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On the stability of stationary solutions in diffusion models of oncological processes

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Abstract We prove a sufficient condition for the stability of a stationary solution to a system of nonlinear partial differential equations of the diffusion model describing the growth of malignant tumors. We also numerically simulate stable and unstable scenarios involving the interaction between tumor and immune cells.

1 Introduction

Cancer is a generic term for a group of diseases and figures as a leading cause of death globally. Responsible for one in every six deaths, it lays a significant burden on healthcare systems and continues to be among the major health problems worldwide [1]. One defining characteristic in cancer diseases is the appearence of abnormal cells that hijack control checks and proliferates abnormally, which leads to a neoplasm that can occur in almost any part of the body [2,3].

Increasing knowledge of cancer evolution has improved the understanding of anticancer treatment resistance. A better characterization of cancer evolution and subsequent use of this knowledge for personalized treatment would increase the chance to overcome cancer treatment resistance. On this matter, mathematical oncology has surfaced as an area that comprehends both ellaboration and application of model-based approaches to describe cancer-related phenomena and help improve personalized treatment [4–6]. Currently, there are many mathematical models of tumor growth displayed by ordinary and partial differential equations [7–9]. Exact and numerical methods have been developed for solving the initial and initial boundary value problems generated by these models [10], as well as methods for studying

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the qualitative properties of such models. The latter, in particular, include studies on stability of a stationary state. Below, in the description of the models, we essentially use the results of [11] and the literature review given there.

The first mathematical tumor growth models were Cauchy problem for a system of ordinary differential equations. The models took into account tumor cells, normal cells, dead cells, nutrition, various inhibitory substances, immune system response [12]. Later, a tumor was considered as a system with distributed parameters in advection–diffusion–reaction models [13–26]. Tissue formed by three types of cells is considered incompressible; therefore, their total concentration is assumed to be constant. The growth rate of tumor tissue based on the second Newton's law is determined through the excess internal pressure arising during the generation of new cells. Models taking into account not only diffusional tumor growth but also tumor invasion by blood vessels were presented in the works [13–15]. The cells of a healthy organism are mortal, and apoptosis is the end of the life cycle. In turn, the main feature of tumor cells is the absence of apoptosis [22–26].

Since tumor cells look similar to healthy ones, it is difficult for the immune system to recognize them [23,27,28]. An increase in the number of tumor cells is accompanied by their association and leads to the formation of various spatial structures (spheroids, tubes, threads, disks, etc.) [22–26]. Internal cells of the emerging structure begin to die due to lack of nutrition, external tumor cells continue to multiply, pushing healthy ones away from themselves. In the process of tumor growth, both tumor cells and all the dead cells are not removed from the body, forming a solid tumor [25,26]. A solid tumor is a nucleus of dead cells surrounded by a layer of continuously multiplying tumor cells [22,26]. The tumor becomes autonomous and its cells begin penetrate into surrounding tissues, destroying them and creating new growth points.

Overall, these remarking characteristics show how different the proliferation of early tumor cells or the tissue invasion of specialized ones can be. Such distinctness reinforces the importance of approaching such phenomena with mathematical and physical tools, exploring their dynamics and analyzing possible interesting scenarios [29,30]. This paper is devoted to the stability of a stationary solution to a system of partial differential equation modeling tumor growth. Section 2 grounds the fundamental concepts regarding diffusing phenomena. The main model is presented in Sect. 3, with the stability of a stationary solution being derived in Sect. 4. Additionally, in Sect. 5 the stability of a solution pertaining to a simplified model is verified. Finally, Sect. 6 applies the same approach to analyze another model of interest in oncology dynamics, along with virtualizations provided by numerical simulations.

2 Preliminary and fundamental concepts

Bearing in mind that the present work proposes to investigate the solution and the stability of the stationary problem of the diffusion equation toward oncological processes, this section points out some preliminary and fundamental concepts that address the issue of the uniqueness of the solution for the nonhomogeneous diffusion equation.

Theorem 1 *Consider the nonhomogeneous diffusion equation*

$$\frac{\partial u(x,t)}{\partial t} - D^2 \frac{\partial^2 u(x,t)}{\partial x^2} = f(x,t) \tag{1}$$

and

$$u(x,0) = \phi(x)$$

satisfying any of the well-known Dirichlet, Neumann or Robin boundary conditions and where u and f are functions of two arguments (x, t) *with* $0 < x < L$ *and* $t > 0$ *and* $D \in \Re$ *is a constant, namely, the diffusion coefficient.*

There is a unique solution $u(x, t)$ of the partial differential equation (1).

Proof Let $u_1(x, t)$ and $u_2(x, t)$ be continuous functions in $[0, L] \times [0, +\infty)$ that have continuous partial derivatives in $[0, L] \times [0, +\infty)$ and are solutions of (1).
Suppose that $u_1(x, t)$ and $u_2(x, t)$ also satisfy in $x = 0$ and $x = L$ the Dirichlet, Neumann or Robin boundary conditions. In order to treat all possibilities in the same argument, it will not be specified what condition is fixed on each end of the range.
We consider $z(x, t) = u_1(x, t) - u_2(x, t)$ and define a function $E(t)$ such that

$$E(t) = \int_0^L z(x, t)^2 \, \mathrm{d}x.$$

One can note that

$$\frac{\mathrm{d}E}{\mathrm{d}t} = E'(t) = 2 \int_0^L z(x, t) z_t(x, t) \, \mathrm{d}x = 2D^2 \int_0^L z(x, t) z_{xx}(x, t) \, \mathrm{d}x.$$

Integrating by parts the integral on the right-hand side of the last equality, one can obtain

$$E'(t) = -2D^2 \int_0^L z_x(x, t)^2 \, \mathrm{d}x + 2D^2 \left[z(x, t), z_x(x, t) \right]_{x=0}^{x=L}.$$

Fixing at $x = 0$ and $x = L$ any of the boundary conditions considered (even different types at each end of the range), one obtains

$$\left[z(x, t), z_x(x, t) \right]_{x=0}^{x=L} \leq 0,$$

so that $E'(t) = 0$ for all $t > 0$. Therefore, $E(t) \leq E(0) = 0$ allowing to conclude that $z(x, t) \equiv 0$, for all $t > 0$.

Consequently, the solution obtained from (1) is unique. □

3 Basic model and problem statement

We are not trying to modify the well-known models of oncological processes. Our goal is to study the stability of a stationary solution in the diffusion model considered in [11]. We briefly describe this model, following [11]. The model under consideration contains three kinds of cells: tumor cells, normal cells and dead cells. Assume that there is no apoptosis in tumor cells. In the absence of tumor cells, normal cells multiply according to the logistic law. During growth, tumor cells, releasing toxic substances [23,25], have an inhibitory effect on normal cells. In turn, dead cells provide inhibiting effect on normal and tumor cells. The spread of tumor and normal cells in space occurs due to diffusion [22–26]. Dead cells are motionless. Over time, only dead cells remain in the area of tumor cells in a solid tumor [23,26]. The tissue of the resulting structure is considered to be low compressible. Therefore, the concentration of normal cells in the absence of tumor and dead cells and the concentration of dead cells in the absence of tumor and normal cells should be the same. Below, this limit concentration is

assumed to be equal to one. The mathematical model is based on the fundamental principles of mathematical population biology [12–20,31–39]. Let u_1 be the linear density of tumor cells, u_2 be the linear density of normal cells and u_3 be the linear density of dead cells. Tumor growth occurs on a segment of length l. Taking into account the above notation, the system of differential equations describing the dynamics of three types of cells has the form :

$$\begin{aligned}\frac{\partial u_1}{\partial t} &= D_1\frac{\partial^2 u_1}{\partial x^2} + \mu_1 u_1 - \mu_1 u_1 u_3 - \gamma_1 u_1 u_3,\\ \frac{\partial u_2}{\partial t} &= D_2\frac{\partial^2 u_2}{\partial x^2} + \mu_2 u_2(1-u_2) - \mu_2 u_2 u_3 - \gamma_2 u_1 u_2,\\ \frac{\partial u_3}{\partial t} &= (\gamma_2 u_1 u_2 + \gamma_1 u_1 u_3 + \gamma_3 u_2 u_3)(1-u_3).\end{aligned} \tag{2}$$

In the first equation, $\mu_1 u_1$ is the rate of self-growth of tumor cells, $\gamma_1 u_1 u_3$ is the rate of inhibition of tumor cells by dead cells, and $\mu_1 u_1 u_3$ is the rate of displacement of tumor cells by dead cells. In the second equation, $\mu_2 u_2(1-u_2)$ is the rate of change in the number of normal cells, $\gamma_2 u_1 u_2$ is the rate of inhibition of normal cells by tumor cells , $\gamma_2 u_2 u_3$ is the rate of inhibition of normal cells by dead cells, and $\mu_2 u_2 u_3$ is the rate of displacement of normal cells by dead cells. In the third equation, the rate of increase in the density of dead cells is proportional to $(\gamma_2 u_1 u_2 + \gamma_1 u_1 u_3 + \gamma_3 u_2 u_3)(1-u_3)$, and the factor $(1-u_3)$ reflects the fact that the more the functional space is occupied by dead cells, the slower it occurs. The positive constants $\mu_1,\ \mu_2,\ \gamma_1,\ \gamma_2,\ \gamma_3$ characterize the reaction rates, and D_1 and D_2 are the diffusion coefficients of tumor cells and normal cells, respectively. The boundary conditions have the form:

$$\left.\frac{\partial u_1}{\partial x}\right|_{x=0} = 0,\quad \left.\frac{\partial u_2}{\partial x}\right|_{x=0} = 0,\quad \left.\frac{\partial u_3}{\partial x}\right|_{x=0} = 0, \tag{3}$$

$$\left.\frac{\partial u_1}{\partial x}\right|_{x=l} = 0,\quad \left.\frac{\partial u_2}{\partial x}\right|_{x=l} = 0,\quad \left.\frac{\partial u_3}{\partial x}\right|_{x=l} = 0. \tag{4}$$

These boundary conditions assume that free cell growth occurs at the boundaries of the segment.

In order to study the stability of a stationary solution of system (2)–(4), namely, the solution (v_1, v_2, v_3) of the system, one can write

$$\begin{aligned}D_1\frac{\partial^2 v_1}{\partial x^2} + \mu_1 v_1 - \mu_1 v_1 v_3 - \gamma_1 v_1 v_3 = 0,\\ D_2\frac{\partial^2 v_2}{\partial x^2} + \mu_2 v_2(1-v_2) - \mu_2 v_2 v_3 - \gamma_2 v_1 v_2 = 0,\\ (\gamma_2 v_1 v_2 + \gamma_1 v_1 v_3 + \gamma_3 v_2 v_3)(1-v_3) = 0,\end{aligned} \tag{5}$$

with boundary conditions

$$\left.\frac{\partial v_1}{\partial x}\right|_{x=0} = 0,\quad \left.\frac{\partial v_2}{\partial x}\right|_{x=0} = 0,\quad \left.\frac{\partial v_3}{\partial x}\right|_{x=0} = 0, \tag{6}$$

$$\left.\frac{\partial v_1}{\partial x}\right|_{x=l} = 0,\quad \left.\frac{\partial v_2}{\partial x}\right|_{x=l} = 0,\quad \left.\frac{\partial v_3}{\partial x}\right|_{x=l} = 0. \tag{7}$$

4 Stability of a stationary solution

Let $v = (v_1, v_2, v_3)$ be a stationary solution of system (2)–(4), that is, the solution of system (5)–(7). Let $z_j = u_j - v_j,\ j = 1, 2, 3$. We derive the equations for each of the deviations z_j, multiply the resulting equality by z_j and integrate over the segment $[0, l]$.

From the first equation of system (2), we have:

$$\frac{\partial u_1}{\partial t} = \frac{\partial z_1}{\partial t} = D_1 \frac{\partial^2 (v_1 + z_1)}{\partial x^2} + \mu_1 (v_1 + z_1) - \mu_1 (v_1 + + z_1)(v_3 + z_3) - \gamma_1 (v_1 + + z_1)(v_3 + z_3).$$

Opening the brackets, we get

$$\frac{\partial z_1}{\partial t} = D_1 \frac{\partial^2 z_1}{\partial x^2} + \mu_1 z_1 - \mu_1 z_1 z_3 - \gamma_1 z_1 z_3 - \mu_1 v_1 z_3 - \mu_1 v_3 z_1 - \gamma_1 v_1 z_3 - \gamma_1 v_3 z_1 + D_1 \frac{\partial^2 v_1}{\partial x^2} + \mu_1 v_1 - \mu_1 v_1 v_3 - \gamma_1 v_1 v_3.$$

Due to the fact that $v = (v_1, v_2, v_3)$ is the solution of system (5), the sum of the last four terms on the right side of the last equality is equal to zero. Therefore, we obtain

$$\frac{\partial z_1}{\partial t} = D_1 \frac{\partial^2 z_1}{\partial x^2} + \mu_1 z_1 - \mu_1 z_1 z_3 - \gamma_1 z_1 z_3 - \mu_1 v_1 z_3 - \mu_1 v_3 z_1 - \gamma_1 v_1 z_3 - \gamma_1 v_3 z_1. \tag{8}$$

Multiplying equality (8) by z_1, we get

$$\frac{1}{2} \frac{\partial}{\partial t} (z_1^2) = D_1 \frac{\partial^2 z_1}{\partial x^2} z_1 + \mu_1 z_1^2 - \mu_1 z_1^2 z_3 - \gamma_1 z_1^2 z_3 - \mu_1 v_1 z_1 z_3 - \mu_1 v_3 z_1^2 - \gamma_1 v_1 z_1 z_3 - \gamma_1 v_3 z_1^2.$$

Considering the deviations z_j to be small enough, we discard the monomials of the variables (z_1, z_2, z_3) that have a degree higher than two in the obtained equality. Then the last equality is converted to the form

$$\frac{1}{2} \frac{\partial}{\partial t} (z_1^2) = D_1 \frac{\partial^2 z_1}{\partial x^2} z_1 + \mu_1 z_1^2 - \mu_1 v_1 z_1 z_3 - \mu_1 v_3 z_1^2 - \gamma_1 v_1 z_1 z_3 - \gamma_1 v_3 z_1^2.$$

We integrate the obtained equality over the segment $[0, l]$ and obtain

$$\frac{1}{2} \int_0^l \frac{\partial}{\partial t} (z_1^2)\, \mathrm{d}x = D_1 \int_0^l \frac{\partial^2 z_1}{\partial x^2} z_1\, \mathrm{d}x + \mu_1 \int_0^l z_1^2\, \mathrm{d}x - \mu_1 \int_0^l v_1 z_1 z_3\, \mathrm{d}x - \mu_1 \int_0^l v_3 z_1^2\, \mathrm{d}x - \gamma_1 \int_0^l v_1 z_1 z_3\, \mathrm{d}x - \gamma_1 \int_0^l v_3 z_1^2\, \mathrm{d}x.$$

We integrate by parts the first integral on the right-hand side of the last equality. Taking into account the boundary conditions, we obtain

$$\begin{aligned}\frac{1}{2}\frac{\partial}{\partial t}\int_0^l z_1^2\,\mathrm{d}x = &-D_1\int_0^l\left(\frac{\partial z_1}{\partial x}\right)^2\mathrm{d}x+\mu_1\int_0^l z_1^2\,\mathrm{d}x\\ &-\mu_1\int_0^l v_1z_1z_3\,\mathrm{d}x-\mu_1\int_0^l v_3z_1^2\,\mathrm{d}x\\ &-\gamma_1\int_0^l v_1z_1z_3\,\mathrm{d}x-\gamma_1\int_0^l v_3z_1^2\,\mathrm{d}x.\end{aligned}\tag{9}$$

Similarly, we transform the second equation:

$$\begin{aligned}\frac{1}{2}\frac{\partial}{\partial t}\int_0^l z_2^2\,\mathrm{d}x = &-D_2\int_0^l\left(\frac{\partial z_2}{\partial x}\right)^2\mathrm{d}x+\mu_2\int_0^l(1-2v_2)z_2^2\,\mathrm{d}x\\ &-\mu_2\int_0^l v_2z_2z_3\,\mathrm{d}x-\mu_2\int_0^l v_3z_2^2\,\mathrm{d}x\\ &-\gamma_2\int_0^l v_1z_2^2\,\mathrm{d}x-\gamma_2\int_0^l v_2z_1z_2\,\mathrm{d}x.\end{aligned}\tag{10}$$

And in the same way, we convert the third equation:

$$\begin{aligned}\frac{1}{2}\frac{\partial}{\partial t}\int_0^l z_3^2\,\mathrm{d}x = &\int_0^l(\gamma_2v_2+\gamma_1v_3-\gamma_2v_2v_3-\gamma_1v_3^2)z_1z_3\,\mathrm{d}x\\ &+\int_0^l(\gamma_2v_1+\gamma_3v_3-\gamma_2v_1v_3-\gamma_3v_3^2)z_2z_3\,\mathrm{d}x\\ &+\int_0^l(\gamma_1v_1+\gamma_3v_2-\gamma_2v_1v_2-2\gamma_1v_1v_3-2\gamma_3v_2v_3)z_3^2\,\mathrm{d}x.\end{aligned}\tag{11}$$

Adding equalities (9)–(11), we get

$$\begin{aligned}\frac{1}{2}\frac{\partial}{\partial t}\int_0^l|z|^2\,\mathrm{d}x = &-D_1\int_0^l\left(\frac{\partial z_1}{\partial x}\right)^2\mathrm{d}x-D_2\int_0^l\left(\frac{\partial z_2}{\partial x}\right)^2\mathrm{d}x\\ &+\int_0^l(b_{11}z_1^2+2b_{12}z_1z_2+2b_{13}z_1z_3\\ &+b_{22}z_2^2+2b_{23}z_2z_3+b_{33}z_3^2)\,\mathrm{d}x,\end{aligned}\tag{12}$$

where

$$|z|^2 = z_1^2 + z_2^2 + z_3^2,$$

$$b_{11} = \mu_1 - \mu_1 v_3 - \gamma_1 v_3, \tag{13}$$

$$b_{12} = b_{21} = -\frac{1}{2}\gamma_2 v_2, \tag{14}$$

$$b_{13} = b_{31} = \frac{1}{2}(\gamma_2 v_2 + \gamma_1 v_3 - \gamma_2 v_2 v_3 - \gamma_1 v_3^2 - \mu_1 v_1 - \gamma_1 v_1), \tag{15}$$

$$b_{23} = b_{32} = \frac{1}{2}(\gamma_2 v_1 + \gamma_3 v_3 - \gamma_2 v_1 v_3 - \gamma_3 v_3^2 - \mu_2 v_2), \tag{16}$$

$$b_{22} = \mu_2 - 2\mu_2 v_2 - \mu_2 v_3 - \gamma_2 v_1, \tag{17}$$

$$b_{33} = \gamma_1 v_1 + \gamma_3 v_2 - \gamma_2 v_1 v_2 - 2\gamma_1 v_1 v_3 - 2\gamma_3 v_2 v_3. \tag{18}$$

We are interested in the sign of the expression defined by formula (12). More precisely, we want to establish sufficient conditions for this expression to be negative. Undoubtedly, negative definiteness of the quadratic form

$$\sum_{k=1}^{3}\sum_{j=1}^{3} b_{kj}\,\xi_k\,\xi_j \tag{19}$$

will be this sufficient condition. But there is still a reserve for refinement of sufficient conditions. We will use the method applied in [40]. We will apply the one-dimensional version of the Steklov–Poincare–Friedrichs equality [41–44] to the integrals of the squares of derivatives on the right-hand side of equality (12). Moreover, we prefer to reproduce here the derivation of this inequality in order to clarify the multiplicative "constant," which does not depend on the function included in the inequality, but depends on the length of the segment l, which may turn out to be important. Thus, using the Cauchy–Bunyakovsky–Schwartz inequality, we have

$$\int_0^l y^2\,\mathrm{d}x = \int_0^l \left(\int_0^x 1\cdot\frac{\mathrm{d}y}{\mathrm{d}t}\mathrm{d}t\right)^2 \mathrm{d}x \le \int_0^l \left(\int_0^x 1^2\,\mathrm{d}t \cdot \int_0^x \left(\frac{\mathrm{d}y}{\mathrm{d}t}\right)^2 \mathrm{d}t\right)\mathrm{d}x.$$

It is easily shown that

$$\int_0^l \left(\int_0^x 1^2\,\mathrm{d}t \cdot \int_0^x \left(\frac{\mathrm{d}y}{\mathrm{d}t}\right)^2 \mathrm{d}t\right)\mathrm{d}x = \int_0^l \left(x \cdot \int_0^x \left(\frac{\mathrm{d}y}{\mathrm{d}t}\right)^2 \mathrm{d}t\right)\mathrm{d}x$$
$$\le \int_0^l x\,\mathrm{d}x \int_0^l \left(\frac{\mathrm{d}y}{\mathrm{d}t}\right)^2 \mathrm{d}t = \frac{l^2}{2}\int_0^l \left(\frac{\mathrm{d}y}{\mathrm{d}x}\right)^2 \mathrm{d}x.$$

Therefore, we finally have

$$\int_0^l y^2\,\mathrm{d}x \le \frac{l^2}{2}\int_0^l \left(\frac{\mathrm{d}y}{\mathrm{d}x}\right)^2 \mathrm{d}x. \tag{20}$$

This is the one-dimensional Steklov–Poincare–Friedrichs inequality. From equality (12), we obtain, taking into account (20), the following inequality:

$$\frac{1}{2}\frac{\partial}{\partial t}\int_0^l |z|^2\,\mathrm{d}x \le \int_0^l (a_{11}z_1^2 + 2a_{12}z_1z_2 + 2a_{13}z_1z_3 + a_{22}z_2^2 + 2a_{23}z_2z_3 + a_{33}z_3^2)\,\mathrm{d}x, \tag{21}$$

where

$$a_{11} = \mu_1 - \mu_1 v_3 - \gamma_1 v_3 - \frac{2D_1}{l^2}, \tag{22}$$

$$a_{12} = a_{21} = -\frac{1}{2}\gamma_2 v_2, \tag{23}$$

$$a_{13} = a_{31} = \frac{1}{2}(\gamma_2 v_2 + \gamma_1 v_3 - \gamma_2 v_2 v_3 - \gamma_1 v_3^2 - \mu_1 v_1 - \gamma_1 v_1), \tag{24}$$

$$a_{23} = a_{32} = \frac{1}{2}(\gamma_2 v_1 + \gamma_3 v_3 - \gamma_2 v_1 v_3 - \gamma_3 v_3^2 - \mu_2 v_2), \tag{25}$$

$$a_{22} = \mu_2 - 2\mu_2 v_2 - \mu_2 v_3 - \gamma_2 v_1 - \frac{2D_2}{l^2}, \tag{26}$$

$$a_{33} = \gamma_1 v_1 + \gamma_3 v_2 - \gamma_2 v_1 v_2 - 2\gamma_1 v_1 v_3 - 2\gamma_3 v_2 v_3. \tag{27}$$

A refined sufficient condition for a stationary solution to be asymptotically stable is that the quadratic form

$$\sum_{k=1}^{3}\sum_{j=1}^{3} a_{kj}\,\xi_k\,\xi_j \tag{28}$$

be negatively defined. Of course, the verification of this condition, although somewhat cumbersome, is still quite realizable, especially with the help of a computer.

5 Model without tumor cells and dead cells

Let us give a simpler example of using the technique described above. In the absence of tumor and dead cells, the equation for the growth of the number of normal cells follows from the second equation in system (2)

$$\frac{\partial u_2}{\partial t} = D_2\frac{\partial^2 u_2}{\partial x^2} + \mu_2 u_2(1 - u_2). \tag{29}$$

In this model, it is assumed that the rate of their birth is equal to $\mu_2 u_2$ and the rate of their death is equal to $\mu_2 u_2^2$.

Let v_2 be a stationary solution of Eq. (29) that is the solution of the equation

$$D_2\frac{\partial^2 v_2}{\partial x^2} + \mu_2 v_2(1 - v_2) = 0. \tag{30}$$

Following the plan already worked out above, we substitute the representation $z_2 = u_2 - v_2$ to Eq. (29). As a result, we get the following equality

$$\frac{\partial z_2}{\partial t} = D_2\frac{\partial^2 z_2}{\partial x^2} + \mu_2 z_2(1 - 2v_2) - \mu_2 z_2^2 + D_2\frac{\partial^2 v_2}{\partial x^2} + \mu_2 v_2(1 - v_2),$$

or, taking into account (30),

$$\frac{\partial z_2}{\partial t} = D_2 \frac{\partial^2 z_2}{\partial x^2} + \mu_2 z_2 (1 - 2v_2) - \mu_2 z_2^2.$$

We multiply this equality by z_2 and integrate the resulting equality over the segment $[0, l]$. After integration by parts, we obtain

$$\frac{1}{2}\frac{\partial}{\partial t}\int_0^l z_2^2 \, \mathrm{d}x = -D_2 \int_0^l \left(\frac{\partial z_2}{\partial x}\right)^2 \mathrm{d}x + \mu_2 \int_0^l (1 - 2v_2) z_2^2 \, \mathrm{d}x - \mu_2 \int_0^l z_2^3 \, \mathrm{d}x. \quad (31)$$

Applying the Steklov–Poincare–Friedrichs inequality (20), we get

$$\frac{1}{2}\frac{\partial}{\partial t}\int_0^l z_2^2 \, \mathrm{d}x \le \int_0^l \left(\mu_2(1 - 2v_2) - \frac{2D_2}{l^2}\right) z_2^2 \, \mathrm{d}x - \mu_2 \int_0^l z_2^3 \, \mathrm{d}x. \quad (32)$$

Taking advantage of the fact that the calculations here, unlike the general case, will not be very cumbersome, we show on what basis we can discard the integral from z_2^3. Indeed, if the deviation z_2 is small enough, the following inequality will be executed

$$\left|\mu_2 \int_0^l z_2^3 \, \mathrm{d}x\right| < \frac{1}{2}\left|\int_0^l \left(\mu_2(1 - 2v_2) - \frac{2D_2}{l^2}\right) z_2^2 \, \mathrm{d}x\right|,$$

and therefore, for such deviations, the sign of the right-hand side of inequality (32) coincides with the sign of the first term. Hence, it follows that the inequality

$$\mu_2(1 - 2v_2) - \frac{2D_2}{l^2} < 0 \quad (33)$$

is a sufficient condition for the asymptotic stability of a stationary solution to Eq. (29).

Under boundary conditions (3), (4), solutions $v_2 = 0$ and $v_2 = 1$ satisfy Eq. (29). In the paper [11], it is indicated that the first solution will be unstable and the second solution will be sustainable. Taking into account condition (33), we can clarify this thesis somewhat. The solution $v_2 = 0$ may turn out to be stable under the condition

$$\mu_2 - \frac{2D_2}{l^2} < 0. \quad (34)$$

This is the effect of transition from a point model to a diffusion model. In other words, we observe the effect of switching to the model as a system with distributed parameters from a model with focused parameters.

Equation (29) has been known for a long time. In 1921, G. Hotelling proposed a model of population growth and its spatial distribution. Growth was modeled on the basis of Verhulst's principles as a logistic process, while the source of construction of migration processes in space was the Fourier theory of heat distribution. The concept of saturated population density was introduced. So if the real population density was higher than saturated one, the population decreased, and if the real population density was lower than saturated one, then the population increased. Justification for spatial diffusion was based on the fact that per capita output population reduced with increasing population (labor force); then, there was a decrease in income, and people were leaving from more populated places for less populated ones.

Denoting the population by $p = p(x, y, t)$ and the coefficient of its density by s, we obtain the equation (see [45]):

$$\frac{\partial p}{\partial t} = A(s - p)p + B\Delta p, \tag{35}$$

where A and B are two constants representing, respectively, the growth rate and the spread rate. The time is indicated by t, and x, y are spatial coordinates.

We also note that the above calculations are the development of the method presented in the work [40], and this section simply retells this work, in which condition (33) weakens the condition

$$s - 2p_0 < 0.$$

Puu [45] proved that the last condition was a sufficient condition for the stability of a stationary solution to Eq. (35). In our case, due to the transition to dimensionless variables, $s = 1$. By the way, the zero solution does not satisfy T. Puu's condition. However, we have seen that this does not mean that it is unstable. It is unknown whether the sufficient condition for the stability of the stationary solution can be weakened further.

In the paper [46], the methods of the work [40] were applied to a more complex equation, also considered in [45].

6 Immune response model

In this section, we will study the stability of a stationary solution in the immune response model [11]. Here, we consider a model with a homogeneous population of tumor cells, focusing only on their interaction with lymphocytes.

6.1 Problem statement and stability

At the initial stage of the growth of tumor cells, the immune system in some types of tumors recognizes tumor cells, and lymphocytes begin to destroy them [23,25,27]. Let $q = q(x, t)$ be a linear density of lymphocytes. Then the mathematical model describing the interaction of tumor cells and lymphocytes, assuming the absence of interaction with normal and dead cells, has the form

$$\begin{aligned} \frac{\partial u_1}{\partial t} &= D_1 \frac{\partial^2 u_1}{\partial x^2} + \mu_1 u_1 - \gamma_{12} u_1 q, \\ \frac{\partial q}{\partial t} &= D_4 \frac{\partial^2 q}{\partial x^2} - v \frac{\partial q}{\partial x} - \gamma_{21} u_1 q. \end{aligned} \tag{36}$$

In the first equation, $\gamma_{12} u_1 q$ is the rate of destruction of tumor cells by lymphocytes, in the second equation $\gamma_{21} u_1 q$ is the rate of death of lymphocytes on contact with tumor cells, D_1 is the diffusion coefficient of tumor cells, D_4 is the diffusion coefficient of lymphocytes, γ_{12}, γ_{21} are constants characterizing the interaction of tumor cells and lymphocytes, and v is the rate of lymphocyte migration to the area of accumulation of tumor cells. It is assumed that in the absence of tumor cells, the system is in a stationary state and its concentration of lymphocytes is equal to q^0. Tumor cells appear at the point $x = x_0$. Under these assumptions, the following conditions are taken as initial conditions:

$$u_1(x, 0) = u_1^0 \delta(x_0), \quad q(x, 0) = q^0.$$

We transfer from the model with the point occurrence of tumor cells to the model that assumes their smooth distribution at the initial time. Then we obtain initial conditions of the form

$$u_1(x,0) = u_1^0(x) \in C^\infty([0,l]), \quad q(x,0) = q^0. \tag{37}$$

When we select boundary conditions, it is assumed that

$$\left.\frac{\partial u_1}{\partial x}\right|_{x=0} = 0, \quad \left. q \right|_{x=0} = q^0, \tag{38}$$

$$\left.\frac{\partial u_1}{\partial x}\right|_{x=l} = 0, \quad \left. q \right|_{x=l} = q^0. \tag{39}$$

Let us study the stability of a stationary solution of system (36)–(39), that is, the solution (w_1, w_2) of the system

$$\begin{aligned} D_1 \frac{\partial^2 w_1}{\partial x^2} + \mu_1 w_1 - \gamma_{12} w_1 w_2 = 0, \\ D_4 \frac{\partial^2 w_2}{\partial x^2} - v \frac{\partial w_2}{\partial x} - \gamma_{21} w_1 w_2 = 0, \end{aligned} \tag{40}$$

with the boundary conditions

$$\left.\frac{\partial w_1}{\partial x}\right|_{x=0} = 0, \quad \left. w_2 \right|_{x=0} = q^0, \tag{41}$$

$$\left.\frac{\partial w_1}{\partial x}\right|_{x=l} = 0, \quad \left. w_2 \right|_{x=l} = q^0. \tag{42}$$

Let $w = (w_1, w_2)$ be a stationary solution of system (36)–(39), that is, the solution of system (40)–(42). Let $z_1 = u_1 - w_1, \ z_2 = q - w_2$.

Let

$$\alpha_{11} = \mu_1 - \gamma_{12} w_2 - 2D_1/l^2, \tag{43}$$

$$\alpha_{12} = \alpha_{21} = -\frac{1}{2}(\gamma_{12} w_1 + \gamma_{21} w_2 \exp(-\sigma x)), \tag{44}$$

$$\alpha_{22} = -\exp(-\sigma x)\gamma_{21} w_1 - \frac{\sigma^2 D_4}{\exp(\sigma l) - 1 - l\sigma}. \tag{45}$$

We can use the same estimation method as above. Now a refined sufficient condition for a stationary solution to be asymptotically stable is that the quadratic form

$$\sum_{k=1}^{2} \sum_{j=1}^{2} \alpha_{kj}\, \xi_k\, \xi_j \tag{46}$$

be negatively defined. This condition is equivalent to the system of two conditions

$$\mu_1 - \gamma_{12} w_2 - 2D_1/l^2 < 0, \tag{47}$$

$$\begin{aligned} &4\left(\mu_1 - \gamma_{12} w_2 - 2D_1/l^2\right)\left(-\exp(-\sigma x)\gamma_{21} w_1 - \frac{\sigma^2 D_4}{\exp(\sigma l) - 1 - l\sigma}\right) \\ &\quad - \left(\gamma_{12} w_1 + \exp(\sigma l)\gamma_{21} w_2\right)^2 > 0. \end{aligned} \tag{48}$$

Let us note an important circumstance that distinguishes the considered diffusion model of the immune response from its point analog. If we formally go to a point model from

model (36), discarding the diffusion and convective terms, we obtain the system of ordinary differential equations

$$\begin{aligned} \frac{\mathrm{d}u_1}{\mathrm{d}t} &= \mu_1 u_1 - \gamma_{12} u_1 q, \\ \frac{\mathrm{d}q}{\mathrm{d}t} &= -\gamma_{21} u_1 q. \end{aligned} \tag{49}$$

Obviously, the vector function with coordinates $u_1 = 0, q = 0$ is an unstable stationary solution of system (49). However, this vector function can also be a stable stationary solution of system (36) under condition

$$\mu_1 - 2D_1/l^2 < 0. \tag{50}$$

Condition (48) for the zero solution turns out to be superfluous, since it becomes a consequence of condition (50).

6.2 Numerical simulations

In order to visualize the dynamics of the immunological system and tumor populations, including some possible stable states, the system given by Eq. (36) is numerically simulated. All simulations took into consideration the domain $0 < x < 1$, with boundary conditions given by Eqs. (38) and (39) and initial conditions given by Eq. 37.

The initial state for the population density of lymphocytes was chosen as $q^0 = 1$, implying a maximum density of the immunological cells equality distributed along x at instant $t = 0$. Two different initial conditions for the tumor cells population density were put forward. The initial condition A states that there are tumor cells over all x, but their maximum ($u_1^0 = 1$) is at the center $x = 0.5$ and minimum at the limits of the domain. It is modeled by a periodic function given by $u_1^0(x) = \sin(\pi x)$. On the other hand, condition B states that the tumor cells density is highly concentrated around $x = 0.5$, with no cells outside of the segment $0.45 \leq x \leq 0.55$. It is modeled by an impulse function with maximum $u_1^0 = 1$.

The initial condition A could describe a tumor that actually is quite scattered since it has cells across all considered domain, but has a maximum population density at a certain point. Diffuse tumors, such as brain tumors, may be loosely classified with this description. On the other hand, the initial condition B refers to a very compact and dense tumor that has its extremities close to its maximum cell concentration. Several types of carcinoma can play that role.

The simulation parameters were chosen arbitrarily allowing the visualization of different interesting scenarios pertaining the investigated tumor. Parameters for the stable scenarios have been obtained by means of the stability condition given by Eq. (50), while the other scenarios have obtained by carefully changing these parameters around each other in an empirical way. We herein assume that we are dealing with dimensionless values and that parameters respect their physical meanings and magnitudes of time and space domains. The parameters used in all simulations are listed in Tables 1 and 2 for cases using conditions A and B, respectively.

It is important to consider that although the adopted parameters respect the physics and internal logics of the studied system, they do not necessarily have an individual biological meaning according to the proposed interpretation for each scenario, since they were not measured or estimated directly. In fact, in order to explore a meaning in respect of each parameter, a precisely conducted work of comparison and validation of the studied model

Table 1 Parameters and description for numerical simulations of system (36) with initial condition as a periodic distribution of tumor cells ($u_1^0(x) = \sin(\pi x)$)

Cases (with initial condition A)	D_1	D_4	μ_1	v	γ_{12}	γ_{21}
1A: Lymphocytes overcome tumor cells (stable)	0.0050	0.0050	0.0100	0.2000	1.0000	1.0000
2A: Tumor cells overcome lymphocytes (unstable)	0.0100	0.0100	0.2000	0.0100	1.0000	3.0000
3A: Tumor cells' quiescence (stable)	0.0050	0.0050	0.0100	0.0100	0.0700	2.0600

Table 2 Parameters and description for numerical simulations of system (36) with initial condition an impulse function for the distribution of tumor cells ($u_1^0(x) = 1$ for $0.45 \leq x \leq 0.55$ and $u_1^0(x) = 0$ elsewhere)

Cases (with initial condition B)	D_1	D_4	μ_1	v	γ_{12}	γ_{21}
1B: Lymphocytes overcome tumor cells (stable)	0.0050	0.0050	0.0100	0.2000	0.7500	1.0000
2B: Tumor cells overcome lymphocytes (unstable)	0.0050	0.0050	0.3500	0.0100	0.5000	5.0000
3B: Tumor cells' quiescence (stable)	0.0080	0.0050	0.0150	0.0100	0.0243	1.2500

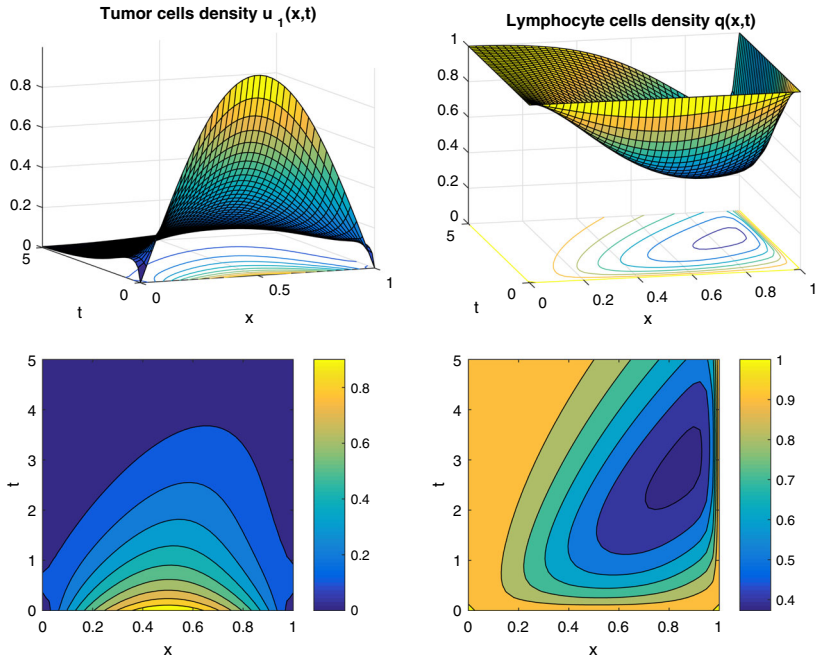

Fig. 1 Case 1A—Lymphocytes overcome tumor cells (periodic initial condition)

would be required. Regardless, although hypothetical, the following virtualized scenarios and their respective interpretations are plausible and compatible to oncology phenomena.

Cases 1A and 1B describe the scenario in which the immunological system prevails against tumor cells after a sufficient amount of time has passed, yielding a stable solution $u_1 = 0$ and $q = 1$. Figures 1 and 2 illustrate the results of the numerical simulation for this case. In

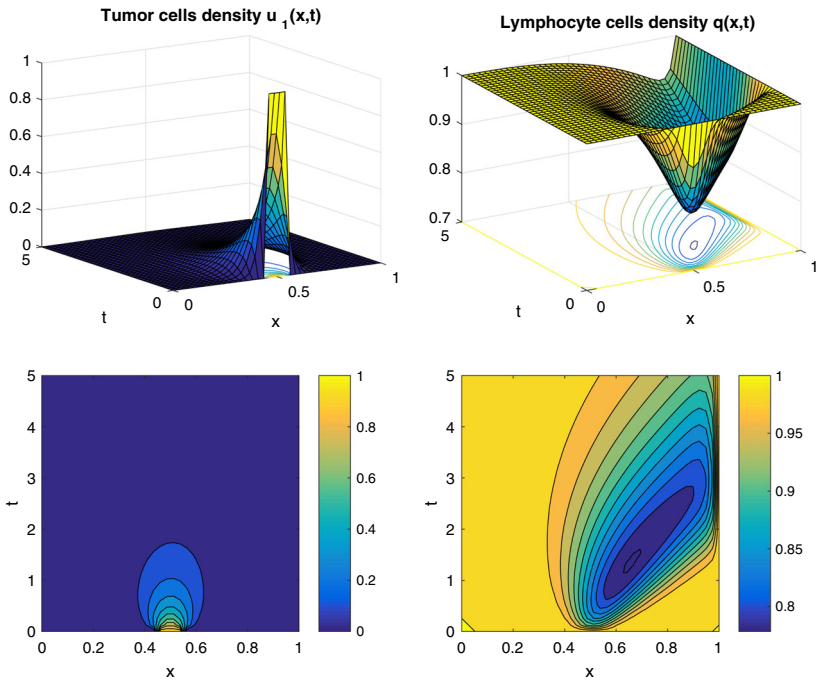

Fig. 2 Case 1B—Lymphocytes overcome tumor cells (impulse initial condition)

that scenario, the lymphocytes are strong enough to kill the tumor cells, gradually decreasing their population density as time passes and restoring their reservoir capacity afterward. One can note that both initial conditions yield very similar results, but in Case 1B the tumor cells are eliminated more quickly due to a reduced total amount of cancerous cells present in the impulse initial condition.

Cases 2A and 2B picture the scenario where the tumor cells growth rate μ_1 and rate of destruction over the lymphocytes γ_{21} are much higher than in the first case. Such change yields an unstable result as the immune cells population is degraded and the tumor cells grow unchecked after some time has passed, as presented in Figs. 3 and 4. In this scenario, the parameter regarding velocity of lymphocytes (v) was purposely kept lower than in the previous case so one can notice the difference between the transport of immune cells being dominated by either convection (Case 1) or diffusion (Case 2).

Cases 3A and 3B present a very interesting scenario in which tumor and immune cells reach an equilibrium, in which their population densities remain constant and nonzero after a sufficient amount of time has passed. Following the stability conditions previously discussed, this case yields a stable result for system (36) that is different from $u_1 = 0$ and $q = 1$, as shown in Figs. 5 and 6. Additionally, comparing Cases 3A and 3B, it is noticeable that the stable levels of tumor cell density are much lower in the latter, which is a trend present on the other cases. This might comparatively suggest that tumors whose cells are more densely concentrated could be treated by the immune system more effectively.

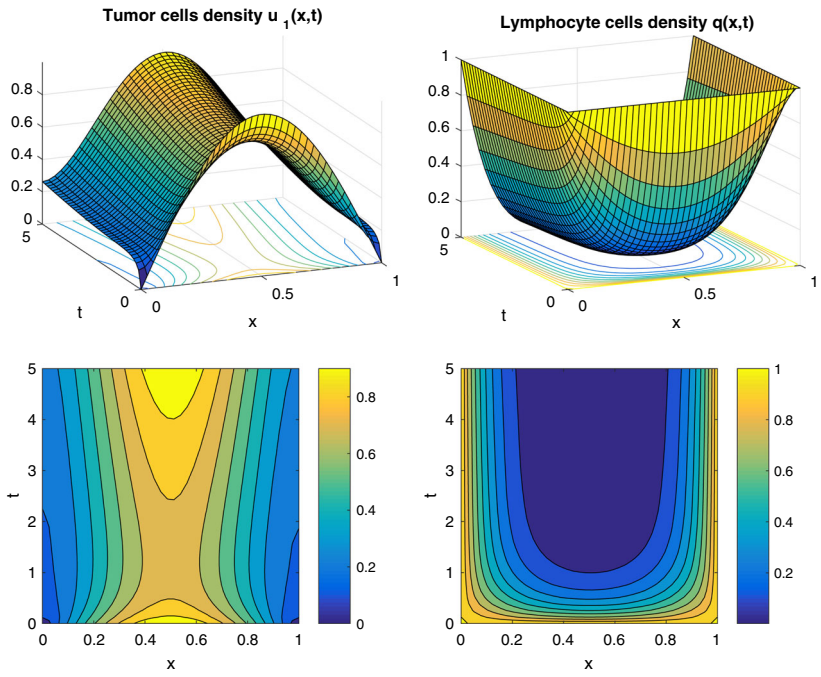

Fig. 3 Case 2A—Tumor cells overcome lymphocytes (periodic initial condition)

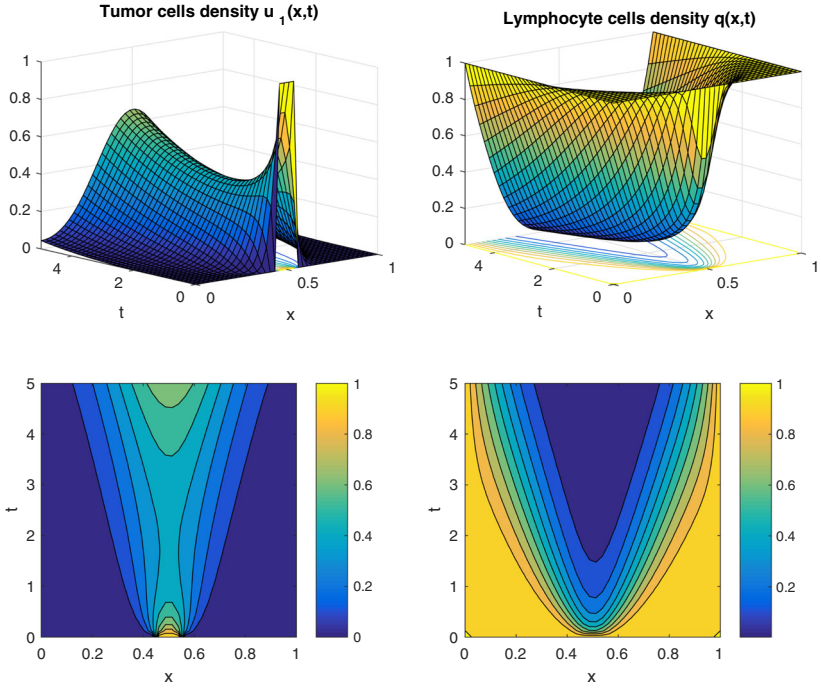

Fig. 4 Case 2B—Tumor cells overcome lymphocytes (impulse initial condition)

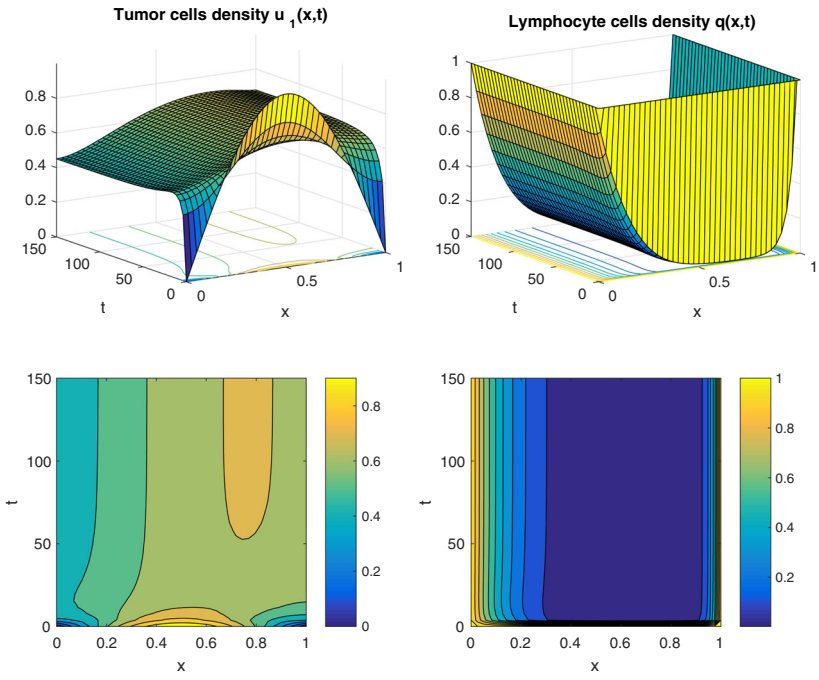

Fig. 5 Case 3A—Quiescence/stability (periodic initial condition)

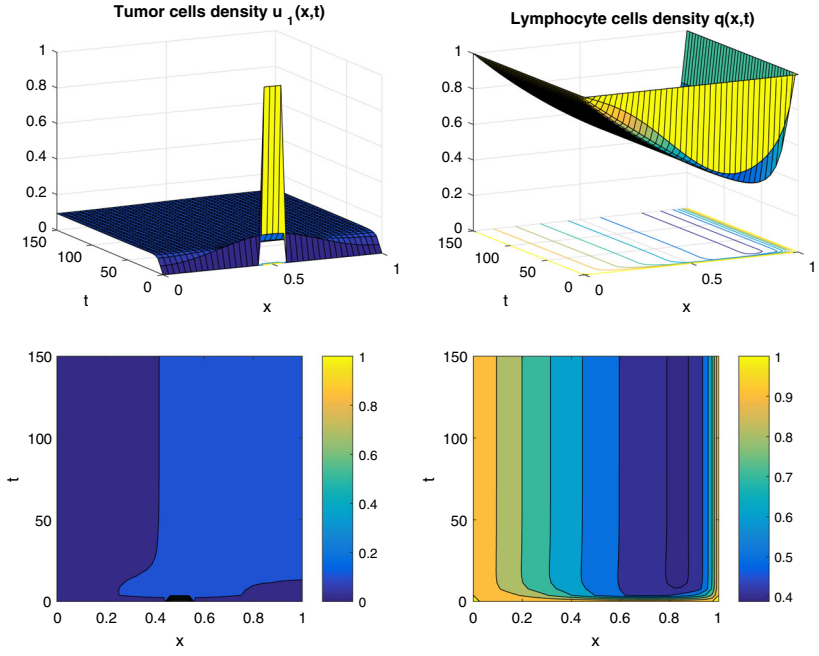

Fig. 6 Case 3B—Quiescence/stability (impulse initial condition)

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