Papers published during the grant period

A. Dénes, G. Röst, Dynamics of an infectious disease including ectoparasites, rodents and humans, in: R. P. Mondaini (Ed.), *Trends in biomathematics: modeling, optimization and computational problems,* Springer, 2018, pp. 59–73.

This paper, published during the first year of the grant period was submitted before the start of the grant. In the paper, we established 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 identified three reproduction numbers for the rodent subsystem and showed 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 determined the possible equilibria of the human subsystem and showed that one of the equilibria of this subsystem is always globally attractive. Hence we completely described the global dynamics of the full system.

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

In this paper, we studied the effects of quarantine on the spread of Ebola virus disease. In the newly established model, we described quarantine in a novel form, unlike several recent studies where the models given for quarantine in fact described isolation. For a special case of the model, we calculated the basic reproduction number R_0 and described the global dynamics depending on this threshold parameter: if $R_0<1$ then the disease-free equilibrium is globally asymptotically stable, while in the opposite case, the endemic equilibrium is globally asymptotically stable. We performed sensitivity analysis to show that the parameters related to the effectiveness of quarantine are the main drivers of the disease transmission dynamics

K. Muqbel, A. Dénes, G. Röst, Optimal temporary vaccination strategies for epidemic outbreaks, in: R. P. Mondaini (Ed.), *Trends in biomathematics: mathematical modeling for health, harvesting, and population dynamics*, Springer, 2019.

In this work, we proposed temporary vaccination strategies in the SIR disease outbreak model, where vaccination starts when the infection level reaches a threshold, and continues until susceptibles drop below a level such that the number of infected hosts is decreasing without further intervention. We assigned costs to vaccination and disease burden, and investigated which one of this two parameter family of VUHIA (vaccinate until herd immunity achieved) strategies gives the minimal cost. When the cost of vaccination is very small compared to the cost of disease burden, the optimal strategy is to start vaccination as early as possible and as high rate as possible. When vaccination is very expensive, the minimal cost is attained without vaccination. When the two costs are close, we found that the total cost can be a non-monotone function of the vaccination rate and the threshold value. We also showed that for different basic reproduction numbers, the corresponding optimal strategies can be very different.

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

In this work, we studied the possible effect of the reduction of the sterile needle exchange program among drug users on the spread of some sexually transmitted diseases. We established a compartmental model and calculated the basic reproduction number. Using stability theory and persistence theory, we have showed that the disease-free equilibrium is globally asymptotically stable if the reproduction number is smaller than 1, while the disease is persistent if the reproduction number is larger than 1.

A. Dénes, M. A. Ibrahim, L. Oluoch, M. Tekeli, T. Tekeli, Impact of weather seasonality and sexual transmission on the spread of Zika fever, *Sci. Rep*. **9**(2019), 17055, 10 pp.

We established a nonautonomous model describing the spread of Zika fever considering all important features of the spread: vector-borne and sexual transmission, asymptomatic carriers, the prolonged capability of sexual transmission after recovery. The main novelty of our model is taking into account the periodic changes of weather. We gave an explanation why the epidemic had different outcomes in various countries of South America and gave estimations for the role of different parameters, especially the role of sexual transmission.

A. Dénes, Y. Muroya, G. Röst, Global stability of a multistrain SIS model with superinfection and patch structure, *Math. Methods Appl. Sci*. **43**(2020), 9671–9680.

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. (7)2006, 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.

P. Boldog, T. Tekeli, Zs. Vizi, A. Dénes, F. A. Bartha, G. Röst, Risk assessment of novel coronavirus COVID-19 outbreaks outside *China, J. Clin. Med*. **9**(2020), No. 571, 12 pp.

We study the risks of novel coronavirus outbreaks outside China. We estimate the dependence of the risk of a major outbreak in a country from imported cases on key parameters such as evolution of the cumulative number of cases in mainland China outside the closed areas, connectivity of the destination country with China, including baseline travel frequencies, effect of travel restrictions, and efficacy of entry screening at destination and efficacy of control measures in the destination country. Risk assessments were illustrated for various countries. We studied how their risks depend on those parameters, and how the risk is increasing in time as the number of cases in China is growing.

A. Dénes, G. Röst, Global analysis of a cancer model with drug resistance due to microvesicle transfer, in: R. P. Mondaini (Ed.), *Trends in biomathematics: modeling cells, flows, epidemics, and the environment*, Springer, Cham, 2020, pp. 71--80.

We model the change of the number of chemotherapy-sensitive and resistant tumour cells. In the model we also consider that, according to the most recent research according to which resistance might be transmitted via microvesicles as well, similarly to the spread of infectious diseases. Using Bendixson–Dulac theory and the Poincaré–Bendixson theorem, in the paper we completely characterize the global dynamics of the system: we determine which of the four possible equilibria is globally asymptotically stable, depending on the four threshold parameters identified. Using numerical simulations, we study the possible effects of an increase in drug concentration, and determine the possible bifurcation sequences.

S. Barua, A. Dénes, M. A. Ibrahim, A seasonal model to assess intervention strategies for preventing periodic recurrence of Lassa fever, *Heliyon* **7**(2021), No. 8, e07760.

We established and studied a new nonautonomous compartmental model for Lassa fever transmission including asymptomatic carriers, quarantine and periodic coefficients to model annual weather changes. We determined parameter values providing the best fit to data from Nigerian states Edo and Ondo from 2018–20 and performed uncertainty analysis and PRCC analysis to assess the importance of different parameters and numerical simulations to estimate the possible effects of control measures in eradicating the disease.

S. Barua, A. Dénes, Global dynamics of a model for anaerobic wastewater treatment process, in: R. P. Mondaini (Ed.), *Trends in biomathematics: chaos and control in epidemics, ecosystems, and cells*, Springer, Cham, 2021, pp. 281–291.

We established a model for an anaerobic wastewater treatment process where microorganisms including hydrolytic, acidogenic, acetogenic and methanogenic bacteria degrade organic substance into biogas in an oxygen free environment. The anaerobic wastewater treatment plant is still rare at the industrial scale because of it is unstable under certain circumstances. We show that under certain conditions, there is a unique positive equilibrium of the system. We use the Bendixson–Dulac criterion and the Poincaré–Bendixson theorem to show that this equilibrium is globally asymptotically stable. We show numerical simulations to support the theoretical results.

M. A. Ibrahim, A. Dénes, Threshold dynamics in a model for Zika virus disease with seasonality, *Bull. Math. Biol*. **83**(2021), Article No. 27, 28 pp.

We established a periodic compartmental model for the spread of Zika fever including sexual and vectorial transmission as well as asymptomatic carriers with time-dependent mosquito birth, death and biting rates to integrate the impact of the periodicity of weather on the spread of Zika. We defined the basic reproduction number as the spectral radius of a linear integral operator and showed that the global dynamics is determined by this threshold parameter: if it is less than 1, then the disease-free periodic solution is globally asymptotically stable, while if it is larger thn 1, then the disease persists. Numerical examples suggest what kind of parameter changes might lead to a periodic recurrence of Zika.

M. V. Barbarossa, N. Bogya, A. Dénes, G. Röst, H. V. Varma, Zs. Vizi, Fleeing lockdown and its impact on the size of epidemic outbreaks in the source and target regions – a COVID-19 lesson, *Sci. Rep*. **11**(2021), 9233.

During the COVID-19 pandemic, in several countries many people fled a region just before lockdown was introduced, hence many infections all at once appeared in regions with small number of cases. In this work, we studied the effect of fleeing on the size of an epidemic outbreak in the region under lockdown, and in the destination establishing a mathematical model suitable to describe the spread of a disease over multiple regions. We showed that timely and stricter intervention could have largely lowered the number of cases and that migration of exposed/undetected cases at the time of lockdown possibly played a minor role in the spread. By constructing two first integrals, we determined a new type of final size relation for the nonautonomous model introduced in our work.

G. Röst, F. A. Bartha, N. Bogya, P. Boldog, A. Dénes, T. Ferenci, K. J. Horváth, A. Juhász, Cs. Nagy, T. Tekeli, Zs. Vizi, B. Oroszi, Early phase of the COVID-19 outbreak in Hungary and post-lockdown scenarios, *Viruses*, **12**(2020) No. 7, 708.

COVID-19 epidemic has been suppressed in Hungary due to timely non-pharmaceutical interventions, prompting a considerable reduction in the number of contacts and transmission of the virus. This strategy was effective in preventing epidemic growth and reducing the incidence of COVID-19 to low levels. In this report, we present the first epidemiological and statistical analysis of the early phase of the COVID-19 outbreak in Hungary. Then, we establish an age-structured compartmental model to explore alternative post-lockdown scenarios. We incorporate various factors, such as age-specific measures, seasonal effects, and spatial heterogeneity to project the possible peak size and disease burden of a COVID-19 epidemic wave after the current measures are relaxed.

A. Dénes, G. Röst, Single species population dynamics in seasonal environment with short reproduction period, *Comm. Pure Appl. Anal.* **20**(2021), 755–762.

We presented a periodic nonlinear scalar delay differential equation model for a population with short reproduction period. By transforming the equation to a discrete dynamical system, we reduced the infinite dimensional problem to one dimension. We determined the basic reproduction number not merely as the spectral radius of an operator, but as an explicit formula and showed that is serves as a threshold parameter for the stability of the trivial equilibrium and for permanence.

A. Dénes, S. Marzban, G. Röst, Global analysis of a cancer model with drug resistance due to Lamarckian induction and microvesicle transfer, *J. Theor. Biol*. **527**(2021), 110812.

Development of resistance to chemotherapy in cancer patients strongly effects the outcome of the treatment. Due to treatment, resistance can emerge by Darwinian evolution. Acquired drug resistance may also arise via changes in gene expression. According to a recent discovery in cancer research, this phenotype conversion can also occur through the transfer of microvesicles from resistant to sensitive cells, a mechanism resembling the spread of an infectious agent. We presented a model describing the evolution of sensitive and resistant tumour cells considering Darwinian selection, Lamarckian induction and microvesicle transfer. We identified three threshold parameters which determine the existence and stability of the three possible equilibria. Using a Dulac function, we completely described the dynamics of the model depending on the three threshold parameters. We also established an agent based model as a spatial version of the ODE model and compared the outputs of the two models to find that although the ODE model does not provide spatial information about the structure of the tumour, it is capable to determine the outcome in terms of tumour size and distribution of cell types. We demonstrated the possible effects of increasing drug concentration, and characterize the possible bifurcation sequences. Our results show that the presence of microvesicle transfer cannot ruin a therapy that otherwise leads to extinction, however it may doom a partially successful therapy to failure

M. A. Ibrahim, A. Dénes, Threshold and stability results in a periodic model for malaria transmission with partial immunity in humans, *Appl. Math. Comput*. **392**(2021), 125711, 19 pp.

We develop a periodic compartmental model for the spread of malaria, dividing the human population into two classes: non-immune and semi-immune. The effect of changes in weather is considered by applying a non-autonomous model where mosquito birth, death and biting rates are time-dependent. We show that the global dynamics of the system is determined by the basic reproduction number, defined as the spectral radius of a linear integral operator: for values less than 1, the disease-free periodic solution is globally asymptotically stable, otherwise, the disease remains endemic. We show simulations in accordance with the analytic results and show that the time-average reproduction rate gives an underestimation for malaria transmission risk.

M. A. Ibrahim, A. Dénes, A mathematical model for Lassa fever transmission dynamics in a seasonal environment with a view to the 2017–20 epidemic in Nigeria, *Nonlinear Anal. Real World Appl.* **60**(2021), 103310.

We study a model for Lassa fever transmission dynamics considering human-to-human, rodent-to-human transmission and vertical transmission in rodents. We introduce a nonautonomous model with time-dependent parameters for rodent birth rate and carrying capacity of the environment with respect to rodents. We introduce the basic reproduction number and show that it is a threshold parameter for the global dynamics. We show numerical studies for Lassa fever in Nigeria and give examples to describe what kind of parameter changes might trigger the periodic recurrence of Lassa fever.

T. Tekeli, A. Dénes, G. Röst, Adaptive group testing in a compartmental model of COVID-19, *Math. Biosci. Eng.***19**(2022), 11018–11033

We study a model for applicability of mass testing and compare pooling strategies. We develop a method to optimize pooling depending on prevalence and establish an adaptive strategy described by a nonautonomous model to select variable pool sizes during the epidemic. Optimizing pool size can avert a significant number of infections. The adaptive strategy is much more efficient and prevents an outbreak even when a fixed pool size strategy cannot.

F. A. Bartha, P. Boldog, T. Tekeli, Zs. Vizi, A. Dénes, G. Röst, Potential severity, mitigation, and control of Omicron waves depending on pre-existing immunity and immune evasion, in: R. P. Mondaini (Ed.), *Trends in biomathematics: Stability and oscillations in environmental, social and biological Models – Selected works from the 21st BIOMAT Consortium Lectures, Rio de Janeiro, Brazil, 2021*, Springer, Cham, 2023, pp. 407–419.

We assess potential consequences of the upcoming SARS-CoV-2 waves caused by the Omicron variant showing that even in regions where the Delta variant is controlled by non-pharmaceutical interventions and population immunity, a significant Omicron wave can be expected. We characterize possible outbreaks depending on pre-existing immunity and immune evasion capability of Omicron. We find that two countries with similar effective reproduction numbers for the Delta variant can experience different Omicron waves in terms of peak time, peak size and total number of infections.

M. A. Ibrahim, A. Dénes, A mathematical model for the spread of Varroa mites in honeybee populations: two simulation scenarios with seasonality, *Heliyon* **8**(2022), e10648.

We developed and studied a new model for the spread of Varroa mites and the pathogens they transmit. The novelty of the model is that instead of the number of mites, we consider groups of bees infected with mites, either virus-carrying or virus-free. Our previous similar model was extended in several aspects. Firstly, we have included forager bees among the infected, and we have made several parameters time-dependent, using periodic parameters to describe the year-to-year variation of each factor. The main properties of the autonomous version of the system were described and numerical simulations were carried out to investigate the risk of bee colony collapse as a function of the parameters.

Papers submitted during the grant period

MA Ibrahim, A Dénes, Mathematical modelling of COVID-19 transmission between humans and minks

We study a model for COVID-19 spread considering human-to-human, human-to-mink and mink-to-human transmission. We divide humans into 2 groups based on contacts with minks and consider measures (culling/vaccination) to control spread among minks. Numerical simulations are used to study the impact of control measures on the number of human/mink infections.

S. Barua, B. Das, A. Dénes, A compartmental model for COVID-19 to assess effects of non-pharmaceutical interventions with emphasis on contact-based quarantine

We have developed a new model to describe the spread of Covid-19 by taking quarantine into account. The model presents the infection rate in a different way than usual, which allows us to more accurately track the effects of different non-pharmaceutical intervention strategies, which are particularly important in the absence of drugs or vaccines when a new outbreak occurs. The model was fitted to Bangladeshi data, sensitivity analysis was used to identify the most important parameters for disease spread and numerical simulations were used to examine the impact of different intervention strategies.

M. A. Ibrahim, A. Dénes, A mathematical model for Zika virus infection and microcephaly risk considering sexual and vertical transmission

We established a compartmental model for Zika virus disease transmission, with particular attention paid to microcephaly, the main threat of the disease, considering separate microcephaly-related compartments for affected infants, as well as the role of asymptomatic carriers, the influence of seasonality, and the transmission through sexual contact. We determined the basic reproduction number of the corresponding time-dependent model and time-constant model and studied the dependence of this value on the mosquito-related parameters. We demonstrated the global stability of the disease-free periodic solution if the basic reproduction number is less than 1, whereas the disease persists otherwise. We fitted our model to data from Colombia between 2015 and 2017 as a case study to figure out how sexual transmission affects the number of cases among women as well as the number of microcephaly cases. Our sensitivity analyses concluded that the most effective ways to prevent Zika-related microcephaly cases are preventing mosquito bites and controlling mosquito populations, as well as providing protection during sexual contact.

I. Nali, A. Dénes, Global dynamics of a within-host model for Usutu virus

We have developed a model to describe the intra-organismal dynamics of Usutu virus, a flavivirus that mainly affects birds. A novel feature compared to previous models is that the new model includes the birth and death of healthy cells and that a Crawley-Martin functional response is used in the term describing the infection of healthy cells. We have determined the basic properties of the system of four differential equations, the reproduction number of the system, and, as a function of this parameter, we have given a complete description of the dynamics of the system using Lyapunov functions and the LaSalle invariance principle.

Ongoing work

A. Dénes, M. A. Ibrahim, G. Röst, A periodic model for malaria dynamics with long incubation period in hosts

Motivated by empirical observation of bimodal distribution of incubation time of P. vivax in Korea, we study a periodic compartmental model of delay differential equations for malaria transmission including 2 distinct exposed classes in humans. Short-term incubation period is modelled by exponential distribution, while the long-term one is assumed to be of fixed length. We identify the reproduction number as the spectral radius of a linear operator and show that it is a threshold parameter for the global dynamics. We apply the model to data from South Korea.

S. Barua, A. Dénes, Global dynamics of a compartmental model for the spread of Nipah fever

A new model has been developed to describe the spread of the disease caused by the Nipah virus, which is classified by the World Health Organisation as a virus of concern. The disease, which is associated with a very high mortality rate, is spread by bats and is usually contracted through ingestion of food contaminated with the virus or direct contact with infected animals. In addition to bats, the model also takes into account pigs, which may also be carriers of the virus. The model also includes the possibility of re-infection and the role of the deceased in the spread of the virus. Following the construction of a compartmental model with eight differential equations, the equilibrium states of the system and the reproduction number as a threshold parameter for the dynamics were determined. A complete description of the global dynamics of the system is currently under way.

A. Dénes, A. B. Gumel, Modelling the impact of uncertainty about COVID-19 vaccines

During the research period, we created a compartmental model incorporating uncertainty about Covid-19 vaccines. During the pandemic, the role of uncertainty caused by vaccine resistance, misinformation and mistrust in vaccination and thus in the spread of the epidemic was demonstrated. In our model, uncertainty varies as a function of prevalence, with a higher propensity to vaccinate when the number of cases is high; and vaccination rates are also a time-dependent parameter in the model. In addition to the basic analytical results, we used sensitivity analysis to determine the most important parameters for the spread of the epidemic and numerical simulations to illustrate the expected effects of different interventions such as dissemination of reliable information, increasing vaccination coverage, and introducing mandatory vaccination cards.

S. Barua, A. Dénes, Global dynamics of a compartmental model to assess the effect of transmission from deceased

During several epidemics, transmission from deceased people significantly contributed to disease spread. Transmission of Ebola during traditional burials was the most well-known example, however, there are several other diseases such as hepatitis, plague or viral haemorrhagic fevers which can potentially be transmitted from disease victims. This is especially true in the case of serious epidemics when health care is overwhelmed and the operative capacity of health sector is diminished, such as it could be seen during the COVID-19 pandemic. We present a compartmental model for the spread of a disease with an imperfect vaccine available, also considering transmission from deceased infected. Using the graph theoretical method by Shuai and van den Driessche, we completely describe the global dynamics of the system. We perform numerical simulations to assess the importance of transmission from deceased.

M. A. Ibrahim. A. Dénes, G. Röst, Dynamics of cancer cell population with logistic growth and cell division delay

We develop a one-phase delay differential equation model to describe the dynamics of the cancer cell concentration in the resting phase assuming that cells leave the resting phase and enter a proliferation phase at a rate that is smoothly dependent on the present concentration and is modelled by a logistic function. In addition, the number of surviving cells that have exited the proliferating phase and the newborn daughter cells resulting from the surviving mother cells are dependent on the cell cycle time. We define a formula derived from the characteristic equation, which ensures the global stability of the trivial equilibrium when the threshold parameter is less than 1, and that of the positive equilibrium otherwise. Furthermore, we show that the system is permanent in the latter case. The most interesting dynamics occur when the positive equilibrium starts losing its stability. Our results suggest that the delay can cause stability switches. In particular, we have shown that if the threshold parameter is larger than 1, then the dynamics is characterized by four threshold values, depending on which the positive equilibrium may be globally asymptotically or the model may admit only the trivial equilibrium, resulting in the decay of the cancer cells. It has been demonstrated that the model has a finite, even number of Hopf bifurcation values. Numerical simulations were carried out to illustrate the model's rich dynamics.

Conference and seminar talks

2022 – Workshop on Epidemiology and Modelling, Kerekegyház, Modelling the impact of uncertainty about COVID-19 vaccines

2022 – Models in Population Dynamics, Ecology and Evolution, Torino, Italy (online talk), Adaptive group testing in a compartmental model of COVID-19

2022 – 13th Conference on Dynamical Systems Applied to Biology and Natural Sciences, online conference (poster presentation), Global dynamics of a compartmental model to assess the effect of transmision from deceased

2021 – BIOMAT 2021 – 21th International Symposium on Mathematical and Computational Biology, online conference, Epidemic model for risk-based testing and quarantine

2021 – BioMATEmathics, online conference, Fleeing lockdown and its impact on the size of epidemic outbreaks in the source and target regions – a COVID-19 lesson

2021 – Workshop on Epidemiology and Modelling, Kecskemét, Impact of people fleeing closures on the size of the outbreak

2021 – Differential equations seminar, Szeged (joint talk with M. V. Barbarossa and H. V. Varma), Fleeing lockdown and its impact on the size of epidemic outbreaks in the source and target regions – a COVID-19 lesson

2021 – 12th Conference on Dynamical Systems Applied to Biology and Natural Sciences, online conference (poster presentation), Malaria dynamics with bimodality of incubation period in hosts in a seasonal environment

2020 – Differential equations seminar, Szeged, Global analysis of a cancer model with drug resistance due to Lamarckian induction and microvesicle transfer

2020 – 11th Conference on Dynamical Systems Applied to Biology and Natural Sciences, Trento, Italy, Global analysis of a cancer model with drug resistance due to Lamarckian induction and microvesicle transfer

2019 – BIOMAT 2019 – 19th International Symposium on Mathematical and Computational Biology, Szeged, Global analysis of a cancer model with drug resistance due to microvesicle transfer

2019 – 9th International Congress on Industrial and Applied Mathematics, Valencia, Spain, A population model in seasonal environment with short reproduction period

2019 – 11th Colloquium on the Qualitative Theory of Differential Equations, Szeged, Global stability of a multistrain SIS models with superinfection and patch structure.

2019 – 10th Conference on Dynamical Systems Applied to Biology and Natural Sciences, Naples, Italy, Global stability of a multistrain SIS models with superinfection and patch structure.

2018 – Matsue Seminar, Shimane University, Matsue, Japan, Two mathematical models for recent epidemics – Ebola and Zika.

2018 – Qualitative theory on ODEs and its applications to mathematical modeling workshop, Kyoto, Japan, Global stability of multistrain SIS models with superinfection and patch structure.

Prizes and awards obtained during the grant period

2022 Research Award of the Faculty of Science and Informatics, University of Szeged

2022 Alexits György Prize

2021 Bolyai Memorial of Hungarian Academy of Sciences

2019–2020 Bolyai+ New National Excellence Program Scholarship

2018–2019 Bolyai+ New National Excellence Program Scholarship