5th Interdisciplinary Workshop on

Modeling in Life Sciences

November 20, 2015

Bolyai Institute, University of Szeged

erc

Hungary-Serbia
IPA Cross-border Co-operation Programme

Program

9:30	**Registration**
10:00	*Gergely Röst*: **Opening**
10:05	*Keynote lecture:* *Hiroshi Nishiura*: **Real time modeling research response to Middle East respiratory syndrome (MERS) outbreak in the Republic of Korea**
11:00	*Diána Knipl*: **The potential impact of vaccination on the dynamics of dengue infections**
11:25	*Zsolt Vizi*: **An agent based modelling framework for indirect disease transmission: Ebola as a case study**
11:45	*Eliza Bánhegyi*: **The effect of the reduction of the needle exchange program on the spread of AIDS**
12:05	*György Bencskó*: **Model for effective case-infection ratio for silent, borderline transmission of poliovirus**
12:30	Lunch break
13:30	*László Nagy:* **Modeling energy conversion in photosynthetic reaction center protein – energy harvesting and biosensor applications**
14:00	*Mihály Vöröslakos*: **Targeted transcranial electrical stimulation protocols: Spatially restricted intracerebral effects via improved stimulation and recording techniques**
14:20	*Gábor Kiss*: ***Lucilia cuprina* population dynamics with heterogeneous maturation sites**
14:40	Coffee break
15:10	*Julia Sánchez Sanz*: **On the computation of stability boundaries in a SIR model**
15:30	*Philipp Getto*: **A maturing and self-regulating cell population – an example for a nonlinear structured population model**
16:00	*János Karsai:* **Closing remarks**

Abstracts

The effect of the reduction of the needle exchange program on the spread of AIDS

Eliza Bánhegyi

Bolyai Institute, University of Szeged, Hungary

Last year, ECDC rated Hungary as an endangered country due to the reduction of the sterile needle exchange program among drug users. Similar reductions had serious consequences in other countries. Can we expect in the future the increased spread of HIV and hepatitis in Hungary?

In the talk, we consider a compartmental model of the problem based on an ODE system. Investigating the reproduction number R_0 uncovers the behaviour of the epidemics.

[1] Edward H. Kaplan, Elaine O'Keefe, Let the Needles Do the Talking! Evaluating the New Haven Needle Exchange, *Interfaces* **23**, No. 1, Franz Edelman Award Papers (Jan. - Feb., 1993), 7–26

[2] D. Hedrich, E. Kalamara, O. Sfetcu, A. Pharris, A. Noor, L. Wiessing, V. Hope, M. Van de Laar, Human immunodeficiency virus among people who inject drugs: Is risk increasing in Europe?, *Eurosurveillance* **18**, Issue 48, 28 November 2013.

Model for effective case-infection ratio for silent, borderline transmission of poliovirus

György Bencskó

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Recent polio outbreaks in Syria and Ukraine, and isolation of poliovirus from asymptomatic carriers in Israel have raised concerns that polio might endanger Europe. A model is devised to calculate the time needed to detect the first case should the disease be imported to Europe, taking the effect of vaccine coverage – both from inactivated and oral polio vaccines, also considering their differences – on the length of silent transmission into account by deriving an "effective" case/infection ratio that is applicable for vaccinated populations. Using vaccine coverage data and the newly developed model, the relationship between this ratio and vaccine coverage is derived theoretically and is also numerically determined for European countries. This shows that unnoticed transmission is longer for countries with higher vaccine coverage and higher proportion of IPV-vaccinated among the vaccinated. Assuming borderline transmission (R=1·1), the expected time to detect the first case is between 326 days and 512 days in different countries, with the number of infected between 235 and 1439. Imperfect surveillance further increases these

numbers, especially the number of infected until detection. While longer silent transmission does not increase the number of clinical diseases, it can make the application of traditional outbreak response methods more complicated, among others.

A maturing and self-regulating cell population – an example for a nonlinear structured population model

Philipp Getto

Bolyai Institute, University of Szeged, Hungary
Technical University Dresden, Gemany

In many models it is relevant to take into account physiological differences among individuals. Examples for these are an individual organisms age or maturity, the time elapsed since it became infected with a disease or its body size. Also relevant are interactions among individuals that influence the physiological development. In this sense a typical nonlinear physiologically structured population model incorporates individual vital rates (birth, development, reproduction, death) that depend on both its physiological state and on the environment defined by the interactions with other individuals. The objective is to relate the consistency of the individual vital rates to population dynamical phenomena like convergence to equilibria and oscillations. Major tools are delay equations to formulate the population dynamics and characteristic equations to analyze stability. I will use one of my current working examples of a maturing and self-regulating cell population to illustrate these issues.

Lucilia cuprina population dynamics with heterogeneous maturation sites

Gábor Kiss

Bolyai Institute, University of Szeged, Hungary

Regular oscillations of *Lucilia cuprina* populations can be modelled with the so-called Nicholson's blowflies equation; a scalar delay differential equation with unimodal feedback incorporating maturation delay. Much is known about the dynamics of the equation when a single population is considered in homogeneous environment for juveniles. In this talk, we report on changes in the regular basic oscillation caused by heterogeneity. More precisely, we are interested in populations where the egg-larvae-pupa part of the life cycle is happening under different environmental conditions. Joint work with Gergely Röst.

The potential impact of vaccination on the dynamics of dengue infections

Diána Knipl

Department of Mathematics, University College London, United Kingdom

We develop a serotype-specific, vector-host compartmental model to evaluate the effect of vaccination on the dynamics of dengue infection. The ODE model incorporates the phenomena of antibody-dependent enhancement and cross-protection following recovery from primary infection, and is able to reproduce the reported multi-annual patterns of dengue infection. Our model projects that vaccination can dramatically reduce the overall incidence of the disease. However, vaccination can potentially increase the incidence of severe infection of dengue hemorrhagic fever following the vaccine introduction due to the effects of antibody-dependent enhancement. The magnitude and timelines for this increase depend strongly on the efficacy and duration of the vaccine-induced protection. Corresponding to the current estimates of vaccine efficacy, we show that dengue eradication is infeasible using an imperfect vaccine. Our findings suggest that other vector control measures may still play a significant role in dengue prevention even when a vaccine with high protection efficacy becomes available.

Joint work with S. M. Moghadas (Agent-Based Modelling Laboratory, York University, Toronto).

Modeling energy conversion in photosynthetic reaction center protein – energy harvesting and biosensor applications

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The evolution of present form of life and even the huge (but not inexhaustible) availability of fossil fuels are thanks to the solar energy. It would be hard to debate that the photosynthetic conversion of solar into chemical energy by the reaction centre protein is one of the most important processes on Earth. The absorption of light initiates separation of positive and negative charges within the protein matrix followed by vectorial kinetic steps of electron transport through well known cofactors. The protein complex and its cofactors (e.g. quinones) can selectively and sensitively interact with exogenous environmental molecules such as pesticides and endocrine disruptor compounds (EDC), therefore the reaction centre may be suitably employed as biosensing element.

Moreover, since we got a solid knowledge about structural and functional details of the reaction center photochemistry, it has been theoretically possible - but very rarely and only partially realised - to work out kinetic models in order to describe the electron transfer processes and other protein functions (e.g. quinone exchange dynamics and competition with exogenous molecole, protein-lipid interactions, etc.). Such models will help to better understand the functions under different conditions and to optimize the efficiency of the energy conversion, as well as, potential applications, to predict the effect of inhibitors (e.g. agriculture pesticides) and to design effective biosensor devices.

Real time modeling research response to Middle East respiratory syndrome (MERS) outbreak in the Republic of Korea

Hiroshi Nishiura

Graduate School of Medicine, The University of Tokyo, Japan

A hospital-centered outbreak of Middle East respiratory syndrome (MERS) has occurred in the Republic of Korea from May to July 2015. Our research team has responded to the outbreak in real time, providing insights into essential risk assessment and countermeasures against the disease. Not only real time estimation of the transmission potential and severity, but also the risk of international transportation and the risk of successful importation have been modeled. Moreover, the end of MERS epidemic has been objectively assessed by employing a mechanistic stochastic model.

On the computation of stability boundaries in a SIR model

Julia Sánchez Sanz

Basque Center for Applied Mathematics, Bilbao, Spain

In this talk a SIR model is presented in which the dynamics of immunity is boosted by reexposure to infection. The model has a disease free equilibrium and an endemic one, which stability depends on a set of parameters. Determining the stability of an equilibrium considering parameter dependence, and presenting the results in a friendly way, can help epidemiologists to improve their knowledge about a disease and to derive conclusions. Here the scheme of a methodology for computing stability charts in parameter planes is introduced, and numerical examples presented. Finally epidemiological conclusions are derived from the obtained stability charts.

An agent based modelling framework for indirect disease transmission: Ebola as a study case

Zsolt Vizi

Bolyai Institute, University of Szeged, Hungary

Agent-based modelling is increasingly being used in the study of disease outbreaks for direct agent-to-agent transmission. However, a number of infectious diseases are indirectly transmitted between agents through vectors or environment. In this talk, we present the first agent-based modelling framework for indirect disease transmission, in which the environment plays the role of vector. The computational multi-agent, multi-layer system developed here incorporates intervention strategies to explore the effect of environmental factors and hospitalization on disease spread and control. We implement the system to study the 2014 outbreaks of Ebola in Africa, and use parameter estimates in the literature provided by the analysis of databases collected for such outbreaks. This is an ongoing project in collaboration with Seyed M. Moghadas from York University (Canada) and Aquino L. Espindola from Instituto de Ciências Exatas – ICEx (Brazil).

Targeted transcranial electrical stimulation protocols: Spatially restricted intracerebral effects via improved stimulation and recording techniques

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Neural activity can be induced or modulated by an exogenous electrical field, which can be generated noninvasively by transcranial electrical stimulation (TES). The physiological effects of TES are determined by the spatial distribution and temporal pattern of the induced intracerebral electrical field. In most cases in human patients there is no direct data accessible about the local neuronal entrainment by TES, but still the *a priori* knowledge on the expectable local intracerebral effects of given stimulation parameters may allow to design targeted treatment plans. In principle, TES can be also spatially selective (similarly to deep brain stimulation) by limiting the extent of the electrical fields. In our experiments, we set out to measure the TES generated electrical fields in human brains and to test the viability of a spatially focused TES protocol. Our assumption is that the effect of repetitively delivered high frequency (>1 kHz) Gaussian pulses on multiple bilateral

electrode pairs may be temporally integrated by the neurons, leading to a stronger neuronal entrainment around the cross point of the diagonal gradients than at the periphery.

We recorded TES-generated field potentials in human cadavers and anesthetized rats. Stimulation was applied by placing Ag/AgCl EEG electrodes over the external surface of the skull. We used independently isolated stimulation pairs to deliver sinusoidally modulated TES with various parameters and repetitive high-frequency Gaussian stimulus trains in various arrangements. Custom made multiple-site electrodes (>200 contact points) and 32-channel silicone probes were used to thoroughly sample the field potentials in the brain. We also measured the shunting effect of the skin and the skull during transcutaneous stimulation by comparing the gradients to the effect of direct stimulation over the surface of the brain.

In addition to our earlier results, we found that the skin dramatically reduced the generated intracranial electrical gradients, and alters its geometry. We recorded the unit activity during the high-frequency pulsed TES, and estimated its effects on neuronal activity. We found that the high-frequency stimulation generates a relatively small diameter axial voltage gradient in the geometrical axis of the stimulator electrodes (<50% gradient strength off-axis vs in-axis). The multiple crossing stimulation pairs protocol resulted in a spatially focal effect after temporal integration (>30% larger gradient strength at the crosspoint than at the periphery). We also suggest a protocol to selectively and unilaterally stimulate the frontal cortex via TES.

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