Systems Medicine Student Research Symposium

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Titles and Abstracts

A Ternary Network Simulating Low Shear Stress and Hypoxic Cell Signaling Pathways in Pulmonary Endothelial Cells

Sharanya Chatterjee[1] and Isabella Delbakhsh[2]

[1]Freedom High School, [2]Lake Highlands High School

Pulmonary endothelial cells (ECs) line the interior of blood vessels, facilitate nutrient circulation and fluid transfer in the lungs, and are essential in regulating angiogenesis, apoptosis, vasodilation, and gap openings. Hypoxia and low shear stress are two interrelated conditions involving the loss of oxygen and blood flow that both impact EC function. To characterize the relationship between low shear stress and hypoxia in ECs, we utilized an asynchronous ternary network with 50 nodes that modeled cell signaling under both conditions. While most of the literature on hypoxia and shear stress only examines one aspect or pathway of the overall signaling cascade, this study involves both factors and the interactions between the different cascades within ECs. Through examining literature, we determined the initial conditions of our model and set that as our equilibrium point. To further validate the model, we tested inputs for the model in R by running through each connection in our model and comparing the results from our ternary network to the corresponding findings in the literature.

Mentors: Henrique de Assis Lopes Ribeiro and Melody Walker

Modeling Bleomycin Induced Pulmonary Fibrosis

Sofia John[1]

[1]Department of Statistics

Pulmonary fibrosis is a disease characterized by chronic injury, which results in inflammation and constant remodeling of the lung tissue. While healing and repair are part of the body's normal processes, pulmonary fibrosis manifests

when these processes get dysregulated. Persistent remodeling and scarring of the lung change its architecture and consequently reduce its function. Patients diagnosed with idiopathic pulmonary fibrosis generally have a poor prognosis after identifying their condition. There has been a multitude of sources linked to the development of pulmonary fibrosis from viral infections to smoking habits to cancer therapies, however, the exact mechanisms which are disrupted remain unknown.

Agent-based modeling provides a unique opportunity to identify these initiating mechanisms by replicating the behaviors of cell types in biology in a computational platform. In order to better understand pulmonary fibrosis, we have developed an agent-based model for studying the interplay of macrophages, fibroblasts, and alveolar epithelial cells in the development of fibrotic disease after bleomycin treatment. The validity of the model will be further verified by comparing the emergent behavior of the model to known clinical hallmarks of fibrosis. Identifying the fibrogenic mechanism is crucial to elucidating effective targets for therapy.

Mentors: Luis Sordo Vieira and Matthew Wheeler

A Boolean Gene Regulatory Network in Airway Epithelial Cells Infected with SARS-Coronavirus: Construction and Validation

Achyudhan Kutuva[1]

[1]Department of Microbiology & Department of Statistics

SARS-CoV-2 is a viral respiratory illness that causes COVID-19, which was first detected in December 2019. Based on the public health crisis involving this disease and with current knowledge of the various biological mechanisms that COVID-19 employs, we developed an integrative Boolean network model. This model discretely represents actions that take place continuously in the human body, specifically focusing on viral effects on pneumocytes. By incorporating elements of various cellular processes, including the AKT-mTOR pathway, the ACE 2-Angiotensin pathway, and other major viral pathways, this model documents how biological mechanisms interact upon infection with COVID-19. With an ensemble of 250 asynchronous networks ran independently, the model currently supports five of seven noted genes, given expression data at 24 hours following infection. Many of these mechanisms also overlap in responses to other major viruses and diseases, providing motivation to generalize this model while maintaining relative simplicity and high accuracy. We also hope to employ novel computational techniques to iteratively improve node connections and regulatory functions based on time-series gene expression data. By developing these model variants, we wish to explore the space of potential networks that can be formed to ascertain how deterministic these networks exist in the real world.

Mentor: Henrique de Assis Lopes Ribeiro

Boolean Networks and Dynamic Modularity

Hemangi Patel[1] and Samyukta Kandarpa[1]

[1]Orlando Science School

The concept of modularity is frequently discussed in biological systems. However, it is difficult to find an agreed upon definition for modularity, especially one that is mathematically rigorous. In this talk we investigate an approach to defining modularity which uses strongly connected components of a Boolean network. We begin by understanding the prevalence of modularity in terms of random Boolean networks. Then, in order to find biological evidence grounding our definition, we consider a specific network which models T-cell survival and study the connections between individual modules of the network and distinct biological processes.

Mentor: Matthew Wheeler

Racial Ethnic Disparities in Post–Lung Transplant Outcomes

Abhinav Penmetcha[1] and Omolola Suleiman[1]

[1]Department of Biology

Lung transplantation is a thoracic procedure where a patient's lung is replaced with a donor's lung. As donor lungs are limited, an organizational system was implemented in 2005 in which waitlisted patients are prioritized by a score calculated from several aspects of the patient's health. This score is predictive of outcomes after transplant, along with other dimensions of health. However, as with other health outcomes, social determinants may also play a role. Of these determinants, the race/ethnicity of the patient is of particular interest.

Our goal in this project is to construct a mediator model describing the relationship between race/ethnicity, a curated set of covariates, and post-transplant outcomes. We conducted a literature review to identify determinants of post-transplant outcomes and we integrated the studies from this review into a causal framework involving four variable sets: race/ethnicity, social determinants, health factors, and outcomes. We are currently conducting a survival analysis on the United Network for Organ Sharing lung transplant dataset which will allow us to validate our causal framework. Finally, we will conduct a mediation survival analysis to quantify the mediating role of social determinants on any racial-ethnic outcome differences.

Collaborator: Divya Patel

Mentor: Jason Cory Brunson

Sarcoidosis Modeling Project: Striving for Solutions to Sarcoidosis

Chhavi Pokharna[1] and Bhavya Kambara[2]

[1]Orlando Science High School, [2]Land O' Lakes High School

Sarcoidosis is a disease that is characterized by the formation of small areas of inflammation, known as granulomas, in multiple organs of the body, most often in the lungs. Common symptoms include, but are not limited to: cough, fatigue, skin rash, chest pain, and joint pain. This disease can develop in adult patients of all ethnicities and sexes, however, its incidence is highest in African American women. The diagnosis of this condition is extremely difficult for doctors since it can affect any organ of the body and has similar symptoms to those of other diseases. So far, we have created a genetic and cellular model for this understudied disease which we can use to evaluate and analyze the parameters that play key roles in this illness. Currently, we are working on developing equations for the cells so that in the future we can create a code to represent the model of this disease and perform a sensitivity analysis to understand which components are the driving factors of sarcoidosis. In this presentation, we will show our progress on the mathematical equations we have created based off our models for the key cells involved in this disease. Overall, our goal is to assist sarcoidosis researchers to better understand the dynamics of this disease to aid in treatment and care for patients.

Collaborator: Divya Patel

Mentor: Helen Moore

The Utility of the Functional Route Modulus for Boolean Network Analysis

Igor Sokolov[1]

[1]Department of Mathematics

Every organism relies on complex biological processes to govern even the simplest of tasks. These processes transpire over a range of components which must effectively communicate. Molecular signals are not always simple activations but may be co-dependent with other signals or may inhibit components downstream rather than activate them. Mathematical representations of such signaling pathways are called signal transduction networks (STNs). We analyze these STNs with tools from two python packages intended to expand the network and compute minimal functional routes, which are analogues to shortest paths that

take synergy and inhibition into account. We then compute the graph modulus for these functional routes, which is a quantity characterized by a norm that unifies many useful notions of richness of the family of routes. This leads to an analysis ofthe network using the modulus, comparing values obtained from families of different objects such as walks and functional routes. Finally, we provide a probabilistic interpretation of the 2-modulus on a family of functional routes as it relates to the most likely paths a stochastic signal will take through the network.

Collaborator: Luis Sordo Vieira

Mentor: Jason Cory Brunson

Localized Prediction to Interpolate between Case-Based Reasoning and Machine Learning

Xinyi Zhang[1]

[1]College of Liberal Arts & Sciences

A major limitation of the prediction models developed for machine learning is the lack of simple and natural interpretations of their components. One of the main goals of our model is to ensure interpretability while increasing accuracy, that usually, simpler models work as well as the complex model. We want to determine whether locally-fitted predictive models improve upon their globally-fitted counterparts at clinical tasks when data sets are small. Also, we want to investigate whether GLMs perform at least as well as "black box" predictive models when locally fitted.

Collaborator: Tara Hashemian

Mentor: Jason Cory Brunson