Applications of Mathematics in Health Research
Mathématiques appliquées à la recherche en santé
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MALIHA AHMED, University of Waterloo
Model for a cortical circuit associated with childhood absence epilepsy

Childhood absence epilepsy is a pediatric epilepsy disorder characterized by brief episodes of impaired consciousness. The thalamocortical circuit is considered to play an important role in the pathophysiology of absence seizures, exhibiting the ability to generate oscillations of different frequencies and a range of synchrony. The purpose of our investigation was to explore of the same of the factors that alter the function of individual neurons in the cerebral cortex, giving rise to an epileptic network. In particular, we investigated the consequence of these alterations on neuronal network activity associated with this disorder. In this regard, we created a small network consisting of deep layer cortical pyramidal neurons and an interneuron, each described by a single-compartment Hodgkin-Huxley style model. We investigated factors that convert a normal network into a hyperexcitable one, including impairment of $GABA_A$ synapses and sodium channel defects resulting from mutations in Scn genes. Our model agrees with experimental results indicating the role of GABA impairment in generating a hyperexcitable network. In particular, our cortical network is capable of generating its own spike-and-wave oscillations analogous to those in a thalamocortical network. Our results also suggest that the co-existence of multiple Na^+-channel mutations alters individual neuronal function to increase or decrease the likelihood of the network exhibiting seizure-like behaviour.

BRYDON EASTMAN, University of Waterloo
Contrasting Chemotherapy Schedules from Reinforcement Learning and Optimal Control

Determining the optimal chemotherapy schedule for a cancer patient is difficult. Increasing the dose of the chemotherapeutic results in both greater cancer kill but also greater toxicity to the patient in the form of red blood cell and bone marrow loss. We present two methods of deriving optimal chemotherapeutic schedules for a particular model of breast cancer treated with paclitaxel. The first, a schedule learned via deep reinforcement learning and the second, a schedule learned via optimal control theory. We demonstrate that the deep RL derived therapy provides a more robust chemotherapeutic schedule when we concern ourselves with interpatient variability.

HERMANN EBERL, Univ. Guelph
Challenges in the modeling of antibiotic effects on gut flora

The experimental study of gut microbiota often uses laboratory reactors that mimick the ecological conditions in the large intestine. Such reactors can be described by large chemostat-like models. We review one such model that is based on the International Water Association's Anaerobic Digestion Model No. 1, and we extend it to account for the side effect of bacteriostatic antibiotics on gut processes. We present some first results and point out modelling challenges due to the mathematical and microbial complexity that are unique to this setting vis-a-vis more traditional chemostat model applications.

MARYAM GHASEMI, Department of Applied Mathematics, University of Waterloo
Computational investigation of influence of Quorum Sensing inhibition on biofilm growth and disinfection

An important feature of biofilms that makes them distinct from freely moving planktonic cells is their resistance against chemical and mechanical washout. It has been reported that Quorum Sensing (QS), cell-cell communication mechanism, can influence the resistance of bacteria against antibiotics and make them more protective. There are several ways, by which QS can increase the biofilm resistance. One connection is that antibiotics are a stressor for the bacteria, and QS has been characterized as a method of stress response, forcing the bacteria for example to more cooperation or other changes in behavior. One strategy to make the biofilms susceptible against antibiotics is QS disruption. We present a mathematical model to describe the interaction

between quorum sensing and quorum quenching, an inhibitory enzyme that can disrupt quorum sensing upregulation, and its effect on biofilm response to antibiotics that act as a stressor. The model is a highly nonlinear system of partial differential equations that we investigate in computer simulations. Our results show that adding QQ at the beginning of treatment or before QS upregulation leaves the biofilms in an unprotected mode of growth. Moreover, our results suggest that periodic administration of antibiotics can remove bacteria if QS is prohibited by QQ whereas in a system without quorum quenching periodic treatment strategy is not efficient in the sense of removing biofilms.

SAMANEH GHOLAMI, Ryerson University
Simplifying Stochastic Discrete Models of Biochemical Networks

Recently, stochastic modelling and simulation of biochemical networks have been the subject of intense research.

Biochemical systems have critical practical applications, in particular to the study of key cellular processes.

In many cases, stochastic cellular dynamics is modelled using jump Markov processes,

whose probability distributions evolve according to the Chemical Master Equation.

These models of biochemical systems depend on a set of kinetic parameters, whose values are sometimes unknown or poorly estimated.

We propose a model reduction technique for the Chemical Master Equation, based on sensitivity analysis.

For sensitivity analysis we apply some existing finite-difference sensitivity estimators, such as the coupled finite-difference or the

coupled random number strategies. The new technique is successfully applied on some complex biochemical networks arising in applications..

The behaviour of the reduced system is in excellent agreement with that of the full system.

This is joint work with S. Ilie.

PRADEEP KUNWAR, Ryerson University
Formation of HIV-1 capsids based on an extended Becker-Döring Model by stochastic self-assembly

The HIV-1 virions include various components such as MA(matrix protein), CA (capsid proteins), NC (nucleocapsid proteins) and RNA (ribonucleic acid) during the period of maturation. The CA monomers play important role to form capsids. Before formation of capsid, CA monomers become the CA hexamers. About 1000-1500 CA monomers are needed to build a typical cone-shaped capsid [5]. The self-assembly of HIV-1 will be modeled here using an extended Becker-Döring model, and the mean first assembly time to form CA hexamers will be determined.

The Becker-Döring model is one of the most popular models to describe aggregation and detachment in the self assembly of molecules.

$$C_r + C_s \underset{k^-_{r+s}}{\overset{k^+_r}{\rightleftharpoons}} C_{r+s}$$

Here, C_r are the concentrations of a cluster of size r, where r can be referred to as aggregation number and, $r = 1, 2, 3...$. The r^{th} forward reaction rate constant is k^+_r, and k^-_{r+s} is the $(r+s)^{st}$ backward reaction rate constant. One of the limitations of the Becker-Döring model is that only monomers can attach or detach to a given cluster. The Becker-Döring model is extended here to include attachment and detachment of molecules of size two or more in a cluster(s=2,3,... in above equation), one at a time, with the help of a chemical master equation and stochastic approaches. The mean first assembly times of molecules of different sizes based on the extended Becker Döring Model will be determined stochastically.

SUZAN FARHANG SARDROODI, Ryerson university
Mathematical Model of Muscle wasting in cancer cachexia

Cancer cachexia is a severe condition, characterized by the irreversible loss of skeletal muscle and adipose tissues, that is estimated to affect more than 50-80The standard understanding of cachexia is based on nutritional arguments, and describes a disregulated cellular metabolism. As such, existing mathematical models focus on metabolic balances. However, a new appreciation is forming for cancer-derived signaling factors that circulate through the host and may disrupt tissue function and homeostasis. Here, we present a novel mathematical model to explore the role of systemic cancer signaling in the development of cachexia. The model describes stem-cell regulated muscle tissue using ordinary differential equations and feedback control. I will discuss our model parameterization strategy, and then present model predictions on potential effects of cancer-derived factors through numerical simulation and sensitivity analysis. We then use our combined modelling results to identify potential treatment options. As no known cure exists for cancer cachexia, it is hoped that uncovering cancer-derived systemic factors that disregulate tissue homeostasis, will lead to the development of new targeted therapies with the potential to impact quality of life for many cancer patients.

ADAM STINCHCOMBE, Math Dept, University of Toronto
Mathematical Modelling of Azacitidine Resistance in Myelodysplastic Syndrome Patients

Myelodysplastic syndrome (MDS) is a group of cancers in which blood cells do not fully mature. A standard chemotherapy for MDS is azacitidine, which has a poorly understood mechanism and many patients ultimately develop resistance to the drug. The dynamic interaction between MDS clones and the non-diseased hematopoietic stem cells, as well as multiple coupled feedback loops within the haematopoietic systems makes identifying the mechanism of disease progression, typically to leukemia, very difficult. We use a compartment model of the haematopoietic system, fit to each patient's blood test measurements using Kalman filtering, to understand disease progression and azacitidine's mechanism. We show how different natural histories of disease can be explained by changes in model parameters over time. This work is a collaboration with Roman Shapiro at the Dana-Farber Cancer Institute and is an excellent example of how clinical data can be used to understand a disease in-vivo.

NA YU, Ryerson University
Mathematical Modeling and Analysis of Dopaminergic Neurons

Midbrain dopaminergic (DA) neurons, the main source of dopamine, are slow intrinsic pacemakers. In response to diverse stimuli or pharmacological manipulations, they exhibit tonic firing, bursting or depolarization block. These activities are associated with human neurological disorders, for example, Parkinson's disease and schizophrenia. We present a mathematical model of DA neurons to uncover the ionic basis of the activities described above. Our model successfully reproduces experimental results. The bifurcation analysis is then applied to study its underlying dynamics.