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MODEL OF AIDS-RELATED TUMOUR WITH TIME DELAY

Abstract. We present and compare two simple models of immune system and cancer cell interactions. The first model reflects simple cancer disease progression and serves as our "control" case. The second describes the progression of a cancer disease in the case of a patient infected with the HIV-1 virus.

1. Introduction. Human immunodeficiency virus (HIV) is a retrovirus often leading to a disease called acquired immunodeficiency syndrome (AIDS) which is estimated to be responsible for killing more than 25 million people since its first recognition in 1981 up to 2005 (cf. data in [12]).

AIDS is characterized by deeply impaired functionality of the immune system and by various clinical expressions. The first target for the virus is the dendritic cells present in the mucous membrane. After being infected, the dendritic cells move to surrounding lymph nodes, where during the antigen presentation the T cells become infected. Cells which are actively producing virus are T helper cells, which are in turn destroyed both by HIV and by T cytotoxic cells. Patients with diagnosed AIDS have fewer than 200 T $CD4^+$ cells/mm^3, while in healthy persons this value is estimated to be between 800 and 1200 T $CD4^+$ cells/mm^3 [8]. Basically four stages of the disease can be distinguished: incubation period, acute infection, latency stage and AIDS. The initial incubation period upon infection is asymptomatic and usually lasts between two and four weeks. The second stage, acute infection, lasts an average of 28 days and can include symptoms similar to those of influenza or infectious mononucleosis. The third, latency stage, that occurs later, shows few or no symptoms and can last anywhere from two weeks to twenty years and beyond. And finally, the fourth stage of HIV infection

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(AIDS) shows symptoms such as various opportunistic infections and various cancers such as Kaposi's sarcoma, cervical cancer and cancers of the immune system known as lymphomas [15].

Defensive immune mechanisms are usually turned on when tumour cells appear. Therefore, patients with chronic state of immunosuppression have substantially increased incidence of some tumours, for instance patients with HIV infection develop lymphoma about hundred times more often and Kaposi's sarcoma about four hundred times more often than people non-infected. Other tumours that have high prevalence among HIV patients are highly malignant cervical cancer, rhabdomyosarcoma among children and rectal carcinoma [3, 4, 8]. It is therefore of great importance to better understand links between HIV-related immunosuppression and cancer prognosis.

A review of various aspects of AIDS and mathematical modelling of HIV infection can be found e.g. in [12]. First mathematical models of the disease were based on the idea of epidemic modelling (see e.g. [1]). Very simple mathematics was used by Ho et al. [7] to interpret experimental data and to show that during the first three stages of the disease which are asymptomatic or symptoms suggest other diseases, replication of HIV-1 is continuous and highly productive. On that basis many mathematical models of HIV infection and therapy were proposed (see e.g. Perelson and Nelson [16] and references therein). Most of these models are formulated as systems of ordinary differential equations. However, delay of reaction was also included, leading to systems of retarded differential equations (see e.g. Nelson [13], Nelson et al. [14]).

On the other hand, the literature devoted to mathematical modelling of tumour growth is even richer than that devoted to AIDS modelling. A review of simple models of tumour dynamics and treatment can be found in Wheldon [17], while a more recent review is presented in [5].

Previous mathematical models for AIDS-related cancers include those of [9, 10]. Both of these papers examine how cancer cells respond to the immune system being infected with HIV virus. However, in our opinion both systems need some modifications to reflect better the clinical reality.

In [2] we have proposed a very simple model of immune response to cancer diseases. On the basis of this model we have also proposed an AIDS-related model. The models studied in this paper essentially follow the ideas of [2]. However, in [2] we have assumed one-to-one tumour-immunocompetent cell encounters. In this paper we generalise it using two different coefficients for encounters in equations describing the dynamics of cancer cells and immunocompetent cells.

1.1. *Presentation of the models.* In the first model which describes interactions between the immune system and cancer cells we use two vari-

ables, $T(t)$ and $E(t)$, reflecting the dynamics of the cancer and immunocompetent cells, respectively. Both components are identified by their concentrations without taking into account their three-dimensional distribution.

The total number of cancer cells in a body depends on the rates of their division and destruction by the immune system. We assume that the number of cancer cells increases by division exponentially and that their decline occurs mainly through the action of NK cells. Therefore, the dynamics of cancer cells is described by the following equation:

$$\frac{dT}{dt} = r_1 T(t) - a k_1 T(t) E(t),$$

where

- $r_1 T(t)$ represents the growth in the number of cancer cells due to proliferation, and r_1 is the tumour's proliferation rate;
- $a k_1 T(t) E(t)$ describes the reduction of tumour cells by the activity of immunocompetent cells (direct destruction of cancer cells and their elimination through production of the tumour necrosis factor TNF, see [8]), while $1/a$ represents the number of immunocompetent cells needed to neutralise one cancer cell.

The number of immunocompetent cells depends on their growth, which we assume is limited (i.e. does not surpass a certain level) and on the processes of inactivation and activation due to immune reactions. As already mentioned, we assume that the decline of cancer cells occurs mainly through the NK cells action. After killing a cancer cell, NK lymphocyte becomes inactive and needs some time to become active again. However, a small percentage (denoted by a constant ε) of NK cells do not survive this cycle and dye after killing a cancer cell (see [8]). Hence, the second equation reads

$$\frac{dE}{dt} = r_2 E(t)\left(1 - \frac{E(t)}{m}\right) - k_1 T(t) E(t) + (1-\varepsilon) k_1 T(t-\tau) E(t-\tau),$$

where

- $r_2 E(t)(1 - E(t)/m)$ denotes the limited growth of immunocompetent cells (a logistic term is used to model this);
- $k_1 T(t) E(t)$ describes inactivation of NK cells that occurs after killing a cancer cell;
- $(1-\varepsilon) k_1 T(t-\tau) E(t-\tau)$ describes subsequent activation of NK cells, where τ is the mean time needed for this activation.

Therefore, the full model without HIV infection is described by the system

$$(1) \quad \begin{cases} \dfrac{dT}{dt} = r_1 T(t) - a k_1 T(t) E(t), \\ \dfrac{dE}{dt} = r_2 E(t)\left(1 - \dfrac{E(t)}{m}\right) - k_1 T(t) E(t) + (1-\varepsilon) k_1 T(t-\tau) E(t-\tau), \end{cases}$$

where T is the density of tumour/cancer cells and E reflects the density of healthy immunocompetent cells. The model presented above differs from that proposed in [2] only in the first equation where the coefficient a is used to distinguish between the instances of NK-cancer cell interactions and cancer-NK cell ones. A biological interpretation of this coefficient implies that $a \leq 1$. This is caused by the fact that typically at least one NK cell is needed to neutralise one cancer cell.

In the model with HIV infection some of the immunocompetent cells become inactive due to the viral infection. Therefore, the model consists of three equations corresponding to the cancer cell density denoted by $T(t)$, non-infected immunocompetent cell density $E(t)$ and inactive immunocompetent cell density $I(t)$. We assume that only non-infected immunocompetent cells are able to kill cancer cells, and therefore the first equation describing the dynamics of cancer cells is the same as in (1).

In the second equation, describing the dynamics of non-infected immunocompetent cells, we assume that the maximal density of immunocompetent cells (denoted by m) is the same for both populations of infected and non-infected immunocompetent cells. The next two terms in the second equation are the same as in the model (1). The last term describes the process of viral infection. This leads to the following equation:

$$\begin{aligned} \frac{dE}{dt} = r_2 E(t)\left(1 - \frac{E(t)+I(t)}{m}\right) - k_1 T(t) E(t) \\ + (1-\varepsilon) k_1 T(t-\tau) E(t-\tau) - k_2 E(t) I(t). \end{aligned}$$

The new, third equation describes the dynamics of immunocompetent cells infected by the HIV virus. The first term of this equation corresponds to the infection rate which we assume is proportional to the amount of virions circulating in bloodstream (which we assume to be proportional to the density of infected cells) and immunocompetent cells. The second (and the last) term corresponds to the death of infected immunocompetent cells. We also assume that infected cells do not proliferate. Hence, the dynamics of I is described by the equation

$$\frac{dI}{dt} = k_2 E(t) I(t) - \mu I(t).$$

This makes the whole model with HIV infection look as follows:

$$(2)\qquad \begin{cases} \dfrac{dT}{dt} = r_1 T(t) - a k_1 T(t) E(t), \\ \dfrac{dE}{dt} = r_2 E(t)\left(1 - \dfrac{E(t)+I(t)}{m}\right) - k_1 T(t) E(t) \\ \qquad\qquad + (1-\varepsilon) k_1 T(t-\tau) E(t-\tau) - k_2 E(t) I(t), \\ \dfrac{dI}{dt} = k_2 E(t) I(t) - \mu I(t), \end{cases}$$

where: T is the density of tumour/cancer cells, E the density of healthy immunocompetent cells, I the immunocompetent cells infected by the HIV virus, and again the system (2) differs from those proposed in [2] only in the first equation, as in the case of the system (1).

2. Asymptotic analysis. We start the asymptotic analysis by determining the steady states of the systems (1) and (2). From the first equation of both systems we have either $\bar{T} = 0$ or $\bar{E} = r_1/(ak_1)$. For (1), if $\bar{T} = 0$, then $\bar{E} = 0$ or $\bar{E} = m$. On the other hand, if $\bar{E} = r_1/(ak_1)$, then $\bar{T} = r_2(ak_1 m - r_1)/(\varepsilon a k_1^2 m)$. Therefore, for (1) there are always two steady states $A = (0,0)$ and $B = (0,m)$, while the third steady state

$$D = \left(\frac{r_2(ak_1 m - r_1)}{\varepsilon a k_1^2 m}, \frac{r_1}{ak_1}\right)$$

exists if $r_1/a < k_1 m$.

From the last equation of (2) we get $\bar{I} = 0$ or $\bar{E} = \mu/k_2$. If $\bar{T} = 0$ and $\bar{I} = 0$, then there are two steady states: the trivial one $A_H = (0,0,0)$ and the state describing the healthy organism $B_H = (0,m,0)$, analogous to the steady states A and B for (1). If $\bar{I} \neq 0$ we get the tumour free – virus present state

$$C_H = \left(0, \frac{\mu}{k_2}, \frac{r_2(k_2 m - \mu)}{k_2(k_2 m + r_2)}\right),$$

existing under the assumption $m > \max\{\mu/k_2, r_2/k_2\}$ or $m < \min\{\mu/k_2, r_2/k_2\}$. Finally, if $\bar{T} \neq 0$ we have the fourth steady state

$$D_H = \left(\frac{r_2(ak_1 m - r_1)}{\varepsilon a k_1^2 m}, \frac{r_1}{ak_1}, 0\right),$$

again existing under the assumption $r_1/a < k_1 m$. The steady state with all coordinates positive does not exist in the generic case but in the non-generic case it exists under the assumption $\mu a k_1 = k_2 r_1$.

2.1. *The case without delay.* First we assume that $\tau = 0$. In the two-dimensional phase space for the system (1) we can restrict our analysis to the subspace $\Omega = \{(T,E) : T \geq 0,\ E \in [0,m]\}$. Similarly, for the system (2) the subspace $\Omega_H = \{(T,E,I) : T \geq 0,\ E \in [0,m],\ I \geq 0\}$ is invariant. Positivity of solutions to both systems in this case is obvious, while the

boundedness of E is implied by the inequality $\dot{E} \leq r_2 E(1 - E/m)$, which yields $E \leq \max\{E_0, m\}$.

The behaviour of both systems depends on the model parameters, namely on the magnitude of r_1/a, that is, the virus reproduction rate and the number of immunocompetent cells needed for neutralising one cancer cell.

PROPOSITION 1. *For the system* (1):

1. *The steady state A is unstable independently of the model parameters.*
2. *If $r_1/a > k_1 m$, then the steady state B is unstable and the positive steady state D does not exist. Moreover, in Ω every solution has the following properties: T increases to ∞ and $E \to 0$ as $t \to \infty$.*
3. *If $r_1/a < k_1 m$, then the semi-trivial steady state B is locally stable and the positive steady state D is a saddle.*

Proof. To study local stability of the steady state $(\bar{T}, \bar{E})$ we calculate the Jacobi matrix:

$$J(\bar{T}, \bar{E}) = \begin{pmatrix} r_1 - ak_1\bar{E} & -ak_1\bar{T} \\ -\varepsilon k_1\bar{E} & r_2(1 - 2\bar{E}/m) - \varepsilon k_1\bar{T} \end{pmatrix}.$$

For the trivial steady state there are two real positive eigenvalues $\lambda_i = r_i$, $i = 1, 2$. Hence, A is an unstable node. For the semi-trivial steady state one gets $\lambda_1 = r_1 - ak_1 m$ and $\lambda_2 = -r_2 < 0$. Therefore, B is a node: stable for $r_1/a < k_1 m$ and unstable for $r_1/a > k_1 m$. If $r_1/a < k_1 m$, then the positive steady state D exists and $\operatorname{tr} J(D) = -r_2\bar{E}/m < 0$, $\det J(D) = -\varepsilon a k_1^2 \bar{E}\bar{T} < 0$, which implies that D is a saddle.

In Ω for $r_1/a > k_1 m$ we have $\dot{T} > (r_1 - ak_1 m)T$ for all $t \geq 0$. Therefore, $T(t) \geq T_0 \exp((r_1 - ak_1 m)t)$ and T increases to ∞ as $t \to \infty$. In fact the growth is exponential, because $\dot{T} \leq r_1 T$. Moreover, for sufficiently large $T > M > r_2/(\varepsilon k_1)$ one gets $\dot{E} < -\alpha E$ for $\alpha = |r_2 - \varepsilon k_1 M| > 0$, which yields $E \to 0$. ∎

Studying the phase space portraits one can say something more about the behaviour of solutions to the system (1) (see Fig. 1). If $r_1/a > k_1 m$, then the null-cline $E = r_1/(ak_1)$ for the variable T lies above the threshold $E = m$, and therefore T is always increasing in Ω. The null-cline $T = r_2(m - E)/\varepsilon k_1 m$ divides the phase space into two regions: for the points lying under it the variable E is increasing, while above it E decreases. Hence, either E increases at the beginning, reaches its maximal value on the null-cline and eventually decreases to 0, or it decreases for all $t \geq 0$.

For $r_1/a < k_1 m$ the dynamics of the system (1) is slightly more complicated. The positive steady state D exists and it is a saddle. The phase space is divided into two subspaces with different dynamics. The separatrix is formed by the unstable manifold of the state D. The solutions for initial

data above this curve tend to the semi-trivial steady state $(0, m)$, which is locally stable. The solutions for initial data below this curve have the same properties as in the first case, that is, $T \to \infty$ and $E \to 0$. In Fig. 2 we see two examples of phase space portraits for the system (1) for $r_1/a < k_1 m$ and different values of a. As can be expected, for larger a the growth of tumour is faster. However, the difference is only quantitative and not qualitative.

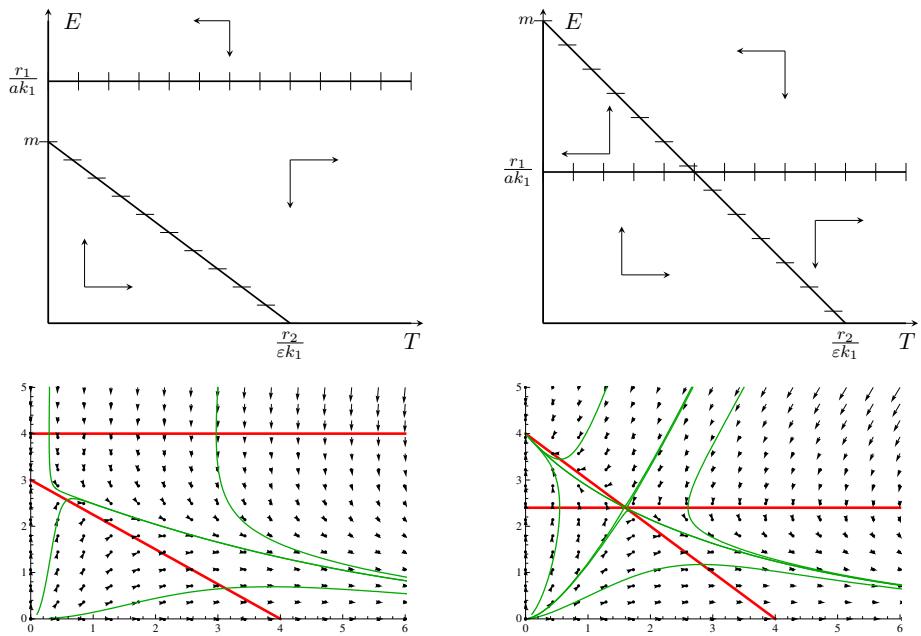

Fig. 1. Phase portraits for the system (1) without time delay

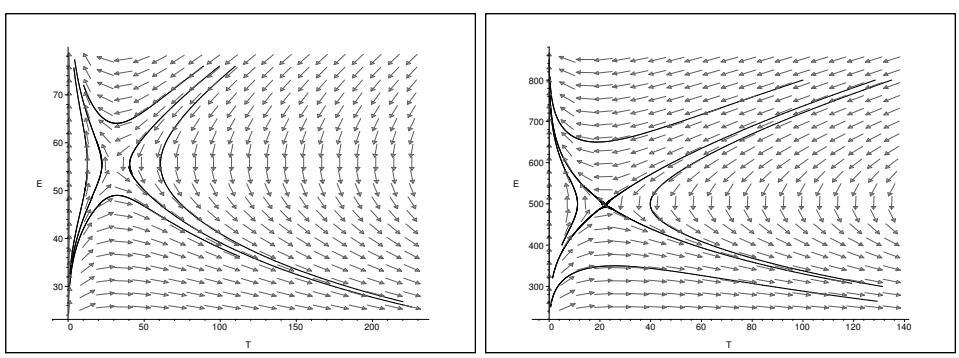

Fig. 2. Phase space portraits for the system (1) and different values of a: $a = 1$ (left) and $a = 1/9$ (right). Other parameter values: $r_1 = 0.5$, $k_1 = 0.009$, $r_2 = 0.03$, $m = 1500$ and $\varepsilon = 0.1$.

Now we turn to the system (2) with $\tau = 0$.

PROPOSITION 2. *For the system* (2):

1. *The trivial steady state A_H is unstable independently of the model parameters.*
2. *The semi-trivial steady state B_H is locally asymptotically stable if $r_1/(ak_1) < m < \mu/k_2$. If $r_1/(ak_1) > m$ or $m > \mu/k_2$, then it is unstable. Moreover, in Ω_H if $r_1/(ak_1) > m$, then for every solution, T increases to ∞, $E \to 0$ and $I \to 0$ as $t \to \infty$.*
3. *The tumour free – virus present steady state C_H is locally asymptotically stable if $r_1/(ak_1\mu) < \mu/k_2 < m$ and unstable if $\mu/k_2 > m$ or $r_1/(ak_1) > \mu/k_2$.*
4. *The tumour present – virus free steady state D_H is stable if $m < r_1/(ak_1) < \mu/k_2$ and unstable if $m > r_1/(ak_1)$ or $r_1/(ak_1) > \mu/k_2$.*

Proof. The Jacobi matrix for this system

$$J_H(T,E,I) = \begin{pmatrix} r_1 - ak_1E & -ak_1T & 0 \\ -\varepsilon k_1E & r_2(1-\frac{2E+I}{m}) - \varepsilon k_1T - k_2I & -\frac{r_2E}{m} - k_2E \\ 0 & k_2I & k_2E - \mu \end{pmatrix}.$$

It is obvious that for A_H the characteristic values are $\lambda_i = r_i$ for $i = 1, 2$ and $\lambda_3 = -\mu$. Thus, A_H is unstable and it is a saddle for (2).

For the state B_H we also easily obtain $\lambda_1 = r_1 - ak_1m$, $\lambda_2 = r_2$ and $\lambda_3 = k_2m - \mu$. Hence, B_H is locally stable for $r_1/(ak_1) < m < \mu/k_2$ and unstable if $r_1/(ak_1) > m$ or $m > \mu/k_2$. If $r_1/(ak_1) > m$, then, just as for (1), we have $T(t) \geq T_0 \exp((r_1 - ak_1m)t)$, which yields $E \to 0$, and similarly $I \to 0$.

For the third steady state C_H we obtain the following characteristic polynomial:

$$W(\lambda) = \left(\lambda - \left(r_1 - \frac{ak_1\mu}{k_2}\right)\right)\left(\lambda^2 + \frac{r_2\mu}{k_2m}\,\lambda - \frac{r_2\mu}{k_2m}\,(k_2m - \mu)\right).$$

It can be easily deduced that the steady state C_H is stable for $k_2r_1 < ak_1\mu$ and $k_2m > \mu$, which is equivalent to $r_1/(ak_1) < \mu/k_2 < m$.

For the steady state D_H the characteristic polynomial is

$$W(\lambda) = \left(\lambda - \left(\frac{k_2r_1}{ak_1} - \mu\right)\right)\left(\lambda^2 + \frac{r_1r_2}{ak_1m}\lambda + \frac{r_1r_2}{ak_1m}\,(ak_1m - r_1)\right).$$

Thus, the steady state D_H is stable for $k_1m < r_1/a < \mu k_1/k_2$. ∎

Now, we would like to compare the dynamics of tumour with and without HIV infection. We follow the idea presented in [2] and obtain the same results. Let $\bar{T}$, $\bar{E}$ denote the variables of the system (1) and T, E, I be the variables for the system (2), as before. We study the dynamics of the differences $x =$

$T - \bar{T}$, $y = \bar{E} - E$. Consider the system of equations for x and y:

$$(3) \quad \begin{cases} \dot{x} = (r_1 - ak_1E)x + k_1\bar{T}y, \\ \dot{y} = (r_2(1 - y/m) - 2r_2E/m - \varepsilon k_1\bar{T})y + \varepsilon k_1Ex + (k_2 + r_2/m)EI, \end{cases}$$

where $\bar{T}$, E and I are non-negative parameters. Assume that $x_0 = 0$, $y_0 = 0$ and $I_0 > 0$, which corresponds to the beginning of HIV infection at $t = 0$. Moreover, $\bar{T}_0 > 0$ and $E_0 > 0$. Therefore, $\dot{x}(0) = 0$ and $\dot{y}(0) = (k_2 + r_2/m)E_0I_0 > 0$, which implies that $y(t)$ increases and is positive on some interval $(0, t_1)$. This entails that $x(t)$ also starts to increase. The form of (2) implies that both variables are positive for all $t > 0$. Hence, we have the same conclusion as in [2] for the system with $a = 1$: in the case without delay the population of cancer cells is larger when the HIV infection occurs.

2.2. *System* (1) *in the case* $\tau > 0$. Studying stability of the steady states for $\tau > 0$ one calculates the characteristic quasi-polynomial looking for solutions in exponential form. Hence, one obtains

$$\det \begin{pmatrix} r_1 - ak_1\bar{E} - \lambda & -ak_1\bar{T} \\ -k_1\bar{E} + (1-\varepsilon)k_1\bar{E}e^{-\lambda\tau} & r_2(1 - 2\bar{E}/m) - k_1\bar{T} + (1-\varepsilon)k_1\bar{T}e^{-\lambda\tau} - \lambda \end{pmatrix} = 0.$$

PROPOSITION 3. *Local stability of the steady states* A, B *and* D *for the system* (1) *does not depend on the magnitude of the delay* τ.

Proof. For A and B the characteristic quasi-polynomials are exactly the same as the characteristic polynomials for $\tau = 0$, and therefore do not depend on τ. Hence, it is obvious that stability does not depend on τ.

For the positive steady state the characteristic quasi-polynomial is

$$\lambda^2 + \lambda\left(k_1(1-\varepsilon)\bar{T} + \frac{r_2\bar{E}}{m}\right) - ak_1^2\bar{E}\bar{T} - \lambda(1-\varepsilon)\bar{T}e^{-\lambda\tau} + (1-\varepsilon)ak_1^2\bar{E}\bar{T}e^{-\lambda\tau}.$$

Defining

$$g_1(\lambda) = \lambda^2 + \lambda\left(k_1(1-\varepsilon)\bar{T} + \frac{r_2\bar{E}}{m}\right) - ak_1^2\bar{E}\bar{T},$$

$$g_2(\lambda) = (\lambda(1-\varepsilon)\bar{T} - (1-\varepsilon)ak_1^2\bar{E}\bar{T})e^{-\lambda\tau},$$

one can see that the characteristic values for D are solutions to the equation $g_1(\lambda) = g_2(\lambda)$. However, looking at the graphs of $g_1(x)$ and $g_2(x)$ for the real variable x it is easy to see that for $\varepsilon \in (0, 1)$ there always exists a positive solution $\bar{x} > 0$, which is a real positive characteristic value. This implies that D is unstable independently of the magnitude of τ. ∎

Now, assume that

$$(4) \quad E_0(h) = m \text{ for } h \in [-\tau, 0], \quad T_0(h) = 0 \text{ for } h < 0, \quad T_0(0) = T^0 > 0,$$

which can be interpreted as the healthy organism in which cancer is recognised at $t = 0$. Therefore, in $[0, \tau]$ the behaviour of (1) is the same as in the case without delay and we would like to study the dynamics for $\tau > 0$.

PROPOSITION 4. *If $r_1/a > mk_1$ and the initial condition is defined by* (4), *then the set Ω is invariant for the system* (1) *for any $\tau > 0$.*

Proof. If $r_1/a > mk_1$, then T is increasing on $[0,\tau]$. We have $\dot{E}(0) = -k_1T^0m < 0$, which implies that E decreases on some interval. Until $E < m$ we also have $E < r_1/(ak_1)$, and therefore T is increasing. Assume that there exists $\bar{t} > 0$ such that $E(\bar{t}) = m$ and $\dot{E}(\bar{t}) > 0$. If $\bar{t}$ is the first point with these properties, then for $t < \bar{t}$ we have $E(t) < m$ and T is increasing on $[0,\bar{t})$, which yields $T(\bar{t}-\tau) < T(\bar{t})$. Hence, $\dot{E}(\bar{t}) < -\varepsilon k_1T(\bar{t})m < 0$ (see [2]), which contradicts the definition of $\bar{t}$. Therefore, $E < m$ for every $t > 0$. ∎

Propositions 3 and 4 suggest that the qualitative behaviour of the system (1) with positive delay is similar to the case without delay.

Now consider the case $r_1/a < mk_1$. Then the dynamics of the system (1) with positive delay is much more complicated. Following the ideas presented in [2] one can show that the subspace Ω may not be invariant for positive delay in this case. Clearly, assume that T_0 is such that the solution lies in the basin of attraction of the steady state B and rewrite the variables of the system as the deviations from the steady state, that is, $T(t) = 0 + u(t)$ and $E(t) = m + v(t)$ with u and v sufficiently small. Consider the first order approximation of the system (1), which reads

$$\begin{cases} \dot{u} = (r_1 - mak_1)u(t), \\ \dot{v} = -r_2v(t) - mk_1u(t) + (1-\varepsilon)mk_1u(t-\tau). \end{cases} \tag{5}$$

The first equation of the system (5) is not coupled with the second and can be easily solved, $u(t) = T^0e^{(r_1-mak_1)t} \to 0$. Then we can solve the second equation of (5) for $v_0 = E_0 - m = 0$:

$$v(t) = mk_1T^0\,\frac{e^{(r_1-mak_1)t} - e^{-r_2t}}{r_2 + r_1 - mak_1}\,((1-\varepsilon)e^{(mak_1-r_1)\tau} - 1) > 0 \tag{6}$$

for $\tau > \frac{1}{r_1-mak_1}\ln(1-\varepsilon)$. This inequality shows that E exceeds the threshold m for such values of delay. Moreover, for any $t > 0$ we can choose T_0 such that $v(t)$ is arbitrarily large. It should be noticed that it is not necessary that the initial value of E is exactly m. If $E(h) \le m$ for $h \in [-\tau, 0]$, then one can obtain the formula

$$v(t) = e^{-r_2t}\left(v_0 + mk_1T_0\,\frac{e^{(r_2+r_1-mak_1)t} - 1}{r_2 + r_1 - mak_1}((1-\varepsilon)e^{(mak_1-r_1)\tau} - 1)\right)$$

for $v_0 = E_0 - m \le 0$. However, it is obvious that for any $t > 0$ the formula above yields $v(t) > 0$ for $\tau > \frac{1}{r_1-mak_1}\ln(1-\varepsilon)$ and T_0 large enough.

2.3. *The system* (2) *in the case $\tau > 0$.* Now, we study the stability of the steady states of the system (2) for $\tau > 0$. To determine it we calculate the characteristic quasi-polynomial depending on the delay parameter τ, that is,

the determinant of

$$\begin{pmatrix} r_1 - ak_1\bar{E} - \lambda & -ak_1\bar{T} & 0 \\ -k_1\bar{E}+(1-\varepsilon)k_1\bar{E}e^{-\lambda\tau} & r_2(1-\frac{2\bar{E}+\bar{I}}{m}) - k_1\bar{T}+(1-\varepsilon)k_1\bar{T}e^{-\lambda\tau} - k_2\bar{I}-\lambda & -\frac{r_2\bar{E}}{m}-k_2\bar{E} \\ 0 & k_2\bar{I} & k_2\bar{E}-\mu-\lambda \end{pmatrix}.$$

PROPOSITION 5. *Local stability of the steady states A_H, B_H, C_H and D for the system* (2) *does not depend on the magnitude of the delay τ.*

Proof. It can be easily seen that for A_H, B_H and C_H the characteristic quasi-polynomials are the same as the characteristic polynomials in the case with $\tau = 0$. Therefore, stability of these states does not depend on τ.

For the steady state D_H we obtain

$$W(\lambda) = \left(\lambda - \left(\frac{k_2 r_1}{ak_1} - \mu\right)\right) W_1(\lambda)$$

with

$$W_1(\lambda) = \lambda^2+\alpha((\varepsilon-1)\beta e^{-\lambda\tau}-(\varepsilon-1)\beta+\varepsilon r_1)\lambda - r_1\alpha((\varepsilon-1)\beta e^{-\lambda\tau}+\beta) \tag{7}$$

where $\alpha = r_2/(ak_1 m\varepsilon)$ and $\beta = ak_1 m - r_1$. We recall that in the case without delay, D_H is stable for $k_1 m < r_1/a < \mu k_1/k_2$. In the case with time delay, we also need $k_2 r_1/a < k_1\mu$. Moreover, the roots of $W_1(\lambda)$ should have its real part negative. Rewrite (7) as $W_1(\lambda) = P(\lambda) + Q(\lambda)e^{-\lambda\tau}$, where

$$\begin{aligned} P(\lambda) &= \lambda^2 + \alpha(\varepsilon r_1 - \beta(\varepsilon - 1))\lambda - \alpha\beta r_1, \\ Q(\lambda) &= \alpha\beta(\varepsilon - 1)(\lambda - r_1)\,. \end{aligned}$$

If the stability switch occurs, by continuity, there must exist a purely imaginary root of W_1. For $\lambda = i\omega$ with $\omega > 0$ the equality $\|P(i\omega)\|^2 = \|Q(i\omega)\|^2$ must hold. After some computations we obtain $F(\omega) = \|P(i\omega)\|^2 - \|Q(i\omega)\|^2$:

$$F(x) = x^2 - \alpha^2\varepsilon r_1\left(2\beta\left(\varepsilon - \left(1+\frac{ak_1 m}{r_2}\right)\right) - r_1\varepsilon\right)x + \alpha^2\beta^2 r_1^2\varepsilon(2-\varepsilon), \quad x = \omega^2\,.$$

Since $\varepsilon < 1$ we have $F(0) > 0$. Therefore, we can have either zero or two positive roots of $F(x) = 0$. Existence of D_H yields $\beta = ak_1 m - r_1 > 0$. Since $\varepsilon < 1$ we have $2\beta(\varepsilon - (1 + ak_1 m/r_2)) - r_1\varepsilon < 0$. This implies that the coefficient of the linear term of F is positive, which together with $F(0) > 0$ shows that F has no real positive roots. ∎

As in the case of the system (1) we can also show that under some conditions the set Ω_H is invariant for any $\tau > 0$. In more detail, if the initial data satisfies (4) (or $E(h) \le m$ for $h \in [-\tau, 0]$) and $r_1/a > mk_1$, then Ω_H is invariant, while if $r_1/a < mk_1$, then it may not be invariant. The proof is the same as for the system (1).

To end this section we summarise the stability results obtained in Subsections 2.2 and 2.3 in the following table:

Steady state	Stability conditions for the system (2)	Stability conditions for the system (1)
$A_H = (0, 0, 0)$	always unstable	always unstable
$B_H = (0, m, 0)$	$r_1/(ak_1) < m < \mu/k_2$	$r_1 < ak_1 m$
$C_H = (0, \frac{\mu}{k_2}, \frac{r_2(k_2 m - \mu)}{k_2(k_2 m - r_2)})$	$\mu/m < k_2 < ak_1\mu/r_1$	does not exist
$D_H = (\frac{r_2(ak_1 m - r_1)}{ak_1^2 m\varepsilon}, \frac{r_1}{ak_1}, 0)$	$\mu/m < r_1/a < k_1\mu/k_2$	$\mu < r_1 m$

3. Numerical simulations. Following [10], in simulations we use the following data:

$$\begin{gathered} r_1 \in [0.05, 0.5], \quad r_2 = 0.03, \quad k_1 \in [10^{-5}, 10^{-3}], \\ k_2 \in [0.5 \cdot 10^{-5}, 5 \cdot 10^{-4}], \\ \mu = 0.3, \quad m = 1500, \quad \varepsilon = 0.1. \end{gathered} \tag{8}$$

We study the case where a healthy organism is infected with HIV virus and at $t_0 = 0$ the presence of tumour cells is recognised. For that reason we choose initial data as follows:

$$\begin{aligned} T_0(t) &= \bar{T}_0(t/\tau + 1) && \text{for } t \in [-\tau, 0], \\ E_0(t) &= m && \text{for } t \in [-\tau, 0], \\ I_0(t) &= \bar{I}_0(t/\tau + 1) && \text{for } t \in [-\tau, 0]\,. \end{aligned}$$

For the same parameters we compare the behaviour of solutions to the models (1) and (2) for $a = 1$ and $a < 1$.

In Fig. 3 we present the behaviour of the solutions when the healthy steady state is stable and the solutions converge to it. It can be easily seen that the presence of HIV as well as the parameter $a < 1$ slows down the recovery. However, in the case $a = 1$, the difference between the solutions to the models (1) and (2) can hardly be seen. On the other hand, for small a, the tumour size is greater and the concentration of the effector cells is smaller in the case of presence of HIV than without it.

In Fig. 4 we present the situation when the size of the tumour increases to infinity. Again, the presence of HIV as well as $a < 1$ speeds up the rate of the tumour increase. In that case the difference between solutions of the model with and without the presence of HIV is visible. However, again the difference is more significant for small a.

In Fig. 5 the situation when the organism recovers for $a = 1$ and the tumour size tends to infinity for some $a < 1$ is presented. For $a < 1$ more frequent oscillations of the concentration of effector cells can be observed, especially for the case with HIV infection.

4. Conclusion. In patients with tumours originating from different viruses, such as Kaposi's sarcoma (virus HHV8), cervical cancer (virus HPV)

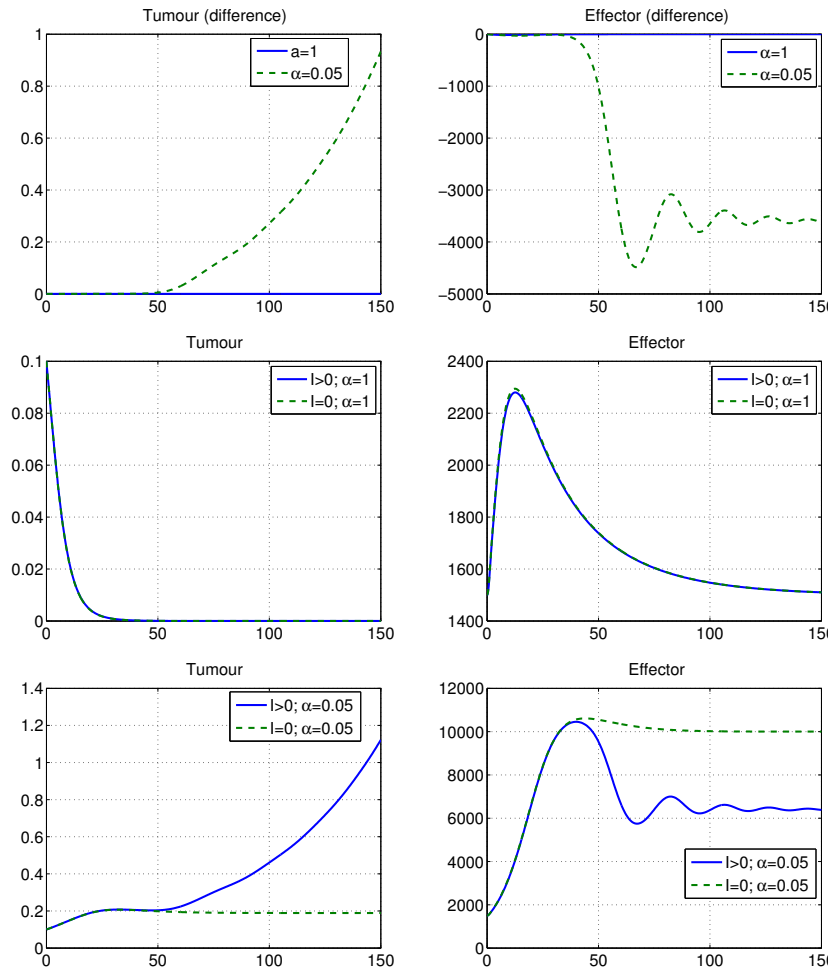

Fig. 3. An example of solution when the organism can recover in the case without HIV as well as in the presence of viruses. The first line shows the difference between the solutions in two cases: for $a = 1$ and $a = 0.05$. The second line shows the behaviour of the tumour and effector cells in the case of $a = 1$ and the third one for $a = 0.05$. Parameter values: $r_1 = 0.05$, $k_1 = 10^{-4}$, $k_2 = 5 \cdot 5 \cdot 10^{-5}$.

or B cell lymphomas (virus EBV) immune response against tumour cells has been detected, and in some cases it turned out to be successful [11]. Unfortunately, this refers only to patients with healthy immune system, which is of course not the case for HIV infected patients. Opportunistic infections and various cancers, which are the main cause of AIDS mortality, are direct results of loss of T helper cells following HIV infection.

In this paper we have presented a mathematical model of AIDS-related cancer and immune system. First, we developed a model which describes

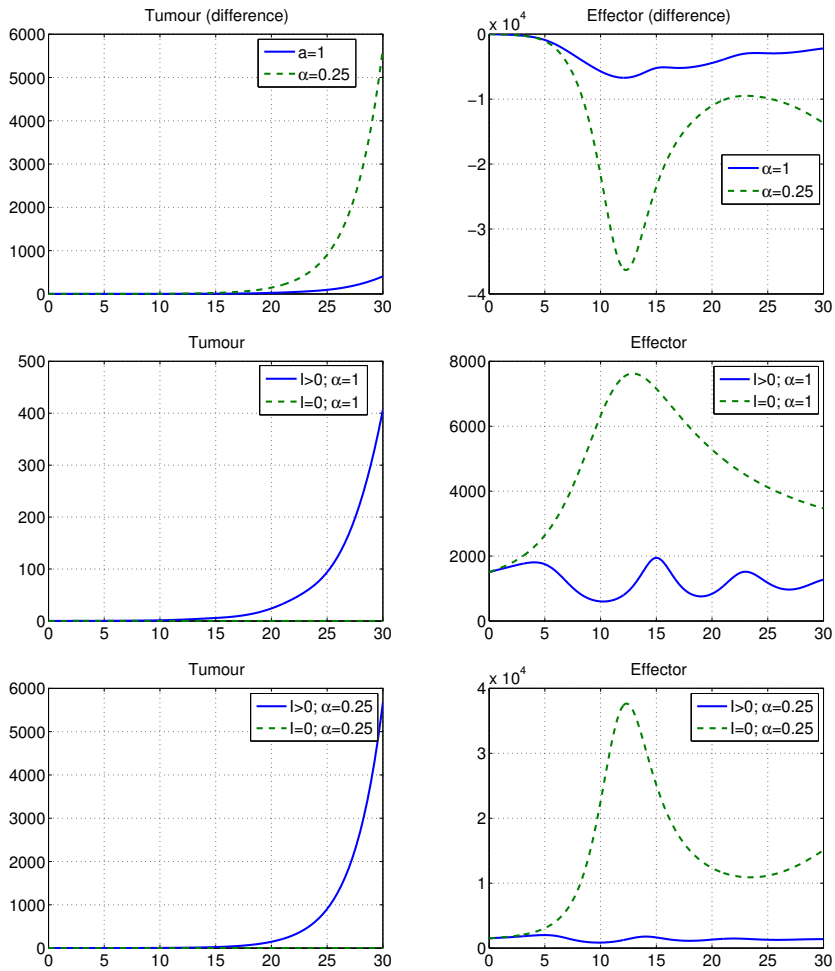

Fig. 4. An example of solution when the organism can recover in the case without HIV in two cases: for $a = 1$ and $a = 0.05$. The second line shows the behaviour of the tumour and effector cells in the case of $a = 1$, and the third one for $a = 0.25$. Parameter values: $r_1 = 0.4$, $k_1 = 10^{-4}$, $k_2 = 5 \cdot 10^{-4}$.

interactions between the immune system and cancer cells. The model differs from previous models of cancer dynamics in that it includes for the first time the effects of inactivation of immunocompetent cells resulting from their activity. It was formulated as a system of ordinary differential equations with a delay term describing the aforementioned temporal inactivation of immune cells. Then we extended the model in order to take into account the effect of HIV infection. In mathematical terms it means that we added to the basic model an equation describing the immunocompetent cells infected by HIV. We have presented some mathematical analysis of the models as well as nu-

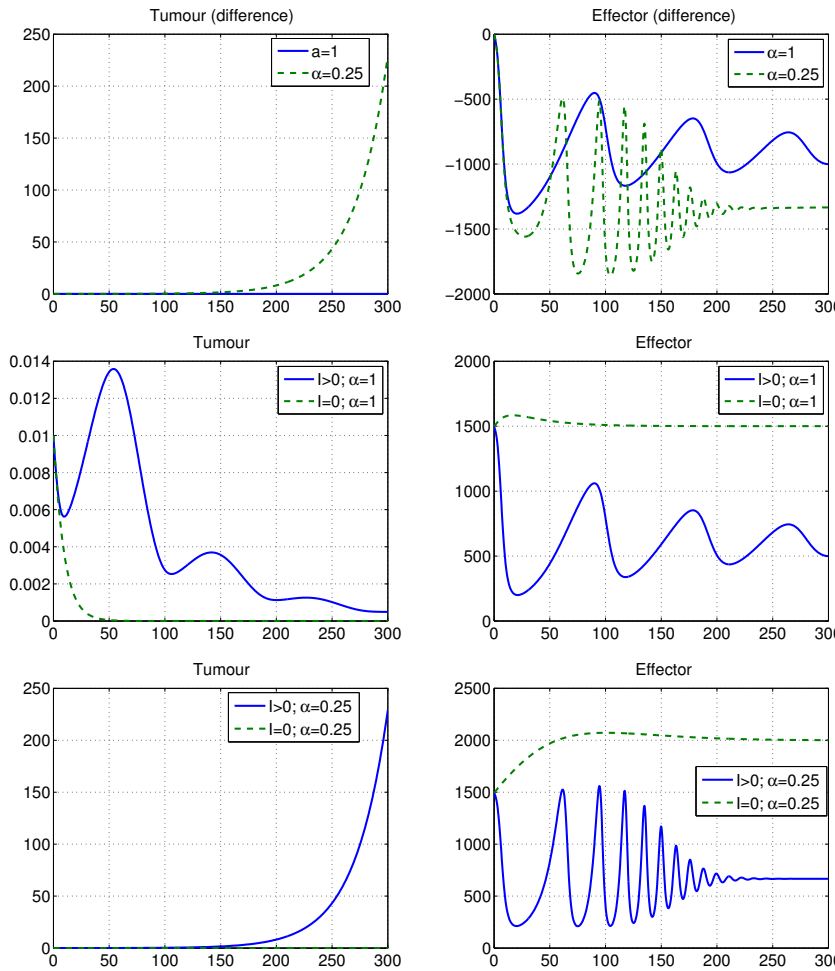

Fig. 5. An example of solution when the organism can recover faster in the case without HIV viruses. The first line shows the difference between the solutions in two cases: for $a = 1$ and $a = 0.05$. The second line shows the behaviour of the tumour and effector cells in the case of $a = 1$ and the third one for $a = 0.25$. Parameter values: $r_1 = 0.05$, $k_1 = 10^{-4}$, $k_2 = 5 \cdot 10^{-4}$.

merical simulations. By comparing the two models presented we confirmed several phenomena known from clinical experience, e.g. our numerical simulations show that significant weakness caused by HIV virus may lead to faster tumour development and spread. We have also shown that in some cases, if not affected by the HIV virus, the organism may recover.

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