
Krajowa Konferencja
Zastosowań Matematyki w Biologii i Medycynie
14 - 18 września 2021
Pałac Załuskich Iwonicz
Uniwersytet Rzeszowski

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List of Abstracts

Mathematical modelling of Covid-19 spread with health care capacity

Agnieszka Bartłomiejczyk[1], ***Monika J. Piotrowska***[2], ***Marek Bodnar***[2] CT

[1] Gdańsk University of Technology
[2] University of Warsaw

Low grade gliomas are primary brain tumours which evolve very slowly in time, however inevitably cause patient death. We are going to study the possibility of existence of travelling waves in the Fisher-Kolmogorov type model describing evolution in time of low grade glioma cells proposed in [1,2]. Considered system describes the evolution in time of functionally alive tumour cells and cells irreversibly damaged by chemotherapy treatment.

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Stochastic model of self-repressing gene with time-delayed protein production

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One of the fundamental processes taking part in living cells is regulation of gene expression. It is a complex process involving many biochemical reactions with proteins being final products and in many cases, these processes take place in small volumes and may involve only few molecules and different time scales are present. In addition, biochemical processes usually involve several sequential steps. It is a common procedure to replace these steps by one fixed time delay.

We analyse a simple model of self-repressing gene with time-delayed protein production. We lump transcription and translation into one process, which is a standard approximation proposed in [1]. Protein molecules may bind to DNA promoters and repress their own transcription. We assume that gene can be in the unbound state or in the bound state with a lower transcription rate, usually assumed to be zero. We model all four biochemical processes, that is production and degradation of protein molecules and switching of gene states, by Markov jump processes.

We derive approximate formulas for time-correlation function of gene being at an occupied and free state. In the mean-field approximation we get approximate formulas for the expected value and the variance of the number of protein molecules in the stationary state. We show that the expected value increases and the variance decreases with time delay. Our approximate analytical results agree with stochastic simulations.

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Some aspects of fuzzy sets theory and their applications

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The concept of a fuzzy set was introduced by L. Zadech in 1965 by extending the value of the characteristic function to the unit interval. Then this concept has received many generalizations, such as Atanasov Intuitionistic fuzzy set and interval-valued fuzzy set allowing mathematical modeling to describe these phenomena and concepts that are ambiguous and imprecise, i.e. modeling the uncertainty existing in many areas of human life. During this presentation, basic information about fuzzy sets will be presented, as well as some of their applications, in particular in the medical decision making process.

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Mathematical modelling of Covid-19 spread with health care capacity

Agnieszka Dzwonkowska*, *Joanna Krawczyk CT

University of Warsaw

In the presentation, we analyse a SEIR model of Covid-19 pandemic spread with health care capacity, based on an article 'Dynamic analysis of mathematical model with health care capacity for COVID-19 pandemic' by S. Cakan (2020). The model is described by a set of four time-delayed differential equations. We proved existence and uniqueness of solutions, we considered the problem of nonnegativity of solutions and we defined an invariant set. We took into consideration the cases of constant and nonconstant health care capacity function. In the first case, we proved global asymptotical stability of steady states of the model depending on the basic reproduction number. Furthermore, in the case when the health care capacity function is a decreasing function of the number of infectious individuals, we determined sufficient conditions of local asymptotical stability of steady states. In addition, we supported the model analysis by numerical simulation and plots created with MATLAB. We illustrated the pandemic spread on plots depending on model parameters for both, constant and nonconstant health care capacity functions.

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Mathematical modelling of prostate cancer development

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Prostate cancer (PC) is the second most common cancer among men all over the world. At an earlier stage, called hormone-sensitive (HSPC), androgen deprivation therapy (ADT) is a standard care. Eventually, the disease transforms to the next stage, called castrate-resistant (CRPC), often resulting in metastasis. In clinical practise, the occurence of PC is measured via surrogate biomarker prostate specific antigen (PSA).

In 2016, Elishmereni et al. proposed a personalized mathematical model describing the development of HSPC and predicitng the time to biochemical failure (BF) of ADT (beeing in general the effect of acquired drug resistance, ADR). In our research, we proposed a new version of this model, better grounded in the biology of the described processes. First, using nonlinear mixed effect modeling (cf. e.g. [2]) we fitted the underlying tumour growth law (more precisely, we proposed a differential equation reflecting the changes in PSA levels) to the data from Mayo hospital. Next, we combined this growth law with a simple model of testosteron secretion obtaining the basic model of HSPC development. On the basis of this model we are able to predict if the level of PSA can be controlled in the ideal scenario (i.e. when there is no ADR) or not [3].

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Unravelling the role of CA9 on immune response via agent-based modelling

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CT

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Immune checkpoint inhibitors have revolutionized the treatment of advanced malignancies such as metastatic melanoma. However, only a subset of patients benefits from the therapy, indicating the need to identify predictive biomarkers [2]. Our aim is to develop a computational model of the tumor microenvironment (TME) in order to investigate the role of CA9, an enzyme which acidifies the TME, in regulating immune response and investigate it as a potential biomarker.

We propose an on-grid agent based model, developped from a well-characterized model from an earlier study [3]. The agents are cancer cells and T cells. Their actions are governed by spatio-temporal concentrations of substances in the TME, modelled via reaction-diffusion equations. We have adapted the model to the current research problem by adding glucose, pH, tumor cell metabolism and CA9 expression, thereby significantly increasing the model's complexity.

Using numerical simulations we were able to to confirm that the model predictions are in accordance with experimental findings concerning tumor growth and immune cell infiltration in CA9-knockout vs control, presented in [1]. In the near future, we plan to study the efficacy of combination therapy of CA9 inhibitors and immune checkpoint inhibitors and to investigate CA9 as a biomarker for immune checkpoint inhibitor therapy.

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Analiza danych aerobiologicznych

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Obiektem badań aerobiologii są ziarna pyłku i zarodniki grzybów swobodnie unoszące się w powietrzu. Dzięki swoim bardzo małym rozmiarom mogą rozprzestrzeniać się na setki a niekiedy tysiące kilometrów. Zgodnie z przyjętą metodyką pomiary aeroplanktonu prowadzone są w sposób ciągły a odczyty prowadzone są co godzinę. Prowadząc wieloletnie badania (w Rzeszowie 24 lata) badacz dysponuje kilkusettysięczną bazą danych. Wpływ na skład ilościowy i jakościowy aeroplanktonu ma szereg czynników (abiotyczne, biotyczne, antropogeniczne), które wyrażone są w różnych skalach (skala nominalna, porządkowa, ilorazowa). Ta mnogość zmiennych oraz fakt, że część z nich charakteryzuje się silną autokorelacją i skrajnie asymetrycznym rozkładem liczebności sprawia, iż prawidłowe opracowanie danych jest wyzwaniem dla aerobiologa. Wątpliwości pojawiają się już przy graficznej prezentacji danych (jaki rodzaj wykresu i jaką wybrać formułę opisującą sezon pyłkowy?) i przy opisie statystycznym próby (średnia czy mediana). Wychodząc naprzeciw tym wątpliwościom i problemom biolodzy we współpracy z matematykami, informatykami opracowują narzędzia dedykowane tylko danym aerobiologicznym. Przykładem jest pakiet AeRobiology dla programu R, zawierający narzędzia do wizualizacji wyników, zarządzania bazami danych, obliczania statystyk, w tym statystyk kołowych dla danych okołodobowych. Dane aerobiologiczne można określić jako wielowymiarowe szeregi czasowe i do ich analizy z powodzeniem wykorzystywane są metody wielowymiarowe, w tym analiza skupień ConsLink czy wielowymiarowa korelacji. Badania nad zawartością pyłku roślin i zarodników grzybów w powietrzu są ważne, gdyż wiele z nich jest alergenne. Dla alergologa i jego pacjenta niezwykle istotne jest nie tylko to co aktualnie jest w powietrzu, ale jakie będzie stężenie w następnych dniach i czy to stężenie będzie przekraczało wartości progowe do wywołania objawów chorobowych. W literaturze przedmiotu prezentowane są różne modele prognostyczne wykorzystujące między innymi metody regresji wielorakiej, ARIMA, sieci neuronowe, sztuczną inteligencję, jednak ich skuteczność, szczególnie dla zarodników grzybów, często nie jest zadowalająca. Wadą tych modeli jest również brak uniwersalności.

W środowisku aerobiologów zwraca się szczególną uwagę na poprawność metodyczną badań, w tym na opracowanie danych liczbowych i jest to częsty temat dyskusji na różnych forach naukowych. Nierzadko powodem negatywnych recenzji artykułu są właśnie błędy w analizie danych, dlatego to środowisko naukowe cechuje otwartość na współpracę z matematykami i informatykami.

Towards a Synthesis of Solutions for Optimizing Combination Therapies in Cancer

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We analyze a mathematical model for the combination of chemotherapy with antiangiogenic treatment as a multi-input optimal control problem. Assuming that the total amounts of both agents to be given have been determined a priori based on a medical assessment of side-effects, we consider the problem to minimize a weighted average of tumor volume and the carrying capacity of the tumor vasculature. The monotherapy problem for an antiangiogenic agent has been solved previously [2] and recently the problem has been analyzed for cancer chemotherapy which also includes antiangiogenic effects of the cytotoxic agent [1]. In each case, lower dose strategies determined by an optimal singular arc with significantly reduced dose rates, are an essential part of the solutions. For both monotherapy problems and for the medically realistic domain of the mathematical model the concatenation structure of optimal controlled trajectories as segments of bang and singular arcs was determined based on a thorough theoretical analysis of first and high-order necessary conditions for optimality. This led to simple numerical minimization procedures for the computation of globally optimal controls. Currently the full combination therapy problem is being analyzed as a multi-input optimal control problem with the goal of determining optimal administration regimens for a simultaneous administration of both treatments.

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Mathematical modelling of bacteria spread in the inter-hospital network

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Diseases caused by multidrug-resistant bacteria are a serious problem in modern healthcare systems. The aim of my master thesis is to use mathematical modelling to realistically describe the patient exchange between hospitals and society, as well as the transmission of bacteria. For this purpose I analyze a system of eight ordinary differential equations describing the spread of bacteria in a network of two hospitals and corresponding society. This system is based on a model of a single hospital-community pair presented in [2].

In order to examine the properties of a disease-free steady state I use the approach utilizing the next generation matrix presented in [1], in which basic reproduction number is computed. Then I analyze the existence of endemic steady states. Moreover, I perform numerical simulations that visualize the properties of the model.

Under certain assumptions there is another interpretation of this model, which describes the dynamics between intensive care units, remaining wards and society. This perspective justifies implementing this model as a part of a network model for a large number of hospitals.

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Study of the time-dependent synergy effect in the models of combined radio-chemotherapy

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The synergy effect in combined radio-chemotherapy usually means a radiosensilisation of tumor cells through by action of concurrent chemotherapy. This radiosensilisation process is a complex time-dependent mechanism, and therefore it is often omitted in mathematical models of radio-chemotherapy. But from the perspective of therapy planning, lack of the radiosensilisation effect in these models may impair their predictive capability. That's why it is relevant to know which of them shows this synergistic behaviour. There are several known methods of detecting synergies in the models of radio-chemotherapy, but they neglect the relationship between the times in which the therapeutic factors act. In the work [1], we propose a method for detection the time-dependent synergy effect based on the second-order sensitivity analysis. We test the proposed approach using four exemplary models of combined radio-chemotherapy of cancer.

Acknowledgements: This work was supported by the Polish National Science Centre under grant UMO-2020/37/B/ST6/01959 (K.F.), and by the Silesian University of Technology statutory research funds (K.Ł.). Calculations were performed using the infrastructure supported by the computer cluster Ziemowit (www.ziemowit.hpc.polsl.pl) funded by the Silesian BIO-FARMA project No. POIG.02.01.00-00-166/08 and expanded in the POIG.02.03.01-00-040/13 in the Computational Biology and Bioinformatics Laboratory of the Biotechnology Centre at the Silesian University of Technology.

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Modelling the spread of multidrug-resistant bacteria by a SIS-type network-based model

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The spread of multidrug-resistant bacteria, such as *Enterobacteriaceae*, in hospitals and thus within community is an increasing problem present in all European countries. Readmissions of patients who were colonized during earlier hospital stays lead to repeated re-introductions of resistant bacteria into hospitals and are considered to be an important factor promoting the resistance. We are going to present our approaches to model bacteria transmission within the healthcare network using a mathematical model that combines a deterministic SIS-type model for within-hospital spread of pathogens with a hospital–community transfer of patient proposed in [1, 2]. Parameters of the mathematical model used to create the hospital–community network and to model movement of patients within the network are obtained from two German health insurance companies. For each considered hospital–community pair we estimated basic reproduction number showing that hospitals with high reproduction numbers represent a continuous source of risk for the whole network.

Co-authors (alphabetic order): J. Horn (University Halle-Wittenberg), A. Karch (Institute for Epidemiology and Social Medicine), M.E. Kretzschmar (Utrecht University), A. Lonc (UW), R.T. Mikolajczyk (University Halle-Wittenberg), K. Sakowski (UW, IHPP PAS), H. Tahir (Utrecht University).

This work was supported by grant no. 2016/22/Z/ST1/00690 of the National Science Centre, Poland within the transnational research programme JPI-EC-AMR co-found grant no 681055 for the consortium EMerGE-Net. We thank the AOK Plus and AOK Lower Saxony for providing anonymized data.

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Computational modeling of pulse wave propagation: how mathematical model can be used to assess the state of patient's cardiovascular system

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Cardiovascular (CV) diseases are the leading cause of death worldwide. Therefore, there is a constant demand for more accurate and non-invasive methods for cardiovascular system state assessment. Therefore, we focused on developing a mathematical model which, after calibration with patient-specific data, would provide new personalized information about CV system state.

To this extent, we model the blood transport in a bifurcating binary tree of fifty-five larger systemic arteries in which individual vessels are axisymmetric elastic cylinders tapering along their length [1, 2]. We describe spatiotemporal changes in the cross-sectional area of the artery (equivalently blood pressure) and blood flow using an 1D approach, i.e. we consider a large system of partial differential equations coupled to a series of non-trivial inflow/outflow conditions.

Proposed model was confronted with the actual recordings of the blood pressures in the peripheral arteries collected in a group of healthy individuals and hemodialysis patients. We show that, after parameter estimation procedure, the model is able to provide new patient-specific insights into CV system state that are unattainable with existing non-invasive methods.

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Volumetric Brain Analyses of Sex- and Age-Related Trends

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The aim of the work was to determine the influence of sex, age and the head/brain size on the compartmental brain volumes in the radiologically verified healthy Polish population (96 subjects). Calculations were conducted on a set of 4 overall brain volumes and volumes of 14 subcortical structures for the left and right cerebral hemispheres. We used statistical general linear models, with and without the volumetric parameters as the covariates, to study the regional vs. global brain atrophy. The majority of sex differences in the specific volumes of interest revealed to be linked to the difference in the brain size parameters. The analysis confirmed the significant effect of the aging process on the brain loss. The general linear model analysis revealed that the sex-related differences should be investigated after normalization of the magnetic resonance imaging data to avoid unnecessary bias. Presented research is mostly based on our published results [1].

This work was supported by Silesian University of Technology statutory research funds.

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A computational platform for performing virtual clinical trials on the example of the SOLO-1 clinical trial in ovarian cancer

Emilia Kozłowska[1], ***Krzysztof Puszyński***[1], ***Anniina Färkkilä***[2]

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CT

Pre-clinical trials and clinical trials are very time-consuming and costly. Additionally, only a small number of drugs that are tested in the preclinical phase successfully enter the pharmaceutical market. Therefore, the cost of clinical trials is not only the cost of research on one drug, but also the cost of research on drugs that have not passed the rigorous process of implementation. The time and cost of clinical trials justifies the need to use computational tools to determine whether a given drug has a chance to be implemented on the market.

We created a computational platform based on a mathematical model to find new drug combinations in ovarian cancer. This platform is based on creating virtual patients using statistical methods, which differ in such parameters as: tumor size during diagnosis, tumor cell growth rate and toxicity. Subsequently, such virtual patient simulations are performed to determine the course of the disease from diagnosis to relapse or death / cure. Such results from individual virtual patients can be used as inputs to statistical models. The built-in computing platform allows to predict the effect of new therapeutics on the patient's prognosis relatively quickly and cheaply.

We tested the created computational platform on a clinical trial, which is a grade III clinical trial of the use of Olaparib (PARP inhibitor) in ovarian cancer. This trial is called SOLO-1 and it tests the possibility of using Olaparib as maintenance therapy after chemotherapy (based on platinum compounds) in primary treatment. As part of the project, we matched the publicly available results from the SOLO-1 trial with the simulation results to reproduce the results of this clinical trial. The obtained results from computer simulations faithfully reflect the actual results that were obtained from the clinicaltrials.gov database.

Then, after fitting the model to the data from the SOLO-1 clinical trial, we used the computing platform to determine the optimal length of Olaparib maintenance treatment, among other things. As a result, not only the toxicity of maintenance therapy can be reduced, but also its cost. As part of further work, it is planned to use the developed platform to test other PARP inhibitors that are not yet approved by the FDA and EMA.

Modelling of tumor growth, metastasis and therapy

Jarosław Śmieja*, *Krzysztof Psiuk-Maksymowicz*, *Andrzej Świerniak CT

Silesian University of Technology

The work is concerned with modeling of tumor growth, taking into account chemo- and radiotherapy and metastasis [1]. We propose a compartmental model of non-small lung cancer growth with metastasis. Two therapies, chemo- and radiotherapy are taken into account with actual clinical protocols. We assume Gompertz-type growth of both primary and metastatic tumor. A population of virtual patients is created by sampling model parameters. Kaplan-Meier survival curves are used to compare simulation results with clinical data.

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Bio-modelling and machine learning in prediction of metastases in non-small cell lung cancerr

***Emilia Kozłowska*[1], *Iwona Dębosz-Suwińska*[2], *Rafał Suwiński*[2], *Andrzej Świerniak*[1]** CT

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Lung cancer is a leading cause of cancer death and the most common type of cancer diagnosed in Poland. There are known two main subtypes of lung cancer non-small cell (NSCLC) and small cell (SCLC) ones, where the NSCLC constitutes 85% of all cases. NSCLC could be divided into Adenocarcinomas, Squamous Cell Carcinomas, and Large Cell carcinomas, where adenocarcinomas are the most frequent subtype of NSCLC. In Poland, the median survival rate of patients with NSCLC is 18 months. High incidence and high mortality of lung cancer justify the choice of this type of cancer in the study. Approximately 60% of patients diagnosed with NSCLC have tumor spread to distant organs. This leads to incurable cancer. Metastases are not only correlating with poor prognosis but are also associated with poor patients' performance. Thus, it justifies tackling the problem of emerging of metastases in non-small cell lung cancer. We applied two types of models: machine learning (ML) and mechanistic ones. We used ML models in the form of Cox proportional hazard (CPH) regression and random survival forest (RSF). CPH model is a standard model of proportional hazard applied in medicine to extract important covariates affecting the survival. RSF however, is a model applying random forest to predict right-censored survival values. Next, we also applied a mechanistic model in the form of mixed-effect model which was published by C. Nicolo et al. (2020) in JCO Cancer Clinical Informatics. The model was applied to develop a predictive model of metastasis survival. Development of metastases in lung cancer is an important event which defines how the patient is treated. Thus, a strong biomarker which could predict MFS is of high interest to clinicians treating cancer patients. In the project we aimed at finding the clinical biomarker(s) based on available clinical data.

Application of entropy-based methods to distinguish healthy individuals with normal sinus rhythm from patients with congestive heart failure

Katarzyna Tessmer CT

Gdańsk University of Technology

We examined whether entropy-based methods are able to differentiate healthy individuals from patients with congestive heart failure. To this aim, we applied two methods: Permutation Entropy and Block Entropy. Long-term ECG recordings (75 000 RR intervals) were analyzed. The results proved that both methods can distinguish those groups on condition that the parameters are appropriately chosen.

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Goodwin model and its extensions

Andrzej Tomski[1], ***Agnieszka Kozdęba***[2] CT

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We analyse stochastic gene expression of a single gene with its dynamics given by the classical Goodwin model. We compare the effect of the presence of positive and negative feedback on the transcription regulation. In such cases we observe two qualitatively different types of asymptotic behaviour of this system. We discuss possible extensions of the model.

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Individualized modeling for Covid-19 pandemic

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During the Covid-19 pandemic, various control policies were applied to limit the spread of the virus. Several studies have been conducted to assess their effectiveness in Europe, most relying on modeling each country independently [1, 2]. While such approach takes into account local specificity, limited amount of data raises problems with the estimation of parameters and, subsequently, result interpretability. A solution is to use data from all countries. However, a common model might not be flexible enough to capture differences between objects. We propose a compromise — simultaneous construction of individualized models. In each one, a subset of parameters is estimated from a combined dataset, while other parameters are estimated separately for each country.

As the basic model of an epidemic, we used the SEIR model, treating the virus transmission intensity as a time-dependent parameter, expressed as a function of the degree of restrictions applied in individual countries. For parameter estimation, we used linear least squares method combined with a gradient approach in which we calculated the derivatives of the objective function with respect to the model parameters using adjoint sensitivity analysis. Compared with independent and common approaches, the individualized solution yields best results for largest number of countries. Analysis of obtained values suggests how control strategies influence transmission speeds.

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Stability of fixed points in an approximate solution of the spring-mass running model

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We consider a classical spring-mass model of human running which is built upon an inverted elastic pendulum (see the seminal papers [2, 4]). Based on our previous results concerning asymptotic solutions for large spring constant (or small angle of attack), we construct analytical approximations of solutions in the considered model based on the perturbation theory (see [5] and compare with [3]). The model itself consists of two sets of differential equations - one set describes the motion of the centre of mass of a runner in contact with the ground (support phase), and the second set describes the phase of no contact with the ground (flight phase). By appropriately concatenating asymptotic solutions for the two phases we are able to reduce the dynamics to a one-dimensional apex to apex return map. We find sufficient conditions for this map to have a unique stable fixed point. By numerical continuation of fixed points with respect to energy, we find a transcritical bifurcation in our model system.

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Topologiczna analiza danych: metody i wyniki

Mykhaylo Zarichnyy

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Topologiczna analiza danych (TAD) jest intensywnie rozwijającym się rozdziałem matematyki stosowanej poświęconym badaniom struktur metrycznych i topologicznych chmur danych. Jednym z najważniejszych metod TAD jest wykorzystywanie techniki topologii algebraicznej, w szczególności homologii uporczywych (persistent homology) [1, 2].

Będą omówione diagramy uporczywości (persistence diagrams), różne metryzacje zbiorów takich diagramów oraz własności topologiczne otrzymanych przestrzeni metrycznych [3].

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Existence and stability of positive solutions for a periodic boundary value problem

Mirosława Zima

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We will discuss sufficient conditions for existence, localization and stability of positive solutions for

$$x''(t) + ax'(t) = r(t)x^{\alpha} - s(t)x^{\beta}$$

subject to periodic boundary conditions $x(0) = x(T)$, $x'(0) = x'(T)$, where $a \geq 0$, α, $\beta \in \mathbb{R}$, and the functions r, s are continuous and T-periodic. Our main tools are the following: the fixed point index of compact operators, the method of lower and upper solutions, the abstract averaging method for semilinear equations and the third approximation method. The talk is based on the recent joint papers [1], [2], [3] and [4].

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Useful Information

Talks will be held at the Palace. It is situated on the ground floor.

Accommodation is on the first floor.

Beakfasts, coffee breaks, lunches and dinners will be offered on the ground floor near the conference hall.

Wi-Fi will be available during the conference.

How to get to Iwonicz?

By bus:

By line NEOBUS
Iwonicz-Zdój – Warszawa (by Rzeszów, Nowa Dęba, Opatów, Ostrowiec Św., Radom) departure at 02:25, 06:10, 09:55,11:45, 15:55, , 23:25

Warszawa – Iwonicz-Zdrój (by Rzeszów, Nowa Dęba, Opatów, Ostrowiec Św., Radom) departure at 00:10, 05:00, 09:00, 13:30, 17:00, 20:40

Iwonicz-Zdój – Łódź departure at 06:10, 9:55, 23:25

Łódź – Iwonicz-Zdrój departure at 08:00, 09:00

Iwonicz-Zdój – Wrocław (by Kraków, Katowice) departure at 02:25, 06:10, 09:55, 15:55, 23:25

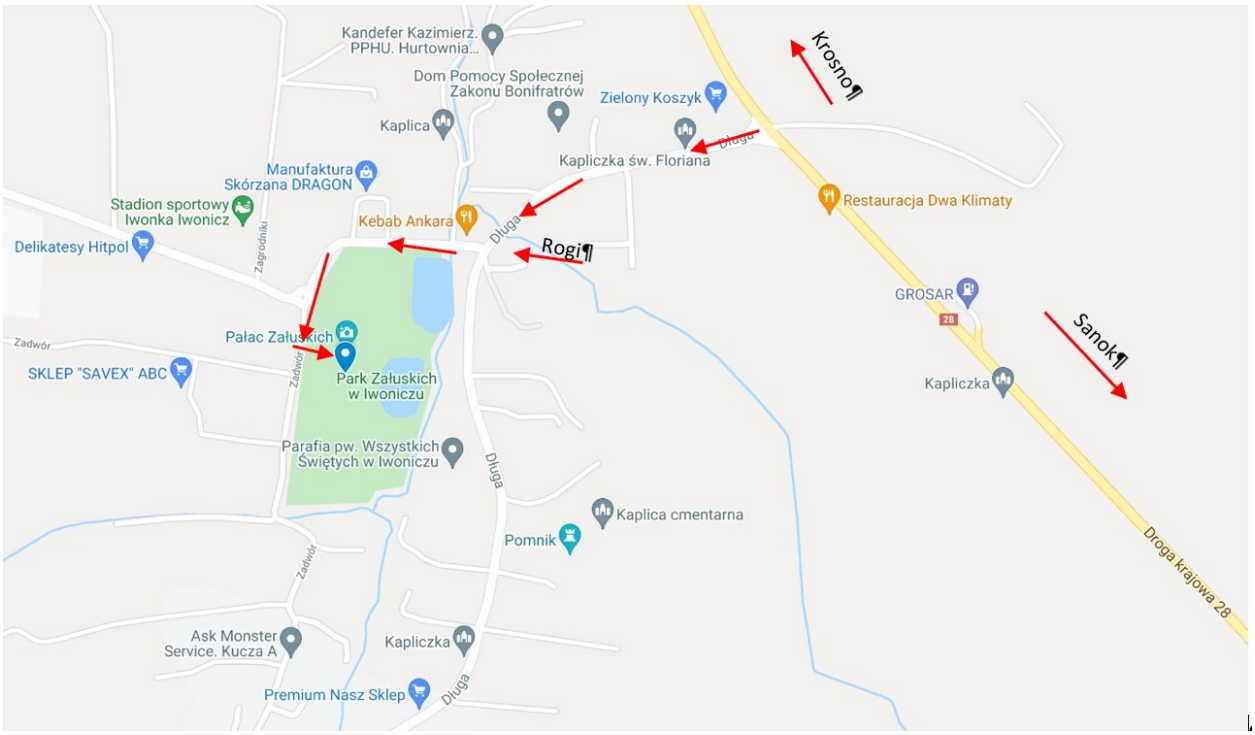
Wrocław – Iwonicz-Zdrój (by Kraków, Katowice) departure at 03:50, 12:20, 16:00, 19:00, 22:40

Iwonicz-Zdój – Bytom (by Kraków, Katowice) departure at 11:00

Bytom – Iwonicz-Zdrój (by Kraków, Katowice)departure at 08:10

or

by car.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