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 Hahnfeldt 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.
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 (dead) tumor cells and the serum level of the applied drug. The combination of these terms give the differential equations representing the necrotic tumor volume and the species representing the proliferating tumor volume, the species represents the drug serum level.

The formal chemical kinetics, this equation results in the term $\dot{x}_2 = -c x_1$, $\dot{x}_3 = -b x_1 x_3 / (E_{D0} + x_3)$, where the parameter $K_D$ is the Michaelis-Menten constant of the drug.

The output $y$ of the system is the measured tumor volume in $\text{mm}^3$ that is the sum of the proliferating ($x_1$) and necrotic ($x_3$) tumor volumes, i.e.

$$y = x_1 + x_3.$$  

(4)

The dynamics of the output is described by the differential equation

$$\dot{y} = ay + \frac{b}{K_D + x_3}.$$  

(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 $X_1 + X_3 \xrightarrow{\text{b}} X_2$, 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 \( X \rightarrow_\text{O} \), that results in the differential equation \( \dot{x}_2 = -w x_2 \), considering mass-action kinetics. Thus, in order to incorporate the effect of washout, (2) should be modified to

\[
\dot{x}_2 = \alpha x_1 + b \frac{x_1 x_3}{ED_{50} + x_3} - w x_2. \tag{6}
\]

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 \( h \) as

\[
h = (b_1 - b) - \beta x_2, \tag{7}
\]

where \( b_1 \) is the maximal value of the drug efficiency, and \( \beta \) 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 consider 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

\[
u = k_1 x_1 - k_2 x_3. \tag{8}
\]

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 \( k_2 \) 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

\[
\begin{align*}
\dot{x}_1 &= (a - n) x_1 - b x_1 x_2 + \frac{ED_{50} x_1 x_3}{ED_{50} + x_3} \\
\dot{x}_3 &= -c_b x_3 \frac{ED_{50} x_1 x_3}{ED_{50} + x_3} + (k_1 x_1 - k_2 x_3).
\end{align*} \tag{9}
\]

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 \( k_2 \) 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

\[
\begin{align*}
\dot{x}_1 &= (a - n) x_1 (ED_{50} + x_3) - b x_1 x_3 \\
\dot{x}_3 &= -c_b x_3 (ED_{50} + x_3) - \frac{b_0 x_1 x_3}{K_B + x_3} \\
&\quad+ (k_1 x_1 - k_2 x_3) (ED_{50} + x_3).
\end{align*} \tag{11}
\]

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

\[
J = \begin{pmatrix}
J_{11} & J_{12} \\
J_{21} & J_{22}
\end{pmatrix}
\]

with

\[
\begin{align*}
J_{11} &= (ED_{50} + x_3)(a - n - \frac{b x_3}{ED_{50} + x_3}) \\
J_{12} &= (a - b - n) x_3 \\
J_{21} &= ED_{50} - (b_0 - k_1) x_2 \\
J_{22} &= -ED_{50} b_0 - b_0 x_2 + b_1 x_1 - 2 b_1 x_1 \\
&\quad- \frac{c_b (ED_{50} K_B + x_3(2K_B + x_3))}{(K_B + x_3)^2}.
\end{align*} \tag{12}
\]

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

\[
\begin{align*}
\lambda_1 &= ED_{50} (a - n) \\
\lambda_2 &= -ED_{50} c + \frac{k_3 K_B}{K_B}
\end{align*} \tag{13}
\]

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 \( \lambda_3 > 0 \) 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

\[
x_3 = -b \frac{x_1 x_3}{ED_{30} + x_3}
\]

(20)

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

\[
x_3(t) = x(0) \exp \left( -\int_0^t \frac{b \kappa_1(t)}{ED_{30} + x_3(t)} \, dt \right),
\]

(21)

thus the equilibrium point is

\[
x_3^* = \lim_{t \to \infty} x_3(t) = \exp \left( -\int_0^\infty \frac{b \kappa_1(t)}{ED_{30} + x_3(t)} \, dt \right)
\]

(22)

The symbolic expression for the eigenvalues of the Jacobian 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 \( \times \) 2 matrix. For a 2 \( \times \) 2 matrix \( J \), the eigenvalues can be expressed in terms of the determinant \( \det(J) \) and trace \( \text{Tr}(J) \) of the matrix as

\[
\lambda_{1,2} = \frac{\text{Tr}(J) \pm \sqrt{\text{Tr}(J)^2 - 4 \det(J)}}{2}
\]

(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

\[
\text{Tr}(J) < 0 \quad \text{and} \quad \det(J) > 0.
\]

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 condition also holds for \( k_3 \) with

\[
\varphi = c (-a + b + n)^2 \alpha^2 \beta \gamma (ED_{30} - K_B) - b^2 k_1 K_B + 2 b_0 \alpha (-ED_{30} + K_B) n + b_0 (ED_{30} - K_B)^2
\]

(36)

the equilibrium of the tumor volume is

\[
x_3^* = \frac{x_3}{x_4}
\]

(25)
In this case, the positive equilibrium is stable, otherwise it is unstable.

Note that in this equilibrium $J_{11} = 0$, thus $\text{Tr}(J) = J_{22}$ and $\text{Det}(J) = -J_{13}J_{21}$, 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 $\alpha - n > 0$ and $a - n - b < 0$. If the parameters $k_1$ and $k_2$ 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 $k_2$ 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 $\alpha - n > 0$, $a - n - b < 0$, (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 $k_1$ is

$$\frac{\partial}{\partial k_1} x_{1,n} = b ED_3 (a - n) [K_y - a (-ED_3 + K_y)] + (-ED_3 + K_y) n$$

which can be used to set an optimal value of the parameter $k_1$ if the value of $u_{\text{max}}$ 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 $k_2 = 1$ 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/day, $b = 0.1685$ 1/day, $c = 0.1825$ 1/day, $n = 0.1030$ 1/day, $b_3 = 1.0839 \cdot 10^{-4}$ mg/(ml mm$^3$ day), $x_1(0) = 49.0497$ mm$^3$, $x_2(0) = 0$ mm$^3$, $x_3(0) = 0$ mg/ml.
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 \( b = 0.2085 \text{ day}^{-1} \), and \( n = 0.30301 \text{ day}^{-1} \). 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 \( k_1 > 6.25 \times 10^{-3} \) and \( k_2 > 0.4130 \). Since the gains are chosen to be \( k_1 = 1 \) and \( k_2 = 1 \), the conditions of Theorem 1 are satisfied. The simulation results are shown for 18 days 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 \( x_1^* = 9.63 \times 10^{-4} \text{ mm}^3 \), \( x_2^* = 6.81 \times 10^{-5} \text{ mg} \) that is verified by the simulation as well.

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

\[ K_T = 0.4409 \text{ mg/ml} \text{ and } ED_{50} = 50 \times 10^{-6} \text{ mg/ml}. \] 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.

\[ K_T = 0.2085 \text{ day}^{-1} \text{ and } n = 0.30301 \text{ day}^{-1}. \] 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 \( k_1 > 6.25 \times 10^{-3} \) and \( k_2 > 0.4130 \). Since the gains are chosen to be \( k_1 = 1 \) and \( k_2 = 1 \), 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.