Final Report of the Research Project FK 124016:

Functional differential equations in mathematical epidemiology
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Overview

Functional differential equations are suitable for modelling phenomena where the rate of change of the system state at a given time depends on past states, i.e. on the history of the system. They are used in several applications from engineering and physics to mathematical biology. In particular, in epidemiology, time delays appear in the model equations naturally for various reasons: in control (it takes time to initiate a treatment or other intervention); due to spatial constraints (it takes time for hosts to move to other location); the duration of disease stages (latency, infectious period); the loss of immunity after some time, or from mathematical transformations of structured population models incorporating within host processes. Functional differential equations generate infinite dimensional dynamical systems, since the state space is a suitable function space. This fact, together with the nonlinearities naturally emerging from epidemiological modelling makes the analysis of such models mathematically challenging.

Our main objective was to construct and analyse new mathematical models motivated by the problems of epidemiology, described by infinite dimensional dynamical systems; to explore the global dynamics of the resulted nonlinear systems and understand their implications to life sciences and public health. With this research we planned to develop and analyse new models that better capture such biological complexities which are currently in the frontier of infectious disease modelling. At the same time, we advanced the abstract mathematical theory of functional differential equations.

Project arrangements

The project ran from 01.12.2017 to 31.12.2022, at the Department of Applied and Numerical Mathematics, Bolyai Institute, University of Szeged. During this period, four PhD students joined the research. Among them, Khalil Muqbel defended his PhD in April 2021 (thesis title: Optimal Interventions for Epidemic Outbreak) and obtained his degree, Tamás Tekeli’s and Péter Boldog's thesis defence is scheduled for March 2023, and Bornali Das is expected to defend his thesis around June 2023. The COVID-19 pandemic has strongly affected the research process in several aspects. As conferences and travel were not possible for a substantial period of time, our budget and activities had to be adapted to the situation. On the other hand, COVID-19 gave rise to a number of urgent research problems that are closely related to the research objectives of this project, but which were obviously not foreseen in this form at the time of the call. Consequently, we also conducted a number of research activities related to the spread of COVID-19. Thirdly, the project’s researchers have been intensely involved in the pandemic response of Hungary, by modelling the spread of the disease, providing forecasts and analysing scenarios, providing invaluable input to policy makers. Unfortunately, there was also a tragic event: the sudden death of our brilliant young colleague Gabriella Vas shook us all, and several of our joint projects were interrupted.

Scientific output of the project

Our results have been published in 35 research papers, 21 of those appeared in Q1 ranked journals, and 6 of those are in D1 ranked journals (Scientific Reports, Epidemics, Nonlinear Dynamics, Proc R Soc A, J Nonlinear Science). Despite the short time elapsed since their publication, our papers already have received hundreds of citations in total. Many of our works have been done in international collaborations with researchers from USA, Canada, United Kingdom, Japan, China, Germany, and some papers on the more applied side were written in interdisciplinary collaborations with epidemiologist, network scientists, engineers, data scientist, social scientists. This way we found avenues of expedited knowledge transfer from pure mathematical theories to practical applications. Our results have been presented at many international meetings and conferences, including several plenary and keynote talks by our researchers. Due to space constraints it is impossible to outline here all the research results, hence below we show a selected set of research results.

Selected results

Below we summarize the research findings from a subset of our publications. The full list of papers can be found in the list attached to this report.

Functional differential equations (FDEs)

Delayed logistic equations, such as Wright's equation and its variants, are one of the most studied yet not fully understood type of equations, and also serve as benchmarks to improve techniques about the nonlinear dynamics of functional differential equations. In [Győri, Nakata, Röst *CPAA* 2018] we study bounded, unbounded and blow-up solutions of a delay logistic equation without assuming the dominance of the instantaneous feedback. It is shown that there can exist an exponential (thus unbounded) solution for the nonlinear problem, and in this case the positive equilibrium is always unstable. We obtain a necessary and sufficient condition for the existence of blow-up solutions, and characterize a wide class of such solutions. There is a parameter set such that the non-trivial equilibrium is locally stable but not globally stable due to the co-existence with blow-up solutions.

In [Baker, Röst *J Nonlinear Sci* 2020], we consider a novel delayed logistic equation with discrete and distributed delays. The equation has clear biological underpinning coming from cell population modelling. The global dynamics is completely described, and it is proven that all feasible non-trivial solutions converge to the positive equilibrium. The main tools of the proof rely on persistence theory, comparison principles and an *L2*-perturbation technique. Using local invariant manifolds, a unique heteroclinic orbit is constructed that connects the unstable zero and the stable positive equilibrium, and we show that these three complete orbits constitute the global attractor of the system. Despite global attractivity, the dynamics is not trivial as we can observe long-lasting transient oscillatory patterns of various shapes. We also discuss the biological implications of these findings and their relations to other logistic-type models of growth with delays.

Generally, the first Lyapunov coefficient, that determines the direction of the Hopf bifurcation, is given by a complicated formula. In [Balázs, Röst *CNSNS* 2020] we point out that for Wright type equations, it can be reduced to a simple inequality to check. By comparing the magnitudes of second and third order terms, we can immediately tell the direction of all the Hopf bifurcations emerging from zero, saving us from the usual lengthy calculations. We further obtain upper and lower estimates of the periods of the bifurcating limit cycles along the Hopf branches. The proof is based on a complete classification of the possible bifurcation sequences and the Cooke transformation that maps branches onto each other. Applying our result to Wright's equation, we show that the Hopf branches have no folds in a well estimated neighbourhood of the bifurcation point. Finally, we show how our results relate to the nonlinearity having negative Schwarzian derivative. The method is extended to delay recruitment models, and we show in [Balázs, Röst *IJBC* 2021] that the Hopf bifurcations in the Nicholson's blowfly equation are always supercritical, as we increase the delay. Earlier results treated only the first bifurcation point and even that was not fully explicit, hence we significantly improved the state-of-the-art in this regard.

[Baker, Röst *J Nonlinear Sci* 2020] Baker RE, Röst G: Global dynamics of a new delay logistic equation arisen in cell biology, JOURNAL OF NONLINEAR SCIENCE, **30**, pages 397–418 (2020)
[Balázs, Röst *CNSNS* 2020] Balázs I, Röst G: Hopf bifurcation for Wright-type delay differential equations: The simplest formula, period estimates, and the absence of folds, COMMUNICATIONS IN NONLINEAR SCIENCE AND NUMERICAL SIMULATION 84: 105188, 2020
[Balázs, Röst *IJBC* 2021] Balázs I, Röst G: Hopf bifurcations in Nicholson's blowfly equation are always supercritical. INTERNATIONAL JOURNAL OF BIFURCATION AND CHAOS. 2021 Apr;31(05):2150071
[Győri, Nakata, Röst *CPAA* 2018] Győri I, Nakata Y, Röst G: Unbounded and blow-up solutions for a delay logistic equation with positive feedback, COMMUNICATIONS ON PURE AND APPLIED ANALYSIS 17(6): 2845-2854, 2018

Functional differential equations in disease modelling

In [Röst, Vizi, Kiss *Proc A* 2018] we present the generalized mean-field and pairwise models for non-Markovian epidemics on networks with arbitrary recovery time distributions. First we consider a hyperbolic partial differential equation (PDE) system, where the population of infective nodes and links are structured by age since infection. We show that the PDE system can be reduced to a system of integro-differential equations, which is analysed analytically and numerically. We investigate the asymptotic behaviour of the generalized model and provide an implicit analytical expression involving the final epidemic size and pairwise reproduction number. As an illustration of the applicability of the general model, we recover known results for the exponentially distributed and fixed recovery time cases. For gamma- and uniformly distributed infectious periods, new pairwise models are derived. Theoretical findings are confirmed by comparing results from the new pairwise model and explicit stochastic network simulation. A major benefit of the generalized pairwise model lies in approximating the time evolution of the epidemic. Continuing this line of research, in [Vizi Kiss Miller Röst *J Math Ind* 2019], we prove that under some mild technical conditions on the distribution of the infectious periods, smaller variance in the recovery time leads to higher reproduction number, and consequently to a larger epidemic outbreak, when the mean infectious period is fixed. We discuss how this result is related to various stochastic orderings of the distributions of infectious periods.

In [Röst, Kuniya, Moghadas, Wu *Ricerche Mat* 2018], we study a model for influenza transmission dynamics, in which antiviral treatment as a single containment strategy was administered within a specified window of opportunity for initiating treatment. We extend this model to a more general framework with age-of-infection dependent treatment rates. The resulting age structured model can be transformed into a closed system of delay differential equations, for which we perform a complete global stability analysis. By constructing suitable Lyapunov functions, we show that the effective reproduction number fully characterizes the possible outcomes of disease dynamics. Our results allow us to evaluate treatment strategies and examine the impact of treatment delays on the potential success of disease control.

In [Barbarossa, Polner, Röst *Complexity* 2018], 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.

The use of multiple vaccine doses has proven to be essential in providing high levels of protection against a number of vaccine-preventable diseases at the individual level. However, the effectiveness of vaccination at the population level depends on several key factors, including the dose-dependent protection efficacy of vaccine, coverage of primary and booster doses, and in particular, the timing of a booster dose. For vaccines that provide transient protection, the optimal scheduling of a booster dose remains an important component of immunization programs and could significantly affect the long-term disease dynamics. In [Wang, Röst, Moghadas *J Math Biol* 2019], we developed a vaccination model as a system of delay differential equations to investigate the effect of booster schedule using a control parameter represented by a fixed time-delay. By exploring the stability analysis of the model based on its reproduction number, we show the disease persistence in scenarios where the booster dose is sub-optimally scheduled. The findings indicate that, depending on the protection efficacy of primary vaccine series and the coverage of booster vaccination, the time-delay in a booster schedule can be a determining factor in disease persistence or elimination. We present model results with simulations for a vaccine-preventable bacterial disease, Heamophilus influenzae serotype b, using parameter estimates from the previous literature. Our study highlights the importance of timelines for multiple-dose vaccination in order to enhance the population-wide benefits of herd immunity.

We propose and analyse a mathematical model for infectious disease dynamics with a discontinuous control function, where the control is activated with some time lag after the density of the infected population reaches a threshold in [Muqbel, Vas, Röst *QTDS* 2020]. The model is mathematically formulated as a delayed relay system, and the dynamics is determined by the switching between two vector fields (the so-called free and control systems) with a time delay with respect to a switching manifold. First we establish the usual threshold dynamics of persistence and eradication with respect to the basic reproduction number. For $R_0>1$, we divide the parameter domain into three regions, and prove results about the global dynamics of the switching system for each case: we find conditions for the global convergence to the endemic equilibrium of the free system, for the global convergence to the endemic equilibrium of the control system, and for the existence of periodic solutions that oscillate between the two sides of the switching manifold. The proof of the latter result is based on the construction of a suitable return map on a subset of the infinite dimensional phase space. Our results provide insight into disease management, by exploring the effect of the interplay of the control efficacy, the triggering threshold and the delay in implementation.

[Barbarossa, Polner, Röst *Complexity* 2018] Barbarossa MV, Polner M, Röst G: Temporal evolution of immunity distributions in a population with waning and boosting, COMPLEXITY, Paper 9264743
[Muqbel, Vas, Röst *QTDS* 2020] Muqbel K, Vas G, Rost G: Periodic Orbits and Global Stability for a Discontinuous SIR Model with Delayed Control, QUALITATIVE THEORY OF DYNAMICAL SYSTEMS 19: (2) 59, 2020
[Röst, Kuniya, Moghadas, Wu *Ricerche Mat* 2018] Röst G, Kuniya T, Moghadas SM, Wu J: Global dynamics of an epidemiological model with age-of-infection dependent treatment rate, RICERCHE DI MATEMATICA 67:(1), pp 125–140, 2018
[Röst, Vizi, Kiss *Proc A* 2018] Röst G, Vizi Zs, Kiss IZ: Pairwise approximation for SIR type network epidemics with non-Markovian recovery, PROC A MATH PHYS ENG SCI 474:(2210) Paper 20170695., 2018
[Vizi Kiss Miller Röst *J Math Ind* 2019] Vizi Zs, Kiss IZ, Miller JC, Röst G: A monotonic relationship between the variability of the infectious period and final size in pairwise epidemic modelling, JOURNAL OF MATHEMATICS IN INDUSTRY, 9:1, 2019
[Wang, Röst, Moghadas *J Math Biol* 2019] Wang Z, Röst G, Moghadas SM: Delay in booster schedule as a control parameter in vaccination dynamics, JOURNAL OF MATHEMATICAL BIOLOGY 79:(5-6), pp 2157–2182, 2019

COVID-19 modelling

During the pandemic, we have used mathematical tools to gain insight into several aspects of COVID-19 dynamics. First, in the early phase of the pandemic, we quantified the risk of global spread to various countries in [Boldog et al. *JCM* 2020], combining three types of models (local transmission dynamics, network of global transportations, branching process starting from immigrations). The model estimates the dependence of the risk of a major outbreak in a country from imported cases on key parameters such as: (i) the evolution of the cumulative number of cases in mainland China outside the closed areas; (ii) the connectivity of the destination country with China, including baseline travel frequencies, the effect of travel restrictions, and the efficacy of entry screening at destination; and (iii) the efficacy of control measures in the destination country (expressed by the local reproduction number). This method already identified Italy as a high risk country of becoming the next hot spot, several weeks in advance. Human mobility became important again when large amount of people were fleeing before lockdown measures were introduced. We also modelled this in [Barbarossa et al. *SciRep* 2021], then fitted the model to Italian data, estimated the final epidemic size in the presence of fleeing (even derived a final size relation analogue), and showed that in the case of Italty, people fleeing from the North to South when measures were implemented had no significant effect on the long term outcome of the outbreak. We have also derived a new final epidemic size relation which can be applied in any situation of abrupt population mobility impulses. Social behaviour has also influenced the pandemic waves, hence we collected large amounts of data to construct contact matrices [Koltai et al. *SciRe*p 2022]. These contact matrices, and also biological parameters constituted important inputs to age structured compartmental models, which has been used to analyse post-lockdown scenarios after the first pandemic wave [Röst et al. *Viruses* 2020]. In this paper, besides analysing the first wave in Hungary and the impact of various intervention measures, we proposed three scenarios for the second wave, and later in the reality the second wave followed very closely our moderate control scenario, producing the same peak size in hospitalizations.

We further used a control theory approach to devise optimal non-pharmaceutical interventions for various objective functions, that are composed of costs associated to healthcare burden, and costs associated to lockdowns [Péni et al. *Nonlinear Dynamics* 2020]. The results also clearly show the key importance of early intervention, the continuous tracking of the susceptible population and that of future work in determining the true costs of restrictive control measures and their quantitative effects. Nevertheless, the optimal strategy highly depends on the objective function, which may be different from country to country. A potential tool to reduce disease transmission is regular mass testing of a high percentage of the population, possibly with pooling (testing a compound of several samples with one single test). In [Tekeli, Dénes, Röst *MBE* 2022] we develop a compartmental model to study the applicability of this method and compare different pooling strategies: regular and Dorfman pooling. The model includes isolated compartments as well, from where individuals rejoin the active population after some time delay, hence the model is formulated as a system of delay differential equations. We develop a method to optimize Dorfman pooling depending on disease prevalence and establish an adaptive strategy to select variable pool sizes during the course of the epidemic. It is shown that optimizing the pool size can avert a significant number of infections. The adaptive strategy is much more efficient, and may prevent an epidemic outbreak even in situations when a fixed pool size strategy can not.

The advent of effective vaccines lead to open questions on how best to vaccinate the population. To address such questions, in [Childs et al. *Epidemics* 2022] we developed a model of COVID-19 infection by age that includes the waning and boosting of immunity against SARS-CoV-2 in the context of infection and vaccination. The model also accounts for changes to infectivity of the virus, such as public health mitigation protocols over time, increases in the transmissibility of variants of concern, changes in compliance to mask wearing and social distancing, and changes in testing rates. The model is employed to study public health mitigation and vaccination of the COVID-19 epidemic in Canada, including different vaccination programs (rollout by age), and delays between doses in a two-dose vaccine. We find that the decision to delay the second dose of vaccine is appropriate in the Canadian context. We found a similar result for Hungary as well, which has not been published yet, but such calculations played a role in forming the Hungarian vaccine rollout programme as well.

[Barbarossa et al. *SciRep* 2021] Barbarossa MV, Bogya N, Dénes A, Röst G, Varma H, Vizi Zs: Fleeing lockdown and its impact on the size of epidemic outbreaks in the source and target regions – a COVID-19 lesson, SCIENTIFIC REPORTS 11: (1) 9233, 2021

[Boldog et al. *JCM* 2020] Boldog P, Tekeli T, Vizi Zs, Dénes A, Bartha F,, Röst G: Risk assessment of novel coronavirus COVID-19 outbreaks outside China, JOURNAL OF CLINICAL MEDICINE 9: (2) 571, 2020

[Childs et al. *Epidemics* 2022] Childs L, Dick D, Feng Zh, Heffernan J, Li J, Röst G: Modeling waning and boosting of COVID-19 in Canada with vaccination, Epidemics 39: p. 100583., 2022

[Koltai et al. *SciRep* 2022] Koltai J, Vásárhelyi O, Röst G, Karsai M: Reconstructing social mixing patterns via weighted contact matrices from online and representative surveys, SCIENTIFIC REPORTS 12: (1) 4690, 2022

[Röst et al. *Viruses* 2020] Röst G, Bartha F, Bogya N, Boldog P, Dénes A, Ferenci T, Horváth K, Juhász A, Nagy Cs, Tekeli T, Vizi Zs, Oroszi B: Early Phase of the COVID-19 Outbreak in Hungary and Post-Lockdown Scenarios, VIRUSES 12: (7) p. 708., 2020

[Péni et al. *Nonlinear Dynamics* 2020] Péni T, Csutak B, Szederkényi G, Röst G: Nonlinear model predictive control with logic constraints for COVID-19 management, NONLINEAR DYNAMICS 102: (4) pp. 1965-1986., 2020

[Tekeli, Dénes, Röst *MBE* 2022] Tekeli T, Dénes A, Röst G: Adaptive group testing in a compartmental model of COVID-19, MATHEMATICAL BIOSCIENCES AND ENGINEERING 19: (11) pp. 11018-11033., 2022

Utilization of the research

Although the research objectives of the project were to further develop mathematical methods, tools, and models on the interface of functional differential equations and mathematical epidemiology, the pandemic highlighted the enormous benefits of such research not only for publioc health, but for society as a whole and the economy as well, since this pandemic caused unprecedented economic damage. Model based optimization of pandemic response policies can save lives, and mitigate the societal and economic costs, hence being extremely valuable. The research results on epidemic models obtained in the FK project have been a very important pillar of the Hungarian COVID-19 Mathematical Modelling and Epidemiological Analysis Task Force, which has been coordinated by the Ministry for Innovation and Technology during this crisis. Throughout the pandemic, the Task Force continuously provided in-depth situation reports, scenario analyses, forecasts and other strategic reports to policy makers to help evidence informed decision making, playing an important role in the pandemic response of the country.

Public engagement

Infectious disease modelling is a suitable topic for public engagement, as it captures the imagination of a general audience, and makes it possible to explain several mathematical concepts and ideas. Even before the pandemic we have been active in this area by giving popular lectures at various events, writing expository articles and so on. For example, the paper Dénes A, Ibrahim MA, Oluoch L, Tekeli M, Tekeli T. Impact of weather seasonality and sexual transmission on the spread of Zika fever. Sci Rep. 2019 Nov 19;9(1):17055 has been widely reported in the media, on platforms like National Geographic Hungarian edition, qubit.hu, origo.hu, ematlap.hu and other outlets. The public interest towards the mathematical modelling of epidemics skyrocketed during the pandemic, and the PI of the project appeared in all kinds of media (TV, radio, newspapers, magazines) countless of times. His interviews and explanatory articles became well known in Hungary, and reached hundreds of thousands of people, occasionally possibly over a million. He also gave many public lectures to diverse audiences such as high school students, university students, businessmen, international investors, ambassadors, security experts, general practitioners, and so on. Overall, the public awareness and appreciation of mathematical modelling of infectious diseases have been dramatically increased in the past years.