

Jacques Cartier workshop, Health and Complex Systems,
november 30 and december 1st 2009,
campus de la Doua, Villeurbanne, France.

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Tuesday december 1st, 2:40

Metapopulation models of infectious diseases

The world is increasingly inter-connected. Merchandises and livestock are constantly transported across countries, continents and oceans. Human beings travel, for work and leisure, more and more and over greater distances. They also are involved in relocations because of economic or political circumstances. In addition to these human-induced movements, there are naturally occurring movements such as animal migrations. All of this implies that the opportunities for an infectious pathogen affecting animals and/or humans to become spatially mobile are multiplying, as was emphasized by the 2003 SARS epidemic and the current A/H1N1 influenza pandemic. Metapopulation models, i.e., models of populations of populations, provide a good tool with which to consider some of these spatial spread problems. I will discuss metapopulations for the description of infectious disease propagation, and will illustrate with a real world application, the Bio. Diaspora Project, which studies the global air transportation network and its link with emerging or re-emerging infections.

Samuel Bernard

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Monday november 30, 10:40

L'âge de nos cellules par essais nucléaires

Certains organes et tissus chez l'humain ont une capacité de régénération limitée, ce qui peut provoquer des maladies chroniques ou liée aux vieillissement. En collaboration avec l'Institut Karolinska, nous appliquons des modèles de prolifération cellulaire pour déterminer, à partir d'une technique de datation au carbone-14, l'âge de nos cellules. Une grande quantité de carbone-14 a été relâchée dans l'atmosphère lors des tests nucléaires de surface dans les années 1950 et 1960. L'intégration du carbone-14 dans l'ADN des cellules en division permet de dater leur naissance de façon très précise. Nous avons déjà appliqué cette méthode avec succès aux cellules du gras, les adipocytes, pour montrer que celles-ci se renouvellent à hauteur de 10% par année, ce qui ouvre la porte à de nouvelles cibles thérapeutiques contre l'obésité.

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Modélisation biophysique de la dynamique des prions infectieux. Application à l'optimisation de protocole experimental

On s'intéresse au modèle proposé par Masel et al., puis développé par Greer et al. dans un cadre continu, et dont le but est de décrire les processus biophysiques d'agrégation de prions infectieux. Au vu de certains résultats récents concernant la distribution en taille des agrégats in vivo, il semble essentiel d'intégrer dans le modèle des paramètres cinétiques dépendant de la taille des oligomères, ce qui rend l'analyse plus complexe. Nous présenterons au cours de cet exposé quelques résultats théoriques et numériques liés à l'optimisation de la croissance d'une population d'agrégats. Ces résultats préliminaires s'inscrivent dans la perspective d'une optimisation de protocole pour l'amplification du prion in vitro (PMCA).

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Mathematical models of diabetes treatment**Philippe Cinquin**

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Augmented Medical Interventions

Augmented Medical Interventions (AIM) propose to use the wealth of multi-modal medical images to help physicians and surgeons quantitatively simulate and plan complex medical and surgical interventions, and to offer them tools for safe and accurate performance of the optimal strategy (these tools include passive- navigational- or active- robotics- aids). This implies facing scientific and technical challenges in various domains (applied mathematics, computer vision, image processing, robotics, ...). We will first overview the major results obtained since this domain was launched more than 20 years ago, together with the remaining challenges. We will then concentrate on the potentialities that are offered

in this domain by the increasing performance of miniaturised sensors and actuators, based on instances of several “body mounted robots”. The notion of Augmented Medical Interventions puts forward medical Quality, with the first challenge of consensually and quantitatively defining this notion. In order to augment medical Quality, the expert’s knowledge and action have to be modelled, providing the basis on which tools improving the efficiency/morbidity ratio of the intervention can be developed. The targeted augmentation is first medical (medical added value) and secondarily technical (methods and tools for assisting planning and performing the intervention or the substitution to the failing function).

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Modélisation mathématique de la prolifération cellulaire et de son contrôle circadien : défis en chronothérapeutique des cancers

Après avoir pointé quelques questions, et des défis mathématiques possibles, soulevés à partir de faits d’observation en biologie et en chronothérapeutique des cancers, liés aux horloges circadiennes, je présenterai quelques modèles mathématiques à base physiologique conçus pour contribuer à optimiser des traitements anticancéreux multicibles et multimédicaments. Ces méthodes se déclinent en :

- a) une modélisation par équations aux dérivées partielles (EDP) structurées en âge pour représenter l’évolution dans le cycle de division de populations cellulaires proliférantes, saines ou tumorales, ainsi que le contrôle de cette évolution par les horloges circadiennes et les médicaments anticancéreux ;
- b) une modélisation par équations différentielles ordinaires (EDO) de la cinétique et du métabolisme des médicaments, non seulement au niveau sanguin et hépatique, mais aussi au niveau intracellulaire, en prenant en compte le contrôle circadien des mécanismes de traitement des médicaments, le polymorphisme génétique enzymatique, les effets toxiques indésirables sur les cellules saines, et l’apparition possible de résistances aux traitements ;
- c) Des algorithmes d’optimisation visant à trouver les meilleurs profils temporels de débit de perfusion, conduisant à maximiser le nombre de cellules tumorales éliminées, sous des contraintes qui peuvent être circadiennes, mais aussi dépendant du sujet, telles que la tolérance au traitement, dépendant de l’état général du patient, le polymorphisme génétique du métabolisme des médicaments et des enzymes de réparation de l’ADN lésé, et l’expression des transporteurs ABC.

Enfin, je passerai en revue un certain nombre de défis et de questions complémentaires à l’adresse des mathématiciens, des biologistes et des médecins, provenant d’observations sur la croissance tumorale et la thérapeutique anticancéreuse.

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Modelling CD8 T-cell Immune Response

The primary CD8 T-cell immune response due to a first encounter with a pathogen is characterized by a fast increase of the number of T-cells (cellular expansion), followed by a contraction phase. This results in the generation of memory CD8 T-cells, specific of the antigen and able to recognize it on a second encounter. We will discuss modelling of this primary response, and in particular the roles and relevance of feedback controls that could regulate this response. The resulting model will be confronted to experimental data on mice.

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Physiologically Based Predictions of the Impact of Inhibition of Intestinal and Hepatic Metabolism on Human Pharmacokinetics of CYP3A Substrates

The early identification and delineation of the pharmacokinetic and clinical consequences of drug interactions is major aspect in drug development. The first objective of the present study was to predict the pharmacokinetics of selected CYP3A substrates administered at a single oral dose to human. The second objective was to predict pharmacokinetics of the selected drugs in presence of inhibitors of the intestinal and/or hepatic CYP3A activity. We developed a whole-body physiologically-based pharmacokinetics (WB-PBPK) model accounting for presystemic elimination of midazolam (MDZ), alprazolam (APZ), triazolam (TRZ), and simvastatin (SMV). The model also accounted for concomitant administration of the above-mentioned drugs with CYP3A inhibitors, namely ketoconazole (KTZ), itraconazole (ITZ), diltiazem (DTZ), saquinavir (SQV), and a furanocoumarin contained in grape-fruit juice (GFJ), namely 6',7'-dihydroxybergamottin (DHB). Model predictions were compared to published clinical data. An uncertainty analysis was performed to account for the variability and uncertainty of model parameters when predicting the model outcomes. We also briefly report on the results of our efforts to develop a global sensitivity analysis and its application to the current WB-PBPK model. Considering the current criterion for a successful prediction, judged satisfied once the clinical data are captured within the 5th and 95th percentiles of the predicted concentration-time profiles, a successful prediction has been obtained for a single oral administration of MDZ and SMV. For APZ and TRZ, however, a slight deviation toward the 95th percentile was observed especially for C_{max} but, overall, the in vivo profiles were well captured by the PBPK model. Moreover, the impact of DHB-mediated inhibition on the extent of intestinal presystemic elimination of MDZ and SMV has been accurately predicted by the proposed PBPK model. For concomitant administrations of MDZ and ITZ, APZ and KTZ, as well as SMV and DTZ, the in vivo concentration-time profiles were accurately captured by the

model. A slight deviation was observed for SMV when co-administered with ITZ, whereas more important deviations have been obtained between the model predictions and in vivo concentration-time profiles of MDZ co-administered with SQV. The same observation was made for TRZ when administered with KTZ. Most of the pharmacokinetic parameters predicted by the PBPK model were successfully predicted within a two-fold error range either in the absence or presence of metabolism-based inhibition. Overall, the present study demonstrated the ability of the PBPK model to predict DDI of CYP3A substrates with promising accuracy.

Vincent Lemaire

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Modeling and simulation to optimize drug disposition of controlled release forms

Ideally, vectors for drug administration should induce rapid rise of drug concentration in blood to an optimal target level and they should be able to maintain this target concentration for the duration of the treatment with minimal fluctuations. Conventional oral administration vectors, such as immediate release tablets, generally produce large concentration fluctuations. These fluctuations generate an unpleasant up and down efficacy pattern and are often the cause of unwanted adverse effects. Controlled release forms offer a way to achieve sustained concentration for a certain period of time. However, releasing the drug at a constant rate is not sufficient to guarantee a steady concentration of drug. The general question we address is to determine the rate of release of a drug from a controlled release device leading to a particular blood concentration profile. It is mainly an optimization problem, but it also relies on the ability to develop an accurate model of the pharmacokinetics of the drug. We present the general methodology that was developed to tackle this problem, as well as the pit falls and challenges we have to deal with, for example the data integration problem and the in vitro / in vivo translational issues. We also present examples of application to illustrate how the use of modeling and simulation methods helps us to design better and safer drug products.

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Do dynamics of the prion protein polymerization explain the infection? Are there possibilities that another protein becomes infectious?

The emergence of new infectious diseases has struck the industrial societies that believed they have dismissed this scourge of the past. The emergent pathogens are generally viruses, bacteria or eukaryotic parasites, but the epidemic BSE has put into the light a new kind of infectious pathogen called prion. Today, human prion diseases (CJD, GS, nvCJD,

FFI) as well as animal prion diseases (Scrapies, BSE, CWD) are well contained but not entirely under control, because these diseases are still poorly understood. Most scientists in the field agree that these infectious diseases are due to the formation of amyloid by the prion protein according to the model of P. Lansbury. However, numerous proteins that form amyloids are not infectious and most of the amyloids build with recombinant prion protein are also not infectious, but the reasons why only some amyloids are infectious are presently unknown. Besides, recent results clearly demonstrate that some non-infectious proteins produce amyloids that can behave as infectious under experimental laboratory conditions. This is true for A- β peptide (of Alzheimer) or the serum-amyloid-A (SAA) protein. Moreover, certain conditions favor amyloid formation from proteins that normally do not behave this way, for instance interaction with mica or over expression. These observations ask the question: Can new infectious agents of prion type emerge from new industrial, medical, pharmaceutical or agricultural practices? To answer this question it is necessary to identify the conditions that lead a protein to infectious amyloids. To fulfill these objectives, we have developed a collaboration between mathematicians and biologists to understand the dynamics of prion protein polymerization and to find out what characteristics of polymerization would explain infectivity.

Michael Mackey

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G-CSF therapy in cyclical neutropenia and following chemotherapy: Insight from mathematical models of the hematopoietic system

In this talk I will discuss the use of a comprehensive mathematical model for the regulation of mammalian hematopoiesis in tailoring the G-CSF treatment of patients with cyclical neutropenia, and recent work investigating the effects of different patterns of G-CSF administration to alleviate the deleterious effects of chemotherapy.

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A Model of Antibiotic Resistant Bacterial Epidemics in Hospitals

The development of drug-resistant strains of bacteria is an increasing threat to society, especially in hospital settings. Many antibiotics that were formerly effective in combating bacterial infections in hospital patients are no longer effective due to the evolution of resistant strains. The evolution of these resistant strains compromises medical care worldwide. In presentation, we will formulate a two-level population model to quantify

key elements in nosocomial infections. We will first discuss the evolution of the resistant strain at the level of one patient, and we will discuss the multi-drug resistant problem. Then we will turn to the epidemic problem at the level of one hospital. We will consider the population of patient and the population of healthcare workers. We will conclude the presentation with some practical consequences of the analysis of the models.

John Milton

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Stabilizing human balance using low–amplitude, low frequency vibrations

Humans are continuously exposed to vibration both in their living and work space. Here we show that vibration has a stabilizing effect in two paradigms of human balance control: stick balancing at the fingertip while standing on a periodically vibrating platform and postural sway while the Achilles tendon is vibrated. Surprisingly the critical parameter for the stabilizing balance is the peak-to-peak amplitude of the vibrations. These observations can be explained by a simple “drift and act” mechanism in which controlling movements are made only when the vertical displacement angle exceeds a threshold. In particular it is suggested that the stabilized upright position does not represent equilibrium, but rather a more complex and bounded time-dependent behavior such as a limit cycle. Periodic forcing results in a behavior with a smaller peak to peak amplitude; stabilization occurs once the amplitude becomes lower than the threshold. The fact that the amplitude of the vibrations is important for stabilizing balance suggests falls may not always be simply related to “slips and trips”, but may be encouraged by modern day society’s efforts to filter out the effects of surface–induced vibrations through shoe and walking surface design. Thus it may be possible to reduce the risk of falling in the elderly by making appropriate changes in walking shoes and surfaces.

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Modeling the architecture and dynamics of hematopoiesis

Hematopoiesis is a multistep process that results in the production of a variety of blood cells with different morphologies and diverse functions. All of these cells have their origin in hematopoietic stem cells (HSC) that replicate slowly to self-renew and give rise to progeny cells that proceed along the path of differentiation. The process is complex with the cells responding to a wide variety of cytokines and growth factors. We discuss a model of hematopoiesis based on stochastic cell behavior. Multiple compartments are introduced to keep track of each cell division process and increasing differentiation. Despite its

simplicity, the model is able to account for the salient features of hematopoiesis and is compatible with considerable and independent experimental data. The model is applicable to hematopoiesis across mammals and can be used to understand the dynamics of various disorders both in humans and in animal models.

Sandy Pang

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Physiologically-based pharmacokinetic modeling for drug and metabolite kinetics

Physiologically-based pharmacokinetic (PBPK) models relate to the mass transfer of drugs within organs and tissues of discrete physiologic volumes, and the well-mixed organs are in turn connected by flow. Such a strategy is shown to be successful in the prediction of drug levels in target tissues, for the scale-up from animals to man, and in risk assessment of environmental chemicals. Recently, the involvement of enzymes and transporters for elimination (metabolism and excretion) and transport have been included to describe the kinetics of the drug and metabolite with the liver, intestine, and kidney in PBPK modeling. Analytical solutions on the areas under the curve (AUCs) of the metabolites and extraction ratios, based on PBPK modeling showed that the AUC of the preformed, administered metabolite was only dependent of metabolite parameters, whereas the AUC of the formed metabolite was modulated additionally by the metabolic, secretory and intestinal absorptive intrinsic clearance of the precursor drug. The AUCs of formed and preformed metabolites derived from these theoretical examinations showed differences in their extraction ratios within eliminating organs. Recent PBPK model development that incorporated renal excretion of drug and metabolite, and the metabolism of drug by the intestine or liver to multiple metabolites, revealed useful area ratios for drug and metabolite after oral and intravenous drug administration that are useful in bioavailability estimations. Furthermore, these relations are extremely useful in understanding the mechanism of drug-drug interactions.

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Contribution to a mathematical analysis of prion proliferation

How do the normal prion protein Pr^{PC} and infectious prion protein Pr^{PSc} populations interact in an infected host? To answer this question, we analyze the behavior of the two populations by studying a system of differential equations. The system is constructed under the assumption that Pr^{PSc} proliferates using the mechanism of nucleated polymer-

ization. We prove that with parameter input consistent with experimentally determined values, we obtain the persistence of PrPSc. We also prove local and global stability results for steady states. We also give numerical simulations, which are confirmed by experimental data. We show the link between this theoretical work and some epidemics theory for SEIS and HIV models. Finally, a close collaboration with biologists will be pointed out through several experiments and new theoretical approaches.

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Methods and Theories of Model Identification and Parameter Estimation for Complex Nonlinear Dynamic Systems in Infectious Disease Research

Nonlinear dynamic models or differential equation (DE) models are widely used to quantitatively study complex systems in many scientific fields. These models now receive substantial attention from mathematicians who apply complex and nonlinear DE models to modeling biological processes, in particular infectious diseases. Over the past two decades, nonlinear dynamic models, in particular nonlinear differential equation models, have emerged as essential tools to describe and quantify interactions between virions, proteins, cells, organs and individual persons, and thus have significantly advanced our understanding of pathogenesis and epidemiology of important infectious diseases. In this talk, I will present our recent development of identifiability analysis theories and methodologies for nonlinear dynamic systems, including structural, practical and sensitivity-based identifiability analysis tools. Our approach incorporates both biological understanding and available information such that mechanism models, biological knowledge and experimental data can be appropriately interpreted, represented, and supported. Secondly, I'll present novel statistical estimation methods and theories for unknown parameters in complex dynamic models with sophisticated structures (including time-varying parameters). Data from an influenza research will be used to demonstrate the usefulness of the developed methodologies.