Qualitative analysis of a closed-loop model of tumor growth control

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***Abstract*—Tumor volume modeling and control is a promising way to design more efficient, personalized tumor treatment. This requires a model of tumor growth dynamics, and a control law to design the therapy. Tumor growth models are usually nonlinear, while most control laws are linear, and the controllers are designed for approximate linear models thus stable operation is guaranteed only locally. We consider the application of a linear state feedback for a nonlinear tumor growth model, and carry out the qualitative analysis of the closed-loop model. We give conditions for the control law parameters to have a globally stable closed-loop system, and analyze the effect of the control law parameters on the steady-state tumor volume and the maximal drug injection.**

***Index Terms*—tumor therapy, cancer therapy, tumor control**

I. Introduction

Modeling tumor growth under the effect of some drugs is motivated by the potential of optimizing tumor therapies. One of the first models was the Hahnfeldt model [1], extended and analyzed in [2], which describes antiangiogenic therapy, and models the tumor volume and endothelial volume dynamics. A bilinear model was given in [3], that was extended in [4] to model tumor growth dynamics, tumor necrosis dynamics, drug pharmacodynamics and pharmacokinetics. The model parameters were identified based on experiments with an angiogenic inhibitor in [4], but the model is formalized such that it can be used to model the effect of many different drugs, as we will discuss in Section II. We create the closed-loop model by applying a linear state feedback control law, and analyze the properties of the closed-loop system in Section III.

Control of tumor models have been considered as a tool to generate optimal therapeutic protocols. In [5], [6], control of the Hahnfeld model was considered using linear control techniques. In [7], the authors apply impulsive control of chemotherapy, and carry out the analysis using Ljapunov functions. Impulsive control of antiangiogenic therapy based on the Hahnfeldt model is done in the recent work [8]. Benefits of using discrete-time controller for therapy design based on the Hahnfeld model were examined in [9]. Multiobjective optimization is used in [10]. In [11], the control of combined therapy is done with the consideration of time delays. Here, we use the model from [4] with a linear control law, and analyse the effect of the control law parameters on the qualitative properties of the closed-loop system.

The qualitative analysis of a dynamical system means the investigation of qualitative properties of the system, like stability of equilibrium points, local behavior of a system around an equilibrium, determining of invariant manifolds etc. For instance, qualitative analysis of the Moon-Rand system was carried out in [12], while a gene model was analyzed using these techniques in [13]. Here, we use qualitative analysis to determine the behavior of the closed-loop system based on the values of the model and control law parameters.

The analysis of the closed-loop model is carried out in Section III, where the equilibrium points of the closed-loop system are determined, and the stability (by which we mean asymptotic stability) is analyzed by checking the eigenvalues of the system matrix of the linearized model in the equilibrium. All the computations are carried out symbolically using Mathematica [14]. We give conditions for the model parameters in the form of inequalities that define when the tumor grows without treatment and in which cases can the treatment be effective. We give conditions for the parameters of the control law that ensure that the closed-loop system has a globally stable positive equilibrium point. In Section IV we show how the value of the control law parameters effect the value of the positive equilibrium of the system. The results can be used both for the analysis and synthesis of control algorithms using state feedback.

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II. Tumor growth model

The tumor growth model used here was created to model the effect of bevacizumab [4] and the parameters of the model were identified based on mice experiments [15]. The tumor growth model has three state variables: the volume of the proliferating (living) tumor cells, the volume of the necrotic (dead) tumor cells and the serum level of the applied drug. The terms in the model can be explained using an analogy to chemical reactions [16], [17], [18]. Suppose that the species X_1 represents the proliferating tumor volume, the species X_2 represents the necrotic tumor volume and the species X_3 represents the drug serum level. The formal chemical equations of the model are:

- $\mathrm{X}_1 \xrightarrow{a} 2\,\mathrm{X}_1$ that defines that the tumor cells proliferate (divide) with a tumor growth rate a. Using mass-action kinetics, this equation results in the term $\dot{x}_1 = ax_1$;
- $\mathrm{X}_1 \xrightarrow{n} \mathrm{X}_2$ that defines the necrosis (death) of tumor cells with necrosis rate n. Note that this necrosis is independent of the treatment. Using mass-action kinetics, this equation modifies the dynamics of the proliferating and necrotic tumor volumes with the terms $\dot{x}_1 = -nx_1$, $\dot{x}_2 = nx_1$;
- $\mathrm{X}_3 \xrightarrow{c} \mathrm{O}$ that defines that there is an outflow of the drug with a reaction rate coefficient c, i.e. the clearance of the drug. Instead of the mass-action type, here we use Michaelis–Menten kinetics in order to have a mixed-order model for the pharmacokinetics, so this equation results in the term $\dot{x}_3 = -cx_3/(K_B + x_3)$, where the parameter K_B is the Michaelis–Menten constant of the drug;
- $\mathrm{X}_1 + \mathrm{X}_3 \xrightarrow{b} \mathrm{X}_2$ that defines that the effect of the drug depends on the concentration of the drug and the tumor volume, and the result is that proliferating tumor cells become necrotic. The effect of the drug is considered with Michaelis–Menten kinetics with Michaelis–Menten constant ED_{50} (called the median effective dose [19]) resulting in the velocity term $x_1x_3/(ED_{50} + x_3)$. This effect on the volumes is considered with reaction rate coefficient b. The effect of this equation on the dynamics of the proliferating and necrotic tumor volumes is expressed by the terms $\dot{x}_1 = -bx_1x_3/(ED_{50} + x_3)$ and $\dot{x}_2 = bx_1x_3/(ED_{50} + x_3)$. Since these terms have the dimension $\mathrm{mm}^3/\mathrm{day}$, these terms can not be directly used to modify the dynamics of the drug serum level, since that has the dimension $\mathrm{mg}/(\mathrm{ml}\cdot\mathrm{day})$. Thus, we use the constant κ with dimension $\mathrm{mg}/(\mathrm{ml}\cdot\mathrm{mm}^3)$ to define the term $\dot{x}_3 = -\kappa bx_1x_3/(ED_{50}+x_3)$. Instead of κ, we will use the constant $b_\kappa = \kappa b$ in the remaining of the paper.

The combination of these terms give the differential equations of the tumor growth model:

$$\dot{x}_1 = (a-n)\,x_1 - b\frac{x_1x_3}{ED_{50}+x_3} \quad (1)$$

$$\dot{x}_2 = nx_1 + b\frac{x_1x_3}{ED_{50}+x_3} \quad (2)$$

$$\dot{x}_3 = -c\frac{x_3}{K_B+x_3} - b_\kappa\frac{x_1x_3}{ED_{50}+x_3} + u, \quad (3)$$

Parameter notation	Parameter name	Parameter dimension
a	tumor growth rate	$\frac{1}{\mathrm{day}}$
b	drug efficiency rate	$\frac{1}{\mathrm{day}}$
c	clearance	$\frac{1}{\mathrm{day}}$
n	necrosis rate	$\frac{1}{\mathrm{day}}$
b_κ	modified drug efficiency rate	$\frac{\mathrm{mg}}{\mathrm{ml}\cdot\mathrm{day}\cdot\mathrm{mm}^3}$
K_B	Michaelis–Menten constant of the drug	$\frac{\mathrm{mg}}{\mathrm{ml}}$
ED_{50}	median effective dose of the drug	$\frac{\mathrm{mg}}{\mathrm{ml}}$

TABLE I
The notations, names and dimensions of the parameters of the tumor growth model

where x_1 is the time function of proliferating tumor volume in mm^3, x_2 is the time function of necrotic tumor volume in mm^3, x_3 is the time function of drug serum level in mg/ml, u is the input that is the time function of drug injection rate in $\mathrm{mg}/(\mathrm{ml}\cdot\mathrm{day})$. The notations, names and dimensions of the model parameters are summarized in Table I. The model is formulated such that in a phsyiologically meaningful case all the parameters are positive.

The output y of the system is the measured tumor volume in mm^3 that is the sum of the proliferating (x_1) and necrotic (x_2) tumor volumes, i.e.

$$y = x_1 + x_2. \quad (4)$$

The dynamics of the output is described by the differential equation

$$\dot{y} = ax_1 \quad (5)$$

that is the sum of (1) and (2), thus the change of the measured tumor volume depends only on the tumor growth rate constant a and the actual volume of the proliferating tumor volume.

As a result by Volpert [20], also discussed in [18, pp. 153–154], the dynamical system described by (1)–(3) is nonnegative since it is kinetic. We will also use the positivity of the system in the qualitative analysis in the following section.

A. Generalizations of the tumor growth model

The tumor growth model was validated using mice experiments [15] with an angiogenic inhibitor called bevacizumab [19], however this does not limit the application of the model only for angiogenic inhibition. The model can be used to describe the effect of any drug whose effect can be simplified to the formal chemical equation $\mathrm{X}_1 + \mathrm{X}_3 \xrightarrow{b} \mathrm{X}_2$, i.e. if the drug and a living tumor cell meets, the result is a dead tumor cell. Although various drugs applied in cancer therapies may act throughout different pathways, the final result can be expressed by this simple equation. As a result, the tumor growth model can be used to model the effect of any therapeutic drug.

There are two important physiological phenomena that were not considered in [4] due to the nature of angiogenic inhibition that are not negligible when chemotherapeutic agents are used. The first phenomenon is the washout of the necrotic tumor cells, i.e. the decrease of necrotic tumor volume as the patients body decomposes and removes these cells. This phenomenon was not characteristic when angiogenic therapy was applied [15], the tumor was composed of proliferating and necrotic regions, however washout may be present if a chemotherapeutic drug is applied [21].

The washout can be modeled with the chemical reaction equivalent $\mathrm{X}_2 \xrightarrow{w} \mathrm{O}$, that results in the differential equation $\dot{x}_2 = -wx_2$, considering mass-action kinetics. Thus, in order to incorporate the effect of washout, (2) should be modified to

$$\dot{x}_2 = nx_1 + b\frac{x_1x_3}{ED_{50} + x_3} - wx_2. \tag{6}$$

However, the necrotic tumor cell volume does not affect the dynamics of the closed-loop system discussed in the following subsection, so we will omit the necrotic tumor volume dynamics in the qualitative analysis (i.e. the results will be valid independent of washout).

The other important phenomenon is that the tumor cells may become resistant to the drug. However, this resistance is only temporary. This effect can be modeled by adding an extra dynamics for the drug efficiency rate b as

$$\dot{b} = (b_0 - b) - \beta b x_3, \tag{7}$$

where b_0 is the maximal value of the drug efficiency, and β characterizes the speed of the development of resistance. Since this increases the dimension of the system, it complicates the qualitative analysis, thus we will not use this extension in this article, but we will considered it in future research.

B. The closed-loop system dynamics

The right-hand side of the differential equations (1)–(3) does not depend on x_2, thus we may omit the dynamics of the necrotic tumor volume, and only use the dynamics of the proliferating tumor volume (1) and the drug serum level (3) in the following analysis.

In order to get a closed-loop system and eliminate the control input u to be able to carry out the analysis of the model, we use the state feedback

$$u = k_1x_1 - k_3x_3. \tag{8}$$

The state feedback is a general control law used widely in control theory (for its application in tumor control, see e.g. [5], [6]). The signs in the control law are chosen such that for positive k_1 and k_3 values the feedback is negative.

The dynamics of the closed-loop system is acquired after substituting the control law into the tumor growth model, i.e. the closed-loop system dynamics is governed by

$$\dot{x}_1 = (a-n)\,x_1 - b\frac{x_1x_3}{ED_{50} + x_3} \tag{9}$$

$$\dot{x}_3 = -c\frac{x_3}{K_B + x_3} - b_\kappa\frac{x_1x_3}{ED_{50} + x_3} + k_1x_1 - k_3x_3. \tag{10}$$

In the following section we analyze the equilibria of the closed-loop system, and the stability of the equilibria, and give conditions for the parameter values k_1 and k_3 that ensure the existence of a positive equilibrium and stability of that equilibrium.

III. Qualitative analysis of the closed-loop tumor growth model

In this section we analyze the equilibrium points of the system described by (9)–(10) and the stability of those equilibrium points. In order to simplify the equations, we multiply both equations by the term $x_3 + ED_{50}$ to eliminate some of the rational terms and get

$$\dot{x}_1 = (a-n)\,x_1(ED_{50} + x_3) - bx_1x_3 \tag{11}$$

$$\dot{x}_3 = -c\frac{x_3(ED_{50} + x_3)}{K_B + x_3} - b_\kappa x_1x_3 + (k_1x_1 - k_3x_3)(ED_{50} + x_3). \tag{12}$$

Multiplication with $x_3 + ED_{50}$ will result in an extra equilibrium $x_3 = -ED_{50}$, however this case is not valid physiologically due to the positivity of the parameters and the variables. The system has three more equilibrium points that are the same as the equilibrium points of the original system. The signs of the real parts of the eigenvalues of the Jacobian of the system at the equilibrium points are also unaffected by multiplication by the positive term $ED_{50} + x_3$. The Jacobian of the modified closed-loop system model is

$$J = \begin{pmatrix} J_{11} & J_{12} \\ J_{21} & J_{22} \end{pmatrix} \tag{13}$$

with

$$J_{11} = (ED_{50} + x_3)(a - n - \frac{bx_3}{ED_{50} + x_3}) \tag{14}$$

$$J_{12} = (a - b - n)x_1 \tag{15}$$

$$J_{21} = ED_{50}k_1 - (b_\kappa - k_1)x_3 \tag{16}$$

$$J_{22} = -ED_{50}k_3 - b_\kappa x_1 + k_1x_1 - 2k_3x_3 - \frac{c(ED_{50}K_B + x_3(2K_B + x_3))}{(K_B + x_3)^2}. \tag{17}$$

A. Equilibrium # 1

In the first equilibrium point $x_1^* = 0$ mm^3 and $x_3^* = 0$ mg/ml. This equilibrium point describes the trivial case when there is no (living) tumor and no drug. The eigenvalues of the Jacobian (13) at this equilibrium point are

$$\lambda_1 = ED_{50}\,(a - n) \tag{18}$$

$$\lambda_2 = -ED_{50}\frac{c + k_3K_B}{K_B}. \tag{19}$$

Since we suppose that the parameters of the model are positive, and if we suppose that $k_3 > 0$, we have that $\lambda_2 < 0$. This eigenvalue describes the dynamics of the drug clearance, which, if considered as a subsystem independent of the tumor volume dynamics, is stable, so the zero drug level is a stable equilibrium. Note that if k_3 could be negative (i.e. we would

have positive feedback in the control law), then it could be chosen such that $\lambda_2 > 0$ resulting in increasing drug level.

The other eigenvalue is the difference of the tumor growth rate and the necrosis rate. If this difference is negative, i.e. the tumor grows slower than it dies, then the equilibrium is stable, i.e. the tumor is self-healing, it is being absorbed, and therapy is not required.

In the special, degenerate case if $a = n$, the tumor growth dynamics is described by

$$\dot{x}_1 = -b\frac{x_1 x_3}{ED_{50} + x_3} \tag{20}$$

thus for the initial tumor volume $x(0)$, the tumor volume at time instant t is

$$x_1(t) = x_1(0)\exp\left(-\int_0^t \frac{bx_3(\tau)}{ED_{50} + x_3(\tau)}\,\mathrm{d}\,\tau\right), \tag{21}$$

thus the equilibrium point is

$$x_1^* = \lim_{t\to\infty} x_1(0)\exp\left(-\int_0^t \frac{bx_3(\tau)}{ED_{50} + x_3(\tau)}\,\mathrm{d}\,\tau\right) \tag{22}$$

if the limit at the right-hand side exists. In that case, since $x_3 \in \mathcal{C}^1([0,\infty], \mathbb{R}_0^+)$, we have that $x_1^* \leq x_1(0)$, i.e. if there is no drug in the patient, then the equilibrium remains $x_1(0)$, but if there is some drug injected, then the equilibrium volume decreases: greater drug dose results in smaller equilibrium.

In the case $a > n$, the tumor grows faster than it dies, and $\lambda_1 > 0$, thus this equilibrium is unstable. In what follows we will suppose that $a > n$, thus the tumor is not self-healing and therapy is required, but $k_3 > 0$, which implies that the dynamics of the drug is stable around the zero equilibrium. Such an equilibrium point is called a saddle.

B. Equilibrium # 2

In the second equilibrium point $x_1^* = 0$ mm^3 and $x_3^* = -(c + k_3K_B)/k_3$ mg/ml. For positive parameter values and positive k_3, the equilibrium point for the drug level is negative, which is physiologically unfeasible, so we neglect this equilibrium.

C. Equilibrium # 3

In the third equilibrium point, the drug serum level is

$$x_3^* = -ED_{50}\frac{a-n}{a-b-n}. \tag{23}$$

If the tumor is not self-healing, i.e. $a > n$, then this value is positive if and only if

$$a - n - b < 0, \tag{24}$$

which is the condition that ensures that tumor volume can be decreased using the drug, as it was shown in [4]. From now on, we suppose that the parameters satisfy (24).

The equilibrium of the tumor volume is

$$x_1^* = \frac{x_{1,n}}{x_{1,d}} \tag{25}$$

with

$$\begin{aligned} x_{1,n} &= bED_{50}(a-n)\,(b(c+k_3K_B) \\ &\quad -a(c+k_3(-ED_{50}+K_B)) \\ &\quad +(c-ED_{50}k_3+k_3K_B)n) \end{aligned} \tag{26}$$

$$\begin{aligned} x_{1,d} &= (a-b-n)(ab_\kappa - bk_1 - b_\kappa n)\cdot \\ &\quad \cdot(a(ED_{50}-K_B)+bK_B \\ &\quad +(-ED_{50}+K_B)n). \end{aligned} \tag{27}$$

Taking into account the previous conditions, this equilibrium is positive if either

$$k_1 > b_\kappa\frac{a-n}{b} \tag{28}$$

$$k_3 > c\frac{a-b-n}{aED_{50} - aK_B + bK_B - ED_{50}n + K_Bn} \tag{29}$$

or

$$k_1 < b_\kappa\frac{a-n}{b} \tag{30}$$

$$k_3 < c\frac{a-b-n}{aED_{50} - aK_B + bK_B - ED_{50}n + K_Bn}. \tag{31}$$

The symbolic expression for the eigenvalues of the Jacoban in this equilibrium point contain more than 2000 terms after simplification, thus analysis of this equilibrium point is not possible this way even with the use of computer algebra software. In order to overcome this problem, we utilize the fact that the system is planar, thus the Jacobian is a 2×2 matrix. For a 2×2 matrix J, the eigenvalues can be expressed in terms of the determinant ($\mathrm{Det}(J)$) and trace ($\mathrm{Tr}(J)$) of the matrix as

$$\lambda_{1,2} = \frac{\mathrm{Tr}(J) \pm \sqrt{\mathrm{Tr}(J)^2 - 4\,\mathrm{Det}(J)}}{2}. \tag{32}$$

In order to have eigenvalues with negative real parts (i.e. to guarantee that the equilibrium point is stable) the parameters should be chosen such that

$$\mathrm{Tr}(J) < 0 \tag{33}$$

$$\mathrm{Det}(J) > 0. \tag{34}$$

Using computer algebra software (e.g. Mathematica with Reduce command) one can verify the following. The determinant of the Jacobian is positive if (28)–(29) hold, but negative if (30)–(31) are true. Thus, if the parameters of the control law are chosen to satisfy (30)–(31), the equilibrium is unstable. If conditions (28)–(29) are true, then the trace of the Jacobian is negative, if the additional

$$k_3 > \frac{\varphi}{\omega} \tag{35}$$

condition also holds for k_3 with

$$\begin{aligned} \varphi &= c(-a+b+n)^2(a^2b_\kappa(ED_{50}-K_B) \\ &\quad -b^2k_1K_B + 2ab_\kappa(-ED_{50}+K_B)n \\ &\quad +b_\kappa(ED_{50}-K_B)n^2) \end{aligned} \tag{36}$$

$$\begin{aligned} \omega &= (a(ED_{50}-K_B)+bK_B \\ &\quad +(-ED_{50}+K_B)n)^2(a^2b_\kappa \\ &\quad +b^2k_1 - 2ab_\kappa n + b_\kappa n^2). \end{aligned} \tag{37}$$

In this case, the positive equilibrium is stable, otherwise it is unstable.

Note that in this equilibrium $J_{11} = 0$, thus $\mathrm{Tr}(J) = J_{22}$ and $\mathrm{Det}(J) = -J_{12}J_{21}$, which further simplifies the expressions. However, the expressions still contain many terms (but they can be handled with Mathematica, i.e. the commands are executed in a reasonable time), so we omit the intermediate results here. We summarize our main result in the following theorem.

Theorem 1. *Consider the closed-loop tumor growth model given by the differential equations (9)–(10). Suppose that the parameters of the model are positive and they satisfy* $a-n > 0$ *and* $a - n - b < 0$. *If the parameters* k_1 *and* k_3 *are chosen such that (28)–(29) or (30)–(31) are satisfied, then there exists a positive equilibrium of the system. Moreover, if* k_1 *satisfies (28) and* k_3 *satisfies (35), then this equilibrium is stable.*

IV. Discussion and Conclusion

In the previous section we have analyzed the qualitative properties of the closed-loop tumor control model with the application of state feedback. The results of the analysis give us symbolic tools to either check if the closed-loop system is stable for a previously designed state feedback controller even in the presence of parametric perturbations, or to design a controller using (28) and (35) and the known values (or intervals if there is parametric uncertainty) of the parameters. This way, we can guarantee that the resulting closed-loop system is stable (even in the presence of parametric uncertainties).

Stability is a crucial property of the closed-loop system, however, the steady-state value of the tumor volume is also important. The equilibrium value is affected by the parameters of the model and the parameters of the control law as well. It can be verified using computer algebra that if the positivity conditions of the parameters, the conditions $a - n > 0$, $a - n - b < 0$, (28) and (35) hold, then the numerator and the denominator of (25) are positive (i.e. $x_{1,n} > 0$ and $x_{1,d} > 0$). The numerator depends on k_3, but does not depend on k_1, while the denominator depends on k_1 and does not depend on k_3.

The derivative of the numerator of (25) with respect to k_3 is

$$\begin{aligned}\partial_{k_3} x_{1,n} &= bED_{50}(a-n)(bK_B - a(-ED_{50} + K_B) \\ &\quad +(-ED_{50} + K_B)n) \end{aligned} \tag{38}$$

that is always positive with the given conditions, thus increasing k_3 means increasing steady-state tumor volume. This is physiologically feasible too, since increasing k_3 means faster depletion of the drug, thus the effect of the drug will be smaller. Decreasing k_3 would result in smaller steady-state tumor volume, however, too small k_3 (i.e. which violates (35)) would result in an unstable equilibrium point. As a conclusion, k_3 should be small enough to have small steady-state tumor volume, but large enough to have stable operation.

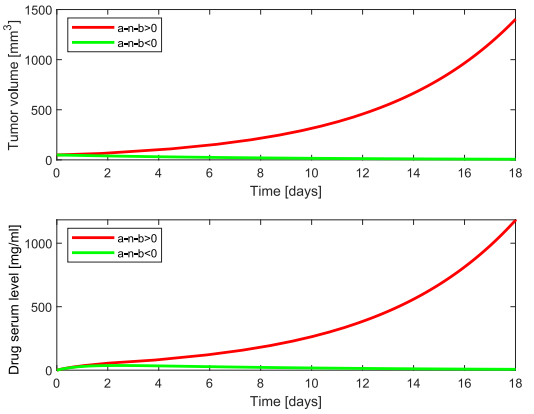

Fig. 1. The tumor volume (up) and drug serum level (bottom) in the case of a scenario when there is no positive equilibrium (i.e., $a - n - b > 0$, the red curves) and in the case when there exists a positive equilibrium and it is asymptotically stable (green curve)

The derivative of the denominator of (25) with respect to k_1 is

$$\begin{aligned}\partial_{k_1} x_{1,d} &= b(-a+b+n)(a(ED_{50} - K_B) + bK_B \\ &\quad +(-ED_{50} + K_B)n) \end{aligned} \tag{39}$$

that is always positive with the given conditions, so increasing k_1 results in decreasing steady-state tumor volume. This shows that larger values of k_1 are desirable, moreover, increasing the value of k_1 does not violate the conditions for the stable equilibrium. However, considering the control law (8), increasing k_1 means increasing control input, thus larger doses of the drug, which may be toxic. An upper bound for the maximal value of the input can be given as

$$u_{max} = \max_{x_1,x_3,k_1,k_3>0} k_1 x_1 - k_3 x_3 \leq k_1 x_{1,max} \tag{40}$$

which can be used to set an optimal value of the parameter k_1, if the value of u_{max} is known.

The closed-loop system has only two valid equilibrium points, the first valid equilibrium is $x_1 = 0$ mm^3, the second valid equilibrium point is given by (25). If $a - n > 0$, i.e. the first equilibrium is not stable, but the drug is effective against the tumor (i.e. $a-n-b < 0$), then if the control law parameters are chosen to satisfy (28) and (35), the second equilibrium is stable, and there are no other positive equilibrium points. As a result, for any positive initial tumor volume, the trajectories of the system converge to the stable positive equilibrium, thus that equilibrium is globally stable.

The simulation results of the closed-loop system with $k_1 = 1$ and $k_3 = 1$ with two different parameter sets are shown in Figure 1. The first parameter set is from [4], i.e., the parameters were identified based on mice experiments carried out using bevacizumab. The values of the parameters are: $a = 0.4579\,1/\text{day}$, $b = 0.1685\,1/\text{day}$, $c = 0.1825\,1/\text{day}$, $n = 0.1030\,1/\text{day}$, $b_\kappa = 1.0839 \cdot 10^{-6}\,\text{mg}/(\text{ml} \cdot \text{mm}^3 \cdot \text{day})$, $x_1(0) = 49.0497\,\text{mm}^3$, $x_2(0) = 0\,\text{mm}^3$, $x_3(0) = 0\,\text{mg/ml}$,

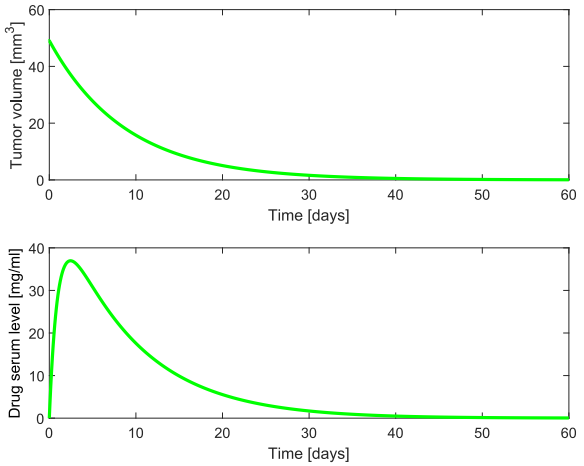

Fig. 2. The tumor volume (up) and drug serum level (bottom) in the case of existence of an asymptotically stable positive equilibrium

$K_B = 0.4409\,\mathrm{mg/ml}$ and $ED_{50} = 50 \cdot 10^{-6}\,\mathrm{mg/ml}$. In this case, there is no positive equilibrium, since $a - n - b = 0.1864 > 0$. The simulation results for this parameter set are shown by the red curves in Figure 1.

The second parameter set is a modified version of the first one where the parameter values b and n are modified in order to ensure that $a - n - b < 0$. The modified values are $b = 0.2685\,1/\mathrm{day}$, and $n = 0.3030\,1/\mathrm{day}$. In this case $a - n - b = -0.1136 < 0$, thus there exists a positive equilibrium. In order to have an asymptotically stable positive equilibrium based on Theorem 1, the feedback gains should satisfy (28) and (35). For the second parameter set, these bounds are $k_1 > 6.25 \cdot 10^{-7}$and $k_3 > -0.4139$. Since the gains are chosen to be $k_1 = 1$ and $k_3 = 1$, the conditions of Theorem 1 are satisfied. The simulation results are shown for 18 day in Figure 1 by the green curves. The simulation is repeated for 60 days and the results are shown separately from the unstable case in Figure 2. The results show that there is a stable positive equilibrium, and the trajectories converge to this equilibrium. The value of this equilibrium based on (25) and (23) is $x_1^* = 9.63 \cdot 10^{-5}\,\mathrm{mm}^3$, $x_3^* = 6.81 \cdot 10^{-5}\,\mathrm{mg/ml}$ that is verified by the simulation as well.

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