

Special Session 43: Dynamical systems in Biology and Medicine

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Models of glucose/insulin regulation

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Simona Panunzi and Pasquale Palumbo

The recently published SDM model for the glucose/insulin system regulation during an Intra-Venous Glucose Tolerance Test will be presented and its performance will be compared to that of the Minimal Model. Conclusions will be drawn with respect to incorrect schemes of parameter estimation by decoupling, and the connection between physiological appropriateness, acceptable qualitative behavior of the solutions, and statistical robustness will be highlighted.

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Probiotic control of bacterial biofilms

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Traditionally probiotics have been used as functional foods, e.g. as health promoting agents in dairy products. More recently their potential as an alternative to antibiotics is being investigated. We present a model in which probiotic biofilm formers are used to control pathogenic biofilms. This model is based on a system of degenerate diffusion-reaction systems. The control mechanism itself is modification of environmental conditions, in particular lowering the pH and increasing the concentrations of growth limiting lactic acids.

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An Introductory Mathematical Model of Chronic Skin Inflammation

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Miranda Teboh-Ewungkem and Alison Wise

Chronic inflammation is a process where Dendritic Cells (DCs) are constantly sampling antigen in the skin and migrating to lymph nodes where they induce the activation and proliferation of T cells. The T cells then travel back to the skin where they release cytokines that induce/maintain the inflammatory condition. This process is cyclic and ongoing. In the case of chronic inflammation, we wish to interrupt DC migration using the viral chemokine binding protein. What insight can mathematics lend in order to solve this problem?

This talk presents work in progress based on a problem posed at a workshop on "The Application of Mathematics to Biomedical Problems" held at the School of Pharmacy, University of Otago, Dunedin, NZ. We gratefully acknowledge the support of the NSF, Grant No. 0737537.

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An Improved Optimistic Three-Stage Model for the Spread of HIV amongst Injecting Intravenous Drug-Users

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Wafa Al-Fwzan

This talk aims to show how mathematical models describing the spread of HIV/AIDS in a population of injecting drug users over time can be improved by including the assumption that infectious needles lose infectivity over time with per needle rate σ_i for $i=1,2,3$. We start with a short introduction. This is followed by the derivation of a model of a relatively optimistic scenario using addict-needle interaction assumptions. This assumes that a needle is always left in the infectious state of the last infected addict to use it. The model incorporates assumptions describing the spread of disease through the three stages of infectivity. We describe the results of an equilibrium and stability analysis on the model and obtain some global stability results. There is a threshold

parameter R_0 which determines the behaviour of the model. If $R_0 > 1$ then there is a unique endemic equilibrium which an approximation argument and later numerical results suggest is locally asymptotically stable. Otherwise if $R_0 \leq 1$ then system will tend to the unique equilibrium where the disease has died out. Finally we present some numerical simulations which confirm the results. We conclude with a brief discussion.

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Desynchronization of subthalamic bursting clusters and the application in Parkinson's disease

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High frequency deep brain stimulation (DBS) has been proven clinically effective to relieve motor symptoms for Parkinsonian patients. To investigate the mechanism underlying DBS, we study a network including the subthalamic nucleus (STN), the external segment of the globus pallidus (GPe), the internal segment of globus pallidus and the thalamic cortical (TC) neurons. Both the excitatory STN and inhibitory GPe neurons form synchronized bursting clusters. These synchronized clusters induce downstream GPi bursting activity that impairs the relay ability of TC neuron. We first consider DBS applied to STN with spatial distance between the stimulation site and the surrounding STN neurons. In this case, DBS replaces the GPi bursting pattern by tonic high frequency firing. Therefore, the TC relay fidelity is restored. More importantly, We show that TC relay ability can also be improved by applying various type of stimulation to break the synchrony within the STN cluster. Stimulations that can break the pathological synchronized bursting cluster within STN could be an alternative way to relieve motor symptoms in Parkinson's disease.

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Pattern Formation in Chemotaxis Models

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K. Painter

In this talk, I will discuss typical versions of chemotaxis PDE models. Some show finite time blow-up solutions, others have global solutions and show interesting pattern formation. I will focus on pattern formation. It turns out that most models show a typical dynamic of merging or merging and emerging of local maxima. A behavior, that is also known from physical models. The systematic analysis of these complicated patterns has just begun.

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On a nonlocal problem arising from phytoplankton blooms: incomplete mixing and competition for light

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Yihong Du

In this talk we present a mathematical model of n species competing for light under an environment of abundant nutrients. The model takes the form of parabolic partial differential equations with nonlocal terms. First we present a complete result of steady state problem for the case of one species. Then we consider the case of the system of parabolic PDEs for two species competing for light. We obtain a partial results of extinction when diffusion coefficients are equal.

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Modelling the dynamic response of oxygen uptake to exercise

Alex James

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Bi-phasal oxygen uptake responses to exercise have been seen in clinical trials. Here we use a simple model based on muscle motor units to give a possible explanation of the mechanisms that may cause this response.

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Qualitatively Stable Numerical Methods for Autonomous Dynamical Systems in Ecology

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Dobromir T. Dimitrov

A new class of one-step nonstandard finite difference (NSFD) methods is developed for first-order ordinary differential equations. The proposed numerical techniques are based on a nonlocal modeling of the right-hand side function and a nonstandard discretization of the time-derivative. This approach leads to significant qualitative improvements in the behavior of the numerical solution. For multi-dimensional autonomous dynamical systems, positive and elementary-stable NSFD methods are formulated and analyzed, based on an extension of the nonstandard discretization rules. Applications of the NSFD methods to specific biological systems are also presented.

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Saturation in predation and predation-transmitted infections

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Many predators are opportunistic feeders who prefer one type of prey when it is available but can eat other things when the prey is scarce. We therefore consider a per-predator predation rate which is roughly linear for small prey densities but saturates for large prey densities, and show that sufficiently sharp (e.g., piecewise linear) saturation can cause a bistable state with two locally stable prey densities. For diseases transmitted through predation, this generates two different values for the basic reproductive number, which may fall on different sides of unity, in which case a momentary discontinuity in population size can enable or prevent the persistence of the infection in both populations. We consider a spectrum of saturation functions from Holling Type II (Verhulst) to piecewise linear, in order to establish a sharpness threshold.

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Pharmacokinetical models of subcutaneous injection of insulin analogues for type 1 diabetes

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Yang Kuang

Subcutaneous injection of exogenous insulin or insulin analogues needs to be performed one or more times daily for type 1 diabetics. The timing and dosage of insulin administration have been a critical

research area since the invention of insulin analogues. In this talk, we present two systematic and simplified models to model the subcutaneous injection of rapid-acting insulin analogues and long-acting insulin analogues. We analyze the dynamics of the plasma insulin concentrations and show the numerical simulations that demonstrate the agreement with experimental data and improvement over the existing models.

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Biochemical, ecological, and dynamical origins of Redfield ratio N:P=16 in oceans

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Among the largest patterns in the biosphere is nitrogen to phosphorus ratio, N:P=16 by atoms found throughout deep ocean; though N:P of individual phytoplankton species can range from 6 to 60, the average N:P of phytoplankton is also 16. Discovered empirically by Redfield over 70 years ago, this pattern is central to carbon sequestration models and marine biogeochemical cycling. However, the rationale behind N:P=16 is not known. Here, we derive N:P=16 by linking cellular processes with competition among phytoplankton species and upwelling of nutrients. First, we show that N:P=16 arises from five fundamental molecular constants: N in amino acids, N and P in nucleotides, and maximal translation and transcription rates; it corresponds to biochemically optimal RNA:Protein ratio. Next, we integrate this biochemical optimum into our dynamic competition model that shows how N:P=16 establishes itself on a community level. The necessary condition for this to happen is a long residence time of nutrients in deep ocean and upwelling. Our work shows that N:P=16 originates on a molecular scale, but evolutionary forcing and positive feedback of upwelling propagate the pattern to the global scale.

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Modeling glycemic change in individuals who develop type 2 diabetes

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Yang Kuang and Robert L. Hanson

The prevalence of type 2 diabetes continues to increase worldwide with related increases in obesity levels. The interrelationship of these maladies has been shown, though direct modeling attempts to correlate them have been limited. Recent modeling work has shown rapid changes in an individual's glucose levels as diabetes ensues over a relatively short time frame. Yet rapid changes in other metabolic variables (insulin, body mass index, etc.) over the same time-frame are lacking. Whether the cause of rapid glucose increase is due to a threshold effect of these variables or to a direct relationship with some unmeasured factor is currently unknown. Modeling efforts to investigate the causal pathway are presented. Studies which may elucidate the pathogenesis are also proposed.

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Natural selection on cell ATP allocation may constrain evolutionary suicide in cancer

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John D. Nagy and Kelley Thompson

Many types of malignant tumors are characterized by regions of necrosis, and some—for example, neuroblastoma—occasionally regress spontaneously. Recent theoretical studies of dynamical models of cancer have spawned a unique hypothesis that may explain at least some necrosis and spontaneous regression as an ecological collapse initiated by a hypertumor. In essence, a hypertumor arises from evolutionary suicide. In an established tumor, an aggressively proliferative mutant cell strain arises that is favored by natural selection because of its reproductive potential. If that strain also damages the tumor's ecological infrastructure—by failing to secrete angiogenesis factors or depleting the local environment of a critical nutrient, for example—selection for the aggressive strain may paradoxically damage the entire tumor. Here we present work in progress on an extension of an earlier model in which hypertumors were first suggested. This model adds smaller scale considerations to the simple system of ordinary differential equations originally used. In particular, we now model ATP production and allocation among cellular tasks, including TAF secretion, proliferation and other energetically needy physiological functions, which creates a tradeoff among growth potential, angiogenesis factor secretion and survivability. This tradeoff constrains the conditions under which selec-

tion can favor hypertumor development.

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Multi-strain virus dynamics with mutations: A global analysis

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B | 3 0 J We consider within-host virus models with $n \geq 2$ strains and allow mutation between the strains. If there is no mutation, a Lyapunov function establishes global stability of the steady state corresponding to the fittest strain. For small perturbations, this steady state persists, perhaps with small concentrations of some or all other strains, depending on the connectivity of the graph describing all possible mutations. Moreover, using a global perturbation result, we show that this steady state also preserves global stability.

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Predicting the Release Kinetics of Matrix Tablets

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Many drugs are most effective when the concentration at the site of action is kept between specific thresholds, but it is not practical to administer the drug continuously. Thus there is a need to produce delivery mechanisms that ensure a particular release profile of the drug over time. One such mechanism uses compression and heating to create a tablet consisting of the drug in powder form, a polymer and other substances. Once ingested, the fused polymers create a porous medium through which the dissolved drug particles must diffuse. In this talk we will describe a mathematical model whose goal is to understand the relationship between the porosity of the medium, which can be controlled by the heating temperature and the concentration of polymer, and the release profile. The mathematical model uses random sphere packing and the distribution of first passage times of random walks on weighted graphs.

Results from the preliminary model will be compared to data from actual tablets, and model refinements will be discussed briefly.

This talk presents work in progress based on a problem posed at a workshop on "The Application of Mathematics to Biomedical Problems" held at the School of Pharmacy, University of Otago, Dunedin, NZ. The problem was proposed by Ian Tucker and Thomas Rades of the School of Pharmacy. Members of the working group also included: Mousab Arafat, U. of Otago; Boris Baumer, U. of Otago; Chris DuBois, UC Irvine, USA; Bram Evans, U. of Otago; Peter Hinow, U. of Minnesota, USA; Ami Radunskaya, Pomona College, USA; Emma Spiro, Pomona College, USA. We gratefully acknowledge the support of the NSF, Grant No. 0737537.

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Delivery of Growth Factors to Wounds

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see abstract

An open wound represents a loss of the main barrier to drug absorption and thus provides the opportunity for direct application of therapeutic agents such as growth factors to assist wound healing. The aim is to release the growth factor into the wound slowly over extended periods to elevate the free fraction of growth factors (e.g., FGF-2, fibroblast growth factor 2) within the wound. In this talk a preliminary mathematical model for the tissue concentration of growth factors under topical delivery is presented. It is hoped that the model can be used to determine optimal dosage and duration of release for topical FGF-2.

This talk presents recent results of a workshop "Application of Mathematics to Biomedical Problems" held at the University of Otago in Dunedin, New Zealand, to the problem of drug penetration in wounds. The problem was proposed by Natalie Medicott of the School of Pharmacy at the University of Otago and the following members participated in this group of the workshop: Natalie Medicott, University of Otago, New Zealand; Graeme Wake, Massey University, New Zealand; Andrzej Swierniak, Silesian University of Technology, Poland; Michal Swierniak, Memorial Cancer Centre, Poland; Yang Kuang, Arizona State University, USA; Dann Mallett, University of Queensland, Australia; Emma Spiro, Pomona College, USA; Urszula Ledzewicz of

Southern Illinois University, USA and Heinz Schaettler of Washington University, USA.

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Species decline and extinction: synergy of infectious disease and Allee effect?

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Host-parasite models with density-dependent (mass action) incidence and a critical Allee effect in host growth can explain both species decline and disappearance (extinction). The behavior of the model is consistent with both the novel pathogen hypothesis and the endemic pathogen hypothesis for chytridiomycosis. Mathematically, the transition from decline to disappearance is mediated by a Hopf bifurcation and is marked by the occurrence of a heteroclinic orbit. The Hopf bifurcation is supercritical if intraspecific host competition is strong and subcritical if it is weak. In the supercritical case, host-parasite coexistence can be at equilibrium or periodic; in the subcritical case it is only at equilibrium.

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Germline stem cell competition

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In the ovarian niche of drosophila, there are two to three germline stem cells. They compete each other for occupancy. The experiment data show cadherin serve as a signal molecule to play an important role in this process. We use mathematical model to study the competition within the niche and the maintenance of the niche.

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Modelling the Interaction of Cytotoxic T Lymphocytes and Epithelial Cells in Influenza

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The aim of this work is to investigate the mechanisms involved in the clearance of viral infection of the influenza virus at the epithelium level by modeling and analyzing the interaction of the influenza virus-specific cytotoxic T Lymphocytes (CTL cells, T-cells) and the epithelial cells. Since detailed and definite mechanisms that trigger T-cell production and death are still controversial, we formulate different models for the T-cell response to influenza infection for three plausible scenarios. We present a systematic analysis of these model systems and we compare their dynamics.

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A Reservoir Mediated Infectious Disease Model with Threshold

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Human pathogens are prevalent virtually everywhere, but people do not become infected by contacting few pathogens. Frequently, the number of pathogens which one ingests or contacts must be above a critical threshold to cause infection in susceptible individuals, and this infection dose is a consequence of body's immune response. A disease, such as cholera, is transmitted when a susceptible individual ingests water containing pathogenic bacteria. The infected individuals transmit indirectly by shedding bacteria back into the aquatic reservoir and transmittability increases for higher bacteria density in the reservoir. Assuming a fixed daily intake of water, susceptible individuals can become infected if the pathogen density they encounter in the aquatic reservoir is sufficiently high. Therefore, it is pivotal to understand the interaction between infected individuals and pathogens in the reservoir as well as the threshold density for infection. In this manuscript, we introduce and analyze a family of reservoir mediated SIR models with a threshold pathogen density for infection, which represents the effect of human immune system. An epidemic can result from the introduction of infected individuals or the density fluctuation of pathogens in the reservoir. We devise two new measures of how close such a disease is to becoming an epidemic or endemic: the minimum ratio of infected individuals and the minimum fluctuation of pathogen density to induce an epidemic. Our model predicts that in the case of waterborne diseases, suppressing the pathogen or parasite density in aquatic reservoirs may be more effective than minimizing the number

of infected individuals.

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A mathematical model for calcium regulation in yeast cells

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Francisco Solis and Pamela Marshall

In eukaryotic cells, one of the functions of calcium is to serve as an intracellular messenger in response to extracellular factors. We present a model for the regulation of cytosolic calcium concentration (calcium homeostasis) in yeast cells. The model considers sequestration into the endoplasmic reticulum and vacuole as the regulatory mechanisms. We study the equilibration of internal calcium concentration after an external concentration change and discuss the stability of the final equilibrium state.

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On the role of schistosome mating structure in the maintenance of drug resistant strains

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The effects of drug treatment of human hosts upon a population of schistosome parasites depend upon a variety of factors. Previous models have shown that multiple strains of drug-resistant parasites are likely to be favored as the treatment rate increases. However, such models have neglected to account for the complex nature of schistosome mating biology. To more accurately account for the biology of these parasites, a simple mating structure is included in a multi-strain schistosome model, with parasites under the influence of drug treatment of their human hosts. Parasites are assumed to pay a cost for drug resistance in terms of reduced reproduction and transmission. The dynamics of the parasite population are described by system of homogeneous differential equations with and without time delays, and the existence and stability of the exponential solutions for the systems are used to infer the impact of drug treatment on the maintenance of schistosome genetic diversity.

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