Final report of the project KH 125628

General summary

The general theme of the proposal is the formulation and analysis of metapopulation models expressed by high dimensional differential equations, arising from various problems in population dynamics and mathematical epidemiology. After developing a suitable model that captures in sufficient details the required biological complexity, the key questions are centering around how combined local control strategies can provide a successful global control strategy. In mathematical terms, we are looking for meaningful conditions for local and global stability of equilibria, persistence of species, and the global bifurcation structure with respect to model parameters. Also, we parametrize the systems, numerically solve, visualize and interpret their solutions, and apply them to the original real world problems.

Participants

There was the following change in personnel: it was planned that Gábor Kiss will be employed on this project, but he gained employment in another way before the project started. Hence, Attila Dénes was employed instead. Both of them are original participants of the projects, so we only needed to tune their FTEs according to their changed roles. After Attila Dénes won a NKFIH PD grant, we have employed Ferenc Bartha to replace him. For a short period we employed Francesca Scarabel who came to work with us from Helsinki on numerical bifurcation analysis of some infinite dimensional dynamical systems.

Scientific results

In [1] we investigate the temporal evolution of the distribution of immunities in a population, which is determined by various epidemiological, immunological, and demographical phenomena: after a disease outbreak, recovered individuals constitute a large immune population; however, their immunity is waning in the long term and they may become susceptible again. Meanwhile, their immunity can be boosted by repeated exposure to the pathogen, which is linked to the density of infected individuals present in the population. This prolongs the length of their immunity. We consider a mathematical model formulated as a coupled system of ordinary and partial differential equations that connects all these processes and systematically compare a number of boosting assumptions proposed in the literature, showing that different boosting mechanisms lead

to very different stationary distributions of the immunity at the endemic steady state. In the situation of periodic disease outbreaks, the waveforms of immunity distributions are studied and visualized. Our results show that there is a possibility to infer the boosting mechanism from the population level immune dynamics. We continued this research by combining analytical results with cutting-edge techniques of numerical bifurcation analysis for infinite-dimensional dynamical systems, and uncovered a surprisingly complicated and very interesting global bifurcation structure for models with waning and boosting of immunity, including torus bifurcations and coexistence of stable periodic orbits [14].

In [2] we present a mathematical model describing the spread of an infectious disease spread by ectoparasites which are harboured by rodents (e.g. plague transmitted by fleas spread by rats). We identify three reproduction numbers for the rodent subsystem and show that these three reproduction numbers completely characterize the global dynamics of this subsystem. Depending on which of the four equilibria of the rodent subsystem is globally attractive, we determine the possible equilibria of the human subsystem and show that one of the equilibria of this subsystem is always globally attractive. Hence we completely describe the global dynamics of the full system.

In [3] we study the global stability of a multistrain SIS model with superinfection and patch structure. We establish an iterative procedure to obtain a sequence of threshold parameters. By a repeated application of a result by Takeuchi et al. [Nonlinear Anal Real World Appl. 2006;7:235-247], we show that these parameters completely determine the global dynamics of the system: for any number of patches and strains with different infectivities, any subset of the strains can stably coexist depending on the particular choice of the parameters. Finally, we return to the special case of one patch examined in [Math Biosci Eng. 2017;14:421-435] and give a correction to the proof of Theorem 2.2 of that paper. Let us point out that [3] completely solved Problem 4 proposed in the research plan.

Paper [4] is concerned with some aspects of numerical methods. Maximal stability regions of explicit Runge-Kutta methods are derived. Explicit one-parameter power form representation of the proper Zolotarev sextic polynomials is found in [7], which is major advance as such explicit representation had been known only up to degree five.

[8] considers a model for the spread of a sexually transmitted disease considering sexual transmission and spread via infected needles among intravenous drug users. Besides the transmission among drug users, we also consider sexual contacts between intravenous drug users and non-drug users. Furthermore, the needles are considered as a vector population. For several European countries, a sharp increase of sexually transmitted diseases was reported and several others are rated as endangered based on the number of syringes given out per intravenous drug users per year. The main purpose of the paper is to investigate the dynamics of this model including the effect of needle exchange and study the risk of an increased transmission among non-drug users, induced by the

reduction of the needle exchange program. Following the determination of the basic reproduction number R_0 it is shown that all solutions tend to the unique disease-free equilibrium if $R_0 < 1$. We also prove that the disease persists in the human population if $R_0 > 1$. Our numerical simulations, based on real life and hypothetical data for HIV, suggest that a decrease in the rate of the distribution and discharge rate of new needles might imply that the considered disease is becoming endemic in the considered human population of drug users and non-drug users. A variant of our model with time- variable needle distribution parameter is fitted to recent HIV data from Hungary to give a forecast for the number of infected in the following years.

The impact of quarantine during an outbreak of Ebola virus disease was modelled in [9]. The quarantine of people suspected of being exposed to an infectious agent is one of the most basic public health measure that has historically been used to combat the spread of communicable diseases in human communities. This study presents a new deterministic model for assessing the population-level impact of the quarantine of individuals suspected of being exposed to disease on the spread of the 2014–2015 outbreaks of Ebola viral disease. It is assumed that quarantine is imperfect (i.e., individuals can acquire infection during quarantine). In the absence of quarantine, the model is shown to exhibit global dynamics with respect to the disease-free and its unique endemic equilibrium when a certain epidemiological threshold is either less than or greater than unity. Thus, unlike the full model with imperfect quarantine (which is known to exhibit the phenomenon of backward bifurcation), the version of the model with no quarantine does not undergo a backward bifurcation. Using data relevant to the 2014–2015 Ebola transmission dynamics in the three West African countries (Guinea, Liberia and Sierra Leone), uncertainty analysis of the model show that, although the current level and effectiveness of quarantine can lead to significant reduction in disease burden, they fail to bring the associated *quarantine reproduction number* to a value less than unity (which is needed to make effective disease control or elimination feasible). This reduction of this number is, however, very possible with a modest increase in quarantine rate and effectiveness. It is further shown, *via* sensitivity analysis, that the parameters related to the effectiveness of quarantine (namely the parameter associated with the reduction in infectiousness of infected quarantined individuals and the contact rate during quarantine) are the main drivers of the disease transmission dynamics. Overall, this study shows that the singular implementation of a quarantine intervention strategy can lead to the effective control or elimination of Ebola viral disease in a community if its coverage and effectiveness levels are high enough.

[10] established a new four-dimensional system of differential equations for a honeybee colony to simultaneously model the spread of *Varroa* mites among the bees and the spread of a virus transmitted by the mites. The bee population is divided to forager and hive bees, while the latter are further divided into three compartments: susceptibles, those infested by non-infectious vectors and those infested by infectious vectors. The system

has four potential equilibria. We identify three reproduction numbers that determine the global asymptotic stability of the four possible equilibria. By using Dulac's criterion, Poincaré–Bendixson and persistence theory, we show that the solutions always converge to one of the equilibria, depending on those three reproduction numbers. Hence we completely described the global dynamics of the system.

To solve Problem 1 of the research plan, we adapted a recent approach of disease control by constructing alternative next generation matrices to vector borne diseases with spatial patch structure. The method allows us to determine if a given vector control strategy is capable of controlling the disease. This way we can construct local strategies of vector contol on selected patches that translates into successful disease control on the global scale. Our manuscript on this is still in preparation [11].

Problem 3 of the research plan has been mostly solved in [12]. The manuscript is under finalization, but the results have already been presented at a number of international conferences. The existence and local stability of equilibria in the two patch delayed logistic equation is fully described. We found stability switches with respect to the migration parameters. We achieved global attractivity results in the case of one-way migration, and we could formulate a generalized Wright-conjecture.

Regarding Problem 2 of the research plan, we considered first single species dynamics in seasonal environment with maturation delay. With the assumption of short reproductive period, we were able to reduce the system to a discrete map, where seasonal and delayed effects are distorting the recruitment function, thus generating different dynamics than a corresponding discret time model with the given recruitment function (Ricker, Beverton-Holt, etc.). We gave sufficient conditions for the population extinction as well as the existence and stability of a non-trivial periodic solution, and constructed periodic solutions of any period which is an integer multiple of the system coefficients periodicity (in ecological models typically one year). We are working on extending this approach to patch models, and finding ways to reduce the coninuous model to iterating discrete time maps. Our manuscript is in preparation [13], but the resulst have already been presented at international conferences.

The introduction of varicella-zoster virus (VZV) vaccines into the routine vaccination schedule is under introduction in Hungary, hence it is important to understand the current transmission dynamics and to estimate the key parameters of the disease. Mathematical models can be greatly useful in advising public health policy decision making by comparing predictions for different scenarios. Our works are summarized in [5],[6],[15]. First we consider a simple compartmental model that includes key features of VZV such as latency and reactivation of the virus as zoster, and exogeneous boosting of immunity. After deriving the basic reproduction number R0, the model is analysed mathematically

and the threshold dynamics is proven: if R0 ≤ 1 then the virus will be eradicated, while if R0 > 1 then an endemic equilibrium exists and the virus uniformly persists in the population. Then we extend the model to include seasonality, and fit it to monthly incidence data from Hungary. It is shown that besides the seasonality, the disease dynamics has intrinsic multi-annual periodicity. We also investigate the sensitivity of the model outputs to the system parameters and the underreporting ratio, and provide estimates for R0. We investigated different vaccination strategies with the simple compartmental model, and pointed out the expected increase in zoster cases after introducing the varicella vaccinations, as well as the outstanding danger of ceasing the vaccination campaign some years after of its introduction. Based on our simple model the global effects and strategic goals can be already visible. To build a realistic model which can be used to evaluate the impact of vaccination policies, our model should be significantly extended by an other modelling arm representing vaccinated compartments, the parameters and the specifics of the given vaccination strategy, seasonal effects, and a metapopulation model with detailed age structure, age specific parameters and contact patterns. We are currently working on this challenging and highly important task, and have achieved significant preliminary results.

Publications

[1] M.V. Barbarossa, M. Polner and G. Röst, Temporal Evolution of Immunity Distributions in a Population with Waning and Boosting, ***Complexity***, 2018: Paper 9264743. (2018), doi: 10.1155/2018/9264743

[2] A. Dénes, G. Röst, Dynamics of an infectious disease including ectoparasites, rodents and humans, in: ***Trends in Biomathematics: Modeling, Optimization and Computational Problems*** (ed. R. Mondaini), Springer, 2018, pp. 59–73. doi: 10.1007/978-3-319-91092-5_5

[3] A. Dénes, Y. Muroya, G. Röst: Global stability of a multistrain SIS model with superinfection and patch structure, arXiv:1805.06552 (in revision in ***Mathematical Methods in the Applied Sciences***)

[4] R. Vajda: Maximal Radius for Stability Regions for Explicit Runge Kutta Methods by Real Quantifier Elimination, 19th International Symposium on Symbolic and Numeric Algorithms for Scientific Computing, (**SYNASC 2017**), pp. 49-54., 2017

[5] Karsai J, Csuma-Kovács R, Dudás J, Dánielisz Á, Molnár Zs, Röst G, On the impact of vaccination on the epidemiology of varicella in Hungary ***APLIMAT 2019***, 617-627

[6] Csuma-Kovács R, Dudás J, Karsai J, Dánielisz Á, Molnár Zs, Röst G, Challenges in the modelling and control of varicella in Hungary, in: ***Progress in Industrial Mathematics at ECMI 2018*** (eds. I. Faragó, F. Izsák, P. Simon), Springer 2019

[7] H.-J. Rack, R. Vajda: An Explicit Univariate and Radical Parametrization of the Sextic Proper Zolotarev Polynomials in Power Form, ***Dolomites Research Notes on Approximation*** Padova University Press, 12(1), pp. 43-50, 2019.

[8] E. Bánhegyi, A. Dénes, J. Karsai, L. Székely, The effect of the needle exchange program on the spread of some sexually transmitted diseases, ***Math. Biosci. Eng.*** 16(2019), No. 5, 4506–4525.

[9] A. Dénes, A. B. Gumel, Modeling the impact of quarantine during an outbreak of Ebola virus disease, ***Infect. Dis. Model.*** 4(2019), 12–27.

[10] A. Dénes, M. A. Ibrahim, Global dynamics of a mathematical model for a honeybee colony infested by virus-carrying Varroa mites, ***J. Appl. Math. Comput.*** 61(2019), 349–371.

[11] A. Dénes, D. Knipl, G. Röst, Spatial strategies of vector control for the eradication of vector borne diseases, in preparation

[12] F. Bartha, D. Knipl, G. Röst, X. Zou, Dynamics of the delayed logistic equation on two patches, manuscript. Results were already presented at 11QTDE, ICIAM 2019, BIOMAT 2019.

[13] A. Dénes, G. Röst, Single species dynamics in seasonal environment with maturation delay and short reproductive period, manuscript. Results were already presented at ICIAM 2019.

[14] MV Barbarossa, M Polner, G Röst, F Scarabel, Global bifurcation diagram of an epidemiological model of waning and boosting of immunity with discrete and distributed delays, in preparation. Results were already presented at ICIAM 2019.

[15] J Karsai, R Csuma-Kovács, Á Dánielisz, Zs Molnár, J Dudás, T Borsos, G Röst, Modeling the transmission dynamics of varicella in Hungary, submitted to ***Journal of Mathematics in Industry.*** Results were already presented at 11QTDE and BIOMAT 2019.