

Closed-loop control of tumor growth by means of anti-angiogenic administration

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Abstract—A tumor growth model accounting for angiogenic stimulation and inhibition is here considered, and a closed-loop control law is presented with the aim of tumor volume reduction by means of anti-angiogenic administration. To this end the output-feedback linearization theory is exploited, with the feedback designed on the basis of a state observer for nonlinear systems. The control scheme allows to set independently the control and the observer parameters thanks to the special structural properties of the tumor growth model that guarantee the separability of estimation and feedback control algorithms. Preliminary results seem extremely promising, showing a noticeable level of robustness against a wide range of the initial state estimate.

I. INTRODUCTION

Anti-angiogenic therapies are relatively new cancer treatments, proposed at first by Folkman [?] in the early seventies, consolidated along the nineties by several discoveries on the main principles regulating tumor angiogenesis [?] and widely debated in several theoretical and experimental studies throughout the last decade. Anti-angiogenic treatments aim at inhibiting the development of the vascular network necessary to support tumor growth during the vascular phase, so providing a way to control the heterogeneous and growth-unconstrained tumor population throughout the control of the homogeneous and growth-constrained population of endothelial cells [?], [?]. Tumors have the capability to develop resistance to the conventional chemotherapeutic drugs mainly because of the rapidity of tumor cells in evolving towards new resistant phenotypes. Due to the indirect action of the anti-angiogenic drugs, the outcome of the therapy should not be impaired by the capability of tumor cells to generate resistant phenotypic variants [?], [?], and the effectiveness of anti-angiogenic treatments on the control and possible remission of experimental tumors has been demonstrated [?]. Moreover, anti-angiogenic therapies have limited side effects respect to the conventional chemotherapies and radiotherapies. Conventional chemotherapies may also have anti-angiogenic effects on the vascular network [?], [?], [?].

This note aims to investigate and design a closed-loop model-based anti-angiogenic therapy. The adopted model refers to [?], where a quantitative model describing the growth of experimental tumors under the control of the vascular network is presented. In [?], Hahnfeld and coworkers introduced the concept of the *carrying capacity* of the

vasculature, i.e. the tumor volume potentially sustainable by the vasculature, in order to account for the vascular control on the tumor growth. As the carrying capacity is strictly dependent on the vasculature extension, its dynamics can be assumed to represent the dynamics of the vascular network. Moreover, the effect on the carrying capacity of stimulatory and inhibitory angiogenic signals produced by the tumor itself and of administered anti-angiogenic drugs are explicitly accounted by the model formulation. The paper represents one of the first attempts to model, with a minimal number of parameters, the interplay between the dynamics of the tumor volume and of the carrying capacity, with or without administration of anti-angiogenic drugs. In [?] the predictions of the model have also been successfully compared with experimental data on anti-angiogenically treated and untreated Lewis lung tumors in mice.

Besides experimental frameworks, the model proposed in [?] has been widely exploited in theoretical studies in order to predict the effectiveness of new anti-angiogenic therapies and some model extensions have also been proposed in the related scientific literature. In [?] some model modifications are proposed and conditions for the eradication of the tumor under a periodic anti-angiogenic treatment are provided. In [?], [?] problems addressing the optimal scheduling of a given amount of angiogenic inhibitors are presented, while in [?] the optimal scheduling problem of a combined radiotherapy and anti-angiogenic treatment is formulated by exploiting a suitable modified version of the original model. Further extensions are also proposed in [?], where the Authors aim to describe the interplay between the populations of tumor cells and endothelial cells subject to a combined therapy of chemotherapeutic and anti-angiogenic drugs. In [?] an optimal scheduling problem for the combined chemotherapeutic/anti-angiogenic treatment is presented. The model in [?] has been recently exploited to design closed-loop model-based feedback control laws in [?], [?], where robust control strategies are proposed by exploiting a Linear Quadratic controller and an H_∞ methodology applied to the linearized model.

By suitably exploiting the model in [?], the aim of tumor volume reduction is here pursued according to a closed-loop, model-based approach, with the control strategy making use of the feedback linearization theory [?]. To this end only available tumor volume measurements are exploited, with the carrying capacity estimated by means of a state observer for nonlinear system [?], [?], and the regulator is synthesized as a feedback from the observed state. The closed-loop control law is designed to track a desired low level of tumor volume,

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possibly starting from a high level situation. It is proven that the control scheme allows to set independently the control and the observer parameters, thanks to the special structural properties of the tumor growth model that guarantee the separability of estimation and feedback control algorithms. Numerical simulations revealed to be extremely promising, showing a noticeable level of robustness against a wide range of the initial state estimate and of the actual value of the carrying capacity.

The paper is organized as follows. The next section is devoted to detail the tumor growth mathematical model chosen to design the closed-loop control law, which is defined in Section 3, where the main theorem is proposed. Simulations are reported in Section 4. Conclusions follow.

II. THE TUMOR GROWTH MODEL

The model under investigation is a nonlinear model accounting for angiogenic stimulation and inhibition [?], and is given by the following Ordinary Differential Equations (ODE) system:

$$\begin{cases} \dot{x}_1 &= -\lambda x_1 \ln\left(\frac{x_1}{x_2}\right) \\ \dot{x}_2 &= bx_1 - (\mu + dx_1^{2/3})x_2 - cx_2x_3 \end{cases} \quad (1)$$

where x_1 , [mm³], and x_2 , [mm³], denote the tumor volume and the carrying capacity of the vasculature, respectively. The first equation describes the phenomenology of tumor growth slowdown, as the tumor grows and resorts its available support with λ , [day⁻¹], denoting the tumour growth rate. In the second equation the first term represents the stimulatory capacity of the tumor upon the inducible vasculature (bx_1), the second term accounts for spontaneous loss (μx_2) and for tumor-dependent endogenous inhibition ($dx_1^{2/3}x_2$) of previously generated vasculature; the third term refers to the vasculature inhibitory action performed by an exogenous drug administration (cx_2x_3) with x_3 , [mg/kg], denoting the serum level of the administered angiogenic inhibitor (i.e. the drug concentration). As far as the parameters, b , [day⁻¹], is the vascular birth rate, d , [day⁻¹mm⁻²], is the endothelial cell death, μ , [day⁻¹], is the spontaneous vascular inactivation rate, and c , [day⁻¹(mg/kg)⁻¹], is the sensitivity to the drug. According to the model literature [?], without loss of generality, parameter μ will be set equal to zero in the following.

Being the anti-angiogenic drug not directly administered in vein, a further compartment is considered to account for drug diffusion:

$$x_3(t) = \int_0^t e^{-\eta(t-t')} u(t') dt' \quad (2)$$

with u , [day⁻¹(mg/kg)], being the actual control law and η , [day⁻¹], being the diffusion rate into serum. As a matter of fact, the whole system (1)-(2) (with $\mu = 0$) may be written in a compact ODE form:

$$\begin{cases} \dot{x}_1 &= -\lambda x_1 \ln\left(\frac{x_1}{x_2}\right) \\ \dot{x}_2 &= bx_1 - dx_1^{2/3}x_2 - cx_2x_3 \\ \dot{x}_3 &= -\eta x_3 + u \end{cases} \quad (3)$$

In the following, system (3) will be also referred to as:

$$\dot{x} = f(x) + g(x)u \quad (4)$$

with $f : \mathbb{R}^3 \mapsto \mathbb{R}^3$ and $g : \mathbb{R}^3 \mapsto \mathbb{R}^{3 \times 1}$ defined by:

$$f(x) = \begin{bmatrix} -\lambda x_1 \ln\left(\frac{x_1}{x_2}\right) \\ bx_1 - dx_1^{2/3}x_2 - cx_2x_3 \\ -\eta x_3 \end{bmatrix} \quad g(x) = \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix} \quad (5)$$

III. THE CONTROL ALGORITHM

The goal of the control law is to design a feedback control input that allows to stabilize the closed-loop system and let the tumor volume (state variable x_1) to track a desired level. The feedback is synthesized by exploiting only the tumor volume output, which is the available measurement from the model:

$$y = h(x), \quad h : \mathbb{R}^3 \mapsto \mathbb{R}, \quad h(x) = x_1. \quad (6)$$

Let r be the desired level of tumor volume to be tracked, smaller and safer than the non-trivial equilibrium state coming from the uncontrolled system (i.e. with $u = 0$):

$$x_{1,ss} = x_{2,ss} = (b/d)^{3/2} \quad (7)$$

The control algorithm is synthesized by applying the feedback linearization theory to the nonlinear system [?], with the feedback synthesized by means of a state observer [?], [?]. To this end, consider a domain D in \mathbb{R}^3 that excludes $x_1 = 0$ and $x_2 = 0$. Then, the working hypothesis concerning the state feedback linearization is satisfied, since the *single-input single-output* system has full relative degree in D . Indeed, $\forall x \in D$ it is:

$$\begin{aligned} L_g h(x) &= L_g L_f h(x) = 0 \\ L_g L_f^2 h(x) &= -\lambda c x_1 \neq 0 \end{aligned} \quad (8)$$

with $L_f^k h(x)$, $k = 1, 2, \dots$ denoting the Lie derivative of order k of the scalar function $h : \mathbb{R}^3 \mapsto \mathbb{R}$ along the vector field $f : \mathbb{R}^3 \mapsto \mathbb{R}^3$, [?].

As a matter of fact [?], the following nonlinear map $\Theta : \mathbb{R}^3 \mapsto \mathbb{R}^3$:

$$\Theta(x) = \begin{bmatrix} h(x) - r \\ L_f h(x) \\ L_f^2 h(x) \end{bmatrix} = \begin{bmatrix} x_1 - r \\ -\lambda x_1 \ln(x_1/x_2) \\ \Theta_3(x) \end{bmatrix} \quad (9)$$

with

$$\begin{aligned} \Theta_3(x) &= \lambda^2 x_1 \left(\ln\left(\frac{x_1}{x_2}\right) \right)^2 + \lambda^2 x_1 \ln\left(\frac{x_1}{x_2}\right) + b \lambda \frac{x_1^2}{x_2} \\ &\quad - \lambda d x_1^{2/3} x_1 - \lambda c x_1 x_3 \end{aligned} \quad (10)$$

is a diffeomorphism in D with the Jacobian matrix given by

$$J_\Theta = \frac{d\Theta}{dx} = \begin{bmatrix} 1 & 0 & 0 \\ -\lambda(1 + \ln(x_1/x_2)) & \lambda x_1/x_2 & 0 \\ J_{31}(x) & J_{32}(x) & -\lambda c x_1 \end{bmatrix} \quad (11)$$

(see the Appendix for the explicit expression of entries $J_{31}(x)$ and $J_{32}(x)$). Therefore, $z = \Theta(x)$ is a state transformation, and system (4) becomes, in the z -coordinates:

$$\dot{z} = A_b z + B_b [L_f^3 h(\Theta^{-1}(z)) + L_g L_f^2 h(\Theta^{-1}(z))u(t)] \quad (12)$$

where A_b and B_b are the following Brunowski matrices

$$A_b = \begin{bmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ 0 & 0 & 0 \end{bmatrix} \quad B_b = \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix} \quad (13)$$

with the explicit computation of $L_f^3 h(x)$ in Appendix.

Since $L_g L_f^2 h(x) \neq 0$, the following state feedback control law is well defined

$$u(t) = \frac{K_c z(t) - L_f^3 h(x(t))}{L_g L_f^2 h(x(t))} \quad z = \Theta(x) \quad (14)$$

and allows to write the closed-loop system in the z -coordinates as follows:

$$\dot{z} = (A_b + B_b K_c)z \quad (15)$$

The pair of Brunowski matrices (A_b, B_b) is controllable, therefore matrix K_c can be designed in order to make Hurwitz (i.e. eigenvalues with negative real part) the closed-loop matrix $A_b + B_b K_c$. This fact ensures that the z components asymptotically converge to zero and, as a matter of fact, so does the first component $z_1 = x_1 - r$, thus ensuring the convergence of the tumor growth x_1 to the desired level $r > 0$.

The drawback of such a control law is that it requires a complete knowledge of the state $x(t)$; however the carrying capacity (x_2) and the third component (x_3), are not directly measurable. A need exists, therefore, to exploit a state observer to overcome the problem. To this end we exploit the observer for nonlinear systems [?], [?], whose equations are:

$$\dot{\hat{x}} = f(\hat{x}) + g(\hat{x})u(t) + J_{\Theta}(\hat{x})^{-1} K_o (y(t) - h(\hat{x})) \quad (16)$$

where $K_o \in \mathbb{R}^{3 \times 1}$ is the observer gain to be designed, and J_{Θ}^{-1} is the inverse of the Jacobian matrix defined in (11), whose existence is ensured in D by the full relative degree hypothesis, which implies that Θ is an *observability map*, and system (4) is *drift-observable*.

According to [?], by applying the observer equations (16) to (4) (which is drift-observable), provided that the following additional sufficient conditions hold true:

H1) $L_f^3 h(\Theta^{-1}(z))$ is uniformly Lipschitz in $\Theta(D)$, that is, there exists γ_1 such that $\forall z, \bar{z} \in \Theta(D)$

$$\|L_f^3 h(\Theta^{-1}(z)) - L_f^3 h(\Theta^{-1}(\bar{z}))\| \leq \gamma_1 \|z - \bar{z}\| \quad (17)$$

H2) $L_g L_f^2 h(\Theta^{-1}(z))$ is uniformly Lipschitz in $\Theta(D)$, that is, there exists γ_2 such that $\forall z, \bar{z} \in \Theta(D)$

$$\|L_g L_f^2 h(\Theta^{-1}(z)) - L_g L_f^2 h(\Theta^{-1}(\bar{z}))\| \leq \gamma_2 \|z - \bar{z}\| \quad (18)$$

H3) the input u is uniformly bounded, that is:

$$\sup_{t \geq 0} \|u(t)\| < M < +\infty \quad (19)$$

then, there exists an observer matrix $K_o \in \mathbb{R}^{3 \times 1}$, such that the state estimate converges asymptotically to the real state if the initial error is sufficiently small.

Differently than (14), by straightforwardly applying the state observer (16) to design the closed loop control, the control input would be given by:

$$\hat{u}(t) = \frac{K_c \hat{z}(t) - L_f^3 h(\hat{x}(t))}{L_g L_f^2 h(\hat{x}(t))} \quad \hat{z} = \Theta(\hat{x}) \quad (20)$$

Though implementable by means of only measured state variables, such a control law would not ensure the separability principle, since it is well known that the separability principle does not hold true for nonlinear systems, unless special cases. The following Theorem shows how to modify the control scheme in order to elude such a drawback.

Theorem 1. Consider the control input:

$$u(t) = \frac{K_c \hat{z}(t) - L_f^3 h(\hat{x}(t))}{H(y(t))}, \quad \hat{z} = \Theta(\hat{x}) \quad (21)$$

with $H(y) = -\lambda c y$ and $\hat{x}(t)$ provided by:

$$\dot{\hat{x}} = f(\hat{x}) + J_{\Theta}(\hat{x})^{-1} B_b H(y) u(t) + J_{\Theta}(\hat{x})^{-1} K_o (y(t) - h(\hat{x})) \quad (22)$$

Then, provided that hypothesis H1) holds true, it is possible to design the gain matrix K_c in (21) and the observer gain K_o in (22) in order to ensure the asymptotic convergence of the observer (by means of K_o) independently of the exponential convergence of $x_1(t) \mapsto r$ (by means of K_c).

Proof: The proof is organized in two steps. Step 1 shows that it is possible to design the observer gain in order to ensure the asymptotic convergence to zero of the observer error; Step 2 shows how to design the control gain K_c independently of K_o in order to ensure the exponential convergence of the tumor growth x_1 to the desired level r .

Step 1. Define $C_b = [1 \ 0 \ 0]$. By exploiting the definition of \hat{z} in (21), the observer equation (22) can be written in the \hat{z} -coordinates as:

$$\begin{aligned} \dot{\hat{z}} &= \left[\frac{d\Theta}{dx} \dot{\hat{x}}(t) \right]_{\hat{x}=\Theta^{-1}(\hat{z})} = \left[J_{\Theta}(\hat{x}) \dot{\hat{x}}(t) \right]_{\hat{x}=\Theta^{-1}(\hat{z})} \\ &= A_b \hat{z} + B_b L_f^3 h(\Theta^{-1}(\hat{z})) + B_b H(y) u(t) \\ &\quad + K_o (y(t) - C_b \hat{z}) \end{aligned} \quad (23)$$

where the identity

$$\left[J_{\Theta}(x) f(x) \right]_{x=\Theta^{-1}(z)} = A_b z + B_b L_f^3 h(\Theta^{-1}(z)) \quad (24)$$

has been properly used.

Notice that the nonlinear function $H(y)$ coincides with $L_g L_f^2 h(x)$, since this Lie derivative only depends on the first (measured) coordinate x_1 , see (8). As a matter of fact, the z -coordinate system (12) can be rewritten as:

$$\dot{z} = A_b z + B_b L_f^3 h(\Theta^{-1}(z)) + B_b H(y) u(t) \quad (25)$$

Hence, we readily obtain that the observer error in the z -coordinates $e_z(t) = z(t) - \hat{z}(t)$ does not depend on the control input u :

$$\dot{e}_z = (A_b - K_o C_b) e_z + B_b [L_f^3 h(\Theta^{-1}(z)) - L_f^3 h(\Theta^{-1}(\hat{z}))] \quad (26)$$

By exploiting (26), it has been proven in [?] that:

- (i) according to the sufficient hypothesis H1), the e_z dynamics obeys the following inequality:

$$\|e_z(t)\| \leq e^{(\sigma_1 + \sqrt{3}\gamma_1 \|V^{-1}(\sigma)\|)t} \|V^{-1}(\sigma)\| \cdot \|V(\sigma)\| \cdot \|e_z(0)\| \quad (27)$$

where $\sigma = \{\sigma_1, \sigma_2, \sigma_3\}$ are distinct real eigenvalues properly assigned by K_o to matrix $A_b - K_o C_b$, with σ_1 the greater eigenvalue and

$$V(\sigma) = \begin{bmatrix} \sigma_1^2 & \sigma_1 & 1 \\ \sigma_2^2 & \sigma_2 & 1 \\ \sigma_3^2 & \sigma_3 & 1 \end{bmatrix} \quad (28)$$

is the Vandermonde matrix associate to spectrum σ ;

- (ii) for any chosen $\alpha > 0$, there exist a way to choose negative real eigenvalues $\sigma_3 < \sigma_2 < \sigma_1 < 0$ such that:

$$\sigma_1 + \sqrt{3}\gamma_1 \|V(\sigma)\| < -\alpha \quad (29)$$

These facts ensure that the observer gain K_o can be designed in order to have exponential convergence to zero of the e_z error, (27), and, therefore, asymptotic convergence to zero of the error $e(t) = x(t) - \hat{x}(t)$, according to the continuity of Θ^{-1} .

Step 2. By substituting the control input (21) in (25), we obtain:

$$\begin{aligned} \dot{z} = & (A_b + B_b K_c)z - B_b K_c e_z \\ & + B_b \left[L_f^3 h(\Theta^{-1}(z)) - L_f^3 h(\Theta^{-1}(\hat{z})) \right] \end{aligned} \quad (30)$$

According to (30), we can write the following integral equation

$$\begin{aligned} z(t) = & e^{(A_b + B_b K_c)t} z(0) - \int_0^t e^{(A_b + B_b K_c)(t-\tau)} B_b K_c e_z(\tau) d\tau \\ & + \int_0^t e^{(A_b + B_b K_c)(t-\tau)} B_b [\alpha(z(\tau)) - \alpha(\hat{z}(\tau))] d\tau \end{aligned} \quad (31)$$

where $\alpha(\cdot) = L_f^3 h(\Theta^{-1}(\cdot))$. Now, let $\nu = U(\xi)z$ with $U(\xi)$ the Vandermonde matrix associated to the spectrum $\xi = \{\xi_1, \xi_2, \xi_3\}$ of distinct real eigenvalues assigned by the gain matrix K_c to $A_b + K_c B_b$. Then, by denoting

$$\Xi = \text{diag}\{\xi_1, \xi_2, \xi_3\} = U(\xi)(A_b + B_b K_c)U^{-1}(\xi) \quad (32)$$

we have:

$$\begin{aligned} \nu(t) = & e^{\Xi t} \nu(0) - \int_0^t e^{\Xi(t-\tau)} U(\xi) B_b K_c e_z(\tau) d\tau \\ & + \int_0^t e^{\Xi(t-\tau)} U(\xi) B_b [\alpha(z(\tau)) - \alpha(\hat{z}(\tau))] d\tau \end{aligned} \quad (33)$$

and, according to hypothesis H1):

$$\begin{aligned} \|\nu(t)\| \leq & e^{\xi_1 t} \left(\|\nu(0)\| \right. \\ & \left. + \int_0^t e^{-\xi_1 \tau} \sqrt{3}(\gamma_1 + \|K_c\|) \|e_z(\tau)\| d\tau \right) \end{aligned} \quad (34)$$

where ξ_1 is the greatest eigenvalue in ξ and the identity $\|U(\xi)B_b\| = \sqrt{3}$ (straightforwardly coming from the definitions of the Vandermonde matrix, (28), and B_b , (13)) has

been properly considered. Finally, by exploiting inequality (27), and according to a proper choice for K_o in order to ensure inequality (29), (34) becomes

$$\|\nu(t)\| \leq e^{\xi_1 t} \left(\|\nu(0)\| + \int_0^t \Omega e^{-(\xi_1 + \alpha)\tau} d\tau \right) \quad (35)$$

with

$$\Omega = \sqrt{3}(\gamma_1 + \|K_c\|) \cdot \|V^{-1}(\sigma)\| \cdot \|V(\sigma)\| \cdot \|e_z(0)\| \quad (36)$$

After the computation of the integral:

$$\|\nu(t)\| \leq e^{\xi_1 t} \|\nu(0)\| + \frac{\Omega}{\alpha + \xi_1} (e^{\xi_1 t} - e^{-\alpha t}) \quad (37)$$

Therefore, by properly designing K_c , independently from K_o , in order to have $\xi_1 < 0$, it is $\|\nu(t)\| \mapsto 0$. Thus $z(t)$ converges to zero exponentially since:

$$\|z(t)\| \leq \|U^{-1}(\xi)\| \cdot \|\nu(t)\| \quad (38)$$

and this implies that $x_1(t) \mapsto r$ exponentially as well, since $x_1 - r$ is the first component of z . ■

Remark 2. Notice that, in case Θ^{-1} is Lipschitz in $\Theta(D)$, that is

$$\|\Theta^{-1}(z) - \Theta^{-1}(\bar{z})\| \leq \gamma_3 \|z - \bar{z}\| \quad \forall z, \bar{z} \in \Theta(D) \quad (39)$$

then the observer error $e(t) = x(t) - \hat{x}(t)$ converges to zero exponentially, since

$$\|e(t)\| \leq \gamma_3 \|e_z(t)\| \mapsto 0 \quad (40)$$

IV. SIMULATION RESULTS

To demonstrate the validity of the algorithm, simulations are performed setting the model parameters to the values estimated in [?]. Such an estimation was based on experimental data of Lewis lung carcinoma implanted in C57BL/6 mice. The data referred to volume measurements of both untreated control tumors and treated tumors under a regimen with endostatin. Treatment was initiated when tumors were $\sim 200 \text{ mm}^3$ in size and it ended after 13 days. The treatment regimen was 20 mg/kg/day. The produced fitting curve showed a final tumor volume of $\sim 135 \text{ mm}^3$, setting the initial value of the carrying capacity to 625 mm^3 . The parameters estimated in [?], are reported in Table IV.

TABLE I
MODEL PARAMETERS

λ day ⁻¹	b day ⁻¹	d day ⁻¹ mm ⁻²	μ day ⁻¹	c day ⁻¹ (mg/kg) ⁻¹
0.192	5.85	0.00873	0	0.66

According to [?], the treatment length has been fixed to 13 days, and the desired tumor level r has been set equal to 135 mm^3 with the goal to get close to r at the end of the treatment.

Simulations have been carried out by setting the initial tumor volume $x_1(0)$ equal to 200 mm^3 and by varying the initial value of the carrying capacity $x_2(0)$ in the percentage

range of $[-40, +200]\%$ with respect to the reference value of 625 mm^3 . The initial value of the serum level of the administered angiogenic inhibitor $x_3(0)$ is set equal to zero. Also these initial values are consistent with real data coming from [?].

For the observer initialization, $\hat{x}_1(0)$ is set equal to the measurement of the tumor volume at day zero, $\hat{x}_3(0)$ is set equal to zero, and $\hat{x}_2(0)$ is allowed to vary in the percentage range of $[-40, +200]\%$ with respect to real value $x_2(0)$.

For each pair of initial conditions $(x_2(0), \hat{x}_2(0))$, three different targets have been address that is:

- 1) to keep the final value of the tumor volume within 10% of variation of the reference level:

$$x_1(13\Delta) \in [0.9r, 1.1r], \quad \Delta = 1 \text{ day} \quad (41)$$

- 2) to keep the total amount of the administered drug smaller than 260 mg/kg (i.e. 20mg/kg per 13 day):

$$m = \int_0^{13\Delta} u(t)dt \leq 260, \quad (42)$$

- 3) to keep the average daily amount of the administered drug within 40% of variation with respect to 20 mg/kg/day:

$$m_d = \frac{1}{\Delta} \int_T^{(T+1)\Delta} u(t)dt = 20 \cdot (1 \pm 40\%) \quad (43)$$

with $T = 0, \dots, 12$,

Matrices K_c and K_o are designed in order to ensure the eigenvalues of $A_b - K_o C_b$ and $A_b - B_b K_c$ to be equal to $[-0.45, -0.9, -1.35]$ and $[-1, -2, -3]$, respectively. The same set of control parameters has been considered for all simulations reported.

Accounting for different initial conditions of x_2 and \hat{x}_2 , Table II and Table III report the values of $x_1(13\Delta)$ and m , respectively, and Table IV refers to the maximum value (out of 13 average daily delivered amounts) of m_d .

TABLE II
FINAL VALUE OF TUMOR VOLUME $x_1(13\Delta)$, AT THE END OF THE TREATMENT

		$\Delta x_2(0) (\%)$					
		-40	-20	0	50	100	200
$\Delta \hat{x}_2(0) (\%)$	-40	139.13	139.19	139.25	139.35	139.36	139.39
	-20	139.09	138.97	138.94	138.62	138.46	138.80
	0	138.73	138.62	138.34	137.82	137.86	138.42
	50	137.76	137.11	136.88	136.95	137.23	137.96
	100	136.45	136.17	136.15	136.46	136.87	137.66
	200	135.15	135.21	135.39	135.91	136.40	137.25

The tables demonstrate the good performance of the algorithm, in spite of the great range of variability of the carrying capacity and of its estimate. Looking at Table II it may be appreciated that the final value of the tumor volume is very close to the desired value of 135 mm^3 , with its variability lower than 4%. Table III ensures a total amount smaller than the upper bound of 260 mm^3 , compatible with the total amount delivered in the experiments of [?]. As far as Table IV, even if it tells of an average daily delivery

TABLE III

TOTAL AMOUNT m OF THE ADMINISTERED ANTI-ANGIOGENIC DRUG

		$\Delta x_2(0) (\%)$					
		-40	-20	0	50	100	200
$\Delta \hat{x}_2(0) (\%)$	-40	247.78	249.34	250.90	253.89	256.10	259.35
	-20	247.39	248.82	249.73	251.68	253.37	257.53
	0	247.00	247.65	248.04	249.47	251.81	256.36
	50	242.97	242.71	243.62	246.61	249.60	254.67
	100	238.94	240.11	241.54	245.18	248.43	253.76
	200	235.95	237.90	239.85	243.88	247.26	252.59

TABLE IV

MAXIMUM AVERAGE DAILY AMOUNT m_d OF ANTI-ANGIOGENIC DRUG

		$\Delta x_2(0) (\%)$					
		-40	-20	0	50	100	200
$\Delta \hat{x}_2(0) (\%)$	-40	26.24	26.44	26.61	26.95	27.16	27.50
	-20	26.14	26.30	26.36	26.47	26.59	27.13
	0	26.03	26.02	25.98	25.96	26.21	26.91
	50	25.16	24.85	24.83	25.17	25.65	26.51
	100	24.10	24.06	24.20	24.77	25.34	26.27
	200	22.98	23.24	23.56	24.33	24.98	25.96

greater than 20 mm^3 , such delivery never shows a variability greater than 40%. A further comment is that best results in terms of Table II and Table IV are obtained when $\hat{x}_2(0)$ is overestimated. As expected the performance of the controller worsen when $x_2(0)$ is high.

Finally, all tables deal with a control algorithm that shows a noticeable level of robustness with respect to the initial condition of the carrying capacity, as well as to its estimate.

In Fig.1 an example of the system dynamics is presented.

V. CONCLUSIONS

Based on a mathematical model of tumor growth, this work proposes a closed-loop control law aiming to reduce the tumor volume. The model accounts for angiogenic stimulation and inhibition, and is one of the most adopted in the literature to simulate and predict the effects of anti-angiogenic drug delivery. Based on the feedback linearization theory, the control law makes use of an observer for nonlinear systems in order to design the model-based control by means of only available measurements. Theoretical results ensure that the control gain of the regulator can be set independently of the observer gain, thanks to the structural properties of the tumor growth model. Numerical simulations show the effectiveness of the control law in spite of a wide range of variation of the (not measured) carrying capacity.

APPENDIX

In this section the explicit expression of entries $J_{31}(x)$, $J_{32}(x)$ in (11) and $L_f^3 h(x)$ are reported.

$$J_{31}(x) = \lambda^2 \left(3 \ln \left(\frac{x_1}{x_2} \right) + \ln \left(\frac{x_1}{x_2} \right)^2 \right) - \frac{5}{3} \lambda dx_1^{\left(\frac{2}{3}\right)} + \lambda^2 - \lambda c x_3 + \frac{2\lambda b x_1}{x_2}; \quad (44)$$

$$J_{32}(x) = -\frac{\lambda^2 x_1}{x_2} \left(2 \ln \left(\frac{x_1}{x_2} \right) + 1 \right) - \frac{\lambda b x_1^2}{x_2^2}; \quad (45)$$

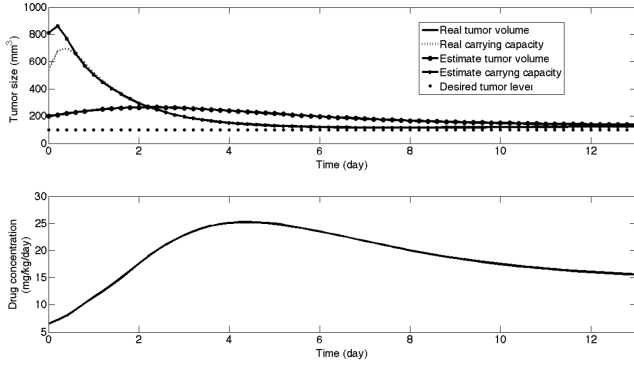


Fig. 1. Graphical comparison of the real and estimate state under the action of the closed loop control law

$$\begin{aligned}
 L_f^3 h(x) = & \phi(x) \lambda \frac{x_1}{x_2} \left(2\lambda \ln \left(\frac{x_1}{x_2} \right) - \phi(x) + cx_3 + dx_1^{\frac{2}{3}} + \lambda \right) \\
 & - \lambda^2 \frac{x_1^2}{x_2} \left[\lambda \frac{x_1}{x_2} + \lambda \left(1 + 2 \ln \left(\frac{x_1}{x_2} \right) + \left(\ln \left(\frac{x_1}{x_2} \right) \right)^2 \right) \right. \\
 & \quad \left. - \frac{5}{3} dx_1^{\frac{2}{3}} + 2b \frac{x_1}{x_2} - cx_3 \right] - \lambda c \eta x_1 x_3
 \end{aligned} \tag{46}$$

with

$$\phi(x) = dx_1^{\frac{2}{3}} x_2 - bx_1 + cx_2 x_3 \tag{47}$$

REFERENCES