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Model of AIDS-related tumour with time delay

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Resumen

We present and compare two simple models of immune system and cancer cells interactions. The first model reflects simple cancer disease progression and stands for our "control" case. The second one describes the progression of a cancer disease in the case of a patient infected with the HIV-1 virus. For the first time the model includes the effects of inactivation of immunocompetent cells resulting from its activity. We present some mathematical analysis as well as numerical simulations.

1. Introduction: presentation of the models

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 (compare data in [9]).

The review of the different aspects of AIDS and mathematical modelling of HIV infection can be found eg. in [9]. First mathematical models of the disease was based on the idea of epidemic modelling (compare eg. [1]). Most of the models of HIV infection and therapy are formulated as systems of ordinary differential equations (compare e.g. [12] and references therein). However, delay of reaction was also included leading to systems of retarded differential equations (compare e.g. [10] or [11]).

On the other hand, the literature devoted to mathematical modeling of tumour growth is even more reach than those devoted to AIDS modelling. Review of simple models of tumour dynamics and treatment can be found in [13], while more recent review is presented in [3].

Previous mathematical models for AIDS-related cancers include those of [6, 7]. Both of these papers examine how cancer cells respond to immune system infected with HIV

virus. 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 AIDS-related model. However, in [2] we have assumed one-to-one tumour-immunocompetent cell encounters. Now, we generalise it using two different coefficients for encounters in equations describing the dynamics of cancer cells and immunocompetent ones.

In the first model which describes interactions between the immune system and cancer cells we have used two variables reflecting the dynamics of 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. The number of immunocompetent cells depends on its growth, which we assume is limited and on the processes of inactivation and activation due to immune reactions. 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, small percentage (denoted by constant ε) of NK cells do not survive this cycle and dies after killing a cancer cell (see [5]).

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

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

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 encounters of NK – cancer cells interactions and cancer – NK cells ones. Biological interpretation of this coefficient implies that $a \leq 1$. It 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, this model consists of the three equations corresponding to cancer cells, non-infected immunocompetent cells and inactive immunocompetent cells density, respectively. 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 the system (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) refers to both population of infected and non-infected immunocompetent cells. Next two terms in the second equation are the same as in the model (1). The last term describes the process of viral infection.

The new, third equation describes the dynamics of immunocompetent cells infected by 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 already infected cells) and immunocompetent cells. The

second term referees to the death of infected immunocompetent cells. We assume also that infected cells do not proliferate.

Thus the whole model with HIV infection reads

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

where: T — density of tumour/cancer cells, E — density of healthy immunocommpetent cells, I — immunocompetent cells infected by 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 from determining the steady states of the systems (1) and (2). From the first equation of both systems we have either $\bar{T} = 0$ or $\bar{E} = \frac{r_1}{ak_1}$. For Eqs. (1) if $\bar{T} = 0$, then $\bar{E} = 0$ or $\bar{E} = m$. On the other hand, if $\bar{E} = \frac{r_1}{ak_1}$, then $\bar{T} = \frac{r_2(ak_1 m - r_1)}{\varepsilon a\ k_1^2 m}$. Therefore, for Eqs. (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 Eqs. (2) we get $\bar{I} = 0$ or $\bar{E} = \frac{\mu}{k_2}$. 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 Eqs. (1), respectively. 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 $m > \max\{\frac{\mu}{k_2}, \frac{r_2}{k_2}\}$ or $m < \min\{\frac{\mu}{k_2}, \frac{r_2}{k_2}\}$. 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 $\mu a k_1 = k_2 r_1$.

The case without delay. At the beginning we assume that $\tau = 0$. In the two-dimensional phase space for the system (1) we can restrict our analysis to the sub-space $\Omega = \{(T,E) : T \geq 0,\ E \in [0,m]\}$. Similarly, for the system (2) the sub-space $\Omega_H = \{(T,E,I) :\ T \geq 0,\ E \in [0,m],\ I\ \geq 0\}$ 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.

For the system (1) with $\tau = 0$ we have:

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.

Studying the phase space portraits one can say something more about the behaviour of solutions to the system (1). If $r_1/a > k_1 m$, then the null-cline $E = \frac{r_1}{ak_1}$ for the variable T lies above the threshold $E = m$ and therefore, T is always increasing in Ω. The null-cline $T = \frac{r_2(m-E)}{\varepsilon k_1 m}$ 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 decreases eventually 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. There exists the positive steady state D and it is a saddle. The phase space is divided into two sub-spaces with the different system dynamics. The separatrix is formed by the unstable manifold of the state D. The solutions the for initial data above this curve tends to the semi-trivial steady state $(0, m)$ which is locally stable. The solutions for the initial data below this curve have the same properties as in the first case, that is $T \to \infty$ and $E \to 0$.

For the system (2) with $\tau = 0$ we have:

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 $\frac{r_1}{ak_1} < m < \frac{\mu}{k_2}$. If $r_1/a > k_1 m$ or $k_2 m > \mu$, then it is unstable. Moreover, in Ω_H if $r_1/a > k_1 m$, then for every solution T increases to ∞, $E \to 0$ and $I \ \to 0$ $t \to \infty$.

3. The tumour free - virus present steady state C_H is locally asymptotically stable if $\frac{r_1}{ak_1\mu} < \frac{\mu}{k_2} < m$ and unstable if $\mu/k_2 > m$ or $r_1/a > k_1\mu/k_2$.

4. The tumour present - virus free steady state D_H is stable if $m < \frac{r_1}{ak_1} < \frac{\mu}{k_2}$ and unstable if $k_1 m > r_1/a$ or $r_1/a > k_1\mu/k_2$.

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

$$\begin{cases} \dot{x} &= (r_1 - ak_1 E)x + k_1 \bar{T} y, \\ \dot{y} &= \left(r_2(1 - y/m) - 2r_2 E/m - \varepsilon k_1 \bar{T}\right) y + \varepsilon k_1 E x + (k_2 + r_2/m) E I \ , \end{cases} \tag{3}$$

where $\bar{T}$, E and I are the non-negative parameters. Assume that $x_0 = 0$, $y_0 = 0$ and $I_0 > 0$, which reflect the beginning of HIV infection at $t = 0$. Moreover, $\bar{T}_0 > 0$, $E_0 > 0$. Therefore, $\dot{x}(0) = 0$ and $\dot{y}(0) = (k_2 + r_2/m) E_0 I_0 > 0$, which implies that $y(t)$ increases and it is positive on some interval $(0, t_1)$. This yields that $x(t)$ also starts to increase. The form of Eqs. (3) 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 in larger when the HIV infection appears.

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

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

Now, assume that

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

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 2 *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 $\tau > 0$.*

Propositions 1 and 2 suggest that the qualitative behaviour of the system (1) with positive delay is similar as in 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 can be not 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 re-write 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

$$\begin{cases} \dot{u} &= (r_1 - ma\ k_1)u(t), \\ \dot{v} &= -r_2 v(t) - mk_1 u(t) + (1-\varepsilon)mk_1 u(t-\tau). \end{cases} \tag{5}$$

The first equation of the system (5) is uncoupled with the second one and it can be easily solved, $u(t) = T^0 e^{(r_1 - ma\ k_1)t} \to 0$, obviously. Then, we can solve the second equation of (5) for $v_0 = E_0 - m = 0$:

$$v(t) = mk_1 T^0 e^{-r_2 t} \frac{e^{(r_1 - ma\ k_1)t} - e^{-r_2 t}}{r_2 + r_1 - ma\ k_1} \left((1-\varepsilon) e^{(ma\ k_1 - r_1)\tau} - 1 \right) > 0, \tag{6}$$

for $\tau > \frac{1}{r_1 - ma\ k_1} \ln(1-\varepsilon)$. This inequality shows that E exceeds the threshold m for such values of delay. Moreover, for every arbitrary $t > 0$ 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 $E(h) \leq m$ for $h \in [-\tau, 0]$, then one can obtain the formula

$$v(t) = e^{-r_2 t} \left(v_0 + mk_1 T_0 \frac{e^{-(r_2 + r_1 - mak_1)t} - 1}{r_2 + r_1 - mak_1} \left((1-\varepsilon) e^{(mak_1 - r_1)\tau} - 1 \right) \right),$$

for $v_0 = E_0 - m \leq 0$. However, it is obvious that for every arbitrary $t > 0$ the formula above yields $v(t) > 0$ for $\tau > \frac{1}{r_1 - ma\ k_1} \ln(1-\varepsilon)$ and T_0 large enough.

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 this stability we calculate the characteristic quasi-polynomial depending on the delay parameter τ. This yields

Proposition 3 *Local stability of the steady states A_H, B_H, C_H and D_H for the system* (2) *does not depend on the magnitude of the delay τ.*

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 details, if the initial data satisfies (4) (or $E(h) \leq m$ 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 can be not invariant. The proof is the same as for the system (1).

3. Numerical simulations

Following the ideas presented in [7] in simulations we use the following data: $r_1 \in [0{,}05, 0{,}5]$, $r_2 = 0{,}03$, $k_1 \in [10^{-5}, 10^{-3}]$, $k_2 \in [0{,}5 \cdot 10^{-5}, 5 \cdot 10^{-4}]$, $\mu = 0{,}3$, $m = 1500$, $\varepsilon = 0{,}1$. We have decided to study in the simulations the case where a healthy organism is infected with HIV viruses and at some time which we assume to be $t_0 = 0$, the presence of tumour cells is recognised. For that reason we have choose initial data as follows

$$T_0(t) = \bar{T}_0(\frac{t}{\tau} + 1)\,, \quad E_0(t) = m\,, \quad I_0(t) = \bar{I}_0(\frac{t}{\tau} + 1) \qquad \text{for } t \in [-\tau, 0]\,.$$

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

In Figs. 1 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 be hardly 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 Figs. 2 we present the situation when the size of 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 can be seen. However, again the difference is more significant for the case of small a.

In Figs. 3 the situation when the organism recover for $a = 1$ and the tumour size tends to infinity for some $a < 1$ is presented. In the case $a < 1$ more frequent oscillations of the concentration of effector cells can be observed, especially for the case with HIV infection.

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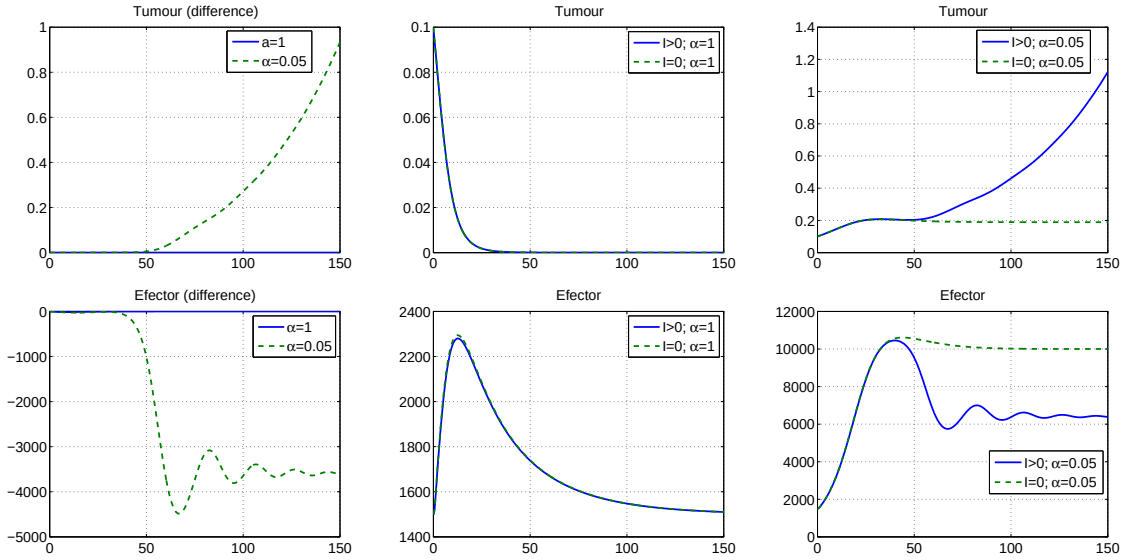

Figura 1: The example of the solution, when organism can recover in the case without HIV as well as in the case of presence of viruses. The first column shows the difference between solution in this two cases for $a = 1$ and $a = 0{,}05$. The second column show the behavior of the tumour and effector cells in the case of $a = 1$ and the third one for $a = 0{,}05$. Values of parameters: $r_1 = 0{,}05$, $k_1 = 10^{-4}$, $k_2 = 5 \cdot 5 \cdot 10^{-5}$.

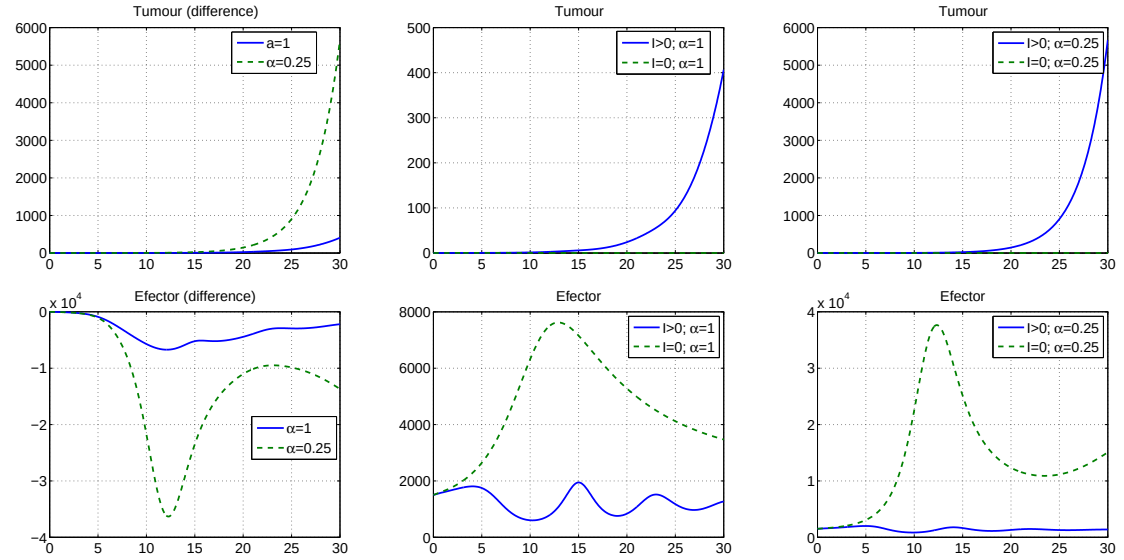

Figura 2: The example of the solution, when organism can recover in the case without HIV this two cases for $a = 1$ and $a = 0{,}05$. The second column shows the behavior of the tumour and effector cells in the case of $a = 1$ and the third one for $a = 0{,}25$. Values of parameters: $r_1 = 0{,}4$, $k_1 = 10^{-4}$, $k_2 = 5 \cdot 10^{-4}$.

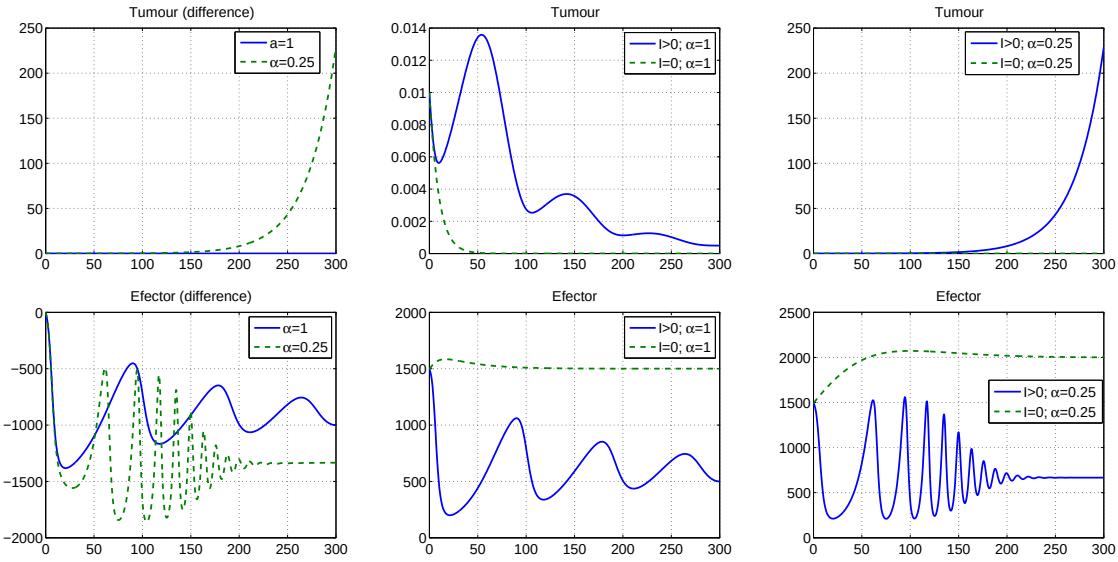

Figura 3: The example of the solution, when organism can recover faster in the case without HIV viruses. The first column shows the difference between solution in this two cases for $a = 1$ and $a = 0{,}05$. The second column shows the behavior of the tumour and effector cells in the case of $a = 1$ and the third one for $a = 0{,}25$. Values of parameters: $r_1 = 0{,}05$, $k_1 = 10^{-4}$, $k_2 = 5 \cdot 10^{-4}$.

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