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A DELAY–DIFFERENTIAL EQUATION MODEL OF HIV RELATED CANCER–IMMUNE SYSTEM DYNAMICS

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Abstract. In the human body, the appearance of tumor cells usually turns on the defensive immune mechanisms. It is therefore of great importance to understand links between HIV related immunosuppression and cancer prognosis. In the paper we present a simple model of HIV related cancer – immune system interactions *in vivo* which takes into account a delay describing the time needed by $CD4^+$ T lymphocyte to regenerate after eliminating a cancer cell. The model assumes also the linear response of immune system to tumor presence. We perform a mathematical analysis of the steady states stability and discuss the biological meanings of these steady states. Numerical simulations are also presented to illustrate the predictions of the model.

1. **Introduction.** AIDS (acquired immunodeficiency syndrome) was first recognized in 1981 and in the period 1981–2005 it is estimated that in the world, more than 25 million people died after contracting it (compare data in [16]). AIDS is characterized by deeply impaired functionality of immune system and various clinical expressions. In 1981, during examinations of gay males with AIDS in Southern California and New York City, American public health scientists noticed clusters of Kaposi's sarcoma (skin cancer) and Pneumocystis pneumonia (PCP) – a form of pneumonia, caused by the yeast-like fungus. Although pneumocystis is common and specific for humans it can be dangerous for people with a weak immune system as a source of opportunistic infection, including lung infection.

In 1983, two separate research groups led by Robert Gallo and Luc Montagnier independently declared that a novel retrovirus may have been infecting AIDS patients. In 1986, that retrovirus was subsequently named human immunodeficiency virus or HIV. HIV targets, among others, the $CD4^+$ T lymphocytes, which are the most abundant white blood cells of the immune system. It is thought that HIV, although attacking many different cells, wreaks the most havoc on the $CD4^+$ T-cells by causing their destruction and decline, and thus decreases the body's ability to fight infection [8]. The last stage of HIV infection (AIDS) shows symptoms of various opportunistic infections and cancers such as Kaposis's sarcoma, cervical cancer and cancers of the immune system known as lymphomas, compare [19] and also [3, 4]. In the cancer cells of HIV infected patients no viral sequence in the DNA was found, therefore it seems the virus doesn't induce cancer itself. Moreover, it has been discovered that there exist tumor-specific antigens and the immune system has the ability to prevent cancer development. It is a common ability not only for

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human immune system. Thus, it appears that the role of the immune system is to prevent development of tumors that arise on a frequent basis (immune surveillance hypothesis [14]).

In current bio-mathematical literature there appear many papers focused on either the tumor growth modeling (compare [21, 6] and the references therein) or the HIV virus dynamics (compare [8, 17, 18, 20] and the references therein). Due to the occurrence of several types of cancers related to the presence of the HIV virus it is important to combine these two types of models to describe such a combined disease. In the papers of Lou et al. [14, 15] the basic model of this phenomenon in the tissue cultures (*in vitro*) was proposed and studied without ([14]) and with ([15]) time delay. They describe the HIV related cancer – immune system interactions using three populations of cells: cancer cells, healthy and infected $CD4^+$ T lymphocytes. Their model concerns the cell-to-cell spread of the HIV virus because that transfer mechanism has been estimated to be much more important in areas such as the brain and lymph tissue, where 98% of the $CD4^+$ T cells *in vivo* are found [14]. In [15] there is taken into account the time delay for the incubation phase when the target cells are infected. In [1, 2] some modification of the model of Lou et al. was proposed. The main idea of this modification was to change the intrinsic cellular dynamics of cancer/effector cells. Moreover, the time delay in another process was taken into account. In [11, 10] it is claimed that after killing a tumor cell the effector cell is able to have cytotoxic effect on other tumor cells but it needs some time for regeneration. The delay considered in [1, 2] describes the time needed by $CD4^+$ T lymphocyte for regeneration after eliminating the cancer cell.

In this paper we consider the next modification of the cancer – immune system interactions dynamics in which we address the issue of immune reaction against tumor *in vivo*. It is known that there is a second way for HIV to disseminate *in vivo*: circulating free viral particles to T cells directly [14]. On this basis, we consider an additional variable in our model: the concentration of free HIV viral particles. Moreover, it occurs that effector cells (which are mainly $CD4^+$ T lymphocytes) in the compartments other than brain or lymph tissue are mainly recruited from outside of the antigen – effector cells system. This suggest that the logistic dynamics proposed by Lou et al. [14, 15] and Bodnar et al. [1, 2] in the description of effector cells evolution should be changed.

Apart from the current Section 1, the paper is organized in the following way. In Section 2, we propose the model that reflects this external recruitment and incorporates both ways of HIV dissemination. We also identify the model parameters. In Section 3, we perform the basic mathematical analysis of the proposed model and discuss the biological meaning of steady states and their stability. In Section 4, we show numerical simulations which complete and extend the analytical results. In the last Section 5 we discuss the presented results and predictions of the model.

2. **The model.** We propose the following system of differential equations as a model of the HIV related cancer–immune system dynamics *in vivo*:

$$\begin{cases} \dfrac{dT}{dt} = r_1 T(t) - k_1 T(t) E(t)\,, \\ \dfrac{dE}{dt} = r_2 T(t) + \alpha - \mu_1 E(t) - k_1 T(t) E(t) + \\ \qquad +(1-\varepsilon) k_1 T(t-\tau) E(t-\tau) - k_2' E(t) I(t) - k_3 E(t) V(t)\,, \\ \dfrac{dI}{dt} = k_2' E(t) I(t) + k_3 E(t) V(t) - \mu_2 I(t)\,, \\ \dfrac{dV}{dt} = N\delta I(t) - cV(t)\,, \end{cases} \tag{1}$$

where all parameters are non-negative and the variables $T(t)$, $E(t)$, $I(t)$, $V(t)$ denote the concentration of cancer cells, healthy effector cells (mainly $CD4^+$ T-cells), effector cells infected by the HIV virus, and the free HIV viral particles, respectively. We do not consider any space dependency in the model and all concentrations reflect averages at time t.

We assume that the dynamics of cancer cells is governed by two processes: cancer cells proliferation and their interactions with the immune system. Similarly to [9] we assume the cancer cell proliferation term is linear with respect to the cancer cell concentration $T(t)$. This means that in the absence of the immune system surveillance the tumor grows exponentially. Such type of tumor growth is experimentally observed at the beginning of the tumor development [21]. We take the term describing the influence of effector cells on cancer cells dynamics as proportional to the product of both concentrations. The same simple form of this term was proposed by Lou et al. [14]. A slightly more complicated form of it can be found in [12].

The concentration of effector cells increases due to the direct presence of the tumor, where the parameter r_2 reflects the antigenicity of the tumor and the term $r_2 T(t)$ models the recruitment of effector cells, compare [12]. Antigenicity can be thought of as a measure of the difference between the tumor and the normal tissue. The parameter α is the "normal" (non-enhanced by cancer cells presence) rate of the flow of mature effector cells into the region of cancer cells localization [13]. Parameter μ_1 is the positive constant representing the rate of elimination of effector cells, resulting from their destruction and migration. Following the ideas presented in [1, 2], the fourth and fifth terms in the equation for effector cells dynamics describe the process of effector cells regeneration after the injection of lytic granules into the target cells. Cytotoxic T-cells kill target cells mainly using lytic granules containing perforin, granzymes and TNF. They bind to the surface of the target cell and trigger the extracellular release of perforin molecules from the granules; these polymerize to form transmembrane channels which may facilitate lysis of the target by permitting entry of granzymes which induce apoptotic cell death through activation of the caspase protease cascade and ultimate fragmentation of nuclear DNA [10]. We assume that the delay τ describes the time needed by effector cells to regenerate lytic granules. In addition, we incorporate the fact that the small percentage (denoted by ε) of effector cells do not survive the attempt to eliminate target cell, as the granzymes released from lytic granules may breach into the T-cell.

The last two terms in the equation determining evolution of the healthy effector cells concentration describe the transition of the healthy effector cell into the infected one due to the direct contact with infected cells or by the infiltration by the free viral particles. Like in the papers by Lou et al., we assume that cells which

have been infected by the HIV virus may only migrate or undergo spontaneous destruction, which is described by the parameter μ_2 in the third equation of the model.

Following Perelson et. al [20], we assume that the dynamics of the free viral particles is governed by two processes: secretion of new viral particles by infected effector cells and loss of that particles due to migration or other processes [8]. The term describing the release of the new free viral particles by the infected cells is multiplied by the additional parameter N to represent the number of those particles released by the single infected cell. Furthermore, we assume that the rate of change of the free HIV viral particles is high relative to the rate of change of the concentration of considered cellular populations. Thus, we assume that during the whole process $dV/dt \equiv 0$, that is $V(t) \equiv N\delta/c\, I(t)$. Under that assumption Eqs. (1) reduce to the following system of three differential equations:

$$\begin{cases} \dfrac{dT}{dt} = r_1 T(t) - k_1 T(t) E(t)\,, \\ \dfrac{dE}{dt} = r_2 T(t) + \alpha - \mu_1 E(t) - k_1 T(t) E(t) + \\ \qquad +(1-\varepsilon) k_1 T(t-\tau) E(t-\tau) - k_2 E(t) I(t)\,, \\ \dfrac{dI}{dt} = k_2 E(t) I(t) - \mu_2 I(t)\,, \end{cases} \tag{2}$$

where

$$k_2 = k_2' + k_3 \frac{N\delta}{c}\,.$$

In the following, we consider the simplified form (2) of the full model (1). To complete the mathematical model of the biological process we should specify the ranges for values of the parameters. If we consider Eqs. (2) in the absence of the tumor and the HIV infected cells, that is $T(t) \equiv I(t) \equiv 0$, we see that the solution $E(t)$ converges to the ratio α/μ_1 as $t \to \infty$. Thus, the ratio α/μ_1 reflects the normal physiological level of the effector cells. According to the literature [11], in healthy persons this value is estimated to be between 800 and 1200 $CD4^+$ T-cells/mm^3. As most of the terms in our model are similar to those of the models in [12], [14], [8], [20] and [2], we explored the choices for most of the parameters as presented in those studies. The ranges of parameters values and corresponding references are given in Table 1.

r_1 [14]	k_1 [14]	r_2 [12]	α/μ_1 [11]	k_2' [14]	k_3 [8]
0,05 $\sim$ 0.5	$10^{-5} \sim 10^{-3}$	0 $\sim$ 0.05	800$\sim$1200	$10^{-5} \sim 5 \times 10^{-4}$	2.4×10^{-5}

μ_2 [14]	δ [20]	c [20]	μ_1 [12]	ε [2]	N [8]
0.3	0.3 $\sim$ 0.7	2.1 $\sim$ 3.8	0.03	0.1	100 $\sim$ 2000

TABLE 1. The ranges of parameters values and corresponding references.

Following the ideas from [1, 2], we focus on comparing the cancer–immune system interactions dynamics in two cases: when there is no HIV infection and when the HIV virus is present in the system. Thus, Eqs. (2) for $I(t) \equiv 0$, that is when there is no HIV virus in the system, stands for our control case. In the control case we

verify the immune surveillance hypothesis, that is the possibility of preventing the tumor development by the immune system. Then, in the following sections, we consider introduction of the HIV virus to the model and focus on its influence of the tumor development under surveillance of the impaired immune system.

3. Mathematical analysis.

3.1. Control case.

We begin with the analysis of the control case, that is when $I(t) \equiv 0$, in order to verify if the healthy immune system is able to prevent the cancer development. We consider the following two–variable system:

$$\begin{cases} \dfrac{dT}{dt} = r_1 T(t) - k_1 T(t) E(t)\,, \\ \dfrac{dE}{dt} = r_2 T(t) + \alpha - \mu_1 E(t) - k_1 T(t) E(t) + (1-\varepsilon) k_1 T(t-\tau) E(t-\tau)\,. \end{cases} \tag{3}$$

where parameters values are the same as in the full model (2) (see Table 1).

3.1.1. *Analysis for* $\tau = 0$. In the case when there is no delay in the system, that is for $\tau = 0$, the model (3) reduces to the following set of equations:

$$\begin{cases} \dfrac{dT}{dt} = r_1 T(t) - k_1 T(t) E(t)\,, \\ \dfrac{dE}{dt} = r_2 T(t) + \alpha - \mu_1 E(t) - \varepsilon k_1 T(t) E(t)\,. \end{cases} \tag{4}$$

Several different types of that system dynamics are possible depending on the model parameters. We start from the analysis of the null-clines which are described by the following equalities

$$\begin{aligned} \dot{T} = 0 \quad &\Longleftrightarrow \quad T = 0 \quad \text{or} \quad E = \tfrac{r_1}{k_1}, \\ \dot{E} = 0 \quad &\Longleftrightarrow \quad E = \frac{\alpha + r_2 T}{\mu_1 + \varepsilon k_1 T}. \end{aligned}$$

It can be easily seen that there always exists a cancer free steady state:

$$(\tilde{T}, \tilde{E}) = \left(0, \frac{\alpha}{\mu_1}\right),$$

in which the concentration of the healthy effector cells is at the physiological level α/μ_1. We can also see that, if $r_2 > \frac{\alpha\varepsilon k_1}{\mu_1}$, then the null-cline for E is an increasing function, while for $r_2 < \frac{\alpha\varepsilon k_1}{\mu_1}$ it is decreasing. Moreover, it takes all the values in the range $\left(\min(\frac{\alpha}{\mu_1}, \frac{r_1}{\varepsilon k_1}), \max(\frac{\alpha}{\mu_1}, \frac{r_1}{\varepsilon k_1})\right)$. Hence, if

$$\frac{r_2}{\varepsilon} < r_1 < \frac{\alpha k_1}{\mu_1} \quad \text{or} \quad \frac{\alpha k_1}{\mu_1} < r_1 < \frac{r_2}{\varepsilon}\,, \tag{5}$$

then the null-cline for E crosses the non-trivial null-cline for T once, which means that there exists the unique strictly positive steady state:

$$(\bar{T}, \bar{E}) = \left(\frac{\mu_1 r_1 - \alpha k_1}{k_1(r_2 - \varepsilon r_1)}, \frac{r_1}{k_1}\right).$$

If non of Ineqs. (5) hold, then the null-cline for E lies above or under the non-trivial null-cline for T, which means that there does not exist any strictly positive steady state. We can interpret the strictly positive steady state as the case when the immune system is able to successfully prevent further cancer development.

It should be mentioned that for the parameters values presented in Table 1 all the considered above types of the system behavior are possible. However, we are mainly interested in the case when the rate of tumor growth reflected by the parameter r_1 is relatively large comparing to the rate of cancer elimination by the immune system, that is k_1.

Theorem 3.1. *The set $\mathcal{D} = \mathbb{R}^2_+$ is invariant for system (4). Moreover, for every solution in $\mathcal{D}$ there is $E(t) \le \max\{E(0), \frac{r_2}{\varepsilon k_1}, \frac{r_1}{k_1}\}$.*

If $r_1 > \frac{\alpha k_1}{\mu_1}$ and

- *$\varepsilon < \frac{r_2}{r_1}$, then there exists the unique positive steady state $(\bar{T}, \bar{E})$, which is globally stable in $\mathcal{D}$;*
- *$\varepsilon > \frac{r_2}{r_1}$, then there is no positive steady state and for all solutions $T(t) \to \infty$ as $t \to \infty$.*

Proof. Invariance of $\mathcal{D}$ is obvious due to the form of the right-hand side of Eqs. (4). Boundedness of E is a consequence of the phase-space analysis, compare Fig. 1. Moreover, the phase-space analysis for $\varepsilon < \frac{r_2}{r_1}$ shows that every orbit of Eqs. (4) is bounded, compare the left-hand graph in Fig. 1.

Local stability of $(\bar{T}, \bar{E})$ for $\varepsilon < \frac{r_2}{r_1}$ follows from the form of the Jacobi matrix:

$$MJ(\bar{T}, \bar{E}) = \begin{pmatrix} 0 & -k_1\bar{T} \\ r_2 - \varepsilon r_1 & -\mu_1 - \varepsilon k_1 \bar{T} \end{pmatrix}$$

with $\mathrm{tr} MJ < 0$ and $\det MJ > 0$. Global stability is a corollary from the Dulac – Bendixson criterion. More precisely, defining $B(T, E) = \frac{1}{TE}$ one gets

$$\frac{\partial}{\partial T} B(T,E) G_1(T,E) + \frac{\partial}{\partial E} B(T,E) G_2(T,E) = -\frac{1}{E^2}\left(\frac{\alpha}{T} + r_2\right) < 0$$

in $\mathcal{D}$, where $G = (G_1, G_2)$ denotes the right-hand side of Eqs. (4). This implies that there is no closed orbit in $\mathcal{D}$ yielding global stability of $(\bar{T}, \bar{E})$ according to the Poincaré – Bendixson theorem.

On the other hand, if $\varepsilon > \frac{r_2}{r_1}$, then the analysis of the phase-space portrait yields $T \to \infty$ for $t \to \infty$ and T is either increasing for all $t > 0$ or has one minimum, compare the middle graph in Fig. 1. □

Remark 1. Similarly we can show that for $r_1 < \frac{\alpha k_1}{\mu_1}$ when r_2 is large, that is $r_2 > \frac{\alpha \varepsilon k_1}{\mu_1}$, there is no positive steady state and all solutions are attracted by the cancer free state $(\tilde{T}, \tilde{E})$, compare the right-hand graph in Fig. 1, while if $(\bar{T}, \bar{E})$ exists, then it is a saddle and we observe two types of the system dynamics: either $(\tilde{T}, \tilde{E})$ attracts the solution (for solutions above the stable manifold for the saddle point) or $T \to +\infty$ as $t \to +\infty$.

3.2. **Analysis of the full system for $\tau = 0$.** It is obvious that for $I(0) \neq 0$ there is $I(t) \neq 0$ for $t > 0$, which yields that the set $\mathbb{R}^3_+$ is invariant for Eqs. (2) with $\tau = 0$. Studying the behavior of the full system (2) for $\tau = 0$ we see that there can be three steady states:

1. $T = 0$ and $I = 0 \Longrightarrow \bar{E}_1 = \frac{\alpha}{\mu_1}$, that is $S_1 = (0, \frac{\alpha}{\mu_1}, 0)$ describes the healthy state;
2. $T = 0$ and $I \neq 0 \Longrightarrow \bar{E}_2 = \frac{\mu_2}{k_2}$ and $\bar{I}_2 = \frac{\alpha k_2 - \mu_1 \mu_2}{\mu_2 k_2}$, that is the steady state $S_2 = \left(0, \frac{\mu_2}{k_2}, \frac{\alpha k_2 - \mu_1 \mu_2}{\mu_2 k_2}\right)$ describes the HIV infection without cancer;

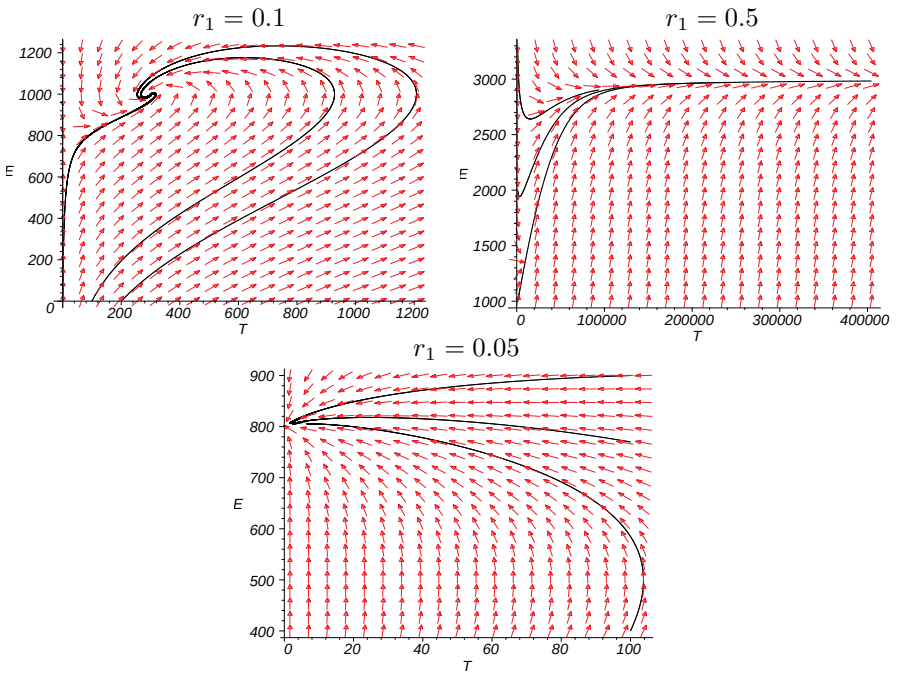

FIGURE 1. Exemplary phase-space portraits for Eqs. (3) for different values of r_1 and with parameters values used in numerical simulations presented in Section 4.

3. $T \neq 0 \Longrightarrow \bar{E}_3 = \frac{r_1}{k_1} \Longrightarrow I = 0$ and $\bar{T}_3 = \frac{\mu_1 r_1 - \alpha k_1}{k_1(r_2 - \varepsilon r_1)}$, that is the steady state $S_3 = \left(\frac{\mu_1 r_1 - \alpha k_1}{k_1(r_2 - \varepsilon r_1)}, \frac{r_1}{k_1}, 0\right)$ describes the cancer – immune system interactions without the HIV infection.

We see that S_2 exists only if $\alpha > \frac{\mu_1 \mu_2}{k_2}$ and S_3 has the same T and E coordinates as $(\bar{T}, \bar{E})$, that is the positive steady state of Eqs. (4). On the other hand, there is no positive steady state describing the coexistence of the tumor and the HIV virus.

Recalling that r_1 is relatively large comparing to k_1, as in the control case, we prove the following.

Proposition 1. *The set $\mathcal{D} = (\mathbb{R}^+)^3$ is invariant for Eqs. (2).*
If $r_1 > \frac{\alpha k_1}{\mu_1}$, then S_1 is unstable (a saddle point). Moreover

- *if $\varepsilon < \frac{r_2}{r_1}$, then S_3 exists; if additionally $r_1 < \frac{\mu_2 k_1}{k_2}$, then it is locally asymptotically stable;*
- *if $\alpha > \frac{\mu_1 \mu_2}{k_2}$, then S_2 exists; if additionally $r_1 < \frac{\mu_2 k_1}{k_2}$, then this state is stable.*

Proof. Studying local stability we calculate the Jacobi matrix of Eqs. (2). We have

$$\begin{pmatrix} r_1 - k_1 E & -k_1 T & 0 \\ r_2 - \varepsilon k_1 E & -\mu_1 - \varepsilon k_1 T - k_2 I & -k_2 E \\ 0 & k_2 I & k_2 E - \mu_2 \end{pmatrix}.$$

For S_1 we easily see that the characteristic values are equal to $\lambda_1 = r_1 - \frac{\alpha k_1}{\mu_1}$, $\lambda_2 = \mu_1$, $\lambda_3 = \frac{\alpha k_2}{\mu_1} - \mu_2$ and the stability requires $r_1 \leq \frac{\alpha k_1}{\mu_1}$, which contradicts the assumption.

For S_2 the characteristic polynomial has the form

$$P_{S_2}(\lambda) = \left(r_1 - \frac{\mu_2 k_1}{k_2} - \lambda\right)\left(\lambda^2 + \lambda\frac{\alpha k_2}{\mu_2} + \alpha k_2 - \mu_1\mu_2\right)$$

and we know that for $\alpha k_2 > \mu_1\mu_2$ this state exists. This implies that the quadratic term of P_{S_2} has either real negative roots or complex roots with negative real part. Hence, if $\lambda_1 = r_1 - \frac{\mu_2 k_1}{k_2} < 0$, then S_2 is locally stable.

For S_3 there is

$$P_{S_3}(\lambda) = \left(\lambda^2 + \lambda(\mu_1 + \varepsilon k_1\bar{T}_3) + k_1\bar{T}(r_2 - \varepsilon r_1)\right)\left(\frac{r_1 k_2}{k_1} - \mu_2 - \lambda\right)$$

and similarly as for the state S_2, if $\lambda_3 = \frac{r_1 k_2}{k_1} - \mu_2 < 0$, then S_3 is stable assuming $\varepsilon < \frac{r_1}{r_2}$ which yields that S_3 exists. □

Remark 2. If the states S_2 and S_3 do not exist, then we easily calculate eigenvalues for S_1 as $\lambda_1 = r_1 - \frac{k_1\alpha}{\mu_1}$, $\lambda_2 = -\mu_1$, $\lambda = \frac{k_2\alpha}{\mu_1} - \mu_2$ and see that they are negative, which yields local stability of S_1. We also suspect global stability in this case, because the immune system is strong.

For the parameters values used in simulations in Section 4 the state S_2 does not exist. We have performed the series of simulations for the full system and observe that the type of dynamics for both Eqs. (2) and (3) for $\tau = 0$ is similar.

3.3. **Case $\tau > 0$.** In this subsection we look for the stability switches with increasing delay. Because we are interested in comparing the control case of the cancer – immune system interactions to the HIV related cancer – immune system interactions we are mainly interested in the case when inequality $r_1 > \frac{\alpha k_1}{\mu_1}$ holds. The same inequality is assumed in Theorem 3.1 and Proposition 1.

We perform the analysis for the full system (2) but the analysis for Eqs. (3) is a part of that analysis. Moreover, stability changes for the steady state S_3, which we study below, are the same as stability changes for the positive steady state $(\bar{T}, \bar{E})$ for Eqs. (3).

We focus on the stability of S_3 and hence we calculate the characteristic matrix for Eqs. (2) at S_3, which reads

$$\Delta(\lambda,\tau) =$$

$$\begin{pmatrix} -\lambda & -k_1\bar{T}_3 & 0 \\ r_2 - r_1 + (1-\varepsilon)r_1 e^{-\lambda\tau} & -\mu_1 - k_1\bar{T}_3 + (1-\varepsilon)k_1\bar{T}_3 e^{-\lambda\tau} - \lambda & -k_2\bar{E}_3 \\ 0 & 0 & k_2\bar{E}_3 - \mu_2 - \lambda \end{pmatrix}$$

We see that

$$\begin{aligned} W(\lambda,\tau) &= \det\Delta(\lambda,\tau) = (k_2\bar{E}_3 - \mu_2 - \lambda)W_2(\lambda,\tau)\,, \\ W_2(\lambda,\tau) &= P(\lambda) + Q(\lambda)e^{-\lambda\tau}\,, \end{aligned} \tag{6}$$

where

$$P(\lambda) = \lambda^2 + (\mu_1 + k_1\bar{T}_3)\lambda + (r_2 - r_1)k_1\bar{T}_3, \quad Q(\lambda) = k_1\bar{T}_3(1-\varepsilon)(-\lambda + r_1)$$

and W_2 is the characteristic quasi-polynomial for the reduced two-variable system (2) with $I \equiv 0$.

From the form (6) of the characteristic quasi-polynomial we have the following.

Corollary 1. *If $r_2 < \varepsilon k_1$ and*

- $\mu_2 < k_2\bar{E}$, *then if* $(\bar{T}, \bar{E})$ *is stable as a steady state in the two-variable system, then* S_3 *is stable as a steady state for system* (2)*;*
- $\mu_2 > k_2\bar{E}$, *then* S_3 *is unstable.*

Let us study the stability changes in the two-variable system with the characteristic quasi-polynomial W_2. If $r_2 < \varepsilon k_1$, then $(\bar{T}, \bar{E})$ is stable for $\tau = 0$. Studying stability switches we follow the ideas from [7]. The necessary condition for stability switches is the existence of purely imaginary eigenvalue:

$$\lambda = i\omega, \quad \omega > 0, \quad \text{for some threshold value } \tau_{th}.$$

If $i\omega$ is an eigenvalue for τ_{th}, then

$$W_2(i\omega, \tau_{th}) = 0 \Longrightarrow P(i\omega) = -Q(i\omega)\mathrm{e}^{-i\omega\tau_{th}}$$

which implies

$$||P(i\omega)|| = ||Q(i\omega)||.$$

Defining

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

we get the auxiliary function F which positive zeros define eigenvalues $i\omega$. Let $y = \omega^2$. There is

$$F(y) = y^2 + Ay + B$$

with

$$A = \varepsilon(2-\varepsilon)k_1^2\bar{T}^2 + 2(\mu_1 - r_2 + r_1)k_1\bar{T} + \mu_1^2$$

and

$$B = (r_2 - r_1(2-\varepsilon))(r_2 - r_1\varepsilon)k_1^2\bar{T}^2.$$

We have $r_2 - r_1\varepsilon > 0$ and $\varepsilon < 1$. We can show that $A > 0$. Hence,

1. if $r_2 - r_1(2-\varepsilon) > 0$, then there is no positive roots of F;
2. if $r_2 - r_1(2-\varepsilon) < 0$, then F has exactly one positive root $\bar{y}$.

Theorem 3.2. *Assume that the steady state* S_3 *of system* (2) *exists, that is the state* $(\bar{T}, \bar{E})$ *for the system* (3) *also exists.*

If $r_2 - r_1(2-\varepsilon) > 0$, *then* $(\bar{T}, \bar{E})$ *is stable for any positive delay* $\tau > 0$.

If $r_2 - r_1(2-\varepsilon) < 0$, *then there exists the threshold dealy* $\tau_{th} > 0$ *such that* $(\bar{T}, \bar{E})$ *is stable for* $\tau < \tau_{th}$, *loses stability at* $\tau = \tau_{th}$ *in which Hopf bifurcation occurs.*

Proof. If $r_2 - r_1(2-\varepsilon) < 0$, then there exists a pair of purely imaginary eigenvalues $\pm i\omega_0$ with $\omega_0 = \sqrt{\bar{y}}$ which is the unique positive root of the auxiliary function F. For these eigenvalues we calculate the sinus and cosine of $\omega_0\tau_{th}$ from the identity

$$\cos(\omega_0\tau_{th}) - i\sin(\omega_0\tau_{th}) = e^{-i\omega_0\tau_{th}} = \frac{P(i\omega_0)}{Q(i\omega_0)} =$$

$$\frac{\Re P(i\omega_0)\Re Q(i\omega_0) + \Im P(i\omega_0)\Im Q(i\omega_0)}{||Q(i\omega_0)||^2} - i\frac{\Re P(i\omega_0)\Im Q(i\omega_0) - \Im P(i\omega_0)\Re Q(i\omega_0)}{||Q(i\omega_0)||^2}.$$

Hence,

$$\tau_{th} = \frac{\arg\left(\frac{\Re P(i\omega_0)\Re Q(i\omega_0)+\Im P(i\omega_0)\Im Q(i\omega_0)}{||Q(i\omega_0)||^2} - i\frac{\Re P(i\omega_0)\Im Q(i\omega_0)-\Im P(i\omega_0)\Re Q(i\omega_0)}{||Q(i\omega_0)||^2}\right)}{\omega_0}.$$

Finally, the change of stability occurs when

$$\frac{d\Re\lambda}{d\tau}\Big|_{\tau=\tau_{th}} > 0.$$

However, this value has the same sign, compare [7], as

$$F'(y)\Big|_{y=\omega_0^2}$$

and it is positive when F has only one positive zero.

Thus, $(\bar{T}, \bar{E})$ loses stability at τ_{th} and Hopf bifurcation occurs.

If $r_2 - r_1(2-\varepsilon) > 0$, then the characteristic quasi-polynomial W_2 has no purely imaginary roots and therefore the change of stability is impossible. □

Remark 3. From the analysis presented above it is obvious that the state S_3 cannot recover stability for larger values of τ.

Remark 4. Studying stability of S_1 when S_2 and S_3 do not exist we easily see that the eigenvalues at S_1 do not depend on the delay. This implies that there is no stability changes for S_1 with increasing delay.

4. **Numerical simulations.** In this section we would like to illustrate the analytical results presented in the previous section. We consider two cases: infection by the HIV virus after the development of primary tumor and the tumor development in the host already infected by the HIV virus. In the first case we address the issue of the tumor whose further growth has been successfully prevented by the healthy (not infected by the HIV virus) immune system. Thus, we consider the case when

$$\frac{\alpha k_1}{\mu_1} < r_1 < \frac{r_2}{\varepsilon}\,,$$

that is when the unique positive steady state for Eqs. (4) exists and is globally asymptotically stable (see Theorem 3.1). The set of parameters we have chosen for the simulations is presented in Table 2. For the simulations we assume constant

r_1	k_1	r_2	α/μ_1	k_2'	k_3	μ_2	δ	c	μ_1	ε	N
0.1	10^{-4}	0.03	800	5×10^{-5}	2.4×10^{-5}	0.3	0.3	3.8	0.03	0.1	275

TABLE 2. Parameters values chosen for the numerical simulations.

initial functions

$$T(t) = 50 \quad \text{and} \quad E(t) = 780 \quad \text{for} \quad t \le 0\,.$$

In Fig. 2 we present the solutions to Eqs. (3) for the chosen set of parameters and different values of delay. As we can see, for the chosen values of the time delay growth of the tumor is successfully prevented by the immune system and the time delay causes only the appearance of oscillations around the steady state. Thus, in this case the tumor is under the healthy immune system surveillance.

Now we assume that at the time moment $t = 250$ the HIV infected effector cells appear in the system. The results of that kind of the virus introduction are presented in Fig. 3. It can be seen that for each value of delay the tumor starts to grow rapidly due to the presence of the infecting cells. The virus causes the decrease of the healthy effector cells concentration which allows the tumor to escape from the surveillance of the immune system.

That kind of numerical result is consistent with the analytical results presented in previous section, that is if before the HIV infection there exists globally stable positive steady state, then after the introduction of the infected effector cells, the

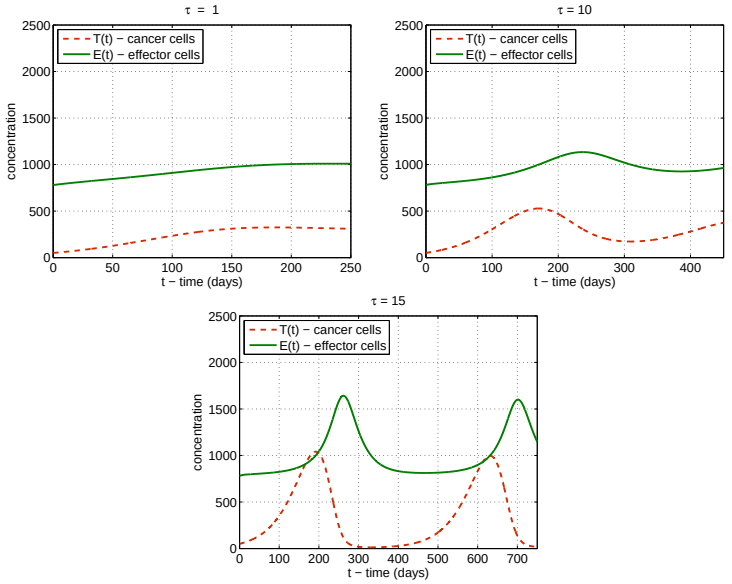

FIGURE 2. Solution to Eqs. (3) for the parameters values presented in Table 2 and for different values of the time delay.

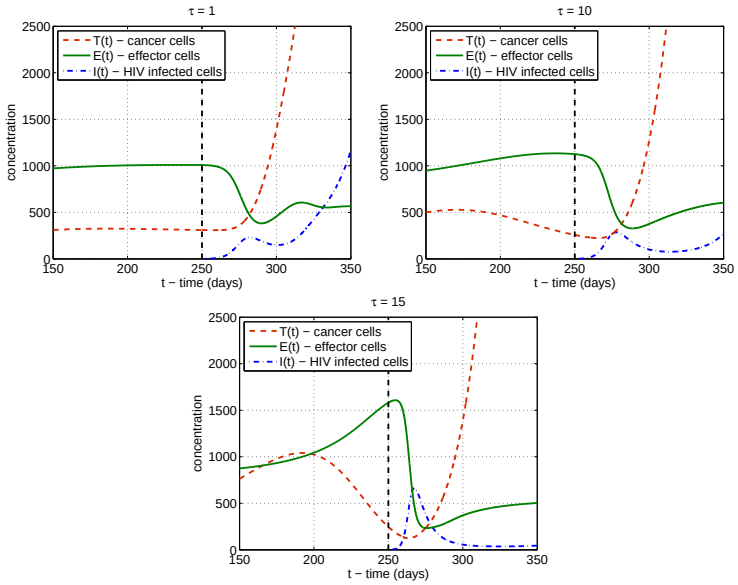

FIGURE 3. Solutions to Eqs. (2) in the case when the HIV infected cells of the initial amount $E_0 = 1$ are introduced at $t = 250$.

concentration of the cancer cells tends to infinity with $t \to +\infty$. In other words, if before the infection the patient has the primary tumor which is kept by the immune system under control, then the HIV infection causes the development of that tumor. Although the analytical results predict unbounded tumor growth, it

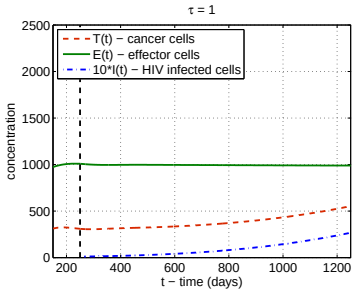

FIGURE 4. Solutions to Eqs. (2) in the case when the HIV infected cells of the initial amount $E_0 = 1$ are introduced at $t = 250$ and the following parameters are fixed at: $k_2' = 0.000015$, $N = 100$.

should be marked that it is the asymptotic behavior. As we can see in Fig. 4, the long lasting coexistence of the HIV virus and the tumor cells is possible, depending on the model parameters. Hence, it is obvious that such type of the dynamics can be observed in a clinical practise.

Now, we study the case of the primary HIV infection. We use the same parameters set as in the previous case except the value of k_1 parameter

$$k_1 = 0.00022\,,$$

that is we assume higher efficacy of the immune system in eliminating the cancer cells. If the tumor is not present in the system, we need only to specify the initial conditions for the healthy and infected effector cells at $t = 0$

$$E_0 = 780 \quad \text{and} \quad I_0 = 10\,.$$

In Fig. 5 the result of numerical simulation in that case is presented. As it can be seen the presence of the HIV virus causes the long lasting decrease in the concentration of the healthy effector cells. Thus, in this case the immune system is impaired by the virus. Now we consider the introduction of the cancer cells to the

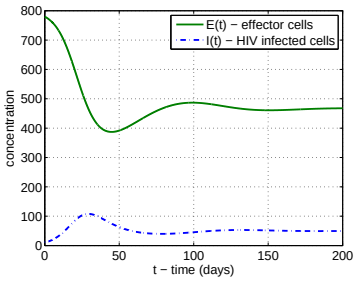

FIGURE 5. Solution to Eqs. (2) in a cancer free case for the parameters values presented in Table. 2 and for $k_1 = 0.00022$.

HIV infected system as we would like to verify if the immune system is able to prevent the tumor development. In Fig. 6 the numerical simulations in that case are presented. As we can see for each chosen value of the time delay the partially impaired immune system is still able to successfully eradicate the tumor. Thus, even in a patient with the HIV virus the immune system might be still able to keep

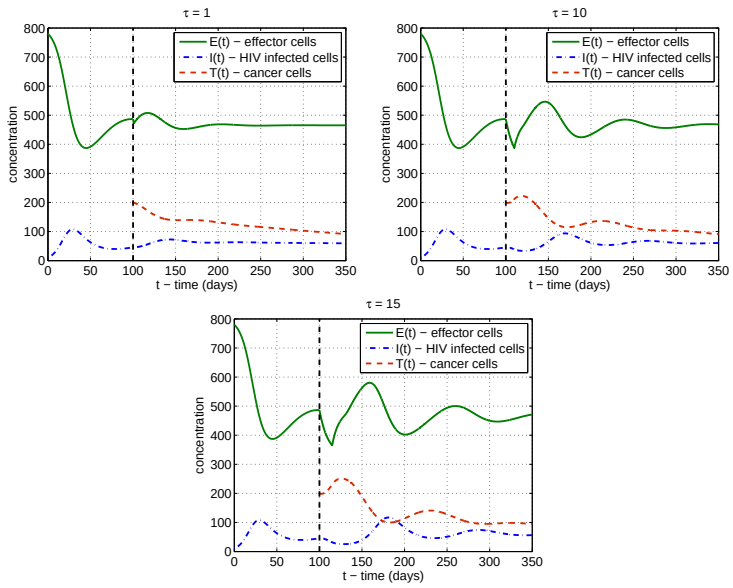

FIGURE 6. Solutions to Eqs. (2) in the case when the cancer cells in the initial amount of $T_0 = 200$ are introduced at $t = 100$.

the tumor under surveillance. This may explain the large time lag between the primary infection by the HIV virus and the occurrence of the first AIDS syndromes as not every cancer is able to escape from the surveillance of even impaired immune system.

5. **Discussion.** Virus related cancers, such as Kaposi's sarcoma, cervical cancer or B cell lymphoma are significant burden to the patients infected by HIV. It is important to understand the causes of higher incidence of those cancers in individuals with the immune deficiency related to the HIV virus. It is known that there exists the immune response against cancer cells and in some cases the immune system can prevent the cancer development. It is argued that the HIV virus decreases the immune system ability to fight the cancer and this allows the cancer to escape from the surveillance of the immune system.

In this paper we have developed the mathematical model of the HIV related cancer–immune system interactions *in vivo* which takes into account the delay describing the time needed by $CD4^+$ T lymphocyte to regenerate after eliminating one cancer cell. The model assumes also the linear response of the immune system to the tumor presence. We perform the basic mathematical analysis of the model which is very preliminary and should be extended for the cases when the HIV infection is primary and the cancer is its consequence.

In the absence of the HIV virus the model successfully reproduces the immune surveillance phenomenon. Depending on the parameters values we have three possible cases: the healthy immune system eradicate the tumor completely, the tumor is kept at some level of development or the tumor escapes from the immune surveillance and grows unlimitedly. We are especially interested in first two cases as it appears that their existence is compromised by the immune deficiency related to the HIV virus. In the presence of the infected effector cells the model predicts two

interesting phenomenas concerning both cases. In the first case it occurs that, if before the infection the patient has the primary tumor which is kept by the immune system under control, then the HIV infection causes the rapid development of that tumor. However, depending on the model parameters the concentrations of the tumor cells and the HIV virus can be kept on the relatively small level for a long time and such type of the behavior is also observed in reality. In the second case it appears that even in a patient with the HIV virus the immune system might be still able to eradicate the tumor. This may explain the large time lag between the primary infection by the HIV virus and the occurrence of the first AIDS syndromes as not every cancer is able to escape from the surveillance of even impaired immune system.

The next step should be to investigate the influence of several kinds of cancer/HIV therapies on the systems dynamics. It is crucial that the influence of such kind of treatments cannot be studied separately as it is well known that the immune therapy causes the recruitment of additional effector cells that might be subsequently infected by the HIV virus and chemotherapy is not selective to the cancer cells.

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