Linear state-feedback control synthesis of tumor growth control in antiangiogenic therapy

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***Abstract*—Cancer diseases are one of the most lethal, incurable diseases today, thus fighting cancer is an actual and urgent problem in clinical practice. Beside classical therapies, a new approach is represented by model-based therapies, where human body works as a complex system. These therapies are called targeted molecular therapies (TMTs). TMTs are fighting specifically against different cancer mechanisms and usually don't eliminate the whole tumor, but control the tumor into a given state and keep it there. The aim of antiangiogenic cancer therapy is to prevent tumors from forming new blood vessels, because without angiogenesis tumor growth is inhibited. In this paper we analyze a nonlinear tumor growth model and design linear controllers based on a linear model acquired from working point linearization. Realized controllers are state feedback with pole placement, LQ control method and both controllers with state observer. Simulations are carried out and the controllers are analyzed in many aspects, including the working points used at linearization.**

I. INTRODUCTION

Cancer diseases are one of the most lethal, incurable diseases today [1], [2], [3], which often cause death within a short time after making the diagnosis. Therefore, in cancer fighting therapies beside classical therapies [4] (such as chemotherapy, radiotherapy, surgical intervention) a new line have appeared, called *targeted molecular therapy* [5]. Targeted molecular therapies were developed specifically against different cancer mechanisms (drugs based on receptor inhibition [6], revertant therapy [7], inhibitions of DNA replication [8], drugs effecting apoptosis [9], drugs effecting different cell organelles [10]). To develop these therapies, it's required to analyze tumor growth and explore causal factors – this process belongs to the science of molecular oncology. Successful investigation creates the possibility of specific drug intervention into detected injured processes or pathological mechanisms. The aim of targeted molecular therapies is not to eliminate the whole tumor, but to control the tumor into a given state and keep it there. This task belongs to the science of control engineering that can provide effective assistance to model-based therapies, which examine the human body as a complex system [11]. Therefore, it's required to elaborate an optimal control algorithm for developed medical therapies, so that patients could have the most effective treatment. The main goal of this paper is to find optimal control for antiangiogenic therapy [12].

Rapidly dividing tumor cells need lots of oxygen. When proliferation begins, small sized tumor can pick up oxygen from near capillaries. After a certain size (1-2 mm diameter) tumor development stops, because a part of the tumor gets too far from capillaries and can't pick up enough oxygen. Tumor needs own blood vessels – the process of forming new blood vessels is called angiogenesis [13], [14]. Angiogenesis occurs normally in the human body at specific times in embryonic development and growth (a developing child in a mother's womb must create the vast network of arteries, veins, and capillaries that are found in the human body). Angiogenesis also takes place in adults, although it is a relatively infrequent event (in case of high altitude (low oxygen concentration), regeneration of tissue during wound healing and in women during certain phases of the menstrual cycle) [15]. In such cases, angiogenesis starts due to typical molecular triggers and ends when the necessary processes are completed. Tumors can break through this precise control. The aim of antiangiogenic cancer therapy is to prevent tumors from forming new blood vessels, because without angiogenesis tumor growth is inhibited. Several angiogenic inhibitors are known in medical practice, for example endostatin [16] or bevacizumab [17].

A nonlinear model of tumor growth under angiogenic inhibition was published in [18], and was analyzed and simplified in [19]. The properties of the nonlinear tumor growth model were analyzed, and optimal control was designed in terms of tumor volume with a constraint on the maximal amount of control input in [20]. In [21] angiogenic inhibition is combined with radiotherapy, and the aim of antiangiogenic control is to maintain a fixed tumor-vasculature ratio. Antiangiogenic therapy is also considered in [22] along with chemotherapy and immunotherapy. In this article we deal with a simplified model of tumor growth under angiogenic inhibition, and seek by a linear control synthesis for optimal therapeutic protocols that use the least amount of drug.

The paper is organized as follows. In Section II, we review a model of tumor growth and present a simplified model which we have been working on. In Section III, we analyze the steady states of the nonlinear model, and then we use working point linearization and examine non-zero steady states, stability, observability and controllability of the linearized model. In Section IV, we design four controllers and present simulation results. The paper ends with the conclusion in Section V.

II. THE MODEL OF TUMOR GROWTH UNDER ANGIOGENIC INHIBITION

A. The original model

Hahnfeldt et al. elaborated a dynamic model for tumor growth in antiangiogenic therapy [18]. In their experiments mice were injected with Lewis lung carcinoma cells. After about 3–10 days, mice were randomized into four groups. Three groups received different angiogenic inhibitors (angiostatin, endostatin and TNP-470), the fourth group was the control group (received injections of the vehicle alone) [18].

The nonlinear model is defined by the equations:

$$V' = -\lambda_1 V \ln\left(\frac{V}{K}\right) \tag{1}$$

$$K' = -\lambda_2 K + bV - dKV^{2/3} - eKg(t) \tag{2}$$

$$g(t) = \int_0^t c(t')\exp(-clr(t-t'))dt' \tag{3}$$

The model possesses the following variables [18]: V is the tumor volume (mm^3), K is the endothelial volume (mm^3), g is the concentration of the administered inhibitor (mg/kg) and c is the inhibitor administration rate ($mg/kg/day$).

The model possesses the following parameters: λ_1 is the tumor growth rate ($1/day$), λ_2 is the parameter of spontaneous loss of functional vasculature ($1/day$), b is the stimulatory capacity of the tumor to the vasculature ($1/day$), d is the endogenous inhibition of previously generated vasculature ($1/day \cdot mm^2$), e is the angiogenic inhibitor's inhibition of tumor vasculature ($kg/day \cdot mg$) and clr is the clearance rate ($1/day$).

The specific parameters for the considered Lewis lung carcinoma and the used mice type are [18]: $\lambda_1 = 0.192$ 1/day, $\lambda_2 = 0.0$ 1/day (experiments show that this parameter is always zero), $b = 5.85$ 1/day, $d = 0.00873$ 1/day·mm^2. Parameter values for the inhibitors are: $e_{endostatin} = 0.66$ kg/day·mg, $e_{angiostatin} = 0.15$ kg/day·mg, $e_{TNP\text{-}470} = 1.3$ kg/day·mg.

B. The simplified model

The original model was analyzed and transformed in several studies [19], [20], [23]. One of the most important modifications is the continuous infusion therapy [20], where the input (the inhibitor administration rate) is equal to the concentration of administered inhibitor (serum level of inhibitor), therefore equation (3) is removed from the model.

Hence, the simplified model which we have been working on is:

$$\dot{x}_1 = -\lambda_1 x_1 \ln\left(\frac{x_1}{x_2}\right) \tag{4}$$

$$\dot{x}_2 = bx_1 - dx_1^{2/3}x_2 - ex_2 g \tag{5}$$

$$y = x_1 \tag{6}$$

where x_1 is the tumor volume and x_2 is the endothelial volume and g is the concentration of the administered inhibitor.

III. MODEL ANALYSIS

A. Steady state analysis of the simplified model

The system is in a steady state, if the changing of the state variables is zero. The steady state of the model defined by (4)-(6) is:

$$0 = -\lambda_1 x_{10} \ln\left(\frac{x_{10}}{x_{20}}\right) \tag{7}$$

$$0 = bx_{10} - dx_{10}^{2/3}x_{20} - ex_2 g_0 \tag{8}$$

where x_{10} is the tumor volume, x_{20} is the endothelial volume and g_0 is the constant concentration of administered inhibitor in the steady state.

The trivial solution is $x_{10} = x_{20} = 0$, but in this case there is no tumor. Non-trivial solution is $x_{10} = x_{20}$, in this case:

$$x_{10} = \left(\frac{b - eg_0}{d}\right)^{\frac{3}{2}} \tag{9}$$

If the therapy is successful, tumor volume is reduced to zero with angiogenic inhibitor. From (9) we can express g_0, which keeps up zero steady state (if the inhibitor is endostatin, $g_{0,max} = 8.863$ mg/kg).

If the therapy is constant inhibitor dosage with $g_0 < g_{0,max}$, the steady state is not zero. Fig. 1 presents the evolution of tumor and endothelial volume with constant dose $g_0 = 5$ mg/kg of endostatin. The steady state volume is 4992 mm^3.

If there are no inhibitors present ($g_0 = 0$), tumor and endothelial cells grow with no control input, and the steady state volume is a very high value. In this case steady state volume depends only on the type of the tumor and the patient:

$$x_{10} = \left(\frac{b}{d}\right)^{\frac{3}{2}} \tag{10}$$

Tumor and endothelial cell growth with no control input can be seen on Fig. 2. The numerical value of the steady state volume is $1.734 \cdot 10^4$ mm^3.

B. Working point linearization

For linear controller design, it's required to linearize the model. Using working point linearization [24] in the $g_0 = 0$ working point, the matrices of the linear model are:

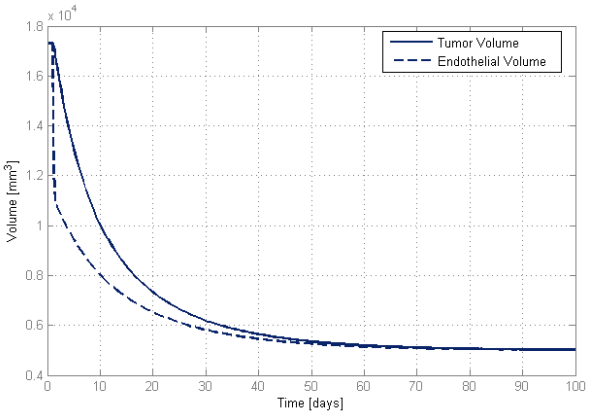

Figure 1. Constant inhibitor dosage therapy (*5 mg/kg* endostatin)

$$A = \begin{bmatrix} -\lambda_1 \log\left(\frac{x_1}{x_2}\right) - \lambda_1 & \lambda_1 \frac{x_1}{x_2} \\ b - \frac{2}{3} d \cdot x_1^{-\frac{1}{3}} \cdot x_2 & -d \cdot x_1^{\frac{2}{3}} \end{bmatrix} \quad (11)$$

$$B = \begin{bmatrix} 0 \\ -ex_2 \end{bmatrix} \quad (12)$$

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

$$D = \begin{bmatrix} 0 \end{bmatrix} \quad (14)$$

C. Non-zero steady states of the linearized model

As we have mentioned, the aim of targeted molecular therapies is to control the tumor into a given state and keep it there. Thus, we have analyzed the model around non-zero steady states. In this case $x_1 = x_2$, which we have marked as x_{10}. The system matrix A in the steady state is:

$$A_{ss0} = \begin{bmatrix} -\lambda_1 & \lambda_1 \\ b - \frac{2}{3} d \cdot x_{10}^{\frac{2}{3}} & -d \cdot x_{10}^{\frac{2}{3}} \end{bmatrix} \quad (15)$$

Eigenvalues of the system matrix are:

$$s_{1,2} = \frac{-(d \cdot \sqrt[3]{x_{10}^2} + \lambda_1) \pm \sqrt{(d \cdot \sqrt[3]{x_{10}^2} + \lambda_1)^2 - 4 \cdot (\frac{5}{3} d\lambda_1 \cdot \sqrt[3]{x_{10}^2} - \lambda_1 b)}}{2} \quad (16)$$

If $x_{10} = 0$, there is a stable and an unstable pole in the system. Increasing the x_{10} working point, the stable pole accelerates and the unstable pole becomes stable [25]. For high x_{10} values the poles will form stable complex conjugate pairs.

D. Stability, observability and controllability of the linearized model

Stability, observability and controllability were analyzed in three different working points (using endostatin as inhibitor). The linearized system in non-zero steady state has the following controllability and observability matrices:

$$M_C = \begin{bmatrix} 0 & -e\lambda_1 x_{10} \\ -ex_{10} & ed \cdot x_{10}^{\frac{5}{3}} \end{bmatrix} \quad (17)$$

$$M_O = \begin{bmatrix} 1 & 0 \\ -\lambda_1 & \lambda_1 \end{bmatrix} \quad (18)$$

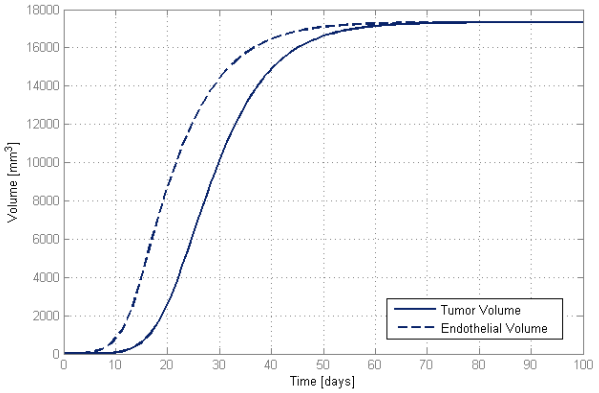

Figure 2. Tumor and endothelial cell growth with no control input

The matrices in (17) and (18) are full rank for every $x_{10} \neq 0$, so the linearized system is controllable and observable in every working point.

In a low working point, the system (defined by equations (4)-(6)) can be poorly approximated by the linear model, so first we have examined a "worst-case" working point from this range. The system matrix of the model linearized at the $x_{10} = 100\ mm^3$ working point is:

$$A_{100} = \begin{bmatrix} -0.1920 & 0.1920 \\ 5.7246 & -0.1881 \end{bmatrix} \quad (19)$$

This system is unstable, but controllable and observable.

The second analyzed working point is $x_{10} = 4992\ mm^3$, this is the steady state volume of $5\ mg/kg$ constant endostatin dosage. The system matrix of this model is:

$$A_{4992} = \begin{bmatrix} -0.1920 & 0.1920 \\ 4.1500 & -2.5499 \end{bmatrix} \quad (20)$$

This system is unstable, but controllable and observable.

The third examined working point is $x_{10} = 8062\ mm^3$. Increasing the working point from zero, the unstable pole becomes zero at this point and it is stable for $x_{10} > 8062\ mm^3$. The system matrix of this model is:

$$A_{8062} = \begin{bmatrix} -0.1920 & 0.1920 \\ 3.5100 & -3.5100 \end{bmatrix} \quad (21)$$

This system is on the boundary of stability, but it is controllable and observable.

IV. Controller Design and Simulation Results

A. Controller design

We have designed controllers for the linearized model, but we have used them for controlling the nonlinear model.

As we have seen, the stability of the linearized model depends on the working point. There are several working points, where the system has an unstable pole. The aim of the control is to accelerate the unstable pole to be stable. One solution can be the *state feedback with pole placement* [24]:

$$u_{PP}(t) = -K_{PP} \cdot x(t) \quad (22)$$

The feedback matrix K_{PP} can be determined by the Ackermann's formula:

$$K_{PP} = \begin{bmatrix} 0 & 0 & \dots & 0 & 1 \end{bmatrix} \cdot M_c^{-1} \cdot \varphi_{closed}(A) \quad (23)$$

where M_c is the controllability matrix and φ_{closed} is the characteristic equation of the closed loop. The poles of the closed loop system were chosen as:

$$p_{new} = -a \cdot sign(p_{old}) |p_{old}| \quad (24)$$

where p_{new} is the new pole of the closed system, p_{old} is the pole of the original system, and a is the amount of acceleration. We have analyzed several scenarios with different a parameters varying from 0.5 to 1.2.

Since angiogenic inhibitors are quite expensive, our goal is to minimize the tumor volume (x_1) using the least possible control signal (u_{opt}). Consequently, the problem statement represents an optimization problem, and the literature offers a wide spectrum for solution staring from classical control theory [24], modern robust control theory [26], or even soft computing applications [27].

For our preliminary investigation we have focused on the *LQ control method* [24] with the cost function:

$$J(t,x) = \int_0^\infty \{x^T(t)Qx(t) + u^T(t)Ru(t)\}dt \quad (25)$$

We have chosen to minimize the square of the output (in our model this is $x_1^2 = y^2$), thus the Q weighting matrix is:

$$Q = C^T C \quad (26)$$

By the R weighting matrix we can affect the input, so $R = \rho$ is chosen to have a great value (during simulations we have examined the $\rho = [10^3, 10^6]$ range) reflecting also the idea that the input (inhibitor dosage is expensive). The solution of the optimal control problem is a state feedback

$$u_{opt}(t) = -K_{LQ} \cdot x(t) \quad (27)$$

K_{LQ} can be determined by:

$$K_{LQ} = R^{-1}B^T P \quad (28)$$

where P is the solution of the Control Algebraic Ricatti Equation (CARE):

$$PA + A^T P + Q - PBR^{-1}B^T P = 0 \quad (29)$$

We are unable to measure all states of the system, hence we have designed a *state observer* [24] defined by the differential equation:

$$\dot{\hat{x}} = F\hat{x} + Gy + Hu \quad (30)$$

where the $\hat{x}$ observer states are the estimated state variables. Polynomial G is designed by pole placement with poles five times faster than the poles of the closed loop system. Matrices F and H are:

$$F = A - GC \quad (31)$$

$$H = B \quad (32)$$

In all cases we have placed saturation between the tumor model and the controller. The control input has a lower limit in order to exclude negative inputs, since they have no physiological meaning; and an upper limit, because too high input could be injurious in biological systems.

B. Simulation results

We have realized four *controllers* under *MATLAB 7.9.0 (R2009b)*: (C1) state feedback with pole placement, (C2) LQ control method, (C3) state feedback with pole placement and observer, (C4) LQ control method with observer. Controllers were designed for the linearized model, but were used for the nonlinear model.

TABLE I.
RESULTS OF THE OPTIMAL CONTROLLERS

Crit.	Optimal controllers		
	LQ control method (x_{10}=8062 mm^3, sat=25 mg/kg, $R = 10^3$)	LQ control method (x_{10}=100 mm^3, sat=100 mg/kg, $R = 10^6$)	State feedback with pole placement (x_{10}=100 mm^3, sat=100 mg/kg, a=1.1)
(i)[a]	1131	1202	1207
(ii)[b]	8.348	2.833	2.986
(iii)[c]	264.1	7.922	7.774

[a] Total concentration of the administered inhibitor during the treatment (*mg/kg*)
[b] Steady state inhibitor concentration at the end of the treatment (*mg/kg*)
[c] Steady state tumor volume at the end of the treatment (mm^3)

We have examined the effect of several *parameters*. Three working points were analyzed (x_{10} = 100 mm^3, x_{10} = 4992 mm^3, x_{10} = 8062 mm^3). Impact of saturation was examined through three values (u_{max} = 100 mg/kg, u_{max} = 50 mg/kg,u_{max} = 25 mg/kg).

Three amount of acceleration were used in state feedback with pole placement ($a = 0.5$, $a = 1.1$, $a = 1.2$). R weighting matrix in LQ control method was analyzed at the $\rho = [10^3, 10^6]$ range. If the controller contained state observer, acceleration of the controller was $a_o = 5$ all the time. Simulation periods were 100 days in all cases and endostatin was used as angiogenic inhibitor. Initial value of tumor volume and endothelial volume was the steady state volume in case of no control input ($1.734 \cdot 10^4$ mm^3).

Controls were evaluated by three *criterions*: (i) the total concentration of the administered inhibitor during the treatment (*mg/kg*), (ii) the steady state inhibitor concentration at the end of the treatment (*mg/kg*), (iii) the steady state tumor volume at the end of the treatment (mm^3).

Simulation results are divided into six groups. In the evaluation of the controls we use two different terms: efficient control (tumor volume was reduced, but not up to the required volume (around 300 mm^3)) and successful control (examined parameter's value is in the required range).

Group 1: controllers (C1) and (C3) in medium (around 4992 mm^3) working points (except controller (C3) with $a = 0.5$ acceleration). These controls were efficient, but not successful, because tumor volume was reduced to about 5000 mm^3. The explanation is the following. Gain K in state feedback can be determined by the Ackermann's formula (equation (23)), where the controllability matrix is

$$M_c = \begin{bmatrix} B & AB & A^2B & \dots & A^{n-1}B \end{bmatrix} \quad (33)$$

Increasing the working point, the norm of matrix B quickly increases, but the norm of matrix A doesn't change substantially. Therefore, norm of matrix M_c also increases; hence, norm of matrix M_c^{-1} decreases. Ackermann's formula contains M_c^{-1}, thus the smaller the norm of the matrix M_c^{-1}, the smaller the norm of gain K *is*. This means that increasing the working point, the control signals become too low to reduce the tumor volume (because of the nonlinearity).

Group 2: controllers (C1) and (C3) in high (around 8062 mm^3) working points (except controller (C3) with $a = 0.5$ acceleration). These controls were inefficient and unsuccessful, because the tumor volume didn't decrease at all. The explanation is the same as in Group 1, but there is therapeutic difference between these groups.

In Group 1, tumor volume was reduced with antiangiogenic treatment to a certain size, where chemotherapy can be used with high clinical efficacy in combined therapy [28].

Group 3: controllers (C2) and (C4) in medium and high working points with weighting matrix $R = 10^6$. These controls were efficient; however, not successful like in Group 1, but with different reason. In this case (in LQ control method) we can affect the input by matrix R and since angiogenic inhibitors are expensive, we choose it to have the largest value in the range (10^6). However, this lowers control signal that is unable to ensure the required tumor volume at the end of the treatment.

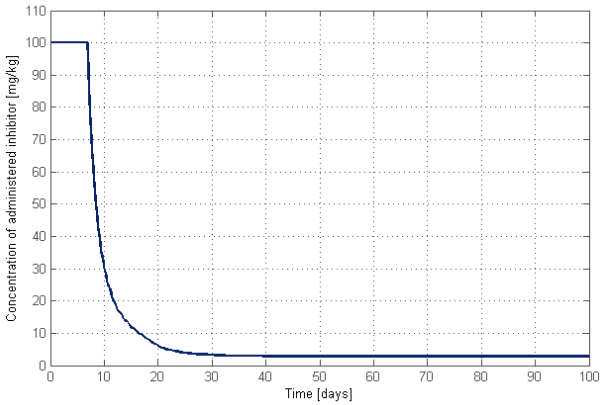

Figure 3. Output of the controller
Controller: LQ control method, inhibitor: endostatin, working point: *100 mm*^{3}, saturation: *100 mg/kg*, weighting matrix $R = 10^6$, simulation time: *100 days*

Group 4: controllers (C4) in medium and high working points with weighting matrix $R = 10^3$ and each controllers with low (u_{max} = *25 mg/kg*) saturation. Different from Group 3, here we choose R to have the smallest value in the range (10^3) in LQ control method. As we have expected, with more inhibitor dosage, controllers are able to reduce tumor volume to the required value. However, in case of LQ controllers with state observer a new problem appeared: oscillation at the steady state inhibitor concentration. All controllers with low saturation have the same problem.

Group 5: controllers (C3) in medium and high working points with *a = 0.5* acceleration. Considering only the steady state tumor volumes, this group seems optimal, because tumor volumes are *1 mm*^{3} at the end of the treatment. Investigating the outputs of the controllers, it can be seen that the control signal have the maximum value (saturation upper limit) during all the simulation time. Therefore, the total concentration of the administered inhibitor during the treatment is extremely high. The explanation is that these observers are unstable: the estimation error continuously grows. Thus these controllers are useless.

Group 6: each controllers in low (around *100 mm*^{3}) working points with high and medium (*100* and *50 mg/kg*) saturation and controllers (C2) with weighting matrix $R = 10^3$ (except one in *100 mm*^{3} working point with *25 mg/kg* saturation). These controls are successful for each criterion. From successful controllers optimal controllers can be chosen which have the best result for a certain criterion. Results of the optimal controllers can be seen in Tab. I.

For criterion (i) the best result (*1131 mg/kg*) was achieved by controller (C2) with working point *8062 mm*^{3}, saturation *25 mg/kg* and weighting matrix $R = 10^3$.

For criterion (ii) the best result (*2.833 mg/kg*) was achieved by controller (C2) with working point *100 mm*^{3}, saturation *100 mg/kg* and weighting matrix $R = 10^6$ (output of the controller can be seen on Fig. 3., output of the system can be seen on Fig. 4.).

Finally, for criterion (iii) the best result (*7.774 mm*^{3}) was achieved by controller (C1) with working point *100 mm*^{3}, saturation *100 mg/kg* and acceleration *a = 1.1*.

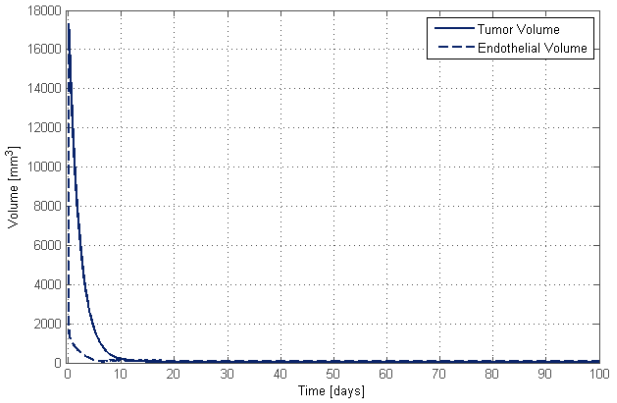

Figure 4. Output of the system
Controller: LQ control method, inhibitor: endostatin, working point: *100 mm*^{3}, saturation: *100 mg/kg*, weighting matrix $R = 10^6$, simulation time: *100 days*

We can see that controllers which are optimal for one criterion have near-optimal values for the other criterions [25].

V. Conclusion

Simulation results showed that the lowest steady state tumor volume at the end of the treatment can be reached by using state feedback with pole placement. However, according to various aspects, the most effective control is LQ control method: (a) for two criterions (total concentration of the administered inhibitor during the treatment and steady state inhibitor concentration at the end of the treatment) this controller had the best results; (b) the minimal value of the third criterion can be well approximated with LQ control method; (c) this is the only controller, which ensures successful control for high working points. Besides this we can conclude that small value of weighting matrix R is useful for high working points, high value of weighting matrix R is useful for low working points.

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