Application of Mathematics to Medicine and Biology
Applications des mathématiques en médecine et en biologie
(Org: **Sivabal Sivaloganathan** (University of Waterloo))

JANE HEFFERNAN, York University
Virus dynamics and the immune system

The outcome of viral infection ultimately depends on the efficacy of interactions between the pathogen and different components of the immune system. In this talk I will discuss our recent work in modelling HIV and influenza infections where one or more activated component of the immune system is explicitly included in the model structure. Briefly, depending on model assumptions (i.e. killing of infected cells, virus loss term), we find that a model of CD4 T-cell activation and memory generation in HIV infection can produce one or more backward bifurcations and one or more Hopf bifurcations at low viral load. We will discuss these outcomes in the context of HIV viral clearance and viral blips. In collaborative work, we have found that mathematical models of influenza infection that include the innate and/or adaptive immune response can generate similar viral hierarchy infection outcomes as those observed in laboratory studies of influenza cross-reactivity. Finally, we will discuss extensions of in-host models of virus and immune system dynamics to a multi-scale study of the effects of immunity on susceptibility and transmissibility at the population level.

BRIAN INGALLS, University of Waterloo
Synthetic biology approaches to suppression of antibiotic resistance: toward model-based design

Antibiotic-resistant pathogens present an increasing global health concern. Our group is investigating synthetic biology-based strategies for suppression of resistance in environmental bacterial populations. This approach involves the delivery of engineered genetic elements to target populations. We are developing models of the dynamics of this system, at both the genetic and population level, to be used for model-based design of potential implementations. Analysis of proof-of-principle scenarios and accompanying experimental results will be presented.

KAMRAN KAVEH, Harvard University
Evolution in heterogeneous and random environments

Many theoretical models of evolution assume that all competing individuals experience the same environment. Here, we consider the more realistic scenario of evolution in heterogeneous environments. We introduce a novel formalism to approach any form of spatial fitness heterogeneity in an evolutionary graph. We calculate the condition for natural selection to favor the mutant type relative to the resident on a complete graph structure. Environmental heterogeneity elucidates an interesting asymmetry between the mutant and resident types. Mutant heterogeneity suppresses fixation probability, and if strong enough, it can completely offset the effects of natural selection. In contrast, resident heterogeneity can amplify a mutant's fixation probability if population is small and has no effect on mutant fixation probability otherwise. Our results hold for any environmental heterogeneity and selection intensity. We address generalization of the above observations to other graph structures, as well as heterogeneous evolutionary games.

XINZHI LIU, University of Waterloo
Infectious Disease Modeling by a Hybrid System Approach

Mathematical models for infectious disease are crucial in gaining knowledge of the underlying mechanism that drives an epidemic. They are often used for implementing and evaluating control schemes in order to eradicate a disease. This talk discusses a hybrid dynamical system approach for infectious disease modeling. Seasonality and pulse control are considered in the epidemic models. Hybrid control schemes are examined, and, in doing so, we hope to gain insight into the effects of a time-varying contact rate on critical control levels required for eradication.

ALI MAHDIPOUR, University Health Network
Cell Cycle Significance in the Evolutionary Dynamics of Cancer

Proliferation has known as one of the main building blocks of almost any evolutionary mechanism in living species. More specifically, during cell replication, each cell undergoes various phases within the cell cycle. The average time of successful divisions and the frequency of cells within each of the cell cycle phases determine their fitness within a population. In continuation to recent researches on the role of various cell-cycle-compartments in the evolution of biological systems, we suggest a general framework which highlights the significance of cell cycle in a heterogeneous system. More precisely, we investigate how the cell cycle mechanism may affect the dynamics of malignancy in such a system. We find the speed of initiation/progression of malignancy and its survival rate in diverse cell-cycle phases. Our findings may provide a better understanding of malignancy development in infectious diseases and different types of cancer where various phenotypes behave differently during mitosis and replication. This research may also affect current treatment schedules in order to provide more intense therapies.

VICTOR OLUWOLE OLOBATUYI, University of Alberta
Modeling the effects of G2-checkpoint dynamics on the low-dose hyper-radiosensitivity

In experimental studies, it has been found that certain cell lines are more sensitive to low-dose radiation than it is expected by the classical linear-quadratic model (LQ model). In fact, it is frequently observed that cells incur more damage at low doses than at higher dose. This effect has been termed hyper-radiosensitivity (HRS) and increased radio-resistance (IRR). The effect depends on the type of cells and on their phase in the cell cycle. In this talk, I will present the analysis of a differential equation model for the cell cycle that includes G2-checkpoint dynamics and radiation treatment. We fit the model to surviving fraction data for different cell lines including glioma cells, prostate cancer cells, as well as to cell populations that are enriched in certain cell-cycle phases. The HRS/IRR effect is measured in the literature through a ratio of the slope of the surviving curve at zero doses versus the slope of the corresponding LQ model. Using our model, we are able to derive an explicit formula for this ratio and we show that it corresponds very closely to experimental observations. Finally, we identify the dependence of this ratio on the surviving fraction at 2 Gy. It was speculated in the literature that such a relation exists. Our theoretical analysis will help to more systematically identify the HRS/IRR in cell lines and opens doors to analyzing its use in cancer treatment.

This is a joint work with Thomas Hillen and Gerda de Vries.

LAWRENCE OPREA, McGill University
Modeling perisaccadic traveling wave dynamics in the visual cortex

In normal vision our eyes rapidly flicker (saccade) between behaviourally pertinent objects in the environment. During ocular transit we become effectively blind as processing of motion-blurred images is suppressed in all parts of the visual system. Recent work in primates has shown that traveling waves of electrical activity occur in the visual brain area V4, after a saccade. These waves help to increase visual sensitivity and therefore may alleviate suppression. Our research goal is to create a neural network model to investigate the rapid dynamics of wave initiation and interaction with neurons. Previously, work has shown very fast switching between wave and synchronous states through the modulation of coupling kernels. We investigate the wave dynamics using an optical flow methodology that allows models of any dimensionality to be analyzed as 2D flows.

KATRIN ROHLF, Ryerson University
Reactive Multi-particle Collision (RMPC) dynamics for stochastic simulations of biochemical systems

Stochastic simulation methods are popular means to simulate reaction mechanisms, and can be used to explore biochemical systems for which traditional well-mixed chemical kinetics rate laws no longer apply. The Gillespie algorithm, or other related stochastic simulation algorithms, have had a lot of success in capturing both the well-mixed system dynamics in agreement with well-mixed chemical rate laws and reaction-diffusion mechanisms, as well as effects beyond the applicability of ODE/PDE models. Coupling of the reactive dynamics to fluid flow, however, is a challenge in this framework, and other simulation

methods, such as Reactive Multi-particle Collision dynamics (RMPC) can allow for a means to model chemically reactive systems coupled to flow conditions.

This talk will introduce the Reactive Multi-particle Collision (RMPC) dynamics, as well as its generalized Master equation. Simulation results for the Selkov reaction mechanism, as well as those of an intracellular signaling pathway for bacterial chemotaxis in E. coli will be presented. As part of the talk, the theoretical calculation for the self-diffusion coefficient for the different chemical species will be derived from the RMPC dynamics. The talk will conclude with current work, and future studies for which RMPC can be an important simulation tool.

FRANCES SKINNER, Krembil Research Institute, UHN and University of Toronto
Mathematically modeling theta oscillations in the hippocampus

It is clear that oscillatory brain activities are a ubiquitous feature of brain recordings. In particular, theta rhythms (3-12Hz) in the hippocampus play fundamental roles in memory processing. Is it possible to have a cellular-based understanding of these activities? In this talk, I will describe some of our recent modeling work from the perspective of a particular cell type in the hippocampus and its contribution to theta rhythms by virtue of its biophysical characteristics.

ROBERT SMITH?, The University of Ottawa
Comparing malaria surveillance with periodic spraying in the presence of insecticide-resistant mosquitoes

There is an urgent need for more understanding of the effects of surveillance on malaria control. Indoor residual spraying has had beneficial effects on global malaria reduction, but resistance to the insecticide poses a threat to eradication. We develop a model of impulsive differential equations to account for a resistant strain of mosquitoes that is entirely immune to the insecticide. The impulse is triggered either due to periodic spraying or when a critical number of malaria cases are detected. For small mutation rates, the mosquito-only submodel exhibits either a single mutant-only equilibrium, a mutant-only equilibrium and a single coexistence equilibrium, or a mutant-only equilibrium and a pair of coexistence equilibria. Bistability is a likely outcome, while the effect of impulses is to introduce a saddle-node bifurcation, resulting in persistence of malaria in the form of impulsive periodic orbits. If certain parameters are small, triggering the insecticide based on number of malaria cases is asymptotically equivalent to spraying periodically.

MADJID SOLTANI, KNTOOSI University
Intracellular events regulate tissue scale phenomena in sprouting angiogenesis, A mathematical model

During sprouting angiogenesis, endothelial cells (EC) grow and migrate in extracellular matrix (ECM) to build new capillaries for delivery of oxygen and nutrients to the tumor. When sprouts start to grow from parent vessel, biochemical and biomechanical signals in the ECM regulate EC behavior; however, after anastomosis of sprouts and formation of a loop, blood flow induced shear stress is the main regulator of EC behavior. In this work, a multiscale mathematical model is developed to show endothelial cells collective behavior in a single sprout or a loop. Results show that when the loop forms, its hemostasis and elongation strongly depend on the intracellular events. Activation of different signaling cascades due to shear stress on ECs changes the cell behavior and also the behavior of ECs as a whole in the loop. This is the main reason that in the presence of blood flow, the loop keeps its integrity and elongates while in the absence of blood flow, the loop collapses.

ADAM STINCHCOMBE, University of Toronto
Understanding Myelodysplastic Syndromes from Blood Cell Counts

Haematopoietic stem cells, found in the bone marrow, are progenitors for the nearly 10^{12} blood cells, of all types, produced daily in an adult human. The blood cell production process, haematopoiesis, is important to understand in its relation to myelodysplastic syndromes (MDS), a group of cancers in which blood cells do not fully mature. In this short talk, I will describe a model of haematopoiesis given by a system of delay-differential equations. By fitting the parameters of this model to blood cell counts in MDS patients, I can identify and provide a mechanism for different types of MDS. I will address

the statistical question of the frequency of blood samples needed to identify the MDS type and consider some type-specific treatment options.

KATHLEEN WILKIE, Ryerson University

Classifying Cancer Types for Treat-ability Using PPI Network Structure

The existence of a correlation between cancer protein-protein interaction (PPI) network degree-entropy and cancer 5-year survival probability has been shown (Breitkreutz *et al.*, PNAS, 2012). We investigate the correlation between epidemiological survival data and the molecular details of specific cancers further through higher levels of degree-connectedness and through the evolution of cancer network connections compared to a random graph evolution. By comparing the cancer networks to random graphs of the same size, we create a new metric that correlates with 5-year survival and may act as a classifier. The correlative relationship suggests that our method is able to surpass individual variabilities such as cancer site, disease stage, and structural features of the PPI network, through the use of proxy measurements: 5-year survival data and our entropy-based metrics. Our findings suggest that the underlying structure of cancer protein-protein interaction networks may be used to classify cancer types into two groups: those that are more treatable for various reasons and those that are not. Furthermore, using spectral analysis techniques we present a new method to identify potential drug targets, and discuss their effects on residual network structure.

This is joint work with Dr. M La Croix and Dr. P Hahnfeldt