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EXISTENCE AND UNIQUENESS OF A SOLUTION FOR NONLINEAR ODE AND PDE SYSTEMS WITH DELAY. AN APPLICATION

Abstract. In this paper, we study the existence and uniqueness of a solution for a system of nonlinear differential equations with delay. We show its application using a mathematical model that describes tumor-immune interactions in the bladder as a result of BCG therapy. We also study a mathematical model that uses a system of nonlinear partial differential equations with delay while considering the geometrical configuration of the human bladder. We use two-dimensional grid discretization to find the numerical solution of the systems describing the tumor-immune interaction.

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რეზიუმე. ნაშრომში შესწავლილია დაგვიანებულარგუმენტიანი არაწრფივი დიფერენციალური განტოლებათა სისტემის ამონახსნის არსებობა და ერთადერთობა. ნაჩვენებია მისი გამოყენება მათემატიკურ მოდელზე, რომელიც აღწერს სიმსივნურ-იმუნურ ურთიერთქმედებებს შარდის ბუშტში BCG თერაპიის შედეგად. აგრეთვე შესწავლილია მათემატიკური მოდელი, რომელიც ადამიანის შარდის ბუშტის გეომეტრიული კონფიგურაციის განხილვისას იყენებს დაგვიანებულარგუმენტიან არაწრფივ კერძოწარმოებულიან დიფერენციალურ განტოლებათა სისტემას. გამოყენებულია დისკრეტიზაცია ორგანზომილებიანი ბადით იმ სისტემის რიცხვითი ამოხსნის მოსაძებნად, რომელიც აღწერს სიმსივნურ-იმუნურ ურთიერთქმედებას.

1 Introduction

Differential equations with delay have attracted the attention of many researchers. Note the monographs [2, 3, 6, 8, 10], in which the problems of existence, uniqueness and stability are considered.

In this paper, we study a system of nonlinear ODEs with delay and a system of nonlinear PDEs with delay. In the first part of the paper, we reduce these problems to a system of equations without delay by generalizing the approach proposed in [7], and use the approach proposed in [17] in order to prove the uniqueness and existence of their solutions. This approach is based on the Galerkin approximations method. In the second part of this paper, we present an application to these systems with delay.

Bladder cancer is among the top ten most common cancers around the world [16]. Immunotherapy with Bacillus Calmette–Guerin (BCG) has been used to treat non-invasive bladder cancer for several decades [14]. It is considered to be one of the most successful treatments for non-invasive cancer currently in use with around 60% success rate according to [11]. Even though researchers have a lot of experience with BCG, it is still under research for its therapeutic effects. Shortening the dwell time and dose differences are the well studied and important topics and much research on the topics has been done via clinical trials [1,13,15]. In this paper, we try to approach this topic using a mathematical model. According to Prof. Mary Bakhanashvili, Head of AIDS Lab Infectious Diseases Unit, Sheba Medical Center, Tel-Hashomer, Israel (`https://eng.sheba.co.il/bakhanashvili_mary`), there is a period of time from the initial BCG instillation until all the various cells react to the BCG. The time it takes for all the cells in the bladder to react to the BCG introduces a delay into this model.

Several attempts of modeling the problem have taken under consideration the population's size of different cells in the system over time, based on the biological dynamics of the system using ordinary differential equations [4, 5, 9]. An attempt to improve the model has been done by taking under consideration an approximation of the geometric configuration of the bladder in the mathematical modeling yielding partial differential equations. The PDEs Model's parameters sensitivity and solution's stability for the given parameters was the main focus of [12]. In this paper, we add delay which describes more precisely the process when the various cells are being infected after BCG instillation. We use a grid based discretization approach to solve the PDEs system numerically.

2 Preliminaries

Let us consider the following system of ordinary differential equations with delay:

$$\frac{dx_1(t)}{dt} = \Big[a_{11} + a_{12}x_2(t-\tau_2(t)) + a_{13}x_3(t-\tau_3(t)) + a_{14}x_4(t-\tau_4(t))\Big]x_1(t-\tau_1(t)) + a_{15}, \tag{2.1}$$

$$\frac{dx_2(t)}{dt} = \Big[a_{21}x_1(t-\tau_1(t)) + a_{22} + a_{23}x_3(t-\tau_3(t)) + a_{24}x_4(t-\tau_4(t))\Big]x_2(t-\tau_2(t)) + a_{25} + \alpha x_3(t-\tau_3(t)), \tag{2.2}$$

$$\frac{dx_3(t)}{dt} = \Big[a_{31}x_1(t-\tau_1(t)) + a_{32}x_2(t-\tau_2(t)) + a_{33} + a_{34}x_4(t-\tau_4(t))\Big]x_3(t-\tau_3(t)) + a_{35} + \beta x_1(t-\tau_1(t))x_4(t-\tau_4(t)), \tag{2.3}$$

$$\frac{dx_4(t)}{dt} = \Big[a_{41}x_1(t-\tau_1(t)) + a_{42}x_2(t-\tau_2(t)) + a_{43}x_3(t-\tau_3(t)) + a_{44}\Big]x_4(t-\tau_4(t)) + a_{45}, \tag{2.4}$$

with the initial conditions

$$x_1(0) = c_1, \quad x_2(0) = c_2, \quad x_3(0) = c_3, \quad x_4(0) = c_4, \tag{2.5}$$

and with the condition

$$x_1(t) = 0, \quad x_2(t) = 0, \quad x_3(t) = 0, \quad x_4(t) = 0 \ \text{ for all } \ t < 0. \tag{2.6}$$

We understand a solution $x = (x_1, x_2, x_3, x_4)$ as a vector of differentiable functions satisfying (2.1)–(2.4) and (2.5), (2.6).

Furthermore, let us consider the following system of partial differential equations with delay:

$$\frac{\partial x_1(r,t)}{\partial t} = \Big[a_{11} + a_{12}x_2(r,t-\tau_2(t)) + a_{13}x_3(r,t-\tau_3(t)) + a_{14}x_4(r,t-\tau_4(t))\Big]x_1(r,t-\tau_1(t)) + a_{15} + D_1\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial x_1(r,t)}{\partial r}\Big), \tag{2.7}$$

$$\frac{\partial x_2(r,t)}{\partial t} = \Big[a_{21}x_1(r,t-\tau_1(t)) + a_{22} + a_{23}x_3(r,t-\tau_3(t)) + a_{24}x_4(r,t-\tau_4(t))\Big]x_2(r,t-\tau_2(t)) + a_{25} + \alpha x_3(r,t-\tau_3(t)) + D_2\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial x_2(r,t)}{\partial r}\Big), \tag{2.8}$$

$$\frac{\partial x_3(r,t)}{\partial t} = \Big[a_{31}x_1(r,t-\tau_1(t)) + a_{32}x_2(r,t-\tau_2(t)) + a_{33} + a_{34}x_4(r,t-\tau_4(t))\Big]x_3(r,t-\tau_3(t)) + a_{35} + \beta x_1(r,t-\tau_1(t))x_4(r,t-\tau_4(t)) + D_3\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial x_3(r,t)}{\partial r}\Big), \tag{2.9}$$

$$\frac{\partial x_4(r,t)}{\partial t} = \Big[a_{41}x_1(r,t-\tau_1(t)) + a_{42}x_2(r,t-\tau_2(t)) + a_{43}x_3(r,t-\tau_3(t)) + a_{44}\Big]x_4(r,t-\tau_4(t)) + a_{45} + D_4\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial x_4(r,t)}{\partial r}\Big), \tag{2.10}$$

with the boundary conditions

$$\frac{\partial x_1(0,t)}{\partial t} = b_1, \quad \frac{\partial x_2(0,t)}{\partial t} = b_2, \quad \frac{\partial x_3(0,t)}{\partial t} = b_3, \quad \frac{\partial x_4(0,t)}{\partial t} = b_4, \tag{2.11}$$

and with the initial conditions

$$x_1(r,0) = c_1, \quad x_2(r,0) = c_2, \quad x_3(r,0) = c_3, \quad x_4(r,0) = c_4. \tag{2.12}$$

We understand a solution $x = (x_1, x_2, x_3, x_4)$ as a vector of differentiable functions up to the second order satisfying (2.7)–(2.10) and (2.11), (2.12); $a_{ij}, \alpha, \beta \in \mathbb{R}$ for all $1 \le i, j \le 5$, D_1, D_2, D_3, D_4 are positive real numbers, and $\tau_1(t)$, $\tau_2(t)$, $\tau_3(t)$, $\tau_4(t)$ are nonnegative measurable functions.

Let x_1, x_2, x_3 and x_4 be the functions defined in a bounded smooth domain Ω in $\mathbb{R}^n$ (in our cases, $n = 1$ for the ODE system and $n = 2$ for the PDE system). Introduce the following operators:

$$L_1(x) = a_{12}x_2 + a_{13}x_3 + a_{14}x_4, \quad L_2(x) = a_{21}x_1 + a_{23}x_3 + a_{24}x_4,$$
$$L_3(x) = a_{31}x_1 + a_{32}x_2 + a_{34}x_4, \quad L_4(x) = a_{41}x_1 + a_{42}x_2 + a_{43}x_3.$$

Let us also denote the operator $L = (L_1, L_2, L_3, L_4)$.

Let A be the matrix of coefficients

$$A = \begin{pmatrix} 0 & a_{12} & a_{13} & a_{14} \\ a_{21} & 0 & a_{23} & a_{24} \\ a_{31} & a_{32} & 0 & a_{34} \\ a_{41} & a_{42} & a_{43} & 0 \end{pmatrix} \tag{2.13}$$

and let $H = L^2(\Omega)$ and $V = H_0^1(\Omega)$. The scalar products and the norms are denoted, respectively, by $((\,\cdot\,,\,\cdot\,))$, $(\,\cdot\,,\,\cdot\,)$, $\|\cdot\|$, $|\cdot|$. Identifying H with its dual, we have $V \subset H \subset V'$ with continuous inclusions. We also associate with the continuous linear operator $L : V \to V'$, $L \in \mathcal{L}(V, V')$, a continuous bilinear form on $V \times V$ given by the formula:

$$\forall\, v, u \in V, \quad a(v,u) = (Lv, u)_{V',V}.$$

Thanks to the continuity of L, we have

$$\forall\, v, u \in V, \quad |a(v,u)| \le M\|v\|\,\|u\|.$$

Recall that a bilinear form will be called coercive if

$$\exists\, \gamma > 0 \;\; \forall\, v \in V, \quad a(v,v) \ge \gamma\|v\|^2.$$

If $a(v,u) = ((v,u))$ defines the scalar product in V, then L is a canonical isomorphism of V onto V'. We have the well-known Lax–Milgram lemma.

Lemma 2.1. *If a is a bilinear continuous and coercive form on V, then L defines an isomorphism from V onto V':*

$$\forall\, L \in \mathcal{L}(V, V')\ \ \exists\, !f \in V, \quad a(x, f) = L(x)\ \ \textit{for all}\ \ x \in V.$$

The operator L also defines an isomorphism of its domain $D(A) \subset H$ onto H.

2.1 Uniqueness and existence of solutions of systems with delay

In order to prove the uniqueness and existence of solutions we reduce our systems with delays to systems without delay, by generalizing the approach used in [7]. According to the generalized mean value theorem for definite integrals, for every differentiable function $f(x)$, there exists $c \in [a, b]$ such that

$$\int_a^b f(x)g(x)\,dx = f(c)\int_a^b g(x)\,dx,$$

under the condition that $g(x)$ is an integrable function that does not change sign. Our approach assumes this theorem according to which there exists $\widetilde{\tau}_i(t)$ obeying

$$x_i(t-\tau_i(t))\int_{-\infty}^{t} e^{\frac{u-t}{\widetilde{\tau}_i(t)}}\,du = \int_{-\infty}^{t} e^{\frac{u-t}{\widetilde{\tau}_i(t)}}x_i(u)\,du.$$

Calculating the integral in the left-hand side, we obtain

$$\int_{-\infty}^{t} e^{\frac{u-t}{\widetilde{\tau}_i(t)}}\,du = \lim_{a\to-\infty}\left[\widetilde{\tau}_i(t)e^{\frac{u-t}{\widetilde{\tau}_i(t)}}\right]_a^t = \lim_{a\to-\infty}\left[\widetilde{\tau}_i(t) - \widetilde{\tau}_i(t)e^{\frac{a-t}{\widetilde{\tau}_i(t)}}\right] = \widetilde{\tau}_i(t).$$

Thus

$$x_i(t-\tau_i(t)) = \frac{1}{\widetilde{\tau}_i(t)}\int_{-\infty}^{t} e^{\frac{u-t}{\widetilde{\tau}_i(t)}}x_i(u)\,du.$$

From this construction we can conclude that $\widetilde{\tau}_i(t) \neq 0$ for all t. Assuming that $\widetilde{\tau}_i(t)$ is differentiable, we observe that $v_i(t) := x_i(t-\tau_i(t))$ obeys

$$\frac{dv_i}{dt} = -\frac{v_i}{\widetilde{\tau}_i(t)} + \frac{x_i(t)}{\widetilde{\tau}_i(t)} - \frac{v_i}{\widetilde{\tau}_i(t)}\,\frac{d\widetilde{\tau}_i(t)}{dt}\,.$$

This equation allows us to represent the ODE system (2.1)–(2.4) as

$$\frac{dx_1}{dt} = L_1(v)v_1(t) + a_{11}v_1(t) + a_{15}, \tag{2.14}$$

$$\frac{dx_2}{dt} = L_2(v)v_2(t) + a_{22}v_2(t) + a_{25} + \alpha v_3(t), \tag{2.15}$$

$$\frac{dx_3}{dt} = L_3(v)v_3(t) + a_{33}v_3(t) + a_{35} + \beta v_1(t)v_4(t), \tag{2.16}$$

$$\frac{dx_4}{dt} = L_4(v)v_4(t) + a_{44}v_4(t) + a_{45}, \tag{2.17}$$

where

$$\frac{dv_i}{dt} = -\frac{v_i(t)}{\widetilde{\tau}_i(t)} + \frac{x_i(t)}{\widetilde{\tau}_i(t)} - \frac{v_i(t)}{\widetilde{\tau}_i(t)}\,\frac{d\widetilde{\tau}_i(t)}{dt}$$

for $i = 1, 2, 3, 4$. This reduces the problem with delay to the usual local in time system where we will study the uniqueness and existence of solutions by the usual methods. Multiplying both sides of the last equation by $\widetilde{\tau}_i(t)$, we get

$$\widetilde{\tau}_i(t)\,\frac{dv_i}{dt} = -v_i(t) + x_i(t) - v_i(t)\,\frac{d\widetilde{\tau}_i(t)}{dt}\,,$$

and we can write this equation in the following simple form:

$$\frac{d}{dt}\left[\widetilde{\tau}_i(t)v_i(t)\right] = x_i(t) - v_i(t). \tag{2.18}$$

Following a similar process, we can represent the PDE system (2.7)–(2.10) as

$$\begin{aligned}
\frac{\partial x_1}{\partial t} &= L_1(v)v_1(r,t) + a_{11}v_1(r,t) + a_{15} + D_1\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial x_1(r,t)}{\partial r}\Big),\\
\frac{\partial x_2}{\partial t} &= L_2(v)v_2(r,t) + a_{22}v_2(r,t) + a_{25} + \alpha v_3(r,t) + D_2\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial x_2(r,t)}{\partial r}\Big),\\
\frac{\partial x_3}{\partial t} &= L_3(v)v_3(r,t) + a_{33}v_3(r,t) + a_{35} + \beta v_1(r,t)v_4(r,t) + D_3\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial x_3(r,t)}{\partial r}\Big),\\
\frac{\partial x_4}{\partial t} &= L_4(v)v_4(r,t) + a_{44}v_4(r,t) + a_{45} + D_4\frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2\frac{\partial x_4(r,t)}{\partial r}\Big),
\end{aligned}$$

where

$$\frac{\partial v_i}{\partial t} = -\frac{v_i(r,t)}{\widetilde{\tau}_i(t)} + \frac{x_i(r,t)}{\widetilde{\tau}_i(t)} - \frac{v_i(r,t)}{\widetilde{\tau}_i(t)}\frac{d\widetilde{\tau}_i(t)}{dt}$$

for $i = 1, 2, 3, 4$.

For the following theorems, we denote

$$f_1 = (a_{11}, a_{22}, a_{33}, a_{44}), \quad f_2 = (a_{15}, a_{25}, a_{35}, a_{45});$$
$$\widetilde{\alpha} = (0, \alpha, 0, 0), \quad \widetilde{\beta} = (0, 0, \beta, 0).$$

Using similar approach proposed in [17], we formulate and prove the following statement.

Theorem 2.1. *If the matrix A defined by* (2.13) *is a symmetric invertible matrix, then there exists a unique weak solution x of* (2.1)–(2.4) *and* (2.5), (2.6) *such that*

$$x \in L^2(0, T : V) \cap L^\infty(0, T : H), \quad x' \in L^2(0, T : V').$$

Remark 2.1. In the context of this theorem and the following proof, we use the notations x', v', $\frac{dx}{dt}$, $\frac{dv}{dt}$ for the weak derivatives of the corresponding functions.

Proof. In the first part of the proof, we use the eigenfunctions and eigenvalues in order to obtain a system of linear ordinary differential equations where its global existence and uniqueness results are known. First of all, we have to prove that such eigenfunctions and eigenvalues exist.

Since for all $v \in V$,

$$a(v, v) = (Lv, v)_{V',V} = (Av, v),$$

from the assumption that A is a symmetric invertible matrix, there exists a scalar $\gamma > 0$ such that

$$a(v, v) \geq \gamma\|v\|^2$$

for all $v \in V$. Thus a is a bilinear continuous and coercive form on V; hence we can use Lemma 2.1. Since A is a symmetric matrix, we get

$$a(v, u) = (Au, v) = (u, A^T v) = (u, Av) = (Av, u) = a(u, v),$$

which means that the form $a(v, u)$ is symmetric. Since the inclusion $V \subset H$ is compact and the form is symmetric, we can consider an orthonormal base of V that consists of eigenfunctions of the operator L:

$$\forall\, j \in \mathbb{N}, \quad Lw_j = \lambda_j w_j.$$

For each fixed m, define an approximated solution x_m, v_m of (2.14)–(2.17) and (2.18):

$$x_m = \sum_{i=1}^{m} g_{im}w_i, \quad v_m = \sum_{i=1}^{m} h_{im}w_i$$

such that

$$\frac{d}{dt}(x_m, w_j) = (L(v_m)v_m, w_j)+(f_1 v_m, w_j)+(f_2, w_j)+(\widetilde{\alpha}v_{3m}, w_j)+(\widetilde{\beta}v_{1m}v_{4m}, w_j), \quad j=1,\dots,m,$$
$$\frac{d}{dt}(\widetilde{\tau}v_m, w_j) = (x_m, w_j) - (v_m, w_j), \quad j=1,\dots,m.$$

By the definition of the form $a(v,u)$, we can write this system as follows:

$$\frac{d}{dt}(x_m, w_j) = a(v_m, w_j) + (f_1 v_m, w_j) + (f_2, w_j) + (\widetilde{\alpha}v_{3m}, w_j) + (\widetilde{\beta}v_{1m}v_{4m}, w_j), \quad j=1,\dots,m, \tag{2.19}$$
$$\frac{d}{dt}(\widetilde{\tau}v_m, w_j) = (x_m, w_j) - (v_m, w_j), \quad j=1,\dots,m. \tag{2.20}$$

With the assumption of $\{w_1,\dots,w_m,\dots\}$ being an orthonormal base of eigenfunctions and the assumption of x_m, v_m being the functions satisfying this system of ordinary differential equations, we can conclude that the functions g_{jm}, h_{jm} are differentiable. We get

$$\frac{d}{dt}\,g_{jm}(t)(w_j,w_j) = \lambda_j h_{jm}(t)(w_j,w_j) + f_1 h_{jm}(t)(w_j,w_j) + (f_2, w_j) + \widetilde{\alpha}h_{3jm}(t)(w_j,w_j) + \widetilde{\beta}h_{1jm}(t)h_{4jm}(t)(w_j,w_j), \quad j=1,\dots,m,$$
$$\frac{d}{dt}\left[h_{jm}(t)\widetilde{\tau}\right](w_j,w_j) = g_{jm}(t)(w_j,w_j) - h_{jm}(t)(w_j,w_j), \quad j=1,\dots,m.$$

We have obtained a linear system of $2m$ ordinary differential equations for the unknown functions $g_{im}(t)$, $h_{im}(t)$, $i=1,\dots,m$. Thus the global existence and uniqueness of its solution is known. The functions x_m, v_m belong to $C([0,T]:V)$, and the derivatives x'_m, $v'_m \in L^2(0,T:V)$. Multiplying equations (2.19), (2.20) by g_{jm} and h_{jm}, adding the results for $j=1,\dots,m$, we get

$$(x'_m, x_m) = a(v_m, x_m) + (f_1 v_m, x_m) + (f_2, x_m) + (\widetilde{\alpha}v_{3m}, x_m) + (\widetilde{\beta}v_{1m}v_{4m}, x_m),$$
$$\big((\widetilde{\tau}v_m)', v_m\big) = (x_m, v_m) - (v_m, v_m),$$

or

$$\frac{1}{2}\frac{d}{dt}(x_m, x_m) \le ((v_m, x_m)) + \|f_1\|\cdot\|v_m\|\cdot\|x_m\| + \|f_2\|\cdot\|x_m\| + |\alpha|\cdot\|v_m\|\cdot\|x_m\| + |\beta|\cdot\|v_m\|\cdot\|x_m\|,$$
$$\frac{1}{2}\frac{d}{dt}(\widetilde{\tau}v_m, v_m) + \|v_m\|^2 \le \|x_m\|\cdot\|v_m\|,$$
$$\frac{1}{2}\frac{d}{dt}|x_m|^2 \le M\|v_m\|\cdot\|x_m\| + \|f_1\|\cdot\|v_m\|\cdot\|x_m\| + \|f_2\|\cdot\|x_m\| + |\alpha|\cdot\|v_m\|\cdot\|x_m\| + |\beta|\cdot\|v_m\|\cdot\|x_m\|,$$
$$\frac{1}{2}\frac{d}{dt}|v_m|^2 + \|v_m\|^2 \le \|x_m\|\cdot\|v_m\|.$$

Integrating the above over $[0,t]$ and using the Cauchy inequality to the left-hand side, we get

$$|x_m(t)|^2 \le |x_m(0)|^2 + 2M\int_0^t (\|v_m\|^2 + \|x_m\|^2)\,du + \int_0^t \left(\|f_1\|^2 + \|v_m\|^2 + \|x_m\|^2\right)du + \int_0^t \left(\|f_2\|^2 + \|x_m\|^2\right)du + \int_0^t \left(\alpha^2 + \|v_m\|^2 + \|x_m\|^2\right)du + \int_0^t \left(\beta^2 + \|v_m\|^2 + \|x_m\|^2\right)du,$$

$$|v_m|^2 + 2\int_0^t \|v_m\|^2\,du \le \int_0^t \left(\|x_m\|^2 + \|v_m\|^2\right) du,$$

or

$$|x_m(t)|^2 \le |x_m(0)|^2 + (2M+3)\int_0^t \|v_m\|^2\,du + (2M+4)\int_0^t \|x_m\|^2\,du + \int_0^t \left(\|f_1\|^2 + \|f_2\|^2 + \alpha^2 + \beta^2\right) du,$$

$$|v_m(t)|^2 + \int_0^t \|v_m\|^2\,du \le \int_0^t \|x_m\|^2\,du.$$

Hence the sequences x_m and v_m are bounded in $L^2(0,T:V)\cap L^\infty(0,T:H)$ uniformly in m.

The space $L^2(0,T:V)$ is the Hilbert space (and hence reflexive), $L^\infty(0,T:H)$ is a conjugate of $L^1(0,T:H)$, which is separable. Therefore, from sequences x_m, v_m bounded in such spaces we can extract subsequences x_{m_k} and v_{m_k}, respectively, such that

$$\begin{aligned} x_{m_k} &\to x \ \text{ in } L^2(0,T:V) \text{ weakly},\\ v_{m_k} &\to v \ \text{ in } L^2(0,T:V) \text{ weakly},\\ x_{m_k} &\to x \ \text{ in } L^\infty(0,T:H) \text{ weak*},\\ v_{m_k} &\to v \ \text{ in } L^\infty(0,T:H) \text{ weak*}. \end{aligned}$$

Passing in (2.19), (2.20) to the limit, we obtain

$$\begin{aligned} &\frac{d}{dt}(x,w_j) = a(v,w_j) + (f_1 v,w_j) + (f_2,w_j) + (\widetilde{\alpha}v_3,w_j) + (\widetilde{\beta}v_1v_4,w_j), \quad j=1,\dots,m,\\ &\frac{d}{dt}(\widetilde{\tau}v,w_j) = (x,w_j) - (v,w_j), \quad j=1,\dots,m, \end{aligned}$$

and, since w_j forms a basis in V, we also have

$$\begin{aligned} &\forall\, u\in V, \quad \frac{d}{dt}(x,u) = a(v,u) + (f_1 v,u) + (f_2,u) + (\widetilde{\alpha}v_3,u) + (\widetilde{\beta}v_1v_4,u),\\ &\forall\, u\in V, \quad \frac{d}{dt}(\widetilde{\tau}v,u) = (x,u) - (v,u), \end{aligned}$$

where the equality is understood in the sense of distributions in $(0,T)$. According to Lemma 3.1 from [17, p. 69], $\frac{d}{dt}(x,u) = (x',u)$, $\frac{d}{dt}(\widetilde{\tau}v,u) = ((\widetilde{\tau}v)',u)$, and we find that system (2.14)–(2.17) and (2.18) is satisfied. But since $L(v)\in L^2(0,T:V)$, we have $\frac{dx}{dt}\in L^2(0,T:V')$. Now, since $L^2\subset L^1$, the solution x is a.e. equal to a continuous function from $[0,T]$ into V'. □

3 Application to mathematical modeling of bladder cancer treatment by using bcg immunotherapy

In this section, we introduce an application to the systems of differential equations with delay that we studied.

3.1 Mathematical modeling

We develop the mathematical model described in [4] in the following two directions. The first one is considers the delay for the ordinary differential equations

$$\frac{dB(t)}{dt} = -p_1E(t-\tau_2(t))B(t-\tau_1(t)) - p_2B(t-\tau_1(t))T_u(t-\tau_3(t)) - \mu_1B(t-\tau_1(t)) + b,$$

$$\begin{aligned}
\frac{dE(t)}{dt} &= -\mu_2 E(t-\tau_2(t)) + \alpha T_i(t-\tau_3(t)) + p_4 E(t-\tau_2(t))B(t-\tau_1(t)) \\
&\quad - p_5 E(t-\tau_2(t))T_i(t-\tau_3(t)), \\
\frac{dT_i(t)}{dt} &= p_2 B(t-\tau_1(t))T_u(t-\tau_3(t)) - p_3 T_i(t-\tau_3(t))E(t-\tau_2(t)), \\
\frac{dT_u(t)}{dt} &= \lambda T_u(t-\tau_3(t)) - p_2 B(t-\tau_1(t))T_u(t-\tau_3(t)),
\end{aligned}$$

where $\tau_1(t)$, $\tau_2(t)$ are the delays in $B(t)$, $E(t)$, respectively, and $\tau_3(t)$ is the delay in $T_i(t)$ and $T_u(t)$. The state variables $B(t)$, $E(t)$, $T_i(t)$ and $T_u(t)$ represent the concentration of BCG in the bladder, effector cell population, tumor cell population that has been infected with BCG, and tumor cell population that is uninfected with BCG, respectively.

The second direction of our development considers the geometrical configuration of the human bladder (see [12]). This model can be described by the following system of partial differential equations with delay:

$$\begin{aligned}
\frac{\partial B(r,t)}{\partial t} &= -p_1 E(r,t-\tau_2(t))B(r,t-\tau_1(t)) - p_2 B(r,t-\tau_1(t))T_u(r,t-\tau_3(t)) \\
&\quad - \mu_1 B(r,t-\tau_1(t)) + b + D_1 \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 \frac{\partial B(r,t)}{\partial r}\Big), \\
\frac{\partial E(r,t)}{\partial t} &= -\mu_2 E(r,t-\tau_2(t)) + \alpha T_i(r,t-\tau_3(t)) + p_4 E(r,t-\tau_2(t))B(r,t-\tau_1(t)) \\
&\quad - p_5 E(r,t-\tau_2(t))T_i(r,t-\tau_3(t)) + D_2 \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 \frac{\partial E(r,t)}{\partial r}\Big), \\
\frac{\partial T_i(r,t)}{\partial t} &= p_2 B(r,t-\tau_1(t))T_u(r,t-\tau_3(t)) - p_3 T_i(r,t-\tau_3(t))E(r,t-\tau_2(t)) \\
&\quad + D_3 \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 \frac{\partial T_i(r,t)}{\partial r}\Big), \\
\frac{\partial T_u(r,t)}{\partial t} &= \lambda T_u(t-\tau_3(t)) - p_2 B(r,t-\tau_1(t))T_u(r,t-\tau_3(t)) + D_4 \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2 \frac{\partial T_u(r,t)}{\partial r}\Big),
\end{aligned}$$

D_1, D_2, D_3, D_4 are the diffusion rates in the system for $B(r,t)$, $E(r,t)$, $T_i(r,t)$ and $T_u(r,t)$, respectively. The variable r stands for the Euclidean distance in $\mathbb{R}^3$ from the point $(0,0,0)$ in the polar coordinates. The center of the system's geometry is defined to be $(0,0,0)$.

In the scope of this paper, it is assumed that the bladder has a form of a perfect sphere ring satisfying the condition

$$r_0^2 \le x^2 + y^2 + z^2 \le R^2.$$

The variables x, y, z are the Cartesian coordinates system. r_0 and R are the radii of the internal and external spheres of the geometrical configuration, respectively.

The boundary condition of the inner sphere is given by

$$\frac{\partial B(r_0,t)}{\partial t} = b, \quad \frac{\partial E(r_0,t)}{\partial t} = 0, \quad \frac{\partial T_i(r_0,t)}{\partial t} = 0, \quad \frac{\partial T_u(r_0,t)}{\partial t} = 0.$$

In addition, the initial conditions are assumed to be

$$B(r,t_0) = 0, \quad E(r,t_0) = 0, \quad T_i(r,t_0) = 0, \quad T_u(r,t_0) = \frac{cr}{R-r_0},$$

where $c > 0$ is the tumor cells equal distribution factor.

3.2 Discretization

Our approach consists in a discretization of our system of differential equations, by dividing the domain into a two-dimensional grid in r and t. Our t-axis partition is

$$t_{start} = t_0 < t_1 < \cdots < t_n = t_{end},$$

while the r-axis partition is

$$r_0 < r_1 < \cdots < r_n = R.$$

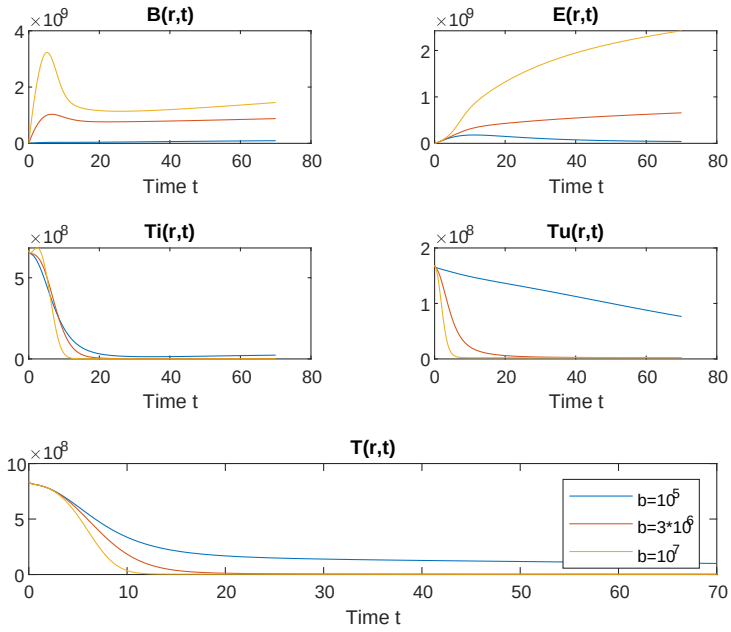

Figure 1. Effect of different dosages on PDE.

For a general function $f(r,t)$, we can use this grid system to get the following approximation of its derivatives:

$$\frac{\partial f_{i,j}}{\partial t} = \frac{f_{i,j+1} - f_{i,j}}{t_{j+1} - t_j},$$
$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial f_{i,j}}{\partial r}\right) = \frac{2f_{i+1,j} - 2f_{i,j}}{r_i(r_{i+1} - r_i)} + \frac{f_{i+2,j} - 2f_{i+1,j} + f_{i,j}}{(r_{i+2} - r_{i+1})(r_{i+1} - r_i)}.$$

Substituting these approximations into our system of partial differential equations with delay, we get

$$\begin{aligned}
\frac{B_{i,j+1} - B_{i,j}}{t_{j+1} - t_j} &= -p_1 E_{i,j-\tau_2} B_{i,j-\tau_1} - p_2 B_{i,j-\tau_1} T u_{i,j-\tau_3} - \mu_1 B_{i,j-\tau_1} + b \\
&\quad + D_1 \frac{2B_{i+1,j} - 2B_{i,j}}{r_i(r_{i+1} - r_i)} + D_1 \frac{B_{i+2,j} - 2B_{i+1,j} + B_{i,j}}{(r_{i+2} - r_{i+1})(r_{i+1} - r_i)}, \\
\frac{E_{i,j+1} - E_{i,j}}{t_{j+1} - t_j} &= -\mu_2 E_{i,j-\tau_2} + \alpha T I_{i,j-\tau_3} + p_4 E_{i,j-\tau_2} B_{i,j-\tau_1} - p_5 E_{i,j-\tau_2} T I_{i,j-\tau_3} \\
&\quad + D_2 \frac{2E_{i+1,j} - 2E_{i,j}}{r_i(r_{i+1} - r_i)} + D_2 \frac{E_{i+2,j} - 2E_{i+1,j} + E_{i,j}}{(r_{i+2} - r_{i+1})(r_{i+1} - r_i)}, \\
\frac{T I_{i,j+1} - T I_{i,j}}{t_{j+1} - t_j} &= p_2 B_{i,j-\tau_1} T u_{i,j-\tau_3} - p_3 T I_{i,j-\tau_3} E_{i,j-\tau_2} \\
&\quad + D_3 \frac{2T I_{i+1,j} - 2T I_{i,j}}{r_i(r_{i+1} - r_i)} + D_3 \frac{T I_{i+2,j} - 2T I_{i+1,j} + T I_{i,j}}{(r_{i+2} - r_{i+1})(r_{i+1} - r_i)}, \\
\frac{T u_{i,j+1} - T u_{i,j}}{t_{j+1} - t_j} &= \lambda T u_{i,j-\tau_3} - p_2 B_{i,j-\tau_1} T u_{i,j-\tau_3} \\
&\quad + D_4 \frac{2T u_{i+1,j} - 2T u_{i,j}}{r_i(r_{i+1} - r_i)} + D_4 \frac{T u_{i+2,j} - 2T u_{i+1,j} + T u_{i,j}}{(r_{i+2} - r_{i+1})(r_{i+1} - r_i)}.
\end{aligned}$$

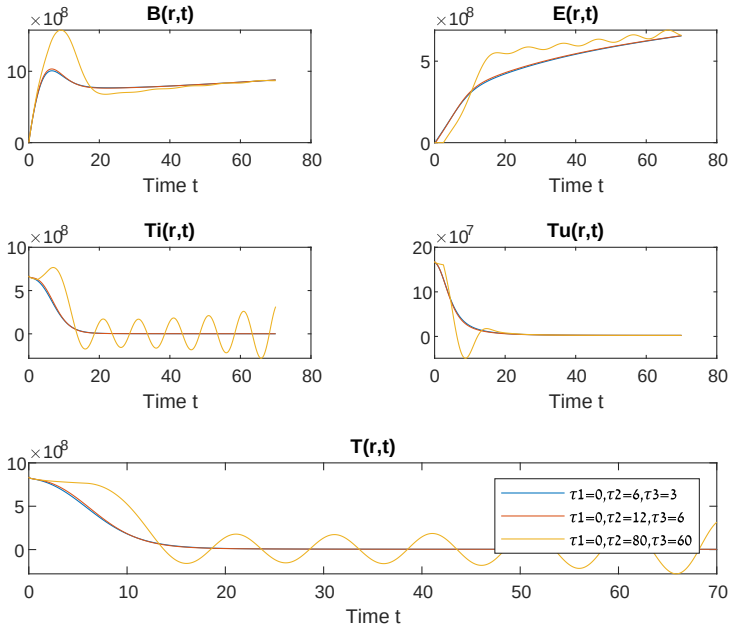

Figure 2. Effect of different delays on PDE.

Our discretization consists of a two-dimensional grid where for every $i, j < 0$, we assume

$$B_{i,j} = 0, \quad E_{i,j} = 0, \quad TI_{i,j} = 0, \quad Tu_{i,j} = 0.$$

Discretization of the initial condition is given by

$$B_{i,0} = 0, \quad E_{i,0} = 0, \quad TI_{i,0} = 0, \quad Tu_{i,0} = \frac{cr_i}{R - r_0}$$

for every i, while discretization of the boundary condition is given by

$$B_{0,j+1} = B_{0,j} + b, \quad E_{0,j+1} = E_{0,j}, \quad TI_{0,j+1} = TI_{0,j}, \quad Tu_{0,j+1} = Tu_{0,j}.$$

For the system of ordinary differential equations with delay, we use a one-dimensional grid in t,

$$t_{start} = t_0 < t_1 < \cdots < t_n = t_{end}.$$

For a general function $f(t)$, we can use this grid system to get the following approximation of its derivative:

$$\frac{df_j}{dt} = \frac{f_{j+1} - f_j}{t_{j+1} - t_j}.$$

Substituting this into our system of ordinary differential equations with delay, we get

$$\begin{aligned}
\frac{B_{j+1} - B_j}{t_{j+1} - t_j} &= -p_1 E_{j-\tau_2} B_{j-\tau_1} - p_2 B_{j-\tau_1} Tu_{j-\tau_3} - \mu_1 B_{j-\tau_1} + b, \\
\frac{E_{j+1} - E_j}{t_{j+1} - t_j} &= -\mu_2 E_{j-\tau_2} + \alpha TI_{j-\tau_3} + p_4 E_{j-\tau_2} B_{j-\tau_1} - p_5 E_{j-\tau_2} TI_{j-\tau_3}, \\
\frac{TI_{j+1} - TI_j}{t_{j+1} - t_j} &= p_2 B_{j-\tau_1} Tu_{j-\tau_3} - p_3 TI_{j-\tau_3} E_{j-\tau_2}, \\
\frac{Tu_{j+1} - Tu_j}{t_{j+1} - t_j} &= \lambda Tu_{j-\tau_3} - p_2 B_{j-\tau_1} Tu_{j-\tau_3}.
\end{aligned}$$

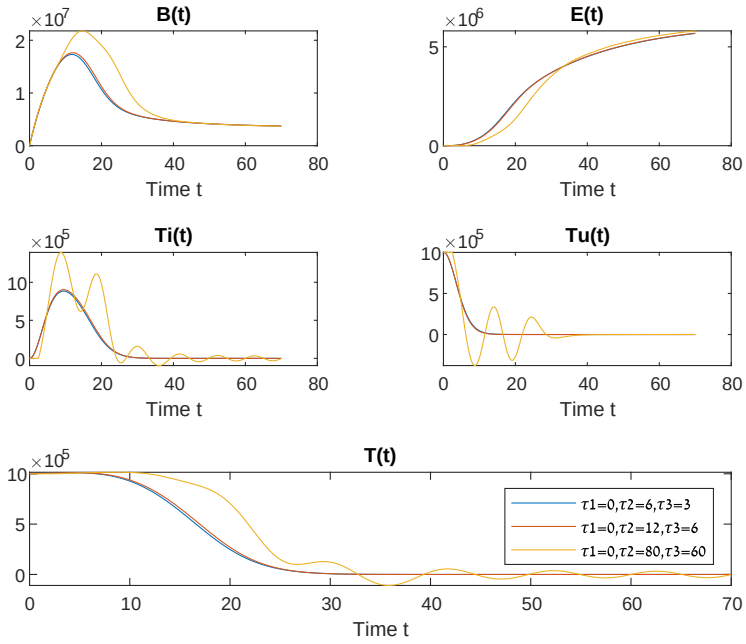

Figure 3. Effect of different delays on ODE.

Discretization of the initial condition is given by

$$B_0 = 0, \quad E_0 = 0, TI_0 = 0, \quad Tu_0 = \frac{c}{R - r_0}.$$

The calculation has been performed using *Matlab* software (version R2020a). Several tests have been conducted to examine the results, the effect of the delay and different dosage on the PDE and the ODE models, and the differences between the PDE and the ODE models.

In each figure, the x-axis respresents the time that has been passed from the beginning of the treatment and the y-axis is the size of the cell population. In Figure 1, we compare different dosages of BCG injected and how it affects the PDE model. In Figures 2 and 3, we compare different values of delay for the PDE model and ODE model, respectively. Lastly, Figure 4 shows the absolute difference between the PDE and ODE models.

4 Conclusions

This study develops a numerical method for the analysis of the solutions for the system of partial differential equations with delay of a mathematical model with pulsed BCG immunotherapy based on a two-dimensional grid discretization. Using this numerical method, we created graphs describing the difference of the system behavior based on specific parameters change. From these graphs, we can come to the conclusion that the bigger the delay, the less stable these systems become. Furthermore, we can observe that the partial differential system allows us to get more accurate presentation of how the BCG affects the bladder early on. This is a result of the geometry of the bladder taking part in the system using diffusion. Later on, we have got similar behavior for both.

In addition, we can use these calculations to help us determine the dosage needed for each treatment. As can be observed in Figure 1, low dosage of $b = 10^5$ has no effect on the cancer cells and will not result in the cancer being cured. Once we increase the dosage, we can observe that there is an effect and the cancer is cured. For example, for $b = 3 \cdot 10^6$, the cancer takes double the time to get cured compared to $b = 10^7$.

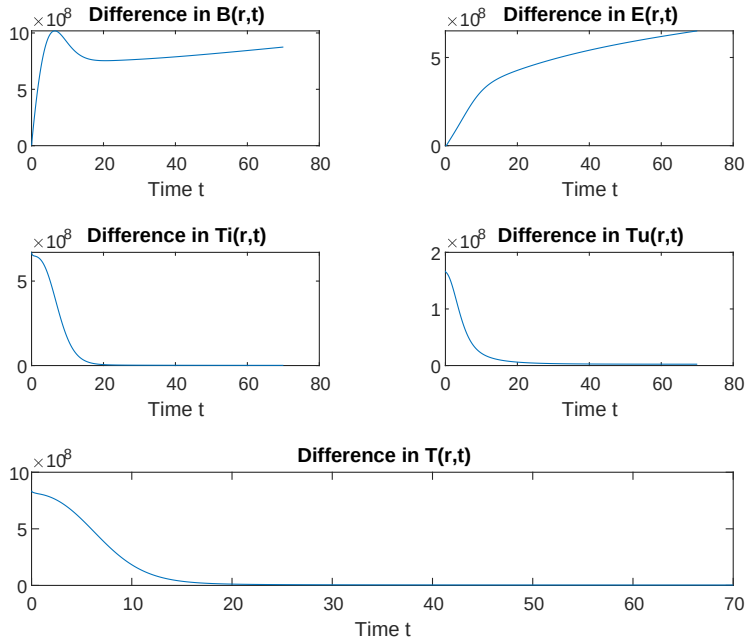

Figure 4. Difference between PDE and ODE.

In Figure 4, it can be observed that the difference between the PDE and ODE models in all cell populations at the start of the treatment is of a high magnitude. Later on, the delta between the models converges to a constant for all cell populations which indicates linear correlation between the PDE and ODE models. This difference between the models can be explained by the introduction of the geometry which is reflected in the diffusion coefficients of the system. For the PDE model, there is diffusion dynamics as opposed to the ODE model where there is an instant reaction to the introduction of BCG. After the diffusion spreads throughout the bladder, it behaves like an instant reaction, and therefore the PDE and ODE models eventually behave identically, as can be seen in Figure 4. However, the PDE model will provide us with a more accurate analysis of the treatment effect.

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