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Model-based Angiogenic Inhibition of Tumor Growth using Feedback Linearization

Annamária Szeles, Dániel András Drexler, Johanna Sápi, István Harmati and Levente Kovács

Abstract— **In the last decades beside conventional cancer treatment methods, molecular targeted therapies show prosperous results. These therapies have limited side-effects, and in comparison to chemotherapy, tumorous cells show lower tendency of becoming resistant to the applied antiangiogenic drugs. In clinical research, antiangiogenic therapy is one of the most promising cancer treatment methods. Using a simplified model of the reference dynamical model for tumor growth under angiogenic inhibition from the literature, exact linearization is performed in the paper to handle the nonlinear behavior of the model. Two different control methods are applied on the linearized model: flat control and switching control. Simulations are performed on the nonlinear model to show the characteristics of the therapies carried out using the presented control methods.**

I. INTRODUCTION

Cancer is one of the most destructive illnesses in the world, and Europe has a leading position in world-wide statistics [1]. Developing effective cancer treatment methods is one of the most important objects of modern medicine. Conventional therapies as radiotherapy or chemotherapy are supposed to directly kill tumor cells. These treatment methods have many side-effects, the entire body is affected during the therapy. Modern therapies, called targeted molecular therapies, influence the life cycle of the cancerous cells; thus, have limited side-effects. The therapy presented and simulated in this paper is the antiangiogenic therapy which takes effect on the vascular growth of the tumor [2]. Angiogenic inhibitors prevent tumor cells from growing own blood vessels; thus, antiangiogenic therapy keeps the tumor in an avascular state with nontoxic inhibitor concentrations [3], [4].

The mathematical formalism of tumor growth under angiogenic stimulator and inhibitor effects was investigated by Philip Hahnfeldt et al. at the Harvard University [5]. This paper uses a simplified model to design and compare different control strategies. Bang-singular-bang control was implemented for the simplified model in [6], and optimal control was elaborated in bang-singular-bang structure for the original model in [7]. Optimal linear control was designed and investigated in [8], [9].

There are more different approaches to handle the nonlinearity of the system. Working point linearization, state-space and robust control techniques were designed and analyzed in former papers, [8], [10]. In this paper, exact linearization is performed to transform the nonlinear model into a series of integrators. For the linearized system, flat control and switch control is designed to investigate path tracking.

In Section II, the onco-pathological background of tumor growth and medical treatments is described. Section III presents the nonlinear model of tumor growth under angiogenic inhibition and the controllability analysis of the system. In Section IV, the theoretical background of exact linearization is shortly introduced, and Section V gives a detailed presentation of the controllers designed and related simulations. In Section VI, control techniques are compared based on the simulation results, relevant characteristics are compared, and Section VII gives a brief conclusion.

II. BIOMEDICAL BACKGROUND

Cancer treatment is one of the most important research field of medicine. Surgical intervention [11], chemotherapy [12] and radiotherapy [13] are referred as conventional treatments in medical practice [14]. These techniques prevent the most significant characteristics of tumors, that tumor cells divide and proliferate rapidly. However, in case of curative surgery healthy tissue has to be removed as well; in case of chemotherapy the entire body is affected and tumor cells can become resistant to the applied drugs; in case of radiotherapy the DNA of nearby tissue can be damaged.

Antiangiogenic therapy [15] influences the vascular growth of tumors. Nutritiants and oxygen needed by the dividing tumor cells are taken from the host body until a given size of the tumor (generally 1-2 mm^3). When the tumor exceeds this size, angiogenesis is stimulated by the tumor itself and new blood vessels will be grown to nourish the tumor. This mechanism is called tumor indicated angiogenesis [16]. Antiangiogenic therapy inhibits this stimulatory effect, and eliminates tumor grown vascularity.

Several angiogenic inhibitors are known in medical practice, such as endostatin [17] or bevacizumab [18]. Clinical results present another advantage of antiangiogenic drugs in point of resistance. While tumor cells develop intrinsic resistance to chemotherapy, in case of antiangiogenic treatment resistance is induced by the drug (acquired resistance). Intrinsic resistance means pre-existing resistance – approximately 50% of all cancer cases, resistance to chemotherapy already

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A. Szeles, D. A. Drexler and I. Harmati is with the Budapest University of Technology and Economics, Dept. of Control Engineering and Information Technology, Magyar tudósok krt. 2., H-1117 Budapest, Hungary; szeles.annam@gmail.com, {drexler, harmati}@iit.bme.hu

J. Sápi and L. Kovács is with the Óbuda University, John von Neumann Faculty of Informatics, Bécsi út 96/B, H-1034 Budapest, Hungary, sapi.johanna@phd.uni-obuda.hu, kovacs.levente@nik.uni-obuda.hu

exists before drug treatment starts [19]. It is difficult to manage intrinsic resistance; however, there are alternative targets (based on normalization of the tumor microenvironment) to overcome acquired resistance [20].

III. DYNAMICAL MODEL OF TUMOR GROWTH

In 1999, a research was carried out at the Harvard Medical University by Philip Hahnfeldt et al. to investigate experimentally and theoretically the effects of angiogenic inhibitors on tumor growth dynamics. They posed a quantitative theory for tumor growth under angiogenic stimulator/inhibitor control [5]. In their experiments, mice were injected with Lewis lung carcinoma cells. The following equations comprise the entire model formulation:

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

$$\dot{x}_2 = bx_1 - dx_1^{\frac{2}{3}} x_2 - ex_2 x_3 \tag{2}$$

$$\dot{x}_3 = \int_0^t u(t') \exp\left(-\lambda_3 (t - t')\right) dt' \tag{3}$$

$$y = x_1, \tag{4}$$

where x_1 is the tumor volume (mm^3), x_2 is the supporting vasculature volume (mm^3), x_3 is the inhibitor serum level (mg/kg), and u is the inhibitor administration rate (mg/kg/day). The complete model formulation describes the phenomenology of tumor growth slowdown, as the tumor consumes its available support; stimulatory and inhibitory influences from the tumor cells; inhibition due to administered inhibitors; and the clearance of the administered inhibitor. In the simplified model, the latter effect is not described, only the serum level of the inhibitor to be maintained is represented, so a second-order system is to be analyzed:

$$\dot{x}_1 = -\lambda x_1 \ln\left(\frac{x_1}{x_2}\right) \tag{5}$$

$$\dot{x}_2 = bx_1 - dx_1^{\frac{2}{3}} x_2 - ex_2 u \tag{6}$$

$$y = x_1 \tag{7}$$

where x_1 is the tumor volume (mm^3), x_2 is the vasculature volume (mm^3), and u is the serum level of the inhibitor (mg/kg). Equation (7) represents that tumor volume is the measured output of the system. The characteristics of the parameters for the Lewis lung carcinoma and the mice used in the experiment are: $\lambda = 0.192\,(\text{day}^{-1})$, $b = 5.85\,(\text{day}^{-1})$, $d = 0.00873\,(\text{day}^{-1}\text{mm}^{-2})$, while the parameter characteristic for the inhibitor (endostatin) is: $e = 0.66\,(\text{day}^{-1}(\text{mg/kg})^{-1})$. For further calculations and controller design, the nonlinear model described in (5)-(7) will be used. Fig. 1 shows the nonlinear behavior of the simplified model.

A. Lie Algebra Rank Condition

The controllability of the system needs to be investigated before the controller design is carried out. For this purpose,

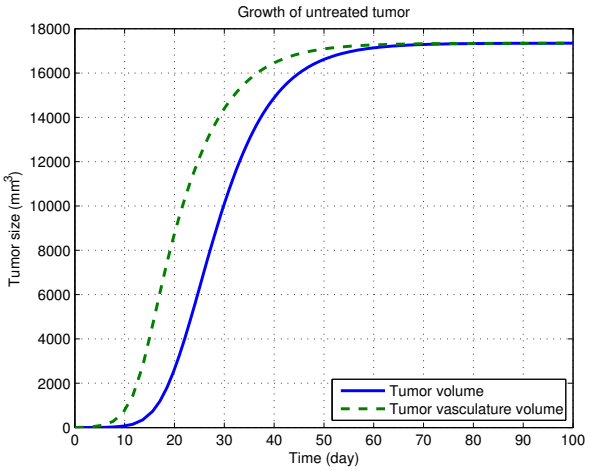

Fig. 1. Growth of untreated tumor

Lie Algebra Rank Condition is evaluated. The general formalism of input affine nonlinear systems is:

$$\dot{x} = f(x) + g(x)u \tag{8}$$

$$y = h(x) \tag{9}$$

where the drift vector field f, the control vector field g, and the output expression h can be formulated in the current case as:

$$f(x) = \begin{bmatrix} -\lambda x_1 \ln\left(\frac{x_1}{x_2}\right) \\ bx_1 - dx_1^{\frac{2}{3}} x_2 \end{bmatrix} \quad g(x) = \begin{bmatrix} 0 \\ -ex_2 \end{bmatrix}$$

$$h(x) = x_1. \tag{10}$$

The Δ distribution [21], where state variables x_1, x_2 are declared, has to fulfill the following criteria:

- Δ is involutive;
- Δ contains the distribution $\text{span}\{g\}$;
- Δ is invariant under the vector fields f, g.

To reach these properties, a construction is given in [21].

1) Initialization: $\Delta_0 = \Delta$ a distribution expanded by a set of the vector fields $\tau_1 \dots \tau_q$;
2) Expansion: $\Delta_{k+1} = \Delta_k + \sum_{i=1}^{q} [\tau_i, \Delta_k]$, where Δ_{k+1} contains Δ_k and is invariant for τ_i $i = 1 \dots q$ vector fields;
3) Stop condition: $\dim(\Delta_{k+1}) = m$ or $\dim(\Delta_{k+1}) = \dim(\Delta_k)$.

In our case (Single Input Single Output system), the drift vector field is f, the control vector field is g, $m = 2$, and the following steps have to be done:

1) Initialization: $\Delta_0 = \{g\}$;
2) Expansion: $\Delta_1 = \Delta_0 + [f, g] + [g, g] = \{g, [f, g]\}$, since $[g, g] = 0$; involutivity has to be investigated.

The system is controllable if the set $\Delta = \{f, [f, g]\}$ is involutive, which can be assessed by checking if the constructed

matrix is full rank. The Lie-bracket of the drift vector field f, and the control vector field g, can be calculated as follows:

$$[f,g] = \frac{\partial f}{\partial x}g - \frac{\partial g}{\partial x}f = \begin{bmatrix} -\lambda e x_1 \\ e b x_1 \end{bmatrix} \tag{11}$$

The constructed matrix to check Lie Algebra Rank Condition is:

$$\Delta = \{g,[f,g]\} = \begin{bmatrix} 0 & -\lambda e x_1 \\ -e x_2 & e b x_1 \end{bmatrix} \tag{12}$$

The determinant of the matrix to determine singularities is:

$$D = -(-\lambda e x_1)(-e x_2) = -\lambda e^2 x_1 x_2. \tag{13}$$

The determinant becomes zero, if x_1 or x_2 equals to zero. $x_1 = 0$ means that there is no tumor and no treatment is needed. $x_2 = 0$ means that the tumor has no endothelium grown by itself, no control is needed and constant serum level is required to maintain avascular state. In any other cases ($x_1 \neq 0$ and $x_2 \neq 0$) the system is controllable.

IV. FLATNESS BASED SWITCH CONTROL

This section presents how exact linearization was performed on the nonlinear system. Linearizing feedback can be calculated based on the output and the transformed coordinates of the nonlinear system. If this linearizing feedback exists, the linearized system between input v and output y can be handled as a series of integrators.

First of all, the relative degree of the measured output has to be calculated to determine if the system can be linearized using static feedback linearization.

A. Relative degree of the output

The relative degree of the output $y = h(x)$ is $r \in \mathbb{N}$ for which:

$$\begin{aligned} L_g L_f^k h(x) &= 0 \quad \text{if} \quad 0 \leq k < r-1 \\ L_g L_f^{r-1} h(x) &\neq 0. \end{aligned} \tag{14}$$

In our case, the following calculations have to be carried out:

$$L_g h(x) = \frac{\partial h(x)}{\partial x} g = 0 \tag{15}$$

$$L_g L_f h(x) = \frac{\partial}{\partial x}\left(\frac{\partial h(x)}{\partial x} f\right) g = -e\lambda x_1 \tag{16}$$

which means that the relative degree of the measured output is equal to the order of the system, $r = 2$, thus exact linearization can be carried out.

B. Linearizing feedback

The first $r = 2$ elements of the coordinate transformation $x \mapsto \phi(x) \in R^n \mapsto R^n$ can be defined accordingly:

$$z_1 = \phi_1(x) = h(x) = x_1 \tag{17}$$

$$z_2 = \phi_2(x) = L_f h(x) = \frac{\partial h(x)}{\partial x} f = -\lambda x_1 \ln \frac{x_1}{x_2}. \tag{18}$$

Since $\dim(x) = n = r$, no further variables are needed, the zero dynamics of the system is trivial, static linearizing feedback can be designed. Otherwise, the last $n-r$ elements should be constructed such that $L_g \phi_i(x) = 0$ and ϕ^{-1} exists. The differential equations of the system in the new coordinates are:

$$\dot{z}_1 = \frac{\partial \phi_1}{\partial x}\dot{x} = L_f h(x) = \phi_2(x) = z_2 \tag{19}$$

$$\begin{aligned} \dot{z}_2 &= \frac{\partial \phi_2}{\partial x}\dot{x} = L_f^2 h(x) + L_g L_f h(x) u = \\ &:= a(x) + b(x)u(t) \end{aligned} \tag{20}$$

where

$$\begin{aligned} a(x) = (\lambda \ln \frac{x_1}{x_2} + \lambda)\lambda x_1 \ln \frac{x_1}{x_2} + \\ \lambda x_1 \frac{1}{x_2}(b x_1 - d x_1^{\frac{2}{3}} x_2) \end{aligned} \tag{21}$$

$$b(x) = -e\lambda x_1. \tag{22}$$

The linearizing feedback can be calculated accordingly:

$$v = L_f^2(h(x)) + L_g L_f(h(x))u = a(x) + b(x)u \tag{23}$$

$$u = \frac{v - a(x)}{b(x)}. \tag{24}$$

Exact linearization can be executed using the coordinate transformation and linearizing feedback presented in (17), (18) and (23). In the following, the linearized model will be controlled, using switching strategy for the flat control.

C. Flat control

Flat control realizes path tracking with a control behaviour determined by the predefined error dynamics. The reference signal [22] is given with its derivatives as well, $\{y_{ref}, \dot{y}_{ref}, \ddot{y}_{ref}\}$. In this case, the reference signal decreases exponentially from an initial tumor volume (2000 mm^3) to the desired plateau (1 mm^3). The reference signal and its derivatives are:

$$y_{ref} = (x_{init} - 1)e^{-\frac{t}{T}} + 1 \tag{25}$$

$$\dot{y}_{ref} = -\frac{1}{T}(x_{init} - 1)e^{-\frac{t}{T}} \tag{26}$$

$$\ddot{y}_{ref} = \frac{1}{T^2}(x_{init} - 1)e^{-\frac{t}{T}}. \tag{27}$$

The control law is designed by prescribing the error dynamics. Error dynamics is chosen to be faster than the poles of the system obtained with working point linearization at the initial tumor volume. The control law is:

$$\begin{aligned} v &= \ddot{y}_{ref} + k_2(\dot{y}_{ref} - \dot{y}) + k_1(y_{ref} - y) \\ &= \ddot{y}_{ref} + k_2(\dot{y}_{ref} - z_2) + k_1(y_{ref} - z_1) \end{aligned} \tag{28}$$

which means that the solutions of the following equation characterizes the error dynamics:

$$s^2 + k_2 s + k_1 = 0. \tag{29}$$

The nonlinear model was investigated using working point linearization at the initial tumor volume, the poles of the linearized model are 6.2526 and -0.3436. The control shall

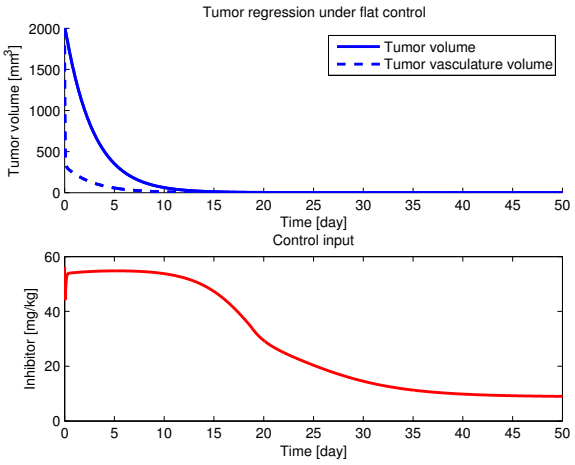

Fig. 2. Flat control

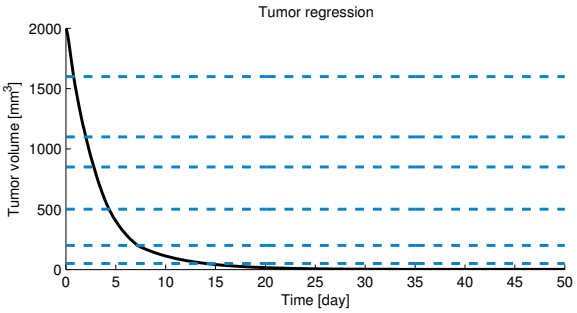

Fig. 3. Division of tumor domain

TABLE I
SIMULATION PARAMETERS

	Domain					
Parameter	1	2	3	4	5	6-7
sys_poles	+6.25 -0.34	+3.89 -0.44	+2.39 -0.58	+0.10 -3.91	+0.02 -5.38	+0.0006 -5.99
err_poles	-0.15 -8	-0.25 -8.75	-0.3 -11	-0.35 -12.5	-0.32 -12.7	-0.2 -19
T	1/0.35	1/0.45	1/0.5	1/0.7	1/0.8	1

stabilize the unstable pole and fasten the closed-loop system. The error dynamics are prescribed with the poles $-4 \pm 1.5i$, and time constant of the reference signal is set to $1/0.35$. Using these parameters, the control results in fast tumor regression such that the control input does not exceed the physiological limit (50-65 mg/kg). If error dynamics are set significantly faster, control input shall be saturated.

The tumor regression under reference flat control with parameters $T = 1/0.35$ (day), $x_{init} = 2000$ (mm^3), $k_1 = 18.25$, $k_2 = 8$ is depicted in Fig. 2. The total inhibitor consumption during a 50 days long therapy was 1412 mg/kg. In the next subsection, a switch control strategy is proposed that maintains the performance, but decreases the total inhibitor consumption (and the cost) of the therapy.

D. Switching control

The nonlinear model shows different behavior in different regions of the tumor domain. Simulations show that faster error dynamics are compatible with the model as the tumor volume decreases, using different controllers in different regions can be prosperous. Thus, the tumor volume domain was divided into several parts as shown in Fig. 3. These regions are the following: [2000-1600, 1600-1150, 1150-850, 850-500, 500-200, 200-50, 50-0] mm^3. In the low regions, tumor growth dynamics change faster, thus a more stiff division was necessary. In each domain differently parametrized flat control is designed to follow the dynamics of the original nonlinear system such that the fastest controller is applied which corresponds to the physiological conditions (maximal serum level does not exceed 50-65 mg/kg) and the performance criteria.

The nonlinear model was linearized using working point linearization at the points: 2000, 1200, 1000, 700, 300, 100; and the poles of the system were calculated ('sys_poles') to parameterize flat control, i.e. error dynamics ('err_poles') with the corresponding coefficients in (29) in each domain accordingly, see 'sys_poles' and 'err_poles' in detail in Table I. Two groups of simulations are discussed:

1) only error dynamics is fastened
2) both the reference signal and the error dynamics are fastened,

for the latter case see time constants in Table I.

V. SIMULATION RESULTS

Simulations are carried out in the 0-2000 mm^3 tumor domain, since experiments show that this is the tumor range where most of the mice are alive, above 2500 mm^3 less than 10% of the animals survive. Antiangiogenic therapy can reduce tumor volume only to a minimal size (1-2 mm^3) where the tumor cells obtain oxigen and nutritiants from the host body without growing own blood vessels. In simulations, 1 mm^3 is set to minimal tumor volume. This minimal volume (the avascular state of the tumor cells) can be maintained using a given serum level (8.85 mg/kg), derived from steady state equations of the model [9]. Thus, the expectations to the designed contollers are the following:

- tumor volume decreases to the minimal volume;
- the applied serum level does not exceed 50-65 mg/kg;
- tumor volume decreases to the 1% of the initial tumor volume as fast as possible;
- total inhibitor inlet is as low as possible.

The aim of applying switching control is to secure fast tumor regression to 1% of the initial tumor volume and low total inhibitor inlet. Switching control was performed using two solutions in both groups:

- in each domain control input is calculated according to the modified parameters;
- the control inputs calculated in neighboring domains are mixed using their affine combination ($u = \lambda u_i + (1-\lambda)u_{i+1}$), in the middle of the given domain, the precalculated control input will effect.

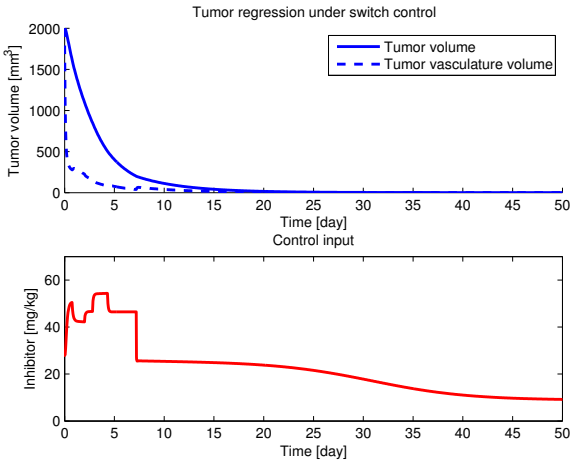

Fig. 4. Switch control – No affine combination of control inputs

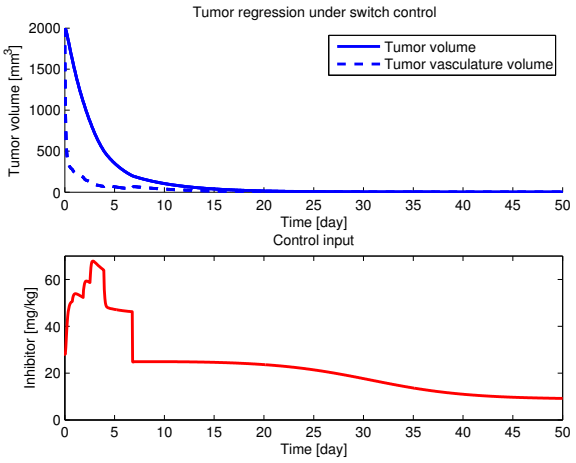

Fig. 6. Switch control – No affine combination of control inputs, reference signal fastened

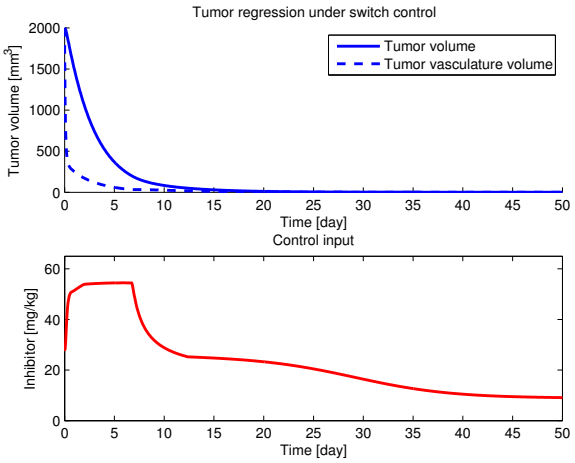

Fig. 5. Switch control – Using affine combination of control inputs

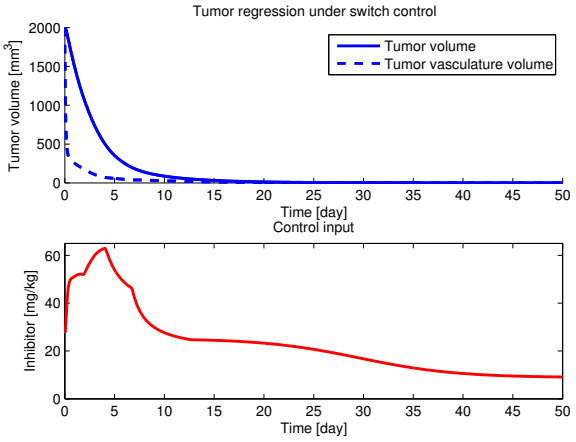

Fig. 7. Switch control – Using affine combination of control inputs, reference signal fastened

In the first group of simulations only error dynamics were set faster in each domain (Fig. 4). Using affinely combined control inputs secures continuous control input in the entire time domain (Fig. 5). In case of affinely combined inputs, tumor regression is faster. Total inhibitor inlet is 1111 mg/kg if no affine combination of control inputs is used, and 1153 mg/kg if affine combination is calculated.

In the second group of simulations, both error dynamics and reference signal were fastened in each domain. Total inhibitor inlet is 1131 mg/kg when no affine combination of control inputs is used (Fig. 6), and 1148 mg/kg when affine combination is calculated (Fig. 7). Total inhibitor inlet does not show relevant increasement, however faster tumor regression could be achieved.

The controller was fastened considering the physiological limit in each domain except the last one, where slow-down was needed to achieve decreasement in the total inhibitor inlet. Using switching control, the characteristics of therapy and tumor regression can be tuned according to the external constraints as maximal serum level, costs, total inhibitor inlet. However, there is a trade-off between maximal serum level and length of therapy (speed of tumor regression). Though, total and daily inhibitor inlet is impressively lower than in the case of flat control and shows nearly the same performance until regression to the 10% of the initial tumor volume, both 1% of the initial tumor volume and minimal tumor volume are reached slower.

VI. DISCUSSION

Simulation results show that using switch control, parameters can be tuned according to the regression and inhibitor inlet desired; thus, total inihibitor inlet could be minimized with appriopriate parameters. Using flat control, fast tumor regression can be achieved with higher inhibitor consumption. The designed controllers are compared in this section according to the following aspects (Table II):

1) Time while tumor volume decreased to 1% (20 mm^3) of initial tumor volume;
2) Time to achieve the plateau of 1 mm^3;

TABLE II

COMPARISON OF DIFFERENT CONTROL METHODS

Property	Flat	I-NA	I-A	II-NA	II-A
Time to 1% (days)	13.3	18.7	17	18.5	17.4
Time to 1 mm^3 (days)	18.7	42.6	40.1	40.3	38.9
Daily inlet high (days)	17.4	7.2	7.6	6.7	7.2
Total inlet (mg/kg)	1412	1111	1153	1131	1148

3) Daily endostatin inlet is over 40 mg/kg measured in days;
4) Total endostatin inlet.

Abbreviations in Table II: I-NA – First group without affine combination, I-A – First group with affine combination, II-NA – Second group without affine combination and II-A – Second group with affine combination.

All controllers fulfill the physiological condition i.e. the control input of highest magnitude is not over 50-65 mg/kg. Furthermore, all controllers achieve the desired plateau of 1 mm^3. The least inhibitor is required by switching control, both in total and daily inlets. A consequence of this is that total regression takes longer. Tuning the control in the last domains, tumor regression can be fastened though resulting in higher total inhibitor inlet. Generally, it can be stated that fast tumor regression requires higher inhibitor levels in daily and in total inlet.

VII. CONCLUSION

Fast tumor regression was achieved using relatively low daily and total inhibitor inlet using the control techniques presented in the paper. The minimal tumor volume was reached by both control methods, that is a really impressive result compared to the performance achieved in [10]. Using linearizing feedback and an appropriate reference signal, the control input fits the physiological constraints without saturation that facilitates more precise parameter tuning.

Performing exact linearization makes all linear control methods applicable and further methods could be investigated as well. Another issue to investigate is using other nonlinear control methods, for example State Dependent Riccati Equation or adaptive control methods.

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