platelet detail. A discrete model of platelet aggregation represents both platelets and flow by many discrete particles, which is computationally intensive. We aim to create a hybrid discrete-continuum model of platelet aggregation where platelets are individual, discrete particles coupled to a continuum flow that can efficiently model physiological timescales. Simulating adhesion is the first stage of this model development. The critical interaction for adhesion is between wall-adherent collagen, von Willebrand factor (vWF), and platelet receptor GPIb. Each platelet is represented as a single particle within the molecular dynamics software, LAMMPS. Platelet motion is driven by a prescribed flow field in addition to random Brownian motion. Each platelet has a discrete set of bonding points with which they can adhere to fixed molecules embedded in the wall akin to the GPIb-vWF bonding. Adhesion parameters were validated against single-platelet rolling experiments conducted in microfluidic channels. Current and future work will model additional bonding interactions key to platelet aggregation and computationally couple this discrete platelet model to a dynamic flow.

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MP2

Integrating Mechanistic Modeling and Machine Learning to Predict Bleeding Phenotype in FXI Deficiency

Bleeding risk in factor (F)XI deficiency correlates poorly with FXI antigen or activity, making identification of bleeding-phenotype difficult, leading to possible over- or under-treatment. Plasma-based functional assays can discriminate between bleeding phenotypes; however, activation of the contact pathway masks this discrimination. We developed a mechanistic mathematical model of coagulation using a reaction network constructed from established coagulation mechanisms. Patient-specific plasma factor levels were used as model inputs and coagulation dynamics were simulated with and without triggering the contact pathway. The model generated metrics that improved discrimination and enabled visualization of species concentrations that cannot be visualized with functional assays. When used as features for a machine-learning classifier, model-derived features improved prediction of bleeding phenotype in FXI-deficient patients, outperforming classifiers based on functional assay metrics alone.

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MP3

Developing Discrete-to-Continuum Nerve Net Models for Jellyfish Locomotion

Jellyfish, or rather Scyphomedusae, lack a central nervous system. Instead, they utilize a system nerve nets, whose communication is mediated by a symmetrical arrangement of multiple pacemaker like structures called rhopalia, that are responsible for propagating action potential. One of the nerve nets, dubbed the Motor Nerve Net, interacts with the subumbrellar musculature and produces complex macroscopic behaviors such as turning and swimming. This study explores how small scale action potential and transmission dynamics can lead to large-scale behavior. We employ a set of Hodgkin-Huxley type equations to model the ion channels of a nerves axon as conductance that change according to probabilities based on transmembrane voltage. Regression on a Chebyshev polynomial basis the simulation data is coupled with an Immersed Boundary Adaptive Mesh Refinement (IBAMR) fluid simulation of the pumping of a jellyfish bell. A simulation starting from neuron dynamics up allows for finer control of temporal asymmetries, allowing for our analysis of delayed pacemaker firings and their impact on turning and swimming.

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PP1

How Interneuron Subtypes Shape Working Memory Dynamics

The maintenance of continuous variable information in working memory is thought to rely on persistent patterns of cortical activity. In delayed estimation tasks, neural activity has been observed to form localized activity peaks whose centers track the memory of the variable. These bumps of neural activity are well capture by neuronal network models organized to produce continuous attractors. However, most existing models neglect the role and interaction of distinct interneuron subtypes on the memory dynamics. Past work has investigated broadly the stability and interactions of excitatory and inhibitory neuron subpopulation dynamics, finding the variance of predicted response error distributions to be strongly dependent on the neural architecture. This work refines neuron subpopulations into excitatory (E), parvalbumin-expressing (PV), and somatotostatin-expressing (SOM) neuron types. We explore the resulting linear stability of the model and its dependence on changes in the network architecture as well as computationally examine the wandering dynamics of memories in this system. From this model we are able to gain insight on how characteristics of different neuron subpopulations can influence the dynamics of memories.

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PP1

Sci-LLMs for Molecular Hypothesis Generation: Bridging Sequence, Structure, and Assays

We present a workflow that adapts scientific large language models (Sci-LLMs) to propose experimentally testable molecular hypotheses by jointly conditioning on protein/nucleotide sequence, predicted structure, and biochemical assay metadata. The system uses multimodal encoders to translate structural and assay descriptors into token-like embeddings and a masked-generation objective to propose residue-level mutations or small-molecule modifications predicted to change a phenotype of interest. We demonstrate case studies on (i) enzyme specificity switching and (ii) small-molecule affinity modulation, validated against held-out experimental datasets and simple wet-lab assays. The results show Sci-LLMs can produce high-value candidate hypotheses that prioritise experiments and reduce screening burden.

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PP1

Weak-Form Upscaling of Agent-Based Models

Agent-based models (ABMs) are a flexible framework for simulating complex biological systems that are often difficult or impossible to model with traditional methods. However, their computational cost and inherent stochasticity limit their utility for inference. Classic compartmental models like the Susceptible-Infected-Recovered (SIR) model are deterministic and analytically tractable, but they rely on significant simplifying assumptions. We employ weak-form sparse identification of nonlinear dynamics (WSINDy), a data-driven algorithm for model selection, in order to infer deterministic mean-field ordinary differential equations (ODEs) from SIR-type ABMs with multiple levels of population mixing and distributed infectivity. We study convergence of the ABM processes to the learned equations, contrasting it with the classical SIR dynamics, and characterizing the deviations arising as a result of multi-scale interactions and heterogeneous transmission rates. The results demonstrate that WSINDy is able to recover deterministic mean-field equations from stochastic simulations that differ from the traditional mean field limits of interacting particle systems. This work demonstrates the usefulness of WSINDy for coarse-graining ABMs in order to find interpretable and computationally efficient lower-order models of complex biological systems.

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PP1

Benchmarking Scientific Llms for Biomedical Reasoning: Tasks, Metrics, and Dataset Suite

We propose a standardized benchmark suite for evaluating Sci-LLMs on biomedical reasoning tasks: pathway inference, assay outcome prediction, causal claim extraction, and therapeutic repurposing suggestion. The suite contains curated datasets, multi-scale evaluation metrics (factuality, plausibility, experimental utility), and a human-in-the-loop evaluation protocol that emphasises experimental follow-up value. We test several open and closed Sci-LLMs and identify systematic failure modes (confabulation on rare variants, overconfident mechanistic claims). We release the benchmark and evaluation scripts to cultivate reproducible progress.

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PP1

Reproducing Paramecium Behavior Via Changes in Ciliary Beat Patterns

Paramecia are single-celled organisms covered in dense arrays of motile cilia and are widely considered model organisms within the ciliate group. They exhibit complex swimming and surface-interaction behaviors arising from coordinated waves of ciliary beating, or beat patterns. These organisms dynamically change their spatiotemporal ciliary activity to produce different behaviors. During free swimming, asymmetric beat patterns generate helical swimming trajectories. When encountering an obstacle, paramecia undergo an avoidance reaction, reversing their swimming direction and reorienting before resuming forward motion. During feeding and surface attachment, cilia in specific regions, such as the oral groove, beat at higher frequencies to generate feeding currents and maintain proximity to surfaces. We develop a swimming model that reproduces these behaviors using real cell geometry with prescribed traction stresses on the ciliary surface that are related to the spatiotemporal organization of the beating pattern obtained from experimental data. Using numerical fluid simulations, we demonstrate how swimming and surface-interaction behaviors arise from different beat patterns. We couple the swimming model with an existing electrophysiological model, enabling an integrated description of how the cell behavior results from environmental cues.

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PP1

Modulating Bursting in Unidirectionally Coupled Neurons

Bursting is a common firing pattern of interest in neurons which is characterized by an alternating pattern of a sequence of spikes followed by quiescence. Two related concerns are the transition between spiking and bursting as well as the process of adding/removing spikes within a burst. Previous work has shown that by changing the amplitude and frequency of a lower frequency oscillatory input, one can modulate bursting behavior in higher frequency neurons. Using this relationship as inspiration, we wish to look at how changing the same features in an input neuron in a unidirectionally coupled system would generate and modulate bursting. Neuronal model can be coupled through inhibitory, excitatory, or gap junction coupling. We will start by investigating how these three couplings can generate bursts. Then, we will look at how changing coupling strength as well as the pre-synaptic neuron's frequency can add or remove spikes. We will use techniques from geometric singular perturbation theory and bifurcation theory for fastslow systems with multiple time scales to explore the underlying spike adding/subtracting mechanism for coupled neurons.

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PP1

Agent-Based Modeling of Wheat-Blast Transmission in Fields

Diseases can affect plants across the world, leading to a decrease in the production of edible crops. Here we are focused on wheat blast, which is a fungal plant disease that has the capacity to destroy wheat fields in a few weeks. Working with data on wheat in Bolivia, we develop an on-lattice agent-based model that treats each plant as an individual grid site and describes the spread of disease in the field. Using approximate Bayesian computation, we estimate parameter values associated with different experimental conditions. We discuss our model and ongoing results, highlighting different dynamics observed in wheat leaves and spikes and comparing the role of spatial and non-spatial data in parameter estimation.

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PP1

Cellular and Subcellular-Scale Modeling of Cardiac Excitation Propagation with Dynamic Extracellular Cleft Concentrations

In cardiac electrophysiology, ionic currents at the subcellular scale drive electrical activity at the tissue scale, making accurate cellular modeling essential for understand-

ing cardiac function. Experimental inaccessibility of subcellular compartments in intact tissue positions mathematical models as essential tools for studying excitation propagation and motivates the development of multiscale frameworks. We present a biophysically derived computational model for action potential propagation in linear strands of cardiac myocytes that explicitly couples gap junction and ephaptic mechanisms. The model incorporates a biophysically detailed ionic model (Luo-Rudy dynamic) with intracellular concentration dynamics, coupled to a continuum PDEDAE system governing transmembrane voltage and cleft ion concentrations. Cleft concentration dynamics, governed by conservation of mass, balance spatially localized transmembrane ionic currents at intercalated discs from adjacent myocytes with Goldman-Hodgkin-Katz electrodiffusive exchange to the bulk extracellular space. Equations are discretized using finite volume methods to preserve conservation and integrated using operator splitting with a multirate GARK method to resolve the multiple temporal scales. This framework enables mechanistic investigation of ephaptic coupling through dynamic ion concentrations in the extracellular cleft and demonstrates stable propagation with recovery of known conduction limits in ventricular tissue.

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PP1

Protein Cluster Formation As a Moving Boundary Problem

Protein aggregation plays a key role in the formation of many subcellular structures, ranging from lipid raft formation to protein cluster formation in postsynaptic domains. In many cases the underlying mechanism of protein aggregation involves diffusing particles being assimilated into protein clusters in the presence of a recycling process that exchanges particles with the cytosol. The resulting models support non-equilibrium stationary states (NESS) due to the dynamical balance between particle recycling, diffusion and absorption at cluster interfaces. In this paper we investigate protein aggregation models from the wider perspective of moving boundary problems. Given the complexity of the spectral problem underlying the stability of stationary protein clusters, we develop the theory in terms of a single one-dimensional (1D) cluster. This also allows us to exploit certain analogies with a model of tubulin-based neurite elongation, in which the tip of the neurite is treated as a moving boundary subject to polymerization/depolymeriztion. We derive conditions for the existence and stability of a stationary cluster and compare the predictions of the spectral theory with direct numerical simulations of the full reaction-diffusion equations. One main result is that a low density cluster in a sea of higher density diffusing proteins can become unstable via a Hopf-like instability. Finally, we show that analogous results hold for a circularly symmetric cluster in $\mathbb{R}^2$.

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PP1

Telling Time with a Circadian Clock: Light and Temperature Integration in Cyanobacteria

A simple circadian clock enables cyanobacteria to align photosynthesis, photoprotection, and metabolism with the Earths varying day-night cycles. Recent work models the clock as an encoderdecoder that estimates biologically relevant quantities like time to sunset or future light levels, thereby providing a principled explanation for non-24-hour internal periods and their dependence on seasonal structure and latitude. Building on this mechanism, we simulate the KaiABC oscillator with a StuartLandau equation, which describes the dynamics of limit-cycle attractors near a Hopf bifurcation. By harnessing environmental signals like temperature and solar radiation as inputs to the model, we can chart the oscillators trajectory in clock phase space. In particular, luminance changes drive shifts in the limit cycle's origin during day-to-night transitions, while temperature scales the oscillation amplitude. This entrainment over time can be modeled as movement between orbits, providing a statistical basis for downstream prediction of crucial physiological variables. The models predictive power is enhanced by encoding oscillation nullification at sufficiently low temperatures, informed by experimental observations of lab-strain cyanobacteria. This additional temperature dependence on the bifurcation parameter more clearly captures seasonal variations in clock behavior across climates, prompting further investigation into the wide variety of circadian structures in nature.

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PP1

Multivariate Correlations Between Functional and Structural Connectivity and Longitudinal Cognitive Outcomes for Older Autistic and Non-Autistic Adults

Recent studies suggest people with autism (ASD) have higher risk of experiencing cognitive decline and neurodegenerative diseases compared to non-autistic (non-ASD) counterparts (Vivanti et al, 2021; Starkstein et al, 2015). We investigated the functional and structural connectivity patterns that correlate to longitudinal cognitive change in ASD (n=40) and non-ASD adults (n=33), aged 40-71. Brain networks were constructed from multimodal MRI data from first visits in a longitudinal study; long-term cognitive outcomes were calculated using the slope of a linear mixed effects model of the long-term memory score of the Auditory Verbal Learning Test across 2-10 years of follow-up for each participant. Brain connectivity was quantified through network measures using the Brain Connectivity Toolbox in MATLAB and residualized using age and sex as covariates. Behavioral partial least squares was used to identify significant multivariate correlations between network measures and long-term cognitive outcomes. For the non-ASD group, we found that long-term cognitive outcomes correlated to structural connectivity patterns involving classic memory regions (e.g. hippocampus). For the ASD group, we found that long-term cognitive outcomes correlated to functional connectivity patterns across a wide range of brain regions, as well as the whole brain. These findings suggest potential biomarkers and brain mecha-

nisms of risk for accelerated cognitive decline in the ASD population.

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PP1

Learning Noise Models and Growth Laws Using Biologically-Informed Neural Networks

Neural ordinary differential equation frameworks such as Biologically-Informed Neural Networks (BINNs) have shown promise for learning mechanistic laws from sparse data. However, most assume homoscedastic Gaussian noise, ignoring the biologically meaningful structure in data variability. In this work, we extend BINNs to include a learnable noise model, allowing discovery of additive, multiplicative, or mixed noise directly from data. Using synthetic population growth systems, we demonstrate that the framework correctly identifies the noise type, scales uncertainty with state, and yields calibrated variance estimates. This work establishes a general approach for incorporating data-driven noise learning into mechanistic neural-ODE architectures.

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PP1

Scalable Network Algorithms for Multi-Omics Prioritization and Therapeutic Discovery

We introduce a compact pipeline that uses network analytics and lightweight AI to prioritize biomarkers and therapeutic hypotheses from integrated multi-omics and clinical data. Key components are: (1) construction of multi-layer biological graphs linking genes, proteins, metabolites, and phenotypic terms, (2) fast network propagation to diffuse signal from sparse clinical labels, and (3) embedding-based ranking augmented with uncertainty scores to guide experimental follow-up. In retrospective benchmarks the pipeline improves recall of validated targets and reduces candidate lists by an order of magnitude, enabling more focused experimental screening. The poster highlights algorithmic scalability, parameter choices that preserve biological interpretability, and a short case study demonstrating rapid prioritization for a disease cohort. All code, CI recipes, and reproducible notebooks will be made available to facilitate adoption.

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PP1

In-Host Modeling of Bacterial Coinfection

Bacterial coinfection can reshape within-host immune dynamics and shift a host from effective control to persistent infection and tissue injury. We build on an established mechanistic model of bacterial infection that couples pathogen burden with activated neutrophils, anti-inflammatory mediators, and tissue damage, and extend it to include two bacterial populations with explicit interaction mechanisms. This framework captures how competition or facilitation between bacteriatogether with immune feedbackcan generate distinct outcomes, including clearance with recovery, persistent infection, and high-inflammation/high-damage states. We identify key parameters and interaction pathways that shift thresholds between these outcomes and reveal history dependence, such as priority effects in which the order or timing of acquisition changes the long-term trajectory. Overall, the model provides a quantitative platform for investigating how bacterial interactions within the host influence disease severity and recovery under coinfection.

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PP1

Antibiotic Resistance Dynamics and Viral Control Intervention Strategies

Antibiotic resistance represents a major public health challenge, complicating the treatment of bacterial infections. This study explores Antibiotic Resistance Dynamics and Viral Control Intervention Strategies by developing a mathematical framework that integrates virus interactions into a system of differential equations. We focus on the interaction between wild-type bacteria, antibiotic-resistant bacteria, and virus infected bacteria populations, using optimal control theory to guide virus-infected bacterial interventions. The model accounts for key biological factors, including bacterial growth rates, mutation rate, and viral infection dynamics. Numerical simulations demonstrate how introducing viral infection influences the stability of bacterial populations and reduces the dominance of resistant strains. Furthermore, an optimal control approach is employed to identify effective intervention strategies, with the goal of minimizing the antibiotic-resistant population while maintaining the population of wild bacteria. Our findings emphasize the importance of incorporating viral dynamics in resistance management and propose a balanced approach to control resistant infections without exacerbating the emergence of more resistant strains. Crucially, we extend this framework into a reaction-diffusion model to account for spatial heterogeneity and the localized spread of

resistance.

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PP1

Webng: A Templating Tool for Weighted Ensemble Sampling of Rule-Based Models

Mechanistic models of biochemical systems defined via Rule-Based Modeling (RBM) are essential for capturing the combinatorial complexity of protein signaling. However, calculating the kinetics of rare events, such as cell-fate switching or signal propagation, remains computationally challenging using standard stochastic simulation. While the Weighted Ensemble (WE) algorithm provides a mathematically rigorous framework for enhancing the sampling of these rare events, its integration with RBM software like BioNetGen (BNG) has historically required intensive custom engineering. We introduce WEBNG, an open-source framework that couples BNGs rule-based models with the WESTPA simulation engine. WEBNG automates the simulation pipeline, including state serialization, propagation, data-driven clustering, and kinetic analysis. We demonstrate WEBNGs accuracy across four benchmarks, including an 8 gene network for stem cell differentiation. We show that WEBNG probes dynamic regimes inaccessible to brute-force methods. By bridging the gap between RBM and WE, WEBNG enables the broader systems biology community to quantify the transition kinetics of complex models of cell signaling and gene expression dynamics.

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PP1

Modeling of Multipartite Virus Particles

Most viruses transmit their genetic material in a single package, such that when a cell is infected by a virion, all the information needed for replication is available and the virus replicates. However, some viruses, known as multipartite viruses, have their genetic material contained in several different viral particles. In this case, a cell needs to be infected with at least one copy of each package in order to have all the information needed for viral replication. Requiring infection by multiple distinct particles would seem to present a barrier to successful viral replication, so should be an evolutionary dead end. Yet multipartite viruses exist and seem able to persist. We use mathematical modeling to explore the effect of having multiple viral particles on a virus' ability to establish and maintain an infection. We find that viruses split into more particles require a higher infection rate in order to establish an infection. These findings can help develop an understanding into the adaptive mechanisms of multipartite viruses and contribute to a broader understanding of viral evolution and host-virus interactions.

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PP1

A New Perspective on Phase Tumbling with Slow Manifold

"Phase Tumbling" in the context of circadian physiology refers to the phenomenon whereby phase shifting occurs more rapidly in response to external inputs when the oscillators are initially less synchronized. We investigate this phenomenon using slow manifold reduction in a population of coupled circadian oscillators; here a slow manifold can be considered as the intersection of the unstable manifold of the periodic orbit and the stable manifold of the periodic orbit. Phase and isostable response curves computed on the slow manifold ultimately yield new insights about the phase tumbling phenomenon.

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PP1

The Cardinal Framework for Cardiovascular Modeling and Simulation

Cardinal is an open-source software library that provides modeling and simulation infrastructure for all major aspects of heart function, including cardiac mechanics, electrophysiology, electromechanical coupling, valvular dynamics, fluid dynamics, and fluid-structure interaction (FSI). Cardinal builds on the IBAMR software framework for modeling FSI using the immersed boundary (IB) method and its extensions, with support for adaptive mesh refinement (AMR). Unlike IBAMR, which is designed to support a broad range of FSI applications across engineering and applied science, Cardinal targets high-fidelity cardiac digital twins. To enable such models, it includes cardiovascular constitutive laws and reduced-order representations that provide physiological driving and loading conditions, such as Windkessel models and simplified descriptions of the pericardium. Cardinal also leverages the deal.II finite element library to provide substantial capabilities beyond those available in IBAMR, particularly for cardiac electrophysiology based on the monodomain and bidomain equations. In addition, it supports integrated models that combine volumetric descriptions of the myocardium with cable-based representations of specialized conduction system components, such as the His bundle and the Purkinje network. This poster will provide an overview of Cardinals design, capabilities, and the physiological modeling applications it enables.

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PP1

Modeling Amyloid-Beta Clearance Across the Blood-Brain Barrier with Nonlinear Receptor Kinetics

Impaired clearance of amyloid-beta (A) from the brain has been implicated in the pathogenesis of neurodegenerative diseases such as Alzheimer's. A large portion of this clearance occurs through the blood-brain barrier (BBB) via receptor-mediated transport, yet current models fail to capture the complex kinetics and heterogeneity of receptors at the BBB. Here, we derive a nonlinear homogenized boundary condition for solute transport across the BBB that accounts for finite receptor kinetics, receptor density, and bidirectional transport. The boundary condition incorporates Michaelis-Menten kinetics for two distinct receptor populations: LRP1, which mediates A efflux from brain to blood, and RAGE, which mediates influx from blood to brain. We implement this boundary condition in a cylindrical geometry representing a capillary surrounded by brain tissue and verify the numerical model against a steady-state analytical solution. Simulations reveal that A concentrations in the brain are highly sensitive to the receptor number ratio, while concentrations in the blood are primarily governed by the blood clearance rate. These findings carry therapeutic implications, as aging is associated with large changes in both receptor expression and cerebral blood flow. Using this model, we provide numerical evidence that non-rapid eye movement (non-REM) and REM sleep may be structured to enhance brain waste clearance via complementary function of the glymphatic and BBB efflux routes.

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PP1

Robustness and Stability in a Closed-Loop Respiratory Network with Heterogeneous Populations

The pre-Btzinger complex (preBtc) serves as the kernel for the mammalian inspiratory rhythm. While single-neuron models capture fundamental pacemaking properties, they fail to account for population-level dynamics within the closed physiological feedback loop. This study extends the closed-loop breathing framework of Diekman, Thomas, and Wilson (2017) by replacing their single-neuron controller with a heterogeneous population of $N = 20$ Butera-Rinzel-Smith bursting neurons. The model couples conductance-based differential equations for neuronal voltage to first-order motor kinetics and gas exchange dynamics. We analyze the system's homeostatic robustness against increasing metabolic demand (M). In homogeneous networks, closed-loop chemosensory feedback flattens the response curve, maintaining eupnea across a broad metabolic range before a sharp bifurcation leads to tachypneic collapse. We demonstrate that recurrent excitatory synaptic coupling significantly extends this stability margin by enhancing integrated inspiratory drive. Furthermore, introducing Gaussian parameter heterogeneity (coefficient of variation $\approx 3\%$) transforms the failure mode from a sharp "cliff" to a distributed, sigmoidal threshold. The system also exhibits robust period-n alternans and irregular recruitment patterns near stability boundaries. These findings provide a mechanistic account of how intrinsic diversity and network topology may modulate respiratory resilience in vivo.

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PP1

Baseline Firing Rate of Dopaminergic Neurons Modulates the Characteristics of the Dopamine Level Response to Stimuli

The dopamine (DA) system plays a key role in arousal, movement, memory, and reward-related behavior. Electrical brain stimulation (EBS) is an important tool for investigating dopamine circuits and developing potential for treating conditions, such as addiction, depression and schizophrenia; however, factors of electrical stimulation that regulate dopamine response remain unclear. Using fast-scan cyclic voltammetry (FSCV), we detected the rapid change in DA responses in the nucleus accumbens evoked by medial forebrain bundle stimulation in anesthetized rats. We observed a highly variable dopamine response to identical stimuli across stimulus conditions, for both 10?Hz and 20?Hz stimulation. To investigate the source of this variability, we develop a model that captures the observed fluctuations in dopamine response by adding background firing rate (BFR) and presynaptic D2 autoreceptor inhibition to the previously developed Montague et al. model and fit the model to an extensive FSCV dataset. We found that changes in the BFR of DA neurons can substantially alter the DA response to identical stimuli. We also employ phase-plane analysis to explore the dynamical mechanisms of this phenomenon and explore how physiological parameters modulate dopamine dynamics. These findings underscore the important role of the BFR of DA neurons in modulating dopamine response to EBS and its potential impact on the treatment of conditions, such as depression, Parkinsons disease, and schizophrenia.

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PP1

Modeling Infectious Diseases with Immune Mem-

ory

For many infectious diseases, immunity acquired from infection (or vaccination) wanes over time and is boosted by re-exposure to the pathogen (or antigen). For multi-strain pathogens with immune-mediated interactions, such as cross-protective immunity and antibody-dependent enhancement (ADE), modeling waning immunity is complicated by the need to track infection history. Here we extend a differential equations modeling framework that explicitly tracks population-level antibody dynamics, a measurable quantity of the immune system, to multi-strain pathogens and cross-reactive antibodies. Specifically, we model primary and secondary infections with infection risks modulated by an antibody-dependent susceptibility probability function that distinguishes naive, partially cross-protected, and ADE-prone immune states. We systematically explore how the duration and strength of cross-immunity and ADE determine the amplitude and periodicity of epidemic behavior. Applied to dengue virus transmission, our model generates multi-annual cycles consistent with empirical observations and under similar conditions to prior work, although the influence of short-lived cross-immunity is much greater than that of ADE. Our model provides a flexible framework that bridges individual-level immunity and population-level transmission for investigating the dynamics of immune-mediated interactions of dengue and other multi-variant diseases.

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PP1

Healthcare Agents: Language Model Agents in Health Prediction and Decision-Making

We present a research program building language-model agents for health: from single-agent clinical assistants to multi-agent systems integrating wearable streams, clinical records, and domain knowledge. We address core challengessafety, hallucination, long-horizon reasoning, and continual learningby combining constrained generative models, explicit planner modules, and verifiable decision logs. Case studies include diagnostic support, medication adherence coaching, and longitudinal risk monitoring. We evaluate safety via adversarial prompts, prospective pilot simulations, and human-in-the-loop checks. The research outlines evaluation criteria and path toward certified clinical-grade agents.

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PP1

From Nucleus to Migration: Linking Nuclear Mechanics with Predictive Models of Cell Motility

Nuclear mechanics directs cell locomotion by integrating mechanical cues from the tug-of-war between the extracellular matrix (ECM), cell-matrix adhesions, and cytoskeletal architecture. Recent experiments uncover that A-type lamins engage with both F-actin and vimentin, and A-type lamin knockout promotes nuclear expansion, whereas B-type lamins predominantly engage with perinuclear vimentin and its absence compresses the nucleus. These results reveal an intricate link between mechanics of F-actin cytoskeleton, vimentin intermediate filaments, and nuclear envelope via LINC complexes. To further investigate the mechanisms, we develop a mathematical model of the nucleus-cytoskeleton system using a 2D elastic, deformable cable-network description. Model simulations reproduce the morphological shape changes of the nucleus in response to A- and B-type lamin knockouts and recapitulate traction force trends. We then transition from static adherent geometry to an unconstrained geometry to account for dynamic cell spreading. In addition, we model the localization of key transcriptional proteins such as YAP with partial differential equations (PDEs). This modeling of nucleus-cytoskeleton dynamics allows us to understand the mechanisms of the initial stages of cell movement, starting from nuclear mechanics.

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PP1

Agent-Based Modeling of Chemokine-Driven Chemotaxis in the Pancreatic Cancer Microenvironment

Pancreatic ductal adenocarcinoma (PDAC) is among the deadliest cancers, with poor survival rates and limited therapeutic responsiveness. A major contributor to this poor prognosis is the tumors complex and heterogeneous microenvironment. The purpose of this study is to investigate chemokine-mediated immune cell chemotaxis within the PDAC tumor microenvironment, with the goal of improving mechanistic understanding of how spatial immune organization emerges in pancreatic tumors. This work examines how cellcell and cellenvironment feedback loops regulate immune cell migration, localization, and persistence within tumor tissue. The study also investigates how variations in chemokine signaling, cellular interaction networks, and microenvironmental structure contribute to immune exclusion versus immune infiltration states, which are thought to play important roles in tumor immune evasion and therapeutic response. To accomplish these objectives, this work employs agent-based modeling to simulate the behavior of individual tumor and immune cells within a spatially explicit microenvironment. Simulations are implemented using the PhysiCell modeling framework, enabling integration of chemokine gradients, cellular decision rules, and environmental constraints.

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PP1

Photoadaptation and a Continuous Pulse Function Accurately Depict the Mammalian Circadian Response to Light Induction

The circadian rhythm is the bodys internal clock that regulates daily physiological and behavioral processes on a 24-hour cycle. At the molecular level, this rhythm appears from interacting proteins. Experimental studies suggest that certain clock proteins may play distinct functional roles with their unique responses to light induction; the circadian time shifts due to external light pulses are amplified in clock mutated mice. We developed a mathematical model using a system of ordinary differential equations to capture how the mammalian circadian system responds to external light cues measured by phase response curves (PRCs), which quantify shifts in biological timing. By analyzing the numerical simulations, we elucidate that the incorporation of photoadaptation, with a secondary negative feedback loop where increased protein levels suppress their own production, and a time-dependent light pulse function, allows the model to reproduce experimentally observed PRCs. Variations in such design can mimic the experimental response to the clock mutated mice. These results suggest that more detailed mathematical representations are necessary to accurately model mammalian circadian regulation, possibly with unique functional roles of certain proteins in relation to light.

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PP1

Efficient Parameter Estimation in Agent-Based Models of Collective Cell Invasion Via Gaussian Process Surrogates and Bayesian Optimization

Cell migration and invasion are key processes underlying cancer metastasis. These behaviors are driven by cellcell adhesion, chemotaxis, and matrix remodeling. CompuCell3D is a platform for agent-based modeling of cell migration; however, a limitation is that it does not natively support systematic parameter estimation for the stochastic simulations. Traditional Monte Carlo sampling-based approaches to parameter tuning are time-consuming and computational demanding. This work focuses on parameter estimation for agent-based modeling of collective cell invasion for two phenotypes: a network (invasive) phenotype and a spheroid (non-invasive) phenotype emerging from growth of tumor spheroids simulated using CompuCell3D. We adopt a data-centric approach based on Gaussian process surrogate models and Bayesian optimization, leveraging simulation outputs alongside experimental data for invasion dynamics and circularity of cell clusters. This framework efficiently operates with limited simulation data and sequentially proposes new parameter sets to evaluate, prioritizing those expected to provide maximal information gain. Through sequential rounds of parameter selection, agent-based simulations, and comparison with experimental data, the calibrated model reproduces experimental invasion dynamics and circularity. This framework provides an efficient approach for producing realistic invasion dynamics while reducing the need for extensive trial-and-error simulations.

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PP1

Smad3 Complex Formation Drives Cytokine Receptor Synergy in Cd4+ T Cell Fate Decisions: A Systems Perspective

¡P¿ In CD4? T cells, the Treg-Th17 fate choice shapes susceptibility to autoimmune disorders such as rheumatoid arthritis and multiple sclerosis. This decision reflects receptor synergy: both lineages require coordinated TCR and TGF-R signals, while Th17 additionally depends on IL-6R. Signaling proceeds through alternate SMAD3-containing complexes that rewire early phosphorylation networks. SMAD3/4 promotes PKA and CSK activity strengthening negative feedback in Treg contexts. With IL-6, STAT3 binds SMAD3, blocks SMAD3/4 formation, and elevates PI3K/AKT/mTOR signaling toward Th17. To define this at systems scale, phosphoproteomic and IL-6 dose-response data [Prado, Cattley, Shipman et al., J. Biol. Chem. 297(6), 2021] are combined with a rule-based BioNetGen model of SMAD complex formation, compiled to PEtab for reproducible multistart optimization with identifiability and sloppiness diagnostics. The calibrated model reproduces signaling dynamics under Treg- and Th17-like conditions and reciprocal IL-6 dose dependence of SMAD3/SMAD4 versus SMAD3/STAT3d abundance, recapitulating the competitive-binding switch experimentally. Disrupting STAT3-SMAD3 binding restores SMAD3/4-dependent negative feedback, shifting dynamics toward Treg. Information-geometry analysis isolates stiff parameter combinations dominating predictions, enabling model reduction. This framework explains how receptor synergy reconfigures kinase-network topology to bias cell fate.

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PP1

Cellular Foundation Models in Biology: Towards Understanding Disease and Therapeutic Targets

Cellular foundation models (CFMs) learn generalizable cell representations from large-scale, multi-modal single-cell datasets and can be fine-tuned for perturbation prediction and therapeutic target prioritization. Here, we survey CFM architectures, data-scale requirements, and evaluation practices, highlighting key pitfalls in benchmarking and interpretability that limit fair model comparison. Through case studies, we demonstrate that CFMs can generalize across tissues and perturbation contexts, underscoring their potential for disease biology and drug discovery. However, inconsistent evaluation frameworks obscure true model utility and hinder progress. We therefore call for standardized benchmarks and biologically meaningful challenge datasets to enable rigorous assessment of perturbation prediction and downstream therapeutic applications.

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PP1

From Ai for Biological and Medical Science to Virtual Cells

Advances in single-cell multi-omics and self-supervised learning make constructing computational virtual cells increasingly feasible. The poster maps the pipeline for building virtual cells from multi-omics: data ingestion, representation learning, perturbation modelling, and validation. It summarizes case studies demonstrating response prediction and discusses benchmarks, interpretability strategies, and resource requirements. Practical guidance for dataset curation and model evaluation is included. Concluding remarks highlight future directions for scalable, validated virtual-cell systems.

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PP1

Mathematical Modeling of PER Dimerization in Mammalian Circadian Clock

The mammalian circadian clock is driven by a transcription-translation negative feedback loop in which PERIOD (PER) proteins act as key repressors. While dimerization of repressor proteins has been observed across species, its functional advantage over monomeric activity remains poorly understood. To investigate the role of dimerization, we constructed and compared two mathematical models of the mammalian circadian clock: a monomer and a dimer model. We employed bifurcation analysis and MCMC-based sensitivity analysis to characterize the robustness and parameter sensitivity of each model. Both approaches consistently showed that dimerization enhances robustness and provides an additional regulatory handle for period control through the dimerization rate. Additionally, joint perturbations of model parameters reproduced experimentally observed phenotypes and provided mechanistic insight into complex biological scenarios where multiple mechanisms are inevitably coupled and difficult to disentangle experimentally.

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PP1

A Dynamical Systems Model for the Total Fission Rate in Drp1-Dependent Mitochondrial Fission

Mitochondrial hyperfission in response to cellular insult is associated with reduced energy production and programmed cell death. We develop a nonlinear dynamical systems model of dynamin related protein one (Drp1)-dependent mitochondrial fission and use it to identify parameters which can regulate the total fission rate (TFR) as a function of time. The TFR defined from a nondimensionalization of the model undergoes a Hopf bifurcation with bifurcation parameter $\mu = \frac{k_+ \mathcal{M}}{k_-}$ where $\mathcal{M}$ is the total concentration of mitochondrial fission factor (Mff) and k_+ and k_- are the association and dissociation rate constants between oligomers on the outer mitochondrial membrane. The variable μ can be thought of as the maximum build rate over the disassembling rate of oligomers. Though the nondimensionalization of the system results in four dimensionless parameters, we found the TFR and the cumulative total fission (TF) depend strongly on only one, μ. Interestingly, the cumulative TF does not monotonically increase as μ increases. Instead it increases with μ to a certain point and then begins to decrease as μ continues to increase. This non-monotone dependence on μ suggests interventions targeting k_+, k_-, or $\mathcal{M}$ may have a non-intuitive impact on the fission mechanism. Thus understanding the impact of regulatory parameters, such as μ, may assist future therapeutic target selection.

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PP1

Optimal Organization of Cilia at Different Scales

Cilia are used in many biological systems to transport fluid and to power locomotion. At small Reynolds numbers (Re) cilia are typically organized into ciliary carpets, consisting of arrays of individual cilia. Cilia also drive locomotion at nonzero Re, but exhibit a different spatial organization. *Ctenophores* swim at $Re \sim 10-100$ by beating comb plates consisting of 1000's of cilia fused together. To investigate whether this difference in organization is the result of an evolutionary adaptation to different flow regimes, we quantify the performance of both arrays of individual cilia and bundled plates using numerical simulations over a range of Reynolds numbers. We prescribe kinematics of cilia beats from data and vary the spatial arrangement and phasing between different individual and fused cilia to predict how the optimal organization depends on Re.

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PP1

Systems Biology Approaches to Unravel Gut-Immune-Bone Pathways Altered by Estrogen Loss and Dietary Intervention

Aging in women is associated with estrogen loss, an inflammatory process that affects tissues throughout the body. This inflammation has widespread effects on women's health, increasing their risk of postmenopausal osteoporosis, stroke, and heart disease. Prebiotic dietary fibers are a promising treatment modality to reduce gut, bone, and systemic inflammation. However, there is a gap in our mechanistic understanding of how estrogen and prebiotic fibers affect these tissues separately and in combination. Computational models, paired with targeted experiments, can accelerate the discovery process by providing mechanistic insights to guide experimental design. To this end, we are using systems biology methods to explore heterogeneous data from the bone, serum, and gut tissue during estrogen loss and dietary intervention experiments. Gut measurements include bulk RNA sequence results. We are using deconvolution to infer cell composition and provide insight into cell-type-specific signals. These results will enable systems-level analysis of tissue, cellular, and genetic responses that we will use to inform and constrain mechanistic models of estrogen inflammation and fiber-based treatments. Finally, we are exploring data-driven models that can leverage our multi-modal -omics, molecular, and phenotypic data to provide additional insights.

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PP1

Catalyst: Fast and Flexible Modeling of Reaction Networks

Chemical reaction networks (CRNs) are a commonly used model type in biology and chemistry (with applications in e.g. systems biology, pharmacology, and epidemiology). Here, we demonstrate Catalyst.jl, a flexible and feature-filled Julia library for the creation, simulation, and analysis of CRN models. Models can be created both using the Catalyst DSL (which enables the implementation of CRNs in their native reaction format), or built programmatically. Next, they can be simulated using ODE, SDE, and jump process (e.g. Gillespie simulation) approaches. Internally, models are represented symbolically, enabling e.g. automatic symbolic simplifications and Jacobian constructions to improve simulation performance. Finally, Catalysts internal CRN model representation enables it to compose with many additional modelling packages. This facilitates features such as steady state computations, bifurcation analysis, identifiability analysis, and parameter fitting.

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PP1

Revealing Overlapping Results from Sobol and Bifurcation Analysis

Sobol and bifurcation analyses are distinct methods for studying dynamical systems, but preliminary results suggest greater overlap in their results than previously thought. Contrary to conventional use, our results suggest that bifurcation analysis can quantify relative parameter importance, while Sobol analysis can estimate the location of bifurcations. We compared these methods for a model with saddle/cusp-like bifurcations and three single-bifurcation models (transcritical, supercritical Hopf, subcritical Hopf). The Sobol sensitivity index calculations used the same parameters that were used in bifurcation analysis, and the results were compared over identical ranges. Results showed that (1) the absolute values of the relative slopes of bifurcation diagrams correlate with Sobol indices (steeper slopes correlate to higher indices), allowing bifurcation analysis to quantify relative parameter importance, and (2) non-zero second-order indices and large index changes occur only near bifurcations, allowing Sobol analysis to locate bifurcations. Future work will determine if Sobol analysis can determine bifurcation types, enabling the study of dynamics using Sobol analysis without prior bifurcation knowledge.

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PP1

Comparison of Sex-Specific Host Mechanisms Across 3 Viruses Infecting Human Respiratory Epithelial Cells

Host proteins involved in viral infection have emerged as compelling drug targets that can be more resilient to viral evasion by mutation. 40% of new FDA drug petitions reuse previous approved drugs for different contexts, are about half as costly, and greatly reduce the drug certification risk associated with translating animal results to human trials. Therefore, we explore potential human host targets for treating viral infection. We investigate publicly available datasets of human lung cell lines infected by the SARS-CoV-2 USA-WA1 variant and influenza viruses H1N1 and H3N2. We apply the algorithm of detecting mechanism action by network dysregulation (DeMAND) to RNA-seq gene expression at 24 hours post-infection (hpi). We then compare these results across viruses to estradiol sex-specific responses in H3N2 assayed by microarrays to identify the conservation of sex-specificity in viral infection-host response pathways at 24 hpi. Challenges of this study include normalization between gene expression technologies, respiratory cell types, and experimental batch effects. Thus, we analyze individual and collective host responses to viruses of significant interest to public health.

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PP1

Network Analysis for the Detection of Antiviral Drug Targets Against Sars-CoV-2 and Influenza A Viruses

Seasonal viruses, including SARS-CoV-2 and influenza A, present a significant public health risk, with the CDC reporting 32,000-72,000 deaths annually from these viruses. Antiviral drugs are expensive to develop, and few broad-spectrum antivirals are approved by the FDA. Differential gene expression analysis and host factor screens have been used historically to identify possible drug targets. While useful, these methods cannot identify critical host mechanisms that are not differentially regulated or do not directly interact with viral proteins. In this work, we apply the network analysis algorithm DeMAND (Detecting Mechanism of Action by Network Dysregulation) to publicly available SARS-CoV-2/USA/WA1 and H3N2/A/Udorn/72 RNA-seq datasets. This approach integrates gene expression data with the set of all possible interaction pathways, allowing for a higher-level view of infection mechanisms. To refine this application of network analysis, we will compare the results of only using a host protein-protein interaction (PPI) network to those using a combined host and virus-host PPI network. We hypothesize that these statistical approaches will help establish inexpensive means of understanding host-pathogen interactions at a high level. Additionally, we hope to identify novel drug targets shared by both viruses for the development of generalized antivirals.

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PP1

Mathematical Modeling of the Medea Gene-Drive Mechanism for the Mosquito Population Control

Mosquitoes cause millions of deaths annually, presenting a severe public health problem. A promising mosquito control strategy is population replacement, in which native mosquitoes are replaced by transgenic mosquitoes that are unable to spread disease. We consider a genetically modified mechanism called maternal-effect dominant embryonic arrest (Medea), where the progeny of a Medea-carrying mother that does not inherit the Medea allele will die. This facilitates the spread of the modified allele, which is further linked to a disease-refractory trait. Due to the fitness cost induced by the genetic modification, there exists a threshold condition for the Medea gene-drive mechanism to persist and spread. In this project, we develop and analyze an ordinary differential equation model that tracks mosquitoes across multiple life stages, including eggs, adult females, and males, as well as across genotypes. We derive the basic reproduction number of the modified allele along with other dimensionless quantities that characterize the inheritance dynamics. To identify the threshold condition for the persistence of the Medea allele, we derive the equilibria and perform the corresponding stability analysis. Our bifurcation analysis indicates bistable behavior in the proposed model, revealing the threshold condition. We derive an analytical expression for this threshold and quantify its dependence on mosquito life traits and the Medea-induced fitness cost.

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PP1

Kinetic-Mamba: Mamba-Assisted Predictions of Stiff Chemical Kinetics

We introduce Kinetic-Mamba, a Mamba-based neural operator framework for accurate chemical kinetics modeling. The framework comprises three models: (i) a standalone Mamba model; (ii) a constrained Mamba model that enforces mass conservation; and (iii) a regime-informed architecture. We also develop a latent Kinetic-Mamba variant that evolves dynamics in a reduced latent space and reconstructs the full state on the physical manifold. Computational experiments on Syngas and GRI-Mech 3.0 reaction mechanisms demonstrate that our framework achieves high fidelity in predicting complex kinetic behavior using only the initial conditions of the state variables.

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PP1

Ocular Pharmacokinetic/Pharmacodynamic Modeling of Ranibizumab Released from Single and Bi-Layered Polymeric Microspheres

Age-related macular degeneration (AMD) is the leading cause of vision loss with aging and is triggered by vascular endothelial growth factor (VEGF). Various drugs with short half-lives inhibit VEGF. Current treatments require frequent intravitreal (IVT) injections. We considered drug delivery systems (DDSs) to extend the release of the anti-VEGF drug ranibizumab. We developed a mathematical model of drug release dynamics from chitosan-polycaprolactone (PCL) bi-layered core-shell polymeric microspheres parameterized with published release data. The DDS model involves diffusion from concentric layers of a sphere and is solved by finite differences to yield the release rate of the ranibizumab from different DDS configurations. We combined this release rate with a three-compartment PK/PD model of ranibizumab and VEGF interactions from the literature to simulate the biodistribution of drug and VEGF in three eye regions after release from the DDSs. We used the combined model to determine how design parameters influence the duration of VEGF pharmacodynamic suppression for single- and bi-layered microspheres. The DDSs provide longer VEGF suppression than direct IVT administration in all simulated scenarios. We found that the radii of single-layered microspheres of chitosan and PCL and bi-layered chitosan-PCL microspheres affect drug release biodistribution and duration of VEGF pharmacodynamic suppression non-monotonically.

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PP1

Comparing Insulin Secretion Responses During An Oral Glucose Tolerance Test in Adolescents With and Without Metabolic Dysfunction-Associated Steotic Liver Disease

Most research on the progression to type 2 diabetes (T2D) has focused on adults. However, with rising T2D prevalence in adolescents, there is a growing need for methods applicable in this metabolically distinct population. In previous work, we developed a Bayesian hierarchical modeling framework to infer insulin secretion rate (ISR) with uncertainty from frequently sampled plasma C-peptide during an oral glucose tolerance test (OGTT). By accounting for uncertainty, this method is well-suited for adolescent populations where kinetic parameters for C-peptide have not been determined. We adapted our original method to infer ISR in adolescents with metabolic dysfunction-associated steatotic liver disease (MASLD), characterized by insulin resistance. Among adolescent participants without T2D classified as normal weight, with obesity, or with obesity and MASLD, we quantified differences in beta cell function with ISR-based metrics: early (first 30 min) insulin secretion, four-hour insulin secretion, and time to peak insulin secretion. The MASLD group secreted more insulin in the early period compared to the normal weight group and more than both normal weight and obese groups over the four-hour period (p ¡ 0.05). This modeling approach enabled sensitive detection of increased insulin secretion across an OGTT in participants with MASLD and may facilitate the development of therapeutic approaches targeted to the needs of this population at high risk for progression to T2D.

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PP1

Mathematical Modeling of Glioblastoma-Induced Hyperexcitability in Spatially Structured Neural Networks

Recent experimental evidence demonstrates that high-grade gliomas integrate into neural circuits through AMPA receptor-dependent synapses and activity-dependent potassium currents, forming an electrically coupled network that increases neuronal excitability. How this pathological integration reshapes the collective dynamics of cortical populations remains theoretically unexplored. We extend spatially structured balanced network frameworks to incorporate glioma-induced heterogeneities, modeling the tumor as a localized region of neuronal hyperexcitability consistent with the elevated firing rates observed in glioma-infiltrated cortex. Through large-scale spiking network simulations, we systematically vary tumor geometry, comparing compact spherical masses, tumors with branch-like appendages mimicking microtubule-mediated infiltration, and spatially disjointed multi-focal configurations, to characterize how each morphology differentially disrupts the cancellation of excitatory and inhibitory input correlations that maintains the asynchronous balanced state. Our simulations provide a mathematical framework linking tumor morphology and single-cell tumor-neuron interactions to emergent population-level disruptions in correlated variability,

offering mechanistic predictions for how glioma infiltration may degrade neural circuit function.

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PP1

Towards Biological Discovery with Foundation Models: Applications in Neuroscience

Foundation models can learn rich representations of biological systems; we apply them to neuroscience to discover biomarkers and therapeutic hypotheses for neurodegenerative disease. We describe infrastructure for scalable model training, representation analysis, and downstream biomarker identification, and present case studies identifying candidate signatures for Alzheimers and Parkinsons. Methods combine multimodal data fusion, interpretable embeddings, and perturbation simulations to propose experimentally testable mechanisms. We discuss validation strategies and limitations for translation to clinical interventions.

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PP1

Pinpointing Sex-Specific Immune Responses Driving Severe Influenza Outcomes in Females Using Mathematical Modeling

In humans, differences in immune response between males and females influence influenza infection outcomes. During the 2009 H1N1 pandemic, Eshima et al. (2011) found that adult females were $\sim$ 40% more likely to be hospitalized than their male, age-matched counterparts. With collaborators at UW Madison, experiments on male and female mice infected with CA04-H1N1 influenza infection have shown increased viral production and disease severity at 36 hours post infection for females, resulting in early, excessive innate immune activation characterized by proinflammatory cytokine profiles, and critical differences in macrophage counts. Histopathology shows lesions in the alveolar region of female, but not male mice, indicating influenza virus penetrates more deeply in female lungs. We developed a novel mathematical model of influenza infection to better understand how differences emerge during infection and identify mechanisms responsible for observed increases in disease severity in female mice. The model represents influenza infection, and the subsequent innate immune response, in the left lobe of mouse lung. We have, with significant evidence, identified two models with differing sex-based parameters by using Bayesian Model Selection (AICc). Each model points to a possible mechanism responsible for the unique immune response and pathology observed in female animals.

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PP1

Graph Reduction of a Competitive Inhibitor Stimulation Reaction Network

A competitive inhibitor is a molecule that can slow an enzymatic reaction by binding in the place of substrate. However, in more complicated reactions, a competitive inhibitor can act to stimulate or inhibit a reaction depending on the kinetics of the enzyme and dosage. This project applies concepts from chemical reaction network theory and singular perturbation theory to the reaction network for alcohol dehydrogenase (ADH), an enzyme that exhibits a dose-dependent activation or inhibition through binding the competitive inhibitor imidazole, a phenomenon called competitive inhibitor stimulation (CIS). Given a reaction network, a graph can be constructed with the edges being reactions and vertices being the combinations of chemical species that are reactants or products of a reaction. The vertices are called complexes and are encoded in the matrix ν, while the fast and slow reactions are encoded in incidence matrices $\mathcal{E}^f$ and $\mathcal{E}^s$. Given vectors $R^f(c)$ and $R^s(c)$ that encode the rates of the reactions, we write the differential equation on the fast time scale as

$$\frac{dc}{d\tau} = \nu\mathcal{E}^f R^f(c) + \varepsilon\nu\mathcal{E}^s R^s(c)$$

The solution of this perturbative problem is then used to create an initial rate equation for the reaction that depends on the concentration of inhibitor used and confirms that the model exhibits CIS.

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PP1

Dynamical Systems Modeling to Determine the Role of Crosstalk in Shaping STAT Signaling Profiles

Macrophages use the JAK/STAT signaling pathway to integrate cytokine cues into context-specific functional decisions. Understanding the mechanisms underlying this process is complicated by the observation that the same JAK kinases and STAT transcription factors can direct a range of gene expression programs depending on the activating cytokine. The high degree of regulatory symmetry in this pathway led us to hypothesize that the cytokine-environment controls the relative contribution of parallel network arms and that asymmetric kinetics determine its capacity to appropriately discriminate stimuli. Our group previously developed a computational workflow that links features of cytokine-induced STAT phosphorylation profiles to downstream gene expression. While the ODE model is able to recapitulate experimental observations and correctly predict the impact of JAK2 variation on gene expression, many of the 40+ model parameters are poorly constrained by the available data. Thus, our ability to understand how context-specific variation impacts signal transduction is limited. Here we present work toward optimizing parameter estimation and predicting data necessary to constrain individual model parameters. We also discuss the role of cross-talk and kinetic asymmetries in shaping cytokine-specific STAT phosphorylation profiles. Our aim

is to predict the impact of network component perturbations on phospho-STAT trajectories and ultimately downstream gene expression profiles.

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Machine Learning Guided Mechanistic Modelling for Respiratory Viral Infections

The immune response to influenza is varies widely by viral strain, biological sex, and age. While pandemic H1N1 demonstrates high transmissibility, avian strains such as H5N1 and H7N9 cause fewer infections but significantly higher mortality. Clinical observations further indicate that reproductive-aged females suffer increased severity compared to males, and children remain disproportionately susceptible despite comparable viral loads. To elucidate the mechanisms underlying these disparities, we propose using AI-Aristotle, a machine learning-guided mechanistic modeling paradigm. It generates ensembles of interpretable ordinary differential equation (ODE) models, each representing a biological hypothesis that explains observed kinetic data, enabling straightforward validation. Preliminary work suggests the framework to be capable of recovering the underlying model from noisy, synthetic test datasets. However, the frameworks ability to generate sensible models using real-world data is yet to be fully understood. Specifically, the impact of amount of data available along with its composition is to be tested. Moreover, the ability of this framework, in its current state, to uncover complex interactions between biological cohorts and underlying mechanisms is limited. This research aims to benchmark AI-Aristotles performance and improve it to be used on real-world IAV infection datasets to understand drivers of sex and strain-specific drivers of immune responses.

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In Silico Parametrized Predictive Mathematical Modeling of Oncological Drug Transport Through the Blood Brain Barrier

The Blood Brain Barrier (BBB) is a network of tight-junction brain endothelial cells that restricts pharmaceutical diffusion into the brain and leads to inaccurate dosage. This research focuses on using a novel predictive model to simulate transport for 25 commonly used drugs in brain dysfunctions. Paper emphasizes the integration of Ficks and Einstein-Stokes Laws to derive a parametrized function representing drug diffusivity. The function is constructed on calculated values of j-flux, diffusion coefficient, radius, and polarity; viscosity is a constant to model BBB fluidity. The equation is integrated from t in [0, alpha], the barrier at t = alpha, and yields a measure of moles limited when diffused. We devise a rank formula, denoted SN(x), to weight drugs with respect to numerical diffusibility. Inputs employ min-max normalization to ensure the domain occupies [0,1], standardizing values. Weight scores produced are shown through heatmaps to measure total diffusivity. Results showed Levodopa and Temozolomide scored highest, with weighted scores of 5.22 and 5.13 respectively. Conversely, Vancomycin and Paclitaxel attained the lowest. These results are consistent through viscosity modulation, achieving similar rank distributions. This validates the model's accuracy. The model weighs chemical factors to produce predictive permeability scores, avoiding in vitro costs and time. Future adaptations follow inclusion of Markov Chains to model BBB movement.

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Investigating the Hedgehog Pathways Role in Cancer Through Data-Driven Mathematical Models

The Hedgehog pathway is a gene regulatory network essential for the development of organs and tissues in vertebrates. Various cancers are associated with mutations in the pathway, such as medulloblastoma, the most common form of pediatric brain cancer. The central dynamics of the pathway occur in the primary cilium- a small antenna-shaped microtubular organelle. Researching the pathway often requires indirect methods due to the small size of the cilium, leaving parts of the architecture unknown. We develop a mathematical model of the pathway to bridge the gap in current technology and to investigate its dynamics. Furthermore, we incorporate RNA sequencing data from a zebrafish medulloblastoma study into the model to uncover influential genes in the cancer and examine their roles in the Hedgehog pathway.

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PP1

Clawing Toward Threshold: How the Dynamic Interplay of Cortico-Basal Ganglia-Thalamic Pathways Shapes the Decision-Making Process

Significant effort has been spent looking at specific roles that specific neural populations in the cortico-basal ganglia pathways play in guiding decisions and learning from them. In this study, we take on the much less investigated questions of how activity evolves within the whole circuit during the course of individual decisions, the nature of variability within this process, and how this dynamic evolution changes with learning. To address these questions, we developed and used a novel computational framework that we call CLAW (Circuit Logic Assessed via Walks) to trace the instantaneous flow of neural activity as it progresses through stochastic, spiking cortico-basal ganglia-thalamic (CBGT) networks engaged in a virtual decision-making task. Our results uncover distinct deliberation and commitment phases characterized by which CBGT components are dominant and suggest how differences in subpopulation dominance underlie distinct decision strategies. Moreover, we show how dopamine-dependent synaptic plasticity based on decision outcomes can alter the nature of CBGT activity during decisions and shift the likelihood of decision strategies from deliberation to reward-directed commitment. Finally, we map these results to the drift-diffusion model (DDM) framework, recasting them in terms of gradual changes in DDM parameters that provide an algorithmic interpretation of how learning leads to improved decision speed and accuracy while preserving the capacity for caution.

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PP1

Ubiquitous Ai for Health

Ubiquitous AI leverages smartphone and wearable data streams to model circadian rhythms, activity, and other biobehavioural states for personalized health interventions. In this postr, we describe multimodal modelling pipelines, methods for robust feature extraction from noisy mobile signals, and intervention design examples (e.g., personalized music for state modulation). Emphasis is placed on privacy-preserving engineering, long-term engagement metrics, and evaluation using longitudinal cohorts. We present pilot results showing improved detection of circadian disruptions and effective personalized interventions.

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Cerebrospinal Fluid Adrenocortical-Brain Steroid Concentrations and Dynamics : Physiologically-Based Hormone Dynamic Modeling

Background: Dehydroepiandrosterone (DHEA) and cortisol are key adrenal hormones whose concentrations dynamically fluctuate in response to stress. These hormones can be measured across multiple physiologic compartments. Measuring them in cerebrospinal fluid (CSF) provides insight into central neuroendocrine regulation but is technically challenging and invasive, whereas saliva sampling offers a noninvasive alternative. Understanding the relationship between CSF and salivary concentrations of cortisol and DHEA therefore holds substantial clinical relevance. However, the dynamic and asynchronous nature of these measurements makes it challenging to characterize their interrelationships. Methods: Cortisol and DHEA were sampled and quantified. Associations between CSF and salivary concentrations were examined using correlation analyses. A three-compartment physiologically based hormone dynamic (PBHD) model (plasmaCSFsaliva) was developed to characterize compartmental exchange and temporal delays. Results: PBHD modeling reproduced observed concentrationtime profiles and demonstrated nonlinear, time-dependent relationships. Exposure-based analyses using model-derived area-under-the-curve measures showed strong centralperipheral coupling. Conclusions: Salivary cortisol and DHEA reflect central neuroendocrine activity in a temporally lagged manner. Integrating physiologically based modeling improves interpretation of noninvasive biomarkers of stress-axis function.

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Hidden Spirals in Human Local Field Potentials

Traveling oscillatory (phase) waves are commonly observed in multi-electrode recordings in the brains of many species, including humans. In collaboration with the Jacobs lab, we obtained local field potential recordings from human subjects performing 8 cognitive tasks. The recordings consist of spatial phase patterns on a square array of electrodes. Statistical methods were used to identify epochs where the patterns were stationary. We hypothesized that these patterns can be described as phase-locked solutions of a network of locally coupled oscillators, $\dot{\theta}_i = \omega_i + \sum_{j \in N(i)} H(\theta_j - \theta_i)$. We developed an optimization method to determine the local intrinsic frequencies ω_i and the interaction function $H(\phi)$ that best fit the observed patterns while ensuring stability. We further hypothesized that the observed structures arise from local frequency differences combined with activity driven solely by network connectivity and the interaction function. To uncover this

underlying activity, we gradually flattened the frequency distribution until all oscillators became identical. In a subset of recordings, this procedure revealed hidden spiral waves. These spiral waves were associated with certain cognitive tasks but not with others.

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