Overview

I develop and analyse mathematical models to understand the mechanisms underlying treatment resistance. The major theme of my research program is developing physiologically appropriate mathematical models to understand the role of intra- and inter-patient heterogeneity in disease progression and treatment response. In my experience, successful mathematical biology research leads to new understanding in both mathematics and biology. Through the development of analytical and numerical techniques, I leverage these mathematical models to identify the biological mechanisms that drive disease progression and the evolution of treatment resistance. These mathematical models then allow for the development of evolutionarily-inspired and clinically-actionable therapeutic strategies to mitigate treatment resistance and the resulting disease progression.

My prior work has shown that including individual heterogeneity in mathematical models naturally leads to *physiologically structured equations*. Structured equations, typically in the form of partial differential equations (PDEs), provide a mathematical framework to study how individual-level heterogeneity drives population level dynamics. In this framework, individuals are continuously distributed according to the physiological "trait" of interest (mutational burden, age, maturity, ...). The population is thus a density p distributed over the space of possible traits, Ω. This framework naturally encodes intra-individual heterogeneity into mathematical models and allows researchers to address questions at both the individual level, by considering p, and at the population level, by considering the time evolution of the entire population

$$N(t) = \int_\Omega p(t,x)\mathrm{d}x.$$

Modelling the role of heterogeneity in disease response will necessarily entail new techniques in the development, simulation, and analysis of structured population models. These include numerical methods to simulate and parametrize these models, bifurcation techniques to study these infinite dimensional dynamical systems, and analytical approaches to identify key model properties. Moreover, I have recently addressed questions of treatment resistance in human immunodeficiency virus-1 (HIV-1) [33], the impact of phenotypic plasticity and identification of dose limiting toxicities in non-small cell lung cancer (NSCLC) [15, 16], and the optimization of treatment scheduling in melanoma [11, 22] by using these structured models.

The numerous areas of application and variety of techniques involved in the implementation of structured equations in mathematical biology provides a number of possible research avenues for students. While my research trainees will develop their own lines of inquiry and scientific taste, they will also acquire expertise in a wide variety of applied mathematics techniques and become familiar with the multi-faceted approaches underlying model development and analysis. Further, by working at the intersection of mathematics and biology, they will develop communication skills necessary to translate their mathematical understanding into new biological knowledge. In what follows, I summarize the broad themes of my proposed research into the use of structured equations to investigate the physiological determinants of treatment success in viral infection and cancer.

Future directions: Structured equations in mathematical biology

Structured equations typically model the evolution of a population density through trait space. These models often include interactions between individuals with different traits via nonlocal terms and are non-trivial to develop, simulate, and analyse [17]. Accordingly, mathematical biologists often artificially bin individuals with similar traits and use simpler compartmental ordinary differ-

ential equation (ODE) models [21, 36]. To address these difficulties, I established equivalences between certain structured PDE models and delay equations (DEs) that are simpler to analyse and simulate [10, 16, 12]. These equivalences facilitate comparison to biological data, formalize model assumptions [7], and allow modelers to use distinct perspectives to analyse the same model.

Numerical methods for structured models:

A significant obstacle in the use of structured equations in mathematical biology is the lack of appropriate numerical tools to facilitate their study and simulation [23, 27]. However, numerical techniques for these structured models, and delay differential equations (DDEs) in particular, are limited and rely on non-biological assumptions [13]. Existing numerical methods for DDEs are complicated by the evaluation of delay term, which necessarily induces overlapping in each Runge-Kutta step. To address this, numerical methods must output a continuous extension of the solution to calculate the intermediate RK steps. The theory of these functionally continuous Runge-Kutta (FCRK) methods is beginning to be developed [5] but has not been extended to infinite delay DDEs. My research will address this gap in the literature and facilitate the use of these infinite delay DDE models in mathematical biology by developing appropriate FCRK methods. An undergraduate researcher under my supervision recently developed a FCRK for the simulation of generic gamma distributed DDEs [13]. Extensions of this work to other specific infinite delay DDEs are well-suited for undergraduate researchers. The more general FCRK framework for structured models is a multi-summer research direction for trainees interested in numerical analysis.

Numerical bifurcation techniques:

The bifurcation structure of these structured models can shed light on possible therapeutic strategies. Pseudospectral approximates are being developed for the numerical bifurcation analysis of these infinite dimensional dynamical systems [20, 18]. My collaborator, Francesca Scarabel, and I will extend existing pseudospectral techniques to study bifurcations in structured epidemic models. Our preliminary work shows that structuring the infected class by infection age and including waning infectivity to increase biological relevance can cause waves of infection rather than endemic infection. Our results have consequences in the development of vaccination strategies and must be confirmed through the development of novel rigourous numerical bifurcation techniques.

Equivalent model formulations:

As a long term goal, my research group will extend the equivalences between structured PDE models and DEs by fully classifying the conditions under which these equivalences exist. However, it is likely that there are models for which it is not possible to establish true equivalence between solutions of the PDE and DE formulations. In these cases, we will develop finite dimensional, thus analytically and numerically tractable, approximations to physiologically structured models. These approximations will allow mathematical biologists to include the biologically-relevant heterogeneity that is present in structured models without sacrificing the tractability of ODE models. We will then quantify the accuracy of these approximations compared to the underlying full model. Properly quantifying the accuracy of these approximations is crucial to developing confidence in model predictions and testing the biological assumptions underlying the approximation. Developing these approximations will require perspectives from analysis, probability theory, and dynamical systems. Accordingly, this proposed research allows for students with diverse interests and expertise across applied mathematics to work simultaneously and collaboratively.

Future directions: Structured models of HIV dynamics

Despite remarkably effective antiretroviral therapies that rapidly control circulating viral loads, there is still no functional cure available for individuals with HIV-1. Accordingly, broadly neutralizing antibodies (bNAbs) have become increasingly important in the search for a functional cure [32, 9, 24]. While these antibodies induce a transient decrease in viral load in HIV infected individuals [6, 33], existing bNAbs have *not* led to sustained viral control and viral rebound occurs following the emergence of an antibody resistance rather than antibody washout [29, 8, 24]. I developed a mathematical model to understand the evolution of resistance in a recent phase I/II clinical trial of the novel bNAb PGT121 [33]. My work illuminated the mechanisms by which PGT121 led to long-term virological control in two patients and indicated that treatment induced competitive release of a resistant viral strain leads to treatment failure.

Combination bNAb therapies:

If the competitive release of resistant viral sub-populations can be avoided through combination therapies, then highly potent bNAbs, such as PGT121, may induce long-term viral suppression in HIV-1 positive individuals. Genetic profiling and *in vitro* neutralization assays of escape virus indicates that sensitivity to other bNAbs is maintained or possibly enhanced following PGT121 therapy. Accordingly, I will investigate this population-level resistance by using structured models to explicitly consider the dynamic pathways leading to resistance against bNAb therapies. These models will use the strain-specific *in vitro* neutralization efficacy as the physiological "trait" to structure the viral population. Working with students with interests in viral dynamics, we will validate these models against temporal sequencing data and predict viral response and resistance development during bNAb therapy. Leveraging these models to determine combination strategies to inhibit the development of resistance by maintaining distinct evolutionary selection pressure on resistant viral subspecies will require techniques from pharmcometrics, dynamical systems, and control theory. These students will benefit from opportunities for summer research positions arising from my collaboration with the Viral Dynamics group at the Los Alamos National Laboratory.

Future directions: Structured models of oncolytic viruses

Genetically engineered viruses designed to preferentially infect tumour cells have recently been approved for the treatment of late-stage melanoma [2]. In addition to the killing of infected cells, these oncolytic viruses (OV) elicit a potent anti-tumour immune response. However, this immune response also attenuates viral replication and limits secondary OV infections. I developed a mathematical model of the virus-tumour interactions [14] and a virtual clinical trial platform capable of replicating a phase III clinical trial of the OV T-VEC [11, 2]. I supervised an undergraduate researcher who extended our model to include OVs with pro- and anti-inflammatory effects. We then identified a relationship between patient specific tumour growth rates and individualized optimal combination OV treatment strategy [22].

Spatial structure in oncolytic virus treatment:

OVs are injected intra-lesionally before diffusing throughout the tumour micro-environment. Including this spatial component in models of OVs raises two parallel avenues for future research: 1) using parabolic PDEs to model diffusion at a macro-scale or 2) using an agent based approach to model individual cells, both of which will be undertaken by my group. It appears possible to obtain a parabolic PDE from an agent based model by considering the expected behavior of individual cells. By formalizing the conditions under which this "mean field" approximation holds, we will identify the biological mechanisms that are intrinsic to the individual level scale. In particular,

predictions from the two modelling approaches will be validated by experimental collaborators to further understand the role of virus infiltration in OV therapy. This work is well situated for support from interdisciplinary funding mechanisms.

Future directions: Shaping evolution in cancer

Despite advances in targeted medicine, most patients with advanced cancer experience drug resistance, treatment failure and, ultimately, disease recurrence [28, 26]. This resistance, long thought to result from genetic heterogeneity, is increasingly understood as the result of non-mutational evolutionary adaptations to therapy [25, 4]. Recent studies have indicated that epigenetic regulation of genetically identical NSCLC cells induces a reversible drug-tolerant phenotype that expands during chemotherapy [31, 19]. This phenotypic heterogeneity is modulated by a number of complex physiological factors, including the current state of the tumour microenvironment [30, 35]. As systems-level experiments of these complex interactions are currently intractable, physiologically-structured mathematical models are integral to our understanding of how therapeutic selection pressure shapes the epigenetic evolution of malignant tumours. My recent work has identified non-genetic phenotypic inheritance as a possible driver of treatment resistance in NSCLC [16].

Directing phenotypic evolution in solid cancers:

My research will interrogate the systemic determinants of epigenetic resistance to therapy through the development of mechanistic mathematical models of tumour evolution. These models will be structured in phenotype space to explicitly study intra-clonal population heterogeneity during treatment. By validating these models against *in vitro* and mouse xenograft data, the models will facilitate understanding of how therapeutic selection shapes the epigenetic evolution of malignant tumours [30, 3]. In particular, my research will identify the evolutionary and physiological mechanisms underlying transient resistance to therapy observed in many solid cancers [34, 19]. By using perspectives from dynamical systems and pharmacometrics, I will derive treatment strategies that direct epigenetic evolution of drug resistance.

Combination therapies and collateral sensitivities in solid cancers:

This mechanistic understanding of epigenetic adaptation to therapy will be particularly important when considering large heterogeneous tumours. In these tumours, single drug therapies are unlikely to be successful. Treatment therefore involves combination therapies, whose scheduling includes the timing and ordering of each combination partner. My research group will adapt and extend our existing models to determine optimal scheduling of drug combinations. Developing models continuously structured in phenotype space is particularly important when considering the multifactorial adaptation pathways to combination therapies. Predicting this evolutionary path will identify the precise timing of collateral sensitivies, wherein resistance to certain therapies increases sensitivity to others [1]. The models we develop during this work will identify treatment strategies to maintain a drug-sensitive population of cells and thus induce collateral sensitivity. My collaboration with the Integrated Mathematical Oncology department at the Moffitt Cancer Center and my industrial experience in treatment scheduling at Pfizer will furnish collaboration and internship opportunities for my trainees. These projects offer a number of distinct and complimentary axes for undergraduate students interested in Mathematical Oncology. Trainees will learn how to use experimental data to build confidence in mathematical models by collaborating outside the Mathematics department. This work also offers avenues to apply for interdisciplinary funding.

Outlook

Research in my group will make original contributions by developing mathematical methodologies with real clinical implications. Structured population models permit the explicit study of heterogeneity in disease progression. Through the development of physiologically realistic models, my work will address questions of treatment resistance and optimal treatment scheduling. Answering these questions will require the development of novel mathematical models and techniques for their simulation and analysis. Consequently, my research offers numerous opportunities for trainees at the undergraduate level in fields ranging from mathematical analysis to mathematical modelling. These trainees will benefit from my existing collaborations and industrial experience for post-graduate positions.

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