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Positive nonlinear control of tumor growth using angiogenic inhibition ⋆

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Abstract: The input of physiological control systems is positive in almost every case (i.e. it is the concentration of a drug), thus the application of controllers which guarantee positive input is crucial. However, most of the controller design methods can not incorporate the constraint that the input has to be positive. We propose a method based on the dynamic extension of the system that guarantees that the output of the controller is always positive, and design nonlinear controller and observer for the extended system. The extended system is linearized using exact linearization, and path tracking control law is applied to ensure the desired tumor volume regression. The output of the resulting controller is always positive, and achieves the desired tumor regression with low control inputs that are desirable in physiological point of view. The results show that the proposed dynamical extension can be sufficiently used along with exact linearization to control nonlinear dynamic systems with positive inputs.

Keywords: Physiological models, Feedback linearization, Tumor therapy, Biomedical control, Nonlinear control systems, Observers.

1. INTRODUCTION

1.1 Oncopathological background

Tumor cells can appear in the human body after a somatic mutation. As tumor cells proliferate, the number of cells increase, and the tumor volume grows. This growth, however, is limited since blood supply is provided by the nearby capillaries, and if the tumor cells get farther than the diffusion distance (150 μm), nutrition and oxygen access decrease. In order to overcome this problem, tumor cells need own blood supply. There are two main ways to form new blood vessels. The formation of the first primitive vascular plexus is called as vasculogenesis, while the formation of new blood vessels from the preexisting microvasculature is angiogenesis (Distler et al. (2003)). In the case of tumor growth, angiogenesis takes place which is regulated by pro- and antiangiogenic factors. The most important proangiogenic factor is the vascular endothelial growth factor (VEGF) since it specifically regulates endothelial proliferation (Ferrara (2000)) which is essential for angiogenesis. Therefore VEGF inhibition is an important therapeutic target (Harris (2003)); and to control angiogenesis, anti-VEGF agents and other VEGF inhibitors are being used all over the world (Saha et al. (2013)). However, the best angiogenic inhibition administration method is still unknown in clinical practice (Distler et al. (2002)).

1.2 Background of the control problem

In many physiological problems that are considered as a control problem, the control input is usually the level of some drug, and as a result, the control input can not be negative. This is the same case when one wants to control tumor growth: antiangiogenic factors (anti-VEGF) should be delivered as an external input which is positive during the whole treatment. Designing controllers that guarantee positive input is thus crucial for the control of physiological systems.

The situation when the inputs are constrained to a certain set, e.g. they can only have positive values, is a constrained control problem. Such a problem can be formalized as a constrained optimization problem that can be solved e.g. using dynamic programming (Bertsekas (2005, 2012)), direct shooting methods (Osborne (1969)) or collocation methods (Biegler (1984)). However, these solutions may require lots of computation, and in many situations they may not be suitable for real-time applications.

We consider the control problem of a tumor growth model created by Hahnfeldt et al. (1999) defined in Section 2 whose input is the level of a drug, which must always be positive. In our previous works (Sápi et al. (2015, 2013); Drexler et al. (2011, 2012); Szeles et al. (2014); Kovács et al. (2014)), this constraint was not incorporated into the controller design process, and positivity was ensured by using a discontinuous saturation on the input of the tumor model, which distorts the model of the closed-loop system, making model-based techniques less reliable. We introduce a technique here that guarantees positive input that is also incorporated into the model of the system in the controller design phase.

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We introduce the input dynamics that is a first-order bilinear positive dynamic system whose state-variable is the control input in Section 3. The differential equation of this system is formulated such that for positive initial conditions the solutions remain positive regardless of the input of this new system. We extend the original tumor model with this new dynamics, and consider the input of this new dynamics as the new fictive control input that can have negative values as well. This yields that we can design any type of controller that acts on the fictive input of this extended system, the positivity of the real input will be guaranteed by the dynamics of the extended system.

We carry out exact linearization on the extended system, design path tracking control and a globally exponentially stable nonlinear state observer in Section 3. The resulting controller is extended with the input dynamics, resulting in a positive nonlinear path tracking controller.

The closed-loop system is evaluated using simulations in Section 4. We demand an exponential tumor regression and analyze the results of path tracking control with different time constants for the desired tumor regression. We find that the inputs of the system are always positive, and they have significantly lower values compared to the earlier results. The low value of drug inputs is promising for real clinical applications.

2. A MODEL OF TUMOR GROWTH UNDER ANGIOGENIC INHIBITION

A model of tumor growth under angiogenic inhibition was proposed by Hahnfeldt et al. (1999), and it describes the tumor growth dynamics in time t with the equations

$$\dot{x}_1(t) = -\lambda_1 x_1(t) \log\left(\frac{x_1(t)}{x_2(t)}\right) \tag{1}$$

$$\dot{x}_2(t) = b x_1(t) - d x_1^{2/3}(t) x_2(t) - \eta x_2(t) I(t), \tag{2}$$

with $x_1(t)$ being the tumor volume in time instant t given in mm^3, $x_2(t)$ is the volume of the supporting vasculature in time instant t given in mm^3, and $I(t)$ being the inhibitor serum level in time instant t given in mg/kg. The parameters acquired in Hahnfeldt et al. (1999) from mice experiments with Lewis lung carcinoma used as tumor and endostatin as the inhibitor are $\lambda_1 = 0.192\,1/\mathrm{day}$, $b = 5.85\,1/\mathrm{day}$, $d = 0.0087\,1/(\mathrm{mm}^2 \cdot \mathrm{day})$ and $\eta = 0.66\,\mathrm{kg}/(\mathrm{mg} \cdot \mathrm{day})$.

The equilibria of the system defined by (1) and (2) with constant inhibitor serum level $I \equiv I_\infty$ are the points $x_{1,\infty} = x_{2,\infty}$, and given a desired equilibrium tumor volume $x_{1,\infty}$, one can calculate the required steady-state drug concentration using

$$I_\infty = \frac{b - x_{1,\infty}^{2/3} d}{\eta}, \tag{3}$$

see e.g. Sápi et al. (2015).

In practice, angiogenesis takes place in tumors whose volume is big enough (above a few mm^3), below that volume the tumor can use the blood vessels of the host, and does not have to induce angiogenesis. However, this critical tumor volume is not known exactly, and may be different for each situation (depending on the type of tumor and the vascularization level of the host organ), we will suppose later that the tumor volume is greater than or equal to $1\,\mathrm{mm}^3$ (i.e. the critical volume is $1\,\mathrm{mm}^3$), so the smallest steady-state tumor volume will be $1\,\mathrm{mm}^3$. Since the supporting vasculature volume corresponding to this steady-state is $x_{2,\infty} = 1\,\mathrm{mm}^3$, and lower volume would result in decreasing tumor volume based on (1), we suppose that the supporting vasculature volume is greater than or equal to $1\,\mathrm{mm}^3$ as well. Note that if this critical tumor volume is greater or less than $1\,\mathrm{mm}^3$, then the differential equations can be rescaled such that this critical tumor volume becomes one, and the results of this paper still hold.

3. POSITIVE NONLINEAR CONTROLLER

3.1 The positive input dynamics

The input of the tumor model is the inhibitor serum level that is the function I in (2). Here, we extend the dynamics of the tumor model with the input dynamics governed by the differential equation

$$\dot{I}(t) = -I(t)u(t), \tag{4}$$

where $u(t)$ is a new, fictive input. If the initial state of the dynamical system defined by (4) is positive, i.e. $I(t_0) > 0$ for some $t_0 \in \mathbb{R}$, then the solution of the differential equation (4) is also positive, i.e. $\forall t \geq t_0$, $I(t) > 0$, regardless of the values of u, since the solution of the differential equation is

$$I(t) = I(t_0) e^{-\int_{t_0}^{t} u(\tau) d\tau}, \quad t \geq t_0. \tag{5}$$

Thus, if we extend the tumor growth model with the dynamic system given by (4), and design controller with output u for the extended system, then we can guarantee that the function I will be positive. Note that the new dynamics is added to the tumor model when we consider the controller design process, but it is added to the controller in the implementation process.

3.2 Exact linearization and path tracking control of the extended system

In order to simplify the expressions we use for controller design, we introduce the new variables

$$y_1 = \log(x_1) \tag{6}$$

$$y_2 = \log(x_2). \tag{7}$$

Since we have supposed that $x_1 \geq 1\,\mathrm{mm}^3$ and $x_2 \geq 1\,\mathrm{mm}^3$, it follows that the new variables are nonnegative. The differential equations of the transformed system are

$$\dot{y}_1 = \frac{1}{x_1}\dot{x}_1 = -\lambda_1(\log(x_1) - \log(x_2)) \tag{8}$$

$$\dot{y}_2 = \frac{1}{x_2}\dot{x}_2 = b\frac{x_1}{x_2} - d x_1^{2/3} - \eta I, \tag{9}$$

and after some manipulation we get that the differential equations of the extended system in the new variables are

$$\dot{y}_1 = -\lambda_1 y_1 + \lambda_1 y_2 \tag{10}$$

$$\dot{y}_2 = b e^{y_1 - y_2} - d e^{2y_1/3} - \eta I \tag{11}$$

$$\dot{I} = -Iu. \tag{12}$$

This system can be transformed to a linear dynamic system governed by the differential equation

$$\dot{z}_1 = z_2 \tag{13}$$
$$\dot{z}_2 = z_3 \tag{14}$$
$$\dot{z}_3 = v, \tag{15}$$

with $z_1 := y_1$ using the transformations

$$\dot{z}_1 = L_f h \tag{16}$$
$$\dot{z}_2 = L_f^2 h \tag{17}$$
$$\dot{z}_3 = L_f^3 h + L_g L_f^2 h u := v \tag{18}$$

with $L_f h$ being the Lie-derivative of the vector field f along the scalar field h (see e.g. Isidori (1995)), and the vector fields f and g are defined as

$$f = \begin{pmatrix} -\lambda_1 y_1 + \lambda_1 y_2 \\ be^{y_1 - y_2} - de^{2y_1/3} - \eta I \\ 0 \end{pmatrix} \; g = \begin{pmatrix} 0 \\ 0 \\ -I \end{pmatrix} \tag{19}$$

while the scalar field h is defined as $h = y_1$, and the definition of the Lie-derivative is

$$L_f h = h' f \tag{20}$$

where h' is the total derivative of h. The repeated application of the Lie-derivative is denoted by a superscipt, i.e. $L_f^k h = L_f(L_f^{k-1} h)$. The symbolic expressions for the Lie-derivatives in the transformation are

$$\begin{aligned} L_f h &= -\lambda_1 y_1 + \lambda_1 y_2 \\ L_f^2 h &= -\lambda_1 \left(de^{2y_1/3} + \eta I - \lambda_1 y_1 + \lambda_1 y_2 - be^{y_1 - y_2} \right) \\ L_f^3 h &= \lambda_1 \left(\lambda_1 + be^{y_1 - y_2} \right) \left(de^{2y_1/3} + \eta I - be^{y_1 - y_2} \right) \\ &\quad -\lambda_1^2 \left(y_1 - y_2 \right) \left(\lambda_1 - 2/3 de^{2y_1/3} + be^{y_1 - y_2} \right) \\ L_g L_f^2 h &= -\lambda_1 \eta I. \end{aligned} \tag{21}$$

The resulting system after the application of these transformations is a series of integrators, i.e. $z_1 = y_1$, $z_2 = \dot{y}_1$ and $z_3 = \ddot{y}_1$, so it is plausible to design path tracking control for the transformed system.

We define the logarithm of the desired tumor regression $y_{1,d}$ and its derivatives $\dot{y}_{1,d}$, $\ddot{y}_{1,d}$ and $\dddot{y}_{1,d}$, and define the control law as

$$v = \dddot{y}_{1,d} + k_2 \left(\ddot{y}_{1,d} - z_3 \right) + k_1 \left(\dot{y}_{1,d} - z_2 \right) + k_0 \left(y_{1,d} - z_1 \right) \tag{22}$$

that leads to the error dynamics

$$\dddot{e} + k_2 \ddot{e} + k_1 \dot{e} + k_0 e = 0 \tag{23}$$

where e is the function of path tracking error defined by $e = y_{1,d} - z_1 = y_{1,d} - y_1$. If we choose the coefficients k_0, k_1, k_2 such that (23) is stable with equilibrium $e_\infty = 0$, then the closed-loop system is also stable, and the path tracking error tends to the zero equilibrium. The control law for the input u can be expressed from (18) as

$$u = \frac{v - L_f^3 h}{L_g L_f^2 h} \tag{24}$$

which we will write as

$$u = \frac{\phi(y_1, y_2, I, y_{1,d}, \dot{y}_{1,d}, \ddot{y}_{1,d}, \dddot{y}_{1,d})}{\beta(I)} \tag{25}$$

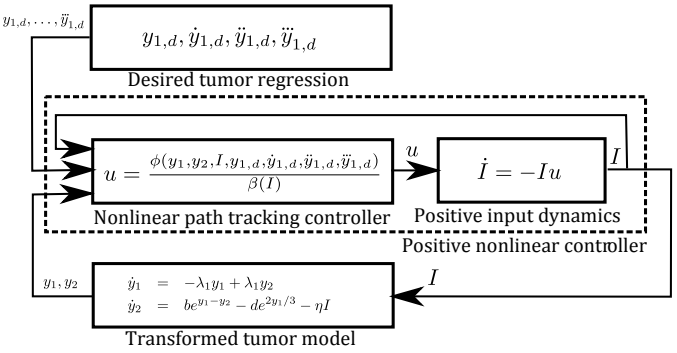

Fig. 1. Positive, nonlinear path tracking control of the transformed tumor model

with the function ϕ defined as

$$\begin{aligned} \phi(y_1, y_2, I, y_{1,d}, \dot{y}_{1,d}, \ddot{y}_{1,d}, \dddot{y}_{1,d})) = \\ \dddot{y}_{1,d} + k_2 \left(\ddot{y}_{1,d} - L_f^2 h \right) + k_1 \left(\dot{y}_{1,d} - L_f h \right) \\ + k_0 \left(y_{1,d} - h \right) - L_f^3 h \end{aligned} \tag{26}$$

while the function β being defined by

$$\beta(I) = -\lambda_1 \eta I. \tag{27}$$

The closed-loop system with the nonlinear, positive path tracking control is in Fig. 1. The inputs of the nonlinear path tracking controller with control law (25) are the current inhibitor level, the logarithm of the reference tumor volume and its derivatives, and the logarithm of the current tumor volume and supporting vasculature volume. The output of the nonlinear path tracking controller is connected to the positive input dynamics block that simulates the differential equation (4) that ensures that the inhibitor level (the input of the tumor model) is positive. The positive input dynamics block is also implemented inside the controller. The output of the positive input dynamics block is the output of the controller that is the inhibitor serum level which is connected to the transformed tumor growth model. Note that the inhibitor serum level is also required for the control law (25) that results in an inner loop in the controller.

3.3 State estimation

Now we consider the physiologically relevant situation where the supporting vasculature volume can not be measured, only the tumor volume and the inhibitor level is known, and design a nonlinear state observer to estimate the logarithm of the supporting vasculature volume. The differential equations of the state observer are

$$\dot{\hat{y}}_1 = -\lambda_1 \hat{y}_1 + \lambda_1 \hat{y}_2 + G_1 (y_1 - \hat{y}_1) \tag{28}$$
$$\dot{\hat{y}}_2 = be^{\hat{y}_1 - \hat{y}_2} - de^{2\hat{y}_1/3} + \eta I + G_2 (y_1 - \hat{y}_1), \tag{29}$$

where y_1 is the logarithm of the measured tumor volume, and $G = (G_1, G_2)^\top$ is the gain vector, so with $y = (y_1, y_2)^\top$ being the real system states and $\hat{y} = (\hat{y}_1, \hat{y}_2)^\top$ being the estimated system states we have that the observer dynamics is governed by

$$\dot{\hat{y}} = f(\hat{y}) + g(\hat{y}) I + G(y_1 - \hat{y}_1) \tag{30}$$

with the vector fields f and g defined this case as

$$f(\hat{y}) = \begin{pmatrix} -\lambda_1 \hat{y}_1 + \lambda_1 \hat{y}_2 \\ be^{\hat{y}_1 - \hat{y}_2} - de^{2/3 \hat{y}_1} \end{pmatrix}, \; g = \begin{pmatrix} 0 \\ -\eta \end{pmatrix}. \tag{31}$$

The differential equation of the estimation error $\hat{e} = y - \hat{y}$ is

$$\begin{aligned}\dot{\hat{e}} &= f(y) - f(\hat{y}) + g(y)I - g(\hat{y})I - G(h(y) - h(\hat{y})) \\ &= f(y) - f(\hat{y}) - G(h(y) - h(\hat{y})). \end{aligned} \quad (32)$$

A sufficient condition for this state estimator to be globally exponentially stable is given by the following theorem.

Theorem 1. (Primbs (1996); Kou et al. (1975)) If there exists a constant matrix G and a positive definite symmetric matrix P such that

$$P\,(f' - Gh') < 0 \quad (33)$$

holds in every point, then for any initial estimate $\hat{y}(t_0)$ we have for all $t \geq t_0$ that

$$\|\hat{y}(t) - y(t)\| \leq \alpha_1 \|\hat{y}(t_0) - y(t_0)\| e^{-\alpha_2 (t - t_0)}, \quad (34)$$

with α_1 and α_2 being some positive numbers, i.e. the states of the estimator converge exponentially to the states of the original system.

Next, we give sufficient conditions for the values of G such that the estimator with dynamics (30) is globally exponentially stable.

Theorem 2. The nonlinear state estimator governed by the differential equation (30) is globally exponentially stable and the estimated states converge to the original states if the conditions

$$G_1 > -\lambda_1 \quad (35)$$

$$G_2 > -G_1 \frac{b}{\lambda_1} e^{y_1 - y_2} - \frac{2}{3} d e^{2/3 y_1} \quad (36)$$

hold for any value of y_1 and y_2.

Proof. Consider $P = I_2$, i.e. let P be the 2×2 identity matrix (which is a positive definite symmetric matrix). Thus, according to Theorem 1, the sufficient condition for (30) to be globally exponentially stable is that

$$(f' - Gh') < 0 \quad (37)$$

holds in every point. Expanding the terms in this inequality yields

$$\begin{pmatrix} -\lambda_1 - G_1 & \lambda_1 \\ b e^{y_1 - y_2} - 2/3 d e^{2/3 y_1} - G_2 & -b e^{y_1 - y_2} \end{pmatrix} < 0. \quad (38)$$

The eigenvalues of the matrix in the left-hand side of (38) are the roots of the polynomial equation

$$s^2 + \underbrace{\left(b e^{y_1 - y_2} + \lambda_1 + G_1\right)}_{\beta} s + \underbrace{\lambda_1 G_2 + b e^{y_1 - y_2} G_1 + 2/3 \lambda_1 d e^{2/3 y_1}}_{\gamma} = 0 \quad (39)$$

that can be written as

$$s_{1,2} = \frac{-\beta \pm \sqrt{\beta^2 - 4\gamma}}{2}. \quad (40)$$

So, the matrix in the left-hand side of (38) is negative definite – thus the inequality (37) holds – if and only if (40) has negative real parts. A necessary condition for (40) to have negative real part is that $\beta > 0$ that can be expanded to get

$$b e^{y_1 - y_2} + \lambda_1 + G_1 > 0 \quad (41)$$

which can be rearranged to get

$$G_1 > -b e^{y_1 - y_2} - \lambda_1. \quad (42)$$

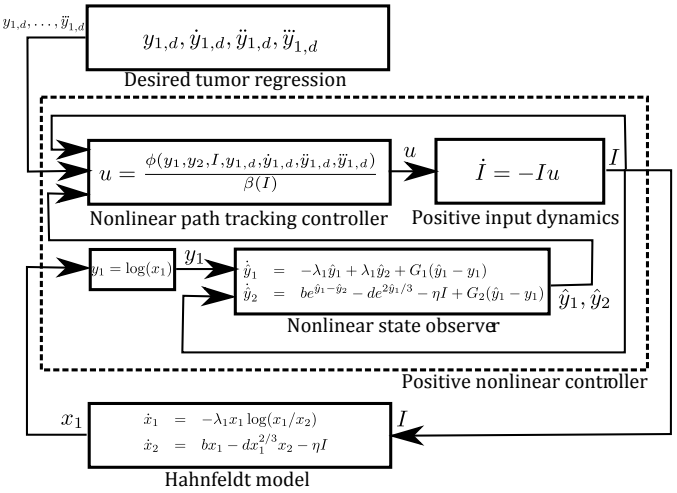

Fig. 2. Positive, nonlinear, path tracking control of the original tumor model with state estimation

Note that $e^{y_1 - y_2}$ is always positive, while b is also always positive, so if $G_1 > -\lambda_1$, then this necessary condition is always satisfied that verifies condition (35).

If $\beta > 0$ holds, then a necessary and sufficient condition for (40) to have negative real part is that $\gamma > 0$ (since in this case the absolute value of the result of the square root function in (40) will be less than β), which can be formulated as

$$\lambda_1 G_2 + b e^{y_1 - y_2} G_1 + \lambda_1 2/3 d e^{2/3 y_1} > 0 \quad (43)$$

that can be rearranged to get

$$G_2 > -G_1 b/\lambda_1 e^{y_1 - y_2} - 2/3 e^{2/3 y_1} \quad (44)$$

that verifies condition (36) and thus concludes the proof.

Note that the conditions of this theorem are satisfied for every value of y_1 and y_2 if $G_1 > 0$ and $G_2 \geq 0$.

The block diagram of the closed-loop system containing the original Hahnfeldt-model, the positive nonlinear controller, the state estimator and the reference signals are in Fig. 2.

4. SIMULATION RESULTS

In this section we show results of the simulation of the closed-loop system in Fig. 2. The path tracking control was designed such that the characteristic equation of the tracking error dynamics has the root -1 with multiplicity of 3, so the error dynamics is governed by the differential equation

$$\dddot{e} + 3\ddot{e} + 3\dot{e} + e = 0 \quad (45)$$

thus $k_2 = 3$, $k_1 = 3$, $k_0 = 1$ in the control law (25). The gain parameter G in the differential equation of the state estimator was chosen to $G = (1, 1)^\top$ that results in a globally exponentially stable estimator according to Theorem 2. The initial conditions for the tumor model were $x_1(0) = x_2(0) = 1.74 \cdot 10^4\,\mathrm{mm}^3$, while the initial condition for the positive input dynamic subsystem was $I(0) = 0.1\,\mathrm{mg/kg}$.

The reference signals are given by

$$y_{1,d} = \log\left((x_1(0) - 1)\exp(-t/T_{id}) + 1\right) \quad (46)$$

and its derivatives. Note that due to the transformations (6)-(7) on the states variables of the Hahnfeldt-model, y_1 is

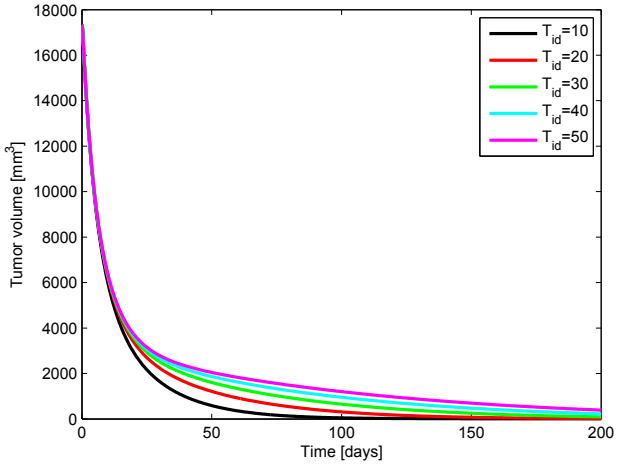

Fig. 3. Tumor volumes during the simulations with different time constants for the reference signal

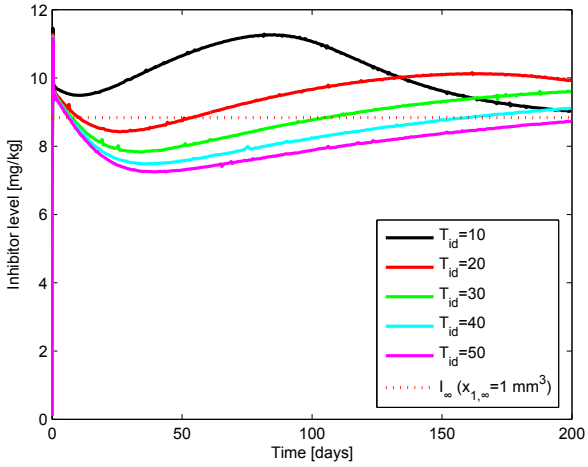

Fig. 4. Inhibitor levels during the simulations with different time constants for the reference signal (solid curves), and the serum level I_∞ required for maintaining the $x_{1,\infty} = 1\,\mathrm{mm}^3$ steady-state tumor volume (dotted line)

the logarithm of the tumor volume, so this reference signal ensures an exponential regression of the tumor volume in the closed-loop system with time constant T_{id}. The simulations started at $t = 0$ and ended at $t = 200$ days.

We have run simulations for five different values of time constants with $T_{id} \in \{10, 20, 30, 40, 50\}$ days. The results are in Figs 3 and 4. The smaller time constant results in faster tumor regression, but higher inhibitor levels. Increasing the time constant results in lower inhibitor levels that are physiologically desirable, while they still yield sufficiently fast tumor regression. The serum level $I_\infty = 8.85\,\mathrm{mg/kg}$ required for maintaining the $x_{1,\infty} = 1\,\mathrm{mm}^3$ steady-state tumor volume acquired using (3) is the red dotted line in Fig 4.

In Drexler et al. (2011, 2012), the second-order Hahnfeldt-model was extended with the pharmakokinetics of the drug. In Drexler et al. (2011) an LQ regulator and a linear observer was designed for a linear model acquired by linearization of the Hahnfeldt-model in an operation point, and the positivity and low value of the drug input was guaranteed by a discontinuous saturation. The input for the model with pharmakokinetics is the rate of injection, this was extremely high without saturation ($3 \cdot 10^4$mg/kg/day at the beginning), and was still high with saturation (80mg/kg/day at the beginning), and it decreased during the therapy, until it reached the steady-state required for maintaining the steady-state of $1\,\mathrm{mm}^3$ tumor volume. In Drexler et al. (2012) path tracking control was applied to the Hahnfeldt-model extended with the pharmakokinetics using exact linearization, and the simulation results showed that no upper limit for the saturation of the controller output were needed. The inhibitor injection rate increased to approximately 30 mg/kg/day at the beginning, and after it reached its maximum, it decreased to the value required for maintaining the steady-state of $1\,\mathrm{mm}^3$ tumor volume. The desired tumor volume regression was exponential, with time constant of 6 days.

In Sápi et al. (2013) a robust controller was designed using H_∞-synthesis for the second-order Hahnfeldt-model (without pharmakokinetics) that was linearized in an operation point. In order to guarantee low inputs and positive inputs, we used a saturation on the output of the controller with lower limit of 0 mg/kg and upper limit of 13 mg/kg. The simulation results showed that initially the inhibitor level was the upper limit of the saturation (i.e. the real signal was saturated) for about 60 days, and after that period it decreased towards the value required for maintaining the steady-state of $1\,\mathrm{mm}^3$ tumor volume. In Sápi et al. (2015), linear controllers using LQ regulators, pole-placement and linear observers were designed for the Hahnfeldt-model without pharmakokinetics linearized in different operation points, and the results were compared. The output level of the controllers were very high in this case as well, thus we had to apply saturation on the controller output. We used a saturation with lower limit of 0 mg/kg and upper limit of 13 mg/kg. Even with the best parameter settings, the control output was saturated for $60 - 80$ days, and after that it converged towards the value required for maintaining the steady-state of $1\,\mathrm{mm}^3$ tumor volume.

In Kovács et al. (2014) a robust controller was designed for the Hahnfeldt-model without pharmakokinetics linearized in an operation point. The inputs had to be saturated in this case as well, and the inhibitor level was the maximal allowed level (depending on the upper level used for the saturation) for a long period of time (the smaller the level of the saturation, the longer this period is), and then it decreased to the steady-state inhibitor level required to maintain the $1\,\mathrm{mm}^3$ steady-state tumor volume. In Szeles et al. (2014), using a tumor volume dependent switching paradigm for the controller parameters, path tracking control was designed for the exact linearized Hahnfeldt-model, while LQ regulator and robust controller based on H_∞ synthesis was designed for the Hahnfeldt-model linearized in an operation point. The parameters of the controllers depended on the current tumor volume. However, in this case the maximal inhibitor levels were still $50 - 60$ mg/kg, and we needed a saturation for the

controller output of the LQ regulator and the robust controller.

5. CONCLUSION

The results of inhibitor levels during the simulations show that we do not need a saturation on the controller output if we use the controller discussed in this paper, moreover, the serum levels are always below 13 mg/kg, and they can also go below the value required for maintaining the steady-state of 1 mm^3 tumor volume that never happened in our previous works. However, in exchange, the tumor regression is slower, but that is negligible if we consider the gain of having physiologically valid controller outputs without any saturation.

The potential clinical impact of this positive nonlinear control is considerable. Several studies examined the anti-tumor effect of endostatin as a function of delivery (for instance in the case of pancreatic cancer Kisker et al. (2001), Capillo et al. (2003)). Continuous administration (using micro-osmotic pumps) was found to be more effective (97% inhibition of tumor growth) than daily bolus doses (66% inhibition of tumor growth), using the same dosage (20 mg/kg/day). The controller which can handle the continuous administration guaranteeing positive inputs would result in even more effective treatment, not just in regard to the therapeutic effectiveness, but to the cost-effectiveness aspect as well.

6. ACKNOWLEDGMENT

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