Workshop on Mathematical Perspectives on Immunobiology

Book of Abstracts
Institute of Mathematics and Informatics

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Society for Mathematical Biology

ПИКОМ
ПОВИШАВАНЕ НА ИЗСЛЕДОВАТЕЛСКИЯ КАПАЦИТЕТ В ОБЛАСТТА НА МАТЕМАТИЧЕСКИТЕ НАУКИ

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About the Workshop

Advances in genetics and biochemistry have opened novel opportunities for accumulating knowledge about the organization, dynamics, and regulation of the human immune system. The importance of mathematics in qualitative and quantitative analysis is manifested in those cases where experimental methods or clinical observations reach their limit.

The Workshop on Mathematical Perspectives on Immunobiology brings together researchers who do research on one of the most complex systems of the human organism: the immune system. The focus will be on mathematical modeling and computational analysis applied to immunology, host-pathogen interactions, onset and progress in human diseases.

Topics of the workshop include:

- within-host models of host-pathogen interactions
- models of immune response in cancers
- models of immune system regulation
- models of autoimmunity and inflammation
- signalling pathways, regulatory networks and the immune response
- models of therapy and vaccination
- multiscale immuno-epidemiological models

with applications of deterministic models, probabilistic models, agent-based models, and their mathematical analysis and biological interpretation.

Special attention will be paid to how applications of mathematics help expand the understanding of in-host response to infectious diseases, cancer and chronic inflammatory diseases. Among those are model-driven experimental design, model validation against experimental and clinical data, mechanistic understanding of immunological processes and causality, disease progression and prognosis, in silico development of therapy, etc.

To the knowledge of the organisers, this forum focusing on mathematical and computational modeling in the context of immunological processes is the first one of its kind in recent years in Bulgaria. The workshop programme includes keynote invited talks, contributed talks and a poster session. It also includes a round-table discussion on current problems, hot topics, and perspectives for the applications of mathematics in the analysis of immunological processes.

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Contents

Plenary Talks

Viruses, hosts, and the immune response: the eternal dance in nature and evolution

Talk

Radostina Alexandrova

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We are used to seeing viruses as the bad guys in the neighborhood. And this is completely understandable after all the pain, suffering and death they have brought to humanity. The recent COVID 19 pandemic has once again reinforced our opinion in this regard. But is that the whole truth about them?

How many viruses are there on the planet, what fraction of them do we know, how do the new viruses emerge and how do epidemics and pandemics appear?

The presentation will briefly summarize the events that occur when the virus meets its host; the antiviral immune response, and the cat-and-mouse game between human and animal defense mechanisms on the one hand and viral survival strategies on the other. How does this eternal dance of microworld and macroworld affect evolution and nature? Will the world survive if the viruses disappear? What is the role of vaccines, monoclonal antibodies and antiviral agents in the fight against viral infections and why do we need mathematical models.

KIRs, T cell dynamics and human health

Talk

Becca Asquith

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Studying immunology in humans is extremely challenging, for obvious ethical reasons. Mathematics, combined with experiment, can provide a unique and valuable insight. We will focus on a family of immune receptors called KIRs (killer immunoglobulin like receptors). We combine analysis of genetic data from large patient cohorts with mechanistic mathematical modelling and assays of in vitro and in vivo T cell dynamics to gain insight into the relationship between iKIRs, T cell dynamics and human health. We suggest that KIRs enhance T cell survival and that this in turn impacts on clinical outcome in viral infection (HCV, HTLV-1, HIV-1) and autoimmunity (type I diabetes).

Systems Pharmacology to optimize anticancer therapies

Talk

Annabelle Ballesta
INSERM & Institut Curie

Abstract text

Mathematical Modelling of Neutrophil Heterogeneity

Talk

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Neutrophils, also known as polymorphonuclear leukocytes, are the most abundant type of granulocytes in many mammals, including humans. They are key players in the innate immune response due to their ability to execute various effector functions at sites of infection or injury. While classically perceived as short-lived cells with limited plasticity and diversity, they are now recognized as highly heterogeneous and unconventional immune cells with the capacity to adapt to diverse environmental cues [1]. In addition to playing a central role in host defense, neutrophils are implicated in pathological contexts such as inflammatory diseases and cancer. The prevalence of neutrophils in these conditions is typically associated with detrimental responses and poor clinical outcomes. However, emerging evidence suggests a beneficial role for neutrophils in several pathological contexts, including cancer. From a mathematical modeling perspective, neutrophils have not been as extensively studied as other immune cells, such as lymphocytes [2]. In this talk, I will review current understanding of neutrophil biology and describe various modelling approaches that have been used to study them.

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Modeling viral dynamics of SARS-CoV2: treatment and transmission

Talk

Jérémie Guedj

INSERM/Université de Paris Cité
UMR 1137 "Infection, Antimicrobials, Modelling, Evolution", France

In this talk I will discuss how we used mathematical modeling to unravel some key aspects of SARS-CoV-2 transmission. I will also show how modeling was used to optimize antiviral treatment and what models tell us in terms of protection against infection in the future.

Immunotherapy: Using Math to Help the Immune System Fight Cancer

Talk

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In recent years, immunotherapy has been taking a central role in cancer therapies. In this talk we will provide an overview of some of our recent works in mathematical modeling of immunotherapy. Among the topics we will discuss are engineered T cell therapy, transforming growth factors, checkpoint inhibitors, and cellular exhaustion.

Scientific Abstracts

Phenotype-driven Mathematical Approaches for T-cell Activation

Poster

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The first comprehensive approach to model T-cell activation and signalling was KPR (kinetic proof reading) scheme introduced in [1]. It was built on the assumption that the TCR (T-cell receptor) complex does not immediately signal when it binds pMHC (peptide-major histocompatibility complex), but that it must undergo a series of modifications before it reaches a signalling-competent state. According to this mechanism pMHC ligands bind to TCRs to form a TCR-pMHC complex (C_0) which goes through a sequence of N biochemical modifications complexes ($C_1, ..., C_N$) which form the proof-reading or activation chain until a signaling-competent state C_N is attained. However the kinetic proof reading mechanism cannot account for the sensitivity of T-cell activation. This was addressed by assuming that TCRs that have reached the signaling-competent state (the C_N complex) only signal for a limited period of time [2] . The KPR model with limited signal proposed that there will be optimal dissociation time for T-cell activation at all concentrations. However this assumption was found to be inconsistent with some modified proof reading models. It was found that at low pMHC concentration there is an optimal dissociation time for T-cell activation but at high pMHC concentration there is no such requirement. Hence instead of assuming that signal is limited, KPR with sustained signalling model was introduced which makes an assumption that signalling competent TCRs are able to maintain signaling for a prescribed time even after pMHC unbinding[3].

Further when it was found that induced rebinding enhances the sensitivity of the basic KPR model while retaining specificity and it was ascribed to processes "such as TCR clustering, conformational changes, and/or membrane alignment". In this induced rebinding model, the initial binding of TCR with pMHC undergo a series of modifications as per KPR scheme and this modification also includes TCR clustering, which follows that when pMHC dissociate from an intermediate state, its likely to rebind[4]. In all these approaches taken based upon the phenotypic characteristics, little was explored about the dynamics of the differential system based upon these assumptions. The existence, uniqueness, equilibrium points, stability, and sensitivity of the solutions associated with these differential systems are yet to be fully explored. My aim is to classify all the models based on phenotypic characteristics and analytically observe the mathematical properties of the dynamical systems of T-cell activation, which has the potential to provide new insights into the process of T-cell activation.

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PDE models of cell interactions in Multiple Sclerosis

Talk

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Multiple sclerosis (MS) the most widespread neurological autoimmune disease in the world with young adults being the most frequently diagnosed group. As with other autoimmune diseases, the causes and potential cures for MS remain elusive with mathematical modeling offering a promising pathway to gain insight into the more abstract nature of MS.

This talk focuses on a PDE reaction—diffusion—chemotaxis model [1] of the dynamics of three cell types. In order to simulate the rich dynamics of the different disease types, modifications such as time-varying coefficients and a time-delay term are incorporated as a modification to the original model.

We consider a subtype of MS called Baló's concentric disease which lends itself to numerical analysis in a much easier manner. We present results from numerical simulations of the different MS types. These are obtained thanks to the modifications of the original model, the results of which could aid us to better understand the disease's pathogenesis. We also discuss the computational challenges that we face when simulating the different variants of the model.

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Quantifying the activation of the pregnane X receptor and the expression kinetics of its up-regulated xenobiotic-handling target genes

Talk

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Pregnane X receptor (PXR) is a liver-enriched ligand-activated transcription factor and is considered to be a crucial sensor in xenobiotic response [1]. Moreover, it was revealed to be involved in the pathogenesis of immune disorders and inflammatory responses [2]. PXR controls transcription of drug-handling genes such as those from the cytochrome P450 family, including CYP3A4, CYP2C9, and CYP2B6. For example, CYP3A4 is the most important enzyme that is involved in metabolism of approximately 50% of all clinically used drugs [3].

Several mathematical models (MMs) exist that describe the effect of ligands on PXR-activated CYP3A4 gene expression in primary human hepotocytes (PHHs) [4, 5]. However, these studies have employed data evaluated from PHHs monolayer cultures, which are prone to degenerative changes shortly after exposure to ligands. We propose a MM to describe the activation of PXR and the expression kinetics of its up-regulated target genes and consider efflux of a drug from the cell via the multidrug resistance protein 1 (MDR1), which is also regulated by PXR. The MM is fitted to in-house generated experimental data. A state-of-the-art *in vitro* system of PHH spheroids was employed instead of PHH monolayer culture which allowed us to monitor the changes in the target gene messenger RNA (mRNA) expression for up to two weeks. The cells were treated with the antibiotic rifampicin, a potent PXR activator, which is used to treat several types of bacterial infections, including tuberculosis. mRNA of CYP3A4, CYP2C9, CYP2B6 and MDR1 were quantified at the early and late phases of PXR activation.

Our MM suggests that MDR1 is depleted during the PXR activation as it transports rifampicin out of the cell. This takes place despite an increased transcription of MDR1; MDR1 mRNA is up-regulated, but the rate at which it is translated is not sufficient to replenish the protein concentration. This saturation of MDR1 might pose a risk at high rifampicin doses or during a combination therapy when the efflux transporter is saturated and the drug accumulates in the system. Thus, it is crucial to quantify the mechanisms of PXR activation and the resulting interplay with MDR1 to be able to optimize the dose of a drug during the mono- or multi-drug therapy.

Keywords: rifampicin, PXR, cytochrome P450, multidrug resistance protein 1, parameter estimation, mathematical model

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Mechanistic Mathematical Modelling of Immune-Based Blood Cancer Therapy

Poster

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The Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs) are a group of slowly developing blood cancers that are triggered by chronic inflammation and are primarily characterised by an overproduction of blood cells [1]. Without treatment, they result in severe complications such as thrombosis and bleeding [1]. Different treatments exist for MPN patients. In the COMBI-I ($n = 50$ patients, #EudraCT 2013-003295-12 [2]) and COMBI-II ($n = 25$ patients, #EudraCT 2018-004150-13 [3]) studies, the effects of combination treatment using interferon-α-2a (IFN), a mediator of the immune system, and ruxolitinib (RUXO), a compound with anti-inflammatory effects, were studied [4]. Using data from these studies, this poster explores a mechanistic mathematical modelling approach to study the effects of IFN and RUXO on the malignant cell burden of the patients. The mathematical model is based on the Cancitis model [5], [6] and consists of coupled ordinary nonlinear differential equations. The effects of combination therapy is included in the model as changes to parameters describing cell kinetics, and the model is then fitted to the time course of the malignant cell burden of individual patients. The preliminary results suggest that the model fits well to a large number of patients and can potentially contribute to prediction of the course of the disease.

This work was supported by the fellowship "Personalized prediction of blood cancer progression using clinical data and mathematical modeling" (R335-2019-2020) from the Lundbeck Foundation (PI: T.S.).

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Statistical methods for clinical trials: Analyzing the impact of circadian timing on cancer patient outcomes

Talk

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The time-of-day administration of cancer treatments can affect their effectiveness and tolerability, hence the patient's survival and response rates, as a result [1]. This time-of-day variability results from the circadian timing system, that controls most physiological functions of the organism ensuring optimal adaptation to the light/dark cycles on earth. Exploiting this circadian changes, cancer chrono-chemotherapy has been studied for several decades now, addressing treatment optimization by selecting the most beneficial time-of-day for administration [2]. More recently, also immunotherapy has shown circadian dependent outcomes, particularly in the survival of cancer patients whenever treated in the "early" part of the day [3]. Determining the morning/afternoon cut-off, however, is still debated: ranging from 12.55pm to 4.30pm across studies. Its definition is critical and requires the design of robust analytical approaches that will allow to extract meaningful and actionable insights from circadian timing investigation in clinical studies.

The aim of this study was to retrospectively investigate the effect of treatment timing on patient survival, neoplastic response and toxicities, in a population treated with immune checkpoint inhibitors (ICI). The patients were classified into two infusion groups, "morning" and "afternoon", according to the threshold obtained with the predictiveness curve method. Such an optimal timing cut-off was then confirmed by an alternative approach based on the area under the survival curves (RMST). Notably, morning patients showed a longer median overall survival than the afternoon group, which was significantly associated with three factors: patient performance status, ICI administration timing, and line of treatment. Overall, these findings were in agreement with previous research suggesting a benefit for "morning" immunotherapy infusion [3].

Further, we challenged the binary definition of morning/afternoon infusion groups in order to account for the continuous and periodic nature of the timing variable. We thus

developed a sinusoidal Cox model which allowed us to extrapolate the worst ICI time-of-day infusion, that we then validated with another independent method (based on the RMST).

We therefore provided new tools for optimizing the checkpoint inhibitor schedule, with the aim to promote a clinical practice able to maximize immunotherapy efficacy and survival. Eventually, future prospective trials will be needed to confirm our predictions.

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The effect of model structure and data availability on multiscale model predictions - Usutu virus case study

Talk

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Understanding the epidemiology of emerging pathogens, such as Usutu virus infections, requires systems investigation at each scale involved in the host-virus ecology, from individual bird infections, to bird-to-vector transmissions, to disease incidence in bird and vector populations, and eventually to spillover probability in humans. For new pathogens wild data is sparse, and predictions are based on laboratory-type inoculation and transmission experiments combined with dynamical mathematical modeling. In this study, we developed a multiscale vector-borne epidemiological model of Usutu virus infection in birds and mosquitoes and used individual within-host viral load data and host-to-vector probability of transmission data to predict disease incidence in bird and mosquito populations exposed to two different Usutu viral strains. We addressed the role of model structure, data uncertainty and optimal experimental design on model predictions. We found that within-host peak viremia levels do not always correlate with infection incidence levels in host and vector populations and that uncertainty in predictions at one scale may change predicted results at another scale. We showed that optimal experimental design and increased frequency of data collection vastly improves these correlations. The results may be useful for predicting spillover events.

Resource limitation in an immuno-epidemiological model with vaccination and testing

Talk

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During emergent outbreaks of viral infections, public health policy decisions are made on the basis of incomplete information in a changing landscape of scientific knowledge and budgetary and infrastructure constraints. We developed a multi-scale immuno-epidemiological model of the spread of COVID-19 to explore efficacy of testing and vaccination for preventing outbreaks. Our model indicates that in budget constrained situations, less sensitive but cheaper tests can be more effective at outbreak preventions. Our finding further indicate that population vaccination prevalence has a strong influence on the efficacy of testing regimes.

In emerging pandemic scenarios, limited public health resources must be apportioned to different control methods. Accounting for the trade-offs necessitated by the resource limitation is essential when formulating an optimal policy response. Using our immuno-epidemiological model, we pose optimal control problems to explore the implications of several such trade-off, focusing on testing vs. vaccination and long-term vs. short-term public health objectives. We also explore the how these optimal controls are influenced by the efficacy of the interventions and the frequency with which policy changes can be made.

Mechanism-based mathematical modelling of chimeric antigen receptor T cell treatment of cancer

Talk

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In chimeric antigen receptor (CAR)-T cell treatment of cancer, T cells are engineered to express transgenic artificial CARs that can recognize antigens of choice. The CAR-T cells become activated when encountering cells bearing the antigen and use their intrinsic ability to kill the given cells[7].

The T cells are taken from the peripheral blood of the cancer patient[6] or a matched donor[2]. Afterwards, the T cells are engineered to express CARs, expanded, and infused back into the patient[4]. The CAR-T cell products given to the patients are quite heterogeneous and the pharmacology is different from traditional small molecule and biomolecules drugs[4, 7], which makes it difficult to decipher the underlying reasons why some patients respond well to CAR-T cell treatment, while others do not.

A key aspect of improving CAR-T cell treatment efficacy is understanding how patient variability in T cell differentiation phenotypes and exhaustion influence the battle against the cancer cells[1]. Studies have shown significant differences between patients responding well to treatment and non-responding patients when looking at the distribution of phenotypes of the T cells taken from the peripheral blood of the patients and later in the CAR-T cells in the infusion products[1, 3].

Only few mathematical modelling papers have investigated the important aspects of phenotypes of the CAR-T cells[7, 5]. In this mechanism-based mathematical modelling work, we explore the patient specific differences in CAR-T cell immunophenotypic differentiation and expansion, and how these aspects influence the treatment efficacy. The model consists of ordinary differential equations (ODEs) describing the dynamics of CAR-T cells on different differentiation phenotypes and how these influence the extent of expansion and persistence of CAR-T cells in the patient during treatment. The model is compared to CAR-T cell data from patients suffering from different B cell malignancies found in the literature[2, 6].

Keywords: chimeric antigen receptor T cell, cancer, mechanism-based mathematical modelling, ordinary differential equations

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Unexpected linearity: a first-order drug response curve observed and explained for SARS-CoV-2 in a hybrid mathematical model

Talk

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We observe, analyze and explain a pharmacokinetical phenomenon of extraordinary simplicity. Specifically, we show that the probability of infection extinction in a complex, non-deterministic hybrid mathematical model is a linear function of the virus removal rate under rather general circumstances. Joint work with Ferenc Bartha, Sadegh Marzban, Renji Han and Gergely Röst.

Modelling the dynamics of small heterodimer partner expression in response to pregnane X receptor activation: implications of drug-drug interactions in cancer treatment

Poster

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The pregnane X receptor (PXR) contributes to cancer treatment failure by being strongly implicated in drug-drug interactions (DDIs) [1]. The interaction between PXR and the small heterodimer partner (SHP) is a major contributor to DDIs. SHP represses PXR's transcriptional activity, limiting its ability to induce the expression of genes responsible for hepatic drug clearance [2, 1], thus preventing DDIs. However, PXR activation by rifampicin decreases the expression of SHP [3], thereby increasing PXR activity and decreasing the efficacy of concomitantly administered anticancer drugs due to DDIs [1]. Interestingly, existing computational models of PXR activity in hepatocytes [4] do not account for the effects of PXR activation on SHP expression.

Here, we formulated a novel mechanistic model to capture the temporal dynamics of SHP expression upon PXR activation by rifampicin. The model suggests that the decrease in SHP protein upon PXR activation is due to the inhibition of the background production of SHP mRNA and the absence of SHP mRNA synthesized via the PXR transcriptional pathway. Using experimental data from 3D primary human hepatocyte spheroids [5], we estimated the model parameters by fitting the model to SHP mRNA levels obtained under low and high doses of rifampicin. The model is consistent with previous experimental results, confirming its accuracy, and the estimated parameters show reasonable values.

With further refinement, this parameterized model is a promising tool for capturing the dynamic relationship between PXR activation and SHP expression, enabling the identification of new approaches to improve therapeutic outcomes and minimize the impact of drug-drug interactions in cancer treatment.

Keywords: pregnane X receptor, rifampicin, small heterodimer partner, drug-drug interactions, mechanistic model, parameter estimation

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A model of tumour-immune response with immunotherapy

Talk

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We present a mathematical model for tumour-immune response interactions in the perspective of immunotherapy by immune checkpoint inhibitors (ICIs). The model is of the integro-differential Lotka-Volterra type, in which heterogeneity of the cell populations is taken into account by structuring variables that are continuous internal traits (aka phenotypes). These represent a lumped "aggressiveness", i.e., for tumour cells, malignancy understood as the ability to thrive in a viable state under attack by immune cells or drugs - which we propose to identify as a potential of de-differentiation -, and for immune cells, ability to kill tumour cells, in other words, anti-tumour efficacy. We analyse the asymptotic behaviour of the model in the absence of treatment. By means of two theorems, we characterise the limits of the integro-differential system under an a priori convergence hypothesis. We illustrate our results with a few numerical simulations, which show that our model exemplifies the three Es of immunoediting: elimination, equilibrium, and escape.

Keywords: Tumour-Immune interactions, Phenotype-structured model, Asymptotic analysis, Immune checkpoint inhibitors.

MSC2020: 35B40, 35F50, 35Q92, 92-10, 92C50, 92D25

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Data matches and mismatches: parameterizing a compartmental viral and immune kinetics model with ADE effect to sequential Dengue virus infections

Talk

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Dengue, a neglected tropical disease, is a globally distributed arboviral (genus *Flavivirus*) pathogen primarily spread by *Aedes* mosquitoes and infecting approximately 390 million individuals each year. Subsequent to primary infection immune memory is cross-protective for two to three months after which protection is serotype-specific, and secondarily infected patients have an elevated risk of severe dengue. A hypothesis for this increased risk, known as antibody-dependent enhancement (ADE), is that antibodies increase dengue severity and boost virus replication. One hypothesized mechanistic explanation for this effect is, *hypothesis 1: that ADE occurs during an intermediate risk window with respect to decay of cross-reactive antibody titer.*

In addition to the increased risk of severe dengue for secondarily infected DENV patients, there are a number of empirically observed differences in the time course of events between primary and secondary infection. A proposed explanation for this is *hypothesis 2: differences in initial cross-reactive antibody level mechanistically explain observed differences between primary and secondary infection in the timing of within-host events.* Here we fit a viral-immune kinetics model from our prior work [1] which encapsulates these hypotheses to viral kinetics data collected from the Hospital for Tropical Diseases (Ho Chi Minh City, Vietnam) between May 2007 and July 2008. Our results provide further support for these hypotheses in that (i) they recapitulate the data well while including explicit data-backed dependence of infection severity on pre-existent cross-reactive antibody concentration (hypothesis 1) not produced by other mechanistic models, and (ii) capture the clinically observed differences between primary and secondary infection in a unified modeling framework (hypothesis 2).

Ultimately, we leverage our modeling results and long-term NS1-specific IgG antibody decay data from Recife, Northeast Brazil, to estimate both the decay rate of Dengue IgG antibodies and the time frame of the risk window for escalated disease severity due to ADE from hypothesis 1.

Keywords: Dengue, ADE, viral kinetics, immune kinetics

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Learning dynamical models of the interactions between the immune receptor NLRP3 and the circadian clock – application to lung cancer

Poster

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Lung cancer is a major health problem, with high mortality rates, due to an absence of effective treatment strategies. In this work, we focus on two deregulated mechanisms in cancer: the immune system and the circadian clock. At the cell level, the circadian clock is a biological oscillator composed of regulatory network with intertwine feedback loops that generate sustained oscillations with a period between 20 and 35h. Besides, NLRP3 is a sensor of innate immunity whose role in the immune response has been well studied which was recently identified as an interesting gene altered in lung tumors. Previous studies have shown that NLRP3 transcription is regulated indirectly by REV-ERB α (a nuclear receptor of the circadian clock) in macrophages [1, 2]. However, the links between NLRP3 and the circadian clock have been rarely investigated. Our goal is then to characterize the interactions between NLRP3 and the circadian clock that are emerging as major components in the pathophysiology of lung cancer.

To this end, we have undertaken a combined experimental and mathematical approach. We have studied the interactions of NLRP3 and the circadian clock in human bronchial epithelial cells (HBEC) which were synchronized by serum shock. RNA-Sequencing and Western blot data as well as intracellular localization (nucleus/cytoplasm) were assessed. Clock gene components were defined using the Reactome database (v84). Circadian rhythms were studied using cosine wave fitting and using CMAES for the minimization task. Model learning method was developed to automatically learn the structure of quantitative systems biology models based on ordinary differential equations from multimodal data. Parameter estimation was performed using a modified least-square approach using CMAES for minimization.

The analysis of mRNA levels of 70 clock genes revealed a functional clock in HBEC cells with a period of 33h+/-2h . NLRP3 can interact with clock proteins and the data suggest that they could regulate the intracellular localization of NLRP3 to orchestrate its functions. On the other hand, loss of NLRP3 expression may disrupt the circadian regulation necessary for normal lung function. An existing circadian clock model [3] using ordinary differential equations (ODE) was extended by adding equations describing the influence of the clock on NLRP3 transcription and interactions of clock and NLRP3 proteins. As a start, a collection of models were considered that included a single additional reaction as compared to the initial clock model. A systematic fit to the data of each model

was performed which allowed to eliminate unlikely reactions. Models involving more than one additional reaction are being investigated. Such model learning pipeline will help prioritize future experiments to fully determine NLRP3 interactions with the clock and identify potential drug targets to restore NLRP3 functions in NLRP3-altered cancer cells.

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Dynamical analysis of an HIV infection model including quiescent cells and immune response

Talk

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This paper presents a comprehensive analysis of an HIV infection model that incorporates quiescent cells and immune response dynamics within the host. The model, represented by a system of ordinary differential equations, captures the intricate interplay between the host's immune response and the viral infection. The study investigates the fundamental properties of the model, including equilibrium analysis, the computation of the basic reproduction number $\mathcal{R}_0$, stability analysis, bifurcation phenomena, numerical simulations, and sensitivity analysis. An infection equilibrium, which reflects the persistence of the infection, and a disease-free equilibrium, which represents the possibility of disease control, are both revealed by the analysis. By applying matrix-theoretical methods, stability analysis confirmed that the disease-free equilibrium is both locally and globally stable for $\mathcal{R}_0 < 1$. The research also reveals a transcritical forward-type bifurcation at $\mathcal{R}_0 = 1$, which denotes a critical threshold that affects the behavior of the system. The temporal dynamics of the model are investigated through numerical simulations, and sensitivity analysis determines the most important variables by examining the effects of parameter changes on the system's behavior.

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Within-host dynamics of lysogen and non-lysogen bacteria with spontaneous prophage induction phenomenon

Talk

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Bacteriophages or phages (viruses of bacteria) play numerous roles in shaping the diversity of bacterial communities within the human gut. Either a phage-infected bacterial cell immediately starts a lysis mechanisms (virulent/lytic infection), or it enters a stable state within the host as a prophage (lysogeny), until a trigger event, called Spontaneous Prophage Induction (SPI), allows the lysis phenomenon. We develop an approach to address the role of SPI within phage-bacteria interactions and the influence of lysogeny on the success of phage therapy. This is based on a model structure in terms of time since infection. Our analysis suggests that SPI allows lysogen bacteria to have a competitive advantage over their non-lysogenic counterparts. Moreover, the model exhibits the bistability phenomenon such that, depending on the initial conditions, the dynamic can either converge towards a purely temperate state (only lysogens and temperate phages persist) or a purely lytic state (only nonlysogens and virulent phages persist). We also highlight the existence of SPI's critical values leading to the coexistence of all states through periodic oscillations. Finally, the model suggests that efficient bacteria control through phage therapy can be achieved by minimizing lysogens' offspring.

Keywords: Within-host competition; Nonlinear dynamical systems; SPI; Age structured model; Phage therapy; Hopf bifurcation.

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Analysis of a biochemical model with recycling in case of negative cooperativity

Talk

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The objective of this theoretical study is to evaluate the role of cooperativity, captured by the Hill coefficient, in a biochemical model with recycling. We have based the present model on that of [1, 2, 3] in which the dimensionless concentration of the substrate s and the dimensionless concentration of the product p are described by the following system of nonlinear ODEs:

$$\begin{aligned} \dot{s} &= \frac{ds}{dt} = v + \frac{\sigma_i p^g}{K^g + p^g} - \sigma \frac{s(1+s)(1+p)^2}{\alpha + (1+s)^2(1+p)^2}, \\ \dot{p} &= \frac{dp}{dt} = -k_s p - \frac{\beta \sigma_i p^g}{K^g + p^g} + \beta\sigma \frac{s(1+s)(1+p)^2}{\alpha + (1+s)^2(1+p)^2}, \end{aligned} \tag{1}$$

where $\alpha > 0$ is the allosteric constant of the enzyme, v is the normalized substrate injection rate, K is a constant equal to the product concentration for which the recycling rate reaches its half-maximum value, g is the degree of cooperativity (Hill coefficient), σ_i denotes the maximum rate of recycling, divided by the Michaelis constant of the substrate for the autocatalytically regulated allosteric enzyme, $\beta = K_R/K_p$ (where K_R and K_p are the Michaelis constant for the substrate s and the dissociation constant for binding of the product p to the regulatory site of the enzyme), σ is the maximum rate of the enzyme reaction, and k_s is the rate constant of product degradation by a first order reaction.

The model equations are analyzed for negative cooperativity using a specific version of bifurcation theory and they are solved numerically. Special attention is paid to the sign of so-called first and second Lyapunov values. Interpretations of the results are given, both according to dynamic theory and in biological terms.

Keywords: cooperativity, qualitative analysis, numerical analysis
MSC2020: 34C23, 34C60, 92B05

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Inflammation, comorbidity, and aging in cancer

Talk

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Pathogens generally provoke the immune system to respond. Classically this may cause one out of three outcomes, the pathogen may be eradicated by the immune response, the immune response may be insufficient and disease progression emerges, or the immune response may keep the pathogen at such a low burden that related disease symptoms are not realized, which we denote a dormant pre-disease state. We aim in presenting a uniform explanation of the following four challenging observations

- Many diseases may be latent i.e., evolving from a dormant pre-disease state as seen in blood cancers, a concept denoted Clonal Hematopoiesis of Indeterminate Potential (CHIP) [1, 2].
- In large cohort screening of citizens, 31% of the observed JAK2V617F positive citizens carry the malignant mutation in a dormant pre-disease state, while the remaining develop blood cancer [3, 4].
- Auto-immune diseases increase the risk of developing cancer. [5]
- Inflammation may be a frequent cause of cancer escape [6, 7, 8].

We present a general mechanism-based mathematical model for con- sidering inflammatory comorbidities during cancer progression focusing on the immuno-coupling between the respective inflammatory responses. The model explains the four observations and does propose an explanation of how the probability of cancer escape increases with age, a phenomenon referred to as immuno-aging for which the model was not constructed [9]. That the prevalence for JAK2V617F positive myeloproliferative neoplasm increases approximately linearly with age also serves as an independent validation of the model [10]

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Deciphering the Complexity of the Antibody Repertoire: Novel Insights from IgOme Studies and Graph Theory

Talk

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We explore the transformative potential of IgOme, a comprehensive global antibody reactivity map, to illuminate the depth and breadth of the antibody repertoire [1]. Leveraging a "deep panning" approach with phage display peptide libraries and next-generation sequencing, the IgOme encapsulates the antibody repertoire's complexity [2].

Our study breaks new ground by focusing on the IgM repertoires, a non-traditional area of exploration due to its physiological autoreactivity. We posit these repertoires as potential biosensors for the internal environment and source of biomarkers for diverse autoimmune, infectious, and malignant disorders.

In a significant finding, our analysis of antiphospholipid syndrome patients' sera supported previous suggestions of a restricted IgM repertoire, characterized by "holes". Notably, these restrictions were associated with the emergence of domains in the IgG repertoires with matching reactivity, indicating general alterations in the antibody repertoire.

In the field of infectious diseases, the concept of IgOme graph helped identify candidate epitopes on the spike of SARS-CoV-2 virus. The set of 7-mer mimotope peptides representing the IgM repertoire of healthy donors proved to contain sequences which are homologous to parts of that antigen [3].

Utilizing sequence graphs and graph theory tools proved instrumental in these investigations. Paired with high-throughput binding tests, the IgOme mimotope libraries used alongside peptide microarrays allowed us to construct a cross-reactivity graph from patients' binding data [4]. This approach facilitated the distinction between IgOme profiles of Alzheimer's disease and frontotemporal dementia. Employing graph-aided feature selection, we extracted meaningful IgM reactivity profiles, effectively serving as classifiers for brain malignancies.

In conclusion, our findings underscore that IgOme studies, enriched by graph theory tools, could offer a pioneering platform for diagnostic tests. This cutting-edge methodology promises to catalyze advancements in the development of more sophisticated diagnostic and therapeutic interventions across a wide range of diseases.

Keywords: IgM, IgG, antibody repertoire, graph theory

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Effect of infectious and noninfections DENV on plasmacytoid dendritic cells and the immune response

Poster

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According to the WHO, every year nearly 400 million people worldwide become infected with the dengue fever virus after being bitten by an Aedes mosquito. Dengue virus belongs to the Flaviviridae family and has four different coexisting variants (serotypes DENV1-4). The first infection is usually quite mild, but a subsequent infection with a different serotype often results in a much more severe life-threatening illness.

Virus synthesis in infected human cells requires cleavage of the prM protein from the viral envelope to the M protein, catalyzed by the enzyme furin, which completes the formation of the mature virus. However, blood samples of dengue patients contain about 30% immature dengue viruses that contain uncleaved prM. Immature virus is essentially non-infectious because the structure of the envelope prevents it from attaching to a target cell. Results of in vitro studies show that immature viruses regain full infectivity upon interaction with anti-prM antibodies. This phenomenon is called antibody-dependent enhancement (ADE) and is the basis of reinfections with DENV of different serotypes causing fatal complications.

The role of immature DENV viruses that are produced during infection and the immune response to them have not been studied in detail using mathematical modeling. Experimental results reveal that plasmacytoid dendritic cells respond differently to cells infected with DENV, which synthesize a spectrum of viruses with different degrees of maturity. We present a mathematical model of within-host infection that includes plasmacytoid dendritic cells and mature infectious and immature dengue virus [1].

Due to insufficient elucidation of the underlying biological mechanism in the literature, we consider two scenarios of possible interactions between the pathogen and the immune response. For each we then use numerical simulations to compare the immune response in the first and the secondary infection with different DENV serotypes, with the help of which we generate different indicators of infection and immune response.

The model contains a large number of ODEs with a large number of parameters, many of which have not been evaluated experimentally, so we use random sampling of parameters from a uniform distribu- tion for the numerical experiment.

The model exhibits one of the main challenges, typically encountered in the modelling of complex biological phenomena, namely, the number of parameters whose values are uncertain grows rapidly if one wants to realistically describe the biological complexity.

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Monotonicity of the response function for the initiation of T cell activation

Talk

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A model for the initial stages of T cell activation was introduced in [1]. It combines a kinetic proofreading module with a negative feedback due to the phosphatase SHP-1. There are experimental observations indicating that sometimes the level of activation is a decreasing function of the signal strength. It was suggested in [3] that this phenomenon could not be reproduced by the model of [1]. In [2] we carried out a mathematical analysis of the model of [1]. On the basis of this work we were able to do simulations showing that the model of [1] can exhibit the phenomenon mentioned above. In [2] we also proved that the model of [1] can exhibit more than one steady state for given values of the parameters. The kinetic proofreading module alone has a unique steady state. More recently it has been proved that in a more elaborate model where the role of Lck is included explicitly even the kinetic proofreading module can exhibit more than one steady state.

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Dynamics of an SIRWS model with waning of immunity and varying immune boosting period

Talk

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SIRS models capture transmission dynamics of infectious diseases for which immunity is not lifelong. Extending these models by a W compartment for individuals with waning immunity, the boosting of the immune system upon repeated exposure may be incorporated. Previous analyses assumed identical waning rates from R to W and from W to S. This implicitly assumes equal length for the period of full immunity and of waned immunity. We relax this restriction, and allow an asymmetric partitioning of the total immune period. Stability switches of the endemic equilibrium are investigated with a combination of analytic and numerical tools. Then, continuation methods are applied to track bifurcations along the equilibrium branch. We find rich dynamics: Hopf bifurcations, endemic double bubbles, and regions of bistability. Our results highlight that the length of the period in which waning immunity can be boosted is a crucial parameter significantly influencing long term epidemiological dynamics.

Joint work with F. Bartha, M. Polner, and R. Okopu-Sarkodie.

Monkeypox Viral Transmission Dynamics and Fractional Order Modeling with Vaccination Intervention

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A current outbreak of the monkeypox viral infection, which started in Nigeria, has spread to other areas of the globe. This affects over 28 nations, including the United Kingdom and the United States. The monkeypox virus causes monkeypox (MPX), which is comparable to smallpox and cowpox (MPXV). The monkeypox virus is a member of the Poxviridae family and belongs to the Orthopoxvirus genus. In this work, a novel fractional model for Monkeypox based on the Caputo derivative is explored. For the model, two equilibria have been established: disease-free and endemic equilibrium. Using the next-generation matrix and Castillo's technique, if $R_0 < 1$ the global asymptotic stability of disease-free equilibrium is shown. The linearization demonstrated that the endemic equilibrium point is locally asymptotically stable if $R_0 > 1$. Using the parameter values, the model's fundamental reproduction rates for both humans and non-humans are calculated. The existence and uniqueness of the solution are proved using fixed point theory. The model's numerical simulations demonstrate that the recommended actions will cause the infected people in the human and non-human populations to disappear.

Keywords: Monkeypox; Caputo Fractional derivative; Reproduction Number; Stability Analysis; Fractional Euler's Method; Fixed Point Theory; Next-Generation Matrix; Existence and Uniqueness.

Key factors and parameter ranges for immune control of equine infectious anemia virus infection

Talk

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Equine Infectious Anemia Virus (EIAV) is an important infection in equids whose similarity to HIV holds hope for a potential vaccine. We analyze a within-host model of EIAV infection with antibody and cytotoxic T lymphocyte (CTL) responses. In this model, the stability of the biologically relevant endemic equilibrium, characterized by coexistence of long-term antibody and CTL levels, relies upon a balance between CTL and antibody growth rates, needed to allow existence of persistent CTL levels. We determine model parameter ranges in which CTL and antibody proliferation rates are simultaneously most influential in leading the system towards coexistence and derive a mathematical relationship between CTL and antibody production rates in order to explore the bifurcation curve that leads to coexistence. We employ Latin hypercube sampling and least squares to find parameter ranges that equally divide the endemic and boundary equilibria. We then examine this relationship numerically via a local sensitivity analysis of the parameters. Our analysis is consistent with previous results showing that an intervention, such as a vaccine, intended to control a persistent viral infection with both immune responses should moderate the antibody response to allow for stimulation of the CTL response. Finally, we show that the CTL production rate can entirely determine the long-term outcome, regardless of the effect of other parameters, and we provide the conditions for this result in terms of identified ranges for all model parameters.

Keywords: Equine Infectious Anemia Virus; cytotoxic T lymphocytes; antibodies; bifurcations; Latin hypercube sampling; partial rank correlation coefficients; least squares

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Mathematical model for NETosis in Systemic Lupus Erythematosus

Talk

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Neutrophils account for about 70% of human leukocytes, and participate in the host's first line of defense against pathogens. Their role in innate immunity is to neutralize them and to initiate the adaptive immune response. Neutrophils can act in several ways: degranulation (release of cytotoxic molecules), phagocytosis (removal by engulfment and ingestion), and NETosis [1].

NETosis is a regulated form of neutrophil death, which causes extrusion of chromatin, nuclear, cytoplasmic and granular material, proinflammatory cytokines, and antimicrobial peptides from the cell, resulting in its death and the formation of neutrophil extracellular traps (NETs). These traps have a web-like structure which prevent the pathogen from spreading in the organism [2]. NETosis has been reported in infectious diseases such as RSV, HIV, Chikungunya virus, SARS-Cov-2 [3], but it may a sign of an inadequate immune response in chronic diseases such as systemic lupus erythematosus (SLE) [4].

In SLE patients, NETs expose numerous autoantigens leading to a reaction directed towards the organism itself. Furthermore, microparticles derived from apoptotic cells in the case of SLE have been found to enhance the formation of NETs, leading to a feed-forward effect on the autoimmune response [5, 6, 7, 8].

We propose a simple mathematical model for the network of interactions between neutrophils, apoptotic particles, autoantigen resulting from necrotic residue and NETosis, and macrophages. Bifurcation analysis is used to characterise the effect of several parameters on the asymptotic behaviour of the model.

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Keywords: SLE, NETosis, macrophages, Bifurcation analysis

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Fractional ordered model for cell level viral transmission dynamics with adaptive immunity

Talk

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In this paper we proposed fractional ordered model of cell level pathogen transmission dynamics by considering adaptive immunity. Infected and latently infected cells are considered in the model. The model assumed as infection occur from virus to health cell and from infected cell to health cells. The qualitative behavior of the model is analyzed. From the qualitative analysis basic threshold parameters that affect clearance and maintenance of infection are determined. Effect memory as well as some parameters on the expansion of the infection is done in numerical simulations.

Keywords: Fractional Order; Modeling; Cell level; Adaptive immunity

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