Discrete time state feedback with setpoint control, actual state observer and load estimation for a tumor growth model

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***Abstract*— With the current scientific knowledge, there is no medical device which can handle continuous infusion cancer therapy. Hence, only a quasi continuous infusion therapy can be achieved using discrete drug administration (which can be sufficiently frequent). Therefore, a discrete time control has to be designed for a tumor growth model for real-life application. We designed state feedback control, augmented with setpoint control to follow nonzero reference signal, and also augmented with actual state observer due to the fact that we are unable to measure all states of the system. In addition, the control system contains load estimation as well to investigate the effect of disturbance on the input of the model.**

I. INTRODUCTION

Nowadays in cancer treatment there is a wide scale of available therapies. A recent treatment type is called as Targeted Molecular Therapies (TMTs) which aim to fight directly against specific, identified cancer mechanisms. A promising target method is to inhibit tumor vascularization because if we can cease the process of angiogenesis (new blood vessel formation), tumor growth is limited. This leads to a new approach where the point is not to eliminate the whole cancer but to keep it in a controlled steady state.

We investigated a well-known tumor growth model under antiangiogenic therapy [1] and designed several continuous time controllers like LQ control method and state observer [2-4], flat control [5-7], modern robust control method [8-10], feedback linearization method [11], and adaptive fuzzy techniques [12]. However, with the current scientific knowledge, there is no medical device which can handle continuous infusion cancer therapy [13]; hence we oriented in the current research work on discrete time control.

The paper is organized as follows. In Section II, we present the nonlinear model of tumor growth under angiogenic inhibition, and describe a linear model which is acquired by working point linearization. Section III contains the description of the design structure including state feedback, setpoint control, actual state observer and load estimation. In Section IV, we present the simulation results. The paper ends with the conclusion in Section V.

II. THE APPLIED MODEL OF TUMOR GROWTH

P. Hahnfeldt et al. created a dynamic model for tumor growth under antiangiogenic therapy [1]. In their experiment mice were injected with Lewis lung carcinoma cells and they have investigated the effect of three different angiogenic inhibitors (angiostatin, endostatin and TNP-470). The original model was analyzed and modified in several studies [14-16]. The most important alteration is the continuous infusion therapy [15], where the input (the inhibitor administration rate) is equal to the concentration of administered inhibitor (serum level of inhibitor).

The model which takes into account the continuous infusion therapy is the following second-order system:

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

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

$$y = x_1, \tag{3}$$

where x_1 is the tumor volume (mm^3), x_2 is the endothelial/ vascular volume (mm^3) and g is the concentration of the administered inhibitor (mg/kg). The model contains the following parameters: λ_1 is the tumor growth rate (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 antiangiogenic effect of the administered inhibitor on the tumor vasculature ($kg/(day \cdot mg)$).

Parameter values for the considered Lewis lung carcinoma and the mice used in the experiment are [1]: $\lambda_1 = 0.192$ 1/day, $b = 5.85$ 1/day, $d = 0.00873$ $1/day \cdot mm^2$. The experiment has shown that the most effective inhibitor was endostatin; therefore, we have applied this antiangiogenic drug in controller design ($e_{endostatin} = 0.66$ $kg/(day \cdot mg)$).

From equation (1) it is clear that the system is in steady-state when tumor and vascular volumes are equal. Tumor growth without antiangiogenic therapy leads to high steady-state tumor volume ($1.734 \cdot 10^4$ mm^3) and it represents the lethal steady-state case.

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Since state feedback control design requires linear model, we have applied operating point linearization in the $g_0 = 0$ working point. The matrices of the linear model are:

$$A = \begin{bmatrix} -\lambda_1 \log\left(\frac{x_1}{x_2}\right) - \lambda_1 & \lambda_1 \frac{x_1}{x_2} \\ b - \frac{2}{3} d \cdot x_1^{-\frac{1}{3}} \cdot x_2 & -d \cdot x_1^{\frac{2}{3}} \end{bmatrix} \quad (4)$$

$$B = \begin{bmatrix} 0 \\ -ex_2 \end{bmatrix} \quad (5)$$

$$C = \begin{bmatrix} 1 & 0 \end{bmatrix} \quad (6)$$

$$D = \begin{bmatrix} 0 \end{bmatrix} \quad (7)$$

III. CONTROLLER DESIGN

In the case of discrete time controller design, the closed loop contains a DAC (digital to analog converter) right before the tumor model in the feedforward branch, which is modeled by a zero-order hold. In the feedback branch, right after the model, an ADC (analog to digital converter) can be found (Fig.1). The whole controller structure was designed for the linearized and discretized tumor growth model; however, the simulations were carried out with the original nonlinear continuous model. Controller design was executed in Matlab 7.9.0 (R2009b).

A. Sampling time, observability and controllability of the linearized discrete model

Sampling time (T_d) was chosen to fulfill the conditions of Shannon theorem for every signal of the accelerated system.

Taking into account a discrete time model which can be represented by the following state space and output equations:

$$x_{i+1} = A_d x_i + B_d u_i \quad (8)$$

$$y_i = C x_i, \quad (9)$$

the controllability and observability matrices are as follows:

$$M_C = [B_d \quad A_d B_d \quad \ldots \quad A_d^{n-1} B_d] \quad (10)$$

$$M_O = \begin{bmatrix} C \\ CA_d \\ \ldots \\ CA_d^{n-1} \end{bmatrix}, \quad (11)$$

where n is the dimension of the state variables. To fulfill the conditions of controllability and observability, M_C and M_O have to be full rank (rank $M_C = n$ = dim x, rank $M_O = n$ = dim x). The matrices are full rank for every nonzero operating point; thus, the system is controllable and observable.

B. State feedback

The general state feedback law is given by :

$$u_i = -K x_i, \quad (12)$$

where K can be calculated based on pole placement or LQ control method. The state equation of the closed loop system using state feedback is:

$$x_{i+1} = (A_d - B_d K) x_i. \quad (13)$$

In the case of pole placement, the feedback matrix K can be determined by the Ackermann's formula, i.e.

$$K_{PP} = e_n^T \cdot M_C^{-1} \cdot \varphi_{closed}(A_d), \quad (14)$$

where e_n is the nth unit vector and $\varphi_{closed}(A)$ is the characteristic polynomial of the closed loop evaluated at the matrix A_d. The poles of the closed loop are determined by accelerating the poles of the linear continuous model and then using Z-transform method (pole–zero mapping):

$$z = e^{sT_d}, \quad (15)$$

where z is the discrete time pole, s is the continuous time pole.

LQ control method aims to minimize the tumor volume (x_1) using the least possible control signal. The discrete time cost function which has to be minimized with the constraint (8) is the following:

$$J(u) = \sum_{i=1}^{T} \left\{ x_i^T Q x_i + u_i^T R u_i \right\}, \quad (16)$$

where Q and R are positive definite weighting matrices.

We chose to minimize the square of the output ($x_1^2 = y^2$), thus the Q weighting matrix is:

$$Q = C^T C. \quad (17)$$

The feedback matrix K for the discrete time LQ problem can be calculated by the formula:

$$K_{LQ} = \left(R + B_d^T P B_d\right)^{-1} B_d^T P A_d, \quad (18)$$

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

$$P = A_d^T P A_d - \left(A_d^T P B_d\right)\left(R + B_d^T P B_d\right)^{-1}\left(B_d^T P A_d\right) + Q \quad (19)$$

C. Setpoint control

The solution of the state equation in steady state is characterized by the equivalence of the previous and actual states:

$$x_\infty = A_d x_\infty + B_d u_\infty \quad (20)$$

$$y_\infty = C x_\infty. \quad (21)$$

Taking into account a constant reference signal, two matrices (N_x and N_u) are needed to extend the control structure for setpoint control. For zero steady state error on the output, the following equations need to be satisfied:

$$x_\infty = N_x r \quad (22)$$

$$y_\infty = r \quad (23)$$

$$u_\infty = N_u r. \quad (24)$$

Considering on the one hand (21), (22) and (23) equations, one can express:

$$C N_x = I_m, \quad (25)$$

where dim y = dim r = dim u = m. On the other hand, substituting (22) and (24) into (20) leads to the:

$$(A_d - I)N_x + B_d N_u = 0_{nxm}. \quad (26)$$

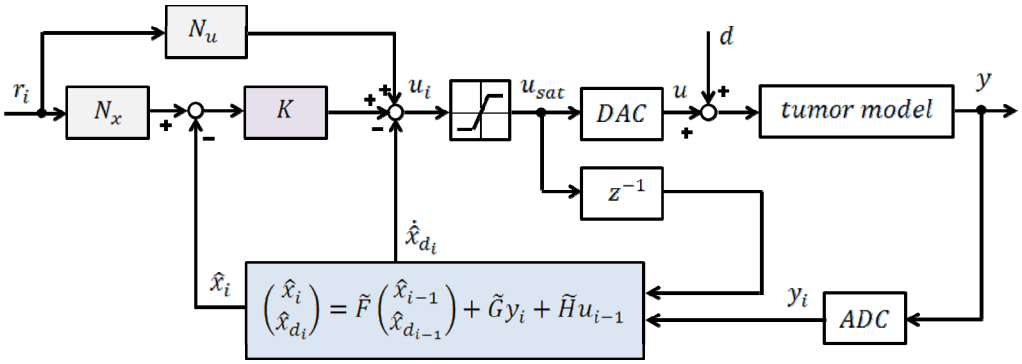

Figure 1. Block diagram of the discrete time control containing state feedback, setpoint control, actual state observer and load estimation.

Finally, equation (25) and (26) can be written in matrix equation form that expresses the vector which contains the required N_x and N_u matrices:

$$\begin{pmatrix} N_x \\ N_u \end{pmatrix} = \begin{bmatrix} A_d - I & B_d \\ C & 0 \end{bmatrix}^{-1} \begin{pmatrix} 0_{nxm} \\ I_m \end{pmatrix}. \quad (27)$$

D. Actual state observer

In discrete time, an actual state observer can be used to estimate the non-measurable state variables.

Let us consider that the matrix $M_o A_d$ is full rank, i.e. the discrete time system is observable with an actual observer. In this case we can choose an actual state observer which is described by the difference equation:

$$\hat{x}_i = F\hat{x}_{i-1} + Gy_i + Hu_{i-1}. \quad (28)$$

Let $\tilde{x}_i$ be the error of estimation:

$$\tilde{x}_i = x_i - \hat{x}_i, \quad (29)$$

then

$$\tilde{x}_i = F(x_{i-1} - \hat{x}_{i-1}) + (B_d - GCB_d - H)u_{i-1} + \\ + (A_d - GCA_d - F)x_{i-1}. \quad (30)$$

In order to assure $\tilde{x}_i \to 0$, we choose the following parameters for the actual state observer:

$$F = A_d - GCA_d \quad (31)$$

$$H = B_d - GCB_d \quad (32)$$

$$\tilde{x}_i = F\tilde{x}_{i-1}. \quad (33)$$

Finally, gain G can be calculated using the Ackermann's formula by substituting $A_d := A_d^T$ and $B_d := A_d^T C^T$ into (14) and using the prescribed poles of the observer to defined the characteristic polynomial in (14).

E. Load estimation

We assume that the disturbance is reduced to the input of the system (load change) and has a constant value. Consequently the differential equation of the disturbance is:

$$d_{i+1} = d_i. \quad (34)$$

Extending the system with the state variable of the disturbance (x_d) and using the notation $\tilde{x} = \left(x^T, {x_d}^T\right)^T$, the state equation becomes:

$$\begin{pmatrix} x_{i+1} \\ x_{d\,i+1} \end{pmatrix} = \begin{bmatrix} A_d & B_d \\ 0 & I \end{bmatrix} \begin{pmatrix} x_i \\ x_{d_i} \end{pmatrix} + \begin{bmatrix} B_d \\ 0 \end{bmatrix} u_i \quad (35.a)$$

$$\tilde{x}_{i+1} = \tilde{A}_d \tilde{x}_i + \tilde{B}_d u_i \quad (35.b)$$

$$y_i = \begin{bmatrix} C & 0 \end{bmatrix} \begin{pmatrix} x_i \\ x_{d\,i} \end{pmatrix} \quad (36.a)$$

$$y_i = \tilde{C}\tilde{x}_i. \quad (36.b)$$

The state feedback and the setpoint control is designed for the original system; however, the actual state observer has to calculate not only the estimation of the state variables ($\hat{x}$), but the estimation of the disturbance ($\hat{x}_d$) as well. Therefore, actual state observer was designed for the extended system [17] whose difference equation is:

$$\begin{pmatrix} \hat{x}_i \\ \hat{x}_{d\,i} \end{pmatrix} = \tilde{F} \begin{pmatrix} \hat{x}_{i-1} \\ \hat{x}_{d\,i-1} \end{pmatrix} + \tilde{G}y_i + \tilde{H}u_{i-1}. \quad (37)$$

Fig. 1 depicts the whole closed-loop control system containing the controller and the nonlinear system. We 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 dangerous in biological systems.

IV. Simulation Results

Simulations were executed in Simulink 7.9.0. Simulation periods were *150* days in all cases and endostatin was used as angiogenic inhibitor. Initial value of tumor volume and endothelial volume was the steady state volume without control input ($1.734 \cdot 10^4$ mm^3). Acceleration of the actual state observer was $a_o = 5$.

Control strategies were evaluated based on three *criteria*: (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).

We found that operating point (x_{10}) has a determinative effect on the control since the appropriate operating point can be chosen only from a narrow range.

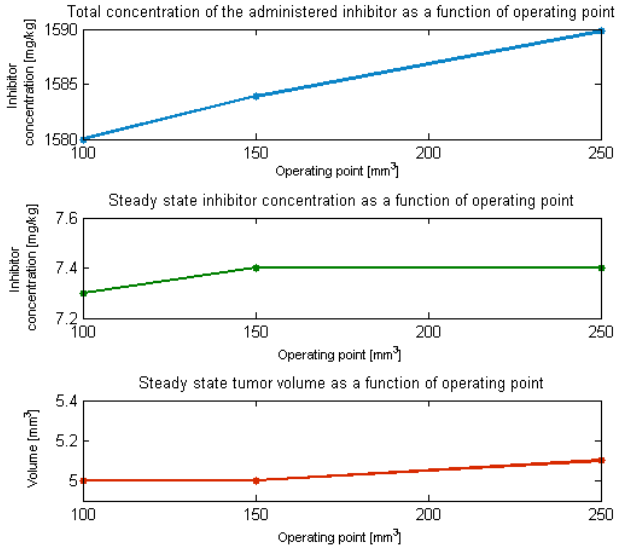

Figure 2. Effect of operating point on the evaluation criteria (LQ control, saturation: 15 mg/kg; *R* weighting matrix: 10; reference signal: 5 mm^3; disturbance: 10%).

If $x_{10} < 100$ mm^3 or $x_{10} > 250$ mm^3, the control is not effective. For $x_{10} < 100$ mm^3, the control input before the saturation (u_i according to Fig. 1) is unusable because its amplitude is high and it oscillates with high frequency; for $x_{10} > 250$ mm^3, the *150* days simulation period is not enough to reach the steady state. If 100 $mm^3 < x_{10} < 250$ mm^3, the control strategy is effective and the smallest amount of inhibitor is needed in the case of $x_{10} = 100$ mm^3 operating point (Fig. 2).

If the gain of state feedback is calculated based on LQ control method, the most important parameter to be chosen is the *R* weighting matrix. Theoretically large *R* attempts to minimize the input, while small *R* allows high inputs; however, we found that larger *R* values resulted in larger total inhibitor concentration (Fig. 3). This behavior can be explained by the effect of saturation. Similarly to the operating point, *R* also has a range in which case the control strategy is effective ($1 < R < 100$).

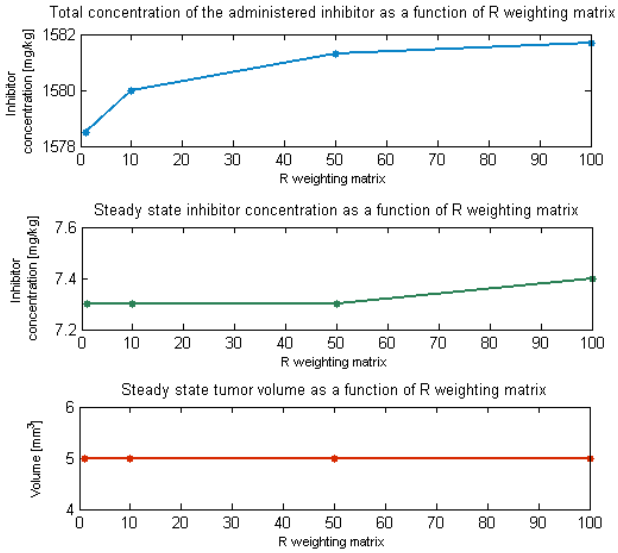

Figure 3. Effect of *R* weighting matrix on the evaluation criteria (LQ control, operating point: 100 mm^3; saturation: 15 mg/kg; reference signal: 5 mm^3; disturbance: 10%).

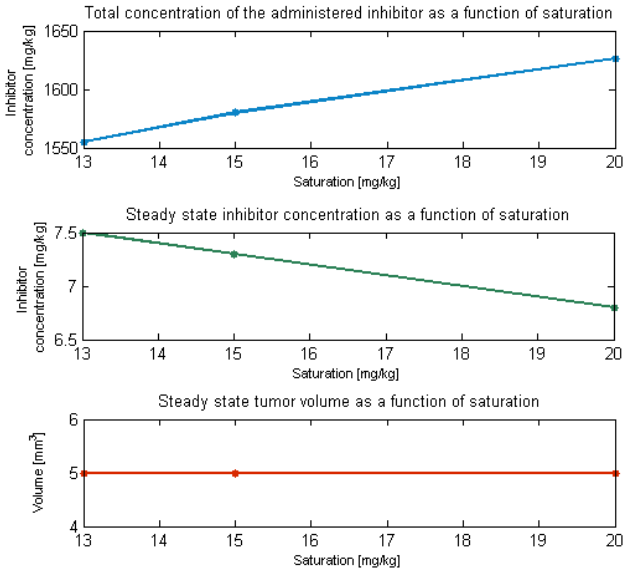

Figure 4. Effect of saturation on the evaluation criteria (LQ control, operating point: 100 mm^3; *R* weighting matrix: 10; reference signal: 5 mm^3; disturbance: 10%).

The effect of saturation was found to be very similar to the continuous time state feedback [4]. Increasing the saturation limit, the total concentration of the administered inhibitor also increases, whilst the steady state inhibitor concentration slightly decreases and the steady state tumor volume remains the same value (Fig. 4). It means that lower saturation value is not only appropriate due to physiological aspects (less side effects) and economic considerations (better cost-effectiveness), but also because of engineering point of view.

In real-life applicability, a key question is the prescribed value of reference signal. Evidently, small steady state tumor volume has smaller cytotoxic and other harmful physiological effect than larger ones; however, the problem is more complicated. In cancer treatment, we have to take into account cost-effectiveness aspect as well which can be accomplished in the following way.

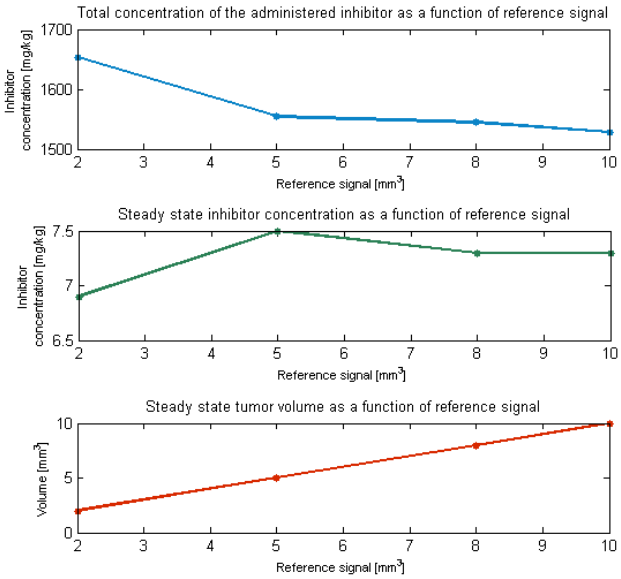

Figure 5. Effect of reference signal on the evaluation criteria (LQ control, operating point: 100 mm^3; saturation: 15 mg/kg; *R* weighting matrix: 10; disturbance: 10%).

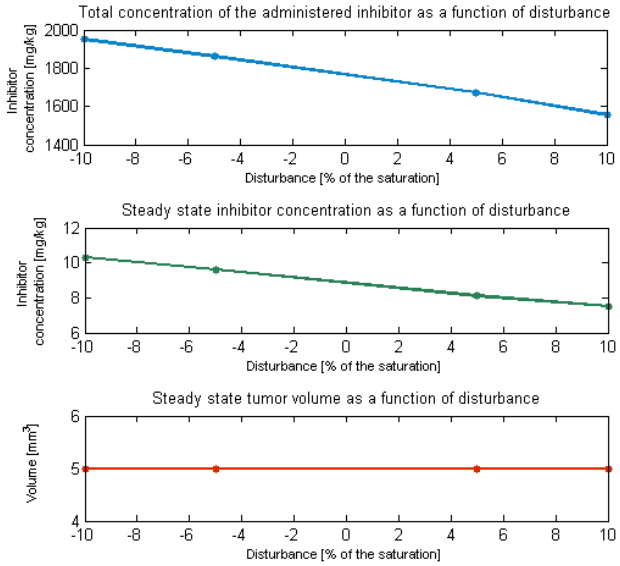

Figure 6. Effect of disturbance on the evaluation criteria (LQ control, operating point: 100 mm^3; saturation: 15 mg/kg; *R* weighting matrix: 10; reference signal: 5 mm^3).

One has to define oncologically homogenous groups which contain a set of cases (e.g. a set of steady state tumor volumes) which have nearly the same physiological effect to the host organism. Within a certain homogenous group, the most cost-effective treatment should be chosen. If we can count the *2* mm^3 < *r* < *10* mm^3 reference signal range as an oncologically homogenous group, the selection criterion should be the *r* which results in the smallest total inhibitor concentration, viz. *r* = *10* mm^3 (Fig. 5).

The effect of disturbance (*d*) is also not negligible. A possible type of disturbance which is reduced to the input of the system can be the error caused by the non-precise tumor volume measurement [13]. Fig. 6 shows the effect of the disturbance when *d* is [*-10%,+10%*] of the saturation. One can see that the corresponding total inhibitor concentration values vary in a large range (*1952* mg/kg and *1555* mg/kg for *-10%* and *+10%*, respectively). In addition, the steady state inhibitor concentration also varies in a relatively wide range (*10.3* mg/kg and *7.5* mg/kg for *-10%* and *+10%*, respectively).

Finally, if the gain of state feedback is calculated based on pole placement, the acceleration (*a*) of the poles has to be set as a parameter. If *a* < *2*, the *150* days simulation period is not enough to reach the steady state. Otherwise, if *a* > *5*, the system is over-accelerated. Within this range, the higher the acceleration, the lower the total inhibitor concentration becomes (Fig. 7).

Fig. 8 shows the reference, input and output signals of the tumor growth model in the case of LQ control. One can see that the parameters have significant effect on the input signal. If the input has large over- and undershoot, it will cause larger total inhibitor concentration on the one hand, and on the other hand it may result in side-effects for the patient.

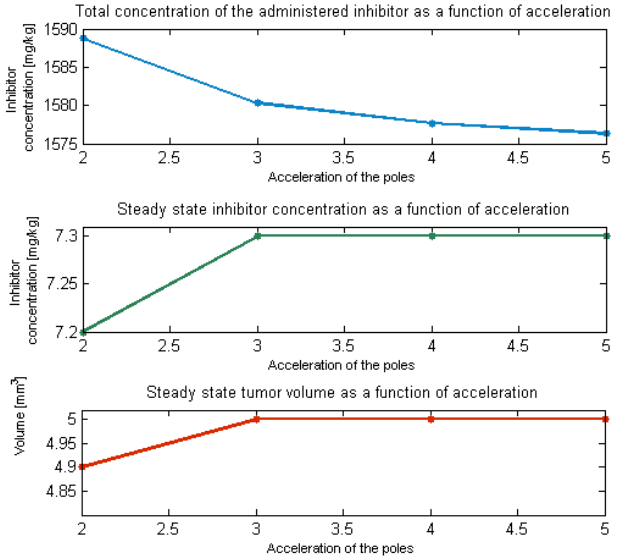

Figure 7. Effect of acceleration on the evaluation criteria (pole placement, operating point: 100 mm^3; saturation: 15 mg/kg; reference signal: 5 mm^3; disturbance: 10%).

V. CONCLUSION

We designed state feedback control, augmented with setpoint control to follow nonzero reference signal. State feedback was realized using both pole placement and LQ control method. The control structure is also augmented with an actual state observer and load estimation. We examined the effect of several parameters on the control such as operating point, *R* weighting matrix, saturation, reference signal, disturbance and acceleration. We found that a current set of parameters can be chosen in order to reduce total inhibitor concentration and avoid side-effect as much as possible.

Further work will focus on the investigation of LPV-based modeling [18].

REFERENCES

[1] P. Hahnfeldt, D. Panigrahy, J. Folkman, and L. Hlatky, "Tumor development under angiogenic signaling: A dynamical theory of tumor growth, treatment response, and postvascular dormancy", *Cancer research*, vol. 59, pp. 4770–4775, 1999.

[2] D. A. Drexler, L. Kovács, J. Sápi, I. Harmati, and Z. Benyó, "Model-based analysis and synthesis of tumor growth under angiogenic inhibition: a case study." *IFAC WC 2011 – 18th World Congress of the International Federation of Automatic Control*, pp. 3753–3758, August 2011, Milano, Italy.

[3] J. Sápi, D. A. Drexler, I. Harmati, Z. Sápi, and L. Kovács, "Linear state-feedback control synthesis of tumor growth control in antiangiogenic therapy," *SAMI 2012 – 10th IEEE International Symposium on Applied Machine Intelligence and Informatics*, pp. 143–148, January 2012, Herlany, Slovakia.

[4] J. Sápi, D. A. Drexler, I. Harmati, Z. Sápi, and L. Kovács, "Qualitative analysis of tumor growth model under antiangiogenic therapy – choosing the effective operating point and design parameters for controller design," *Optimal Control Applications and Methods*, Article first published online: 9 SEP 2015, DOI: 10.1002/oca.2196.

[5] D. A. Drexler, J. Sápi, A. Szeles, I. Harmati, A. Kovács, and L. Kovács, "Flat control of tumor growth with angiogenic inhibition", *SACI 2012 – 6th IEEE International Symposium on Applied Computational Intelligence and Informatics*, pp. 179–183, May 2012, Timisoara, Romania.

[6] D. A. Drexler, J. Sápi, A. Szeles, I. Harmati, L. Kovács, "Comparison of Path Tracking Flat Control and Working Point Linearization Based Set Point Control of Tumor Growth with Angiogenic Inhibition", *Scientific Bulletin of the "Politehnica" University of Timisoara, Transactions on Automatic Control and Computer Science*, vol. 57 (71):(2), pp. 113–120, 2012.

[7] A. Szeles, D. A. Drexler, J. Sápi, I. Harmati, and L. Kovács, "Study of Modern Control Methodologies Applied to Tumor Growth under Angiogenic Inhibition", *IFAC WC 2014 – 19th World Congress of the International Federation of Automatic Control,* pp. 9271–9276, August 2014, Cape Town, South Africa.

[8] A. Szeles, J. Sápi, D. A. Drexler, I. Harmati, Z. Sápi, and L. Kovács, "Model-based angiogenic inhibition of tumor growth using modern robust control method", *IFAC BMS 2012 – 8th IFAC Symposium on Biological and Medical Systems*, pp. 113–118, August 2012, Budapest, Hungary.

[9] J. Sápi, D. A. Drexler, L. Kovács, "Parameter optimization of H∞ controller designed for tumor growth in the light of physiological aspects", *CINTI 2013 – 14th IEEE International Symposium on Computational Intelligence and Informatics*, pp. 19–24, November 2013, Budapest, Hungary.

[10] L. Kovács, A. Szeles, J. Sápi, D. A. Drexler, I. Rudas, I. Harmati, and Z. Sápi, "Model-based angiogenic inhibition of tumor growth using modern robust control method", *Computer Methods and Programs in Biomedicine*, vol. 114, pp. 98–110, 2014.

[11] A. Szeles, D. A. Drexler, J. Sápi, I. Harmati, Z. Sápi, and L. Kovács, "Model-based Angiogenic Inhibition of Tumor Growth using Feedback Linearization", *CDC 2013 – 52nd IEEE Conference on Decision and Control*, pp. 2054–2059, December 2013, Florence, Italy.

[12] A. Szeles, D. A. Drexler, J. Sápi, I. Harmati, and L. Kovács, "Model-based Angiogenic Inhibition of Tumor Growth using Adaptive Fuzzy Techniques", *Periodica Polytechnica: Electrical Engineering and Computer Science,* vol. 58:(1), pp. 29–36, 2014.

[13] J. Sápi, L. Kovács, D.A. Drexler, P. Kocsis, D. Gajári, Z. Sápi, "Tumor Volume Estimation and Quasi-Continuous Administration for Most Effective Bevacizumab Therapy", *Plos One*, vol. 10:(11), Paper e0142190. 20 p, 2015.

[14] A. d'Onofrio, and P. Cerrai, "A bi-parametric model for the tumour angiogenesis and antiangiogenesis therapy", *Mathematical and Computer Modelling*, vol. 49, pp. 1156–1163, 2009.

[15] U. Ledzewicz, and H. Schätler, "A synthesis of optimal controls for a model of tumor growth under angiogenic inhibitors", *CDC 2005 – 44th IEEE Conference on Decision and Control, and the European Control Conference*, pp. 934–939, December 2005, Sevilla, Spain.

[16] A. d'Onofrio, A. Gandolfi, and A. Rocca, "The dynamics of tumour-vasculature interaction suggests low-dose, time-dense antiangiogenic scheduling", *Cell Proliferation*, vol. 42, pp. 317–329, 2009.

[17] B. Lantos, "Theory and Design of Control Systems I-II" (in Hungarian), *Akadémia Kiadó*, Budapest, 2005.

[18] Gy. Eigner, J. K. Tar, I. Rudas, and L. Kovács, "LPV-based quality interpretations on modeling and control of diabetes", *Acta Polytechnica Hungarica*, vol. 13(1), pp. 171–190, 2016.

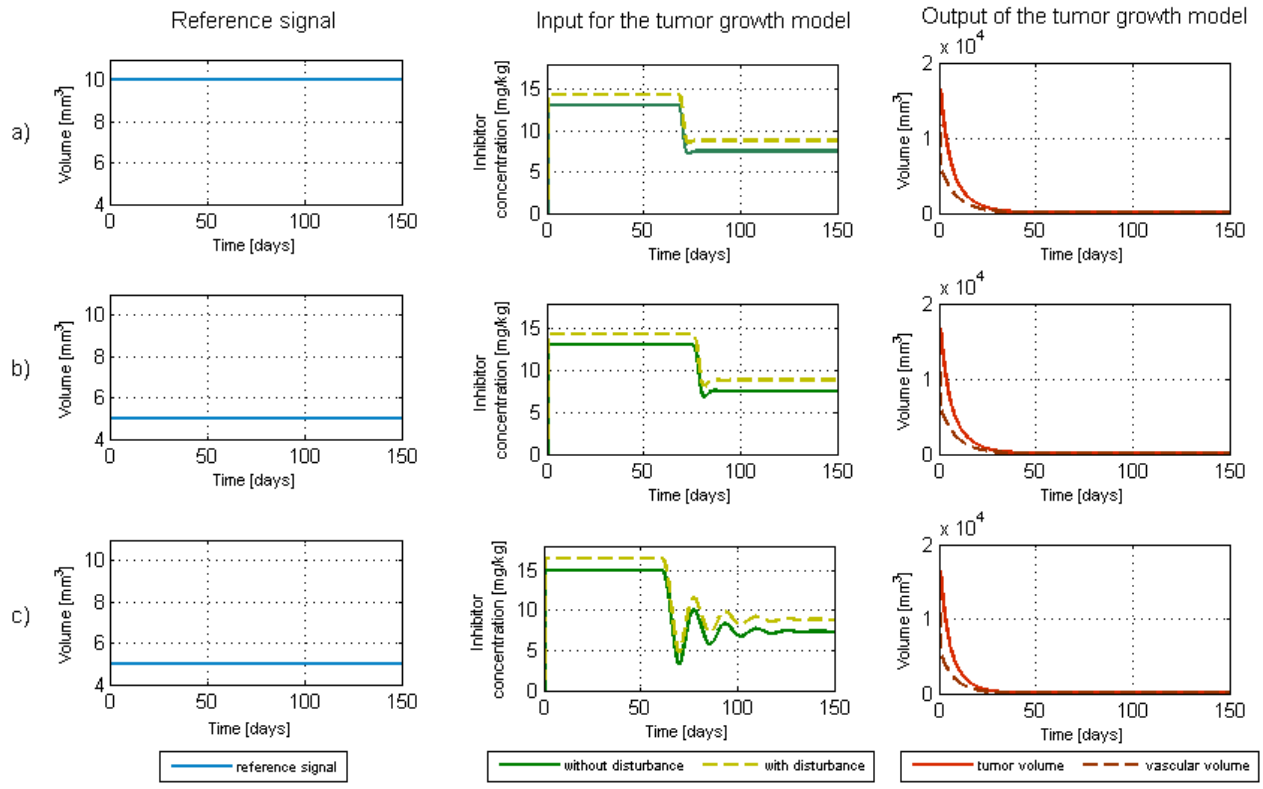

Figure 8. Reference, input and output signals of the tumor growth model in the case of LQ control.
a) Parameters: operating point: 10 mm^3; saturation: 13 mg/kg; R: 1; reference signal: 10 mm^3; disturbance: 10%.

Total inhibitor concentration: 1506 mg/kg, steady state inhibitor concentration: 7.5 mg/kg, steady state tumor volume: 10 mm^3.
b) Parameters: operating point: 10 mm^3; saturation: 13 mg/kg; R: 1; reference signal: 5 mm^3; disturbance: 10%.
Total inhibitor concentration: 1550 mg/kg, steady state inhibitor concentration: 7.5 mg/kg, steady state tumor volume: 5 mm^3.
c) Parameters: operating point: 100 mm^3; saturation: 15 mg/kg; R: 10; reference signal: 5 mm^3; disturbance: 10%.
Total inhibitor concentration: 1580 mg/kg, steady state inhibitor concentration: 7.3 mg/kg, steady state tumor volume: 5 mm^3.