Final report

Asymptotic behaviour of population dynamical models

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Papers published during the grant period

The following two papers, connected to the topic of modelling ectoparasite-borne diseases, and submitted before the start of the grant were published during the first year of the grant.

- A. Dénes, G. Röst, Global dynamics of a compartmental system modeling ectoparasite-borne diseases, *Acta Sci. Math. (Szeged)* **80**(2014), 553–572.
- A. Dénes, G. Röst, Impact of excess mortality on the dynamics of diseases spread by ectoparasites, in: M. Cojocaru, I. S. Kotsireas, R. Makarov, R. V. N. Melnik, H. Shodiev (Eds.), *Interdisciplinary Topics in Applied Mathematics, Modeling and Computational Science*, Springer Proceedings in Mathematics & Statistics, Vol. 117, Springer International Publishing, 2015.

The following papers were submitted and/or published during the grant period.

- M. V. Barbarossa, A. Dénes, G. Kiss, Y. Nakata, G. Röst, Zs. Vizi, Transmission dynamics and final epidemic size of Ebola Virus Disease outbreaks with varying interventions, *PLoS ONE* **10**(7)(2015) e0131398.

  We proposed a compartmental model to describe the dynamics of the ongoing Ebola epidemic in West Africa, including virus transmission in the community, at hospitals, and at funerals. Using two frameworks (time-dependent parameters and impulsive change in the parameters), we incorporated the increasing intensity of intervention efforts. Fitting the system to the early phase of the 2014 West Africa Ebola outbreak, we estimated the basic reproduction number as 1.44. We derived a final size relation which allows us to forecast the total number of cases during the outbreak when effective interventions are in place. Our model predictions showed that, as long as cases are reported in any country, intervention strategies cannot be dismissed. We also showed that, since the main driver in the slowdown of the epidemic is not the depletion of susceptibles, future waves of infection might be possible, if control measures or population behavior are relaxed.

- A. Dénes, G. Röst, Global stability for SIR and SIRS models with nonlinear incidence and removal terms via Dulac functions, *Discrete Contin. Dyn. Syst. Ser. B* **21**(2016), 1101–1117.

  We proved the global asymptotic stability of the disease-free and the endemic equilibrium for general SIR and SIRS models with nonlinear incidence. Instead of the popular Volterra-type Lyapunov functions, we used the method of Dulac functions, which allowed us to extend the previous global stability results to a wider class of SIR and SIRS systems, including nonlinear (density-dependent) removal terms as well. We showed that this method is useful in cases that cannot be covered by Lyapunov functions, such as bistable situations. We completely described the global attractor even in the scenario of a backward bifurcation, when multiple endemic equilibria coexist.

- A. Dénes, L. Hatvani, On the asymptotic behaviour of solutions of an asymptotically Lotka–Volterra model, *Electron. J. Qual. Theory Differ. Equ.* **2016**, No. 67, 1–10.

  We made more realistic our model [1] on the coexistence of fishes and plants in Lake Tanganyika. The new model is an asymptotically autonomous system whose limiting equation is a Lotka–Volterra system. We give conditions for the phenomenon that the trajectory of any solution of the original non-autonomous system "rolls up" onto a cycle of the limiting Lotka–Volterra equatios, which means that the limit set of the solution of the non-autonomous system coincides with the cycle. We constructed a counterexample showing that the key integral condition on the coefficient function in the original non-autonomous model cannot be dropped and provided computer simulations to illustrate the results.

- A. Dénes, Y. Muroya, G. Röst, Global stability of a multistrain SIS model with superinfection, *Math. Biosci. Eng.* **14**(2017), No. 2, 421–435.

  The basic model for the spread of ectoparasites and diseases transmitted by them, established in [2], was generalized in a joint work with Yoshiaki Muroya and Gergely Röst where we considered a multistrain

SIS model with superinfection with n different strains having different virulences. We established an iterative procedure to calculate a sequence of reproduction numbers, and we proved that this sequence completely determines the global dynamics of the system. We showed that for any number of strains with different virulences, the stable coexistence of any subset of the strains is possible, and we completely characterized all scenarios.

- A. DÉNES, L. SZÉKELY, Global dynamics of a mathematical model for the possible re-emergence of polio, *Math. Biosci.* **293**(2017), 64–74.

  This work was motivated by some studies warning about a possible re-emergence of poliomyelitis in Europe, due to a decreased vaccination rate in several European countries and the arrival of refugees from war-torn areas where polio vaccination was reduced or completely stopped. The use of inactivated polio vaccine can also contribute to the unobserved spread of polio, as this vaccine only partly prevents vaccinees from infection, and even vaccinated people might become carriers and in regions with low vaccination coverage, herd immunity might be insufficient to prevent sustained transmission. As only one in every 200 infected develops acute flaccid paralysis, it might take one year of silent transmission before one paralysis case is identified and an outbreak is detected, although hundreds of individuals would carry the infection. In our work, we established a compartmental model with seven compartments including those who may become carriers of the disease in spite of being vaccinated. We calculated the basic reproduction number $\mathcal{R}_0$, and showed that (depending on the reproduction number) the system may have two equilibria, a disease-free and an endemic one. By constructing an appropriate Lyapunov function, we proved that for $\mathcal{R}_0 < 1$, the disease-free equilibrium is globally asymptotically stable. Using persistence theory, we showed that for $\mathcal{R}_0 > 1$, all the infected compartments are strongly uniformly persistent. Using the results on persistence, and applying a Volterra-type Lyapunov function, we showed that for $\mathcal{R}_0 > 1$, the unique endemic equilibrium is globally asymptotically stable. Hence we determined the global dynamics of the system: we showed that, depending on the parameters, one of the two equilibria is globally asymptotically stable. Based on our results and some numerical experiments, we gave suggestions on how vaccination should be performed: our results suggest that vaccinating the immigrant population is insufficient to stop the spread of the disease, also the vaccination rate of the European population should be increased to reach the level which is sufficient to obtain herd immunity.

- A. Dénes, G. Röst, Dynamics of an infectious disease including ectoparasites, rodents and humans (submitted)

  This work was motivated by our basic model for the spread of ectoparasites and diseases transmitted by them, established in [2]. It is well known, that in the case of several ectoparasite-borne diseases, the parasites are spread to humans by rodents (the most commonly known example for this is plague transmitted by fleas spread by rats). We present a mathematical model describing the spread of an infectious disease spread by ectoparasites which are harboured by rodents. The compartmental model consists of two parts: there are three rodent compartments and three human compartments; for both parts we have susceptibles, those who are infested with non-infectious parasites and those who are infested by infectious parasites. The two parts of the model are coupled by the parasite transmission from rodents to humans. As it is assumed that the parasites are not transmitted the opposite way, the three rodent equations can be decoupled from the rest of the equations, forming a three-dimensional system similar to the one studied in [2]. First we identify three reproduction numbers for the rodent subsystem and show that these three reproduction numbers completely characterize the global dynamics of this subsystem. In the proof we use persistence theory, Dulac–Bendixson theory and the Poincaré–Bendixson theorem. The latter two methods can be applied because the three-dimensional system can be reduced to a two-dimensional one by the introduction of a new variable. 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. Also in the case of the human subsystem, a reduction to two dimensions is possible, and similar methods can be applied. Hence we completely describe the global dynamics of the full system.

Ongoing work

- *Global stability of a multistrain SIS model with superinfection and patch structure*

  The paper entitled Global stability of a multistrain SIS model with superinfection and patch structure, which is a joint work with Yoshiaki Muroya and Gergely Röst is before submission. In this paper, which is a continuation of our previous work, a generalization of the results published earlier this year in *Math. Biosci. Eng.*, we study the global stability of a multistrain SIS model with superinfection and patch structure: we consider a model with p patches, and on each patch the population is divided into $n+1$ compartments according to infections by a virus with n strains with different virulences such that the more virulent strains may superinfect individuals infected by weaker strains. We establish an iterative procedure to obtain a sequence of threshold parameters. Applying the result of [10], we show that these threshold 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. We will probably submit the paper based on the result in the first week of November 2017.

- *The relation between attractivity and stability*

  The manuscript entitled From attractivity to stability (joint work with Gergely Röst) is before submission. In this work we study the connection between attractivity and stability of an equilibrium of a system of ordinary differential equations: using notions and results from [9], we show that if a system has a single equilibrium which is globally attractive, then, it is stable if and only if there are no homoclinic orbits. The submission of the manuscript is expected within 1–2 weeks.

- *The effect of the needle exchange program on the spread of HIV*

  The manuscript The effect of the needle exchange program on the spread of HIV, a joint work with Eliza Bánhegyi and János Karsai is before submission. In the paper we study the possible effect of the reduction of the sterile needle exchange program among drug users on the spread of HIV. The work was motivated by some recent studies We have established a compartmental model consisting of six compartments, in which, following the idea of some earlier work by Kaplan et al. [3–5], the needle population acts as a vector. In the model, there is a susceptible and an infected compartment for those who do not use drugs, for the drug users and for the needles, respectively. We have calculated the basic reproduction number $\mathcal{R}_0$. By constructing an appropriate Lyapunov function, we have showed that the unique disease-free equilibrium is always globally asymptotically stable is $\mathcal{R}_0 < 1$. Using persistence theory, we have showed that the disease is persistent if the reproduction number is larger than 1. We conjecture that there is a unique endemic equilibrium is $\mathcal{R}_0 > 1$. We are currently working on the nonautonomous case when the needle distribution is changing in time. The paper based on the results will probably be submitted within 1–2 months.

- *Stability threshold for scalar periodic delay differential equations*

  In a joint work with Gergely Röst, we study the stability properties of the equation
  $$x'(t) = g(t, x(t), x(t-1)),$$
  where $g(t, 0, 0) = 0$ and $g(t, \xi, \eta) = g(t + P, \xi, \eta)$ for all $t, \xi, \eta \in \mathbb{R}$. This type of equation arises in several mathematical models, such as neural networks, or transmission dynamics of vector-borne diseases, and population growth models with seasonality. The linear variational equation of this equation has the form
  $$x'(t) = -a(t)x(t) + b(t)x(t-1),$$
  where $a(t)$ and $b(t)$ are nonnegative, P-periodic continuous real functions. The linear equation was studied in [7]. So far, we have generalized the results given in that paper by proving that if $b(t)$ has the form
  $$\begin{cases} b(t) = 0, & \text{if } kP \leq t \leq kP + L,\ k = 0, 1, 2, \dots, \\ b(t) > 0, & \text{elsewhere,} \end{cases},$$
  where $1 \leq L < P < L+1$, then the zero solution of the linear equation is stable if and only if for the stability threshold $\gamma := -\int_{-1}^{P-1} a(s)\mathrm{d}s + \ln\big(\int_{L-P}^{0} b(u)e^{\int_{u-1}^{u} a(s)\mathrm{d}s}\mathrm{d}u + 1\big)$, the relation $\gamma \leq 0$ holds. We are currently working on the original nonlinear equation, we would like to try conditions on the function g such that extinction follows from linear stability and persistence follows from linear instability. In the case of persistence we would like to find conditions for the existence of periodic solutions. The manuscript based on our results is expected to be submitted this year.

- *Mathematical models for the sterile insect technique*

  In a joint work with Maria Vittoria Barbarossa, we work on modelling the sterile insect technique. This environmentally nonpolluting technique has been used to control the populations of harmful insects since the middle of the 20th century. The method consists in releasing large numbers of sterile male insects, which compete for the females with the fertile males. Females mating with sterile males will not have offspring, thus reducing the population in the next generation.

We have established basic ordinary, resp. delay differential equation models. We have obtained results on existence, uniqueness, nonnegativity of solutions, as well as numerical simulations and qualitative comparison with previous models. We have established a new model for sterile insect technique, based on the Nicholson's blowflies equation. We constructed the basic model for sterile insect technique, including time delay for maturation lags and periodic, resp. impulsive release of sterile males and we have established a malaria transmission model including the model. Submission of results about the topic are expected for next year.

- *Malaria dynamics with long incubation period in hosts in a periodically changing environment*

  In a joint work with Gergely Röst, we study a compartmental model for the transmission dynamics of malaria. Our new model is based on the model established in [6] which features two distinct exposed classes in human population, motivated by empirical observation of the bimodal distribution of the incubation time of *P. vivax* in Korea. To make the model more realistic, in our new model the mosquito birth and death rates as well as the transmission rates are assumed to be periodic. The periodic delay model takes into account the climate factors, by assuming the birth and death rates of mosquitoes and the transmission coefficients to be periodic functions. Applying methods established in [12], we have calculated the basic reproduction number as the spectral radius of a linear integral operator on a space of periodic functions. To apply the methods established in [12], one needs to transform the system to have a cooperative transition matrix. We are now working on showing that the reproduction number serves as a threshold parameter for the global dynamics of the system. We plan to include simulations with data from South Korea. The paper based on the results is expected in the first half on next year.

- *Modelling of Koi herpes in carps*

  The highly virulent Koi herpesvirus (KHV) infecting carps has seasonal outbreaks in spring and autumn. The mechanism of seasonality is seasonal variation in the length of sojourn time between the host immune states. After a fish is infected with KHV, there is a temperature-dependent delay before it becomes infectious, and a further delay before mortality, i.e. KHV epidemiology is driven by seasonal changes in water temperature. A mathematical model was given in [8], but no deep mathematical analysis has been done yet. In a joint work with Toshikazu Kuniya, Ryosuke Omori and Gergely Röst, we have established a model with two periodic delays to study this phenomenon. In [16], a similar model was studied, however, the paper contains only local stability results. We plan to extend the results to global stability. The paper based on the results is expected for next year.

Conference and seminar talks

I gave the following conference and seminar talks during the grant period.

- On the risk of polio re-emergence in Europe due to unvaccinated war refugees, *Pannonian Mathematical Modelling Conference*, 25–28 April, 2015, Novi Sad, Serbia

- Global stability for SIR and SIRS models via Dulac functions, *10th Colloquium on the Qualitative Theory of Differential Equations*, 1–4 July, 2015, Szeged

- Transmission dynamics and final epidemic size of Ebola Virus Disease outbreaks with varying interventions, *Mathematical and Computational Epidemiology of Infectious diseases*, 30 August–5 September, 2015, Erice, Italy

- Transmission dynamics and final epidemic size of Ebola Virus Disease outbreaks with varying interventions, *Conference on Mathematical Modeling and Control of Communicable Diseases*, 11–14 January, 2016, Rio de Janeiro, Brazil

- Global stability for SIR and SIRS models via Dulac functions, *International Conference on Applications of Mathematics to Nonlinear Sciences*, 26–29 May, Kathmandu, Nepal (invited talk)

- Transmission dynamics and final epidemic size of Ebola Virus Disease outbreaks with varying interventions, *The 11th AIMS Conference on Dynamical Systems, Differential Equations and Applications*, 1–5 July, 2016, Orlando, USA (invited talk)

- Global stability of a multistrain SIS model with superinfection, *The 11th AIMS Conference on Dynamical Systems, Differential Equations and Applications*, 1–5 July, 2016, Orlando, USA (invited talk)

- Járványtani modellek (Models from mathematical epidemiology), seminar talk, Eötvös Loránd University, 10 April 2017
- Global stability of a multistrain SIS model with superinfection, *XXV Congreso de Ecuaciones Diferenciales y Aplicaciones / XV Congreso de Matemática Aplicada*, 26–30 June 2017, Cartagena, Spain (invited talk)

The following talk was given shortly after the end of the grant period, based on result obtained during the grant period.

- Dynamics of an infectious disease including fleas, rodents and humans, *17th International Symposium on Mathematical and Computational Biology*, 29 October–3 November, 2017, Moscow

Awards obtained during the grant period

I received the following prize and scholarship during the grant period

- In 2015, I was awarded the Farkas Gyula Memorial Prize, given by the János Bolyai Mathematical Society
- In 2017, I obtained the János Bolyai Research Scholarship of the Hungarian Academy of Sciences for the period 2017–2020. The title of my grant proposal was *Asymptotic behaviour of non-autonomous models from population dynamics and mathematical epidemiology*. During the three years of the scholarship, I plan to continue working on the topics concerning periodic epidemic models started during the past three years of my grant and to further develop the models to more general time-dependencies.

References

[1] A. Dénes, L. Hatvani, L. L. Stachó, Eventual stability properties in a non-autonomous model of population dynamics, *Nonlinear Anal.* **73**(2010), 650–659.

[2] A. Dénes, G. Röst, Global dynamics for the spread of ectoparasite-borne diseases, *Nonlinear Anal. Real World Appl.* **18**(2014), 100–107.

[3] E. H. Kaplan, R. Heimer, HIV prevalence among intravenous drug users: model-based estimates from New Haven's legal needle exchange, *J. Acquir. Immune Defic. Syndr.*, **5**(1992), 163–169.

[4] E. H. Kaplan, E. O'Keefe, Let the Needles Do the Talking! Evaluating the New Haven Needle Exchange, *Interfaces*, 1993, No. 1, Franz Edelman Award Papers, 7-26.

[5] E. H. Kaplan, R. Heimer, The model based estimate of HIV infectivity via needle sharing, *J. Acquir. Immune Defic. Syndr.*, 1992, 1116–1118.

[6] K. Nah, Y. Nakata, G. Röst, Malaria dynamics with long incubation period in hosts, *Comput. Math. Appl.* **68**(2014), No. 9, 915–930.

[7] K. Nah, G. Röst, Stability threshold for scalar linear periodic delay differential equations, *Canad. Math. Bull.* **59**(2016), 849–857.

[8] R. Omori, B. Adams, Disrupting seasonality to control disease outbreaks: The case of koi herpes virus, *J. Theoret. Biol.* **271**(2011), 159–165.

[9] P. Poláčik, Existence of unstable sets for invariant sets in compact semiflows. Applications in order-preserving semiflows, *Comment. Math. Univ. Carolin.* **31**(1990), 263–276.

[10] Y. Takeuchi, W. Wang, Y. Saito, Global stability of population models with patch structure. *Nonlinear Anal. Real World Appl.* **7**(2006), 235–247.

[11] X. Wu, F. M. Magpantay, J. Wu, X. Zou, Stage-structured population systems with temporally periodic delay, *Math. Methods Appl. Sci.* **38**(2015), 3464–3481.

[12] X.-Q. Zhao, Basic reproduction ratios for periodic compartmental models with time delay, *J. Dynam. Differential Equations* **29**(2015), 67–82.