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DELAYED EQUATIONS IN APPLICATIONS

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ABSTRACT. In this paper we make a review of analysis of delay differential equations in the context of applications. We illustrate described methods using simple examples known from biomathematical literature.

1. INTRODUCTION

Recently, delay differential equations (DDEs) are frequently used in the description of various natural phenomena. There are models known from years, like the Hutchinson equation (cf. [52]), which was proposed in 1948 and has been studied in many paper and text-books [46, 49, 55], as well as many newer models; cf. [3, 11] in the context of romantic relationships, [5, 6, 24–28, 32] in the description of immune reactions, [13, 15, 35, 62] for biochemical reactions modelling, and many papers devoted to various stages of tumour growth and treatment, such as [7, 8, 17, 33, 34, 36, 38, 39, 44, 65–68] describing avascular stage of tumour growth, [37, 41, 42] for vascular stage, [12, 14, 31] for carcinogenic mutations, [40, 43] for immunotherapy of cancers, and [10, 30] describing dynamics of some class of DDEs resulting from the analysis of tumour growth. Notice, that most of the cited papers are the results of research in our group, but the number of papers involving models with delays still increase tremendously.

Although many properties of DDEs are similar to ordinary differential equations (ODEs), there are also significant differences between these types of equations. In this article we present some basic mathematical properties of DDEs in the general context of dynamical systems. We compare these properties with standard theory of ODEs and give some remarks on the theory of functional differential equations defined in Banach spaces.

2. FINITE AND INFINITE DIMENSIONAL CONTINUOUS DYNAMICAL SYSTEMS

Finite dimensional dynamical systems are typically generated by ODEs of the following form

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n,\ n \in \mathbb{N}, \tag{2.1}$$

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where $\dot{x} = \frac{dx}{dt}$, n is the number of equations in the system and the dimension of the dynamical system as well. Any solution of system (2.1) can be expressed as a function of time $x_{x_0}(t)$ for fixed initial vector x_0, but from the other hand, as a function of initial data $x_t(x_0)$ for fixed t. If the solution is defined for any initial data $x_0 \in \mathbb{R}^n$ and $t \in \mathbb{R}$, then $x_t : \mathbb{R}^n \to \mathbb{R}^n$, $t \in \mathbb{R}$, defines a family of functions. This family forms a dynamical system of dimension n. In the context of biomedical applications typically initial data and solutions should be non-negative. In this case the dynamical system is defined on $(\mathbb{R}^+)^n$, where $\mathbb{R}^+ = \{(x_1, \ldots, x_n) \in \mathbb{R}^n : x_i \geq 0,\ i = 1, \ldots, n\}$. Moreover, we look for forward solutions as we are interested in predictions of the future system dynamics. Hence, assuming that initially $t = 0$, we are looking for solutions of the system for $t > 0$ and the family of solutions is defined for $t \geq 0$. Formally, we distinguish between dynamical and semi-dynamical systems that are defined for every $t \in \mathbb{R}$ or $t \in \mathbb{R}^+$, respectively, cf. [74]. However, we call such families dynamical systems, for simplicity, although they are defined only for $t \geq 0$.

Infinite dynamical systems, cf. [51], can be generated by delay differential equations or reaction-diffusion equations. Such systems are generated in the same way as in case of ODEs, the only difference is connected with the functional space on that the system is defined. In this case the functional space is infinite dimensional.

The most typical system of DDEs applied in biomedical modelling reads

$$\dot{x} = f(x(t), x(t-\tau)), \tag{2.2}$$

where $\dot{x}$ is the right-hand side derivative with respect to time t, $\tau > 0$ denotes time delay, cf. e.g. [22, 49, 50] and [46, 55, 57] in the context of biomedical modelling. Typically, for system (2.2) we define initial data $(0, x_0)$ for $x_0 : [-\tau, 0] \to (\mathbb{R}^+)^n$ continuous, where n is the number of equations, as before. To obtain a dynamical system we need to have solutions of the same functional form defined on the same space as initial data. Let $x(t)$, $t \geq 0$, be the solution of Eq. (2.2) for some initial data x_0 and define

$$x_t(h) = x(t+h),\ h \in [-\tau, 0],\ t \geq 0.$$

Then $x_t : [-\tau, 0] \to \mathbb{R}^n$ is the part of solution defined on $[t-\tau, t]$, but it has a functional form we are interested in. Therefore, we define our dynamical system on the space of continuous functions defined on the interval $[-\tau, 0]$.

Similarly, we can generate infinite dimensional dynamical system on the basis of reaction-diffusion equations, cf. e.g. [16, 23, 51, 70, 73]. RDEs belongs to the class of partial differential equations. In the context of biomedical applications such equations describe not only the population size but also the dependence on space, age or other important quantities. We have two independent variables: time t and position p, while the dependent variable is $x = x(t, p)$. In general, for PDEs, apart from initial data we need to define boundary conditions. Typically, for bounded region $\mathcal{U}$, that is equivalent to a box in $\mathbb{R}^n$, depending on the number of equations, we consider two types of boundary conditions:

- the Neumann BC, when the normal outside derivative of x equals 0 at the boundary of $\mathcal{U}$ (zero-flux bc);
- the Dirichlet BC, when x equals 0 at the boundary of $\mathcal{U}$.

It should be noticed that there are also mixed BC like the Robin BC, used in more complex cases.

The process of diffusion means a random movement of individuals and is described by the Laplace operator $\Delta x = \sum_{i=1}^{k} \frac{\partial^2 x}{\partial p_i^2}$, where $p = (p_1, \ldots, p_k)$ denotes the position and k is the dimension of space, where individuals live, in reality $k = 1$, $k = 2$ or $k = 3$. In RDEs we combine the process of diffusion with some reaction described by a function $f(x)$ reflecting the mean system dynamics (that is the dynamics without diffusion described by ODEs). This function is called a kinetic function or just kinetics. Hence, the simplest RDE reads

$$\frac{\partial x}{\partial t} = f(x) + D\Delta x, \tag{2.3}$$

where $D > 0$ is the diffusion coefficient and we consider Eq. (2.3) with the appropriate BC on the boundary of $\mathcal{U}$. To solve Eq. (2.3) with some BC we also need to describe initial data, that mean t_0, typically $t_0 = 0$, and x_0 which is a function defined on $\mathcal{U}$ and fulfilling the assumed BC[1]. Therefore, similarly to DDEs, we can define some dynamical system in the appropriate functional space, e.g. in Sobolev space H^1 or H^1_0, depending on the BC, the Neumann or Dirichlet BC, respectively.

Figure 1 illustrate the schematic difference between initial data and solutions of single ODE, $n = 1$, (Eq. (2.1), left), DDE (Eq. (2.2), middle) and RDE (Eq. (2.3), right).

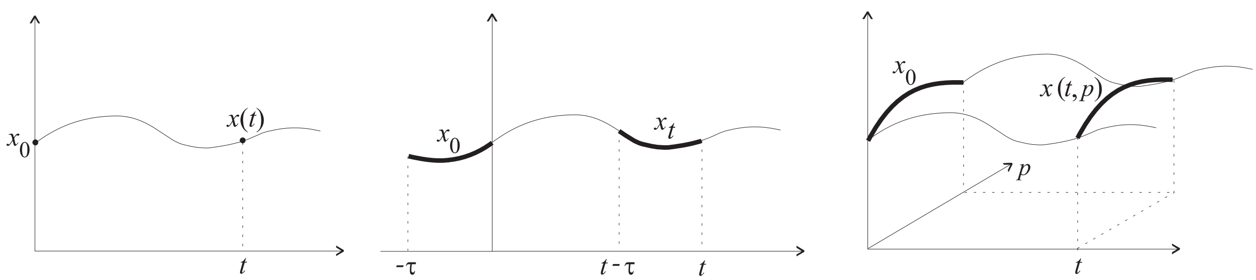

FIGURE 1. The difference between initial data and solutions of ODE (left), DDE (middle) and RDE (right). For ODE it is a point (in $\mathbb{R}$): x_0 is the initial point and $x(t)$ is the solution at some time t, both point are marked by dots in the graph. For DDE it is a (continuous) function x_0 defined on $[-\tau, 0]$. The solution x_t for this initial data is also a function defined in the same interval. Both functions (the initial function x_0 and the part the part of solution reflecting x_t after the shift to $[-\tau, 0]$) are indicated by bold lines. Similarly for RDE, both initial data and solutions are functions. However, now initial data x_0 is a function of p and the solution at time t is also such function. Hence, we have $x(t, p)$. The initial data and solution at time t are indicated by solid lines, again.

2.1. **How to analyse mathematical models based on dynamical systems?** Every mathematical model should be analysed in the context of correctness. Therefore, we need to study basic properties like:

- existence and uniqueness of solutions;
- non-negativity for non-negative initial data;

[1]In biomedical applications an initial function frequently does not satisfy the BC, however diffusion quickly "smooths" so we can assume the BC is satisfied from the very beginning.

- possibility of a solution extension[2];
- local stability of steady states[3];
- possibility of global stability[4];
- existence of periodic solutions;
- bifurcations[5].

It should be noticed that global (in $\mathbb{R}^+$) existence, uniqueness and non-negativity of solutions allow to define an appropriate dynamical system and use the dynamical systems tools.

2.1.1. *Existence, uniqueness and non-negativity of solutions of DDEs.* Existence and uniqueness of solutions are typically a simple consequence of the form of right-hand side of the system. For autonomous DDEs in general form

$$\dot{x}(t) = f(x_t), \tag{2.4}$$

where f is an operator defined on Banach space $\mathcal{C}$ of continuous functions $\varphi : [-\tau, 0] \to \mathbb{R}^n$ equipped with standard supremum norm, we are able to prove similar theorems as for autonomous ODEs of the form (2.1), cf. e.g. [49]. Hence, if f is continuous, then solutions of Eqs. (2.4) exist, while if it locally Lipschitz[6], then solutions are unique.

On the other hand, non-negativity and global existence of solutions should be study for every model separately. However, for systems of the form (2.2) we can use so-called step method, that is the method of mathematical induction adapted for DDEs. More precisely, let $\varphi \in \mathcal{C}$ be an initial function and consider $t \in [0, \tau]$. Then Eq. (2.2) reads

$$\dot{x}(t) = f(x(t), \varphi(t-\tau)) \tag{2.5}$$

because $t - \tau \in [-\tau, 0]$ and $x = \varphi$ in this interval. We see that Eq. (2.5) is non-autonomous ODE and we can analyse it using standard tools of ODEs. Hence, if the solution of Eq. (2.5) with initial data $(0, \varphi(0))$ exists for all $t \in [0, \tau]$, then we can continue such procedure for $t \in [\tau, 2\tau]$. In general, assume that $x_k : [(k-1)\tau, k\tau] \to \mathbb{R}^n$ is a continuous solution of Eq. (2.2) in the interval $[(k-1)\tau, k\tau]$ and consider

$$\dot{x}(t) = f(x(t), x_k(t-\tau)), \quad t \in [k\tau, (k+1)\tau]. \tag{2.6}$$

If for arbitrary k there exists a continuous solution $x_{k+1} : [k\tau, (k+1)\tau] \to \mathbb{R}^n$, then the method of mathematical induction implies that the solution for initial data $(0, \varphi)$ exists globally (in $\mathbb{R}^+$). Similarly, we can use this method to study uniqueness and non-negativity of solutions.

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[2]For semi-dynamical systems it means that we can extend solutions for every $t \geq 0$. Notice, that even for ODE it is sometimes not possible to extend the solution for every $t \geq 0$. If the right-hand side of ODE increases more than linearly, then the solution can blow up. Equation $\dot{x} = x^2$ is probably the best known example of such dynamics: for any positive x_0 the solution $x(t) = x_0/(1 - x_0 t)$ tends to ∞ for $t \to \tilde{t} = 1/x_0$, that is there is a blow up at $\tilde{t}$.

[3]Local stability means that for initial data near the steady state the solution remains near this state for $t > 0$. If additionally all solutions from some neighbourhood of the steady state tends to it for $t \to +\infty$, then this state is locally asymptotically stable.

[4]Global stability means that all solutions from some set have the properties described above.

[5]Bifurcation means the qualitative change of solution dynamics with the change of some parameter of the model.

[6]Operator f is locally Lipschitz if for any compact set $U \subset \mathcal{C}$ there exists such $L > 0$ that $|f(\phi) - f(\psi)| \leq L|\phi - \psi|$ for every $\phi, \psi \in U$.

Notice that, if $f(x(t), x(t-\tau)) = f(x(t-\tau))$, that is the right-hand side depend only on the past time $t-\tau$, then the step method immediately yields global existence and uniqueness for continuous functions f[7]. Moreover, if f is non-negative, then any solution remains non-negative in this case, cf. [4] and the discussion on non-negativity presented there.

Example 1. Let us consider a scalar linear equation

$$\dot{x} = ax(t) + bx(t-\tau), \quad a,\ b \in \mathbb{R},\ \ b \neq 0, \tag{2.7}$$

with initial function $\varphi \in \mathcal{C}$ for $t \in [-\tau, 0]$. Then for $t \in [0, \tau]$ we have

$$\dot{x} = ax(t) + b\varphi(t-\tau) \implies x(t) = \varphi(0)\mathrm{e}^{at} + b\mathrm{e}^{at}\int_0^t \mathrm{e}^{-as}\varphi(s-\tau)ds$$

and we see that the solution exists, is unique and non-negative assuming $b > 0$ and $\varphi(0) \geq 0$. Next, assuming that $x_k : [(k-1)\tau, k\tau] \to \mathbb{R}^+$ is the solution of Eq. (2.7) in $[(k-1)\tau, k\tau]$ we obtain

$$\dot{x} = ax(t) + bx_k(t-\tau) \implies x(t) = x_k(k\tau)\mathrm{e}^{a(t-k\tau)} + b\mathrm{e}^{at}\int_{k\tau}^t \mathrm{e}^{-as}x_k(s-\tau)ds$$

for $t \in [k\tau, (k+1)\tau]$. The step method yields the existence and uniqueness of solution for all $t \geq 0$. Moreover, solutions are non-negative for $b > 0$ and $\varphi(0) \geq 0$.

2.1.2. *Steady states and local stability for DDEs.* Looking for steady states of Eqs. (2.2) we notice, that a steady state is a solution that does not depend on time, and therefore $x(t) = x(t-\tau) = \bar{x}$ for every t. This means that any steady state $\bar{x}$ satisfies the system of algebraic equations

$$0 = f(\bar{x}, \bar{x}). \tag{2.8}$$

Again similarly to local stability analysis for ODEs, we use the linearisation method[8]. Let us recall that for ODEs of the form (2.1), cf. e.g. [1], it can be proved that near a non-hyperbolic[9] steady state the phase-space portrait[10] of the original system is topologically conjugated[11] with the phase-space portrait of the linear variational system $\dot{x} = Df(\bar{x})(x - \bar{x})$. Analogously, instead of Eqs. (2.4) we can study this linear system with $Df(\bar{x})$ reflecting the Frechét derivative at $\bar{x}$. However, in case of DDEs the topological conjugation is not necessarily observed. On the other hand, we can still study the linearised system instead the original one. Moreover, in case of Eqs. (2.2) calculating the Frechét derivative we can treat the operator f as a function of two variables $x(t)$ and $x(t-\tau)$. Therefore, the linearised system reads

$$\dot{y} = \frac{\partial f}{\partial x_1}(\bar{x}, \bar{x})y(t) + \frac{\partial f}{\partial x_2}(\bar{x}, \bar{x})y(t-\tau), \tag{2.9}$$

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[7]In fact, f needs to be only integrable in this case.

[8]Let us recall the geometrical interpretation of a derivative of $f : \mathbb{R} \to \mathbb{R}$ which allows to understand the notion of "linearisation". The derivative of f at x_0 is equal to the directional coefficient of a tangent to the graph of f at x_0. In small neighbourhood of x_0 the values of f can be approximated by the values of this linear function $x_0 + f'(x_0)(x - x_0)$.

[9]Steady state $\bar{x}$ is hyperbolic if there exists an eigenvalue, that is a solution of the characteristic equation $\det(Df(\bar{x}) - \lambda\mathbb{I}) = 0$ with zero real part.

[10]Phase-space portrait reflects the dynamics of solutions in the vector field described by f in $\mathbb{R}^n$.

[11]This means that orbits of one system can be continuously transformed into orbits of the other one.

where $y(t) = x(t) - \bar{x}$, $\frac{\partial f}{\partial x_1}$ is the derivative of $f(x(t), x(t-\tau))$ with respect to $x(t)$, while $\frac{\partial f}{\partial x_2}$ is the derivative with respect $x(t-\tau)$.

We look for non-trivial solutions of Eqs. (2.9) of the form $y(t) = y_0 \mathrm{e}^{\lambda t}$. Therefore,

$$\lambda y_0 \mathrm{e}^{\lambda t} = M_1 y_0 \mathrm{e}^{\lambda t} + M_2 y_0 \mathrm{e}^{\lambda(t-\tau)}$$

with $M_1 = \frac{\partial f}{\partial x_1}(\bar{x}, \bar{x})$, $M_2 = \frac{\partial f}{\partial x_2}(\bar{x}, \bar{x})$, and the characteristic equation reads

$$\det\left(\lambda \mathbb{I} - M_1 - M_2 \mathrm{e}^{-\lambda\tau}\right) = 0.$$

In general this characteristic equation has the form

$$W(\lambda) = P(\lambda) + Q(\lambda)\mathrm{e}^{-\lambda\tau} = 0, \tag{2.10}$$

where P and Q are polynomials and $\deg P = n > \deg Q$. It should be noticed that Eq. (2.10) has infinitely many zeros, that is the main problem in studying stability for DDEs. However, we do not need to calculate all characteristic values but only check the existence of those with non-negative real parts. If all eigenvalues have negative real parts, then $\bar{x}$ is locally asymptotically stable, while existence of at least one eigenvalue with positive real part yields instability.

For particular system and specific parameter values we can study local stability using different stability criteria. There are several criteria based on the Principle of argument, like the Mikhailov, Nyquist or integral criteria [55]. The Mikhailov criterion has probably the most clear one. It was proposed by Mikhailov for ODEs in [63], while the version for DDEs appeared in [45] and was described in details and proved in [48][12]. In [29] we clearly described the usage of this criterion for several models, completed a small gap in the proof from [29] and extend the criterion for models with integral delays. This criterion yields that in case of non-hyperbolic steady state all zeros of Eq. (2.10) have negative real parts iff the change of argument $\Delta \arg W(i\omega) = n\pi/2$ when ω increases from 0 to $+\infty$. It is easy to see that $\arg W(0) = 0$ or $\arg W(0) = \pi$. Therefore, to obtain stability the vector $(\mathbb{R}e W(i\omega), \Im W(i\omega))$ must encircle the origin in the complex plane properly.

Example 2. Again consider Eq. (2.7) and assume $b > 0$. It has unique (for $a \neq -b$) trivial steady state $\bar{x} = 0$. Studying local stability we look for solutions of exponential form $x(t) = x_0 \mathrm{e}^{\lambda t}$ that yields

$$\lambda = a + b\mathrm{e}^{-\lambda\tau},$$

and hence the characteristic quasi-polynomial reads

$$W(\lambda) = \lambda - a - b\mathrm{e}^{-\lambda\tau}.$$

For $\lambda = i\omega$, $\omega > 0$, we have $W(i\omega) = i\omega - a - b\mathrm{e}^{-i\omega\tau}$ yielding $W(0) = -a - b$. This means that if $-a - b > 0$, then $\arg W(0) = 0$, while if $-a - b < 0$, then $\arg W(0) = \pi$ (for $a + b = 0$ this argument is undefined and assumptions of the Mikhailov criterion are not satisfied). We study the curve $(\Re W(i\omega), \Im W(i\omega))$ for ω increasing from 0 to ∞. This shape depends on a and b, obviously. We have

$$\sin \arg W(i\omega) = \frac{\Im W(i\omega)}{|W(i\omega)|} = \frac{\omega - b\sin(\omega\tau)}{|W(i\omega)|},$$

$$\cos \arg W(i\omega) = \frac{\Re W(i\omega)}{|W(i\omega)|} = \frac{-a - b\cos(\omega\tau)}{|W(i\omega)|}$$

[12]The proof presented in [45] incomplete.

with

$$|W(i\omega)| = \sqrt{\omega^2 + a^2 + b^2 + 2b(a\cos(\omega\tau) - \omega\sin(\omega\tau))}.$$

Therefore, $\sin\arg W(i\omega) \to 1$ and $\cos\arg W(i\omega) \to 0$ implying $\arg W(i\omega) \to \pi/2 + 2l\pi$ as $\omega \to +\infty$. This means that to obtain stability we require $W(0) > 0$ and $l = 0$. Therefore, for $a+b > 0$ the steady state is unstable and it can be stable for $a+b < 0$. Moreover, $\Im W(i\omega) \to +\infty$ and $\Re(i\omega)$ oscillates between $-a-b$ and $-a+b$. Hence, if $a+b < 0$, then $\arg W(i\omega) > 0$ for all $\omega \geq 0$, and therefore $\Delta \arg W(i\omega) = \pi/2$ and the trivial steady state is stable independently of the delay. This means that if the term without delay dominates in the right-hand side, $|a| > b$, and for equation without delay term we have stability, then this stability is preserved in the equation with delay for any arbitrary, even very large, delay. Notice, that for other values of a and b we can get the stability depending on the delay τ.

2.1.3. *Hopf bifurcation and stability switches.* In case of ODEs it is well known that if a steady state loses stability, then a periodic orbit can appear as the result of Hopf bifurcation, cf. [61]. More precisely, Hopf bifurcation is a qualitative change of the model dynamics such that the increase of bifurcation parameter leads to a periodic solution appearance or disappearance. This periodic solution is replaced by a steady state. The orbit of the periodic solution encircles the steady state in the phase-space. Both steady state and periodic orbit can be stable or unstable. The Hopf bifurcation theorem gives sufficient condition for a periodic orbit appearance. Moreover, stability of this orbit can be studied using the central manifold theorem.

Again similarly we can study Hopf bifurcation and arising periodic orbits for DDEs, cf. [22,49]. The necessary condition for Hopf bifurcation is a change of stability of the steady state $\bar{x}$ for that Hopf bifurcation is studied. This change of stability is related to the existence of an eigenvalue with zero real part, because eigenvalues depend continuously on the model parameters. In case of Eqs. (2.2) we can treat time delay as a bifurcation parameter. More precisely, changing the time variable $t \to t/\tau$ we obtain the model with delay equal to 1 and other model parameters rescaled by τ, and therefore the delay is the model parameter as well. Continuous dependance implies that if $\bar{x}$ is asymptotically stable for $\tau = 0$, that is all eigenvalues have negative real parts, then it is stable for small τ. Similarly, if it is unstable for $\tau = 0$, that is there is an eigenvalue with positive real part, then instability for small $\tau > 0$ is guaranteed. When there is an eigenvalue[13] $\lambda = i\omega$, $\omega \in \mathbb{R}^+$, then the change of stability can occur and the characteristic function (2.10) reads

$$W(i\omega) = P(i\omega) + Q(i\omega)\mathrm{e}^{-i\omega\tau},$$

and therefore

$$W(i\omega) = 0 \Longrightarrow |P(i\omega)| = |Q(i\omega)|.$$

Following the ideas presented in [18], cf. also [72], we define the auxiliary function

$$F(y) = |P(i\sqrt{y})|^2 - |Q(i\sqrt{y})|^2, \quad y = \omega^2, \tag{2.11}$$

and study zeros of F. Under some assumptions, cf. [18], any positive zero $\bar{y}$ of F defines the eigenvalue $i\bar{\omega}$, $\bar{\omega} = \sqrt{\bar{y}}$ and there is a corresponding sequence of delays τ_n defined by Eq. (2.10) for $\lambda = i\bar{\omega}$, where the stability switch can occur. Moreover, the sign of $F'(\bar{y})$ determines this stability switch. Clearly, if $\bar{x}$ is stable for $\tau = 0$ and $\bar{y}$ is the only zero of the auxiliary function F, then $F'(\bar{y}) > 0$ implies that $\bar{x}$ loses stability for the first critical delay τ_0 and cannot gain it again for larger delays. Other cases can be analysed similarly.

[13]In fact we have two conjugated eigenvalues $\pm i\omega$ in this case.

Now, we turn to the analysis of bifurcating periodic orbits. We use the approach proposed in [22] basing on normalised bounded variation (NBV) functions.[14] The reason of usage NBV approach instead of standard one, cf. [49], is that for NBV we obtain formulae that are more clear and slightly simpler to calculate than in standard approach. In this analysis we additionally assume that f is of class $\mathbf{C}^3$ and $f(0) = 0$ such that we study the trivial steady state of Eq. (2.4). Moreover, $f = f(x_t, \alpha)$, where α is a bifurcation parameter. Because typically we are interested in bifurcations with respect to the delay, therefore to avoid problems with the space, we rescale time $t \to t/\tau$ obtaining $\tau = 1$ in new time variable. Let now $\mathcal{C}$ denote the Banach space of continuous functions defined on the interval $[-1, 0]$ with the complex values (the real-valued functions can be treated as the functions with zero imaginary part). The non-linear function f can be expressed as

$$f(x_t, \alpha) = L(x_t, \alpha) + G(x_t, \alpha),$$

where L is a linear continuous map on $\mathcal{C}$ and G is a non-linear part of f, $G \neq 0$. According to the Riesz representation theorem, the map L has an unique representation in terms of NBV functions and Riemann-Stjelties integral.[15] Therefore, the exists an unique NBV function ζ such that $L(\phi) = \int_0^1 d\zeta(\theta)\phi(-\theta)$ for every $\phi \in \mathcal{C}$. This yields that NBV with the total variation norm is a representation of the dual space of $\mathcal{C}$. Hence, we can also write $L(\phi) =< \zeta, \phi >$, where $< \cdot, \cdot >$ reflects duality.

We study Hopf bifurcation and stability of periodic orbit arising when the trivial steady loses stability, that is for some threshold value α_0 of the bifurcation parameter. Let $T(t)$, $t \geq 0$ be the semi-group defined by the equation $\dot{z} = L(z_t)$ and A denotes the generator of this semi-group. Hopf bifurcation occurs for α_0 if A has $i\omega_0$ as an eigenvalue. To find eigenvalues we study study the characteristic function

$$\Delta(\lambda, \alpha) = \lambda - \int_0^1 \exp(-\lambda\theta) d\zeta(\theta, \alpha),$$

The generator A has $i\omega_0$ as an eigenvalue, if there exists $\mathbf{p} \in \mathcal{C}$, $\mathbf{p} \neq 0$, such that

$$\Delta(i\omega_0, \alpha_0)\mathbf{p} = 0,$$

and then the function $\phi(\theta) = \exp(i\omega_0\theta)\mathbf{p}$ is the eigenvector for A at the eigenvalue $i\omega_0$. Let $\mathbf{q} \in \mathcal{C}$, $\mathbf{q} \neq 0$ satisfies

$$\mathbf{q}\Delta(i\omega_0, \alpha_0) = 0.$$

If A^* is the adjoint operator, then it has $i\omega_0$ as its eigenvalue and the eigenvector ψ satisfies $< \psi, \phi >= \mathbf{q}D_1\Delta(i\omega_0, \alpha_0)\mathbf{p}$, where $D_1\Delta(\lambda, \alpha)$ is the derivative of Δ with respect to the first variable

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[14] Let $f : [a, b]$ be bounded and $\Pi : a = x_0 < x_1 < \ldots < x_l = b$ be a partition of the interval $[a, b]$. Denote $V(\Pi, f) = \sum_{i=1}^{l} |f(x_i) - f(t_{x-1})|$. The number $V(f) = \sup_\Pi V(\Pi, f) = \sup_\Pi \sum_{i=1}^{l} |f(x_i) - f(t_{x-1})|$ is called the variation of the function f on the interval $[a, b]$.

Let ζ be a function of bounded variation defined on the interval $[0, 1]$. We call this function NBV (normalised bounded variation) if $\zeta(0) = 0$ and ζ is continuous from the right-hand side on the open interval $(0, 1)$.

[15] Let f, $g : [a, b] \to \mathbb{R}$ be bounded. If there exists $K > 0$ such that $\forall\varepsilon > 0\ \exists\delta > 0$ such that for every partition $\Pi :\ a = x_0 < x_1 < \ldots < x_l = b$ of the interval $[a, b]$ with the diameter $\delta(\Pi) < \delta$ and every choice of the intermediate points $\xi_i \in [x_{i-1}, x_i]$, $i = 1, \ldots, l$, there is $|\sum_{i=1}^{l} f(\xi_i)\left(g(x_i) - g(x_i - 1)\right) - K| < \varepsilon$, then K is called the Riemann-Stieltjes integral of f on the interval $[a, b]$ with respect to g.

λ. Moreover, if $\pm i\omega_0$ are simple eigenvalues, then $<\psi,\phi>$ can be normalised to 1. Then we choose $\mathbf{q}$ such that $<\psi,\phi>$ is normalised to 1 obtaining

$$\mathbf{q}D_1\Delta(i\omega_0,\alpha_0)\mathbf{p}=1.$$

To study the type and stability of bifurcating periodic solution within the centre manifold, we determine the third term μ_2 in the Taylor expansion of this solution. If μ_2 is positive, then the bifurcation is called supercritical and periodic solutions exist for $\alpha>\alpha_0$. If additionally the steady state is stable for $\alpha<\alpha_0$, then the bifurcating periodic solution is stable within the centre manifold. Moreover, if no spectrum of A is in the right half-plane, then the centre manifold is attractive. Therefore, the periodic solution is asymptotically stable. If μ_2 is negative, then the bifurcation is called subcritical and periodic solutions exist for $\alpha<\alpha_0$, and if as before the steady state is stable for $\alpha<\alpha_0$, then the periodic solution is unstable.

The third term μ_2 can be calculated as

$$\mu_2=\frac{\mathbb{R}ec}{\mathbb{R}e\left(\mathbf{q}D_2\Delta(i\omega_0,\alpha_0)\mathbf{p}\right)},$$

where $\mathbf{p}$, $\mathbf{q}$ are chosen as above, D_2 denotes the derivative with respect to the bifurcation parameter α, and

$$c=\frac{1}{2}\mathbf{q}D_1^3G(0,\alpha_0)(\phi,\phi,\bar{\phi})+\mathbf{q}D_1^2G(0,\alpha_0)\left(\psi_{\bar{\phi}}(\cdot,0),\phi\right)+\frac{1}{2}\mathbf{q}D_1^2G(0,\alpha_0)\left(\psi_{\phi}(\cdot,2i\omega_0),\bar{\phi}\right),$$

where D_1^i, $i=2,3$ denotes the derivative of the ith order with respect to the first variable z_t and

$$\psi_{\phi_1}(\theta,a)=\exp(a\theta)(\Delta(a,\alpha_0))^{-1}D_1^2G(0,\alpha_0)(\phi,\phi_1).$$

Example 3. As before consider Eq. (2.7) with $b>0$. We have $|i\omega-a|=|b\mathrm{e}^{-i\omega}|$, and therefore $F(y)=y+a^2-b^2$. The auxiliary function F has positive zero $y_0=-a^2+b^2$ iff $a^2-b^2<0$ and then $F'(y_0)>0$. This means that stability switches can occur only when $b>|a|$ and only the switch from stable to unstable steady state is possible. However, for $\tau=0$ the trivial steady state is stable for $a+b<0$ and unstable for $a+b>0$. Let us consider two cases:

- $a>0$ implying $a+b>0$, that is the trivial steady state is unstable for $\tau=0$ and remains unstable for all $\tau>0$;
- $a<0$, $a\neq -b$, implying
  $a+b>0$ and the trivial steady state is unstable for all $\tau\geq 0$ again;
  $a+b<0$ and there is a change of stability from stability to instability for $\tau=\tau_c$, where τ_c is the first delay satisfying $\omega+b\sin(\omega\tau_c)=0$ and $a+b\cos(\omega\tau_c)=0$.

In case of the linear equation Eq. (2.7) Hopf bifurcation cannot occur, obviously. The reader can find examples of Hopf bifurcation analysis in Section 4.

2.1.4. *Global stability and Lyapunov functionals.* Studying global stability we usually apply the method of Lyapunov functionals, cf. e.g. [2] in the context of ODEs and [53] in the context of DDEs. Lyapunov functional is a smooth function defined on the space of solutions having some special properties. The Liapunov theory for ODEs implies that if $L:\mathbb{R}^n\to\mathbb{R}^n$, $L(x)\geq 0$ and $L(x)=0\iff x=\bar{x}$, where $\bar{x}$ is the steady state under study, L is strictly decreasing along the system trajectories, then $\bar{x}$ is globally stable. Slightly more strong conditions are required in case of infinite dimensional dynamical systems like DDEs.

In general, the most typical is Lyapunov-LaSalle theorem that can be used also in case of ODEs e.g. when f is not strictly decreasing. More precisely, in case of DDEs this theorem yields that if the system has Lyapunov functional, then any solution is attracted by M that is an invariant subset of the set $\{\varphi \in \mathcal{C} : L'(\varphi) = 0\}$, where L' is the derivative of the Lyapunov functional along the system trajectory.

Example 4. Coming back to Eq. (2.7) with $b > 0$, we study stability of the trivial steady state, and hence we assume $a < 0$. We define a Lyapunov functional as

$$L(\phi) = \phi^2(0) + C\int_{-\tau}^{0} \phi^2(s)ds, \quad C > 0.$$

It is obvious that for $\phi \in \mathcal{C}$ this functional satisfies $L(\phi) = 0$ iff $\phi = 0$. Moreover,

$$\dot{L}(x(t)) = (2a + C)x^2(t) + 2bx(t)x(t-\tau) - Cx^2(t-\tau),$$

that is $\dot{L}(x(t))$ is a quadratic form of $x(t)$ and $x(t-\tau)$. Now, we need to find $C > 0$ (if possible) such that for chosen a and b $\dot{L}$ is negatively defined. Therefore, we need to study the matrix

$$\begin{pmatrix} -(2a+C) & -b \\ -b & C \end{pmatrix},$$

that is positively defined for $2a + C < 0$ and $(2a + C)C + b^2 < 0$. Let us choose $C = |a|$. Then $2a + |a| = a < 0$ yielding $a|a| + b^2 = -a^2 + b^2 < 0$ for $|a| > b$. We see that $L'(\varphi) = 0$ for every $\varphi \in \mathcal{C}$ such that $\varphi(0) = \varphi(-\tau) = 0$. However, the only invariant subset of $\mathcal{C}$ satisfying this condition is $M = \{0\}$. Therefore, if the trivial steady state is stable independently on the delay, then it is globally stable.

3. Simple models with delay in applied sciences

In this section we present a short introduction to DDEs applied in biology and medicine in general. The beginning of such applications is typically associated with the Hutchinson equation. In 1948 G.E. Hutchinson proposed [52] the delayed version of the logistic equation.

3.1. Classic logistic equation with delay in population dynamics.

In his article [52] Hutchinson applied the logistic equation in the description of oscillatory ecological systems. The Hutchinson equation was used in that context many times in the seventies and eighties of XX century. Moreover, except linear equations, it is the most frequently used example of DDE properties, cf. [46, 49, 55]. On the basis of this equation researchers tried to explain many experiments where the oscillations appeared. The Hutchinson equation reads

$$\frac{dN}{dt}(t) = rN(t)\left(1 - \frac{N(t-\tau)}{K}\right), \tag{3.1}$$

where $N(t)$ denotes the size of population in study in the present time t, the derivative $\frac{dN}{dt}(t)$ describes the change of this size at time t, $N(t-\tau)$ is the size in some past time $t-\tau$, $\tau > 0$ is the magnitude of delay and in population models it is typically related with the maturation time or the length pregnancy period, r reflects fertility of the population and is typically called the (intrinsic) birth or reproduction rate, while K is the carrying capacity for the population.

Now, we present some specific examples of the application of Eq. (3.1), cf. [64]. May (1975) used this equation to model oscillations in the size of population of Australian fly (*Lucilla cuprina*). The experimental period of oscillations was 35–40 days. Maturation from a larva to a fly was taken

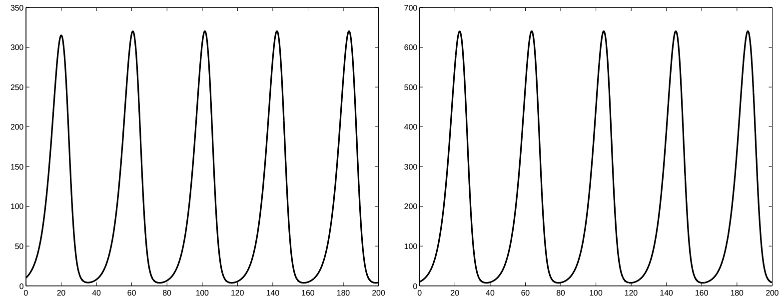

FIGURE 2. Sample solutions of Eq. (3.1) with $r\tau = 2.1$, $\tau = 9$ (right) and $K = 100$ (left), $K = 200$ (right). In both graphs we observe the same quantitative dynamics, however doubling of the carrying capacity K implies doubling of the solution amplitude.

into account in the model. For parameters satisfying $r\tau = 2.1$ and the delay $\tau = 9$ days the period of solutions is equal to 40 days. The solution of Eq. (3.1) with parameters $r\tau = 2.1$, $\tau = 9$ and $K = 100$ is presented in Fig. 2 (left). In reality, the maturation time is near 11 days, however such fitting of that simple models seems to be satisfactory. Better fitting is possible for slightly more complex model (Gurney et al. 1980). It should be noticed that the oscillatory dynamics in the model described by Eq. (3.1) does not depend on the magnitude of carrying capacity and this effect is observed in experiments. Graphs presented in Fig. 2 illustrated this feature: the right-hand graph was prepared for the carrying capacity equal to twice carrying capacity comparing to the left-hand graph. Solutions differ only quantitatively, while the qualitative description is the same in both graphs.

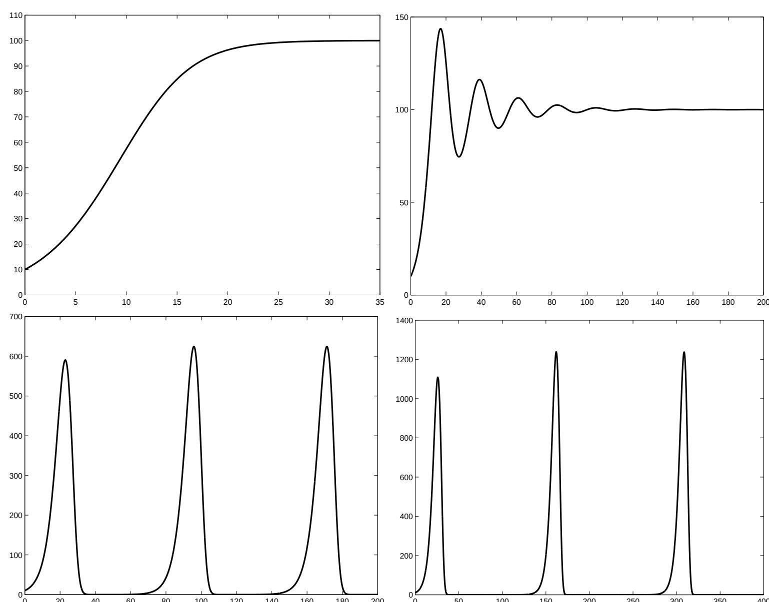

FIGURE 3. Solutions of the Hutchinson equation (3.1) with $r\tau = 2.1$, $K = 100$ and $\tau = 1, 5, 12, 15$, respectively.

Using this simple model we explain the possible influence of time delay on the model dynamics. Fig. 3 shows the solutions of Eq. (3.1) with the same parameters and increasing delay. For small delays the dynamics is similar to the original logistic equation, that is solutions monotonically tend to the carrying capacity K, cf. the left-hand top graph in Fig. 3. With increasing delay oscillations appear. These oscillations are dumping at the beginning (right-hand top graph in Fig. 3), and become un-dumping for larger delays, cf. bottom graphs in Fig. 2. Notice, that increasing delay yields the increasing both the amplitude and period of oscillations. Hence, in this case the delay has an destabilising effect, meaning that the steady state stable for small delays becomes unstable for larger ones. For larger delays solutions oscillate around the steady state. More precisely, if $x(t)$ is a periodic solution of Eq. (3.1), then

$$\int_{x(0)}^{x(T)} \frac{dx}{x} = r\int_0^T \left(1 - \frac{x(s-\tau)}{K}\right) ds \Longrightarrow \ln\frac{x(T)}{x(0)} = r\left(T - \int_0^T \frac{x(s-\tau)}{K} ds\right),$$

where T is the period of solution, and therefore $x(0) = x(T)$. We obtain

$$x_{\text{mean}} = \frac{1}{T}\int_0^T x(t)dt = K.$$

The same Hutchinson equation was used by May (1981) to describe the dynamics of lemming population in the Churchil District in Canada. In this model the delay reflect a pregnancy period (about 0.72 year). Similarly Stritzaker (1975) modelled vole population in Scottish Mountains, however he used more complex system with the predation effect included. Myers and Krebs (1974) studied cycles for rodent populations that last typically 3, 4 years.

Another type of the delayed logistic equation was proposed by Schuster & Schuster [71] to reflect the cancer cells dynamics, we describe it in the next section. Moreover, from mathematical point of view we can introduce the delay in several different ways, cf. [54], however from biological point of view only specific models can be justified. We discuss that topic in the last section.

Except the simple models based on the Huntchinson equation many other models was used in population dynamics, the interested readers can refer to the text-books of Gopalsamy [46] and Kuang [55], cf. also [20, 75, 78].

3.2. **Simple models of red blood cell production.** Many physiological disorders appear in association with periodic or oscillatory dynamics. Such dynamics can be caused by time delays in the physiological process taken into account. Hence, DDEs are often used in modelling of different diseases with oscillatory dynamics.

One of the most important processes for which the time delay is undoubtedly present and causes oscillations is a red blood cell production. There is the delay about 6 days between the decrease in red blood cells number in blood and the release of new ones from bone marrow to fill this loss. Probably the first model proposed in this context was constructed by Ważewska-Czyżewska and Lasota in [77]. However, at the same time Mackey and Glass studied a similar model, cf. [58, 59, 64]. It should be noticed that the delayed model proposed in [77] is a reduced version of more complex model that has good biological justification. However, Mackey & Glass model has become popular because chaotic dynamics is observed for some parameter values. Both Ważewska-Czyżewska & Lasota and Mackey & Glass equations describe changes of red blood cells number in circulating blood. Let $c(t)$ denote the total number (density) of red blood cells in blood at time t. Both models can be written in the following general form

$$\frac{dc}{dt}(t) = -\gamma c(t) + f(c(t-\tau)), \tag{3.2}$$

where γ reflects the mean death rate of red blood cells and f describes the release from bone marrow. In case of Ważewska-Czyżewska & Lasota model $f_{WL}(x) = \varrho \exp(-\gamma x)$ (where γ characterises excitability of a hematopoietic system, and ϱ reflects an organism oxygen demand), while Mackey and Glass chose $f_{MG}(x) = \lambda \frac{a^m x}{a^m + x^m}$ with the Hill parameter m yielding the diversity of the model dynamics.

One of the symptoms of leukemia is oscillatory behaviour of while blood cells. In [58] the reader can find the comparison between clinical data for a patient with chronic leukemia and solutions of Eq. (3.2) with the function f_{MG}. For this model the sequence of bifurcation leading to chaotic[16] dynamics is observed. Fig. 4 presents solutions of this model with parameters $\gamma = a = 1$, $\lambda = \tau = 2$ and m changing from $m = 7$ to $m = 19$. With increasing bifurcation parameter m we observe qualitative change of the model dynamics from simple sinus-type oscillations for $m = 7$, through more complex periodic solutions, to aperiodic solutions for $m = 10$, 11, and again to periodic dynamics. Graphs in Fig. 4 reflect the dependance between $c(t)$ at present time t and $c(t-\tau)$ at previous time $t-\tau$. Such type of graphs are sometimes called phase-portraits for DDEs. However, it should be noticed that the real phase-space is infinite-dimensional in this case, and therefore cannot be reflected graphically. For comparison in Fig. 5 we present graphs of solutions $c(t)$ as functions of time t for $m = 7$ and $m = 10$. It should be emphasised that Eq. (3.2) with f_{WL} was used by M. Ważewska-Czyżewska to propose a better treatment of patients with drug-induced anemia, cf. [76]. She helped many patients using this method[17].

Similarly, dynamics of CO_2 density in blood vessels can be modelled. On that basis we can try to explain respiratory disorders in Cheyne-Stokes respiration. In this case the delay reflects the gap between oxygenation of blood in lungs and getting the signal of this oxygenation by chemoreceptors in the brain stem.

3.3. **Other models.** DDEs are extensively used in epidemiological and immunological modelling. Some results on immune system modelling are presented in the next section. Introduction to the description of the role of time delays in immune system modelling can be found e.g. in [21] and [60].

Interesting combination of population dynamics, economic growth and epidemiological model was proposed by Cooke and Yorke in [19]. Many interesting examples of delayed epidemiological models can be found in [64], in particular models of HIV dynamics by Nelson are very interesting and bringing some insight in the general knowledge about AIDS.

[16]There is no one accepted definition of chaos. Here, we use the notion of deterministic chaos which is observed in case of deterministic models having both regular, periodic and irregular, aperiodic solutions.

[17]The method is based on the model conclusions. The drug-induced anemia can be treated maintaining a low level of red blood cells that cab be achieved by influencing the rate of maturation. In order to decrease the speed of maturation of red blood cells a patient should breathe oxygen-enriched air.

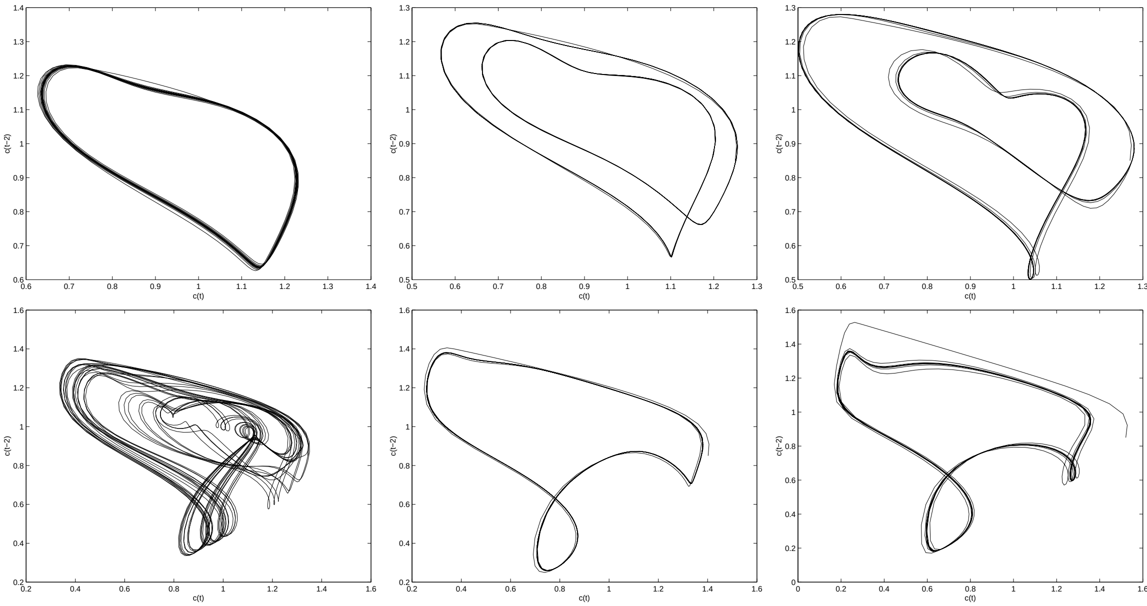

FIGURE 4. Solutions of Eq. (3.2) in the space $(c(t), c(t-\tau))$ with f_{MG} and parameters $\gamma = a = 1$, $\lambda = \tau = 2$ and $m = 7$, 7.5, 8, 10, 12 and 19, respectively.

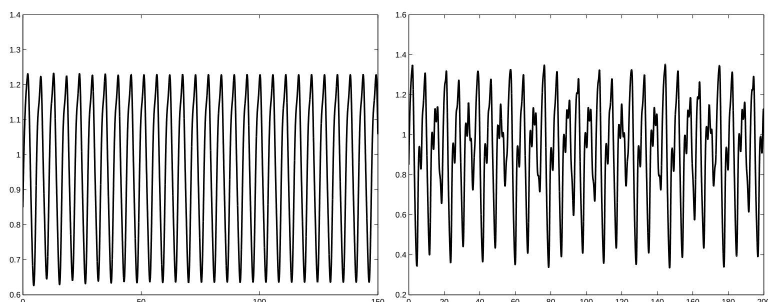

FIGURE 5. Solutions of Eq. (3.2) with the function f_{MG} and parameters $\gamma = a = 1$, $\lambda = \tau = 2$ and $m = 7$ (left), $m = 10$ (right).

New interesting branch of dynamical systems applications is connected with interpersonal relationships and love affairs dynamics. Simple linear approach on the basis of ODEs system of equations was described by Rinaldi [69]. Probably the best known are results of Gottman et al. [47] popularised by Murray in his text-book [64], where the approach of discrete dynamical systems to model the dynamics of marriage was used. In the context of human relationships DDEs was used in [56]. Our study presented in [3] was focused on possible stability switches with increasing delay[18]. It should be noticed that to obtain multiple stability switches we need to consider at least two delays for single DDE equation or a system of two DDEs with one discrete delay, while for one equation with one discrete delay only one stability switch is possible.

[18] Stability switch for some critical values of delay means the change from stable steady state to unstable one or vice versa. Typically in case of non-linear models it is associated with Hopf bifurcation.

Below we include one more example of linear system of two equations with more than one stability switch, for more details cf. [3].

Let us consider

$$\begin{cases} \dot{x}(t) = a_{11}x(t-\tau) + a_{12}y(t), \\ \dot{y}(t) = a_{21}x(t) + a_{22}y(t). \end{cases} \tag{3.3}$$

The dynamics of Eqs. (3.3) depends on the coefficients a_{ij}, obviously. We can prove that if $|a_{12}a_{21}| > |a_{11}a_{22}|$, then multiple stability switches are possible. In Fig. 6 we see examples of such switches for the set of parameters $[a_{11}, a_{12}, a_{21}, a_{22}] = [5, -4, 3, -1]$. For $\tau = 0$ and small values of delays the origin is unstable, then the first change of stability occurs for $\tau_{th}^1 \approx 0.522$ at which periodic solutions are present. Between $(\tau_{th}^1, \tau_{th}^2)$, $\tau_{th}^2 \approx 0.722$, the origin is stable, and after the second switch it remains unstable for larger delays.

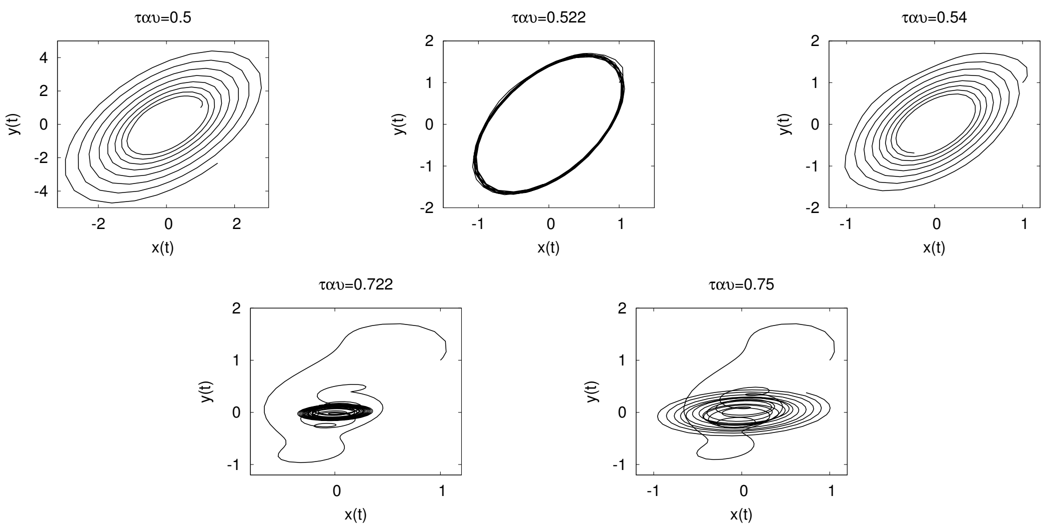

FIGURE 6. Trajectories of Eqs. (3.3) in the space (x, y) around two stability switches. For small delays we observe instability (left-top), then stability switch (middle-top) to stability (right-top), again stability switch (left-bottom) to instability (right-bottom).

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