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Research statement
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My research interests are related to widely understood applications of mathematics in biology and medicine. From the mathematical point of view I successfully use dynamical systems to analyze models describing mainly various processes associated with tumor growth and treatment, as well as immune system (also in the context of tumor-immune system interactions), heart action pathologies, epidemiological and ecological processes, and dyadic interactions.

In all real processes there appear delays that reflect e.g. feedback loops or time necessary to obtain the reaction of a given system to specific external signal, especially in systems with control; c.f. Fig. 1. Delays are mainly used to reflect the time of duration of some process composed of several

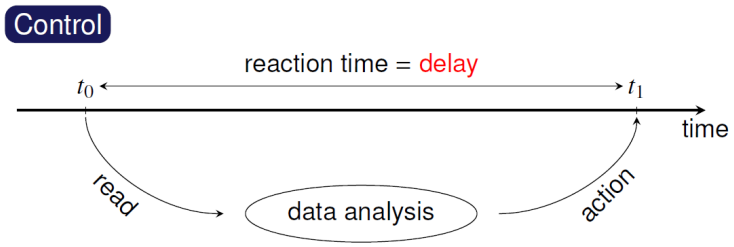

Figure 1.

subprocesses we do not want to describe in more details. The reason for omitting these subprocesses could be different, e.g. we would like to decrease the number of equations in the system or the details of the heuristic description are not known; c.f. Fig. 2.

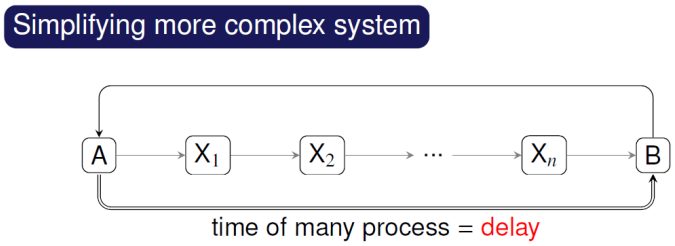

Figure 2.

Therefore, I frequently use infinite-dimensional semi-dynamical systems generated by delay differential equations. That is why I include below some necessary information about such equations and notation used in the theory of DDEs.

The book by J. Hale from 1977 [18] remains the main text-book on the theory of functional- differential equations (which we call DDEs) for years. Completed version of this book was published in 1993 [19], and the next edition appeared in 1997. From application point of view other text-books are important. I can mention the book of Y. Kuang [26] which includes, apart from theoretical base, many

examples of models coming from applications. Similarly, in the text-book [14] many specific models with delays are studied. Although recently new books on that topic have appeared, in particular by O. Diekmann et al. [9], the text-book by Hale is still considered as the one to be cited in articles of other researchers. In my papers I also gave citations to this book, although while studying a Hopf bifurcation I apply the approach of Diekmann et al.

Let Ω denote an arbitrary space and $\varphi : [a, b] \to \Omega$, $[a, b] \subset \mathbb{R}$ be an arbitrary function. Let us fix $\tau > 0$ and $t \in [a + \tau, b]$, under the assumption $b > a + \tau$. We define a new function φ_t as a translation of the function φ restricted to the interval $[t - \tau, t]$ into the interval $[-\tau, 0]$, that is

$$\varphi_t(s) = \varphi(s + t) \quad \text{dla} \quad s \in [-\tau, 0]\,.$$

Figure 3 presents schematic construction of the function φ_t.

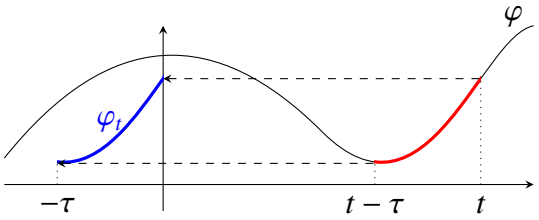

Figure 3. Construction of φ_t.

This translation allows to define semi-dynamical system in a Banach space $\mathscr{C}_\tau$ of continuous functions with a domain $[-\tau, 0]$ (with values in $\mathbb{R}^n$ with standard supremum norm) associated with an autonomous system of delay differential equations (DDEs)

$$\dot{x}(t) = F(x_t) \quad \text{for} \quad t \geq 0\,, \tag{1}$$

where $x(t) \in \mathbb{R}^n$, $F\colon \mathscr{C}_\tau \to \mathbb{R}^n$ is a given operator, $\dot{x}$ denotes a right-hand side derivative of $x(\cdot)$ with respect to time. If a solution of System (1) with an arbitrary initial function $\varphi_0 \in \mathscr{C}_\tau$ is defined for all $t \geq 0$, then orbits form a semi-dynamical system $\{x_t,\ t \geq 0\} \subset \mathscr{C}_\tau$. DDEs generate semi-dynamical systems as in general they are irreversible in time. This means that for a given initial function φ_0 we are not able to prolog a solution on the interval $[-2\tau, -\tau]$ without additional assumptions, and prolongation on the next intervals of the delay length needs more and more assumptions.

In general, non-autonomous equations are also an object of theoretical study. In this type of equations the right-hand side depends on time explicitly, $F = F(t, x_t)$, which may be important in specific applications (in particular for processes with parameters depending on time, like in the case of seasonal changes). Nevertheless, even for such equations we consider the space $\mathscr{C}_\tau$, in which most of theorems known from ODEs have their analogues (like theorems about existence, uniqueness and backward prolongation of solutions, as well as linearization theorem).

Let us notice that for any arbitrary $\tau > 0$ one can always make time scaling taking $\tau s = t$ and obtain unit delay as a result. We should also stress that the assumption that the delay is finite is important and the case $\tau = +\infty$ should be treated separately (c.f. [20]).

In my research I mainly use equations with discrete delays. In this case general system reads

$$\dot{x}(t) = G(t, x(t), x(t - \tau_1), x(t - \tau_2), \ldots, x(t - \tau_k)), \tag{2}$$

where $G\colon \mathbb{R} \times \mathbb{R}^{nk} \to \mathbb{R}^n$ is some function. Notice that $x(t - \tau_i) = x_t(-\tau_i)$, and hence (2) could be easily rewritten as an equation defined in $\mathbb{R} \times \mathscr{C}_\tau$. Introducing only delays in discrete form does not simplify the theory or reduce the space dimension, which is still infinite dimensional Banach space of continuous functions defined on $[-\bar{\tau}, 0]$ (where $\bar{\tau} = \max_{j\in\{1,\ldots,k\}} \tau_j$), but allows to use the so-called step method. This method is just a method of mathematical induction adapted for DDEs which is useful

for proving specific properties of the considered equation on the interval of the length of the smallest delay, $I_\ell = [\ell \min_{j\in\{1,\dots,k\}} \tau_j, (\ell+1)\min_{j\in\{1,\dots,k\}} \tau_j]$, basing on the theory of ODEs. Clearly, in each interval I_ℓ Equation (2) becomes non-autonomous ODE with known functions $x(t-\tau_j)$, $j = 1,\dots,k$, as $t - \tau_j \in I_m$ for some $m < \ell$. Most frequently, this methods is used to prove prolonagability of solutions for all $t > 0$, and is easier to exploit, as it allows to conduct the analysis in the space $\mathbb{R}^n$ instead of $\mathscr{C}_\tau$. Moreover, for DDEs with discrete delays the stability analysis simplifies even more comparing to the general case, because a characteristic function allows to consider

$$\sum_{j=0}^{n} a_n \lambda^j + \sum_{\ell} \sum_{j=0}^{n-1} b_{\ell,j}\, \mathrm{e}^{-\lambda\tilde{\tau}_\ell},$$

where $\tilde{\tau}_\ell = \alpha_1\tau_1 + \alpha_2\tau_2 + \dots + \alpha_k\tau_k$, and moreover $\alpha_j \in \mathbb{N}$, $j = 1,\dots,k$, $\alpha_1 + \alpha_2 + \dots + \alpha_k \le n$.

Indeed, stability analysis, especially in the context of global stability, is one of the most important topics in analysis of DDEs describing real processes occurring in nature. On the other hand, nonnegativity for nonnegative initial functions is important as well. This is because of the interpretation of the model variables. We should remember that by introducing time delays we may lose nonnegativity of solutions. More precisely, if the original model without delay preserves nonnegativity, when a delay is introduced into some negative term, then typically solutions become negative for large delays (c.f. [4]). In biomathematical literature there nevertheless appear articles in which the authors seem do not know or do not remember about this property, e.g. [5, 12].

I shall present a very simple example. Consider the Cauchy problem $\dot{x} = a - x(t)$, $a > 0$, $x(0) = x_0 > 0$ for which we obtain the solution $x(t) = a + (x_0 - a)\,\mathrm{e}^{-t} > 0$. The same equation with delay, that is $\dot{x} = a - x(t-\tau)$, and with initial function $x(t) = a + \beta\cos t$, $t \in [-\tau, 0]$ for $\tau = \frac{\pi}{2}$, has the solution $x(t) = a + \beta\cos t$ for all $t > 0$, and this solution takes negative values for $a > \beta$; c.f. Fig. 4.

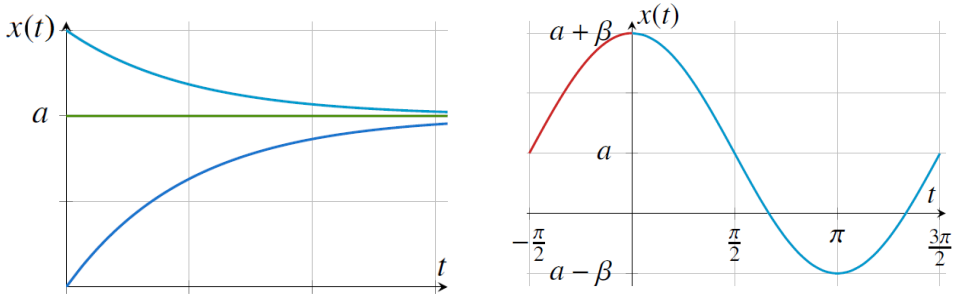

Figure 4.

In general, studying global stability for DDEs is difficult, if at all possible, for example it is hard to propose an appropriate Lyapunov functional. As an example I can mention the well known Hutchinson equation [22] (classic logistic equation with delay). This equation has been proposed in 1948, but even until today its dynamics is not completely known and is still an object of research (see the discussion in [26]) and the Wright hypothesis [39] proposed more than 60 years ago has not been settled yet. Short introduction to the theory of DDEs in the context of applications to simple biomedical models was presented in my review work [M4], while main problems associated with the introducing of delays are described in [A17].

Apart from semi-dynamical systems generated by DDEs in my research I also used finite-dimensional systems generated by ODEs (which could be treated as equations of the form (1) with $F(\phi) = f(\phi(0))$ for some function f) or discrete dynamical systems. Moreover, when the space distribution seemed to be important, I studied the influence of diffusion on the dynamics of the systems considered. However, reaction-diffusion equations also generate dynamical systems, and therefore could be analyzed within this framework.

More precisely, from the analytical point of view in my research I use following approaches:

— nonlinear systems of ordinary differential equations studied in the context of global existence of unique nonnegative solutions, local and global stability of steady states (with the usage of Lyapunov functions or other techniques dedicated for specific models), occurrence of limit cycles and other bifurcations, including Hopf bifurcation;
— linear and nonlinear systems of delay differential equations in the same context as above, in particular studying bifurcations (including stability switches) with respect to increasing delay;
— nonlinear equations with diffusion, both without and with delays, in the contexts as above;
— systems including external influence on the dynamics, like impulses or control (including optimal control problems).

From the application point of view my research has been focused on the following topics:
— modeling of immune reactions, including the influence of vaccinations and tumor immunotherapy together with its effectiveness;
— modeling of avascular tumor growth, studying the influence of delays onto that growth, necrotic core formation;
— tumor angiogenesis process, antiangiogenic therapy and combined therapies;
— cancer mutations;
— radiation induced bystander effect;
— chemotherapy of tumors: acquired drug resistance and optimal control in the context of ADR;
— modeling of androgen deprivation therapy in prostate cancers;
— delays in biochemical reactions;
— modeling of dyadic interactions;
— modeling of heart action;
— epidemiological models: influence of vaccines, heterogeneous populations – modeling of the spread of tuberculosis;
— eco-epidemiological models;
— modeling in neurosciences: recognition in ambivalent situations.

1. Modeling of immune reaction

My earliest research was focused on modeling immune reaction. I studied this process on the basis of simplest Marchuk's model [30].

1.1. Marchuk's model

The model was proposed by G.I. Marchuk in 1980 and in the simplest form it describes humoral immune reaction, that is the type of immune reaction in which antigen (that cause this reaction) is eliminated by antibodies (proteins transmitted in lymph and blood, which is the reason of the name "humoral"). We describe the evolution of three variables V, C and F in time. These variables represent the density of antigen, plasma cells, which produces antibodies, and antibodies, respectively. The system dynamics is described by a system of ordinary differential equations with discrete delay

$$\begin{aligned} \dot{V}(t) &= (\beta - \gamma F(t))\, V(t), \\ \dot{C}(t) &= \alpha V(t-\tau) F(t-\tau) - \mu_C \left(C(t) - C^*\right), \\ \dot{F}(t) &= \rho C(t) - (\mu_F + \eta\gamma V(t))\, F(t). \end{aligned} \tag{3}$$

In this model the rate of change of the antigen density depends on this density (parameter β is interpreted as the growth rate, but also as the antigen aggressiveness) and on immune reaction (term FV stands for elimination of the antigen by antibodies, parameter γ reflects probability of meeting, recognizing and eliminating the antigen). Antibodies are produced by plasma cells, while the process of plasma cell production is triggered by signals which are sent by antigen-antibody complexes. Time

delay τ reflects the time needed to send the signal and produce new plasma cells. Parameter C^* describes the so-called physiological level of plasma cells, while μ_C^{-1} is the mean life-span for these cells. Antibodies are produced by plasma cells, die in immune reaction against antigens (parameter η reflects the mean number of antibodies necessary to eliminate one antigen), and their mean life-span is equal to μ_F^{-1}.

Basic properties of System (3) were studied by the team of Marchuk [30], c.f. also [M1, M3]. Global dynamics of the model without delay was analyzed by my supervisor, Prof. Wiesław Szlenk, but the results have not been published by him. On the basis of his notes, my bachelor's students, Jarosław Badowski and Tomasz Trabszys, prepared their bachelor's thesis, and moreover the main results were published by us in [C15, C16].

In [Z1, A1] I presented the result of my master's thesis. I studied the model with distributed time delay (interestingly, my earliest papers [Z1, A1] and one of the newest works [C57] are devoted to similar topics – analysis of the influence of distributed delay onto the dynamics of some specific model) and proposed conditions of local stability of steady states. System (3) has two steady states: $A = (0, C^*, F^*)$, $F^* = \rho C^*/\mu_F$, describing healthy organism (meaning that there is no antigen, while plasma cells and antibodies remain on their physiological levels), and positive state $B = (\bar{V}, \bar{C}, \bar{F})$, which reflects chronic disease. This state exists under the assumption $\alpha\rho > \eta\gamma\mu_C$ and $\beta > \gamma F^*$ or for inverse inequalities.

It turns out that the distributed form of delay does not change conditions of stability much. These conditions remain similar to the ones for discrete delay. The only difference is that the mean delay appears in it. In the proof I used generalized Mikhailov criterion which is presented in Subsection 14.

I also considered other modifications and generalizations of Marchuk's model (3). Immunologists working with us that time were interested in the influence of interleukins (cytokines that regulate various immune processes), and that is why I proposed the modification of (3) which includes this influence [A2]. However, this model proved itself too complex to study anything else than local stability under some specific conditions. Together with Marek Bodnar we revisited the topic in [Z24]. The next idea of immunologists was to consider the influence of vaccines [Z4, C1, C2]. After "bad" experience with high complexity of the interleukin model, I proposed simplified model of vaccinations studied its global stability in [A4]. Another idea was to propose discrete time model [Z2], which could be easier to understood for medicals, but it had no effect.

In parallel, I conducted research on global dynamics of System (3), including bifurcations with respect to increasing delay. I focused on those topics in [Z3, A3, A5, Z8, A8, C3, A14]; notice that in [A3, A5] I presented main results of my PhD thesis. In particular, I proved that if $\alpha\rho > \eta\gamma\,(\mu_C + \beta)\,\mathrm{e}^{\beta\tau}$ and $\beta < \gamma F^*$, then any solution of System (3) with initial data reflecting healthy organism infected by some dose of an antigen at time $t = 0$ (that is $V_0(s) = 0$ for $s < 0$, $V_0(0) = V^0 > 0$, $C_0(s) = C^*$, $F_0(s) = F^*$, we call it "standard initial condition") tends to the steady state A. Notice, that the standard initial condition is not continuous (and therefore does not belong to $\mathscr{C}_\tau$), however the step method allows to find the solution on the interval $[\tau, 2\tau]$, and after that the standard theory may be used (that is the theory for an initial function from $\mathscr{C}_\tau$). As for the steady state B, assuming that $\beta > \gamma F^*$ i $\alpha\rho > \eta\gamma\,(\mu_c + \beta)\,\mathrm{e}^{\beta\tau}$, we can prove that any solution of System (3) has its mean value (i.e. there exists $\lim_{t\to+\infty} \frac{1}{t}\int_0^t X(s)ds$, where $X(t)$ denotes the solution) and this mean is equal to B. This theorem could be interpreted in the following way. Independently of an initial dose of the antigen the solution oscillates around the state B, which means that there is no possibility of recovery. On the other hand, we should remember that this result is purely analytic, while in reality we are not able to detect densities (not only in the case of considered antigen) below some threshold value, and this should be considered as cure in practice.

In my last article devoted to Marchuk's model [A14] I proved that there is a stable supercritical Hopf bifurcation when the positive steady state loses stability. In this analysis I based on the approach from [9]. I present this approach below.

In general we consider a system of the form

$$\dot{z} = H(z_t, \alpha) = L(z_t, \alpha) + G(z_t, \alpha), \quad H(0, \alpha) = 0, \tag{4}$$

where $z_t = x_t - \bar{x} \in \mathbb{C}$ (in this approach we formally extend the values from $\mathbb{R}$ into $\mathbb{C}$), $\bar{x}$ is the steady state that changes stability with increasing bifurcation parameter $\alpha \in \mathbb{I}$, where $\mathbb{I}$ denotes the interval of admissible values of α, operator $H : \mathscr{C} \times \mathbb{I} \to \mathbb{C}$ is sufficiently smooth, $L, G : \mathscr{C} \times \mathbb{I} \to \mathbb{C}$ are linear and non-linear part of (4) in the neighborhood of the steady state $\bar{z} = 0$, respectively.

The approach of Diekmann et al. is based on the theory of normalised bounded variation functions (NBV) defined on $[0, 1]$ (for the Banach space $\mathscr{C}$ of functions defined on $[-1, 0]$). Riesz representation theorem implies that for every $\phi \in \mathscr{C}$ and continuous operator L there exists exactly one NBV ζ, such that $L(\phi) = \int_0^1 d\zeta(\theta)\phi(-\theta)$ (this is a Riemann-Stieltjes integral). This means that NBV with maximal variation norm is a space adjoint to $\mathscr{C}$. Hence, $L(\phi) = \langle \zeta, \phi \rangle$, and the form $\zeta(\theta, \alpha)$, with α being a bifurcation parameter, is uniquely determined by the linear operator L.

With the equation $\dot{z} = L(z_t)$ the operator $T(t) : \mathscr{C} \to \mathscr{C}$, $T(t)\phi = z_t$ could be related. Here z is a solution of our equation with some initial function $\phi \in \mathscr{C}$. Then $T(t)$, $t \geq 0$, is a strongly continuous semi-group generated by an infinitesimal generator A, with the domain dense in $\mathscr{C}$ [18, 19], which allows to use the semi-group theory. If for some critical α_0 the generator A has a pair of purely imaginary eigenvalues $\pm i\omega_0$, where $\pm i\ \omega_0$ are single and do not cross the imaginary axis with non-zero speed as α increases, then a Hopf bifurcation occurs. In order to calculate eigenvalues of the characteristic equations

$$\Delta(\lambda, \alpha) = \lambda - \int_0^1 d\zeta(\theta, \alpha)\, \mathrm{e}^{-\lambda\theta}.$$

The generator A has purely imaginary eigenvalue $i\omega_0$, if there exist $\mathbf{p} \in \mathbb{C}$, $\mathbf{p} \neq 0$, such that $\Delta(i\omega_0, \alpha_0)\mathbf{p} = 0$, and a function $\Phi(\theta) = \mathrm{e}^{i\omega_0\theta}\,\mathbf{p}$, while A is for eigenvalue $i\omega_0$. On the other hand, if A^* is the adjoint operator, then the eigenvector reads $\Psi(\theta) = \mathbf{q}\,\mathrm{e}^{i\omega_0\theta}$, where $\mathbf{q} \in \mathbb{C}$, $\mathbf{q} \neq 0$, $\mathbf{q}\Delta(i\omega_0, \alpha_0) = 0$ and $\langle \Psi, \Phi \rangle = \mathbf{q}d_1\Delta(i\omega_0, \alpha_0)\mathbf{p}$, where d_1 is a derivative with respect to the first coordinate, which is λ here. If $\pm i\omega_0$ are single eigenvalues, then we can normalize $\langle \Psi, \Phi \rangle$ to 1 and choose $\mathbf{q}$, such that $\langle \Psi, \Phi \rangle = 1$, which means $\mathbf{q}d_1\Delta(i\omega_0, \alpha_0)\mathbf{p} = 1$.

Stability of periodic solutions appearing on the central manifold as a result of bifurcation is determined by the coefficient μ_2 of the third term in Taylor expansion [9]. This coefficient can be calculated as

$$\mu_2 = \frac{\mathrm{Re}c}{\mathrm{Re}\left(\mathbf{q}d_2\Delta(i\omega_0, \alpha_0)\mathbf{p}\right)}, \tag{5}$$

where d_2 is the second derivative with respect to the second variable (bifurcation parametr), which is α here, while $c = c_I + c_{II} + c_{III}$,

$$\begin{aligned} c_I &= \tfrac{1}{2}\mathbf{q}d_1^3G(0, \alpha_0)(\Phi, \Phi, \bar{\Phi}), \\ c_{II} &= \mathbf{q}d_1^2G(0, \alpha_0)\left(\Psi_{\bar{\Phi}}(\cdot, 0), \Phi\right), \\ c_{III} &= \tfrac{1}{2}\mathbf{q}d_1^2G(0, \alpha_0)\left(\Psi_{\Phi}(\cdot, 2i\omega_0), \bar{\Phi}\right), \end{aligned}$$

where d_1^i, $i = 2, 3$, denote ith derivatives with respect to the first variable (z_t) and

$$\Psi_{\Phi_1}(\theta, a) = \mathrm{e}^{a\theta}(\Delta(a, \alpha_0))^{-1}d_1^2G(0, \alpha_0)(\Phi, \Phi_1),$$

with $\Phi_1 = \bar{\Phi}$ and $\Phi_1 = \Phi$ for c_{II} or c_{III}, respectively.

If $\mu_2 > 0$, then supercritical Hopf bifurcation is present. In particular, periodic solutions exist for $\alpha > \alpha_0$. If additionally the steady state is stable for $\alpha < \alpha_0$, then bifurcating periodic solutions are stable within the central manifold. Moreover, if the generator A has no eigenvalues in the right-hand complex half-plane, then the central manifold is attracting, and this means that the periodic orbits are stable. If $\mu_2 < 0$, then the bifurcation is subcritical and periodic orbits exists for $\alpha < \alpha_0$. If the steady state is stable for $\alpha < \alpha_0$, then the periodic orbits are unstable, obviously.

I used the method described above in [A14], as well as in [C14, C24, C28, C42]. I would like to emphasize that calculation of Coefficient (5) for systems of DDEs is challenging in general.

Subsequent research projects within this topic were conducted together with M. Bodnar and concerned seasonality of immune reactions, especially in the context seasonal changes of the weather. In such a case it is natural to consider main parameters of the model to be periodic functions. This topic was considered in [Z6, C3, C4, Z19]. First, in [Z6, C3, C4] we focused on System (3) with coefficient α depending on time, while in [C18] these preliminary results were extended to the case when both α and ρ are time dependent. We assumed that these functions are continuous and bounded. Under this assumption it is easy to show that unique solutions exist globally in time (for $t \geq 0$). If ρ is periodic with period T, then we can prove (applying appropriate estimations and Gronwall's Lemma) that for any t_0 there is exactly one value f_0 for which a solution of the problem

$$\dot{F} = C^*\rho(t) - \mu_F F, \quad F(t_0) = f_0,$$

is periodic with period T. Moreover, if β and V^0 are sufficiently small, while f_0 is large enough, then solutions of System (3) tend to some periodic function as $t \to +\infty$. If both functions $\alpha(t)$ and $\rho(t)$ are periodic, then we are able to prove the existence of periodic solutions for small delays. The proof is based on the Leray-Schauder fixed point theorem. Compactness of the operator (which is one of the important assumptions of this theorem) is a consequence of compact embedding of $\mathbf{C}([-\tau, 0], \mathbb{R}^3)$ into $\mathbf{C}^1([-\tau, 0], \mathbb{R}^3)$.

1.2. Immunotherapy of tumors

My experience in modeling of immune reaction turned out to be very useful in mathematical analysis of immune reaction against tumors and tumor immunotherapy. In particular, in [A10] I focused on such interpretation of Marchuk's model. My main research in this field was conducted with the team of Prof. Zvia Agur from the Institute of Medical Biomathematics (Bene, Atharot, Israel). I was involved in mathematical analysis of immunotherapy of brain tumors (articles [C23, C37, C43] are related to that topic), and immunotherapy of prostate cancer [C56]. Tumor immunotherapy is a wide topic and it includes many actions focused on stimulation of immune reaction against tumor cells. It is still a nonstandard therapy, as clinical trials are very expensive. However, some of these trials showed that this therapy could be useful, and allows to predict doses for successful treatment. Therefore, I think these articles are among my most important achievements from application point of view. The review article [C67] on the personalized immunotherapy of cancers was prepared by us during the COVID-19 pandemic.

In [C12], together with Jacek Waniewski and Petar Zhivkov, we studied simplified model, in which we took into account two variables: size of specific immune response X and size of tumor Y. In this model a function describing immune reaction plays an important role. We assumed that the equation describing tumor cells dynamics is of "standard" predator-prey form (c.f. [31]), that is underlying growth is exponential, while the term XY reflects elimination of tumor cells due to immune reaction. If there is no antigen (tumor cells in this model), then we observe constant production of precursor cells and their natural mortality. Consequently, if there are no tumor cells the specific immunity is kept on a constant level which is called background immunity. The presence of antigen causes an increase of immunity proportionally to X, with proportionality coefficient being a function (F). We assume that F is bounded either with respect to both variables, or with respect to tumor size only. Formation of complexes tumor cell-cytotoxic T lymphocyte could lead to the lymphocyte death, which is again expressed by the bilinear term XY. We considered two types of F – in both cases it was a Hill function with some coefficient α, but it could be the function of the variable Y or Y/X. In [C12] asymptotic dynamics of that model depending on parameter values was studied. What is important, this model was used by Monika Joanna Piotrowska [33] to describe a specific (mice) experiment. This shows a

power of such approach – although the model is very simple, it is able to reflect immune reaction in the experiment.

Next, together with M. Bodnar we focused on more complex model of immune reaction against tumors. Our research was inspired by the paper [12], were the authors obtained false results which are associated with the fact that solutions of that model could take negative values. More on that topic could be found below in Subsection 9 where I describe biochemical reactions with delay. In [C53] we proved that the model proposed in [12] has undesired properties, and therefore we proposed a modification together with global analysis in the case of non-immunogenic tumor (that is the tumor does not cause immune response).

1.2.1. Immunotherapy of glioma

Glioma is a name of the family of brain tumors, and high grade (III and IV) gliomas give very poor prognosis – for grade IV the mean survival does not exceed 1.5 years even with highest standard therapy. My first work [C23] (together with Y. Kogan, Natalie Kalev-Kronik and other members of the team) considers those cancers.

Basic model of glioma immunotherapy (with the focus on most aggressive GBM – glioblastoma multiforme) was proposed in [24] and generalized in our article [C23]. Immune reaction was described by six nonlinear ODEs, and although part of them has a simple structure, the structure of the equation describing changes of tumor size is so complex, that it is difficult to analyse this model. More precisely, the first equation reads

$$\dot{T} = r(T)T - f_T(x)g_T(u)h(T)CT,$$

where T and C reflect the size of tumor and effector cells, i.e. cytotoxic lymphocytes (CTLs) population, respectively, $r(T)$ is the tumor growth rate, $f_T(x)$ describes reduction of the effectiveness of effector cells due to the presence of TGF-β (transforming growth factor-beta), $g_T(u)$ reflects the dependence of effector cells on the number of MHC class I receptors presented by one tumor cell, and $h(T)$ describes "overcrowding" effect associated with the tumor growth. Other model equations describe changes in time of effector cells density, number of MHC class I and II receptors, and densities of TGF-β and interferon-*gamma* (INF-γ).

In the article we focused on the existence of steady states and their stability, as well as proposing conditions of effective treatment, that is conditions of stability of the healthy state. We also have prepared the analysis of reduced (assuming quasi-steady approximation) model consisting of four equations for which we studied global stability and obtained as simple as possible formulas reflecting therapeutic doses. This awaits for the approval of Prof. Z. Agur.

In next papers [C37, C43, Z28] together with my collaborators from the UW (M. Bodnar, M.J. Piotrowska and J. Poleszczuk) we tried to propose a simplified model in which complexity of immune reaction was reflected by time delay (as it was done in Marchuk's model). Among these articles the most important is [C37], where we studied sensitivity of the model with respect to parameters changes and the reduction has been proposed on that basis.

In [Z23, A16] I studied simplified model with the influence of space reflected by diffusion process. There are interested numerical simulations showing the spread of tumor depending on the number of primary sites.

1.2.2. Immunotherapy of prostate cancer

One of my newest articles (together with M. Bodnar and Y. Kogan) [C56] describes the results of mathematical analysis of a model proposed in [25]. The model reflects the cascade of immune reactions appearing as a result of vaccine for PC (prostate cancer). Our analysis showed that asymptotic dynamics could be described by one equation which allows to estimate the results of therapy in

an easy way. In the first part of this article we proposed a general equation which in a specific case reduces to the one for PC immunotherapy. We considered the following Cauchy problem

$$\dot{x} = x\,F(t,x), \quad x(t_0) = x_0, \quad x_0,\ t_0 \geq 0, \tag{6}$$

with F satisfying conditions: F is continuous and uniformly bounded, increasing with respect to x and locally Lipschitz with respect to x in $\mathcal{D} = \mathbb{R}^2_+$ ($\mathbb{R}_+ = [0, +\infty)$ here), $F(t+1, x) = F(t, x)$, that is F is t-periodic with period 1.

Notice, that for t-periodic function it is enough to consider initial data with $t_0 \in [0, 1)$, while proposed assumptions guarantee existence of unique, global in time (for $t \geq 0$) solutions of (6). Moreover, for $x_0 > 0$ there is $x(t) > 0$ for $t \geq 0$.

Our main analytical result presented in [C56] is the theorem relating asymptotic dynamics of Problem 6 to mean value of F for $t = 0$.

Under our assumptions:

— if $F_A = \int_0^1 F(s,0)ds > 0$, then any solution of Problem (6) with $x_0 > 0$ tends to $+\infty$ as $t \to +\infty$;

— if $F_A = \int_0^1 F(s,0)ds < 0$ and $F(t,x) \to f(t) > 0$ uniformly as $x \to +\infty$, then there exists a curve $\gamma : [0,1) \to (0, +\infty)$, such that if

$x_0 < \gamma(t_0)$, then solutions of Problem (6) tend to 0;

$x_0 > \gamma(t_0)$, then solutions of Problem (6) tend to $+\infty$;

$x_0 = \gamma(t_0)$, then $x(t_0 + 1) = \gamma(t_0)$ and γ extended periodically to $[1, +\infty)$ is a periodic solution of Problem (6).

The proof of this theorem is based on integrating the equation on the interval $[t+n, t+n+1]$ for fixed $t \in [0,1)$ and $n \in \mathbb{N}$ and applying assumed properties of F and its mean in the second part of the proof.

Notice that if $F(t,x)$ does not depend on t, that is $F(t,x) = G(x)$ for some continuous, locally Lipschitz function G, then

1. either there exists $\tilde{x} > 0$ such that $G(\tilde{x}) = 0$ and then $x(t) \to 0$ for $0 < x_0 < \tilde{x}$, while $x(t) \to +\infty$ for $x_0 > \tilde{x}$;
2. either $G(x) > 0$ for $x > 0$ and then $x(t) \to +\infty$ for every $x_0 > 0$.

Second part of [C56] is devoted to the description of PC immunotherapy model (seven equations reflecting specific immune response and tumor growth) and the influence of vaccine. First we considered single vaccine, and next a series of vaccines included as impulses to the model. We applied the theorem proved in the first part and showed that to achieve cure after single vaccine the tumor growth rate must be sufficiently small, while natural influx of mature dendritic cells should be large enough. It is not possible in the case of parameters estimated in [25]. Therefore, the series of vaccinations is needed. In the final part of the article we proposed a condition guaranteeing cure.

1.3. Modeling of immune reaction in the presence of HIV virus

Some of my results were also related to the analysis of immune reaction against tumor cells in the situation when a patient has AIDS. Articles [Z22, C21, C30] (together with M. Bodnar and Zuzanna Szymańska or with J. Poleszczuk) are focused on that topic in the context of delayed reaction according to the presence of HIV. However, comparing to other results I obtained in the area of tumor modeling and treatment, I think that these results are more theoretical, probably without chances for application.

Lastly, inspired by Prof. Priti Kumar Roy (during his stay at the UW), we studied (together with my PhD student Marcin Choiski, and then also with Mariusz Bodzioch from Warmian- Masursian University in Olsztyn) CD4+T lymphocyte immunotherapy of patients with HIV virus ([C60]).

2. Modeling avascular tumor growth

Next research topic I was involved considers the growth of tumor during the first stage of development, that is avascular tumor growth. My interests in carcinogenesis were directly related to my participation in international grants within 5. and 6. EU Programmes. More precise description of processes associated with tumor development may be found in my monograph [M2].

It is assumed that at the initial stage of the growth tumor forms a compact structure in which cells are nourished via diffusion of nutrients from outside into the tumor. This is avascular stage of the growth. It is obvious that during the growth this structure must reach a size in which the amount of nutrients inside the tumor is not sufficient for all cells to proliferate. This leads to formation of so called necrotic core – cells for which there is not enough nutrient become quiescent (do not proliferate) and eventually die due to hunger. This type of death is called necrosis. The final, stable structure has about 2 mm of diameter, and its destabilization is strongly related to the begging of the next stage of tumor growth, that is angiogenesis process.

Initially I conducted the research on tumor growth modeling together with M. Bodnar. First articles were devoted to the first avascular stage of this growth in the context of time delay influence. Simple models of that type are based on the idea of multicellular spheroids (MCS). This is the idea of spatially symmetric growth of cellular colony described by H.P. Greenspan [16]. I explain this idea in Subsection 3 considering relations with the logistic equation. Our research was based on [6], where the author proposed to include time delay into cellular processes, in particular to the term describing proliferation, and next to regulatory apoptosis. Apoptosis is a kind of cell death which is natural in such a sense that it is not caused by external conditions (like lack of nutrients in the case of necrosis) but is programmed (like "suicide") to keep an organism in good condition. In [C6] we dealt with the model with time delay in proliferation process which is described by

$$\dot{x}(t) = -cx(t) + \sigma_e x(t-\tau) - \frac{a}{15}x^{5/3}(t-\tau), \tag{7}$$

where $x(t) = R^3(t)$ reflects tumor volume ($R(t)$ is MCS radius at time t), apoptosis is constant with coefficient c, σ_e reflects constant density of nutrients outside MCS (as well as on the surface, that is for $r = R(t)$, where r denotes the distance from the centre of MCS), τ is the delay od proliferation with respect to diffusion of nutrients, and a is a constant reflecting the balance between consumption and diffusion of nutrients. It also means that all nutrients appearing inside MCS are consumed. This is obvious that such equation could describe only that type of MCS in which all cell proliferate. Notice, that for $\tau = 0$, the inequality $\sigma_e > c$ must be fulfilled in order to keep the tumor in proliferating state. Therefore, the tumor must stabilize at the level $\bar{x} = \left(\frac{15(\sigma_e - c)}{a}\right)^{3/2}$.

When introducing delay we see that the right-hand side of Equation (7) includes a negative term with delay, and therefore it is of great importance to study nonnegativity of solutions. We proved the following properties of Equation (7).

— If initial function satisfies $x_0(s) \in \left[0, \left(\frac{15\sigma_e}{a}\right)^{3/2}\right]$ for $s \in [-\tau, 0]$ and $\frac{\sigma_e}{c} < \frac{25}{18}\sqrt{15}$, then the solution remains in the same interval for $t \geq 0$. On the other hand, if $\frac{15^{3/2}}{27} > \sigma_e > \frac{5^{5/2}}{2\cdot 3^{3/2}}c$, then there are solutions exceeding the value $\left(\frac{15\sigma_e}{a}\right)^{3/2}$.

— Equation (7) has two steady states. Trivial state ($x = 0$) is unstable regardless of delay. Stability of the positive state $\bar{x} = \left(15\frac{\sigma_e - c}{a}\right)^{3/2}$ depends on the model parameters, including delay. If $\sigma_e < 4c$, then $\bar{x}$ is stable independently of the delay. If $\sigma_e > 4c$, then there exists critical τ_c, such that for $\tau < \tau_c$ the sate $\bar{x}$ is stable, for $\tau = \tau_c$ there is a Hopf bifurcation and periodic solutions appear.

— If $2\sigma_e < 5c$ and initial function satisfies $x_0(s) \in \left(0, \left(\frac{15\sigma_e}{a}\right)^{3/2}\right)$ for $s \in [-\tau, 0]$, then any solution tends to $\bar{x}$ as $t \to \infty$.

In [C7] we introduced delay into regulatory apoptosis. In this case the models reads

$$\dot{x}(t) = \sigma x(t) - \hat{a}x^{5/3}(t) + \theta f(x(t-\tau)), \tag{8}$$

where $f(z) = -\hat{\sigma}z + \hat{a}z^{5/3}$, $\hat{a} = \frac{a}{15}$, $\hat{\sigma} = \sigma_e - \sigma_h$, and σ_h is a coefficient reflecting the influence of regulatory apoptosis, an therefore it could be positive and negative as well.

We also studied the range of parameter values for which solutions of Equation (8) remain non-negative, positive steady state exists, steady states are stable/unstable and Hopf bifurcation appears. Delays in both processes were considered in [Z9, Z13, Z16].

The next stage is formation of necrotic core which is associated with MCS exceeding the critical value for which the density of nutrients inside MCS in insufficient for all cell to proliferate. This was considered in [C9] (together with Anna Mokwa-Borkowska). In particular we were interested in the thickness of the proliferating rim. It depends on the parameters, obviously, but in most of the cases considered it was really slim. In [Z15, C10] we again (together with M. Bodnar) introduced delay to the model considered in [C9]. We studied the influence of delay onto that model dynamics, as in [C6, C7]. The results of mentioned papers [C6, C7, C9, C10] were included into my habilitation monograph [M2].

3. Logistic equation and its generalizations in the description of tumor dynamics

Logistic equation and its various generalizations where used by me and my collaborators many times. In particular, we used this equation to describe avascular tumor growth. Currently, it is assumed that the logistic equation has no biological interpretation (c.f. the discussion in [31]), while its common usage is associated only with its simplicity and well known properties. In the description of tumor growth the Gompertz model [13] is most often applied. This is probably connected with the fact that it was used for the first time as the mathematical model describing tumor growth in some experiment [27, 28]. On the other hand, the Greenspan model [16] is (or seems to be) biologically approved. In line with this, I think that the result obtained by me together with M. Bodnar in [C13] is important. We showed that the logistic equation could be derived as underlying law for cellular colony growth on Petri dish (that is in $\mathbb{R}^2$).

3.1. Derivation of the logistic equation in the context of tumor growth

In [C13] we based on reaction-diffusion equation proposed by [16]

$$\begin{cases} \dfrac{\partial}{\partial t}\sigma(t,x) = D\Delta_x\sigma(t,x) - P, & \text{for } t \geq 0, |x| \leq R(t), \\ \sigma(t,R(t)) = \sigma_e, \end{cases}$$

where $x \in \mathbb{R}^n$ (in Greenspan case $n = 3$, we decided to generalize his idea to the abstract n-dimensional case), $|x|$ is Euclidean norm, σ represents the density of nutrients, $R(t)$ is the outside MCS radius, P is the rate of consumption of nutrients by tumor cells, and Greenspan assumed $P = \text{const}$. We also assume that outside MCS the density of nutrients is constant, equal to σ_e, which means that it is constant at the boundary of MCS. tumor volume changes proportionally to the proliferation of cells, as well as natural cells death (with coefficient σ).

Next, we assume that the diffusion of nutrients is much faster than the tumor doubling time. Hence, we can (formally) use quasi-steady approximation and assume that $\sigma(t,x)$ is radially symmetric (more precise analysis of similar approximation but for more complex model is described in [Z27] – for the Hahnfeldt et al. model [17]). In our case, solving ordinary equation of the second order we obtain

$$\sigma(t,r) = \sigma_e - \frac{a}{2n}\left(R^2(t) - r^2\right),$$

with $a = P/D$. Using this formula for σ we derive the equation

$$\dot{V} = \alpha V\left(\sigma_e - c - \frac{a}{n(n+2)}V^{2/n}\right),$$

with α reflecting the growth rate, and $V = R^n$ could be interpreted as tumor volume. Moreover, for $n = 2$ we obtain the logistic equation, also known as the Verhulst equation [37]. In classic case, for $n = 3$ we obtain the exponent $2/3$, and the Greenspan equation [16].

3.2. Logistic equation and similar equations

Main topic of our research described in [C13] was to compare several theoretical equations with the experimental data. We considered two equations

$$\dot{x}(t) = \begin{cases} -r\,x(t-\tau)\ln|x(t-\tau)| & \text{for } x(t-\tau) \neq 0, \\ 0 & \text{for } x(t-\tau) = 0, \end{cases} \tag{9}$$

$$\dot{x}(t) = rx(t-\tau)\left(1 - (x(t-\tau))^{\gamma}\right), \tag{10}$$

that is the Gompertz equation (that could be obtained by generalization of the logistic equation) and the equation which becomes logistic for $\gamma = 1$ or Greenspan for $\gamma = 2/3$.

Notice that both models (9) and (10) belong to the class of those equations (c.f. [4]), for which the right-hand side takes negative values. This means that one of the main points of our analysis has been to check if it is possible to remain in positive region, because only then the models have biological meaning. We proved the following properties of the equations above.

1. For Equation (10) with $\gamma = 1$, if $\tau < \tau_0$, where $r\tau_0$ is the smallest positive root of $W(r\tau) = (r\tau)^3 + 4(r\tau)^2 - 16$, then all solutions remain positive under the assumption that initial values belong to the interval $[0, 1]$. The state $\bar{x} = 1$ is locally asymptotically stable for $\tau < \frac{\pi}{2r\gamma}$, and for $\tau = \frac{\pi}{2r\gamma}$ there is a Hopf bifurcation.
   If $\tau < \frac{1}{r\gamma}$, then the state $\bar{x} = 1$ is globally stable in the set

$$\mathcal{A} := \{\varphi \in \mathscr{C}_\tau : 0 \leq \varphi(t) \leq 1\,,\ t \in [-\tau, 0]\}\,.$$

2. For Equation (9), if $\tau < \tau_0$, where $r\tau_0$ is the smallest positive root of $F(r\tau) = 1 - r\tau\left(\frac{r\tau}{\mathrm{e}}\right)\ln\left(1 + \frac{r\tau}{\mathrm{e}}\right)$, then all solutions remain positive under the assumption that initial values belong to the interval $[0, 1]$. The state $\bar{x} = 1$ is locally asymptotically stable for $\tau < \frac{\pi}{2r}$, and for $\tau = \frac{\pi}{2r}$ there is a Hopf bifurcation.
   If $\tau < \frac{1}{r}$, then the state $\bar{x} = 1$ is globally stable in the set $\mathcal{A}$.

An important part of this research was to construct a specific algorithm which allowed to find parameters to best reproduce experimental results from [34]. The results seem to confirm that the Gompertz equation reflects these data in the best way.

The earliest article devoted to the logistic equation with delay [C5] presents results of master's thesis of Remigiusz Kowalczyk. We studied the influence of delays introduced to various terms of the right-hand side, taking into account the classic version of the Verhulst equation $\dot{x} = rx(1 - x)$ (with $K = 1$), as well as the competitive version $\dot{x} = rx - ax$, where a reflects intraspecific competition. It occurs that the best properties from application point of view have equations with single (that is classic one) and double delay (as in Equation (10)). Moreover, the last model was proposed in [34] to describe experimental data for tumor growth, and therefore it is an object of my research.

I continued a research on various types of equations (like logistic and Gompertz) in the context of tumor growth and treatment. In [Z29, C39] we (together with M. Bodnar and M.J. Piotrowska) studied the logistic equation with delay and quasi-periodic treatment function, while in [C40] we conducted a

study of the Gompertz model in the same context. In [C28] together with M.J. Piotrowska I analyzed existence and a type of Hopf bifurcation for the Gompertz model with delay. In [C49] we (with Jan Poleszczuk and Ting Liu) studied the logistic equation with delay and treatment reflected by impulses, which seems to be closer to reality than other forms of treatment description (like in [Z29, C39, C40]).

3.3. Logistic equation with delay and diffusion

In [Z10, C8] together with Anna Marciniak-Czochra I studied logistic equation with delay and diffusion. We considered both classic and double delayed equation as a reaction-diffusion problem with zero-flux boundary conditions. Similarly to the case without diffusion – until the solutions of double delayed model remain positive, they have similar dynamics to the classic version. What is important, our analysis showed that diffusion has no effect on the stability of the positive steady state and destabilization is related to the delay and not diffusion.

4. Modeling of tumor angiogenesis

When the tumor exceeds critical size, necrotic core is formed inside MCS. In this stage tumor cells secrete biochemical signals and these signals initiate the process of tumor angiogenesis. This is a process of new blood vessels formation from existing ones. This process is very complex, obviously, in particular complex space structures are formed during it. However, we can consider average quantities and use dynamical systems in the description of that process dynamics.

My first article [C11] on that topic was prepared in the framework of cooperation of Prof. Z. Agur and her team from the IMBM (Israel). It was based on articles of this team [2, 3]. This article [C11] was included into my habilitation, where I also analyzed its simplified version; c.f. also [Z18]. In [C11] together with Yuri Kogan and Yuri Kheifetz I focused on proving that there are always oscillatory solutions in the considered model. The model is described by a system of three DDEs describing tumor size, size of vessels network and amount of regulating proteins. It should be emphasized that reflecting oscillations by a mathematical model was the main idea of the authors of the original papers [2, 3], as such type of the behavior was observed in experiments. However, in the proposed model there is no possibility of non-oscillatory solutions, while simple monotonic dynamics of the system is observed in nature as well, or even more often. In line with that we (together with M. Bodnar) proposed ([C17]) a modification of the model studied in [C11]. We considered 3 equations with discrete delays of the form

$$\begin{aligned}
\dot{N}(t) &= \alpha N(t)\left(1 - \frac{N(t)}{1 + f_1(E(t-\tau_1))}\right),\\
\dot{P}(t) &= f_2(E(t))N(t) - \delta P(t),\\
\dot{E}(t) &= \left(f_3(P(t-\tau_2)) - \alpha\left(1 - \frac{N(t)}{1 + f_1(E(t-\tau_1))}\right)\right)E(t),
\end{aligned} \tag{11}$$

where N reflects tumor size, P stands for density of proteins regulating growth and maturation of blood vessels, E is effective vessel density (measured in terms of vessels volume divided by tumor size).

Functions f_j, $j = 1, 2, 3$, are continuous and fulfill the following conditions. Functions f_1, f_3 are increasing, $f_1(0) = 0$, $\lim_{x\to\infty} f_1(x) = b_1 > 0$, $f_3(0) < 0$, $f_3(c_3) = 0$, $\lim_{x\to\infty} f_3(x) = b_3 > 0$, while f_2 is decreasing, $\lim_{x\to\infty} f_2(x) = 0$.

Analysis of the existence and stability of steady states under the assumption $\tau_1 = \tau_2 = 0$ proved complicated. Analytical results we obtained could be summarized as follows. Let us denote $g(x) = f_2(x)(1 + f_1(x)) - \delta c_3$. System (11) has the following steady states:

$$A = (0, 0, 0), \quad B = (1, a_2/\delta, 0), \quad C_j = (\bar{N}_j, c_3, \bar{E}_j),$$

where $\bar{N}_j = 1 + f_1(\bar{E}_j)$, while $\bar{E}_j$ are positive solutions of the equation $g(\bar{E}) = 0$.

For $\tau_1, \tau_2 = 0$, assuming differentiability of f_1, f_2, f_3, we obtain:

1. the steady state A is a saddle;
2. the steady state B is:
   locally asymptotically stable for $a_2 < c_3\delta$,
   unstable for $a_2 > c_3\delta$;
3. the steady state C_j is:
   locally asymptotically stable for $g(\bar{E}_j) < 0$,
   unstable for $g(\bar{E}_j) > 0$.

Points 1. and 2. are a simple consequence of the Jacobian matrix form. Stability of C_j depends on the sign of the free term of the characteristic function. We showed that this sign is related to the sign of the derivative of g which defines states C_j.

Let us assume $C_j = (\bar{N}_j, \bar{P}_j, \bar{E}_j)$, $j = 1, 2, ...$ and $0 < \bar{E}_1 < \bar{E}_2 < \dots$.

Depending on the model parameters, in generic cases we obtain:

— either the number of positive steady states is even, and then those with even indexes are locally asymptotically stable,

— either the number of positive steady states is odd, and then those with odd indexes are locally asymptotically stable.

Assuming specific forms of f_j, that is

$$f_1(E) = \frac{b_1 E^2}{c_1 + E^2}, \quad f_2(E) = \frac{a_2}{1 + d_2 E}, \quad f_3(P) = \frac{(a_3 + b_3)P^2}{\frac{c_3^2 b_3}{a_3} + P^2} - a_3,$$

we showed that in the space of parameters (a_2, b_1) a hysteresis loop appears. In numerical simulations, with increasing delay we observed destabilization of the positive steady state and Hopf bifurcation.

In [C36] we came back to the problem of dependence of System (11) on delays. Portion of the results presented in this paper was obtained by Ewa Nizińska in her master's thesis, while the rest of the research was conducted together with M.J. Piotrowska and M. Bodnar. It turned out that the stability of the states A and B does not depend on the magnitude of delay (which is again a simple consequence of the form of characteristic functions), while stability of positive states depends on the sign of the derivative $g'(\bar{E}_j)$. If $g'(\bar{E}_j) > 0$, then the state C_j is unstable regardless of the delay. The proof is based on the Mikhailov criterion (c.f. Subsection 14). We showed that the state is unstable in the case without delays and the change of the argument for positive delays could not be equal to $3\pi/2$, which implies instability. For specific cases when one of the delays is equal to 0, we proved theorems on stability of positive steady states. We used the method described in Subsection 14. The results are complex, and therefore I do not present them here. Analytical results were completed by numerical simulations, in particular for basins of attraction for two positive states in the case of bistability.

My newest article on that model [C57] was written together with Emad Attia and M. Bodnar. In this article the results from [C36] were extended to the case of Erlang distributed delays. In that case the delay is infinite, so another space must be considered; c.f. [20].

In our case distributed delays are of the form

$$\int_0^\infty f(\tau)G(x(t-\tau))d\tau,$$

where $f : [0, \infty) \to \mathbb{R}_0^+$ is a probability density with finite mean. We need to control the behavior of functions $\varphi : (-\infty, 0] \to \mathbb{R}^2$ for $t \to -\infty$. Now, $\mathscr{C} = \mathbf{C}((-\infty, 0], \mathbb{R}^n)$ and it seems natural to choose the space of bounded continuous functions $BC = \{\varphi \in \mathscr{C} : \sup|\varphi| < \infty\}$. However, the space BC does not fulfill one of the assumptions guaranteeing local existence of unique solutions. Therefore, for an

arbitrary continuous nondecreasing positive function $\eta : (-\infty, 0] \to \mathbb{R}^+$, $\lim_{\theta\to-\infty} \eta(\theta) = 0$ we define Banach space

$$\mathcal{K}_\eta = \left\{\varphi \in \mathscr{C} : \lim_{\theta\to-\infty} \varphi(\theta)\eta(\theta) = 0 \text{ and } \sup_{\theta\in(-\infty,0]} |\varphi(\theta)\eta(\theta)| < \infty\right\},$$

with the norm $\|\varphi\|_\eta = \sup_{\theta\in(-\infty,0]} |\varphi(\theta)\eta(\theta)|$ for $\varphi \in \mathcal{K}_\eta$. Function η must be chosen in such a way that we control the behavior of initial functions at $-\infty$. If delays are finite, that is densities have compact supports, initial functions fulfill $\varphi \in \mathscr{C}_\tau$, $\tau = \tau_{\max}$, where $[-\tau_{\max}, 0]$ includes the supports, which is equivalent to considering the space $\mathcal{K}_\eta$ with the function $\eta = 1$ on the interval $[-\tau_{\max}, 0]$ and decreasing to 0 at $-\infty$. If supports are unbounded and initial functions φ are unbounded, then we need to choose an appropriate function η. One of the possibilities is to choose $\eta(\theta) = \mathrm{e}^\theta$. However, this assumption does not simplify the analysis, and therefore we presented our results in general case, without assuming specific form of η. However, it is important that the chosen space fulfills all axioms postulated in [20].

Some of the results concerning the delay in tumor growth were presented in [Z36]. Some results, in particular those in which there is no dependence on the delays, were extended to any integral delay without assuming its specific form. However, for most of the results we needed to assume the specific form of the density function. Applied tools are not very different from those for discrete delays, however specific calculations and estimations are very laborious.

Yet another article [C19] considers the process of angiogenesis. It is based on the results of bachelor's thesis of J. Poleszczuk. In [C19] we proposed a model of angiogenesis taking into account that vessels created during angiogenesis are irregular, tangled and leaky. Therefore, it is estimated that large amount of chemotherapy does not enter inside of the tumor, while the part that enters is not spread evenly. The model taking into account these features could possibly allow to plan normalization of the vessels structure.

4.1. Articles related to the Hahnfeldt et al. model

Part of the most important results obtained by me and my team was inspired by the Hahnfeldt et al. model [17]. This model was proposed in 1999 and describes the process of angiogenesis using two ODEs. The first equation reflects the dynamics of tumor on the basis of Gompertz law, but instead of constant carrying capacity a variable reflecting size of vessels network was used. More precisely, this variable reflects the size of vessels network necessary to nourish the tumor of given volume. The second equation describes the changes of vessels network in time. In the general form the model reads

$$\begin{aligned} \dot{p} &= -rp \ln \tfrac{p}{q}, \\ \dot{q} &= -\mu q + bS(p,q) - dI(p,q), \end{aligned} \tag{12}$$

where r is the tumor growth rate, μq is spontaneous loss of vessels, the term $bS(p(t), q(t))$ stands for stimulation of vessels formation, while $-dI(p(t), q(t))$ reflects inhibition of this formation. In [17] the authors derived the following relation between $I(p,q)$ and $S(p,q)$:

$$\frac{I(p,q)}{S(p,q)} = p^\alpha q^\beta, \quad \text{where } \alpha + \beta = 2/3.$$

Eventually, comparing speeds of various processes, Hahnfeldt et al. [17] proposed the equation

$$\dot{q} = bp^\alpha q^{1-\alpha} - (ap^{2/3} + \mu)q.$$

In the literature, System (12) with $\alpha = 1$ is mainly called Hahnfeldt et al. model [17], as it was eventually studied in this paper. The model with $\alpha = 0$ (and with delay) ws analyzed by A. d'Onofrio and A. Gandolfi [10]. Similar model was also proposed by Ergun et al. [11].

Analyzing the space portrait of System (12) and using the Dulac-Bendixson criterion and the Poincaré-Bendixon theorem it is easy to check that for $b > \mu$ there is a positive steady state of System (12) which is globally stable in the set $(\mathbb{R}^+)^2$ (we study System (12) under the assumption $0 < \alpha \leq 1$, because for $\alpha > 1$ the term describing stimulation of the vessels formation loses biological meaning). Stability of steady states was studied by me and M. Bodnar in [Z20, C20], mainly in the context of the influence of delay introduced into the model on this model dynamics. After the change of variable $u = p/q$ and a proper scaling we studied the model that reads

$$\begin{aligned} \dot{p}(t) &= -rp(t)\ln u(t-\tau_1), \\ \dot{u}(t) &= -u(t)\left(r\ln u(t-\tau_1) + b\,(u(t-\tau_2))^{\alpha} - a\,(p(t-\tau_3))^{2/3}\right), \end{aligned} \tag{13}$$

where τ_j, $j = 1, 2, 3$, reflect delays present on the macroscopic level in the considered processes, that is tumor growth, vessels stimulation and vessels inhibition. Applying the method described in Subsection 14 we proved the following properties of System (13).

— If $\tau_1 = \tau > 0$ and $\tau_2 = \tau_3 = 0$ or $\tau_2 = \tau_3 = \tau > 0$ and $\tau_1 = 0$, then there exists $\tau_c > 0$, such that the positive steady state is stable for $\tau < \tau_c$ and unstable for $\tau > \tau_c$.

— If $\tau_2 > 0$ and $\tau_1 = \tau_3 = 0$, then

if $r < \alpha b$, then the positive steady state is stable for all delays $\tau_2 > 0$;

if $r > \alpha b$, then the positive steady sate is stable for small τ_2 and loses stability for some threshold value $\tau_{2,c} > 0$.

Next, in [C24, C42] together with M.J. Piotrowska I studied a Hopf bifurcation for the Hahnfeldt et al. and d'Onofrio-Gandolfi models, first for only one delay appearing in the model (that is either the growth of tumor is delayed or the vessels formation is delayed; c.f. [C24]), and next for both non-zero delays ([C42]). In the second paper we based on numerical analysis partially, as analytical formulae for Coefficient (5) are too complex in this case.

It should be noted that the macroscopic model (12) was derived in [17] from the microscopic model – Hahnfeldt et al. described the process of diffusion-consumption of stimulators and inhbitors of angiogenesis, which under some assumptions (e.g. radial symmetric) could be simplified to ODE (similarly to the Greenspan model; c.f. Subsection 3). However, in [17] the derivation was described very briefly and formally, without proper reasoning. In [Z27] we presented the results of research on that derivation (main results of J. Poleszczuk master's thesis). We proved that formal steps presented in [17] are well-founded from mathematical point of view. Understanding of the microscopic processes governing tumor angiogenesis allowed to propose in [C27] (together with J. Poleszczuk and M. Bodnar) alternative way of the mathematical description of anti-angiogenic treatment. In standard description (like in [17]) this therapy is reflected by additional death term in the equation describing changes of vessels. However, from the microscopic model we concluded that the therapy should be described differently in the case when drugs inhibits stimulation or stimulate inhibition of the vessels formation. In our research we focused on the class of drugs directly blocking proteins stimulating angiogenesis, which reflects in blocking blokuje VEGF (vascular endothelial growth factor). Bevacizumab (Avastin®) is a drug belonging to this class.

More precisely, in general case the second equation of System (12) with standard treatment term reads

$$\dot{q} = -\mu q + bS(p,q) - dI(p,q) - equ,$$

where u reflects the amount of drug applied. In [C27] we proposed alternative modification of the Hahnfeldt et al. model

$$\begin{aligned} \dot{p} &= -rp\ln\frac{p}{q}, \\ \dot{q} &= -\mu q + \frac{l}{a+u}S(p,q) - dI(p,q). \end{aligned}$$

In [Z30] and [C44] (with J. Poleszczuk and M.J. Piotrowska) we studied optimal treatment having in mind combined treatment, where anti-angiogenic therapy could be used as a complement of stan-

dard therapy. In that context, it seems that proposing a proper objective functional is of the most importance, as it is important what we optimize. We proposed the following objective functional

$$P[u(\cdot)] = p(T) - k_1 \frac{q(T)}{p(T)} + k_2 \int_0^T u(t)dt,$$

where T (> 0) describes (fixed) duration of treatment, k_1, k_2 reflects the decision which of the therapeutic goals is more important, while the last term stands for side effects of the drug application. In line with this we additionally assume that $\int_0^T u(t)dt \leq A_{\max}$ for some constant $A_{\max}$. In our opinion, this functional emphasized the role of vessels normalization in better distribution of the drug inside the tumor.

We proved that the optimal strategy consists of intervals in which we apply full dose, no dose, as well as intermediate doses, while bang-bang strategies are not optimal, and the change between full and no dose is always through intermediate doses.

More recently, with my PhD student Piotr Bajger and M. Bodzioch, I focused on sensitivity of tumor cells with respect to therapy ([Z37]). In System (12) we divided the whole cellular population into two groups – sensitive and resistant to therapy (chemotherapy, but we can also consider other types of tumor therapies). The result that seems to be most important from a patient point of view is connected with simulations in which we plotted survival times. In clinics the typical therapeutic scheme is "full dose – no dose", while in our model of competition between sensitive and resistant cells this scheme dose not lead to highest survival. Maximal survival time is obtained for intermediate doses.

Last papers on the process of angiogenesis ([C27], [C44], [Z37]) are important in my opinion, because of their potential impact on the tumor treatment.

5. Modeling of cancer mutations

Due to hypotheses, carcinogenesis is a multistage process, and the formation of cancer is preceded by the sequence of mutations. Typically there are 3 to 7 mutations; c.f. [32]. In several of my research papers I analyzed models of cancer mutations on the basis of [1]. This topic was also included into my habilitaion monograph, but only two-stage mutation was considered there (c.f. also [A13]). Simplified version (only one mutation) I presented in [Z14], while in [Z17] I studied the influence of delay onto the one-stage model dynamics. Later, in [A15] I extended some results to the general n-dimensional case. More precisely, I analyzed three models

$$\begin{aligned} \dot{y}_0 &= y_0(a_0(1-y_0) - \mu_1 y_1), \\ \dot{y}_i &= y_i(a_i(1-y_i) - \mu_{i+1}y_{i+1} + \eta_i y_{i-1}), \text{ for } i = 1,\dots,n-1, \\ \dot{y}_n &= y_n(\,\mathbf{1+}\, \eta_n y_{n-1}), \end{aligned} \tag{14}$$

$$\begin{aligned} \dot{y}_0 &= y_0(a_0(1-y_0) - \mu_1 y_1), \\ \dot{y}_i &= y_i(a_i(1-y_i) - \mu_{i+1}y_{i+1} + \eta_i y_{i-1}), \text{ for } i = 1,\dots,n-1, \\ \dot{y}_n &= y_n(\,\mathbf{1-}\, \eta_n y_{n-1}), \end{aligned} \tag{15}$$

$$\begin{aligned} \dot{y}_0 &= y_0(a_0(1-y_0) - \mu_1 y_1), \\ \dot{y}_i &= y_i(a_i(1-y_i) - \mu_{i+1}y_{i+1} + \eta_i y_{i-1}), \text{ for } i = 1,\dots,n-1, \\ \dot{y}_n &= y_n(\mathbf{-1} + \eta_n y_{n-1}), \end{aligned} \tag{16}$$

where y_0 stands for healthy cells population, while y_i, $i = 1,\dots,n$, describes the size of cellular population on the ith stage of mutations. Systems (14), (15) and (16) differ in the influence of the

environment on the last stage of mutations, and reflect favorable, competitive and unfavorable environment, respectively.

In [A15] I studied global dynamics of these models. I showed that $\dot{y}_i$ grows at most linearly for all $i \in \{0, 1, \ldots, n\}$, which yields global existence of solutions in time. For System (16) there is also $\dot{y}_n \geq y_n$, and therefore $y_n \to \infty$, which means that in favorable environment cancer cells grow to infinity. The rest of the paper focused on other systems. In (15) the same effect as for (14) could be observed. However, we are able to choose such parameter values for which y_n is bounded. I also studied various kinds of steady states that could be present in these models. Using the method of Lyapunov functionals I analyzed global stability. For System (16) I proved that if there is unique positive steady state, then it is globally stable. On the other hand, for System (15) the positive steady state is unstable, if exists, which is a simple consequence of the Jacobian matrix form. The stable state is reflected by $y_n = 0$ and other coordinates are nonzero (again if this state exists). Notice, that this state is unstable for System (16). If both the states do not exists, we should focus on the states with more zero coordinates.

In the basic article [1] the authors studied reaction-diffusion equations, so I decided to study the influence of diffusion as well. It turns out that these systems belongs to the class of equations for which Lyapunov functions for ODEs could be easily translated into the functional for reaction-diffusion equations with zero-flux boundary conditions by integration. Hence, the results for global stability remain unchanged.

In [Z31, C41] we considered the influence of delay and diffusion on the model dynamics. In [Z32, C48] the influence of delays into two-stage model dynamics was analyzed.

6. Radiation induced bystander effect

Article [C52] presents main results of the first PhD thesis of J. Poleszczuk. The thesis was prepared on the basis of experiments conducted in Silesian Technical University under the supervision of Prof. Maria Wideł. Experiments were related to so called bystander effect and was conducted to study radiation induced bystander effect (that is the influence of radiation on cells not directly exposed to radiation) and appearance of senescent cells (this means cells that are not able to proliferate but do not follow apoptotic path and remain in the organism). It turns out that depending on the dose of radiotherapy there appear various kinds of bystander effects. In the article results of the experiments were analyzed statistically and we proposed a modification of standard linear-quadratic model describing effects of radiotherapy with the influence of bystander effect. Although from mathematical point of view we used simple tools, the results presented in [C52] could potentially have some practical impact, as they could be used to propose better radiotherapeutic protocols, and therefore I think they belong to my most important results.

7. Chemotherapy of tumors: acquired drug resistance

Last several years I have focused on chemotherapy of tumors in the context of acquired drug resistance (ADR). Together with M. Bodnar we considered two simple models of ADR syndrom to compare two hypotheses on acquiring drug resistance ([Z39], [C66]). Analytical results are not sufficient to decide which hypothesis is more probable. We can only conclude that more experiments focusing on the problem are needed.

Another problem in this direction is related to optimal control. This research has been conducted together with P. Bajger and M. Bodzioch, and started with the Hahnfeldt et al. model for heterogeneous tumors ([Z37]) described above. Then we considered simplified model without angiogenesis, focusing on competition between sensitive and resistant tumor cells subpopulations [C62]. The most important part of our work is optimal control problem in which we propose to minimize not only

tumor size (during and at the end of treatment) and drug side-effects but also to penalize presence of resistance subpopulation. In this research we considered the following optimal control problem:

Minimize

$$J(u(\cdot)) = \omega_1 n_1(T) + \omega_2 n_2(T) + \int_0^T \left(\eta_1 n_1(t) + \eta_2 n_2(t) + \xi G\left(\tfrac{n_2(t)-n_1(t)}{\epsilon}\right) + \theta u(t)\right) dt \tag{17}$$

over all measurable functions $u : [0, T] \to [0, 1]$ with respect to the dynamics

$$\begin{aligned} \dot{n}_1 &= \gamma_1 n_1 (1 - n_1 - n_2) - \tau_1 n_1 + \tau_2 n_2 - n_1 u(t), \\ \dot{n}_2 &= \gamma_2 n_2 (1 - n_2 - n_1) + \tau_1 n_1 - \tau_2 n_2, \end{aligned} \tag{18}$$

where n_1, n_2 are the non-dimensional volumes of cells respectively sensitive and resistant to chemotherapy, $u : [0, T] \to [0, 1]$ is the non-dimensional chemotherapy dose (or control), and G reflects penalty related to the presence of resistant cells (in simulations we used $G(z) = \frac{1}{2}(1 + \tanh(z))$). Coefficients γ_1, γ_2 are the non-dimensional proliferation rates, τ_1, τ_2 are the non-dimensional mutation rates, ω_1, ω_2, η_1, η_2, ξ and θ are non-negative weights. The timescale in (18) was chosen so that the coefficient in front of the chemotherapy-induced cell death is 1 and the cell populations were rescaled by the maximal size (arrying capacity in population models). In order to penalize the resistant population even further, one can chose the weights so that $\omega_2 > \omega_1$ and $\eta_2 > \eta_1$.

In C62 we presented some analytical results about the structure of optimal control. In particular we showed that there exist singular controls which satisfy Legendre-Clebsch condition and thus locally optimal. The singular arc and the singular control may also be calculated explicitly in terms of the state variables. We identified four regions in the phase space and classified them according to a possibility of locally optimal "no dose – full dose" and "full dose – no dose" switches occurring in each of them. Finally, we showed that the optimal control has to end with a full dose interval under some additional restriction. Next, we referred to a numerical method to find the optimal control. It occurred to be of the form "full dose – singular – full dose". The singular interval in the middle – during which the control is applied at about 10% of the full dose – is crucial in preserving the sensitive phenotype. The singular control maintains the number of sensitive cells just above the number of resistant cells. Note that the singular interval stems directly from the resistance penalty function G being present in the objective functional (17). These results support our hypothesis that inclusion of explicit resistance penalty in the objective functional leads to the low-dose metronomic-type protocols being optimal.

These results have been further extended: analytically, for simpler model, without mutation components, and numerically, for the Hahnfeldt et al. type of model with angiogenesis process included. Two manuscripts are in review now.

8. Androgen deprivation therapy in prostate cancers

This is my newest research topic related to the Bekker Program financed by the National Agency for Academic Exchange (NAWA). The research has been conducted in Israel with IMBM team. Within the project - based on clinical data from Mayo Clinic - we developed mathematical model for the growth of prostate cancer in hormone-sensitive stage (HSPC) and its treatment with androgen deprivation therapy (ADT). Tumor size is reflected by measured amount of prostate specific antigen (PSA). We proposed and fitted to the data an underlying tumor growth model (using the data of those patients for whom records of PSA before the start of ADT were available); proposed a pharmacokinetic model of the administered drug (leuprolide) and fitted it to the data available from FDA records; proposed a testosterone secretion model and fitted it to the available data. Then we combined the above models into one model and fitted it to the data from patients treated with continuous ADT. Next, we proposed a model which includes two resistance mechanism: one influencing the

testosterone path and second influencing PSA. At all stages of the model development I performed mathematical analysis confirming our choices. Mathematical analysis of the full model for constant drug amount was performed as well and a manuscript presenting the process described above has been prepared. I plan to send it to publication after final approval by other authors (Alon Nahshoni and Moran Elishmereni).

9. Biochemical reactions with time delay

As it has been mentioned in the introduction, sometimes authors of articles on modeling real phenomena using DDEs do not pay attention to basic mathematical properties of such equations, like nonnegativity of solutions. One of such articles is [5], where the authors claimed that oscillations observed in some simple biochemical reactions channels appear as a result of delays. They described the first of considered channels by one linear DDE, which is known to have negative solutions [4]. Discussing the models proposed in [5] we noticed (with J. Poleszczuk and M. Bodnar) [C31] that solutions not only can have negative values but always take negative values when the delay exceeds critical value for which Hopf bifurcation occurs. It considers one DDE of the form

$$\dot{x}(t) = A \ - Bx(t) - Cx(t-\tau) \tag{19}$$

with initial data

$$x(t) = \begin{cases} 0 & \text{for } t \in [-\tau, 0), \\ x_0 & \text{for } t = 0, \end{cases} \tag{20}$$

and whenever negative solutions appear, they have no biological meaning. In [5] Equation (19) describes a reaction channel for some protein which could degrade either instantaneously or with some delay – this means that the second reaction lasts significantly longer (with mean value equal to τ). Scheme of this channel reads

$$\emptyset \xrightarrow{A} X, \quad X \xrightarrow{B} \emptyset, \quad X \xRightarrow{C} \emptyset, \tag{21}$$

where X denote the considered protein. Scheme (21) means that the protein is produced by DNA with constant rate A, while intensities of degradation are B and C, for instantaneous and delayed degradation, respectively.

In [5] the authors presented results of stochastic simulations and formally calculated correlation function for stationary distribution, which in their opinion confirmed oscillations caused by the delay. On the other hand, it is known that for $C > B$ and $\tau > \tau_c := \frac{\arccos(-B/C)}{\sqrt{C^2-B^2}}$ Equation (19) has oscillatory solutions (c.f. [18, 19, 26]). In our article [C31] we proved that if $\tau > \tau_c$ then for every $x_0 \geq 0$ there exists such time point $\bar{t} < 4\tau$ at which the solution of (19)–(20) takes negative value. The proof of that fact is based on proposing the formula for solution on each interval $[n\tau, (n+1)\tau)$, which could be proved by mathematical induction. However, formulas are complex, and necessary calculations are tedious. This is probably the reason that it was not clearly stated in the literature before.

Notice that initial data (20) covers all cases important from biochemical point of view, so we concluded that Equation (19) is not a proper mathematical description of biochemical reaction. In line with that in [C25] (together with Jacek Miękisz, J. Poleszczuk and M. Bodnar) we proposed an alternative description of biochemical reactions with delays, while in [C26] we presented mathematical analysis of the models describing Reaction 21 and two other reaction channels from [5].

The description of Reaction (21) proposed by us reads

$$\begin{aligned} \dot{x}(t) &= A - (B+C)x(t), \\ \dot{u}(t) &= Cx(t) - Cx(t-\tau)\,\mathrm{e}^{-D\tau} - Du(t), \end{aligned} \tag{22}$$

where D is the rate of instantaneous degradation of those reactants which are in the path of delayed degradation. Clearly, in Scheme 21 we do not exclude the situation when a protein chosen for delayed

degradation at time $t-\tau$ is degraded in the path of instantaneous reaction before t. We see that the first equation of System (22) is linear, and the whole system is separable. Therefore, although the delay appears in the second equation, our system could be solved analytically, and the delay plays a role of a "usual" parameter. We calculated analytical solutions of System (22) and showed that permanent oscillations are not possible. Hence we concluded that one reaction of this kind is not able to cause oscillatory dynamics.

Second reaction channel considered in [5] is a protein production with negative feedback, which could be described by the following system

$$\begin{aligned} \dot{x}(t) &= Ad_0(t-\tau) - Bx(t), \\ \dot{d}_0(t) &= -k_1 x(t) d_0(t) + k_{-1}(\gamma - d_0(t)), \end{aligned} \tag{23}$$

where x reflects the amount of proteins, d_0 stands for active DNA, while γ is the overall amount of DNA. Usually $\gamma = 1$ and then d_0 is a proportion of active DNA. For System (23) we proposed initial data

$$x(t) = x^0(t), \quad d_0(t) = d^0(t) \quad \text{for} \quad t \in [-\tau, 0].$$

In Supplement to the article of Bratsun et al. [5] the formulation of this model appeared, but there is no mathematical analysis there.

Denote

$$\Omega = [0, +\infty) \times [0, \gamma], \qquad \Omega_1 = \left[0, \frac{A\gamma}{B}\right] \times [0, \gamma],$$
$$C_\Omega = \{\varphi \in \mathscr{C}_\tau : \varphi(t) \in \Omega\}, \quad C_{\Omega_1} = \{\varphi \in \mathscr{C}_\tau : \varphi(t) \in \Omega_1\}.$$

We showed that C_Ω is positively invariant for System (23) and proved that if all coefficients are positive, then there exists exactly one positive steady state $(\bar{x}, \bar{d}_0)$ which is locally asymptotically stable for all $\tau > 0$. For $\tau = 0$ this state is globally stable in $\mathbb{R}^+$, while if $Ak_1\gamma < 2Bk_{-1}$ and $\tau > 0$ this state is also globally stable in C_Ω. Local stability was proved using standard linearization method, while for global stability we proposed Lyapunov functions for $\tau = 0$ and $\tau > 0$ separately. For $\tau = 0$ the functional is defined in $(\mathbb{R}^2)^+$, while for $\tau > 0$ we need to define it in $\mathbb{C}_\Omega$. Discrete form of the delay allows for reducing the problem of negativity of the derivative along the solution of (23) to the problem of positivity of some real matrix (3×3 in this case).

Third reaction channel considered in [5] is a modification of the previous reaction. In addition, it is assumed that a protein is able to bind to DNA and block its own production only in the form of dimer. Therefore, it is necessary to from two-protein complexes (dimers). The model describing this channel reads

$$\begin{aligned} \dot{x}(t) &= Ad_0(t-\tau) - Bx(t) - k_2 x^2(t) + 2k_{-2}x_2(t), \\ \dot{x}_2(t) &= \frac{k_2}{2}x^2(t) - k_{-2}x_2(t) - k_1 x_2(t) d_0(t) + k_{-1}(\gamma - d_0(t)), \\ \dot{d}_0(t) &= -k_1 x_2(t) d_0(t) + k_{-1}(\gamma - d_0(t)). \end{aligned} \tag{24}$$

Notation is the same as for System (23), and x_2 stands for density of dimers. As before, we proposed proper initial data on $[-\tau, 0]$. We again showed the existence of unique positive steady state $(\bar{x}, \bar{x}_2, \bar{d}_0)$ which is locally asymptotically stable for $\tau = 0$. Moreover,

1. if $\sqrt{2\frac{k_{-1}k_{-2}}{k_1 k_2}} > \frac{A\gamma}{2B}$ then the steady state is locally asymptotically stable for all $\tau > 0$;
2. if $\sqrt{2\frac{k_{-1}k_{-2}}{k_1 k_2}} < \frac{A\gamma}{2B}$ then the steady state is locally asymptotically stable for $\tau \in [0, \tau_0)$, and for $\tau = \tau_0$ a Hopf bifurcation appears.

Other stability changes for the steady state of System (24) are not possible.

Results presented in [C26] showed that to obtain oscillatory behavior one should consider not only the delay, but the delay together with feedback and dimers formation. Therefore, the hypothesis formulated in [5] is false and at least three reactions of the considered type (that is of bilinear form)

are necessary for oscillations. The series of our papers is meaningful, because it showed that using DDEs one needs to be careful, and moreover, only detailed mathematical analysis could lead to proper conclusions. Therefore, I also singled out and attached these articles.

10. Modeling of dyadic interactions

Interesting part of my research is related to modeling of dyadic interactions, commonly known as "Romeo and Juliet" models. The main paper on that topic is [C35] in my opinion, as it was published in a journal of sociological scope. In this article (together with Natalia Bielczyk and Tadeusz Płatkowski) we studied the influence of delays into the relationship between partners. The model variables were interpreted as intensities of emotions of partners in their relationship. For the first time a model of such type was proposed by Strogatz [35, 36]. In [C35] we studied the linear system, as studying stability we usually make linearization, so analysis of stability is typically associated with linear analysis. The delay reflects slower reaction of one of the partners either to its own emotions or to the emotions of a partner. In most general case the model we considered reads

$$\begin{aligned} \dot{r}(t) &= a_{11} r(t-\tau_{11}) + a_{12} j(t-\tau_{12}), \\ \dot{j}(t) &= a_{21} r(t-\tau_{21}) + a_{22} j(t-\tau_{22}), \end{aligned} \tag{25}$$

where r and j stand for the partners emotions, while $\tau_{kl} \geq 0$, $k, l \in \{1, 2\}$ are the delays of reactions. It is obvious that if $\tau_{kl} = 0$ for some $k, l \in \{1, 2\}$ then this reaction is instantaneous. In the cases we considered one of the delays τ_{kl} was nonzero.

This way we made a systematic study of linear DDEs with single discrete delay in the context of possible stability switches. In the proofs we used the methods described in Subsection 14. In line with that this article could also be included to my analytical results, however these results were also interpreted in psychological language.

Taking into account the fact that real relationships are not linear in [C32] we (together with M. Bodnar and N. Bielczyk) proposed nonlinear model in which stabilization due to the presence of delay (for specific values of the delay) is possible. We concluded that for some type of couples it is beneficial if one of the partners does not react immediately but will think a little bit (but not too long) before reaction. It could lead to stabilization of this couple. Introductory results on that topic were presented in [Z26]. Next, in [Z33] together with Małgorzata Półtorak we proposed a model in which we are able to describe positive and negative emotions separately (in classic models the mean emotion is described). This model needs further discussion as it has some undesirable mathematical properties (it is not defined in the whole $(\mathbb{R}^+)^2$).

Next article [C59] (together with M.J. Piotrowska and Joanna Górecka) is related to the influence of optimism and pessimism into our social life (when and which persons have a chance to constitute and maintain a relationship, not necessarily romantic one).

I also considered an influence of time delays into the classic discrete model of Gottman, Murray et al. [15] of marital interactions ([Z38], [A19]). Lastly, the research on the influence of time delays has been continued together with my master's students Katarzyna Cytlak and Natalia Jankowska. We obtained interesting results, again related to the actors attitude to life (optimism/pessimism) [C68] (together with M.J. Piotrowska).

11. Modeling of heart action

Another research topic I was involved came due to cooperation with Beata Jackowska-Zduniak. This topic is modeling of heart action and its pathologies. In [C45] we used (together with M. Bodnar) van der Pol equation with delay to reconstruct abnormal heart action observed in tachycardia. Van der Pol equation is a prototype ODE of the second order used in the description of oscillators, as it

has a limit cycle for some range of parameter values. More precisely, we used this equation in its first order form that reads

$$\begin{aligned} \dot{x} &= y, \\ \dot{y} &= -a(x^2-1)y - fx(x+d)(x+e), \end{aligned} \tag{26}$$

where parameter values were fixed in such a way that System (26) reflects real frequencies of heart beat. Abnormal heart action was described by feedback with delay:

$$\begin{aligned} \dot{x} &= y(t) + k(x(t-T) - x(t)), \\ \dot{y} &= -a(x^2(t)-1)y(t) - fx(t)(x(t)+d)(x(t)+e). \end{aligned}$$

We analytically studied the influence of delay ans numerically reproduced abnormal heart action observed in tachycardia.

Next article [C55] presented research on various types of tachycardia on the basis of more complex models, like Hodgkin-Huxley model [21] (well known model used in the description of action potentials) or Yanagihara-Noma-Irisawa model [40]. We again introduced delays to reflect pathologies in heart action. It turns out that proposed models successfully reproduce differences between various types of tachycardias.

12. Ecological, epidemiological and eco-epidemiological models

My interests related to ecological problems were initiated during my cooperation with National Forest Research Institute. I was involved in investigation of possible prognostic abilities of mathematical models in the context of forests pest gradations. Article [Z7] (with M. Bodnar) is devoted to that topic. Next, I modeled coral reefs. The model was based on diffusion-consumption idea, the same as for avascular tumor growth ([Z11], [Z12]). Together with Zuzanna Szymańska ([Z21, C22]) I came back to ecological problems and studied relations between heterothropic and autotrophic organisms. In [C47] together with my bachelor's student Paweł Matejek I studied the possibility of explaining an unusual disproportion in predator species in Australia on the basis of the prey-predator model with carrying capacity for preys. The article has mainly a review character, but the presented interpretation is interesting and I used it in popularizing way many times, in particular I prepared an article for "Delta" (which was awarded the Deans Award for the best article in 2014).

In turn, my interests of epidemiological models have started with my cooperation with the team of Prof. Anping Liu from China University of Geosciences in Wuhan. The first work on that topic [C34] prepared together with Meihong Qiao was devoted to SICR model, in the context of vaccinations against Hepatitis B.

Last time I focused on the spread of epidemics in heterogeneous populations ([C64], [C65]). I has been inspired by M. Bodzioch (UWM in Olsztyn) and his research on active case founding of tuberculosis in a subpopulation of homeless people in Warmian- Masurian Province of Poland.

12.1. Modeling of vaccinations

In [C34] we studied a model in which the whole population is divided into four classes: S, I, C i R – susceptible, infected, carriers and resistant. As usual in such type of models, as variables reflect fractions of persons in each of the considered classes, we were able to reduce the model and consider the system of three ODEs

$$\begin{aligned} \dot{S} &= \mu - (\beta I + \varepsilon\beta C)S - \mu S, \\ \dot{I} &= (\beta I + \varepsilon\beta C)S - \gamma_1 I - \mu I, \\ \dot{C} &= q\gamma_1 I - \gamma_2 C - \mu C, \end{aligned} \tag{27}$$

with positive parameters. This system was considered in the set

$$\Omega = \{(S, I, C) \in \mathbb{R}^3_+ : S + I + C \leq 1\}, \tag{28}$$

which is positively invariant for (27).

One of the most important parameters in epidemiological models is so called basic reproduction number $\mathcal{R}_0$. It gives the information about the threshold of epidemic. If the value if $\mathcal{R}_0$ is less than 1, then the disease does not spread as one infected individual is able to infect less than one susceptible. In our model

$$\mathcal{R}_0 = \frac{\beta}{\gamma_1+\mu} + \frac{q\gamma_1}{(\gamma_1+\mu)}\frac{\varepsilon\beta}{(\gamma_2+\mu)}.$$

We proved that if $\mathcal{R}_0 \le 1$ then the only steady state $(1,0,0)$ (disease free equilibrium, DFE) is globally stable, while for $\mathcal{R}_0 > 1$ there exists positive steady state

$$S^* = \frac{1}{\mathcal{R}_0} = \frac{(\gamma_1+\mu)(\gamma_2+\mu)}{\beta(\mu+\gamma_2+\varepsilon q\gamma_1)}, \quad I^* = \frac{\mu(\mu+\gamma_2)}{\beta(\mu+\gamma_2+\varepsilon q\gamma_1)}(\mathcal{R}_0-1),$$
$$C^* = \frac{\mu q\gamma_1}{\beta(\mu+\gamma_2+\varepsilon q\gamma_1)}(\mathcal{R}_0-1),$$

which is locally stable, and moreover it is globally stable under some additional assumptions.

Global stability of DFE was investigated using the method proposed in [23]. In this method the system should be rewritten in the form

$$\begin{aligned} \dot{X}_1 &= A_1(X)(X_1 - X_1^*) + A_{12}(X)X_2, \\ \dot{X}_2 &= A_2(X)X_2, \end{aligned} \tag{29}$$

where $X_1 \in \mathbb{R}_+^{n_1}$, $X_2 \in \mathbb{R}_+^{n_2}$, $X = (X_1, X_2)$ and System (29) is defined in positively invariant set $\Omega_X \subset \mathbb{R}_+^{n_1+n_2}$. In general, X_1 stands for all uninfected classes, while X_2 reflects other ones. For System (29) we assume:

1. (29) is dissipative in positively invariant set Ω_X;
2. steady state X_1^* of subsystem
$$\dot{X}_1 = A_1(X_1, 0)(X_1 - X_1^*)$$
is globally stable in the canonical projection of Ω_X into $\mathbb{R}_+^{n_1}$;
3. matrix $A_2(X)$ is Metzler (that is all off-diagonal terms are nonnegative) and irreducible for any $X \in \Omega_X$;
4. there exists a matrix A_2^u which bounds from above all matrices from the set $\mathcal{M} = \{A_2(X) : X \in \Omega_X\}$, and either $A_2^u \notin \mathcal{M}$ or if $A_2^u \in \mathcal{M}$, that is $A_2^u = \max_{\Omega_X} \mathcal{M}$, then for any $X \in \Omega_X$ such that $A_2^u = A_2(X)$ we have $X \in \mathbb{R}_+^{n_1} \times \{0\}$ (meaning that the points realizing maximum lie in the submanifold of disease free states);
5. $\alpha\left(A_2^u\right) \le 0$, where $\alpha\left(A_2^u\right)$, is the spectral bound for A_2^u.

In [23] it was proved that if Assumptions 1.–5. are satisfied then DFE is globally stable for System (29). We showed that for $\mathcal{R}_0 < 1$ these assumptions and fulfilled for System (27), which implies global stability of DFE.

For positive state (S^*, I^*, C^*) we proved global stability (inside the set Ω) proposing a Lyapunov function, assuming that

$$\beta < \min\{2\mu+\gamma_1+\gamma_2, 2\mu+(1-q)\gamma_1, (2\mu+\gamma_2)/\varepsilon\}.$$

The main topic of [C34] was to study the influence of vaccines onto the model dynamics. These vaccines were modeled using impulses. We assumed that vaccines are given at times $n\tau$, $n \in \mathbb{N}$, where τ is the time interval between two impulses (vaccines), while $S(n\tau^-)$ reflects the size of susceptible class just before nth vaccine. For a given fraction $p \in [0,1]$ of vaccinated individuals we wanted to find an optimal distance τ between two subsequent impulses. Hence, we studied the system

$$\left.\begin{aligned} \dot{S} &= \mu - (\beta I + \varepsilon\beta C)S - \mu S, \\ \dot{I} &= (\beta I + \varepsilon\beta C)S - \gamma_1 I - \mu I, \\ \dot{C} &= q\gamma_1 I - \gamma_2 C - \mu C, \end{aligned}\right\} t \neq n\tau,$$
$$S(t^+) = (1-p)S(t), \; t = n\tau, \; n \in \mathbb{N}^+. \tag{30}$$

We used the comparison method for equations with impulses [29]. We proved that if

$$\mathcal{R}_1 = \frac{\beta}{\mu+\delta} \cdot \frac{1-\mathrm{e}^{-\mu\tau}}{1-(1-p)\,\mathrm{e}^{-\mu\tau}} < 1,\ \delta = \min\{(1-q)\gamma_1, \gamma_2\},\ q < 1,$$

then solutions of System (30) tend to $(S^*(t), 0, 0)$, where

$$S^*(t) = 1 - \frac{p}{1-(1-p)\,\mathrm{e}^{-\mu\tau}}\,\mathrm{e}^{-\mu(t-n\tau)},\ \ n\tau < t \le (n+1)\tau,\ \ n \in \mathbb{N}^+.$$

We concluded that the condition of effective vaccination is:

$$\tau < \frac{1}{\mu}\ln\frac{\beta-(1-p)(\mu+\delta)}{\beta-\mu-\delta} \quad \text{or} \quad p > (1-\frac{\beta}{\mu+\delta})(1-\mathrm{e}^{\mu\tau}).$$

In [C51] we studied epidemiological model with delay and impulsive birth rate (such type of birth rate could be explained in the framework of external influence onto the considered ecosystem).

12.2. Modeling the spread of epidemic in heterogeneous populations

Research on the spread of epidemic in heterogeneous populations (e.g. we considered tuberculosis for homeless and non-homeless people) is conducted by me together with M. Bodzioch, in the framework of PhD of M. Choiski. We based on a simple SIS model, because the data for other groups in the populations are not available. We studied a class of models assuming Malthusian growth of the population [C65] as well as a constant influx of individuals to the population [C64]. To describe the spread of the disease in the heterogeneous population we used criss-cross type models. The most important conclusion from our analysis is related to the fact that conditions that are sufficient to eliminate the disease from the single subpopulations could not act in the same way in the case of the whole heterogeneous population. Hence, the presence of (even small) subgroup of people with higher rate of the disease spread could lead to the pandemic in the whole population, which seems to be important in the context of COVID-19.

12.3. Eco-epidemiological models

Subsequent papers with the team of Prof. A. Liu focused on combination of ecological and epidemiological topics. Such a combination has been a new trend of eco-epidemiological studies. We analyzed the prey-predator model with infection in the prey species. In [C46] the system of reaction-diffusion equations was considered and we studied this system in the context of influence of diffusion on the model dynamics. It turns out that for this model we were able to propose a Lyapunov function as the system belongs to that class of problems for which the Lyapunov function for ODE version could be adapted for diffusion version via integration. Additional analysis of that model was performed in [C61] (together with Piotr Radziski – this was partially his bachelor's thesis). In [C50] we studied the influence of stochastic effects.

13. Modeling in neurosciences

Analysis of the influence of time delays into the dynamics of simple systems of equations leads also to interesting results in the context of neurosciences. In [C58], [C63], together with N. Bielczyk and master's students Katarzyna Piskała and Natalia Płomecka (also with other coauthors) we studied a system of two equations describing interactions between two neuronal populations. The system describes an ambivalent situation, where "win" of one population means the choice of one of the two available options. Including delays we show that sometimes such choice is not easy, and the brain considers both options subsequently. In particular, it could be related to the increasing age and, consequently, delays.

In [Z42] I presented several real situations which could be described by similar simple models.

14. Analytical results for some classes of DDEs

In this subsection I present results obtained by me and my collaborators for some general classes of DDEs, however these results were also motivated by specific applications. I consider these results an important part of my research because it is not a frequent case to obtain analytical results for general equations in the case of DDEs. Therefore these articles are attached to this statement.

14.1. General equation motivated by the logistic model

In many problems studied by me (and not only by me, c.f. [31, 34]), like avascular tumor growth, there appeared an equation which could be generalized as

$$\begin{cases} \dot{x}(t) = \alpha f(x(t-1)), & t \geq 0, \\ x(t) = \varphi(t), & t \in [-1, 0], \end{cases} \tag{31}$$

where $f\colon \mathbb{R}^+ \to \mathbb{R}$ is a continuous function satisfying the following conditions: $f(0) = f(1) = 0$, f is positive in the open interval $(0, 1)$ and has one positive maximum. In particular, in [34] such type of equation with logistic f (that is $f(x) = x(1-x)$) was proposed to describe the change of tumor cells population in the experiment on mice.

First analytical results obtained by me under some stronger assumptions (in particular for unimodal function f fulfilling inequalities $\alpha \leq 1$ and $|f'(1)| \leq 1$) I published in [A11]. In [C14] we (with M. Bodnar) weakened the conditions on f assuming only that f is nonincreasing on the interval $(c, +\infty)$, where $c \in (0, 1)$ is the point at which f achieves its maximum. In turn, inequalities assumed in [A11] were replaced by the condition of positivity of the function $1 - x + \alpha f(1 + \alpha f(x))$ on the interval $(c, 1]$.

More precisely, if the function $g(x, \alpha) = 1 - x + \alpha f(1 + \alpha f(x))$ is positive in the interval $[c, 1)$ then for any initial function φ with the values in $[0, 1]$ there exists a global nonnegative solution $x(t)$ of Problem (31), and if $\varphi \not\equiv 0$ then $x(t) \to 1$ as $t \to +\infty$. We also showed that g is decreasing with respect to the second variable, so there exists unique critical α_c such that $g(x, \alpha) > 0$ for all $\alpha < \alpha_c$ and $x \in [c, 1)$, while for $\alpha > \alpha_c$ there exists such $\bar{x} \in [c, 1)$ that $g(\bar{x}, \alpha) < 0$.

The proof is based on considering two possibilities. Either a solution remains above or below 1 starting form some time point $\bar{t}$, and then this solution tends to 1, obviously. If not, then there exists an infinite sequence $(t_n)_{n=0}^{\infty}$ such that $x(t_n) = 1$, $x(t) \geq 1$ for $t \in (t_{2k}, t_{2k+1})$ and $x(t) \leq 1$ for $t \in (t_{2k+1}, t_{2k+2})$. Moreover, $t_n \to +\infty$. Estimating the solution on subsequent intervals (t_n, t_{n+1}), separately for even and odd natural number n, we obtained two sequences: x_k bounds $x(t)$ from below in the intervals (t_{2k-1}, t_{2k}) and y_k bounds $x(t)$ from above in the intervals (t_{2k}, t_{2k+1}). We derived the recurrent formula and concluded that x_n is convergent under the assumption, which also implies the convergence of y_n.

Notice, that the assumption of this theorem are weaker then those in [A11], which could be checked e.g. for the Gompertz function (that is for $f(x) = -x \ln x$). Assuming that f is sufficiently regular we were able to simplify these assumptions. We proposed such simplifications in [C14], and we used some of them in [C13] in the analysis of specific models.

Second part of [C14] was devoted to the study of possible destabilization of positive steady state and the appearance of Hopf bifurcation. We used the method proposed by Diekmann et al. [9]; c.f. (5). We showed that the steady state $\bar{x}_2 \equiv 1$ of Equation (31) is destabilized when α exceeds critical value $\alpha_0 = \pi/(2|f'(1)|)$ and if f is of class $\mathbf{C}^3$ and

$$(11\pi - 4)\,(f''(1))^2 > \pi f'''(1) f'(1)$$

then for $\alpha = \alpha_0$ there is a stable Hopf bifurcation.

This work was also complemented with several examples of application of the theorems we proved; c.f. also [C13].

As I mentioned before, Equation (31) was motivated by the version of delayed logistic equation considered in [34]. This equation, in contrary to the classic version (c.f. [31]), has some undesirable properties, in particular it has negative solutions for large values of the delay. Because during our studies it turned out that there are no significant qualitative and quantitative differences between the classic equation and that proposed in [34] until the solution to the second one remains positive, therefore in specific applications we can try to fit both of the equations as well. Sometimes it is important to introduce death term to the model explicitly, for example in tumor growth modeling such term could reflect some form of a treatment. On the other hand, as time after which the triggered death is observed is much shorter comparing to the cell cycle length or time of pregnancy, we usually assume that the death term is not delayed. That is why we (with M. J. Piotrowska and M. Bodnar) decided to study in [C38] equations of the form

$$\begin{cases} \dot{x}(t) = \alpha\Big(f(x(t-1)) - g(x(t))\Big), & t \geq 0\,, \\ x(t) = \varphi(t)\,, & t \in [-1,0] \end{cases} \tag{32}$$

and

$$\begin{cases} \dot{x}(t) = \alpha\Big(x(t)f(x(t-1)) - g(x(t))\Big), & t \geq 0\,, \\ x(t) = \varphi(t)\,, & t \in [-1,0]\,, \end{cases} \tag{33}$$

where the function g reflects death, while $xf(x)$ in (33) plays the same role as f in Equations (32) and (31).

One of our aims was to study Hopf bifurcation, as we assumed that functions f and g are of class $\mathbf{C}^3$. However, in the proof of existence and uniqueness of solutions for linear g we used the step method, so it is enough to assume that f is integrable. Moreover, in general case $g(0) = 0$ and g is nondecreasing. It is known that solutions of Equation (32) could be negative, and therefore in the analysis presented in [C38] we assumed the existence of nonnegative solutions defined for all $t \geq 0$. Next, to guarantee existence of positive steady state $\bar{x} = 1$ we assume $f(1) = g(1)$. Main results obtained by us on that topic were presented in [C38]. They were concerned with the occurrence of (degenerated or nondegenerated) Hopf bifurcation and stability of periodic orbits appearing due to the bifurcation; c.f. (5).

General results are rather complex, and obtained conditions have no clear biological interpretation. Depending on the parameters, which are the derivatives of f and g up to the third order, we are able to show that there is a Hopf bifurcation may be super- or subcritical. For example I present below one of the results obtained for Equation (33) under the assumption that the derivatives of the second and third order of both f and g are zero at $\bar{x} = 1$ (we can interpret it as functions that are linear near the positive steady state). Let us define

$$\alpha_0 = \frac{\arccos\frac{a_0-b_1}{a_1}}{\sqrt{a_1^2-(b_1-a_0)^2}}, \text{ where } a_0 = f(1),\ a_1 = -f'(1),\ b_1 = g'(1).$$

If $b_1 - a_1 < a_0 < b_1 + a_1$ then the positive steady state $\bar{x} = 1$ of Equation (33) is locally asymptotically stable for $0 < \alpha < \alpha_0$, unstable for $\alpha > \alpha_0$ and for $\alpha = \alpha_0$ there is a Hopf bifurcation. Moreover,

1. if $b_1 - a_1\xi_0 < a_0 < b_1 + a_1$ then the bifurcation is supercritical;
2. if $b_1 - a_1 < a_0 < b_1 - a_1\xi_0$ then the bifurcation is subcritical;

where $\xi_0 \approx -0.145$ is the only zero of the function

$$F(\xi) = -\Big(12\xi^2 - 10\xi - 1\Big)\sqrt{1-\xi^2} - \Big(8\xi^2 - 16\xi - 3\Big)\arccos(-\xi),\ \xi \in [-1,1].$$

Although in the literature partial results on that topic could be found – for example in [38] a version of Poincaré-Bendixson theorem for Equation (32) with decreasing f fulfilling $xf(x) < 0$ and $g(x) = x$, there were no systematic study for Equations (32) and (33) with general functions f and g, especially in the context of the type of Hopf bifurcation which was our main aim. I therefore think that this research is important.

14.2. Equation motivated by the Cooke model

In [C54], motivated by the article [7], together with Gang Huang and A. Liu we considered the following equation

$$y'(t) = F(y_t(0), y_t(-\tau)) - cy_t(0), \quad c > 0, \tag{34}$$

where $F : \mathbb{R}^2 \to \mathbb{R}$ is of class $\mathbf{C}^1$. We studied Equation (34) in the set

$$\Omega = \{\phi \in \mathscr{C}_\tau : \ \forall t \in [-\tau, 0], \ \ 0 \le \phi(t) \le 1\},$$

under the assumption that F fulfills:
1. $F(u, v) \ge 0$ for $u, v \in [0, 1]$ and $F(1, v) < c$ for $v \in [0, 1]$;
2. $F(u, 0) = 0$ for $u \in [0, 1]$.

Assumption 1. implies that Ω is positively invariant with respect to Equation (34), while 2. is sufficient for $y = 0$ to be a steady state (it is stronger than necessary condition $F(0, 0) = 0$, however is important in the proof of global stability).

Often in specific situations instead of strong inequality in 1. it is enough to assume $F(1, v) \le c$ for $v \in [0, 1]$. In such a case if y reaches the value $y(t) = 1$ and $y''(t) \le 0$ then Ω is still invariant.

In [C54] we studied global stability using proper Lyapunov functionals and the Lyapunov-LaSalle theory; c.f. [19]. First using $U_1 : \Omega \to \mathbb{R}$ defined as

$$U_1(\phi) = \int_0^{\phi(0)} \lim_{v \to 0} \frac{F(0, v)}{F(\sigma, v)} d\sigma + \int_{-\tau}^{0} c\phi(\theta) d\theta, \tag{35}$$

under additional assumptions: F is of class $\mathbf{C}^2$ and partial derivatives of F satisfy inequalities $F_u(u, v) \le 0$, $F_v(u, v) \ge 0$, $F_{uv}(u, v) \le 0$, $F_{vv}(u, v) \le 0$, $F_v(0, 0) \le c$, we proved that the state $y = 0$ is globally stable in Ω.

Next we considered positive steady state under the assumptions guaranteeing the existence of that state (e.g. it is enough to assume $F_v(0, 0) > c$). Defining

$$U_2(\phi) = \int_{y^*}^{\phi(0)} \frac{F(y^*, y^*)}{F(\sigma, y^*)} d\sigma - y^* \ln \frac{\phi(0)}{y^*} + c \int_{-\tau}^{0} \left(\phi(\theta) - y^* - y^* \ln \frac{\phi(\theta)}{y^*} \right) d\theta, \tag{36}$$

we were able to prove global stability of the positive steady state inside the set Ω.

As analysis of global stability for DDEs is not an easy task, in particular proposing a proper Lyapunov functional is not obvious, I decided to mention this paper as important in my research.

15. Other analytic results

In papers [A12] and [Z25, C29] I presented two useful tools for analysis of stability of DDEs. The methods are known in literature, however are not commonly used in biomedical applications, and therefore I decided to popularize them showing their powerful on some specific examples. In [A12] I considered the so called Mikhailov criterion which originally was proposed for ODEs, and as a tool for DDEs has been known mainly for engineers.

In the simplest version this criterion allows to localize roots of a pseudopolynomial

$$W(\lambda) = P(\lambda) + Q(\lambda)\, \mathrm{e}^{-\lambda\tau}, \tag{37}$$

where P and Q are polynomials, deg.P is greater than deg.Q and W has no roots on the imaginary axis. Then the change of the argument of the vector $W(i\omega)$ as ω increases from 0 to ∞ is equal to

$\frac{\pi}{2}$deg.P if and only if all roots of W are located in left-hand complex half-plane. More general – this statement is true for any number of discrete delays, as well as distributed delays on finite intervals (for infinite intervals some additional assumptions could be necessary). In [A12] I presented precise proof for several discrete delays (the poof is base on the Principle of Argument) and discussed several examples of application showing that this is a useful tool.

In [C29] together with Joanna Skonieczna I presented the method of destabilization analysis coming from the article [8]. This method is based on continuity of eigenvalues with respect to the parameters. This means that stable steady state may be destabilized when some parameters (typically delay) changes if eigenvalues cross imaginary axis from left to right-hand complex half-plane with nonzero speed. To this end we define an auxiliary function which is build on the basis of the characteristic quasipolynomial (37) in the following way

$$F(\omega) = |P(i\omega)|^2 - |Q(i\omega)|^2.$$

Looking for zeros of this function F we are able to establish destabilization (if F has positive zero then purely imaginary eigenvalues exist) and possibility of stability switches (if F has more positive zeros). In [C29] we presented simple version of the proof and examples of practical applications of this method.

16. Other articles

Papers [A6] and [A9] are review articles devoted to mathematical modeling of disease transmission both on the level of single individual and the whole population, as well as development of cancerous diseases.

In [A18] I listed several interesting examples of application of dynamical systems to the description of natural phenomena. It is also a review article.

Papers [Z5, A7] are devoted to the life and achievements of Prof. Wiesław Szlenk.

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