Mathematics: Source of New Solutions to Old Problems in Pharmaceutical Research and Therapy
Mathématiques: source de nouvelles solutions à de vieux problèmes en recherche pharmaceutique et en pharma
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JACQUES BÉLAIR, Université de Montréal
Circadian variability in a two-compartment pharmacokinetic model

Circadian variability of a number of physiological parameters is well documented. Attempts have been made to incorporate these fluctuations into one-compartment pharmacokinetic models, but some of the fundamental parameters, notably C_{max}, were shown to remain constant. We introduce a bi-compartmental, time-varying model to represent responses to intravenous and oral drug administration. The effects of the parameters representing circadian changes on a single dose, and on multiple doses, are investigated, and are found to potentially, but not systematically, induce significant changes in C_{max}.

Joint work with Florence Véronneau-Veilleux.

TONI BOURAMA, Virginia State University

MORGAN CRAIG, Université de Montréal
Physiological modelling of neutrophil development guides regimen optimisation during chemotherapy

Chemotherapeutic regimens are toxicity-limited due to the uncontrolled anti-mitotic effects on healthy cells, including the blood cells. Acute neutropenia, brought on by the destruction of neutrophils by chemotherapy, necessitates future lower doses and/or complete cessation of the protocol until the absolute neutrophil count (ANC) returns to acceptable levels. To counteract declining ANCs, granulocyte colony-stimulating factor (G-CSF) is administered following chemotherapeutic agents to recover neutrophils by stimulating their differentiation from the hematopoietic stem cells (HSCs), their proliferation, and the speed of their maturation. Through mathematical modelling and analysis, several authors have proposed dose-adaptation regimens for the concurrent administration of chemotherapeutic agents and G-CSF. In this talk, I will discuss a completely physiological model for granulopoiesis which is used to study the concomittant administration of Zalypsis and G-CSF and the optimisation of chemotherapeutic regimens resulting from our work. Further, I will demonstrate how this DDE model, derived from an age-structured PDE model with variable aging rate, also serves as the basis of the refinement of the pharmacokinetic model of G-CSF.

HERMANN EBERL, Univ. Guelph
compuGUT

The compuGUT is a mathematical modeling framework and computer simulation platform for transport processes, anaerobic digestion, and microbial population and resource dynamics in the human colon that we have developed as an in silico tool for studies in gut health. While the model had its origin in the field of food and nutrition, it should also be applicable in health and pharmacological research (e.g. in the the context of PBPK). In this talk we will give an overview of the model and show simple examples how it could be used to study the effects of antibiotics on gut ecology (e.g. supported by probiotics), or in bacteriotherapy. The compuGUT modeling framework is based on the IWA Anaerobic Digestion Model No. 1, adapted to the biological conditions in the colon, spatially extended by accounting for transport along the main flow direction in the lumen, ecologically extended by allowing for multiple representation of functional groups of microorganisms in lumen and mucus. The resulting model is a system of first order partial differential equations that are coupled through the reaction terms. The number of equations is context dependent. In its basic form it consists of 28, if a more complex microbiological description is desired the number of equations can go into the hundreds. This flexibility of the modeling framework poses considerable challenges for the

computer implementation, which are addressed in the compuGUT software development (http://compugut.sourceforge.net). This is joint work with Arun Moorthy (Guelph), Martin Kalmokoff (AAFC), Steve Brooks (HC).

JANE HEFFERNAN, York University
HPV: vaccination, screening and treatment

HPV is a common sexually transmitted infection found worldwide which can lead to serious health effects. While HPV has a high regression rate, if it does progress, it can cause various cancers (i.e. cervical, penile, throat). It is possible to minimize the mal-effects of HPV with tools such as screening, vaccination and treatment. We have developed a series of mathematical models of HPV screening, vaccination and treatment. These include examining the outcomes of screening vs. vaccination programs, comparing different screening programs, as well as, studying the concept of infection vs. re-infection with HPV.

XI HUO, Ryerson University and York University
The evolutionary ecology of antimicrobial de-escalation

We model the transmission of P. aeruginosa in intensive care units (ICUs) with de-escalation as the major antibiotic treatment strategy. That is, empirical therapy is initiated when a patient is infected with P. aeruginosa, right after the laboratory test results become available, the definitive therapy will be de-escalated - the broad-spectrum antibiotic for empirical therapy is switched to a narrow-spectrum antibiotic if possible. De-escalation is a treatment strategy that have been applied widely in ICUs, with the aim of reducing the risk of super-infection and preserve the efficacy of broad spectrum drugs. It has been considered as a potential way of reducing antibiotic use and antimicrobial resistance in ICUs.

This is a project from the Development of an Antimicrobial Resistance Diversity Index (ARDI) led by Prof. Jianhong Wu.

JUN LI, Université de Montréal
Influence of mathematical model structure on the estimation of phamacokinetic parameters : the example of Vdss

The steady-state volume of distribution (Vdss) is an important pharmacokinetic (PK) parameter that is used to estimate the drug efficacy and toxicity. However, non-compartmental analysis (NCA), based on mammillary models with central linear elimination, is still at the heart of the primary method to estimate this parameter.

However, the suitability of this NCA approach is questioned for complex drug eliminations, as it is the case for simultaneous first-order and Michaelis-Menten eliminations.

In this talk I will discuss two indistinguishable PK models having a structure of two compartments and different elimination pathways.

As results I will show the corresponding exact model based expressions of Vdss directly derived from its physiological definition and discuss their relationship to the NCA counterparts. As proof of concept, the important difference will be shown on various real drug models.

Moreover, considering the issue of model identifiability, the evaluation of Vdss will be discussed.

This is a joint work with X.T. Wu and F. Nekka

MARTIN LYSY, University of Waterloo
Bayesian Inference for Stochastic PK/PD Models

Differential equations (DEs) occupy a central role in the modeling of many pharmacokinetic and pharmacodynamic (PK/PD) processes. To estimate the parameters of these equations from empirical data, a statistical approach might augment the deterministic DE with a stochastic simulation model, and attempt to solve the corresponding inverse problem. We present a Bayesian methodology and its software implementation for PK/PD parameter inference, accounting for three sources of stochastic variability: (1) instrumental measurement error, (2) within-subject process fluctuations, and (3) between-subject

random effects. Through numerical experiments with a small-sample PK study, we explore the effect of increased model complexity on the bias-variance trade-off.

Joint work with Joel Dubin and Kamal Rai, University of Waterloo.

COLIN PHIPPS, University of Waterloo
Parameter identifiability and sensitivity in large molecule PBPK models

One of the primary utilities of physiologically-based pharmacokinetic (PBPK) models is to perform interspecies (e.g. human from animal), or intraspecies (e.g. child from adult) prediction. In many cases the model prediction task is estimating an output of interest, such as the area under the curve (AUC) or the maximum concentration (Cmax), in a specific model compartment or organ (e.g. blood, brain, liver). Ensuring accurate prediction of these outputs in populations where little to no data exists, as is the case in pediatrics or in certain disease states (e.g. renally-impaired), is imperative. During this talk, I will outline a workflow for identifying potential issues that can be encountered during PBPK model prediction using the example of a large molecule model. Unlike the perfusion-limited and permeability-limited frameworks that have been established for small molecules, there remain a number of issues that pervade large molecule models. Once the differential equation system has been mechanistically established there are various parameters related to this process that vary in each organ (e.g. transvascular fluid flow and lymphatic uptake rates) and depend on molecular properties (e.g. vascular and lymphatic reflection coefficients). Estimating these parameters from existing data is challenging due to parameter sensitivity and identifiability issues. If a relatively uncertain model parameter is not identifiable then confidence in the model could be weakened. In this case we will evaluate whether various outputs of interest for the pediatric model are sensitive to non-identifiable parameters in the adult model. If so, model reformulation or further experimentation may be required.

JIANHONG WU, York
Modelling insights for new thearpy issues in emerging infection outbreaks

I will present some recent work, in collaboration with Xi Huo, Xiaodan Sun and Kunquan Lan, on modelling and simulating treatment-donation-stockpile dynamics in Ebola convalescent blood transfusion therapy.