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A SIMPLE MODEL OF CARCINOGENIC MUTATIONS WITH TIME DELAY AND DIFFUSION

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Abstract. In the paper we consider a system of delay differential equations (DDEs) of Lotka-Volterra type with diffusion reflecting mutations from normal to malignant cells. The model essentially follows the idea of Ahangar and Lin (2003) where mutations in three different environmental conditions, namely favorable, competitive and unfavorable, were considered. We focus on the unfavorable conditions that can result from a given treatment, e.g. chemotherapy. Included delay stands for the interactions between benign and other cells. We compare the dynamics of ODEs system, the system with delay and the system with delay and diffusion. We mainly focus on the dynamics when a positive steady state exists. The system which is globally stable in the case without the delay and diffusion is destabilized by increasing delay, and therefore the underlying kinetic dynamics becomes oscillatory due to a Hopf bifurcation for appropriate values of the delay. This suggests the occurrence of spatially non-homogeneous periodic solutions for the system with the delay and diffusion.

1. **Introduction.** Studying of different stages of tumor growth and carcinogenic mutations is one of the most challenging problems in biomedical sciences, while modeling of these processes is a very important topic for applied mathematics at present. It can bring some insight into the medical knowledge, suggests appropriate experiments and/or decreasing their costs, see e.g. [1].

Carcinogenesis is a very complex and still not completely understood process. It is known that tumor is developed from one mutated cell. However, several subsequent mutations are required for transformation from healthy to malignant cells. Therefore, to describe the process of carcinogenesis one needs to consider several different clones of cells, starting from the healthy cells, through benign cells and ending with malignant ones. Thus, interactions between at least three types of cells should be considered. The number of mutations that should be considered depends on the type of tumor. Typically, from 4 to 7 steps are needed, cf. [2], and therefore when modeling using the system of ODEs at least 4 equations are required.

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In this paper, we focus on the analysis of a simple model describing the process of mutations in the framework of the Lotka-Volterra type of interactions between species. As a basis we choose the model proposed in [2] and later studied in [6, 7, 8, 9]. It consist of a system of partial differential equations where it is assumed that cells at the last stage of mutation (i.e. malignant cells) are in the unfavorable environment. Clearly, in the original article two other environmental conditions, that is favorable and competitive, were considered. However, in the case of favorable conditions there is no other possibility than the unbounded tumor growth, and therefore the disease cannot be cured without some external influence, that is a treatment, e.g. by chemotherapy or immunotherapy. On the other hand, unfavorable conditions either mean that immune reaction against the tumor is sufficiently strong, or there is a treatment changing the natural favorable conditions into unfavorable. The analysis performed in [2] is focused on traveling wave solutions. On the other hand, it is obvious that tumors develop in a bounded domain. Thus, the analysis of the system in such domain seems to be more relevant, cf. [6, 7, 8, 9].

In the analysis presented below, we reduce the system of $n+1$ ordinary differential equations with diffusion into only two equations but with time delay. Instead of describing each stage of mutation we approximate this process by appropriate introduction of time delay. Because the dynamics of the system of ODEs corresponding to the model is well know, see e.g. [11], we only recall it and first, we focus on the model with delay and then with delay and diffusion. We should notice that similar type of ODE models are present in population dynamics, biochemical reactions or immune response and clonal selection modeling, compare e.g. [11, 13] and the references therein. It should be also pointed out that some type of delayed Lotka-Volterra models with diffusion was studied previously, cf. e.g [5], where the model with delay in a per capita growth rate and density dependent mortality for predators and similar relations for preys was considered. In the case considered in [5], if the positive steady state exists, then there is always a change of stability with increasing delay, which is the main difference between the dynamics of that model and the model presented in this paper.

1.1. **Model description.** The models proposed in [2] and studied in [9] read

$$\begin{aligned}
\frac{\partial}{\partial s}Y_0 &= Y_0\left(a_0\left(1-\frac{Y_0}{K_0}\right)-\mu_1 Y_1\right)+D_0\Delta Y_0\,,\\
\frac{\partial}{\partial s}Y_j &= Y_j\left(a_j\left(1-\frac{Y_j}{K_j}\right)-\mu_{j+1}Y_{j+1}\right)+\eta_j Y_j Y_{j-1}+D_j\Delta y_j\,, \quad j=1,2,3\ldots,n-1,\\
\frac{\partial}{\partial s}Y_n &= F(Y_{n-1}(t,x),Y_n(t,x))+D_n\Delta Y_n\,,
\end{aligned} \tag{1.1}$$

where the specific function F depends on the environmental conditions of the tumor development. In the case of unfavorable conditions we focus on, this function reads

$$F(u,v)=\eta_n uv-a_n v\,. \tag{1.2}$$

In this paper, we study the dynamics of the simplification of system (1.1). We substitute a multistep mutations described by equations from $j=1$ to $j=n-1$ by a time delay. Thus, the simplified model reads

$$\begin{aligned}
\frac{\partial}{\partial s}Y_0(s,x) &= Y_0(s,x)\left(a_0\left(1-\frac{Y_0(s,x)}{K_0}\right)-\mu_1 Y_1(s,x)\right)+D_0\Delta Y_0(s,x)\,,\\
\frac{\partial}{\partial s}Y_1(s,x) &= -a_1 Y_1(s,x)+\eta_1 Y_0(s-\tau_s,x)Y_1(s-\tau_s,x)+D_1\Delta Y_1(s,x)\,,
\end{aligned} \tag{1.3}$$

where $Y_0(s,x)$ and $Y_1(s,x)$ represent the amount of normal and malignant cells, respectively, at time s and position $x \in \overline{\Omega}$, where $\Omega \subset \mathbb{R}^n$ is an open subset with a smooth boundary. Although most of analytical results presented in this paper are valid for a general set Ω, for the sake of clarity and to make our arguments easier to follow, we decided to assume that $\overline{\Omega} = [0,\pi]$. In fact, only the results concerning local stability cannot be very easily transfered for higher dimensional more general case. In system (1.3), the parameter a_0 describes the growth rate for normal cells, a_1 is the death rate for malignant cells, η_1 expresses the strength of biochemical reactions between normal and malignant cells which stimulate the production of cancer cells, while μ_1 expresses the strength of biochemical reactions between normal and malignant cells which inhibit the production of cancer cells. Clearly, in the second equation we describe the situation when malignant cells need to face the unfavorable environmental conditions. Mobility of cells is reflected by parameters D_0 and D_1 that are diffusion coefficients for normal and malignant cells, respectively. Therefore, it seems to be reasonable to assume $D_0 < D_1$.

Following [9], we rescale Y_0 by K_0 and time s by a_1 obtaining new variables

$$t = a_1 s, \quad y_0(t,x) = \frac{Y_0(s,x)}{K_0}, \qquad y_1(t,x) = Y_1(s,x),$$

and the model of the form

$$\begin{aligned} \frac{\partial}{\partial t} y_0(t,x) &= y_0(t,x)\Big(a\big(1 - y_0(t,x)\big) - \mu y_1(t,x)\Big) + d_0 \Delta y_0(t,x)\,, \\ \frac{\partial}{\partial t} y_1(t,x) &= -y_1(t,x) + \eta y_0(t-\tau,x) y_1(t-\tau,x) + d_1 \Delta y_1(t,x)\,, \end{aligned} \tag{1.4}$$

where y_0 represents the density of normal cells at time t and position x, y_1 stands for malignant cells, constants $a = \frac{a_0}{a_1}$, $\mu = \frac{\mu_1}{a_1}$, $\eta = \frac{\eta_1}{a_1}$, $d_0 = \frac{d_0}{a_1}$, $d_1 = \frac{D_1}{a_1}$ are positive, delay $\tau = \frac{\tau_s}{a_1}$ is non-negative and $x \in [0,\pi]$. We consider the Neumann boundary condition

$$\frac{\partial}{\partial x} y_i(t,x)|_{x=0,\pi} = 0, \quad i = 0,1,$$

and an initial condition

$$y_i(t,x) = \varphi_i(t,x) > 0 \qquad \text{for} \quad t \in [-\tau,0],\ x \in [0,\pi],\ i = 0,1.$$

1.2. **Model without delay.** In [9] more general models describing the carcinogenesis mutation without delay, that take into account n stages of mutations were considered. It has been shown that for each of the three models for different environmental conditions there exists a unique solution. Moreover, it has been proved that there exists the non-negative invariant set, and hence for any initial condition from this set there exists a unique, non-negative and global solution of the considered model. Additionally, in the case of unfavorable environmental conditions and zero flux boundary condition it has been proved that if there exists a positive steady state, then solutions with positive initial data are attracted by this point. Clearly, in system (1.4) with $\tau = 0$ we consider only normal and malignant cells, thus $n = 1$ and all statements proved in [9] holds. The full analysis of the three models for different environment conditions without delay and without diffusion was presented in [8]. On the other hand, it should be marked that in this case system (1.4) is just the classic predator-prey model with carrying capacity for preys, and therefore its dynamics is well known, compare e.g. [11]. Typically, this dynamics is considered as dependent on the carrying capacity, but in system (1.4) it is equal to 1. Therefore, the existence of the positive steady state depends on the magnitude of η. Namely, if $\eta > 1$, then a positive steady state exists and is globally stable, while for $\eta \le 1$ it does not exist and a semi-trivial steady state reflecting the healthy state is globally stable.

2. **Model with delay.** Now, we study basic properties of system (1.4) in the case of positive delay. We prove that the problem is well-posed, and moreover solutions are global.

2.1. **Existence, uniqueness and non-negativity.** Let Ω be any subset of $\mathbb{R}^n$. For any $n, k \in \mathbb{N}$ and $\alpha, \beta \in (0,1)$ by $\mathbf{C}^{k+\alpha}(\Omega)$ we denote a Banach space of functions defined in Ω that are differentiable k times with kth derivative being Hölder with a coefficient α. We say that a function $u \in \mathbf{C}^{n+\beta,k+\alpha}([0,T]\times\Omega)$ if it is differentiable n times with respect to time and its nth time derivative is Hölder with a coefficient β and for any $t \in [0,T]$ the function $u(t,\cdot) \in \mathbf{C}^{k+\alpha}$. Spaces $\mathbf{C}^{k+\alpha}(\Omega)$ and $\mathbf{C}^{n+\beta,k+\alpha}([0,T]\times\Omega)$ are equipped with a standard supremum norm. Let us denote $C = \left(\mathbf{C}^{1+\alpha/2,2+\alpha}([-\tau,0]\times[0,\pi])\right) \times \left(\mathbf{C}^{1+\alpha/2,2+\alpha}([-\tau,0]\times[0,\pi])\right)$.

Theorem 2.1. *Assume that initial functions $(\varphi_0,\varphi_1) \in C$. Then if $\varphi_0(t,\cdot) \geq 0$ and $\varphi_1(t,\cdot) \geq 0$ for all $t \in [-\tau,0]$, then there exists a unique positive and global solution of system (1.4) with the Neumann boundary condition. Moreover this solution belongs to $\mathbf{C}^{1+\alpha/2,2+\alpha}([0,T]\times[0,\pi])$ for any $T>0$.*

Proof. For $t \in [0,\tau]$ system (1.4) reads

$$\begin{aligned} \frac{\partial}{\partial t} y_0(t,x) &= y_0(t,x)(a(1-y_0(t,x)) - \mu y_1(t,x)) + d_0 \Delta y_0(t,x), \\ \frac{\partial}{\partial t} y_1(t,x) &= -y_1(t,x) + \eta \varphi_0(t-\tau,x)\varphi_1(t-\tau,x) + d_1 \Delta y_1(t,x), \end{aligned} \tag{2.1}$$

with the Neumann boundary condition. Notice, that the second equation of (2.1) is a linear non-autonomous diffusion equation. Thus, due to assumptions on φ_0 and φ_1, a standard theory of parabolic equations implies that there exists a unique non-negative solution $y_1 \in \mathbf{C}^{1+\alpha/2,2+\alpha}([0,\tau]\times[0,\pi])$.

The local existence, uniqueness and desired smoothness of solution of the first equation of system (2.1) follows immediately from the fact that the right-hand side is locally Lipschitz continuous and $y_1(t,x) \geq 0$ is a classical solution of the second equation of system (2.1). Knowing that $y_1(t,x) \geq 0$ for $(t,x) \in [0,\tau]\times[0,\pi]$, we deduce that the solution of the standard Fisher-Kolmogorov equation ([3])

$$\frac{\partial}{\partial t} u(t,x) = a\, u(t,x)(1-u(t,x)) - d_0 \Delta u(t,x)$$

with the Neumann boundary condition is an upper solution of the first equation of system (2.1). Similarly $v(t,x) \equiv 0$ is a lower solution. Therefore, y_0 is non-negative and defined for all $t \in [0,\tau]$.

The use of mathematical induction completes the proof. □

Theorem 2.1 allows to consider a dynamical system defined by system (1.4). More precisely, let $\tilde{C} \subset C$ be a Banach space of functions (φ_0,φ_1) such that $\frac{\partial \varphi_i}{\partial x}\big|_{x=0,\pi} = 0$, $i = 0$, 1, and

$$(y_0)_t(h,x) := y_0(t+h,x), \quad (y_1)_t(h,x) := y_1(t+h,x), \quad t \geq 0,\ h \in [-\tau,0]$$

be a solution of system (1.4) for initial data $(\varphi_0,\varphi_1) \in \tilde{C}$. Then, $(\varphi_0,\varphi_1) \to ((y_0)_t,(y_1)_t)$ defines a semigroup in $\tilde{C}$ which is associated with Eqs. (1.4). Moreover, this implies that we are able to use a standard theory of functional-differential equations, see e.g. [10].

Remark 1. Notice, that the results as well as the proof presented in this subsection remain valid if we substitute the interval $[0,\pi]$ by any closed subset of $\mathbb{R}^n$ with a smooth boundary.

2.2. **Steady States.** In this subsection, we study spatially homogeneous steady states of system (1.4). The possible existence of spatially non-homogeneous steady states for delayed non-linear diffusion systems is a difficult problem and we do not consider it in this paper. For $\eta > 1$, system (1.4) has three non-negative spatially homogeneous steady states

$$A = (0,0), \quad B = (1,0), \quad C = \left(\frac{1}{\eta}, \frac{a}{\mu}\Big(1 - \frac{1}{\eta}\Big)\right).$$

For $0 < \eta \leq 1$, it has two non-negative spatially homogeneous steady states A and B. Linearising system (1.4) around the steady state $(\bar{y}_0, \bar{y}_1)$ we obtain

$$\begin{aligned}\frac{\partial}{\partial t}\begin{bmatrix} y_0(t,x) \\ y_1(t,x)\end{bmatrix} &= \begin{bmatrix} a - 2a\bar{y}_0 - \mu\bar{y}_1 & -\mu\bar{y}_0 \\ 0 & -1\end{bmatrix}\begin{bmatrix} y_0(t,x) \\ y_1(t,x)\end{bmatrix} \\ &+ \begin{bmatrix} 0 & 0 \\ \eta\bar{y}_1 & \eta\bar{y}_0\end{bmatrix}\begin{bmatrix} y_0(t-\tau,x) \\ y_1(t-\tau,x)\end{bmatrix} + \begin{bmatrix} d_0 & 0 \\ 0 & d_1\end{bmatrix}\begin{bmatrix} \Delta y_0(t,x) \\ \Delta y_1(t,x)\end{bmatrix}. \end{aligned} \tag{2.2}$$

The characteristic quasi-polynomial for system (1.4) has the following form

$$\begin{aligned} W(\lambda) &= (a - 2a\bar{y}_0 - \mu\bar{y}_1 - d_0k^2 - \lambda)(-1 + \eta\bar{y}_0\,\mathrm{e}^{-\lambda\tau} - d_1k^2 - \lambda) + \mu\eta\bar{y}_0\bar{y}_1\,\mathrm{e}^{-\lambda\tau} = \\ &= \lambda^2 + \lambda\Big(1 + (d_1 + d_0)k^2 - a + 2a\bar{y}_0 + \mu\bar{y}_1\Big) - \Big(a - 2a\bar{y}_0 - \mu\bar{y}_1 - d_0k^2\Big)\Big(1 + d_1k^2\Big) \\ &\quad - \eta\bar{y}_0\Big(\lambda - (a - 2a\bar{y}_0 - d_0k^2)\Big)\mathrm{e}^{-\lambda\tau}, \end{aligned} \tag{2.3}$$

where k is the wavenumber and according to the zero flux boundary condition on the spatial domain $[0,\pi]$ we have $k = \pm 1, \pm 2, \ldots$.

For $(\bar{y}_0, \bar{y}_1) = (0,0)$ we have

$$W(\lambda) = \lambda^2 + \lambda(1 + (d_1 + d_0)k^2 - a) - (a - d_0k^2)(1 + d_1k^2),$$

and the characteristic quasi-polynomial does not depend on τ. Clearly, the trivial steady state A is unstable for the system without diffusion, and hence it is unstable for any arbitrary chosen diffusion coefficients.

For $(\bar{y}_0, \bar{y}_1) = (1,0)$ we have

$$W(\lambda) = \det\begin{bmatrix} -a - d_0k^2 - \lambda & -\mu \\ 0 & -1 + \eta\,\mathrm{e}^{-\lambda\tau} - d_1k^2 - \lambda\end{bmatrix} = (\lambda + a + d_0k^2)\Big(\lambda + 1 + d_1k^2 - \eta\,\mathrm{e}^{-\lambda\tau}\Big).$$

For $1 - \eta > 0$, the semi-trivial steady state B is stable independently of the delay and diffusion coefficients. On the other hand, for $1 - \eta < 0$, $\tau \geq 0$ and $d_1 = d_0 = 0$, this state is unstable, because there always exists a real positive root of the characteristic quasi-polynomial. Therefore, it is also unstable for all $\tau, d_1, d_2 \geq 0$. This means that stability of B depends neither on the delay nor on the magnitude of diffusion.

For $(\bar{y}_0, \bar{y}_1) = \left(\frac{1}{\eta}, \frac{a}{\mu}\Big(1 - \frac{1}{\eta}\Big)\right)$ the characteristic quasi-polynomial (2.3) has the following form

$$W(\lambda) = \lambda^2 + \lambda\alpha_1 + \alpha_0 + \mathrm{e}^{-\lambda\tau}(-\lambda + \beta_0), \tag{2.4}$$

where

$$\alpha_1 = 1 + (d_1 + d_0)k^2 + \frac{a}{\eta} > 0, \quad \alpha_0 = \Big(\frac{a}{\eta} + d_0k^2\Big)\Big(1 + d_1k^2\Big) > 0, \quad \beta_0 = a - \frac{2a}{\eta} - d_0k^2.$$

We see that for the positive steady state C stability can depend on the magnitude of delay.

2.3. **Stability changes for the space homogeneous case.** First, we study if stability changes are possible in the case of the absence of diffusion. Assuming $d_0 = d_1 = 0$ we have

$$\alpha_1 = 1 + \frac{a}{\eta}, \quad \alpha_0 = \frac{a}{\eta}, \quad \beta_0 = a\left(1 - \frac{2}{\eta}\right).$$

For $\tau = 0$, the characteristic quasi-polynomial reads

$$W(\lambda) = \lambda^2 + \frac{a}{\eta}\lambda + a\left(1 - \frac{1}{\eta}\right)$$

and this yields the following Lemma.

Lemma 2.2. *If the positive steady state C for system (1.4) exists, then it is stable for $\tau = d_1 = d_0 = 0$.*

This result is very well know in the literature, compare [11]. Moreover, this state is globally stable in this case. Now, we examine if the stability switches are possible. To get the change of stability when τ is treated as a bifurcation parameter, by a continuity argument, a pair of pure imaginary roots $\lambda = \pm i\omega_0$ of W for some $\tau_0 > 0$ must appear. Clearly, if for some $\omega_0 > 0$ the equality $W(i\omega_0) = 0$ holds, then the function

$$F(\omega) = \omega^4 + (\alpha_1^2 - 2\alpha_0 - 1)\omega^2 + \alpha_0^2 - \beta_0^2 \tag{2.5}$$

has a positive root, see [4] for details. Since

$$\alpha_1^2 - 2\alpha_0 - 1 = \frac{a^2}{\eta^2} > 0,$$

real positive roots of $F(\omega)$ exist if and only if $\alpha_0^2 - \beta_0^2 < 0$. Hence, calculating

$$\alpha_0^2 - \beta_0^2 = a^2\left(1 - \frac{1}{\eta}\right)\left(\frac{3}{\eta} - 1\right),$$

we see that $\alpha_0^2 - \beta_0^2 < 0$ if and only if $\eta < 1$ or $\eta > 3$. Clearly, for $\eta < 1$, the positive steady state does not exist. Hence, consider $\eta > 3$. Substituting $\omega_0^2 = y_0$ in (2.5) we calculate

$$F'(y_0) = 2y_0 + \alpha_1^2 - 2\alpha_0 - 1 > 0.$$

Hence, following [4] we conclude that if there exists $\tau_0 > 0$ for which there exist purely imaginary roots of the characteristic quasi-polynomial (2.4), then they cross the imaginary axis from left to right when the bifurcation parameter increases. Therefore, we state the following theorem.

Theorem 2.3. *Let $d_1 = d_0 = 0$. Stability switches of the positive steady state C are possible for $\eta > 3$ and impossible for $1 < \eta < 3$. Moreover, for $\eta < 1$ there exists no positive steady state.*

Studying stability of the steady state C in the case with non-zero diffusion coefficients we get that adding diffusion does not change the stability of this steady state. In fact, constructing the function F as before we get the following results. The parameter by ω^2 is

$$\alpha_1^2 - 2\alpha_0 - 1 = \frac{a^2}{\eta^2} + k^2\left(\frac{2a\,d_0}{\eta} + 2d_1\right) + \left(d_0^2 + d_1^2\right)k^4 > 0,$$

while the free term reads

$$\alpha_0^2 - \beta_0^2 = a^2\left(\frac{3}{\eta} - 1\right)\left(1 - \frac{1}{\eta}\right) + k^2\left(\left(d_1^2k^2 + 2d_1\right)\left(\frac{a}{\eta} + d_0k^2\right)^2 + 2ad_0\left(1 - \frac{1}{\eta}\right)\right).$$

Thus, for $k = 1, 2, 3, \ldots$ and $\eta > 1$, the expression $\alpha_0^2 - \beta_0^2$ is greater than for the case without diffusion, while for $k = 0$, it has exactly the same value as in the case without diffusion. Therefore, non-negative diffusion coefficients do not change the stability of the steady state C.

2.4. **Global stability.** Consider system (1.4) with $\tau = 0$. In [9], it has been shown that in this case there exists an invariant set

$$\mathbf{\Sigma} = [0, 1] \times [0, \infty). \tag{2.6}$$

Moreover, for the model with the zero-flux boundary condition there exist appropriate Lyapunov functionals implying that for $\eta < 1$, the state B is globally attractive in $\mathbf{\Sigma}$, while for $\eta > 1$, it loses stability and the state C becomes globally attractive inside of $\mathbf{\Sigma}$. The functionals used in [9] have been based on the standard Lyapunov functions for Lotka-Volterra as well as linear systems. Below we follow this idea in proving global stability of the steady state B for $\eta < 1$.

Theorem 2.4. *If $\eta < 1$, then the steady state $B = (1, 0)$ is globally attractive in the invariant set $\mathbf{\Sigma_1} = (0, 1] \times [0, \infty)$ for system (1.4) with the zero-flux boundary condition.*

Proof. Consider first the case without diffusion, that is $d_0 = d_1 = 0$. Because $y_0 \equiv 0$ is the solution of the first equation of system (1.4) for any initial function φ_1 and the first equation is ODE, the solution for initial data from $\mathbf{\Sigma_1}$ remains in this set. Hence, for any solution in this set we have $y_0(t) > 0$ for all $t \geq 0$. Let us define

$$L(\varphi_0, \varphi_1) = \varphi_0(0) - 1 - \ln \varphi_0(0) + \frac{A}{2}(\varphi_1(0))^2 + B \int_{-\tau}^{0} (\varphi_1(s))^2 ds, \ A > 0, \ B > 0, \ \varphi_i \in C, \ i = 0, 1.$$

It is obvious that $L((y_0)_t, (y_1)_t) \geq 0$ and $L((y_0)_t, (y_1)_t) = 0$ iff $y_0(t) = 1$ and $y_1(t) = 0$ a.e. Continuity of the solution yields $y(0) = 1$ and $y_1(t) = 0$ for all t. The derivative of L along the solution of system (1.4) with $d_0 = d_1 = 0$ reads

$$\dot{L}((y_0)_t, (y_1)_t) = \frac{y_0(t) - 1}{y_0(t)} \Big(a y_0(t)(1 - y_0(t)) - \mu y_0(t) y_1(t) \Big) + \\ + A y_i(t) \Big(\eta y_0(t - \tau) y_1(t - \tau) - y_1(t) \Big) + B \Big(y_1^2(t) - y_1^2(t - \tau) \Big).$$

Hence,

$$\dot{L}((y_0)_t, (y_1)_t) = \Big(y_0(t) - 1, y_1(t), y_1(t - \tau) \Big) \mathbb{A} \begin{pmatrix} y_0(t) - 1 \\ y_1(t) \\ y_1(t - \tau) \end{pmatrix},$$

where

$$\mathbb{A} = - \begin{pmatrix} a & \frac{\mu}{2} & 0 \\ \frac{\mu}{2} & A - B & \frac{\eta A}{2} y_0(t - \tau) \\ 0 & \frac{\eta A}{2} y_0(t - \tau) & B \end{pmatrix}.$$

We need to check if there exist A, $B > 0$ such that the matrix $\mathbb{A}$ is positively defined. Analyzing the main minors we see that $D_1 = a > 0$. Moreover,

$$D_2 = a(A - B) - \frac{\mu^2}{4} > 0 \quad \text{iff} \quad A - B > \frac{\mu^2}{4a},$$

and

$$D_3 = aB(A - B) - a \frac{\eta^2 A^2}{4} y_0(t) y_0^2(t - \tau) - B \frac{\mu^2}{4}.$$

We see that

$$D_3 > 0 \quad \text{for all} \quad y_0 \in (0,1] \quad \text{iff} \quad aB(A-B) > a\frac{\eta^2 A^2}{4} + B\frac{\mu^2}{4}\,.$$

Let $A = 2B$. Then $D_2 > 0$ iff $B > \frac{\mu^2}{4a}$ and $D_3 > 0$ iff

$$aB(1-\eta^2) > \frac{\mu^2}{4} \iff B > \frac{\mu^2}{4a(1-\eta^2)}\,,$$

due to the assumption $\eta < 1$. Therefore, it is enough to assume $B > \frac{\mu^2}{4a(1-\eta^2)}$ and $A = 2B$ to get the matrix $\mathbb{A}$ positively defined. Let us consider the set $\mathcal{A} = \{(\varphi_0, \varphi_1) \in C : \dot{L}(\varphi_0, \varphi_1) = 0\}$. We see that the only invariant (with respect to system (1.4)) subset of $\mathcal{A}$ is the steady state B, and therefore B is globally attractive, see e.g. [10].

Now, let us consider $d_0, d_1 > 0$ and define

$$V(\varphi_0, \varphi_1) = \int_0^\pi L(\varphi_0, \varphi_1)dx\,,$$

for $\varphi_i \in \tilde{C}$, $i = 0, 1$. It is again obvious that $V((y_0)_t, (y_1)_t)$ is non-negative and equals 0 iff $y_0 \equiv 1$ and $y_1 \equiv 0$ due to the smoothness of solutions of system (1.4). Calculating the derivative of V along solutions one gets

$$\begin{aligned}
\dot{V}((y_0)_t, (y_1)_t) &= \int_0^\pi \dot{L}((y_0)_t, (y_1)_t)\,dx + d_0 \int_0^\pi \frac{y_0(t,x)-1}{y_0(t,x)}\frac{\partial^2 y_0}{\partial x^2}dx + d_1 A \int_0^\pi y_1(t,x)\frac{\partial^2 y_1}{\partial x^2}dx \\
&= \int_0^\pi \dot{L}((y_0)_t, (y_1)_t)\,dx + d_0 \frac{y_0(t,x)-1}{y_0(t,x)}\frac{\partial y_0}{\partial x}\Big|_0^\pi - d_0 \int_0^\pi \frac{1}{y_0^2(t,x)}\left(\frac{\partial y_0}{\partial x}\right)^2 dx \\
&\quad + d_1 A\ y_1(t,x)\frac{\partial y_1}{\partial x}\Big|_0^\pi - d_1 A \int_0^\pi \left(\frac{\partial y_1}{\partial x}\right)^2 dx\,.
\end{aligned}$$

Therefore,

$$\dot{V}((y_0)_t, (y_1)_t) = \int_0^\pi \dot{L}((y_0)_t, (y_1)_t)\,dx - d_0 \int_0^\pi \frac{1}{y_0^2(t,x)}\left(\frac{\partial y_0}{\partial x}\right)^2 dx - A d_1 \int_0^\pi \left(\frac{\partial y_1}{\partial x}\right)^2 dx\,,$$

implying that $\dot{V}$ is negatively defined and again B is the only invariant subset of $\tilde{\mathcal{A}} = \{(\varphi_0, \varphi_1) \in \tilde{C} : \dot{L}(\varphi_0, \varphi_1) = 0\}$ due to the smoothness of solutions. Hence, B is globally stable. □

This theorem shows that the dynamics of system (1.4) for $\eta < 1$ depends neither on the delay nor on the diffusion coefficient and the system remains globally stable with the semi-trivial steady state B being globally attractive.

Remark 2. Notice, that Theorem 2.4 is also true if we consider system (1.4) in some subset Ω of $\mathbb{R}^n$ with a smooth boundary. In this case, the Lyapunov functional does not change. However, in the proof, one needs to apply the Stokes Theorem instead of just integration by parts.

3. **Numerical simulations.** The analysis presented in previous sections shows that the diffusion itself cannot destabilize the positive steady state and stability switches can be caused only by sufficiently large time-lag. In the following we numerically investigate, for arbitrary set of parameters, behavior of system (1.4) in different regimes of time delay τ. For all of the simulations, we choose the following set of parameters

$$a = 2,\ \mu = 0.9,\ \eta = 5,\ d_0 = 10^{-6},\ d_1 = 4 \cdot 10^{-6}\,. \tag{3.1}$$

This choice yields the existence of the positive steady state C with possibility of the delay induced stability switches. Low values of the diffusion coefficient do not allow for rapid spatial homogenization of the solutions and allows us to observe complicated and rich solution behavior. We assume the following initial functions for both healthy and cancer cells

$$\varphi_0(t,x) = 0.2 + 0.1\cos(4x\pi), \quad \varphi_1(t,x) = 1.77, \qquad \text{for} \quad t \in [-\tau, 0],\ x \in [0,1]\,,$$

that reflect the spatial perturbation in the value of the space homogeneous positive steady state. As it is typically assumed, at any point in the spatial domain, a constant history function is assumed. Considered system (1.4) was discretized in the spatial domain, and then the extended system of time dependent DDEs was solved along each line using standard MATLAB tools.

In order to illustrate destabilization of the positive steady state, we start the numerical investigation with the diffusion free system, that is we solve system (1.4) for $d_0 = d_1 = 0$. Fig. 1 shows the behavior of solutions for different values of time delay $\tau \in \{0, 0.3, 5\}$. It is well known that in the delay free case the solution tends to the positive steady state [11], and the convergence is oscillatory for the chosen parameter values. That kind of behavior does not change for $\tau = 0.3$ and we observe only decrease in the rate of convergence to the steady state. For sufficiently large values of the delay ($\tau = 5$ in the presented simulations), it follows from our mathematical analysis as well as the numerical simulations that the positive steady state is no longer stable and solutions behave in far more complicated manner.

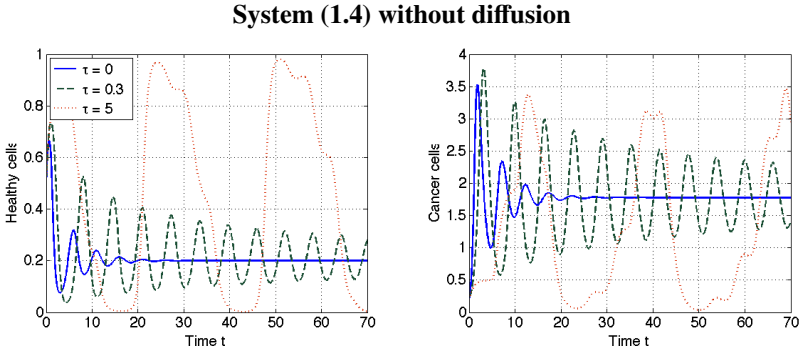

FIGURE 1. Solutions of system (1.4) without diffusion for parameters $a = 2$, $\mu = 0.9$, $\eta = 5$ and different values of time delay. We observe destabilization of the positive steady state with increasing delay.

In addition to investigating the diffusion free system, we solve system (1.4) without delay. It follows from the analysis performed in [9] that there is no possibility for Turing destabilization and we only observe fast convergence of the solution to the spatially homogeneous steady state, compare Fig. 2.

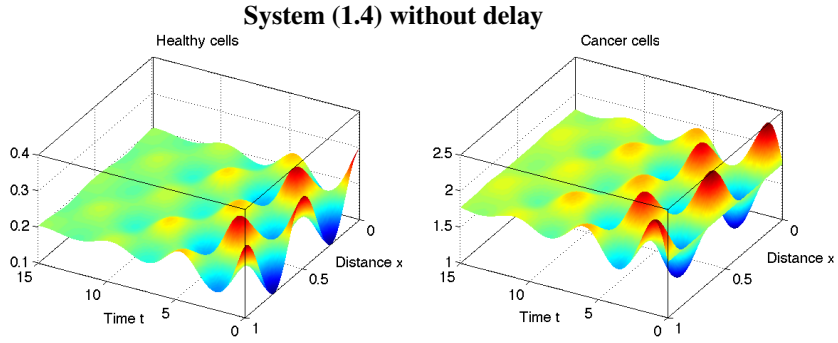

FIGURE 2. Solution of system (1.4) for parameters (3.1) and $\tau = 0$. The positive steady state is stable and the solution converges toward it in an oscillatory manner.

We start numerical investigation of the full system (1.4) with the regime of small delays, in which the positive steady state remains stable. Fig. 3 shows that the solution of system (1.4) tends in an oscillatory manner to the spatially homogeneous steady state. We observe that initially at each point in the spatial domain the solution oscillates with different frequency. Oscillations are then dumped mainly because of the stability of the steady state. For higher values of both diffusion coefficients we observe quicker spatial homogenization of the solution (data not shown).

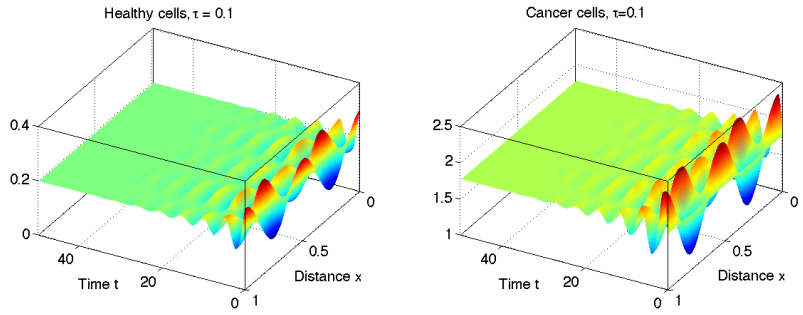

FIGURE 3. Solution of system (1.4) for parameters (3.1) and $\tau = 0.1$. For such a small value of time delay the positive steady state remains stable and the solution converges toward it in an oscillatory manner.

For larger values of time delay, solutions of system (1.4) behave in the completely different manner, see Fig. 4. We observe sustained oscillations with peaks clearly separated in both time and space.

For even larger values of time delay, we observe even more complicated behavior of the solution, compare Fig. 5. Despite the oscillatory behavior at each point in the spatial dimension, we observe spatially non-homogeneous periodic solutions. The highest values of solution are arranged in a half moon shapes, with arm lengths elongating in time.

4. **Discussion.** In the paper we have studied the simplified model of mutations from normal to malignant cells in which instead of multistep mutations a time delay is introduced. The analysis performed for the full system (1.1) in [9] shows global stability of one of

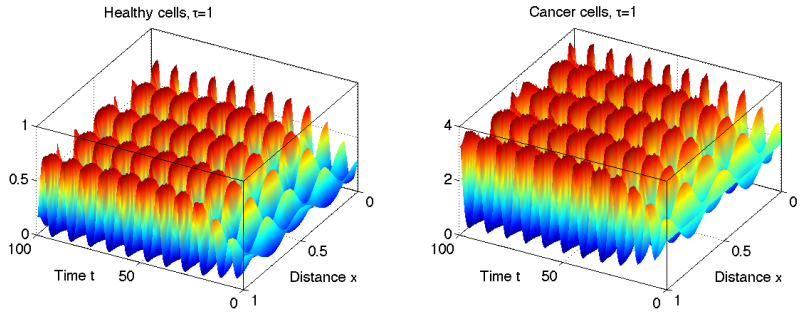

FIGURE 4. Solution of system (1.4) for parameters (3.1) and the value of time delay sufficient to destabilize the positive steady state, that is $\tau = 1$.

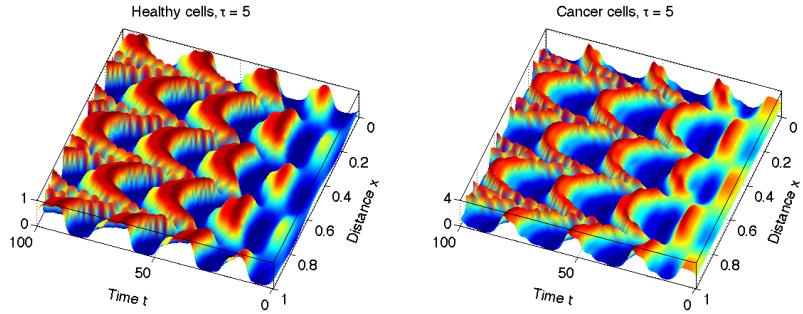

FIGURE 5. Solution of system (1.4) for large value of time delay ($\tau = 5$). Other model parameters as given by (3.1).

existing homogeneous steady state. Although the simplified system (1.3) consists only of two equations an introduction of the delay causes a richer dynamics of solutions. For some parameter values, with increasing delay we observe the appearance of sustained spatially non-homogeneous oscillating solutions.

System (1.3) reflects the mutation process in an unfavorable environment described by the function (1.2). On the other hand, for most of malignant tumors the conditions are favorable, that is instead of (1.2) we have

$$F(u, v) = \alpha v + \eta_1 u\, v,$$

where $\alpha > 0$ is the tumor growth rate. This means that without external interference the tumor grows boundlessly. This result does not depend on the delay, because $F(u, v) \geq \alpha v$ and this inequality is independent of the bilinear term which is delayed in system (1.4). Therefore, to achieve recovery some treatment is needed. Let us consider constant chemotherapy, that can be reflected by additional death term in both equations for normal and malignant cells. This means that for sufficiently large dose of chemotherapy, the environment can be changed from favorable to unfavorable and the dynamics of mutations is then described by system (1.4). Let us consider the model in the favorable conditions with chemotherapy.

Hence, instead of system (1.3) we obtain

$$\frac{\partial}{\partial s}Y_0(s,x) = Y_0(s,x)\left(a_0\left(1-Y_0(s,x)\right)-\mu_1 Y_1(s,x)\right) - r_0 Y_0(s,x) + D_0\Delta Y_0(s,x),$$
$$\frac{\partial}{\partial s}Y_1(s,x) = \alpha Y_1(s,x) + \eta_1 Y_0(s-\tau_s,x)Y_1(s-\tau_s,x) - r_1 Y_1(s,x) + D_1\Delta Y_1(s,x),$$

where $K_0 = 1$ for simplicity, and $r_i > 0$, $i = 0, 1$, denote the additional death term due to chemotherapy for normal and malignant cells, respectively, and typically it is assumed that $r_0 = r_1\varepsilon$, $\varepsilon < 1$. To achieve success in changing of environmental conditions inequalities $r_1\varepsilon < a_0$ and $r_1 > \alpha$ are required. In the model with chemotherapy changing the environment, the positive steady state C exists iff $\eta_1 > \eta_1^{\text{th}} := a_0\frac{r_1-\alpha}{a_0-r_1\varepsilon}$. On the other hand, the analysis performed in this paper implies that for $\eta_1 < \eta_1^{\text{th}}$ the semi trivial steady state B is globally stable, meaning complete cure of the disease. It is obvious that if r_1 is sufficiently large, then $\eta_1 < \eta_1^{\text{th}}$ until $a_0 - r_1\varepsilon$ remains positive. Hence, either it is possible to apply such chemotherapy that $r_1 > \alpha$, $\varepsilon < \frac{a_0}{r_1}$ and $\eta_1 < \eta_1^{\text{th}}$ yielding the cure, or $\eta_1 > \eta_1^{\text{th}}$ and the additional treatment is required to decrease the strength of biochemical reactions stimulating the process of mutations.

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