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Linear Matrix Inequality based Control of Tumor Growth

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***Abstract*—In this paper we examine how can be combined the Linear Parameter Varying (LPV) modeling technique with the Linear Matrix Inequality (LMI) based controller and observer design methodology in order to control the tumor growth via anti-angiogenic inhibition. We introduce the important physiological knowledge regard to the control problem together with the design procedure. We used a recently developed minimal model which describes the tumor growth dynamics beside anti-angiogenic inhibition and we transformed this model into the difference based qLPV model. After, LMI based controller and observer were designed by pole clustering LMIs and we realized the control structure. Our aim was to develop a control environment which is – however – advanced, but it can be easily used and provides good performance from the designing properties and the robustization possibilities points of view, respectively. As our results showed, the framework provides appropriate results for tumor control.**

***Index Terms*—Linear Matrix Inequality, Liner Parameter Varying, LPV-LMI-based control, Anti-angiogenic therapy, Tumor growth control**

I. Introduction

Different type of cancer cells can be occurred in the human body due to somatic mutations, which may caused by external effects (eg. radiation, chemical materials, diseases) or internal effects (eg. natural point mutations, error of DNA replicating mechanisms). If the mutant cells are not eliminated by the programmed apoptosis and/or the immune system, than the cell proliferation starts and a concourse is formed by cancer cells [1]. At the beginning of the tumor growth progression the concourse is supplied by the local nutrients and oxygen through diffusion. The growth continuing until its size reach a limit where the nutrition via diffusion becomes insufficient for supply the further growing (this appeared when the mutant cells grow over than the distance of diffusion, namely, 150 μm. To bypass this problem, the tumor starts to build up its own blood vessels which connects it to the central circulatory system and provides appropriate nutrition. From the tumor growth point of view, the important process to form new blood vessels is the angiogenesis, while the supporting vasculature is evolving from preexisting microvasulature [2]. The process of angiogenesis is regulated by different pro- and anti-angiogen factors. The vascular endothelial growth factor (VEGF) is a crucial pro-angiogen factor, which stimulates the endothelial cell proliferation, in other words, animates the reproduction of endothelial cells which form the blood vessels [3], [4]. In this way, the hamper of angiogenesis through the inhibition of the VEGF is an important therapeutic target. Thus, anti-VEGF agents, effectors and VEGF inhibitors can be used as supplementary therapy beside regular treatments [5]. However, to determine the appropriate administration of the anti-angiogenic inhibitors is still questionable and widely researched by the scientific community [3].

An advanced way for the inhibition of the VEGF and other factors is the Targeted Molecular Therapies (TMT), which became one of the most important directions among the cancer treatments in the recent decades [4]. In case of TMT, drugs or other substances are used to block or eliminate specific molecules involved into the growth, progression and spread of the cancer. Several TMTs exist, for example the apoptosis inducers, signal transmission inhibitors, gene expression modulators and anti-angiogenic therapies [5]. Beside killing the cancer cells by hamper of the gene expression or enforce to destroy itself by apoptosis, the inhibition of angiogenesis can be an effective way to decrease or maintain the volume of the tumor. However, the anti-angiogenic therapy cannot totally eliminate the cancer concourse, but it can "tame" the tumor. The main benefit compared to other type of treatments are the anti-angiogenic TMTs cause less side effects and lower load for the human body – since, in healthy adults, the angiogenesis is infrequent and the most vivid angiogenic processes are connected to the tumor growth.

Mostly, the anti-angiogenic treatments can be used as complementer remedy beside regular treatments such as chemotherapy or radiotherapy. Although, the usage of them as monotherapy is an intensively researched area, promising great outcomes, however, the amount of needed drugs is critical and hard to determine [6]. In the daily clinical practice three drug administration protocols occur: the bolus doses therapy (BDT), the metronomic low dose therapy (MLDT) and the

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continuous infusion therapy (CIT). The BDT protocol operates with the maximum tolerable doses at scheduled time and between them no injections are used. The main benefit is that the injected drugs – thank to the high concentration – acts rapidly, although, side-effects appear more likely than other protocols. Significant drawbacks are that because the applied drugs do not reach the desolation all of the cancer cells, the remaining cells may rebuild the tumor concourse under the longer periods between when injections are not applied. Moreover, there is a risk that because of their fast evolution and proliferation the tumor cells become resistant to the given drug [7]. MLDT does provide particular solution against the problems of BDT. In this case, the anti-tumor drugs are delivered in minimal dosage. The administration is based on given schedule over longer period and it is adjusted to maximize the effectiveness [8]. In the recent times, the application of CIT came to the fore because animal- and in-silico-experiments showed that this treatment can be the most effective one among the current anti-cancer therapies [9]–[11]. Although, to use the CIT in daily practice highly advanced biomedical modeling and controller design tools are needed which are able to deal with the challenges regard to this field (eg. example intra- and inter-patient variability, nonlinearities, etc.).

In the recent years, several advanced control engineering solutions appeared to handle the mentioned issues. One of them is the Linear Parameter Varying theorems which does allow to hide the nonlinearities and uncertainties into the structure of the LPV model and apply linear controller design methods [12], [13]. LPV theorems can be combined with the so-called Linear Matrix Inequality based methods at which the controller design can be formulated as an optimization problem with convex objective functions and LMI constraints [14]. The recently developed Robust Fixed Point Theorem (RFPT) based controller design also can be used for physiological related controls [15], [16]. [17] reported the successfully adaptation of the LMI-based Robust Nonlinear Model Predictive Control (RNMPC) in case of tumor control. Tensor Product (TP) based modeling and control is also suitable for biological problems [18], [19].

In this study, we focused to the LPV-LMI methods and we developed a LMI-based controller and observer for given tumor control problem. In our previous research we have approached the controller design problems in other ways. In this way to compare our current achievements with other solutions will be the part of our further work.

The paper is structured, as follows. First, the used tumor growth model is introduced. After, the controller and observer design are detailed. In Sec. IV, the results are presented which is followed by our conclusions.

II. The Minimal Model

In this study we applied the minimal model developed by Drexler et al [20]. The model describes the dynamics of the tumor's volume growth beside anti-angiogenic inhibition.

$$\begin{aligned} \dot{x}(t) &= ax(t) - bx(t)y(t) \\ \dot{y}(t) &= -cy(t) + u(t) \end{aligned} \quad , \tag{1}$$

where $x(t)$ mm^3 is the tumor volume (and the output of the model), $y(t)$ mg/kg is the inhibitor serum level and $u(t)$ mg/kg/day is the input of the model (inhibitor intake). The used model parameters and their values were the following: $a = 0.27$ 1/day (the tumor growth rate), $b = 0.0074$ kg/mg/day (the inhibition rate) and $c = log(2)/3.9$ 1/day (the clearance of the inhibitor). The handling of the model is quite challenging despite that is has only two states. The main issues are its instability (without external inhibitor the $x(t)$ increases with a and the nonlinear connection between the states).

III. Controller and Observer Design

A. LMI Regions by Pole Clustering

Convex constraints can be defined as LMIs concerning to the controller and observer designing procedures. That means, LMI-based design is possible through numerical optimization of convex objective (cost) functions alongside given LMI constraints to reach predefined satisfactory criteria. If the LMI constraints include Lyapunov-, Ricatti-, or other theorems control related design becomes possible [14].

The general form of a LMI is the following:

$$F(x) := F_0 + \sum_{i=1}^{m} x_i F_i > 0 \ , \tag{2}$$

where $x \in \mathbb{R}^m$, $F_i = F_i^\top \in \mathbb{R}^{n \times n}$ and $i = 1, .., m$. The inequality in means (2) that $F(x)$ is positive definite, thus, $z^\top F(x) z > 0 \ \forall \ z \in \mathbb{R}^n$ [21].

Following the findings of Chilali and Gahinet [22], [23] it is possible to determine such LMI constraints based on the Lyapunov theorems which allow the pole placement of the closed loop system into a desired convex region. This technique is the so-called pole clustering by LMI which suitable for controller and observer design and can be combined with other – mostly robust control related – LMIs efficiently. In the following, we introduce the definition of LMI regions, moreover, we present the important LMIs from this study point of view.

Definition 1. In the complex plane a subset $\mathcal{D}$ is called as LMI region if there exist the $\alpha = [\alpha_{ij}] \in \mathbb{R}^{m \times m}$ symmetric matrix and $\beta = [\beta_{ij}] \in \mathbb{R}^{m \times m}$ matrix that the criteria below is satisfied [23]:

$$\mathcal{D} := \{ z \in \mathbb{C} : f_{\mathcal{D}}(z) = \alpha + \beta z + \beta^\top \bar{z} < 0 \} \ . \tag{3}$$

Definition 2. Let $\mathcal{D}$ a subregion on the left (negative) complex half-plane. A dynamical system $\dot{x}(t) = Ax(t)$ is called $\mathcal{D}$-stable if all its poles lie inside the region $\mathcal{D}$ [23].

Theorem 1. *A matrix A is $\mathcal{D}$-stable if and only if there exists a symmetric positive definite $X > 0$ matrix that the criteria below is satisfied (proof can be found in [23]):*

$$M_{\mathcal{D}}(A, X) := \alpha \otimes X + \beta \otimes AX + (\beta \otimes AX)^\top < 0 \ , \tag{4}$$

where $\otimes$ means the Kronecker-product.

The connection between $f_{\mathcal{D}}(z)$ from (3) and $M_{\mathcal{D}}(A,X)$ from (4) is the following substitution: $(1, z, \bar{z}) \leftrightarrow (X, AX, XA^\top)$ [22], [23].

In this work we considered the following LMIs, which represent vertical strips and imaginary bounding in the complex left half plane and encapsulates the poles of given system.

Definition 3. Vertical strips [23]: The real part of the poles of the matrix A lies between h_1 and h_2 ($\mathcal{D}$ region), thus $-h_1 < Re(\lambda(A)) < -h_2 < 0$ if there exist a symmetric $X > 0$ matrix such that

$$AX + (AX)^\top + 2h_1X > 0, \;\; AX + (AX)^\top + 2h_2X < 0 \;\; . \tag{5}$$

Definition 4. Imaginary bounding [23]: The imaginary part of the poles of the matrix A lie between $-\delta$ and δ ($\mathcal{D}$ region), thus $-\delta < Im(\lambda(A)) < \delta$ if there exist a symmetric $X > 0$ matrix such that

$$\begin{bmatrix} -\delta X & (AX)^\top - AX \\ AX - (AX)^\top & -\delta X \end{bmatrix} < 0 \;\; . \tag{6}$$

The (3)-(6) equations can represent closed loop cases as well.

According to [23]–[25] it is possible to design such state feedback controller and K feedback gain, which enforces that all of the closed loop poles of the controlled dynamical system $\dot{x}(t) = Ax(t) + Bu(t) = (A + BK)x(t)$, $u(t) = Kx(t)$ lie in the predefined $\mathcal{D}$-region ($\mathcal{D}$-stable). Due to this substitution should be applied in (3)-(6): $(AX, (AX)^\top \leftrightarrow (AX + BR), (AX + BR)^\top)$, where R is a matrix variable and K can be calculated as $K := RX^{-1}$.

The same is true in case of observer design as well. Accordingly to [25], the state feedback observer design is possible and L observer gain can be calculated which enforces that all of the closed loop poles of the dynamical observer $\dot{\hat{x}}(t) = A\hat{x}(t) + Bu(t) + L(y(t) - C\hat{x}) = (A + BK - LC)\hat{x}(t) + Ly(t)$, $u(t) = K\hat{x}(t)$ lie in the predefined $\mathcal{D}$-region ($\mathcal{D}$-stable). Due to this substitution should be applied in (3)-(6): $(AX, (AX)^\top \leftrightarrow (AX - RC), (AX - RC)^\top)$, where R is a matrix variable and L can be calculated as $L := X^{-1}R$.

The aforementioned methods can be extended to LPV case as follows [23].

$$\begin{aligned} &\dot{x}(t) = A(p(t))x(t) + B(p(t))u(t) \\ &(A,B) \in \left\{ \left(\sum_{i=1}^{N} p(t)_i A_i, \sum_{i=1}^{N} p(t)_i B_i \right) : \right. \\ &\qquad \left. \sum_{i=1}^{N} p(t)_i = 1, p(t)_i \geq 0 \right\} < 0 \end{aligned} \;\; , \tag{7}$$

where $p(t)$ is the parameter vector of the LPV system ($p(t)$ includes the selected scheduling variables from the system which causes nonlinearities) and $A(p(t)), B(p(t))$ are affine matrix-valued functions of $p(t)$. The parameter vector $p(t) \in \Omega \in \mathbb{R}^N$, where $\Omega = [p_{1,min}, p_{1,max}] \times [p_{2,min}, p_{2,max}] \times ... \times [p_{N,min}, p_{N,max}] \in \mathbb{R}^N$ formalizes a limited hypercube in the N-dimensional hyperspace defined by the extremes of the scheduling variables. Accordingly to [23] the (4) should be modified for controller and observer design, respectively:

$$\begin{aligned} &M_{\mathcal{D}}(A_i + B_iK, X) := \\ &\alpha \otimes X + \beta \otimes (A_iX + B_iR) + (\beta \otimes (A_iX + B_iR))^\top < 0 \\ &M_{\mathcal{D}}(A_i - LC_i, X) := \\ &\alpha \otimes X + \beta \otimes (A_iX - RC_i) + (\beta \otimes (AX - RC_i))^\top < 0 \end{aligned} \;\; . \tag{8}$$

Consequently, via (8) it is possible to design a general K feedback and L observer gains, respectively. These gains are able to control and observe the original nonlinear system via LPV framework if $p(t)$ is inside the Ω parameter domain.

B. Applied qLPV Model

We applied difference based qLPV model – which means we transformed the original model to a qLPV variant which models the error dynamics, thus the deviation of the states of the model from a given "enforced" equilibrium. Due to the lack of natural equilibrium, only the use of an enforced one is possible. The new states in this case will be the deviation from this equilibrium, namely, $\Delta x(t)$ and $\Delta y(t)$.

The qLPV model has to be controllable and observable on the whole Ω parameter domain. Due to the model properties only $p(t) := p_i(t) = y(t)$ can be selected as scheduling variable, otherwise the controllability and observability criteria is not satisfied everywhere on Ω – if $x(t)$ is selected as $p_i(t)$ then the rank of the controlability and observability matrices will be lower than 2 at the extremes of $x(t)$. The selected model equilibrium is $x_e = 0.1$, $y_e = a/b$ and $u_e = cy_e$. (It can be seen in (9) that if x_e is zero than the controllability and observability criteria is not satisfied. Further, $x_e = 0$ is not necessary from physiological reasons, since the target is to decrease the volume of the tumor, not to eliminate it. In this manner, we selected $x_e = 0.1$ as enforced equilibrium which should be reached by the state over time. It has to be noted, the x_e is independent from the equilibria of other states which is clear from (1) – that means, x_e can be arbitrarily selected, but y_e and u_e are determined by the model's structure).

The transformed difference based qLPV model with the introduced new states is the following:

$$\begin{aligned} &\Delta\dot{x}(t) = \dot{x}(t) - 0 = \\ &ax(t) - bx(t)y(t) - [ax_e - bx_ey_e] + 0 = \\ &a(x(t) - x_e) - bx(t)y(t) + bx_ey_e + \\ &\qquad + bx_ey(t) - bx_ey(t) = \\ &(a - by(t))(x(t) - x_e) - bx_e(y(t) - y_e) = \\ &(a - by(t))\Delta x(t) - bx_e\Delta y(t) \end{aligned} \;\; .$$

$$\begin{aligned} &\Delta\dot{y}(t) = \dot{y}(t) - 0 = -cy(t) + u(t) - [-cy_e + u_e] = \\ &-c(y(t) - y_e) + (u(t) - u_e) = -c\Delta y(t) + \Delta u(t) \end{aligned}$$

$$\begin{pmatrix} \Delta\dot{x}(t) \\ \Delta\dot{y}(t) \end{pmatrix} = \begin{bmatrix} (a - by(t)) & -bx_e \\ 0 & -c \end{bmatrix} \begin{pmatrix} \Delta x(t) \\ \Delta y(t) \end{pmatrix} + \begin{bmatrix} 0 \\ 1 \end{bmatrix} \Delta u(t) \tag{9}$$

C. Controller and Observer Design

Due to the applied (9) the aim of the control is to enforce that the states of the model become equal to the selected

model equilibrium. The parameter domain was: $p(t) = y(t) = [y_{min}, y_{max}] = [0, 200]$.

To design the controller we applied the (5) and (6) on the basis of (8) and solve the LMI feasibility problem beside $h_1 = 1$, $h_2 = 10$ and $\delta = 5$:

$$\text{Subjects}: X, R$$

$$\begin{cases} X > 0 \\ (A_iX + B_iR) + (A_iX + B_iR)^\top + 2h_1X < 0 \\ (A_iX + B_iR) + (A_iX + B_iR)^\top + 2h_2X > 0 \\ \begin{bmatrix} -\delta X & (A_iX + B_iR) - (A_iX + B_iR)^\top \\ (A_iX + B_iR)^\top - (A_iX + B_iR) & -\delta X \end{bmatrix} < 0 \end{cases} . \tag{10}$$

In order to solve the LMIs under MATLAB environment the YALMIP [26] framework and the MOSEK [27] convex optimization tool were used.

The occurred $K = RX^{-1}$ feedback gain was $K = [6.3802, -0.0033]$. We tested the compliance of K – namely, that all of the eigenvalues $\lambda(A + BK)$ lie in the $\mathcal{D}$ region or not. We examined $\lambda(A + BK)$ at $p(k) = p_{min} : (p_{max} - p_{min})/N : p_{max}$, where k step size was $k = (p_{max} - p_{min})/N$, $N = 50$, which resolution is fine enough to filter any violations. The result was satisfying (Fig. 1), namely, all of the $\lambda(A + BK)$ lied in the predefined $\mathcal{D}$ region.

Figure 1. $\lambda(A + BK)$ poles of the closed system inside the $\mathcal{D}$ region

The observer can be designed in the same manner. Although, we modified the previous process and applied only (5) on the basis of (8) and solve the LMI feasibility problem beside $h_1 = 1$, $h_2 = 50$. We omitted the imaginary boundary LMI, because we experienced that it does not improve the reached results, just increase the numerical inaccuracy.

$$\text{Subjects}: X, R$$

$$\begin{cases} X > 0 \\ (A_iX - RC_i) + (A_iX - RC_i)^\top + 2h_1X < 0 \\ (A_iX - RC_i) + (A_iX - RC_i)^\top + 2h_2X > 0 \end{cases} . \tag{11}$$

The occurred $L = X^{-1}R$ observer gain was $L = [25.0300, -0.0007]^\top$. We used the same test as in the previous case: $\lambda(A + BK - LC)$ at $p(k) = p_{min} : (p_{max} - p_{min})/N : p_{max}$, where k step size was $k = (p_{max} - p_{min})/N$, $N = 50$. The result was satisfying as it can be seen on Fig. 2, namely, not just all of the $\lambda(A + BK - LC)$ lied in the predefined $\mathcal{D}$ region, but also the poles were faster than the controller case without complex parts.

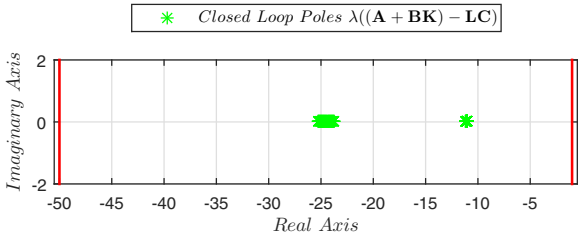

Figure 2. $\lambda(A+BK-LC)$ poles of the closed observer inside the $\mathcal{D}$ region

After the K and L occurred, the realization of the control loop became possible, as it is represented on Fig. 3. In order to avoid the physiologically irrelevant control signals (extraction of inhibitor is not possible), we applied saturation regard to $u(t)$, namely, $u(t)$ cannot be lower than 0.

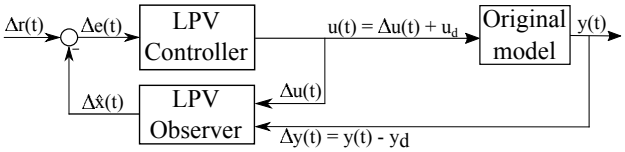

Figure 3. Closed Control Loop

IV. Results

In clinical practice, the therapy starts after the tumor volume reaches the observability border, thus the higher initial value for the tumor volume is reasonable. According to physiological reasons, we applied high initial value for the tumor volume $x(0) = 10000$ mm^3 and zero initial value for the serum inhibitor level $y(0) = 0$ mg/kg (which represents the beginning of the therapy).

Due to the properties of state feedback control, the application of constant reference signal cause issues when the initial values are high. To bypass this problem and provide appropriate reference, we used a smoothly decreasing reference signal for $x_{ref}(t)$, which was generated by the function from (12). Similar to the difference based state, compensation was applied on it as well.

$$x_{ref}(t) = -tanh(ct)x(0) + x(0) + x_e \ , \tag{12}$$

where c is a given tuning parameter and not the parameter of the model.

During the simulations we examined the efficiency of the control beside rapidly and slowly decreasing reference signals which can be tuned by c (higher c responsible for fast decreasing).

We simulated 100 days in all cases, since, from application point of view (and physiological reasons) the first 100 days are the most critical period [1].

Beside $x_{ref}(t)$ reference signal, the y_{ref} was considered as constant $y_{ref} = 0$.

The applied initial values of the states of the observer were different than the system's initial values. Since the observer is difference based, the applied initial values were: $\Delta x_{obs}(0) = x(0) - x_e + 30$ and $\Delta y_{obs}(0) = y(0) - y_e + 1$, where the 30 and 1 were arbitrarily selected to model the imprecise initial measurement.

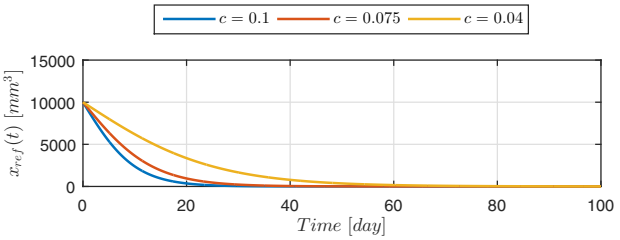

Figure 4. Used reference signal $x_{ref}(t)$ – in this case c is a given tuning parameter and not the parameter of the model

Figure 5 represents the vary of the states and input signal over the simulated time horizon. It can be seen that the properties of the $x_{ref}(t)$ determines the behavior of the model.

The $x(t)$ reached the predefined x_e over the simulated time horizon regardless the reference signal, although the decay is affected by the c tuning parameter.

As it was mentioned above, the model has instable behavior and required continuous control in order to compensate the instability. According to this circumstance, $y(t)$ did not reach the reference value as it was expected – the controller compensating via the control signal in order to avoid the increase of $x(t)$. The c tuning parameter significantly determines the vary of the state.

The applied control signal $u(t)$ is different accordingly to the c tuning parameter. Thus, there is a difference between the states provided by the observer and the initial values of the reference signals, the controller injects inhibitor at the beginning of the therapy. The degree of difference is influenced by the c tuning parameter, thus in case of higher c – eg. $c = 0.1$ –, the controller injects higher amount of inhibitor, further, the later actions become earlier than other cases, when c is lower.

Further, the vary of $p(t)$ had been investigated. Since, $p(t) = y(t)$ in the given case, $p(t)(= \Omega) = [0, 200]$. Fig. 5 shows that there is no domain violation by $p(t)$ over the simulation period.

The observation error is shown by Fig. 6. As it can see, there is a high observation error $(x(t) - x_{obs}(t))$ in case of the tumor volume at the beginning of the simulation. Over time, the observation error decreases and fluctuating in the small environment of zero. Although, the situation is different in case of the second state $(y(t) - y_{obs}(t))$, at which the initial observation error is smaller, but it aggregates over time and only in case of $c = 0.04$ converged to zero over the simulated time horizon, which reflects the previous findings concerning to the intake demands. However, over longer simulation period it converged to zero in all three cases. This behavior of the observer was expected due to the LMI rules (the controller

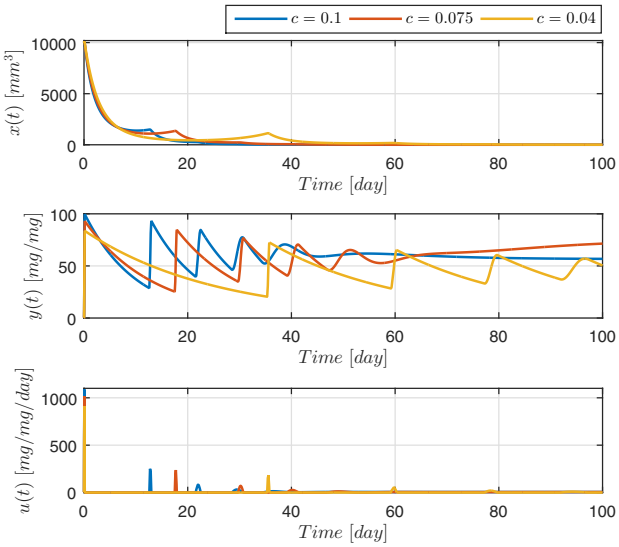

Figure 5. Vary of the sates and input of the original nonlinear model beside different $x_{ref}(t)$ reference signals

and observer has similar rules, although the controller based on more rules than the observer) and the fast observer poles (the higher distance of the poles of the observer in case of any $p(t)$ than the closed controlled system). These facts cause that the observer worked proper in all cases. Probably, the velocity of converging can be increased if the poles are farther from zero – this option will be investigated in our future work.

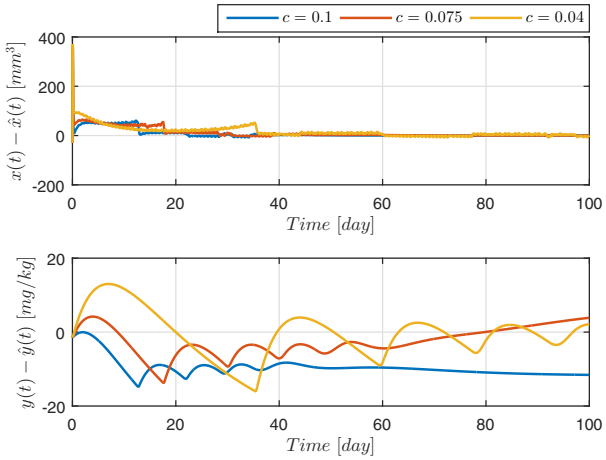

Figure 6. Observation error over the simulated time horizon

V. Conclusion

In this study we investigated the applicability of LPV-LMI-based controller design in case of a difference based qLPV model originated from a nonlinear minimal model of tumor growth. We developed such a state feedback kind controller and observer, which is able to handle the original system via the LPV framework if the LPV's parameter vector $p(t)$ is

inside the predefined Ω parameter domain. According to the results, the developed controller and observer structure is able to deal with the control task and the tumor volume decreased in the expected way. Although, due to the properties of the original model – causes that the continuous inhibitor intake is needed – and because of the applied smaller observer gain – causes slower convergence – the observation error decreases slower at $y(t)$ state. Probably, the effect of the second issue can be improved with faster observer poles, which will be investigated in our future work.

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REFERENCES

[1] R. Weinberg, *The biology of cancer*, 2nd ed. New York, USA: Garland Science, Taylor and Francis, 2014.

[2] J. Distler, A. Hirth, M. Kurowska-Stolarska, R. Gay, S. Gay, and O. Distler, "Angiogenic and Angiostatic Factors in the Molecular Control of Angiogenesis," *Quart J Nucl Med*, vol. 47, no. 3, pp. 149–161, 2003.

[3] B. Al-Husein, M. Abdalla, M. Trepte, D. DeRemer, and P. Somanat, "Anti-angiogenic therapy for cancer: An update," *Pharmacotherapy*, vol. 32, no. 12, pp. 1095–1111, 2012.

[4] Y. Kubota, "Tumor angiogenesis and antiangiogenic therapy," *Keio J Med*, vol. 61, pp. 47 – 56, 2012.

[5] N. Vasudev and A. Reynolds, "Anti-angiogenic therapy for cancer: current progress, unresolved questions and future directions," *Angiogenesis*, vol. 17, no. 3, pp. 471–494, 2014.

[6] A. El-Kenawi and A. El-Remessyn, "Angiogenesis inhibitors in cancer therapy: mechanistic perspective on classification and treatment rationales," *Brit J Pharmacol*, vol. 170, p. 712–729, 2013.

[7] O. Scharovsky, L. Mainetti, and V. Rozados, "Metronomic chemotherapy: changing the paradigm that more is better," *Curr Oncol*, vol. 16, no. 2, pp. 7–15, 2009.

[8] T. Browder, C. Butterfield, B. Kraling, B. Shi, B. Marshall, M. O'Reilly, and J. Folkman, "Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer," *Cancer Res*, vol. 60, no. 7, pp. 1878–1886, 2000.

[9] J. Sápi, L. Kovács, D. Drexler, P. Kocsis, D. Gaári, and Z. Sápi, "Tumor volume estimation and quasi-continuous administration for most effective bevacizumab therapy," *PLoS ONE*, vol. 10, no. 11, 2015.

[10] J. Sápi, D. Drexler, I. Harmati, Z. Sápi, and L. Kovács, "Qualitative analysis of tumor growth model under antiangiogenic therapy: choosing the operating point and design parameters for controller design," *Optim Contr Appl Met*, vol. 37, p. 848–866, 2015.

[11] J. Sápi, D. Drexler, and L. Kovács, "Comparison of Protocol-based Cancer Therapies and Discrete Controller-based Treatments in the Case of Endostatin Administration," in *SMC 2016 - IEEE International Conference on Systems, Man, and Cybernetics*. IEEE, pp. 3830–3835.

[12] G. Eigner, "Novel LPV-based Control Approach for Nonlinear Physiological Systems ," *ACTA Pol Hung*, vol. 14, no. 1, pp. 45–61, 2017.

[13] L. Kovács, "Linear parameter varying (LPV) based robust control of type-I diabetes driven for real patient data," *Knowl-Based Syst*, vol. 122, pp. 199–213, 2017.

[14] J. VanAntwerp and R. Braatz, "A tutorial on linear and bilinear matrix inequalities," *J Proc Con*, vol. 10, pp. 363 – 385, 2000.

[15] G. Eigner, P. Horváth, J. Tar, I. Rudas, and L. Kovács, "Application of Robust Fixed Point control in case of T1DM," in *SMC 2015 - IEEE International Conference on Systems, Man, and Cybernetics*. IEEE, p. 2459–2464.

[16] J.K. Tar, J.F. Bitó, L. Nádai, and J.A.T. Machado, "Robust fixed point transformations in adaptive control using local basin of attraction," *ACTA Pol Hung*, vol. 6, no. 1, pp. 21–37, 2009.

[17] P. Bumroongsri and S. Kheawhom, "Optimal dosing of breast cancer chemotherapy using robust mpc based on linear matrix inequalities," *Modern Engin Tech*, vol. 19, no. 1, pp. 97 – 106, 2015.

[18] J. Kuti, P. Galambos, and P. Baranyi, "Minimal volume simplex (mvs) convex hull generation and manipulation methodology for tp model transformation," *Asian J Control*, vol. 19, no. 1, pages = 289 - -301,, 2017.

[19] P. Baranyi, Y. Yam, and P. Varlaki, *Tensor Product Model Transformation in Polytopic Model-Based Control*, 1st ed., ser. Series: Automation and Control Engineering. Boca Raton, USA: CRC Press, 2013.

[20] D. Drexler, J. Sápi, and L. Kovács, "A minimal model of tumor growth with angiogenic inhibition using bevacizumab," in *SAMI 2017 - IEEE 15th International Symposium on Applied Machine Intelligence and Informatics*. IEEE, p. 185–190.

[21] S. Boyd, L. El Ghaoui, E. Feron, and V. Balakrishnan, *Linear Matrix Inequalities in System and Control Theory*, ser. Studies in Applied Mathematics. Philadelphia, PA: SIAM, 1994, vol. 15.

[22] M. Chilali and P. Gahinet, "H_∞ Design with Pole Placement Constraints: An LMI Approach," IEEE Transactions on Automatic Control," *IEEE T Automat Contr*, vol. 41, no. 3, pp. 358 – 367, 1996.

[23] P. G. M. Chilali and P. Apkarian, "Robust Pole Placement in LMI Regions," *IEEE T Automat Contr*, vol. 44, no. 12, pp. 2257 – 2270, 1999.

[24] M. Bouazizi, A. Kochbati, and M. Ksouri, "LPV Control with Observer and Dynamic Compensator," in *Proceedings of the European Control Conference 2001*. IFAC, pp. 444 – 450.

[25] W. El Messoussi, O. Pagés, and A. El Hajjaji, "Observer-based robust control of uncertain fuzzy dynamic systems with pole placement constraints: an LMI approach," in *2006 American Control Conference*, 2006, pp. 6 pp.–.

[26] J. Löfberg, "Yalmip : A toolbox for modeling and optimization in matlab," in *Proceedings of the CACSD Conference, Taipei, Taiwan*, 2004.

[27] M. ApS, *The MOSEK optimization toolbox for MATLAB manual. Version 7.1 (Revision 28).*, 2015. [Online]. Available: http://docs.mosek.com/7.1/toolbox/index.html