SMB MathEpiOnco Abstracts

Plenary Talks

The impact of eggs quiescence on the efficiency of *Wolbachia*-carrying mosquito release to control arbovirus transmission

Claudia Pio Ferreira, São Paulo State University

Abstract. An ordinary differential model is proposed to understand the role of egg quiescence on the efficiency of releasing *Wolbachia*-carrying mosquito to control arbovirus transmission. The model has four steady states, the persistence of the uninfected population and the extinction of the infected one, the persistence of the infected population and the extinction of the uninfected one, the extinction of both populations, and the persistence of both populations. Their stability is given by four thresholds; two of them are the fitness of uninfected and infected populations when isolated, and the other two are the relative fitness when they are competing. Bifurcation diagrams, phase, and parameter spaces are shaped by the sex ratio that can be manipulated by the *Wolbachia* symbiont. A sensitive analysis shows that the uninfected population always maximizes its fitness according to the environmental conditions throughout the modification of the quiescence rate. Because *Wolbachia*- infected eggs do not survive quiescence or adults emerging from it are infertile, the risk of arbovirus transmission increases during or after environmental stress. This can jeopardize the use of *Wolbachia*-infected mosquitoes to control arbovirus transmissions in regions where quiescence occurs at a high rate.

Mathematical methods in evolution and medicine

Natalia Komarova, University of California, San Diego

Abstract. Evolutionary dynamics permeates life and life-like systems. Mathematical methods can be used to study evolutionary processes, such as selection, mutation, and drift, and to make sense of many phenomena in the life sciences. How likely is a single mutant to take over a population of individuals? What is the speed of evolution, if things have to get worse before they can get better (aka, fitness valley crossing)? Can cooperation, hierarchical relationships between individuals, spatial interactions, or randomness influence the speed or direction of evolution? Applications to biomedicine will be discussed.

Identifiability and interventions: exploring when uncertainty matters

Marisa Eisenberg, University of Michigan

Abstract. Identifiability, estimability, and parameter reduction methods provide tools to understand the interactions between parameters, model structure, and outputs—and how these interactions determine what inferences and predictions are possible for a given system. In particular, issues of identifiability and uncertainty can affect whether it is possible to select an optimal intervention—an important question for both cancer and infectious disease modeling. In this talk, we will explore how identifiability can be used in practice to help inform decision-making, and when intervention strategies are or are not robust to uncertainty in the model parameters and structure.

Contributed Talks

Abstracts are listed in alphabetical order by first/given name.

A Comparison of Mutation and Amplification-Driven Resistance Mechanisms and Their Impacts on Tumor Recurrence

Aaron Li, University of Minnesota

Abstract. Tumor recurrence, driven by the evolution of drug resistance is a major barrier to therapeutic success in cancer. Resistance is often caused by genetic alterations such as point mutation, which refers to the modification of a single genomic base pair, or gene amplification, which refers to the duplication of a region of DNA that contains a gene. Here we investigate the dependence of tumor recurrence dynamics on these mechanisms of resistance, using stochastic multi-type branching process models. We derive tumor extinction probabilities and deterministic estimates for the tumor recurrence time, defined as the time when an initially drug sensitive tumor surpasses its original size after developing resistance. For models of amplification-driven and mutation-driven resistance, we prove law of large numbers results regarding the convergence of the stochastic recurrence times to their mean. Additionally, we prove sufficient and necessary conditions for a tumor to escape extinction under the gene amplification model, discuss behavior under biologically relevant parameters, and compare the recurrence time and tumor composition in the mutation and amplification models both analytically and using simulations. In comparing these mechanisms, we find that the ratio between recurrence times driven by amplification vs. mutation depends linearly on the number of amplification events required to acquire the same degree of resistance as a mutation event, and we find that the relative frequency of amplification and mutation events plays a key role in determining the mechanism under which recurrence is more rapid. In the amplification-driven resistance model, we also observe that increasing drug concentration leads to a stronger initial reduction in tumor burden, but that the eventual recurrent tumor population is less heterogeneous, more aggressive, and harbors higher levels of drug-resistance.

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Incorporating phenotype-structured modeling into epidemiological models to gain insights into variant emergence and competition

Anass Bouchnita, The University of Texas at El Paso

Abstract. Phenotype-structured models were developed to gain crucial insights into the cancer intraclonal heterogeneity and drug resistance. They offer a flexible way of integrating the evolutionary mechanisms into population dynamics models. In this work, we propose for the first time to integrate phenotype-structure into infectious disease models. We extend a previously developed SIR model with immunity by structuring infected individuals according to the phenotype of the virus that they are harbording and describe virus evolution as a diffusion process. After calibrating the model, we apply it to identify the factors that promote variant emergence. We demonstrate that factors such as a high basic reproduction rate, an increased mutation rate, broader cross-protection, and reduced genotypic differences between variants all contribute to the emergence of new variants. Then, we use the model to quantify the impact of variant emergence depending on the characteristics of the original and emerging variants, population-immunity, and the mutation rate. Our simulations reveal that broad cross-immunity is necessary for the eradication of the original variant following the emergence of a more transmissible one. Finally, we show that a robust and cross-variant immunity reduces the frequency of waves driven by virus evolution and immune waning. This approach can be adapted for different viruses and utilized to predict the emergence of specific variants based on genomic data, such as phylogenetic trees.

Global dynamics of an SIR model with post-infection mortality and partial immunity

Brendan Shrader, University of Central Florida

Abstract. The recent COVID-19 pandemic highlights the importance of understanding how post-infection mortality affects disease dynamics. This is because a significant proportion of COVID-19 survivors continue to experience persistent symptoms, known as "Long-Covid," enduring for years after initial infection. In this paper, we discuss an epidemiological model that incorporates post-infection mortality and partial immunity. Additionally, our model assumes the disease is transmitted by the standard incidence rate. We prove the existence and uniqueness of the endemic equilibrium and provide preliminary results on the stability of the endemic and disease-free equilibria. We compare our model to a similar model that uses the mass-action incidence rate, with particular attention to the existence of limit cycles. We find that in cases where limit cycles occur in the mass-action, they do not occur in our standard incidence model. Our findings highlight how incidence rates qualitatively change the dynamics of disease models and how partial immunity impacts disease severity.

A mathematical modeling reveals Crizotinib, a class of medication for metastatic non-small cell lung cancer causes cardiac toxicity

Chitaranjan Mahapatra, Paris Saclay University, France

Abstract. Purpose: Crizotinib is orally used as a multitargeted receptor tyrosine kinase inhibitor for the treatment of metastatic non-small cell lung cancer (NSCLC). The purpose of this study is to investigate the propensity of Crizotinib to modulate cardiac electrophysiological properties using a mathematical model. Methods: The sinoatrial node (SAN) cell is described as an equivalent electrical circuit with ion channels, which are established using the ordinary differential equations in HH formalism. The biophysically altered funny current is integrated into the single SA node electrophysiological model to investigate Crizotinib's modulating properties. Results: The resting membrane potential (RMP) is set at -80mV. A current pulse of 2 nA for 10 ms is injected to evoke the AP. The steady-state value of the activation parameter of the funny current (if) is shifted to the negative side after applying Crizotinib of 1 μ mol/L. The action potential timing is altered when we incorporate the biophysically modified funny current. The results show that the modified funny current plays an important role in reducing the frequency of the spontaneous action potentials at the SA node. Conclusions: Our simulations suggest that Crizotinib reduces the frequency rate of the spontaneous action potential firing by reducing the funny current density. Therefore, the dosage of Crizotinib should be controlled to avoid cardiac toxicity. Keywords: Crizotinib, antiarrhythmic drugs, action potential, ion channel, computational model

A hybrid discrete-continuum modelling approach for the interactions of the immune system with oncolytic viral infections

David Morselli, Politecnico di Torino and Swinburne University of Technology

Abstract. The spatial dynamics between cancer cells, oncolytic viruses and the immune system is still poorly understood. In a previous work we have developed a stochastic agent-based model describing infected and uninfected cells for solid tumors. We here present an extension of that by including interactions with the immune system; the agents' dynamics are coupled with a balance equation for the concentration of the chemoattractant that guides the movement of immune cells. We formally derive the continuum limit of the model and carry out a systematic quantitative comparison between this system of PDEs and the individual-based model, both in one and two spatial dimensions. Furthermore, we study the one-dimensional traveling waves of the two populations, with the uninfected proliferative cells trying to escape from the infected cells while immune cells infiltrate inside the tumor.

Our simulations show a good agreement between agent-based simulations with a sufficiently large cell number and the numerical results for the continuum model. Some parameter ranges give rise to oscillations in both models, in line with the behavior of the corresponding nonspatial model, which presents Hopf bifurcations. Nevertheless, in some situations the stochasticity originates asymmetric or disperse patterns in the discrete model that cannot be described by the continuum model. Our results highlight that an excessive immune response before the infection is well-established appears to decrease the efficacy of the therapy and thus some care is needed when oncolytic virotherapy is combined with immunotherapy.

Modelling Bystander Effect in CAR-T Cell Therapies

Erdi Kara, Spelman College

Abstract. As an adoptive cellular therapy, Chimeric Antigen Receptor T-cell (CAR T-cell) therapy has shown remarkable success in hematological malignancies but only limited efficacy against solid tumors. Compared with blood cancers, solid tumors present a series of challenges that ultimately combine to neutralize the function of CAR T-cells. These challenges include, but are not limited to, antigen heterogeneity - variability in the expression of the antigen on tumor cells, as well as trafficking and infiltration into the solid tumor tissue. A critical question for solving the heterogeneity problem is whether CAR T therapy induces bystander effects, such as antigen spreading. Antigen spreading occurs when CAR T-cells activate other endogenous antitumor CD8 T cells against antigens that were not originally targeted. In this work, we develop a mathematical model of CAR T-cell therapy for solid tumors that considers both antigen heterogeneity and bystander effects. Our model is based on in vivo treatment data that includes a mixture of target antigen-positive and target antigen-negative tumor cells. We use our model to simulate large cohorts of virtual patients to better understand the relationship involving bystander killing. We also investigate several strategies for enhancing bystander effects, thus increasing CAR T-cell therapy's overall efficacy for solid tumor.

Hypoxia-related radiotherapy resistance in tumours: treatment efficacy investigation in an eco-evolutionary perspective.

Giulia Chiari, Politecnico di Torino

Abstract. In the study of therapeutic strategies for the treatment of cancer, eco-evolutionary dynamics are of particular interest, since characteristics of the tumour population, interaction with the environment and effects of the treatment, influence the geometric and epigenetic characterization of the tumour with direct consequences on the efficacy of the therapy and possible relapses. In particular, when considering radiotherapy, oxygen concentration plays a central role both in determining the effectiveness of the treatment and the selective pressure due to hypoxia. We propose a mathematical model, settled in the framework of epigenetically-structured population dynamics and formulated in terms of systems of coupled non-linear integro-differential equations, that aims to catch these phenomena and to provide a predictive tool for the tumour mass evolution and therapeutic effects. The outcomes of the simulations show how the model is able to explain the impact of environmental selection and therapies on the evolution of the mass, motivating observed dynamics such as relapses and therapeutic failures. Furthermore it offers a first hint for the development of therapies which can be adapted to overcome problems of resistance and relapses.

Mathematical Modelling of Infectious Bursal Disease in Commercial Flocks

Hammed Olawale Fatoyinbo, EpiCentre, School of Veterinary Science, Massey University, New Zealand

Abstract. Infectious Bursal Disease (IBD) poses a significant threat to the poultry industry, leading to economic losses and impacting food security. In this work, we formulate a mathematical model to explore the dynamics of IBD within commercial flocks, aiming to enhance our understanding of the disease spread and assist in the development of effective control strategies. Through numerical simulations, we investigate the impact of transmission rate and contaminated environment on the spread of IBD. Furthermore, sensitivity analysis is carried out to identify key parameters that impact disease dynamics, guiding the development of targeted intervention strategies.

Overcoming CCI+ET resistance in ER+ breast cancer by restoring immune surveillance and tumor control

Jiyeon Park, University of Utah

Abstract. We study the resistance mechanisms of high risk estrogen receptor positive (ER+) breast cancer patients to cell cycle inhibitors (CCI) or endocrine therapy (ET). Working with patient samples, our working group has found that resistance to CCI+ET combination treatment involves tumor escape from cytotoxic CD8+ T cell surveillance. This escape is associated with the reduced cytokine signaling, such as through IL-15, by macrophages and other cell types in tumor microenvironment (TME). We leveraged single cell RNA-sequencing (scRNAseq) of clinically annotated ER+ breast cancer with long-term follow-up and analysis of the tumor-wide integrative signaling network to show the fact that signaling drives macrophage polarization from immune-activating M1 to pro-tumor M2 phenotype. Based on these results, we have developed mathematical models of cancer ecology and evolution to predict immune response and treatment effect. These models can be used to design an optimal combination therapy dosing schedules, and to evaluate new treatment approaches, such as CAR-T cells engineered with IL-15, in order to modulate tissue immunity by activating innate (i.e., macrophage) and adaptive (i.e., T cell) immune cells to restore a cancer-surveillant homeostatic state that can control the tumor.

Influenza Vaccination Timing

Julie Allison Spencer, Los Alamos National Laboratory

Abstract. Seasonal influenza infects 5%-20% of people every year in the United States, resulting in deaths, hospitalizations, and economic impacts. To mitigate these impacts, influenza vaccines are developed and distributed annually; however, growing evidence suggests intra-seasonal waning of influenza vaccine effectiveness (VE). Delaying influenza vaccination for older adults has attracted attention as a potential public health option. However, given the uncertainties in seasonal peak, vaccine effectiveness, and waning rate, postponing vaccination could lead to increased morbidity. We systematically investigated various vaccination start times for different age groups under four hypothetical VE scenarios and six combinations of initial effectiveness and waning rates, across 10 influenza seasons. We defined the most favorable vaccination schedule as the one that resulted in the greatest proportion of disease burden prevented. In some scenarios, delayed vaccination appears to be beneficial, while in others, earlier vaccination appears to be beneficial. The most favorable vaccination schedule is sensitive to changes in initial VE value and waning rate. Without knowing the VE and waning in a particular year, it is challenging to determine the best vaccination timing for any age group. Our results suggest that an accurate forecast of influenza peak timing may be important in guiding schedules that avert the most cases.

From COVID-19 to Melanoma: Modeling time-varying treatment response using an Epidemiology-informed Neural Network

Kayode Olumoyin, Moffitt Cancer Center

Abstract. The COVID-19 pandemic has had a significant impact on the United States since it was first reported in January 2020. In 2021, new variants of the virus emerged across many US states, some of which were reported to be more infectious but less deadly than the original strain. In the fight against COVID-19, public health policy across the US combined pharmaceutical and non-pharmaceutical mitigation measures. It became imperative to study time-varying transmission rates in COVID-19 models. We developed a novel approach that use an epidemiology-informed neural network to learn time-varying transmission rates for each variant in the presence of pharmaceutical (vaccine) and non-pharmaceutical mitigation measures (contact tracing and social distancing). The accuracy of the model is demonstrated using error metrics in data-driven simulation for COVID-19 variants in the US states of Florida, Alabama, Tennessee, and Missouri. In recent years, mathematical models have found applications in cancer Immunotherapy and in predicting response to treatment in cancers such as melanoma. Cancer Immunotherapy equips the body's immune system with the ability to eliminate Cancer. One major advance in Immunotherapy has been the success of adoptive cell therapy (ACT) with tumor-infiltrating T lymphocytes (TIL). A patient's own activated T cells can recognize and kill tumor cells; however, they are rarely effective in fighting large tumors. There is a need to boost the patient's immune system. One of the ways this is done is the administration of therapeutic cancer vaccines that can transfect tumor cells and induce signals that activate an immune system response. To determine the optimal experimentally feasible vaccination protocols, we adapt the time-varying epidemiology-informed neural network for the COVID-19 model and integrate laboratory experimental data to modeling treatment response to melanoma tumors.

Mathematical formulations of human risk response in COVID models

Leah LeJeune, Virginia Tech

Abstract. Since the onset of the pandemic, many models have been created to understand the spread of COVID-19 throughout different populations. However, COVID-19 has a variety of complexities impacting its trajectory; as a result, many models have poor predictive abilities for estimating caseloads and deaths. One major component central to improving forecasting is developing an effective method for considering the impact of human behavior on disease transmission. A variety of models emerged which explicitly built human behavior into disease models, often coupling models for human behavior dynamics and disease dynamics. Here, we consider models which consider risk response, where humans change their actions in response to their perception of likelihood of infection (or death due to infection). We classify models based on how human response to new information (risk responsiveness) affects disease transmission within the model, either exogenously or endogenously. We examine how different incorporations of risk response affect model dynamics and provide analysis of a particular model [1] which performed well in epidemic forecasting despite its relative simplicity.

[1] Rahmandad H, Xu R, Ghaffarzadegan N. Enhancing long-term forecasting: Learning from COVID-19models. PLOS Computational Biology. 2022;18(5):e1010100.

Personalized Cancer Care through Digital Twin Technology: Integrating Patient-Specific Data with Quantitative Systems Pharmacology

Leili Shahriyari, University of Massachusetts Amherst

Abstract. Our work explores the possibility of creating a digital twin (DT) platform for cancer to better understand the progression of an individual's cancer. By simulating the unique characteristics of each tumor and its response to treatments, we aim to offer insights into personalized cancer care. Our method combines elements of mechanistic modeling, machine learning, and stochastic techniques to develop a DT platform. This platform makes use of diverse data types, such as biological information, biomedical data, and electronic health records (EHR), to create individualized predictions.

A central aspect of our approach is the use of a mechanistic model based on quantitative systems pharmacology (QSP). QSP is a computational method used to analyze drug interactions and effects, and it plays a crucial role in our project. We acknowledge that a common challenge in QSP modeling is accurately determining parameters, especially since traditional models often assume a general uniformity across different patients' diseases. This assumption can lead to limitations when calibrating parameters using varied data sources.

Our objective is to build a more personalized DT by concentrating on individual patient data for parameter estimation. We adjust the QSP model parameters for each patient based on their unique data. Through detailed sensitivity analysis and uncertainty quantification, we identify key interactions in the model and define the range of our predictions. By integrating this tailored QSP model with insights into cellular and molecular interactions, we hope to better predict how cancer evolves and responds to specific treatments. We are excited about the potential this has for advancing personalized cancer therapy, though we are aware of the challenges and complexities involved in this endeavor.

Synergizing Health Strategies: Exploring the Interplay of Treatment and Vaccination in an Age-Structured Malaria Model

Mahmudul Bari Hridoy, Texas Tech University

Abstract. Malaria persists globally, especially in tropical regions of Africa, Asia, and South America. The transmission of Plasmodium from endemic to non-endemic areas, facilitated by increased human mobility, poses a significant challenge. In 2021, the World Health Organization (WHO) recommended the widespread use of the RTS,S malaria vaccine among children living in malaria-endemic regions. We have developed an extended SEIR age-structured model that includes malaria vaccination for children. This research focuses on the interaction between treatment and vaccination. Our goal is to assess the impact of malaria vaccination coverage on disease prevalence and transmission dynamics. Additionally, we aim to explore the roles of treatment and the vaccine in saving lives, along with their potential contribution to drug resistance. Our observations indicate that while treatment contributes to reducing the malaria disease burden, it also results in an increase in the proportion of malaria cases that are drug-resistant. In contrast, higher vaccination rates are associated with a lower percentage of the population being infected with either strain. These findings suggest that a synergistic approach, involving both vaccination and treatment, could effectively decrease the overall proportion of the population that is infected.

Immune escape: from individual differences to the population-level

Maria A. Gutierrez, University of Cambridge

Abstract. Host immunity drives the evolution of many pathogens towards antigenic escape. However, the contribution towards this escape may not be uniform across the population: different types of hosts may contribute more or less in terms of both immune pressure and onward transmission. Here we investigate the population-level consequences of this heterogeneity, focussing on vaccine escape. This heterogeneity depends on the immune status of each host, primarily through (i) vaccination, (ii) previous infection history, and (iii) general immunocompetence. Existing host immunity may increase or decrease the contribution to escape, as in other phylodynamic phenomena. We define the escape pressure as a linear combination of infections in different groups over an epidemic. We find the escape pressure using SIR-style models with imperfect vaccines and variable vaccination coverage. We also consider the stochastic invasion dynamics of escape strains and their antigenic evolution over multiple epidemic waves. The effects of vaccination on the escape pressure depend on the relative role of vaccinated hosts. If they do not contribute much more than unvaccinated hosts to the escape pressure, increasing vaccination will always reduce the overall escape pressure. However, if vaccinated hosts contribute to escape significantly more, the escape pressure will peak at intermediate vaccination levels. However, these patterns are more complicated with more heterogenous population immunity. The different individual contributions to antigenic escape will shape pathogen evolution. At the population-level, these heterogeneous escape contributions can lead to unintuitive effects in the escape pressure, particularly on its dependence on vaccine coverage. Therefore, it is important to understand better these individual escape contributions and their dependence on host immunity. The considerations here have implications for the design of surveillance and vaccination strategies, and may help to mitigate the risk of vaccine immune escape in a population.

Infection-Age Structured West Nile Virus Model

Marina Mancuso, Los Alamos National Laboratory

Abstract. West Nile Virus (WNV) is the most common vector-borne disease in the continental United States. Over 2,400 human WNV cases were reported in the US in 2023 alone, with nearly 1,600 of these cases being neuroinvasive. The WNV transmission cycle circulates primarily between *Culex* mosquito vectors and avian hosts, with occasional transmission to human dead-end hosts. We present a three population, partial differential equations WNV transmission model between mosquito vectors, bird hosts, and human dead-end hosts. This model incorporates infection-age (or time-since-infection) structure for mosquito vector and bird host populations, which was motivated by experimental studies that showed infection-age dependence on epidemiological processes. The model is well-posed under simplifying assumptions, and a sensitivity analysis shows which processes have the most influence on WNV outbreaks. We further discuss the importance of including temperature-dependent processes on WNV transmission, as climate change is expected to affect the expansion and spread of vector-borne diseases.

Virtual clinical trials of BMP4-induced differentiation therapy identify strategies for combination with radiation therapy for glioblastoma (GBM) patients

Nicholas Harbour, University of Nottingham

Abstract. GBM is the most aggressive and most common primary brain tumour in adults and is uniformly fatal, with a poor median survival time of 15 months. Standard of care for GBM consist of surgical resection followed by radio and chemotherapy, despite this resistance to treatment almost always occurs making recurrence inevitable. Failure of the current standard of care has been partly attributed to a special sub-population, the glioma stem cells (GSCs), which initiate and drive tumour growth. Treatment cannot be successful unless all GSCs are eliminated. However, GSCs are known to be highly resistant to radiotherapy. New treatments that specifically target GSCs could have a potentially large benefit. BMP4 is known to induce differentiation of GSCs towards a less malignant, astrocytic-like lineage. Furthermore, new delivery systems (non-virally engineered adipose mesenchymal cells) provide a potential mechanism by which BMP4 could be successfully administered to reverse the GSC state and increase radio-sensitivity in patients. We develop a data-driven mechanistic mathematical model to create digital twins from patient data on which we perform in silico clinical trials to identify patient specific optimised treatment strategies.

Identifying Critical Immunological Features of Tumor Control and Escape Using Mathematical Modeling

Rachel Sousa, University of California, Irvine

Abstract. The immune system can eradicate cancer, but various immuno-suppressive mechanisms active within a tumor curb this beneficial response. Cytotoxic T cells (CD8s), regulatory T cells (Tregs), and antigen-presenting dendritic cells (DCs) play an important role in the immune response; however, it is very cumbersome to unravel the effects of multimodal interactions between tumor and immune cells and their contributions to tumor control using an experimental approach alone. Thus, to better understand the mechanisms that govern the interactions between immune cells and tumor cells and to identify the critical immunological features associated with tumor control and tumor escape, we built a mechanistic mathematical model of CD8s, Tregs, DCs, and tumor cells. We used an automated model selection procedure known as Design Space Analysis to identify regulatory feedback mechanisms sufficient to reproduce experimentally observed behaviors that regulate the immune system and determined stable regions of parameter space. The model accounts for tumor immunogenicity, the effects of IL-2 prolonging T cell lifespan, Treg suppression of antitumor immune response through CTLA-4, recruitment of immune cells into the tumor environment, and interferon-gamma upregulation of PD-L1 on DCs and tumor cells to deactivate T cells. Our tumor-immune model exhibits bistability in which both a tumor-free and a tumor state exist and are stable. We use the model to explore how the initial immunological conditions dictate the final tumor state and ultimately impinge the success of immunotherapy. We also use the model to make inferences on the mechanisms of resistance to various immunotherapies and identify immunotherapy scheduling to stimulate CD8 but not Treg activation. We are currently expanding our model to include spatial dynamics of cellular interactions, guided by intravital imaging data, to understand how the spatial distribution of T cells contributes to tumor control and how that can be exploited to develop more efficacious immunotherapies.

Multiscale stochastic disease transmission from within-host dynamics to between-host spread

Rodolfo Guadalupe Blanco Rodriguez, University of Idaho

Abstract. This research used a stochastic multiscale modeling approach to unravel the complex dynamics of infectious disease transmission. At the within-host scale, we used a mathematical model of viral particle replication and immune responses, specifically T-cell and antibody dynamics. Our case study focused on a mathematical within-host model for COVID-19 developed in a previous paper. The probability of infection was modeled by linking viral dynamics and immune response on a sigmoidal probability function, where infection depends on the day of contact between a susceptible and an infected individual. Within a linear contact network with varying encounter frequencies, our investigation revealed that the timing of host encounters is a more critical factor in disease spread than the number of encounters. Furthermore, we found that antibody dynamics play a critical role in reinfection cases, underscoring the importance of well-timed vaccination of previously infected nodes. Our numerical results highlight the importance of intra-host dynamics in influencing infectiousness and emphasize the critical role of well-timed encounters in disease spread.

Formation and Growth of Co-Culture Tumour Spheroids: New Compartment-Based Mathematical Models and Experiments

Ryan Murphy, University of Melbourne

Abstract. Co-culture tumour spheroid experiments are routinely performed to investigate cancer progression and test anti-cancer therapies. Therefore, methods to quantitatively characterise and interpret co-culture spheroid growth are of great interest. However, co-culture spheroid growth is complex. Multiple biological processes occur on overlapping timescales and different cell types within the spheroid may have different characteristics, such as differing proliferation rates or responses to nutrient availability. At present there is no standard, widely-accepted mathematical model of such complex spatio-temporal growth processes. Typical approaches to analyse these experiments focus on the late-time temporal evolution of spheroid size and overlook early-time spheroid formation, spheroid structure and geometry. Here, using a range of ordinary differential equation-based mathematical models and parameter estimation, we interpret new co-culture experimental data. We provide new biological insights about spheroid formation, growth, and structure. As part of this analysis we connect Greenspan's seminal mathematical model to co-culture data for the first time. Furthermore, we generalise a class of compartment-based spheroid mathematical models that have previously been restricted to one population so they can be applied to multiple populations. As special cases of the general model, we explore multiple natural two population extensions to Greenspan's seminal model and reveal biological mechanisms that can describe the internal dynamics of growing co-culture spheroids and those that cannot. This mathematical and statistical modelling-based framework is well-suited to analyse spheroids grown with multiple different cell types and the new class of mathematical models provide opportunities for further mathematical and biological insights.

Modeling the Tumor Microenvironment and Optimizing Immunotherapies in Glioblastoma

Tracy Stepien, University of Florida

Abstract. While immunotherapy has shown to be effective in treating some cancer types, the highly immunosuppressive tumor microenvironment of glioblastoma (GBM) provides unique challenges. As an example, immune checkpoint inhibitors, such as for the programmed-death-1 (PD-L1/PD-1) pathway, have had promising pre-clinical outcomes but failed to show efficacy in phase III clinical trials. One potential explanation is the infiltration of the tumor microenvironment by immune-suppressive cells such as myeloid-derived suppressor cells (MDSCs). Encouragingly, in experimental studies where MDSCs are targeted by drugs in combination with PD-1 blockade in mice, median survival increased. In this talk, we'll give an overview of models our group is developing to understand the interactions between cancer cells, T cells, and MDSCs specific to the glioma microenvironment and potential treatment regimens.

Follower the leader: modeling collective cancer invasion

Yi Jiang, Georgia State University

Abstract. A major reason for cancer disease progression and treatment failure is the heterogeneous composition of tumor cells at the genetic, epigenetic, and phenotypic levels. Despite extensive efforts to characterize the makeup of individual cells, there is still much to be learned about the interactions between heterogeneous cancer cells and between cancer cells and the microenvironment in the context of cancer invasion. Clinical studies and in vivo models have shown that cancer invasion predominantly occurs through collective invasion packs, which invade more aggressively and result in worse outcomes. In vitro experiments on non-small cell lung cancer spheroids have demonstrated that the invasion packs consist of leaders and followers who engage in mutualistic social interactions during collective invasion. Many fundamental questions remain unanswered: What is the division of labor within the heterogeneous invasion pack? How does the leader phenotype emerge? Are the phenotypes plastic? What's the role of the individual "cheaters"? How does the invasion pack interact with the stroma? Can the social interaction network be exploited to devise novel treatment strategies? I will discuss recent modeling efforts to address these questions and hope to convince you that identifying and perturbing the "weak links" within the social interaction network can disrupt collective invasion and potentially prevent the malignant progression of cancer.